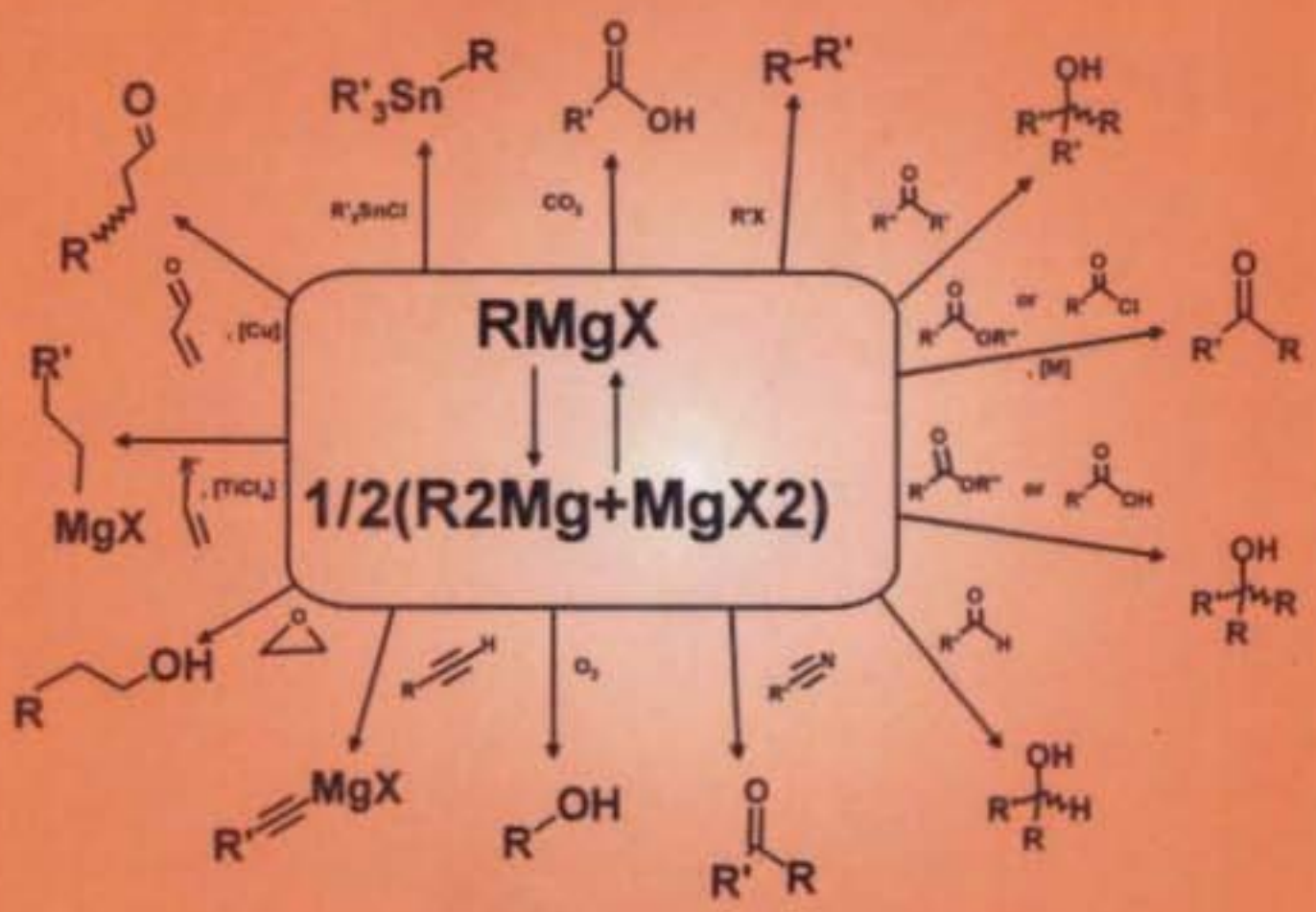
HANDBOOK OF GRIGNARD REAGENTS



edited by
Gary S. Silverman
Philip E. Rakita

Materiał chroniony prawem autorskim

Contents

Preface *iii*
Contributors *xxi*

PART I: INTRODUCTION

1. Introduction **1**
Philip E. Rakita

I. Historical Background 1
II. The Nature of the Grignard Reagent 3
III. Scope of the Grignard Reaction 3
IV. Organization of this Book 6
References 7

PART II: METHODS OF GRIGNARD REAGENT PREPARATION

2. Common Methods of Grignard Reagent Preparation **9**
Gary S. Silverman

I. General Discussion on the Reaction of Magnesium and RX 9
II. Effect of Water and Oxygen on Grignard Reagent Preparation 10

III. Effect of Solvent on Grignard Reagent Preparation 10
IV. Effect of RX on Grignard Reagent Preparation 13
V. Preparation of *n*-Butylmagnesium Chloride 15
VI. Alternative Methods for Grignard Reagent Preparation 17
References 20

3. Preparation of Grignard Reagents from Olefins and Acetylenes 23
Fumie Sato and Hirokazu Urabe

I. Introduction 23
II. Hydromagnesation of Olefins and Acetylenes 24
III. Carbomagnesation of Olefins and Acetylenes 33
IV. Reductive Metallation of Dienes 42
V. Isomerization of Olefinic and Acetylenic Grignard Reagents 45
VI. Conclusion 49
References 49

4. Magnesium Activation 53
Reuben D. Rieke and Matthew S. Sell

I. Introduction 53
II. General Methods of Magnesium Activation 54
A. Removal of Oxide Layers 54
B. The "Dry-Stir" Method 54
C. Gilman Catalyst 57
D. Vitride Addition 58
E. Magnesium Activation by Entrainment 58
F. Metal Atom Vaporization 60
G. Ultrasound Magnesium Activation 61
H. Magnesium–Anthracene Methods 62
I. Choice of Solvent 64
III. Magnesium Activation by the Rieke Methods 64
A. History 64
B. Contemporary Methods 65
C. Grignard Reactions Using Rieke Magnesium 69
References 75

PART III: SAFE HANDLING PRACTICES

5. Safe Handling Practices of Industrial Scale Grignard Reagents 79
Philip E. Rakita

I. Introduction 79
II. Principles of the Industrial Manufacturing Process 80
A. Formation of the Grignard Reagent 80
B. Reaction of the Grignard Reagent with a Substrate 80
C. Hydrolysis of the Reaction Mixture 82

III. Safety Considerations 82
A. Scale-up 82
B. Handling and Storage Procedures 82
C. Transfer Procedures 83
D. Disposal of Waste 83
IV. Hazard Control and Management 85
A. Spills 85
B. Fires 85
C. Toxicity and Toxic By-products 85
V. Regulatory Compliance 86
A. Commercial Use 86
B. Air, Water, Solid Waste Compliance 86
C. Transportation 87
D. Storage 87
References 87

PART IV: ANALYSES OF GRIGNARD REAGENTS

6. Wet Analyses of Grignard Reagents 89
Gary S. Silverman
I. Quantitative Wet Analyses 89
II. Procedures for Quantitative Wet Analyses 90
A. Preparation and Standardization of 2-Butanol Solution 90
B. Determination of Grignard Reagent Activity 91
C. Determination of Grignard Reagent Acid–Base Value 91
References 92

7. Infrared and Raman Spectroscopy 93
Paul Chabot
I. Aliphatic Grignard Reagents 93
II. Allylic Grignard Reagents 98
III. Other Grignard Complexes 100
References 102

8. Nuclear Magnetic Resonance Analyses of Grignard Reagents 103
Jo-Anne K. Bonesteel
I. Introduction 103
II. Proton Chemical Shifts in Grignard Reagents 103
A. Overview 103
B. Internal Dynamics of Organic Molecules 104
III. Magnesium-25 108
A. Overview 108
B. Chemical Shifts and Line Widths 108
C. Schlenk Equilibrium 109

IV. Carbon-13 111
A. Overview 111
B. Chemical Shifts 112
References 115

9. Crystal Structures of Grignard Reagents 117
Haewon L. Uhm

I. Introduction 117
II. Structures of Haloorganomagnesium Compounds 118
A. Tricoordinated Haloorganomagnesium 118
B. Tetracoordinated Haloorganomagnesium 118
C. Pentacoordinated Haloorganomagnesium 122
D. Hexacoordinated Haloorganomagnesium 123
III. Structures of Diorganomagnesium Compounds 124
A. Di- and Tricoordinated Diorganomagnesium 125
B. Tetracoordinated Diorganomagnesium 127
C. Penta- and Hexacoordinated Diorganomagnesium 131
D. Polyether-Containing Organomagnesium 133
IV. Bimetallic Magnesium Compounds 136
V. Structures of Magnesium Dihalide and other Magnesium Compounds 139
References 141

PART V: MECHANISMS AND STRUCTURE–REACTIVITY RELATIONSHIPS

10. Mechanism of Grignard Reagent Formation 145
Chafiq Hamdouchi and Harry M. Walborsky

I. Introduction 145
II. Why Were Chiral Cyclopropyl and Vinyl Systems Selected for Investigating the Mechanism of Organometallic Compound Formation 147
A. Cyclopropyl and Vinyl Radicals 147
B. Cyclopropyl and Vinyl Carbanions and Organometallic Reagent 152
III. The Mechanism of Grignard Reagent Formation 155
A. Intermediacy of Radicals and Pathways Leading to Radicals and to Grignard Reagent: Optically Active Grignard Reagent 155
B. Halogen Effect on the Stereochemistry of the Grignard Formation Reaction 159
C. Nature of the Radicals 160
D. Kharasch–Reinmuth–Walborsky Mechanism for Grignard Reagent Formation 163
E. General Acceptance and Support 164
IV. A Mathematical Approach to Establishing a Mechanism 185
A. Diffusion Model Calculation and Assumptions 185
B. D-Model Accommodation in the Kinetic Treatment and Error in Both Diffusion Concept and Nature of the Reactive Surface 187

C. Disagreement Between the Calculated and the Experimental Results 189
V. Further Evidence for the Surface Nature of Grignard Reagent Formation 195
A. Formation of Grignard Reagent in the Presence of Monodeuterated Alcohols 195
B. Radical-Trapping Experiments 203
VI. The Question of an Anion Radical 206
A. Background 206
B. Criticism 207
C. Only the Surface Nature of the Reaction Could Predict Retention 208
D. Electrochemical Approach 209
VII. Conclusion 213
References 214

11. Mechanisms of Reactions in Grignard Reagents 219
Cornelis Blomberg

I. Introduction 219
II. Mechanism of the Carbonyl Addition Reaction 222
A. Homolytic Versus Concerted Mechanisms 222
B. Development of a Reactivity Spectrum 227
C. Concerted Mechanism 237
D. Reactivity of Various Magnesium Species 242
III. Conclusion 246
References 246

12. Structure-Reactivity Relationships 249
Cornelis Blomberg

I. Introduction 249
II. Specific Features of Reactivity 251
A. Reactivity in General 251
References 268

13. The Composition of Grignard Reagents in Solution: The Schlenk Equilibrium and Its Effect on Reactivity 271
Kevin C. Cannon and Grant R. Krow

I. Introduction 271
II. Factors Affecting the Composition of Grignard Reagents in Solution 273
A. Solvent and Concentration Effects 273
B. Anionic Nonalkyl Ligand Effects 276
C. Alkyl and Aryl Ligand Effects 278
D. Temperature Effects 281
III. Synthetic Usefulness of Schlenk Equilibria Manipulations 283
A. 1,2-Carbonyl Additions 283
B. Conjugate Additions 285
C. Displacement Reactions 287
D. Reductive Dehalogenation 287
References 288

14. Effect of Tris(pyrazolyl)hydroborato Ligation **291**
Gerard Parkin

I. Introduction 291
II. Syntheses and Structures of Monomeric Four-Coordinate Tris(pyrazolyl)hydroborato Magnesium Alkyl Derivatives 292
A. Tris(pyrazolyl)hydroborato Ligands 292
B. Syntheses of $[Tp^{R,R'}]MgR$ Complexes 293
C. Structures and Spectroscopic Properties of $[Tp^{R,R'}]MgR$ Complexes 294
III. Reactivity Studies of $[Tp^{R,R'}]MgR$ Complexes 297
A. Ligand Redistribution 297
B. Reactions with Carbonyl Derivatives 298
C. Reactions with Oxygen 299
D. Reactions with HX and RX 302
IV. Comparison of $[Tp^{R,R'}]MgR$ with Other Alkyl and Hydride Derivatives 304
V. Summary 304
References 305

PART VI: GENERAL REACTIONS OF GRIGNARD REAGENTS

15. Nucleophilic Substitution with Electrophilic Organic, Main Group, and Transition Metal Species **307**
Gary S. Silverman

I. Introduction 307
II. Electrophilic Organic Species 307
A. Potential Problems 307
B. Effect of Leaving Groups 309
C. Nucleophilic Aromatic Substitution 317
D. Epoxide (Oxirane) Ring Openings 322
III. Electrophilic Main Group Species 325
A. Potential Problems 325
B. Potential Solutions to Minimize Competing Reactions 326
IV. Electrophilic Transition Metal Species 334
A. Potential Problems 334
B. Potential Solutions to Minimize Competing Reactions 340
C. Examples of Applications 343
V. Summary 349
References 349

16. Nucleophilic Addition to Unconjugated C–C Multiple Bonds **355**
Philip E. Rakita

I. Introduction 355
II. Factors Affecting the Addition of RMgX to Unconjugated C–C Multiple Bonds 355
III. Intramolecular "Magnesium-ene" Reaction 356

IV. Stereochemistry of Addition 357
V. Addition to Simple Alkenes 357
VI. Addition to Alkynes 358
A. Terminal Alkynes 358
B. Internal Alkynes 358
References 359

17. Nucleophilic Addition to Carbon–Heteroatom Multiple Bonds: O, S, N, P 361
Léone Miginiac

I. Introduction 361
II. Nucleophilic Addition to C=O Bonds 361
A. Aldehydes and Ketones 361
B. Esters, Acyl Chlorides, Anhydrides, and Amides 363
C. Carbon Dioxide and Derivatives 364
III. Nucleophilic Addition to C=S Bonds 364
A. Thioketones 364
B. Dithioesters 365
C. Carbon Disulfide and Carbon Sulfide 366
IV. Nucleophilic Addition to C=N Bonds 366
A. Aldimines and Ketimines 366
B. Iminium Salts 367
C. Iminoethers and Iminothioethers 368
D. Iminocarbonates 368
E. Carbodiimides 369
V. Nucleophilic Addition to C≡N Bonds 369
VI. Nucleophilic Addition to C=P or C≡P Bonds 369
References 370

18. Nucleophilic Addition to Metal–Carbon Multiple Bonds 373
Lisa A. Mercando and Paul Mercando

I. Introduction 373
II. Transition Metal Carbene Complexes 373
III. Transition Metal Carbyne Complexes 377
IV. Conclusion 379
References 379

19. Nucleophilic Addition to Conjugated Carbon–Carbon Multiple Bonds 381
Philip E. Rakita

I. Introduction 381
II. Factors Affecting the Addition 381
III. Stereochemistry 382
IV. Addition to Alkenes 383
A. 1,3-Dienes 383
B. Other Conjugated Olefins 385
C. Enones 385
D. Metal-Complexed Systems 386
V. Addition to Aromatic Nuclei 386
A. Substituted Arenes 386

B. Aryne Quenching 386
VI. Miscellaneous 387
References 388

20. Nucleophilic Addition to Conjugated Carbon–Heteroatom Multiple Bonds: O, S, N 391
Léone Miginiac

I. Introduction 391
II. Nucleophilic Addition to Conjugated C=O Bonds 391
A. Conjugated Aldehydes and Ketones 391
B. Conjugated Esters 392
C. Conjugated Amides 393
D. Alkylidene Malonates and Cyanacetates 393
III. Nucleophilic Addition to Conjugated C=S Bonds 393
IV. Nucleophilic Addition to Conjugated C=N Bonds 394
V. Nucleophilic Addition to Conjugated C≡N Bonds 394
VI. Conclusion 395
References 395

21. Nucleophillic Addition to Organometallic Vinylidene and Allyl Complexes 397
Lisa A. Mercando and Paul Mercando

I. Introduction 397
II. Transition Metal Vinylidene Complexes 397
III. Transition Metal Allyl Complexes 400
IV. Conclusion 403
References 403

PART VII: SPECIAL TOPICS: APPLICATIONS AND REACTIONS OF GRIGNARD REAGENTS

22. The Barbier Reaction 405
David A. Russo

I. Introduction 405
II. Mechanism 406
III. Addition Reactions 407
A. With Aldehydes and Unsaturated Halides 407
B. With Aldehydes and Saturated Halides 408
C. With Ketones and Unsaturated Halides 409
D. With Ketones and Saturated Halides 411
E. With Esters, Amides, Nitriles, Epoxides 412
F. With Other Unsaturation 413
IV. Cyclization Reactions 414
V. Coupling Reactions 417
VI. Dimerizations 417
VII. Wittig-Type Reactions 418

VIII. Phosphorus and Other Metals 418
A. Phosphorus 418
B. Tin 418
C. Germanium 419
D. Lead and Gallium 420
IX. Organosilane Reactions 420
A. Addition Reactions 420
B. Carbon and Oxygen Silylation 425
C. Cyclization Reactions 426
D. Coupling Reactions 428
X. Ultrasonic Reactions 434
XI. Reaction with Other Metals and Metal Halides 435
References 435

23. Grignard Reagents as Bases **441**
Walter Kosar

I. Introduction 441
II. Basicity Theory and Measurement 442
III. Metallation 443
A. Intramolecular Rearrangements 443
B. Enolates 445
C. Miscellaneous Reactions 450
IV. Eliminations 451
V. Summary 452
References 452

24. S_N2 Versus S_N2' **455**
Bruno Figadère and Xavier Franck

I. Introduction 455
II. Reactions with Organomagnesium Reagents 457
A. Allylic Halides 457
B. Allylic Phosphates 458
C. Allylic Ethers 459
D. Allylic Ammonium Salts 459
E. Propargyl Alcohols 460
F. Propargyl Halides 460
G. Propargyl Acetates 461
H. Propargyl Ethers 462
I. Propargyl Oxiranes 462
J. Vinyl Oxiranes 463
K. Intramolecular Reactions 463
III. Reactions Catalyzed by Copper 464
A. Allylic Halides 464
B. Allylic Phosphates 467
C. Allylic Ethers 469
D. Allylic Carboxylates 471
E. Vinyl Oxiranes 476
F. Allylic Aziridines 478

Material chroniony prawem autorskim

G. Allylic Ammonium Salts 479
H. Allylic Sulfides 479
I. Allylic Sulfones 481
J. Allylic Tosylates 483
K. Propargyl Oxiranes 483
L. Propargyl Ethers 485
M. Propargyl Acetates 487
N. Propargyl Sulfinates 488
O. Propargyl Tosylates 488
IV. Reactions Catalyzed by Palladium 489
A. Allylic Halides 489
B. Allylic Acetates 489
C. Allylic Ethers 489
D. Allylic Sulfides 489
E. Propargyl Halides 490
V. Reactions Catalyzed by Other Transition Metals (Ni, Fe, Co, Mn) 490
A. Allylic Alcohols 490
B. Allylic Phosphates 491
C. Allylic Sulfides 492
D. Propargyl Chlorides 492
VI. Conclusion 493
References 494

25. Dihalide-Derived Di-Grignard Reagents: Preparation and Reactions 497
Kevin C. Cannon and Grant R. Krow

I. Introduction 497
II. Alkyl Di-Grignard Reagents 497
III. Reactions of Benzyl and Mixed Benzyl-Aryl Di-Grignard Reagents 511
IV. Reaction of Vinyl and Mixed Vinyl-Alkyl Di-Grignard Reagents 515
V. Reaction of Diaryl Di-Grignard Reagents 517
VI. Reactions of Acetylenic and Mixed Aryl-Acetylenic Di-Grignard Reagents 520
VII. Reactions of Allyl Di-Grignard Reagents 521
References 522

26. Formation and Reactions of Substituted (2-Butene-1,4-diyl)magnesium Complexes 527
Reuben D. Rieke and Matthew S. Sell

I. Introduction 527
II. Reactivity 528
III. Regioselectivity 529
IV. Preparation of Heterocycles and Spiro Compounds 533
V. Preparation of 1,3-Dienes 534
VI. Preparation of Cyclic Dienes 537
References 538

Materiał chroniony prawem autorskim

27. Spiroannulations Using Substituted (2-Butene-1,4-diyl)magnesium Complexes 539
Reuben D. Rieke and Matthew S. Sell

I. Introduction 539
II. Reactions of 1,2-Dimethylene Cyclohexane-Magnesium Complex 539
A. With Bis-electrophiles 539
B. With Bromoalkylnitriles 540
C. Reaction with Ethyl Acetate 542
III. Synthesis of Fused Carbocycles 543
A. Synthesis of Spiro γ-Lactones 546
B. Synthesis of Spiro δ-Lactones 548
IV. Generation of Quaternary Carbon Centers 549
A. Synthesis of Alcohols 549
B. Synthesis of γ-Lactams 550
References 554

28. Asymmetric Synthesis Using Grignard Reagents 557
John T. Roberts

I. Introduction 557
II. Addition to Carbonyl Derivatives 558
A. 1,2-Additions 558
B. 1,4-Additions 565
III. Nucleophilic Substitution Reactions with Grignard Reagents 568
IV. Miscellaneous Reactions 570
V. Summary 573
References 573

29. Metal-Catalyzed Reactions 577
Hirokazu Urabe and Fumie Sato

I. Introduction 577
II. Copper-Catalyzed Reactions 578
A. Substitution Reaction 578
B. 1,2-Addition Reactions to Carbonyl Compounds 592
C. 1,4-Addition Reaction to α,β-Unsaturated Carbonyl Compounds 592
D. Carbonmagnesation of Olefins and Acetylenes 599
III. Nickel-Catalyzed Reactions 599
A. Substitution Reaction 599
B. Carbonyl Addition 611
C. Hydro- and Carbomagnesation of Olefins and Acetylenes 611
IV. Palladium-Catalyzed Reactions 611
V. Titanium-Catalyzed Reactions 615
VI. Miscellaneous Metal-Catalyzed Reactions 617
Glossary 621
References 622

30. The Preparation of 1,1-Bimetallics of Magnesium and Zinc 633
Paul Knochel

I. Introduction 633

Materiał chroniony prawem autorskim

II. Preparation of Mixed 1,1-Bimetallics of Magnesium and Zinc 634
III. Reactions of Mixed 1,1-Bimetallics of Magnesium and Zinc 636
A. Selective Reactions with Electrophiles 636
B. Olefination Reactions 637
C. Oxidation of 1,1-Bimetallics of Magnesium and Zinc 640
IV. Related Reagents 641
References 642

31. Alkynyl Grignard Reagents and Their Uses 645
Masayuki Umeno and Akio Suzuki

I. Introduction: Future of Acetylenic Compounds 645
II. General Methods of Preparation for Acetylenic Compounds 646
A. Elimination of Hydrogen Halogenide and Dehalogenation of Alkylhalogen Compounds 646
B. Introduction to Acetylenic Group with Metal Acetylide and Acetylenic Compounds 646
III. Preparation of Acetylenic Grignard Reagents 647
A. Preparations and Properties 647
B. Ethynylmagnesium Halides, Bis(halogenomagnesium)-acetylene 650
IV. Reactions of Acetylenic Grignard Reagents 650
A. 1,2-Addition Reactions with Carbonyl Compounds 653
B. Nucleophilic Addition to Epoxy Compounds 654
C. Nucleophilic Substitution with Acetals and Aldehydes 655
D. Acetylenic Carboxylation and Acylation 655
E. Nucleophilic Substitution Reactions 656
F. Conjugated Alkynes and Polyalkynes 657
G. Organometallic Acetylene Compounds with Metal Halides 658
H. Reactions of Propargyl and Its Protected Grignard Reagents 660
V. Protecting Methods for Acetylenic Compounds 661
References 662

32. Grignard Reagents and Silanes 667
Barry Arkles

I. Introduction 667
II. Formation of the Silicon–Carbon Bond 667
A. Background 667
B. Reactivity Trends for Grignards and Silanes 669
C. Process Chemistry with Ethers 671
D. Process Chemistry Without Ethers 672
III. Silane-Blocking Agents 672
IV. Conclusion 673
References 674

33. Ziegler–Natta Catalysis 677
Brian W. S. Kolthammer

I. Introduction 677
II. Grignard Reagents as a Second Component 678

III. Grignard Reagents as Precursors to Catalyst Supports 679
IV. Modification of Heterogeneous Surfaces 681
V. Dialkylmagnesium Reagents in Ziegler–Natta Catalysis 682
References 683

34. Organomagnesium Compounds as Polymerization Initiators 685
Xavier Drujon

I. Introduction 685
II. Polymerization of Methyl Methacrylate Using Organomagnesium Initiators 686
A. Description of Stereoregularity in Poly(methyl methacrylate) 686
B. Forces of Stereoregulation in Methyl Methacrylate Polymerization 686
C. Polymerization of Methyl Methacrylate Using Organomagnesium Initiators 688
III. Polymerization of Other Acrylic and Methacrylic Esters Using Grignard Reagents 692
IV. Anionic Polymerization of Other Unsaturated Monomers Using Organomagnesium Compounds 694
A. Nitrogen-Containing Monomers 695
B. Halogenated Monomers 697
C. Styrenic Monomers 697
D. Hydrocarbon Monomers 698
References 698

Index 703

Contributors

Barry Arkles, Ph.D. President, Gelest Inc., Tullytown, Pennsylvania

Cornelis Blomberg, Ph.D. Free University, Amsterdam, The Netherlands

Jo-Anne K. Bonesteel, Ph.D. Group Supervisor, Molecular and Polymer Characterization, Department of Research and Development-Central Analytical Chemistry, Elf Atochem North America, Inc., King of Prussia, Pennsylvania

Kevin C. Cannon, Ph.D. Research Scientist, Specialty Chemicals Group, Elf Atochem North America, Inc., King of Prussia, Pennsylvania

Paul Chabot, Ph.D. Research Scientist, Department of Central Analytical Chemistry, Elf Atochem North America, Inc., King of Prussia, Pennsylvania

Xavier Drujon, Ph.D. Groupement de Recherches de Lacq, Elf Atochem S.A., Lacq, France

Bruno Figadère, Dr.Sc. Department of Organic Chemistry, Faculté de Pharmacie, Université Paris-Sud, Châtenay-Malabry, France

Xavier Franck Doctoral Candidate, Department of Organic Chemistry, Faculté de Pharmacie, Université Paris-Sud, Châtenay-Malabry, France

Chafiq Hamdouchi, Ph.D. Research Scientist, Lilly Research Center, S.A., Madrid, Spain

Material chroniony prawem autorskim

Paul Knochel Professor Doctor, Department of Chemistry, University of Marburg, Marburg, Germany

Brian W. S. Kolthammer, Ph.D. Associate Scientist, Department of Polyolefins and Elastomers Research, The Dow Chemical Company, Freeport, Texas

Walter Kosar, Ph.D. Research Scientist, Department of Industrial Specialties, Elf Atochem North America, Inc., King of Prussia, Pennsylvania

Grant R. Krow, Ph.D. Professor, Department of Chemistry, Temple University, Philadelphia, Pennsylvania

Lisa A. Mercando, Ph.D. Senior Research Chemist, Air Products and Chemicals, Inc., Allentown, Pennsylvania

Paul Mercando, Ph.D. Scientist, Specialty Chemicals Group, Elf Atochem North America, Inc., King of Prussia, Pennsylvania

Léone Miginiac Professor, Laboratoire de Synthèse Organique, Faculté des Sciences, Université de Poitiers, Poitiers, France

Gerard Parkin, D.Phil. Professor, Department of Chemistry, Columbia University, New York, New York

Philip E. Rakita, Ph.D.* Business Manager, Elf Atochem Agri, S.A., Plaisir, France

Reuben D. Rieke, Ph.D. Professor, Department of Chemistry, University of Nebraska and Rieke Metals, Inc., Lincoln, Nebraska

John T. Roberts, Ph.D. Director, Chemicals Research, Chemical Specialties and Plastic Additives, Elf Atochem North America, Inc., King of Prussia, Pennsylvania

David A. Russo, Ph.D. Research Scientist, Specialty Chemicals Group, Elf Atochem North America, Inc., King of Prussia, Pennsylvania

Fumie Sato, Ph.D. Professor, Department of Biomolecular Engineering, Tokyo Institute of Technology, Yokohama, Kanagawa, Japan

Matthew S. Sell Research Chemist, Rieke Metals, Inc., Lincoln, Nebraska

Gary S. Silverman, Ph.D. Principal Scientist, Specialty Chemicals Group, Elf Atochem North America, Inc., King of Prussia, Pennsylvania

Akio Suzuki, Ph.D. Senior Technical Advisor, Fine Chemicals Division, Hokko Chemical Industry Co., Ltd., Tokyo, Japan

---

**Former affiliation*: Akishima Chemical Industries Co., Ltd., Tokyo, Japan

Material chroniony prawem autorskim

Haewon L. Uhm, Ph.D. Scientist, Specialty Chemicals Group, Elf Atochem North America, Inc., King of Prussia, Pennsylvania

Masayuki Umeno Manager, Process Research, Fine Chemicals Research Laboratories, Hokko Chemical Industry Co., Ltd., Atugi, Kanagawa, Japan

Hirokazu Urabe, Ph.D. Assistant Professor, Department of Biomolecular Engineering, Tokyo Institute of Technology, Yokohama, Kanagawa, Japan

Harry M. Walborsky, Ph.D. Professor, Department of Chemistry, The Florida State University, Tallahassee, Florida

Materiał chroniony prawem autorskim

1

Introduction

PHILIP E. RAKITA
Akishima Chemical Industries Co., Ltd., Tokyo, Japan

I. HISTORICAL BACKGROUND

Of all the "name reactions" in chemistry, there is arguably none better known than the "Grignard reaction." It is hardly an exaggeration to say that virtually every chemist, at some time or another in his or her professional life, has carried out a Grignard reaction. The great scope and the versatility of this reaction has made it a frequent choice for laboratory synthesis and, increasingly, for the industrial production of high–value-added specialty chemicals used as catalysts or for intermediates in the food, flavor, fragrance, and pharmaceutical industries.

The term *Grignard reaction* actually refers to two separate steps:

1. The formation of a Grignard reagent from the reaction of magnesium with an organic halide in a suitable solvent [Eq. (1)].

$$RX + Mg + nS \rightarrow RMgX \cdot S_n \quad (1)$$

2. The subsequent reaction of this reagent with an organic or inorganic substrate to yield a product by either addition [Eq. (2)] or substitution [Eq. (3)].

$$RMgX \cdot S_n + AZ \rightarrow RAZMgX \cdot S_n$$
$$RAZMgX \cdot S_n + H_2O \rightarrow RAZH + MgXOH + S_n \quad (2)$$

$$RMgX \cdot S_n + AZ \rightarrow RAZMgX \cdot S_n$$
$$RAZMgX \cdot S_n \rightarrow RA + ZMgX \cdot S_n \quad (3)$$

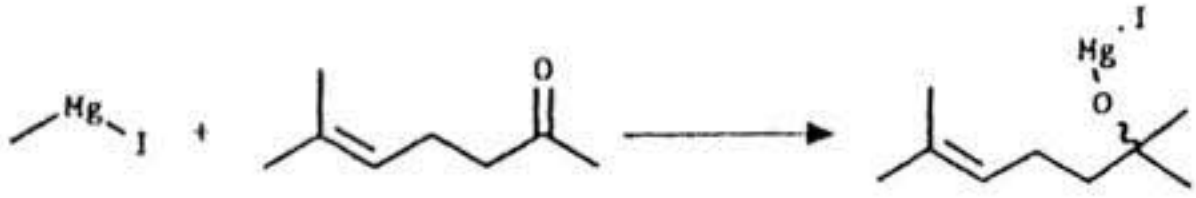
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In Eq. (2), the workup typically involves a water cleavage of the Mg-Z bond, whereas for Eq. (3), there is a spontaneous elimination of the magnesium-containing fragment. Together (either 1+2 or 1+3) these steps constitute what today is meant by a Grignard reaction.

The first example of what is now known as a Grignard reaction was observed, in 1899, by Barbier [1]. He reported that a mixture of methyl iodide, a methyl ketone, and magnesium metal in diethyl ether produced a tertiary alcohol. He assigned to his student, Victor Grignard, the task of unraveling the mechanism of this unusual result. The detailed studies by Grignard [2], first published in 1900 and presented in his doctoral thesis in 1901, established that the reaction observed by Barbier could be separated into three distinct steps:



(4)



(5)



(6)

The great value of his observation was the recognition that this sequence was quite general and could be used to prepare an extraordinary variety of new compounds. Grignard devoted much of the rest of his career to broadening the scope and understanding of this reaction and was recognized for his achievements with the Nobel Prize in Chemistry in 1912 at the age of 39. In the years that followed, the Grignard reaction was increasingly employed as a convenient and versatile tool for laboratory synthesis. However, the relatively high cost of magnesium and the more reactive organic bromides and iodides, as well as the hazards associated with diethyl ether as a solvent, proved to be limitations to commercialization on an industrial scale.

Starting in the 1950s, several developments lead to improved industrial procedures. These included the substitution of tetrahydrofuran (THF) [3] for diethyl ether, together with the recognition that the less reactive, but significantly less expensive, organic chlorides could be successfully used in place of the bromides or iodides [4–7]. Several companies, including Arapahoe Chemicals (now part of Syntex) and M&T Chemicals (now part of Elf Atochem) among others, became merchant suppliers of Grignard reagents in production quantities to the fine chemical industry for the manufacture of flavor, fragrance, and pharmaceutical intermediates.

Today, less than 100 years after the first discovery of this reaction, the chemical literature contains tens of thousands of references to this reaction, and the industrial production of Grignard reagents for captive use or merchant sale is estimated to exceed 50,000 tons annually [8]. The scope and potential for the Grignard reaction continues to grow and new discoveries and improvements in method are regularly reported. The balance of this book is devoted to detailed reports on the preparation, analysis, structure, and reactivity of Grignard reagents and a selection of topics and applications of current interest.

Material chroniony prawem autorskim

II. THE NATURE OF THE GRIGNARD REAGENT

The original formula, **RMgX**, first proposed for the Grignard reagent, by Victor Grignard himself, has a convenience and economy of style that belies its true nature. Following the initial reports, it became quickly apparent that the actual structure is far more complex, both in solution and in the solid state. One early suggestion [9] was an equilibrium of the type:

$$2RMgX \Leftrightarrow R_2Mg + MgX_2 \tag{7}$$

Supporting this view was the observation that dioxane could be used to precipitate MgX_2 from Grignard solutions. (This is, in fact, a convenient method for the preparation of solutions of dialkyl magnesium.) What followed was an extensive series of studies by Schlenk and Schlenk [10]. They proposed a set of equilibria, in which Eq. (7) was accompanied by Eq. (8),

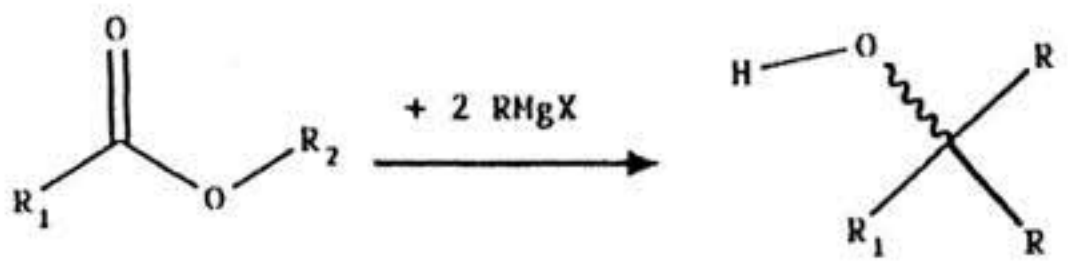
$$R_2Mg + MgX_2 \Leftrightarrow R_2Mg{\bullet}MgX_2 \tag{8}$$

to describe the behavior of the Grignard reagent in solution. Other studies, including conductivity, electrolysis, and isotopic exchange reactions, gave results that could variously be interpreted as supporting or contradicting the classic Schlenk equilibria. The earlier work was reviewed by Ashby, in 1974 [11], and supported the conclusion that all of the reported compositions of the Grignard reagent could be found, to some degree, depending on the nature of organic group, halide, solvent, concentration, and so forth. Nevertheless, for virtually all practical purposes, the simple, stoichiometric structure, **RMgX**, is sufficient to describe the Grignard reagent.

III. SCOPE OF THE GRIGNARD REACTION

The great value of the Grignard reaction to the synthetic chemist is its generality as a building block for an impressive range of structures and functional groups. Similar to other organometallic compounds of the group I, II, and III elements (for example, organolithium and organoaluminum compounds), Grignard reagents act as both (1) prototypical carbon nucleophiles that can undergo addition or substitution reactions and (2) strong bases that can deprotonate acidic substrates, giving conjugate bases or products of elimination reactions. A classic, if by now somewhat dated compendium of the reactions of Grignard compounds with non metallic substances is the volume by Kharasch and Reinmuth [12].

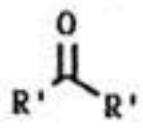
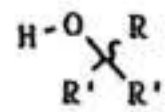
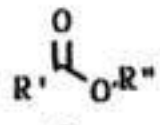
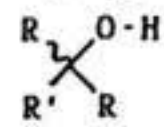
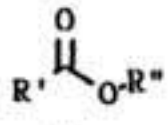
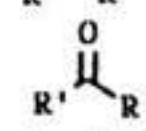
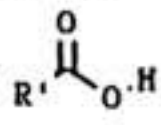
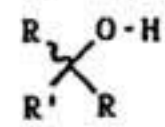
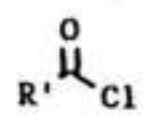
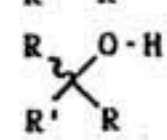
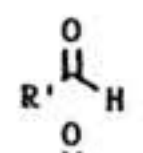
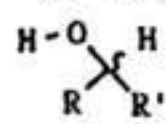
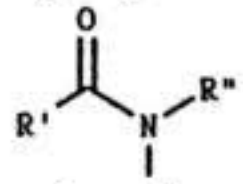
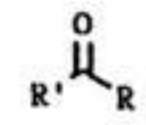
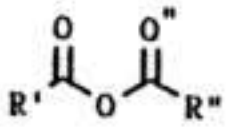
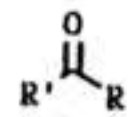
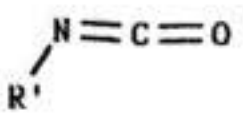
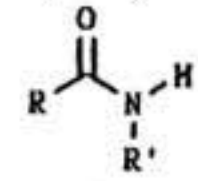
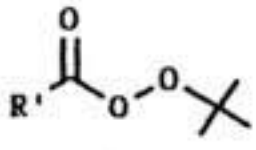
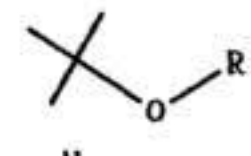
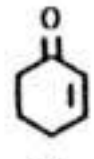
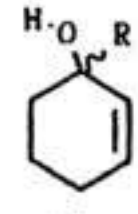
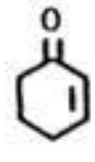
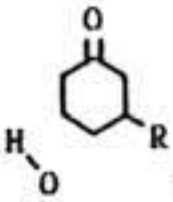
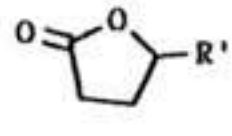
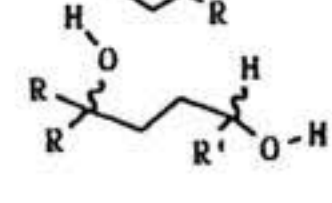
Grignard reagents react with most organic functional groups containing polar multiple bonds (e.g., ketones, nitriles, sulfones, imines), highly strained rings (e.g., epoxides and some cycloalkenes), acidic hydrogens (e.g., alkynes), and some highly polar single bonds (e.g., carbon–halogen or metal–halogen). A summary list is presented in Table 1. Although this table is by no means exhaustive, it illustrates the breadth and richness of possibilities available with the Grignard reaction. To give only two examples, a variation of reaction conditions permits the conversion of an ester to either a tertiary alcohol (see Table 1, entry 9)



(9)

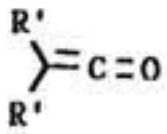
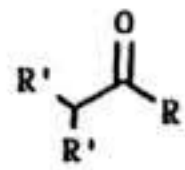
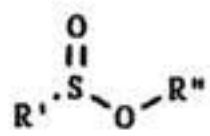
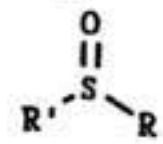
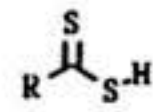
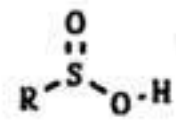
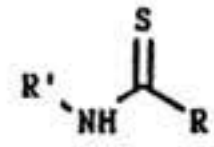
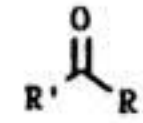
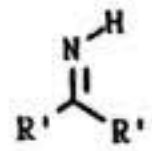
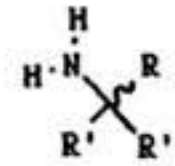
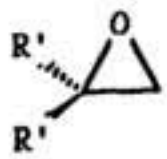
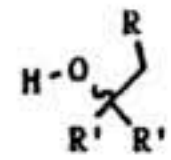
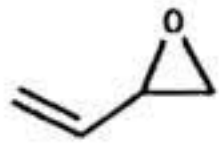
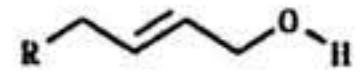
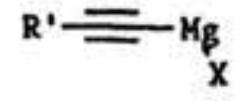
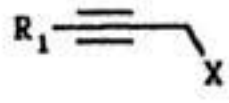
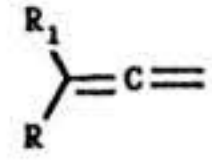
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Table 1 Reaction of RMgX with Substrates

Entry	Reactant	Comments	Product
1[12]	H_2O		RH
2[13]	O_2/H_2O		ROH
3[14]	CO_2/H_2O		RCO_2H
4[12]	I_2		RI
5[12]	R^1X		$R\text{-}R^1$
6[15]	MX_n	n RMgX	MR_n
7[12]	$COCl_2$	3 RMgX	R_3COH
8[11,16]			
9[12]		2 RMgX	
10[17]		catalyst	
11[12]		2 RMgX	
12[18]		2 RMgX	
13[11,16]			
14[17]			
15[17]			
16[19]			
17[20]			
18[21,22]			
19[23]		CuI, < -40°C	
20[24]		2 RMgX	

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Table 1 Continued

Entry	Reactant	Comments	Product
21[12]			
22[25]			
23[21]	R'SSR'	2 RMgX	RSR'
24[26]	S		RSH
25[26]	S	2 RMgX	RSR
26[27]	CS_2		
27[28,29]	SO_2		
28[12]	R'-N-C-S		
29[12,30]	R'—C≡N		
30[31]			
31[12,19,32]			
32[33]			
33[12]			
34[34]			

Source: All of the general reactions were taken from Elf Atochem, *The Handbook of Grignard Reactions*, 2nd ed. 1992, or Ref. 12.

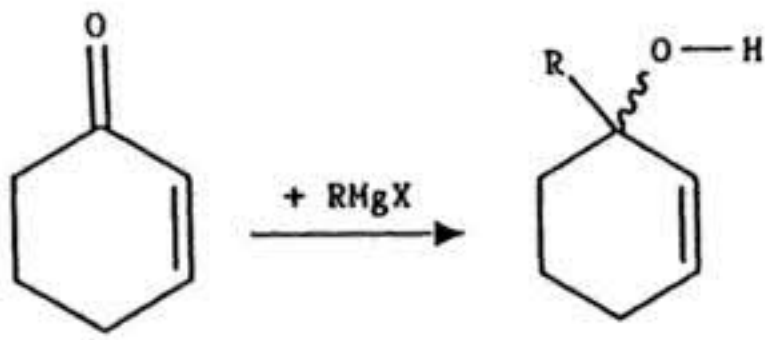
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or a ketone (see Table 1, entry 10).



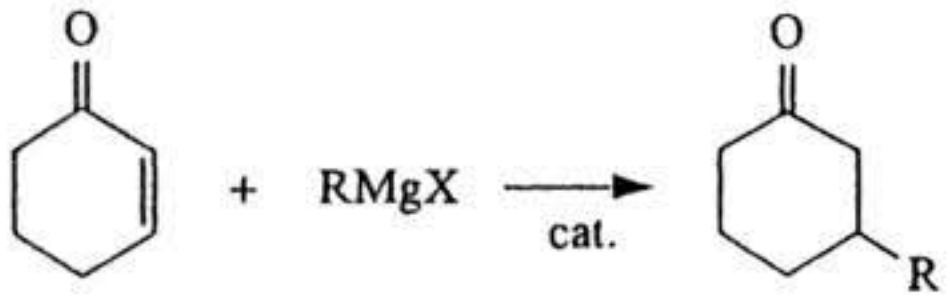
(10)

Likewise, the reaction of a Grignard reagent with a cyclohexenone can result in either 1,2-addition to produce a substituted cyclohexenol (see Table 1, entry 18)



(11)

or 1,4-addition to give a 3-substituted cyclohexanone (see Table 1, entry 19).



(12)

The specific reactions, classified according to type, are discussed in greater detail in Section VI (Chapters 15–21).

IV. ORGANIZATION OF THIS BOOK

General methods for the preparation of Grignard reagents are discussed in Chapter 2, their preparation from olefins in Chapter 3, and the special features of magnesium activation in Chapter 4. Safe-handling procedures are described in Chapter 5 and classic wet methods of analysis in Chapter 6. The spectroscopic analysis of Grignards by infrared (Chapter 7) and nuclear magnetic resonance (Chapter 8) reveal information concerning the structures present in solution, whereas X-ray crystallographic studies (Chapter 9) present the results in the solid state.

Further insight to the nature of the Grignand reagent can be obtained from studies of the mechanism of formation (Chapter 10) and reaction (Chapter 11) of Grignard reagents, and the relationships between structure and reactivity (Chapter 12). These are presented in Part V, along with a review of the Schlenk equilibrium (Chapter 13) and the effect of polypyrazoylborate ligands (Chapter 14). This is followed by discussions of the general classes of reactions (both substitution and addition reactions) in Part VI. Substitution reactions at single bonds are reviewed according to whether the electrophilic substrate is an organic main group element (Chapter 15) or a transition metal compound. Nucleophilic addition reactions at multiple bonds are classified according to whether the multiple bond is unconjugated carbon–carbon (Chapter 16), carbon–heteroatom (Chapter 17), or carbon–metal (Chapter 18); or conjugated carbon–carbon (Chapter 19), carbon–heteroatom (Chapter 20), or carbon–metal (Chapter 21).

Materiał chroniony prawem autorskim

Finally, Part VII (Chapters 22-34) is devoted to a series of special topics in Grignard chemistry, highlighting several areas of current research interest, activities, and applications.

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2

Common Methods of Grignard Reagent Preparation

GARY S. SILVERMAN
Elf Atochem North America, Inc., King of Prussia, Pennsylvania

I. GENERAL DISCUSSION ON THE REACTION OF MAGNESIUM AND RX

The prototypical Grignard reagent preparation involves the reaction of an alkyl or aryl halide (RX) with magnesium (Mg) in an ethereal solvent, under reflux conditions [1,2]. Initiation of this reaction should occur within the first 10–20 wt% addition of the RX solution. Evidence for this initiation is a large exotherm, and a visual change of the magnesium turnings from a bright-shiny silver color to a dull gray-black. Many chemists look for this color change in the magnesium or solution, but this can be misleading if the agitation is strong enough to shear the magnesium (see Chapter 4). Until initiation has been confirmed, no more than 20 wt% of the RX charge should be added to the reactor. Otherwise, one risks initiation of this exothermic reaction after all of the RX has been added. This is one of the major hazards in the Grignard reagent preparation, because the resulting rapid exotherm will cause a release of the reactor contents into the atmosphere. Therefore, an appropriate hazard review should be conducted before carrying out this reaction [3,4]. From a laboratory safety point of view the following precautions are recommended:

1. Isolate reaction setup in a hood.
2. Place a spill tray beneath the flask.
3. Install a vent relief and a surge flask to prevent the release of the RX–solvent mixture to the environment.
4. Use tetrahydrofuran (THF) instead of diethyl ether (Et_2O).
5. Use activity measurements (see Chapter 6) to determine if initiation has occurred.

Materiał chroniony prawem autorskim

The handling technique and choice of RX, solvent, and magnesium can have a significant effect on the preparation and yield of the Grignard reagent. Some of the potential problems are homocoupled product, intramolecular reactions, formation of "$RMgO_2X$," and the noninitiated reaction of RX with Mg. Therefore, proper manipulation and drying of each component must be carried out.

II. EFFECT OF WATER AND OXYGEN ON GRIGNARD REAGENT PREPARATION

The reaction apparatus, RX, solvent, and Mg must be dry (less than 0.02 wt% of H_2O) and free of O_2. If the H_2O content is above 0.02 wt%, then the reaction of Mg and RX will not initiate properly, except for an extremely reactive RX species, such as benzyl bromide.

Unfortunately, the presence of H_2O typically leads to a sudden initiation after all of the RX has been added. This takes place because the residual H_2O is azeotroped out of the mixture during reflux, or the H_2O is actually consumed by residual Grignard reagent in the flask, and the solution eventually reaches a dry, inert state, at which the reaction can initiate. The consequence is a sudden initiation, with a large exotherm that cannot be handled by the condenser, resulting in the reaction flask contents being spewed into the atmosphere. This is one of the most common mistakes that a novice Grignard chemist will make.

To prevent the foregoing scenario, all solvents and reactants should be dried and manipulated under nitrogen (argon) by standard Schlenk or glovebox techniques [5]. Since H_2O reacts with Grignard reagents to form the resulting protonated product [Eq. (1)] [1,2], then H_2O can be eliminated by the addition of the same Grignard reagent from a previous reaction. In fact this method of eliminating H_2O is the most cost-effective way to make Grignard reagents on an industrial scale [6].

$$RMgX + H_2O \longrightarrow R{-}H + MgX(OH) \tag{1}$$

Other precautions that should be taken are to confirm initiation (exotherm and an activity titration) and, under all circumstances, no more than 20 wt% of the RX should be added until initiation has been confirmed.

Although adventitious O_2 will not retard the initiation process, the O_2 will react with the Grignard reagent to form an $RMgO_2X$ species (see Chapter 14). This peroxo-species can oxidize other reactants, ligands, catalyst, or final product in the subsequent coupling reaction. Furthermore, upon hydrolysis, the oxidized Grignard reagent will form an ROH species that may cause purification problems.

An example of this oxidation problem is observed in the preparation of triphenylphosphine using 3.15 equivalents of Grignard reagent [Eq. (2)] [7–9]. If this reaction is hydrolyzed in air instead of an inert N_2 atmosphere, then the amount of triphenylphosphine oxide will increase from less than 1 mol% to greater than 15 mol%. When there is no excess of the Grignard reagent, there is no increase in the amount of triphenylphosphine oxide formed in air (less than 1 mol%). This indicates that oxidation of the Grignard reagent is fast, probably diffusion-controlled, and that the peroxo-species is a better oxidant for triphenylphosphine than O_2.

$$Cl_3P + 3.15C_6H_5MgCl \longrightarrow 0.15(C_6H_5)_3PO + 0.85(C_6H_5)_3P \tag{2}$$

III. EFFECT OF SOLVENT ON GRIGNARD REAGENT PREPARATION

Diethyl ether has been the solvent of choice until alternative ethers became commercially available, in particular THF [10,11]. Virtually all ethereal solvents have been evaluated

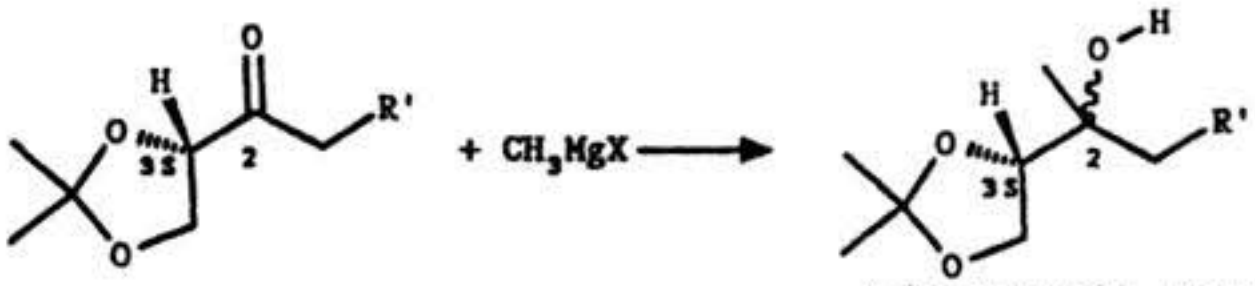
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as well as various nonpolar hydrocarbons. Therefore, preliminary thought should be spent on choosing the appropriate solvent for the Grignard reagent preparation and subsequent coupling reaction. There are four key considerations in choosing a solvent: chemistry, safety, economics, and reactivity.

The solvent can significantly affect the chemistry of the Grignard reagent, such as yield improvements [Eq. (3); 12], stereochemical [Eq. (4); 13] and regiochemical control [Eq. (5); 14], and the formation of dialkylmagnesium species [Eq. (6); 15]. These solvent effects can be attributed to the solvent's polarity, basicity, steric hinderance and shifts in the Schlenk equilibrium (see Chapter 13).

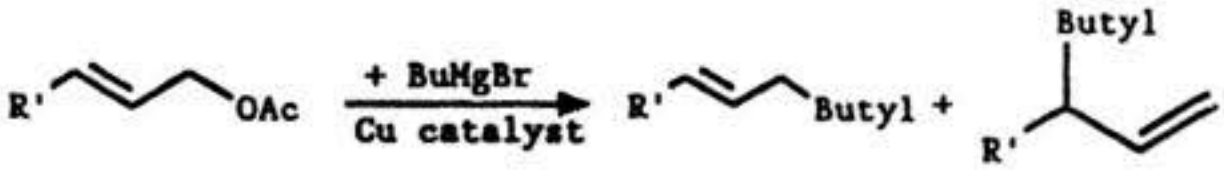
$$4C_6H_5Br + 4Mg + BF_3{\cdot}O(Et)_2 \longrightarrow (C_6H_5)_4BMgBr + 3MgBr(F) \qquad (3)$$

yield
THF = 96%
Et_2O = 4%



Solvent	Yield	SS:SR
THF	85 %	18:82
Et_2O	89 %	62:38

(4)



Product	Distribution,	mole %
THF -	99	1
Et_2O -	0	100

(5)

$$C_2H_5Cl + C_4H_9Cl + 2Mg \xrightarrow{\text{heptane}} C_2H_5MgC_4H_9 + MgCl_2 \qquad (6)$$

Safety issues are directly related to the solvent's flash point [6,16]. From this point of view, diethyl ether is the worst choice for a solvent (Table 1). Most industrial Grignard

Table 1 Selected Solvent Properties[a]

Property	THF	Et_2O	*n*-Hexane	Toluene	Xylene	1,4-Dioxane
Flash point (°C)	−14	−45	−22	4	27	12
TLV (ppm)	200	400	50	100	100	25
Basicity (B) [17,18]	142	129	—	—	—	—
Dielectric constant ($\varepsilon^{20°C}$)	7.54	4.34	1.89	2.378	2.3–2.5	2.20
Boiling point (°C)	66	34	68	111	135	101
Density (g/m)	0.89	0.71	0.66	0.87	0.87	1.04

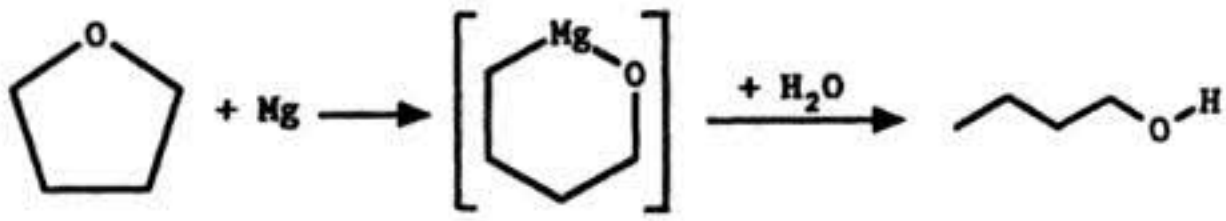
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processes have switched to THF in lieu of diethyl ether because of the flash point issue. Other safety considerations are the following: the raw materials (TLV), the reactive Grignard reagent, and peroxide formation in the ethers. Therefore, the Material Safety Data Sheet of the solvent and all of the reactants should be carefully read and understood by the chemist, so that the appropriate precautions are taken.

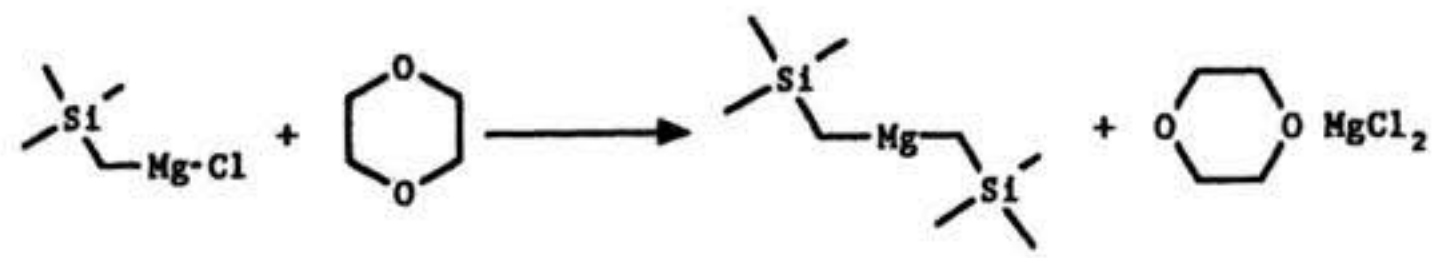
Economic considerations are not an issue for exploratory work carried out in the laboratory. However, these issues are pertinent from a business perspective. The following factors need to be evaluated: cost of the solvent, ease and cost of recycling the solvent, volume efficiency (solubility, especially for RMgCl derivatives), and required temperatures for preparation and subsequent coupling reactions. Given these criteria, diethyl ether falls short because of inefficient recovery, low reflux temperature limit at atmospheric pressure, and low RMgCl solubility relative to THF. The RMgCl is required because of the significant economic advantage that RCl has over RBr or RI.

The last consideration is the reactivity of the Grignard reagent with the solvent itself. Deleterious reactions of the Grignard reagent with ethereal solvents occurs only under extreme conditions and has been observed, to some extent, in diethyl ether, di-*n*-butyl ether, THF, *t*-butylmethyl ether, anisole (155°C), DME, and allylphenyl ether [Eq. (7); 19–24]. Since these reactions occur only under extreme conditions, the ethereal solvents are preferred because of the high Grignard reagent solubility (up to 4 *M*).



(7)

Amines can be used for Grignard reagent preparation, but the solubility is poor (less than 1 *M*) and, occasionally, formation of the ammonium salt will cause problems [1,25,26]. Hydrocarbon solvents, such as hexane and toluene, do not solubilize MgX_2 effectively, resulting in the formation of diorganomagnesium derivatives. This is a cost-effective method to prepare diorganomagnesium derivatives [15,27–30]. The insolubility of the MgX_2 is also observed with 1,4-dioxane and, to some degree, with chelating solvents such as TMEDA and hexamethylphosphoramide (HMPA). In fact the addition of 1,4-dioxane is a common technique to make halide-free R_2Mg [Eq. (8); 31–33)].



(8)

Taking the chemistry, safety, economics, and reactivity into account complicates the solvent choice and typically compromises must be made in at least one of the factors to meet the requirements for the application. The ethereal solvents are typically preferred because of the Grignard reagent's high solubility. From a safety, economic, and usually, a chemical perspective, THF is the best all-around solvent for Grignard reagents. However, THF does have limitations similar to the nonpolar solvents when RMgI species are desired (i.e., low solubility of MgI_2 resulting in the formation of R_2Mg).

Materiał chroniony prawem autorskim

IV. EFFECT OF RX ON GRIGNARD REAGENT PREPARATION

Both the halogen and the R group will affect the Grignard reagent preparation. For the halogen, the rate of disappearance of Mg follows the general order I > Br > Cl ≫ F. Unfortunately, the rate of disappearance of Mg does not always correlate with the formation of active Grignard. Typically, the more reactive the RX is, the higher the probability of forming a homocoupled product. Therefore, when choosing X, the rate of reactivity, solubility, product selectivity, and cost must be taken into account.

The general effect of R on the rate of disappearance of Mg is allyl, benzyl > primary alkyl > secondary alkyl, cycloalkyl ≥ tertiary alkyl, aromatic > vinyl. Again, the more reactive R is, the more probable the formation of homocoupled product. Another important consideration for the R group is the compatibility of functional groups in the organic halide. Because of the reactivity of the Grignard reagent (see Chapters 1, 15–21), noncompatible functional groups need to be protected. However, some chemists design a reactive functionality into the organic halide to carry out an intramolecular cyclization (see Chapters 25–27).

Since the reaction of RX with Mg to generate RMgX is a formal oxidative addition, then a better way to look at the reactivity is to consider the reduction potential of the RX. For the reaction to be thermodynamically feasible, ΔE must be positive (i.e., $a - \Delta G$). This means that the reduction potential for RX must be more positive than the reduction potential of Mg^{2+} to Mg, which has a standard reduction potential of −2.375 V [34]. Since the reduction potentials are greatly affected by solvent and reference electrode, comparisons and discussion of trends must be made under the same electrochemical system (Table 2).

The reduction potentials, within the same electrochemical system, are consistent with the previously stated trends for the halogens (see Table 2, entries 8–10 or 19–21) and R groups (see Table 2, entries 26, 9, 13, 14, 15, 17, 7). Use of the reduction potentials allows the chemist to combine the reactivity effects of the halogen and the R-group to anticipate the potential difficulty in making a Grignard reagent. Generalities about these reduction potentials (DMF/SCE) for Grignard reagent preparation are

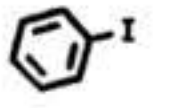
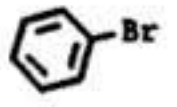
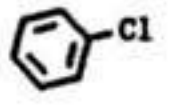
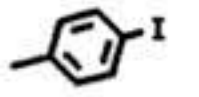
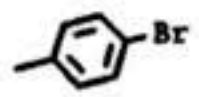
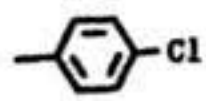
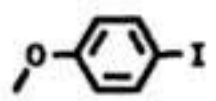
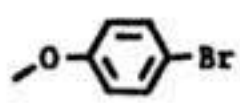
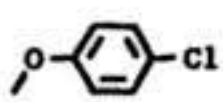
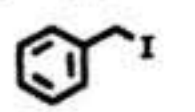
Greater than −2.0:	facile reaction and high homocoupling
−2.0 to −2.3:	moderate reactivity and low homocoupling
Less than −2.3:	sluggish reaction and no homocoupling

In highly reactive RX species, such as benzyl bromide (BzBr), the formation of high levels of dibenzyl (Bz_2) is typical. In fact, Bz_2 can be made quantitatively from this reaction. The level of Bz_2 can be minimized by decreasing the following reaction parameters: temperature, concentration, and addition rate. Increasing the Mg surface area and mass transfer will also decrease the Bz_2 formation. All of these parameter adjustments are aimed at favoring an intermolecular reaction of Mg and BzBr versus the intermolecular reaction of BzMgBr with BzBr.

In sluggish reactions, such as the reaction of magnesium with chlorobenzene (PhCl), there are several process conditions that can help facilitate the reaction. As in the preceding example, the following reaction parameters can be used: agitation rate, temperature, addition rate, concentration, Mg surface area, and mass transfer. To optimize the reaction of RX and Mg a high Mg surface area (see Chapter 4) and high agitation (good mass transfer) is required. The temperature can be raised to near reflux (60°C in THF) to provide the activation energy for the reaction. This technique is particularly effective with aromatic chlorides. These aromatic reactions can be run at a higher concentration and faster addition

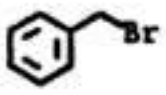
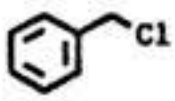
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Table 2 Selected Reduction Potentials of RX[a]

Entry	Compound	Solvent/ Reference Electrode	Halfwave Potential V	Reference
1	CH_3I	CH_3CN(TEAI)/SCE	-1.37	35
2	CH_3Br	DMF(TEAB)/SCE	-1.96	35
3	CH_3Cl	DMF(TEAP)/SCE	-2.76	35
4	CH_3CH_2I	CH_3CN(TEAI)/SCE	-1.36	35
5	CH_3CH_2Br	CH_3CN(TEAB)/SCE	-1.92	35
		DMF(TEAB)/SCE	-2.17	35
6	$BrCH_2CH_2Br$	75% DO(TEAB)/SCE	-1.52	36
7		75% DO(TEAB)/SCE	-2.47	36
8		75% DO(TEAP)/SCE	-1.16	36
9		75% DO(TEAP)/SCE	-1.29	36
		DMF(TEATs)/SCE	-1.29	35
10		75% DO(TEAP)/SCE	-1.94	36
		DMF(TEATs)/SCE	-2.03	35
11	$CH_3CH_2CH_2Br$	DMF(TEAB)/SCE	-2.22	37
12	$CH_3CH(Br)CH_3$	DMF(TEAB)/SCE	-2.27	37
13	$CH_3(CH_2)_3Br$	DMF(TMAP)/SCE	-1.99	35
14	$CH_3CH(Br)CH_2CH_3$	DMF(TEAB)/SCE	-2.34	35
15	$(CH_3)_3CBr$	glyme(TBAP)/SCE	-2.39	35
		DMF(TEAB)/SCE	-2.19	38
16		75% DO(TEAB)/SCE	-1.62	36
		DMF(TBAB)/Hg pool	-1.31	35
		CH_3CN(TEAB)/Ag/Ag^+	-1.23	35
17		75% DO(TEAB)/SCE	-2.32	36
		DMF(TEAB)/Ag/AgBr	-1.81	35
18		DMF(TEAB)/SCE	-2.58	39
		DMF(TEAB)/Ag/AgBr	-2.13	35
19		DMF(TEAB)/Ag/AgBr	-1.26	35
20		DMF(TEAB)/Ag/AgBr	-1.84	35
21		DMF(TEAB)/Ag/AgBr	-2.16	35
22		DMF(TEAB)/Ag/AgBr	-1.25	35
23		DMF(TEAB)/Ag/AgBr	-1.84	35
24		DMF(TEAB)/Ag/AgBr	-2.15	35
25		CH_3CN(TBAB)/Hg pool	-0.24	35

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Table 2 Continued

Entry	Compound	Solvent/ Reference Electrode	Halfwave Potential V	Reference
26		DMF(TEAB)/SCE	-1.22	40
		DMF(TBAB)/Hg pool	-0.83	35
27		75% DO(TEAP)/SCE	-1.91	36
		DMF(TEAC)/Ag/AgCl	-1.54	35

[a]In general the halfwave potentials were measured by a polaragraph using a Pt working electrode, the supporting electrolyte, in parenthesis, concentration varied from 0.01 *M* to saturation and 75% DO is 75% dioxane with 25% H_2O. For more information see reference.

rate relative to the benzylic systems. However, the addition rate should never be faster than the reflux rate.

Typically, Grignard reagents made from the addition of RX to magnesium can be made in higher than 90% yield as long as any reactive functionality in the substrate has been protected and the parameters discussed previously have been optimized through statistical experimental design. Although the solvent system may vary, owing to solubility problems, some commercial examples of this high yield reaction follow (greater than 90% yield and concentrations of 1–3 mol/kg).

CH_3MgCl (Br, I)
CH_3CH_2MgCl (Br)
$CH_2=CHMgCl$ (Br)
$CH_2=CHCH_2MgCl$
$CH_3CH_2CH_2MgCl$
$(CH_3)CHMgCl$
$CH_3(CH_2)_2CH_2MgCl$
$CH_3CH_2CH(CH_3)MgCl$
$(CH_3)_3CMgCl$
$CH_3(CH_2)_3CH_2MgBr$
$CH_3(CH_2)_4CH_2MgBr$
$C_6H_{11}MgCl$
C_6H_5MgCl (Br)
4—ClC_6H_5MgCl
$C_6H_5CH_2MgCl$
2—$CH_3C_6H_5MgCl$ (Br)
4—$CH_3C_6H_5MgCl$ (Br)
$CH_3(CH_2)_6CH_2MgCl$
$C_6H_5CH_2CH_2MgCl$
$C_6H_5C(CH_3)_2CH_2MgCl$

V. PREPARATION OF *n*-BUTYLMAGNESIUM CHLORIDE

This section describes the preparation of a prototypical Grignard reagent, n-butylmagnesium chloride. The removal of O_2 and H_2O from the reaction flask setup, solvent, RX, and Mg is essential. Therefore, all operations were performed under a dry nitrogen or argon atmosphere, using a standard Schlenk line or dry box techniques [5].

The THF was distilled from sodium/benzophenone and stored under an argon atmosphere. Chlorobutane and 1,2-dibromoethane were dried with 4Å molecular sieves (0.02 wt% by Karl Fisher titration), followed by freeze–pump–thaw degasing of RX (repeated 3 times). The dry and degased RX reactants were then placed under an argon atmosphere. The Mg turnings and the glassware for the reaction were placed in a 110°C oven overnight (10–14 h). The glassware was then assembled hot with a strong stream of argon flushing the reaction flask setup (Fig. 1).

A 53.5-G (2.2 mol) sample of magnesium turnings was added hot to the flask, with a strong stream of argon flowing through an open joint that was subsequently capped with a septum. The reaction flask setup was placed under vacuum (less than 0.1 torr) for 10 min and the vacuum was broken with argon (repeat three times). A total of 581.4 g of THF was added to the flask and the mechanical stirrer was turned on. To ensure the

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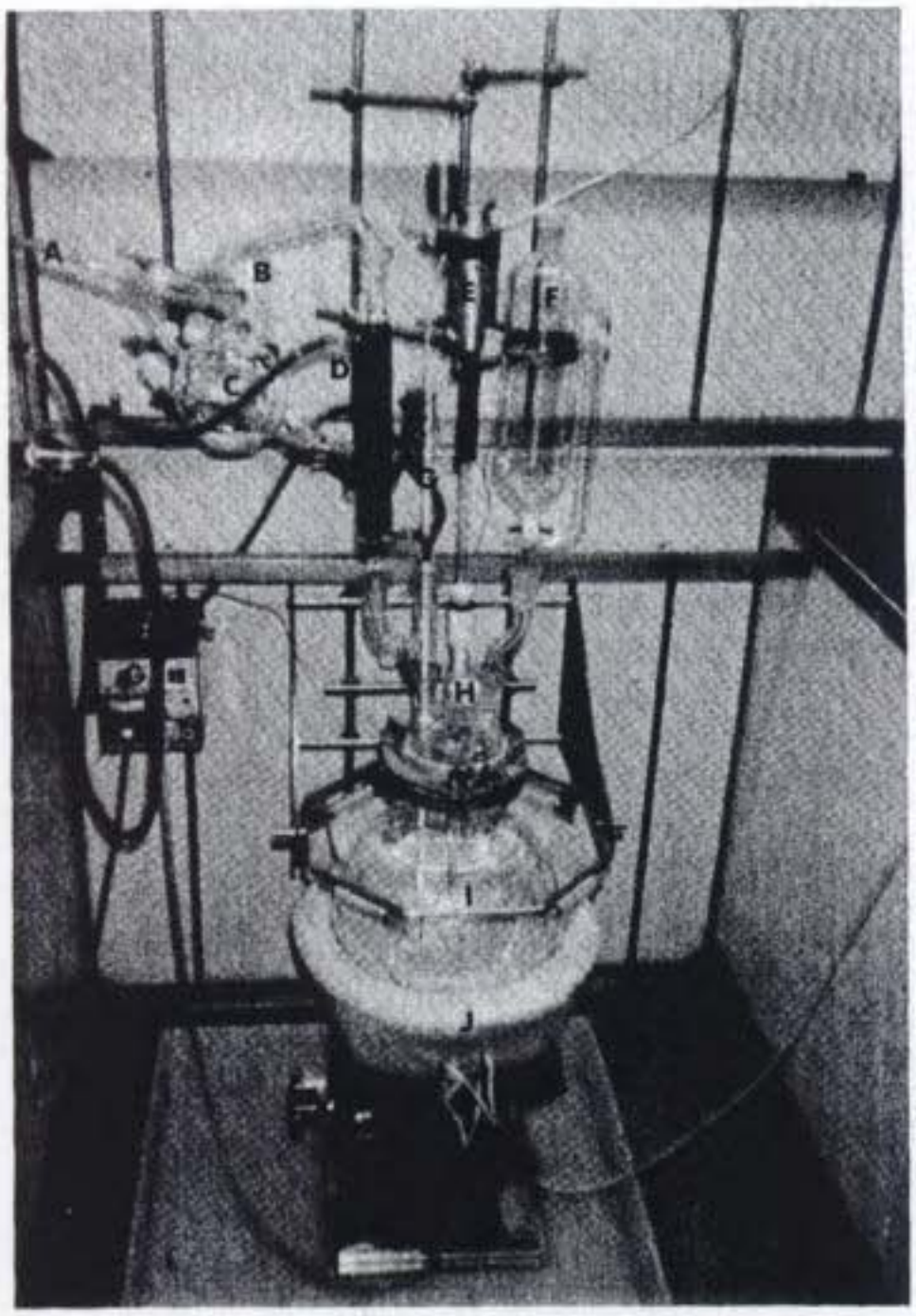


Figure 1 Reaction flask setup for standard Grignard reagent preparation.
A. Vacuum/N_2 inlet
B. Bubbler for pressure relief
C. Surge flask
D. Condenser (inert cooling solvent)
E. Mechanical agitator (explosion-proof)
F. Addition funnel
G. Thermometer or thermocouple with heat controller
H. Septum-covered port for Mg addition
I. Sealed reaction flask with proper support
J. Heating mantle
K. Laboratory jack
L. Spill tray (sufficient for reactor contents)

activation of magnesium (see Chapter 4), 5.0 g (0.027 mol) of 1,2-dibromoethane was added to the flask by syringe. A 5°C exotherm was observed, with an increase in gas flow through the bubbler (i.e., the release of ethene). A mixture of 185 g (2.0 mol) of chlorobutane and 185 g THF was added to the addition funnel. An initial charge of approximately 30 g of this mixture was added to the flask and the exotherm drove the reaction to reflux. The activity analysis confirmed that, indeed, some Grignard reagent had formed. The remainder of the mixture was added at a rate to control the reflux rate at the condenser (2-h addition time). After the addition was complete, external heating was applied for 2 h to maintain

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the reaction at reflux. The reaction was allowed to cool to ambient temperature. Subsequently, the mechanical stirrer was turned off and the residual magnesium was allowed to settle. The solution was transferred by cannula to obtain 994 g of *n*-butylmagnesium chloride solution. The solution was analyzed for activity (1.93 mol/kg) and acid–base titration (2.01 mol/kg) to give a 96% ratio and a 95.9% yield, based on chlorobutane. No chlorobutane was detected by gas chromatography (GC) analysis.

This procedure has been repeated in our laboratory and in production (modified version) hundreds of times, and the average for 1993 activity/acid–base ratio was 96%, with a standard deviation of 2%. This indicates that, if the proper procedure is followed, then a reproducible yield of Grignard reagent can be attained. The most common variation on this preparation is the type of Mg activation (see Chapter 4). Other recommended preparations can be found within this book (see especially Chapters 3 and 4) and in the literature [continuous process Ref. 41 and batch process Refs. 42, 43].

VI. ALTERNATIVE METHODS FOR GRIGNARD REAGENT PREPARATION

By far the most common way of making a Grignard reagent is the oxidative addition of RX to magnesium. However, because of homocoupling difficulties (benzylic systems), unavailable or non-accessible RX species, and economic benefits, other synthetic routes are more favourable. There are several practical alternative synthetic methods to making Grignard reagents: metal–metal exchange reactions [Eq. (9); Table 3, entries 1–7], acid–base reactions of RH with a Grignard reagent [Eq. (10); see Table 3, entries 8–12], oxidative–reductive transmetallation [Eq. (11); see Table 3, entries 13–15], metal$X$–X^1 exchange [Eq. (12); see Table 3 entries 16–20] and preparation from olefins (see Chapter 3). The Grignard reagents generated by these methods are rarely isolated, and the yields reported in Table 3 refer to the coupling reaction of the resulting Grignard reagent intermediate and the substrate of interest. Therefore, the yields actually reflect the coupling reaction of Grignard reagent and substrate. Since there are high yields with some of the substrates, it is reasonable to assume that the yields of these methods can approach the greater than 90% yields of the oxidative addition of RX to magnesium.

$$R_nM + nMgCl_2 \longrightarrow nRMgCl + MCl_n \quad (9)$$
$$M = Na, Li, Hg$$

$$RH + R^1MgX \longrightarrow RMgX + R^1H \quad (10)$$

$$RMX + Mg \longrightarrow RMgX + M \quad (11)$$

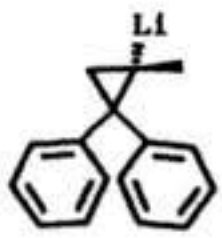
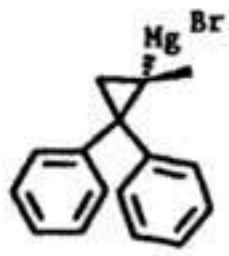
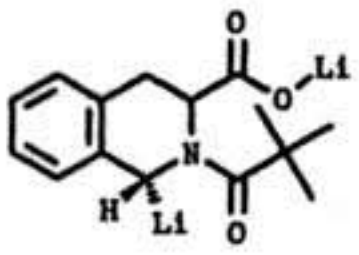
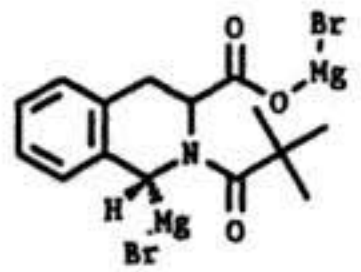
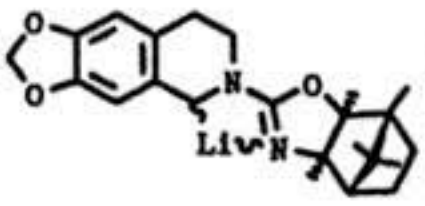
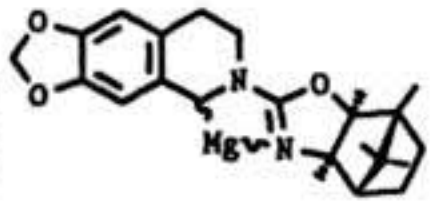
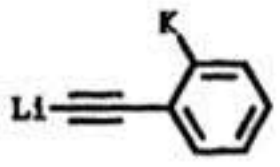
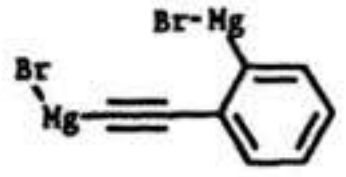
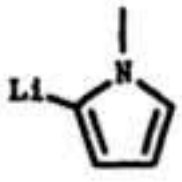
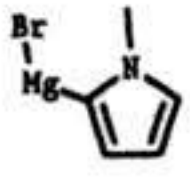
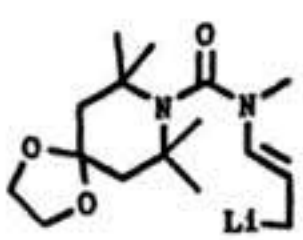
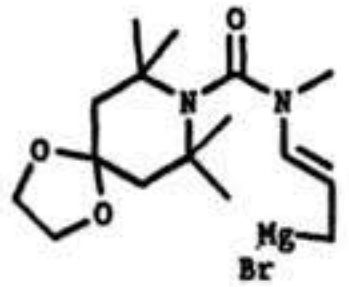
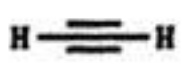
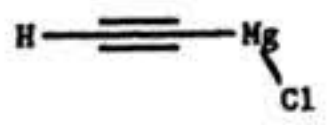
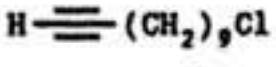
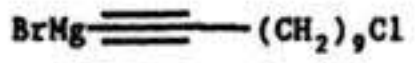
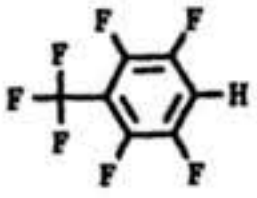
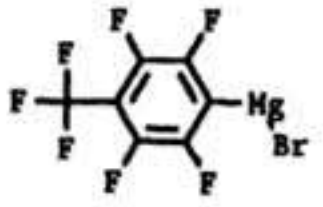
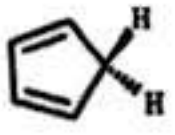
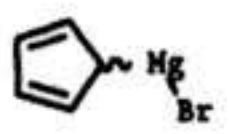
$$RMgX + R^1X^1 \longrightarrow RX^1 + R^1MgX \quad (12)$$

The metal exchange reactions are straightforward, and one can easily prepare MgR_2 by this route. This method is typically used when the Grignard reagent is difficult to prepare from RX, susceptible to homocoupling, or a diorganomagnesium reagent is desired. An interesting application is in asymmetric synthesis by which chiral Grignard reagents can be prepared (see Table 3, entries 1–3). The obvious disadvantage is that this route is not economically favorable relative to the standard method of preparation and adds a step in the synthesis (i.e., preparation of the organometallic reactant, R_nM).

The acid–base preparation method is typically used to make Grignard reagents of terminal alkynes. The advantage is that an inexpensive Grignard reagent can be used to make an unaccessible or prohibitively expensive Grignard reagent. The major limitation is that RH must be more acidic than R^1H for this reaction to occur (see Chapter 31).

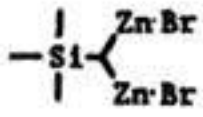
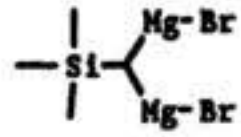
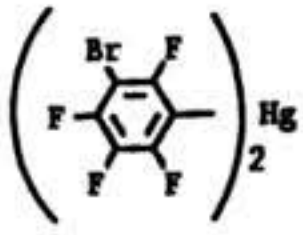
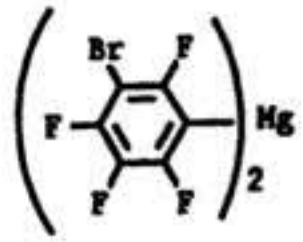
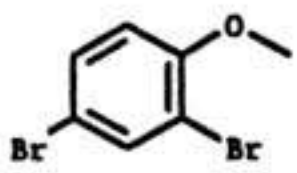
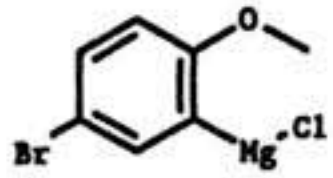
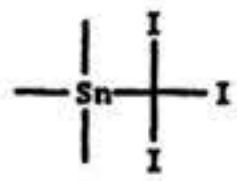
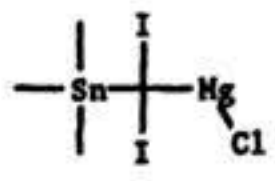
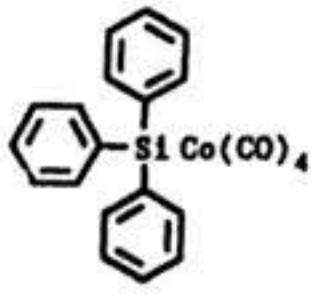
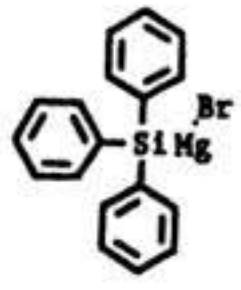
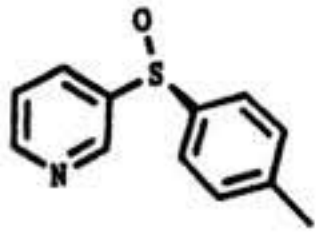
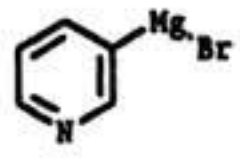
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Table 3 Selected Examples of Alternative Methods for Grignard Reagent Preparation

Entry	Reactant	Intermediate	Yield (%)	Reference
1[A]			32 - 40	44
2[A]			60 (100 DS)	45
3[A]			50 - 58	46
4[B]			71	47
5[A]			15 - 93	48
6[A,C]			31	49
7[A]			54 - 87	50
8[D]			60 - 75	43
9[E]			56 - 80	51
10[F,G]	Cp_2MoH_2	$Cp_2Mo(H)MgCl$	89	52
11[E]			65	53
12[E]			50 - 80	54

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Table 3 Continued

Entry	Reactant	Intermediate	Yield (%)	Reference
13[H]	$CH_3Hg(CH_2)_3HgCH_3$	$BrMg(CH_2)_3MgBr$	66 - 98	55
14[H]			> 95	56
15[F]			20	57
16[F]			80 - 95	58
17[F]			32	59
18[J]	$C_6F_{13}CF{-}C(F)Br$	$C_6F_{13}CF{-}C(F)MgBr$	10 - 65	60
19[K]			40 - 50	61
20[J]				62

[A] $MgBr_2$
[B] 2 equivalents $MgBr_2$
[C] $Na_2C_{10}H_8$
[D] $CH_3(CH_2)_3MgCl$
[E] CH_3CH_2MgBr
[F] $(CH_3)_2CHMgCl$
[G] Reported yield is the Grignard–THF complex
[H] 2 equivalents of Mg
[I] Mg
[J] C_6H_5MgBr
[K] CH_3MgBr

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The oxidative–reductive transmetallation can be carried out with organometallic reagents that have a reduction potential more positive than magnesium (−2.375 V). Since these reactions are typically carried out with organomercury derivatives, there is a major environmental issue with formation of Hg^0, resulting in this method rarely being used, even in the laboratory.

The metal $X–X^1$ exchange reaction is dependent on the polarization of R^1X^1. Therefore, the better the leaving group X^1 is, the more probable this reaction will work. The advantages of this method are the same as those for the metal exchange reaction. The disadvantages are that potentially two different Grignard reagents are in solution [the reaction in Eq. (12) is an equilibrium between the two Grignard species] and the actual coupling reaction to form $R—R^1$.

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3

Preparation of Grignard Reagents from Olefins and Acetylenes

FUMIE SATO and HIROKAZU URABE

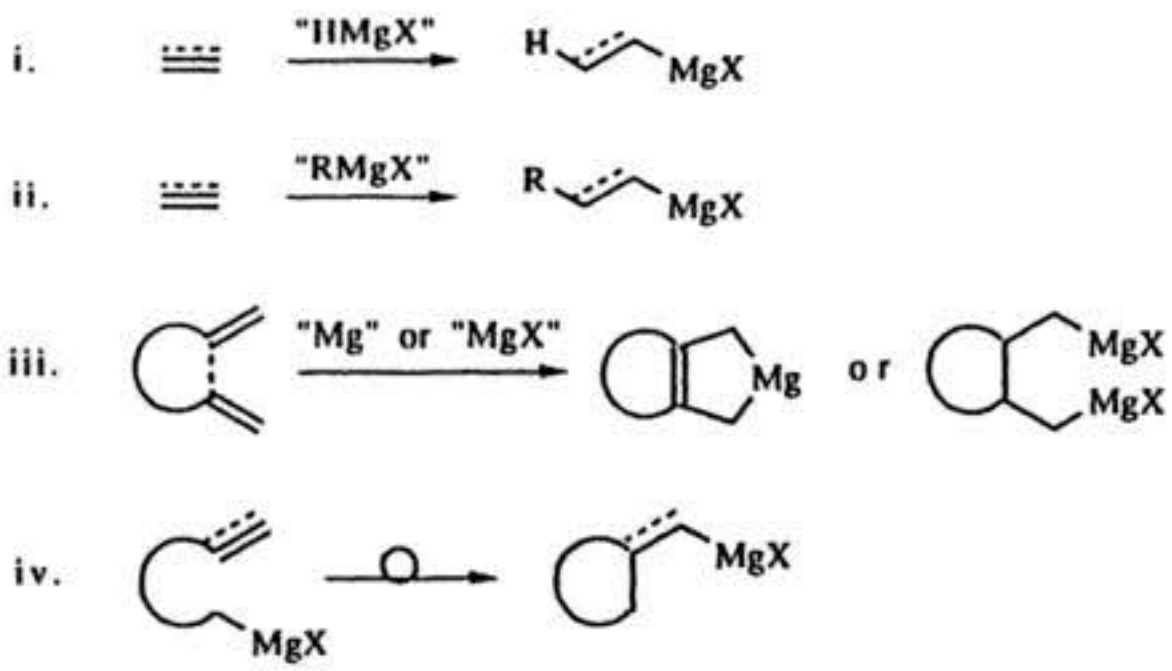
Tokyo Institute of Technology, Yokohama, Kanagawa, Japan

I. INTRODUCTION

The synthesis of Grignard reagents from olefins or acetylenes complements the standard reductive method for preparation of these reagents from alkyl halides and magnesium metal [1, 2]. When alkyl or alkenyl halides are rather difficult to obtain relative to the corresponding olefins or acetylenes, or when a Grignard reagent is hard to prepare by the action of magnesium on an organic halide, this methodology is especially useful. Moreover, chemo-, regio-, and stereochemical considerations often favor this methodology. The reactions described in this chapter will be limited to the direct formation of carbon–magnesium bonds using olefin or acetylenic substrates. Generation of Grignard reagents from any isolable intermediates, such as alkyl (alkenyl) halides or other organometallic compounds obtained from olefins or acetylenes, and formation of magnesium acetylides from terminal acetylenes are excluded.

The reactions appearing in this chapter will be classified into four types: (1) hydromagnesation of olefins or acetylenes, (2) carbomagnesation of olefins or acetylenes, (3) reductive magnesation of dienes, and (4) isomerization of unsaturated Grignard reagents. Scheme 1 shows an illustrative description of these reactions. Some of these topics had been already discussed in review articles [1-17]; herein particular attention will be paid to current literature reports. The reagent of the type R_2Mg is, strictly speaking, not a Grignard reagent (RMgX), but it is discussed together in this section, because RMgX and R_2Mg are often closely related through the Schlenk equilibrium.

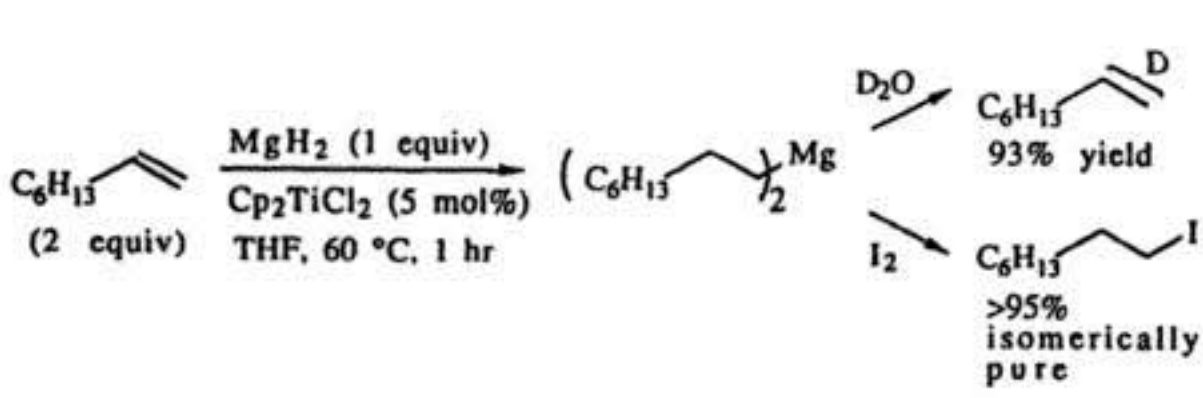
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Scheme 1 Preparation of Grignard reagents from olefins and acetylenes

II. HYDROMAGNESATION OF OLEFINS AND ACETYLENES

The most simple method for the preparation of Grignard reagents from olefins or acetylenes is the formal addition of H-MgX species to such unsaturated carbon–carbon bonds. In fact, the most fundamental inorganic magnesium salt, MgH_2, has been reported to add ethylene under drastic reaction conditions [18]. However, as the double bond is usually resistant to such addition reactions, the method of this reaction is not general. However, in 1978 Ashby *et al.* [19] reported that hydrometallation of 1-octene with MgH_2 was greatly promoted by the addition of a catalytic amount of Cp_2TiCl_2, as evidenced by the fact that quenching the resultant organomagnesium reagent with deuterium oxide or I_2 gave deuterated octane or 1-iodooctane according to Eq. (1). Titanium trichloride and $ZrCl_4$ were reported not to be effective catalysts for this reaction.

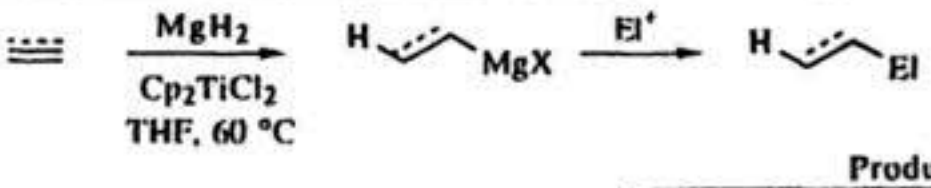


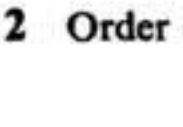
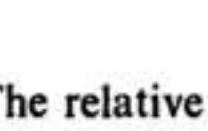
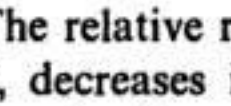
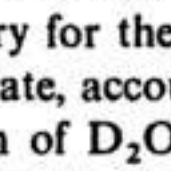
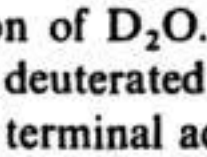
(1)

Other examples are summarized in Table 1. Terminal olefins nicely participated in this reaction as shown in Eq. (1) and entries 1 and 2 in Table 1. Styrene showed a reversal of regioselection relative to the position of the newly formed carbon–magnesium bond. However, sterically hindered olefins afforded an increasing amount of hydrogenated product, even after treatment of the reaction mixture with D_2O (see Table 1, entries 3 and 4). Finally, no deuterated hydrocarbons were obtained from *trans*- and trisubstituted olefins, even though the starting materials were almost completely consumed (see Table 1, entries 5 and 6).

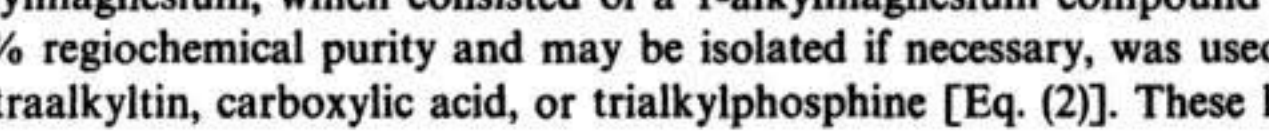
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Table 1 Cp_2TiCl_2-Catalyzed Hydromagnesation of Olefins and Acetylenes



Entry	Substrate	Period (hr)	Product (%) El^+ : H_2O	Product (%) D_2O
1		1	hexane (94)	d_1-hexane (89)
2		1 (r.t.)	PhEt (100)	$PhCHDCH_3$ (90) $PhCH_2CH_2D$ (10)
3		48	methyl-cyclohexane (95)	d_1-methyl-cyclohexane (60)
4		68	hexane (66) *trans*-2-hexene (26)	d_1-hexane (20)
5		92	hexane (70) *cis*-2-hexene (2.5)	d_1-hexane (0)
6		92	3-methyl-heptane (85)	d_1-3-methyl-heptane (0)
7		no reaction		
8	C_6H_{13}—•≡	1 (r.t.)	1-octene (60) 1-octyne (40)	d_1-1-octene (50) d_1-1-octyne (40)
9	C_3H_7—•≡•—C_3H_7	1 (r.t.)	*cis*-4-octene (100)	*cis*-d_1-4-octene (65)

Source: Ref 19.



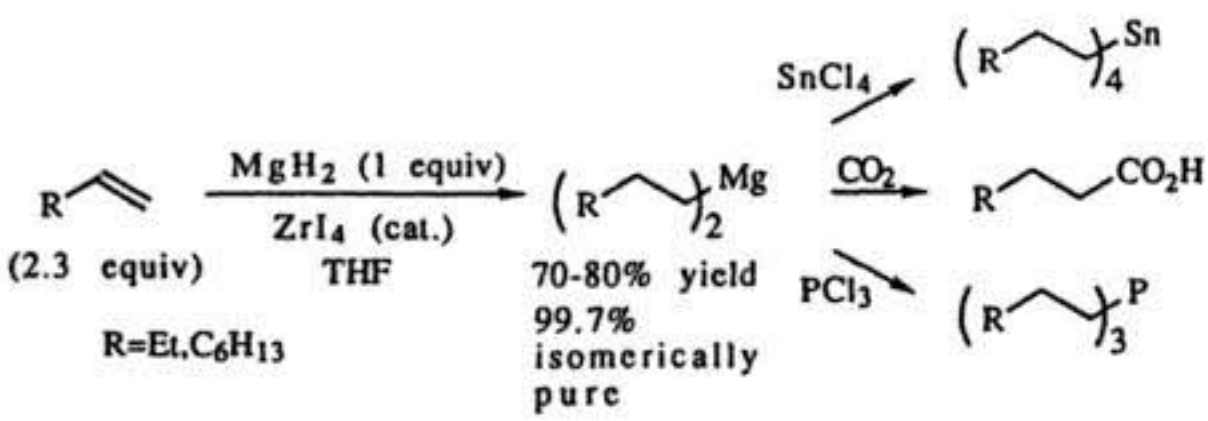
Scheme 2 Order of reactivity for hydromagnesation

The relative reactivity for hydromagnesation of olefins, as estimated by deuteration studies, decreases in the following order (Scheme 2). Relatively long reaction periods necessary for the conversion of hindered olefins, during which active magnesium species deteriorate, account for the low or no uptake of deuterium in the products following the addition of D_2O. Although an internal acetylene underwent this hydromagnesation to give a deuterated *cis*-olefin in good yield after exposure to D_2O (see Table 1, entry 9), with a terminal acetylene, formation of magnesium acetylide hindered further conversion of the substrate (see Table 1, entry 8).

It was also reported [6,20] that MgH_2 prepared from Mg and H_2 under chromium or titanium catalysis hydromagnesiated 1-alkenes in good yields in the presence of a zirconium salt, for which ZrI_4 was particularly useful. As in the earlier example reported by Ashby [19], the reactions with 1,1- and 1,2-dialkylethylenes were very slow. The resulting dialkylmagnesium, which consisted of a 1-alkylmagnesium compound with greater than 99.7% regiochemical purity and may be isolated if necessary, was used for the synthesis of tetraalkyltin, carboxylic acid, or trialkylphosphine [Eq. (2)]. These hydromagnesation

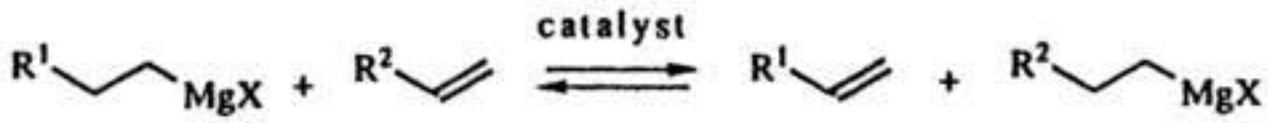
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reactions were also applied to a functionalized olefin [21] and to dienes [22]. Other magnesium hydrides, such as Et_2NMgH, were examined, but were less useful than MgH_2 [6].



(2)

Grignard reagents having a β-hydrogen are known to be in equilibrium with another olefin and a second Grignard reagent in the presence of a certain transition metal catalyst, as shown in Eq. (3).



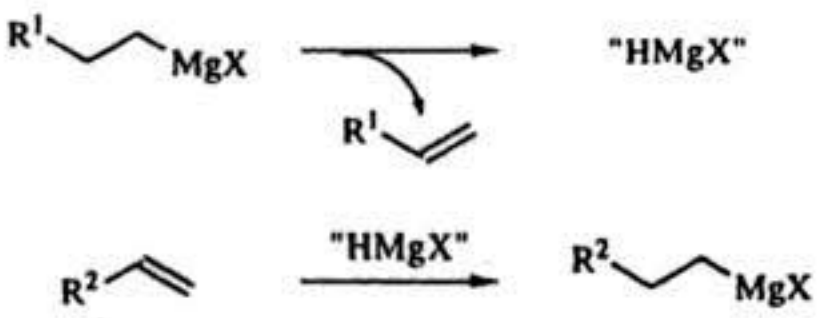
(3)

This reaction is superficially understood as a formal delivery of "H-MgX" element from a Grignard reagent to an olefin under catalysis of such a transition metal complex (Scheme 3).

In 1962 [23], Cooper and Finkbeiner studied this reaction in detail by taking several transition metal catalysts involving $TiCl_4$, $Ti(O\text{-}i\text{-}Pr)_4$, Cp_2TiCl_2, $ZrCl_4$, and VCl_4 [24]. Typically, a mixture of an olefin and PrMgBr in ether was heated at reflux in the presence of $TiCl_4$ to afford the new Grignard reagent resulting from the added olefin. The mechanism of this reaction was proposed, as shown in Scheme 4, in which a titanium hydride, Cl_3TiH, played an important role [25].

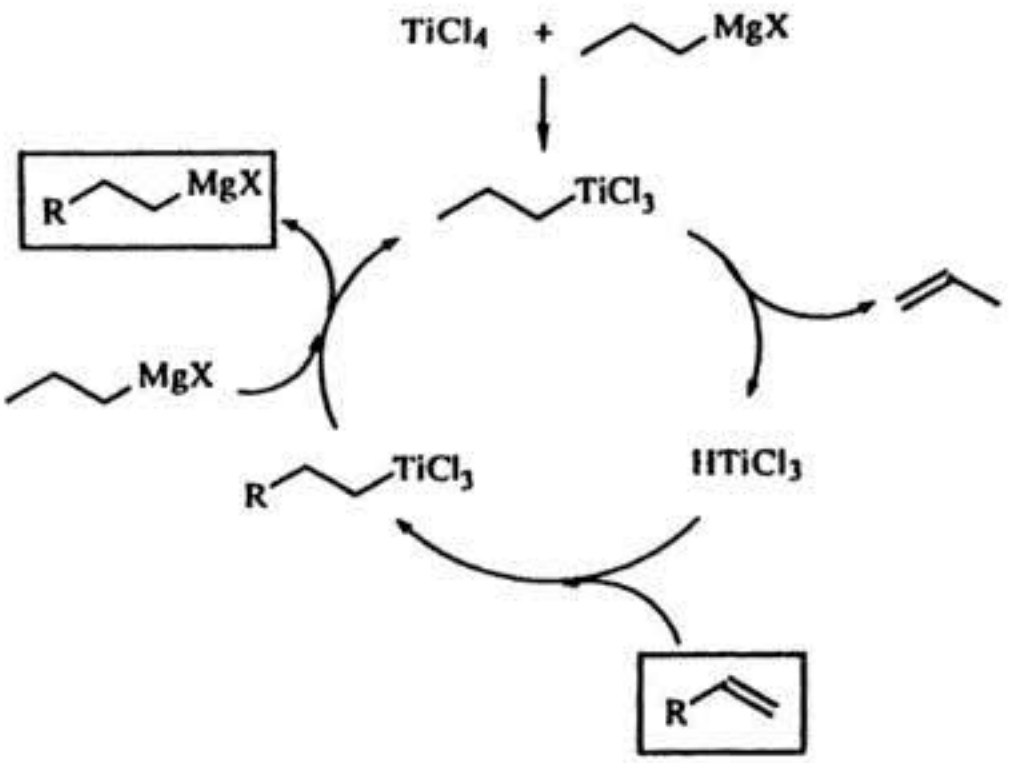
The newly formed Grignard reagent can be trapped regioselectively with a variety of electrophiles, such as aldehydes, ketones, carbon dioxide, orthoesters, silyl chloride, and oxygen. Tables 2 and 3 summarize the results of these and several additional examples.

The use of a low molecular weight Grignard reagent, such as Et-, Pr-, *i*-Pr-, or *i*-Bu-MgX is recommended as the $R^1CH_2CH_2MgX$ in Eq. (3), since the olefin formed by the Grignard equilibrium ($R^1CH{=}CH_2$; ethylene, propylene, or isobutene, respectively)



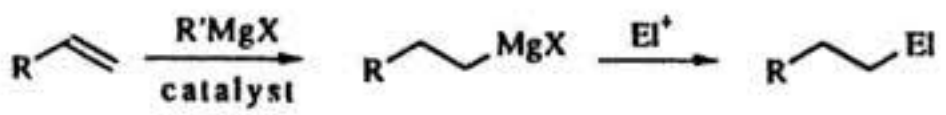
Scheme 3 Transfer of "HMgX"

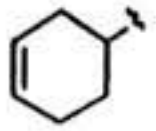
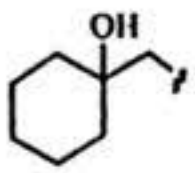
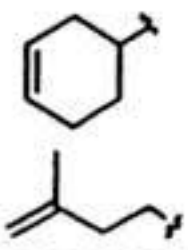
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Scheme 4 Proposed reaction course for titanium-catalyzed Grignard exchange reaction

Table 2 Generation and Reactions of 1-Alkyl Grignard Reagents from Alkenes by Hydromagnesation

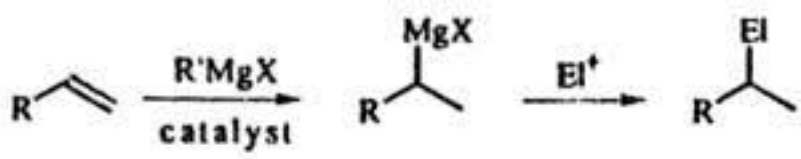


Entry	R	R'MgX	Catalyst	El^+	El	Yield (%)	Ref.
1	Pr, Bu, *i*-Pr, *i*-Bu	PrMgBr	$TiCl_4$	R^1R^2CO	$R^1R^2C(OH)$-	24-45	24
2	$R^1R^2C(OH)CH_2$-	*i*-BuMgCl	Cp_2TiCl_2	R^3R^4CO	$R^3R^4C(OH)$-	42-71	26
3	C_6H_{13}, $ArCH_2$-, *c*-C_6H_{11}, 	PrMgBr	$TiCl_4$	CO_2	CO_2H	28-62	24,27
4	$R^1R^2C(OH)$-, $R^1R^2C(OH)CH_2$-, $R^1R^2C(OH)(CH_2)_2$-	EtMgCl	Cp_2TiCl_2	CO_2	CO_2H[a]	55-64	28
5	C_6H_{13}	PrMgBr	$TiCl_4$	$(EtO)_3CH$	$(EtO)_2CH$-	19	24
6		EtMgBr	Cp_2TiCl_2	Me_3SiCl	Me_3Si	59	28
7		PrMgBr	$TiCl_4$	O_2	OH	40-45	24

[a]The products are lactones if possible.

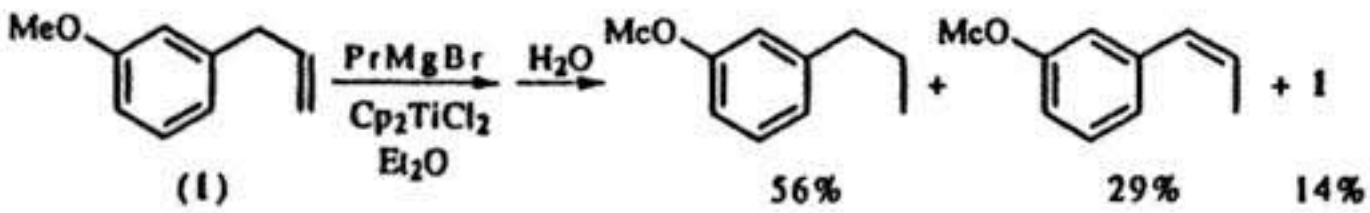
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Table 3 Generation and Reactions of α-Aryl- or α-Silylalkyl Grignard Reagents from Styrenes or a Vinylsilane by Hydromagnesation



Entry	R	R'MgX	Catalyst	El^+	El	Yield (%)	Ref.
1	Ph, Ar	PrMgBr, *i*-PrMgBr, *t*-BuMgBr	Cp_2TiCl_2	H_2O	H	40-98	29,30, 31
2	Ph, *p*-(MeO)C_6H_4-	*n*-PrMgBr	$TiCl_4$	CO_2	CO_2H	22-51	24
3	*p*-(Me_2C=$CHCH_2$)C_6H_4-	PrMgBr	Cp_2TiCl_2	CO_2	CO_2H	82	31
4	Ph	"	$TiCl_4$	O_2	OH	40	24
5	"	"	Cp_2TiCl_2	O_2	OH	80	29
6	$(PhCH_2)_3Si$	*i*-PrMgBr	Cp_2TiCl_2	H_2O	H	--	30
7	"	"		D_2O	D	--	"
8	"	"		Me_3SiCl	Me_3Si	--	"

can be expelled from the reaction mixture to shift the equilibrium to the right [see Eq. (3)]. For the titanium catalyst, Cp_2TiCl_2 could be used equally well. The exclusive formation of 1-alkyl Grignard reagents was noted for the terminal alkenes (see Table 2) except for styrenes and a silylethylene that afforded secondary (i.e., benzyl or 1-silylalkyl) Grignard reagents (see Table 3). Similar to the aforementioned hydromagnesation with MgH_2, terminal olefins also underwent the metallation quite rapidly, which enables a chemoselective hydromagesation between different types of olefins (see entries 3 and 7, Table 2; entry 3, Table 3). None of the following olefins—cyclohexene, 2-pentene, *trans*-stilbene, α-methylstyrene, β-methylstyrene, or 2-methyl-1-pentene—entered the Grignard exchange reaction, even under forcing reaction conditions (PrMgBr, $TiCl_4$) [24]. A few functional groups in the olefinic substrate, such as ether, hydroxyl (which exists as alkoxide in reaction media), or internal olefin, did not interfere with the reaction (see entries 2, 4, and 6, Table 2). Titanium catalyzed isomerization of terminal olefins to unreactive, internal ones as illustrated in Eq. (4) [27] can lower the yield of the exchanged Grignard reagent.

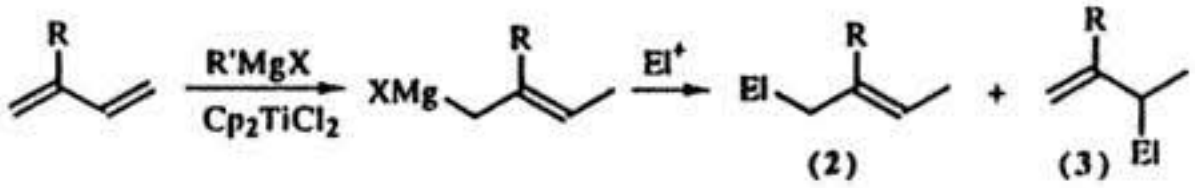


(4)

Thus, the reported product yields so far are moderate to good (usually lower than 50%). This disadvantage was circumvented by the use of dienes or acetylenes as described later, since these substrates afford structurally or electronically more stable intermediates, such as allyl- or alkenylmetals, compared with alkylmetals, which not only

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Table 4 Generation and Reactions of Allyl Grignard Reagents from Dienes by Hydromagnesation



Entry	R	R'MgX	El^+	El	Products (%)	Ref.
1	H	PrMgBr	H_2O	H	*trans*-2 (13), *cis*-2 (13), 3 (53)	29
2	Me	"	H_2O	H	2 (21), 3 (76)	"
3	H, Me	"	Me_2CO	$Me_2C(OH)$-	3 (79-95)	"
4	Me, Et, Bu	*i*-BuMgBr	EtCN	EtCO	3 (71-81)	32
5	Me, Et, Bu, Me_3Si	"	HCO_2MgBr	CHO	3 (33-66)	32,33

makes the reaction of Eq. (3) no longer in equilibrium [29], but also prevents the foregoing undesired isomerization.

Sato *et al.* showed that this titanium-catalyzed reaction of olefins and low molecular weight Grignard reagents could be extended to conjugated dienes and acetylenes, provided that Cp_2TiCl_2 was used as the catalyst in place of $TiCl_4$ [5]. The expected product from 2-alkyl-1,3-butadiene is an allyl Grignard reagent and, in fact, the clean formation of a single allyl Grignard reagent, as shown in Eq. (5), was verified by the subsequent reactions with electrophiles [29] (Table 4).



(5)

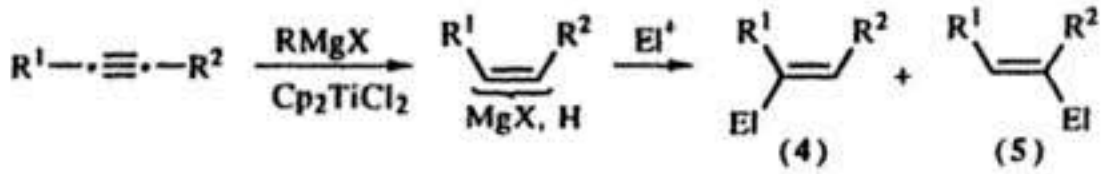
The high yields and the excellent regioselectivities of this hydromagnesation, as well as the versatility of the resultant allylmetal reagents [34,35], make this method valuable in organic synthesis.

Acetylenes also underwent a similar hydromagnesation reaction in the presence of Cp_2TiCl_2 to give alkenyl Grignard reagents having a defined regio- and stereochemistry, dependent upon the substrate [36]. The reactions are collected in Tables 5 and 6. A few points are noteworthy. Disubstituted acetylenes selectively afforded 1,2-*cis*-disubstituted vinyl Grignard reagents, in which the carbon–magnesium bond occupies the position close to phenyl or trimethylsilyl, but remote from 1-hydroxyalkyl (see Table 5). The directing effect of phenyl prevailed over that of the silyl (see entries 11 and 12, Table 5). Trimethylsilyl-propargyl alcohols are exceptional to obtain the 1,2-*trans*-disubstituted vinyl Grignard reagent, even though the regioselection satisfies the foregoing rule (see Table 6). These selective methods for the preparation of alkenyl Grignard reagents have found widespread use in organic synthesis.

The mechanism of the foregoing reactions of dienes and acetylenes should resemble that of the olefinic case (see Scheme 4, on the assumption that the catalytically active

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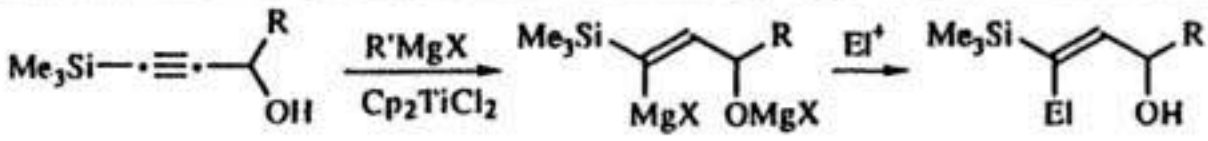
Table 5 Generation and Reactions of Alkenyl Grignard Reagents from Acetylene



Entry	R^1	R^2	RMgX	El^+	El	Yield (%)	Ref.
1	Me	Pr	*i*-BuMgBr	H_2O	H	4 (92-100) [100%Z]	37
2	"	"	"	I_2	I	4+5 [42:58] (90)	"
3	Et	Et	"	H_2O	H	4 (92-100) [>99%Z]	37,38
4	C_6H_{13}	$(CH_2)_8OH$	various Grignards	H_2O	H	4 (100) [>98%Z]	38
5	Et	Et	*i*-BuMgBr	PhCHO	PhCH(OH)-	4 (90)	37
6	Ph	Me	"	H_2O	H	4 (92-100) [>99%Z]	"
7	"	"	"	D_2O	D	4+5 (85) [88:12]	"
8	"	"	"	MeI	Me	4+5 (80) [90:10]	"
9	Me_3Si	Bu	"	H_2O	H	4 (76) [>98%Z]	"
10	"	"	"	D_2O	D	4+5 (--) [95:5]	"
11	Ph	Me_3Si	"	H_2O	H	4 (95) [>94%Z]	"
12	"	"	"	D_2O	D	4+5 (--) [96:4]	"
13	Me_3Si	Bu	*i*-BuMgBr	MeI	Me	4 (91) [97%Z]	39
14	"	"	"	allyl-Br	allyl	4 (89)	"
15	"	"	"	BuI/CuI	Bu	4 (87) [98%Z]	"
16	"	"	"	MeCHBrCHO	-CHMeCHO	4 (*ca.* 50)	33
17	"	$-(CH_2)_6OH$	"	BuI/CuI	Bu	4 (84)	39
18	"	C_5H_{11}	"	$C_5H_{11}CHO$	$C_5H_{11}CH(OH)$-	4 (--)	40
19	"	"	"	3-butenyl-I	3-butenyl	4 (86)	39
20	Me, Bu, Ph, *t*-Bu	CH_2OH	"	H_2O	H	4 (60-100)	41,42
21	Me	CH(Et)OH	"	"	"	4 (96-100)	41
22	"	CMe_2OH	"	"	"	4 (96-100)	"
23	Bu	CH_2OH	"	I_2	I	4 (78-86)	"
24	Bu,  geranylmethyl	"	*i*-BuMgBr, *i*-BuMgCl	MeI	Me	4 (88-92)	"
25	C_5H_{11}	"	*i*-BuMgCl	$C_5H_{11}CHO$	$C_5H_{11}CH(OH)$-	4 (59-62)	36

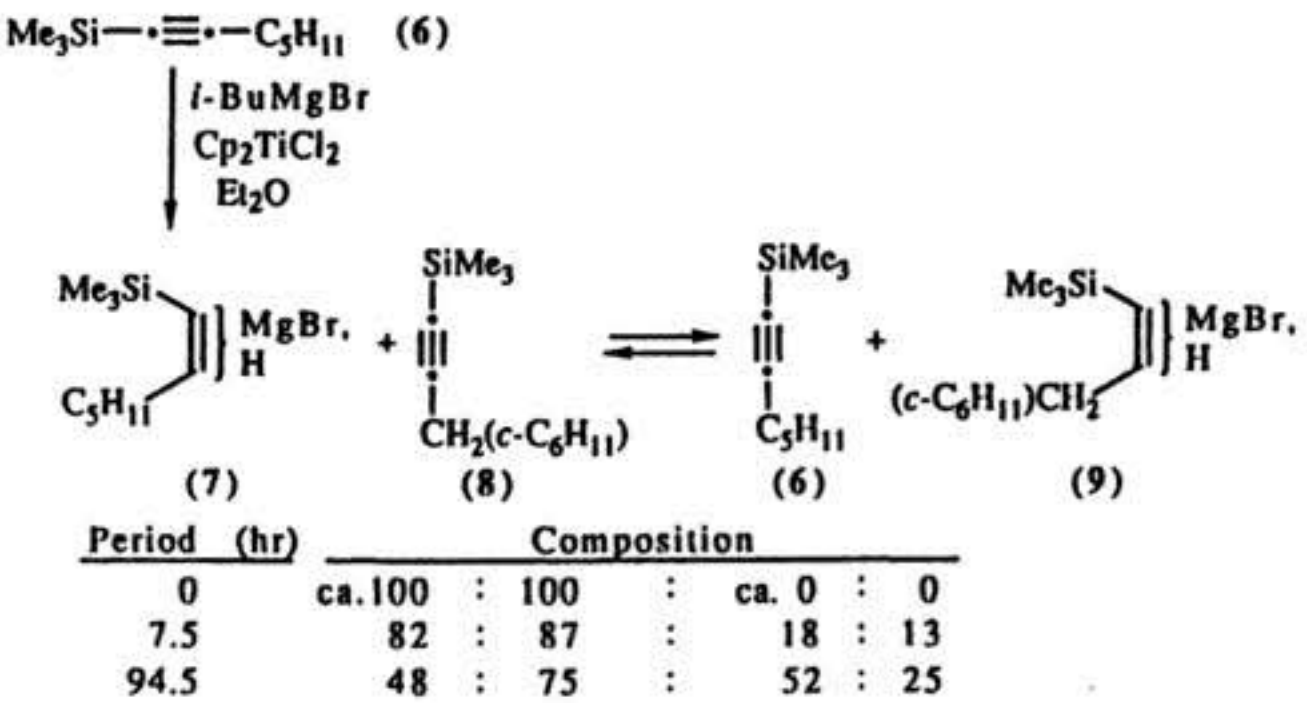
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Table 6 Hydromagnesation of Trimethylsilylpropargyl Alcohols



Entry	R	R'MgX	El^+	El	Yield (%)	Ref.
1	H	*i*-BuMgCl	H_2O	H	100	42
			MeI	Me	88	"
			BuI/CuI	Bu	89 [*E* >95%]	"
2	H	*i*-BuMgBr	R^1R^2CO	$R^1R^2C(OH)$-	80-85	43
3	H, Pr, EtCH(OH)-, PhCH(OH)-	"	R"CN	(R"C(=NH)-[a])	32-86	44,45
4	Me, C_5H_{11}, *c*-C_6H_{11}-, $PhCH_2OCH_2$-, PhCH(OH)-	"	CO_2	(CO_2H[b])	74-92	45,46

[a]The products isolated were corresponding furans.
[b]The products isolated were corresponding lactones.

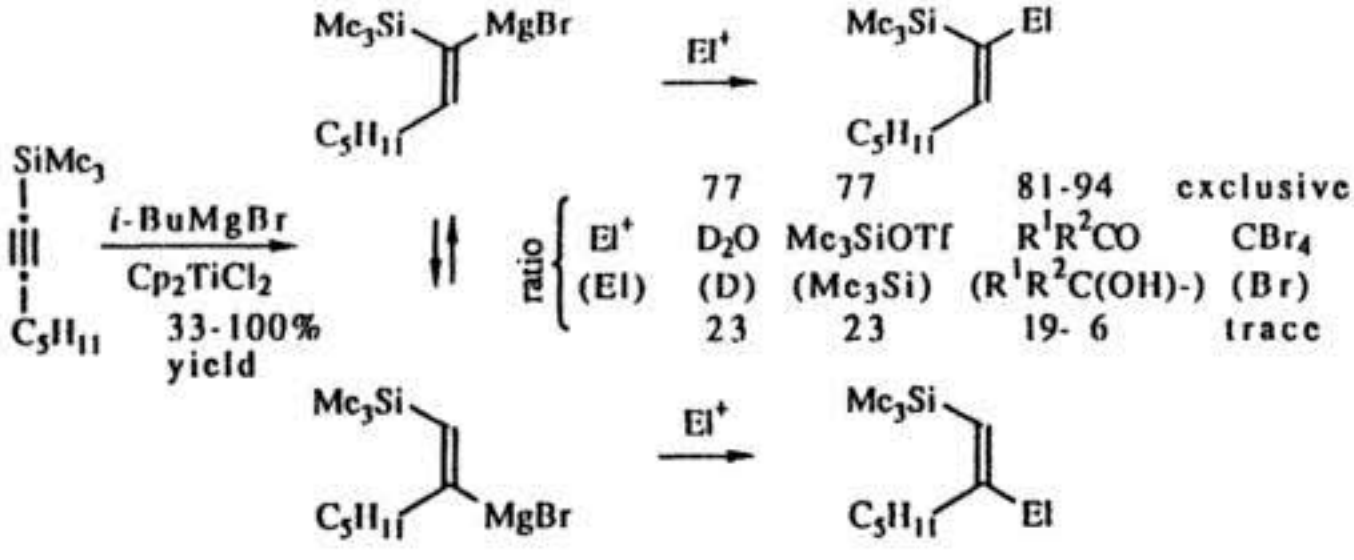


Scheme 5 Equilibration of acetylene and alkenyl Grignard reagent under hydromagnesation conditions

species is Cp_2TiH in place of Cl_3TiH) [29]. Recent study showed that there was an equilibrium between a starting acetylene and the alkenyl Grignard reagent produced by the hydromagnesation, provided the acetylene was silylated [47]. Thus, the addition of a different acetylene **8** to the silylalkenyl Grignard reagent **7**, pre-formed from the corresponding silylacetylene **6** and *i*-BuMgBr under Cp_2TiCl_2 catalysis, formed a new alkenyl Grignard reagent **9** and the initial acetylene **6** in the course of prolonged reaction period (Scheme 5).

More interestingly, the same study showed that change of electrophiles (thus, that of the periods necessary for the completion of the reaction) altered the regioselectivity

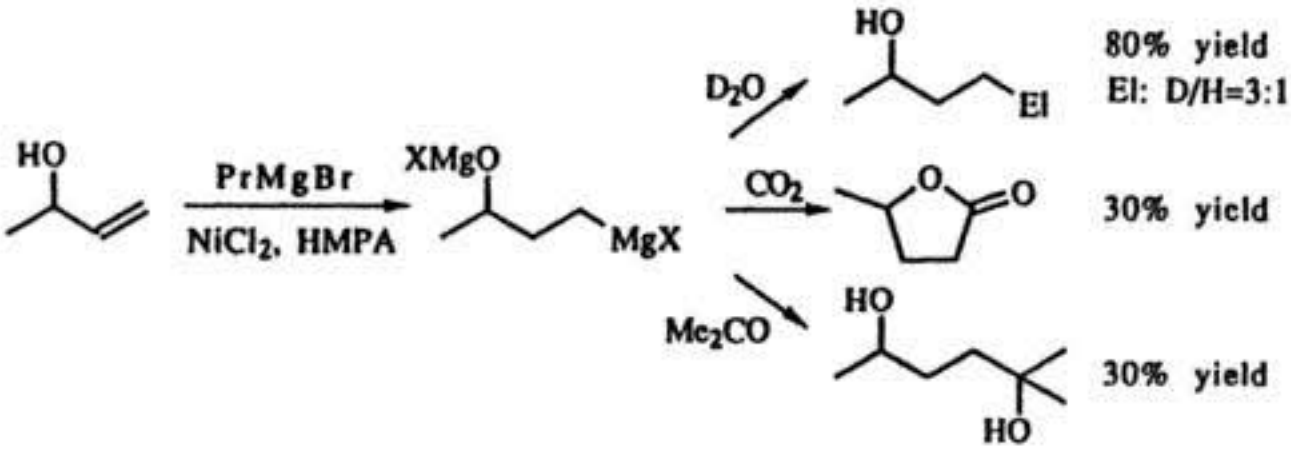
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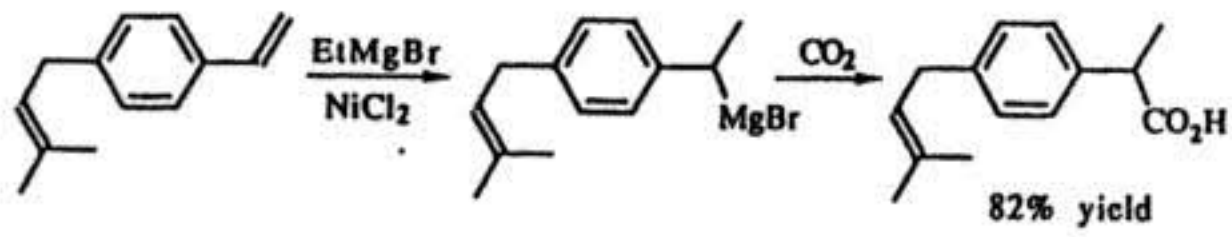
Scheme 6 Regioselectivity depending on electrophiles

found in the final products owing to a rapid equilibrium between the two regioisomers of the alkenyl Grignard reagent through their parent acetylene (Scheme 6).

In 1969 [23], Markó reported detailed investigation on a similar hydromagnesation of 1-alkenes and styrene with PrMgBr, catalyzed by $NiCl_2$ [48–50]. From the former, a 1-alkyl Grignard reagent was obtained, whereas styrene gave the secondary (benzylic) Grignard reagent. Simple olefins gave moderate yields of the Grignard reagents, but the yields of the products were somewhat improved with an allyl alcohol and a styrene, which were used as starting materials in the preparation of a lactone [Eq. (6); 4], and an α-arylalkanoic acid [Eq. (7); 31]. In the last transformation, the yield was maximized.



(6)

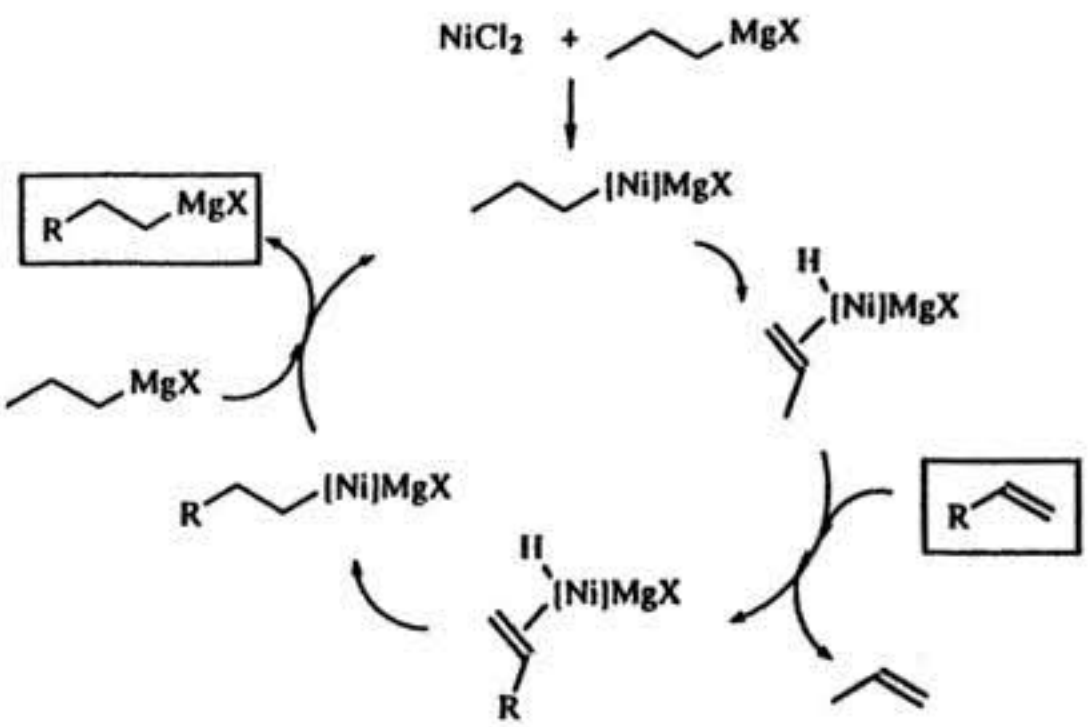


(7)

The mechanisms of the reaction has been considered to be as shown in Scheme 7, in which a Ni-H species, produced by β-hydride elimination from an alkyl-nickel intermediate, catalyzes the key step [4].

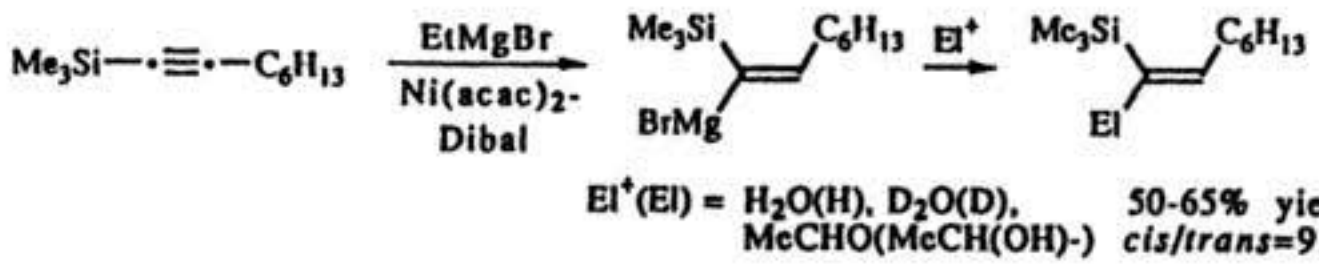
A silylacetylene was reported to enter the similar nickel-catalyzed reaction [Eq. (8); 51]. However, butadiene gave a cyclic Grignard reagent, rather than the simple allyl

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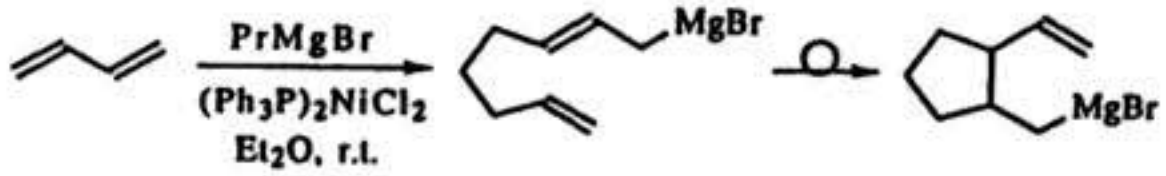


Scheme 7 Proposed reaction course for nickel-catalyzed Grignard exchange reactions

Grignard reagent after its telomerization followed by cycloisomerization [Eq. (9); 52].



(8)



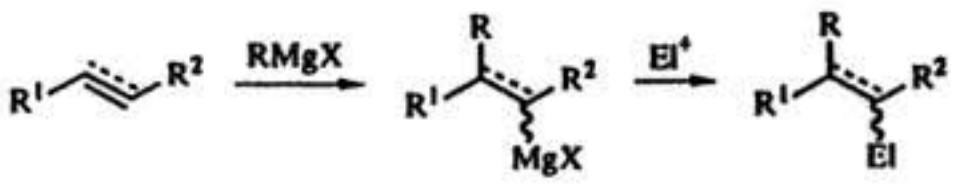
(9)

Like other hydromagnesations catalyzed by iron [3,53,54] or cobalt [55], further synthetic applications of these nickel-catalyzed Grignard exchange reactions were not examined in more detail.

Of the aforementioned transition metal-catalyzed Grignard exchange reactions, the most standard method that has the broadest applications in organic synthesis is perhaps a titanium-catalyzed hydromagnesation of olefins and acetylenes with low molecular weight Grignard reagents.

III. CARBOMAGNESATION OF OLEFINS AND ACETYLENES

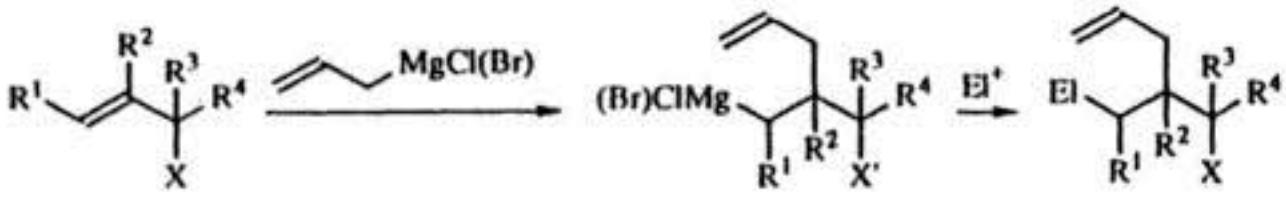
Vicinal functionalization of olefins or acetylenes is an efficient manipulation of these functional groups, as they have two consecutive reactive centers. From this standpoint, carbometallation of olefins and acetylenes is an attractive transformation, owing to the concomitant formation of a new carbon–carbon bond at one terminus and a Grignard reagent at another position, the latter of which permits an introduction of a variety of carbon or heteroatom electrophiles [Eq. (10)].



(10)

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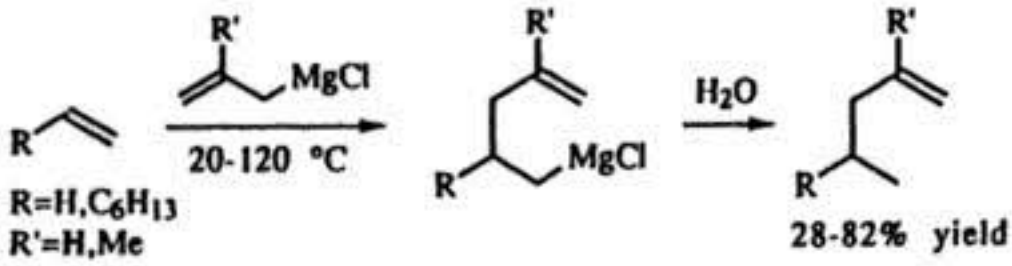
Table 7 Allylmagnesation of Allyl Alcohols and Amines[a]



Entry	R^1	R^2	R^3	R^4	X	El^+	El	Yield (%)	Ref.
1	H	H	H	H	OH	H_2O	H	50	57
2	"	"	"	"	"	D_2O	D	--	"
3	"	"	"	"	"	CO_2	CO_2H	--	"
4	"	"	"	"	"	Me_2CO	$Me_2C(OH)$-	--	"
5	Me	"	"	"	"	H_2O	H	<5	"
6	H	Me	"	"	"	"	"	<5	"
7	"	H	Me	"	"	"	"	16 [*erythro*/*threo*=8:1]	"
8	Ph	"	H	"	"	"	"	99	58
9	H	"	Ph	Ph	"	"	"	0[b]	59,60
10	"	"	H	H	NHPh	"	"	32	61
11	Ph	"	"	"	NH_2	"	"	23	61,62
12	Ph	"	"	"	NMe_2	"	"	44	"

[a]Reactions of entries 1–10 were performed in ether at r.t.-reflux, while those of entries 11–12 in refluxing THF or THF-toluene.
[b]The product obtained in a low yield showed the reversed regioselectivity.

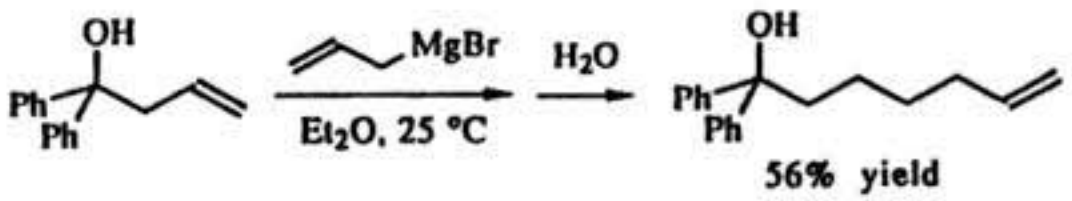
Olefins are generally quite inert against the addition of Grignard reagents under ordinary reaction conditions. Additions of Grignards to unactivated olefins usually require such drastic reaction conditions that they are of limited use [2,7]. However, proper choice in substrates allowed such reactions to proceed under acceptable conditions. Examples include the reactions of allyl Grignard reagents with olefins or dienes [2,7,8,11,12,34], and intramolecular delivery of Grignard reagents to multiple bonds (i.e., isomerization of unsaturated Grignards, see the following section) [2,7,9,10,16,17]. Equation (11) shows allyl Grignard addition to ethylene and 1-octene, the yields of which varied widely [56]. Higher yields were recorded for ethylene. Polymerization and rearrangement of the resultant unsaturated Grignard reagents under the reaction conditions may account for the moderate yields in these reactions.



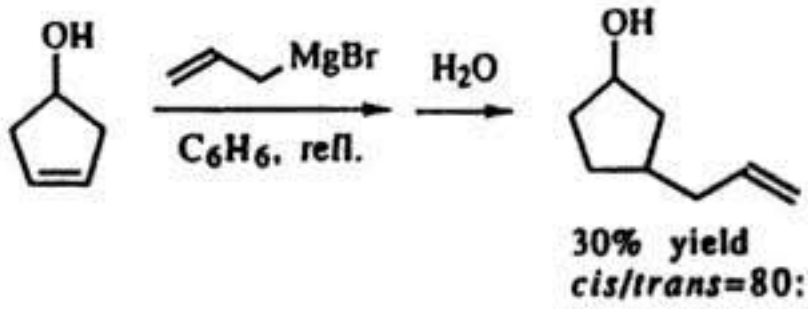
(11)

A certain substituent close to or on the reacting double bond further enhances its reactivity. These substituents involve allylic (Table 7) or homoallylic [Eqs. (12), 59,63; (13), 64; and (14) 64] hydroxy, allylic amino (see Table 7), and the vinylic phenyl (see entry 8, Table 7) groups.

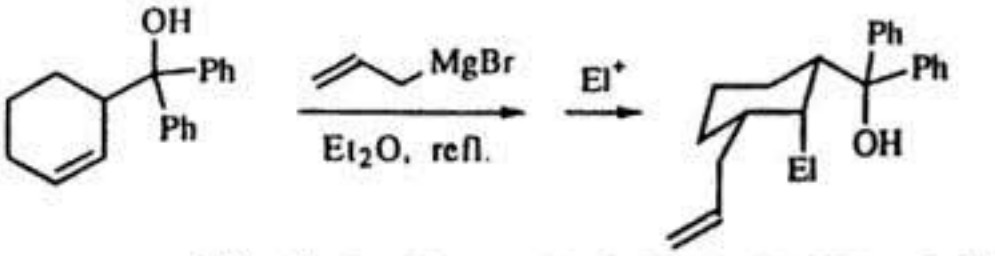
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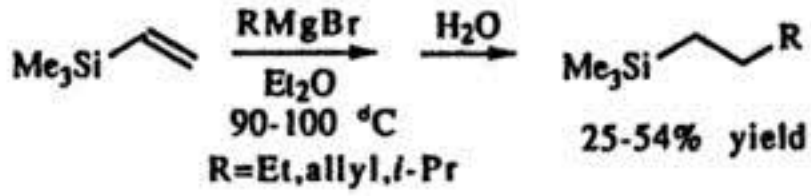


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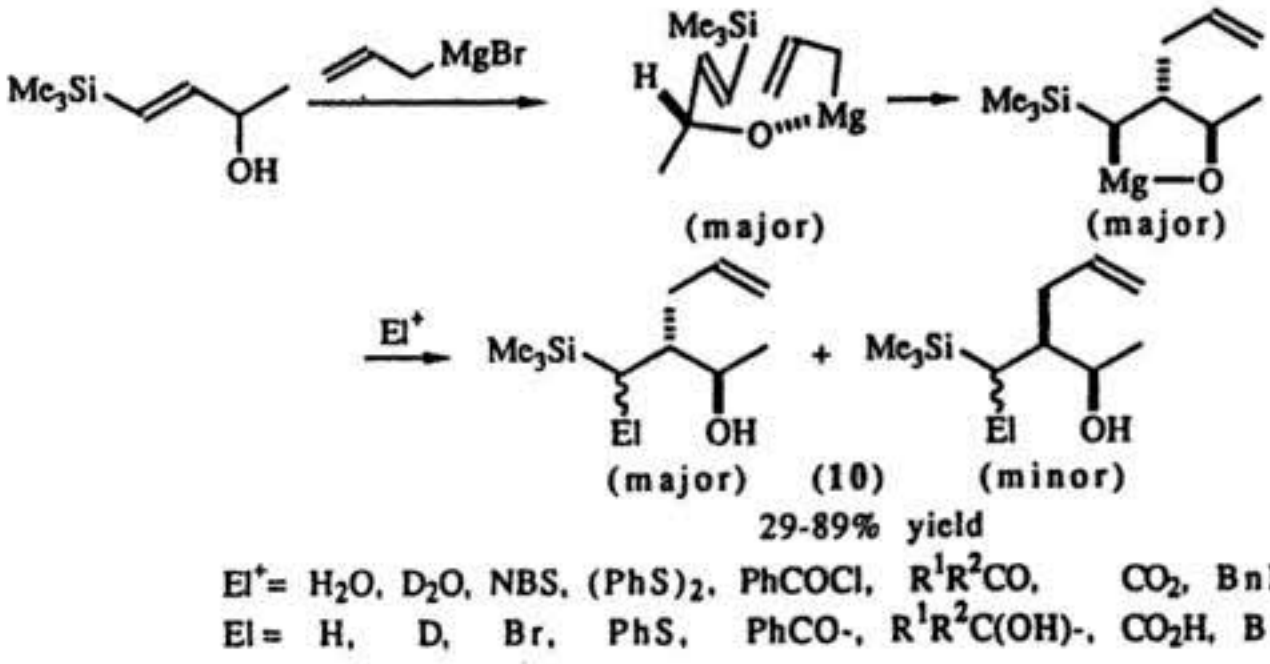
(14)

The stereochemical outcome of the foregoing reactions was discussed in terms of the hydroxyl-assisted mechanism. A vinylic silyl group seemed to promote the addition step and definitely controlled the regiochemistry of the reaction [Eq. (15); 65].



(15)

A synthetically useful transformation, in which the allylic hydroxy and vinylic silyl substituents doubly facilitate the allyl Grignard addition, is noteworthy and is shown in Eq. (16) [66] (see entry 7, Table 7).

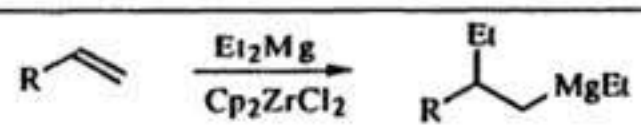


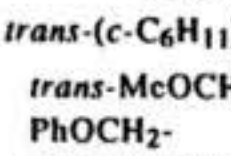
(16)

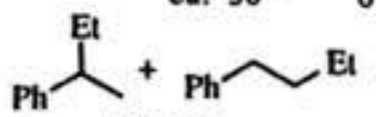
The diastereoselectivity of the protonated product [**10**; El=H] was about 9:1, and the major isomer was proposed to arise from the intramolecular delivery of the allyl group, as shown in Eq. (16). Moreover, the deuterated product (El=D) showed an 8:1

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Table 8 Ethylmagnesation of Olefins with Et_2Mg



Entry	R	Yield (%)	Ref.
1	*cis*-$CH_3CH{=}CHCH_2$-	ca. 90	6
2	Me_3SiCH_2-	96	"
3	$BuOCH_2$-	30	"
4	$CH_2{=}CHCH_2OCH_2$-	30	"
5		95	"
6	*trans*- $CH_2CH{=}CH(CH_2)_3$-	98	"
7	*trans*-(*c*-C_6H_{11})$OCH_2CH{=}CH(CH_2)_3$-	95	"
8	*trans*-$MeOCH_2CH{=}CH(CH_2)_3$-	95	"
9	$PhOCH_2$-	0	"
10	*trans*-$PhOCH_2CH{=}CH(CH_2)_3$-	90	"
11	$HOCH_2$-	0	"
12	*trans*-$HOCH_2CH{=}CH(CH_2)_3$-	98	"
13	Et_2NCH_2-	100	"
14	*trans*-  $NCH_2CH{=}CH(CH_2)_3$-	98	"
15	$CH_2{=}CHCH_2SCH_2$-	25	"
16	Ph	ca. 30[a]	67



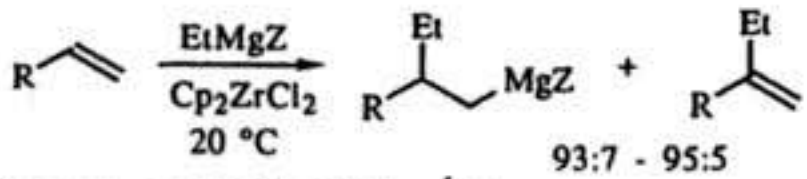
[13:87]

[a]The products and the yield shown are those after hydrolysis of magnesium reagent.

diastereoselectivity for deuterium and the allyl group. A variety of electrophiles could react with the resultant magnesium reagent.

In addition to these uncatalyzed reactions, certain transition metals are known to promote the addition of Grignard reagent to olefins. For example, nickel-catalyzed addition of PhMgBr to ethylene has been documented, but the reaction itself was rather messy and of a low synthetic utility [23,48,49,50]. Whereas a titanium catalyst, such as $TiCl_4$ or Cp_2TiCl_2, effected the *hydro*magnesation of olefins and acetylenes with Grignard reagents, as described in the preceding section, use of a suitable zirconium catalyst allowed a *carbo*magnesation under similar reaction conditions.

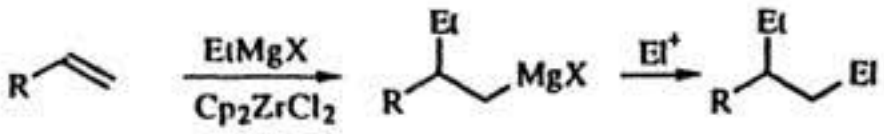
The first report on carbomagnesation catalyzed by zirconium was made by Dzhemilev *et al.*, who carried out the reaction by taking olefin, EtMgZ [Z, see Eq. (17)], and a catalytic amount of Cp_2ZrCl_2 at near room temperature to obtain 2-ethylalkylmagnesium reagent with a good selectivity [Eq. (17); 6].

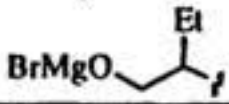


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Table 9 Generation and Reactions of Grignard Reagents by Zirconium-Catalyzed Ethylmagnesation



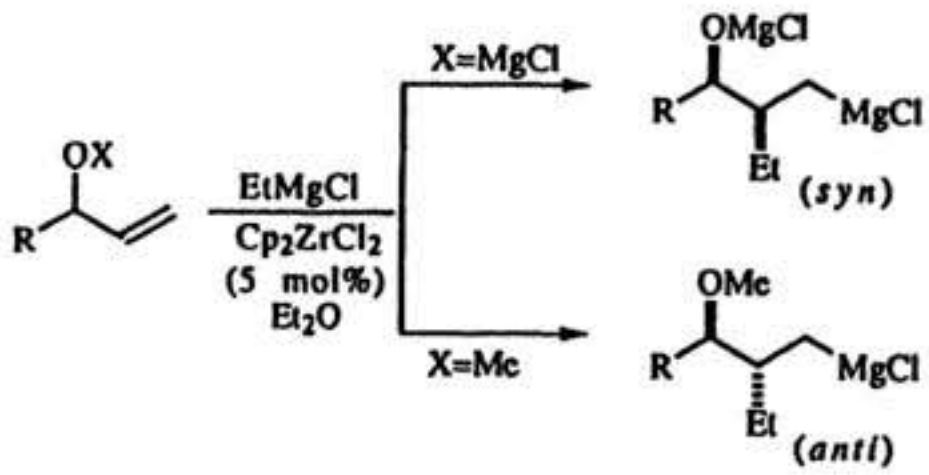
Entry	R	X	El^+	El	Yield(%)	Ref.
1	C_6H_{13}	Br	H_2O	H	96	67
2	C_8H_{17}	Cl	MeCHO	MeCH(OH)-	55	71
3	"	"	$B(OMe)_3/H_2O_2$	OH	60	"
4	"	"	NBS	Br	60	"
5	"	"	I_2	I	65-74	69,71
6	"	Br	MeI	Me	80	69
7	"	"	allyl-Br	allyl	71	"
8		"	$(MeS)_2$	MeS	89	68
9	"	"	R^1R^2CO	$R^1R^2C(OH)$-	38-58	"
10	"	"	$(EtO)_2CO$	CO_2Et	45	"
11		"	--	--	53[a]	72

[a]Yield refers to that of Grignard reagent.

This carbomagnesation was examined mostly with Et_2Mg as EtMgZ and, accordingly, the products are dialkylmagnesiums, which are shown in Table 8. As the aforementioned, titanium-catalyzed hydromagnesations, this zirconium-catalyzed ethylmagnesation was also most successfully applied to terminal olefins and permitted a chemoselective metallation of bis-olefinic substances. Many such examples can be seen in Table 8. Moreover, several functional groups containing ether, amine, sulfide, and silicon groups did not block the reaction. However, allylic phenoxy and hydroxy groups of the reacting terminal olefinic moieties totally inhibited the reaction (entries 9 and 11, Table 8). Styrene showed a reversal regioselectivity against alkenes (see entry 16, Table 8), which is in accord with the tendency of this particular substrate, as also noted in the previous hydromagnesation.

In addition to the basic research just described, a few different groups [67–70] quite recently investigated this reaction in more detail by using ethyl Grignard reagent, rather than diethylmagnesium. This brought the value of this series of reactions to the attention of organic chemists. The resultant Grignard reagents have reacted nicely with a variety of electrophiles, as summarized in Table 9.

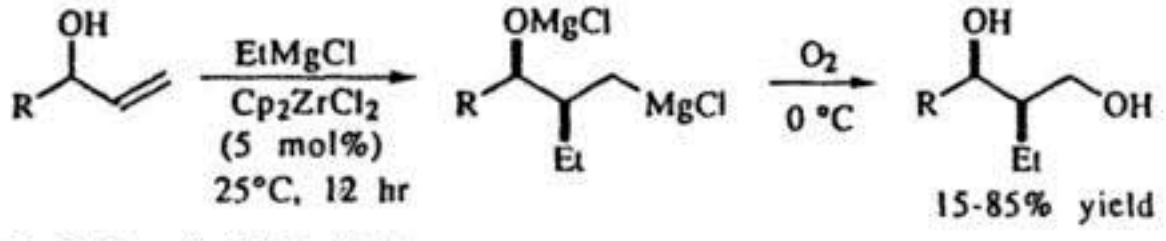
Hoveyda *et al.* further oriented their investigation on this zirconium-catalyzed ethylmagnesation to the issue of 1,2-asymmetric induction in the step of ethyl addition to substituted olefin as exemplified in Eq. (18) [70]. Thus, ethylmagnesation of various allyl



(18)

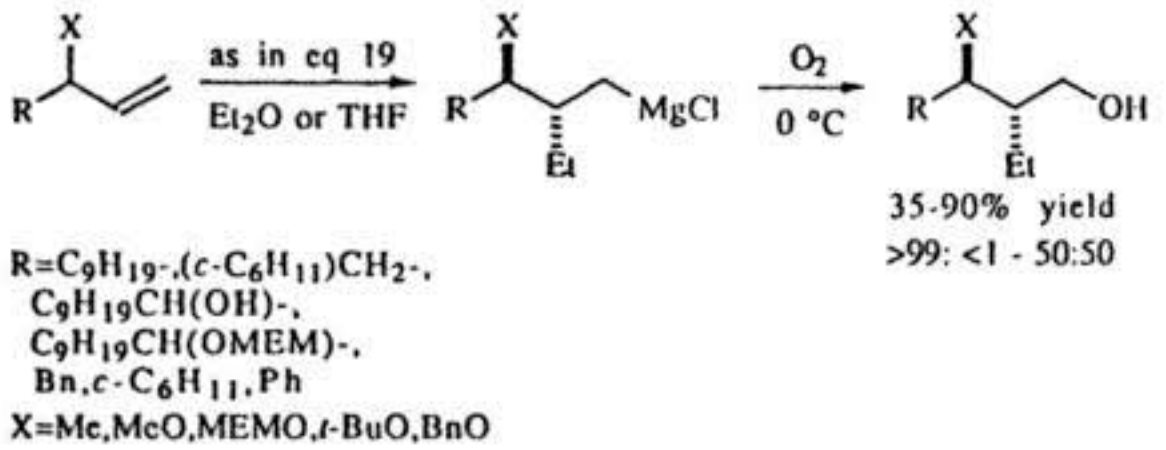
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alcohols afforded *syn*-diol after the oxidative workup of the produced Grignard reagent with O_2 [Eq. (19)]. The *syn*-selectivity was reinforced when the reaction was performed in a solvent with less coordination ability (from THF, to 2,5-DMTHF, to ether), which suggests that the selectivity was controled by chelation between the hydroxy group (alkoxide in the reaction media) and the reacting metal center.



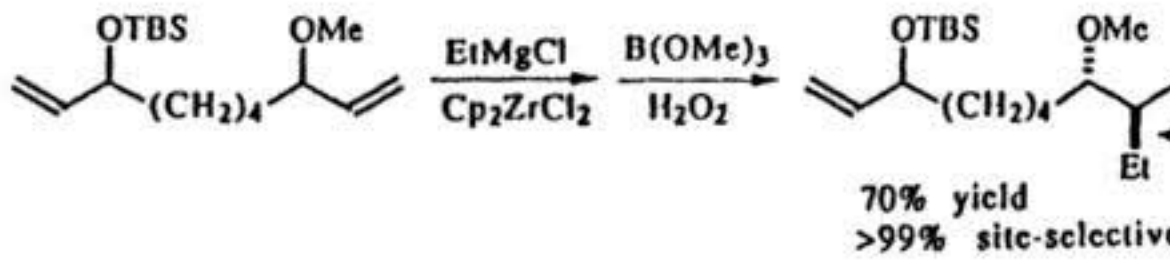
(19)

On the contrary, a wide variety of other terminal alkenes having allylic alkoxy or methyl group afforded *anti*-diols after the ethylmagnesation followed by the same workup [Eq. (20)]. In these cases, virtually no change of diastereoselectivities was observed by switching the solvent from THF to ether, showing that the origin of this diastereoselection comes from steric repulsion of substituents around the reaction center.

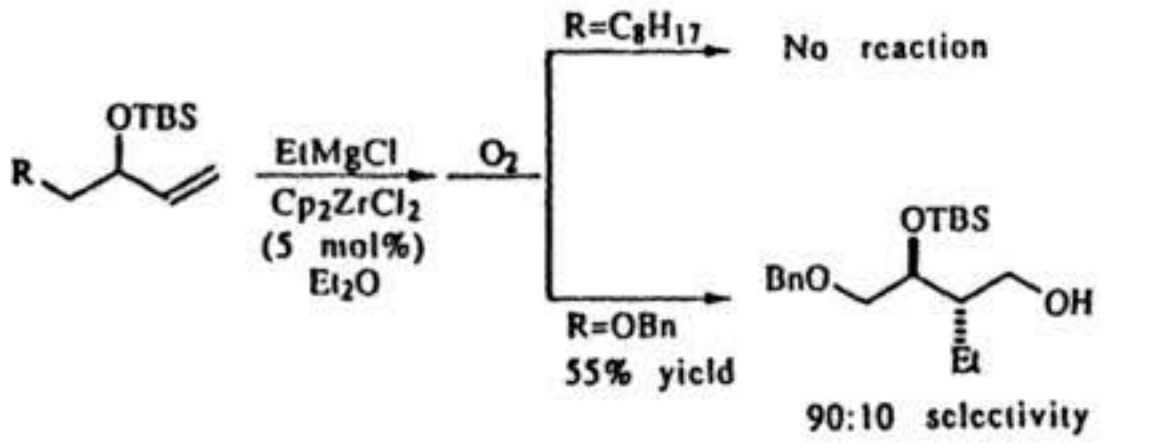


(20)

A bulky TBS group proximal to the terminal olefin blocked the reaction, which enabled the following chemoselective reaction [Eq. (21); 71]. However, an additional oxygen functionality near the reaction center assists the ethylmagnesation to again proceed [Eqs. (22) and (23); 70].

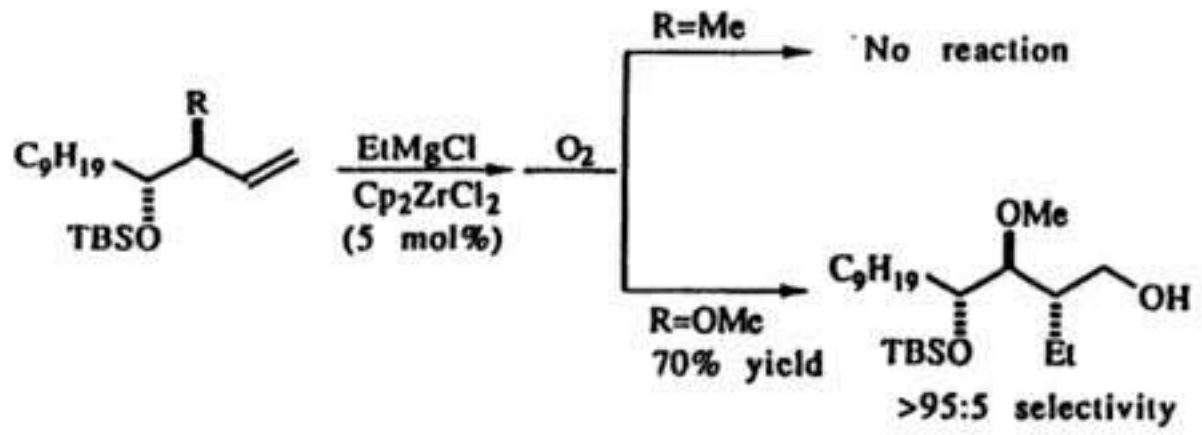


(21)



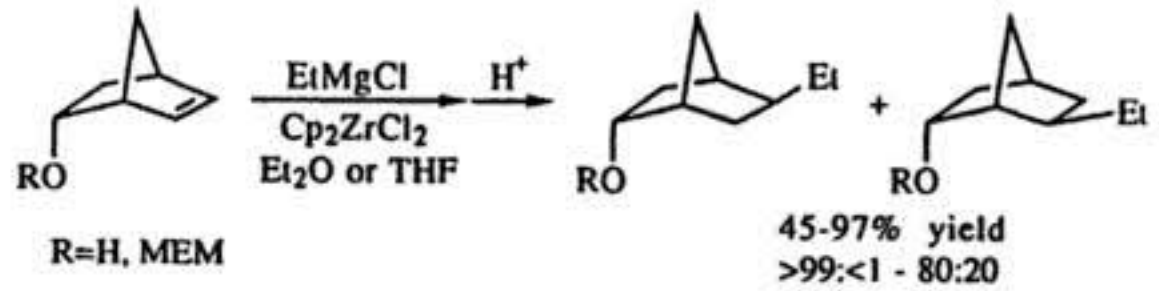
(22)

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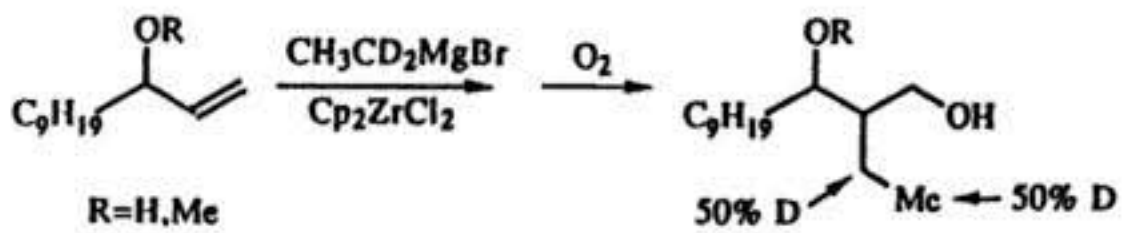
(23)

Norbornenes also underwent regio- and stereoselective ethylmagnesation, even though the synthetic applicability is rather restricted [Eq. (24); 73].

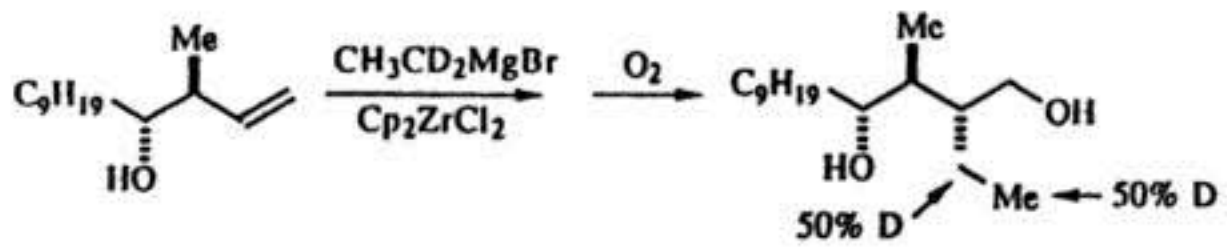


(24)

Study on the mechanism of this reaction revealed a reaction pathway involving reorganizations of several active species. A study using deuterium-labeled CH_3CD_2MgBr revealed that deuterium was incorporated on both carbons of the newly introduced ethyl group at a ratio of 50:50 [Eq. (25) and (26); 70].



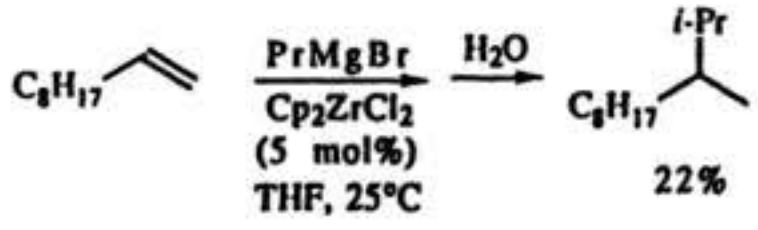
(25)



(26)

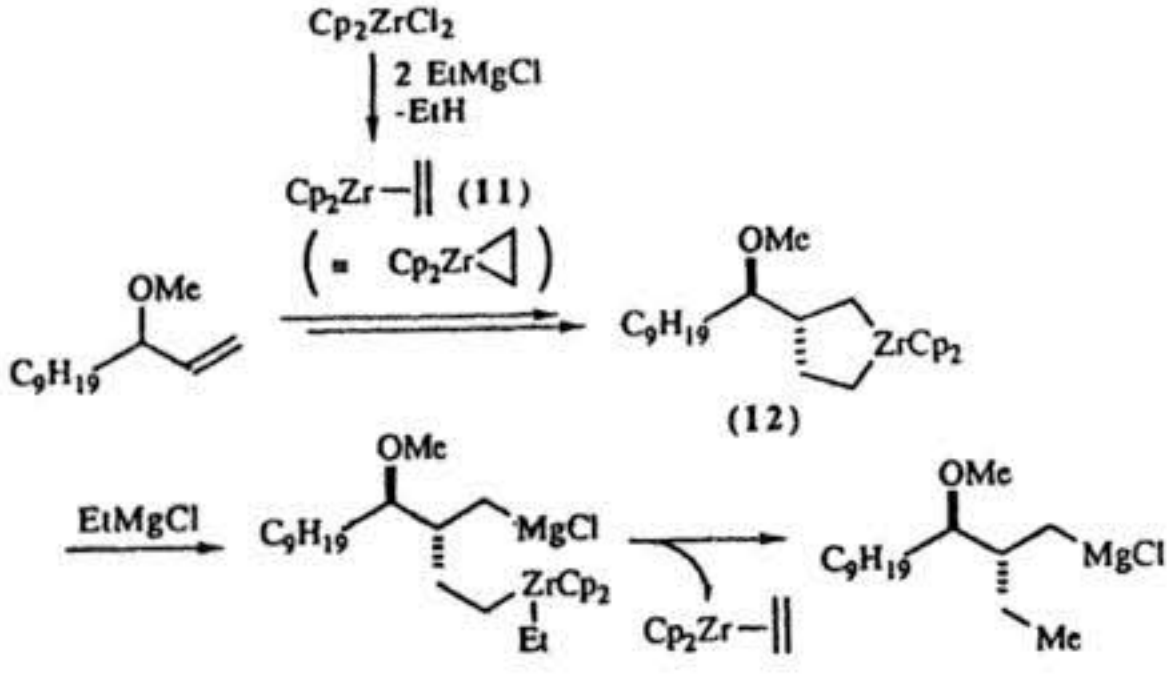
The most likely reaction course through the intermediary zircona-cyclopropane **11** and -cyclopentane **12** was proposed (Scheme 8) and could rationalize the loss of positional identity of both carbons of the ethyl Grignard reagent. Moreover, the origin of the aforementioned stereoselections [see Eqs. (18–20)] has been well explained in terms of chelation or steric repulsion in the intermediate species in this mechanism [70].

When ethyl Grignard reagent in the foregoing carbomagnesation was replaced by PrMgBr, the reaction probably took place through zircona(methylcyclopropane), to yield a mixture of products having *n*- and *i*-propyl groups. The latter is the major or exclusive constituent [Eq. (27); 69,74].



(27)

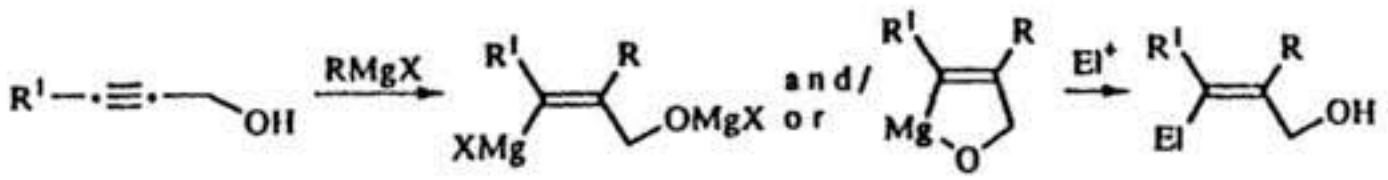
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Scheme 8 Proposed reaction course for zirconium-catalyzed ethylmagnesation

The use of a chiral zirconium catalyst may extend these reactions to asymmetric synthesis. An example that achieved a chiral transfer at a very high level was reported, but a Grignard reagent was involved in only a transient species, not in the final product [74].

Carbomagnesation of acetylenes with Grignard reagents affords the corresponding alkenyl Grignard reagents, possibly with a defined regio- and stereo-chemistry [2,7,11,13,34]. This reaction works well for internal acetylenes having a hydroxy or amino group proximal to the triple bond, as in the olefinic substrates discussed earlier. Equation (28) formulates the reactions, in which the regio- and stereochemistries of the resulting magnesium species have been controlled, as depicted by high selectivities. Table 10 summarizes typical reactions.



(28)

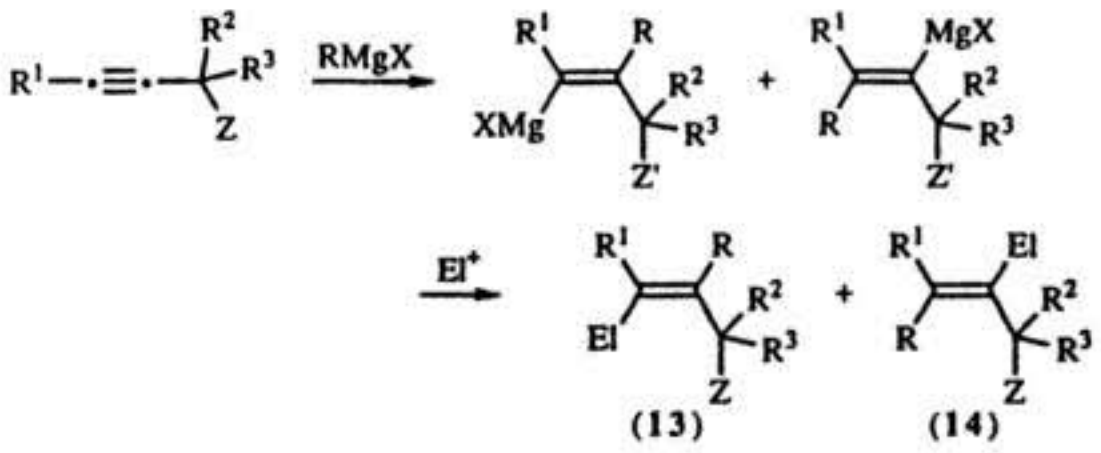
Although propargylic hydroxy groups nicely directed the regioselective addition of Grignard reagents, amino groups seemed to be less effective, and even reversed the regioselection. The addition of Grignard reagents to acetylenes having a functional group, such as hydroxy, amino, or alkylthio, at each of both propargylic termini was also investigated [78–81]. Homopropargyl alcohols are still susceptible to the allyl Grignard addition, but the high regio- and stereoselectivities obtained with propargyl derivatives are often lost [60,64,76,77]. The substrate having a hydroxyl remote from the triple bond by more than three methylenes seemed not to be attacked by allyl Grignard reagent under conditions comparable with those applied to the reactions of Eq. (28) [76].

A transition metal catalyzes a similar carbomagnesation reaction, which has broaden the synthetic usefulness of this method for synthesis of alkenyl Grignard reagents. Among several transition metal salts that were reported to catalyze carbomagnesation of acetylenes [7,51,82–84], copper salts are most popular [7,13–15]. A variety of acetylenes, including acetylene itself [85], as well as substituted ones participated in this reaction. Some representative reactions are summarized in Table 11.

Although the applicability is limited to Grignards having no β-hydrogen, namely MeMgX and PhMgX, nickel-catalyzed carbomagnesations of acetylenes have been documented [Eqs. (29); 84 and (30); 51].

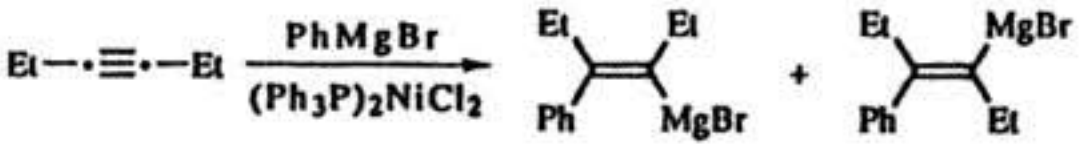
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Table 10 Carbomagnesation of Propargyl Alcohols and Amines with Grignard Reagents

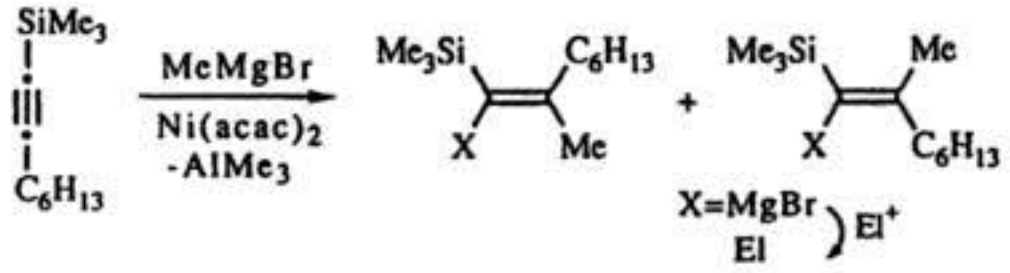


Entry	R^1	R^2	R^3	Z	RMgX	El^+	El	Yield (%)	Ref.
1	H	H	H	OH	EtMgBr	H_2O	H	13 (20)	75
2	Me	"	"	"	allyl-MgCl	"	"	13 (26-85)	75,76,77
3	"	"	"	"	"	CO_2	CO_2H[a]	--	77
4	"	"	"	"	Me-,*t*-Bu-, Ph-MgX	H_2O	H	13 (0)	"
5	"	"	"	"	vinyl-MgCl	"	"	13 (60)	"
6	Bu	"	"	"	Me-,Et-, *i*-Pr-, Ph-MgX	"	"	13 (45-59)	78
7	Me_3Si	"	"	"	allyl-MgCl	"	"	13 (54)	75
8	Me	Me	"	"	allyl-, vinyl-MgCl	"	"	13 (22)	76
9	Me	-$(CH_2)_5$-			allyl-MgBr	"	"	0[b]	60,64
10	Me,Et	H	H	NMe_2	EtMgBr	"	"	13+14 (45-50) [10:90-5:95]	78
11	Me	"	"	NPr_2	Et-, *i*-Pr-MgBr	"	"	13+14 (40-60) [15:85]	"
12	Ph	"	"	NMe_2	allyl-MgCl	"	"	13 (49-51)[c]	61,62

[a] Lactonized.
[b] See references for detailed discussion.
[c] *Z*/*E* not specified.



(29)

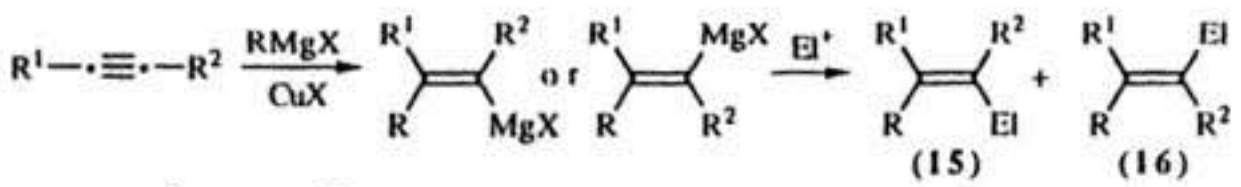


(30)

El^+	El	Ratio	Yield(%)
D_2O	D	9 : 1	75
RCHO	RCH(OH)-	85:15-90:10	66-70
CO_2	CO_2H	4 : 1	61
I_2	I	9 : 1	71

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Table 11 Carbomagnesation of Alkynes with Grignard Reagents Catalyzed by Copper



Entry	R^1	R^2	RMgX	CuX	El^+	El	Yield (%)	Ref.
1	H	H	$C_7H_{15}MgBr$	CuBr	EtCHO	EtCH(OH)-	31	85
2	Me,Et,*i*-Pr, Ph,R'CH=CH-, R'C≡C-	MeS	Me-,Et-, *i*-Pr-, Ph-MgX	CuBr, CuI	H_2O	H	15 (76-95)	86
3	CH_2OH	H	alkyl-MgX, PhMgBr	CuI	H_2O	H	16 (53-80)	87
4	"	"	"	"	D_2O	D	16 (53-80)	88
5	"	"	"	"	CO_2	CO_2H^a	16 (30-61)	89
6	"	"	"	"	R^1R^2CO	$R^1R^2C(OH)$-	16 (24-61)	"
7	"	alkyl,alkenyl, alkynyl,Ph	"	"	D_2O	D	16 (20-79)	87,88
8	H	CH(Me)OH	PhMgBr	"	"	"	15 (35)	"
9	H	CMe_2OH	"	"	"	"	15 (31)	"
10	CH_2OMgBr	MgBr	EtMgBr, PhMgBr, allyl-MgBr	"	"	" (R^2=D)	15 (43-51)	90

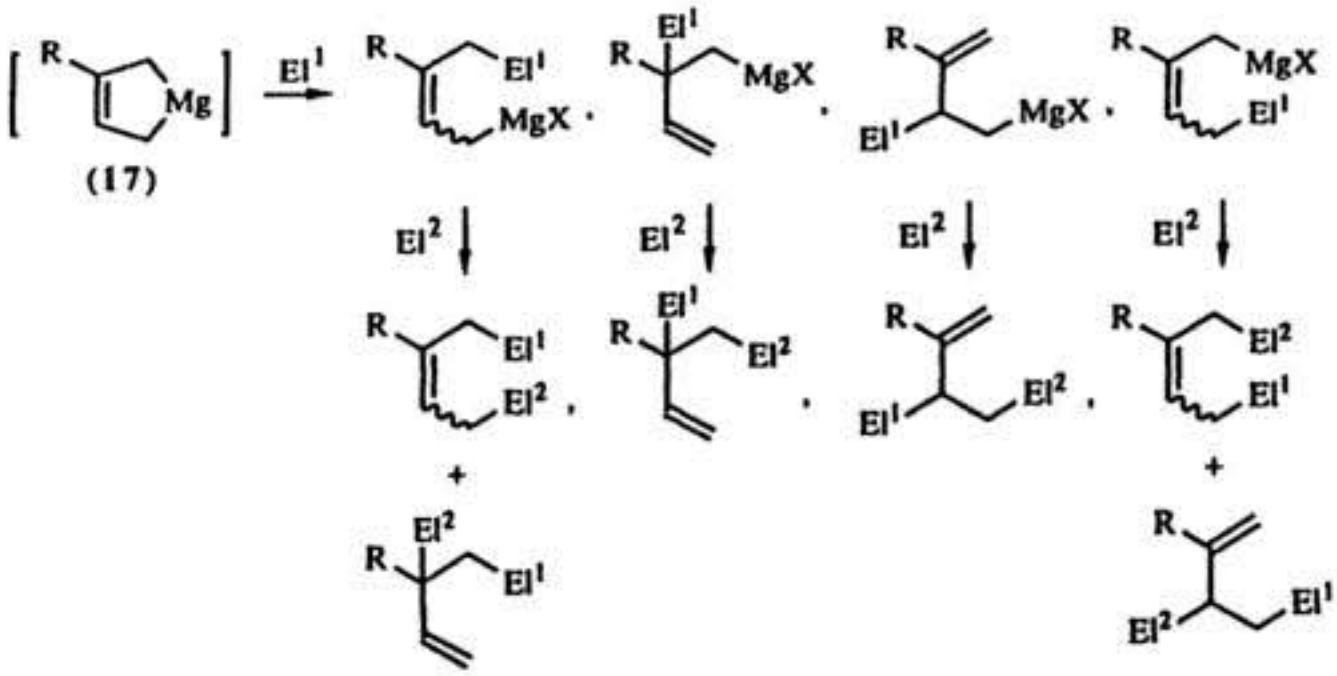
[a]Products isolated are lactones.

These uncatalyzed and transition metal-catalyzed carbometallations enable the use of various Grignard reagents to give alkenyl Grignard reagents of high regio- and stereochemical purities, dependent on substrates. This method enables the synthesis of stereodefined olefins found in many naturally occurring products.

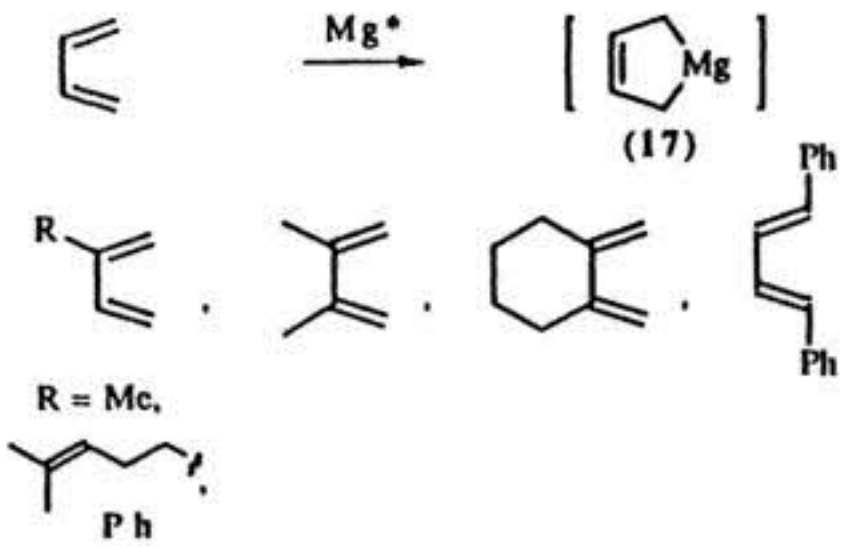
IV. REDUCTIVE METALLATION OF DIENES

Reductive metallation of 1,3-butadiene with magnesium in aprotic media afforded a kind of allylmagnesium reagent, (2-butene-1,4-diyl)magnesium, which has some use as a starting material for other organometallic compounds [91,92]. However, the smooth metallation was limited to butadiene. Other types of 1,3-dienes usually suffered dimerization, polymerization, and other side reactions under similar reaction conditions [93]. Rieke *et al.* circumvented this difficulty by using a very active magnesium, Mg* called "Rieke-Mg" [94], prepared by the reduction of $MgCl_2$ with lithium metal in the presence of naphthalene or lithium naphthalenide in THF. In fact, several typical dienes of the following structures underwent the clean reductive metallation to give the diene–magnesium reagents [**17**; Eq. (31)].

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Scheme 9 Reaction of (2-butene-1,4-diyl)magnesium **17** with two different electrophiles, El^1 and El^2



(31)

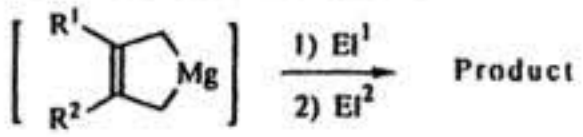
Since these species were difficult to obtain before the development of this improved method, their synthetic application has not been explored [95,96]. As the resulting magnesium species has two carbon–magnesium bonds, it may react with two different electrophiles, El^1 and El^2, in a stepwise manner to give a possible mixture of three regioisomers, if the starting diene is symmetric, or a mixture of six, if it is unsymmetric (Scheme 9). However, the actual reactions of **17** with electrophiles usually take place in a highly regioselective manner to reduce the number of the product(s) to one or two. Table 12 shows representative reactions based on the diene–magnesium reagent.

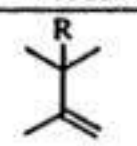
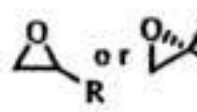
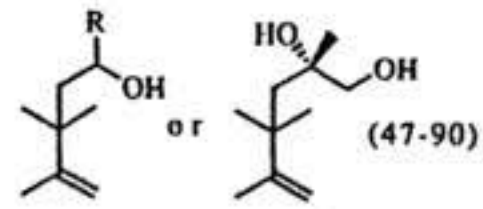
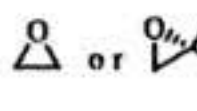
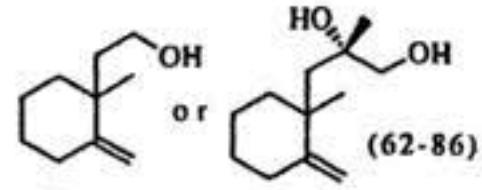
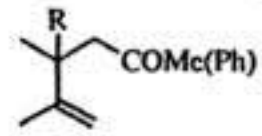
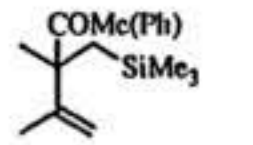
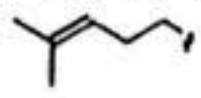
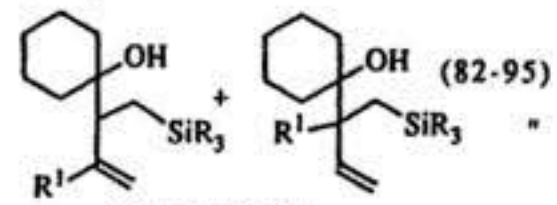
The most interesting applications of **17** are certain cyclizations and spiroannulations [98–100]. The treatment of the reagent with a bifunctional electrophile, such as $X(CH_2)_nX$, $X(CH_2)_nCN$, RBX_2, $RPCl_2$, R_2SiCl_2, or $SiCl_4$, or with a combination of two different ones, including $R^1R^2CO+CO_2$ or ethylene oxide$+CO_2$, effects carbocyclization, heterocyclization, and lactonization, including a spiro-fashion, as shown in Scheme 10.

A superficially analogous cyclomagnesation of 1,6- and 1,7-dienes proceeded with BuMgX or Bu_2MgX in the presence of Cp_2ZrCl_2 catalyst, as shown in Eq. (32) [67,101]. Although most examples include simple hydrolytic workup of the reaction mixture,

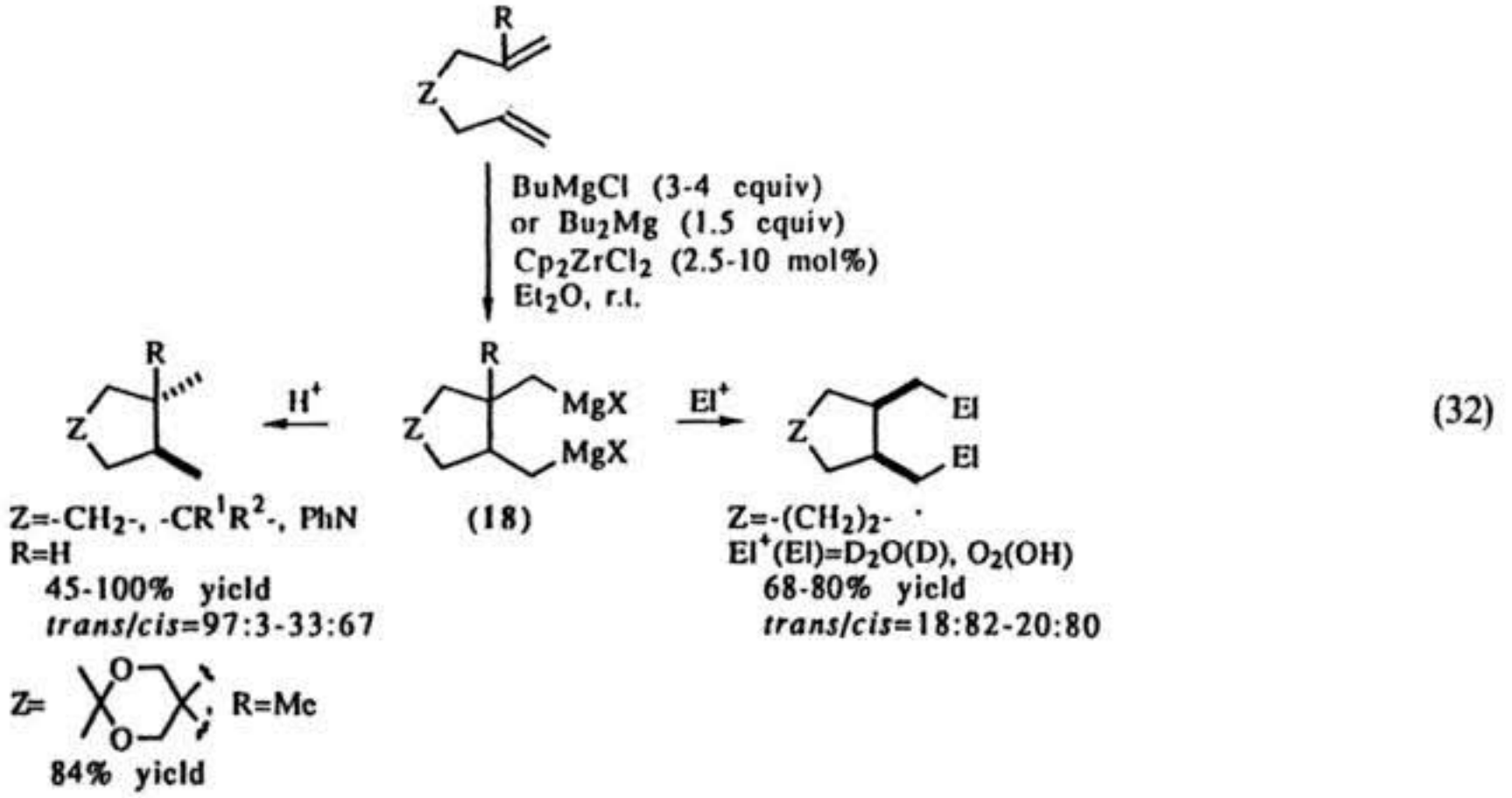
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Table 12 Representative Reactions of (2-Butene-1,4-diyl)magnesiums with Electrophiles



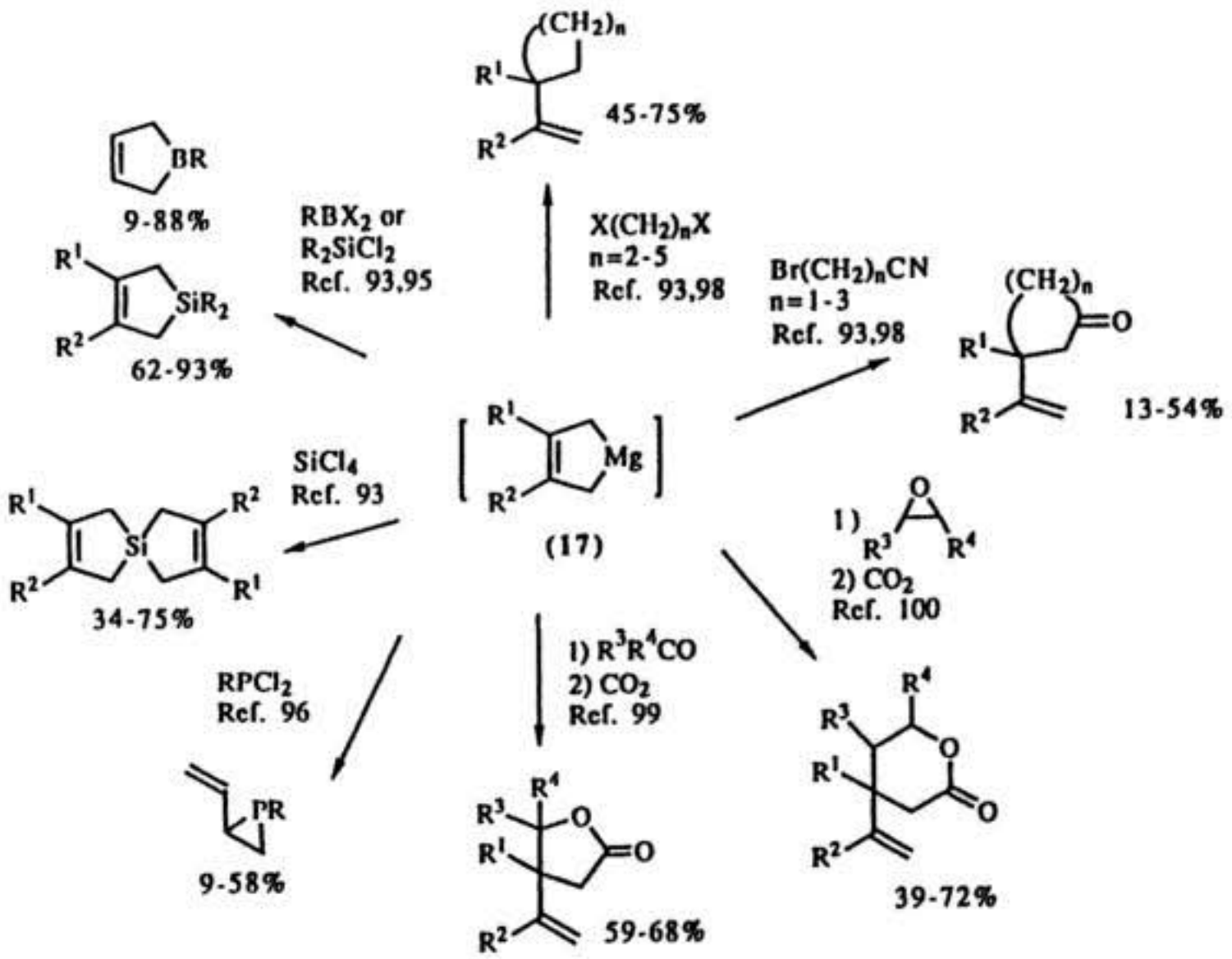
Entry	R^1	R^2	El^1	El^2	Product(s) (%)	Ref.
1	Me	Me	R-Br,-Cl R=alkyl, $ArCH_2$-, $NC(CH_2)_3$-	H^+	 (35-81)	93
2	"	"		H^+	 (47-90)	97
3	$-(CH_2)_4-$			H^+	 (62-86)	"
4	Me	Me	RBr	MeCOCl, PhCOCl	 (60-82)	93
5	"	"	Me_3SiCl	MeCOCl, PhCOCl	 (73-79)	"
6	Me, Ph, 	H	Me_3SiCl, Bu_3SiCl		 [77:23-100:0] (82-95)	"

interception of the intermediate with D_2O or oxygen to yield the corresponding bisdeuterated hydrocarbon or diol confirmed the presence of the bis magnesiated species **18**.



(32)

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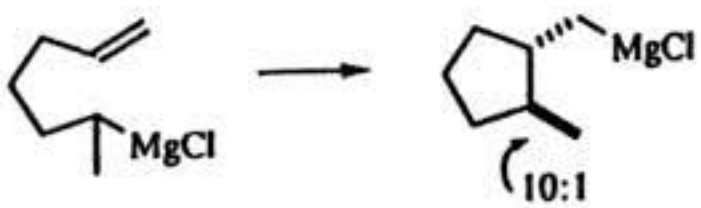


Scheme 10 Cyclization and spiro-annulation based on **17**

The mechanism of this reaction is closely related to that of the ethylmagnesation of olefins with Et_2Mg or EtMgX, as described in the foregoing section, but the use of butylmagnesium reagent, rather than ethyl, is the key. The use of bulkier butylmagnesium reagents prevents the formation of zirconacyclopentane **23** (right half of the Scheme 11). It does allow the ligand exchange between butene and the added 1,6- and 1,7-diene **19** on the zirconium to make the reaction proceed to **22** (left portion of Scheme 11), which finally furnishes a desired bismagnesium reagent **18** [67].

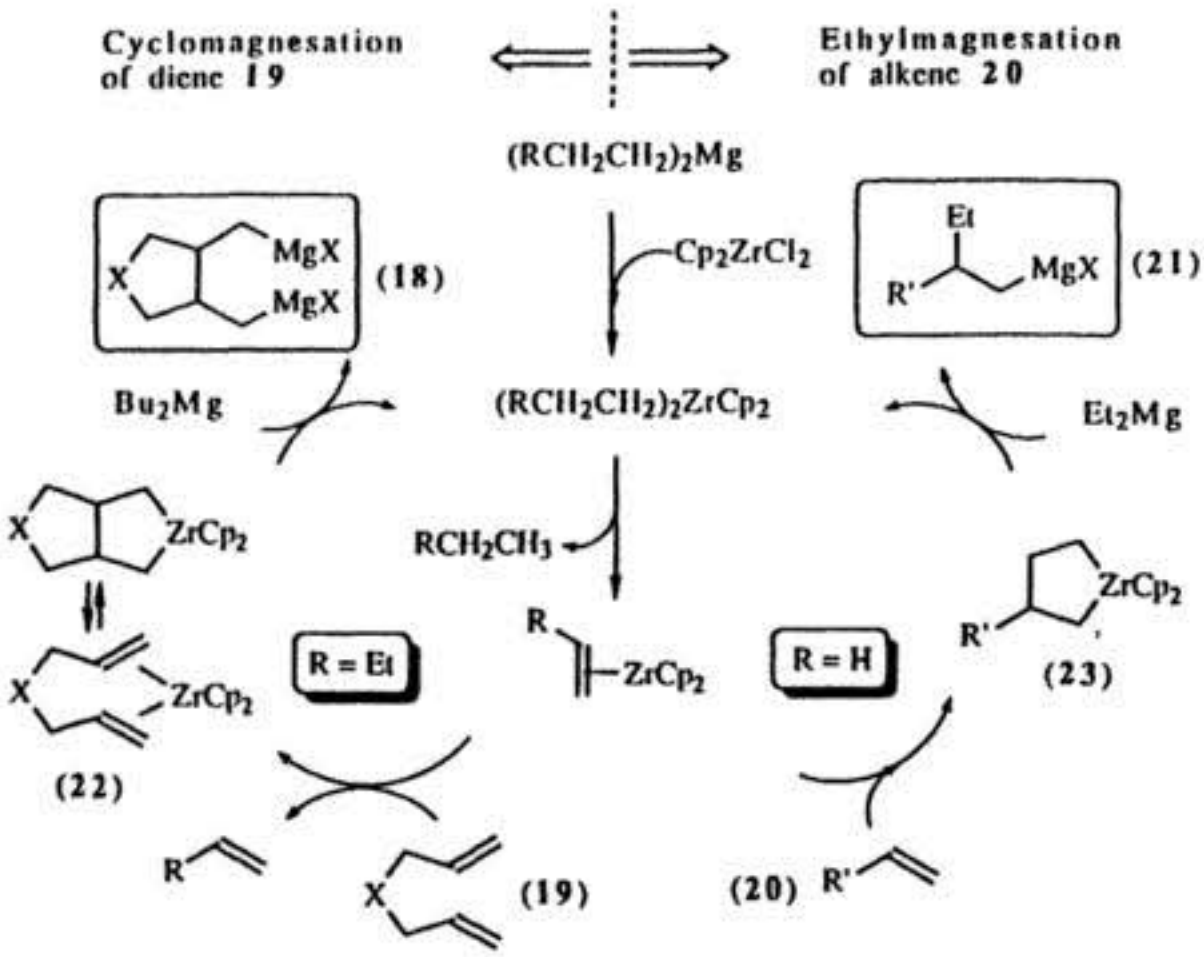
V. ISOMERIZATION OF OLEFINIC AND ACETYLENIC GRIGNARD REAGENTS

In contrast to intermolecular additions of Grignard reagents to unsaturated bonds, the same type of reactions in an intramolecular fashion (i.e., isomerization of olefinic or acetylenic Grignard reagents with an appropriate structure) could proceed much easier [2,7,9,10]. Exhaustive reviews that systematically survey these reactions from the standpoints of organic [10] and physical organic chemistry [9] are quite informative. A general guideline on the rate and direction of the cyclizations has been described in these reviews. A few, synthetically interesting examples are shown in Eqs. (33) [102], (34) [90],

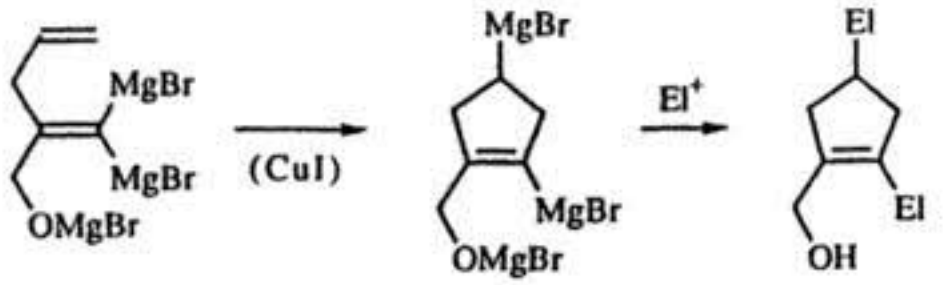


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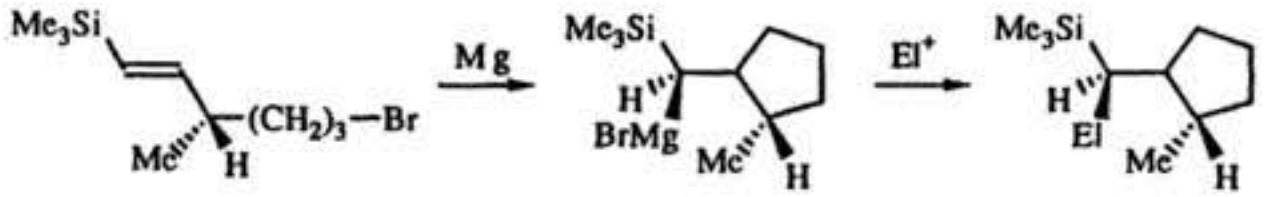


Scheme 11 Difference in proposed catalytic cycles of cyclomagnesation of dienes and ethylmagnesation of alkenes



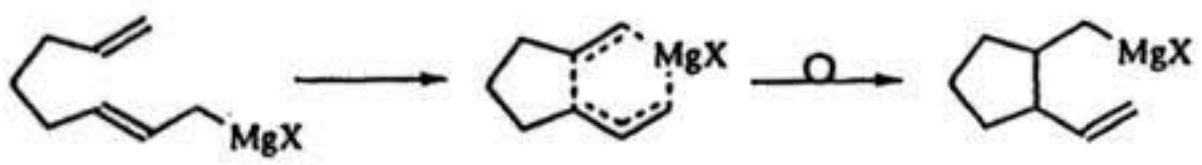
(34)

and (35) [103], which show that both 5-*exo*-trig and 5-*endo*-trig ring closures [104] are possible.



(35)

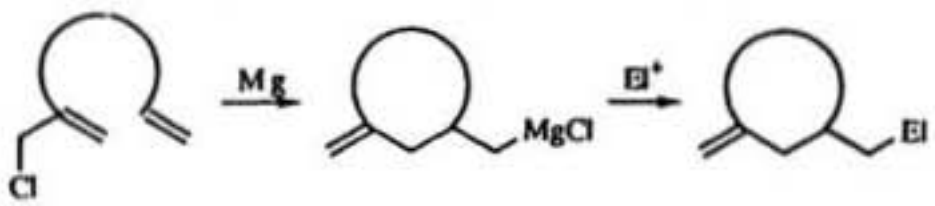
The most synthetically useful transformation belonging to this class of reactions would be the magnesio-ene reaction [Eq. (36); 16,17].

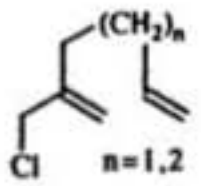
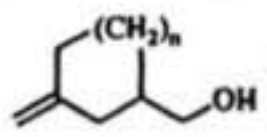
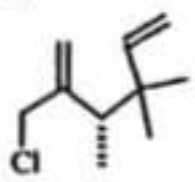
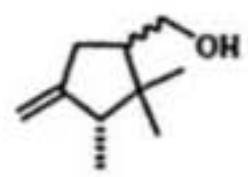
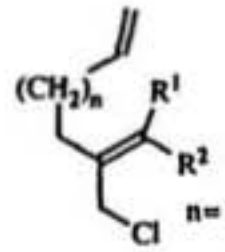
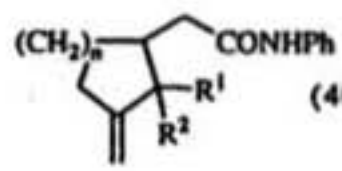
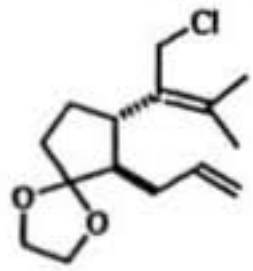
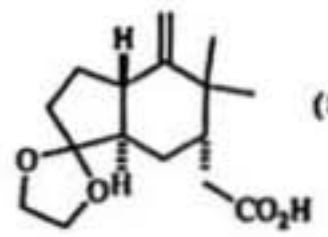
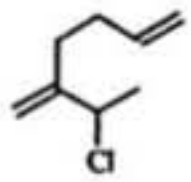
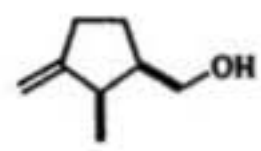
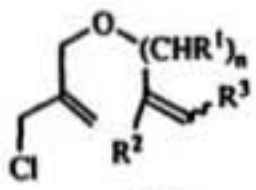
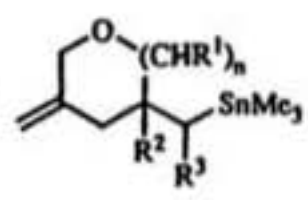
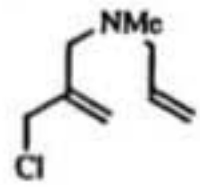
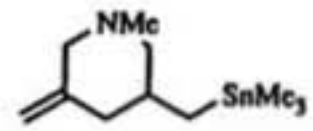
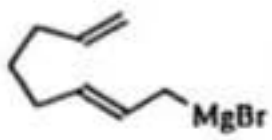
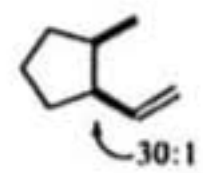
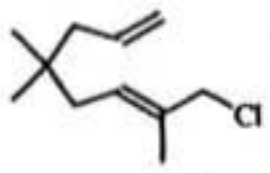
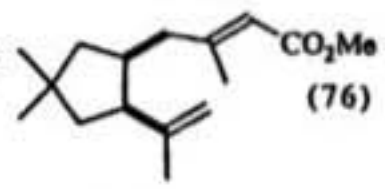
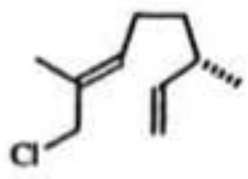
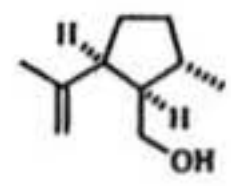


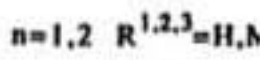
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Table 13 Magnesio-ene and Subsequent Reaction with Electrophiles

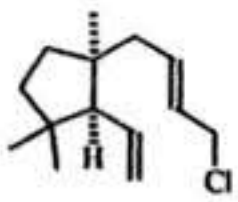
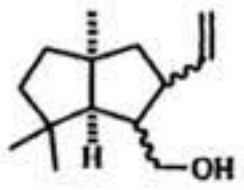
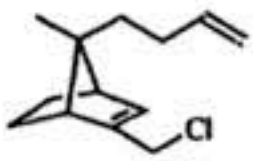
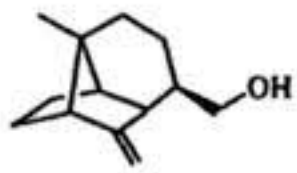
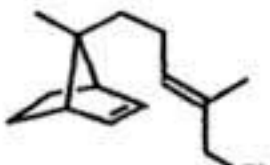
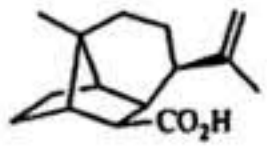


Entry	Substrate	El+	Product (%)	Ref.
1		MoO_5	 (55-57)	94
2		O_2	 (61)	107
3		PhNCO	 (40-86)	94,108
4		CO_2	 (82)	109,110
5		O_2	 (64)	111
6		Me_3SnCl	 (0-15)	112
7		Me_3SnCl	 (76)	-
8[a]		H^+	 (--)	102
9		$MeC{\equiv}CCO_2Me$ CuI, TMEDA	 (76)	113
10		MoO_5	 (58)	114



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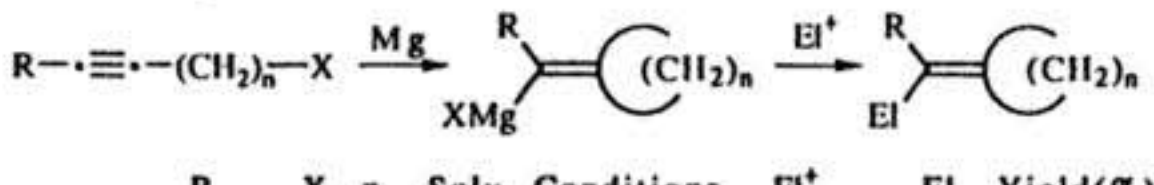
Table 13 Continued

Entry	Substrate	El^+	Product (%)	Ref.
11		O_2	 (70)	115
12		MoO_5	 (62)	116
13		CO_2,	 (47)	117

[a]This Grignard reagent was prepared by other method.

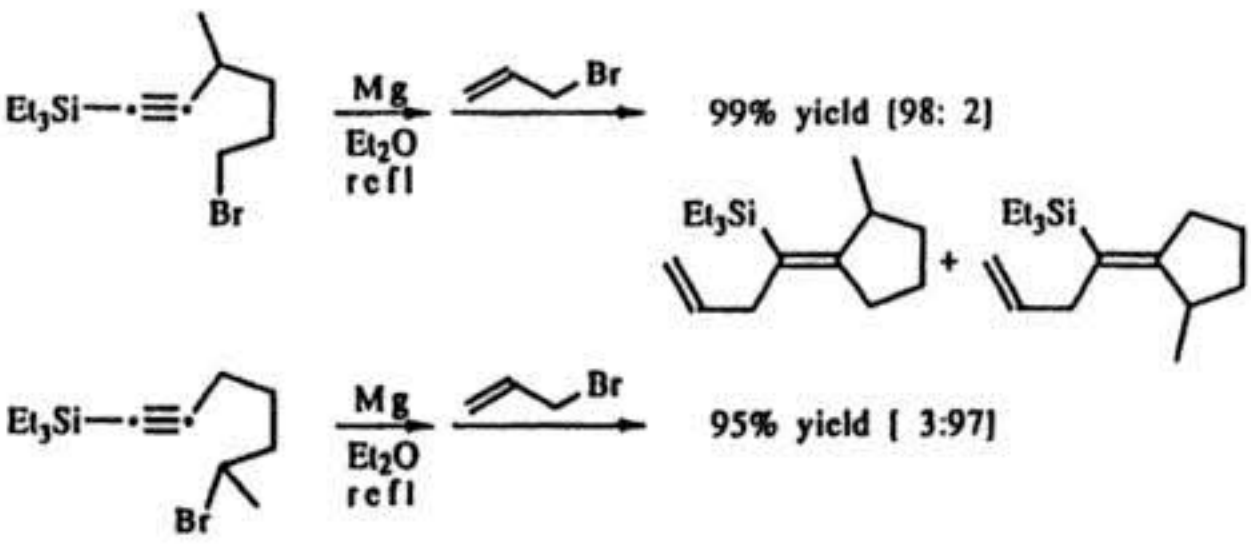
Typically the allylmagnesium reagents are generated from the corresponding allyl chlorides, at a low temperature, with magnesium, which is preferably activated before the reaction by an appropriate method [94,105,106]. The ene reaction was allowed to complete at room temperature or as high as 130°C. Table 13 collects several examples, that demonstrate that this method is particularly useful for the construction of carbocyclic rings. The stereoselectivities of the substituents are often very high and the remaining organometallic moieties are helpful for further synthetic elaboration. These advantages have been amply highlighted in the concise syntheses of terpenes [16,17,107–111,113–117].

Isomerization of acetylenic Grignard reagents affords the corresponding cyclic alkenyl Grignards [2,7]. Many cyclizations of acetylenic Grignard reagents are found in the literature [9]. Equations (37) [118,119] and (38) [119] represent recent, synthetically useful examples, in which the silyl group plays a dual role to facilitate the cyclization and to increase the stereoselectivity.



R	X	n	Solv.	Conditions	El^+	El	Yield(%)
Me_3Si	Br	3	THF	refl.; --	allyl-Br	allyl	9
"	"	4	Et_2O	refl.; 1 hr	"	"	97
Me	Cl	"	THF	100 °C; 6 d	H_2O	H	90
Me_3Si	Br	5	Bu_2O	refl.; --	allyl-Br	allyl	99

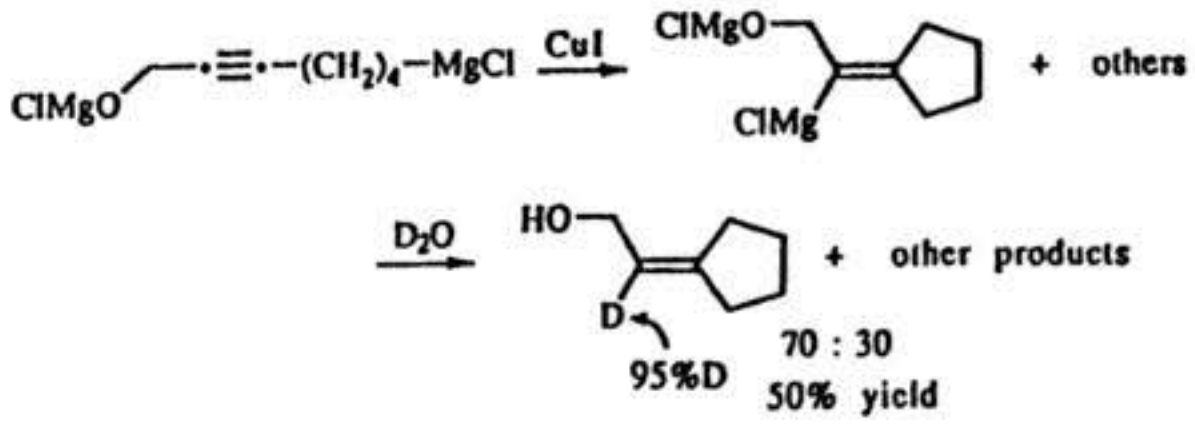
(37)



(38)

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Intramolecular addition of a Grignard to a triple bond is also catalyzed by a copper salt, as in the intermolecular addition [Eq. (39); 15].



(39)

VI. CONCLUSION

Preparation of Grignard reagents from olefins and acetylenes not only complements the conventional methods, but also enables a chemo-, regio-, and stereoselective formation of Grignard reagents that are otherwise difficult to prepare. Moreover, Grignard reagents with stereogenic centers, obtained easily from suitably substituted olefins, contribute an easy access to synthetically versatile intermediates.

ENDNOTE

The following abbreviations are used throughout this section: Et, ethyl; Pr, *n*-propyl unless otherwise indexed; Bu, *n*-butyl unless otherwise indexed; C_nH_{2n+1}, *n*-alkyl unless otherwise indexed; Bn, $PhCH_2$; Ph, phenyl; Ar, aryl; Cp, η^5-cyclopentadienyl, unless otherwise indexed; *n*-, normal; *i*-, iso; s-, secondary; *t*-, tertiary; *c*-, cyclo; *p*-, para; η^m-, m-hapto; THF, tetrahydrofuran; 2,5-DMTHF, 2,5-dimethyltetrahydrofuran; TBS, *t*-$BuMe_2Si$; MEM, methoxyethoxymethyl; Tf, CF_3SO_2-; acac, acetylacetonate; Dibal, diisobutylaluminum hydride. Quite recently, a report on this mechanism of titanium-catalyzed hydromagnesation of acetylenes appeared [120].

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Materiał chroniony prawem autorskim

4

Magnesium Activation

REUBEN D. RIEKE
University of Nebraska and Rieke Metals, Inc., Lincoln , Nebraska

MATTHEW S. SELL
Rieke Metals, Inc., Lincoln, Nebraska

I. INTRODUCTION

Organometallic compounds and metal-mediated transformations are among the most powerful tools in the synthetic organic chemists' arsenal. The literature involving organometallic intermediates has literally exploded in the past 30 years, and the rate of publication in this area continues to accelerate. Although many transformations involve heterogeneous conditions (metal–solution interface), most of these reactions involve discrete organometallic species.

The significance of the Grignard reaction is clearly expressed in the following quotation: "... every chemist has carried out the Grignard reaction at least once in his lifetime ..." [1]. In light of this ubiquity, the generation of new Grignard reagents is indeed a worthwhile endeavor. Although the formation of Grignard reagents is ostensibly thought to be completely general, there are many organic halides that do not form Grignard reagents. The preparation of Grignard reagents from primary, secondary, and tertiary halides, as well as from aryl iodides and bromides using ordinary metallic magnesium turnings can be accomplished in a low-boiling solvent, such as diethyl ether. However, many organic halides, including bicyclic bridgehead halides, aryl chlorides, and vinyl chlorides, exhibit a low propensity for the formation of their corresponding Grignard reagents from ordinary magnesium turnings. Also, there are many alkyl and aryl bromides that appear to be likely candidates for Grignard formation, but fail because of the presence of certain functional groups, such as ethers. Moreover, organic fluorides are generally considered to be inert toward ordinary magnesium. Also, occasionally the Grignard reagents are unstable under the reaction conditions that commonly involve refluxing in tetrahydrofuran (THF).

Clearly, any technique that could make these more difficult organic halides accessible to Grignard reagent formation is desirable. To this end, if ordinary magnesium could

Materiał chroniony prawem autorskim

somehow be "activated" (either physically or chemically), some of these difficultly accessible Grignard reagents could be prepared. Several methods are currently at the disposal of the synthetic chemist, which have greatly expanded the range of organic halides that are amenable to Grignard reagent preparation. It is the "activation" of magnesium that is the scope of this chapter.

II. GENERAL METHODS OF MAGNESIUM ACTIVATION

A. Removal of Oxide Layers

Since Grignard reactions of alkyl iodides and bromides are diffusion-controlled after their "initiation," the reaction rate is directly proportional to the available metal surface area [2]. The simplest "trick" for enforcing the initiation of magnesium-induced reactions by increasing the available surface area is removal of oxide layers by washing with mineral acids; then, filing, grinding, and milling [3]. Although removal of the oxide layers and augmentation of the surface area will increase the reactivity of ordinary magnesium, the production of the finest particles or, in the ideal case, even of large clusters, is far from being achieved using this method.

B. The "Dry–Stir" Method

Scattered reports have appeared in the literature of magnesium activation by stirring the solid under an inert atmosphere. The method is exemplified by the synthesis of the aromatic Grignard reagent shown in Figure 1, which frustrated attempts at its preparation by conventional techniques [4]. The development of this method has proved very effective in the synthesis of several allyl- and benzylmagnesium halides [5].

To test the dry-stirring procedure, a batch of commercial turnings (Fison's) was mechanically stirred with a Teflon bar in a wide-bore Schlenk tube, under a nitrogen atmosphere for 15 hr. This led to gross changes in the appearance of the magnesium. The particle size was reduced, the color was much darker grey-black, and a magnesium mirror had been deposited on the lower walls of the Schlenk tube. At this stage, the metal was covered with dry diethyl ether, maintaining the inert atmosphere. A solution of freshly distilled α-phenethyl chloride in diethyl ether was added dropwise to the center of the vortex of the stirred magnesium slurry and generated the corresponding Grignard reagent shown in Figure 2, at 0°C over a period of 3–4 hr. The quantity of magnesium constituted a fivefold excess over the halide. In this way, a clear solution was maintained. This contrasts with the normal appearance of the reaction mixture during the preparation of the Grignard reagent shown in Figure 2, when substantial precipitation of $MgCl_2$ is formed as a result of homocoupling, leading to cloudiness and eventually a white precipitate.

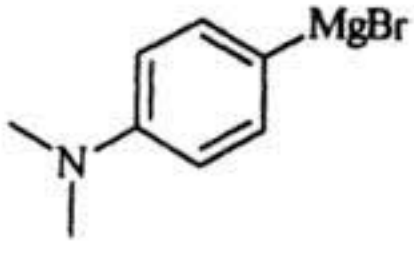


Figure 1 Aromatic Grignard reagent formed using the dry–stir method of magnesium activation.

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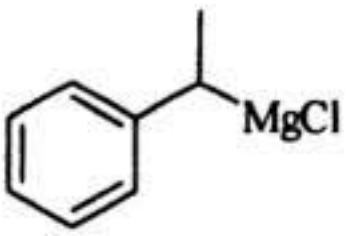


Figure 2 Formation of the Grignard reagent from α-phenethylchloride and magnesium activated by the dry–stir method.

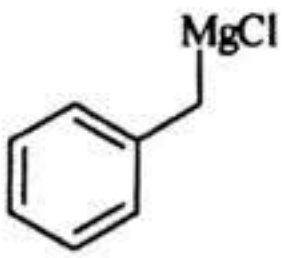


Figure 3 Formation of the benzyl Grignard reagent using magnesium activated by the dry–stir method.

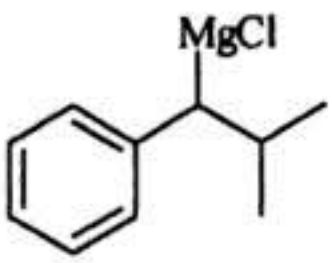


Figure 4 Formation of the benzyl-substituted Grignard reagent using magnesium activated by the dry–stir method.

After addition was complete, the Grignard solution was filtered through a frit, under positive nitrogen pressure, and made up to a standard volume with dry diethyl ether in a second Schlenk tube.

It was established that the nitrogen atmosphere can be replaced with argon, without affecting the activation process. This demonstrates that surface magnesium nitrides do not play a role. The successful application of dry–stir activation to the synthesis of the Grignard reagent shown in Figure 2 spurred a series of experiments in which allyl or benzyl chlorides were converted into their corresponding Grignard reagents.

Among the benzyl magnesium chlorides prepared, the synthesis of the benzyl Grignard reagent shown in Figure 3 was straightforward, whereas the formation of its derivative (Fig. 4) had to be carried out with careful control of the rate of addition to avoid coupling side products.

Cinnamylmagnesium chloride (Fig. 5) can be synthesized very cleanly by present techniques, although reaction of the chloride shown in Figure 6 [6] with dispersed Mg had been reported to yield little or no Grignard reagent [7].

Synthesis of the α-silylated reagent (Fig. 7), widely utilized in asymmetric cross-coupling [8], was straightforward, although, here, the reagent can be prepared in high yield by standard procedures.

The propargyl halide (Fig. 8) can be converted into its corresponding Grignard reagent (Fig. 9) in 63% yield by the dry–stir technique. Previously, this reagent had been

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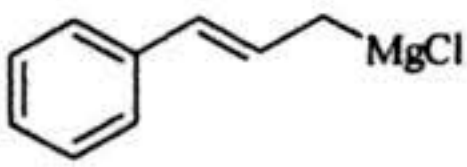


Figure 5 Cinnamylmagnesium chloride prepared using magnesium activated by the dry–stir method.

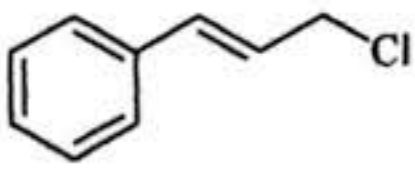


Figure 6 Reaction of cinnamyl chloride with dispersed magnesium has been reported to yield little or no Grignard reagent.

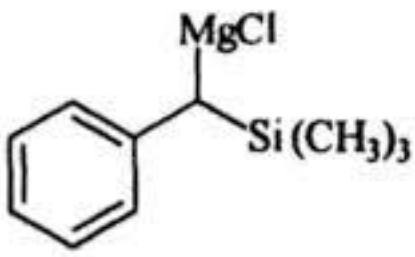


Figure 7 Formation of the α-silylated Grignard reagent using magnesium activated by the dry–stir method.

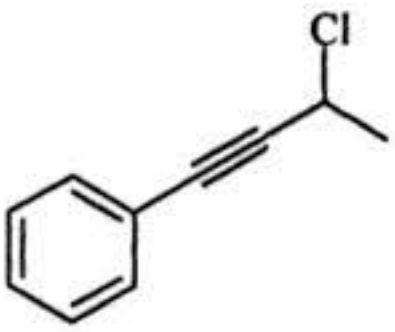


Figure 8 Propargyl chloride can be converted to its corresponding Grignard reagent using the dry–stir technique.

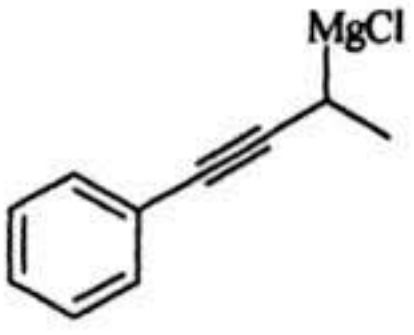


Figure 9 Grignard reagent prepared in 63% yield from its corresponding propargyl chloride (see Fig. 8) using magnesium activated by the dry–stir method.

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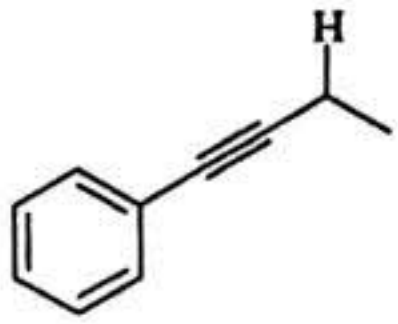


Figure 10 Acetylene was detected as an impurity in the formation of the propargyl Grignard reagent (see Fig. 9).

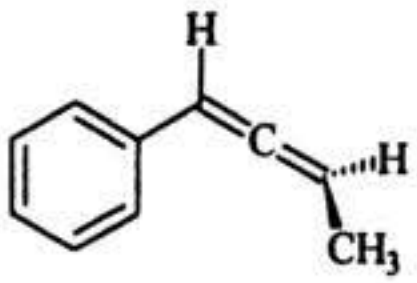


Figure 11 Allene was detected as an impurity in the formation of the propargyl Grignard reagent (see Fig. 9).

prepared only by resource to a cyclic reactor, using amalgamated magnesium [9]. The impurities observed in the ^{13}C-spectrum were acetylene (Fig. 10) and allene (Fig. 11) rather than the homocoupling products; possibly the propargyl radical formed initially is capable of hydrogen atom abstraction from solvent.

Finally, the method was used to prepare allyl- and methallylmagnesium chlorides, the ^{13}C-spectra of which were consistent with the expected dynamic η^1–η^1 allyl structure [10].

C. Gilman Catalyst

One of the earliest magnesium activation methods used in the preparation of Grignard reagents was the Gilman catalyst (I_2) [11]. This method has been widely used, owing to its convenience and safety for large-scale preparation of activated magnesium. Today, it remains the method of choice for activating ordinary magnesium turnings. This method works for a wide variety of organic halides, but not for those halides for which it is traditionally difficult to prepare their corresponding Grignard reagents. Typically, magnesium turnings (5 g) are added under nitrogen to benzene (100 ml), followed by iodine (2.5 g). Diethyl ether (5 ml) is added dropwise to initiate the activation. The mixture is stirred until the iodine color disappears. The solvents are removed to dryness by distillation. The activated magnesium can be stored and reactivated immediately before use by heating until the characteristic iodine color appears. A small amount of iodine may be added to bulk magnesium to initiate difficult reactions. Frequently, Grignard reactions can be initiated simply by the direct addition of a small amount of iodine to the reaction mixture at the beginning stage of the Grignard reagent preparation.

The proposed mechanism to rationalize the enhanced reactivity of iodine-activated magnesium involves the formation of magnesium(I) iodide, which functions as the active agent in the formation of the Grignard reagent [12]. Magnesium(I) iodide is more soluble

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$$Mg + MgI_2 \longrightarrow 2MgI$$

$$R\text{-}X + MgI \longrightarrow R^{\bullet} + XMgI$$

$$XMgI + Mg \longrightarrow MgX + MgI$$

$$R^{\bullet} + MgX \longrightarrow RMgX$$

Figure 12 Proposed mechanism for the activation of magnesium by iodine.

and more reactive than magnesium metal, and since it is regenerated during the reaction, it may act as a catalyst. See Figure 12 for a proposed mechanism for the activation of magnesium by iodine.

D. Vitride Addition

Vitride, which can be purchased from Hexcel Chemical Products, is a reducing agent that has been shown to activate magnesium [13]. Vitride, $NaAlH_2(OCH_2CH_2OCH_3)_2$, is sodium bis(2-methoxyethoxy) aluminum hydride–70% solution in toluene. Vitride is a novel and unique Grignard activator that is generally applicable [14]. It eliminates the need for drying and purification of the solvent, removing quantitatively moisture, alcohols, and peroxides, and it also activates the magnesium. A minute quantity of Vitride is required, and cessation of the hydrogen evolution indicates that the mixture is properly activated. An excess of Vitride does not interfere with the Grignard process. This process is superior to any other Grignard initiation method, and commercial chemicals can be used.

E. Magnesium Activation by Entrainment

Another classic method for magnesium activation is entrainment. Entrainment involves using catalytic amounts of a very reactive alkyl halide in conjunction with an unreactive one to initiate the reaction in the preparation of Grignard reagents. However, in many instances where inert organic halides are used, molar quantities of the very reactive alkyl halides are required as entrainers to provide continuous activation of the metal surface. Thus, two equivalents of magnesium turnings are used when the entrainment of method of magnesium activation is practiced. The reactive organic halide is believed to clean and activate the surface of the magnesium and, thereby, encourage the inert organic halide to subsequently react. Methyl iodide [15] and ethyl bromide [16] have both been used for this purpose. The obvious disadvantage of using these halides is the formation of a second, extrinsic Grignard reagent that will react with added organic substrate.

Pearson *et al.* in 1959 developed an improved method of entrainment [17]. Pearson's method, instead of using reactive alkyl halides, used 1,2-dibromoethane as the entrainer. The advantage of using 1,2-dibromoethane over bromoethane is that upon reaction with the magnesium, magnesium dibromide is formed, with the concomitant liberation of ethylene gas. Hence, no second, extraneous Grignard reagent is present in the reaction mixture. The magnesium dibromide that is formed is an activator. The reaction of 1,2-dibromoethane with magnesium is believed to proceed according to the pathway shown in Figure 13 [18].

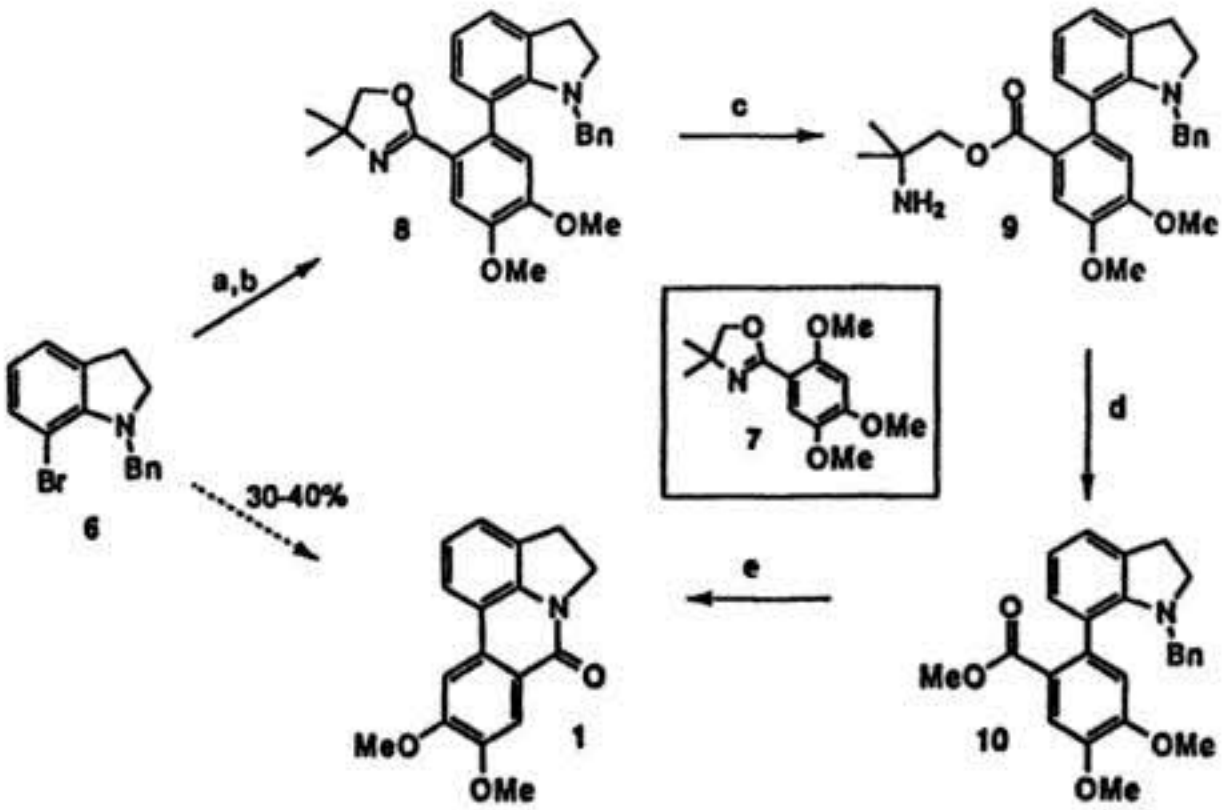
The preactivation of magnesium is a modified entrainment activation procedure that was first developed by Ehrlich and Sachs [19]. This method involves the addition of a

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$$Br\text{-}CH_2\text{-}CH_2\text{-}Br + Mg \longrightarrow Br\text{-}Mg\text{-}CH_2\text{-}CH_2\text{-}Br$$

$$\longrightarrow H_2C{=}CH_2 + MgBr_2$$

Figure 13 Proposed mechanism for the reaction of 1,2-dibromoethane with magnesium in the entrainment method of magnesium activation.



Scheme 1 Synthesis of oxoassoanine using the entrainment method of magnesium activation.

small amount of reactive organic halide to magnesium turnings in diethyl ether. Once the reaction begins, the solution containing the formed Grignard reagent from the reactive organic halide is decanted. The residue is rinsed with diethyl ether several times, followed by the addition of the unreactive halide. The activation of magnesium by this approach may be ascribed to cleaning the metal surface and increasing the number of sites of imperfection.

Recently, Meyers and Hutchings employed the entrainment of magnesium as a key step in the total synthesis of oxoassoanine as shown in Scheme 1 [20].
The corresponding Grignard of bromoindoline **6** was generated by treating **6** with magnesium turnings in THF containing 1,2-dibromotetrafluoroethane as an entrainer. Grignard formation was complete after 1 hr, as evidenced by gas chromatography (GC), showing complete consumption of the starting material. Addition of the oxazoline **7** followed by heating overnight led to the coupled product **8** in 71% yield. This example displays the usefulness of the entrainment method in the synthesis of complex molecules.

In the batch manufacture of Grignard reagents, the most satisfactory procedure is to retain an excess of magnesium from the preceding batch (activated heel) and to add a small amount of the Grignard solution. This process will eliminate H_2O and oxide from the magnesium turnings, subsequently, activating the magnesium. In this fashion little difficulty is usually encountered in initiating the reaction [21].

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F. Metal Atom Vaporization

Several physical techniques for the activation of metals can also be used for activating magnesium. One of these techniques is metal atom vaporization. The first report of the preparation of organometallic compounds by using vaporized metal atoms to react with organic ligands was published by Timms in 1969 [22]. Before Timms' work, a similar technique had been used by Skell and co-workers [23] for the vaporization of reactive carbon species on carbene chemistry. Metals are largely monoatomic after vaporization [24]. The technique that has been generally adopted for reacting thermally generated metal atoms with organic compounds can be summarized as follows: (1) The metal is vaporized at a controlled rate by heating under high vacuum. (2) The metal atoms are trapped by the vapor of an organic substrate or condensed into a solution of the reactant in an inert solvent at low temperature [25].

The first report on the oxidation of metal atoms to form organometallic compounds was made by Skell and Girard [26]. They evaporated magnesium from a crucible at 500°C and condensed the vapor with a variety of straight-chain and branched-chain alkyl halides. The condensate at −196°C was black, but became colorless on warming as the products RMgX, *unsolvated* Grignard reagents, were formed.

A variation of this method is the cocondensation of vaporized metal atoms with solvents such as benzene, THF, or hexane, which was first developed by Klabunde [27]. Klabunde cocondensed magnesium vapors with THF at liquid nitrogen temperature. At −196°C, the magnesium was dark blue when cocondensed with THF. This has been attributed to the formation of a charge-transfer complex. Upon slight warming, the Mg–THF matrix turned into a black slurry. The THF could be pumped off, leaving an extremely reactive powder. Slurries of activated magnesium powders acquired by this technique exhibited high reactivity, particularly toward oxidative-addition reactions [28]. For example, treatment of the magnesium slurry with chlorobenzene at room temperature for 3 h afforded benzene after hydrolysis in 85% yield. In contrast, ordinary magnesium was unreactive toward chlorobenzene under the same conditions.

By using magnesium prepared by the metal atom vaporization method, difficult Grignard reagents have been prepared. For example, the allylic Grignard reagent shown in Figure 14 can be synthesized from the corresponding allyl chloride in 60% yield, although its synthesis proved impossible by conventional techniques [29]. The ability to prepare these difficultly accessible Grignard reagents displays the usefulness of this process.

One advantage this activation method has over other methods is that the generated metal suspensions are completely free of halogens and arenes. With the proper apparatus, even larger amounts of metal can easily be activated. However, comparative study has shown that magnesium activated by such vaporization is not as reactive as Rieke magnesium [30]. Linked with the undoubtedly greater cost of the equipment, this could be responsible for the few recent applications of this technique in organic synthesis [31].

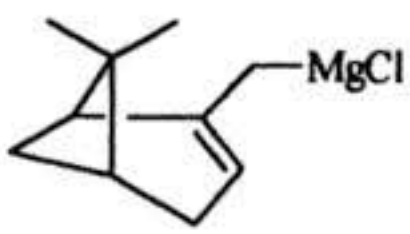


Figure 14 Allylic Grignard reagent formed from the corresponding allyl chloride using magnesium activated by the metal atom vaporization method.

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G. Ultrasound Magnesium Activation

Ultrasound activation is a physical technique that can be employed to activate magnesium. Ultrasound can be delivered safely and conveniently with inexpensive equipment, and this technique has generated a field of study known as sonochemistry. Ultrasound can effect chemical reactions at a metal–solution interface when the sound waves induce "cavitation" or the formation, growth, and sudden collapse of very fine bubbles of gas at the metal–solution interface. This rapid collapse leads to intense, localized pressure and temperature differentials, as well as electric discharges. In multiphase systems, this produces shockwaves, which increase mass transfer and can lead to erosion at the surface of a solid. In addition, the strong turbulence gives rise to collisions of the particles distributed in the solvent, which can lead to considerable morphological changes, either by disintegration of the particles or even by their fusing together owing to local overheating on collision [32]. Such collisions are also believed to be responsible for the degradation, or even the complete destruction, of surface oxide layers. In such cases, sonication of the metal before its use had an activation effect comparable with sonication of the whole reaction mixture. Principal uses have included the generation of organomagnesium reagents [33].

Renaud first reported that improved yields of Grignard reagents could be obtained by sonolysis of the reagents in undried diethyl ether. These results were first published in 1950, but did not stimulate further interest in the use of ultrasound to accelerate chemical reactions [34]. Renaud's initial results were later followed up by Sprich and Lewandos, who examined the reaction between magnesium and 2-bromobutane in diethyl ether containing different percentages of water [35]. The results indicated that ultrasound had a profound effect on the initiation of the reaction, although the overall yield of Grignard reagent was unchanged. Sonication was carried out in a sonicating cleaning bath, and it is significant that sonication of the metal before addition of the organic bromide had no effect on initiation time. This suggests that the primary effect of the ultrasound is to remove adsorbed water from the metal surface, rather than any surface-cleaning effect. A practical advantage of metal activation by ultrasound lies in the fact that frequently the conventional ultrasonic purification baths used in the laboratory already suffice to achieve a satisfactory effect. The resulting magnesium, however, in no way approaches the high level of reactivity demonstrated by Rieke magnesium. The simple and harmless application of ultrasound on a large-scale is sure to guarantee further use and development of this technique in the future. However, at present, sonication has limited use with organic halides that have demonstrated difficulty in Grignard formation (i.e., alkyl and aryl fluorides).

The sonication method of magnesium activation has been employed to initiate sluggish Grignard reactions in ether. Sonication is the preferred technique for effecting the Barbier variation, in which the electrophilic species and organohalide are introduced concomitantly, and the Grignard reagent is then intercepted as fast as it is formed (Fig. 15) [36].

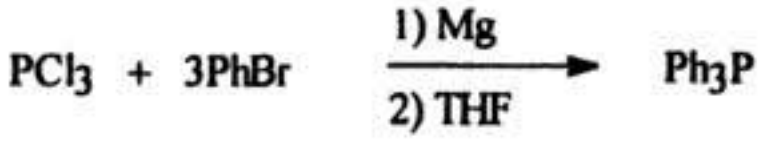


Figure 15 Formation of triphenyl phosphine using sonication.

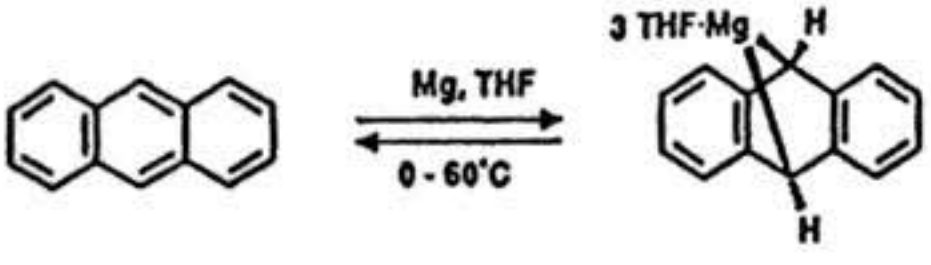
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H. Magnesium–Anthracene Methods

Anthracene and some of its derivatives react with metallic magnesium in THF to form a complex of type **1**, as shown in Figure 16. Spectroscopic and chemical properties of the complex have been investigated in detail [37].

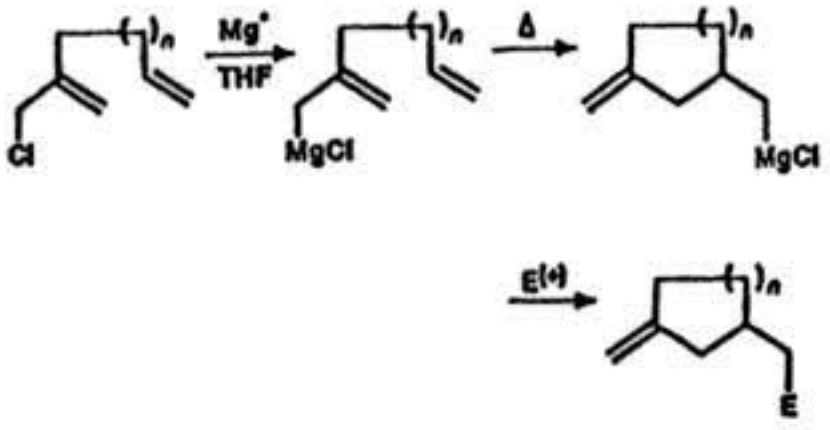
The X-ray structure analysis of a representative of this series shows pentacoordinated magnesium with unusually long bonds to the carbon atoms (2.32 Å) and a significantly bend dihydroanthracene ligand [38]. In view of these structural features, the low thermal stability of the metallacycle is evident, which is further reduced by substituents, especially in the 9- or 10-position, or both, of the anthracene [39]. The unusual structure of this complex is paralleled by its widely diverse chemical behavior. Complex **1** reacts with many electrophiles (e.g., CO_2, alkyl halides, ketones, oxetanes, dichlorosilanes and dichlorostannanes, and Cp_2TiCl_2) as a (di)nucleophile, but acts as an electron donor for aryl halides and as a source of "soluble" magnesium for allyl and benzyl halides, thereby enabling these substrates to be converted efficiently into the corresponding Grignard reagents [40]. Even toluene is suitable as solvent. Furthermore, in contrast to Rieke magnesium, **1** permits the metallation of polystyrene bearing *p*-(chloromethyl) groups [41]. Propargyl chloride is smoothly converted into allenylmagnesium chloride by **1**, which is quite remarkable, given the considerable difficulties with which the preparation of this reagent was formerly associated [40]. This "magnesium source" can also be polymerically bound to a polystyrene functionalized with anthracene residues [47a].

Complex **1** is thermally unstable and affords highly reactive pyrophoric magnesium powders with extraordinarily high specific surface areas (up to 110 $m^2\ g^{-1}$) and correspondingly high reactivity when heated in inert solvents or when heated neat under vacuum [42]. These powders likewise afford Grignard reagents in very good yields on reaction with a series of different halohydrocarbons in THF, toluene, and in some cases,



1

Figure 16 Reaction of anthracene and magnesium.

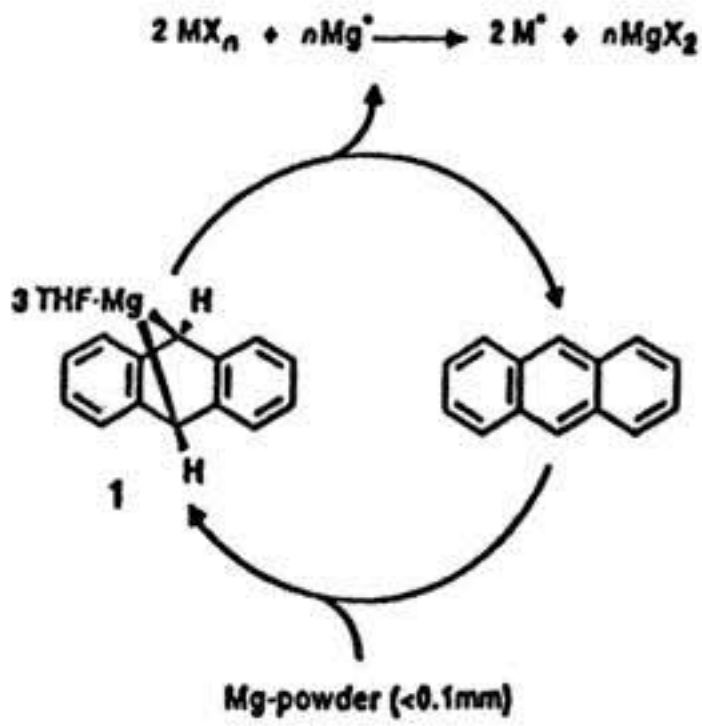


Scheme 2 A magnesium–ene reaction.

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Table 1 Results from the Magnesium-ene Reaction Shown in **Scheme 2** Using Vapor-Activated Magnesium, Anthracene–Magnesium and Rieke Magnesium

n	E	Vapor-activated Mg (%)	Anthracene–Mg (%)	Rieke Mg (%)
1	OH	55	56	55
1	CONHPh	71	67	64
2	OH	57	51	48
2	CONHPh	72	69	64



Scheme 3 Proposed catalytic cycle for the formation of activated metals.

even in heptane. Magnesium powder obtained in the thermal decomposition of activated MgH_2 has proved to be only slightly less reactive [43].

In any event, the activity of such magnesium samples is far superior to that of commercially available metal turnings and compares favorably with that of Rieke magnesium or of magnesium that has been activated by metal vapor techniques. This has been clearly demonstrated, for example, by a comparative study of magnesium–ene reaction shown in Scheme 2 [44]. Table 1 depicts the results obtained in this reaction using vapor-activated magnesium, anthracene–magnesium, and Rieke magnesium.

Since the preparative outlay for each of the individual activation methods differs considerably, yet the results obtained are comparable, their respective "economy" can be estimated.

In the Rieke process for the reduction of salts, magnesium is suitable only in exceptional cases as a substitute for potassium. However, the ready formation of the anthracene complex **1** can also be exploited for this purpose. As shown in Scheme 3, not only activated metals can be generated by a catalytic cycle, but also, in the presence of suitable ligands, complexes with a zero- or low-valent central atom, such as $[M(cod)_2]$ (M = Ni, Pt), $[Cp_2M]$ (M = V, Co, Fe), and $[Pd(PPh_3)_3]$, and [Mo(butadiene)$_3$] can be prepared [45].

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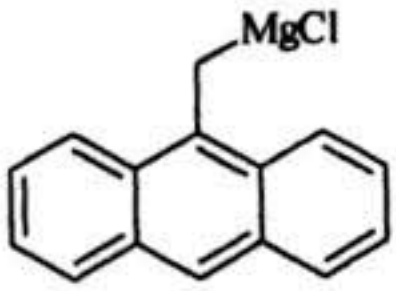


Figure 17 The Grignard reagent of 9-chloromethylanthracene prepared from the magnesium–anthracene complex.

The availability of magnesium–anthracene provided a major advance for the synthesis of reactive Grignard reagents [46]. This orange, THF-soluble adduct is especially effective for the preparation of benzylmagnesium halides, some of which are otherwise difficult to synthesize [47]. The Grignard reagent of 9-chloromethylanthracene (Fig. 17) was prepared by the slow addition of a solution of the organic halide in THF to a suspension of a stoichiometric amount of the magnesium–anthracene complex in THF at 20°C. A deep blue color persists until the addition is complete [48].

This reagent is easily prepared, but the formation of 1 mol of anthracene for each mole of Grignard reagent formed when the stoichiometric reagent is used presents a drawback.

I. Choice of Solvent

Historically, diethyl ether was the common solvent used in the preparation of Grignard reagents [48]. The drawbacks of using diethyl ether include its extreme flammability and relatively low-boiling point, which precludes its use in reactions with high working temperatures.

Since the advent of tetrahydrofuran (THF), work involving diethyl ether has greatly diminished. Tetrahydrofuran is a safer alternative solvent that has been widely used since the 1950s in the commercial-scale production and use of Grignard reagents. It is a cyclic ether with greater solvating power, which renders the formation of Grignard reagents more facile. Also, the boiling point of THF is 15.5°C (60°F) greater than that of diethyl ether. As a result, THF is clearly the solvent of choice for the production of Grignard reagents as well as Rieke magnesium.

Hydrocarbon solvents have also been used for the preparation of Grignard reagents. Advantages have been claimed for the uses of such solvents, but the organomagnesium halide usually precipitates, which renders its transfer and analysis difficult [21]. Tertiary amines have been used to dissolve Grignard reagents in aromatic solvents. Hydrocarbon solvents are, however, frequently used in the subsequent reactions of the Grignard reagent with carbonyl and other substrates. Occasionally, a mixture of THF and toluene is used, as toluene improves the solubility of some Grignard reagents.

III. MAGNESIUM ACTIVATION BY THE RIEKE METHODS

A. History

In 1972, Rieke and associates reported a general approach for preparing highly reactive metal powders by reducing metal salts in ethereal or hydrocarbon solvents using alkali metals as reducing agents [50]. Several basic approaches are possible and each has its own particular advantages. For some metals, all approaches can lead to metal powders

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$$MX_n + nK \longrightarrow M^* + nKX$$

Figure 18 Formation of an activated metal by the reduction of a metal salt using potassium.

of identical reactivity. However, for other metals, one method can lead to far superior reactivity. High reactivity, for the most part, refers to oxidative–addition reactions. Since this initial report, several other reduction methods have been reported, including metal–graphite compounds, magnesium–anthracene complex, and dissolved alkalides [51].

Although Rieke's initial entry into this area of study involved the reduction of $MgCl_2$ with potassium biphenylide, early work concentrated on reductions without the use of electron carriers [52]. In this approach, reductions are conveniently carried out with an alkali metal and a solvent, the boiling point of which exceeds the melting point of the alkali metal. The metal salt to be reduced must also be partially soluble in the solvent and the reductions are carried out under an argon atmosphere (Fig. 18).

The reductions are exothermic and generally are complete within a few hours. In addition to the metal powder, 1 mol, or more, of alkali salt are generated. Convenient systems of reducing agents and solvents include potassium–THF, and sodium–1,2-dimethoxyethane (DME). For many metal salts, solubility considerations restrict reductions to ethereal solvents. Also, for some metal salts, reductive cleavage of the ethereal solvents requires reductions in hydrocarbon solvents, such as benzene or toluene. This is true for Al, In, and Cr [53]. The finely divided metals prepared by this approach are a composite of the metal as well as the alkali salts. The comixture appears to keep the small crystallites from sintering into larger crystals and, thus, attenuating their chemical reactivity. The alkali salts also may serve as electrolytes and facilitate electron transfer in the initial step of the oxidative–addition reaction.

B. Contemporary Methods

A second general approach for the generation of Rieke magnesium involves using an alkali metal in conjunction with an electron carrier, such as naphthalene. The electron carrier is normally used in less than stoichiometric proportions, generally 5–10% by mole, based on the alkali metal. This procedure allows reductions to be carried out at ambient temperatures, or at least at lower temperatures, than with the previous approach, which requires refluxing. A convenient reducing metal is lithium. Not only is the procedure much safer when lithium is used, rather than sodium or potassium, but frequently the reactivity of the metal powder is greater.

The current methods used for the preparation of Rieke magnesium (Mg*) involves a one-pot procedure and uses a catalytic amount of naphthalene. An oven-dried, 50 ml, two-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, an argon/vacuum manifold adapter and a rubber septum is charged with anhydrous magnesium chloride (0.402 g, 4.22 mmol), lithium (cut foil, 0.061 g, 8.86 mmol), and naphthalene (0.170 g, 1.33 mmol) in a Vacuum Atmospheres Company dry box under argon. The flask is then connected through the adapter to a double manifold providing vacuum and purified argon, and the flask is evacuated and back-filled with argon three times. Freshly distilled THF (15 ml) from Na/K alloy under argon is added by syringe. The mixture is vigorously stirred at room temperature under argon until the solution becomes dark green (ca. 3 h). Stirring is continued for another 30 min. The newly formed magnesium slurry is allowed to settle for 3 h and the supernatant is removed by cannula.

Material chroniony prawem autorskim

Freshly distilled THF (10 ml) is added to the active magnesium (black powder), followed by the appropriate substrate. This is the current method of choice for the preparation of Rieke magnesium [54].

A third approach for the generation of Rieke magnesium is to use a stoichiometric amount of preformed lithium naphthalenide. This approach allows a very rapid generation of the metal powders, because the reductions are diffusion-controlled. Very low to ambient temperatures can be used for the reduction. In some cases, the reductions are slower at low temperatures because of the low solubility of the metal salts. In a typical preparation of Rieke magnesium using preformed lithium naphthalenide, the same general procedure, as outlined in the foregoing, is followed, with a few exceptions. Lithium (10.0 mmol) and naphthalene (10.8 mmol) in freshly distilled THF (15 ml) are stirred under argon until the lithium is completely consumed (ca. 2 h). The resulting dark green lithium naphthalenide is then transferred by cannula into a THF solution (10 ml) of anhydrous magnesium chloride (4.8 mmol). The mixture is stirred at room temperature for 30 min. The newly formed active magnesium (black powder) is allowed to settle for 3 h, and the supernatant is drawn off by cannula, followed by replacement with freshly distilled THF (10 ml).

Although each of these methods will generate active magnesium, method 2 is the method of choice, as it facilitates workup. There does not appear to be any appreciable difference in the reactivity of the active magnesium when practicing any of the three methods. The inherent advantages of method 2 are that it is a one-pot process, and it uses a minimum amount of electron carrier, which affords the separations to be more facile. If the reader is using method 2, it is important that the reaction is stirred *vigorously* to prevent the magnesium powders from coating the lithium and thereby retarding the reduction. Also, the stirring was most effective when the reaction flask was set slightly away from the center of the magnetic stirrer.

For all three methods, the finely divided black magnesium powder will settle after standing for a few hours, leaving a clear and, usually, colorless, solution. Thus, the magnesium powder can be washed to remove the electron carrier as well as the alkali salt, especially if it is a lithium salt. Moreover, a different solvent may be added at this point, providing versatility in the solvent choice for subsequent reactions.

A fourth procedure that was developed early in this study involved the reduction of magnesium chloride with potassium in the presence of potassium iodide. Although the optimum ratio of magnesium chloride to potassium iodide is 1:1, much smaller quantities of potassium iodide are nearly as effective (Table 2). This suggests that the potassium iodide is acting in a catalytic fashion. One possible mode of action is that the Rieke magnesium catalyzes a halogen-exchange reaction with the aryl chlorides. In any event, the magnesium prepared by this route is nearly as reactive as the magnesium prepared by the lithium reduction approach. Because the lithium reductions are more convenient and safer, there has been little chemistry carried out with the $MgCl_2$–KI procedure. One of the most notable reactions reported was the conversion of *p*-fluorotoluene to the corresponding Grignard reagent in 1 hr in refluxing THF [50b].

Another interesting variation of the potassium–magnesium chloride reduction is to carry out the reduction in a mixed solvent system of THF and triethylamine (ratio 1:1). This method also yields a form of magnesium that is nearly as reactive as the lithium reduction procedure. Table 3 shows reactions of *p*-chlorotoluene with Rieke magnesium prepared in THF-Et_3N. Few reports have appeared using this form of highly reactive magnesium.

Conceivably, any metal on the periodic table can be activated by the Rieke method.

Materiał chroniony prawem autorskim

Table 2 Reduction of Magnesium Chloride with Potassium in the Presence of Potassium Iodide

Reactn. no.	MX	Mg/ MX	Reactn. temp. (°C)	% yield Grignard at reaction time (min) of				
				5	10	30	60	120
10	None		25	0	0	14	50	75
17	Lif	1	25	0	5	42	76	93
18	LiCl	1	25	0	7	47	74	88
19	NaF	1	25	0	0	30	64	87
20	NaCl	1	25	0	0	23	58	85
21	NaBr	1	25	0	0	13	54	84
22	NaI	1	25	89	93	98	99	100
23	KF	1	25	0	0	7	30	66
24	KCl	1	25	0	5	34	64	83
25	KCl	1	25	0	4	44	67	84
26	KBr	1	25	0	0	11	48	75
27	KBr	1	25	0	0	6	46	78
28	KI	1	25	87	93	98	99	100
29	KI	1	25	0	5	42	71	85
30	KI	1	25	43	66	92	97	100
31	KI	2	25	84	94	97	98	100
32	KI	20	25	51	76	94	97	100
33	KI	0.5	25	86	94	97	99	100
34	None		0	0	0	0	0	0
35	KI	10	0	8	17	55	75	85
36	KI	4	0	14	29	65	76	88
37	KI	2	0	26	46	73	85	91
38	KI	1	0	19	42	74	86	93
39	KI	0.5	0	25	45	74	85	93
40	LiI	2	0	0	0	0	0	11
41	NaI	2	0	0	6	21	49	70
42	CsI	2	0	6	12	41	73	89
43	I_2	20	0	8	10	40	54	64
44	K_2SO_4	1	25	13	33	69	87	95
45	K_2SO_4	20	25	0	6	46	76	90
46	$CuSO_4$	20	25	0	0	0	7	
47	$ZnBr_2$	20	25	0	16	31	64	86
48	$MgCl_2$	0.5	25	0	0	9	22	48
49[b]	$MgCl_2$	0.5	25	0	0	0	0	0

Indeed, many metals other than magnesium have been activated and used in the synthesis of many organic compounds [55]. Most notably, copper, zinc, calcium, indium, cadmium, nickel, aluminum, and barium have been activated and used in the synthesis of many complex molecules [56].

An important aspect of the active magnesium by Rieke methods is its convenient preparation. The apparatus required is very inexpensive and simple. The reductions are normally carried out in a two-neck flask equipped with a condenser (if necessary), magnetic stirrer, under an argon atmosphere. In general, it is not possible to prepare anhydrous

Materiał chroniony prawem autorskim

Table 3 Reactions of *p*-Chlorotoluene with Rieke Magnesium Prepared in THF-Et_3N

Reactn. no.	THF (ml)	Et_3N (ml)	$MgCl_2$, % excess[b]	Reflux time (hr)	Mg/KI	% yield Grignard[b] at reaction time (min) of 5	10	30	60	120
10	50	0	10	3		0	0	14	50	75
55	35	15	10	3		0	12	38	69	85
56	25	25	10	3			47	77	93	99
57	25	25	10	3	1	73	87	97	100	100
58	15	35	10	22		0	0	0	0	0
59	5	45	10	22		0	0	0	0	0
60	0	50	10	22		$MgCl_2$ not reduced				
61	0	50	20	22		$MgCl_2$ not reduced				
62[c]	15	35	10	3		0	0	0	11	32

magnesium halides by heating the corresponding hydrates under vacuum. In general, this will lead to a mixture of oxides and hydroxides that cannot be completely reduced. It is essential that anhydrous magnesium salts be used. The anhydrous magnesium salts can be purchased or can be easily prepared from ordinary magnesium turnings and 1,2-dibromoethane or 1,2-dichloroethane.

A convenient procedure for the preparation of these anhydrous magnesium salts has been published [57]. The magnesium turnings and 1,2-dibromoethane used were purchased from J. T. Baker Chemical Company and Aldrich Chemical Company, Inc., respectively. A 200-ml, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, two stoppers, and a condenser connected to an argon inlet. The flask is charged with 0.35 g (0.0144 mol) of magnesium turnings, 50 ml of tetrahydrofuran, and 3.0 g (0.016 mol) of 1,2-dibromoethane. The suspension is warmed gently to initiate the reaction. After the initially exothermic reaction subsides, the mixture is heated at reflux for 50 min. The solvent is evaporated under a reduced pressure of argon or nitrogen, leaving a white solid. The flask is then evacuated and heated in an oil bath at 150°C for 1 h. The dry magnesium bromide is ready for the ensuing preparation of Rieke magnesium and can be prepared in the same vessel.

Equally important is that extreme caution should be exercised when working with these materials. Although Rieke and co-workers have never had a fire or explosion caused by the active metals, one should handle them with care. Until one becomes familiar with the characteristics of the metal powder involved, careful consideration should be taken at every step. To date, no metal powders that Rieke and co-workers have generated have spontaneously ignited if removed from the reaction vessel while still wet with solvent. They do, however, react rapidly with oxygen and moisture in the air. Accordingly, they should be handled under an argon atmosphere. If the metal powders are dried before being exposed to the air, many will begin to smoke or will ignite. Perhaps the most dangerous step in the preparation of the active metals is the handling of sodium or potassium. This can be avoided for most metals by using lithium as the reducing agent.

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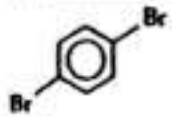
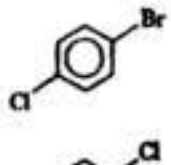
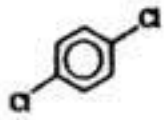
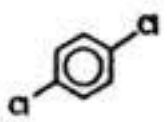
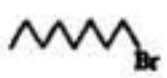
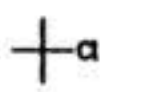
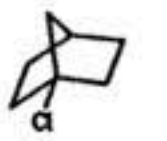
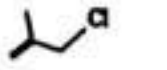
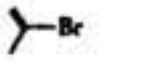
C. Grignard Reactions Using Rieke Magnesium

The reactions of Rieke magnesium with various halides and dihalides, some of which react with difficulty under the conditions of normal Grignard preparations, were investigated [58]. The results are summarized in Table 4. The yields obtained by GC after hydrolysis, and the yields of carboxylic acids obtained after CO_2 quench are shown.

It should be noted that this reported chemistry was performed with Rieke magnesium prepared by the $MgCl_2$—KI—K—THF system. Rieke magnesium prepared by the safer lithium naphthalenide reduction approach should be expected to give the same or even improved results compared with what is reported here.

Previous efforts to prepare dimagnesium derivatives of benzene have been successful only with dibromo- or bromoiodobenzene, required forcing conditions, and typically resulted in the monomagnesium derivative as the major product. This work has been surveyed by Ioffe and Nesmayanov [59]. With the $MgCl_2$—KI—K—THF system, the preparation of the di-Grignard of *p*-dibromobenzene in 100% yield in 15 min at room temperature is possible. The yield was determined by GC after hydrolysis and was based on the disappearance of starting material and bromobenzene and the formation of benzene. In earlier work, only one halogen atom of dichloro derivatives of benzene and naphthalene reacted with magnesium [60], and the chlorine of *p*-chlorobromobenzene was completely unreactive [61]. By using this method, a 100% yield was obtained of the mono-Grignard and a 10% yield of the di-Grignard of *p*-chlorobromobenzene in 15 min at room temperature. After 2 hr the yield of di-Grignard was 100%. With *p*-dichlorobenzene the yield of di-Grignard was 30% in 2 hr. Use of a lower Mg/halide ratio permitted the rapid

Table 4 Reactions of Rieke Magnesium with Various Halides and Dihalides

Halide	Mg/halide	Mg/KI	Reactn temp, °C	Reactn time, min	% yield Grignard Mono	% yield Grignard Di	% yield $-CO_2H$
	4	2	25	15		100	
	4	2	25	15 60 120	100 100 100	10 57 100	
	4	2	25	15 120	100 100	15 30	
	2	2	25	5 60 180	70 86 90	0 0 0	 89
	2		25	5	100		81
	2		25	10 60	100		 52
	1.7	2	66	15 90 360	11 42 74		 63
	2		25	60			82
	2		25	5	100		71

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and selective formation of the mono-Grignard of *p*-dichlorobenzene, which was converted to 4-chlorobenzoic acid in 89% yield by CO_2 quench.

Significantly, when *p*-dibromobenzene was treated with one equivalent of Rieke magnesium at −78°C, only the mono-Grignard was formed quantitatively in 15 min [62]. The yield was determined by GC after hydrolysis and was based on the disappearance of starting material and the formation of bromobenzene. This is in stark contrast to the reaction of *p*-dibromobenzene with ordinary magnesium, which affords a mixture of the mono- and di-Grignards, as well as unreacted starting material [63].

A primary halide, 1-bromooctane, reacted as expected to give 100% yield in 10 min and was converted to pivalic acid in 52% yield after 1 hr of reaction. 1-Chlorobicyclo[2.2.1]heptane reacted slowly at room temperature, so this was rerun in refluxing THF. Again, the Grignard preparation was slow, giving 74% yield after 6 hr of reflux. The Grignard was then quenched with CO_2 to give 1-bicyclo[2.2.1]heptane-carboxylic acid in 63% yield. Bixler and Niemann [64] prepared 1-bicyclo[2.2.1]-heptanecarboxylic acid from 1-chlorobicyclo[2.2.1]heptane by conversion of the chloride to the lithium salt, followed by CO_2 quench. The Rieke method appears to be superior, since it obviates the preparation of the lithium salt used in the procedure of Bixler and Niemann.

An allyl halide, 3-chloro-2-methylpropene, was converted to 3-methyl-3-butenoic acid in 82% yield after 1 hr of reaction at room temperature. Wagner [65] converted 3-chloro-2-methylpropene to the Grignard in 81% yield after 10 hr at 14–16°C, and obtained 3-methyl-3-butenoic acid from the Grignard in 40% yield after CO_2 quench.

Finally, the vinyl bromide 2-bromopropene was converted to the Grignard in 100% yield in only 5 min at room temperature using the $MgCl_2$—K—THF system. The Grignard of vinyl bromide 2-bromopropene was then converted to methacrylic acid in 71% yield. Normant, in his pioneering work on vinyl Grignard preparations, has recommended a 40–50°C range for halide addition to magnesium in THF, followed by heating for 0.5–1 hr at 70–80°C [66]. By this procedure, he was able to obtain yields of 95–97% in the preparation of vinylmagnesium bromide. The Rieke magnesium appears to be an improvement of Normant's method, since it allows the preparation of vinyl Grignard reagents at room temperature and below.

Walborsky has recently reported on the formation of the chiral 1-methylspiro[2.5]-octylmagnesium bromide Grignard reagent, which was generated by Rieke magnesium [67]. Walborsky concluded that the reaction of this chiral Grignard reagent occurs mainly at the surface of the magnesium.

The preparation of 1-bromo-1-methylspiro[2.5]octane (Fig. 19; **13**) was described. To determine product distribution, the racemic bromide **13** was treated with Rieke magnesium in ether [68] in the presence of *t*-BuO-D as shown in Figure 19. The reaction afforded a 70% yield of 1-methylspiro[2.5]octane (**15**), which was 33% deuterated according to NMR analysis, as the main products. This indicates that the yield in the Grignard reagent formation step is 23%. Other products found were 2,3-diethoxybutane (diethyl ether dimer, **16**; 3%), the cyclopropyl radical dimer **17** (3%), and a nonvolatile polymeric residue, which by NMR was shown to contain aliphatic protons and some ether moieties. The volatile products were isolated by preparative gas chromatography, and their structures were proved by spectroscopic analyses and comparison with authentic samples. The authentic sample of spiro hydrocarbon **15** was obtained in 70% yield from bromide **13** by lithium–halogen exchange with *tert*-butyllithium followed by protonation with methanol. The authentic sample of the ethyl dimer **16** was prepared according to a literature procedure [69].

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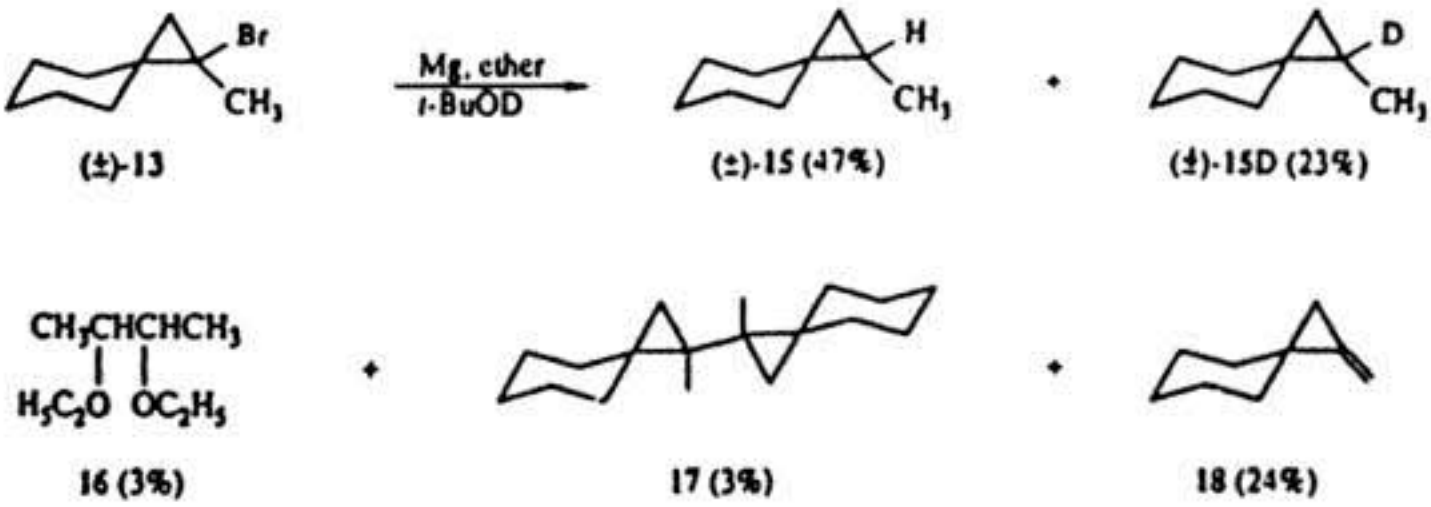
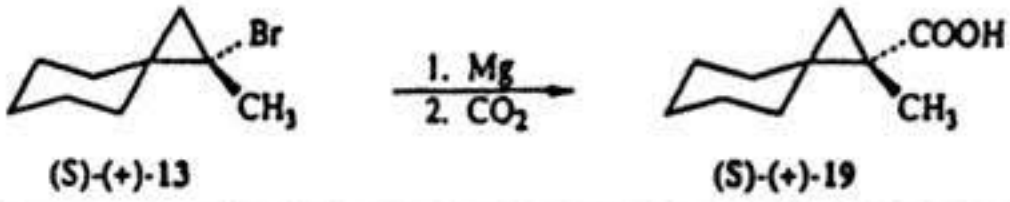


Figure 19 Treatment of racemic bromide **13** with Rieke magnesium in the presence of *t*-BuO-D.



run	solvent	time, h	yield, %	optical purity, %
1	ether	2	25	10
2	THF	2	58	13

Figure 20 Treatment of the optically pure bromide with Rieke magnesium followed by carbonation.

As in the previously investigated Grignard reaction of cyclopropyl bromide [70], the exocyclic cyclopropyl olefin **18** could not be isolated from the reaction mixture. Since it was suspected that olefin **18** would not be stable under the Grignard reaction conditions, an authentic sample was synthesized in 60% yield by zinc-induced elimination of the tosylate precursor in DMF. The Grignard reaction of **13** was repeated in the presence of this olefin and under the same conditions (1 hr at room temperature). The olefin **18** was shown to undergo complete polymerization.

To establish the stereochemistry of the reaction, optically pure (*S*)-(+)-**13** was treated with Rieke magnesium at room temperature in both ether and THF and the reaction mixture carbonated. The results are shown in Figure 20.

The reaction in ether resulted in a 25% yield of optically active acid **19** along with 42% of racemic hydrocarbon **15**. Since the specific rotation of **19** was very small, the optical purity of the acid was determined by the more accurate NMR procedure. Hence, (*S*)-(−)-α-methylbenzylamide was prepared; the diastereoisomeric excess determined by NMR from the signals corresponding to the cyclopropyl protons was 10%. Reaction in THF afforded a much higher yield of the Grignard reagent (58%) and only 20% of racemic hydrocarbon **15**. The optical purity of the acid **19** was 13%.

To establish the absolute configuration of the acid formed after Grignard reaction (Fig. 21) optically pure (*S*)-(+)-**13** was treated with *tert*-butyllithium in ether solution, followed by carbonation to yield optically pure (+)-**19** as determined by NMR analysis of its (*S*)-(−)-α-methylbenzylamide derivative. Since lithium–halogen exchange followed by carbonation proceeds with complete retention of configuration [71] the (*S*) configuration is assigned to (±)-**19**; this establishes that the Grignard reagent formation reaction proceeds with retention of configuration. In contrast, when optically pure bromide **13** was reduced

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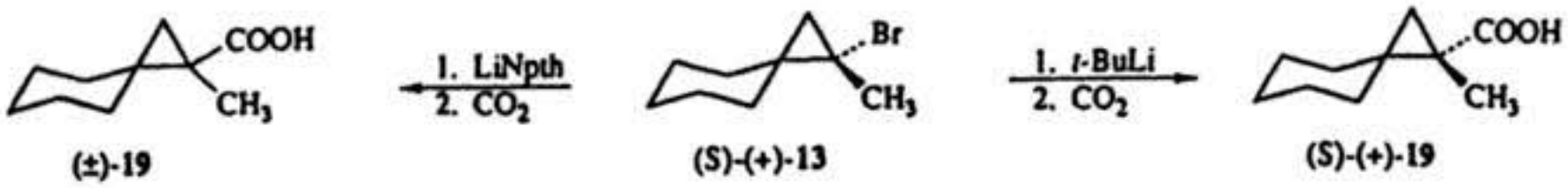
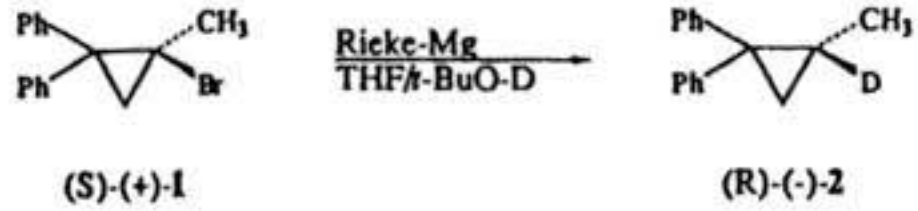


Figure 21 Treatment of the optically pure bromide with *tert*-butyllithium followed by carbonation and the reduction of the optically pure bromide followed by carbonation.

Table 5 Results from the Treatment of the Optically Pure Bromide with Rieke Magnesium in the Presence of *t*-BuO-D



Reaction of (S)-(+)-1 with Rieke-Mg in THF/*t*-BuO-D.

Run	T, °C	t-BuO-D equiv.	Yield, %	D, %	O.P. %
1	-65	2	98	86	41
2	-65	4	94	92	43
3	-65	100	86	92	33
4	+20	4	92	89	18

under homogeneous conditions with lithium naphthalenide (1 eq) [72], in THF at room temperature, the resulting acid **19** isolated in 21% yield after carbonation was completely racemic. These results are consistent with and supportive of the surface nature of the Grignard reagent formation.

Walborsky and Rachon have also reported on the use of Rieke magnesium to obtain reaction with (*S*)-(+)-1-bromo-1-methyl-2,2-diphenylcyclopropane at −65°C to afford a chiral Grignard reagent that is 33–43% optically pure [73]. In 1961, Young and Walborsky [74] demonstrated that the reaction of chiral (*S*)-(+)-1-bromo-1-methyl-2,2-diphenylcyclopropane (Table 5; **1**) with magnesium powder resulted in the formation of a chiral Grignard reagent as evidenced by the fact that on carbonation of the reaction mixture an optically active acid was obtained with an optical purity of approximately 12–18%.

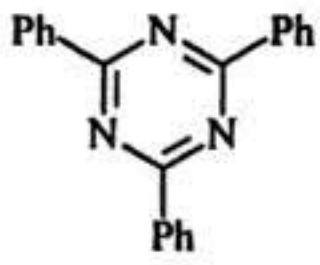
Rieke magnesium, is a highly reactive form of magnesium that enables one to form Grignard reagents at −78°C or lower. The reaction of (*S*)-(+)−**1** with Rieke magnesium was conducted in THF in the presence of *t*-BuO-D. The results are summarized in Table 5. It is clear from Table 5 that the isolated yields of **2** are almost quantitative, with a very high deuterium content. Moreover, at −65°C the optical purity ranges from 33 to 43%. Furthermore, under the foregoing conditions, but using powdered magnesium, instead of Rieke magnesium, no reaction occurred. Also of significance is the decrease in optical purity to 18% when the reaction is carried out at +20°C. The Rieke magnesium, therefore, plays an important role in the initial electron transfer step, since the optical purity of **2** at +20°C is the same for both Rieke magnesium and ordinary powdered magnesium. The high deuterium incorporation is a reflection of the degree of Grignard reagent formation

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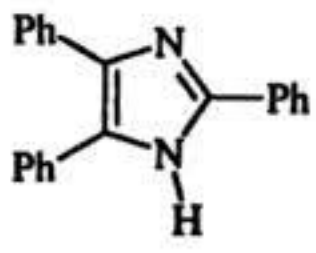
and is a qualitative affirmation that very little reaction of the radical with other hydrogen atom sources occurs under these conditions.

A simple example of the advantage of generating Grignard reagents at low temperatures is the reaction of 3-halophenoxypropane [75]. Although the Grignard reagent is easy to generate at room temperature or above, it displaces the phenoxy group by an S_N2 reaction to generate cyclopropane. This reaction is, in fact, a standard way to prepare cyclopropanes, and the cyclization cannot be stopped; however, by using Rieke magnesium, the Grignard reagent can be prepared at −78°C, and it does not cyclize at these low temperatures. It can then be added to a variety of other substrates in standard Grignard reactions. Other attempts at low-temperature formation of Grignard reagents involved molecules containing nitrile, ketone, and ester functional groups [76]. These reactions were largely unsuccessful, except in the case of 8-bromooctanenitrile. In the alkyl systems, ethyl 3-bromopropionate, 4-bromobutyronitrile, and 5-bromovaleronitrile, the heteroatoms coordinated strongly to the magnesium surface at the temperatures required to prevent attack of Grignard reagents on the functionality present. Thus, Grignard reagent formation was inhibited by the occupation of the active sites on the magnesium surface, although 8-bromooctanenitrile reacted rapidly with Rieke magnesium at −78°C to give 74% conversion to the Grignard reagent. Carbonation gave 8-cyanooctanoic acid in 35% yield, based on Grignard reagent. This appears to be the first example of a Grignard reagent that contains the nitrile functionality. Interestingly, the nitrile functionality coordinates so strongly to the magnesium surface that reaction with organic halides is completely inhibited until 20°C is reached. 4-Bromobutyronitrile did not react at all with Rieke magnesium at −78°C. When the temperature was slowly raised, no reaction was observed until 20°C, at which time polymerization occurred. In confirmatory experiments, 1-bromopentane reacted quantitatively with Rieke magnesium in 1 min at −78°C. The resulting Grignard reagent did not react with subsequently added butyronitrile even after 1 hr at −78°C. If butyronitrile was added to the Rieke magnesium at −78°C, followed by addition of bromopentane, no Grignard reagent was formed after 2 hr. This demonstrates the strong adsorption of the Lewis base (butyronitrile) on the metal surface, which is acting as a Lewis acid.

When benzonitrile was reacted with Rieke magnesium in refluxing glyme, a deep red color developed after 1 hr. Gas chromatography revealed most of the starting material to be unconsumed. After refluxing overnight, the reaction mixture turned brown, and most of the starting material was consumed. An aliquot injected directly into the gas chromatograph did not reveal benzil formation. Workup showed two main products: 2,4,6-triphenyl-1,3,5-triazine and 2,4,5-triphenylimidazole, in 26% and 27%, yields, respectively (Fig. 22).



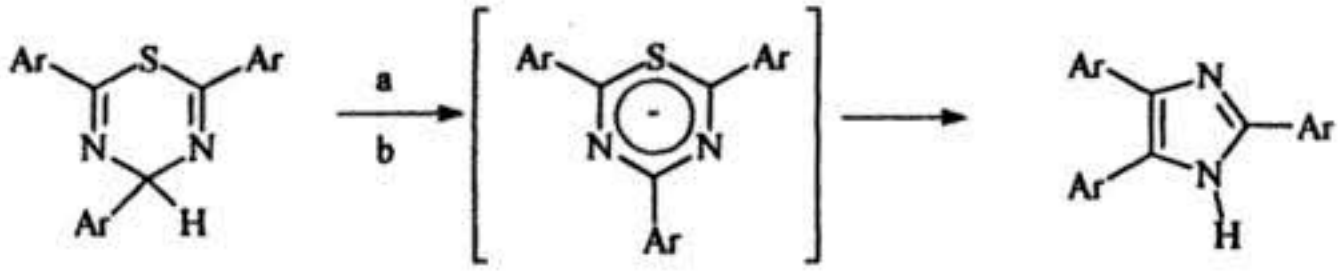
2,4,6-triphenyl-1,3,5-triazine



2,4,5-triphenylimidazole

Figure 22 Two products from the reaction of benzonitrile with Rieke magnesium in refluxing glyme.

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Extrusion reactions used to form imidazoles.
Conditions: (a) aliphatic amines/benzene; (b) *n*-butyllithium

Scheme 4 Two extrusion reactions used to form imidazoles.

Table 6 A Summary of the Various Methods Used in the Trimerization of Aromatic Nitriles

Reagent	Conditions	% yield
Chlorosulfonic acid	0°C, 12 hr	40
$AlCl_3$	140–160°C	1.5
PCl_5/HCl	100–105°C, 24 hr	98
MeOH	100–125°C, 7500 atm	74–82
Na	C_6H_6	None given
RMgX	Boiling xylene	25
RLi		16

The imidazole was quite unexpected, but nevertheless present as the most abundant product. A product with a TLC R_f equivalent to benzil was also present in less than 5 mol% yield, as were numerous other unidentified products in low yields.

The imidazole was shown to arise, at least in part, from the triazine. 2,4,6-Triphenyl-1,3,5-triazine reacted with Rieke magnesium in refluxing THF to afford 2,4,5-triphenylimidazole in 27% yield; 65% was unreacted starting material; 8% was unaccountable.

Giordano and Belli have formed imidazoles from 2,4,6-triaryl-4*H*-1,3,5-thiadiazines by a base-catalyzed extrusion of sulfur [77]. Schmidt *et al.* also refer to an analogous extrusion of oxygen from the 4*H*-1,3-oxazine [78]. Scheme 4 depicts two extrusion reactions used to form imidazoles.

Radzisewski prepared imidazoles by the extrusion of nitrogen from triazines using Zn in refluxing acetic acid [79].

The trimerization of aromatic nitriles to give symmetric triazines is not unknown, but generally, the reactions must be catalyzed by strong acids or a weak base and under extremely high pressure. The action of *preformed* Grignard reagents also gives symmetric triazines. Organoalkalis also give trimers, but not symmetric triazines. A summary of the various methods that have been employed in the trimerization of aromatic nitriles is given in Table 6. This direct reaction of magnesium to afford symmetric triazines is unprecedented in the literature.

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5

Safe Handling Practices of Industrial Scale Grignard Reagents

PHILIP E. RAKITA
Elf Atochem Agri, S.A., Plaisir, France

I. INTRODUCTION

The use of Grignard reagents on an industrial scale poses additional and different concerns from those found in the laboratory. These differences occur at several points during the process of preparation and use of a Grignard reagent. In an industrial situation, often involving several hundred kilograms of reagents, the equipment is different from that employed in the research laboratory. Industrial production typically uses steel vessels of different shapes, with different configurations for the addition or removal of reagents, compared with laboratory glassware. The capability to modify the configuration of the reaction vessel is often less. Agitation methods are different. In the industrial setting, the important engineering parameters, including surface/volume ratios (which influence rates of heat transfer), are substantially different from those in the laboratory. Characteristics and qualities of available reagents may be different. Reaction times may differ substantially, and industrial production may be influenced by such nonscientific considerations as the economics of production scheduling and the exigencies of the industrial workweek.

Although industrial-scale Grignard reagents are often used *in situ* without isolation, an important segment of the worldwide production (estimated at tens of thousands of metric tons annually) is destined for merchant sale. This introduces the additional issues of safe storage and transportation not normally encountered in the laboratory. Also to be considered are matters of compliance with national or international regulatory bodies. Finally, by the sheer volumes of reagents involved, waste disposal for the industrial Grignard chemist is an important economic and safety consideration.

The purpose of this chapter is to identify and outline some of the critical safety issues that must be considered when planning to conduct a Grignard reaction on an industrial scale.

Materiał chroniony prawem autorskim

II. PRINCIPLES OF THE INDUSTRIAL MANUFACTURING PROCESS

In spite of their industrial use for many years, the commercial-scale production of Grignard reagents has not been extensively described in detail. Waugh and Waugh [1] reported the general features of a small production unit, and Colin and Gillin [2] described a pilot-sized operation suitable for pharmaceutical applications. A continuous system, practical for small- or medium-scale production, was patented by Hoffman-La Roche [3], but apparently was never commercialized. The only practically important method is the three-step batch method described by Victor Grignard in 1900, namely (1) formation of the Grignard reagent, (2) reaction with a substrate followed by (3) hydrolysis of the reaction mixture. A simplified schematic diagram of the industrial process is shown in Figure 1.

The equipment can usually be constructed of carbon steel, except for the hydrolysis vessel, which is more typically glass lined to avoid corrosion by aqueous acids. It is preferable to use stainless steel or, ideally, glass-lined vessels throughout. All vessels must be supplied with an inert gas (nitrogen or argon) for purging and blanketing and are to be vented to release off-gases. It is imperative that the reaction vessel be protected with a rupture disk.

A. Formation of the Grignard Reagent

In the classic methodology, for the start-up of a batch process (see Fig. 1), magnesium turnings or chips are charged to vessel R-2. After thorough purging with an inert gas, a portion of the solvent is added, followed by a fraction of the halide charge from vessel R-1. The chief hazard associated with the manufacture of Grignard reagents occurs at this stage—the difficulty in initiating the reaction. If the addition of the halide is continued before initiation takes place, the presence of excess halide when the reaction does begin, will generate such a large exotherm that the cooling system may be overwhelmed. This may result in a dangerous pressure buildup and the potential for an explosion.

To minimize this difficulty, an initiator is frequently employed. Among the numerous suggestions in the literature, the most satisfactory industrial procedure is to retain a portion of the Grignard from the preceding batch and to add this portion to the initial solvent charge. This serves to eliminate residual water and to clean the magnesium surface. Once this "initiator" has been added, the halide is added at a rate determined by the temperature and the pressure in the reaction vessel.

Cooling is routinely applied, either with ambient process water if tetrahydrofuran (THF) is the solvent, or with chilled brine if diethyl ether is used. Since Grignard reagents are particularly reactive with water, liquid hydrocarbon coolants may be preferred, to eliminate the risk that could arise from a cooling system leak.

B. Reaction of the Grignard Reagent with a Substrate

For the process represented by Figure 1, the Grignard reagent is usually transferred from the reaction vessel R-2 to the "coupling" vessel R-3 for the reaction with the substrate. It is usually advisable to remove particles of residual magnesium by filtration. The substrate, dissolved in an ether or hydrocarbon solvent, is then added slowly from the feed tank (with cooling of the reaction vessel). The addition can also be reversed (i.e., addition of the Grignard reagent slowly from vessel R-2 to a solution of the substrate in vessel R-3). The choice of direct or reverse addition is dictated by several factors and is usually established by suitable process and pilot plant studies before reaching the plant stage. After the reaction is complete, most of the solvent is removed by distillation, with or without

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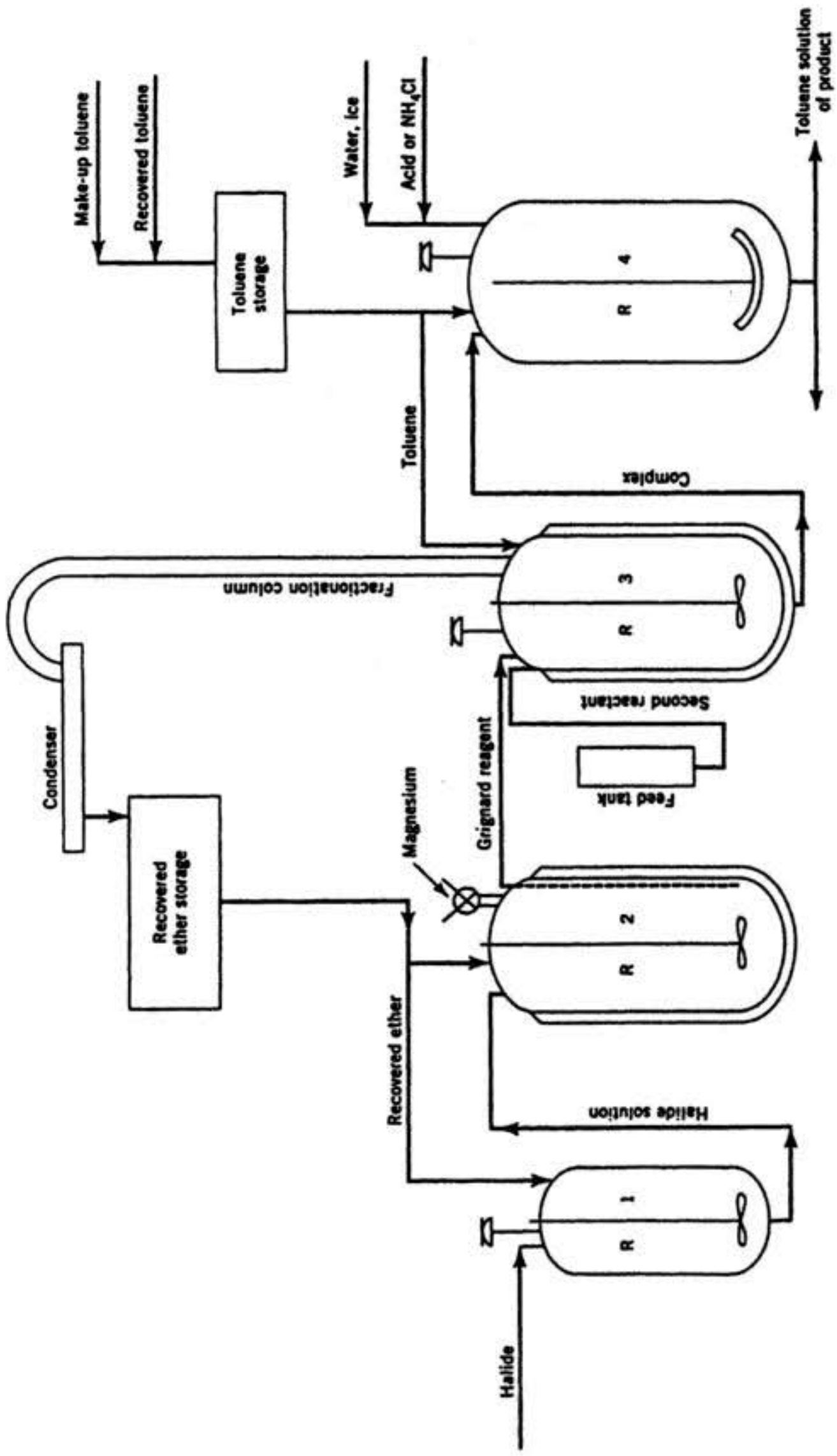


Figure 1 Flow diagram of a Grignard plant.

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the addition of enough hydrocarbon to R-3 to maintain adequate agitation. At this point the contents of R-3 are pumped to R-4 for further processing.

C. Hydrolysis of the Reaction Mixture

Apart from the reaction of Grignard reagents with organic or inorganic halides, the reaction in step 2 gives a complex that requires a "quench" step to release the desired product. Water has sufficient acidity to hydrolyze the complex, but the basic magnesium salts formed in the quenching reaction often produce a gel that can be difficult to manipulate. This problem can be overcome through the addition of a stronger acid to neutralize the basic salts and produce water-soluble magnesium salts. Sulfuric and hydrochloric acids are commonly employed, but may lead, particularly in the case of some tertiary alcohols, to dehydration. In these cases, the use of a weaker acid, such as acetic acid or ammonium chloride, permits the recovery of the desired alcohol. After the hydrolysis step is complete, the aqueous phase is separated from the organic phase and the product is then isolated.

When hydrolysis is not required, the metathetical reaction leads directly to the product (plus magnesium halide) in the solvent. Volatile products may be removed by direct distillation, or the solid magnesium halide may be removed by filtration, before evaporation of the solvent. If the final product is not water-sensitive, water-washing of the final reaction product mixture usually conveniently removes the salts.

Special handling procedures have been described [4] if the Grignard reagent has been purchased commercially (either in drums or bulk) for use in a separate facility.

Several continuous processes for the manufacture and use of Grignard reagents have been proposed [5], but they enjoy no current commercial significance.

III. SAFETY CONSIDERATIONS

A. Scale-up

The transfer of a reaction sequence involving a Grignard reagent from the laboratory through the pilot plant and into production involves the same considerations of scale-up in design and practice as that of other inherently exothermic reactions. Considerations of rates of agitation, heat transfer, pressure buildup, and other safety-related parameters should follow standard chemical engineering design principles.

B. Handling and Storage Procedures

Merchant Grignard reagents are supplied commercially in 55-gallon (200 L), 16-gauge stainless steel tighthead drums (DOT-17C in the United States, IATA 1A2 internationally), with double-welded top and body seams. Heads with a minimum convexity of 3/8 in., but not extending beyond the level of the chimes, are required in the United States. Threaded metal plugs are required and must engage at least three threads with a gasket in place. [Proprietary designs also exist for returnable, refillable bulk containers suitable for shipment of Grignard reagents.]

The propensity of Grignard reagents to react vigorously with water mandates extreme care in drum handling. Any damage to the containers could cause leakage of the contents and contact with water, with the potential of a fast, volatile reaction and the rapid evolution of flammable solvent vapors.

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A blanket of inert gas, such as dry nitrogen or argon, is required for the packaging, handling, and transport of Grignard reagents to reduce reactivity. This inert atmosphere must be maintained throughout the production and use of the reagent, both to maximize safety and optimize yields.

C. Transfer Procedures

When setting up a system to transfer Grignard reagents from drums to a feed tank, the unopened drum of Grignard reagent must be grounded and mechanically bonded before the attachment of any transfer fittings, to ensure a metal-to-metal contact with the ground cable (Fig. 2).

Typically, the 2-in. drum bung is set up as the feed outlet, and the 3/4-in. opening is set up as the vent. This vent is equipped with low-pressure, regulated nitrogen or argon to provide an inert atmosphere in the drum and act as a follower gas in the feed lines.

The 3/4-in. venting system should include a solvent flush for rinsing residual Grignard reagent from the feed lines. This will ensure safe opening of the quick-connect junctions typically found in such systems. A pressure relief valve is also needed to prevent overpressurization of the drum.

D. Disposal of Waste

Before disposal of the drum, it should be flushed with several portions of dry solvent. The line to the receiving tank should be flushed as well. This is followed by a flush of dry inert gas to empty the line. Once the pipe and fittings are removed, the drum is capped and transferred to a waste-handling pad equipped with a grounding system, water, and proper waste solvent-handling facilities. The drum can then be safely filled with cold water. Water should be allowed to overflow for 5 min to flush out any remaining solvent or reagent. After thorough drainage, the drum is ready for safe disposal.

Grignard reactions are generally run using an excess of the reagent to ensure complete consumption of the substrate. Accordingly, when the reaction is complete, there typically remains 5–25% unreacted Grignard reagent in the reaction vessel that must be disposed of properly. Both the quenching of the coupled Grignard reagent and the disposal of the unused reagent left in the drum require an initial hydrolysis step to remove the magnesium halide.

The hydrolysis step required to dispose of excess Grignard reagent is performed in the process vessel, which should be vented through a flame arrestor. Sufficient acidified water (enough to form at least a 25% $MgCl_2$ solution) is added carefully, with good agitation and full cooling on the jacket.

When performed on the reaction mass in the reactor vessel, this hydrolysis step will create two separate, immiscible layers: the product in the organic solvent and aqueous magnesium halide. The (generally) heavier aqueous layer settles to the bottom of the vessel where it can be drained out.

The desired product is then further isolated by removing the volatile solvent. The solvent can be distilled from the product by stripping, or removed mechanically by extraction. The recovered solvent is then burned in an approved facility, or if it is to be reused, is typically distilled to ensure the required purity for the next batch.

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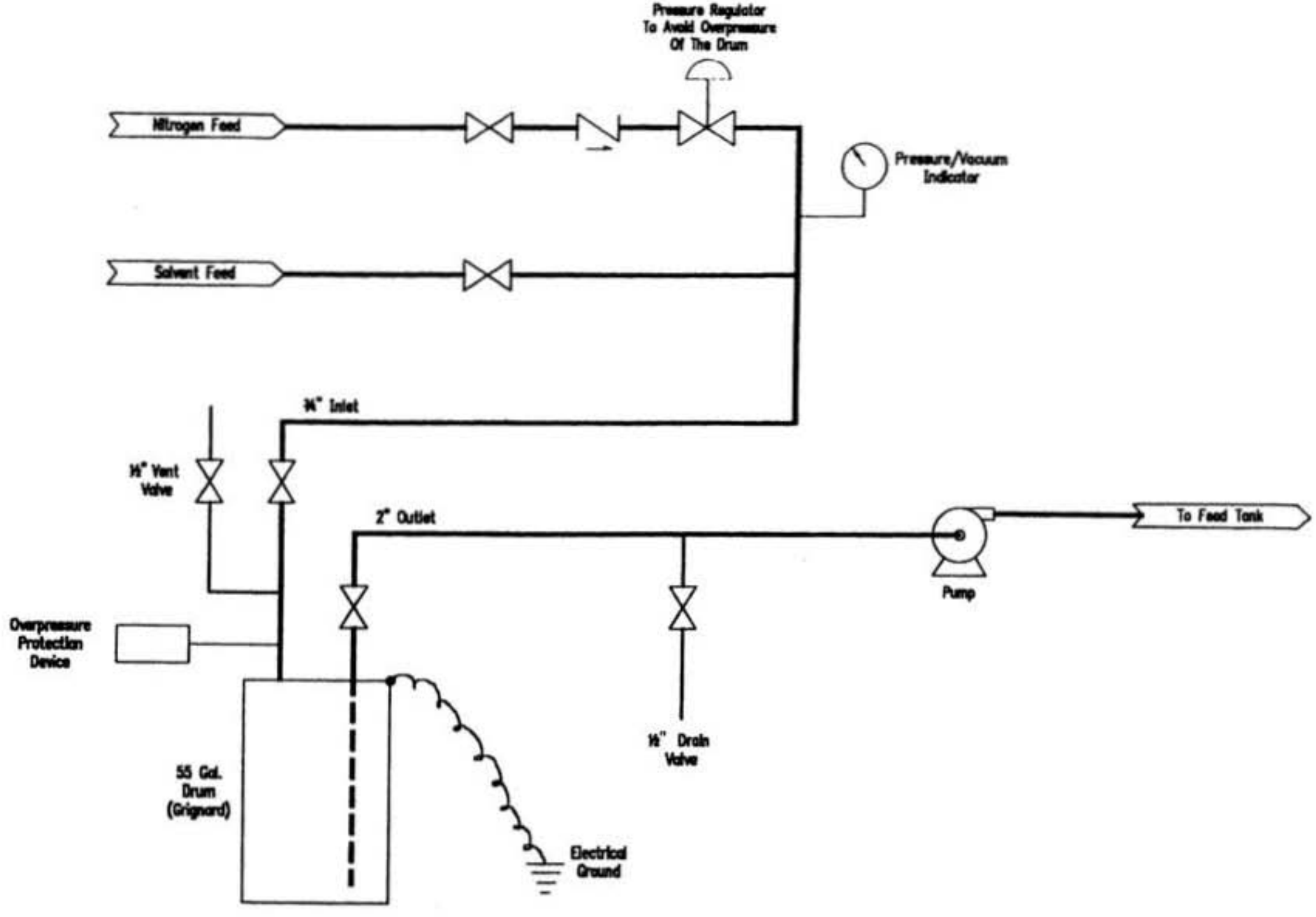


Figure 2 Typical system for transfer of Grignard drum contents.

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IV. HAZARD CONTROL AND MANAGEMENT

A. Spills

Spills of Grignard reagents should be contained with inert absorbent material, such as dry sand or earth, and transferred with nonsparking bronze, brass, or plastic tools, making sure that the container is properly grounded.

Any spilled Grignard reagent must be disposed of as a solid waste, in accordance with all applicable regulations. Spilled Grignard reagents *cannot be salvaged*, since contamination and exposure to air renders them unsuitable for use.

B. Fires

The hazards associated with the manufacture, transport, and use of Grignard reagents are related to the flammability of the solvents employed and the exothermic reactions involved in their preparation and use.

Historically, diethyl ether was the common solvent used in the preparation of Grignard reagents. Commercially, however, its use is limited by its extreme flammability and relatively low-boiling point, which precludes its use in reactions with higher working temperatures. Since the 1950s it has been largely replaced by tetrahydrofuran (THF) in commercial-scale production. Tetrahydrofuran is a cyclic ether, with a boiling point 30°C higher than that of diethyl ether and a flash point of −17°C, compared with −45°C for diethyl ether.

As reactions involving the manufacture and use of Grignard reagents are exothermic, the associated heat must be controlled. Typically, these reactions are carried out in jacketed, glass-lined steel reactors, equipped with cooling, explosion-proof electrical wiring, explosion disks, and inert atmosphere for purging and blanketing. To control the heat of reaction when THF solvent is employed, ambient cold water may suffice. For reactions using diethyl ether, chilled water or brine is required to keep the reaction mass below the boiling point. Since Grignard reagents are particularly reactive with water, liquid hydrocarbon coolants (e.g., kerosene) may be substituted to eliminate the risk of a water leak. Similar precautions apply for the use of commercial Grignard reagents.

Grignard reagents react exothermically with air, water, and CO_2. However, during a reagent fire, the major source of heat generated will be from the burning solvent. As with any solvent fire, the three primary concerns should be

1. Removing the source of ignition
2. Isolating and extinguishing the fire
3. Controlling the evolution of flammable vapors

Because Grignard reagents are highly reactive, extinguishers containing carbon dioxide, chlorinated hydrocarbons, or water must not be used. Dry chemical fire extinguishers are preferred for the fighting of Grignard fires. Additionally, full personal-protective clothing, including self-contained breathing apparatus, is required.

C. Toxicity and Toxic By-products

Because of their high reactivity, there is little meaningful information on the health hazards of Grignard reagents *per se*. Rather, consideration needs to be given to the starting reagents employed, including the solvents and the products (or by-products) of the reaction. Some starting materials, for example, organic halides (notably methyl bromide and vinyl chloride), are particularly toxic. Hydrolysis of a phenylmagnesium halide produces benzene.

Materiał chroniony prawem autorskim

By-products of the decomposition of Grignard reagents are an additional concern. As with flammable organic halides, there is a potential for the release of hazardous hydrogen halide vapors (HCl, HBr). If the fire involves certain Grignard reagents (notable phenylmagnesium halide), the hazardous hydrocarbon, benzene, may be released.

V. REGULATORY COMPLIANCE

A. Commercial Use

Industrial use of a Grignard reagent in the United States requires that it be included on the Environmental Protection Agency (EPA) list of *Chemical Substances in Commerce*. A corresponding registration exists for the European Community and for Japan. Table 1 gives the Chemical Abstracts Service (CAS) numbers of those listed by the EPA as of 1994.

For chemicals that do not appear on the U.S. EPA list of *Chemical Substances in Commerce*, it is necessary to submit a Premanufacture Notification (PMN) to the EPA before making the new material for commercial purposes. The EPA approval is based on adequate documentation of planned manufacturing procedures, anticipated by-products, health and environmental effects test data, and procedures for safe use, handling, and disposal.

B. Air, Water, Solid Waste Compliance

Before a chemical manufacturer in the United States can scale up production of Grignard reagents from the laboratory to the plant, appropriate federal, state, and local air, wastewater, and solid waste permits must be obtained, or existing permits modified. Required approval periods will vary depending on the jurisdiction.

Table 1 Grignard Reagents Listed on the U.S. EPA Toxic Substances Control Act (TSCA) List

Name	RMgX formula	CAS registry number
Methylmagnesium chloride	CH_3MgCl	[646-58-4]
Methylmagnesium bromide	CH_3MgBr	[75-16-1]
Methylmagnesium iodide	CH_3MgI	[917-64-6]
Ethylmagnesium chloride	CH_3CH_2MgCl	[2386-64-3]
Ethylmagnesium bromide	CH_3CH_2MgBr	[925-90-6]
n-Propylmagnesium chloride	$CH_3CH_2CH_2MgCl$	[2234-82-4]
Isopropylmagnesium chloride	$(CH_3)_2CHMgCl$	[1068-55-9]
n-Butylmagnesium chloride	$CH_3(CH_2)_2CH_2MgCl$	[693-04-9]
sec-Butylmagnesium chloride	$CH_3CH_2CH(CH_3)MgCl$	[15366-08-02]
n-Pentylmagnesium bromide	$CH_3(CH_2)_4MgBr$	[693-25-4]
n-Hexylmagnesium bromide	$CH_3(CH_2)_5MgBr$	[3761-92-0]
Vinylmagnesium bromide	$CH_2=CHMgBr$	[1826-67-1]
Phenylmagnesium bromide	C_6H_5MgBr	[100-58-3]
Phenylmagnesium chloride	C_6H_5MgCl	[100-59-4]
Benzylmagnesium chloride	$C_6H_5CH_2MgCl$	[6921-34-2]
p-Tolylmagnesium bromide	$4—CH_3C_6H_4MgBr$	[4294-57-9]
o-Tolylmagnesium chloride	$2—CH_3C_6H_4MgCl$	[33872-80-9]

Material chroniony prawem autorskim

C. Transportation

Since they are classified as flammable liquids, Grignard reagents in the United States must be packaged in drums or other suitable containers bearing a red U.S. Department of Transportation label. The appropriate international designation of Grignard reagents is UN-1993. Container size restrictions apply for ocean shipment of Grignard reagents that generate gaseous by-products (C_1 to C_4 hydrocarbons) on hydrolysis.

When shipping Grignard reagents, one should review international transportation regulations. The United States import and export restrictions on Grignard reagents are listed in the Toxic Substances Control Act (TSCA), Section 12. For export, restrictions may be imposed by the receiving country. Note that the majority of the regulatory considerations for the use of Grignard reagents will apply to the solvents used, rather than the Grignard reagents themselves.

D. Storage

As with any potentially flammable material, the best storage facility is a well-ventilated, fire-resistant building, suitable for flammable chemicals, that is away from main buildings and offices.

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Materiał chroniony prawem autorskim

6

Wet Analyses of Grignard Reagents

GARY S. SILVERMAN
Elf Atochem North America, Inc., King of Prussia, Pennsylvania

I. QUANTITATIVE WET ANALYSES

There are three potential problems that may occur during the Grignard reagent preparation: oxidation by O_2, hydrolysis by H_2O, or homocoupling during the addition of alkyl or aryl halide. Oxidation and hydrolysis will decrease the active Grignard reagent, while maintaining the same equivalents of base. Because of these three problems, the concentration of a Grignard reagent should not be assumed based on the reactants. By not analyzing the Grignard reagent, one or more of the following problems may occur: improper stoichiometry, potential deleterious side reactions, highly exothermic quenching process, phase split, waste disposal, and cost problems. Therefore, the analytical technique must be able to differentiate between active Grignard and total basicity.

There is a plethora of methods available to measure the active Grignard [1–13]. The methods range from titration to electrophilic quenching followed by gas chomatographic (GC) analysis. Potentiometric titration [1–3] using 2-butanol as the titrant is recommended as the general method for determining the activity of Grignard reagents. The advantages of this method are that it does not titrate Mg—OH or Mg—OR species; it gives reproducible results (3 standard deviations = 0.6% of value); direct analysis of solution, and analysis takes less than 10 min.

Standard titration techniques, using indicators [4,5,13] with 2-butanol as the titrant, have greater error (3 standard deviations = 1–5% of value), but usually this is still acceptable. The real advantage of these indicator methods is that virtually no capital investment is required for the equipment. The equipment for the more accurate potentiometric titration method can cost upward of 15,000 dollars. This is why titrations using 2,2′-bipyridyl or 1,10-phenanthroline are more prevalent in the literature.

Electrophilic quench followed by GC analysis can give the accuracy and precision of a potentiometric titration [7–12]. However, each starting material and its product must

Material chroniony prawem autorskim

be calibrated versus a GC standard. This requires a time-consuming GC method development process. Also these methods typically take a minimum of 1 h from the start of the quench procedure to obtaining the final chromatogram. The advantage of the GC method is that a direct measurement of the homocoupled product, oxidized Grignard, hydrolyzed Grignard, and unreacted alkyl or aryl halide, all can be made.

Gas evolution from the hydrolysis of Grignard reagents can be used for the activity analysis. However, care must be taken in the calibration of standards, because the resulting gas will have some solubility in the solvent. Typically, the gas is analyzed by GC, taking the gas from the headspace of a closed system. The obvious limitation in this method is that only a selected amount of Grignard reagents (C_4 or less) can be used, owing to the volatility of the hydrolysis products.

Total basicity is measured by standard acid–base titration techniques. The activity divided by the total basicity should be greater than 90%. If it is not, then the Grignard reagent should be checked for unreacted alkyl or aryl halide, homocoupled product, hydrolysis products, and oxidation products.

II. PROCEDURES FOR QUANTITATIVE WET ANALYSES

This section includes the procedures for the analyses of Grignard reagents. All reagents and solvents were dried (Karl Fischer titration must be less than 0.02 wt% H_2O), degased, and placed under a nitrogen atmosphere. All operations were carried out under an inert atmosphere using a Brinkman 682 titroprocessor, a sealed glass electrode that contained the working and auxiliary electrodes (Pt), and a silver reference electrode. For nonpotentiometric titrations the same buret (Brinkman dosimat 665) and cell were used with the specific indicator.

A. Preparation and Standardization of 2-Butanol Solution

This method is used to standardize 2-butanol solutions in xylenes and is based on acetylation of the alcohol. To make the stock 2-butanol solution, add 74 g of 2-butanol to an inert 1-L volumetric flask and dilute to 1 L with xylenes. Mix thoroughly and transfer under nitrogen to a 1.5-L storage flask containing 4 Å molecular sieves. Degas the solution by the freeze–pump–thaw technique (three times) and place the storage flask under nitrogen.

The titrant is a standardized NaOH solution of approximately 0.5 *N*, and the indicator is a 0.1 wt% 1:1 mix of cresol red and thymol blue in methanol. The color change will be from a light yellow to violet for the end point.

The reagent solution is prepared by pipetting 1 ml of 70% perchloric acid into a 100-ml volumetric flask, add 75 ml of ethyl acetate, and shake well. Add to the mark with acetic anhydride. Note that this is an exothermic dilution and an ice bath may help speed up this process. However, the solution should be at ambient temperature before final dilution and actual use. This reagent is stable for at least 1 week.

Once all of the solutions have been prepared, use the following procedure. Pipette 5 ml of the acetic anhydride reagent solution into each of two oven-dried Erlenmeyer flasks, followed by pipetting 5 ml of the 2-butanol solution into only one of the flasks and mark it flask B. Stopper both flasks and mix thoroughly for at least 15 min. Carefully pipette 45 ml of H_2O over 2–5 min and allow the flask to cool to ambient temperature (5–10 min). Add 5 drops of the indicator solution and titrate with the NaOH solution to the violet

Material chroniony prawem autorskim

end point. Calculate the molarity of the 2-butanol solution using the following equation:

$$M_{\text{2-butanol}} = \frac{M_{\text{NaOH}}(\text{A ml} - \text{B ml})}{5.00\ \text{ml}}$$

The molarity should be approximately 1 based on the mass of 2-butanol and the recommended dilution volume.

B. Determination of Grignard Reagent Activity

Clean, dry, and inert a 50-ml titration flask containing a working/auxiliary electrode, a reference electrode, buret tip for subsurface feed, septum, stir bar, and a nitrogen inlet, with a bubbler for pressure relief. Add enough solvent to the flask to cover the electrodes and the buret tip, which is approximately 25 ml of tetrahydrofuran (THF; less than 0.02 wt% H_2O) and start the stirrer. Weigh out, in milligrams, approximately 2 g of Grignard reagent by syringe and add to the flask. Reweigh the syringe to get the precise mass of Grignard reagent added to the flask. Start the titration with the standardized 2-butanol solution (see Section II.A). A sharp decrease in potential, as well as formation of a white solid, indicate that the endpoint has been reached. The first derivative of the S-shaped curve is the actual endpoint, and the Grignard reagent activity can be calculated by the following equation:

$$\text{Activity (mol/kg)} = \frac{\text{titration volume (L)} \cdot M_{\text{2-butanol}}(\text{mol/L})}{\text{Grignard reagent mass (kg)}}$$

There are several reasons why the Grignard reagent's mass is used instead of the volume (liters) to give the activity. The major reason is mass measurements in most synthetic laboratories are significantly more accurate than volume measurements, owing to the lack of availability of inert volumetric pipettes. For commercial production of Grignard reagents, these comments are magnified, and the mass measurement is the most appropriate.

There are several adequate indicators that can be used instead of the electrode system. The most common are 2,2′-bipyridyl and 1,10-phenathroline. In the presence of active Grignard reagents these indicators will form colored charge-transfer complexes. After quenching with 2-butanol, the complex is broken, subsequently the color disappears. The color will vary from yellow to a dark orange-brown, depending on the Grignard reagent.

An interesting qualitative test for organolithium reagents in the Grignard reagents is to add a few milligrams of 2,2′-bipyridyl to the active reagent [13]. If the solution is red-purple versus a yellow-orange, then there is an organolithium present. This is an important test, especially if Reike Mg, generated from lithium, is used (see Chapter 4).

C. Determination of Grignard Reagent Acid–Base Value

This determination is a standard acid–base titration, and the ratio of activity (see Section II.B)/acid–base should be greater than 93%. An example of this procedure is described in the following.

Clean and inert a 250-ml titration flask containing two buret tips for subsurface feed, septum, stir bar, and a nitrogen inlet, with a bubbler for pressure relief. Add 100 ml of degased H_2O to the flask and turn on stirrer. Weigh out, in milligrams, approximately 5 g of Grignard reagent by syringe and add to the flask slowly. Reweigh the syringe to get the precise mass of Grignard reagent added to the flask. Add approximately 5 ml of 0.5 *M* HCl from buret 1 and rinse the sides of the flask with the solution until there are no visible solids. Add 3 drops of phenolphthalein to the flask and titrate 3–4 ml past the endpoint

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(colorless). Allow the solution to stir for 5 min. Add 3 drops of methyl red indicator. Titrate with standardized 0.1 *M* NaOH in buret 2 to the endpoint (disappearance of red color). To calculate the acid–base value use the following equation:

$$\text{Acid–base (mol/kg)} = \frac{(M_{HCl}V_{HCl} - M_{NaOH}V_{NaOH})}{\text{Grignard reagent mass (kg)}}$$

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7

Infrared and Raman Spectroscopy

Paul Chabot
Elf Atochem North America, Inc., King of Prussia, Pennsylvania

I. ALIPHATIC GRIGNARD REAGENTS

The structure and properties of the Grignard reagents are a function of the organic group attached to the metal atom. Plum, in 1937, was the first to study the influence of the organic group using infrared spectroscopy [1]. The Grignard reagents studied were diethyl ether solutions of ethyl- and phenylmagnesium bromide and iodide. Even though several absorption bands that could be attributed to Grignard reagents were observed, no definite assignments could be made.

The group of Salinger et al. compared the infrared spectra of Grignard reagents "RMgX" in solution in tetrahydrofuran (THF) and diethyl ether (R = Me, Et, or Ph; X = Br(THF, Et_2O), Cl(THF), I(Rt_2O)) [2]. When pure R_2Mg and MgX_2 were mixed, it was observed, after 5 min, that the spectra of the reaction mixtures were identical with that of the Grignard reagents. It was also observed that the nature of the halogen atom did not have a large influence on the infrared spectra. And finally, a change in concentration did not modify the infrared spectra significantly. For the alkyl Grignard reagents, an absorption band was observed between 535 and 500 cm^{-1} and was assigned to the C—Mg stretching vibration. For phenylmagnesium compounds, this band shifted to lower frequencies, and was observed between 383 and 365 cm^{-1}. The results of this study were used to show the existence of the Schlenk equilibrium in Grignard solutions. Furthermore, this study indicates that the nature of the alkyl or aryl group, the halogen atom, and the solvent, all have an effect on the structure of the Grignard reagents.

The effect of the chain length of an aliphatic groups attached to the magnesium atom was studied thoroughly by Kress and Novak [3–5]. The analysis of the infrared and Raman spectra of methyl and ethyl Grignard reagents, combined with the analysis of the corresponding deuterated compounds and different halogen groups has led to a complete vibrational assignment. For $C_2H_5MgX{\cdot}2(C_2H_5)_2O$ (X = Br, I) in the solid state

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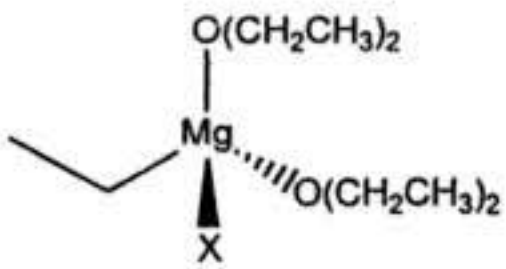


Figure 1 Crystalline structure of $C_2H_5MgX{\cdot}2O(CH_2CH_3)_2$, X = Br or I.

Table 1 Frequencies of the Infrared Bands Observed for the Vibrations Involving the Magnesium Atom in $C_2H_5MgX{\cdot}2(C_2H_5)_2O$ at 90 K

	Infrared		Raman	
Assignment	C_2H_5MgBr	C_2H_5MgI	C_2H_5MgBr	C_2H_5MgI
μ Mg—C	485	481	485	481
μ_{asym} MgO_2	317	314	314	311
μ_{asym} MgO_2	301	295	299	293
μ MgX	253	233	248	223
δ MgCC	—	—	183	179sh
δ MgO_2	—	—	141	145sh

at 90 K, there is a tetrahedral arrangement of the ethyl group, the halogen atom, and the two ethyl ether molecules around the magnesium atom (Fig. 1) [3]. The diethyl ether molecules are always in the CG conformation for these compounds, a conformation that is not known for pure diethyl ether. The reason for the conformational change is the coordination of the diethyl ether molecules with the magnesium atom. The coordination effect increases the frequency of the CH_2 stretching and torsion vibrations and decreases the frequency of the skeleton vibrations through a charge transfer from the oxygen to the metal atom. Diethyl ether absorption bands are not particularly sensitive to the deuteration of the organic group of the Grignard compound or to the chemical substitution of the halogen atom, except for the C—O—C deformation vibration band at 508 cm^{-1}, for which a slight frequency shift can be observed as a function of the compound studied. Accordingly, the ethyl group attached to the magnesium atom is not very sensitive to the deuteration of the diethyl ether, or to the nature of the halogen. But the frequencies observed for the C_2H_5 group were different from those observed for corresponding hydrocarbons. The frequencies of the C—H stretching and deformation vibrations are lower than for hydrocarbons, and the skeleton stretching vibrations frequencies are slightly higher.

The bands corresponding to the vibrations of ethylmagnesium halides involving the magnesium atom are found at frequencies lower than 500 cm^{-1}. Table 1 shows a comparison of these frequencies for the infrared and Raman spectra (X = Br, I). The analysis of the frequencies shows that the tetrahedral arrangement around the metal atom is very similar for both compounds. It also shows that the nature of the halogen has a large influence on the Mg—X stretching vibration, with a shift of 20 cm^{-1} from the bromide to the iodide. The other vibrations involving the Mg atom are only slightly affected.

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Table 2 Frequencies of the Mg—X Stretching Vibration Bands in the Raman Spectra of $C_2H_5MgX{\cdot}2(C_2H_5)_2O$ (X = Br and I) in the Solid (90 K) and Liquid (300 K) State

State	$EtMgBr{\cdot}2(Et)_2O$	$EtMgI{\cdot}2(Et)_2O$	$EtMgCl{\cdot}2(Et)_2O$
Solid	248	224	225
Liquid	244	227	263+241

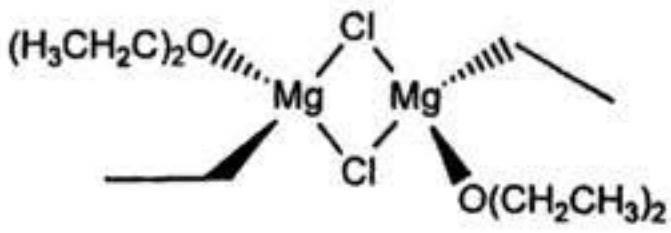


Figure 2 Crystalline structure of $C_2H_5MgCl{\cdot}2O(CH_2CH_3)_2$.

The analysis of the same compounds, in the liquid state, at 300 K did not reveal enough differences to suggest a change in their structure. The spectra of the samples in the solid state (90 K) have a better resolution, which is due to the crystalline correlation effect and the decrease in temperature. The similarity of the frequencies observed for the Mg—X stretching vibration bands in the Raman spectra (Table 2) of the liquids and solids confirm the similarities of the structures. In the liquid state, the diethyl ether molecules are still in the GG conformation.

The Raman spectra of $C_2H_5MgBr{\cdot}2(C_2H_5)_2O$ in the liquid state and in a diethyl ether solution were also compared. The spectrum of the solution corresponds to a superposition of the spectra of pure diethyl ether and of $C_2H_5MgBr{\cdot}2(C_2H_5)_2O$. No concentration effects were observed, indicating that the Schlenk equilibrium favors the Grignard form for the ethylmagnesium bromide.

The compound $C_2H_5MgCl{\cdot}(C_2H_5)_2O$ was also studied in the liquid and crystalline state and in solution in diethyl ether by Kress and Novak, using infrared and Raman spectroscopy [4]. In the liquid state (300 K) and in the vitreous state (90 K), this monoetherate has a dimeric cyclic structure obtained through the formation of chlorine bridges (Fig. 2). The diethyl ether molecules are in a GG conformation.

The Mg—Cl stretching vibration band is located between 290 and 270 cm^{-1} in the infrared spectrum (at 90 K) and at 263 and 241 cm^{-1} in the Raman spectrum (at 300 K). The location of these bands and their multiplicity is compatible with the dimer model proposed for this compound. The bands assigned to other vibrational modes involving the magnesium atom, namely the C—Mg and Mg—O stretching vibrations and the C—C—Mg deformation vibration, are very similar to those observed for $C_2H_5MgBr{\cdot}2(C_2H_5)_2O$. This observation is also consistent with the dimer model. The replacement of the bromine atom by a chlorine atom and the change in the degree of solvation of the molecule initiate only slight frequency shifts of the internal vibrations of the ethyl group attached to the magnesium atom and of the diethyl ether molecules.

The Raman spectra of diethyl ether solutions of ethylmagnesium chloride were very similar to that observed for the liquid. Furthermore, a change in the concentration of the

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solution from 1 to 6 *M* did not modify the spectrum significantly. These results show that the Schlenk equilibrium again favors the Grignard reagent form.

The spectrum of the crystalline form of the ethylmagnesium chloride is different from those observed for the liquid and for diethyl ether solutions. Major frequency shifts were observed for C—H symmetric stretching and CH_2 wagging vibration bands, and also for the C—C and the Mg—C stretching vibration bands of the ethyl group attached to the magnesium atom. Five absorption bands were observed in the Raman spectrum of the crystalline form that could not be found in the spectrum of the liquid. The comparison of the spectrum of the crystalline form with that of Eg_2Mg and $Et_2Mg{\cdot}Et_2O$ shows that the new bands can be assigned to vibrations of the ethyl group attached to the magnesium atom, but in a bridging position. There is also some evidence that the chlorine atoms are still in bridging positions between magnesium atoms. Therefore, it was concluded that the crystaline form consists of a complex association between two or more dimers through the formation of ethyl bridges.

The effect of the length of the organic group on the vibrational spectra of the Grignard reagents was completed by Kress and Novak through the study of $CH_3MgX{\cdot}2(C_2H_5)_2O$ (X = Br, I) [5]. At 90 K, the Raman spectra show that $CH_3MgBr{\cdot}2(C_2H_5)_2O$ exhibits two different crystalline forms (I and II), whereas for $CH_3MgI{\cdot}2(C_2H_5)_2O$, only form I could be observed. The structure of the form I crystals is very similar to that observed for $C_2H_5MgBr{\cdot}2(C_2H_5)_2O$, with a tetrahedral arrangement of the halogen atom, methyl group, and the two diethyl ether molecules around the magnesium atom. For this crystalline form, the diethyl ether molecules are still in a GG conformation. The nature of the halogen atom and the nature of the organic group (deuterated or not) attached to the magnesium atom do not have much influence on the frequencies and intensities of the bands assigned to the internal vibrations of the diethyl ether molecules. The frequency shift observed for the C—O—C deformation vibration is caused by the coupling with the Mg—C stretching vibration.

The deuteration of the methyl group of the methylmagnesium bromide has led to a complete vibrational assignment. The frequencies of the bands assigned to the methyl group are almost identical for the bromide and the iodide; however, their frequencies are much lower than the corresponding vibrations of alkane methyl groups, such as ethane or propane. This is probably due to the ionic character of the methyl group attached to an electropositive magnesium atom.

The vibrations involving the magnesium atom of $CH_3MgBr{\cdot}2(C_2H_5)_2O$ are found below 600 cm^{-1}. Table 3 shows the frequency of these vibrations. From Tables 1 and 3, it can be observed that the frequencies of the infrared and Raman bands corresponding to these vibrations are very similar, except for the Mg—C stretching vibration band, which is higher for the methyl groups than for the ethyl groups, owing to the lower molecular weight of the methyl groups. A slight frequency shift is also observed for the MgO_2 stretching vibrations, which is probably due to a coupling effect of the methyl group.

The large differences observed between the Raman spectra of form I and form II crystals of $CH_3MgBr{\cdot}2(C_2H_5)_2O$ indicate the variations in the molecular structure. Frequency shifts were observed mainly for the bands assigned to vibrations of the diethyl ether molecules. Small shifts were also observed for other vibrations, namely, Mg—C stretching vibration and the MgO_2 asymmetric stretching vibration. It was suggested that, in form II, the diethyl ether molecules adopt a TG or TT conformation. An equilibrium between the *gauche* and *trans* conformations was proposed to explain the spectral results, along with the similarity of the volumes occupied by the Br and CH_3 groups.

The analysis of the spectra obtained for the liquids (at 300 K) and the diethyl ether

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Table 3 Frequencies of the Infrared Bands Observed for the Vibrations Involving the Magnesium Atom in $CH_3MgX \cdot 2(C_2H_5)_2O$ at 90 K

	Infrared		Raman		
Assignment	CH_3MgBr	CH_3MgI	CH_3MgBr (form I)	CH_3MgBr (form II)	CH_3MgI
μ MgC	—	510	508	499	515sh
μ_{asym} MgO_2	304	295sh	303	294	—
μ_{sym} MgO_2	289	287	288	—	286
μ MgX	246	229	248	249	231
δ MgO_2	—	—	—	144	140
δ CMgX	—	—	—	114	113

Table 4 Frequencies of the New Bands Observed from Different Reactions Under Argon

Reaction	μ_{asym} C—H	μ_{sym} C—H	δ_{asym} CH_3	δ_{sym} CH_3
$Mg+CH_3I$	2892	2800	1305	543
$Mg+CD_3I$	2102	2048	990	418
$Mg+CH_3Br$	2886	2800	—	541
$Mg+CD_3Br$	2102	—	—	418
$Mg+CH_3Cl$	—	2805	1306	530
$Ca+CH_3I$	—	—	1305	420, 380
$Sr+CH_3I$	—	—	1305	320
$Sr+CH_d{}^3Br$	—	—	—	320

solutions of form I and II shows that they are similar to the ethylmagnesium bromide spectra. Only a slight difference was observed between the spectra of the liquids at 300 K and those of the form I crystals at 90 K. The structure of the methylmagnesium bromide and iodide in the liquid form is similar to ethylmagnesium bromide. The differences between the liquids and the solids were explained in terms of temperature variations and changes in the physical state. No significant change was observed in the Raman spectra of the solutions as a function of the concentration.

To study unsolvated Grignard species, Ault examined the reaction of magnesium with methyl halides in argon matrices [6]. The reaction of magnesium with CH_3I, CD_3I, CH_3Br, CD_3Br, and CH_3Cl; the reaction of calcium, strongium, or zinc with CH_3I; and the reaction of strontium with CH_3Br, led to infrared spectra with absorption bands that could not be assigned to the parent methyl halide, suggesting a distinct reaction in which the carbon–halogen bond is ruptured. The frequency and proposed assignment of these bands obtained through the different reactions are given in Table 4. From these results, a 1:1 reaction complex was suggested; but no conclusion could be made as far as the structure of the product was concerned, since no carbon–metal or metal–halogen bond could be observed.

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II. ALLYLIC GRIGNARD REAGENTS

The influence of the nature of the halogen, of the solvent, and of the concentration on the C=C stretching vibration region of the vibrational spectra of allylic Grignard reagents (C_3H_5MgX) was studied by Gross [7]. It was found that the concentration of the diethyl ether solution does not have any influence on the frequency of the C=C stretching vibration band of $CH_2=CH—CH_2—Mg—Br$, for concentrations ranging from 0.5 to 2.5 *N*. But unlike what was found for the aliphatic Grignard reagents, the nature of the halogen atom does have a large influence on the vibration of the organic group. The frequency of the C=C stretching vibration band shifts from 1591 cm^{-1} for the allylmagnesium iodide in an ethyl ether solution, to 1588 cm^{-1} for the allylmagnesium bromide, to 1580 cm^{-1} for the chloride derivative.

The solvent also has a strong influence on the position of the C=C stretching vibration band of the allylic Grignard. The frequencies observed for several solvents and different halogen groups are given in Table 5. The role of both the solvent and the halogen atom on the structure of the allylic Grignard was explained by the nucleophilic character of these groups and their action on the empty electronic shells of the magnesium atom. The competition between the donor character of these groups shifts toward the solvent in more basic solvents, and toward the halogen atom in less basic solvents. No conclusion was given for the environment of the magnesium atom and its bonding to the allyl group.

A mixture of 1-bromo-2-butene, *cis*- and *trans*-, and of 3-bromo-1-butene was reacted with magnesium and analyzed using infrared spectroscopy. The crotyl bromide has an absorption band at 1666 cm^{-1}, with shoulders at 1654 and 1637 cm^{-1}. These bands are assigned to the C=C stretching vibration of 1-bromo-2-*trans*-butene, 1-bromo-2-*cis*-butene, and 3-bromo-1-butene, respectively. The infrared spectrum of the Grignard reagent formed from these compounds shows a single band at 1535 cm^{-1} for the unsolvated species, and two bands at 1611 and 1632 cm^{-1} for the solvated species in diethyl ether solution. The smaller shift observed after the formation of the Grignard reagent for the crotylmagnesium bromide than for the allylmagnesium bromide can be explained by the electron donor character of the methyl group of the crotyl. It is even more obvious in the *trans*-crotyl than for the *cis*-form, owing to the easier electron transfer along a *trans*-compound. This assumption is also supported by the single absorption band covered at 1637 cm^{-1} for the Grignard reagent prepared from $(CH_3)_2C=CH—CH_2Br$, where no *cis–trans*-isomers exist.

The crotylmagnesium chloride prepared from the same starting reagents shows infrared spectra in the 1600 cm^{-1} region very similar to the bromide. Only small frequency

Table 5 Influence of the Solvent and of the Halogen Atom on the Frequency of the C=C Stretching Vibration Band of Allylic Grignard Reagents

Solvent	RMgI	RMgBr	RMgCl
Ethyl ether	1591	1588	1580
THF	1578	1571	1565
Butyl ether	—	1589	—
Triethylamine	—	1588	—

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Table 6 Influence of the Nature of the Halogen on the Frequency of the Magnesium–Halides Vibrations for Allylmagnesium Halides

	Infrared		Raman	
Assignment	C_3H_5MgCl	C_3H_5MgBr	C_3H_5MgCl	C_3H_5MgBr
μ Mg—X	250	210	260	210
δ Mg_2X_2	130	110	100	80

shifts (5 cm^{-1}) can be observed, of the same order of magnitude as the shifts observed in the allylmagnesium halides for different halogen atoms.

The vibrational spectra of allylmagnesium chloride and bromide in THF and in diethyl ether, and in the solid state were investigated by Sourisseau et al. [8,9] to obtain more information about the structure of the $C_3H_5^-$ ion, and to verify the nature of the metal–allyl bond. The absence of a C=C stretching vibration band around 1620 cm^{-1}, the absence of the out-of-plane C—H deformation vibration bands between 1000 and 900 cm^{-1} and the absence of characteristic vinyl CH_2 vibrations indicate that the pi electrons are delocalized along the entire allylic skeleton, and that both C—C vibrations and both CH_2 end groups are similar. However, the obtained spectra for these compounds are very different from those obtained for pi allylic complexes of transition metals. Thus, it is suggested that the interactions are of a different type, even though ionic in character.

The study of other allylmetal (magnesium, lithium, sodium) compounds in the solid state showed that the frequency of the stretching vibrations of the allyl group is dependent on the metal. It was proposed that the dependence is due to the negative charge of the ion, which increases from the magnesium compound to the lithium and sodium compounds. The low-frequency infrared spectra of the allylmagnesiums show an intense absorption band near 320 cm^{-1} and another, less intense, band near 160 cm^{-1}. The Raman spectra of the same compounds showed three intense bands between 430 and 310 cm^{-1} and three weaker bands between 190 and 120 cm^{-1}. The higher-frequency absorptions were assigned to allylmagnesium stretching vibrations, whereas the lower-frequency absorptions were assigned to the deformation vibrations.

For the allylmagnesium halides, two other bands were observed in the low-frequency region of the infrared and Raman spectra. The frequency of the bands was dependent on the nature of the halogen group (Table 6). The higher-frequency band was assigned to the Mg—X stretching vibration, although their frequency was much lower than those observed for other magnesium–halide complexes. The presence of halide bridges was proposed to explain the differences. The lower-frequency band was then assigned to the deformation of the Mg_2X_2 bridges.

The THF and diethyl ether solutions of the allylmagnesium halides were also studied between 0.3 and 3 *M*. Differences between the infrared spectra of the two solutions were assigned to the difference of solubility of the Grignard reagents in both solvents. The absorption bands observed for the THF solution were very similar to those observed for the solids, but were located at higher frequencies. Thus, it was proposed that the allyl group has a structure similar to that of the $C_3H_5^-$ anion. Furthermore, two new absorption bands were observed near 470 and 400 cm^{-1}. These bands were assigned to C—Mg stretching vibrations, and were used to explain stronger interactions between some new

Materiał chroniony prawem autorskim

species of the allyl groups and the magnesium atom in the solutions. These stronger interactions do not have a pure covalent assignment.

In another study, Sourisseau et al. compared the infrared and Raman spectra of the allylmagnesium halides with those of cyclopentadiene–metal complexes [9]. Although an average value of 320 cm^{-1} was found for the C—Mg stretching vibration of the allylmagnesium compounds, the $C_5H_5^-$—Mg stretching vibration appears at 360 cm^{-1}. This indicates that the magnesium–cyclopentadiene bonds are stronger than the allyl–magnesium bonds. A covalent bond between the center of the cyclopentadiene group and the metal atom, and an ionic bond between the $C_3H_5^-$ group and the metal atom was suggested to explain the observed difference.

III. OTHER GRIGNARD COMPLEXES

The reaction of benzoyl peroxide (BPO) with phenylmagnesium bromide leads to the formation of two different complexes [10]. Complex I is produced when the molar ratio of [PhMgBr]/[BPO] is 1.33:1.0, and is believed to exist as a dimeric state (Fig. 3), whereas complex II (Fig. 4) is obtained when the molar ratio is 0.66:1.0. The THF solutions of complexs I and II have very similar absorption bands, but differ significantly from the THF solution of BPO. The infrared spectrum of the BPO solution shows three absorption bands at 1792, 1770, and 1214 cm^{-1}. The infrared spectra of the complex I and II solutions show two absorption bands at 1640 and 1415 cm^{-1}. The 1640 cm^{-1} is assigned to the

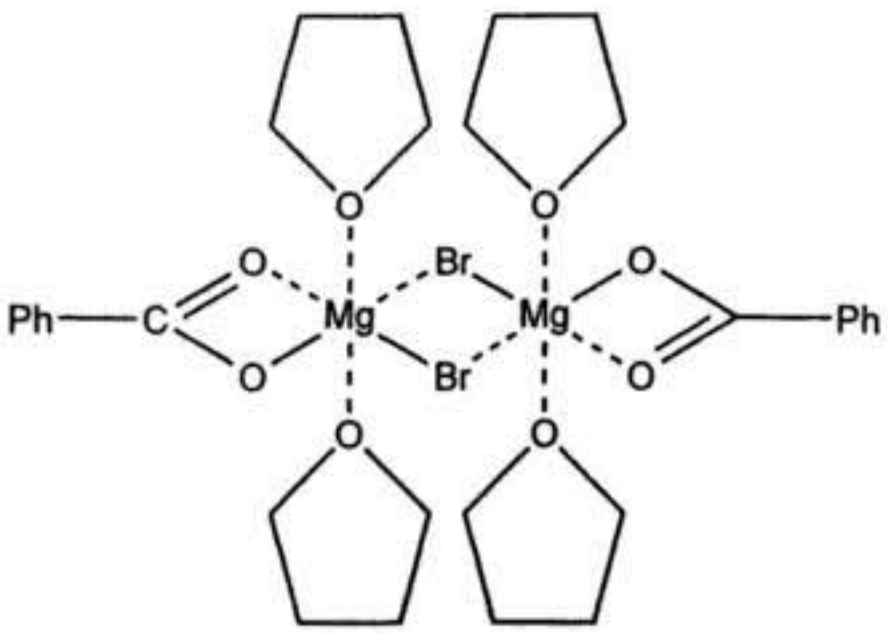


Figure 3 Structure of complex I of [PhMgBr]:[BPO].

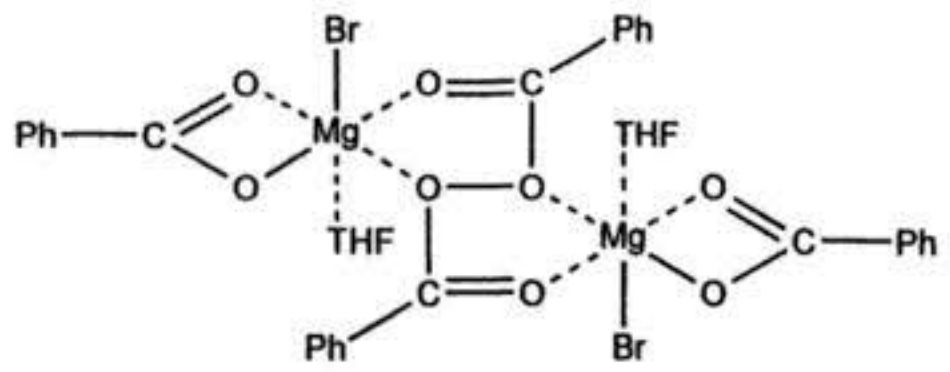


Figure 4 Structure of complex II of [PhMgBr]:[BPO].

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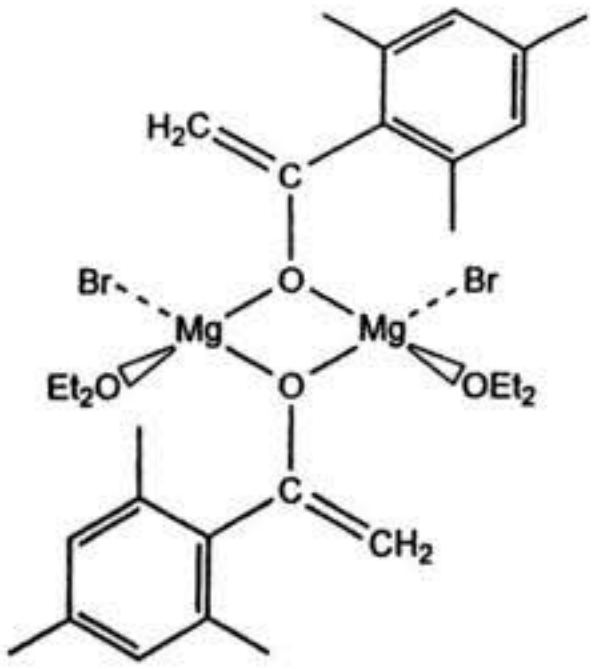


Figure 5 Grignard reagent obtained from the reaction of mesityl methyl ketone and ethylmagnesium bromide.

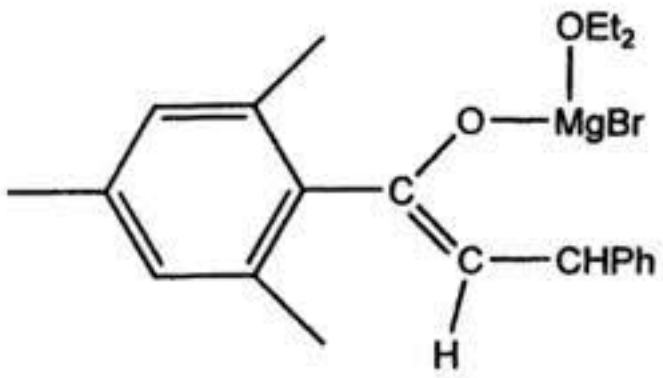


Figure 6 Structure of form I (Z) of the magnesium enolate.

carbonyl stretching vibration (1792- and 1770-cm^{-1} bands in BPO), whereas the 1415-cm^{-1} band is assigned to the C—O stretching vibration (1214 cm^{-1} in BPO). The observed shifts are due to the difference of bonding energies from BPO to the complexes.

The Grignard reagent derived from the reaction of mesityl methyl ketone and ethylmagnesium bromide was studied by Pinkus et al. [11]. From elemental analysis, it was found that the product formed was $C_{15}H_{23}O_2BrMg$ as a monoetherate. The dimeric state of the product was derived from a molecular weight analysis. The infrared analysis of the product showed the absence of a C=O stretching vibration, but the presence of two bands at 1645 and 1667 cm^{-1} that were assigned to a C=C enolic stretching vibration. The aromatic C=C stretching vibration was also observed at 1603 cm^{-1}. From this data, along with the NMR analysis, the dimeric state structure (Fig. 5) was suggested.

The enolization of several ketones using Grignard reagents was followed by Maroni-Barnaud et al. [12]. Several different structures were identified, depending on the starting ketone and the Grignard reagent used. Only the C=C stretching vibration regions of the infrared spectra were investigated. Three different spectral regions were identified. The 1625- to 1635-cm^{-1} region was assigned to the presence of conjugated dienes. The 1650- to 1660-cm^{-1} region was assigned to the C=C stretching vibration of an O-metal species. It was also observed that the intensity of the band found in this spectral region was increasing with the enolate content. A third spectral region was also identified (1670–1690 cm^{-1}), but no correlation with any structure could be derived.

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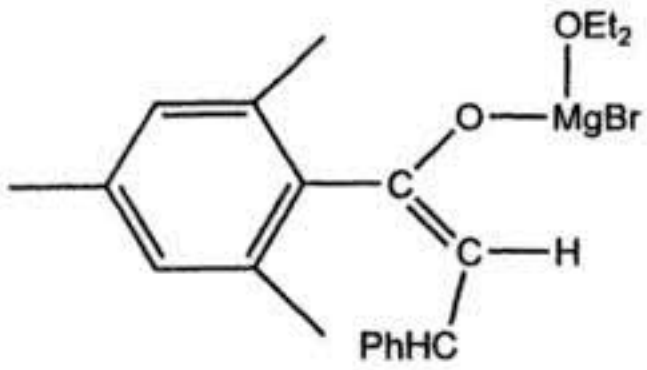


Figure 7 Structure of form II (E) of the magnesium enolate.

The structure of two different magnesium enolates (I and II) was studied by Pinkus and Wu using IR and NMR [13]. Form I (Fig. 6) which has a Z configuration, was obtained through the reaction of benzalacetomesitylene and phenylmagnesium bromide. Form II (Fig. 7) has an E configuration and was obtained from the reaction of 2,2-diphenylethyl 2,4,6-trimethylphenyl ketone with ethylmagnesium bromide. The bands at 1658 and 1650 cm^{-1} observed in the C=C stretching vibration region of the infrared spectra of both magnesium enolates are in excellent agreement with those observed previously for alkylmesityl ketones [11].

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8

Nuclear Magnetic Resonance Analyses of Grignard Reagents

JO-ANNE K. BONESTEEL

Elf Atochem North America, Inc., King of Prussia, Pennsylvania

I. INTRODUCTION

Since the 1950s, nuclear magnetic resonance (NMR) has found wide application in the solution of chemical problems, including numerous applications in the field of Grignard reagents. Chemical shift and spin–spin-coupling data enable the chemist to determine the location of magnetically active nuclei in a molecule of interest, and to obtain preliminary structural information often not readily deducible by other methods of spectroscopy.

Because of the quantum mechanical time scale of the NMR instrument, one can study certain time-dependent phenomena that are not generally accessible to the other branches of spectroscopy. Both molecular motion and chemical exchange may affect the appearance of NMR spectra. This unique characteristic has important implications in the study of Grignard reagents. This chapter is designed to provide information to the chemist who uses NMR as an investigative tool. It is assumed that the reader has a basic understanding of the theory and practice of NMR spectroscopy. Those who do not may find it helpful to consult one of several excellent texts on NMR spectroscopy [1–13].

In the experimental spectra and tables shown in this chapter, the chemical shifts given are those measured from the particular reference, without susceptibility corrections.

II. PROTON CHEMICAL SHIFTS IN GRIGNARD REAGENTS

A. Overview

Two phenomena have the most profound effect on the chemical shifts of protons [19].

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These parameters are:

1. The *local diamagnetic* contribution of the electron cloud around the proton under consideration (σ_{dia}^{local})
2. The effect of *neighboring* atoms and groups on the molecule (σ')

Within this approximation, the influence of substituents and neighboring atoms is twofold. First, they will affect σ_{dia}^{local} through changes of the electron density at the proton, caused by inductive and mesomeric mechanisms. Second, electron circulation induced by the external magnetic field, B_0, within these neighboring atoms and groups will give rise to magnetic moments (i.e., secondary fields that change B_{local} at the proton). Additionally, electric field and van der Waals effects may be considered, as well as the influence of the surrounding medium. Consequently, any change in proton screening may be expressed as a sum of several terms:

$$\Delta\sigma = \Delta\sigma_{dia}^{local} + \Delta\sigma_{magn} + \Delta\sigma_{el} + \Delta\sigma_{v} + \Delta\sigma_{med} \quad (1)$$

where the last four contributions stand for the magnetic field, electric field, van der Waals, and medium effects.

B. Internal Dynamics of Organic Molecules

1. Dynamic Processes in Organomagnesium Compounds and Carbocations

Initial measurements of ether solutions of methylmagnesium bromide and dimethylmagnesium are presented in Table 1 [14]. In agreement with earlier observations for alkylmagnesium bromides and the corresponding dialkylmagnesiums [15–19], the spectra of methylmagnesium bromide and of dimethylmagnesium are very similar, both in position of chemical shift and in ^{13}C–^{1}H-coupling constants. The position of the methyl signal for dimethylmagnesium was dependent on concentration [16,17] and moved to a higher field as the concentration

Table 1 Proton Chemical Shifts of Methyl Magnesium Compounds in Ether Solution[a]

Compound	Conc. mol/L	δ[a]/ppm	$J_{^{13}C\text{-}H/Hz}$	Temp (°C)	$\nu_{1/2}$[b]/Hz
CH_3MgBr	2.40	−1.54	107	~30	≤1
CH_3MgBr	0.70	−1.54	107	~30	≤1
CH_3MgBr	0.20	−1.53	107	~30	≤1
CH_3MgI	1.08	−1.53	107	~30	≤1
$(CH_3)_2Mg$	0.71	−1.38	105.5	~30	≤1
$(CH_3)_2Mg$	0.18	−1.61	105.5	~30	≤1
$(CH_3)_2Mg$	0.090	−1.41	105.5	~30	≤1
$(CH_3)_2Mg$	0.028	−1.50	105.5	~30	≤1
$(CH_3)_2Mg$	0.84	−1.40	105.5	33	≤1
$(CH_3)_2Mg$	0.84	−1.41	105.5	−29	≤1
$(CH_3)_2Mg$	0.84	−1.47	105.5	−54	2.2

[a]The proton NMR data were acquired on a Varian A-60 spectrometer with TMS as an internal standard.
[b]Line width at half height.
Source: Ref. 14.

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was lowered, suggesting that the extent of solvation or the degree of association of dimethylmagnesium varied with concentration.

a. Intramolecular Exchange Processes

The allylmagnesium bromide **1** consists of a quintet at δ 6.2 and a doublet at δ 2.5 ppm in an intensity ratio of 1:4, indicating the presence of an AX_4 system [20]. This observation is consistent with a rapid equilibrium involving the two isomers **1a** and **1b**.

$$\underset{\textbf{1a}}{\overset{1\quad 2\quad 3}{CH_2{=}CH{-}CH_2{-}MgBr}} \rightleftharpoons \underset{\textbf{1b}}{\overset{1\quad 2\quad 3}{BrMg{-}CH{=}CH_2{-}CH_3}}$$

Crotyl bromide and α-methylallyl bromide reacted with magnesium in ether to yield the same butenyl Grignard reagent [21]. Given the extraordinary behavior of the butenyl Grignard reagent in a variety of chemical reactions, Young and Roberts [22, 23] inferred that the correct structure was crotylmagnesium bromide, as confirmed by the infrared evidence [24] and ^{1}H-spectrum [21].

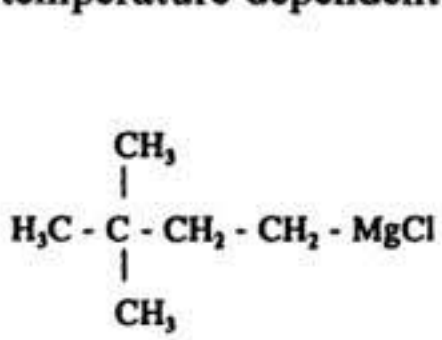
b. Temperature Dependence

The application of ^{1}H-NMR spectroscopy to the study of the structure of Grignard reagents is rendered difficult by the rapid intra- and intermolecular exchange processes that normally occur at room temperature. Evans et al. [25] attempted to overcome this difficulty through the use of fluorine-19 NMR spectroscopy, in the study of fluoroaryl Grignard reagents at low temperatures. Next, they described the low-temperature ^{1}H-spectra of several Grignard reagents in tetrahydrofuran (THF) and diethyl ether (DEE), from which it was possible to distinguish "RMgX" and "R_2Mg" species.

Ashby et al. [27] carried out a similar study on methylmagnesium bromide in diethyl ether. Unfortunately, precipitation precluded any quantitative measurements.

Evans et al. [28] reported the ^{1}H-NMR spectra of a variety of alkyl and aryl reagents in a number of coordinating solvents. These measurements were carried out over a considerable temperature range and, at the lowest temperatures, chemical exchange was on the ^{1}H-resonance time scale.

For 3,3-dimethylbutylmagnesium chloride **2**, the proton spectrum has been observed to be temperature-dependent [29,30]. At −53°C, an AA′BB′ system is obtained, whereas

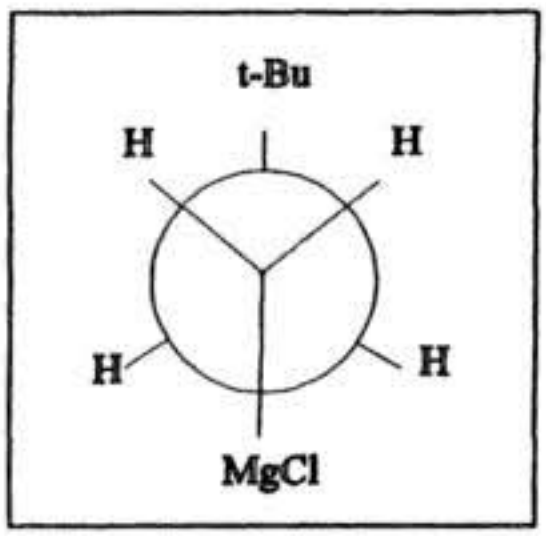


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3,3-dimethylbutylmagnesium chloride

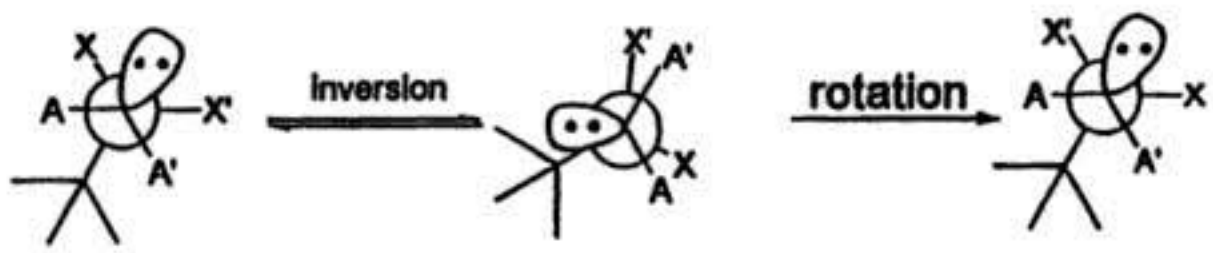
at 32°C, one observes a spectrum of the A_2X_2 type (Figure 1). For a simplified explanation, it may be assumed that, at low temperature, the compound exists predominantly in the *trans conformation* **3**. The observation of an AA′XX′ system is consistent with this conclusion. The transition to an A_2X_2 means that, at high temperatures, the effective chemical shift difference becomes zero. This indicates that for the spin–spin interaction between the A and X protons only one coupling constant exists. Therefore, the protons A and A′ and

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X and X′ must be magnetically equivalent, that is they exchange magnetic sites with one another. The most plausible mechanism for such an exchange is the inversion of the carbanion **4**⇌**5**, that is isoelectronic with an amine. The activation energy for this process



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was determined from the temperature-dependent line shape of the spectrum to be 48 ± 8 kJ mol^{-1} (11 ± 2 kcal mol^{-1}).

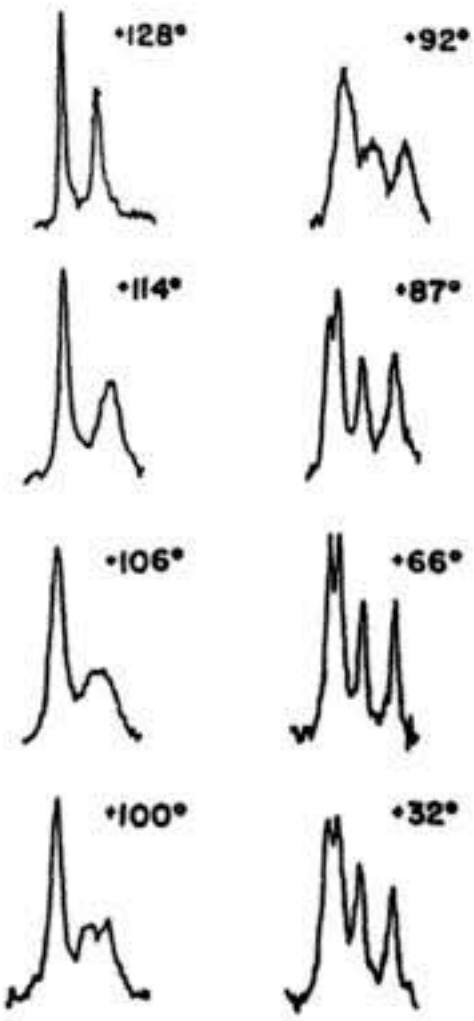


Figure 1 Spectra of CH_3-Mg protons of 2-phenyl-3-methylbutylmagnesium chloride in THF as a function of temperature. (From Ref. 30.)

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Table 2 The H^1-NMR Methyl Signals for Mixtures of Organometallic Compounds in Ether Solution

Compounds (conc., mol/L)	δ^a/ppm	$J_{^{13}C\text{-}H/Hz}$	Temp (°C)
$(CH_3)_2Mg$ (0.26) + LiBr (0.51)	−1.40	...	~30
CH_3MgBr (0.56) + CH_3Li (0.14)	−1.49	99	~30
CH_3MgBr (0.35) + CH_3Li (0.35)	−1.41	...	~30
CH_3MgBr (0.14) + CH_3Li (0.56)	−1.59	...	~30
$MgBr_2$ (1.42) + CH_3Li (0.95)	−1.55	108	~30
$MgBr_2$ (1.13) + CH_3Li (1.14)	−1.52	108	~30
$MgBr_2$ (0.71) + CH_3Li (1.42)	−1.38	105	~30
$MgBr_2$ (0.40) + CH_3Li (1.63)	−1.60	101	~30
$MgBr_2$ (0.07) + CH_3Li (0.70)	−1.75	...	~30

[a]The proton NMR data were acquired on a Varian A-60 Spectrometer with TMS as an internal standard.
Source: Ref. 14.

The ^1H spectrum of the methylene group of 2-phenyl-3-methylbutylmagnesium chloride [30] also shows a temperature variation suggesting changes in the rate of inversion (Fig. 1). In this case, the inverson at the $—CH_2—Mg$ center is slow even at +66°C, and the two methylene protons are magnetically nonequivalent owing to their proximity to a center of molecular asymmetry [31].

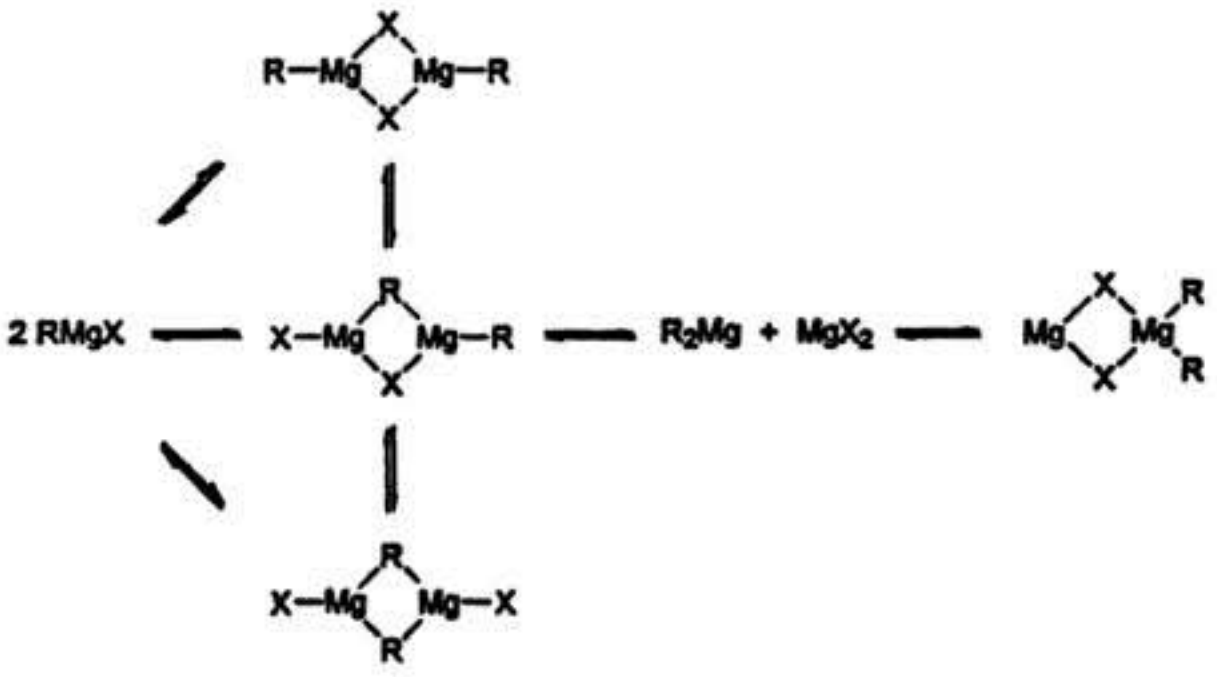
c. Intermolecular Exchange Processes

Whitesides et al. [14] examined the ^1H-NMR methyl signals of ether solutions containing the various mixtures of magnesium and lithium compounds. The data are summarized in Table 2. The chemical shifts and ^{13}C–^1H-coupling constant values observed for the various mixtures containing magnesium bromide suggest the presence of equilibria [Eq. (1 and 2)] that are shifted to the right.

$$2CH_3Li + MgBr_2 \rightleftharpoons 2LiBr + (CH_3)_2Mg \quad (1)$$

$$CH_3Li + MgBr_2 \rightleftharpoons LiBr + CH_3MgBr \quad (2)$$

The possible species present in solutions of Grignard reagents (small concentrations of ions being neglected) can be represented by an extended Schlenk equilibrium [25,32,33].



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Molecular weight determinations [34,35] indicate that Grignard reagents in THF are monomeric; consequently, only the simple Schlenk equilibrium [Eq. (3)] need be considered.

$$R_2Mg + MgX_2 \rightleftharpoons 2RMgX \tag{3}$$

However, in diethyl ether, dimeric or polymeric species are apparently present, except at low concentrations (below 0.1 *M*).

III. MAGNESIUM-25

A. Overview

The earliest studies of ^{25}Mg NMR were largely exploratory and used continuous-wave NMR technology [36–40]. In general, these studies suffered from a lack of instrumental sensitivity. Nevertheless, these exploratory studies demonstrated the ability of ^{25}Mg NMR to provide information on the chemistry of complexation. One of the first applications of Fourier transform techniques to ^{25}Mg-NMR was on aqueous Mg^{II} electrolytes (e.g., $MgBr_2$ and $MgCl_2$) [41]. Fourier transform NMR made it possible to study concentrations as low as 0.002 *M* in natural abundance Mg^{2+} solutions in less than 12 h.

Most earlier ^{25}Mg-NMR investigations concentrated on biological systems and inorganic complexes [3,4,9,12,13]. Recently, the chemical shift range of organomagnesium compounds has been determined [42,43]. The ^{25}Mg chemical shifts and line widths at half height, $\Delta\nu_{1/2}$, can be used to clarify the multiple bonding, coordination, and association behavior of organomagnesium compounds [42]. The importance of the solvent and the temperature at which the NMR measurement is taken should not be underestimated, because these parameters will affect the type of species present in solution, the chemical shift, δ, and the line width of the observed peak of the species.

B. Chemical Shifts and Line Widths

Table 3 presents ^{25}Mg line width and chemical shift data obtained as a function of the concentration of $MgBr_2$ and $MgCl_2$ [41]. Also included in Table 3 are the viscosities of the solutions investigated. The chemical shifts, when corrected for bulk susceptibility effects, vary over a total range of less than 1 ppm.

In THF, the compounds R_2Mg, RMgX, and MgX_2, where R is either an alkyl or an aryl group and X is a halogen, are monomeric over a wide range of concentrations [44]. The values of the ^{25}Mg chemical shifts, δ (^{25}Mg), in THF for the alkyl, aryl MgBr, and dibromide compounds relative to $MgSO_4 \cdot 7H_2O$ in D_2O, are between 0 and +100 ppm, whereas the cyclopentadienyl (Cp) compounds are between −30 and −90 ppm (Fig. 2 and Table 4). The line widths at half height, $\nu_{1/2}$, of the ^{25}Mg NMR signal of $MgBr_2$ in THF varies between 50 Hz at 280 K to 55 Hz at 340 K, with a minimum of 35 Hz at 330 K [45]. This indicates a transition from a quasi-octahedral [46] to a tetrahedral coordinated species as a consequence of the elimination of two molecules of THF at higher temperatures.

The structure for allylmagnesium species has been studied experimentally and theoretically [47, 48]. The ^{25}Mg-NMR of $(C_4H_7)_2Mg$ indicates that the allyl groups are σ-bonded to the magnesium (see ^{13}C-NMR discussion).

Biscyclopentadienyl magnesium species have an unusually narrow $\nu_{1/2}$ of 100–500 Hz. This is rationalized by penta-hapto bonding, $^5\eta$-Cp–Mg [42,43]. In these systems, ^{25}Mg-NMR spectroscopy provides a direct contribution to the discussion of whether the bonding is ionic or covalent [45].

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Table 3 Magnesium-25 NMR Data[a] for Aqueous Magnesium Salt Solutions

Conc. (m)[b]	$\Delta\sigma\nu_{1/2}$ (Hz)[c]	η (cP)	δ (ppm)[d]
$MgBr_2$			
2.70	6.8±0.3	2.04	0.4
2.30	6.1±0.2	1.77	0.5
1.97	5.4±0.2	1.57	0.4
1.64	5.0±0.2	1.43	0.3
0.90	3.9±0.2	1.19	0.1
0.47	3.6±0.2	1.10	0.0
0.10	2.7±0.3	1.01	0.0
$MgCl_2$			
4.10	7.2±0.3	5.5	0.0
3.60	5.9±0.3	4.45	−0.1
3.20	5.3±0.2	3.72	0.0
2.79	4.8±0.2	3.02	0.0
2.30	4.3±0.3	2.40	0.0
1.30	3.8±0.2	1.65	0.0
0.47	3.2±0.2	1.11	0.0
0.10	2.7±0.3	1.05	0.0

[a]Natural abundance ^{25}Mg at 5.51 MHz.
[b]Concentration in molality.
[c]Line widths were determined as the full-width at half-height. Tabulated values represent the average of at least three determinations, with the error limits the standard deviation of the measurement.
[d]Chemical shifts (±0.1 ppm) relative to the signal for $Mg(ClO_4)_2$, extrapolated to infinite dilution. More positive values refer to lower shielding. Bulk susceptibility corrections have been made.
Source: Ref. 41.

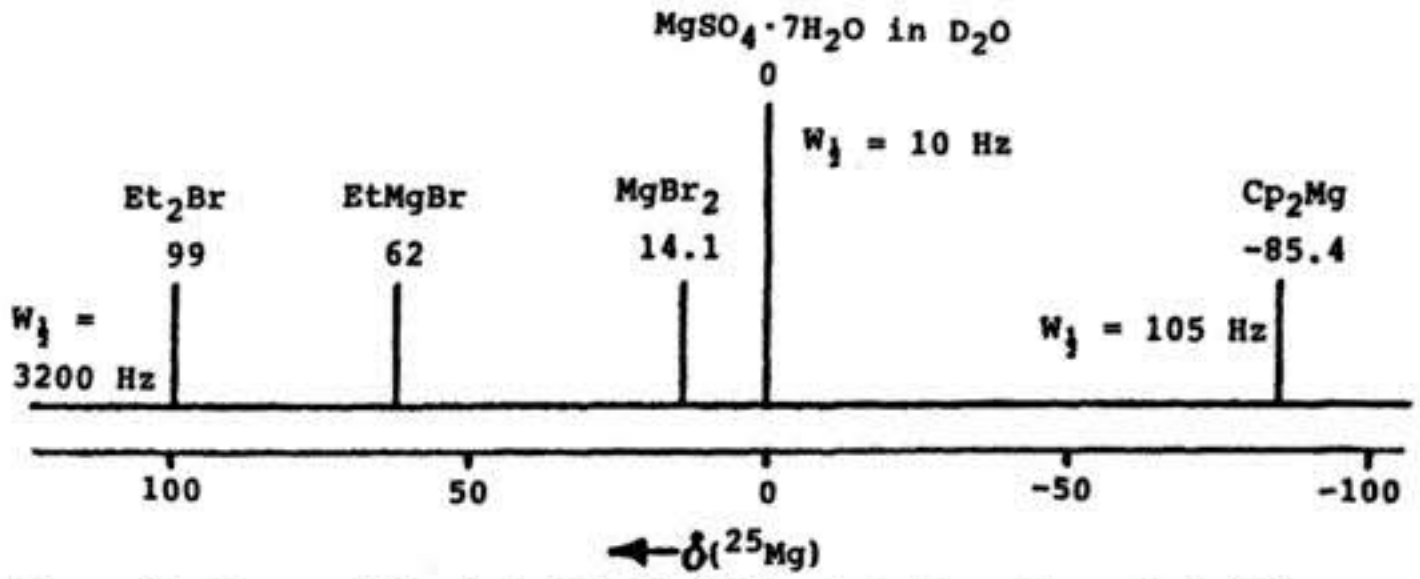


Figure 2 Range of chemical shifts for ^{25}Mg derivatives. (From Ref. 42.)

C. Schlenk Equilibrium

Spectroscopy by ^{25}Mg-NMR has considerable advantages over ^{1}H- and ^{13}C-NMR spectroscopy [47, 49, 50] in the study of the Schlenk equilibria (see Chapter 13), because all three species that are typically associated with the equilibria can be recorded and identified by their characteristic chemical shifts.

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Table 4 Magnesium-25 Nuclear Magnetic Resonance Data[a] for Organic Solutions of Magnesium Compounds Relative to $MgSO_4 \cdot 7H_2O$ (0.18 mol/L) as External Reference

Compound	Solvent	Temp (K)	δ (^{25}Mg) (ppm)	$\Delta\nu_{1/2}$ (Hz)
R_2Mg				
$(C_2H_5)_2Mg$	THF[b]	310	99.2	3200
$(nPr)_2Mg \cdot TMEDA$[c,d]	TMEDA[d]	353	110.0	1700
$(C_4H_7)_2Mg$[e]	THF	310	70.4	2000
$Ph_2Mg \cdot Dioxane$[f]	Dioxane	353	108.0	2800
Cp_2Mg[g]	Toluene[h]	310	−85.4	105
$Cp_2Mg \cdot nTHF$	THF	310	−33.8	90
Cp_2Mg	THF	310	−78.3	350
$Cp_2Mg \cdot TMED$[i]	TMED[i]	310	−25.8	50
$Cp_2Mg \cdot TMBD$[j]	Toluene	213	−31.0	140
$Cp_2Mg \cdot Dioxane$	Dioxane	310	−48.5	~300
$Cp_2Mg \cdot DME$[k]	DME[k]	310	−49.4	75
$Cp_2Mg \cdot nPMe_3$[l]	PMe_3[l]	310	−60.9	220
$Cp_2Mg \cdot nOEt_2$[m]	Et_2O[m]	310	−75.3	150
$^{R}Cp_2Mg$[n]	Toluene[h]	310	−79.6	750
$^{R}Cp_2Mg \cdot nTHF$	THF	310	−36.7	250
$[Mg(acac)_2]$[o]	THF	310	6.3	650
$RMgR'$				
$CpMgEt$[g,p]	THF	310	−4.0	1500
$CpMg(C_4H_7)$[g,e]	THF	310	−14.7	710
Cp^*MgEt[q,p]	THF	310	−10.0	1300
(Indenyl)$MgEt$[p]	THF	343	26.6	900
$CpMgMe \cdot TMEDA$[g,r,d]	TMEDA[d]	310	15.0	1100
$CpMg \cdot OEt_2$[m]	OEt_2[m]	310	−34.1	160
RMgBr				
MeMgBr[r]	THF	310	67.8	1900
EtMgBr[p]	THF	340	56.2	1100
$(C_3H_5)MgBr$[s]	THF	310	29.7	1000
CpMgBr[g]	THF	310	−26.8	60
$^{R}CpMgBr \cdot TMEDA$[n,d]	TMEDA[d]	310	−15.0	300
$(CpMgBr \cdot OEt_2)_2$	Toluene	310	−37.9	140
MgX_2				
$MgCl_2$	THF	310	16.4	350
$MgBr_2$	THF	310	14.1	36

[a]Natural abundance ^{25}Mg at 24.49 MHz (11.4 tesla).
[b]THF = tetrahydrofuran.
[c]nPr = *n*-propyl.
[d]TMEDA = tetramethyl ethylene diamine.
[e]C_4H_7: $H_2C=C(CH_3)CH_2$.
[f]Ph = phenyl.
[g]Cp:cyclopentadienyl = C_5H_5.
[h]Solvent is a mixture of toluene and deuterated toluene.
[i]TMED = 1,2-bis(dimethylamino)ethane.
[j]TMBD = 1,3-bis(dimethylamino)butane.
[k]DME = dimethoxylethane.
[l]PMe_3 = trimethylphosphine.
[m]$OEt_2 = (C_2H_5)_2O$.
[n]^{R}Cp:η^5-1,2,4-$[Si(CH_3)_3]C_5H_2$.
[o]acac = $(CH_3CO)_2CH_2$.
[p]Et = ethyl.
[q]$Cp^* = (CH_3)_5C_5 = Me_5C_5$.
[r]Me = methyl.
[s]$C_3H_5 = H_2C=CHCH_2$.
Source: Refs. 42, 43, 51.

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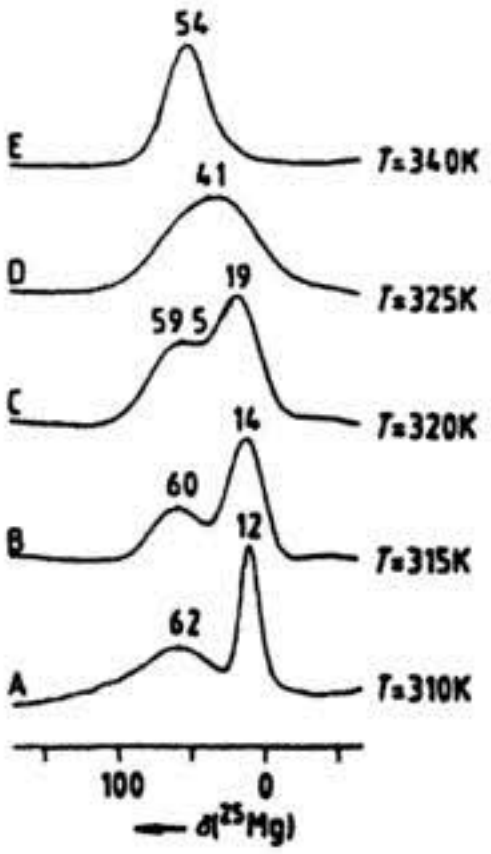


Figure 3 ^{25}Mg-NMR spectra (24.49 MHz) of a 3.6 *M* solution of EtMgBr in THF at various temperatures. At 310 K (A) the RMgX and MgX_2 species are directly identified in the presence of one another. The presence of R_2Mg follows from the coalescence behavior (B–D), and the high-temperature spectrum (E). (From Ref. 42.)

The ^{25}Mg-NMR spectra of organomagnesium halides (Grignard compounds) are a function of the concentration and temperature [44,51]. For EtMgBr, three species of the Schlenk equilibrium can be detected concurrently at 310 K [41] (Fig. 3). The resonances for EtMgBr ($\delta = 62$) and $MgBr_2$ ($\delta = 12$) are resolved. The broader signal of Et_2Mg is overlapped by the EtMgBr signal. Direct evidence for the presence of Et_2Mg is provided by the spectrum at 340 K (see Fig. 3). With increased temperature, the equilibrium shifts in the direction of EtMgBr [28,44], an average signal is found at 54 ppm. Further proof is obtained by comparing the ^{25}Mg-NMR data of EtMgBr with that of MeMgBr. The equilibrium constant for MeMgBr is larger than EtMgBr ($K \approx 30$ vs. $K = 3.1$) [28,44], with the resulting ^{25}Mg-NMR averaged signal for MeMgBr of $\delta = 67.8$, even at 300 K.

For CpMgBr, the ^{25}Mg-NMR signal is further removed from $MgBr_2$, and the line width is narrow enough to quantify the Schlenk equilibria constants [42]. For a 1.38 *M* solution of CpMgBr in THF, there are signals at $\delta = 16.3$ (2 mol%, $MgBr_2$) and -26.8 (98 mol%, CpMgBr). When a 1:1 mixture of Cp_2Mg and $MgBr_2$ is made in THF, the same chemical shifts, line widths, and integration are formed. The equilibrium constant is estimated at $K = 10^5$, which is in agreement with the value obtained by extrapolation to 298 K.

IV. CARBON-13

A. Overview

Carbon-13-NMR is a routine means of characterizing organometallic compounds, as well as a mechanistic probe [52–56]. The sensitivity of ^{13}C-NMR is reflected in the wide range of chemical shifts and scalar coupling constants, J_{C-X}, that allows for evaluation of subtle changes in the organometallic species at the M—C bond. This sensitivity has allowed organometallic chemists to evaluate fluxional processes and electron delocalization in

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paramagnetic species. Some of the advantages of ^{13}C- versus ^{1}H-NMR for organometallic species are direct M–C bond evaluation, evaluation of unsaturated organic species, signal dispersion is much greater (chemical shift), and hybridization of the carbon atoms can be obtained from the $^{1}J_{CH}$-coupling constant.

B. Chemical Shifts

1. Background

To a good approximation, three terms dominate the ^{13}C-NMR chemical shifts: diamagnetic, paramagnetic, and anisotropy shielding terms [57]. Lamb developed a theoretical expression for the *diamagnetic* term that focuses on the electron density at a specific nucleus [58]. Therefore, one would expect the carbon's hybridization to have a large chemical shift effect. Obviously, electron deficiency in a carbocation will profoundly effect the chemical shift [59–62].

The *paramagnetic* term depends on the number of electrons in the 2p orbital and multiple bond contributions as well as the average excitation energy ΔE. Therefore, this term will have a significant deshielding effect on π systems. For further discussion the reader is referred to Pople's reference [63].

The third term *anisotropy* includes the contribution of electron currents on neighboring atoms or functional groups. This neighboring-group effect is most pronounced at the α-carbon and diminishes by the inverse cube of the distance [57]. Molecular geometry also contributes to the anisotropy term. Increasing steric bulk of the alkyl groups or increasing the electron-withdrawing groups generate a downfield shift [64]. Crowding of shielding heteroatoms reinforces an upfield shift. Intramolecular hydrogen bonding will also affect this term. Therefore, there can be significant effects on the chemical shift by changes in concentration, solvent, pH, and such.

2. Experimental

Roberts et al. [65] studied aliphatic Grignard reagents in the presence of hexamethylphosphoramide (HMPA; Table 5). These solutions were thought to exist as RMgX on the basis of ^{13}C-NMR data, which is consistent with the ^{1}H-NMR data. Regiochemical data can be obtained by ^{13}C-NMR analysis, as in the reaction product of *cis*-4-*t*-butylcyclohexyl chloride and magnesium. In this case, there were no 1,3-diaxial steric compression shifts, indicating that only the *trans*-isomer was formed. Initial work on allylmagnesium bromide indicates the existence of an ion pair $(C_3H_5^-)(MgBr^+)$ in diethyl ether solution.

Schlosser et al. [47] attempted to elucidate the bonding between the metal and the carbon skeleton for organometallic allylic species (Structure 4). Using the isotopic perturbation technique developed by Saunders et al. [66–68], Schlosser sought to distinguish between classic and nonclassic carbocations. The lower zero point energy of the C–D bond relative to the C–H bond [69, 70] results in a preference for an olefinic C–D bond versus a saturated C–D bond. Therefore, with the introduction of deuterium into one of the allylic termini, the proportion of the metallomer (Fig. 4b) should increase at the expense of c (see Fig. 4) if they are present in equilibrium (dynamic isotopic effect). Independently of the exchange rate, separate signals should appear for the two terminal carbon nuclei to the right and left of the original signal. In the symmtric structure (see Fig. 4a), the deuterium would lead to a slight, isotopic specific, upfield shift (static isotopic effect).

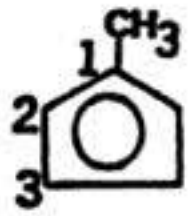
The data from the spectra are shown in Table 6. The monohapto structure (σ-complex) is observed for allylmagnesium bromide in THF or diethyl ether. The chemical shift change

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Table 5 Chemical Shifts of Alkyl Grignard Complexes[a]

Complex	C(1)	C(2)	C(3)	C(4)	C(5)	Ref.
CH_3MgI[b]	14.5					65
C_2H_5MgBr[b]	−2.9	12.2				65
n-C_3H_7MgBr[b]	11.3	21.1	21.1			65
n-C_4H_9MgBr[b]	5.9	31.6	30.6	13.2		65
n-$C_5H_{11}MgBr$[b]	7.4	28.5	40.3	22.7	13.4	65
iso-C_3H_7MgBr[b]	8.9	22.9				65
CyclohexylMgCl[b]	24.4	34.0	30.9	28.6		65
4-*t*-butylcyclohexyl MgCl[b,c]	22.9	34.5	31.8	49.6		65
Allyl MgBr[b]	57.5	113.8	57.5			65
Cyclopentadienyl MgBr[b]	105.5					65
Cyclopentadienyl MgCl	103.8					49
$CH_3C_5H_4MgCl$[d,e]	116.1	104.1	101.6			49
1,3-dimethylcyclopentadienyl MgBr[e,f]	114.4	103.2		101.4		49

[a]All chemical shifts in parts per million.
[b]Data converted from CS_2 standard (192.8 ppm).
[c]$C(CH_3)_3$, $\delta = 32.0$ ppm; $C(CH_3)_3$, $\delta = 27.6$ ppm.
[d]$CH_3\delta = 11.1$ ppm.
[e]See diagrams for numbering.
[f]$CH_3\delta = 11.2$ ppm.





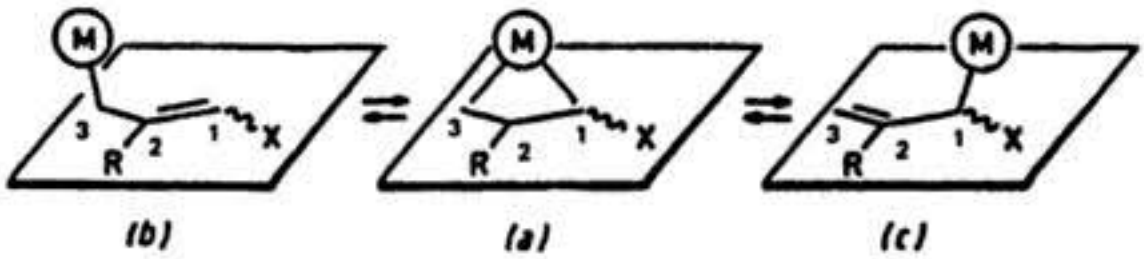


Figure 4 Equilibration of the allyl group in an organometallic complex. (From Ref. 47.)

indicates an equilibrium distribution of (1b)-MgBr/(1(c)-MgBr of 51:49–52:48. The crotyl and prenyl species gave similar results. Thus, as was already determined by Roberts et al. [20,21,71] on the basis of proton NMR, the σ-complex with the magnesium attached to the primary carbon is the preferred allylic Grignard reagent structure. The relative upfield shift of the $\delta(C^3)$ signal suggests a certain accumulation of electron density at the substituted end of the allylic moiety. A polarizing interaction between the metal and double bond (partial valence) may also be considered since the downfield shift of the $\delta(C^2)$ signals is consistent with this effect.

Grant et al. [73] attributed the large chemical shifts of C(1) and C(2,6) in the ^{13}C-NMR of pheylmagnesium chloride to the changes in the average excitation energy (Table 7). Another system, cyclopentadienylmagnesium halide (C_5H_5MgX) does not distinguish any of the intermediate species that might exist, and only one peak is observed

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Table 6 Carbon-13 NMR Chemical Shift Data of Grignard Reagents in THF at 25°C[a,b]

M	X	Structure	δ (C^1)	δ (C^2)	δ (C^3)	δ (CH_3)	δ (C^1)
H[b]	H	Propene	19	13.5	115		
MgBr	H	Allyl	57.5[c]	149.5	57.5[c]		
MgBr	D[d]	Allyl	58.0	149.5	56.6		
MgBr	H[e]	Allyl	58.7	148.2	58.7		
MgBr	D[e]	Allyl	59.1	148.3	57.7		
H[b]	H	2-Butene		124	124	11	
		2-Butene		125	125	16	
MgBr[f]	H	Crotyl		102	141	15	
H[g]	H	3-Methyl-2-butene	17	119	132	17	11
			17	119	132	26	16
MgBr[g]	H	Prenyl	16	135	107	[h]	17

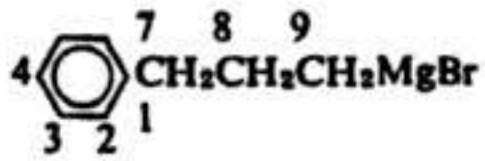
[a]Chemical shifts are relative to TMS.
[b]Chemical shifts of hydrocarbons are given for comparison.
[c]Mixed signals arising by a fast and reversible transition between two mirror-image structures; frozen structures would appear at 22 and 92 ppm for δ (C^1) and δ (C^3), respectively
[d]Deuteration in the X position leads to splitting of the δ(C) signal to a 1:1:1 triplet ($J = 21$–23 Hz).
[e]^{13}C NMR chemical shift in diethyl ether solutions from Ref. 72.
[f]Where two series of numbers are given for a crotyl derivative, the upper values apply to the *endo*-isomer and the lower for the *exo*-isomer.
[g]The upper value in the $\delta(CH_3)$ column of prenyl derivatives refers to the *endo*- and the lower value for the *exo*-isomer.
[h]Not recognizable at 25°C owing to excessive broading by coalescence; on cooling (to −30°C) two separate signals appear at 18 and 26 ppm (the latter masked by THF) and a mixed signal appears at 22 ppm upon warming.
Source: Ref. 47.

Table 7 Chemical Shifts[a] of Alkyl Grignard Complexes

Complex	C(1)	C(2,6)	C(3,5)	C(4)	C(7)	C(8)	C(9)	Ref.
C_6H_5MgBr[b]	164.3	139.9	125.8	124.5				49
$C_6H_5CH_2MgCl$[c,d]	155.1	123.4	127.3	116.1	22.2			65
$(C_6H_5CH_2)_2Mg$[c,d]	155.2	123.2	127.4	115.9	21.9			65
$C_6H_5CH_2MgCl/HMPT$[c,d]	143.0	123.2	127.1	113.1	24.6			65
$C_6H_5CH_2CH_2MgBr$[c,d]	149.6	127.0	127.0	123.1	35.1	10.8		65
$C_6H_5(CH_2)_3MgBr$[c,d]	144.3	127.1	127.9	124.1	44.6	31.9	7.9	65

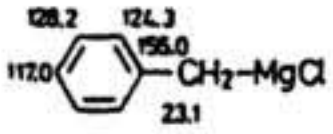
[a]All shifts in ppm.
[b]Data converted from benzene standard (128.5 ppm).
[c]Data converted from CS_2 standard (192.8 ppm).
[d]For numbering system see diagrams.
Source: Ref. 73.



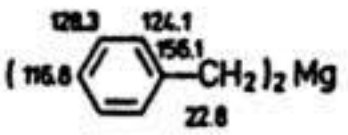


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Benzylmagnesium chloride



Dibenzylmagnesium (ppm)



7

in the ^{13}C-NMR. This is due to the fluxional behavior of the C_5H_5 ring and the NMR experimental time frame being too long to observe the intermediate species.

Roberts et al. [65] found that the chemical shifts of benzylmagnesium chloride and dibenzylmagnesium were nearly identical [Fig. 7]. This suggests that both existed primarily as R_2Mg in diethyl ether solution. The best qualitative description of the benzyl group from the benzyl Grignard reagent is as a benzyl anion. To support this description Roberts [65] calculated the electron density for a benzyl anion and correlated the electron density with a simulated ^{13}C-NMR, which correlates with the observed spectra for benzylmagnesium halide. However, there is some covalent character in the MC–C bond that prevents a precise match.

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9

Crystal Structures of Grignard Reagents

HAEWON L. UHM
Elf Atochem North America, Inc., King of Prussia, Pennsylvania

I. INTRODUCTION

The nature of Grignard reagents has been studied by both physical and spectroscopic techniques. These have shown that the reagent becomes a complex mixture of various magnesium compounds in solution [1]. The isolation and the characterization of these different compounds have helped in understanding the composition of the Grignard reagent solution. In recent years, crystallographic methods have given conclusive evidence for the presence of some of the components.

In simple terms, solutions of the Grignard reagent follow the Schlenk equilibrium [Eq. (1); 1]. The chemistry is dependent on many factors (e.g., solvent used). The compounds present in solution consist of the compounds depicted in Eq. (1) as well as compounds formed from the aggregation of these basic organomagnesium monomers into their dimers, trimers, and so on.

$$R_2Mg \leftrightarrow R_2Mg + MgX_2 \tag{1}$$

A considerable amount of important data can be gained from the crystal structures of organomagnesium compounds. The different bonding and coordination modes of Mg observed in the crystal structures give evidence for the possible structures of the compounds in solution. The reactivity of the complexes can also be inferred from the structure of the organomagnesium complexes. However, it must be realized that the crystals do not necessarily reflect the components in solution, and conclusions should be drawn only in conjunction with other data [e.g., nuclear magnetic resonance; NMR (see Chapter 8) and association measurements].

Briefly, several methods have proved successful in providing X-ray-grade organomagnesium crystals. These methods include slow sublimation, recrystallization from nonpolar solvents (alkanes or toluene), and mixed solvent systems in which a nonpolar

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solvent is added to a Grignard solution. Attempts to remove the coordinated solvent by heating under vacuum usually leads to the decomposition of the R group. Desolvation of RMgX (R = Me, Et; X = Cl, Br) gives a mixture of MgX_2 and $[MgR_2]_n$ [2]. The disproportionation is facile and follows the order Cl > Br > I and Me > Et. This reflects the propensity for ligand bridging.

Grignard reagents refer to compounds of the type RMgX, but the Schlenk equilibrium has indicated that diorganomagnesium compounds and MgX_2 are also present in Grignard solutions. An understanding of the chemical bonding requires the X-ray structures of both organomagnesium compounds and magnesium dihalide compounds; a discussion of all these compounds will be given in this chapter.

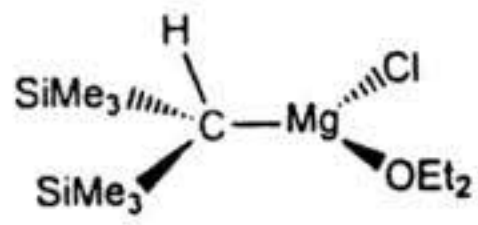
II. STRUCTURES OF HALOORGANOMAGNESIUM COMPOUNDS

The crystalline forms of Grignard reagents are compounds of the type RMgX. However, these compounds have proven to be difficult to crystallize. The crystallization process usually gave a MgX_2 precipitate and a soluble organomagnesium compound with a probable $[Mg_2R_3X]$ composition [3]. Such difficulties were surmounted by studying the Br derivatives.

A list of haloorganomagnesium compounds, with known crystal structures and their bond lengths and angles, is given in Table 1. Also included in Table 1 are compounds of the type RMgX·L, in which the coordinating solvent is replaced by a stabilizing ligand, L.

A. Tricoordinated Haloorganomagnesium

Steric factors lead to deviations from the normal tetrahedral coordination around the Mg atom. The crystal structure of bis(trimethylsilyl)methylmagnesium chloride monodiethyl etherate [Compound **1**] indicates that the compound has a trigonal planar geometry [4]. The unusual coordination results from the steric bulk of the trimethylsilyl group which prevents the coordination of a second ether solvent.



Compound 1

B. Tetracoordinated Halogenoorganomagnesium

Most of the crystal structures of Grignard compounds are four-coordinate and have a distorted tetrahedral structure. The monomeric complex has the structure $RMgXL_2$ [Compound **2**] where R is the organic group, X is the halide, and L is the coordinating solvent (i.e., THF or ethers) [1]. The compounds deviate slightly from ideal tetrahedral geometry. The C—Mg—X bond angle is greater than the regular tetrahedral values and the L—Mg—L bond angle is smaller. An example is the crystal structure of $EtMgBr(OEt_2)_2$ [Compound **3**], which has typical values for the bond lengths of Mg—Br (2.48 Å), Mg—C

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Table 1 Relevant Bond Lengths (Å) and Bond Angles (°) from the Crystal Structures of Haloorgano-magnesium Compounds

Compound	C—Mg—X	L—Mg—L	Mg—C	Mg—X	Mg—L	Ref.
$MgBrEt(OEt_2)_2$	125	101	2.15	2.48	2.04	5
$MgBrPh(OEt_2)_2$	n.a.	n.a.	n.a.	2.44	2.03	58
MgNrEt[(−)-sparteine]	115	84	2.24	2.48	2.15	6
MgCl(*t*-Butyl)-[(−)-sparteine]	115	84	2.19	2.33	2.17	57
MgBrEt-[(−)-α-isosparteine]	112	84	2.22	2.51	2.18	59
MgBrEt-[(+)-6-Bz-sparteine]	111	83	2.34	2.51	2.16	60
$[MgBrEt(NEt_3)]_2$	—	—	2.18	2.566, 2.567	2.15, 2.18	10
$[MgBrEt(OEt_2)]_2$	86.8	93.2	2.09		2.019	61
$[(Np_2Mg)_2\ (NpMgBr)_2]_n$	128.6, 100.6, 108.1, 122.6	—	2.20–2.29, 2.33–2.42	2.808, 2.818	—	12
$[EtMgCl{\cdot}MgCl_2{\cdot}(THF)_3]_2$	95.4, 125.9	89.6	2.19	2.44, 2.60	2.14, 2.11, 2.04	14
[(1-BrMg-2-pivaloyl-tetrahydroquinoline)·$(THF)_3$	104.3	91.9, 82.1	2.245	2.622	2.146, 2.136, 2.236	16
2-BrMg-1,3-xylyl-15-crown-4	128.2	—	2.10	2.517	2.12, 2.13, 2.33, 2.49	17
2-BrMg-1,3-xylyl-18-crown-5	—	—	2.176	2.597	2.126–2.331	17
CpMgBr·$Et_2NCH_2CH_2NEt_2$	125	83	2.21	2.63	—	7
[η^5-1,2,4-$(Me_3Si)_3$Cp]-MgBr·TMEDA	125	83	2.167	2.52	2.269, 2.230	8
[(η^1-Allyl)MgCl·TMEDA]$_2$	125.29	80.28	2.179	2.400, 2.694	2.211, 2.285	15
$(Ph_3C)MgBr{\cdot}(OEt_2)_2$	116.4	101.5	2.25	2.465	2.02, 2.04	9

(2.15 Å), and Mg—O (2.03 and 2.05 Å) as well as bond angles of Br—Mg—C (125.0°) and O—Mg—O (101°) [5].

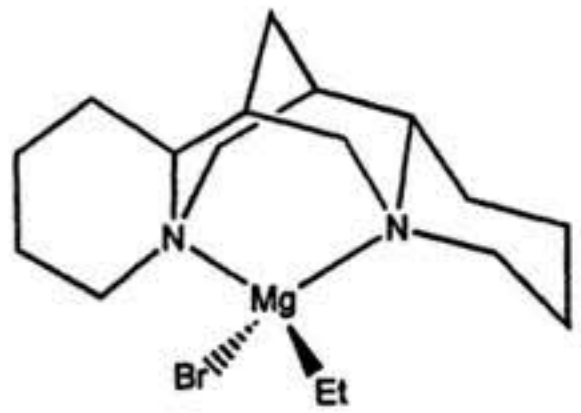


Compounds 2 and 3

Crystal structures are more numerous for compounds of the $RMgXL_2$, in which L is not restricted to coordinating solvents, but can include any neutral ligand. These compounds are generally solids and easier to crystallize into X-ray–grade single crystals.

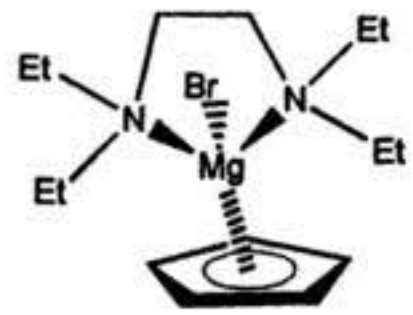
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The crystal structures are pseudotetrahedral, with the distortion being dependent on the steric requirements of the ligand L. The electronic effect of L can also result in variations in the bond lengths. The crystal structures of Grignard complexes with optically active sparteine ligands characterize the variations that can occur [6]. The EtMgBr[(−)-sparteine] compound [Compound **4**] has a typical Mg—Br of 2.48 Å, a longer Mg—C (2.24 Å), and Mg—O bond lengths (2.15 Å). The bond angles are smaller, probably due to the greater steric constraints imposed by the sparteine ligand.



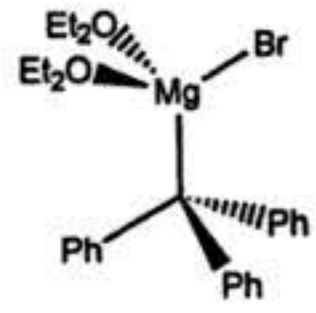
Compound 4

A similar distorted tetrahedral geometry was observed in the crystal structure of Grignard compounds with delocalized anionic ligands. The structure of $CpMgBr(Et_2NCH_2CH_2NEt_2)$ [Compound **5**] has the expected large Cp—Mg—Br angle (125°), but a much smaller N—Mg—N angle (83°) [7]. The ionic Cp ligand results in a longer Mg—Br bond (2.63 Å). A similar crystal structure was determined for the substituted Cp derivative, (η^5-1,2,4-$(Me_3Si)Cp$]MgBr·TMEDA [8].



Compound 5

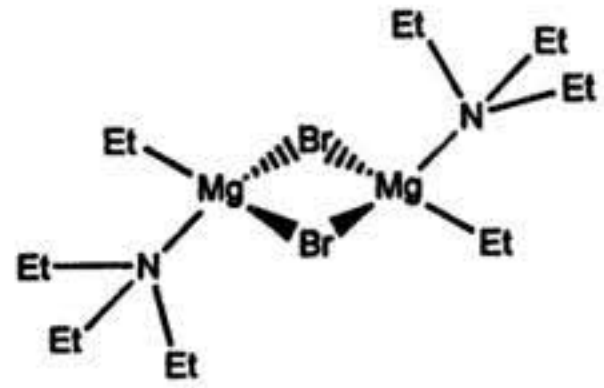
The normal distorted tetrahedral geometry was also determined in the crystal structure of $(Ph_3C)MgBr(OEt_2)_2$ [Compound **6**] [9]. It is of interest because it does not dissociate into its ionic parts (unlike Ph_3CLi), and there is no interaction between the Mg and the phenyl groups. The negative charge from the organic group is partially delocalized and results in a longer Mg—C bond length (2.25 Å).



Compound 6

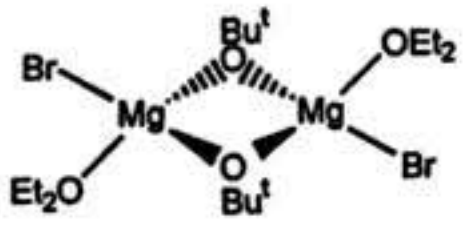
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Grignard compounds can also crystallize as dimers, usually when the recrystallization solvent is weakly coordinating (e.g., triethylamine or isopropyl ether). The structure consists of two tetrahedral Mg atoms that are bridged by two halogen (X) atoms, and each Mg atom has one terminal R group and one coordinating solvent. The crystal structure of [ethylmagnesium bromide·triethylamine]$_2$ [Compound **7**] has Mg—Br bonds of almost equal length (2.566 and 2.567 Å) and the Mg_2Br_2 has a square type formation (Mg—Br—Mg = 86.8° and Br—Mg—Br = 93.2°) [10].



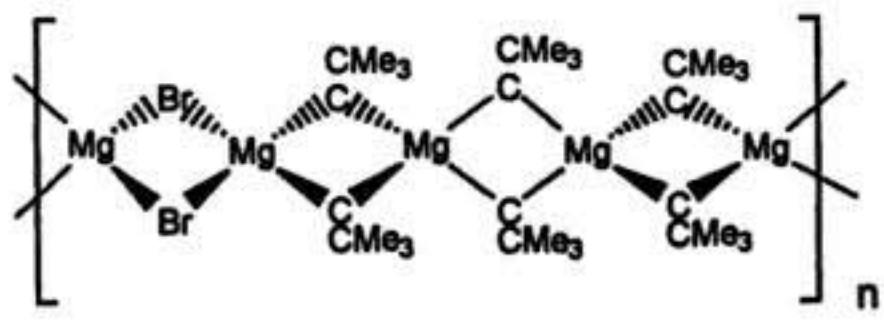
Compound 7

Grignard compounds with alkoxy organic groups do not have the same halogen bridged structure. An X-ray structure of [MgBr(OBu^t)(OEt$_2$)]$_2$ [Compound **8**] has demonstrated that it is an alkoxy-bridged dimer [11].



Compound 8

Grignard compounds of the type RMgX, with no coordinating solvent molecules, are inclined toward polymerization [12]. Growing single crystals of polymers is very difficult. The crystal structure of an adduct, [(Np$_2$Mg)$_2$·(NpMgBr)$_2$]$_n$ [Compound **9**], indicated that it was a polymer chain of three Mg_1Np_2 rings alternating with one Mg_2Br_2 ring [12]. It was the first crystal structure of a simple alkylmagnesium halide with no solvent molecules.

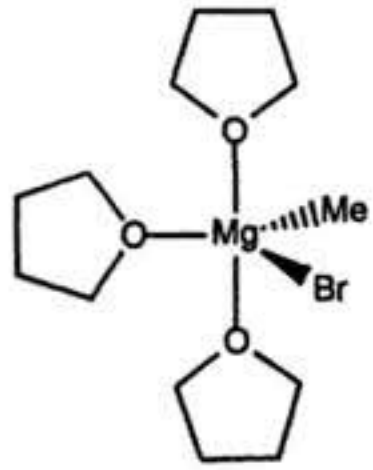


Compound 9

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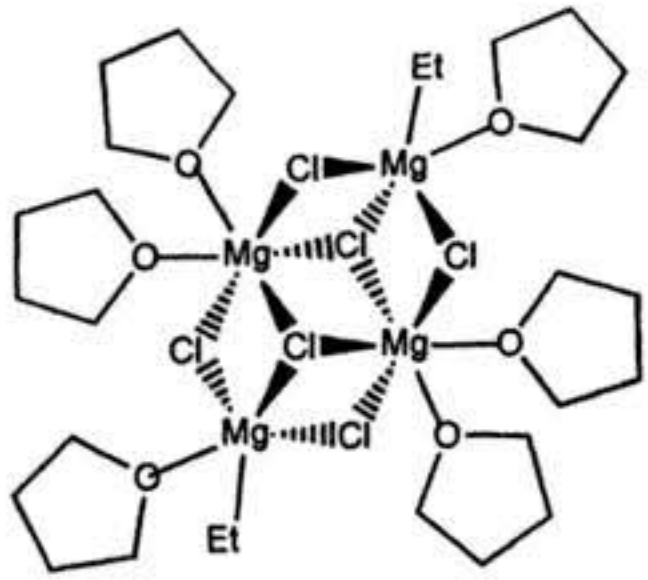
C. Pentacoordinated Haloorganomagnesium

Pentacoordinate geometry is observed for Grignard reagents that include small ligands. They usually attain a distorted trigonal bipyramidal structure and a list of these compounds is given in Table 1. A typical monomeric crystal structure is given by methylmagnesium bromide tris(tetrahydrofuranate) [Compound **10**] [13]. The Me and Br ligands remain in a *cis*-configuration, and they are mutually exchangeable. The Me—Mg—Br angle of 126° is greater than expected.



Compound 10

Pentacoordination can also result from aggregation of Mg compounds. One such compound is an ethylmagnesium chloride–magnesium chloride adduct, $[EtMgCl{\cdot}MgCl_2{\cdot}(THF)_3]_2$ [Compound **11**] [14]. The crystal structure confirms that it is a tetramer with chlorine-bridged Mg atoms. Two of the Mg atoms are pentacoordinated to three Cls, one Et group, and one tetrahydrofuran solvent. The remaining Mg atoms are bound to four Cl ligands and two tetrahydrofuran ligands in an pseudooctahedral symmetry.

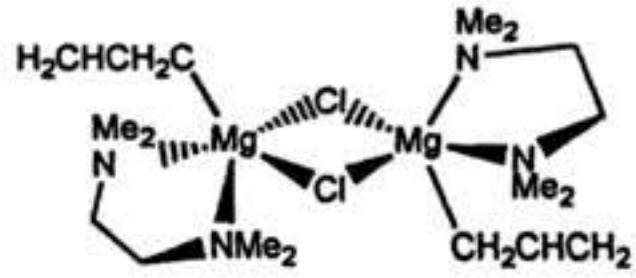


Compound 11

The $[(\eta^1\text{-allyl})MgCl{\cdot}TMEDA]_2$ complex [Compound **12**] has a chlorine-bridged dimeric structure [15]. The compound can be considered as an association of two monomers,

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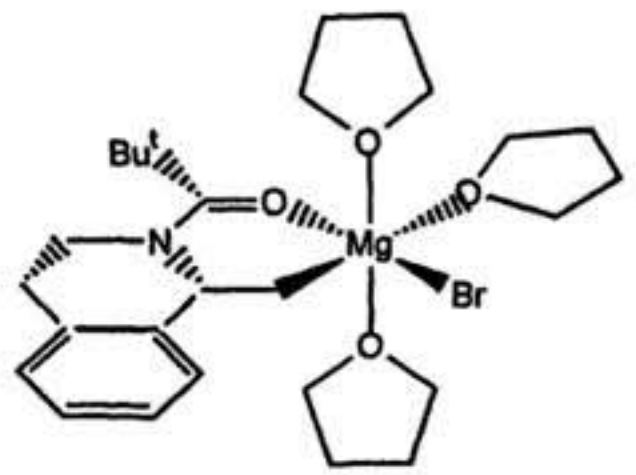
since the Mg—Cl bridges are not symmetric (2.400 and 2.694 Å). The Mg—C bond is typical, and there is no interaction between Mg and the other carbon atoms.



Compound 12

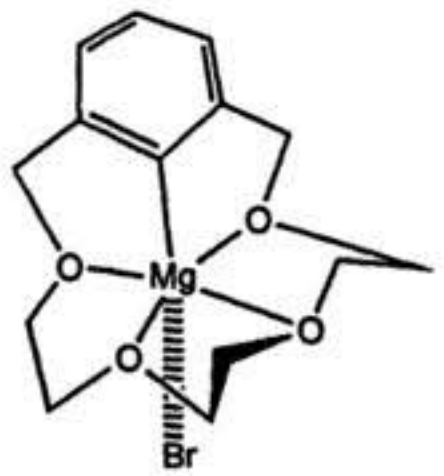
D. Hexacoordinated Haloorganomagnesium

Hexacoordination around the Mg atom occurs when an intramolecular coordination takes place. An example of an octahedral-type structure is given by 1-bromomagnesio-2-pivaloyl-tetrahydroisoquinoline·$(THF)_3$ [Compound **13**] [16]. The Br and organic group of the quinoline are in the *cis*-configuration, which is typical of Grignard reagents. Again, the C—Mg—X angle of 104° is larger than the anticipated 90°. The lack of steric constraints allows for higher coordination. The three THF ligands are in the remaining axial and equatorial positions..The preference for hexacoordination probably also results from the extra stabilization that is achieved by formation of the chelating ring.



Compound 13

One group of crystal structures of hexacoordinated Grignard compounds involves crown ethers, and an example is the compound, 2-bromomagnesio-1,3-xylyl-15-crown-4 [Compound **14**] [17]. The crystal structures of this and other crown ether compounds

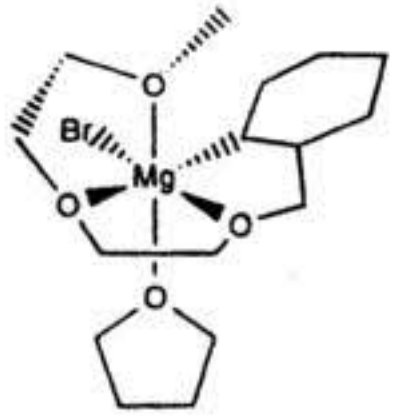


Compound 14

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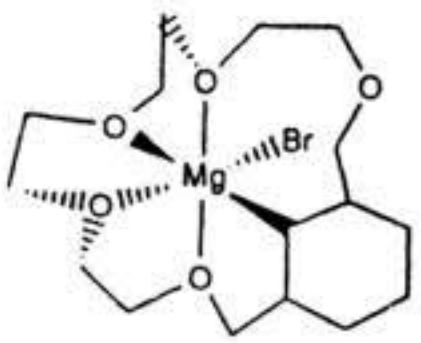
give a distorted octahedron consisting of Br, C, and the four oxygen atoms bound to the Mg atom. The oxygen atoms nearest the xylyl group are only weakly bound to Mg.

Hexacoordinated Mg can also be attained with open polyether ligands. Distorted octahedral geometry results when the polyether group has two, three or four intramolecularly bonded oxygen atoms. A typical crystal structure is given by *o*-[$CH_2(OCH_2CH_2)_2OMe$]-substituted phenylMgBr [Compound **15**][18]. The Mg atom is bound to one phenyl carbon and two oxygen atoms of the polyether ligand in the equatorial plane, with the third oxygen occupying an axial position around the Mg atom. The remaining coordination sites are taken up by the halide (Br) and tetrahydrofuran ligands. The number of coordinated solvent molecules is dependent on the number of free coordination sites around the Mg atom in its pseudooctahedral state.



Compound 15

The highest coordination state of Mg is hexacoordinate, even when further intramolecular coordination is possible. The Mg of the crown ether compound, 2-bromomagnesio-1,3-xylyl-18-crown-5 [Compound **16**] [17], is coordinated to only four of the five oxygen atoms as well as the Br and the aromatic carbon.



Compound 16

Aggregation has not been observed in hexacoordinated Grignard reagents, probably because of both electronic and steric constraints.

III. STRUCTURES OF DIORGANOMAGNESIUM COMPOUNDS

The composition of a Grignard reagent in solution also includes small amounts of diorganomagnesum compounds (MgR_2) in its monomeric, dimeric, and higher aggregate forms [2]. Crystals of diorganomagnesium compounds are much easier to obtain relative to Grignard compounds. The compounds can be crystallized from a polar solvent (ether)

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Table 2 Relevant Bond Lengths (Å) and Bond Angles (°) from the Crystal Structures of Diorganomagnesium Compounds

Compound	C—Mg—C	L—Mg—L	Mg—C	Mg—L	Ref.
$MgMe_2$(TMEDA)	130	82	2.17	2.24	62
$MgPh_2$(TMEDA)	119	83	2.17	2.2	63
Mg(*o*-CH_3carboranyl) (*p*-dioxane)	124	100	2.16	2.04	64
$MgMe_2$(quinuclidine)$_2$	129	108	2.119	2.24	65
$MgPh_2(THF)_2$	122	94	2.13	2.03	25
Mg(*p*-tolyl)$_2(THF)_2$	122.4	94.2	2.127	2.030	26
[Mg(*p*-tolyl)$_2(THF)_2$]	102.5	77.5	2.313, 2.245, 2.130	2.020	26
$[MgMe_2]_n$	105	75	2.24	—	38
$[MgEt_2]_n$	108	72	2.26	—	38
$[(CH_2)_4$Mg·(*p*-dioxane)]$_2$ [*p*-dioxane]	128	90	—	—	32
$[(CH_2)_5Mg·(THF)_2]_2$	141.5	90.8	2.15, 2.13	2.089, 2.110	31
[*o*-XylideneMg·$(THF)_2]_3$	126.8, 130.5	94.1, 94.0	2.154, 5.158, 2.170	2.073, 2.063, 2.081	36
[1,8-NapthalenediylMg·THF]$_4$	—	—	2.15, 2.28, 2.29	2.07	37
$[(Me_3Si)_3]_2Mg$	180	—	2.116	—	21
$[(Me_3Si)_2$NMg(*s*-Bu)]$_2$	—	92.9	2.08	2.118	22
$(Ph—C\equiv C)_2Mg·(THF)_4$	—	88.2	2.175	2.382, 2.374	41
$(Ph—C\equiv C)_2Mg·(TMEDA)_2$	180	80	2.176, 2.200	2.375	42
(*t*-Butylethynyl)$_2$Mg·(TMEDA)$_2$	—	2.175	—	2.372, 2.374	49
[EtMg(2,2,1-cryptand)]$_2$·Et_6Mg_2	106.8, 114.4	—	2.36, 2.238, 2.209	—	43
[NpMg(2,2,1-cryptand)]$_2$·Np_3Mg	116.9, 117.6, 124.8	—	2.125, 2.240, 2.296	—	43
Check name	127.8	89.0	2.127, 2.154	2.142, 2.377	18
[MeMg(15-crown-5)·$Me_5Mg_2]_n$	103.3–115.2	—	2.140, 2.25–2.395, 3.28	—	44
$[Et_2Mg·$(18-crown-6)]	180	—	2.104	2.767, 2.792, 2.778	45
Mg$(Cp)_2$-gas	—	n.a.	2.339	2.008	72
Mg$(Me_5Cp)_2$-gas	—	n.a.	2.341	2.011	19
Mg$(Np)_2$-gas	—	n.a.	2.126	1.541	20
Mg(Cp)(Np)-gas	180	—	2.328	2.12	20

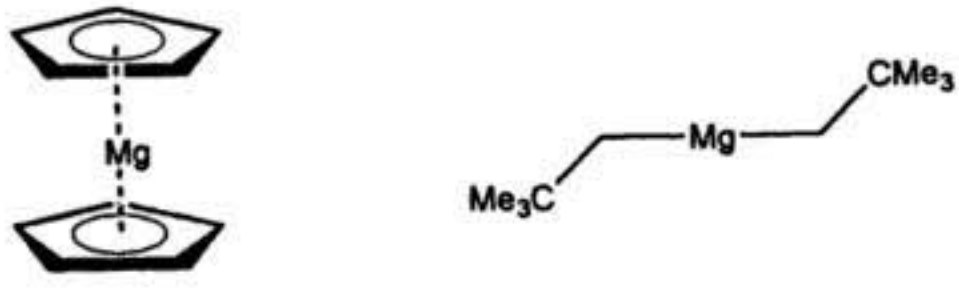
and can also be heated to give unsolvated crystals. Hence, more crystal structures are known for diorganomagnesium compounds than for Grignards. A list of the bond lengths and angles of crystal structures of diorganomagnesium compounds is given in Table 2.

A. Di- and Tricoordinated Diorganomagnesium

The simplest organomagnesium compounds consist of Mg atoms coordinated to two organic groups (MgR_2) in a linear fashion. Gas-phase electron diffraction has been used

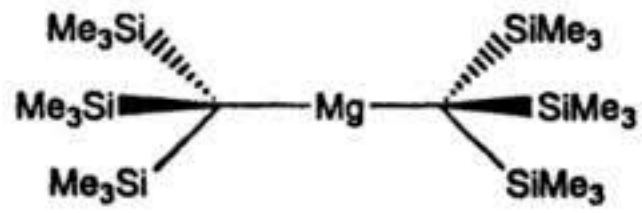
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to study the cyclopentadienyl [Compound **17**] [19] and neopentyl [Compound **18**] [20] derivatives. This method is limited by the thermal instability of many organomagnesium compounds. The heat required for volatilization causes many of the compounds to lose their coordinated solvent and form a nonvolatile polymer.



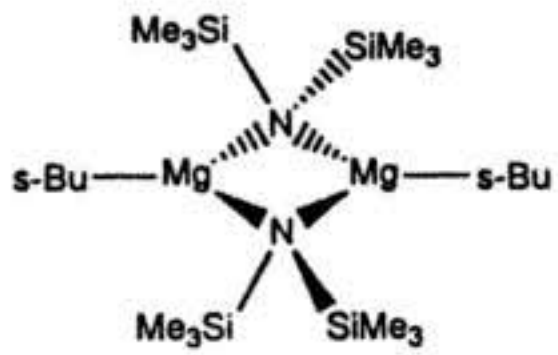
Compounds 17 and 18

Unlike Grignard reagents, crystal structures of dicoordinated organomagnesium compounds are known. These are formed when sterically hindered ligands cause excessive crowding in the environment around the Mg atom and prevent the coordination of any solvent molecules. The X-ray structure of bis[tris(trimethylsilyl)methyl]magnesium [Compound **19**] indicates that the compound is linear (C—Mg—C = 180°) and is centrosymmetric around the Mg atom [21].



Compound 19

Tricoordinated organomagnesium species result from the replacement of the solvent by a sterically constrained R group. Crystals can be obtained by the use of an apolar crystallizing solvent. A typical crystal structure of a tricoordinate species is that of *sec*-butylmagnesium hexamethyldisilazane [Compound **20**], which has a symmetric four-membered Mg_2N_2 cycle (i.e., all Mg—N bond lengths are identical) [22].

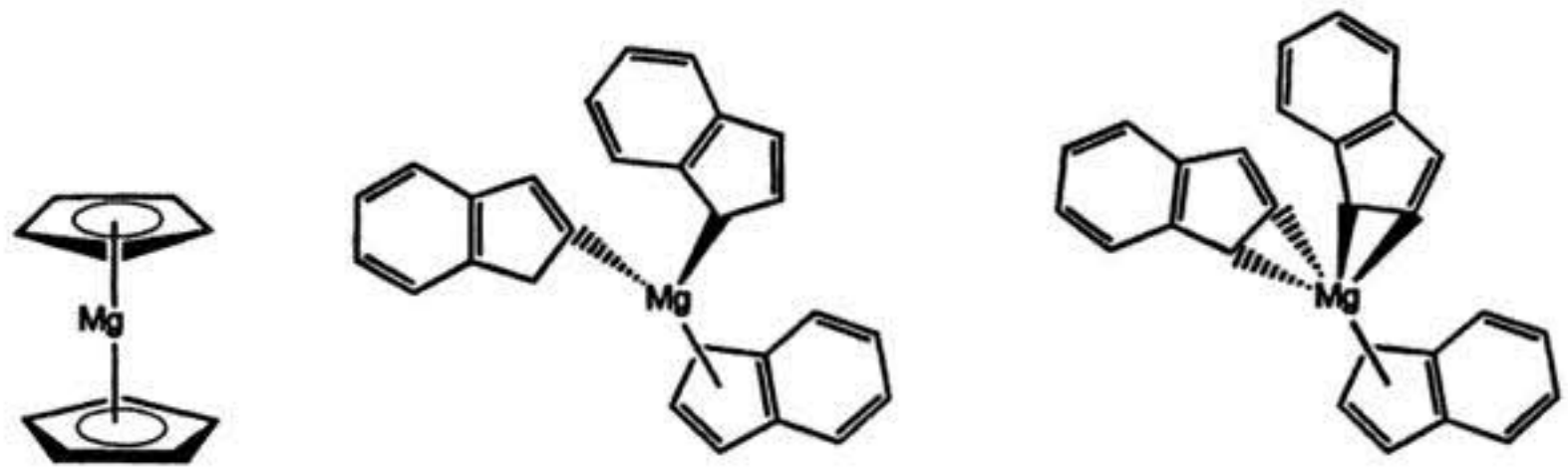


Compound 20

Pseudo di- and tricoordinated crystal structures are known for Mg complexes with cyclopentadienyl and indenyl groups. The magnesocene compound Cp_2Mg [Compound **21**] has a linear Cp—Mg—Cp structure in which the Cp groups are staggered [23]. The tricoordinate indenyl compounds [Compounds **22** and **23**] have two different crystalline

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environments, both of which have a monomeric $Mg(indenyl)_3$ structure [24]. The Mg atom in Compound **22** is η^5-bonded to one indenyl group and η^1-bound to two indenyl groups. Compound **23** has one η^5 Mg-indenyl bond and two η^2 Mg-indenyl bonds. These novel structures probably result from the packing of the indenyl groups in the crystal lattice.

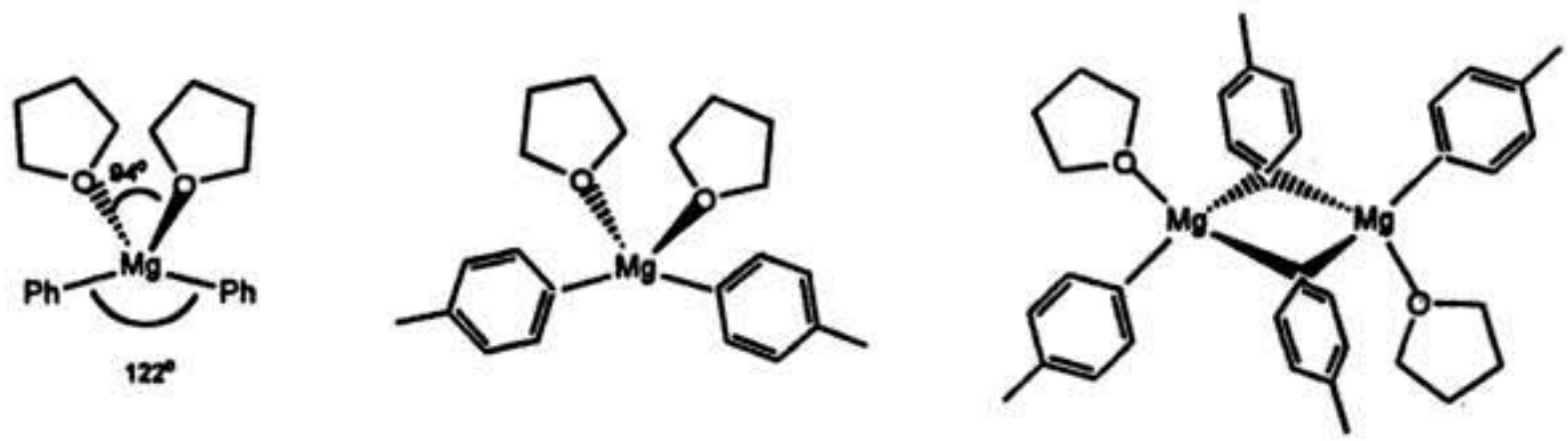


Compounds 21, 22, and 23

B. Tetracoordinated Diorganomagnesium

The normal mode of coordination for organomagnesium is tetrahedral, much the same as for Grignard compounds [1]. The crystal structures are of the form $MgRR'L_2$, in which R and R′ are the same or different organic groups and L refers to a solvent or a neutral ligand.

The crystal structure of diphenylmagnesium·bis(tetrahydrofuranate) [Compound **24**] has bond lengths and angles typical of diorganomagnesium compounds. The C—Mg—C angle of 122.4° is larger than in the Grignard compounds and the O—Mg—O of 94.2° is smaller [25]. An unusual feature of the *p*-tolyl analogue is the presence of both the monomer [Compound **25**] and the dimer [Compound **26**] in the crystalline state [26]. This indicates that both monomers and dimers are present in solution. The crystal structure of the monomer is similar to the phenyl complex. The Mg atoms in the dimer are bridged by the two tolyl groups through a three-center, two-electron bond. However, the bonding is unsymmetric with one long (2.313 Å) and one short (2.245 Å) Mg—C bond per Mg atom and both are longer than the terminal Mg—C bond length of 2.130 Å. The dimer could thus be considered as two strongly associated monomers.



Compounds 24, 25, and 26

The crystal packing of organomagnesium compounds has shown that intramolecular coordination is preferred over solvent coordination. These compounds have a tetrahedral geometry. The crystal structure of $[MeO(CH_2)_4]_2Mg$ [Compound **27**] indicates that the

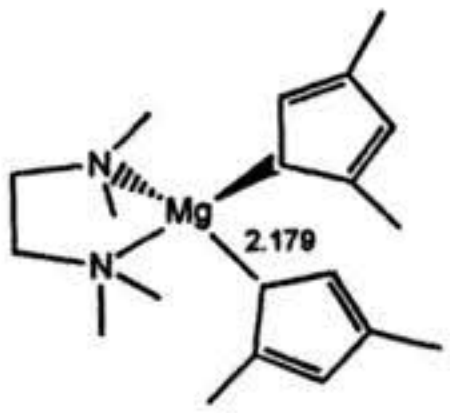
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Mg has a distorted tetrahedral environment, with a large C—Mg—C angle of 140.2° and a small O—Mg—O angle of 96.4° [27]. The [(*o*-pyridyl)$(Me_3Si)_2C]_2Mg$ compound [Compound **28**] also has a distorted tetrahedral geometry around the Mg atom [28]. However, a greater ring strain results from the four-membered rings and, hence, there is a larger variation in the bond angles.



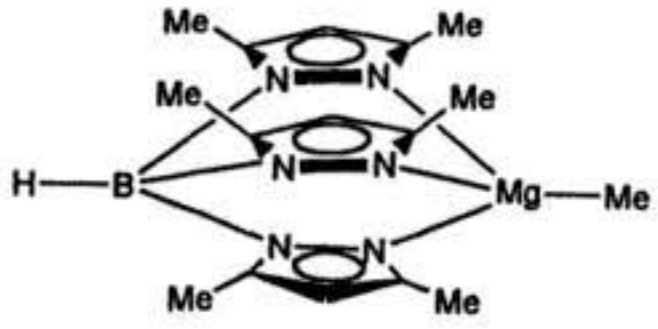
Compounds 27 and 28

The X-ray structure of ([2,4-dimethyl-2,4-pentadienyl)$_2$Mg·TMEDA] [Compound **29**] shows that an η^1-type Mg—C bond is present [29]. No interaction is observed between the Mg atom and the remaining carbon atoms of the pentadienyl ligands. A typical tetrahedral coordination and normal Mg—C and Mg—N bond lengths occurs.



Compound 29

Monomeric tetrahedral compounds can also be achieved by the use of tris-chelating ligands. The crystal structures of several [*tris*(pyrazolyl)hydroborato]alkylmagnesium have shown that they have shorter Mg—C bond lengths (2.10–2.18 Å) and a typical example is given [Compound **30**] [30].

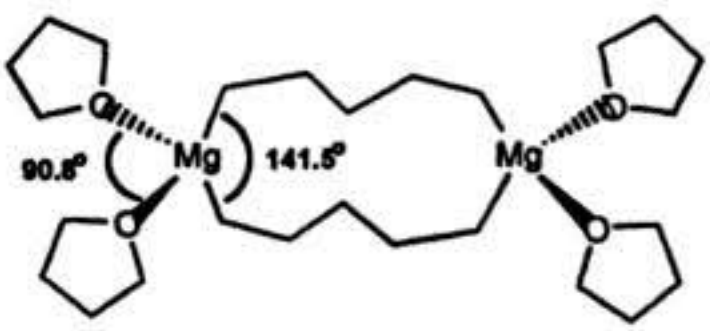


Compound 30

Dimeric diorganorganomagnesium compounds also have distorted tetrahedral geometries. The compounds [$MgPh_2(OEt_2)_2$] and [$MgEt_2[OEt_2)_2$] are known to be

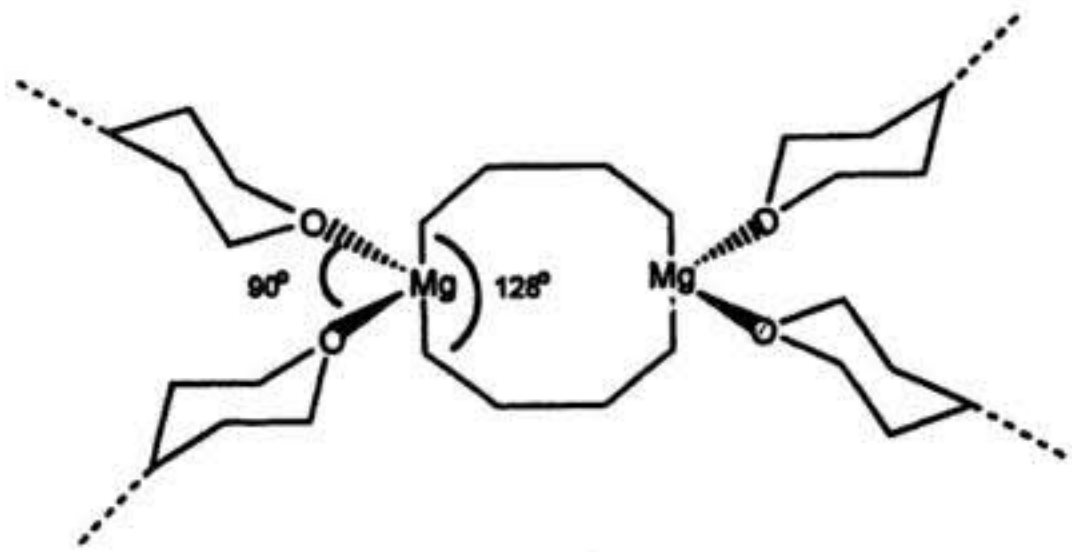
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dimeric in solution, but crystallize as monomers. This predominance for dimeric species in solution usually gives rise to polymeric or cyclic complexes. The crystal structure of $[Mg(CH_2)_5(THF)_2]_2$ [Compound **31**] shows that the Mg atoms are in a 12-membered cycle (i.e., the organic group links the two tetrahedral Mg atoms) [31]. This results from the



Compounds 31

association of the monomers. Thermodynamically, the enthalpy factor (ring strain) prefers the six-membered cyclic monomer, whereas the dimeric compound is favored entropically. A similar compound, $[Mg(CH_2)_4(p\text{-dioxane})_2]_2 \cdot [p\text{-dioxane}]$ [Compound **32**], also has the same dimeric structural base [32]. However, the compound forms a polymer network through the dioxane oxygen atoms. Crystal structures of this type are rare, since the insolubility of noncyclic polymeric species make them difficult to isolate as single crystals.



Compound 32

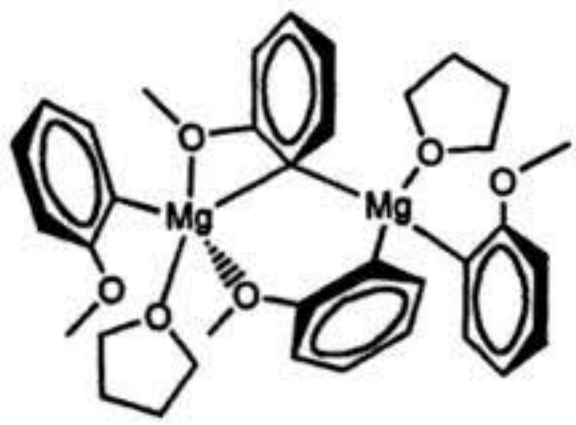
The crystal structure of $[(N,N\text{-dimethyl-3-aminopropyl})MgEt]_2$ [Compound **33**] indicates that the Mg atoms are bridged by the organic group through two-electron, three-center bonds in which the carbon atom has a pendant group that intramolecularly bonds to the Mg atom [33]. This fulfills the tetrahedral geometry around the Mg atom. A nitrogen analogue, $[Me_2NC_2H_4N(Me)MgMe]_2$ [Compound **34**], has a similar structure [34].



Compounds 33 and 34

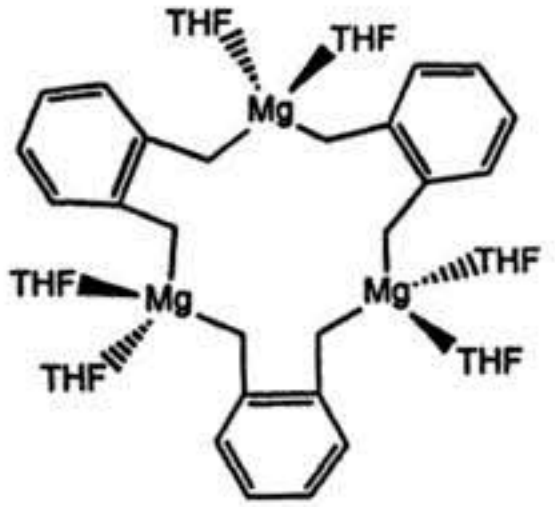
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The $[(o\text{-anisyl})_2Mg(THF)]_2$ complex [Compound **35**] has an unusually complex crystal structure [35]. The unsymmetric dimer contains one tetrahedral Mg and one pentacoordinated Mg atom. Two anisyl groups are bonded solely through the *o*-carbon atom, but the remaining groups are bound through both the oxygen atom and the *o*-carbon atom either to one Mg atom or to both Mg atoms as shown. This results in a partial positive charge on the pentacoordinated Mg atom and a partial negative charge on the other Mg atom.



Compound 35

The cyclic trimeric species, $[o\text{-xylideneMg}(THF)_2]_3$ [Compound **36**], has a trimagnesacyclopentadecane structure [36]. The preference for the trimer probably arises from the greater ability of the Mg atom to achieve a tetrahedral geometry in the trimer relative to the dimer.

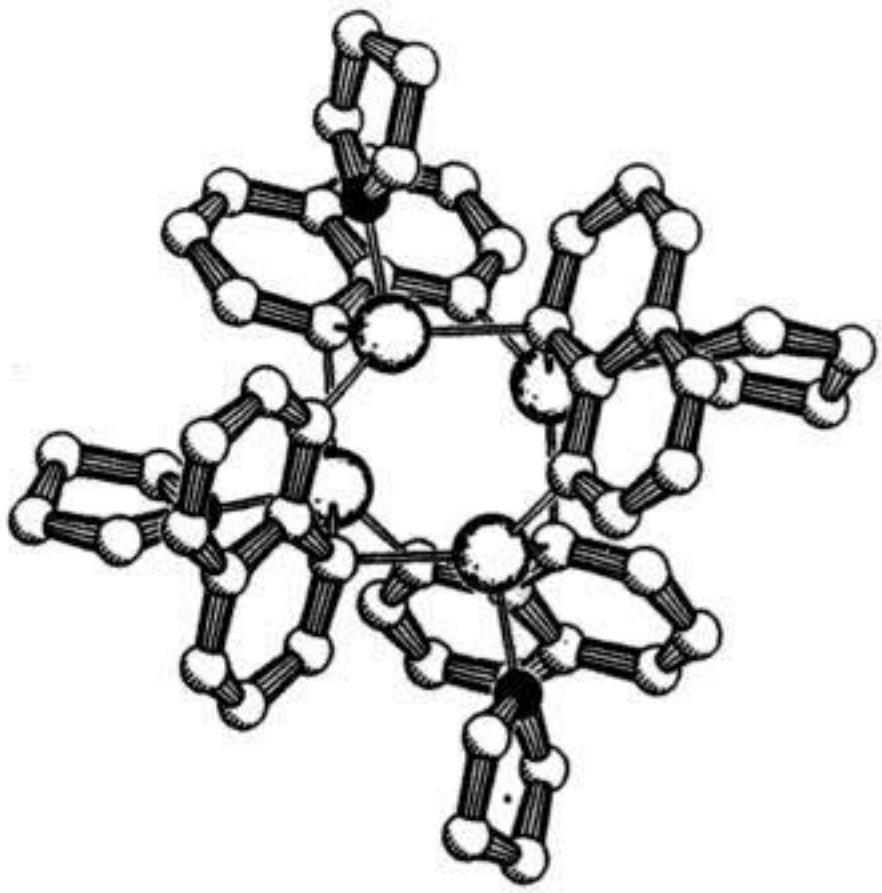


Compound 36

Contrary to the foregoing cyclic compounds, $[(1,8\text{-naphthalenediyl})Mg(THF)]_4$ [Compound **37**] is a tetrameric cluster in which the Mg atoms are bridged through the

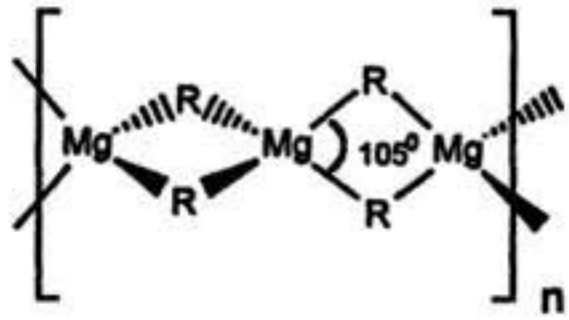
Material chroniony prawem autorskim

napthalene by one σ bond and two three-center, two-electron bonds. Association measurements have shown that this tetrameric species is also present in solution [37].



Compound 37

The nonsolvated compounds, MgR_2 (R = Me or Et) [Compound **38**], are polymers with symmetrically bridging alkyl groups. The Mg—C bond lengths are 2.24 Å for Me derivative and 2.26 Å for the Et derivative [38]. The C—Mg—C angle are constant at 105° and 108°, respectively. The R bridges are three-center, two-electron bonds; therefore, the Mg atoms are able to retain their tetrahedral coordination. The presence of Mg—Mg bonds has not been determined, although some Mg—Mg interaction has been observed in $[MgMe]_n$.



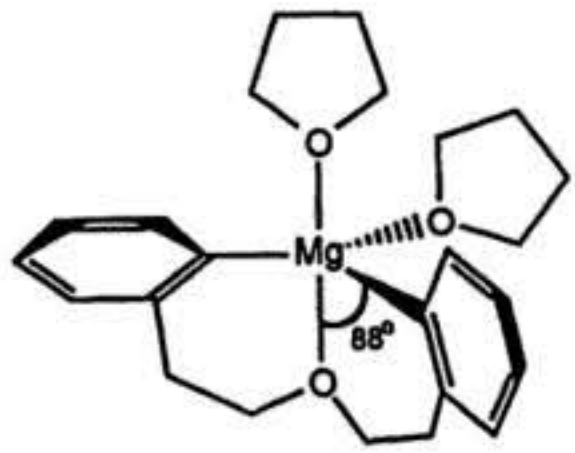
Compound 38

C. Penta- and Hexacoordinated Diorganomagnesium

A pentacoordinated structure exists when an intramolecularly bound ligand is present. The 1-oxa-6-magnesadibenzo(4,5,6)cyclodecadiene·THF_2 compound [Compound **39**]] has a distorted trigonal bipyramidal geometry [39]. The trischelating diphenyl ligand has

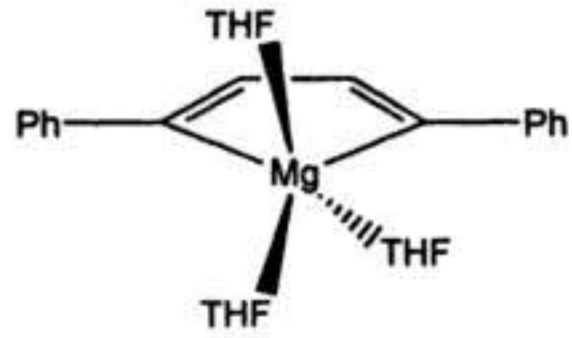
Material chroniony prawem autorskim

small C—Mg—O angles of ~88° and the small bite of the chelate allows the coordination of a second THF molecule.



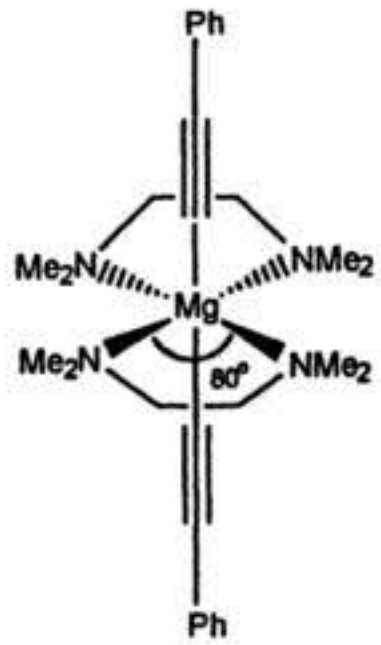
Compound 39

The crystal structure of (*s-cis*-PhCH=CHCH=CHPh)Mg(THF)$_3$ [Compound **40**] has shown that the organic group chelates to the Mg atom and has a distorted trigonal bipyramidal structure [40]. The interesting feature comes from the presence of the double bond which gives the ligand a partial η^4 coordination to the Mg atom.



Compound 40

A hexacoordinate geometry is observed for bis(phenylethynyl)magnesium. An X-ray determination of (Ph—C=C)$_2$Mg(THF)$_4$ demonstrates the presence of two isomeric compounds in which the organic groups are either *trans* or *cis* to each other [41]. The crystal structure of an analogous compound, (Ph—C=C)$_2$Mg(TMEDA)$_2$ [Compound **41**],



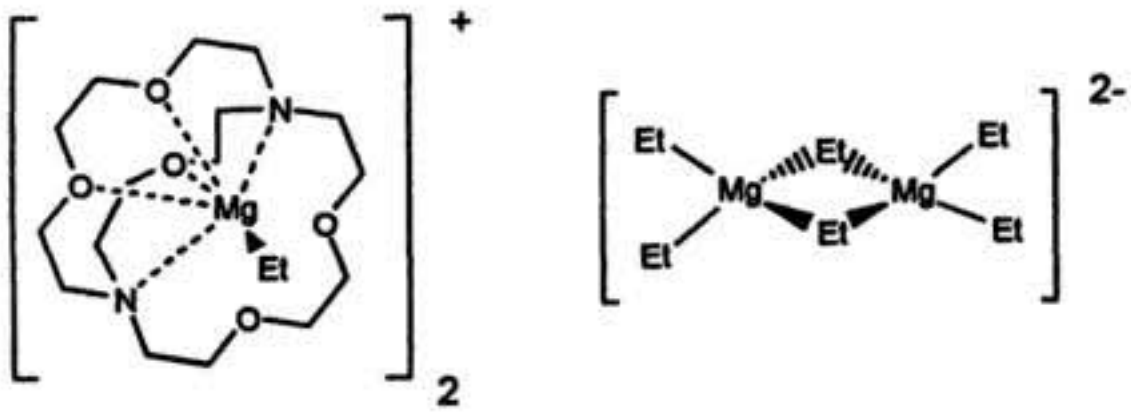
Compound 41

Material chroniony prawem autorskim

shows that it contains only the *trans*-isomer (C—Mg—C of 180°) [42]. Each TMEDA has a N—Mg—N angle of 80°, which results from its chelating effect. Therefore, the equatorial angles are distorted and the Mg—N bond lengths are longer than anticipated.

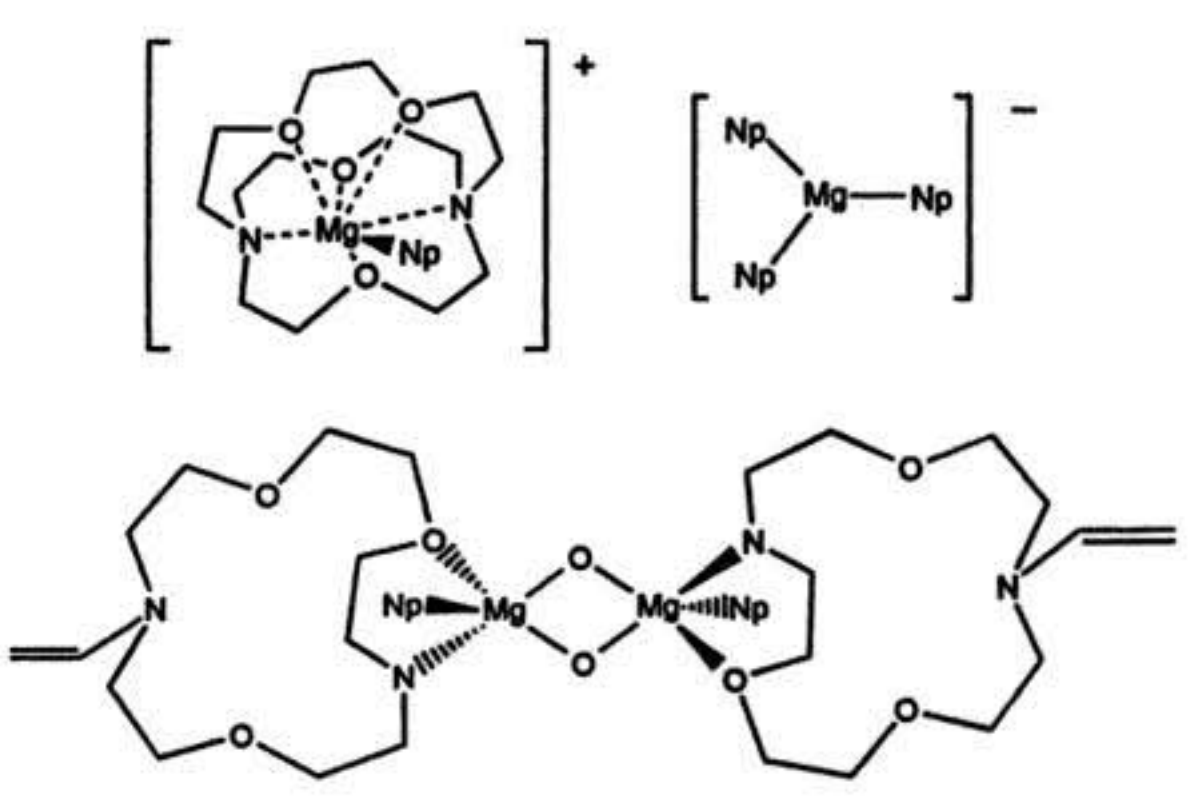
D. Polyether-Containing Organomagnesium

The complexation of organomagnesium compounds with polyether ligands has given rise to unusually high coordination geometries and to a disproportionation into alkylmagnesium cations and magnesate anions. The two effects are exemplified in the crystal structure of $[EtMg(2,2,1\text{-cryptand})]_2[Et_6Mg_2]$ [Compound **42**] [43]. The cryptand facilitates the disproportionation of the Mg dimer into $EtMg^+$ and $Et_6Mg_2^-$. The dialkylmagnesium anion itself has no direct interaction with the cryptand. These compounds have an unusually high reactivity by which rates can be accelerated by several orders of magnitude.



Compound 42

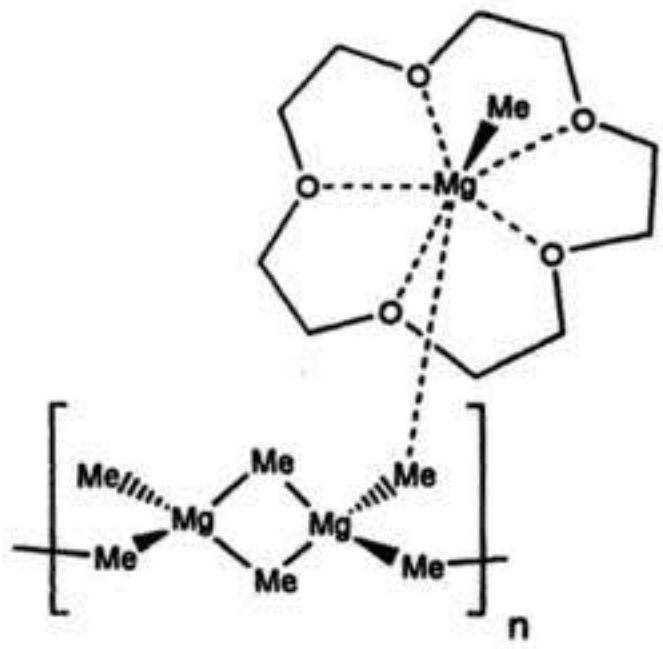
A similar separation of the organomagnesium species occurs in the crystal structure of $[NpMg(2,1,1\text{-cryptand})][Np_3Mg]$ [Compound **43**] [43]. The anion is not symmetric as anticipated, but has a distorted trigonal planar geometry. On heating, the Np_3Mg becomes protonated and a dimeric structure [Compound **44**] is formed. The crystal structure demonstrates that cleavage of some of the bridging ligands has taken place.



Compounds 43 and 44

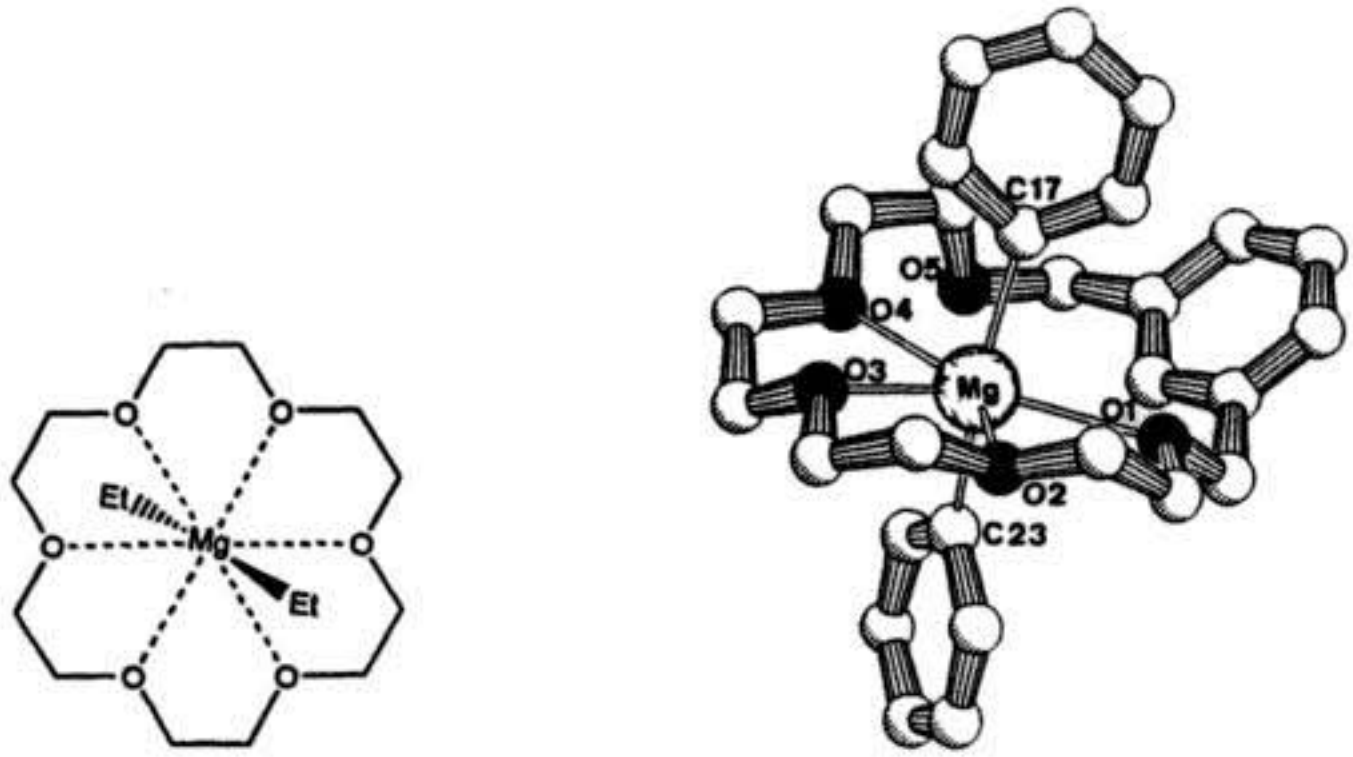
Material chroniony prawem autorskim

The crystal structure of $[MeMg(15\text{-crown-5})\cdot Me_5Mg_2]_n$ [Compound **45**] indicates that a partial dissociation of the compound has taken place [44]. The Mg atom lies 0.42 Å out of the crown ether plane and has a weak interaction with a terminal methyl group of the polymeric magnesate anion.



Compound 45

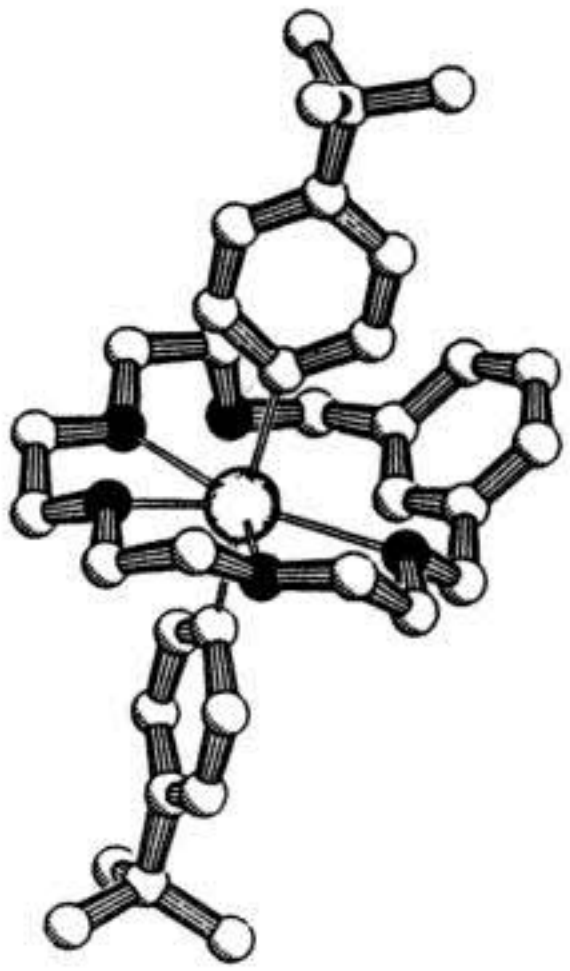
Ionic pairing is not observed for $MgEt_2\cdot$(18-crown-6) [Compound **46**] [45]. The crystal structure reveals a linear C—Mg—C bond, with the crown ether residing in the equatorial plane. The Mg atom occupies the center of the crown ether through weak Mg—O bonds. A similar "threaded" structure is known for $MgPh_2\cdot$(1,3-xylyl-18-crown-5) [Compound **47**] [46]. The Ph—Mg—Ph angle is again linear, although the presence of the xylyl group results in irregular Mg—O bond lengths, with the strongest bonds farthest from the xylyl group. The steric bulk of the phenyl group prevents it from penetrating through the crown ether ring and, therefore, is considered a "rotaxane" structure, in which the $MgPh_2$ undergoes inclusion through "mechanical" means. Its formation probably occurs through an initial dissociation into ion pairs. The rotaxane structure is



Compounds 46 and 47

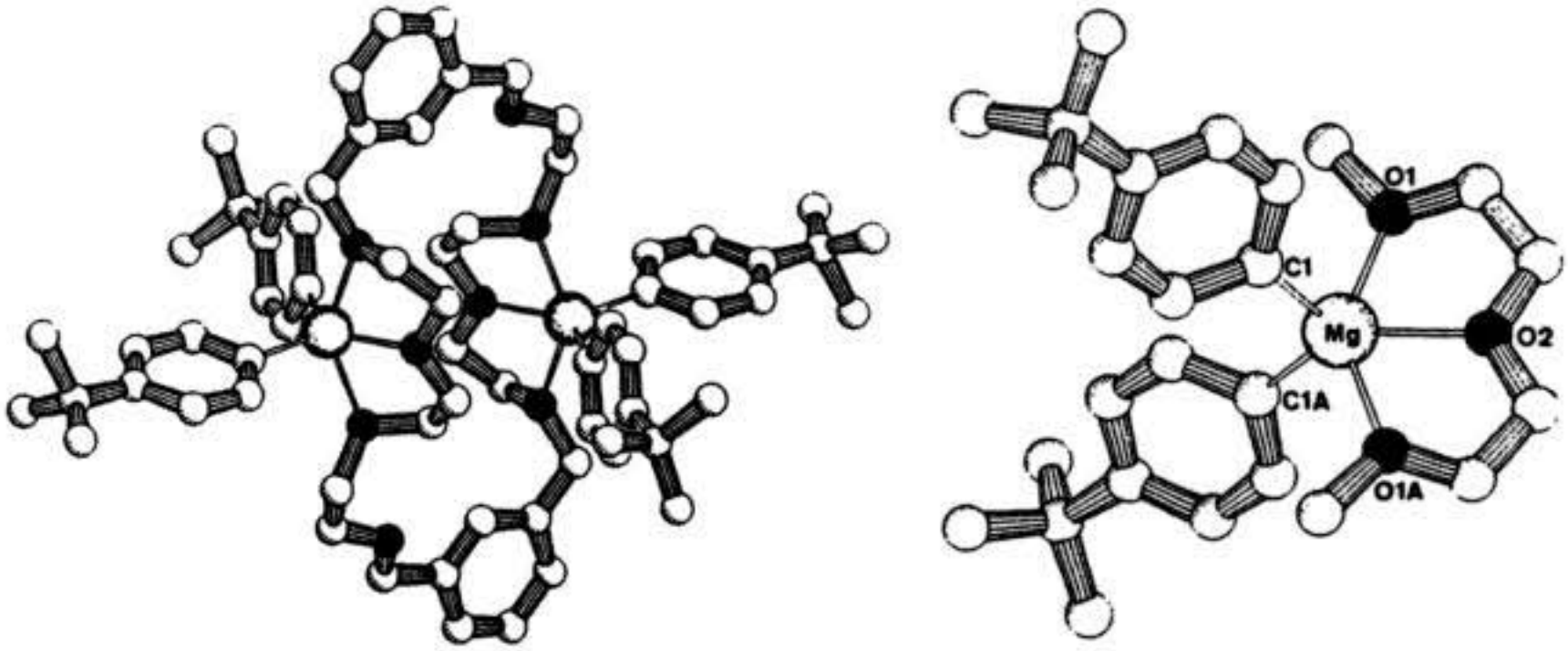
Material chroniony prawem autorskim

observed for Mg(*t*-butylphenyl)$_2$·(1,3-xylyl-18-crown-5) [Compound **48**] [47]. The *t*-butylphenyl group cannot "thread" through the crown ether cavity and, therefore, probably goes through a magnesate species.



Compound 48

The crystal structure of [(*p*-*t*-butylphenyl)$_2$Mg]$_2$(1,3,16,18-dixylyl-30-crown-8) [Compound **49**] indicates that this crown ether has greater flexibility, giving rise to unique coordination environments around Mg [47]. The two diarylmagnesium units bond to the crown ether on either side of the two xylyl groups. The same geometry is observed in the crystal structure of (*p*-*t*-butylphenyl)$_2$Mg(diglyme) [Compound **50**], which is pentacoordinate with Mg and O in one plane [47]. The (*p*-*t*-butylphenyl)$_2$Mg(tetraglyme)

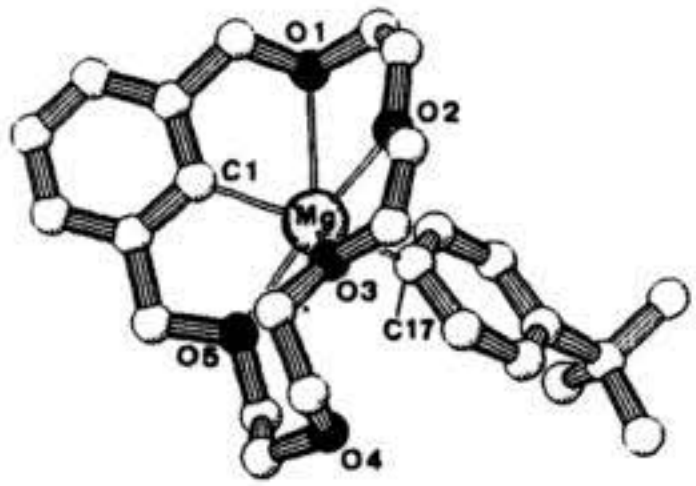


Compounds 49 and 50

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compound has a similar geometry around the Mg atom. Three different conformers result from the different packing of the unbonded ether groups.

Substituted polyether and crown ethers can also undergo intramolecular bonding with Mg through an organic substituent. Derivatives of this nature have greater reactivity relative to other diorganomagnesium compounds. The crystal structure of 2-[(*p*-*t*-butylphenyl)Mg]-1,3-xylyl-18-crown-5 [Compound **51**] displays a distorted trigonal bipyramidal geometry around the Mg atom [47]. Two oxygen atoms have regular bonds to the Mg atom, two others are weakly bound, and one oxygen atom remains nonbonded.

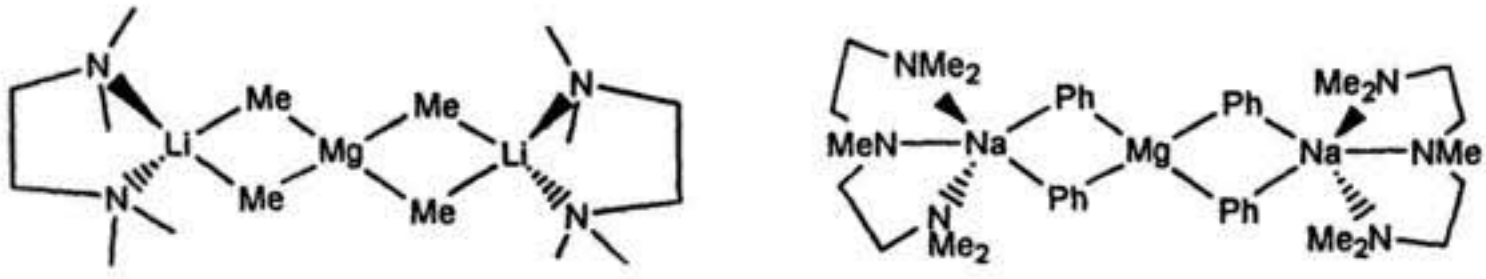


Compound 51

IV. BIMETALLIC MAGNESIUM COMPOUNDS

Several crystal structures of magnesium compounds complexed to either main group or transition metals have been determined in recent years. Since the number of such structures is limited, Grignard and organomagnesium structures will be discussed together. A list of the bond lengths and angles of the compounds are given in Table 3.

Organomagnesium compounds complexed with organolithium complexes are formed through organic bridges between the Mg and Li atoms. The crystal structure of $[TMEDA{\cdot}Li]_2(\mu\text{-}CH_3)_4Mg$ [Compound **52**] shows that the tetrahedral tetramethylmagnesate is capped by two TMEDA-coordinated Li atoms [48]. A true tetrahedral geometry around the Mg is observed where the Mg—C bond lengths range from 2.23 to 2.29 Å and C—Mg—C bond angles range from 108.4 to 109.9°. These values indicate that there is no charge separation into alkali metal cation and magnesate anion species. However, such structures can be perceived as an association of the magnesate unit with the alkali metal solvated by a chelating Lewis base (TMEDA). The sodium analogue has a similar structure, with the only difference arising from the preferred pentacoordination of the sodium [48]. The replacement of TMEDA by the tridentate ligand, PMDTA, gives the $[PMDTA{\cdot}Na]_2(\mu\text{-}Ph)_4Mg$ complex [Compound **53**] [49].



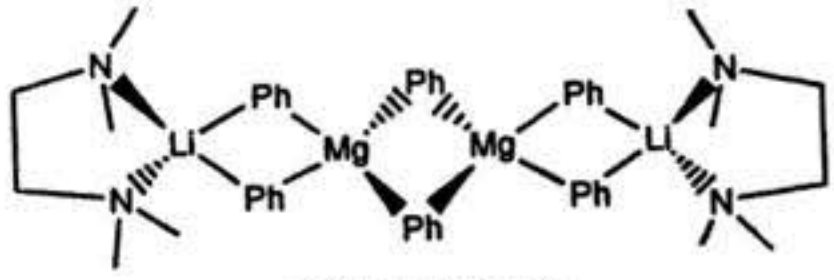
Compounds 52 and 53

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Table 3 Relevant Bond Lengths (Å) and Bond Angles (°) from the Crystal Structures of Bimetallic Magnesium Compounds

Compound	C—Mg—C	Mg—C	Mg—X	Mg—L	Ref.
$[TMEDA{\cdot}Li]_2(\mu\text{-}Me)_4Mg$	108.4–109.9	2.23–2.29	—	2.616, 2.615	48
$[TMEDA{\cdot}Li]_2(\mu\text{-}Ph)_2[Mg(\mu\text{-}Ph)_2]_2$	106.0–112.1	2.29, 2.33	—	—	50
$[PMDTA{\cdot}Na]_2Mg(\mu\text{-}Ph)_4$	107–115	2.27–2.31	—	—	49
$[Li(TMEDA)_2]{\cdot}[(benzyl)_4Mg{\cdot}Li(TMEDA)]$	105–114	2.31, 2.32	—	271.9(Li)	51
$[PhC{\equiv}C)_2Mg{\cdot}Li(TMEDA)]_2$	89.3, 132.8	2.18, 2.31	—	2.35, 2.20	51
$[TMEDA(t\text{-butylethynyl})_3Mg{\cdot}Na]_2$	96.5, 96.9, 134.7	2.167, 2.173, 2.257	—	2.520, 2.254	49
$[PMDTA{\cdot}(t\text{-butylethynyl})_3Mg{\cdot}Na]_2$	97.5, 96.1, 130.3	2.184, 2.247, 2.191	—	2.451, 2.299	49
$(TMEDA)_2Mg(t\text{-butylethynyl})_2$	—	2.175	—	2.382, 237.4	49
$[(Me_3Si)C](THF)Mg(\mu\text{-}Br)_2Li(THF)_2$	—	2.19	2.551, 2.515	2.061	73
$Cu_4Mg(\mu\text{-}Ph)_6$	—	2.35	—	2.046	74
$CpCo(C_2H_4)(\mu\text{-}Ph)MgBr{\cdot}(THF)_2$	n.a.	2.572	—	2.563(Co)	52
$(H_4C_2)_2Ni(\mu\text{-}Me)MgMe{\cdot}TMEDA$	112.5	2.294, 2.150	—	2.252, 2.264	53
$[Cp^*U(O)(CH_2PPh_2CH_2)_2MgCl_2(CH_2PPh_2CH_2)]$	—	2.23	2.79	1.94 (O), 2.23 (C)	75
$[Me_2Sl(\mu\text{-}OMe)_2]_2Mg(p\text{-dioxane})$	—	—	—	2.05, 2.24	76
$(H_4B)_2Mg(THF)_3$	—	—	2.06 B	2.09 (O)	77
$[(o\text{-Xylidene})_2W(O)]_2Mg(THF)_4$	—	—	—	2.07 (O), 2.10 (THF)	78
$[Me_4Re(O)]_2Mg(THF)_4$	—	—	—	2.029, 2.09	79
$[(Me_3Si)_4Re(O)]_2Mg(THF)_4$	—	—	—	1.923 (O), 2.021 (THF)	79
$[MgCl(THF)_5]{\cdot}[FeCl_4]$	—	—	2.384	2.13	80
$[MgCl(THF)_5]{\cdot}[AlCl_4]$	—	—	2.396	2.13	80
$[Mg(THF)_4(\mu\text{-}Cl)_2FeCl_4]$	—	—	2.501	2.09	81
$[(THF)_3Mg(\mu\text{-}Cl)_3Mg{\cdot}(THF)_3]{\cdot}[TiCl_5(THF)]$	—	—	2.50	2.08	82

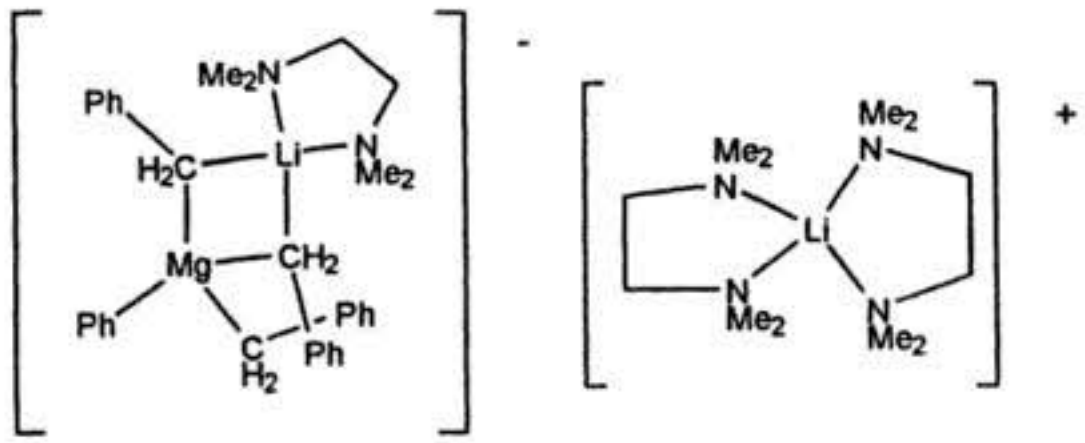
Changing the stoichiometric ratios of the foregoing reagents to equimolar quantities of the magnesium and lithium compounds yields $[TMEDA{\cdot}Li]_2(\mu\text{-}Ph)_2Mg(\mu\text{-}Ph)_2Mg(\mu\text{-}Ph)_2$ [Compound **54**] [50]. The crystal structure shows that the compound is a dimeric



Compound 54

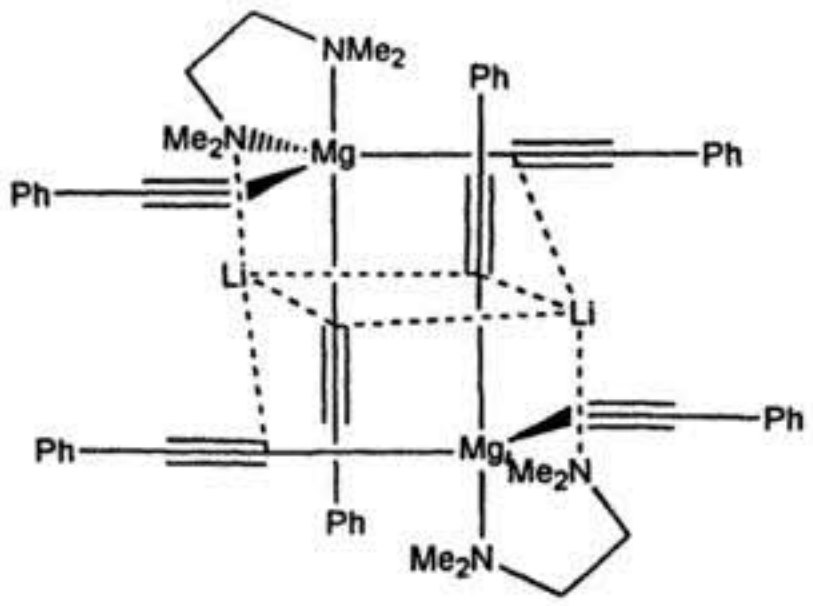
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phenyl-bridged magnesium species that is capped by TMEDA coordinated Li as in Compounds **52** and **53**. A separation of the magnesium and lithium into anionic and cationic species is observed for the benzyl analogue. The crystal structure of $[(TMEDA)_2{\cdot}Li][(benzyl)_4Mg{\cdot}Li(TMEDA)]$ [Compound **55**] reveals that organolithium is present both in the cation and in the anion where it is benzyl-bridged to the magnesium [51]. The geometry around the Mg atom is a distorted tetrahedron with Mg—C bond lengths of 2.32 and 2.31 Å for the bridging benzyl groups and 2.22 and 2.26 Å for the terminal benzyl groups.



Compound 55

Variations on the R group can give rise to pentacoordinated Mg. A typical crystal structure is given by $[(PhC{\equiv}C)_3Mg{\cdot}Li(TMEDA)]_2$ [Compound **56**] [51]. The Mg atom is in a pseudotrigonal bipyramidal geometry with two of the alkynyl ligands in the equatorial plane (Mg—C of 2.18 Å) and a third axial alkynyl group (Mg—C of 2.13 Å). The remaining two positions are occupied by the chelating TMEDA ligand. The two Li atoms bridge the two Mg units through interactions with the π bond of the alkynyl group. A similar crystal structure was observed for $[TMEDA(t\text{-butylethynyl})_3Mg{\cdot}Na]_2$ [49].

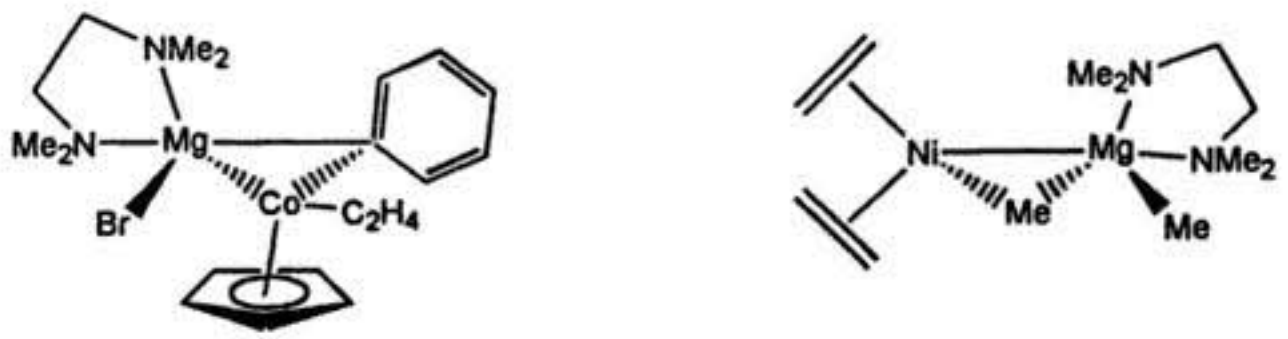


Compound 56

Complexes containing both Mg and a transition metal (M) have been characterized structurally [1]. Bonding usually takes place by bridging organic groups, and through direct Mg—M bonds which are observed when large differences in electronegativities exist between Mg and the transition metal. An example of both types of bonding is seen in the

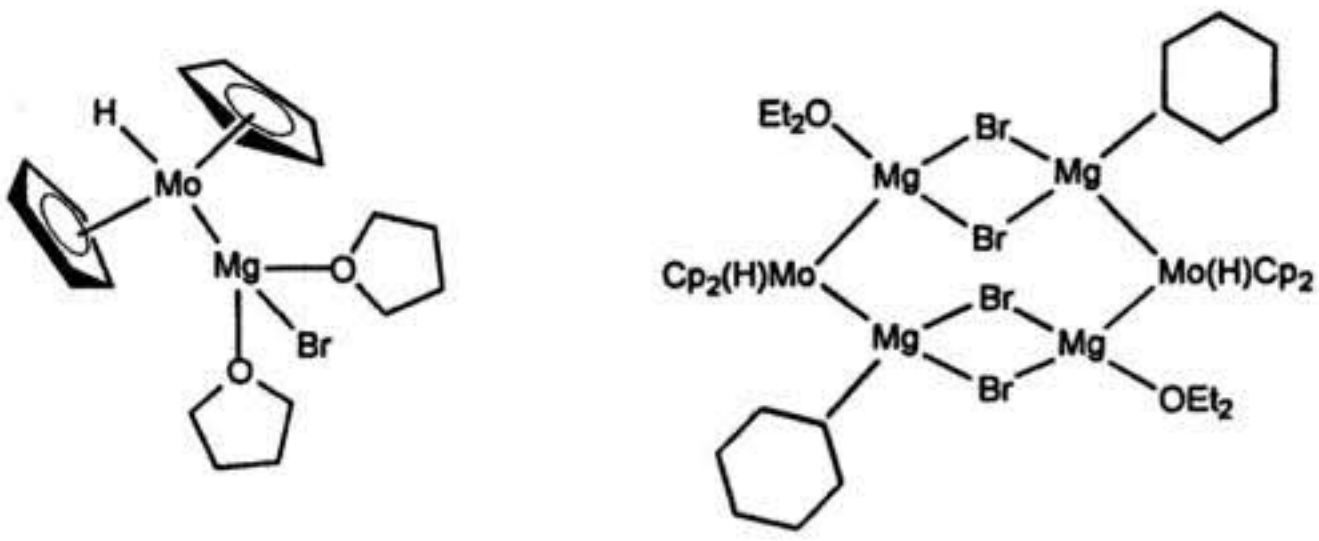
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crystal structure of $CpCo(C_2H_4)(\mu\text{-Ph})MgBr\cdot TMEDA$ [Compound **57**] [52]. A direct Mg—Co of 2.56 Å exists and the phenyl group on the Co is weakly coordinated to the pentacoordinated Mg atom (Mg—C 2.56 Å, Co—C 1.98 Å). The crystal structure of the compound, $(H_4C_2)_2Ni(\mu\text{-Me})MgMe\cdot TMEDA$ [Compound **58**], indicates that there is a direct Mg—Ni bond of 2.615 Å and a bridging Me group (Mg—C 2.295 Å, Ni—C 2.031 Å) [53]. The pentacoordinated Mg atom is also coordinated to TMEDA and a terminal Me group.



Compounds 57 and 58

Two unusual structures are obtained from the coordination of Grignard reagents to Cp_2Mo residues [54,55]. The first crystal structure of $Cp_2Mo(H)MgBr\cdot(OC_4H_8)_2$ [Compound **59**] shows that there is a regular tetrahedral geometry around the Mg atom, but no organic group is bonded to the Mg [54]. A direct Mg—Mo bond replaces the Mg—C bond usually present in organomagnesium compounds. A second set of crystals present gave a cluster in which two Mo and four Mg atoms are present. The crystal structure of $[(Cp_2MoH)\cdot\{RMg(\mu\text{-}Br)_2Mg(OEt_2)\}]_2$ [Compound **60**] contains four-membered Mg_2Br_2 rings bridged by two Cp_2MoH residues with Mg—Mo—Mg angles of 108.8° [55]. Tetrahedral geometries exist around the Mg atoms at which two of the Mg atoms are bound to the cyclohexyl groups and the remaining Mg atoms are coordinated to ether groups.



Compounds 59 and 60

V. STRUCTURES OF MAGNESIUM DIHALIDE AND OTHER MAGNESIUM COMPOUNDS

Although magnesium dihalides are not organomagnesium compounds, they do exist in all Grignard solutions and, therefore, are included in this review. They also give valuable

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Table 4 Relevant Bond Lengths (Å) and Bond Angles (°) from the Crystal Structures of Magnesium Dihalide Compounds

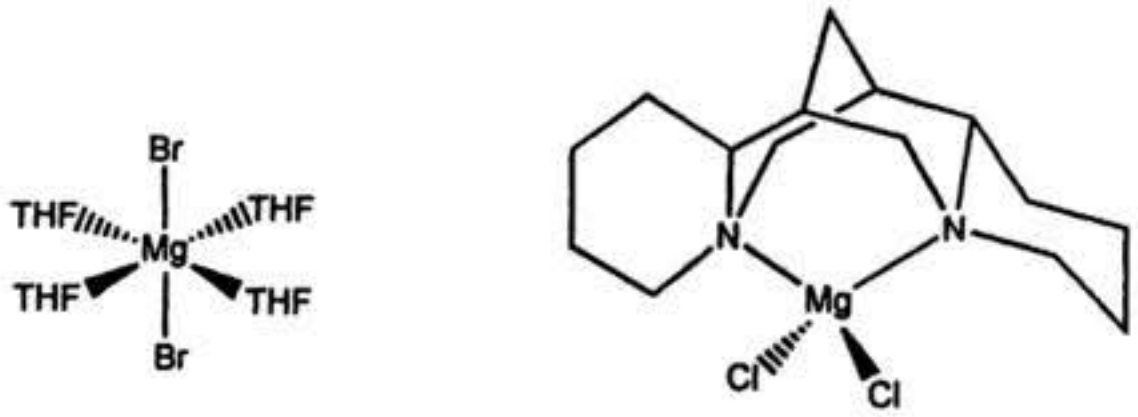
Compound	Mg—X	Mg—L	Ref.
$MgBr_2 \cdot (THF)_4$	2.625	2.16	56
$MgBr_2 \cdot (THF)_2$	2.633, 2.799	2.126	83
$[Mg(THF)_4(H_2O)_2] \cdot Br_2$	4.651	2.042, 2.14	83
$MgCl_2 \cdot (pyridine)_2$	2.463, 2.483	2.26, 2.28	84
$MgBr_2 \cdot (pyridine)_6$	2.767	2.17	85
$MgBr_2 \cdot (5,7\text{-}H_2dibenz[c,e]oxepin)_4$	2.623	2.127, 2.152, 2.183	86
$MgCl_2 \cdot [(-)\text{-sparteine}]$	2.269, 2.279	2.150, 2.160	64
$MgBr_3 \cdot [(+)\text{-6-benzylsparteine}]$	2.45, 2.47	2.08, 2.17	60

Table 5 Relevant Bond Lengths (Å) and Bond Angles (°) from the Crystal Structure of Magnesium Compounds Other than those in Previous Tables

Compound	Mg—X	Mg—L	Ref.
$(Me_3Si)_2Mg \cdot (glyme)$	2.630	2.124	87
$(Me_3Si)_2Mg \cdot TMEDA$	2.628	2.192	88
$(Me_3Ge)_2Mg \cdot (glyme)_2$	2.719	2.22	89
$(H_9B_6)Mg \cdot (THF)_2$	2.38, 2.48	2.019	90
$[\{t\text{-}BuC(O)CHCH_3\}MgBr \cdot (OEt_2)]_2$	2.417	2.049, 1.953	91
$[t\text{-}BuOMgBr \cdot OEt_2]_2$	—	2.01, 1.91	92
$(THF)_2Mg_2Br_2(\mu\text{-}B{=}CPh_2)_9(\mu\text{-THF})$	2.474	2.078, 2.066, 2.453	93
[(*N*,*N*′-Ethylenebis-(acetylacetoneimine-enolate)Mg]$_3$	—	2.12, 2.00	94
(6,8,15,17-Me_4dibenzo-[*b*,*i*]-[1,4,8,11]-N_4-cyclotetradecine)Mg·(THF)	—	2.060(N), 2.041(O)	94
$Mg_6N(NHB^t)_9$	—	2.148, 2.093	95
$[Me_2Xi(Bu^tN)_2Mg \cdot THF]_2$	—	2.049(O), 2.15, 1.993	96
$[(Me_2Al)Me_2Si(NBu^t)_2 \cdot Mg(\mu\text{-I})]_2$	2.83	2.28	96
$[Bu^tNSiN(Bt^t)SiN(Bu^t)]Mg \cdot (THF)_2$	—	2.12(O), 2.05(N)	97
$[(o\text{-}Me_3SiN)_2C_6H_4]Mg \cdot (OEt_2)_2$	—	2.041(O), 1.997, 2.083	98
[Phenazine-*N*,*N*′-(MgBr $THF_3)_2$]·[$MgBr_2THF_4$]	2.513	2.12(O), 2.052	99

Material chroniony prawem autorskim

insight into the reactivity of the Grignard reagents. A list of the bond lengths and angles of some magnesium dihalides is given in Table 4. An example is the crystal structure of $MgBr_2 \cdot (THF)_4$ [Compound **61**], in which the Mg atom is in an octahedral environment with the Br atoms occupying the axial positions and the four THF groups are in the equatorial plane [56]. However, the four equatorial positions are not always occupied by the solvent groups. The crystal structure of $MgCl_2 \cdot$[(−)-sparteine] [Compound **62**] shows that the geometry around the Mg atom is tetrahedral with the sparteine ligand occupying two of the positions [57].



Compounds 61 and 62

The crystal structures of another group of magnesium compounds without Mg—C bonds are also relevant, and some of the bond lengths and angles are given in Table 5.

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10

Mechanism of Grignard Reagent Formation

CHAFIQ HAMDOUCHI
Lilly Research Center, S. A., Madrid, Spain

HARRY M. WALBORSKY
The Florida State University, Tallahassee, Florida

I. INTRODUCTION

The seminal discovery that organic halides react with magnesium metal dates back to the turn of the century [1]. The product of this reaction has been given the appellation of Grignard reagent after its discoverer, the Nobel Laureate Victor Grignard. The question of how this reagent is formed or, to put it another way, how the magnesium is inserted between the carbon–halogen bond is a subject that is still being debated.

$$RCH_2X + Mg \rightarrow RCH_2MgX$$

One of the first suggestions was advanced in 1904 by Tschelinzeff [2], who believed that the intermediates in Grignard reagent formation were oxonium or quaternary ammonium salts. This assumption was quickly rejected by Grignard himself in 1907 [1]. The exclusion of an ionic process for the mechanism of Grignard reagent formation was demonstrated by the work of Kondyrew [3] in 1925 and Brun [4] in 1939, who showed that very little current was passed when magnesium "dissolves" in an etheral solution of ethyl bromide.

An early observation by Grignard [5] that iodine could be used as an activator in initiating the reaction opened up an era of investigations and speculations on the mechanism of Grignard reagent formation. Data collected over a 50-year period were evaluated by Kharasch and Reinmuth [6], who suggested in 1954 that organomagnesium halide formation is a radical reaction involving "surface adherent radicals, at least in part." Kinetic studies on Grignard reagent formation by Kilpatrick and co-workers [7] clearly demonstrated that iodine facilitates the preparation of Grignard reagents by reducing the induction period, without affecting the rate of the reaction. To account for this observation Kharasch and Reinmuth suggested that an activator, such as iodine, must act either by cleansing the magnesium surface, or by introducing free radicals, or both. They also

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concluded that the results of Gomberg and Bachmann [8] as well as those of Gilman and co-workers [9] were consistent with magnesium halide activating the magnesium in the same manner as iodine. Thus, the activator in the presence of iodine could actually have been magnesious iodide:

$$RX + IMg \rightarrow IMgX + R^{\bullet}$$
$$IMgX + Mg \rightarrow {}^{\bullet}MgX + IMg^{\bullet}$$
$$R^{\bullet} + {}^{\bullet}MgX \rightarrow RMgX$$

Without an activator the reaction is assumed to be initiated by a catalytic amount of magnesium halide MgX_2 resulting from a Wurtz-type reaction, which would, following Kharasch and Reinmuth, account for the disproportionation products as well:

$$2RX + Mg \rightarrow MgX_2 + R_2$$
$$2RX + Mg \rightarrow MgX_2 + R_{(+H)} + R_{(-H)}$$
$$MgX_2 + Mg \rightarrow 2XMg^{\bullet}$$
$$RX + XMg^{\bullet} \rightarrow MgX_2 + R^{\bullet}$$
$$R^{\bullet} + XMg^{\bullet} \rightarrow RMgX$$

At this point Kharasch-Reinmuth concluded "there would appear to be no compelling reason to regard these radicals as 'free' in the sense that they occur in significant numbers in the body of the solution. The processes described might very well take place at the solid–liquid interface."

Persuaded by the fact that disproportionation and coupling reactions could not be the result of the reaction of the halide with its Grignard reagent under the conditions used to prepare the reagent, they added that the *surface* accounts for the disproportionation and may involve a free-radical mechanism. The mechanism they suggested, which is a modified version of the Gomberg and Bachman scheme, postulated a surface of magnesium containing "points of surface unsaturation" $(Mg)_x(Mg^{\bullet})_{2y}$. The reaction would be viewed as follows:

1. $$(Mg)_x(Mg^{\bullet})_{2y} + RX \rightarrow [(Mg)_x(Mg^{\bullet})_{2y-1}(MgX) + R^{\bullet}] \rightarrow (Mg)_{x-2}(Mg^{\bullet})_{2y}(MgX)(MgR)$$
2. $$(Mg)_{x-2}(Mg^{\bullet})_{2y}(MgX)(MgR) + RX \rightarrow (Mg)_{x-4}(Mg^{\bullet})_{2y+2} + 2RMgX$$
3. $$(Mg)_{x-2}(Mg^{\bullet})_{2y}(MgX)(MgR) + RX \rightarrow (Mg)_{x-4}(Mg^{\bullet})_{2y+2} + MgX_2 + R_2Mg$$
4. $$(Mg)_{x-2}(Mg^{\bullet})_{2y}(MgX)(MgR) + RX \rightarrow (Mg)_{x-5}(Mg^{\bullet})_{2y+2}(MgX)(MgR) + RMgX$$

Kharasch and Reinmuth also deemed it improbable that highly reactive free radicals in solution would undergo coupling reactions before reacting with the usual Grignard solvents. Thus, surface-attached radicals, by means of their "degree of surface mobility," would account for the Wurtz and disproportionation reactions, and they concluded that "it seems altogether probable that two adjacent radicals might form a dimer."

$$(Mg)_{x-5}(Mg^{\bullet})_{2y+2}(MgR)_2 \rightarrow (Mg)_{x-5}(Mg^{\bullet})_{2y+4} + R_2$$

or/and

$$(Mg)_{x-5}(Mg^{\bullet})_{2y+2}(MgR)_2 + RMgX \rightarrow [(Mg)_{x-5}(Mg^{\bullet})_{2y+3}(MgR) + {}^{\bullet}MgX + R_2] \rightarrow (Mg)_{x-6}(Mg^{\bullet})_{2y+4}(MgX)(MgR) + R_2$$

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The disproportionation reactions being controlled by the same factors as the coupling reaction would be represented by the same equation. Finally, relative to the attack on solvent by radicals that might escape into solution, they merely stated that it would depend on the design of the experiment (i.e., the nature of the free radicals and the nature of the solvent used).

The preceding is a resume of the analysis made by Kharasch and Reinmuth to account for the qualitative and quantitative observations on Grignard reagent formation made over a period of 50 years by the scientific community. Would these speculations be useful in the development of a tenable mechanism for Grignard reagent formation?

It was shortly after publication of the Kharasch and Reinmuth book that our group began their investigations on the mechanism of Grignard reagent formation.

II. WHY WERE CHIRAL CYCLOPROPYL AND VINYL SYSTEMS SELECTED FOR INVESTIGATING THE MECHANISM OF ORGANOMETALLIC COMPOUND FORMATION?

This section provides the rationale for the selection of the chiral cyclopropyl and vinyl systems in the investigation of the mechanism of organometallic compound formation. The absolute configurations and optical purities of these systems have been established. The ability of these systems to perform as effective probes in such mechanistic studies resides in the knowledge of the stereochemistry of their radical and carbanion intermediates. Do the radical and carbanion intermediates retain or lose their configurations?

A. Cyclopropyl and Vinyl Radicals

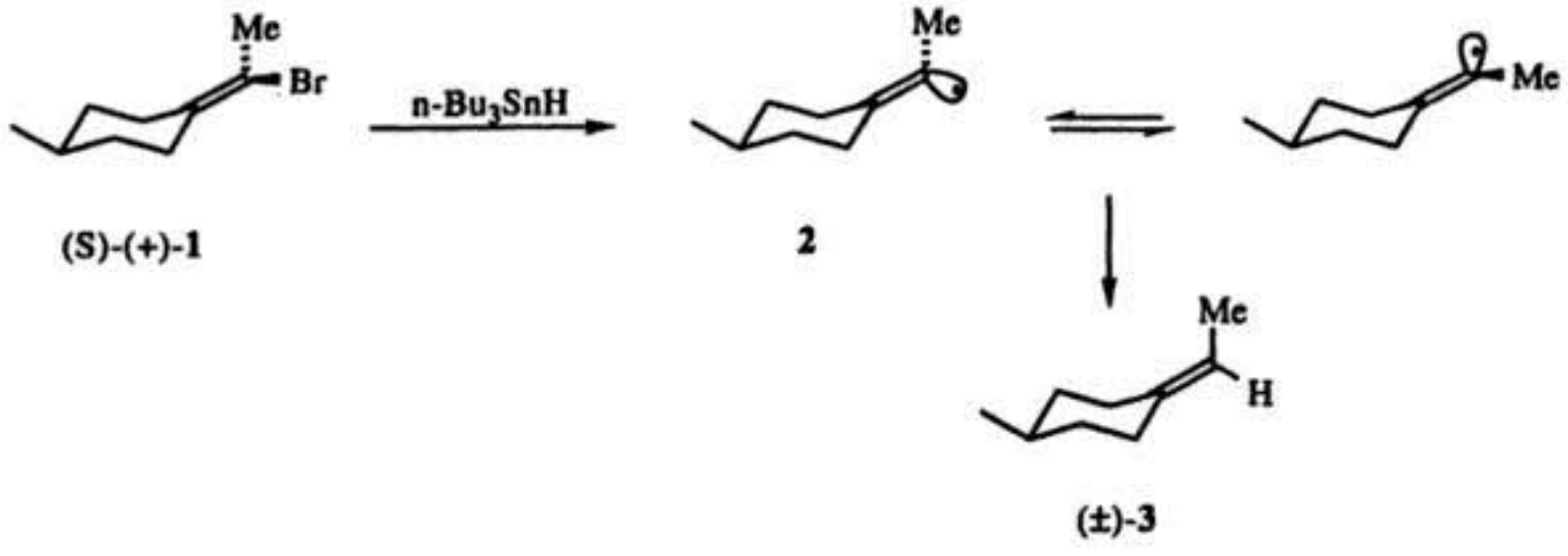
1. Stereochemistry of the Vinyl Radical

The stereochemistry of free radicals and the question of their geometry and reactivity have been the subject of several reviews [10]. Whether the unpaired electron of vinyl radicals is in a p π-orbital (linear) or in an sp^2 σ-orbital (nonlinear) has been a subject of interest for many years.

Electron spin resonance (ESR) studies on vinyl free radicals by Fessenden and Schuler [11] in liquid ethylene-ethane and by Cochran and associates [12] in an argon matrix were conclusive. The ESR spectrum of the vinyl radical reported by the latter group exhibited eight broad overlapping lines that were assigned to the hyperfine interaction of the unpaired electron with three nonequivalent protons. The three protons in this radical were nonequivalent, with values for the coupling constants of $a_{H\alpha}=16$, $a_{H\beta cis}=34$, and $a_{H\beta trans}=68$ G, respectively. Fessenden and Schuler reported two distinct β-couplings constants (58 and 33 G) for the 1-methylvinyl radical at $-172°C$ [11]. This is further evidence that the vinyl radicals are not linear at the radical center and, therefore, have an electronic configuration different from either alkyl radicals or conjugated π radicals. The inversion barrier of the vinyl radical $CH_2{=}CH^{\bullet}$ at the radical center was estimated, in these studies, to be 2 kcal/mol, with a rate of inversion of configuration with upper and lower limits of 3×10^{-8} and 3×10^{-10} sec at $-170°C$, which is on the order of diffusion control. It was also suggested that inversion of the vinyl radical takes place by a tunneling process, which is relatively temperature-insensitive.

The high inversion rate would militate against the trapping of a vinyl radical in solution, even in the presence of a good radical trap and, indeed, this was shown to be true by Walborsky and Rachon [13b]. Thus, the tri-*n*-butyltin hydride radical chain

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(S)-(+)-1 2 (±)-3

Scheme 1

reduction of (*S*)-(+)-**1** gave completely racemic (4-methylcyclohexylidene)-ethane **3** (Scheme 1).

2. *Stereochemistry of the Cyclopropyl Radical*

The high strain in cyclopropyl systems has been attributed to bond angle distortion (Baeyer strain) and nonbonded repulsions (Pitzer strain). To decrease bond angle distortion, the cause of internal strain, the cyclopropyl radical, in contrast with other cyclic and acyclic radicals, is a σ radical [11]. It was on the basis of the earlier electron spin resonance studies carried out by Fessenden and Schuler [11a] that the similarity in the electronic structure of cyclopropyl and vinyl radicals was suggested. The cyclopropyl radical electron paramagnetic resonance (EPR) spectrum exhibited ten lines, characteristic of one α ($a_{H\alpha}=6/51$ G) and four β couplings ($a_{H\beta}=23.42$ G), which indicated that its electronic structure was different from that of alkyl and cycloalkyl radicals and closer to that of a vinyl radical with the α-hydrogen atom out of the plane of the ring. An excellent later article by Ingold and co-workers [14] reported the EPR spectra of both cyclopropyl and 1-methylcyclopropyl radicals. The ^{1}H and ^{13}C hyperfine splitting (hfs) was measured for both radicals and demonstrated, unambiguously, their nonplanarity and their similar degree of deviation from planarity (Table 1).

The hfs caused by the protons on the methyl group of the 1-methylcyclopropyl radical would seem to be quite similar to that of the 1-methylvinyl radical (19.48 G) [11a], which was also shown to be a bent σ radical. The net difference of $a_{H\alpha}$ between the cyclopropyl (−6.7 G) and vinyl radicals (+13.4 G) [11a] also indicates that the vinyl radical is more bent than the cyclopropyl radical. The rate constants for the inversion of both cyclopropyl and 1-methylcyclopropyl radicals were also determined [14] by chemical

Table 1 ^{1}H and ^{13}C Hyperfine Splittings (Gauss; G) for Cyclopropyl and 1-Methylcyclopropyl Radical in Cyclopropane at −70°C

Radical	$a_{H\alpha}$	$a_{H\beta}$	$a_{^{13}C\alpha}$
$C_3H_5\cdot$	6.7(1H)	23.5(4H)	95.9
CH_3-$C_3H_5\cdot$	19.5(3H)	21(4H)	98

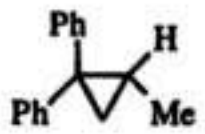
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trapping with CCl_3Br. The inversion process of these radicals was so rapid that it appeared to be impossible, as we will see later, to trap these radicals in solution before complete equilibration. At 71°C the cyclopropyl radical inverts its configuration with rate constant ca. 10^{12} sec^{-1}, slightly faster than 1-methylcyclopropyl radical 2.1×10^{11} sec^{-1} [14] and close to the diffusion rate (10^{11} sec^{-1}) [15].

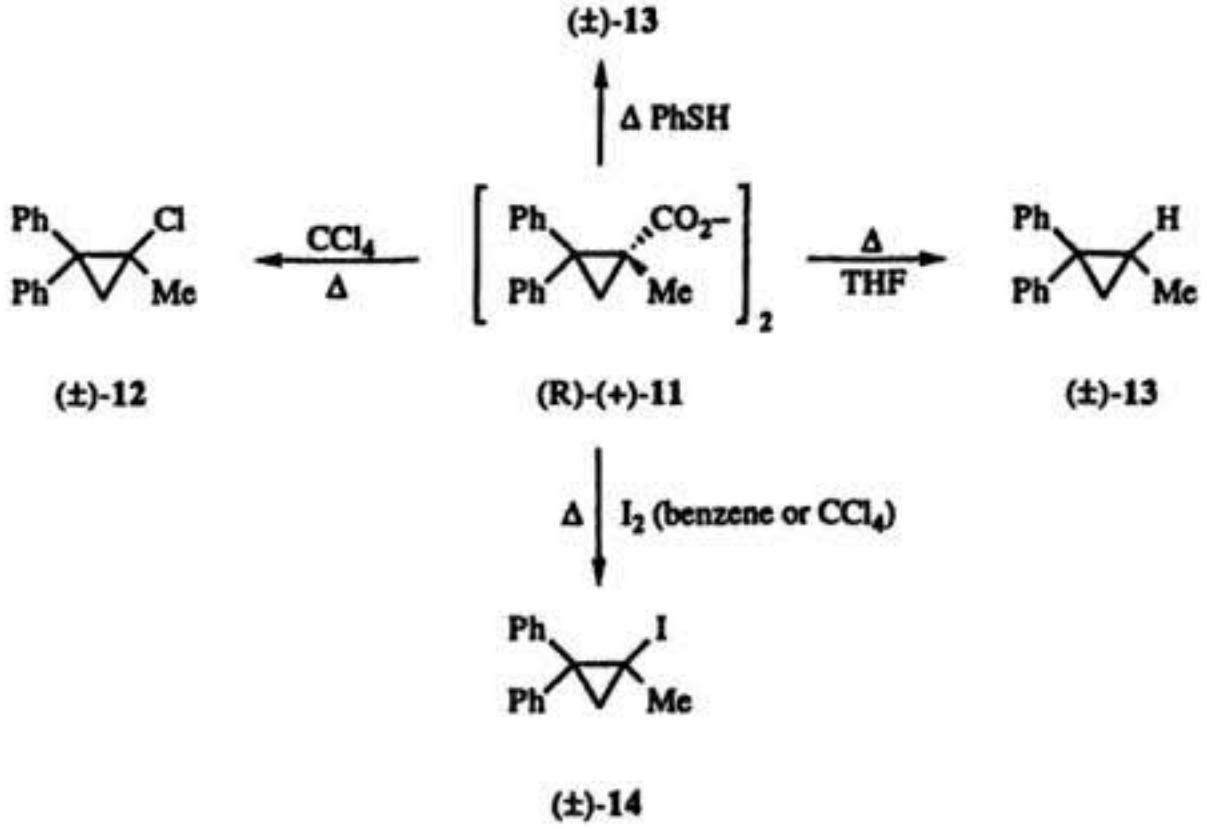
On the other hand, on the basis of ab initio calculations on the cyclopropyl radical, Dupuis and Pacansky [16] showed that the α—CH bond is bent, with an out-of-plane α—CH angle of 39.3° and an inversion barrier of 3.0 kcal mol^{-1}. In addition, their results indicated that the α—CH bond length (1.47 Å) in the cyclopropyl radical was slightly shorter than the C—C bond length (1.501Å) in cyclopropane and that the β—CC bond length (1.54 Å) was longer, which means that the σ radical causes strengthening of the α—CC bond and weakening of the β—CC bond. This is consistent with the observed mode of rearrangement of the cyclopropyl radical to the allyl radical, as will be discussed later. Using an ab initio spin-unrestricted Hartree-Fock (UHF) method, Zgierski and co-workers [17] calculated the geometry and the inversion frequency for the 1-methylcyclopropyl radical. The global minimum exhibited a pyramidalization angle of ($C_4C_1C_2C_3 = 39.5°$), the bond lengths were C_1-C_2=C_1-C_3 = 1.469 and the inversion, which was accompanied by methyl rotation, had a frequency of 9×10^{12} sec^{-1} at −173°C.

Again, given the extraordinary high inversion frequency for the cyclopropyl and methylcyclopropyl radicals, one would expect complete loss of configuration when these radicals are generated in solution, regardless of the radical trap that is present. Hence, it is not surprising that total loss of optical activity was observed when the 1-methyl-2,2-diphenylcyclopropane radical was generated in solution by a variety of methods employing chiral precursors:

1. Thermal decomposition of the diacyl peroxide of (*R*)-(+)-methyl-2,2-diphenylcyclopropane carboxylic acid **11** without or in the presence of a good radical trap, such as iodine or thiophenol [18] (Scheme 2).



(±)-13



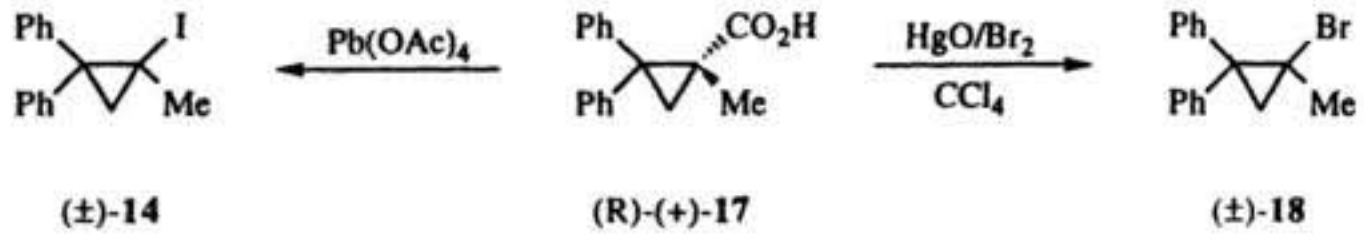
(±)-12 (R)-(+)-11 (±)-13

(±)-14

Scheme 2

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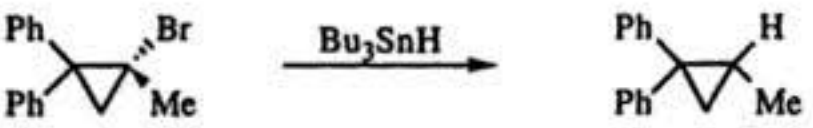
2. Decarboxylation of acid (*R*)-(+)-(**17**) with lead tetraacetate-iodine [19] or with HgO/Br_2 [20] (Scheme 3).



(±)-**14** (R)-(+)-**17** (±)-**18**

Scheme 3

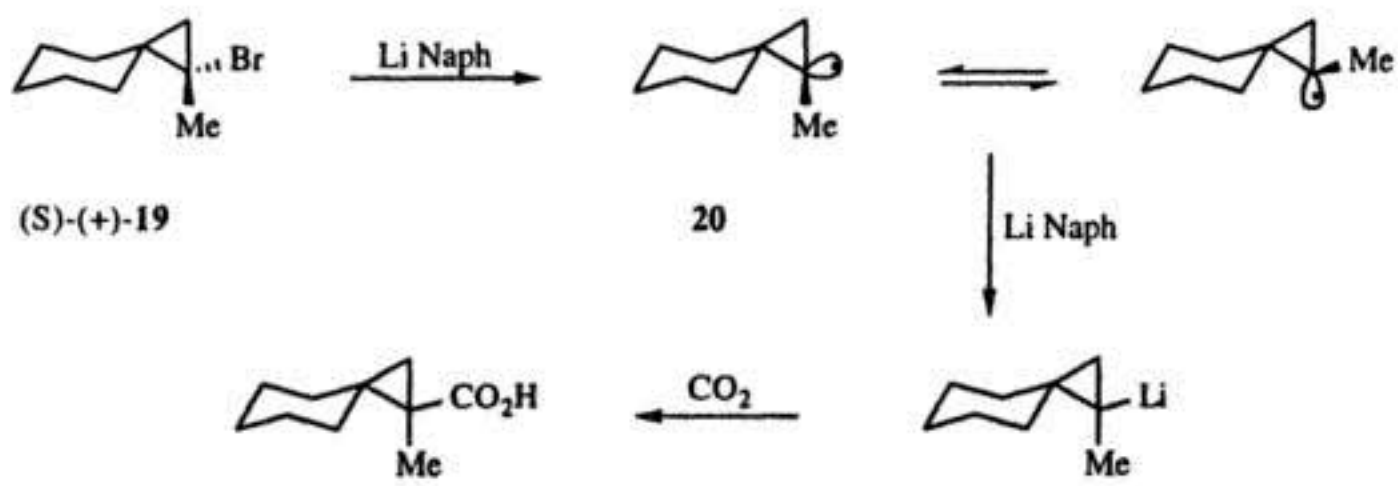
3. Reduction of (*R*)-(+)-1-bromo-1-methyl-2,2-diphenylcyclopropane **18** with tri-*n*-butyltin hydride as solvent [18, 21] (Scheme 4).



(R)-(-)-**18** (±)-**13**

Scheme 4

Total loss of optical activity of the cyclopropyl radical was also reported recently by Walborsky et al. [22] for a chiral aliphatic cyclopropyl system. When optically pure (*S*)-(+)-1-bromo-1-methylspiro[2,5]octane **19** was reduced under homogeneous conditions with lithium naphthalenide in tetrahydrofuran (THF) at room temperature the resulting acid **22**, isolated after carbonation, was completely racemic (Scheme 5).



(S)-(+)-**19** **20** (±)-**22** (±)-**21**

Scheme 5

3. *Reactivity of Cyclopropyl and Vinyl Radical*

Another interesting feature related to the σ nature of the cyclopropyl and vinyl radicals is their reactivity. In general, σ radicals are more reactive and less selective than π radicals. Phenyl, vinyl, and cyclopropyl σ radicals will abstract hydrogen atoms from saturated hydrocarbons at 77 K, conditions under which π radicals are unreactive [23]. In Rüchardt's [24] radical reactivity classification, based on the reaction of a series of σ and π radicals with $BrCCl_3$ and CCl_4, the cyclopropyl radical, an inverting σ radical in an sp^2-hybridized orbital, closely resembled the noninverting phenyl radical. Further support for this finding

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Table 2 Absolute Rate Constants for Reactions of Various Radicals with Tri-*n*-butylgermane at Ambient Temperature

Radical	Temp (°C)	$10^{-6}\ k^{Ge}\ (M^{-1}\ sec^{-1})$	k_H^{Sn}/k_H^{te}
$C_6H_5\cdot$	29	260±28	2
$(Me)_2C{=}CH^{\bullet}$	27	35±5	10
$c\text{-}C_3H_5\cdot$	30	13±2	7
$CH_3\cdot$	27	0.5	20
$RCH_2CH_2\cdot$	27	0.1	24

Source: Ref. 266.

was supplied by experiments of Shono and Nishiguchi [25], who also point out that the cyclopropyl radical behaves more like a phenyl σ radical than a π cyclohexyl radical.

Definitive kinetic data for the reactivity of cyclopropyl and vinyl radicals were provided by work of Ingold and co-workers [26a,b]. Their investigation of the reactivity of some carbon-centered radicals with tri-*n*-butylstannane at 30°C [27] showed that the absolute rate constant for those reactions decreased along the series: $C_6H_5^{\bullet}$ (59[a]) $(CH_3)_2X{=}CH^{\bullet}$ (35) > $c\text{-}C_3H_5^{\bullet}$ (8.5) > $CH_3^{\bullet}$ (1.2) > $RCH_2CH_2^{\bullet}$ (0.27) > $(CH_3)_2CH^{\bullet}$ (0.15) (*a*: rate constant $10^{-7}\ k_{H^{Sn}}$, $M^{-1}\ sec^{-1}$ at 30°C).

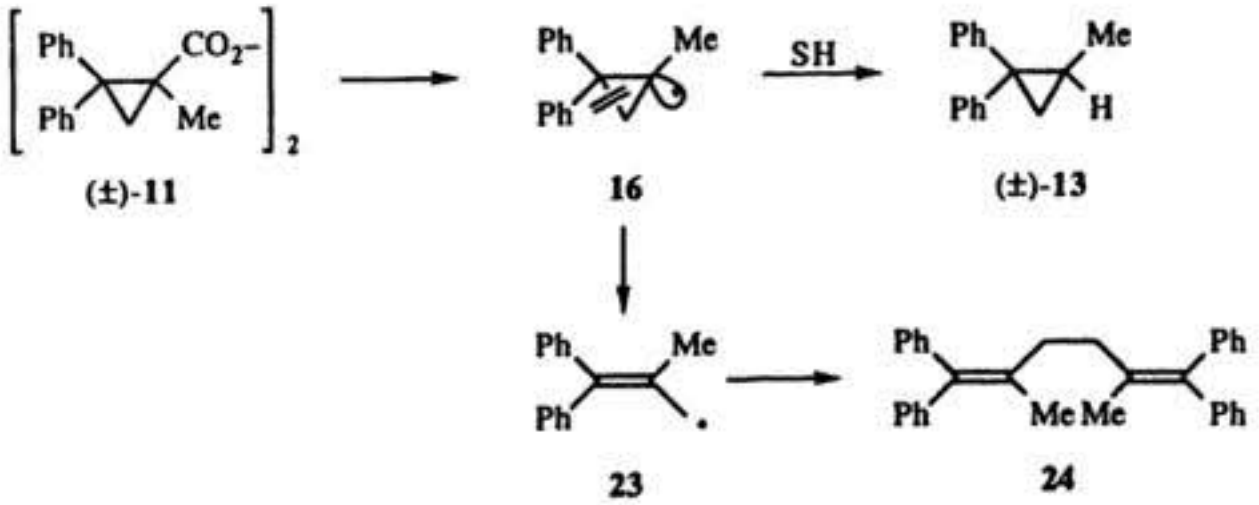
The same order of absolute rate constants was noted for the reactivities of radicals with tri-*n*-butylgermane [27] (Table 2).

4. *Rearrangement of Cyclopropyl Radical*

Another feature that distinguishes the cyclopropyl radical is its propensity to react with solvent before it can rearrange to the more stable allyl radical when it is generated *in solution*. This is because the activation energy for rearrangement is higher than for its reaction with solvent. For example, an unsubstituted cyclopropyl radical requires an energy of 22 kcal mol^{-1} [28,29] to rearrange to an allyl radical, whereas a cyclopropyl radical reacts with solvent by abstracting hydrogen, with an activation energy that is reported [29] to be 7 kcal mol^{-1}.

$$\text{cyclopropane} \xleftarrow{7\ \text{kcal mol}^{-1}} \text{cyclopropyl radical} \xrightarrow{22\ \text{kcal mol}^{-1}} \text{allyl radical}$$

The rearrangement of a cyclopropyl radical to an allyl radical in solution was reported for the first time by Walborsky et al. [18] in the thermal decomposition of 1-methyl-2,2-diphenylcyclopropanecarbonyl peroxide [11] (Scheme 6). The 1-methyl-2,2-diphenylcyclopropyl radical [16] reacted by both abstracting hydrogen from the solvent



Scheme 6

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and by rearranging to the 1,1-diphenyl-2-methylpropenyl radical [23], which dimerized to yield 1,1,6,6-tetraphenyl-2,5-hexadiene [24]. The proportion of dimeric product to that of cyclopropane was dependent on the solvent. If a good radical scavenger, such as chloroform, carbon tetrachloride, or thiophenol, is used, only the unrearranged cyclopropane is obtained. The rearrangement of **16** to **23** has become a useful diagnostic tool, as will be seen in the sequel.

5. *Summary*

Both cyclopropyl and vinyl radicals are σ-radicals with inversion frequencies near or at diffusion control and with similar absolute rate constants, as evidenced by their reactivity toward tri-*n*-butylstannane and tri-*n*-butylgermane.

B. Cyclopropyl and Vinyl Carbanions and Organometallic Reagent

Available methods for generating cyclopropyl and vinyl anions from their corresponding cyclopropyl and vinyl halides are reactions with metal surfaces, with dissolving metals, by halogen–metal exchange, and by electrochemical reduction. In this section we examine the circumstances under which free radicals are not formed as intermediates during the formation of these carbanions and organometallic reagents.

In contrast with the lithium–halogen exchange reactions of tetrahedrally hybridized alkyl iodides in which free alkyl radicals have been detected as intermediates by ESR [30], chemically induced dynamic nuclear polarization (CIDNP) [31], and by chemical trapping of the radicals [32], radicals were not detected for cyclopropyl and vinyl iodides. In general the optical stability of tetrahedrally (sp^3) hybridized organolithium compounds is both temperature- and solvent-dependent. The halogen metal exchange between (−)-(*R*)-2-octyl iodide and *sec*-butyllithium in petroleum ether–ether at −70°C, followed by carbonation, gave (−)-(*R*)-2-methyloctanoic acid that was 80% racemized [33]. The optical purity decreased with increase in temperature, and time allowed for the exchange, thereby indicating the configurational instability of the optically active 2-octyllithium reagent. Also addition of diethyl ether increases the rate of racemization [34].

1. *Stereochemistry of Vinyl Carbanion*

Trigonally hybridized vinyllithium derivatives are characterized by higher configurational stability [34,35]. Panek [36] demonstrated that (*E*) and (*Z*)-1-lithium-1-phenyl-1-butene could be prepared stereospecifically, with retention of configuration, by a lithium–halogen exchange reaction between *n*-butyllithium and (*Z*) and (*E*)-1-bromo-1-phenyl-1-butene, respectively (Scheme 7). Both lithium derivatives are configurationally stable at



25 **26**

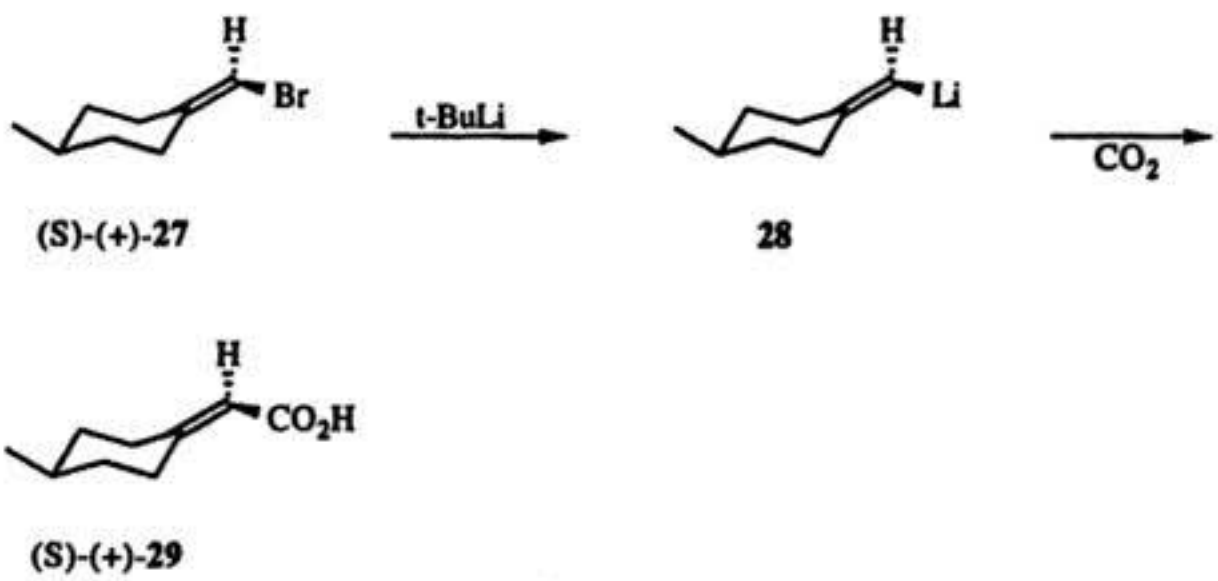
Scheme 7

room temperature in hexane solutions. However, *cis–trans*-isomerization occurred in hexane–THF mixtures.

When the α-substituents are alkyl groups [34,35a] and hydrogen [37], instead of phenyl, the vinyllithiums are configurationally stable, even in coordinating solvents. The

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configurational stability of vinyllithium was examined by Walborsky and Banks [38], who showed that the stereochemical stability of the vinyllithium reagent in diethyl ether was temperature-dependent. Halogen–metal exchange of *t*-butyllithium with opticaly pure (*S*)-(+)-4-methylcyclohexylidenebromomethane **27** in diethyl ether at −65°C produced 4-methylcyclohexylidenemethyllithium, which was carbonated at different temperatures to form the corresponding acid (Scheme 8). Carbonation at −65°C gave an acid, (*S*)-(+)-**29**, with an optical purity greater than 99%. However, when the vinyllithium solution was allowed to warm to 0°C and remain at that temperature for 2 hr, the optical purity of resulting acid, isolated after carbonation, dropped to 79%.



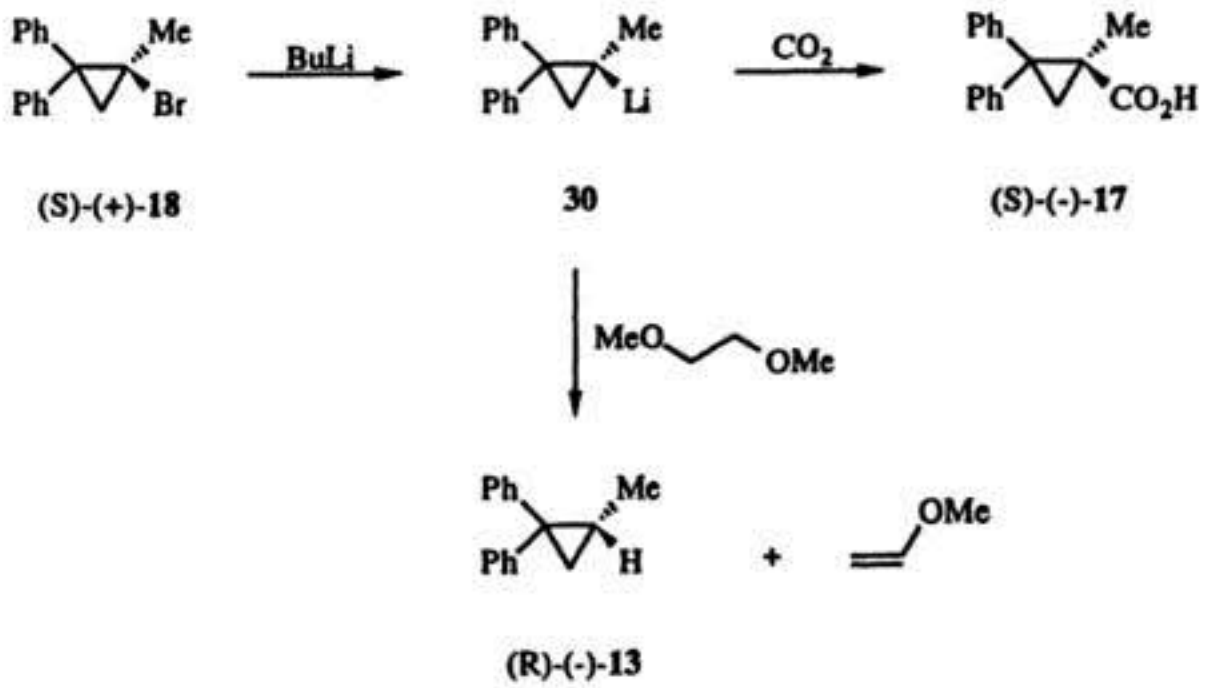
(S)-(+)-27 28

(S)-(+)-29

Scheme 8

2. *Stereochemistry of Cyclopropyl Carbanion*

Because of the greater s character of cyclopropane's excocyclic orbitals [39] ($sp^{2.28}$), the cyclopropyl carbanion might be expected to behave similar to the trigonally hybridized (sp^2) vinyl carbanion. This was indeed shown to be so by Walborsky et al. [40], who investigated the halogen–lithium interchange between (*S*)-(+)-1-bromo-1-methyl-2,2-diphenylcyclopropane **18** and *n*-butyllithium under a variety of conditions (temperature, solvent, and reaction time). They demonstrated that 1-methyl-2,2-diphenylcyclopropyllithium was capable of maintaining its configuration, as judged by the optical purity of the products obtained when it was allowed to react with methanol, water, carbon dioxide, bromine, and iodine (Scheme 9). Moreover, solvent, temperature, and reaction time had very little,



(S)-(+)-18 30 (S)-(-)-17

(R)-(-)-13

Scheme 9

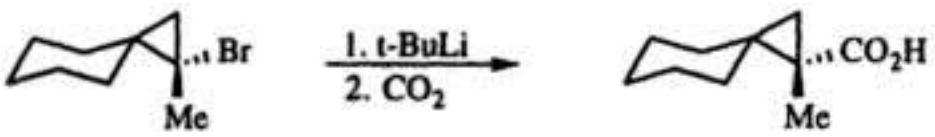
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Table 3 Solvent and Temperature Effect on the Stereochemistry of Cyclopropyl Carbanion

Solvent	Temp (°C)	Time (min)	Yield (%)	Opt. purity (%)
Ether	28	30	53	100
Ether	28–29	10	52	100
Ether	−8	30	49	100
THF	−8	20	39	100

if any, effect on the optical purity (Table 3). The lithium derivative reacted with solvent in the order 1,2-dimethoxyethane > tetrahedrofuran > diethylether. When dimethoxyethane was used, carbonation of the reaction mixture failed to yield any 1-methyl-2,2-diphenylcyclopropanecarboxylic acid **17**. The only product isolated was the hydrocarbon **13** in 85% optical purity. This observation will be used to advantage later.

A similar result was observed with a completely aliphatic substituted cyclopropyl derivative (Scheme 10). When optically pure (*S*)-(+)-1-bromo-1-methylspiro[2,5]octane **19** was treated with *t*-butyllithium in ether solution at −78°C for 30 min, the acid **22** obtained on carbonation was isolated, with complete retention of optical activity and configuration [22]. This indicates that 1-methylcyclopropyllithium derivatives are configurationally more stable than alkyllithium (sp^3) reagents and those vinyllithium reagents that contain a phenyl group in the α-position. Their stability is comparable with that of alkyl-substituted vinyllithium reagents.



(*S*)-(+)-**19** (*S*)-(+)-**22**

Scheme 10

The foregoing technique allows one to prepare other organometallic compounds, such as organomagnesium, organosamarium [41], and organocalcium [42] derivatives, with complete retention of optical activity and configuration. This can be accomplished by simply treating the configurationally stable cyclopropyl or vinyllithium reagent with the corresponding metal halide.

3. *Summary*

It has been demonstrated that cyclopropyl and vinyl radical intermediates cannot maintain their configurations when generated in solution, whereas their corresponding anions, as organometallics, do. Thus, these systems serve as convenient probes for investigating the mechanism of organometallic compound formation. These features were utilized and served as basis for investigating and establishing the mechanism of Grignard reagent formation.

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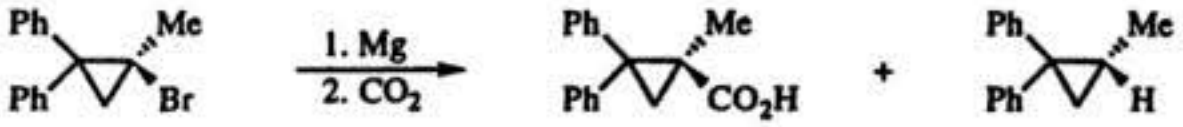
III. THE MECHANISM OF GRIGNARD REAGENT FORMATION

A. Intermediacy of Radicals and Pathways Leading to Radicals and to Grignard Reagent: Optically Active Grignard Reagent

The first successful formation of an optically active Grignard reagent in which the magnesium is directly attached to the chiral center was reported in a short communication in 1961 [43], followed by a full paper in 1964 [44]. Previous attempts to prepare optically active Grignard reagents from acyclic halides such as (−)-2-iodobutane [45], (−)-2-bromooctane [46, 47] and optically active 1-phenylethyl bromide [48], as well as a cyclic halide (−)-3,3-dimethylcyclohexyl chloride [48], all had given rise to racemic products.

The first chiral halides used by Walborsky and Young [43,44] were optically active 1-bromo-1-methyl-2,2-diphenylcyclopropane **18**, 1-chloro-1-methyl-2,2-diphenylcyclopropane **12**, and 1-iodo-1-methyl-2,2-diphenylcyclopropane **14**, the absolute configurations and optical purities of which were established [40,49] as were those of their derivatives, 1-methyl-2,2-diphenylcyclopropane **13** and 1-methyl-2,2-diphenylcyclopropanecarboxylic acid **17**.

When (*S*)-(+)-1-bromo-1-methyl-2,2-diphenylcyclopropane **18** was treated with a powdered magnesium–magnesium bromide mixture in refluxing tetrahydrofuran and the reaction mixture carbonated (Scheme 11), the resulting products 1-methyl-2,2-diphenylcyclopropanecarboxylic acid **17** and 1-methyl-2,2-diphenylcyclopropane **13** were optically active, with predominant retention of configuration. This was the first



(S)-(+)-18 (S)-(-)-17 (R)-(-)-13

Scheme 11

demonstration of an optically active Grignard reagent. Neither solvent, temperature, nor reaction time greatly affected the optical purities of the products (Table 4). The yield of acid increased along with a corresponding decrease in hydrocarbon when going from ether to THF. Also, the particle size and purity of magnesium had little, if any, effect on the stereochemistry of Grignard reagent formation.

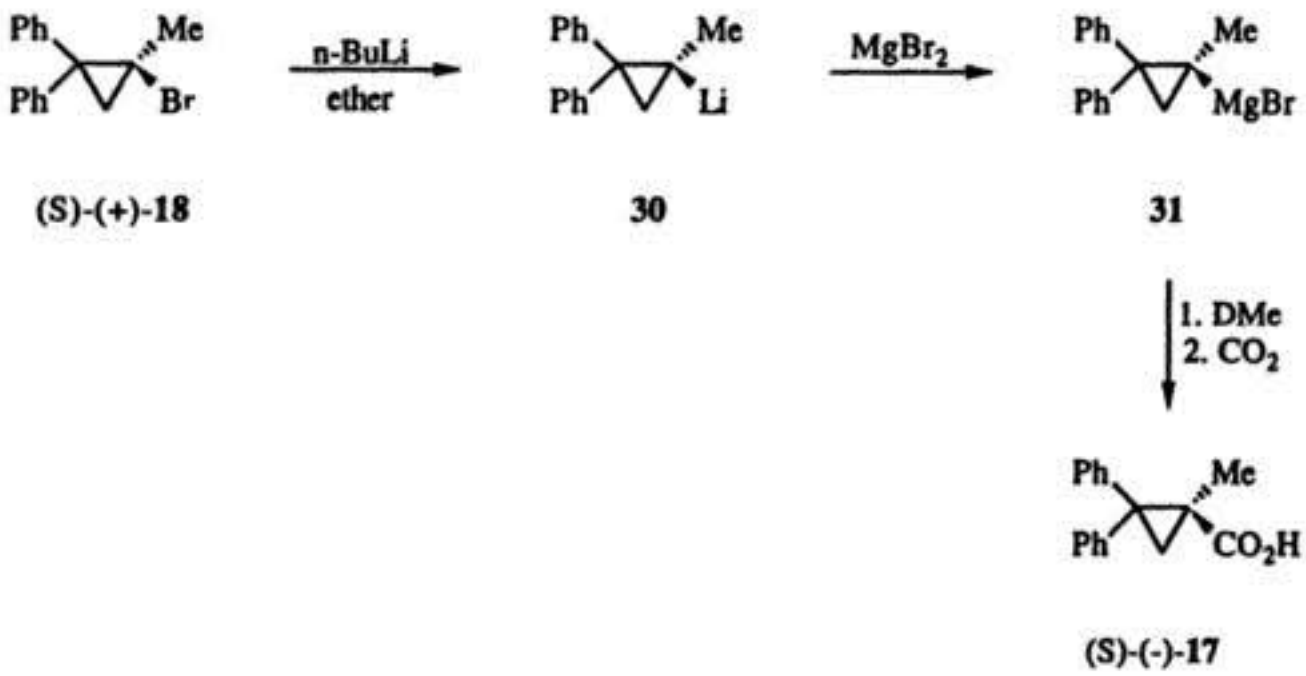
The first question that arose from these results was the following: At which point in the reaction had the racemization occurred? That the unreacted amount of (*R*)-(−)-1-bromo-1-methyl-2,2-diphenylcyclopropane recovered after the reaction had undergone no loss of optical activity removed the possibility that racemization was due to racemization of starting material under the reaction conditions [44]. However, to ascertain whether or not the racemization occurred after the Grignard reagent was formed, it was necessary to prepare an authentic sample of the optically active Grignard reagent. This was achieved by the reaction of optically stable 1-methyl-2,2-diphenylcyclopropyllithium **30** with an etheral solution of anhydrous magnesium bromide (Scheme 12). To assure that no unreacted lithium reagent remained, dimethoxyethane, which was known to decompose **30**, was added. Carbonation of the reaction mixture produced the corresponding acid **17** with complete retention of optical activity and configuration [44], thereby demonstrating that, once formed, the Grignard reagent **31** is

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Table 4 Stereochemistry of Grignard Reagent Formation from Optically Active 1-Methyl-1-bromo-2,2-diphenylcyclopropane

Solvent	Temp. (°C)	Time (min)	Acid		Hydrocarbon	
			Yield (%)	Opt. purity (%)	Yield (%)	Opt. purity (%)
Et_2O[a,b]	35	20	8.3	14.5	59	9.6
Et_2O[b,c]	35	29	26	20.4	22.9	3.7
THF[a,b]	25–27.5	40	45	12.6	36	10.15
THF[a,b]	65	20	38	15.2	38	11.5
THF[a,b,d]	65	30	32	18.8	44	12.3
THF[a,b]	65	30	66	15.5	20	13.7
THF[c,b]	65	35	70	18.5	6.0	6.2
THF[a,b]	65	180	41	15.3	32	12.6
THF[c]	65	180	79	16.2	4.8	4.2
THF[e,c,b]	65		62	16.0	7.8	6.1
THF[f,c,b]	65		45	15.0		

[a]In the earlier studies [43, 44], the reaction mixture was carbonated in the conventional manner by pouring it into a slurry of dry ice, which may have led to a large amount of 1-methyl-2,2-diphenylcyclopropane, resulting from hydrolysis of the Grignard reagent during the carbonation. Under these conditions it was not possible to determine the optical purity of the hydrocarbon formed during Grignard reagent formation.
[b]Magnesium powder was used.
[c]Reactions were carried out in a vacuum manifold system, which enabled the formation and carbonation of the organometallics to be conducted under conditions that excluded moisture mixture and air [50].
[d]Ethylene dibromide was added to bromide and magnesum.
[e]Magnesium turnings were used.
[f]Magnesium of 99.9995% purity was used.



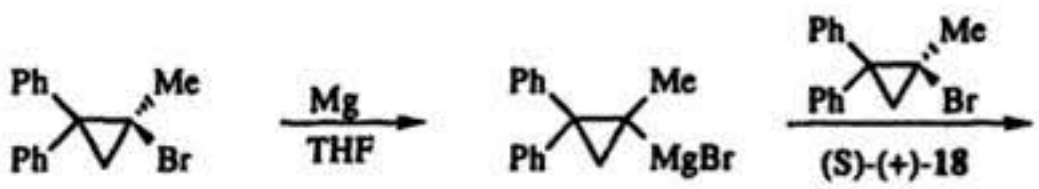
Scheme 12

configurationally stable. Hence, the extensive racemization observed must have occurred in the Grignard reagent formation step in which radicals are known to be involved.

How does one account for the observed retention of configuration? Could retention have been a result of halogen–metal interchange with Grignard reagents? In this manner the formation of Grignard reagents could involve complete racemization, as has been observed with other optically active halides [47], but if the racemic Grignard reagent was

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then to undergo halogen–metal interchange with unreacted optically active halide (a retention step), this would result in the formation of partially active Grignard reagent, as was observed (Scheme 13). Moreover, the results of Zakharin et al. [51] would be in support of this assumption, since their studies on the exchange of Grignard reagents with alkyl and aryl halides suggested that the halogen–metal interchange reaction is the same for both organomagnesium and organolithium compounds. This would imply that the organomagnesium exchange also proceeds with retention of configuration.



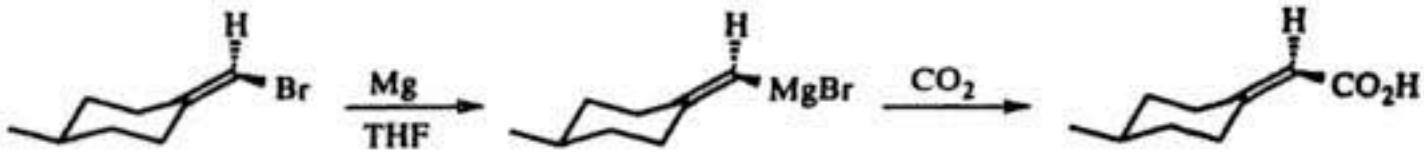
Scheme 13

This question was addressed by Walborsky et al. [50] in the following experiment. A solution of racemic Grignard reagent **31** was prepared from racemic 1-methyl-1-bromo-2,2-diphenylcyclopropane ±**18** in THF and separated from unreacted magnesium. The racemic Grignard reagent was then added to a solution of opticaly active bromide **18**. When the reaction mixture was refluxed for 3 hr and then treated with carbon dioxide, the resulting acid **17** was completely racemic. Thus, halogen–metal interchange can be excluded as a source of the observed optical activity.

At this point, it appeared that the radical intermediate was not entirely free. This resulted in the first proposal for the pathway leading to Grignard reagent formation. It was postulated that electron transfer occurs from the metal surface into the carbon–halogen bond to lead to a *tight anion radical–cation radical pair*, the collapse of which on the surface yielded Grignard reagent with complete retention of configuration. Racemization would result from collapse of the tight anion radical–cation radical pair to a loose radical pair, or might also result directly from initial electron transfer. This proposal was supported by a study of the effect of various halogens on Grignard reagent formation, which will be discussed later.

The other system in which the stereochemistry of Grignard reagent formation was investigated involved use of a chiral vinyl bromide selected for the reasons discussed previously. Walborsky and Banks [38] reported formation of Grignard reagent **32** from chiral (*S*)-(+)-4-methylcyclohexylidenebromomethane **27** (Scheme 14). Optically active (*S*)-(+)-(4-methylcyclohexylidene) bromomethane was converted to the Grignard reagent by reaction with magnesium powder in THF. Carbonation of the Grignard reagent gave the acid **29**, which was 42% optically pure. As with cyclopropyl bromide **18**, the unreacted

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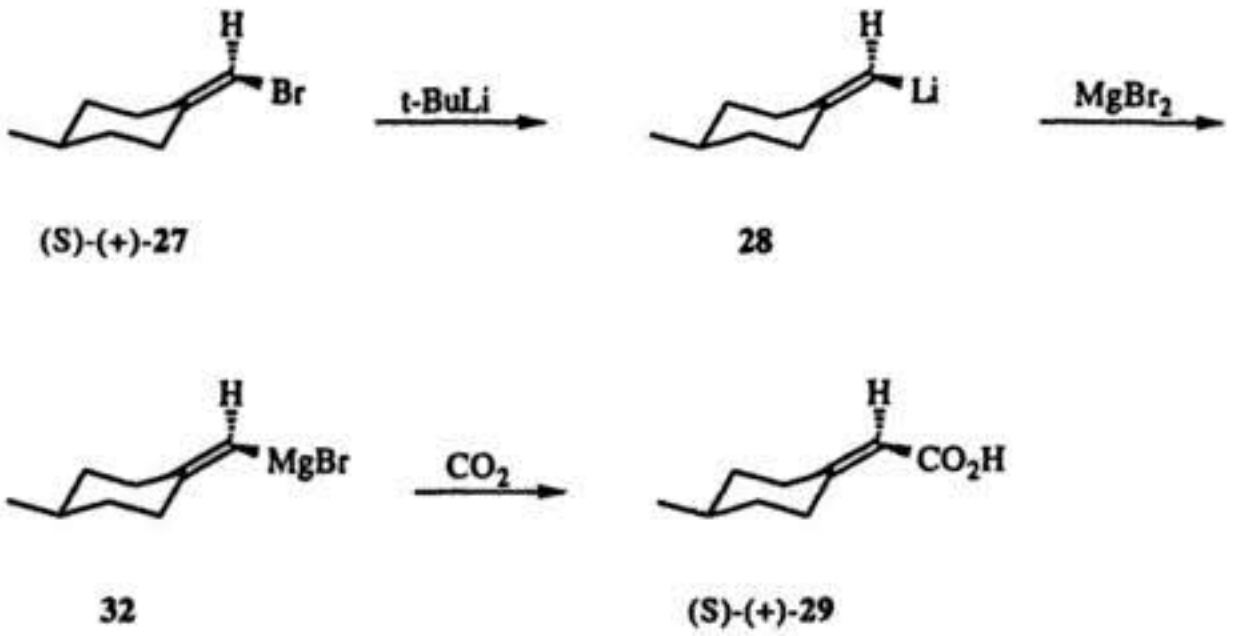


(S)-(+)-27 32 (S)-(+)-29

Scheme 14

bromide could be recovered with complete retention of its initial optical activity. This, again, showed that the loss of optical activity observed in the vinyl Grignard reagent was not due to racemization of the substrate vinyl bromide **27** under the reaction conditions.

As in the cyclopropyl system, to determine whether racemization occurred after the Grignard reagent was formed, the corresponding vinyl Grignard reagent was prepared by treating optically active (4-methylyclohexylidene)methyllithium **28** with excess magnesium promide in THF–hexane solution (Scheme 15). The reaction was allowed to warm to room temperature and then carbonated, whereupon acid **29** was isolated with 91% overall retention of configuration. It is important to recall that the observed small loss of optical activity had actually occurred in the vinyllithium reagent before reaction with magnesium bromide.



(S)-(+)-27 28 32 (S)-(+)-29

Scheme 15

The formation of vinyl Grignard reagent by direct interaction of optically active (4-methylcyclohexylidene)bromomethane **27** with magnesium metal also occurs with partial racemization. Here, too, the racemization occurred in the Grignard formation step.

The stereoselectivity of the reaction of vinyl bromide **27** with magnesium metal is considerably higher than that observed for the cyclopropyl bromide. It has been suggested [38] that the stereoselectivity of the reaction of magnesium metal with chiral organic halides increases with the amount of s-character of the carbon–halogen bond (Table 5). The correlation of carbon–halogen bond strength with the stereoselectivity of chiral Grignard reagent formation implies that electron transfer to vinyl halides is followed by a more concerted collapse of the tight anion radical–cation radical pair leading to retention, rather than in the corresponding step for the reaction of cyclopropyl or alkyl substrates.

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Table 5 Influence of the Hybridization State on the Stereochemistry of Grignard Reagent

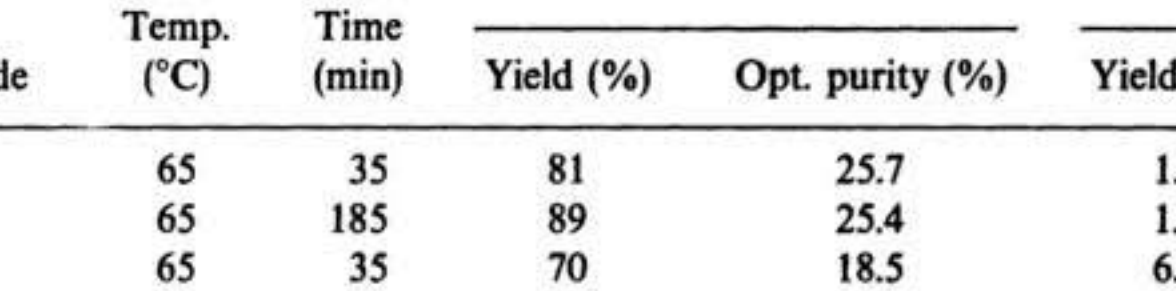
R–X	Temp. (°C)	Solvent	Opt. purity of acid (%)	Hybridization of chiral C
(*S*)-(+)-**27**	25	THF	42	sp^2
(*S*)-(+)-**18**	65	THF	18	$sp^{2.28}$
(c-Hexyl)$CHClCH_3$ [46, 47]	35	Et_2O	0	sp^3

Table 6 Effect of Halogen on the Stereochemistry of Grignard Reagent Formation from Optically Pure 1-Methylcyclopropyl Halides in THF

			Acid		Hydrocarbon	
Halide	Temp. (°C)	Time (min)	Yield (%)	Opt. purity (%)	Yield (%)	Opt. purity (%)
Cl	65	35	81	25.7	1.3	6.6 (inv.)
Cl	65	185	89	25.4	1.0	5.3 (inv.)
Br	65	35	70	18.5	6.0	6.2 (ret.)
Br	65	180	79	16.2	4.8	4.2 (ret.)
I	65	34	40	1.8	(4.4)	0.8 (ret.)
I	65	190	36	1.9	19.0	1.0 (ret.)

B. Halogen Effect on the Stereochemistry of the Grignard Formation Reaction

That halogen has an effect on the stereochemistry of Grignard reagent formation was reported in the earlier studies [44, 50]. Optically active 1-methyl-2,2-diphenylcyclopropyl chloride **12**, bromide **18**, and iodide **14** were converted to their corresponding Grignard reagents and carbonated (Scheme 16). The results are shown in Table 6.



X=Cl, (R)-(-)-**12**
X=Br, (R)-(-)-**18**
X=I, (R)-(-)-**14**

(R)-(+)-**17**

(S)-(-)-**13**

Scheme 16

In all experiments acid **17** was obtained with overall retention of configuration. An interesting effect of the halogen is revealed. Retention of optical activity or configuration decreases in the direction Cl > Br ≫ I, with cyclopropylmagnesium iodide being essentially racemic. The yield of acid varies in the same direction, Cl > Br ≫ I, and the product hydrocarbons are very nearly racemic.

The energy of the carbon–halogen bond as well as the reduction potential decreases in the order Cl > Br > I, as do the optical purities and yields of the Grignard reagents.

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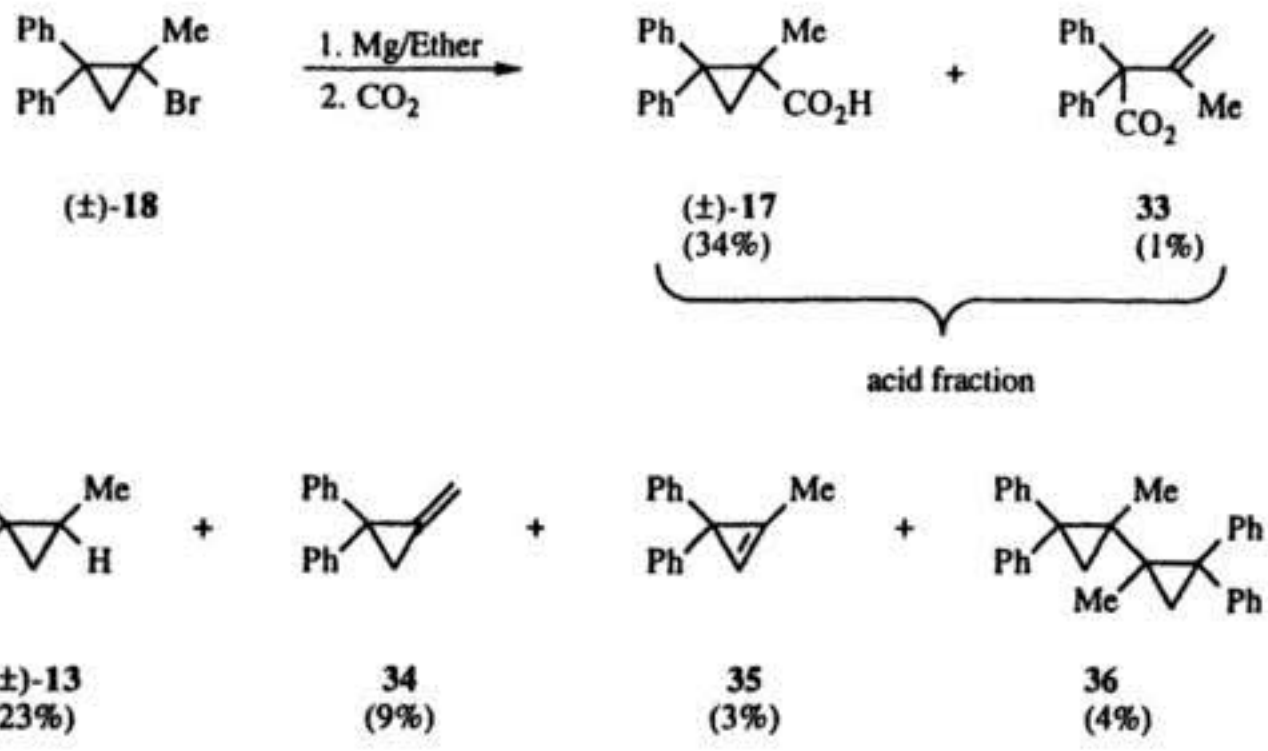
This is consistent with the conclusion that the amount of loose radical pair formed is determined by the strength of the carbon–halogen bond. As the halogen is changed from iodide, to bromide, to chloride, the bond strength increases and more energy is required to add an additional electron to the carbon–halogen bond. Consequently, the lifetime of the intermediate radical ion decreases in this order, and the reaction becomes more concerted, with the consequence that there is less loose radical pair formed and, thus, less racemization and loss of material to side processes.

The foregoing results highlight the questions of the exact nature of the radicals involved in Grignard reagent formation and why the amount of hydrocarbon formed increases when changing solvent from THF to ether.

C. Nature of the Radicals

1. *Product Analysis*

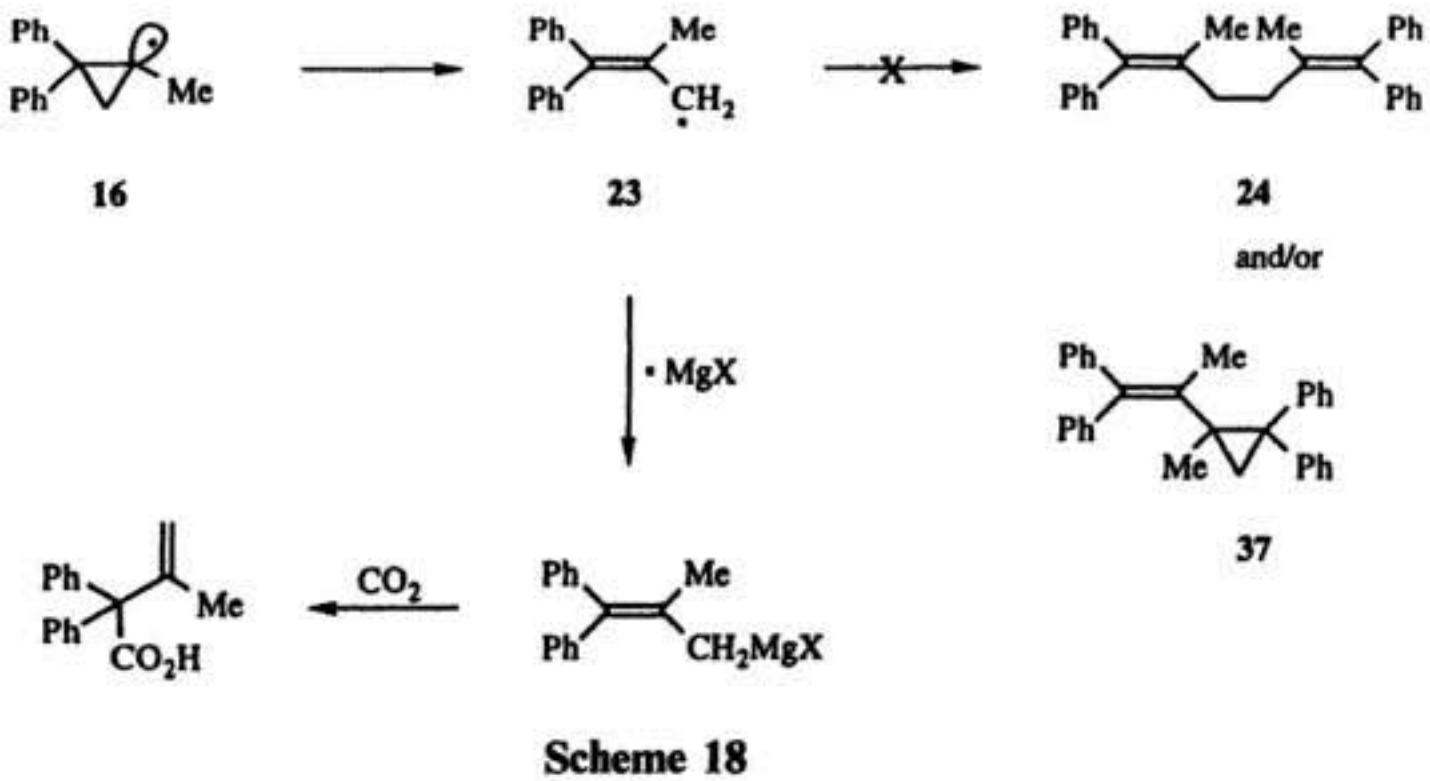
In addition to stereochemical analysis of Grignard reagent formation from optically active 1-methyl-2,2-diphenylcyclopropyl halides, examination and identification of the minor products were thought to provide helpful information for understanding the nature of the radicals involved in this process. Thus, a thorough analysis of the acid and hydrocarbon fractions after carbonation of the Grignard reagent formed from racemic 1-methyl-2,2-diphenylcyclopropyl bromide **18** in ether was undertaken [50] (Scheme 17). Along with 1-methyl-2,2-diphenylcyclopropane carboxylic acid **17**, formed in 34% yield from the cyclopropyl bromide, 1% of 2,2-diphenyl-3-methyl-3-butanoic acid **33** was isolated and identified (Scheme 17), the latter being formed by isomerization of the cyclopropyl radical, either in solution or on the magnesium surface, to form an allylic Grignard reagent (Scheme 18). Although the isomerization might lead to the primary Grignard reagent [52], carbonation would yield tertiary acid **33**.



Scheme 17

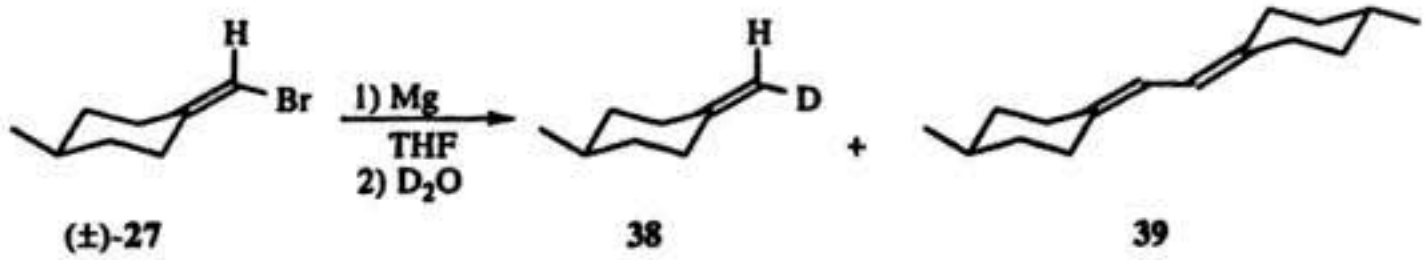
The hydrocarbon fraction was composed of 23% 1-methyl-2,2-diphenylcyclopropane **13**, 9% 2,2-diphenylmethylenecyclopropane **34**, 3% 1-methyl-2,2-diphenylcyclopropene **35**, along with 4% of a higher molecular weight material that turned out to be the "dimer" 1,1-disubstituted-2,2-diphenylcyclopropane **36**. All attempts to detect the presence of other possible dimeric material such as **24** and **37** failed.

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Scheme 18

On the other hand, thorough examination of the products formed after reaction of racemic 4-methylcyclohexylidenebromomethane **27** in THF with magnesium powder followed by hydrolysis of the reaction mixture with deuterium oxide (Scheme 19) furnished 4-methylcyclohexylidenemethane **38** along with bis-1,2-(4-methylcyclohexylidene)ethane **39** in 7:1 ratio. The amount of vinyl Grignard reagent formed was 79%, as judged by approximately 90% deuterium incorporation in olefin **38**.



Scheme 19

Thus, it appears that the side products for both cyclopropyl and vinyl systems differ, in both nature and quantity, from those obtained when the same radicals are generated in solution. This is explained in terms of a *surface-bound radical.*

However, it is difficult to distinguish unambiguously between the amount of hydrocarbon arising from the disproportionation reaction between two radicals and the amount arising from solvent cleavage. To differentiate between the two possibilities, the formation of Grignard reagents in perdeuterated ethers was investigated [50].

2. *Formation of Grignard Reagent in Perdeuterated Ethers*

The extent of solvent cleavage in Grignard reagent formation was determined by Walborsky and Aronoff [50]. In the formation of Grignard reagent from optically active 1-methyl-2,2-diphenylcyclopropyl bromide in THF–D_8 and diethyl ether–D_{10} solvent cleavage was indicated by the amount of deuterium incorporation in the hydrocarbon, 1-methyl-2,2-diphenylcyclopropane **13**. The results (Table 7) show that although solvent cleavage in THF is trivial (only 1%) the amount of deuterium incorporation is 28.5%. In diethyl ether over 20% of **13** is formed, but the amount of deuterium incorporation is low, 6.7%. These observations have a significant bearing on our later discussion of Grignard formation from cyclopropyl bromide.

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Table 7 Formation of Grignard Reagent from (+)-1-Methyl-1-bromo-2,2-diphenylcyclopropane in Deuterated Ethers

		Acid			Hydrocarbon	
Solvent	Temp. (°C)	Yield (%)[a]	Opt. purity (%)[a]	Overall yield RH + RD (%)[a]	RD in HC (%)[a]	Opt. purity (%)[a]
THF-D_8	65	90	13	1.0	28.5	9.0
Et_2O-D_{10}	35	25	18.2	20.2	6.7	4.6

[a]Average.

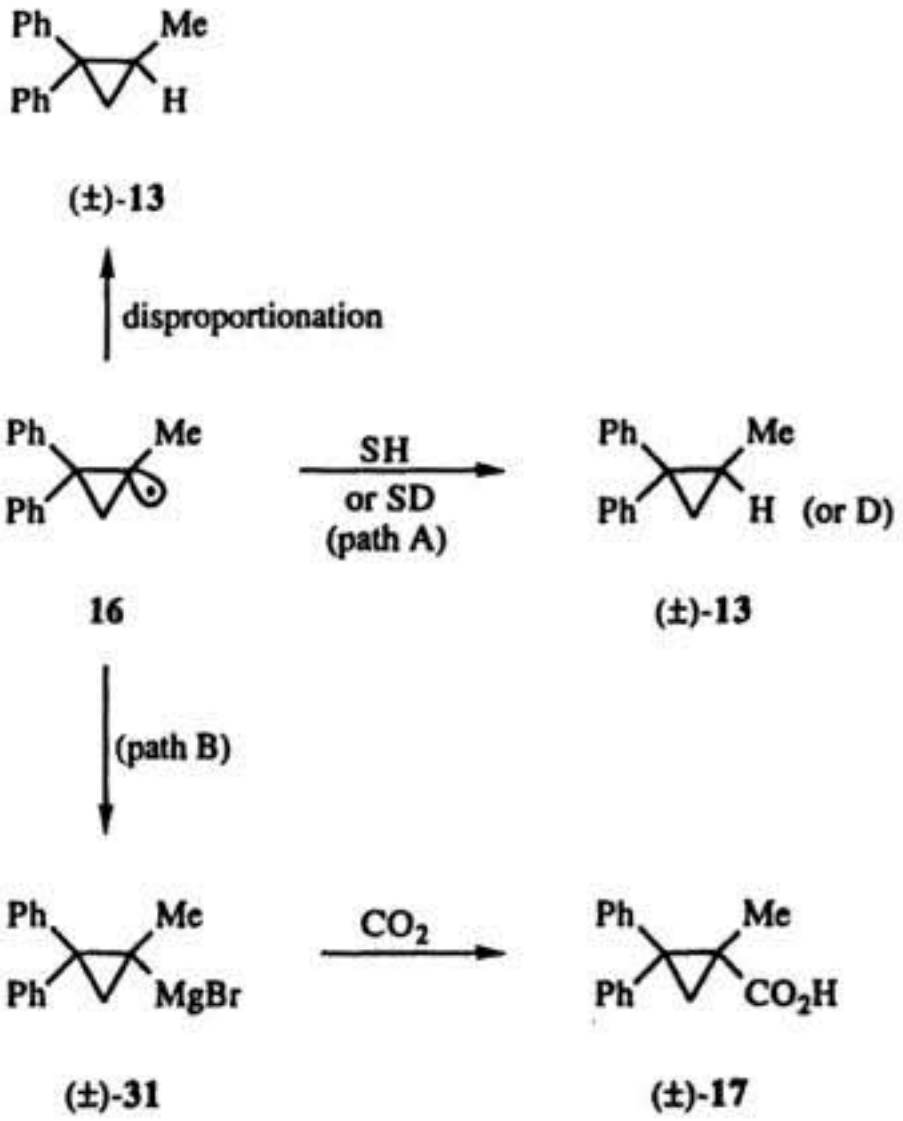
As can be seen, the results obtained in diethyl ether-D_{10} revealed no significant differences in the yields and optical purities of the acids and hydrocarbons from those obtained in nondeuterated ether. This is consistent with the belief that solvent cleavage in this solvent is unimportant, therefore, one would not expect to observe any appreciable kinetic isotopic effect.

However, a significant difference in yield and optical purity of the acid formed on carbonation could be noted between experiments carried out in THF–D_8 and those in ordinary THF. In ordinary THF, the Grignard reagent, as measured by the amount of acid produced, was formed in 15% higher and 5% lower optical purity. By contrast, the yield of 1-methyl-2,2-diphenylcyclopropane in THF–D_8 was significantly lower than in nondeuterated THF, whereas the optical purity increased. The differences in yields and optical purities in THF–D_8 compared with THF are consistent with a deuterium isotopic effect. In protonated THF, solvent cleavage by a racemic intermediate would largely account for the formation of 1-methyl-2,2-diphenylcyclopropane (path A of Scheme 20). On the other hand, a kinetic isotopic effect in THF–D_8 might have resulted in the racemic intermediate being diverted to racemic Grignard reagent, the precursor of racemic acid (path B). Consequently, in the THF–D_8 experiment an increase in the yield of the acid and a decrease in its optical purity would result.

3. *Surface-Bound Radical*

What do both product analysis and the formation of Grignard reagent in perdeuterated solvents, as described in the foregoing, demonstrate? Formation of dimer **36** provides strong evidence for the involvement of radical intermediates that are not free in solution. This, combined with the lack of solvent cleavage, the results of stereochemical analysis, and the nature of products formed in perdeuterated ether, are strong indications of the surface-bound nature of all the intermediates involved in Grignard reagent formation. There is little doubt that if the 1-methyl-2,2-diphenylcyclopropyl radical **16** were generated in solution, it would either cleave the solvent to form cyclopropane **13**, or undergo ring opening to the more stable allyl radical, which would dimerize to yield **24**. Only a very small amount (1%) of product that could be attributed to the allyl radical was detected, and neither dimer **24** nor dimer **37** was observed. Moreover, very little solvent cleavage was found.

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Scheme 20

D. Kharasch–Reinmuth–Walborsky Mechanism for Grignard Reagent Formation

Given the facts outlined in the foregoing detailed discussion, Walborsky and his collaborators proposed the following mechanism of Grignard reagent formation (Fig. 1). All processes involved in formation of the Grignard reagent are assumed to occur at the magnesium surface. The first and rate-determining step involves an electron transfer from the magnesium surface into the σ^* antibonding orbital of the carbon–halogen bond

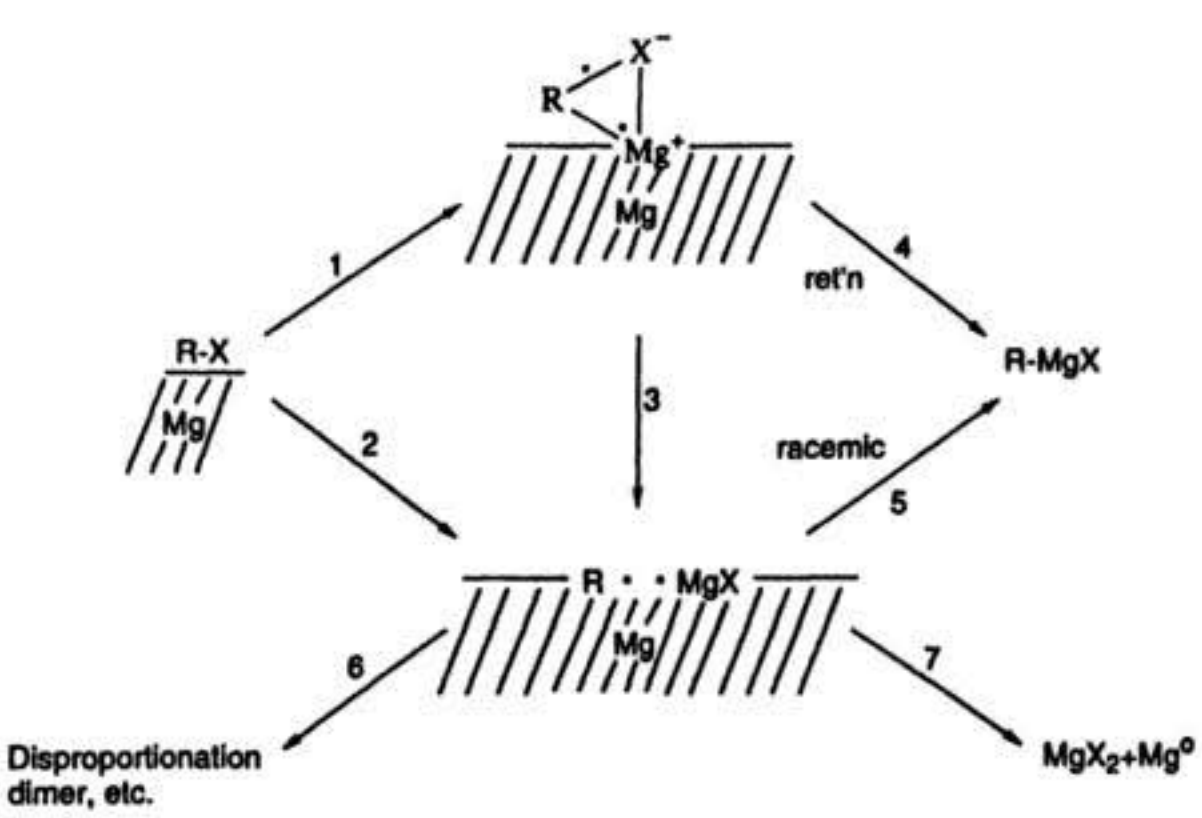


Figure 1 The Kharasch–Reinmuth–Walborsky mechanism of Grignard reagent formation.

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(pathway 1) to produce a tight radical anion–radical cation pair as a transition state or intermediate [55, 56]. Free radicals are generated either by a concerted electron transfer bond breaking from the magnesium surface (pathway 2), or by dissociation—if it is an intermediate—of the tight radical anion–radical cation (pathway 3) to produce a loose radical pair adsorbed on the surface. The amount of the latter depends on the strength of the carbon–halogen bond. The weaker the bond (the lower the reduction potential), the greater the amount of loose radical pairs. In other words, in the mechanism proposed, the amount of these pairs would be predicted to increase in going from C—Cl, to C—Br, to C—I, and to increase from sp^2 character of the carbon bonded to the halide, to $sp^{2.28}$, to sp^3.

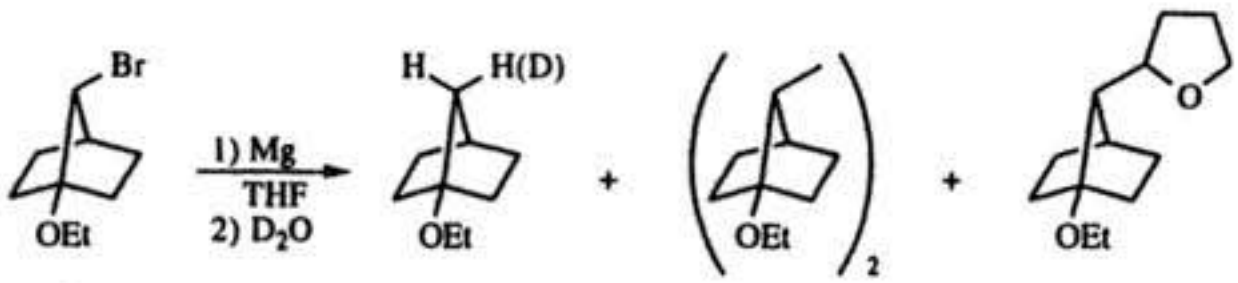
If the halide were at a chiral center and the substrate optically active, collapse of the tight anion radical–cation pair would lead to formation of Grignard reagent with complete retention of configuration (pathway 4). On the other hand, a loose radical pair would mainly lead to racemic Grignard reagent by a 180° rotation of the carbon radical relative to the surface and subsequent combination with the magnesious halide radical (pathway 5). The organic radicals may also escape capture by magnesius halide and undergo disproportionation and dimerization at the surface. Very small amounts of these radicals leave the surface to lose themselves within bulk solvent, and a few (1% in the case of cyclopropyl system, as detected by the amount of Grignard reagent arising from ring opening) may return to the surface to form Grignard reagent.

E. General Acceptance and Support

That radicals are involved in the formation of Grignard reagents has found general acceptance, and further evidence has been provided for the surface-bound nature of the radical. The pathways that describe the mechanism for Grignard reagent formation shown in Figure 1 have been confirmed, either partially or entirely, by several investigators whose work covers various aspects, such as product and stereochemical analyses, kinetic and spectroscopic studies, investigation of the morphology of the magnesium, and initial calculations.

1. Agreement with Other Systems

Formation of biphenyl in the reaction of magnesium with bromobenzene [57] was reported by Bryce-Smith and Cox [58]. Disproportionation and coupling observed in the reaction of β,β-dimethylphenethylchloride with magnesium was reported by Rüchardt et al. [59]. Grootveld, and associates [60] studied the products formed during the reaction of 1-ethoxybromonorbornane with magnesium in THF (Scheme 21). The appreciable amount (12%) of coupling products not only supported the intermediacy of radicals, but was also consistent with the surface nature of Grignard reagent formation.

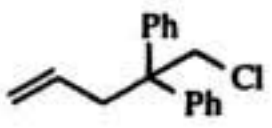


40 **41** (48%) **42** (12%) **43** (1.5%)

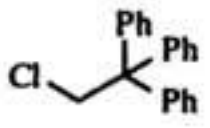
Scheme 21

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The considerable amount of phenyl group migration observed by Grovenstein [61] during the preparation of Grignard reagents from reaction of magnesium with 5-chloro-4,4-diphenyl-1-pentene **44**, 2-chloro-1,1,1-triphenylethane **45**, and 1-chloro-2,2,3-triphenylpropane **46** in diethyl ether and in THF (Scheme 22) is also believed to be the result of intermediate radicals involved in these processes.



44



45



46

6.8 mmol

Mg/Et_2O
5h/27°C

Ph_3CCH_2MgCl ← $Ph_3CCH_2^{\bullet}$ → $Ph_2\dot{C}\text{-}CH_2Ph$

49 **47** **48**

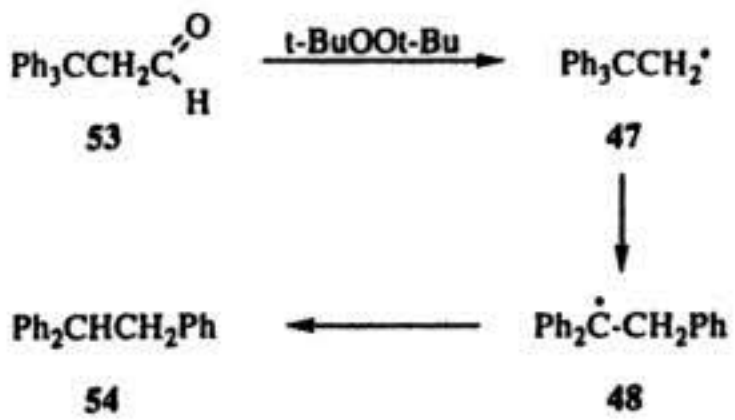
$Ph_3CCH_2CO_2H$ **51** 1.75 mmol

Ph_2CCH_2Ph (I CO_2H) **52** 0.48 mmol ← Ph_2CCH_2Ph (I $MgCl$) **50**

Scheme 22

This hypothesis was actually tested by showing that Grignard reagents **49** and **50**, formed by reaction of 2-chloro-1,1,1-triphenylethane **45** with magnesium in diethyl ether, were stable; therefore, phenyl migration did not occur after the Grignard reagent was formed.

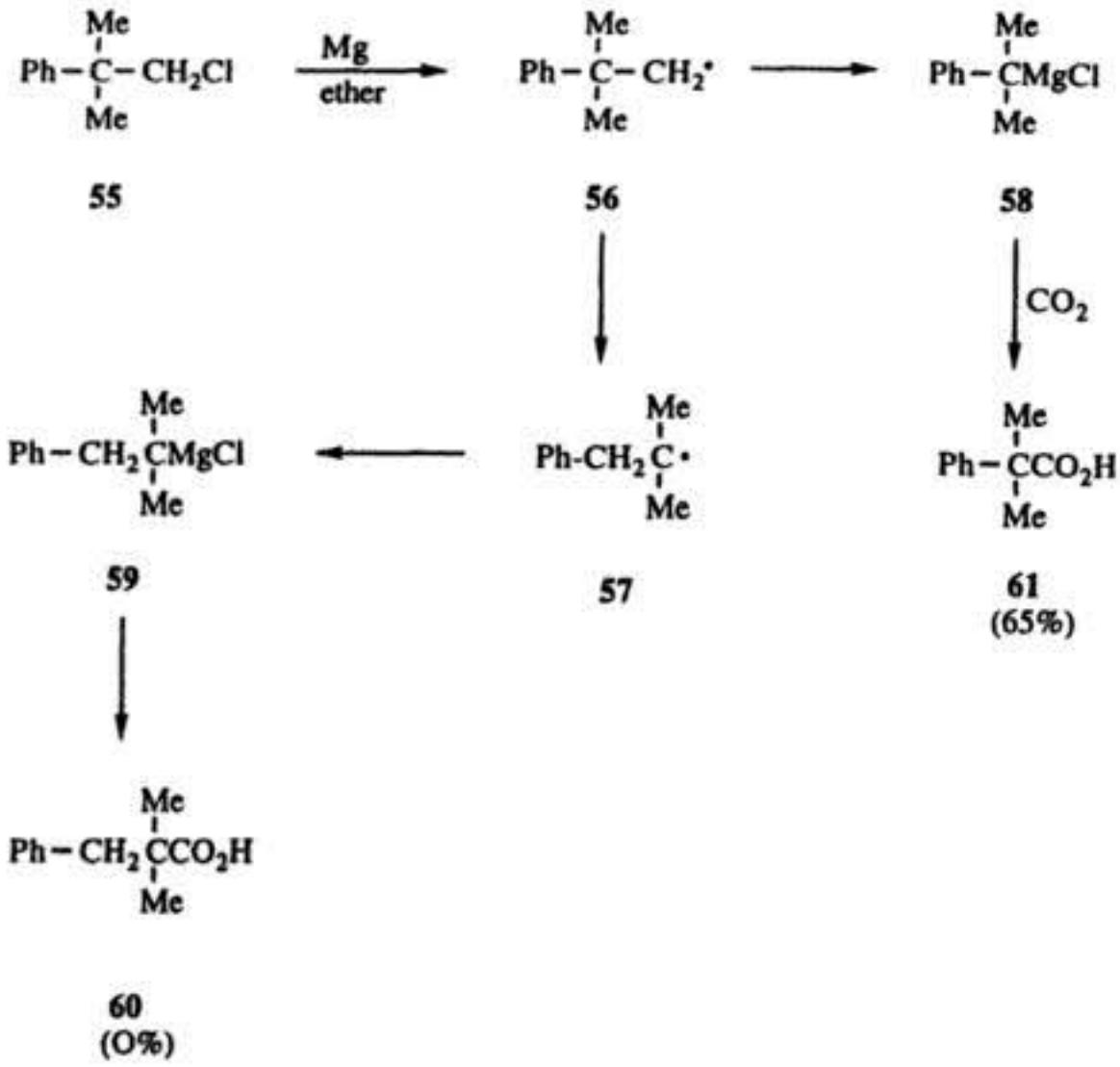
Moreover, strong chemical support for the radical–surface nature of Grignard reagent formation was provided by comparing the results of Grovenstein [61], from experiments in which the radicals were expected to be formed and to remain at the surface of the magnesium, with those of Curtin [62], in which the same radicals were generated in solution (Scheme 23). In the latter case, radical **47** was generated under homogeneous conditions by decarbonylation of the corresponding aldehyde **53**. In contrast with the Grignard reagent, radical **47**, formed by decarbonylation, rearranged completely to radical **48**, as demonstrated by the amount of hydrocarbon **54**.



53 **47** **48** **54**

Scheme 23

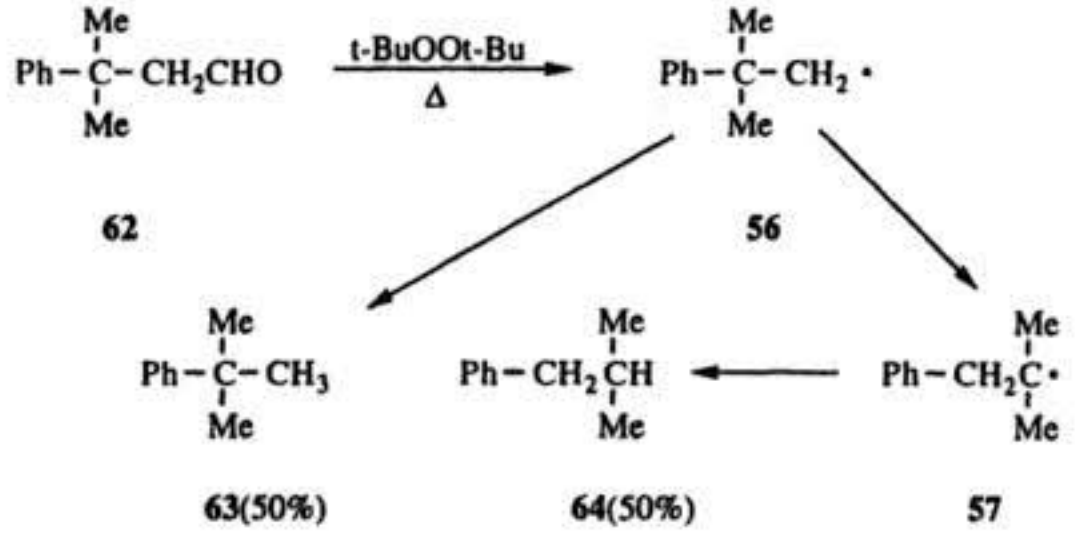
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Scheme 24

Evidence for a surface-bound radical was also provided by work of Rüchardt et al. [59]. Reaction of neophyl chloride **55** with magnesium led, after carbonylation, to acid **61** in 65% yield, without any contamination by acid **60**, which could have arisen by rearrangement of radical **56** to radical **57** (Scheme 24).

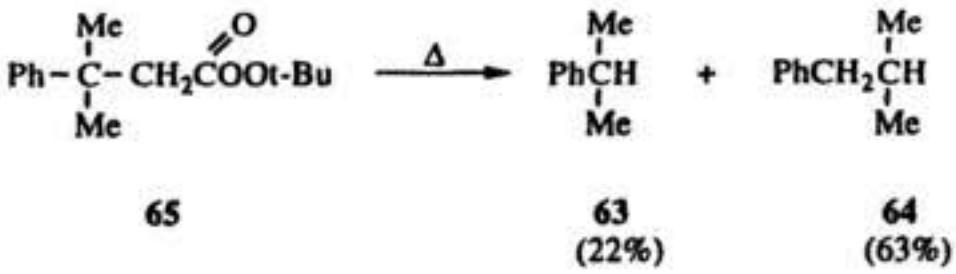
However, when the same radical was generated in solution under homogeneous conditions, either by the radical decarbonylation reaction of Winstein and Seubold [63] of aldehyde **62** (Scheme 25) or by thermal decomposition of the *t*-butyl perester **65** (Scheme 26), the result was different.



Scheme 25

In the former instance, the reaction gave rise to a 1:1 mixture of hydrocarbons **63** and **64**, which indicated that the primary neophyl radical **56** had partially rearranged in solution to the tertiary radical **57**. Similarly, thermal decomposition of perester **65** yielded

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65 → **63** (22%) + **64** (63%)

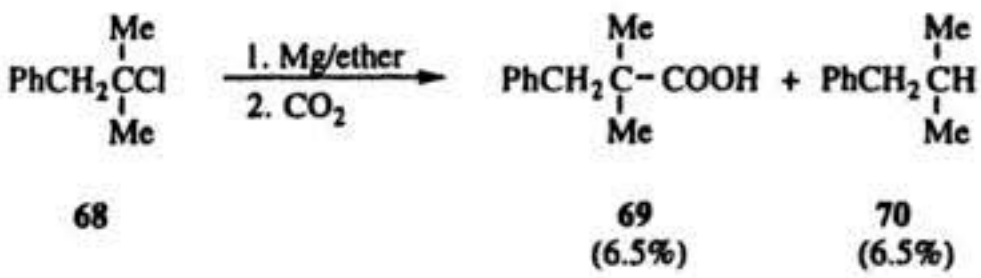


67 (11%) + **66** (4%)

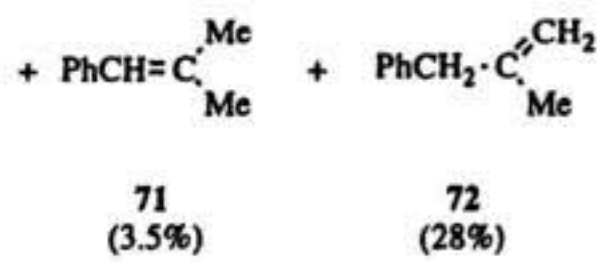
Scheme 26

a mixture of hydrocarbons **63** and **64** as a result of hydrogen capture by unrearranged radical **56** and rearranged radical **57**. These products were not produced under the heterogeneous conditions in which the radicals are bound to the surface.

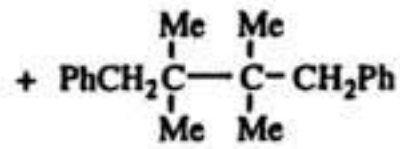
Rüchardt et al. also observed [59], that the product distribution obtained from reaction of 1-chloro-2,2-dimethyl-3-phenylethane [68] with magnesium followed by carbonation (Scheme 27) was quite similar to that obtained in the reaction of racemic 1-methyl-2,2-diphenylcyclopropyl bromide **18** with magnesium in ether, shown in Scheme 17.



68 → **69** (6.5%) + **70** (6.5%)



71 (3.5%) + **72** (28%)



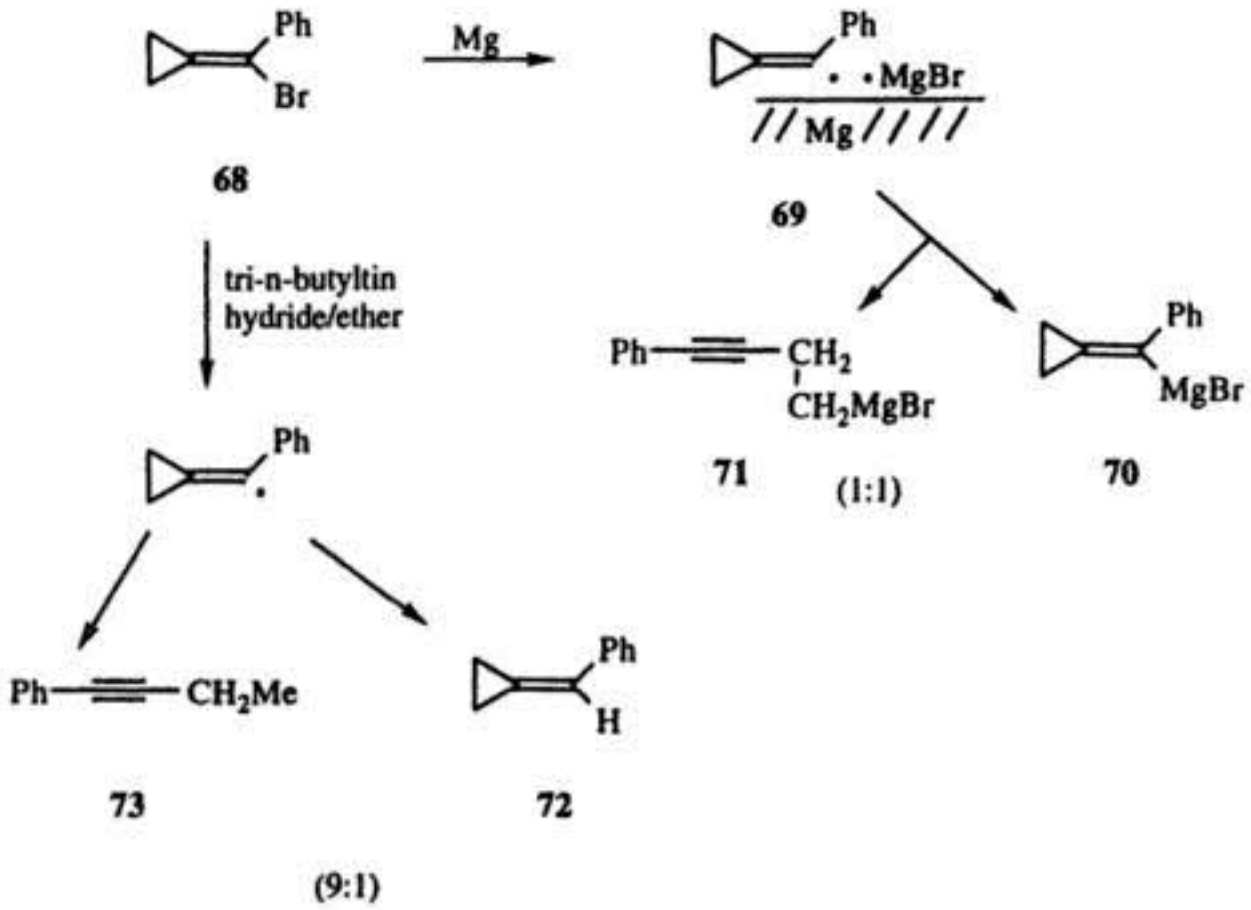
73 (9.5%)

Scheme 27

Only the surface nature of the reaction could account for such a product distribution. Here again, the tertiary radical formed at the surface underwent surface disproportionation and dimerization to give rise to hydrocarbons **73**, **71**, **72**, and part of hydrocarbon **70**. A fraction of the latter might be the result of reaction with solvent.

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Further support for a surface-bound radical can be found in work by Derocque and Sundermann [64] on the reaction of cyclopropylidenemethyl bromide **68** with magnesium in ether (Scheme 28). Under conditions in which radical **69** was generated at the magnesium surface and was expected to remain at the surface, the reaction had led to a mixture of unrearranged Grignard reagent **70** and rearranged Grignard reagent **71** in approximately 1:1 ratio. However, when the same radical intermediate **69** was produced in solution by means of tin hydride reduction in ether, the ratio of hydrocarbons **72** and **73** was considerably different (1:9).



Scheme 28

Grignard reagent formation from geometrically isomeric vinyl halides has been studied by several groups [65a–67], whose results were consistent with the mechanism shown in Figure 1.

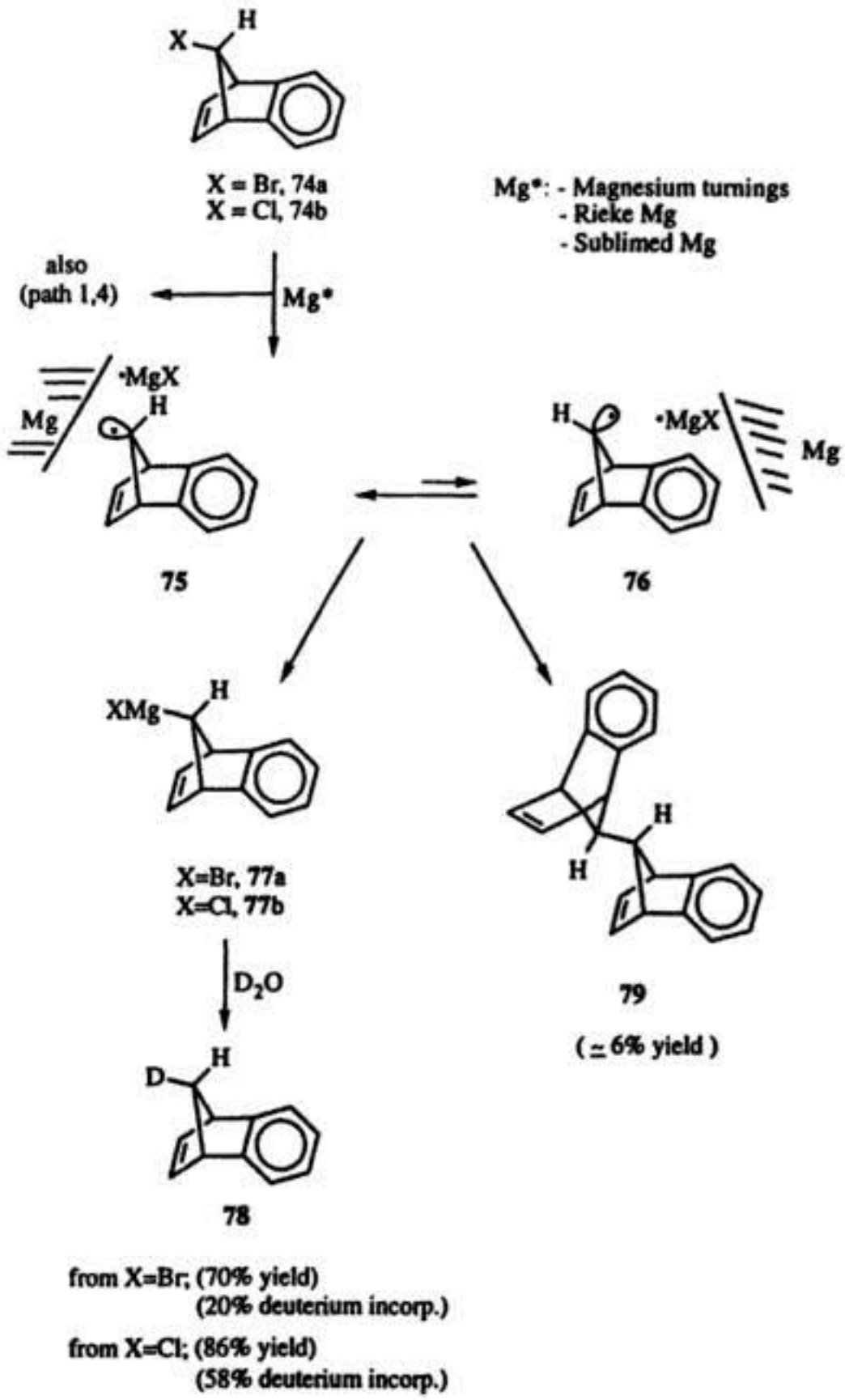
Yoshino and co-workers [65a] reported that reaction of *cis*-β-bromostyrene with magnesium in THF resulted in 95% retention of configuration and that reaction of *trans*-β-bromostyrene proceeded with 91% retention. On the other hand, in diethyl ether, the *cis*-styryl Grignard reagent was formed with only 68% retention of configuration, and the *trans*-isomer was formed with 59% retention. The loss of configuration was shown to take place during formation of the Grignard reagent. They also obtained better yields of Grignard reagent from the β-bromostyrenes and fewer side products in THF, compared with reaction in ether. No deuterium incorporation was detected in the side products when the Grignard reagent was formed in THF-D_8.

A similar nonstereospecificity has been observed in the formation of Grignard reagents from a series of geometric isomers of vinyl bromides. The groups of Martin and Mechin and Martin [66,67] reported the direct measurement of Grignard reagents prepared from such compounds. For example, *cis*-1-bromo-1-hexene gave a Grignard reagent containing 85% of the *cis*-isomer and the *trans*-1-bromo-1-hexene yielded a Grignard reagent 60% *trans*. The data from six vinyl halides provided definitive evidence that the reaction of isomerically pure vinyl bromides with magnesium is nonstereospecific. The stereo-

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selectivity of formation of vinyl Grignard reagents from *cis*- and *trans*-vinyl halides depends on the size of the alkyl substituents; also, the formation of Grignard reagents from *cis*-vinyl halides is more stereoselective than that from *trans*-isomers.

In another study of Grignard reagent formation by Buske and Ford [68], the high stereoselectivity observed in the preparation of *anti*-7-benzonorbornadienyl Grignard reagents **77a** and **77b** (Scheme 29) supports a mechanism in which the rate-limiting step is electron transfer from the metal to the alkyl halide, leading to radicals bound to the magnesium surface. *Anti*-7-bromo- and chloronorbornadiene **74a** and **74b** reacted with various types of magnesium in refluxing THF to yield, after deuterolysis, benzonorbornadiene in 70 and 86% yield, respectively. The unsymmetric dimer **79** was the only side product isolated and identified.



Scheme 29

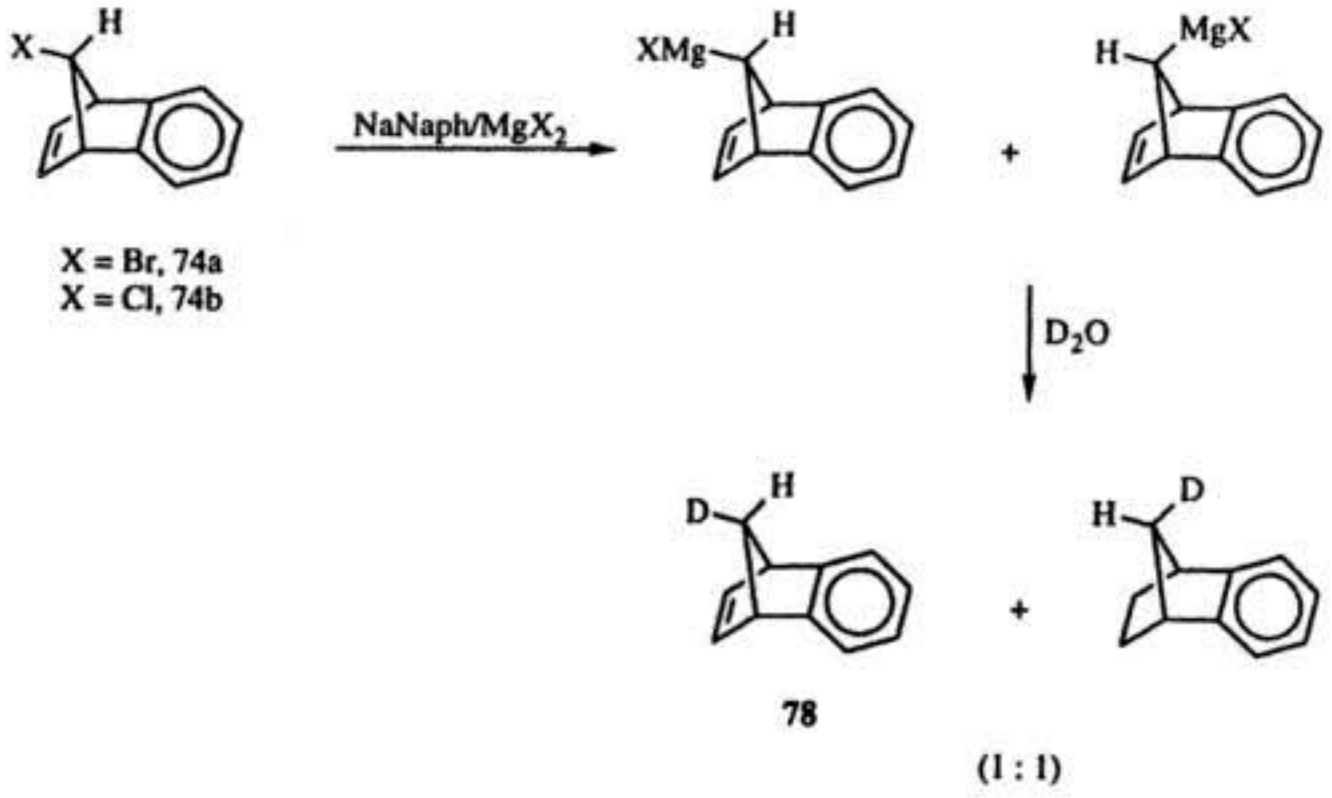
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Two interesting aspects of this work are consistent, with the results listed earlier in Table 6 [50]. First, the yield of Grignard reagent, determined from the amount of deuterium incorporation, turned out to be higher from the *anti*-chloride **74b** (58%) than from the *anti*-bromide **74a** (20%). A second, and more interesting, aspect is the effect of halogen on the stereoselectivity. The Grignard reagent formed from *anti*-bromide was 86% *anti*, whereas that from the *anti*-chloride was more than 90% *anti*. The higher stereoselectivity observed in the latter is also consistent with the greater tendency of RCl to form a tight radical pair (see pathway 1; Fig. 1), rather than a loose radical pair (see pathway 2; Fig. 1), since the strength of the carbon–halogen bond is in the order Cl > Br > I.

It was also made clear in this report [68] that the stereoselectivity did not depend on the particle size nor purity of the magnesium used. This confirms earlier observations [50]. The use of Rieke magnesium also did not change the stereoselectivity significantly.

Did this stereoselectivity occur after the Grignard reagent was formed as a result of equilibrium between a mixture of *syn*- and *anti*-Grignard reagents, as might have been expected from a secondary Grignard reagent [45–47,69]? The answer was no, because the Grignard reagents *anti*-**77a** and **77b**, as well as their corresponding *syn*-isomers were configurationally stable under the conditions of their preparation, as well as under the trapping experiment conditions.

Evidence for a surface-bound radical that had accounted for the stereoselectivity was provided when *anti*-RBr **74a** and **74b** were reacted with a sodium naphthalenide–MgX_2 mixture (NaNaph/MgX_2; Scheme 30). The preparation of Grignard reagents by this method is known to proceed by free radicals in solution. In contrast with reactions occurring at the surface, after deuteriolysis, the NaNaph/MgX_2 reaction yielded a mixture of *anti*-D and *syn*-D product in almost identical yield (Scheme 30). Moreover, the lack of stereoselectivity in this reaction was not due to an isomerization of the Grignard reagent by an excess of NaNaph [68]. Interestingly, Grignard reagent formation from even the saturated *anti*-7-bromobenzonorbornene **74a** proceed with high retention. This excluded the possibility that the double bond in **74a** and **74b** could have stabilized the *anti*-Grignard reagent by coordinating with the magnesium atom.

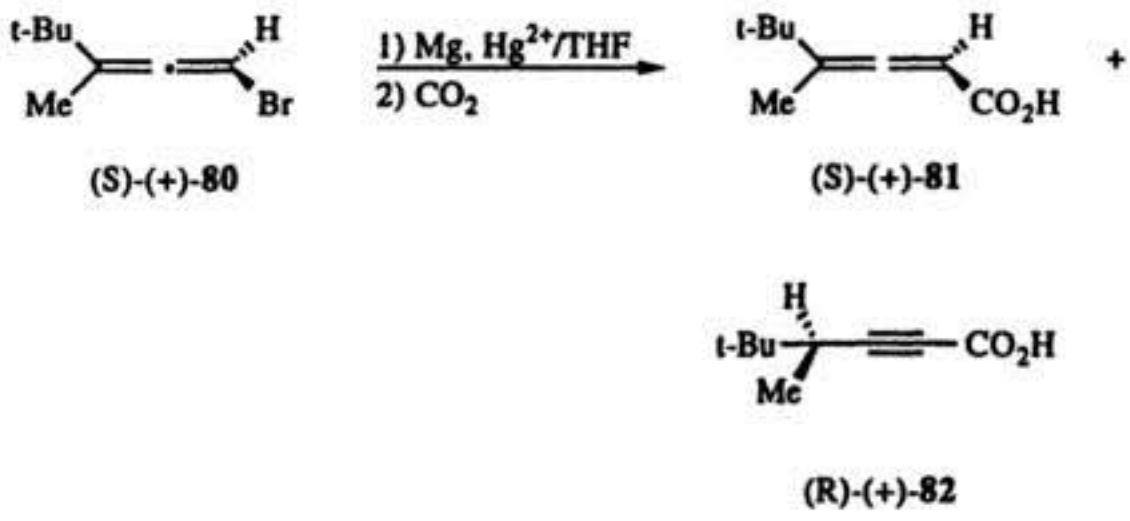


Scheme 30

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The high stereoselectivity could actually have two origins: The first must be due to pathways [1,4] that had accounted for the retention observed in the chiral systems studied by Walborsky et al. [38,43,44,50]. This could explain the effect of halogen on the stereoselectivity. As to the second cause, Buske and Ford [68] suggested that the reaction of *anti*-RBr **74a** and *anti*-RCl **74** might proceed by a rate-limiting electron transfer to form a 7-benzonorbornadienyl radical at the magnesium surface. Here, the magnesium would trap the *anti* surface-bound radical before equilibration to the *syn* surface-bound radical could occur (see Scheme 29).

Landor and co-workers [70] studied the reaction of (*S*)-(+)-1-bromo-4,4,4-trimethylpenta-1,2-diene **80** with magnesium activated by mercuric chloride in THF (Scheme 31). Rearranged and chiral acetylenic acid **82** along with unrearranged chiral allenic acid **81** were obtained after carboxylation. The latter was formed with partial retention of configuration. Both products could be formed through radicals bound to the magnesium surface, but the amount of retention must have been the result of the tight radical anion–radical cation pair formed through pathway 1.



(S)-(+)-80 (S)-(+)-81 (R)-(+)-82

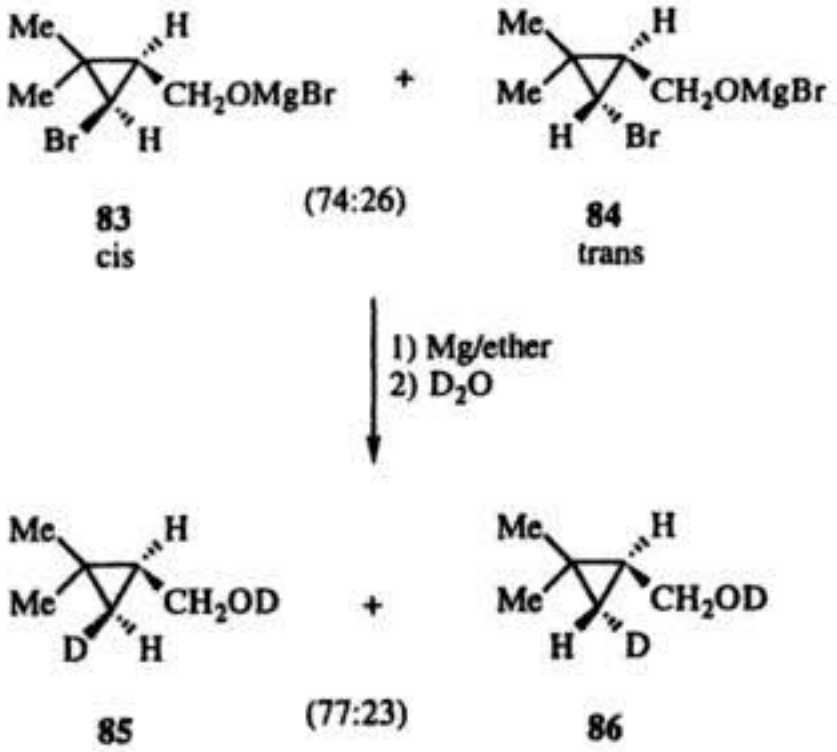
Scheme 31

Additional support for the surface nature of the reaction emerged from a study by Richey and Moses [71] of the configurational stability of a cyclopropyl Grignard reagent, thereby providing a second example [43, 44] of a cyclopropyl Grignard reagent that partially retained its configuration during its formation by direct interaction of cyclopropyl bromide with magnesium. In this case, the magnesium was attached to secondary α-carbon, a 74:26 mixture of **83** and **84** being treated with magnesium in ether at ambient temperature. After deuterolysis the reaction yielded a 77:23 mixture of **85** and **86** (Scheme 32).

This result shows that the Grignard reagents were formed, with almost complete retention of configuration. The **85:86** ratio did not change significantly, even after the solution of Grignard reagent had been heated at reflux for 16 hr (73:27).

The extensive retention observed in this cyclopropyl system, compared with the cyclopropyl systems studied by Walborsky, could be explained in term of different degrees of mobility of the radicals on the metallic surface. Thus, in Walborsky's system [43, 44], the absence of a heteroatom provided for a facile 180° rotation of the cyclopropyl radical, leading after combination with $BrMg^{\bullet}$ to the degree of racemization actually observed, whereas the metallated hydroxyl group present in the radicals formed from **83** and **84** might be involved in chelation with the magnesium surface, thereby keeping the radical from rotating on the surface.

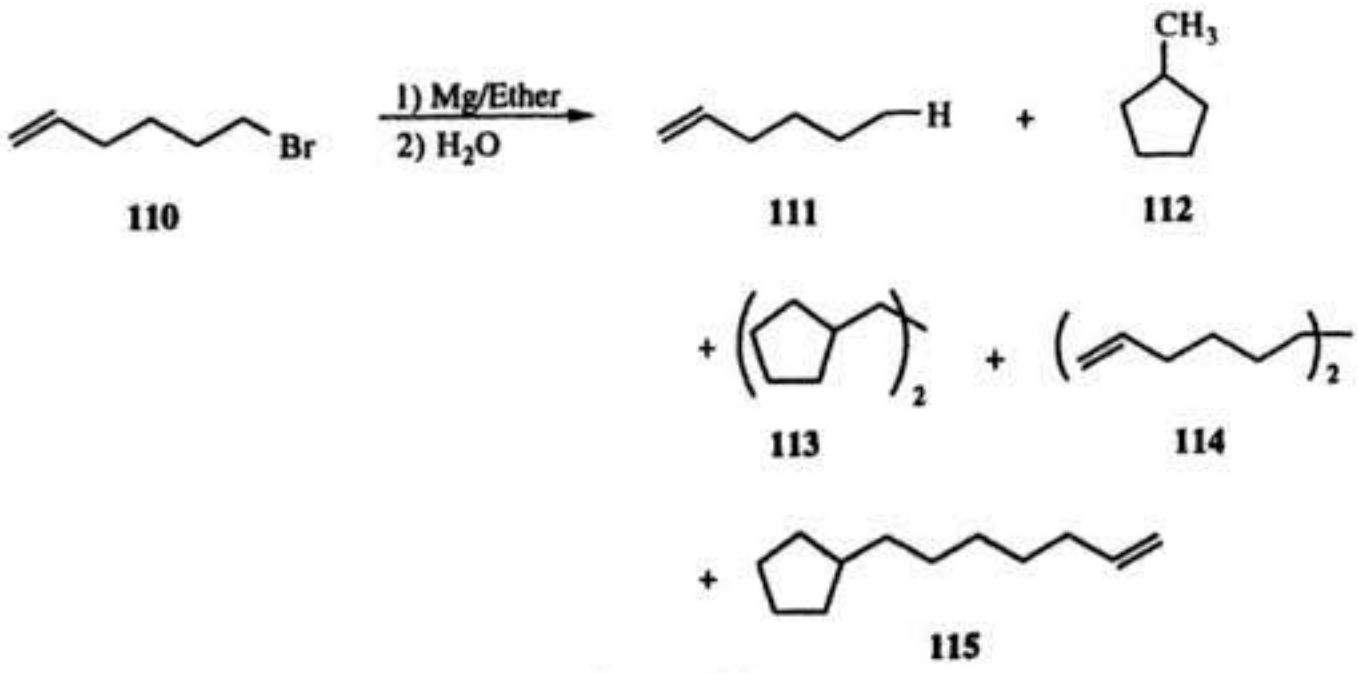
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Scheme 32

2. *Cyclizable Radical Probes*

The reaction of 6-bromo-1-hexene **110** with magnesium was studied by several groups [72], whose results were in perfect agreement with the surface nature of the Grignard reagent formation. The main product formed after hydrolysis was 1-hexene **111** in 85–95% yield, whereas the amount of methylyclopentane **112** was reported to be 3–7% (Scheme 33).



Scheme 33

Interestingly, the 5-hexenyl radical, which is believed to cyclize quickly, with a rate constant on the order of $k_c = 10^5$ sec^{-1} [73,74], had led to a high yield of cyclized product when generated in solution [75]. For example, reduction of **110** with tri-*n*-butyltin hydride provides **112** in 78% yield and only 7% of the straight-chain olefin **111**. This contrasts with what was actually observed in formation of the Grignard reagent by reaction of **110** with magnesium, in spite of the fact that the 5-hexenyl radical is involved in both instances.

The influence of solvent on Grignard reagent formation in the 5-hexenyl system was studied first by Dodewitz and associates [76] and 13 years later by Ashby and Oswald

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Table 8 Yield of Grignard Compounds and Side Products in the Reaction of 6-Bromo-1-hexene with Magnesium

Solvent	Mol. ratio	Viscosity	Absolute yields[a] (%)			Relative yields[a] (%)		
			$R_{sc}MgBr$	R_cMgBr	RR_{tot}	$R_{sc}R_{sc}$	$R_{sc}R_c$	R_cR_c
Et_2O		0.194	85.5	2.5	9.0	64.5	18.0	7.5
THF		0.389	86.0	2.5	4.0	54.5	29.0	17.0
THF/DBE	1/1.77	0.461	84.5	9.0	4.0	45.5	31.5	23.0
DBE		0.506	73.5	18.0	7.0	39.0	40.0	21.0
DPE		0.80	65.5	27.0	4.0	35.0	38.5	26.5
THF/benzene	1/6.7	0.48	54.0	19.5	17.5	46.0	36.0	18.0

[a] R_{sc}, straight chain; R_c, cyclic.
Source: Ref. 76.

[77]. The Dutch group [76] based its conclusions on product distribution and correlation with the intensity of the CIDNP spectra of the Grignard reagent, whereas Ashby and Oswald [77] studied only product distribution after quenching the reaction with D_2O. Similar conclusions were reached by both groups, who found that the nature of the solvent (i.e., its viscosity, basicity, and π-electron-donating ability), influenced, to a certain extent, the evolution of the loose radical pair (R^2 MgX) at the site of the electron transfer, which affects the competition between pathway 5 of Figure 1, leading to Grignard reagent, and pathways 6 and 7, leading to disproportionation, dimerization, isomerization, and so on.

Pathway 5 was more important in more basic solvents, such as THF, which is known to be a good solvent for Grignard reagent formation. Most of the radicals formed in this solvent reacted to form Grignard reagent (85%), whereas lower total yields of dimers (4%) were observed (Table 8). This could be attributed to the ability of this solvent to complex magnesious halide ($XMg^{\bullet}$) at the metal surface, thus facilitating its combination with a 5-hexen-1-yl radical to form $R_{sc}MgX$. However, in less basic solvents, such as diethyl ether and di-*n*-butyl ether, that do not solvate $XMg^{\bullet}$ as well as THF, the radical $R^{\bullet}$ could leave the site of the single-electron transfer, thereby enabling it to react more easily with another radical $R^{\bullet}$ at the surface to produce more side products (see pathway 6; Fig. 1). In accordance with this view, higher yields of dimers and, consequently, lower yields of Grignard reagent were actually observed in such solvents.

On the other hand, the amount of cyclized product depended strongly on the viscosity of the solvent used [76, 77]. An increase in solvent viscosity would be expected to increase the lifetime of radicals, thus facilitating the cyclization process at the site of single-electron transfer (SET), with subsequent formation of cyclized Grignard, and would reduce the mobility of $R^{\bullet}$ at the metal surface, thereby preventing this radical from encountering other radicals (see Table 8).

Dilution of THF with a π-electron-donating solvent, such as benzene [76], decreased the reactivity of $R^{\bullet}$ with $XMg^{\bullet}$ to form Grignard reagent at the site of the single-electron transfer (see Table 8). Consequently, the total yield of straight-chain Grignard reagent decreases, whereas the total yield of dimers increases.

Increase in the benzene/THF ratio would reduce the tendency of THF to complex $XMg^{\bullet}$ necessary for formation of Grignard reagent at the site of the SET, aided by a possible interaction between the radicals and a π-electron-rich solvent. This would increase

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the tendency of the straight-chain radical to leave the side of the SET and move away on the magnesium surface, before cyclization, so that it could meet another radical.

Ashby and Oswald [77] included the effects of activation of the magnesium, temperature, stoichiometry, magnesium purity, and nature of the halide in their study. During the reaction of **110** with magnesium in THF, activated by EtBr, I_2, or sonification, a slight increase (3–4%) in the amount of Grignard reagent took place, as measured by the deuterium content after quenching with D_2O. In fact, an alkyl halide, iodine, or sonification activates magnesium by increasing the number of unsaturated sites, or by cleaning the surface. Varying the temperature from 22 to 61°C, or changing the duration of the reaction, had little effect. On the other hand, an increase in the concentration of **110** slightly decreased the yield of 1-hexene from 94.4% at 0.001 *M*, while increasing the yield of dimer from 0 to 3.5%. However, the relative yields of Grignard reagent, as indicated by the amount of deuterium incorporation, were not affected by a change in concentration of alkyl halide. Increasing the magnesium/alkyl halide ratio did not influence the relative yield of Grignard reagent, but did slightly increase the total yield of 1-hexene, as well as the total yield of methylcyclopentane. Also, more straight-chain Grignard reagent and less cyclic Grignard reagent were formed from chlorohexene, compared with bromohexene.

4. *Kinetic Analysis*

In the late 1970s and early 1980s, two groups attempted by means of kinetic studies to determine the rate-determining steps in the reaction leading to formation of Grignard reagent. At that time, the kinetic studies in question suffered from a lack of information on the reduction of organic halides [78,79].

Volger and co-workers [80] made an attempt to decide between the two alternative rate-determining steps 1 and 2 of Figure 1, pathway 1, which leads to a tight anion radical–cation radical, and pathway 2, which leads to the loose radical pair. Both pathways were viewed as electron-transfer reactions.

$$R\text{-}X + Mg \xrightarrow{\text{SET}} [R\text{-}X^{\bullet -}\, Mg^{2\,\bullet +}] \quad (1)$$

$$R\text{-}X + Mg \xrightarrow{\text{SET}} R^{\bullet} + {}^{\bullet}MgX \quad (2)$$

Measurement of the carbon kinetic isotope effect in the reaction of methyl iodide with magnesium in diethyl ether and comparison with a calculation of the theoretical equilibrium isotopic effect for the homolysis of methyl iodide led Volger and co-workers [8] to suggest that pathway 1, rather than pathway 2 (see Fig. 1), was the rate-determining step in formation of an alkyl Grignard reagent. Arguing that a carbon isotopic effect would be expected if pathway 2 were involved, their experimental results showed that formation of the Grignard reagent proceeded with no detectable isotopic effect ($vk_{12}/k_{13} = 0.9992 \pm 0.0005$). On the other hand, the calculated equilibrium isotopic effect for the equation, $CH_3X \rightarrow CH_3. + X^{\bullet}$, for which the methyl radical was taken as model for the intermediate in pathway 2, lies between 2 and 3%. Although these studies supported the belief that pathway 1 was involved in the rate-determining step, the model used for the calculation to test pathway 2 was really not representative of the pathway in question.

Subsequently, kinetic studies reported by Whitesides and collaborators [81] provided further support for the view that the rate-determining step in formation of alkyl Grignard reagents involves electron transfer from the metal surface. The kinetics of the reaction of an organic halide R_1X with magnesium were described by Eq. (3), in which S_{Mg} accounted for the characteristics of magnesium surface that influence the rate, and an analogous

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expression [Eq. (4)] for another organic halide R_2X, using the same value of S_{Mg}.

$$\frac{-d(R_1X)}{dt} = k_1(R_1X)^{\alpha}S_{Mg} \tag{3}$$

$$\frac{-d(R_2X)}{dt} = k_2(R_2X)^{\alpha}S_{Mg} \tag{4}$$

If two organic halides in the same reaction mixture compete for a common magnesium surface, the expression derived from Eqs (3 and 4) by assuming $\alpha = 1$ and integrating would be Eq. (5).

$$\ln\left[\frac{(R_1X)_t}{(R_1X)_0}\right] = \left(\frac{k_1}{k_2}\right)\ln\left[\frac{(R_2X)_t}{(R_2X)_0}\right] \tag{5}$$

By using this competitive technique for the reaction of alkyl halides with magnesium, the plots of Eq. (5) exhibited a linear character as illustrated in Figure 2. The relative rates (k_1/k_2) were independent of the concentration of alkyl halide or the type of magnesium used, the size, the purity, the surface area, and the quantity.

Of further interest is a comparison [81b] of the structure–reactivity profile for several reaction types (Fig. 3), such as (1) the Grignard reagent of organic halides with magnesium, (2) a reaction involving a carbanion intermediate, such as a metal–halogen interchange; (3) an S_{N^2} reaction such as displacement of bromine ion from an alkyl bromide by iodide ion; (4) an S_{N^1}-type reaction involving a carbocation, such as the solvolysis of 1-methyl-1-chlorocycloalkanes; (5) the free radical reduction of alkyl bromides by tri-*n*-butyltin hydride.

The alkyl iodides and most of the alkyl bromides studied reacted with magnesium in diethyl ether at almost identical rates (see Fig. 3). As can be seen, the rate of the Grignard reagent was least sensitive to the structure of the organic halide. The difference between the structure–reactivity profiles for the Grignard reagent and the

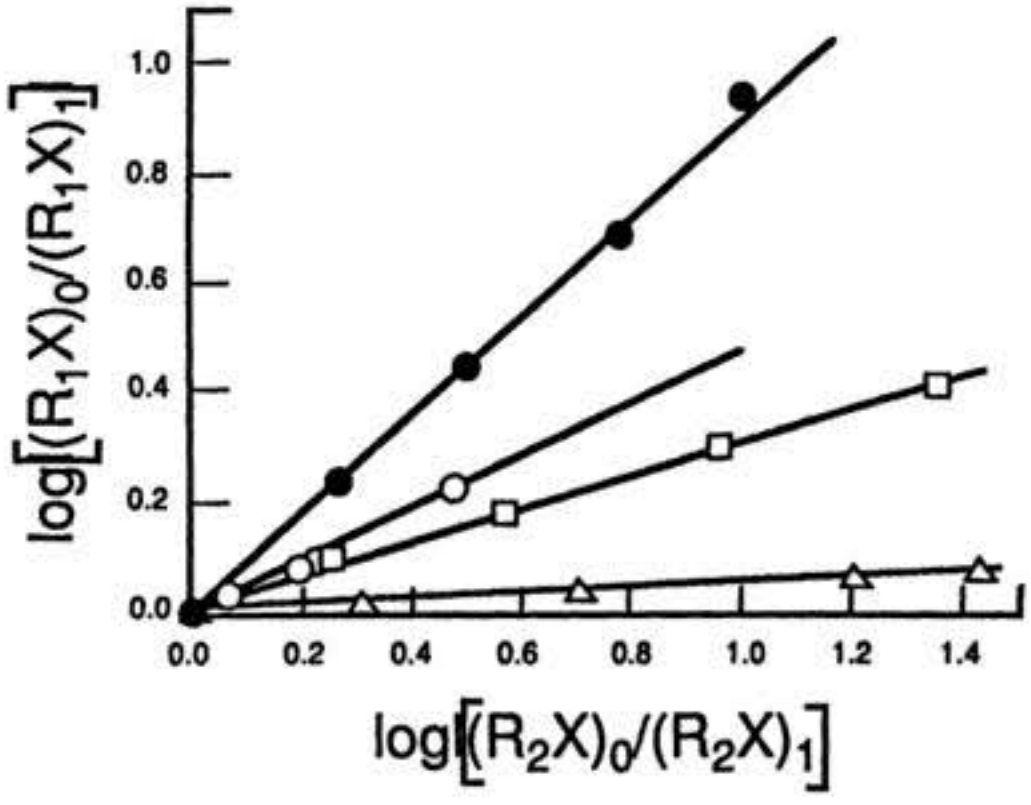


Figure 2 Four representative Grignard reagents plotted according to Eq. (5); cyclohexyl bromide vs. cyclopentyl bromide (●); cyclopentyl chloride vs. cyclopentyl bromide (Δ); *n*-pentyl chloride vs. cyclohexyl chloride (□); neopentyl bromide vs. cyclopentyl bromide (○). (From Ref. 81b.)

Materiał chroniony prawem autorskim

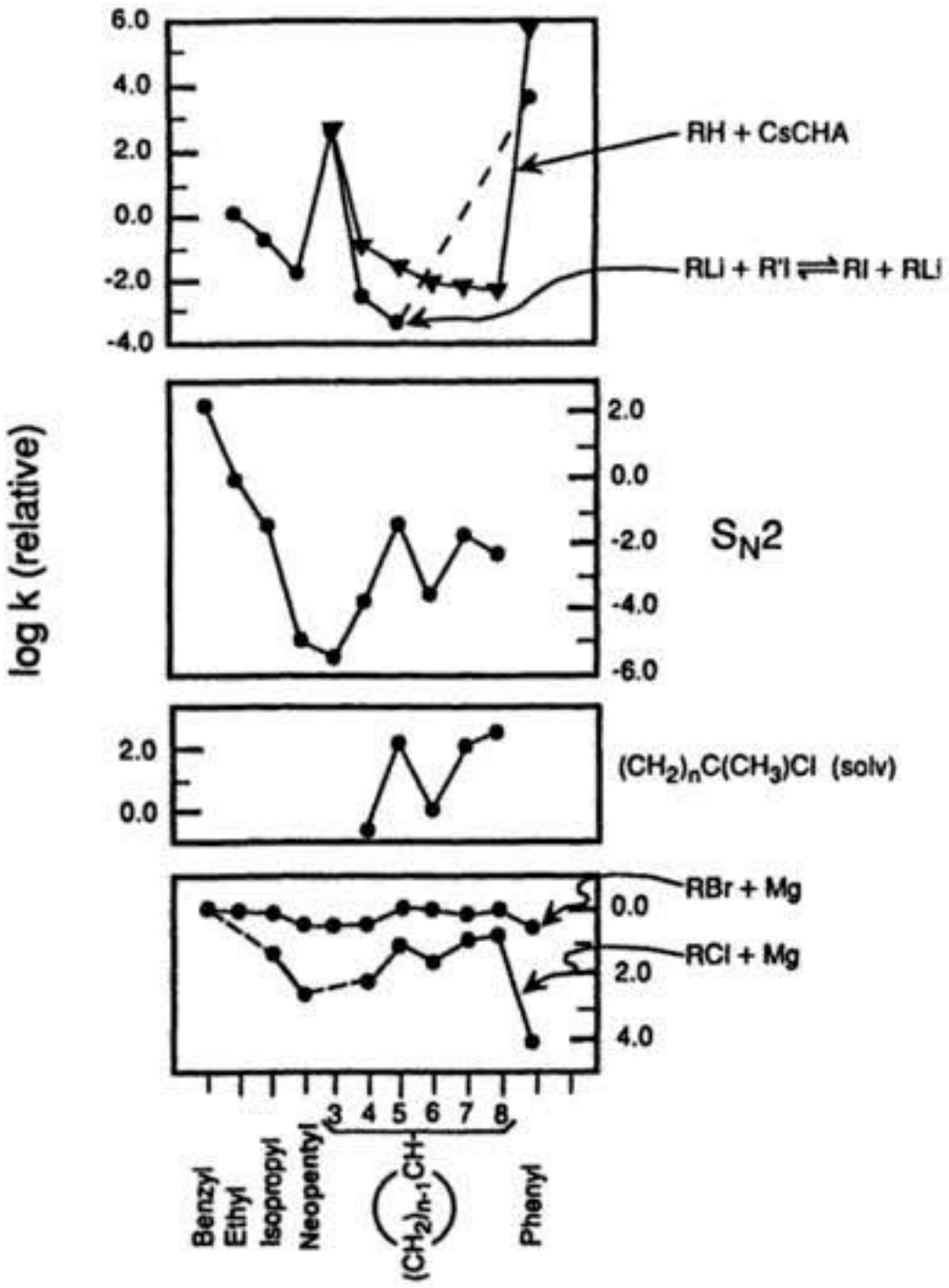


Figure 3 Comparison of the structure–reactivity profile for several reaction types, (CsCHA, cesium cyclohexylamide). (From Ref. 81b.)

structure–reactivity profiles for the reactions of the other models was in agreement with earlier findings of Walborsky et al. [44,50] that Grignard reagent formation does not involve free carbanions or carbonium ions (S_{N1}) as intermediates and that a transition state, such as that involved in an S_{N2} reaction, could also be excluded from the mechanism.

The same authors again concerned themselves [81d] with the question of the existence of alkyl radical anions as discrete intermediates along the reaction coordinate and whether the reaction of alkyl halides with magnesium proceeds by pathway 1 or 2 (see Fig. 1). In contrast to the view of Volger et al. [80], who referred to pathway 2 as an electron-transfer process [Eq. (6)] as originally described, Whitesides et al. viewed pathway 2, if it has an existence, as a halogen abstraction [Eq. (7)].

$$RX + Mg_s \xrightarrow{SET} [R\text{-}X]^{\bullet -} + Mg^{+} \longrightarrow R^{\bullet} + X^{-} \tag{6}$$

$$R\text{-}X + Mg_s \longrightarrow R^{\bullet} + XMg^{\bullet +} \tag{7}$$

To decide between these two models, they compared rate–structure profiles for the disappearance of alkyl halides in contact with magnesium with rate–structure profiles for others models of reduction. These included (1) rate–structure profiles for the free radical reduction of alkyl chlorides with tri-*n*-butyltin hydride in diethyl ether [33], assuming

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Table 9 Correlation Coefficients (and Least-Squares Slopes) Characterizing Linear Free Energy Correlations Between Reactions That reduce Alkyl Halides[a]

	RCl/Mg	RCl/Bu_3SnH	RCl/Bu_3SnH	RBr/$(CH_3C_6H_4)_2COLi$	RCl/($E_{1/2}$)
RCl(Bu_3SnH) (Et_2O, 35°C)	0.9(1.5)				
RBr(Bu_3SnH) (Et_2O, 0°C)	0.82(3.2)	0.97(2.0)			
RBr($CH_3C_6H_4)_2COLi$) (RHF, 24°C)	0.93(0.78)	0.94(0.62)	0.87(0.31)		
RCl($E_{1/2}$) (C, DMF, 25°C)	0.99(6.5)	0.96(6.3)	0.91(3.1)	0.93(9.5)	
RBr($E_{1/2}$) (Hg, DMF, 25°C)	0.74(9.5)	0.73(4.3)	0.81(8.4)	0.93(13)	0.85(0.69)

[a]These parameter are derived from the plots of log k_{rel} vs. log k_{rel}, or from log k_{rel} vs. $E_{1/2}$ for cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, *n*-pentyl, 1-halo-1-alkylethane, and 2-halo-2-alkylpropane.

that this was a model for homogeneous halogen abstraction in an inner-sphere process [84]; (2) rate–structure profiles for the reduction of alkyl bromides with lithium 4,4′dimethylbenzophenone ketyl [85] in THF, assuming that this was a model for homogeneous electron transfer in an outer-sphere process; and (3) potential–structure profiles for the electrochemical reduction of alkyl halides at mercury and glassy carbon electrodes [86], as a model for a heterogeneous electron-transfer process.

Linear correlations were observed between reactions of alkyl halides with all of the reducing agents, as also demonstrated by the correlation coefficients shown in Table 9.

These correlations were taken to indicate that the step(s) involving carbon–halogen bond breaking in all these reduction processes must be similar, which means, following these authors, that there must be a common path that does not involve an intermediate in the rate-determining step. The highest correlation observed was between the potential–structure profile for electrochemical reduction of alkyl chlorides at a glassy carbon electrode and the rate–structure profile for the reaction of alkyl chlorides with magnesium. This point is of significance and will be elaborated on in the electrochemical section.

However, although the results were of interest, these analyses of rate–structure profiles for reactions of organic halides would not distinguish between a path in which carbon–halogen bond-breaking occurs by halogen abstraction from the alkyl group by the metal (an inner-sphere process) and a path that involves a single electron transfer to the organic halide from the metal (an outer-sphere process). Such a decision, it was concluded, "cannot be made made by an experimental approach based on qualitative comparisons of rate–structure profiles with those for reactions which might be expected to exemplify these mechanistic limits since all these profiles appeared to be linearly correlated with each other and since inner and out-sphere processes may exhibit linearly-correlated rate–structure profiles."

A second approach, used by the Whiteside group, employed the constant–surface technique [81b], which involves following the disappearance, with time, of one organic halide in contact with a large mass of magnesium, replacing the solution of the initially formed Grignard reagent with a solution of a second halide and following its disappearance with time, all without changing the surface area of the magnesium. Under these conditions

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Table 10 Relative Rates of Reaction of Cyclopentyl Bromide and Cyclopentyl Chloride with Magnesium in Several Solvents

		Relative rate[a]	
Solvent composition	η, cP	RBr	RCl
Et_2O	0.33	1	
Et_2O–pentane (80:20)	0.33	1.09	
THF	0.55	0.64	
RMgBr (0.6 *M*)			
(Et_2O–pentane, 80:20)	0.58	0.06	0.05
Bu_2O	0.7	0.44	
Et_2O–Nujol (80:20)	0.72	0.47	
Bu_2O–cyclohexane (75:25)	0.77	0.49	
THF–HMPA (75:25)	0.79	0.47	
RMgBr (1.0 *M*)			
Et_2O–pentane (70:30)	0.80	0.58	
RMgBr (1.0 *M*)			
Et_2O–pentane (80:30)	0.86	0.47	
RMgBr (0.6 *M*)			
Et_2O–pentane–Nujol (80:10:10)	0.89	0.36	
RMgBr (0.6 *M*)			
Et_2O–paraffin oil (80:20)	1.2	0.29	
RMgBr (0.6 *M*)			
Et_2O–Nujol (80:20)	1.2	0.27	0.05
RMgBr (1.0 *M*)			
Et_2O–pentane (80:20)	1.8	0.20	

[a]Relative to the rate of diethyl ether.
Source: Ref. 81f.

the rates of reaction of cyclopentyl bromide and cyclopentyl chloride with magnesium were proportional to the exposed surface area S_{Mg}. of the metal.

$$-\frac{d(RX)}{dt} = k_{RX}(RX)S_{Mg} \tag{8}$$

This suggested that the rate-determining step must involve reaction of the organic halide at the surface. Thus, a mechanism involving a soluble magnesium species Mg^I was excluded, and one could conclude that Grignard reagent formation takes place at the metal–solution interface, at least for the rate-determining electron-transfer step.

Further work [81f], which demonstrated that the rates of reaction of cyclopentyl bromide with magnesium fit the kinetic features of a transport-limited heterogeneous reaction, was based on two sets of experiments. First, the relative rates of reaction of cyclopentyl bromide and cyclopentyl chloride with magnesium in solvents of different viscosities [81f] were examined by applying the constant-surface kinetics technique. The results are summarized in Table 10. These demonstrate that the relative rates of reaction of cyclopentyl bromide with magnesium in a series of solvents were proportional to the inverse of the solvent shear viscosity (η^{-1}), whereas the reaction of cyclopentyl chloride was 10^2 slower and insensitive to solvent viscosity. This was taken as evidence that the

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reactions are transport-controlled for cyclopentyl bromide and not for cyclopentyl chloride, even though the latter is known to have a slightly larger diffusion coefficient and is supposed to react more rapidly in a diffusion-controlled process.

Second, the relative rates of the reactions of cyclopentyl bromide and cyclopentyl chloride with magnesium were examined as a function of stirring rate (ω) [81f]. It was assumed that if the reactions were transport-limited, an increase in stirring rate would decrease the thickness of the boundary layer and, therefore, increase the rate at which the alkyl halide reaches the metal surface. Indeed, the rate of disappearance of cyclopentyl bromide was dependent on ω, whereas the rate of reaction of cyclopentyl chloride was independent. In a variation of these experiments, the rate of reaction of cyclopentyl bromide in diethyl ether depended on the angular velocity of a rotating disk of magnesium, which was taken as evidence for a mass transport-limited reaction. These results led to the conclusion [81f] that the rates of reaction of organic iodides and most organic bromides with magnesium are either mass transport- or diffusion-limited. Less reactive organic bromides, such as aryl-, neopentyl-; and cyclopropyl bromide, react at rates less than mass transport. The rates of reaction of alkyl chlorides with magnesium are slower and are not mass transport-limited.

In a similar attempt to determine the nature of the rate-determining step in the reaction of aryl halides with magnesium, the kinetics of the reaction of substituted aryl bromides with magnesium and with tri-*n*-butyltin hydride in ethereal solvents were examined [81c], using competitive kinetics techniques, and were correlated with the substituent effect using Hammett σ parameters. A Hammett plot log $(k_x/k_s)=f(\sigma_x)$ then provided the value of the Hammett constant ρ for the reactions of aryl halides with magnesium and with tri-*n*-butyltin hydride in various solvents (Fig. 4 and Table 11).

Inspection of Table 11 shows that ρ for the reaction of aryl halides with tri-*n*-butyltin hydride was not solvent-dependent, whereas ρ for the reaction with magnesium was. The small values of ρ for the reaction of aryl bromide with magnesium in a polar solvent were again interpreted [81c] in terms of a mass transport-limited process. Thus reactions of aryl bromides would be transport-limited in THF and more polar solvents, but not in diethyl ether and less polar solvent. On the other hand, the rate of reaction of aryl iodides with magnesium seemed to be transport-limited, even in diethyl ether, whereas the rate of reaction of chlorobenzene with magnesium, which was 10^4 slower than that of bromobenzene, was not.

At this point, Whitesides and co-workers concluded [81c] that it was unlikely that the rate-determining step involved transition states, such as starting material, physiosorption, aryl cations, or carbanionic structures. The Hammett values of ρ, together with the observation that the rates of the reaction of aryl bromides with magnesium in ether, correlated with the rates of abstraction of bromine by the tri-*n*-butyltin radical, as well as with the half-wave reduction potentials, led them [81c] to suggest three probable limiting structures for the rate-determining step in Grignard reagent formation from aryl halides. The first possibility was an electron transfer from the metal to aryl bromide, leading to a radical anion, the second was bromine abstraction by magnesium, which produces an aryl radical, and the third an insertion of magnesium into the carbon–bromine bond. Thus, this work did not anser the original question on whether the rate-determining step was pathway 1 or pathway 2 or both (see Fig. 1).

5. *Spectroscopic Studies*

Further and direct evidence for the occurrence of radicals and also proof for radicals pair as intermediates in formation of the Grignard reagent was provided by chemically induced

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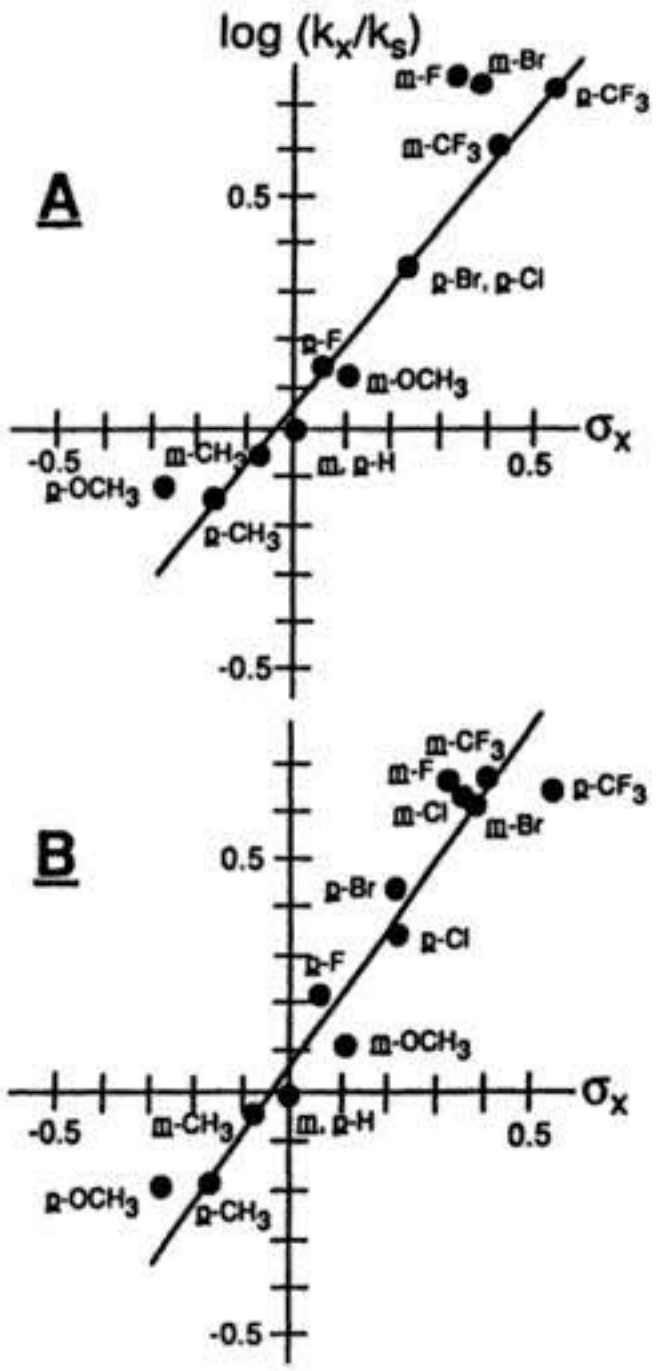


Figure 4 Two examples of Hammett plots; (A) Hammett plots for reactions of substituted bromobenzenes with tri-*n*-butyltin hydride in diethyl ether. (B) Hammett plots for reactions of substituted bromobenzenes with Mg in diethyl ether.

Table 11 Hammett Values for Reactions of Aryl Halides with Magnesium and with Tri-*n*-butyltin Hydride

	Hammett values (ρ)			
Solvent	THF	THP	Et_2O	$3Bu_2O$–$1C_6H_{12}$
ArCl + Mg			2.0 ± 0.2	
ArI + Mg			0.2 ± 0.2	
ArBr + Mg	<0.5	<0.6	1.1 ± 0.2	2.0 ± 0.3
ArBr + Bu_3SnH	1.3 ± 0.2		1.4 ± 0.2	

Source: Ref. 81c.

dynamic nuclear polarization (CIDNP). In a series of reports Bodewitz and associates [60,76,87a–87c] examined the CIDNP ^{1}H-NMR spectra produced during Grignard reagent formation by reaction of various alkyl halides with magnesium in THF and ether. The main feature of this method is that it allows one to recognize the products that are derived

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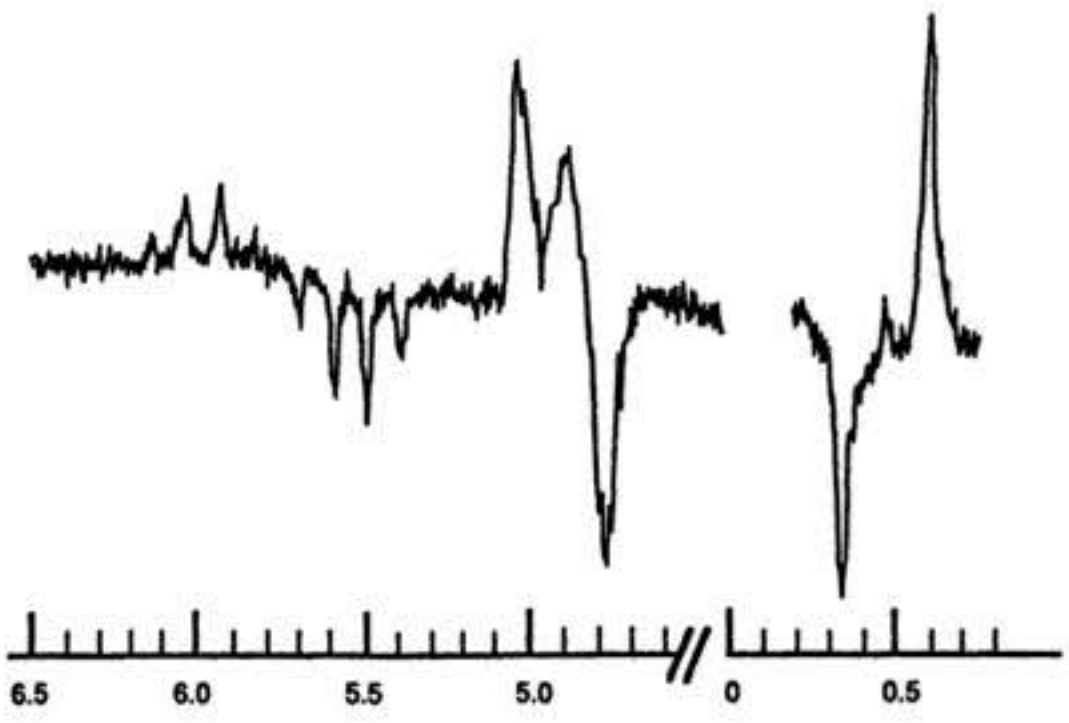


Figure 5 A 60-MHz ^{1}H-NMR CIDNP spectrum during the reaction of 1-iodopropane with magnesium in di-*n*-butyl ether: $CH_3CH_2CH_2MgI$; δ 4.7–6.16—CH_2=CH—CH_3. (From Ref. 87b.)

from radicals. By this means radicals may be detected after a period much longer than their lifetime.

A CIDNP phenomenon was always observed in signals emanating from the α-protons of such Grignard reagents. Moreover, occasionally when the signals of the solvent did not interfere, the effect could also be observed in the proton signals of the disproportionation and coupling products, thereby indicating the position at which the process had occurred. One of these cases is illustrated in Figure 5. This not only strongly supported the radical nature of the reaction, but also provided further proof for the occurrence of radical pairs as intermediates and for a surface-bound radical.

Consistent with pathways 1, 2, 5, 6, and 7 in Figure 1 of the mechanism proposed by Walborsky and co-workers, Bodewitz et al. [60,76,87a–87c] came to the conclusion that the reaction of an aryl halide with magnesium proceeds by a single electron transfer from the surface of the metal to the carbon halogen bond to produce a radical anion absorbed at the metal surface by electrostatic interaction and unipositive magnesium Mg_s^+ (see pathway 1; Fig. 1). Rapid decomposition of this anion radical and combination of X^- with the unipositive magnesium would lead to the radical $R^\bullet$ and the magnesious halide $XMg_s^\bullet$ (see pathway 3; Fig. 1). The latter was described as "s" meaning "a surface-bound non-free radical." In agreement with Walborsky's mechanism, they also indicated that most of the radicals underwent a fast reaction at the site of the electron transfer with $XMg_s^\bullet$ to form the Grignard reagent (see pathway 5; Fig. 1).

However, the CIDNP spectra did not show that the radical pair involved in the formation of the polarized Grignard reagent was $R^\bullet$ $^\bullet MgX$. This was attributed to a lack of the required degrees of freedom of $XMg_s^\bullet$ to take part in singlet triplet mixing in a radical pair $R^\bullet$ $^\bullet MgX$ and the fast process of coupling. Alternatively, radical $R^\bullet$ could escape from the site of the electron transfer where it is formed and undergo hydrogen or halogen abstraction (see pathway 6; Fig. 1). Another route of escape for the radical would be association with another radical to form a radical pair $R^\bullet$ $^\bullet R$, which would result in the polarization observed in the alkyl group (see pathway 5; Fig. 1). Such association would also account for the disproportionation and coupling products (see pathway 6; Fig. 1).

An argument could be made that the radicals diffuse apart when reaction by pathway 6 does not occur. Here, the resulting free radicals might undergo association with $XMg_s^\bullet$

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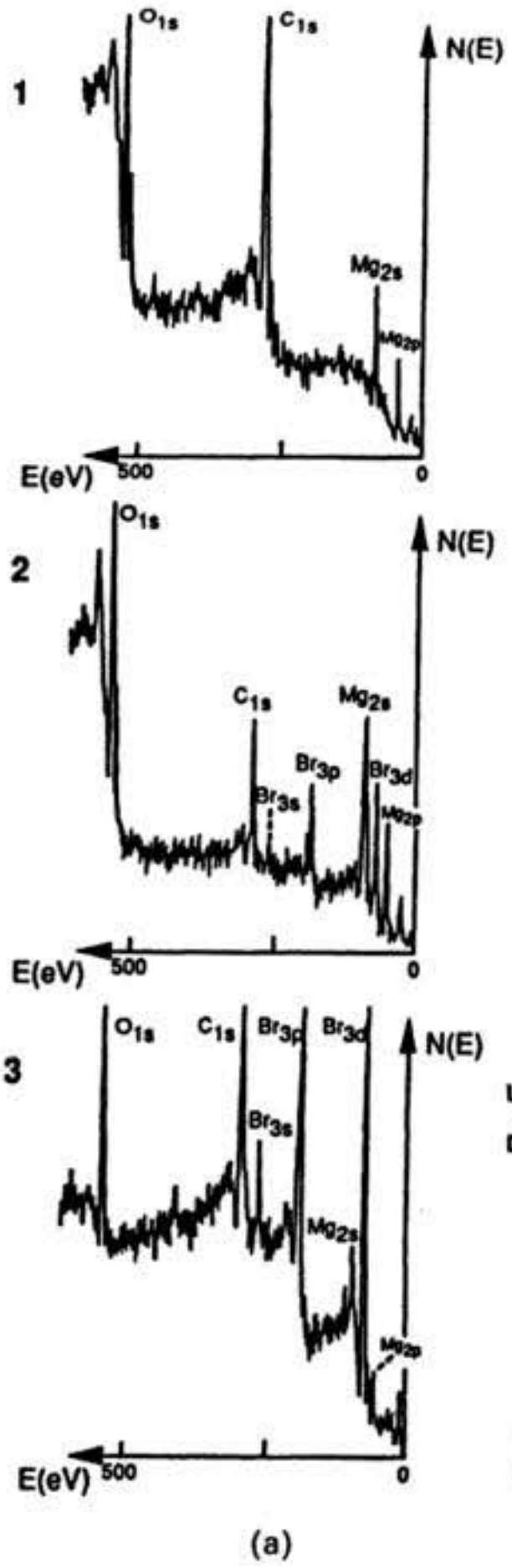
to yield Grignard reagent and hydrogen or halogen abstraction. However, such a possibility appears unlikely, since it would not account for the amount of Grignard reagent formed (98%). As Bodewitz and co-workers pointed out, if the Grignard reagent were formed by radical pairs $R^{\bullet}$ $^{\bullet}R$, or if the radical did not react at the site of its formation, a much lower yield of RMgX would be expected owing to disproportionation, coupling, and such. This provides support for the original mechanism proposed by Walborsky and co-workers in which the surface-bound radical plays the major role in the formation of Grignard reagent, and they comment "we feel that the direct reaction at the site of the electron transfer is by far the most important route leading to the Grignard reagent."

Also of interest are the results of Sergeev and co-workers [88] who investigated the solid-phase reactions of magnesium with aryl and alkyl halides at low temperature by means of EPR. Their investigation of the reaction of magnesium atom with organic chlorides [88b] supports the existence and participation of radical anions and radicals as well as the surface nature of the reaction and provides further evidence that the ratio of intermediates, radical anion–radical pair, formed by pathway 1 and pathway 2 (Fig. 1) is strongly dependent on the carbon–halogen bond strength.

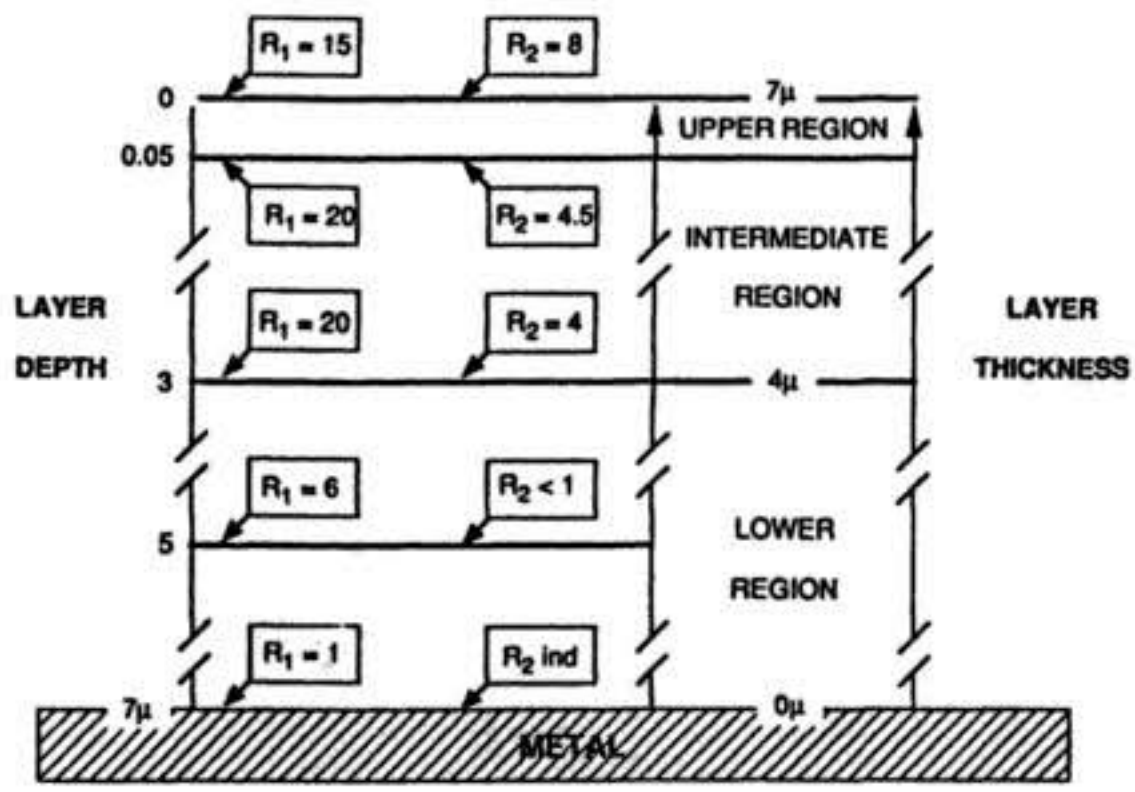
In general, the EPR spectra of condensed magnesium with alkyl and aryl halides exhibited two types of signals, depending mainly on the nature of the halogen. Fluorobenzene, with a carbon–fluorine bond energy of 122 kcal/mol, exhibited a singlet characteristic of the anion radical $RX^{\bullet -}$ $Mg^{\bullet +}$ whereas bromobenzene (75 kcal/mol) showed superposition of a broad signal and a multiplet. The latter was assigned to the radical. On the other hand, the EPR spectrum of condensed magnesium with fluorooctane (carbon–fluorine bond, 107 kcal/mol) showed a sextet, with a superimposed singlet, whereas bromobutane (68 kcal/mol) exhibited a sextet. These data would lead one to the interpretation that an increase in the carbon–halogen bond strength induces an increase in the yield of the tight radical anion–radical cation. Formation of Grignard reagent would occur largely by pathways 1 and 4, (see Fig. 1), with a concomitant decrease in the formation of radical pairs (see pathways 2 and 5). This is reflected in the fact that the highest retention of configuration in Grignard formation in the reaction of 1-halo-1-methyl-2,2-diphenylcyclopropane was observed when the halogen was chlorine. On the other hand, weakening of the carbon–halogen bond would lead to a very low yield of the tight anion radical–cation radical, and formation of the Grignard reagent would occur mainly by pathways 2 and 5. Indeed, this is what was observed; absence in the EPR spectrum of the singlet characteristic of the ion–radical pair in the reaction of magnesium condensed with iodobutane is coupled with the lack of retention of configuration in the reaction of 1-iodo-1-methyl-2,2-diphenylcyclopropane with magnesium.

Support for the surface nature of the reaction was also provided by Molle and co-workers [89a,b] who studied changes in the metal surface during formation of the Grignard reagent from 1-bromoadamantane and observed formation of a black layer on the metal surface, with a thickness reaching 7 μm. The magnesium turnings coated with this deposit were subjected to XPS analysis and ion bombardment [90] to analyze the elements present at different depths and to obtain information on the phenomena occurring at the metal–solution interface when an alkyl halide reacts with magnesium. Figure 6 illustrates the evolution of the signal intensity ratio R_1 of C_{1s} and Mg_{2s} electrons as well as the signal intensity ratio R_2 of Br_{3d} and Mg_{2s} electrons. These ratios correspond to the ratios of the components in the deposit at different depths. The layer at the surface was divided into three important regions. At the outset it should be noted that the XPS spectrum recorded after reaching the surface itself was identical with that of a scoured magnesium turning ($R_1 = R_2 = 0$). The XPS study of the so-called lower region (up to

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(a)



(b)

Figure 6 (a) An example of XPS spectra of Mg turnings before and after the reaction is initiated with dibromoethane and after reaction with 1-bromoadamantane. (b) XPS analysis of the components in the deposit at different depths (R_1, $[C_{1s}]/Mg_{2s}$); R_2, $[Br_{3d}]/[Mg_{2s}]$.

4 μm of thickness) showed that this region was composed mainly of Mg° and 1,1′-diadamantane. In this region both ratios R_1 and R_2 increased, indicating its heterogeneous character. The presence of highly reactive magnesium Mg° along with diadamantane in this region not only showed their common origin, the loose radical (R$^{\bullet}$ $^{\bullet}$MgX) having been formed and reacted largely at the surface, but also supported strongly pathways 6 and 7 (see Fig. 1). Thus, as predicted by the mechanism discussed earlier, the adamantyl radical dimerized (see pathway 6) at the metal surface to give the coupling

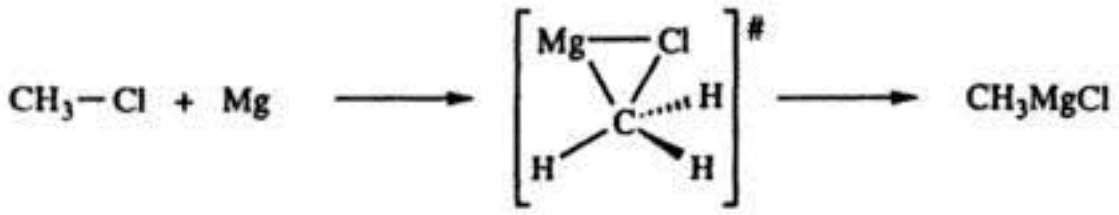
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product, while MgX disproportionated (see pathway 7) to yield highly reactive magnesium Mg^0 and $MgBr_2$. The intermediate region above 4 μm contained the same components, but exhibited homogeneous character, as shown by the constancy of both ratios R_1 and R_2. The third, upper region, which began at 6.95 and ended at 7 μm was mainly composed of $MgBr_2$, as indicated by the increase of R_2 up to the known value of $MgBr_2$ which is 8.

Other work in this area that deserves to be cited is a report by Ault [91] on the formation and spectroscopic characterization of unsolvated Grignard reagents by matrix isolation. Although a gas phase model has little to do with events that occur when the Grignard reagent is prepared in a solvent, the result itself reflects the major role played by the surface of the magnesium. Magnesium metal was codeposited with samples of methyl halides (CH_3X; X=Cl, Br, I) in an argon matrix, and the products formed were analyzed by infrared spectroscopy. New bands (543, 1305, 2800, 2892 cm^{-1}) were detected after every reaction. This suggested that, even in inert matrices, the insertion of magnesium into the carbon–halogen bond takes place to lead to an unsolvated Grignard species.

6. *Ab Initio Study of the Mechanism*

Ab initio calculations by David [92] on the insertion of an isolated magnesium atom into the carbon–halogen bond of fluoromethane and chloromethane included calculations of transition state energies, geometries, and vibrational frequencies. Both systems exhibited similar geometries for the transition state with C_s symmetry (Scheme 34).



Scheme 34

The transition state for the reaction was located at SCF and correlated levels. Geometric parameters and energies for the transition state were compared with those of the Grignard reagent CH_3MgCl, the latter also arrived at after full optimization at both the SCF and correlated levels.

As can be seen from Table 12, the Mg—Cl bond distance in the transition state is quite close to that of the Mg—Cl portion in the Grignard reagent CH_3MgCl. This was

Table 12 Geometrical Parameters and Energies for Transition State $(H_3CClMg)\#$ and the Grignard Molecule CH_3MgCl

	$(H_3CClMg)\#$		CH_3MgCl	
Parameters	SCF	MP2	SCF	MP2
C–Mg (Å)	2.9862	2.7471	2.090	2.0799
C–Cl	2.5174	2.2554		
Mg–Cl	2.392	2.3811	2.217	2.1987
(Mg–C–Cl) (degrees)	50.65	55.81		
(H–C–Mg)			111.7	111.46
Energy (hartrees)	−698.649	−699.182	−698.764	−699.338

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ascribed to the strong interaction between the magnesium and the halogen in the transition state. The net atomic charge was determined by a Mulliken population analysis for the Grignard reagent and for the transition state. The charges found were C, −08.18; Mg, 0.911; Cl, −0.522, for the Grignard reagent, and C, −0.316; Mg, 0.107; Cl, −0.44, for the transition state.

IV. A MATHEMATICAL APPROACH TO ESTABLISHING A MECHANISM

Another view of the mechanism of Grignard reagent formation was advanced by Garst and co-workers in 1986 [93].

A. Diffusion Model Calculation and Assumptions

The view, to be discussed in this section, involved a mathematical model called the diffusion (D) model, based on kinetic data and the product distribution found in several Grignard reagents. It was agreed that the first step in Grignard reagent formation is an electron transfer from the magnesium surface to the carbon–halogen bond, leading to a radical $R^{\bullet}$. The radical is formed in solution at constant flux υ, in a plane parallel to the surface and at a distance s between this plane and the surface at the time of its formation. It was postulated (1) that all radical intermediates diffuse freely in solution at all times as if they were produced in a homogeneous medium, none of them being bound to the metal surface; (2) that isomerization of $R^{\bullet}$ in solution to $R_i^{\bullet}$ (a rearranged radical) is followed by reaction of a fraction of both $R^{\bullet}$ and $R_i^{\bullet}$ with the solvent SH to produce RH, R_iH and $S^{\bullet}$; (3) that a fraction of these three radical intermediates would react with each other, leading to the coupling products RR, RR_i, RS, R_iR_i, R_iS, and SS; and, finally, (4) that those radicals $R^{\bullet}$, $R_i^{\bullet}$, and $S^{\bullet}$, which had escaped reaction with solvent and other side reactions, but were still in the body of the solvent, would return to the magnesium surface to react and form RMgX, R_iMgX, and SMgX (Fig. 7).

The D-model was further based on the assumption that all radical intermediates $R^{\bullet}$, $R_i^{\bullet}$, and $S^{\bullet}$ possessed identical reactivities and rates of diffusion: First, they would all have the same rate constant for reaction with the solvent k_s (sec^{-1}). Second, they would have the same diffusion coefficient D ($cm^2\ sec^{-1}$). Third, they would have the same rate constant k_c ($cm^3\ mol^{-1}$) for reaction with each other. Finally, they would return to the surface to react in an identical manner and with the same reactivity parameter δ (Fig. 8).

The first version of the model [93a] was suggested as an efficient method for predicting the ratios RiMgX/RMgX in the Grignard reaction of alkyl halides. In this version, side reactions, such as solvent attack, coupling, and disproportionation, were not taken into account. On the assumption that all isomerizations took place in the body of the solvent and that both $R^{\bullet}$ and $R_i^{\bullet}$ were free in solution at all times, it was thought plausible to compare the first-order rate constant k for a homogeneous reaction—here, the known rates of isomerization of alkyl radicals and, more specifically, those formed from 5-hexenyl bromide, norbornylethyl bromide, and cyclopropylcarbinyl bromide in homogeneous solution—with the known product distribution for the Grignard reaction of 5-hexenyl bromide [75,95], norbornylethyl bromide [96], and cyclopropylcarbinyl bromide [95,97]. By using, with modification, equations developed by Noyes [98] and Naqvi [99] for the theoretical treatment of diffusion-mediated reactions, Garst et al. arrived at Eq. (9) to describe the relationship of the rate constant k_i to the yield ratio $R_iMgX/RMgX$ where

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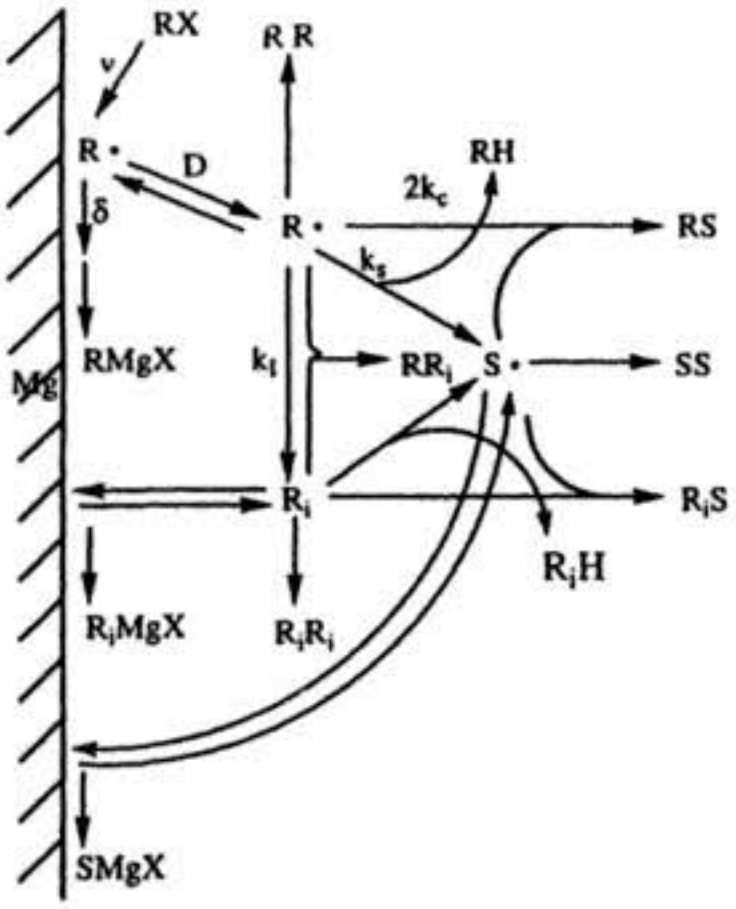


Figure 7 D-model for Grignard reagent formation. Since $R^{\bullet}$, $R_i^{\bullet}$, and $S^{\bullet}$ were assumed to have identical properties, they could be treated as a single intermediate *T*, which may either return to the surface and react with magnesium or undergo coupling in solution. Differences in the nature of the radical intermediates $R^{\bullet}$, $R_{i^{\bullet}}$, and $S^{\bullet}$ were ignored.

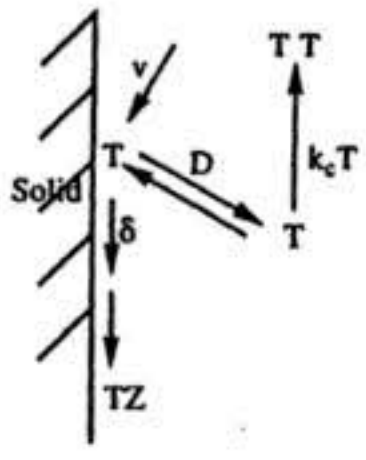


Figure 8 D-model for the single reactive intermediate *T*.

[log $1/\delta + s - 0.5$ log D] is a constant.

$$\log\left(\frac{R_iMgX}{RMgX}\right) = 0.5 \log k_i + \log\left(\frac{1}{\delta + s}\right) - 0.5 \log D \tag{9}$$

In Eq. (9), δ is the reactivity parameter of the radical with the surface, D is the diffusion coefficient and $s <$ or equal 4 Å. The plot of log RiMgX/RMgX versus log k_i for the three alkyl halides was drawn as a straight line, which was taken to imply that δ was equal to 0.01 $Å^{-1}$, since D was taken as 3×10^{11} Å sec^{-1}. However, as may be seen from Figure 9 the error in the value of the constant [log$(1/\delta + s) - 0.5$ log D], from which δ is derived, is almost 25–30%.

On this basis one would conclude that if one knows the rate constant for isomerization of a radical under homogeneous condition, one should be able to predict the yield ratio

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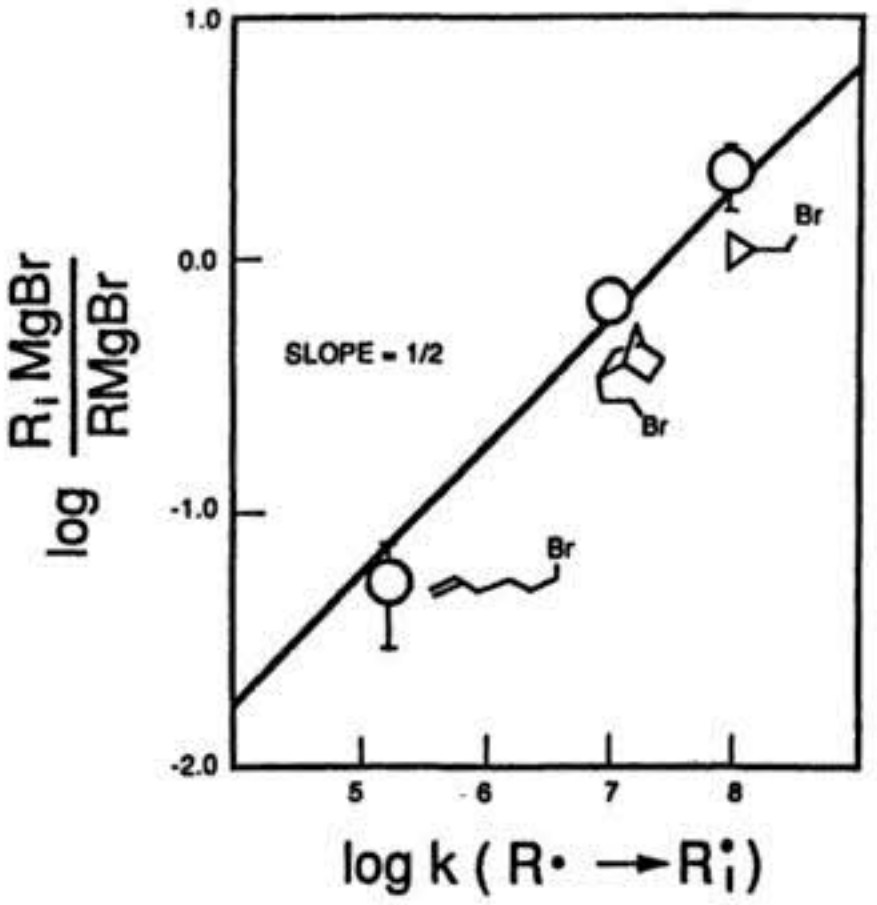


Figure 9 Test of Eq. (9) for isomerizations occurring during the Grignard reagent formation in Et_2O from primary alkyl bromide.

$R_iMgX/RMgX$ for the Grignard reaction of any alkyl halide, either by calculation, using Eq. (9) or directly from the log/log plot of Figure 9.

B. D-Model Accommodation in the Kinetic Treatment and Error in Both Diffusion Concept and Nature of the Reactive Surface

To calculate the product distribution for Grignard reagent formation from 5-hexenyl bromide. Garst et al. [93b,c] used the following equations and compared the results with the experimental data of Bodewitz et al. [76] for the reaction of 5-hexenyl bromide with magnesium (see Sec. III.E.2).

$$G^2-1=k_i/k_s$$
$$V=[4k_c/3(k_s^3D)^{1/2}]v$$
$$\Delta=(D/k_s)^{1/2}\delta$$
$$V_i=[4k_c/3(k_i^3D)^{1/2}]v$$
$$\Delta=(D/k_i)^{1/2}\delta$$

G^2-1 is the scaled radical isomerization rate constant, V represents the scaled initial-step flux, and Δ the scaled reactivity of the surface toward the radical. The parameters k_i, k_s, k_c, and D, were either taken from the literature or estimated when the data were not available. Since a value for the flux v was not known for 5-hexenyl bromide, a value of 2×10^{-5} mol cm^{-2} sec^{-1} was applied to the 2.1 M solution of 5-hexenyl bromide used by Bodewitz et al. [76]. Finally, the value of 0.01 Å^{-1} for δ was taken from the plot of log($R_iMgX/RMgX$) versus log k for the three alkyl halides (see Fig. 9).

Table 13 compares the product distribution calculated in this fashion with the experimental results of Bodewitz et al. It is seen that the calculation where three of the six parameters (v, δ, and k_s) were given estimated values almost exactly reproduces the

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Table 13 Product Distribution for the Reaction of 5-Hexenyl Bromide with Magnesium in Ether at 40°C

Product	Calculated yield (%)	Experimental yield (%)
RMgBr	88	85.5
R_iMgBr	3	2.5
PP[a]	8.7	9.0
RH[b]	0.068	
R_iH[b]	0.059	
RR/PP	66	64.5
RR_i/PP	26	18
R_iR_i/PP	8.2	7.5

[a]P is a collective symbol for R and R_i, thus PP includes RR, R_i, and R_iR_i.
[b]From the reaction of $R^\cdot$ or R_i. with the solvent; the amounts of RH or R_iH that could derive from disproportionation were not taken into account.

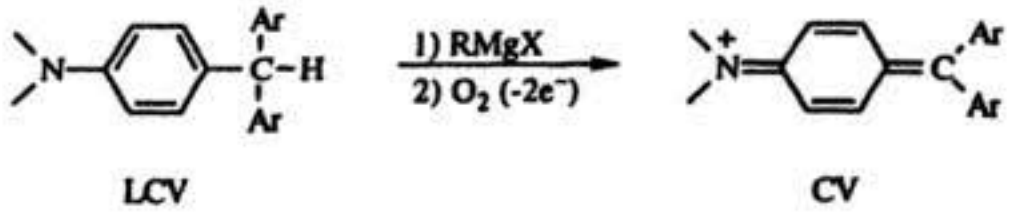
experimental yields and the product distribution. However, as was pointed out [93c], the calculations of product distribution were quite sensitive to variations in the flux υ. The question that may then be asked is where did the value of υ used in the calculations come from? As stated by the authors themselves, it was "simply luck" [93c, p. 245] that the estimated υ value (2×10^{-5} mol cm^{-2} sec^{-1}) was close to the value that gave the best agreement with experiment.

Calculations for Grignard reagent formation from 5-hexenyl bromide and product distribution in other solvents such as THF, DBE, DPE, using similar assumptions and neglecting the reactions of radicals with solvents were also compared in each case with the experimental results of Bodewitz et al. [76] to support the argument for the greater predictive competence of the D-model.

One of the most significant errors in the kinetic treatment leading to the D-model is the assumption of a uniformly reactive surface and linear diffusion. The magnesium surface is treated as if it were uniform [93a–93d], in spite of considerable evidence militating against this. Hill et al. [100] had earlier examined the surface morphology of magnesium, after reaction with organic halides in etheral solution, using optical microscopy and scanning slectron microscopy (SEM). It was demonstrated that the first stage of the reaction took place at small reactive sites caused by defects on the magnesium and dislocations. Small pits were observed on the magnesium surface that grow as the reaction proceeds until they overlap and lose their individual identity. Most of the magnesium surface was unreactive, and the number of sites available for initiation was independent of the action of activators. Also, interestingly, under similar conditions higher pit densities were observed in the alkyl chlorides than with alkyl bromides [100]. The halide ion was involved in the release of some of the magnesium atoms from the surface. Also reactions in diethyl ether produced higher pit densities than in THF.

More recently, Bowyer et al. [101] photographed the magnesium surface area during Grignard reagent formation. Leuco crystal violet [LCV; 4′,4′,4″-methyldiyne-tris(*N*,*N*-dimethylaniline)] (Scheme 35), in the presence of oxygen, was used as an indicator for the Grignard reagent. Thus, Grignard reagent reacts as a base with LCV, which is colorless, to give an intermediate that is oxidized by oxygen to give dark blue CV [101], thus

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Scheme 35

permitting one to detect and follow Grignard reagent formation by observing the dark blue spots that appear on the magnesium surface. In the earlier stages of the reaction, the sites were small. A photomicrograph of the magnesium surface taken after 38 min of the reaction of magnesium with bromoethane clearly demonstrated that most of the surface of the magnesium was unreactive. This contradicts the hypothesis of a uniformly reactive surface assumed by the D-model. Instead the experiments of Bowyer et al. [101] showed the presence of only a few, and very small, reactive sites at the beginning of the reaction and demonstrated that the reaction proceeded mostly by growth of these reactive sites and that, early in the reaction, the diffusion of reactants and products was spherical, rather than linear, as assumed by the D-model. These workers concluded that, based on their experimental observations, "it is remarkable that a model assuming linear diffusion can so accurately predict product ratios."

C. Disagreement Between the Calculated and the Experimental Results

The discussion of the D-model presented in the previous section demonstrated that this model was based on assumptions, accommodations in the kinetic treatment, and error in both diffusion concept and nature of the reactive surface. In this section we present experiments that were designed to test the hypothesis that all radicals diffuse from the magnesium surface and flow freely in solution.

1. Attempts to Trap Free Radicals at the Magnesium Surface

The literature records various studies on the trapping of radicals by metal surfaces. Gaseous methyl free radicals were earlier [102,103] shown to react with metallic mirrors, such as lead, antimony, and zinc, and to oxidize gaseous metal atoms, such as bismuth, tin, mercury, cadmium, germanium [104], as well as calcium and strontium [105]. These findings prompted an interesting question on the reactivity of radicals with magnesium. What would the situation be in solution? In other words, would free radicals generated in solution have enough time to diffuse through the bulk medium, reach the magnesium surface, and form Grignard reagent? The answer to this question would decide the validity of one of the assumptions of the D-model.

It should be pointed out first that, according to the D-model, an alkyl radical may travel 17,000 Å and still retain a high probability of returning to the magnesium surface to form Grignard reagent [93c]. This distance was calculated using the following equations where ϕ is the probability that a

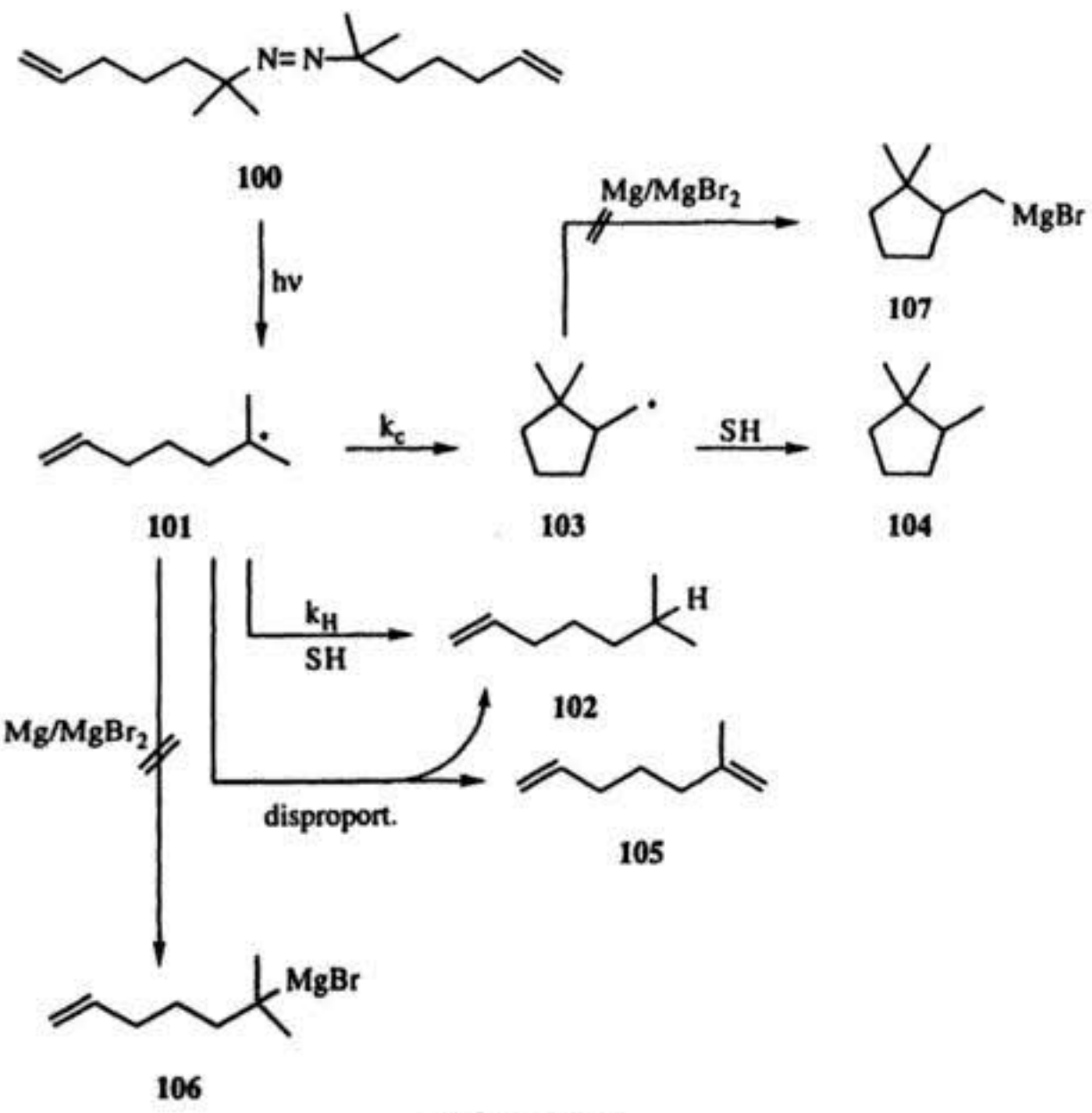
$$\phi = e^{-r/\sigma} \qquad \sigma = (D/k_s)^{1/2}$$

radical at a distance r from a reactive surface will diffuse to the magnesium surface instead

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of reacting with solvent, and σ is called the space constant. The value of k_s, taken from Newcomb's work [106] for the reaction of octyl radicals with Et_2O at 22°C, was 10^3 sec^{-1}, and D was the diffusion constant, which was estimated as 3×10^{11} $Å^2$ sec^{-1}. In this manner, the space constant was calculated to be 17,000 Å. This would mean that an alkyl radical that has traveled a distance $r = 17{,}000$ Å from the surface has a 40% probability to return and form Grignard reagent because ϕ would be equal to e^{-1}.

To test this, we carried out experiments [107] designed to determine if the magnesium surface could serve as an effective radical trap capable of modifying the normal behavior of radicals produced in solution. A free radical clock, radical **101** (Scheme 36), formed by photolytic decomposition of azo precursor **100** [74, 95, 108], was employed as a probe for this investigation [107]. In general, tertiary azo compounds are known to decompose smoothly and with great facility, owing to the stability of the radical formed and the ground-state strain [107], and they also are stable toward Grignard reagents [109]. When **100** was photolyzed in diethyl ether solution at 23°C [107], three hydrocarbon products were formed: 6-methyl-1-heptene **102**; 1,1,2-trimethylcyclopentane **104**; and 2-methyl-1,6-heptadiene (see Scheme 36).



Scheme 36

Product ratios are given in Table 14. Although the total yield was much lower at high concentrations of **100**, the product ratios did not change appreciably with concentration. Evidence that the 1,1-dimethyl-5-hexenyl radical **101** was generated under these conditions was provided (1) by the large amount of cyclized product **104**, and (2) by a trapping experiment with diphenylphosphine. The large amount of **102** observed in the trapping

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Table 14 Photolysis of **100** at 350 nm in Diethyl Ether at 23°C

Entry	Conc. (*M*)	Time (hr)	Total yield (%)	Product ratio (% yield) **104**	**102**	**105**
1	0.025	6	91	1(43)	0.6(26)	0.52(22)
2	0.25	15	57	1(25)	0.72(18)	0.56(14)
3[a]	0.25	15	56	1(3)	12.7(41)	3.7(12)

[a]In the presence of 5 Eq of diphenylphosphine.
Source: Ref. 107.

Table 15 Photolysis of **1** at 350 nm in Diethyl Ether in the Presence of Magnesium

Entry	Conc. (*M*)	Time (hr)	Total yield (%)	Product ratio (% yield) **104**	**102**	**105**
1[a]	0.025	6	91	1(43)	0.6(26)	0.52(22)
2[b]	0.25	15	25	1(11)	0.72(8)	0.55(6)
3[c]	0.25	15	58	1(26)	0.69(18)	0.54(14)
4[d]	0.25	15	59	1(27)	0.68(18)	0.54(14)
5[e]	0.25	15	52	1(23)	0.65(18)	0.60(14)

[a]In the presence of 5 Eq of magnesium powder that was activated by stirring under argon.
[b]In the presence of 5 Eq of magnesium activated by ethylene bromide (0.5 Eq of $MgBr_2$).
[c]In the presence of 5 Eq of magnesium powder activated by ethylene bromide, and the magnesium bromide was washed out.
[d]In the presence of magnesium that was activated by MeI, and MeMgI was washed out.
[e]In the presence of Rieke magnesium.
Source: Ref. 111.

experiment could be explained by assuming that the rate of abstraction of hydrogen from diphenylphosphine ($k_H = 10^7$ sec^{-1}) [106] is higher than the rate of cyclization ($k_H = 10^6$ sec^{-1}) [110]. The close correspondence in the yields of **102** and **105** indicated that these products arose by disproportionation of the intermediate radical **101**.

We now turn to consider the effect that a magnesium surface might have on the rearrangement of free radicals in solution. Does radical **101** or the radical **103**, when generated in the presence of magnesium, react with it? If yes, the formation of some Grignard reagent **106** or **107**, or both, or at least a change in the product ratio would be expected. Table 15 shows what occurs when the photolysis of 100 is carried out under the same conditions, but in the presence of various types of activated magnesium.

A comparison of Tables 14 and 15 demonstrates that the nature, the yields, and the ratio of products are identical, whether **100** has been photolyzed in the presence or absence of the magnesium surface, regardless of how one attempts to activate the magnesium, which includes the use of highly reactive Rieke magnesium [111].

One could argue that the conditions used in these experiments did not exactly resemble the conditions under which the D-model was supposed to operate. Radicals were produced in solution and were captured whether or not they had reached the surface,

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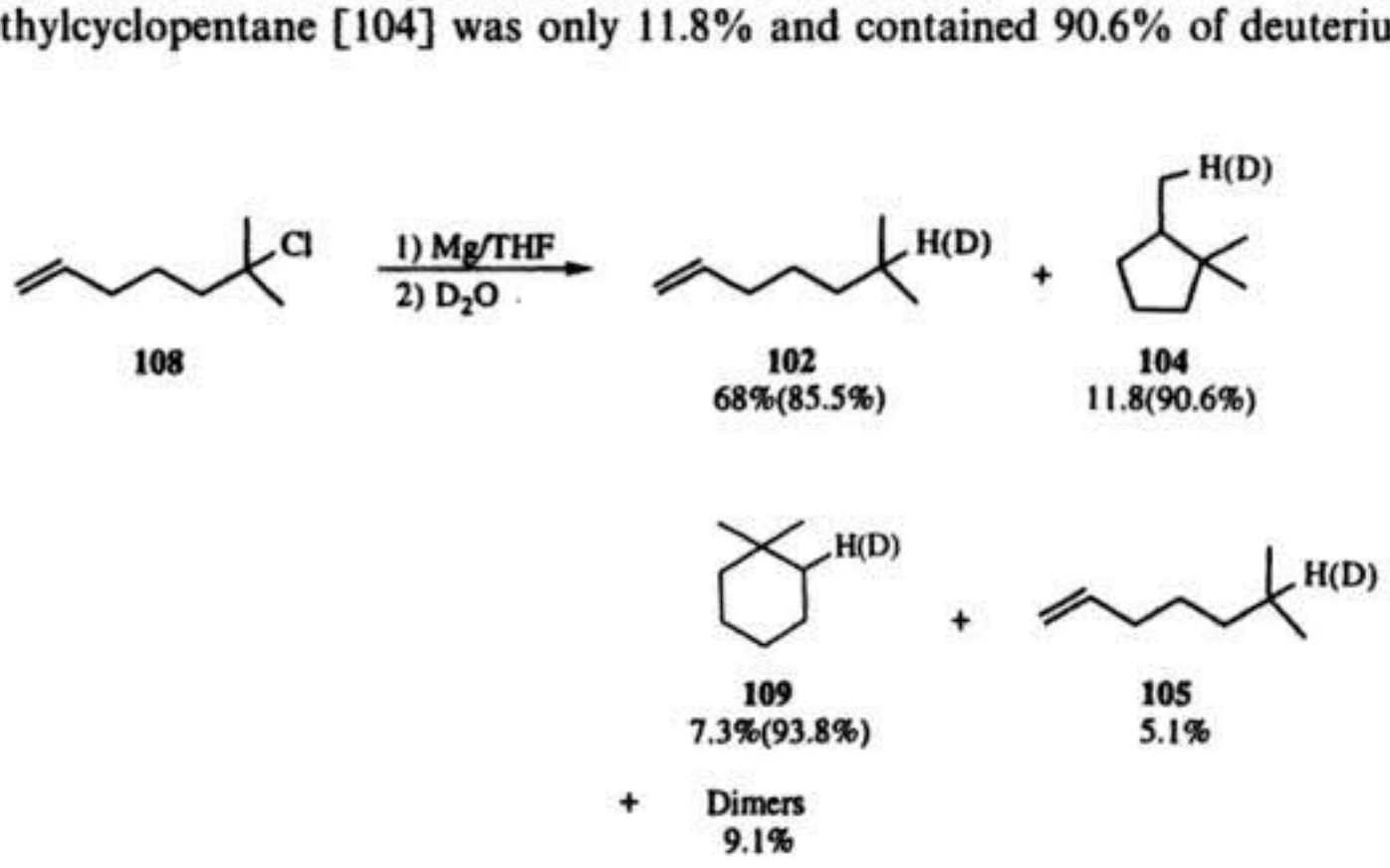
whereas in the D-model, radicals, after being produced at the magnesium surface, are assumed to leave the surface, to diffuse freely in solution, and then to return to form Grignard reagent. The kinetics would obviously be different. However, if one considers two of the assumptions on which the D-model was based, one would have to consider the design of these experiments as a good representation of the model. First, as discussed earlier, the D-model assumes uniformity of the magnesium surface as well as a linear diffusion process; second, it follows from the model that the octyl radical could travel a distance of 17,000 Å into the solution and still have a 40% chance of returning to the magnesium surface before reacting with ether solvent.

Now in the photolysis of **100** in the presence of Rieke magnesium, all radicals were generated close to the magnesium surface within a sphere of radius 1500 Å, as shown by a calculation based on the known values of the average particle size of Rieke magnesium (10^{-5} cm) [111c], the density of magnesium (1.74 g/cm^3), the amount of magnesium used in the experiments, and the total volume of the solution. If we consider these facts, use of Rieke magnesium provided an excellent test for the D-model, since, according to the model, trapping by the surface in this case would be possible. By using the equation on p. 189 for determining the probability ϕ_r that a radical at distance r from the reactive surface will form Grignard reagent instead of reacting with the solvent, with $r=1500$ Å, we obtain $\phi_r=e^{-0.088}=0.92$ which means that the yield of Grignard

$$\phi_r=e^{-1500/\sigma} \qquad \text{and} \qquad \sigma=(D/k_s)^{1/2}$$

reagent expected from this experiment would be 92% if the D-model were correct. Since the octyl radicals did not interact in any way with the magnesium surface, any model that assumes that radicals could travel 1500 Å (or even less [107]) from the surface and return to form Grignard reagent would be excluded.

Let us now consider the behavior of radical **101** when formed at distance zero from the surface, as in the reaction of 6-chloro-6-methyl-1-heptene [108] with magnesium to form the corresponding Grignard reagent [77]. At 22°C in THF and workup with D_2O, **108** furnished the products shown in Scheme 37. 6-Methyl-1-heptene [102], which indicated the amount of the straight-chain Grignard reagent formed during the reaction, was formed in 67% yield and incorporated 85.5% of deuterium, whereas the yield of 1,1,2-trimethylcyclopentane [104] was only 11.8% and contained 90.6% of deuterium.



Scheme 37

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These results seem to show that, if radical **101** had traveled 1500 Å from the magnesium surface, it would not have any chance to form Grignard reagent and that the ratio of products should be similar, to a certain extent, to those shown in Table 14. Instead, 85.5% of Grignard reagent was formed from the straight chain and only 11.8% from the cyclized product.

2. *Cyclopropylmagnesium Bromide: Product Balances, Calculated and Found*

More recently, the authors of the D-model investigated the reaction of bromocyclopropane **133** with magnesium [93e], using again the equations $V=[4k_c/3(k_s^3D)^{1/2}]v$, $\Delta=(D/k_s)^{1/2}\delta$ mentioned earlier to calculate the product distribution, but substituting another composite parameter F for Δ and using the same values, questioned earlier for 5-hexenyl bromide, now for cyclopropyl

$$F=\frac{\Delta^3}{V}=\frac{3D^2\delta^3}{4k_cv}$$

bromide. Thus, the flux r was again estimated as 2×10^{-5} mol cm^{-2} sec^{-1}, the diffusion coefficient D as 3.0×10^{-5} cm^2 sec^{-1}, and the rate constant for the coupling reaction $2k_c$ as 3.0×10^9 M^{-1} sec^{-1}, these values constituting in the authors' words "probably an excellent approximation." The value of the rate constant for the reaction of the cyclopropyl radical with the solvent $k_s=10^6$ sec^{-1} was derived from the D-model analysis (Fig. 10). This was taken to show that the cyclopropyl radical was 1000 times more reactive toward the solvent than a primary alkyl radical. The value of the reactivity parameter δ for cyclopropyl (0.005 Å) is half of the one reported earlier [93a–93c]. These parameters were used to calculate the product distribution for the reaction of cyclopropyl bromide with

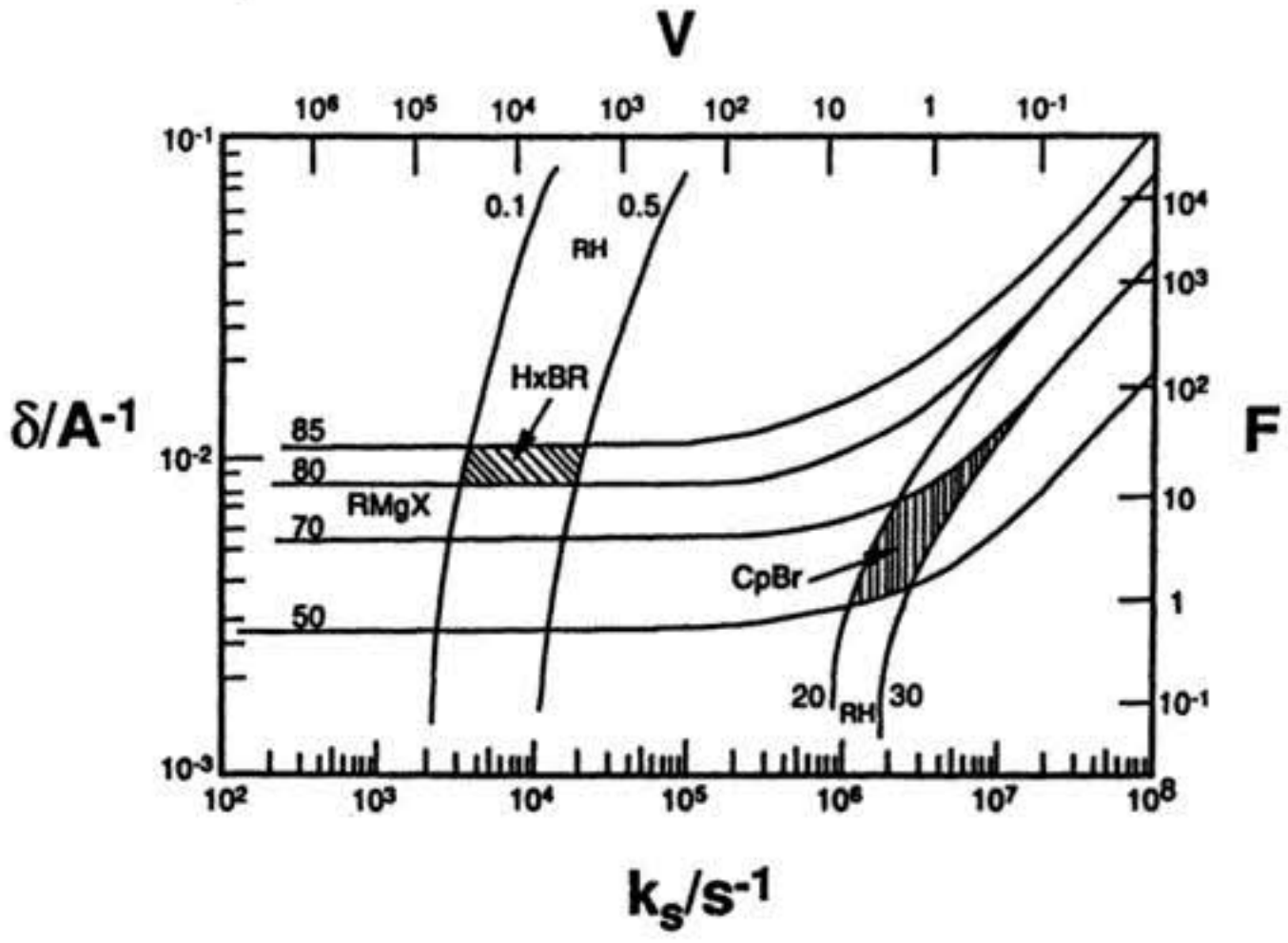


Figure 10 Calculated yields (mol/100 mol of RBr) of RMgX (horizontally trending lines) and RH from solvent attack by R$^\bullet$ (vertically trending lines), according to an idealized D-model in which the intermediate radicals R$^\bullet$ and S$^\bullet$ have the same diffusion coefficients and reactivities in analogous processes.

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Table 16 Comparison of Calculated and Observed Yields for the Reaction of Bromocyclopropane[a] with Magnesium

	CpMgBr	CpH[b]	CpCp[c]	CpS	SS	δ	k_s
Calculated	52	34	3.9	6.2	6.3	0.005	4.4×10^6
Observed	51	20–30	1.5	>4.6	>7.3		

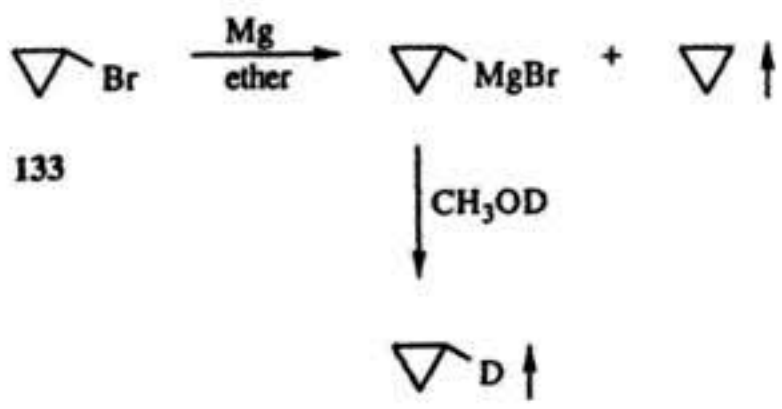
[a]Amount (mol) of product formed for 100 mol of RBr consumed.
[b]Amount of CpH formed from the reaction of Cp$^\bullet$ with diethyl ether.
[c]Includes products of radical disproportionation and coupling.
Source: Ref. 93e.

magnesium and compared with the experimental result for the reaction of magnesium with bromocyclopropane in diethyl ether at reflux. The results are shown in Table 16.

Again, the calculation reproduced almost exactly the experimental results. Moreover, both calculation and experiment accounted for almost 100% of the cyclopropyl group, the possible formation of cyclopropene being completely excluded.

On the basis of these findings, the authors concluded that cyclopropyl bromide is converted to the cyclopropyl radical, which leaves the surface and diffuses into solution, where it reacts mainly by hydrogen abstraction from the solvent ($k_s = 4.4 \times 10^6\ M^{-1}\ \text{sec}^{-1}$) to form cyclopropane and by coupling. The remaining radicals return to the magnesium surface to form Grignard reagent ($\delta = 0.005$).

However, the conclusions based on these experiments and the calculations may be questioned as a result of recent work in our laboratory [112] carried out to find the source of the hydrogen atoms donated to the cyclopropyl radical (Scheme 38). The results are shown in Table 17. In the D-model the main source of these hydrogen atoms would be



Scheme 38

the solvent, whereas on the basis of the mechanism depicted in Figure 1, one would expect that disproportionation on the surface would be the most probable source for cyclopropane formation. The yield of cyclopropane was determined by efficient trapping of the gas (bp −33°C). The amount of Grignard reagent was determined by quenching with methanol-*O*-*D* at 0°C and trapping of the 1-deuteriocyclopropane. Use of ^{1}H-NMR spectrometry easily distinguished between cyclopropane and 1-deuteriocyclopropane.

In these experiments [112], the yields of Grignard reagent and of cyclopropane were significantly different from those published by the authors of the D-model, both by calculation and experiment. The average of five runs showed that only 26% cyclopropane

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Table 17 Yields of Cyclopropane Formed Directly During Formation of Cyclopropylmagnesium Bromide in the Reaction of Cyclopropane with Magnesium

Exp. no.	1	2	3	4	5	Av.
In ether						
Cp, % yield[a]	30	23	24	31	24	26
CpMgBr, % yield[b]	21	27	23	18	31	24
In THF						
Cp, % yield[a]	6	10	11	12		10
CpMgBr, % yield[b]	33	43	23	39		35

[a]Cp, cyclopropane.
[b]Determined by quenching with methanol-O-D.

and 24% cyclopropylmagnesium bromide were formed. The starting material cyclopropyl bromide was not detected after the reaction, so incomplete reaction was not the reason for the difference in the yields. In contrast to the data shown in Table 16, here 40–45% of the cyclopropyl residues were missing, which led to the conclusion that a portion of the loss, ~20%, was the result of disproportionation of the cyclopropyl radical on the magnesium surface that leads to formation of the unstable cyclopropene. Again, these results turned out to be in disagreement with the predictive power of the D-model.

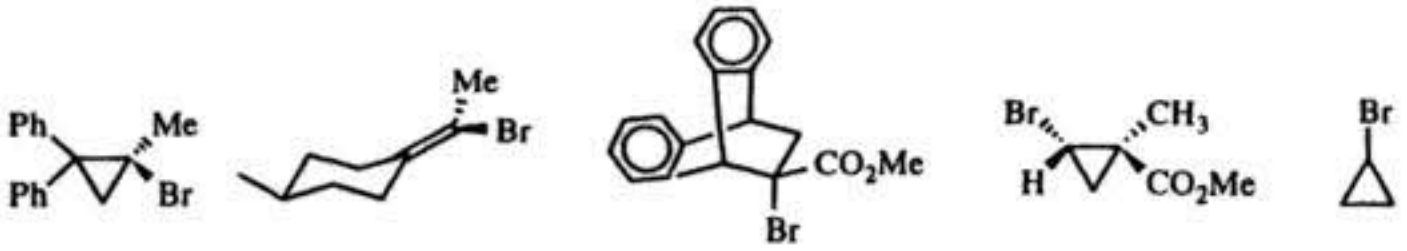
V. FURTHER EVIDENCE FOR THE SURFACE NATURE OF GRIGNARD REAGENT FORMATION

A. Formation of Grignard Reagent in the Presence of Monodeuterated Alcohols

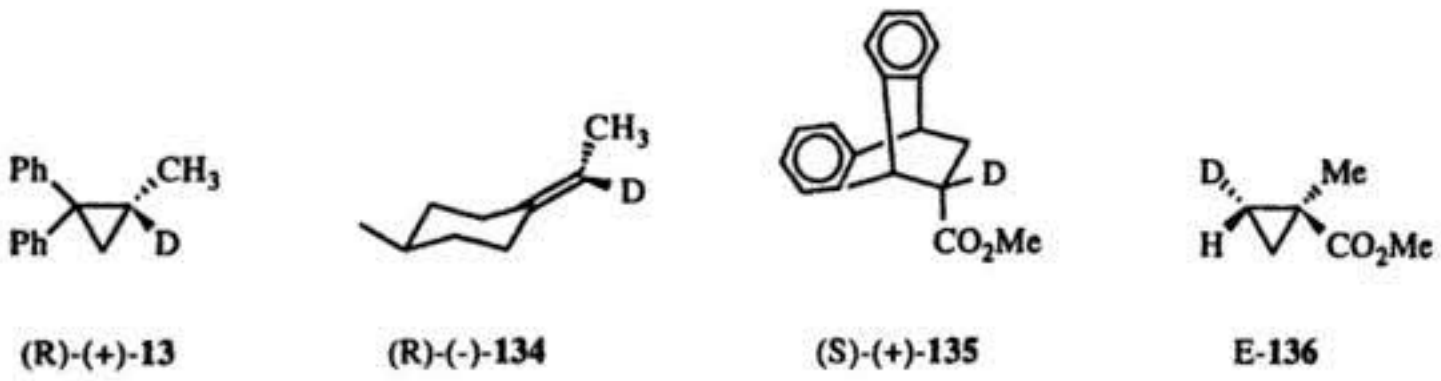
1. Reaction of Organic Bromides Magnesium in Methanol-O-D

It has been demonstrated earlier that the cyclopropyl radical **16**, when generated in methanol by decomposition of the precursor diacyl peroxide [113], on the one hand, abstracts a hydrogen atom from methanol to give **13** and, on the other hand, yields approximately an equal amount of ring-opened dimer **24**. The vinyl radical was even more reactive than the cyclopropyl radical [26]. This led to a further test of the assumption of the D-model that the radicals generated in the reaction of an organic halide with magnesium diffuse freely into the solution at all times and return to the magnesium to form Grignard reagent. The reaction of an organic halide with magnesium in MeOD would be a good probe for this. Thus, if reactive radicals, such as cyclopropyl or vinyl σ radicals left the surface of the magnesium, they would be expected to react with HCH_2OD by abstracting a hydrogen atom [114] from the methyl group, to give RH. Additionally, the hydrocarbon product would be racemic in cases involving chiral compounds and, if a cyclopropyl radical were involved, a considerable amount of ring-opened derivatives would be expected to be formed. If, on the other hand, the radical did not leave the surface, but produced the Grignard reagent on the site of the SET, the reagent would be quenched by CH_3OD to give deuterated product RD. Let us analyze the results of five selected systems, for which

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(S)-(+)-18 (S)-(+)-130 (S)-(+)-131 E-132 133



(R)-(+)-13 (R)-(-)-134 (S)-(+)-135 E-136

Scheme 39

the reactions with magnesium in monodeuterated methanol were studied. The systems are shown in Scheme 39.

Reactions of three optically active organic bromides with magnesium in MeOD were reported by our group in 1989 [13]. (*S*)-(+)-**18** and (*S*)-(+)-**130**, which give rise to σ radicals, and (*S*)-(+)-**131**, which would produce a π planar delocalized radical, were reacted with magnesium powder in methanol-*O*-*D*. The fourth example was reported earlier by Kirmse and co-workers [115], who reduced geometrically pure cyclopropyl bromide (*E*)-**132** with magnesium in MeOD, while the fifth example, the reaction of cyclopropyl bromide **133** with magnesium in methanol-*O*-*D* [112], has already been cited earlier. The results are shown in Table 18.

Consider now the claim that radicals produced during formation of the Grignard reagent diffuse in solution all the time, in view of the results shown in Table 18. In every instance the products incorporated very little if any hydrogen derived from the methyl group of HCH_2OD. There is no law that would have prevented such radicals from forming significant amounts of RH if they were really in solution, regardless of the kinetics. Moreover, no ring-opened products derived from **18** or **132** were detected. Thus, the main products formed in 93–100% yield resulted from deuterolysis for the corresponding

Table 18 Reaction of Organic Bromides (RBr) with Magnesium in Methanol-O-D

RBr	RH + RD (yield %)	RD (yield %)	Opt. purity (%)	Nature	Configuration of major isomer	Ref.
(*S*)-(+)-**18**	87	100	24	Retention	(*R*)-(+)-**13** D	13b
(*S*)-(+)-**130**	70	93	60	Retention	(*R*)-(−)-**134** D	13b
(*S*)-(+)-**131**	94	95	11	Inversion	(*S*)-(+)-**135** D	13b
(*E*)-**132**	93	100	(*E*/*Z* = 95:5)	Retention	*E*-**136** D	115
133	33	98				112

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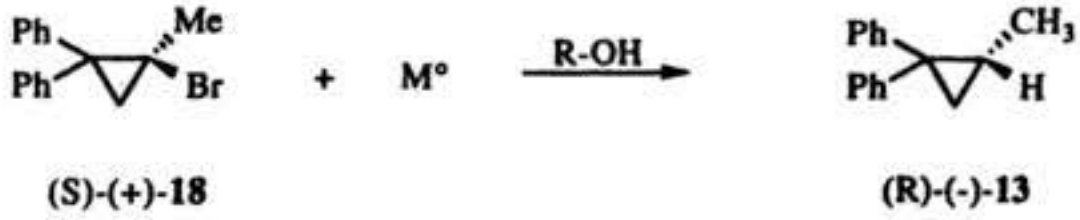
Table 19 Reaction of (*S*)-(+)-**18** with Alkali Metals in Alcohol Solvents

M°	Solvent	(*R*)-(−)-**2** (yield %)	Opt. purity (%)
Li	*i*-PrOH	94	39
Li	*t*-BuOH	100	47
Na	MeOD	100(>95%D)	47
Na	*i*-PrOH	100	47
Na	*t*-BuOH	100	46
K	*i*-PrOH	30	44
K	*t*-BuOH	9	44

Source: Ref. 94.

Grignard reagents. As in the aprotic solvents discussed earlier, hydrocarbons **13** and **134**, the formation of which occurs partially through σ radicals, were formed with significant retention of configuration [13b]. Moreover, in the reaction described by Kirmse [115], product *E*-**136**D, also involving a σ-radical, was formed with almost complete retention of configuration (95:5). Finally, even (*S*)-(+)-**131**, which would undoubtedly give rise to a planar delocalized π radical intermediate, produced (*S*)-(+)-**135D** with significant optical activity (11%). When (*S*)-(+)-**131** was reacted with tri-*n*-butyltin hydride, the resulting product (*S*)-(+)-**135H**, was completely racemic which shows that under homogeneous conditions the radical intermediate was, in fact, achiral.

It is unreasonable to believe that a model that assumes that the radicals diffuse freely in solution could account for such results. On the other hand, a surface-bound radical is fully in accord with them. Compound (*S*)-(+)-**18** behaves similarly when exposed to metal surfaces of alkali metals in hydroxylic solvents [94]. As in the Grignard reagent formation, when a solution of (*S*)-(+)-1-bromo-1-methyl-2,2-diphenylcyclopropane **18** in methanol, isopropyl alcohol, or *t*-butenol was exposed to an alkali metal, such as lithium, sodium, or potassium, the resulting hydrocarbon (*R*)-(−)-1-methyl-2,2-diphenylcyclopropane **13** was shown to be optically active and with retained configuration, as shown in Table 19 and Scheme 40.



(*S*)-(+)-**18** (*R*)-(-)-**13**

Scheme 40

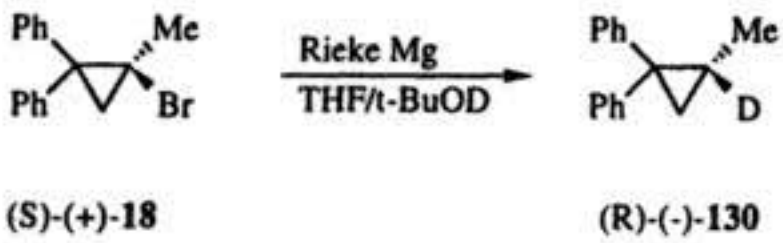
When monodeuterated methanol Me-OD was used as solvent hydrocarbon (*R*)-(−)-**2** was formed, with more than 95% deuterium incorporation in the 1-position.

2. *Reaction of Organic Bromides with Magnesium in Ethers in the Presence of t-Butyl-OD*

The so-called Rieke magnesium [111], which is prepared by reduction of magnesium bromide with potassium, is highly reactive and allows preparation of Grignard reagents

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at very low temperatures (−78°C). This high reactivity is believed to be the result of its greater surface area (particle size 0.1 μm). The reaction of organic halides with Rieke magnesium in the presence of *t*-butyl-OD, using the cyclopropyl system as a probe, has been reported [13a,22]. Here again, the Grignard reagent, once formed would be quenched by *t*-Bu-OD, whereas if the σ radicals diffused in solution, they would be expected to abstract a hydrogen atom from the solvent. Obviously, complete racemization would be expected if the latter occurred. However, when (*S*)-(+)-**18** was exposed to Rieke magnesium in THF in the presence of 4 Eq of *t*-Bu-OD at 65°C, the resulting product (*R*)-(−)-**13D** formed in 94% yield, with 92% deuterium incorporation and 43% optical purity (Scheme 41). The optical activity decreased to 18% when the reaction was conducted under the same conditions, but at 20°C. This implies that, at lower temperatures, the rate differences between pathways 1,4 and 2,5 of Figure 1 are higher and in favor of pathways 1,4, leading to the higher optical purity observed at −65°C versus 20°C. This would be consistent with the relative enthalpies of the two pathways as will be discussed subsequently. The optical purity, using powdered magnesium (200 μM) 20° was similar, but no reaction was observed at −65°C.



(S)-(+)-**18** (R)-(-)-**130**

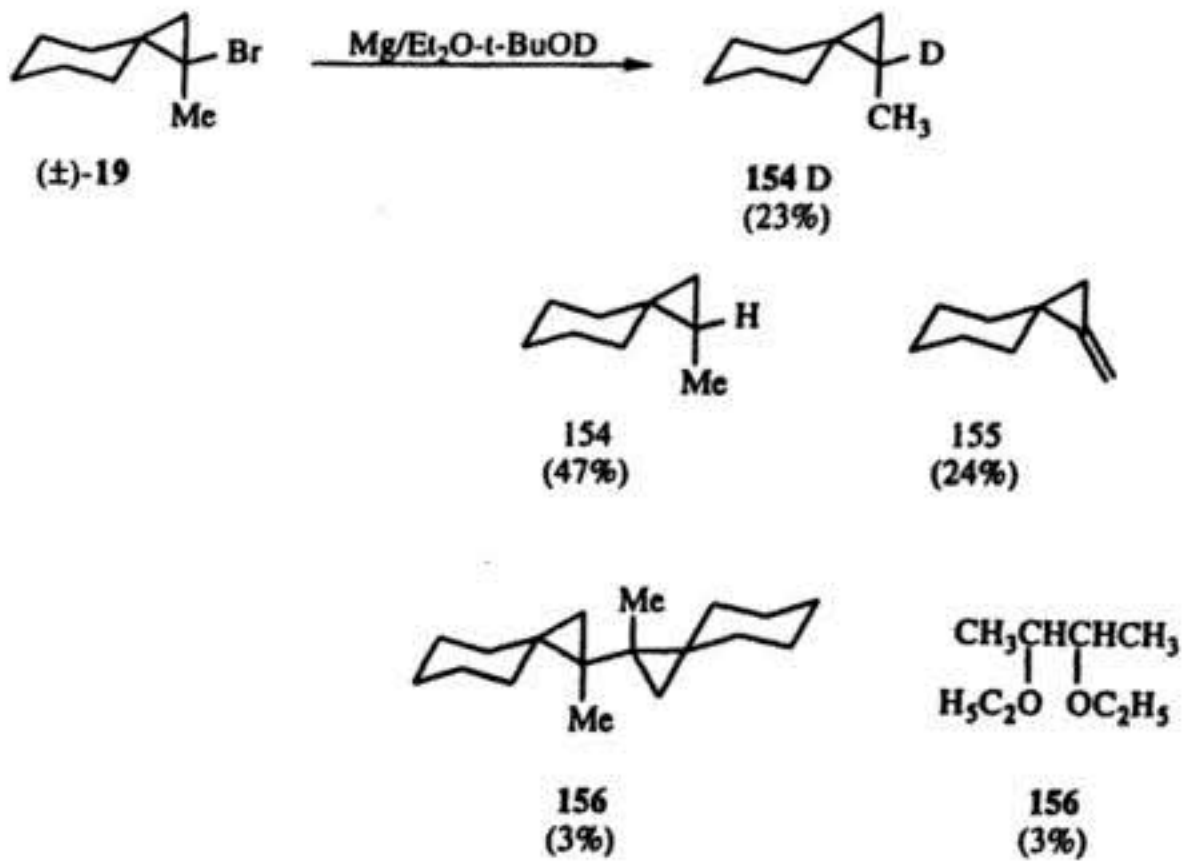
Scheme 41

Grignard reagent formation in the presence of *t*-Bu-OD also allowed the determination of the nature of intermediates for a purely aliphatic cyclopropyl system, as shown in the product distribution from reaction of 1-bromo-1-methylspiro[2,5]octane **19** with magnesium (Scheme 42) [22]. Treatment of (±)-**19** with Rieke magnesium in ether in the presnece of *t*-butyl alcohol-OD gave rise in 70% yield to 1-methylspiro[2,5]octane, **154**, which was 33% deuterated. This indicated that the yield in the Grignard reagent formation step was 23%. Other products detected were 2,3-diethoxybutane (diethyl ether dimer, **157**), the cyclopropyl radical dimer **156** (3%), and a polymeric residue that arose from olefin **155**. The undeuterated cyclopropane **154** arose from disproportionation of the cyclopropyl radical on the surface of magnesium and from reaction with solvent. The % of dimer **156** accounted for 6% of the cyclopropyl groups. The total material balance was 76%, which left up to 24% unaccounted for. This was ascribed to olefin **155**, which once formed, was consumed to give rise to a mixture of polymers. In the Grignard reaction of magnesium with 1-bromo-1-methyl-2,2-diphenylcyclopropane **18** in ether (see Scheme 17), a similar product distribution was observed.

Since the 2-norbornyl radical [117] and the 5-norbornenyl radical [118] have been thoroughly studied and their behavior in solution is well known, studies of Grignard reagent formation using the 2-norbornyl and norbornenyl systems seemed well worthwhile [116]. Relative to the nature of these radicals, they are planar π-radicals.

Let us first consider these radicals under conditions when they are free in solution with a certain lifetime. From the large available data one may conclude that the 2-norbornyl radical **141**, when produced in solution, always reacts more easily from the less-hindered

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(±)-**19**

154 D
(23%)

154
(47%)

155
(24%)

156
(3%)

156
(3%)

Scheme 42

exo-side. The *exo/endo* ratio of the products does not depend on the stereochemistry, whether *exo* or *endo*, of starting material, and the mixture of products always contains more *exo*- than *endo*-adduct. For example the bromodecarboxylation of substituted 2-norbornanecarboxylic acid to the corresponding 2-norbornyl bromides by the Hunsdiecker, or related reactions [119], produces the same product ratio, *exo/endo*, 69:31, independently of starting material. Similar observations were reported by David and Roberts [120] for the oxidation of tri-2-norbornylborane with oxygen, as well as for the auto-oxidation of the 2-norbornylmagnesium halides. In both cases a 76:24 ratio of *exo/endo*-norbornanol was obtained.

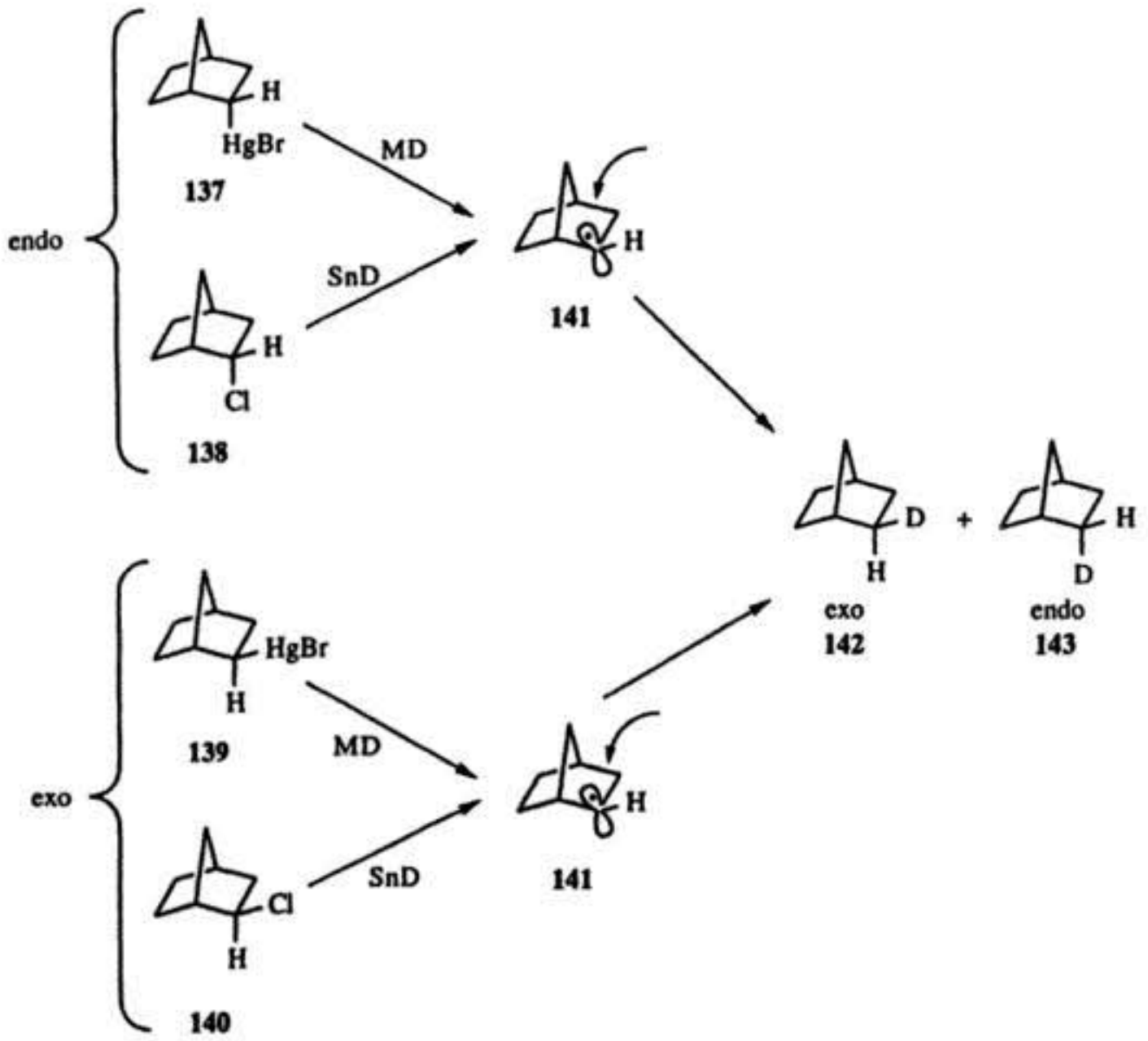
Somewhat later Whitesides and San Filippo [121] studied the behavior of the 2-norbornyl radical **141**, when generated under free radical conditions, by comparing the stereochemistry, yield, and isotopic composition of the mixtures of *endo*- and *exo*-

Table 20 Reduction of **137, 138, 139,** and **140** by Metal Hydrides Under Free-Radical Conditions

RX	Reducing agent	Solvent	Yield (%)	*Exo/endo*	Isotopic composition (%)
139	$NaBD_4$	3:1 THF/H_2O	96	90:10	84
139	Et_2AlD	Et_2O	99	92:8	96
139	$DCuPBu_3$	3:1 THF/Et_2O	63	91:9	84
139	Bu_3SnD	Neat	100	90:10	100
137	$NaBD_4$	3:1 THF/H_2O	96	90:10	87
137	Et_2AlD	Et_2O	99	89:11	92
137	$DCuPBu_3$	3:1 THF/Et_2O	61	91:9	85
137	Bu_3SnD	Neat	100	90:10	95
138	Bu_3SnD	Neat		84:16	94
140	Bu_3SnD	Neat		84:16	94

Source: Ref. 121

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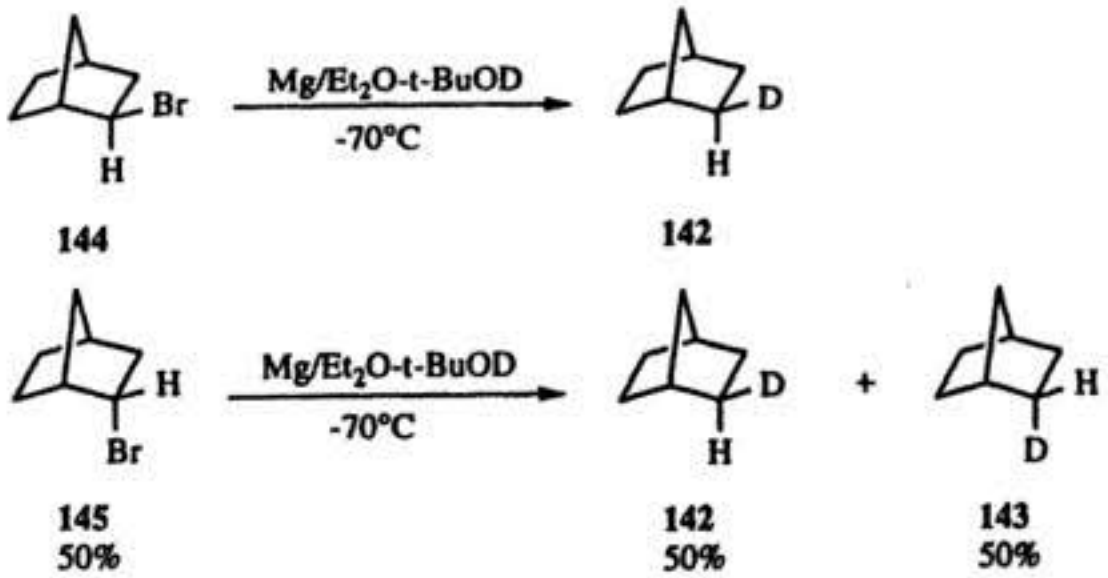
Scheme 43

norbornanes obtained by reduction of **137**, **138**, **139**, and **140** with various reducing agents (Scheme 43). In each case, the pure isomer was used as starting material. The results are summarized in Table 20.

From the data in Table 20, four important points should be kept in mind. First, free radical reduction of **139** and **137** with all reducing agents, as well as the tin hydride reduction of **138** and **140**, occurred with the expected loss of stereochemistry. Second, the ratio of *exo*-/*endo*-norbornane-2-D obtained from these reductions was independent of the stereochemistry of starting material. Third, almost identical ratios of *exo*-/*endo*-norbornane-2-D were obtained from the four starting materials. Finally, the ratio of *exo*-/*endo*-norbornane-2-D was independent of the nature of the metal.

Now that we have a clear idea on how the 2-norbornyl radical **141** behaves in solution, let us return to Grignard reagent formation and see how the same radical behaves. As in the example dealing with the cyclopropyl system [13a,22], both *endo*- and *exo*-2-norbornyl bromide were exposed to Rieke magnesium in ether in the presence of 4 Eq of *t*-butyl alcohol-OD at 70°C. Use of this alcohol not only assures rapid quenching of the organomagnesium species but also provides a marker for analytical purposes. On the other hand, it reduces the possibility that the Grignard reagent might epimerize. In fact, sp^3-hybridized secondary carbon–magnesium bonds are known to undergo slow inversion, even on the NMR time scale. The *endo–exo* equilibrium for 2-norbornyl magnesium halides is actually reached after 1 day at ambient temperature [122]. For 2-norbornylmagnesium bromide, Davies [120] and Jensen [122] found an *exo*/*endo* ratio of 41:59 at equilibrium; in our hands [116], the *exo*/*endo* ratio was 53:47 at equilibrium, starting from the *exo*-bromide, and 52:48, starting from the *endo*-bromide.

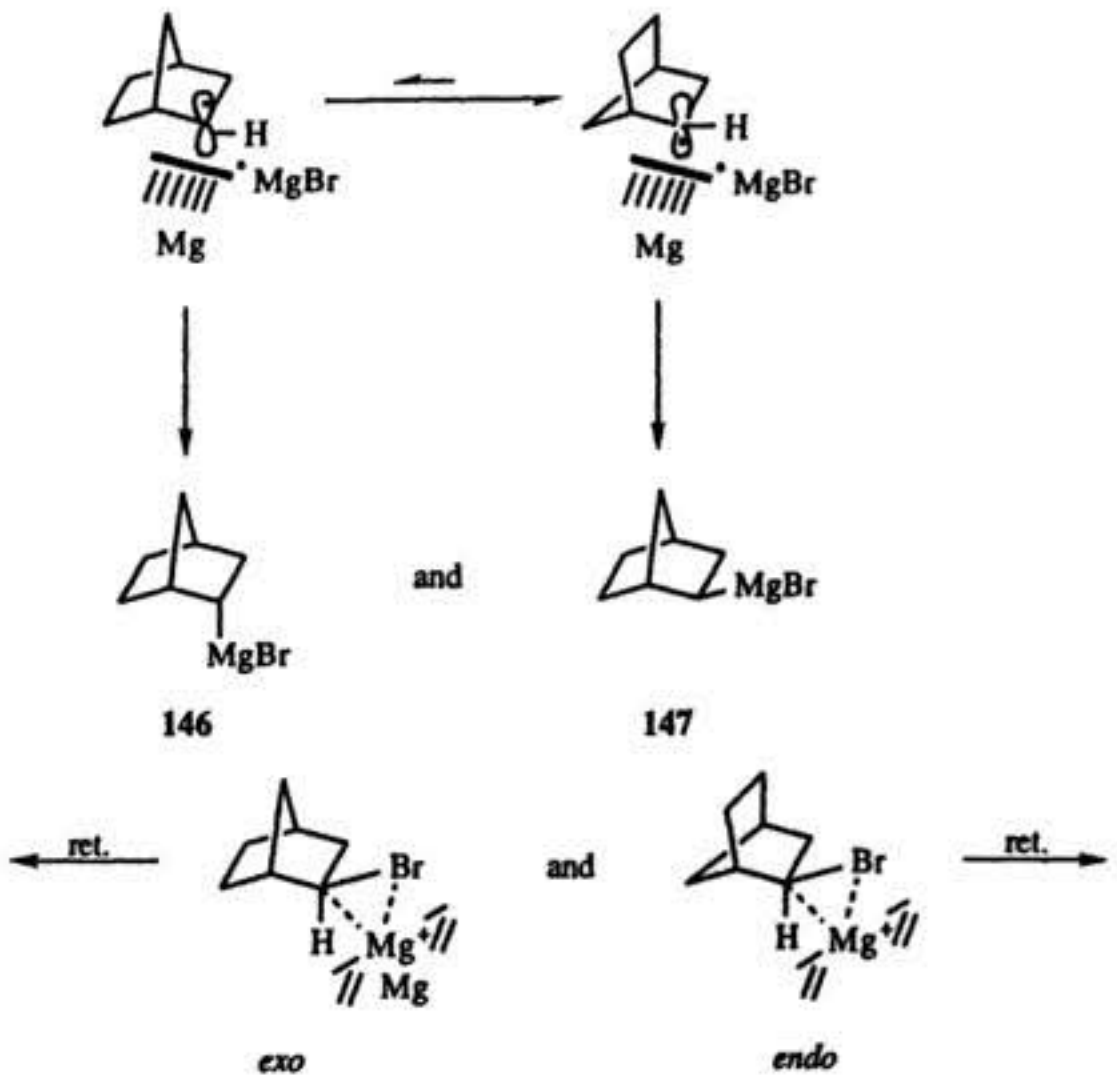
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Scheme 44a

As could be predicted from the surface nature of the reaction, when *exo*-2-norbornyl bromide **144** was exposed to Rieke magnesium at −70°C in the presence of *t*-butyl alcohol-OD, the resulting product was exclusively *exo*-norbornane-2-D, **142**. On the other hand, when *endo*-2-norbornyl bromide was reacted under the same conditions a 50:50 mixture of *endo*- and *exo*-norbornane-2-D, **143** and **142**, was formed (Scheme 44a).

It is clear from this result that the behavior of the radical produced during Grignard reagent formation is quite different from that of the free radical in solution. The exclusive retention observed when starting from *exo*-**144** might be due to more than the simple contribution of pathway 1,4 (see Fig. 1) and might also be due to minimization of the interaction between the π-planar radical **141**, formed by pathway 2 (see Fig. 1), with the surface that leads to equilibration. Consequently, the combination of $R^{\bullet}$ and $XMg^{\bullet}$ to form Grignard reagent would occur predominantly from the less-hindered side, leading to more *exo*-norbornylmagnesium bromide **146** (Scheme 44b).

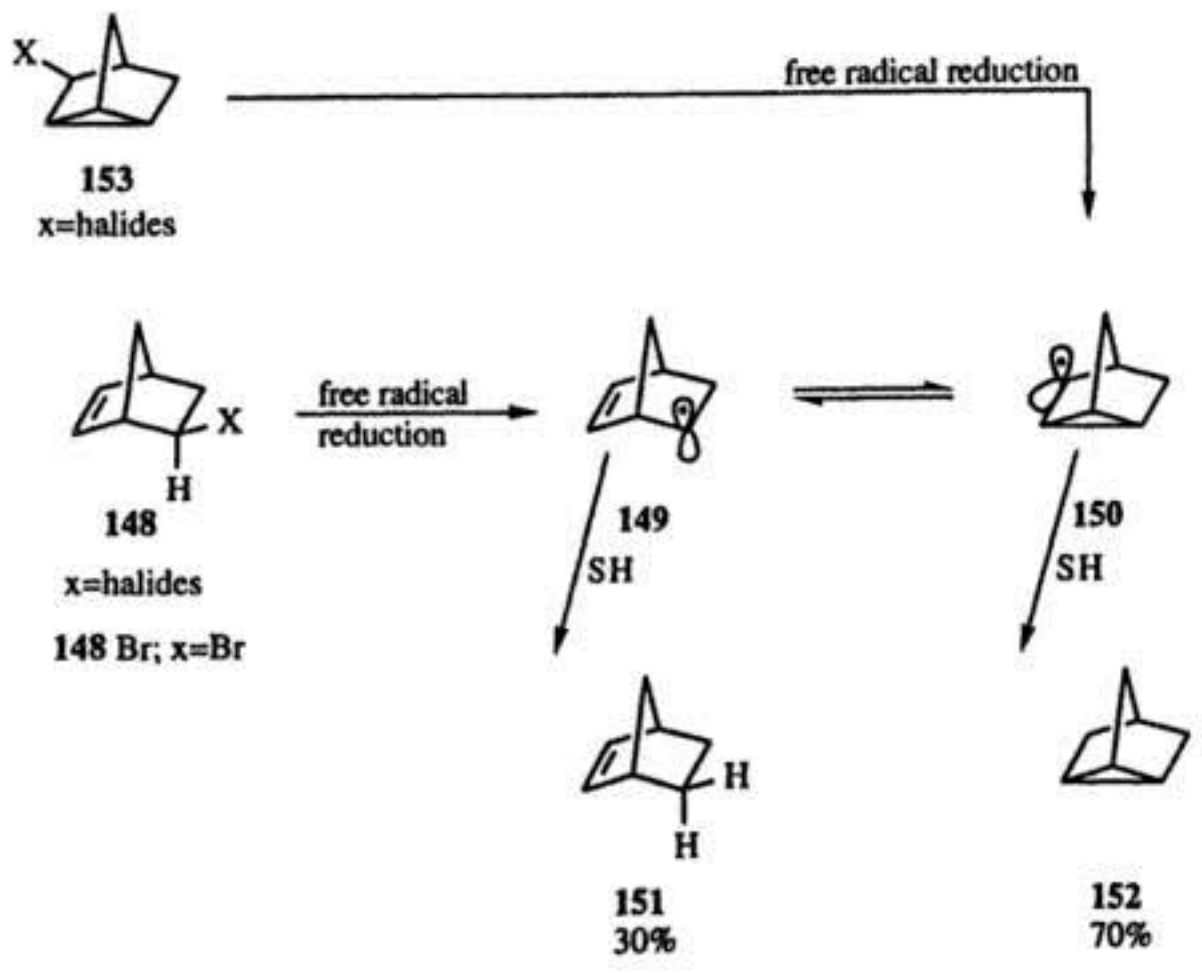


Scheme 44b

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Here again, a temperature effect was noted. When the same reactions were conducted at ambient temperature, *exo*-bromide **144** led to a mixture of 88% of *exo*-**142** and 12% of *endo*-**143**. However, 79% of **142** and 21% of **143** were formed, starting from *endo*-bromide **145**.

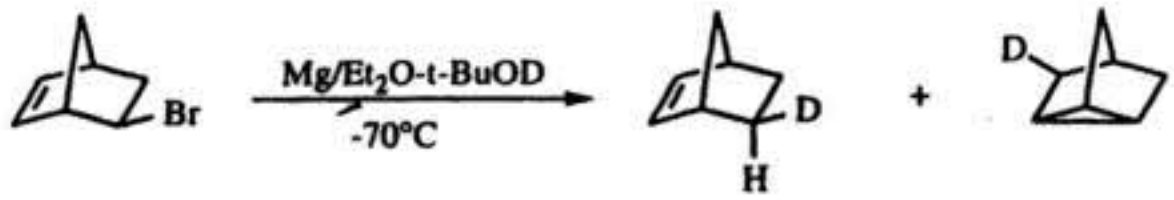
As already mentioned, the second system to be studied [116] was the 5-norbornenyl system. The radical clock-5-norbornenyl **149** [118] is known to rearrange to the 3-nortricyclenyl radical with a rate constant, determined by EPR, on the order of 6×10^2 sec^{-1} at $-30°C$ and 10^6–10^8 sec^{-1} at 25°C [123, 124]. It has been firmly established from numerous examples of free radical reductions involving this system that the equilibrium in solution is in favor of radical **150**. For example, a report by Davies [125] demonstrated that whether one started from 5-bromo-2-norbornene **148** Br or from 3-bromonortricyclene **153** Br when carrying out a cobaltous chloride-catalyzed reaction with methylmagnesium bromide, one obtains a mixture of 30% 2-norbornene **151** and 70% norticyclene **152** (Scheme 45a).



Scheme 45a

A similar equilibrium mixture of products was actually obtained by Kuivila and Alnajjar [124] from the free radical reaction of 5-norbornenyl and 3-nortricyclenyl halides **148** and **153** with trimethyltin sodium, and by Ingold and Carlsson [73] from the tin hydride reduction of the same systems. On the other hand, when *exo*-5-norbornenyl bromide **148** Br was reacted with Rieke magnesium in ether in the presence of *t*-butyl alcohol-OD at $-70°C$ (Scheme 45b) two principal products were obtained, 65% *exo*-5-deuterionorbornene and 35% deuterionortricyclene [116]. Again, the high degree of deuterium incorporation in **151** and **152**, considered together with the considerably large amount of **151** compared with the work shown in Scheme 46a, excludes a mechanism that postulates that the radicals diffuse at all times during Grignard reagent formation.

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148 Br — 151 D 65% — 152 D 35%

Scheme 45b

B. Radical-Trapping Experiments

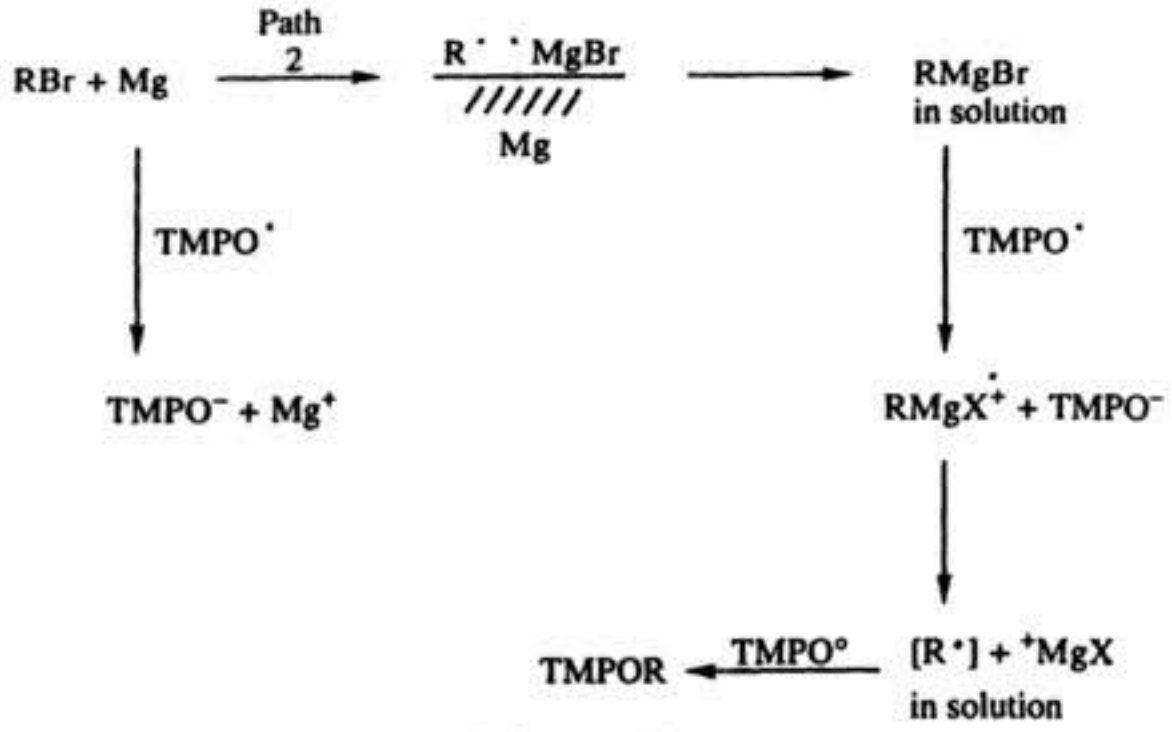
A well-designed radical-trapping experiment could be a means for deciding whether or not radicals, produced during formation of the Grignard reagent, leave the magnesium surface and would also be a way of determining their amount. An attempt to this end was made by Whitesides and co-workers [126], who believed that 2,2,6,6-tetramethylpiperidine nitroxyl (TMPO$^{\bullet}$) was an efficient free-radical scavenger, capable of reacting selectively with an alkyl radical R$^{\bullet}$ to form *O*-alkyl-2,2,6,6-tetramethylhydroxylamine (TMPOR). This reaction is very fast, with a rate constant on the order of 10^9 L mol^{-1} sec^{-1} [128]. Thus, by conducting the reaction of alkyl bromides with magnesium in a solution containing both TMPO$^{\bullet}$ and *t*-butyl alcohol they thought to prevent the Grignard reagents from reacting with the radical scavenger, because it was believed that the reaction of RMgBr with *t*-BuOH was ten times faster than the reaction with TMPO$^{\bullet}$. Their first report [126a] described the reaction of cyclopentyl bromide with magnesium in ether in the presence of TMPO$^{\bullet}$ or *t*-BuOH. In the absence of *t*-BuOH (reaction I), the almost exclusive product was TMPOR (R = cyclopentyl) in 96% yield. TMPOR was also formed in high yield (84%) when the reaction was conducted in the presence of TMPO$^{\bullet}$ together with *t*-BuOH (reaction (II)]. On the hypothesis that RMgBr reacts preferentially with *t*-BuOH, they concluded that more than 80% of the radicals were trapped by TMPO before being converted into cyclopentylmagnesium bromide. Thus, more than 80% of the radicals were supposed to have been free before formation of the Grignard reagent.

$$\text{c-}C_5H_9Br + Mg + 7TMPO^{\bullet} \rightarrow \underset{<2\%}{RH} + \underset{4\%}{R(-H)} + \underset{2\%}{RR} + \underset{96\%}{TMPOR} \quad \text{(I)}$$

$$\text{c-}C_5H_9Br + Mg + 7TMPO^{\bullet} + 10t\text{-BuOH} \rightarrow \underset{15\%}{RH} + \underset{<2\%}{R(-H)} + \underset{<2\%}{RR} + \underset{84\%}{TMPOR} \quad \text{(II)}$$

That cycloheptyl bromide reacts with magnesium in a very similar way as cyclopentyl bromide was reported subsequently [126b]. By using the "constant-surface" kinetic technique to measure the rate of reaction with magnesium, Whitesides and co-workers estimated that the rate of reduction of TMPO$^{\bullet}$ would be three times slower than the rate of reaction of cycloheptyl bromide with magnesium. However, the validity of this estimate is unclear. The kinetics of the system is very complex owing to competition among the several reactions, shown in Scheme 46, which were not considered. The authors [16b] merely plotted the yield of product from the reaction of cycloheptylbromide with magnesium in the presence of TMPO$^{\bullet}$ and *t*-amyl alcohol as function of time, observed the formation of 95% of TMPOc-C_7H_{13}, stated that these results were incompatible with a surface-bound

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Scheme 46

radical and concluded that 95% of the cycloheptyl radicals were free, thereby ignoring processes that compete with trapping by the TEMPO radical.

As admitted by Whitesides and co-workers, Mg^0 reduces TMPO˙ to the anion $TMPO^-$ at a rate competitive with the reaction between RBr and Mg^0 [130], while, on the other hand, oxidation of Grignard reagents in the presence of such agents is also well documented [129, 131]. An example is a recent publication by Greci and Eberson [127], who studied the reaction of a series of Grignard reagents with a nitrone. The process involved a single electron transfer from RMgX to the *N*-oxide and subsequent cleavage of the C–Mg bond, producing radical R˙, which was trapped with a radical scavenger-type aminoxyl. Consequently, one is left with the question of what species has actually reacted with TMPO˙ and these experiments do not answer the question of what percentage of radicals leave the surface during formation of the Grignard reagent.

However, Ashby and Oswald [77] described a solution for this problem by selecting dicyclohexylphosphine (DCPH) as the trapping agent capable of donating a hydrogen atom to a free radical. To ascertain whether or not other reactions competed with the reaction of DCPH with radical, the authors carried out the reaction of bromooctane with magnesium under the conditions described in Table 21. As may be seen, three properties of DCPH were demonstrated convincingly: (1) DCPH did not react with bromooctane,

Table 21 Stability of DCPH Toward Alkyl Halide and Grignard Reagent: Reaction of Bromooctane with Magnesium in the Presence of DCPH

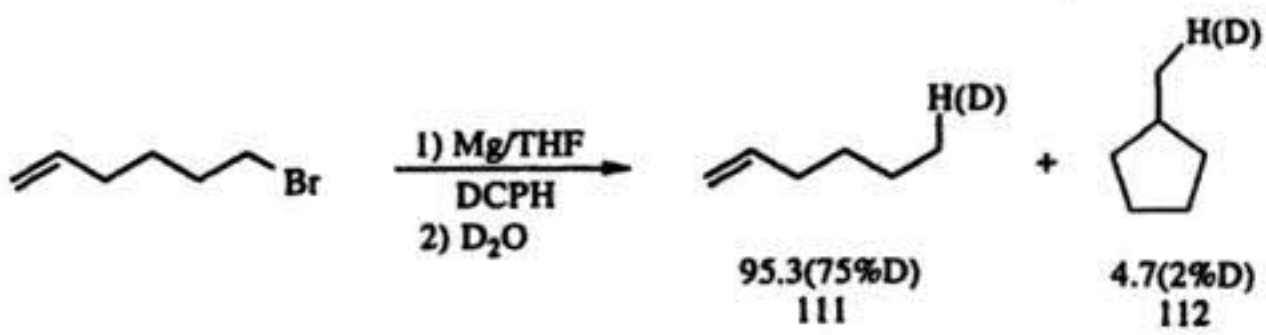
Time (hr)	*n*-Bromooctane (%)	Octane (%) (1D + 1H)[a]	Deuterium (%)
0.5[b]	97.6	0	
0.5	7.8	84.9	80.5
1.0	0	96.1	74.8
16.0	0	92.0	74.0
60.0	0	92.0	74.3

[a]Reactions were carried out in THF at 22°C, then quenched with D_2O.
[b]Blank test to determine the stability of the mixture DCPH/bromooctane.

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(2) DCPH did not react with Grignard reagent, and (3) the Grignard reagent was stable in the presence of DCPH, even after 60 h. Thus, in contrast with TMPO$^{\bullet}$, the properties of DCPH made this radical trap a good candidate for determining the amount of radical on the surface and for further testing the hypothesis of the D-model that all radicals generated during Grignard reagent formation must leave the surface, diffuse freely in solution, and then return to the surface to form the Grignard compounds.

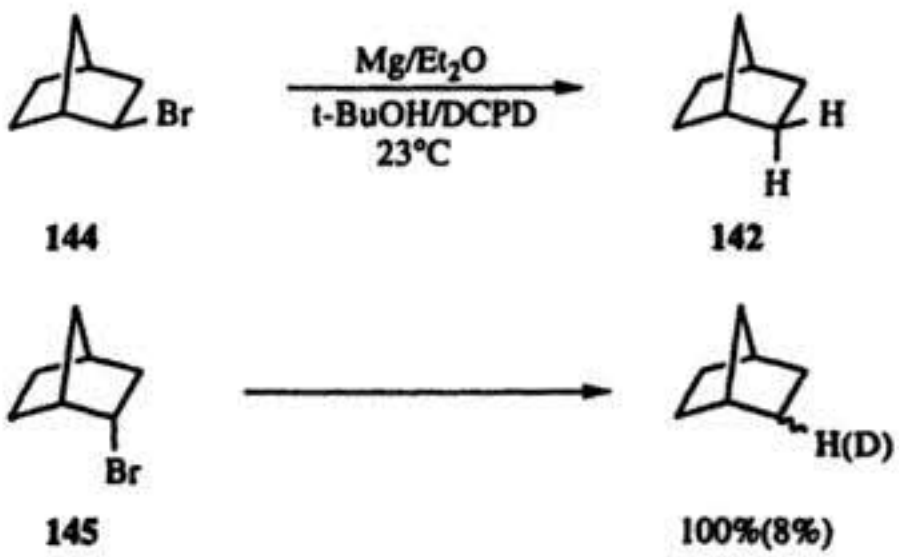
We now turn to the reaction of 6-bromo-1-hexane **110** with magnesium in THF in the presence of DCPH, studied by Ashby and Oswald [77] (Scheme 47). Comparing the result with the earlier discussion in Section III.E.2, it is clear that all radicals that escaped the magnesium surface were trapped by DCPH, which for the hexenyl radical was no more than 25%. The formation of cyclized hydrocarbon **112** (4.7%) was ascribed to cyclization occurring at the surface, since a hexenyl radical leaving the surface was expected to react with DCPH before it could cyclize.



Scheme 47

Other results to be discussed now also suggest that it would be unreasonable to call on freely diffusing radicals in Grignard reagent formation. One of these stemmed from a study of the reaction of **144** and **145** with Rieke magnesium in ether at 23°C [116] in the presence of deuterated dicyclohexylphosphine DCPD, which would be expected to trap free radicals in solution to give **142D** and **143D** respectively. The additional presence of *t*-butyl alcohol would result in rapid quenching of any Grignard reagent formed to give **142** and **143** (Scheme 48).

The *exo*-**144**, under these conditions, furnished norbornane **142**, with no incorporation of deuterium. On the other hand the mixture resulting from *endo*-**145** showed only 8% of deuterium incorporation. Thus, in the latter, 8% of radical has escaped the magnesium to become trapped by DCPD.



Scheme 48

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Similarly, the reaction of *exo*-5-norbornenyl bromide **148** Br (see Scheme 45b) with Rieke magnesium, under the same conditions, gave rise to a mixture of two products, norbornene **151** isolated in 65% yield, containing 2% of deuterium, together with 35% of nortricyclene **152**, which was 22% monodeuterated. This would correspond to about 8% total deuterium incorporation.

Let us now return to the cyclopropyl system, which constituted one of the centers of controversy over the difference between calculated and observed results [93e]. In a test of the prediction of the D-model for the amount of cyclopropyl radical departed from the magnesium surface during the Grignard reagent, it was demonstrated recently [112], using DCPD as the radical trap, that when cyclopropyl bromide **133** reacted with magnesium turnings in ether in the presence of DCPD a 26% yield of cyclopropane containing 15% of deuterium resulted. This constitutes a 4% yield of deuterated material, based on the amount of the cyclopropyl bromide consumed. Thus, again 4% of the cyclopropyl radicals escaped the surface and were trapped by DCPD. When DCPD was replaced by diethyl ether-D_{10}, the reaction of cyclopropyl bromide with magnesium in diethyl ether-D_{10} furnished 23% cyclopropane, of which 13% was deuterated. This again indicates that only 3% of the cyclopropyl bromide consumed has produced radicals that reacted with the solvent.

Trapping experiments in the reaction of (±)-1-bromomethylspiro[2,5]octane **19** with magnesium gave similar results [22]. Reaction with Rieke magnesium in the presence of DCPD resulted in **154**; with 6% incorporation of deuterium in product **154**, whereas in the reaction of **19** with mechanically activated magnesium in diethyl ether-D_{10}, 13% of the radicals left the surface and were trapped by solvent, as judged by the deuterium incorporation into product **154**. Thus, only a small fraction of the radicals leave the surface, and most of the cyclopropane formed resulted from disproportionation on the surface. The D-model predicts that the major source of cyclopropane is reaction of cyclopropyl radical with solvent, which is inconsistent with experiment.

VI. THE QUESTION OF AN ANION RADICAL

A. Background

The reader should first be reminded that pathway 1,4 of Figure 1 involves formation of a tight radical anion–radical cation ion pair on the magnesium surface, which leads to retention of configuration. The literature provides evidence than an anion radical cannot be formed as intermediate by a single electron transfer to alkyl halides. On the basis of experimental data [132] and theoretical calculations [133] single-electron transfer into a carbon–halogen bond is either purely dissociative (pathway 2) or proceeds by extremely short-lived species [134]. Savéant concluded that reductive cleavage of the carbon halogen bond in aliphatic halides, either by direct electrochemical reduction at an inert electrode under heterogeneous conditions, or by electrochemical reduction mediated by aromatic anion radicals, involves a concerted electron transfer bond-breaking mechanism in which the driving force is the standard potential of the $RX/R^{\bullet+}X^-$ and not that of the $RX/RX^{\bullet-}$ couple. Supporters of the D-model [134] also point out that if anion–radical intermediates exist, their lifetimes would be extremely short (10^{-10} sec). Ab initio (gas phase) studies of the insertion of magnesium into the carbon–halogen bond do not predict formation of anion radicals with aliphatic [92], as previously discussed, or vinyl [135] halides.

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B. Criticism

It has been suggested that the retention of configuration observed in the case of 1-bromo-1-methyl-2,2-diphenylcyclopropane **18** resulted from the unusual stability of an intermediate anion radical which, in turn, was due to the phenyl groups. The chiral vinyl systems were also referred to as "atypical" [93d, 93e]. To account for the retention observed in **1**, **12**, **18**, **27**, **131**, and **158** during Grignard reagent formation, they cited work by Boche, who observed partial retention in the reduction of **18**, **12**, and **14** by alkali naphthalenides in homogeneous solution [136] as evidence that the 1-methyl-2,2-diphenylcyclopropyl radical is capable of partially maintaining its configuration in solution. This could account for the Grignard result and may be supportive of the D-model. However, stereochemistry of the radicals generated from these systems in solution indicates that the reduction by means of alkali naphthalenide is halogen-dependent, and that the retention of configuration observed is in the order I > Br > Cl, whereas in Grignard reagent formation it is just the reverse, Cl > Br > I. The retention observed by Boche was attributed to the lower reduction potential of the two geminal aromatic rings, compared with the reduction potential of the carbon–halogen bond, so that the first electron supplied by the reducing agent will enter the aromatic moiety and the second into the σ^* antiboding orbital; therefore, it was proposed that the observed retention was the result of an intramolecular electron transfer to yield the configurationally stable anion. Clearly, Boche's results have no bearing on Grignard reagent formation; it should also be noted that magnesium metal does not react with the geminal phenyl groups in 1-methyl-2,2-diphenylcyclopropane **18**.

Moreover, in our recent study of the formation of organocalcium reagents by direct reaction of the cyclopropyl halides (*S*)-(+)-**18** and (*S*)-(+)-**12** with calcium–aromatic anion radicals (Scheme 49), racemization took place in both instances [42]. As shown in Table 22, reduction of (*S*)-(+)-**18** and (*S*)-(+)-**12** with calcium–aromatic anion radicals, generated by reaction of preformed lithium biphenylide ($LiBPh_2$) and lithium naphthalenide (LiNph) with calcium bromide yielded, after quenching with HCl, 1-methyl-2,2-diphenylcyclopropane [13] or, after carbonation, the corresponding 1-methyl-2,2-diphenylcyclopropanecarboxylic acid [17]. In every instance products were completely racemic. These reactions are believed to occur by electron transfer in a homogeneous medium [42].

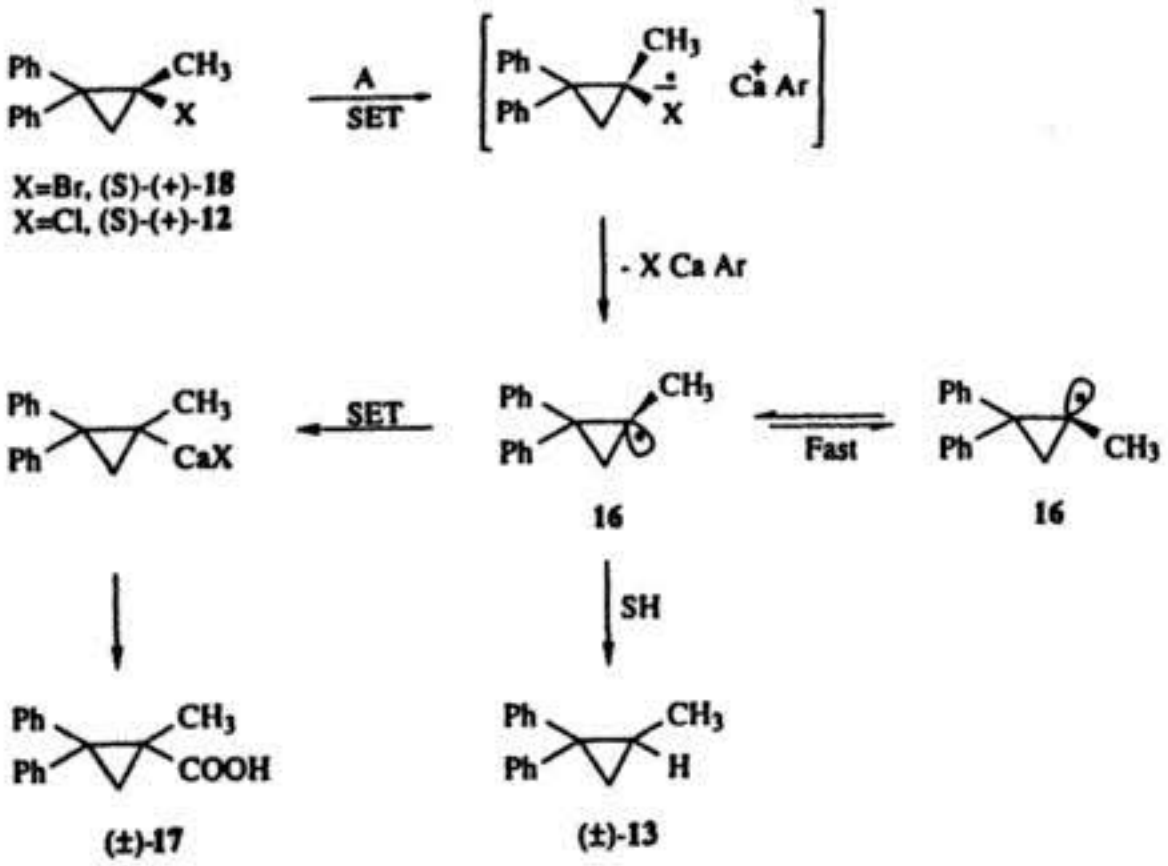
Thus, as detailed in Scheme 49, the racemization involves the intermediacy of cyclopropyl free radical **16** generated by a single electron transfer from the calcium–aromatic anion radical into the carbon-halogen σ^* antibonding orbital. The cyclopropyl radical

Table 22 Reduction of (*S*)-(+)-**18** and (*S*)-(+)-**12** by $Ca(Nph)_2$ and $Ca(Bph)_2$

X	Time (hr)	Temp. (°C)	**13**	**17**
Cl[b,d]	0.5	−20	45(0)	
Br[b,d]	0.5	−20	100(0)	
Br[b,e]	0.75	−78	48(0)	21(0)
Br[c,e]	0.75	−78	49(0)	26(0)

[a]Optical purity.
[b]Reaction with $Ca(Bph)_2$.
[c]Reaction with $Ca(Nph)_2$.
[d]Quenched with H_3O^+.
[e]Carbonated.
Source: Ref. 42.

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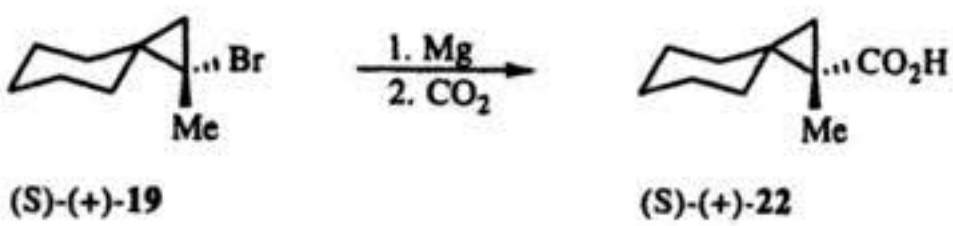
Scheme 49

produced in solution reaches its inversion equilibrium before being trapped by a second electron transfer to yield cyclopropyl calcium, which when quenched with CO_2, gives the racemic carboxylic acid **17**, or by reaction with THF yields racemic **13**.

To complement all the data available from the literature, we designed two additional series of experiments to answer the criticism related to the use of those systems. The first, reported recently [22], dealt with Grignard reagent formation from a purely aliphatic and tertiary chiral cyclopropyl bromide. This molecule does not contain any "pseudoconjugation", owing to an aromatic or vinyl moiety that might be responsible for the alleged unusual stability of an intermediate anion radical during formation of a Grignard reagent. At the same time, the presence of the cyclopropyl ring ensured that the Grignard reagent formed from this bromide would be configurationally stable as had been thoroughly demonstrated earlier. The second was an electrochemical study [56] designed to clarify the question of anion radicals in all systems that had been subject to criticism.

C. Only the Surface Nature of the Reaction Could Predict Retention

To establish the stereochemistry of the reaction, optically pure (*S*)-(+)-1-bromomethylspiro[25]octane **19** was treated with Rieke magnesium at room temperature in both ether and THF, and the reaction mixture was carbonated [22] (Scheme 50). The results are shown in Table 23. The reaction in ether resulted in a 25% yield of optically active acid **22**, the result of optically active Grignard reagent, and 42% of racemic hydrocarbon **154**. Reaction in THF afforded a much higher yield of the optically active Grignard reagent (58%) and only 20% of racemic hydrocarbon **154**. As predicted by the surface nature of



(S)-(+)-19 (S)-(+)-22

Scheme 50

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Table 23 Stereochemistry of Grignard Reagent Formation

Solvent	Time (hr)	Yield (%)	Opt. purity (%)
Et_2O	2	25	10
THF	2	58	13

Source: Ref. 22.

Grignard reagent formation, the reaction of (*S*)-(+)-**19** with Rieke magnesium, at room temperature in ether and in THF, in both cases, gave an optically active Grignard reagent that, after carbonation, gave an acid showing net retention of configuration. This is clear evidence that the surface is necessary for the retention of configuration observed, and that the criticism by the proponents of the D-model was not justified [93d, 93e]. Only the surface nature of the reaction could predict the observed retention.

D. Electrochemical Approach

The questions that needed to be answered [56] were the following: Is bond-breaking a concerted or stepwise process when electrons are transferred from metal surfaces to the carbon–halogen bond? Are radical anions formed as intermediates? Do the π^* orbitals of the aromatic moiety in **18**, **131**, and **158** complete with the σ^* orbital of the carbon–halogen bond during the electron-transfer process from the surface, thereby causing these systems to be atypical [93d, 93e]?

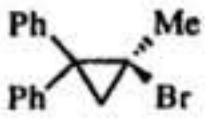
The most conclusive studies devised to ascertain whether electron transfer and bond-breaking are concerted or stepwise have been conducted by Savéant and co-workers, who examined the electrochemical reductive cleavage of the carbon–halogen bond at inert electrodes, using a variety of aromatic and aliphatic halides [132]. An elegant and detailed description of the dissociative electron transfer dynamics, as well as the stepwise version is given in this paper, which also contains a large body of experimental data for testing the model that are based on the electrochemical reduction (under homogeneous and heterogeneous conditions) of alkyl, aryl, and benzyl halides, as well as other organic substrates.

To determine whether or not an anion radical was formed as an intermediate in the experiments used during our investigation of the Grignard reagent formation, we investigated the reductive cleavage of the carbon–halogen bond in our systems by cyclic voltammetry [56].

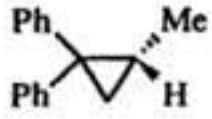
Cyclic voltammetry of the substrates was performed at a glassy carbon electrode which, in contrast with mercury or other reactive electrodes, was believed to be sufficiently inert toward chemical reactions with radical intermediates formed during the reduction process [132]. The compounds studied are shown in Scheme 51. Figure 11 and Table 24 show the most relevant information from the electrochemical reduction of substrates **18**, **158**, **19**, and **131**.

With one exception, that of 1-fluoro-1-methyl-2,2-diphenylcyclopropane **160**, which exhibited no reduction before confomitant reduction of either the solvent or the supporting electrolyte, a single irreversible cathodic wave was always observed. The values of the transfer coefficients were derived from the cyclic voltammetric peaks' widths, assuming that the Butler-Volmer kinetics apply: $\alpha = 1.85(rt/F)(E_{p/2} - E_p)$ [132g,h]. Of interest was

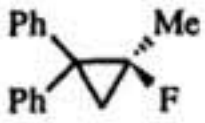
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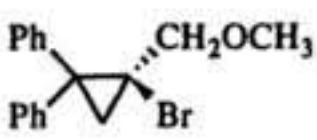
(S)-(+)-**18**



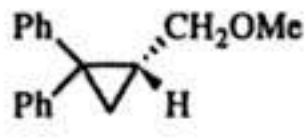
(R)-(-)-**13**



(S)-(+)-**160**



(S)-(+)-**158**



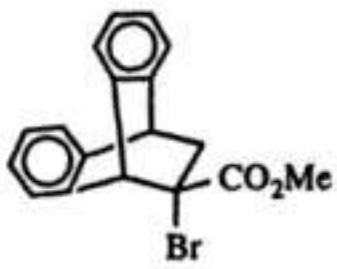
(R)-(-)-**159**



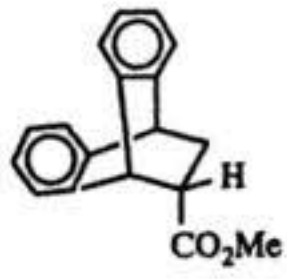
(S)-(+)-**19**



(R)-**154**



(S)-(+)-**131**



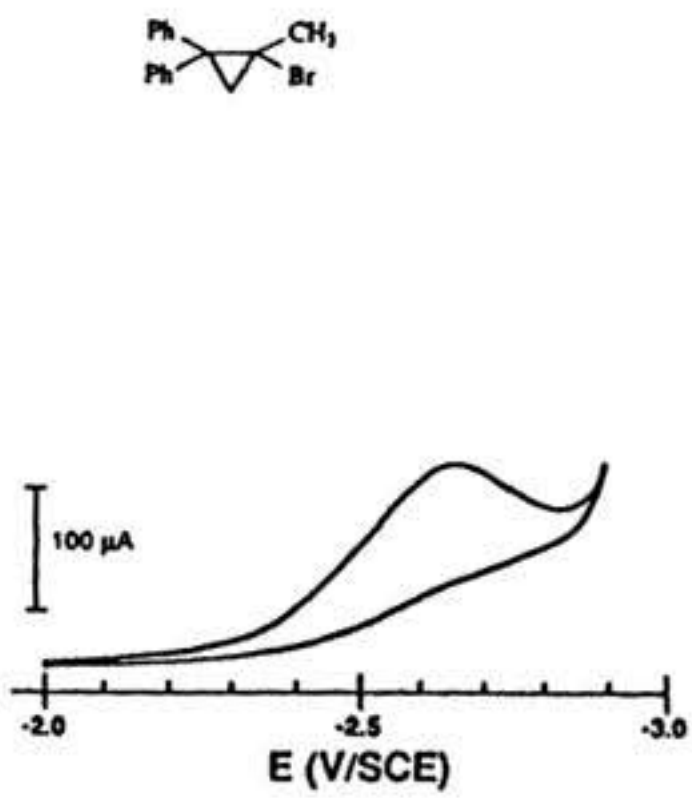
(S)-(+)-**161**

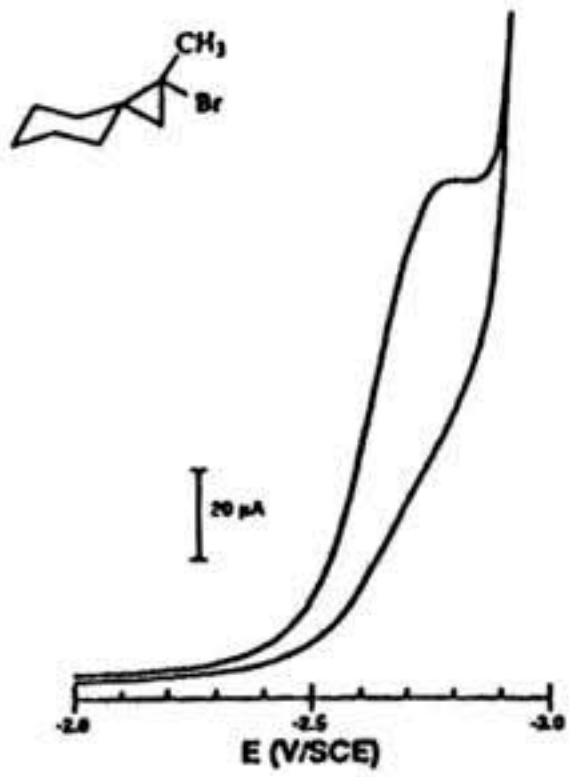
Scheme 51

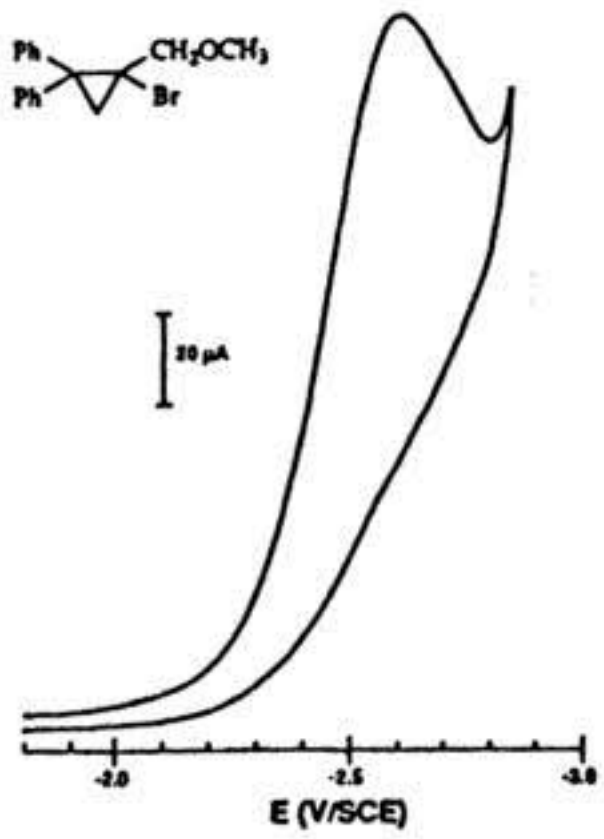
that the values of the transfer coefficient, which were shown to be independent of the scan rate [132g,h], were small for all substrates (between 0.5 and 0.32).

Similar observations have been reported by Savéant et al. in their studies on the electrochemical reduction of simple aliphatic halides [132g] (*n*-, *s*-, and *t*-butyl halides) at a glassy carbon electrode. Cyclic voltammetry of the butyl halides showed one or two irreversible waves, depending on the relative reducibility of the alkyl halide RX and of the radical $R^{\bullet}$. All transfer coefficients reported were smaller than 0.5 (between 0.2 and 0.32). The fact that the transfer coefficient was small was taken as further evidence that the reduction pathways do not involve the $RX^{\bullet-}$ anion radical as an intermediate. Our observations from the electrochemical reduction of **18**, **158**, **19**, and **131** at a glassy carbon electrode are in agreement with this. The cyclic voltammetric shape, the peak width $E_{p/2} - E_p = (180–150)$ mV, and the value of $\alpha = 0.25–0.32$ at different scan rates [137] showed, without question, that electron transfer and decomposition of the anion radical

Material chroniony prawem autorskim







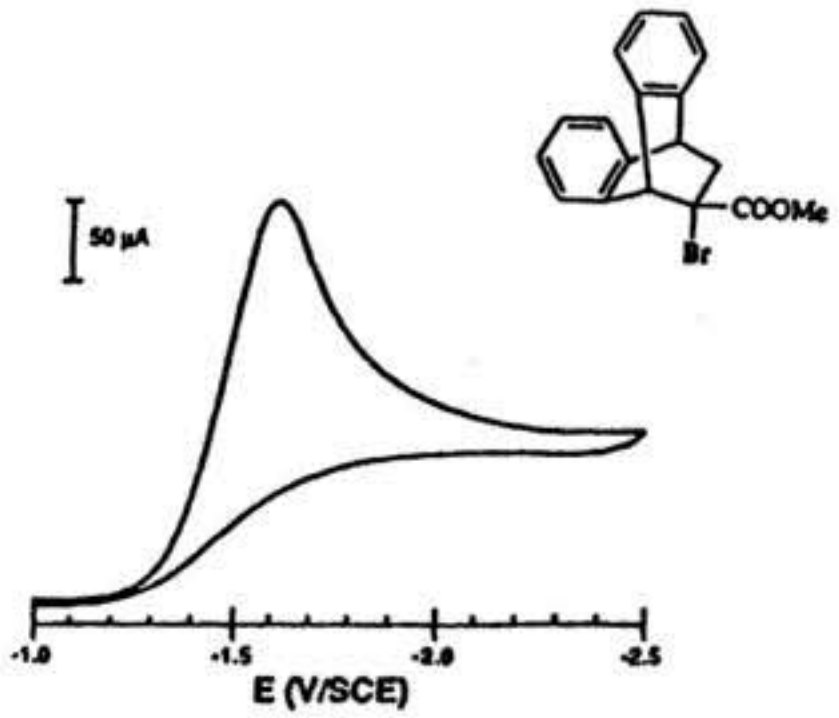


Figure 11 Cyclic voltammetry of substrates **18**, **19**, **158**, and **131** (5 m*M*) on glassy carbon electrode in acetonitrile + 0.1 *M* *n*-Bu_4NBF_4 at 25°C; scan rate 0.1 V sec^{-1}. Vertical scale in μÅ; horizontal scale in V vs. SCE.

for these substrates is concerted. If a radical anion were formed as intermediate, a

$$RX + e^- \rightarrow R^\bullet + X^-$$

transfer coefficient closer to or larger than 0.5 would be observed [132j], since the standard potential of $RX/RX^{\bullet -}$ must be much more negative than that of $RX/R^\bullet + X^-$, as in the case of aromatic halides [132j] and ring-substituted nitrobenzyl halides [132], for which a stepwise mechanism involving the intermediacy of anion radical was shown

$$RX + e^- \rightleftharpoons RX^{\bullet -}$$
$$RX^{\bullet -} \rightarrow R^\bullet + X^-$$

to take place. It is also of interest that the ease of reduction, as shown by the peak potential of the wave, is in the order **131** > **159** > = **18** > **19**.

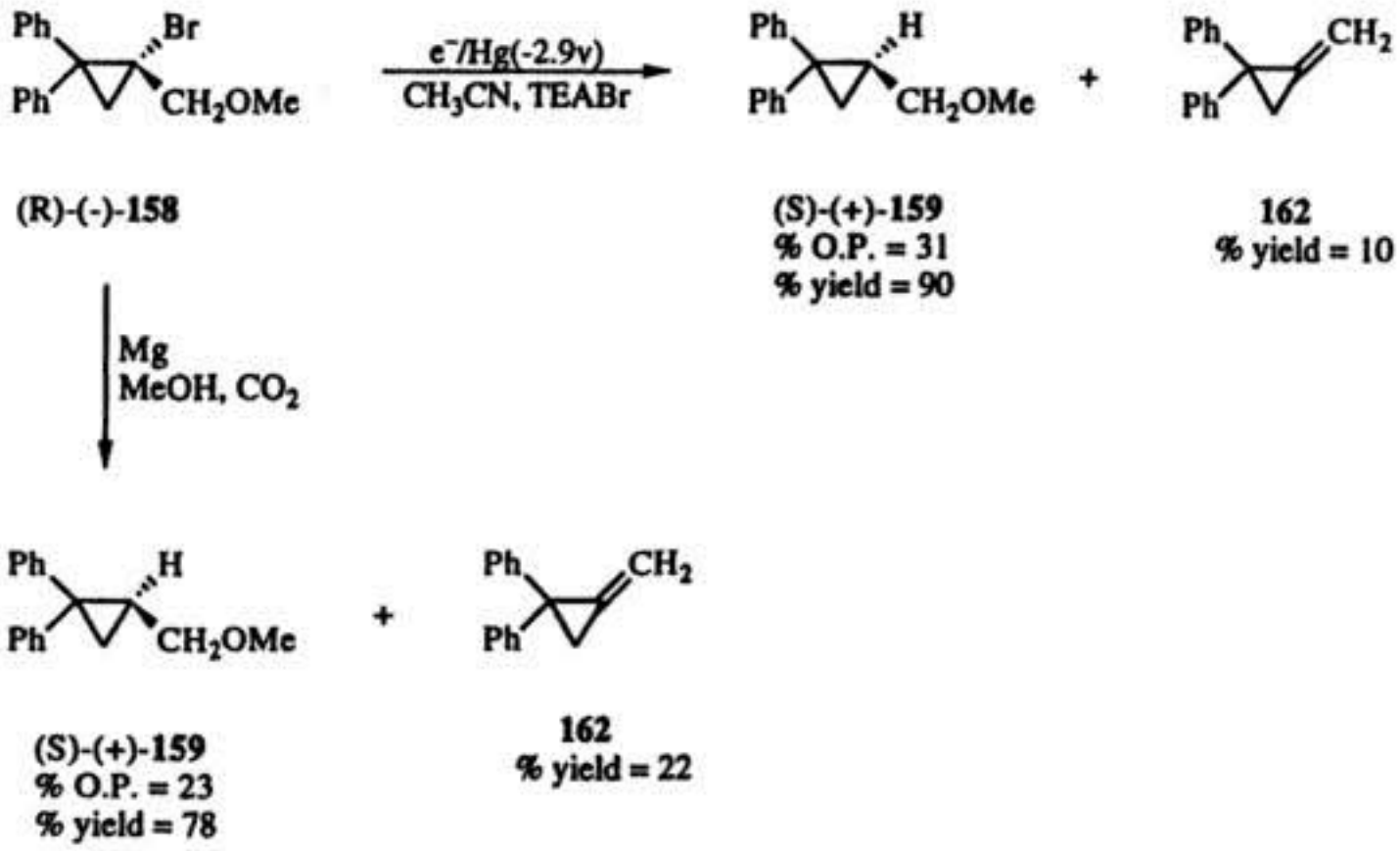
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Table 24 Cyclic Voltammetric Peak Potential[a] and Transfer Coefficient α[b] Determined for Substrates **18**, **158**, **19**, and **131**[c]

Compd.	No. characteristic waves	$-E$ (V vs. SCE)	$E_{p/2}$ (V vs. SCE)	$E_{p/2}-E_p$ (mV)	α
18	1 irreversible	2.65	2.49	160	0.3
158	1 irreversible	2.61	2.43	175	0.27
19	1 irreversible	2.85	2.66	190	0.25

Stereochemical observations also support the analogy between electrochemical reactions [56,138] and orgaometallic reagent formation of organic halides at metal surfaces [22,42–44,94,116].

Reduction of (*R*)-(−)-**158** yields (*S*)-(+)-**159**, with overall retention of configuration and an optical purity of 31% at a mercury electrode [139a] and reduction in methanol on a magnesium surface [140], for which the optical purity is 23% (Scheme 52).



Scheme 52

A similar result is obtained in the reduction of (*S*)-(+)-**18**, leading to the formation of (*R*)-(−)-**6**, with overall retained configuration and optical purities of 26% [139b] and 24% [13b], respectively (Scheme 53).

Scheme 53

Finally, interistingly, even at an unreactive electrode, such as glassy carbon, the retention observed is high, 47% retention of optical activity with overall retention of configuration [139]. This indicates that a very fast second electron transfer, leading to the configurationally stable carbanion, occurs at the surface.

VII. CONCLUSION

The previous pages have described the evidence leading to a description of Grignard reagent formation in terms of the reactions shown in Figure 1. The mechanism, briefly

Materiał chroniony prawem autorskim

referred to as the surface nature of Grignard reagent formation, is based on stereochemical analyses, radical-trapping experiments, and product distribution. Work to counter recent criticisms that the cyclopropyl systems used in establishing and supporting that mechanism are atypical is described as well as experiments that show that the basic assumption of the more recently proposed D-model—that all radicals generated in the reaction leave the magnesium surface and diffuse freely in solution—is untenable.

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11

Mechanisms of Reactions of Grignard Reagents

CORNELIS BLOMBERG
Free University, Amsterdam, The Netherlands

I. INTRODUCTION

Investigations of the mechanistic aspects of the reactions of organomagnesium compounds, in general, and of Grignard reagents, in particular, that have led to our modern insight into these aspects started only rather recently (i.e., in the early 1960s).

Several problems first had to be overcome and several relevant questions to be answered before specific types of reactions could be approached. Among such problems and questions were those concerning the description of the different organometallic species in solution in a variety of solvents (see e.g., Chapter 13); the purity of the material, including the quality of the magnesium used for the preparation of the reagents; and the identity of the different products formed during the reactions.

The role played by the coordinating solvent molecules in the development of intermediates, as well as that of transition states during the progress of the reactions, has been subject of controversy and debate ever since the Grignard reagent was introduced in synthetic organic chemistry at the beginning of this century. The limited understanding of coordination numbers of elements, of main valencies, and of covalent bonds at that time led to an unclear description of the structure of the solvated Grignard reagent and of the mechanistic aspects of its reactions.

In 1901 Blaise [1] suggested the following structure for the Grignard compound

$$RMgX(C_2H_5)_2O$$

in which, as he formulated it:

> the ether is not just an ordinary solvent; it has itself participated in the reaction and the stability of the product shows that it is intimately united with the rest of the molecule.

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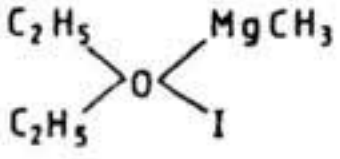


Figure 1 Proposed structure of Bayer and Villiger for a solvated methylmagnesium iodide Grignard reagent. (From Ref. 2.)

Soon other structures were proposed; similar to the one proposed by Bayer and Villiger [2] in 1902, (Fig. 1) for solvated methylmagnesium iodide.

For the first phase of the reaction of RMgX with epoxyethane, Grignard, 1 year later [3], preferred the following structure (Fig. 2) over the one suggested by Bayer and Villiger:

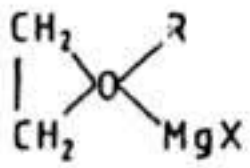
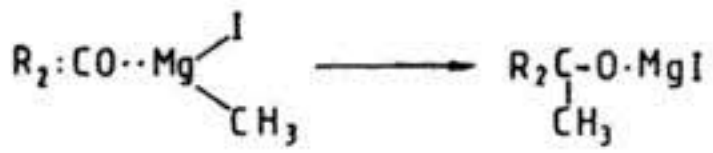


Figure 2 Structure proposed for the first phase of the reaction of epoxyethane with RMgX. (From Ref. 3.)

Through calorimetric measurements, Chelinzeff [4], in 1906 and 1907, found that the addition of 2 molEq of ether to unsolvated Grignard reagents resulted in considerable evolution of heat, which was negligible when more ether was added (see also Lifschitz and Kalberer [5] and Hayes [6]). Heat evolution indicates the formation of a complex between the Grignard reagent and polar molecules, implying competitive solvation–complexation when more than one polar species is present beside the organomagnesium compound.

In 1912, Straus [7] suggested that the first step in the reaction of a Grignard reagent with a carbonyl compound was the replacement of the ether in the complex (analogous to what had earlier been proposed by Kohler [8]; see also Grignard's view on the first step of reactions with epoxyethane as represented in Fig. 2) followed by the formation of the carbon–carbon bond (Scheme 1):



Scheme 1

This concept of replacement of an ether molecule in a Grignard complex by a carbonyl compound as a first step in its reaction gradually became generally accepted (see also Von Braun and co-workers [9]) after results were published by Meisenheimer and Casper [10] as well as by Hess and Rheinboldt [11].

Meisenheimer's complex may be a common first step in the sequence of reactions that may finally lead to the formation of different products (see also Kharasch and Reinmuth's comments [12]). However, the complexity of the following steps in the reactions

Materiał chroniony prawem autorskim

with the many substrates investigated is considerable. And, even then, it was recently suggested that it was not clear whether these complexes are true steps on the reaction path, or whether they represent "blind alleys" [13].

Other complicating factors in the general discussions and systematic investigations of the mechanistic aspects of reactions of Grignard reagents include

1. The wide variety of substrates and of organomagnesium reagents applied in such studies
2. The number of side reactions that seemed to be possible in what originally looked like a straightforward and simple reaction

Concerning point 1, it is not to be expected that reactions of reagents such alkyl-, allylic-, benzylic-, and many other types of organomagnesium halides with substrates as varied as 1-hexyne, benzil, dimesityl ketone, benzonitrile, and so on, should have a similar pattern in their mechanisms. Relative to point 2, neither was it expected at the start of the investigations of the reaction of Grignard reagents with ketones that in the reaction of neopentylmagnesium chloride with benzophenone, a *one-electron transfer* would be observed, leading to a 20% yield of benzopinacol as well as of 2,2-dimethylpropane [14], neopentane.

But apart from "unexpected" side reactions, various well-known competing reactions, such as reduction, conjugated addition, and enolization reactions, may well hinder the studies of mechanistic aspects of Grignard reagent reactions. In view of all such unknown factors, it may not come as a surprise that in one of the latest publications on some mechanistic aspects of Grignard reagent addition reactions, in the *Journal of Organic Chemistry*, the authors started their report with the remark that

> Although the addition of Grignard reagents to carbonyl compounds is a major synthetic reaction and some efforts have been devoted to its mechanism, due to the variable nature of the species present in solution, few positive results have been obtained. [15]

As will be noticed from the contents of this chapter, however, considerably more than "some efforts" have been devoted in the search for a better understanding of the mechanism(s) of the reaction(s) of Grignard reagents. Whether or not these efforts have led to "positive results" is to be judged by those researchers who have made use of them or will be using them for future work.

Developments after the early 1960s in the studies of mechanisms for reactions of Grignard reagents have made it possible to come to a clearer understanding of the general character of these mechanisms. A differentiation between a radical character of such reactions, on the one hand, and a concerted (polar) mechanism, on the extreme other hand, is becoming more and more evident. However, the details on the structure of intermediates and the sequence of the different reaction steps still require more studies.

Earlier reviews on the subject of mechanisms have been presented in such standard works as the Kharasch and Reinmuth textbook [12], which appeared in 1954, as well as in the chapters on organomagnesium chemistry in such general organometallic textbooks as the ones by Joffe and Nesmeyanov [16] and by Nützel [17]. Later reviews in this area are much more characteristic of accounts of investigations by the different specialists in this (and related) field(s) [18–25].

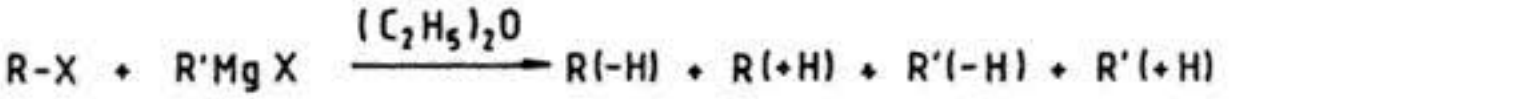
The emphasis of this chapter will be on the mechanistic aspects of the ("normal" ?) addition reaction of Grignard reagents to the carbon–oxygen double bond, as is found for ketones. However, it will become clear that for reactions with other substrates, the general mechanistic aspects of these carbonyl addition reactions are also applicable.

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II. MECHANISM OF THE CARBONYL ADDITION REACTION

A. Homolytic Versus Concerted Mechanisms

Initially, Grignard reagents were considered to be nucleophiles reacting mainly in a polar fashion. However, early in the history of Grignard chemistry the concept originated that the reaction could have a radical character. In 1913 [26] and some years later in 1922 [27] the formation of alkenes and alkanes in the reaction of haloalkanes with Grignard reagents in diethyl ether (Scheme 2) had already been attributed to the intermediacy of what was named, *free* alkyls.



Scheme 2

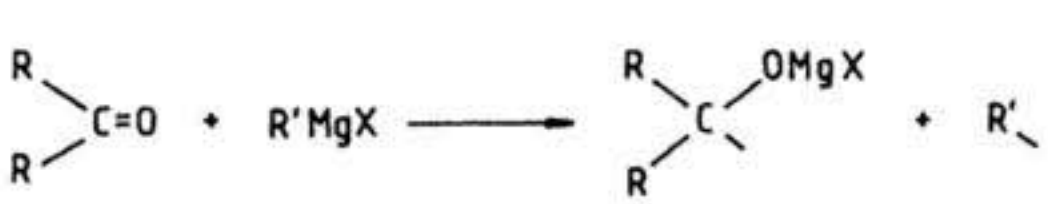
The suggestion that radicals were responsible for the products formed in reactions of alkylmagnesium halides with a ketone was first made in a publication that appeared in 1929 [28]. According to the authors:

> The reducing action of aliphatic Grignard reagents can be accounted for if the assumption is made that trivalent carbon radicals are produced as intermediate reaction products.

They reached the conclusion that

> It would be expected that these trivalent carbon radicals would be very unstable and that they might undergo, spontaneously, one of the types of transformation which have been found to be characteristic for trivalent carbon radicals of the triarylmethyl type, namely, addition, mutual oxidation and reduction, and polarization.

The following reaction scheme was presented (Scheme 3):



Scheme 3

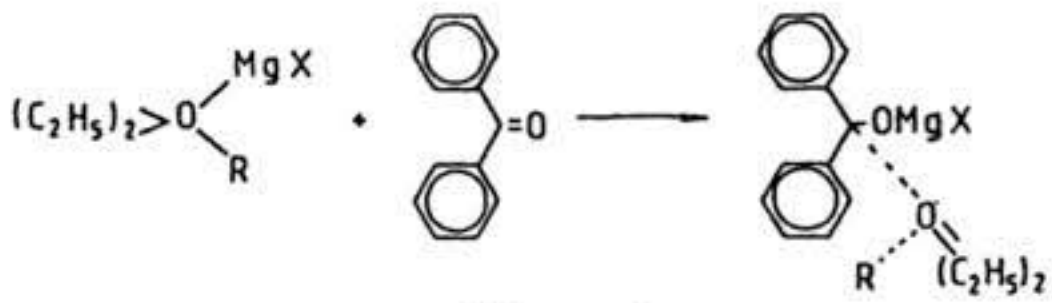
Considerable amounts (often more than 50% yields) of reduced ketones were obtained with Grignard reagents from 1-bromopropane, 2-bromopropane, 1-iodobutane, 2-methyl-1-bromopropane, and 2-methyl-1-bromobutane.

In their article, the authors referred to an earlier paper by Lagrave [29] in 1927, who in his studies of the reduction of benzophenone by Grignard reagents, suggested that the substrate first replaced the solvent molecule in the Grignard etherate (see also earlier work by Grignard [30,31]), after which "the complex changed into a stable form which could then give several different products."

Lagrave presented the following scheme for this reaction (Scheme 4), in which it is

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difficult for modern chemists to grasp what the (dotted-line) bonds actually represent:



Scheme 4

Blicke and Powers referred to this intermediate as being the same type as the radicals they had described in Scheme 3.

Soon after this publication, another report appeared (in 1932) on the (radical) reduction of benzophenone (again!) by cyclohexylmagnesium bromide and iodide [32].

A serious problem arose when it was discovered that trace amounts of transition metals, when added to methylmagnesium bromide, would prevent the formation of the addition reaction product and led to high yields of benzopinacol [33]. In the years that followed, one might even say until the beginning of the 1970s, the whole concept of radical formation in reactions of Grignard reagents was almost exclusively related to the presence of such metal ions in the reaction mixture. So much so, indeed, that in a recently published paper [25], the purpose of which was "to give a brief review on recent studies on the Grignard addition reactions," the remark was made that: "in those days, i.e., the 1960s, unfortunately it was difficult for the radical mechanism of the Grignard reagent to gain general acceptance."

In 1964, thanks to the development of modern techniques, especially electron-spin resonance (ESR), a direct proof could be given of the occurrence of radicals in the reaction of Grignard reagents, such as ethylmagnesium iodide, phenylmagnesium bromide, and *para*-tolylmagnesium bromide, in tetrahydrofuran (THF) with aromatic ketones, such as 4-chlorobenzophenone, 4-aminobenzophenone, 4-methoxybenzophenone, 4,4′-dimethoxybenzophenone, acetophenone, and 4-bromoacetophenone [34].

Radicals were also detected in the reaction mixtures of some aliphatic ketones (such as penta- and hexamethylacetone) and of benzonitrile. At concentrations of 10^{-3}–10^{-4} *M* a yield of 3.4% free radicals was obtained when equimolar amounts of benzophenone and phenylmagnesium bromide were allowed to react at a "dry ice–acetone" temperature. When, in the same reaction, a 20-fold excess of the Grignard reagent was used, 24% radicals (based on the amount of the benzophenone) could be detected. About the nature of these radicals the author stated that

> Although it is clear that the free radical in each Grignard reagent is not the ketyl which is obtained through the reduction of the corresponding carbonyl compound with Mg/Hg, a comparison of their ESR-spectra and visible absorption spectra indicate that they are quite similar.

In that same year, a rather revolutionary publication appeared [35] on *The Scope of the Reaction Between Carbanions or Nitranions and Unsaturated Electron Acceptors.* Many carbanions and nitranions seemed to react with unsaturated molecules, such as nitroaromatics, azobenzene, and diaryl ketones, to form the radical anions derived from the unsaturated compounds. The same effect was observed with *n*-butylmagnesium bromide and *n*-butyllithium. The radical anions were observed with the aid of electron spin resonance

Materiał chroniony prawem autorskim

Table 1 The Influence of Solvent on Radical Formation by Organomagnesium Compounds with Ketones [36]

Solvent	Signal	Radical anions (%)
$(C_2H_5)_2O$	Very weak and unstable	–
THF	Weak but stable signals	<0.1
DME	Rather unstable	0.5
$(C_2H_5)_3N$	Unstable	>0.2
HMPA[a]	Strong and stable	36

[a]HMPA, hexamethylphosphoric acid triamide.

(ESR) spectroscopy, as was seen with the previously mentioned reaction. The conclusion was "... that processes involving one-electron transfer must be important in many reactions involving carbanions."

Of particular interest were the large concentrations of anions formed with organometallic reagents in certain instances. In their discussion of the results the authors stated: "It is of interest to speculate on the importance of electron-transfer processes in the synthetically important addition and condensation reactions of carbanions, nitranions, or organometallic reagents."

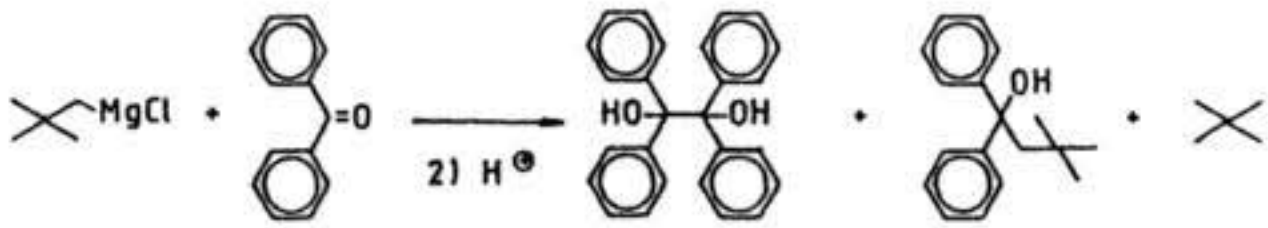
A change in opinion on the rarety of radicals found in what was, until then, considered to be normal carbanionic reactions, was gradually taking place as will be demonstrated in this section.

The influence of the solvent on radical formation by organomagnesium compounds with ketones was made evident a few years later when dibenzylmagnesium was reacted with fluorenone [36] (Table 1).

Since RMgX yields smaller concentrations of radical anions than the corresponding R_2Mg, further investigations by the same authors were carried out with these organomagnesium compounds. It was concluded that the formation of radical anions is favored when the ionic character of the carbon–magnesium bond is increased, as with the strongly basic HMPA. This conclusion was supported by results obtained with several different organomagnesium compounds, when it was found that an increase in the formation of radical anions is caused by a increasing charge on the carbon atom bound to the magnesium atom:

Me < Et < Bu < *i*-Prop < *t*-Bu < benzyl

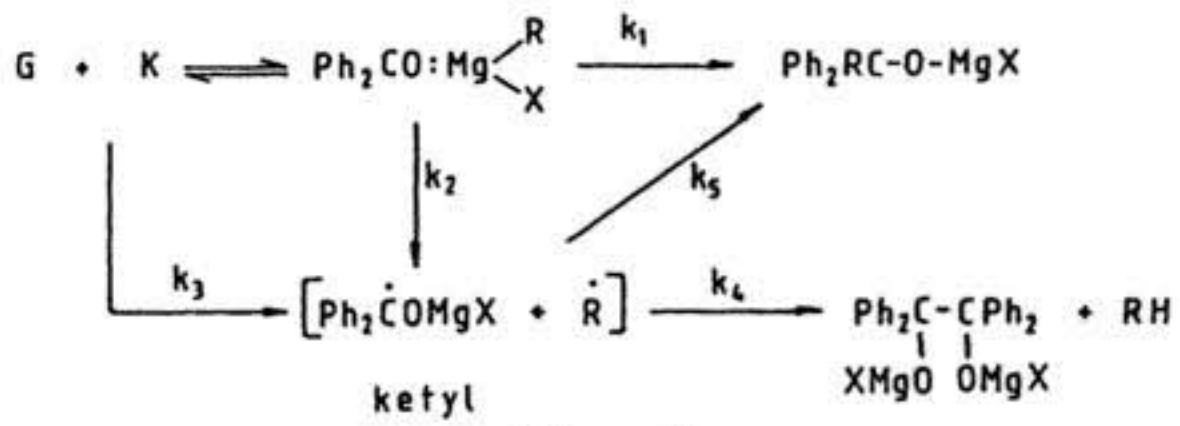
In that same period neopentane, together with benzopinacol, were among the products [14] of the reaction of neopentylmagnesium chloride and benzophenone as well as the "normal" (i.e., the expected) reaction product, the tertiary alcohol (Scheme 5):



Scheme 5

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The proposed mechanism for this reaction included the formation—by a one-electron transfer—of a benzophenone ketyl and a neopentyl radical in a "solvent cage," which then could either collapse to produce the normal product or from which the radicals could escape to form different products, such as benzopinacol and neopentane (Scheme 6):



Scheme 6

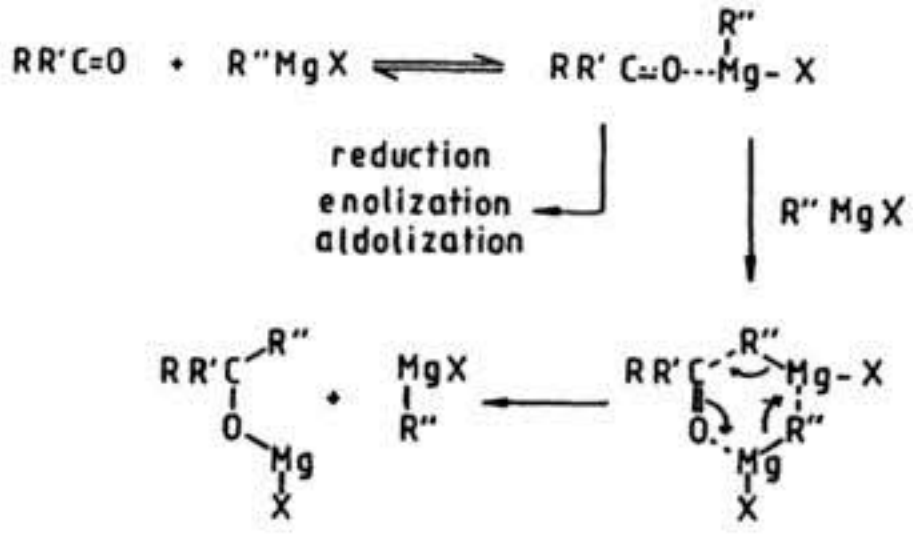
Initially it was thought that the benzopinacol formed in such reactions was just a by-product, produced in a process that was in competition with a polar mechanism. Gradually, the new view developed that the initial electron-transfer process was the common reaction, whereas the polar—or heterolytic—reaction, referred to as "concerted mechanism," took place only when special conditions were fulfilled.

Since (substituted) benzophenone(s) are widely used for mechanistic studies, for different reasons (e.g., no α-hydrogens, so no "enolization" is possible; high molecular weight, so products are easily detectable; slower reaction, and so on), there is a tendency in modern publications to generalize reactions with benzophenone and to announce work as done with ketones in general.

Apart from ESR spectroscopy, kinetic studies have also contributed considerably to a better understanding of the reaction mechanisms of Grignard reagent, as did the studies of the composition and structure of the products of the reactions.

Because of the considerable technical difficulties encountered when monitoring reaction mixtures of Grignard reagents with ketones (the reaction of methylmagnesium bromide and acetone was almost complete within 10 sec, even at $-15°C$), it took a while before reports on such investigations appeared regularly.

In 1961, kinetic studies of methylmagnesium bromide with benzophenone and pinacolone, 3,3-dimethyl-2-butanone [37], confirmed the existing opinion at that time [see Ref. 38, for its origin]. First, a complex was formed between the Grignard reagent and the ketone. The complex was then attacked by a second Grignard molecule to form the addition product (Scheme 7):



Scheme 7

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The reactions (both with benzophenone and with pinacolone) follow a third-order law:

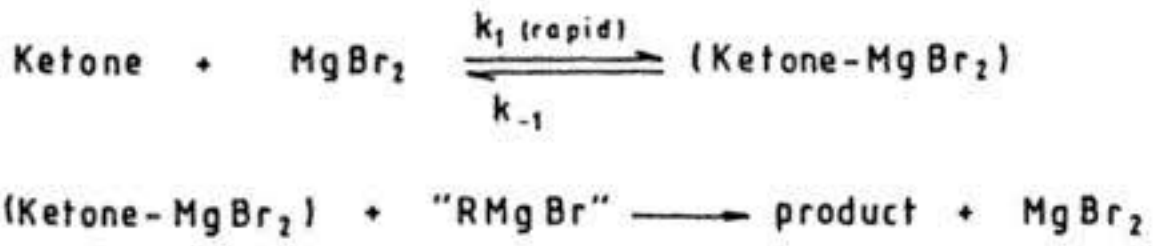
$$V = k_3\ [\text{Grignard}]^2[\text{ketone}]$$

The rate constant for this reaction, however, was dependent on the Grignard reagent concentration, which, as it was formulated, "is probably due to a concentration-dependent self-association as well as with other Grignard reagent forms which are believed to exist, and with the reaction products as the reaction proceeds." Dimethylmagnesium was ten times faster in its reaction with benzophenone [39] than methylmagnesium bromide and stopped half-way when equivalent amounts of both reagents were used. When a double amount of dimethylmagnesium was employed, the reaction was complete.

The initial complexation of magnesium species with ketone could be demonstrated by measuring the rate constants of reactions of methylmagnesium bromide with mixtures of pinacolone and magnesium bromide; the reaction followed second-order law:

$$V = k_2\ [\text{Grignard}][\text{ketone}]$$

"thus demonstrating [according to the author] that the mechanism is closely related to the following" (Scheme 8):



Scheme 8

In this scheme: "the first step is a rapidly established equilibrium, which, in all likelihood, is strongly displaced to the right; the second is rate controlling."

Almost simultaneously, in 1963, another research group reported on the reaction kinetics of methylmagnesium species with benzophenone [40] (a preliminary communication of this work had appeared in 1961). These authors came to conclusions that differed considerably from the previous ones. Very explicitly they expressed as their opinion that "... the concept of the Grignard reaction with a ketone proceeding via a *stable* complex of the type described by Swain [see Ref. 38] is not supported by the published evidence [41] nor by the results of the present investigation."

It is worth reporting here in a modern textbook on Grignard chemistry, that the same authors stated that this whole concept of a stable complex between the Grignard reagent and the ketone was based on a wrong translation and a misunderstanding of a report by Pfeiffer and Blank from 1939 [41] that is often quoted even today. The criticism of the authors continued as follows:

> No quantities, yields, analyses, or isolation were reported to justify in any way the conclusion that the precipitate was a complex of starting materials. It is because of these serious defects that it is felt that the experiment does not merit the importance that has been attached to it. This has already been pointed out by Nesmeyanov and Sazanova [42], who repeated Pfeiffer and Blank's work, but isolated the precipitate immediately. They found that the latter gave, upon hydrolysis, the desired carbinol in 79% yield [40].

However, having said this, they also concluded that the results of their work did not permit them to draw any firm conclusions about a possible substitute. The kinetics were found to be complex, and additional work was still required.

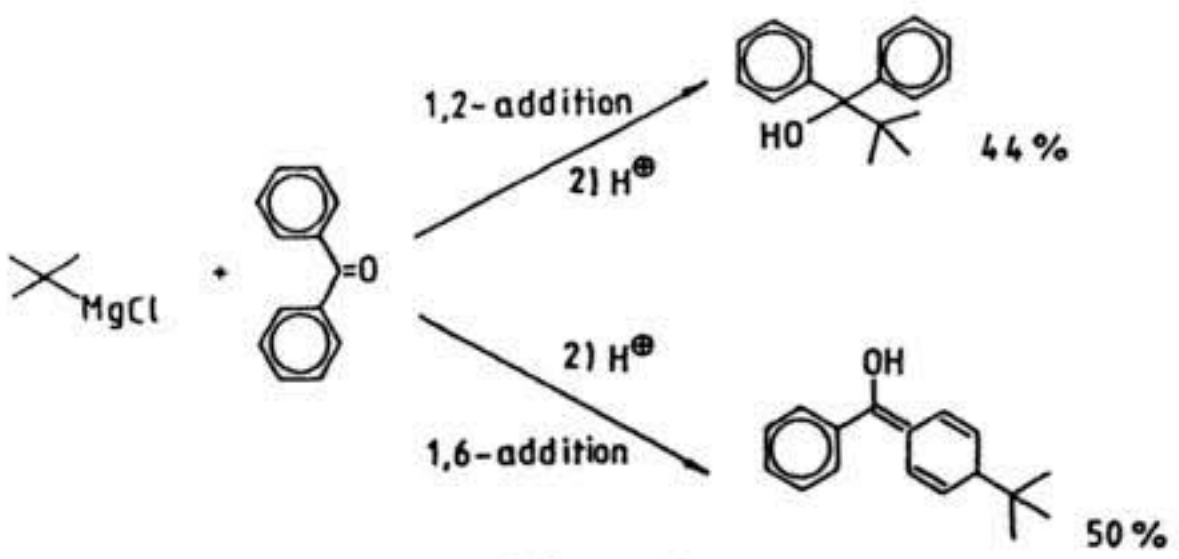
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The proposed concerted mechanisms, containing cyclic intermediates, are no longer of much interest today, since these include complexes with Grignard reagents that were believed to have the $R_2Mg^{\cdot}MgX_2$ structure in accord with the general opinion at that time.

Soon after these kinetic studies, in the early 1960s, aiming at the elucidation of reaction mechanisms, the existence of radicals as intermediates became evident, and it became more and more clear that electron-transfer mechanisms do play an important role in the reactions of Grignard reagents.

Before going into these mechanisms in more detail in the next section (see Sec. II.B), mention should be made of an unexpected side reaction that was published in 1971.

Although the addition of *t*-BuMgCl to benzophenone had been reported [43] to yield 63% of the expected tertiary alcohol, 1,1-diphenyl-2,2-dimethyl-1-propanol, "diphenyl-*t*-butylcarbinol" (no reduction products, such as benzhydrol and benzopinacol, were found then), it was shown that besides the normal addition to the carbon–oxygen double bond, 1,2-addition and also 1,6-addition had taken place, leading to the formation of an alkyldihydrobenzophenone [44] (Scheme 9):



Scheme 9

Also, a small amount of benzopinacol was isolated. The conjugate addition of Grignard reagents to sterically hindered benzophenones had been studied earlier [see, e.g., Ref. 45], but it had never been detected for benzophenone itself. This is probably because of the instability of the dihydrobenzophenone, which at 80–90°C decomposes to form benzophenone and 2-methylpropane. In the presence of oxidizing agents, it undergoes aromatization to form 4-*t*-butylbenzophenone. Further studies in this field showed that with other substituted benzophenones, not only 1,2- and 1,6-addition took place, but, as expected, also 1,4-addition. This happened in particular with 4,4′-di-*t*-butyl- and 4,4′-dichlorobenzophenone.

Kinetic measurements of reactions of *t*-BuMgCl with 19 different substituted benzophenones led the authors to the conclusion that, in all of these reactions, the most probable common rate-limiting step is the electron transfer from the Grignard reagent to the ketone to form the ketyl radical anion and the *t*-butyl radical. This brought them to the statement that: "This would indicate that the radical path is not a side reaction, but rather constitutes the main, if not the only mechanism" [44].

B. Development of a Reactivity Spectrum

Electron transfer is an oxidation–reduction process that leads to the formation of an alkyl radical from the alkylmagnesium halide, and of a ketyl—a radical anion—from the ketone.

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The question can then be raised as to what extent such radicals are "free" to move, either within the solvent cage—a rather vague terminology that hides a certain lack of knowledge about the actual situation—or outside of this solvent cage, farther away from the site of transfer, either to produce the normal product, or to escape and form different, "unexpected," products (such as disproportionation products, solvent-attack products, and others).

On the other hand, in a concerted mechanism, bond formation, which includes the shift of two electrons at a time for each bond to be formed, takes place simultaneously on different sites in the complexed reagents (see, as an example, the cyclic mechanism presented in Scheme 7). These two mechanisms are extremes in a complete picture of how bond formation takes place in reactions of Grignard reagents with whatever substrates is under discussion; a reactivity spectrum then becomes evident.

If the lifetime of the alkyl radical is extremely short, in other words, if a certain given radical is very unstable (i.e., very reactive), the lifetime of a radical pair, consisting of an alkyl and a ketyl radical, after electron transfer and homolysis, would be extremely short. Subsequently, electron transfer and radical combination follow each other, with almost no separation; no differentiation can be made between a two-step electron-transfer mechanism and a one-step polar mechanism. For steric reasons, one would expect the following sequence of reactivities in a concerted mechanism: tertiary < secondary < primary, whereas the reverse is to be expected for an electron-transfer mechanism, in view of the stability of radicals.

A better knowledge of electrochemical properties of the Grignard reagents would allow a more accurate prediction of their reactivities toward one and the same ketone, since electron transfer (ET) involves the transfer of one electron. It was hoped that it would be possible to relate reaction rates to the anodic oxidation potential of RMgX.

To that end, the logarithms of the pseudo–first-order rate constants for reactions of 0.02 *M* Grignard reagent with 0.25 *M* benzophenone were plotted against the (corrected) voltage of an anodic process at a current density of $I_D = 0.06$ A cm^{-2} ($\eta_{0.06}$) [46]. An approximate linear correlation was obtained for methyl-, ethyl-, isopropyl-, *t*-butyl-, and benzylmagnesium bromide, which, as the author carefully worded it,

> might indicate that the ET mechanism which was suggested for *tert*-butylmagnesium bromide [44] may be a relevant model for many simple alkylmagnesium bromides.

However, demonstrating the uncertainty that exists in this area, he continued

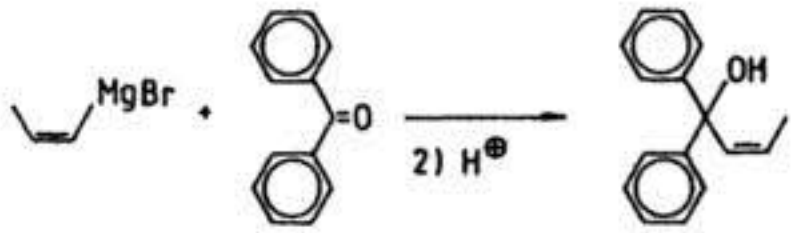
> This would not mean that free radicals are actual intermediates, but only that the alkyl assumes a significant amount of radical character in the transition state [46].

The reactivity of some other Grignard reagents that were investigated was not well correlated with the discharge potential; it seemed that β-branching, as in isobutyl, represents more steric hindrance for the chemical than for the electrode process. For allyl- and cyclopentylmagnesium bromide, the reaction was faster than would be predicted from the discharge potentials. The mechanism of reaction for these reagents may be different, or it may be a hybrid between the stepwise electron-transfer mechanism and the polar (concerted) mechanism.

A few years later, by a different research group, the idea was proposed to "trap," or "observe," the intermediate radical or radical anion [47]. *cis*-Propenylmagnesium bromide, a vinylic Grignard reagent, reacted with benzophenone to yield exclusively the normal,

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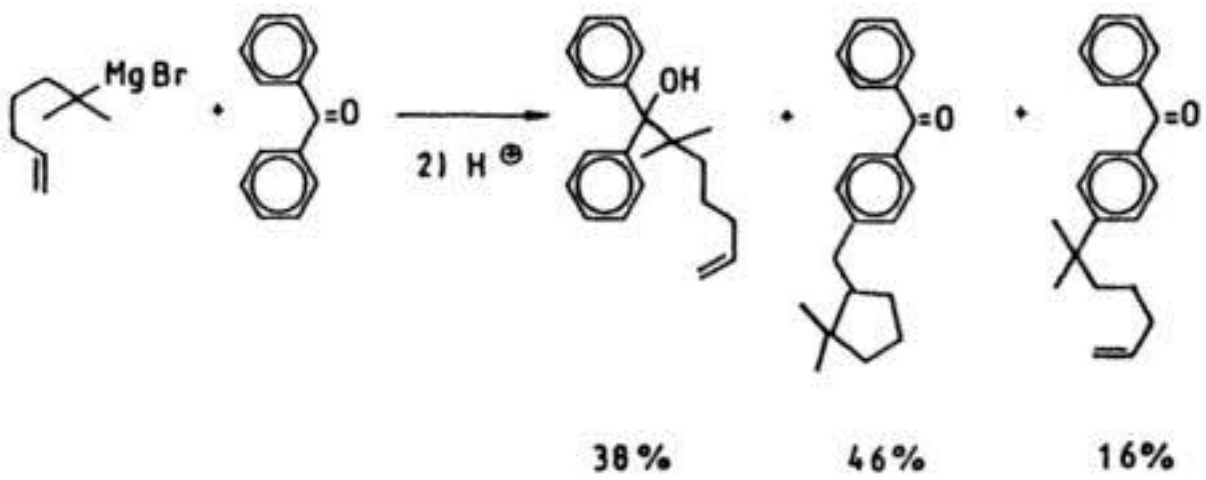
unisomerized, tertiary alcohol (Scheme 10):



Scheme 10

Likewise, no isomerization (cyclization) was observed when 5-hexenylmagnesium bromide, a well-studied radical probe, was reacted with benzophenone. The authors concluded that this "... indicates that either the reaction is polar or, if SET, no "free" radical character is exhibited."

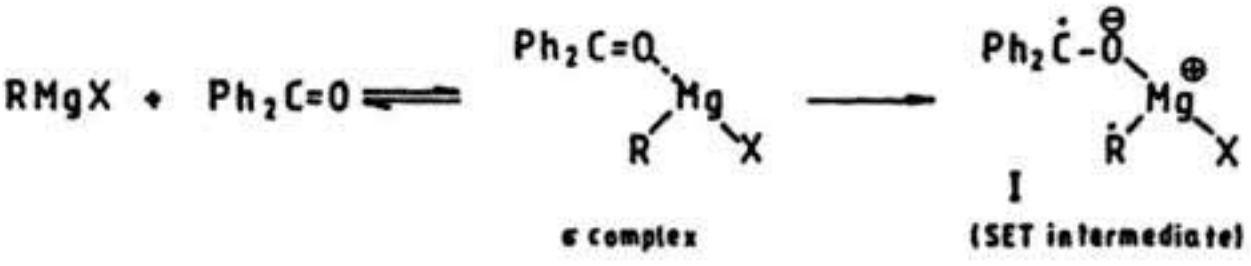
On the other hand, when 1,1-dimethyl-5-hexenylmagnesium chloride was reacted with benzophenone, the following products were obtained (Scheme 11):



Scheme 11

Since products from the 1,6-addition reactions are formed in much larger amounts than those from the 1,2-addition reaction (38:72), and since no cyclization takes place in the latter reaction, the conclusion was made that the 1,2-addition reaction product results from a collapse of a radical anion (ketyl)–radical cation ($RMgX^{\bullet +}$) pair in which the group $R^{\bullet}$ of the Grignard is still tightly bound to the magnesium.

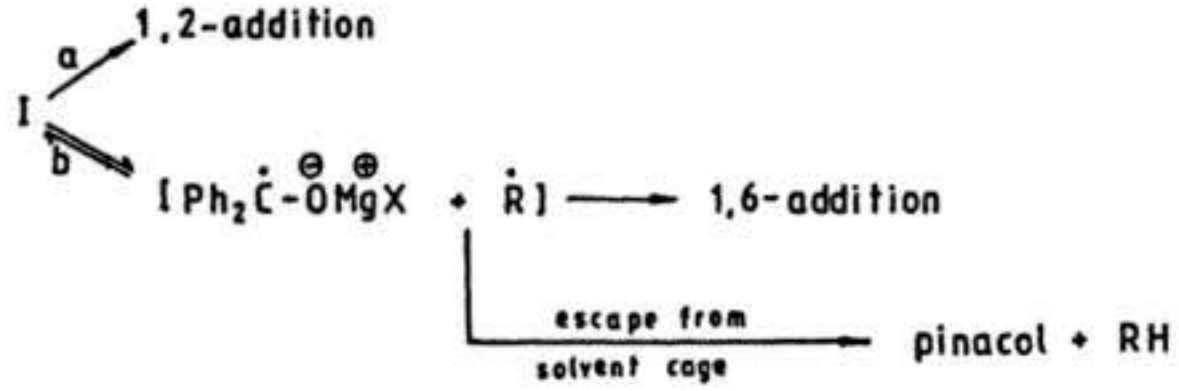
However, how "free," is the radical anion in reactions of benzophenone? In the presence of a radical anion scavenger, such as *p*-dinitrobenzene [48], pinacol formation is totally suppressed in reactions of "CH_3MgBr" and "*t*-C_4H_9MgCl" [49] with 2-methylbenzophenone, but the same scavenger had no effect on the ratio or the rate of 1,2- and 1,6-addition reaction products. Thus, the formation of these products does not involve a "free ketyl." A single-electron transfer (SET) intermediate, **I**, was proposed (Scheme 12)



Scheme 12

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The SET intermediate **I** could either directly form a 1,2-addition reaction product (see Scheme 13 path a; no isomerization) or it could dissociate to form a radical anion and a free radical within the solvent cage. Collapse of the two radicals leads to the formation of the 1,6-addition reaction products, whereas escape from the solvent cage would lead to radical reaction products, such as benzopinacol and R–H, the result of solvent attack (Scheme 13):



Scheme 13

Electron-transfer and polar mechanisms are extremes in a reactivity spectrum of Grignard reagents. All evidence indicates that the reaction of CH_3MgBr with acetone is polar, whereas the reaction of *t*-C_4H_9MgCl with benzophenone proceeds by an electron-transfer mechanism. It is unclear to which of the two possible mechanisms the reactions of the *cis*-vinylic Grignard reagent and 5-hexenylmagnesium bromide belong, since no isomerization took place. From the work presented, it became clear that, if the reaction proceeds through an electron-transfer pathway, a "free" radical is not involved. The authors [47] conclude that

> [T]he mechanism initially proposed by Blomberg-Mosher [14] and Fauvarque [36] and later supported by Holm-Crossland [44] ... needs some modification. A "free" radical and "free ketyl" cannot form in the SET step as was proposed. Apparently an intermediate radical anion–radical cation pair is formed which can collapse to give 1,2 addition product or dissociate to form a radical anion and a free radical within the solvent cage which in turn can collapse to conjugate addition products or escape the solvent cage to form pinacol.

A subtle new element had to be introduced to account for the results obtained: free radicals in a cage, a solvent cage.

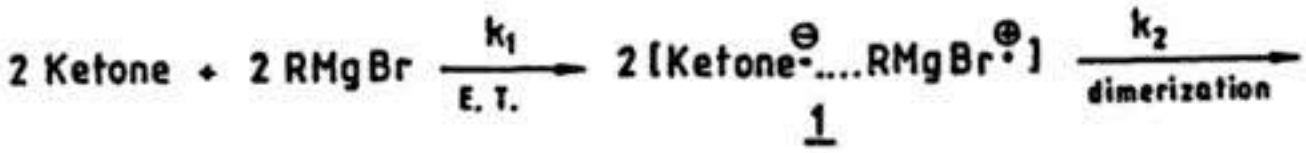
In further work on the elucidation of the mechanism of reactions of Grignard reagents, almost 10 years after the aforementioned refinement of the original electron-transfer mechanism, use was made, among others, of electron paramagnetic resonance of (EPR) techniques [50,51], by the same author who, for the first time, in 1964, found evidence for the occurrence of radicals in such reactions. In the introduction of the paper it was stated that

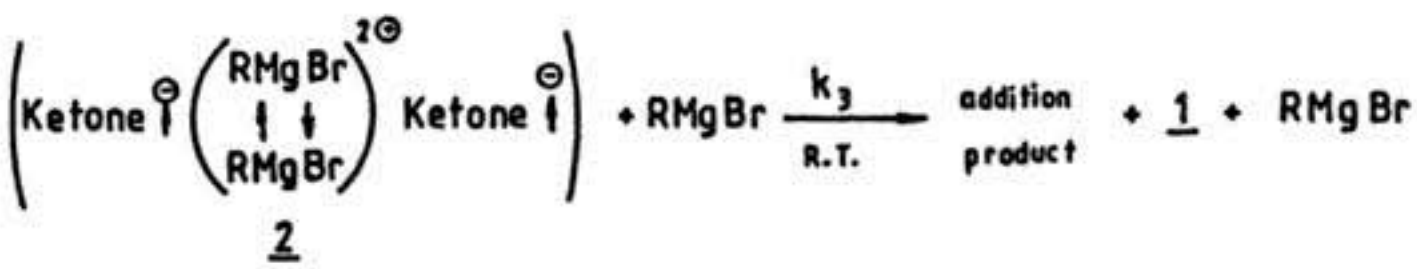
> [T]he mechanism still remains to be clarified since there is almost no definite information on the mechanism by which an alkyl or aryl group is transferred to the initially formed anion radicals.

Again, as before, only aromatic ketones [benzil and (substituted) benzophenones] were the substrates. To measure pseudo–first-order reaction rates a tenfold excess of Grignard reagent over ketone was applied in the measurements. Scheme 14 represents the results

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of these investigations:





Scheme 14

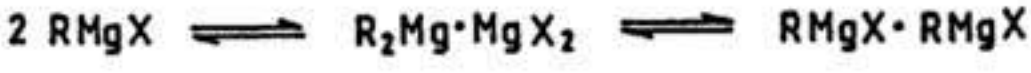
The initial electron transfer from a Grignard reagent to a ketone results in the formation of a monomeric ion radical pair **1**, which instantly forms a stable dimer **2**: the two anion radicals are ion-paired with the dimeric countercation of the Grignard reagent, and the resulting ion pairs exist as a dimeric species. The kinetics of the decay of **2**, followed by stopped-flow technique, showed that the observed pseudo–first-order decay rate constants were proportional to the initial concentrations of the Grignard reagents. This indicates that assistance by another "neutral" molecule of RMgX is necessary for an alkyl (or aryl) group transfer within the complex to complete the addition reaction. The authors were able to determine k_1 and k_3 by direct observation of **2**, which shows a well-resolved ESR spectrum.

A plot of k_1 of the reactions of methylmagnesium bromide, *n*-butylmagnesium bromide, and ethylmagnesium bromide versus the standard oxidation potentials of these Grignard reagents gave a relatively straight line (correlation coefficient $r = 0.998$) [see also Ref. 46], which supports the reliability of the k_1 measurements, as well as the correctness of the proposed mechanism.

A new dimension was given to the study of the radical mechanism by the same group when, rather recently [25], not only the addition reaction but also the reduction reaction were included in the investigations. Whereas the addition reaction required the participation of another neutral Grignard reagent molecule for an alkyl radical-transfer process in the stable anion–radical aggregate, reduction could proceed without such an assistance. This was based on the following two findings:

1. The larger amounts of Grignard reagents, compared with ketones, lead to the formation of greater amounts of addition reaction products.
2. The reactions in diethyl ether, compared with those in tetrahydrofuran, give greater amounts of addition reaction products.

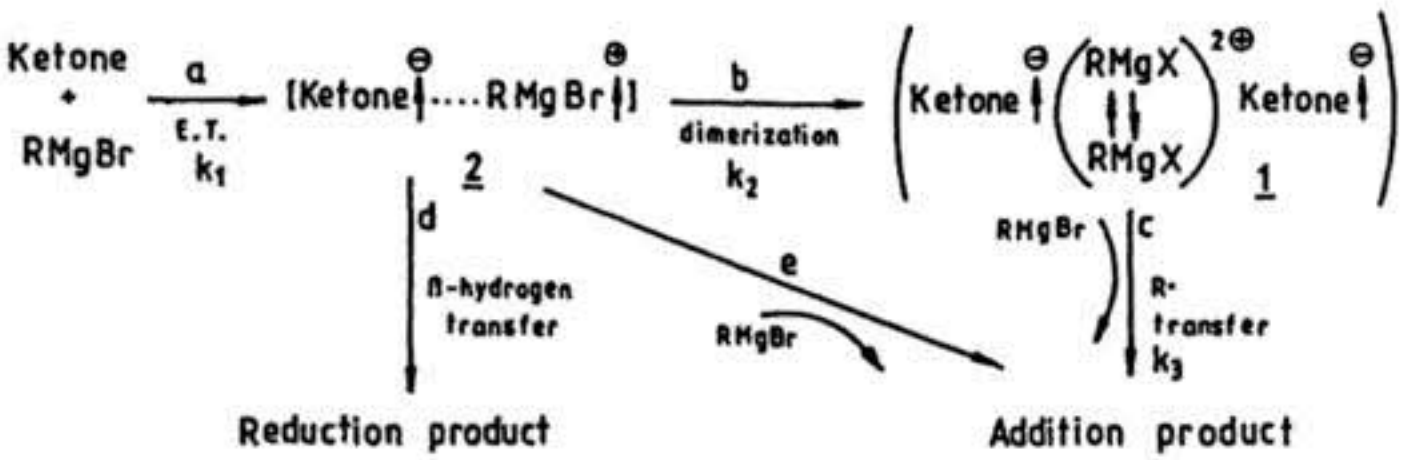
The second finding is explained in terms of the existing Schlenk-type equilibria (Scheme 15) of Grignard reagents in solution (see also Chapter 13):



Scheme 15

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In tetrahydrofuran there will be more monomeric RMgX, whereas in diethyl ether, the equilibrium lies more toward the dimer [52]. According to the reaction scheme, as presented by these authors (Scheme 16), the addition reaction will be favored under a higher concentration of RMgX or in the presence of dimeric Grignard reagent, because alkyl radical transfer in the dimeric anion–radical intermediate will be facilitated by another nearby neutral Grignard reagent (see paths b and c).



Scheme 16

The very last line in this publication, however, leaves open another possible mechanism in which exclusively monomeric RMgX is involved: "A possible participation of *path e* [Scheme 16] cannot be excluded at this stage."

Such an "assistance" by a neutral Grignard molecule to achieve 1,2-addition is a rather surprising new development in recent mechanistic studies of reactions of Grignard reagents. It had been introduced earlier [see Refs. 17,37–39] as the result of kinetic studies, but, in that same period, work by others [see Ref. 40] could not confirm this mechanism. One questions how the assistance by another Grignard molecule from outside the dimeric complex could account for the partial rearrangements in the alkyl group, as was found in reactions of 1,1-dimethyl-5-hexenylmagnesium bromide [see Ref. 47]. Future work will have to answer such questions.

From the same research group, a report recently appeared on studies of the cause for the differences in yields of addition and reduction products in reactions of *n*-propyl- and isopropylmagnesium bromide with substituted benzophenones in three different solvents [e.g., diethyl ether (DEE), tetrahydrofuran (THF), and 1,2-dimethoxyethane (DME); 53]. As to be expected, the main products of reactions of the *n*-propyl Grignard reagent, having two β-hydrogen atoms, were the reduction reaction products, the benzohydrols. In a typical example, the reaction with benzophenone, the following results were reported:

	In THF (%)	In DME (%)	In DEE (%)
n-PropMgBr			
Reduction	83	79	68
Addition	17	21	32
i-PropMgBr			
Reduction	18	31	27
Addition (1,2-; 1,4-; and 1,6-)	82	69	73

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The overall results led the authors to the conclusion that the product distribution was governed by several factors:

1. The oxidizing ability of the benzophenone
2. The degree of association of the Grignard reagent
3. The structure of the alkyl group in this reagent.

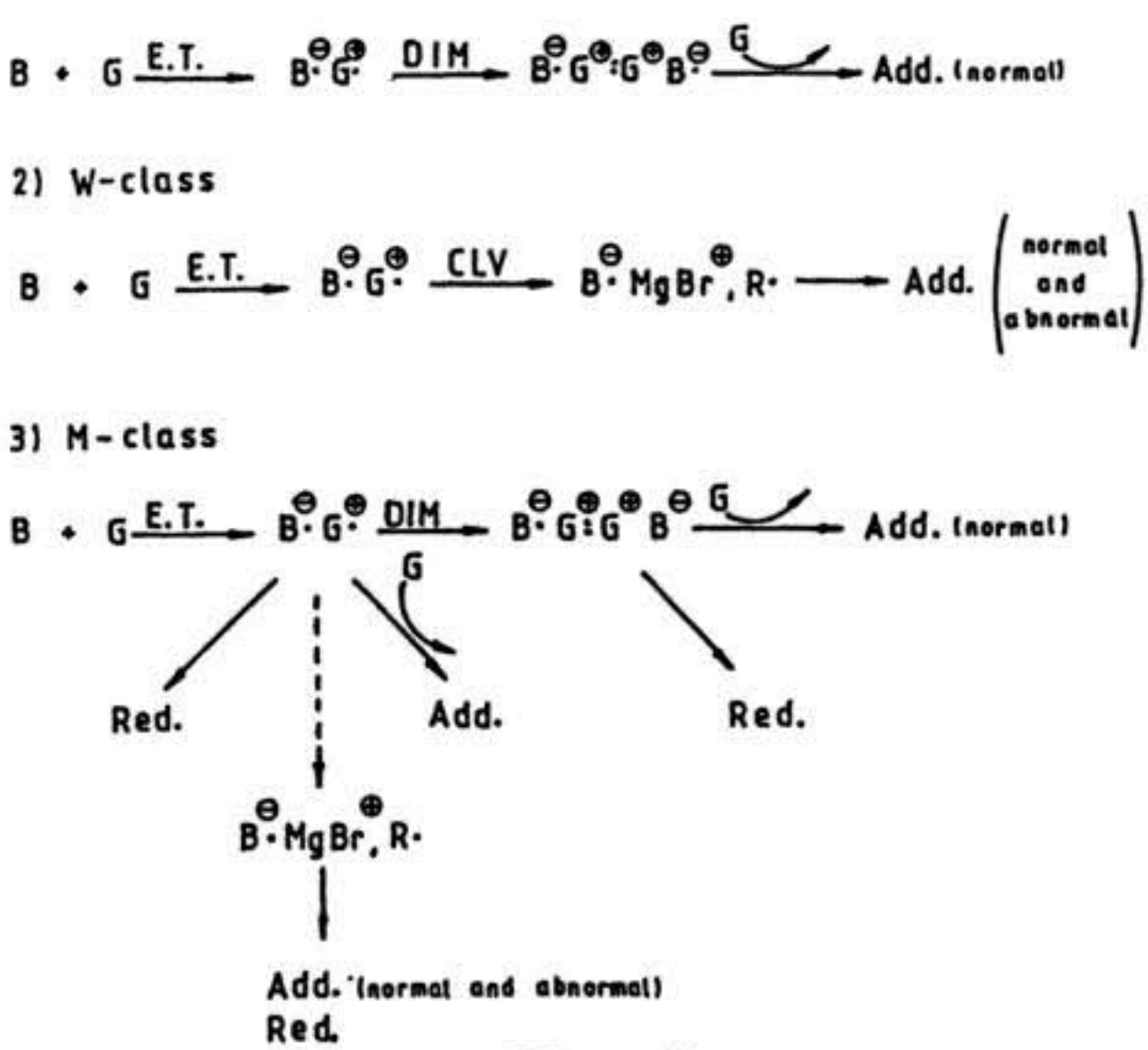
With increasing data on results of reactions and with an increasing number of variables, a growing number of reaction schemes are expected to be introduced. The interpretation of the origin of the differences in the product distribution was based on the following considerations:

The Grignard reagents can be divided into three classes according to the strength of the carbon–magnesium bonds [54].

1. S-class, in which the reagent has a strong C–Mg bond, but has no β-hydrogen atom; the bond energy is higher than 250 kcal/mol: MeMgBr and PhMgBr belong to this class.
2. W-class, in which the reagent has a weak C–Mg bond, with a bond energy below 200 kcal/mol: *t*-BuMgBr belongs to this class.
3. M-class, in which the reagent has a C–Mg bond energy midway between those of the S- and W-classes: EtMgBr and *n*-BuMgBr belong to this class.

For these three classes the reaction pathways can be described as shown in Scheme 17 in which:

B = benzophenone G = Grignard reagent
E.T. = electron transfer DIM = dimerization
CLV = C–Mg bond cleavage

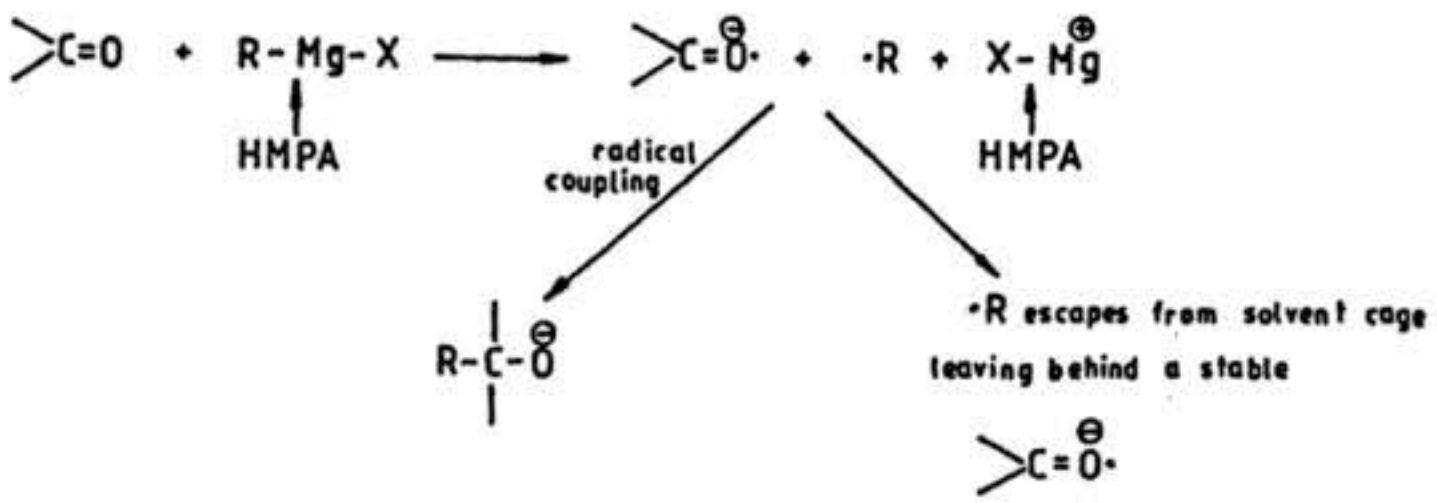


Scheme 17

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In the years that followed after the first time a radical mechanism was suggested for reactions of Grignard reagents and ketones, a few definite steps are to be marked:

1. 1929: Blicke and Powers [28] proposed "trivalent carbon radicals as intermediate reaction products" (see Scheme 2).
2. 1968: Blomberg and Mosher [14] suggest "the transfer of one electron which can take place within the complex formed between the Grignard reagent and the ketone" (see Scheme 6). Their conclusion was that "it seemed possible that many reactions of Grignard compounds have the potential for such a radical course."
3. 1968: Fauvarque and Rouet [36] concluded that "[their] results allowed [them] to propose, in accord with the conclusions of Blomberg and Mosher, that part of the addition reaction developed according to the following scheme (Scheme 18)":

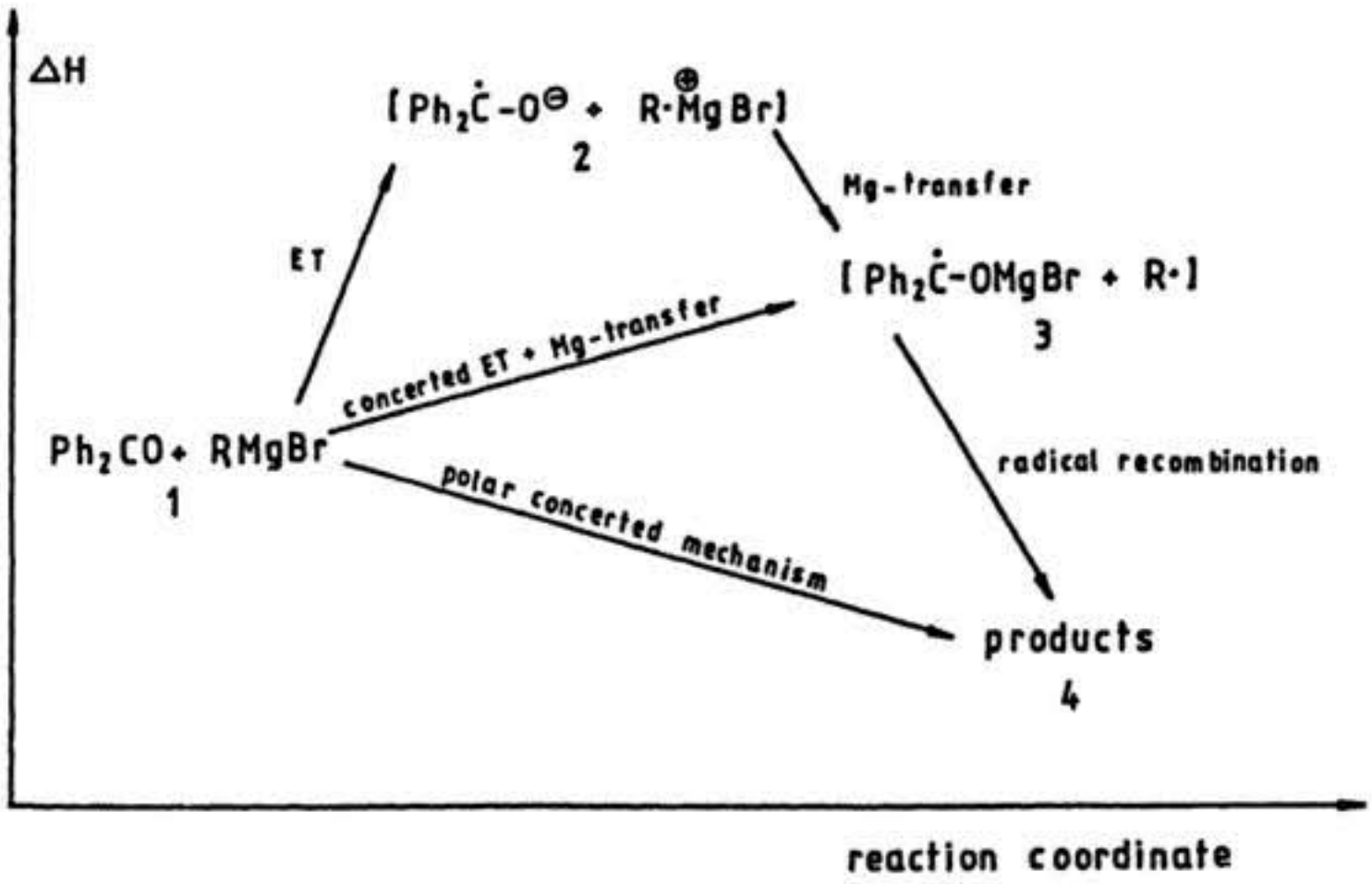


Scheme 18

4. 1977: Ashby and Bowers [47] found that, if the reactions they had studied proceeded by an SET pathway, a free radical is not involved. "Apparently an intermediate radical anion–radical cation pair is formed which can collapse to give 1,2-addition product or dissociate to form a radical anion and a free radical within the solvent cage which in turn can collapse to conjugate addition products or escape the solvent cage to form pinacol" (see Schemes 12 and 13).
5. 1991: Maruyama and associates [53] proposed three mechanisms for reactions of Grignard reagents with benzophenone, in which differentiation is introduced for the C–Mg bond strength in the respective reagent (see Scheme 17).

A refinement of the mechanism was searched for in the more recent literature when a differentiation was made between what was called "inner-sphere" ET and "outer-sphere" ET. It was assumed that, in the reaction of a Grignard reagent with a ketone (i.e., benzophenone), the electron transfer was rate-limiting [44]; furthermore, for a series of Grignard reagents, a correlation had been found between the reaction rates and their oxidation potentials [21], according to the Marcus theory for outer-sphere ET [55]. Nevertheless, it seemed questionable [56] whether the electron transfer was an independent step (steps 1→2→3→4 in Scheme 19), or whether it was concerted with the transfer of the magnesium atom (steps 1→3→4).

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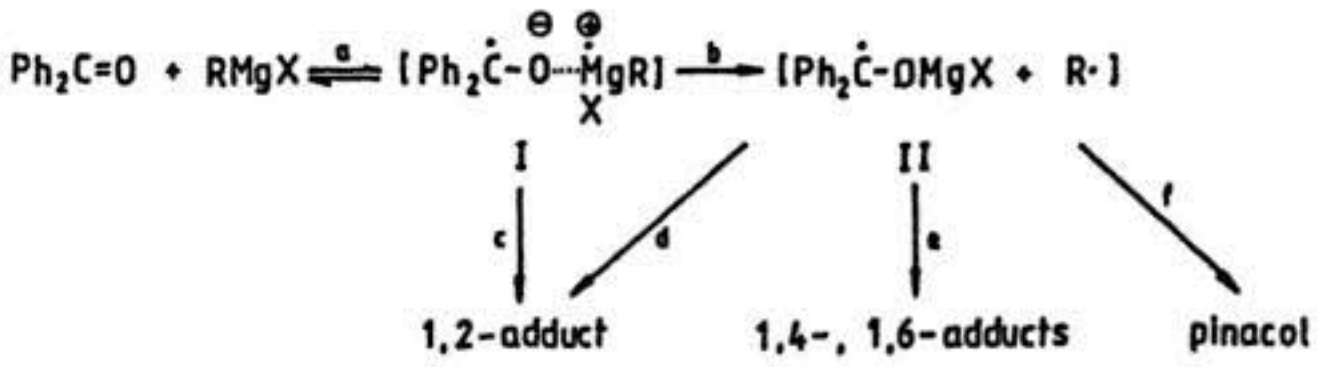


Scheme 19

The outer-sphere electron transfer (step 1→2) mechanism would supposedly require a higher energy of activation than the concerted electron transfer (step 1→3), since magnesium forms a very strong bond to oxygen. On the one hand, from comparison of the heat of formation of the transition states for reactions of alkylmagnesium bromides with benzophenone and, on the other hand, the sum of the heats of formation of the alkyl radicals and magnesium diphenylketyl, the conclusion was drawn that the rate-determining step in these reactions is electron transfer concerted with magnesium transfer from carbon to oxygen. With tertiary and secondary reagents the alkyls were free to diffuse out of the solvent cage, whereas with primary alkyl and methyl reagents, weak bonding exists between the radicals (4–10 kcal/mol), preventing diffusion out of the solvent cage.

A truly concerted mechanism is, however, indicated in the reaction of phenylmagnesium bromide with acetone, since the weak electron donor, phenylmagnesium bromide, is extremely reactive toward this substrate [56].

A different view on the rate-determining step in this type of reactions was published 1 year later [57] after carbonyl carbon kinetic isotope effects and relative reactivities of *ortho*-, *meta*-, and *para*-substituted benzophenones were determined. Scheme 20 presents the reactions proposed by these authors (see also [49] and Schemes 12 and 13):



Scheme 20

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Table 2 Reaction Sequences and the Rate-Determining Step of the Reaction of Benzophenone with Various Grignard Reagents [57]

Reagent	Reaction sequence	Rate-determining step
MeMgI	a→c	c
PhMgBr	a→c	c
AllylMgBr	a→c	a
CrotylMgBr	a→c	a
t-BuMgCl	a→b→(d, e, f)	b

Kinetic isotope effects were positive for methyl-, phenyl-, and *ortho*-tolyl Grignard reagents in diethyl ether, weak for benzylmagnesium bromide, and near zero for allyl-, crotyl-, and *tert*-butylmagnesum halides.

Table 2 lists the reaction sequences and the rate-determining step for the reactions of various Grignard reagents with benzophenone.

> One might ask [the authors end their Concluding Remarks], what will happen if two significantly different ketones were allowed to react with, for example allyl-MgBr; do they always react in similar rates?
>
> The answer is as follows. When the electron-accepting ability of a ketone is lowered by any perturbation, the barrier of step a becomes only slightly higher and the barrier of step b (or c) rises rapidly. As far as SET is the rate-determining step for both ketones, the reactivity difference would be small. However, when the barrier of step b (or c) becomes high enough, the back ET becomes significant and then the reactivity difference of two ketones becomes larger. Further decrease in the electron-accepting ability of the ketone makes step b (or c) the rate-determining step. Finally, the radical ion pair intermediate becomes too unstable to exist in a meaningful lifetime and the mechanism merges with the polar one.
>
> The identification of the rate-determining step for reactions of different ketones is interesting in this context and will be the subject of further study.

In a recent publication [13] of the results of yet another study of carbonyl carbon kinetic isotope effects (KIE), such an effect was found however, for *tert*-butylmagnesium chloride, contrary to what had earlier been reported [57]. The author justified his work as follows

> The presence of a carbon KIE for the reaction of methyl and its absence for the *tert*-butyl Grignard reagent was, however, surprising, since it would indicate that the reaction mechanisms for the two Grignard reagents were qualitatively different, while the linear correlation of E_{ox} and the log rate suggests that they are qualitatively alike. Work was therefore started to determine whether the reported KIEs could be confirmed [13].

The KIE found for the reaction of benzophenone with *tert*-butyl Grignard reagent was not significantly lower than the KIE for the reaction of methylmagnesium bromide. The results indicate that the effect observed is mainly the KIE for the ketyl formation, which includes breaking of the π C=O bond with a simultaneous O–Mg bond formation, *but not* necessarily with a simultaneous C–C bond formation. What is common for the mechanisms is that the fundamental reaction is homolysis of the C–Mg bond, induced by concerted O–Mg bond formation.

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In accord with the previously reported results, indeed no KIE was found for allylmagnesum bromide reacting with benzophenone. Quite opposite earlier conclusions, this indicates that the reaction is not dissociative and that there is no ketyl formation. A concerted six-center reaction, nor an S_E2' mechanism must be imagined with C–C bond formation taking place simultaneously with the breaking of the π C=O bond.

> The finding of KIEs of values around unity must not, as has been done repeatedly, be taken as proof *for*, but rather as proof *against* the participation of ketyl as an intermediate [13].

This being the situation in 1993, it does indeed look (see also Ref. 15 as quoted earlier) as if only "... few positive results have been obtained." However, such a disqualifying statement does not do much justice to the excellent work done in this field in the past 30 years. No doubt some more crucial experiments have to be carried out before most of the mechanistic aspects of the most common of all reactions of Grignard reagents (i.e., the one with ketones) is fully understood.

C. Concerted Mechanism

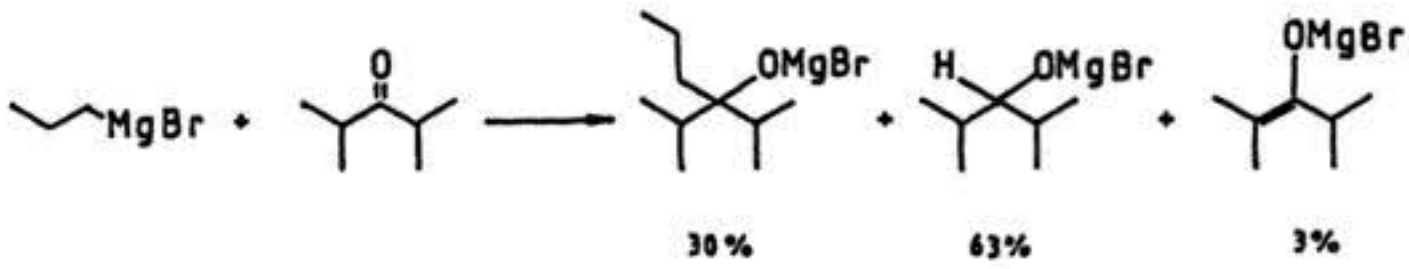
> A truly concerted mechanism is, however, indicated in the reaction of phenylmagnesium bromide with acetone, since the weak electron donor, phenylmagnesium bromide, is extremely reactive toward this substrate [56].

This quotation from the previous section comes from a discussion of the reactions of various Grignard reagents with benzophenone.

Phenylmagnesium bromide is incapable of homolysis, phenyl radicals being extremely unstable. Also, since the reduction of acetone is much less easy than the reduction of an aromatic ketone, such as benzophenone, the transfer of one single electron (as in a reduction reaction) from phenylmagnesium bromide to acetone is very unlikely when other reaction paths are available. A concerted reaction is such a path.

The classic publication of a concerted mechanism appeared in the early 1950s [38]; it picked up the idea of "assistance" by a second molecule of a magnesium species in reactions of Grignard reagents, as suggested earlier [41], based on erroneous observations (see p. 226).

The reaction of 1 molEq of *n*-propylmagnesium bromide with 1 molEq of diisopropyl ketone, a sterically crowded ketone, gave the normal addition reaction product in only low yields; the major product of the reaction was the reduction reaction product, formed by the transfer of a β-hydrogen from the Grignard reagent to the ketone. Owing to an enolization reaction (Scheme 21), 3% unreacted ketone could be isolated:



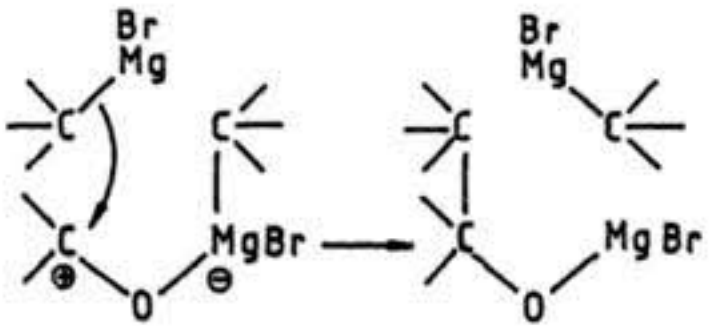
Scheme 21

When, in the same reaction, more than 1 molEq of magnesium bromide was first added to the ketone, followed by the addition of 1 molEq of the Grignard reagent, the yields of

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the products were changed considerably: from 30 to 65% addition reaction product; from 63 to 26% reduction reaction product; and from 3 to 1% enolization reaction product.

The reasoning behind this experiment was the following: The mechanism for addition of Grignard reagents to ketones was supposed to involve reaction of a previously formed Grignard–ketone complex with a second molecule of Grignard reagent (Scheme 22 depicts the mechanistic view of the authors as they presented it in their original paper [35]):



Scheme 22

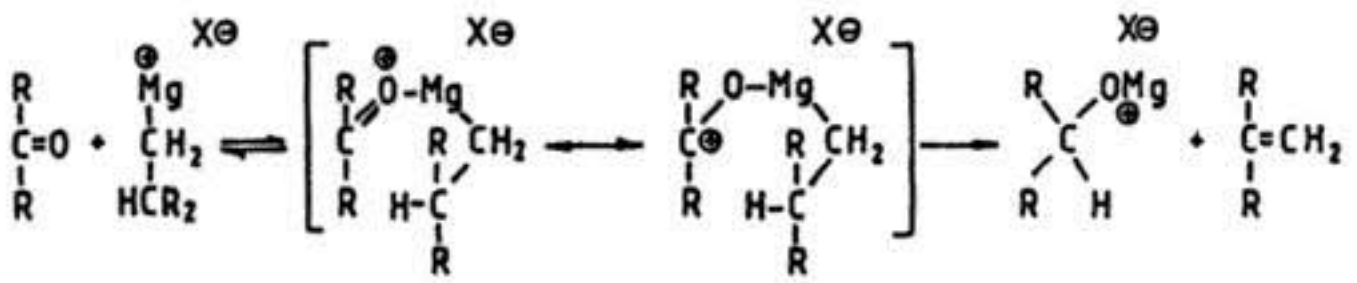
Such a mechanism predicts that one should be able to increase the yield of the addition reaction product to a hindered ketone at the expense of reduction by the simple expedient of adding magnesium bromide to the ketone before addition of the Grignard reagent.

Magnesium bromide is a slightly stronger Lewis acid than the Grignard reagent and should complex preferentially with the ketone. Thus, it would tend to play the role of the first molecule of Grignard reagent (which complexes the ketone). The magnesium bromide–ketone complex would be incapable of reduction by intramolecular rearrangement, but possibly even more susceptible than a Grignard–ketone complex to attack by an external molecule of Grignard reagent.

The authors triumphantly finished their short paper with:

> The success of this prediction is additional evidence for the correctness of the mechanism on which it was based.

The cyclic mechanism, in which the concertedness of the reaction is so clearly depicted, has found applications in several other instances in organomagnesium chemistry. This is particularly true for the reduction reaction with the aid of Grignard compounds. It was reported in 1950, in a paper on the asymmetric reduction of ketones with the aid of chiral Grignard reagents [58], that Whitmore had already presented the idea of a cyclic mechanism (Scheme 23) at an American Chemical Society meeting in 1943 [59]:

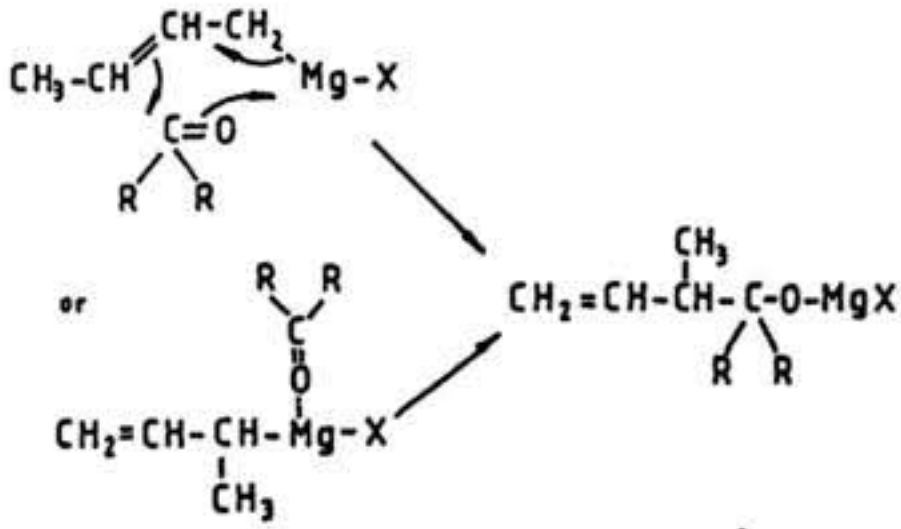


Scheme 23

In that same period, interest had grown in the structure of allylic Grignard reagents in solution and in the mechanism of their reactions. To account for the results of the reaction of ketones with the Grignard reagent prepared from crotyl bromide (1-bromo-

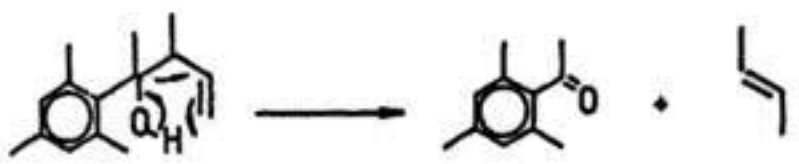
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2-butene), Roberts and Young [60] presented a mechanistic scheme (Scheme 24), with two possible routes to the α-methylallyl derivatives that were obtained:



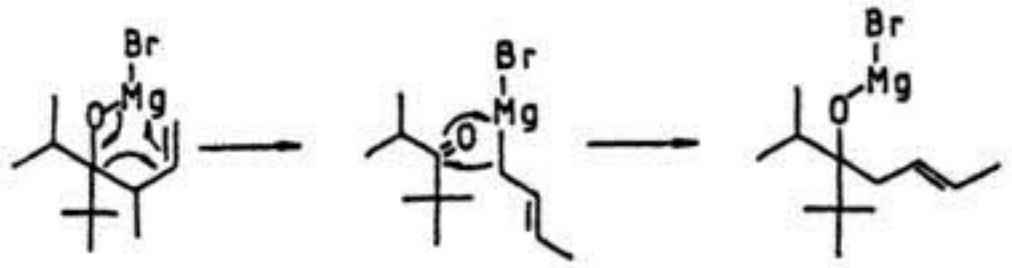
Scheme 24

Such a cyclic mechanism was—in the opinion of these authors—quite similar to that proposed for (what they named) the Claisen allyl ether rearrangement (Scheme 25):



Scheme 25

Quite surprising was the discovery of the reversibility of the addition reaction of crotylmagnesium bromide with sterically hindered ketones [61], in which a cyclic mechanism (Scheme 26) was also suggested to play a role:



Scheme 26

The second step in this scheme involves a four-center concerted mechanism to allow the crotyl structure to be retained in the bromomagnesio alkoxide. After a reaction time of 5 min the α-methylallyl derivative was formed in almost 79% yield, together with 10% of the *cis*- and *trans*-crotyl derivatives. After 193 hr only 0.8% of the α-methylallyl compound had remained among the reaction products, whereas the combined *cis*- and *trans*-products were formed in a yield of 83%: 10% unreacted *tert*-butyl isopropyl ketone was found in the reaction mixture in the presence of presumed excess Grignard reagent. Some years later, such a reversibility was also demonstrated for the reaction of allylmagnesium bromide with *tert*-butyl isopropyl ketone and di-*tert*-butylketone [62, 63].

Material chroniony prawem autorskim

No carbonyl carbon kinetic isotope effect was found for the reaction of allylmagnesium bromide with benzophenone [13,57]. The rate of the homolytic mechanism—which could be predicted on the basis of the oxidation potential of allylmagnesium bromide [46]—is slower than the concerted six-center reaction.

"In keeping with this interpretation," the author concluded that "the reaction of allylmagnesium bromide with benzophenone takes place without any transient coloration [13]."

However, in a recently published, detailed study on the stereochemistry of the addition reaction of allylic Grignard reagents (mainly crotylmagnesium chloride) with α,β-ethylenic ketones [15], addition to aryl-substituted enones occurred without any selectivity at all. The authors suggested that this was due to a single-electron transfer, since poor diastereoselectivity is observed when a carbon–carbon bond is formed by a radical–radical combination [64]. No further mechanistic details on this difference in reactivity were given.

Such results, again, demonstrate that the occurrence of electron transfer is also determined, among other reaction conditions, by the ease of reduction of the substrate.

Proof for single-electron transfer in reactions of allyl- and crotylmagnesium bromide with benzophenone had been reported a few years before, in 1988, based on measurements of carbonyl carbon kinetic isotope effects (which were nonexistent) and substituent effect techniques [65]. Doubt about the correct interpretation of the observed phenomenon was discussed earlier in this chapter (see p. 237 [13]).

The mechanisms of reactions of benzylmagnesium halides can be either homolytic or concerted. As with allylic Grignard reagents, also reversible addition reactions with benzylic Grignard reagents and carbonyl compounds have been reported. In general, yields of normal alcohols are low, and such alcohols are obtained in much better yields by use of dibenzylcadmium [66] or benzyllithium [67]. However, in 1980, it was demonstrated that, by far, the best and quickest results for the synthesis of these normal addition reaction products are obtained by applying benzylic halides in the one-step Li–Barbier reaction under ultrasonic irradiation [68,69].

Benzylmagnesium bromide was among the Grignard reagents found on the straight line when their anodic oxidation potentials were plotted against the logarithm of the pseudo–first-order rate constants of reactions with benzophenone [21,46]. This was considered to be "very good evidence for a rate-limiting electron transfer" [21].

Benzylmagnesium bromide is also reported to react by an electron-transfer mechanism [70] with pyridazin; however, a polar mechanism was involved in the reaction of benzylmagnesium bromide with benzil [71].

Reactions of benzylic Grignard reagents with formaldehyde and with other carbonyl compounds have met with great interest ever since Grignard's first publication in this field [72] in 1903. More recent work has shown that three products are formed in varying amounts, depending on the reaction conditions [73, 74] (Fig. 3): **I**, the normal addition

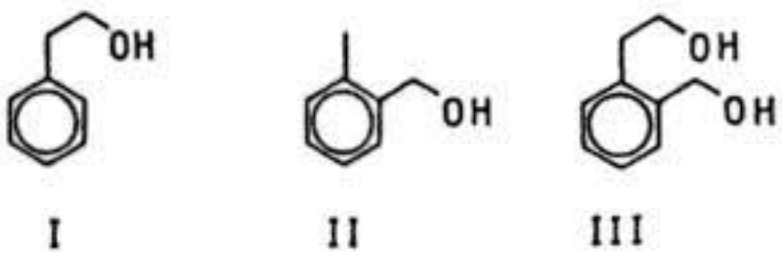
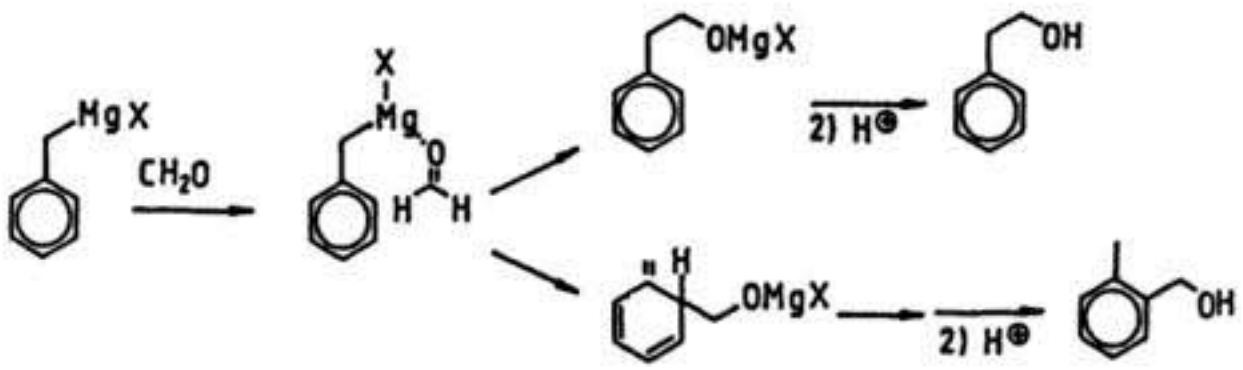


Figure 3 Three products formed from reaction of benzylic Grignard reagents with formaldehyde.

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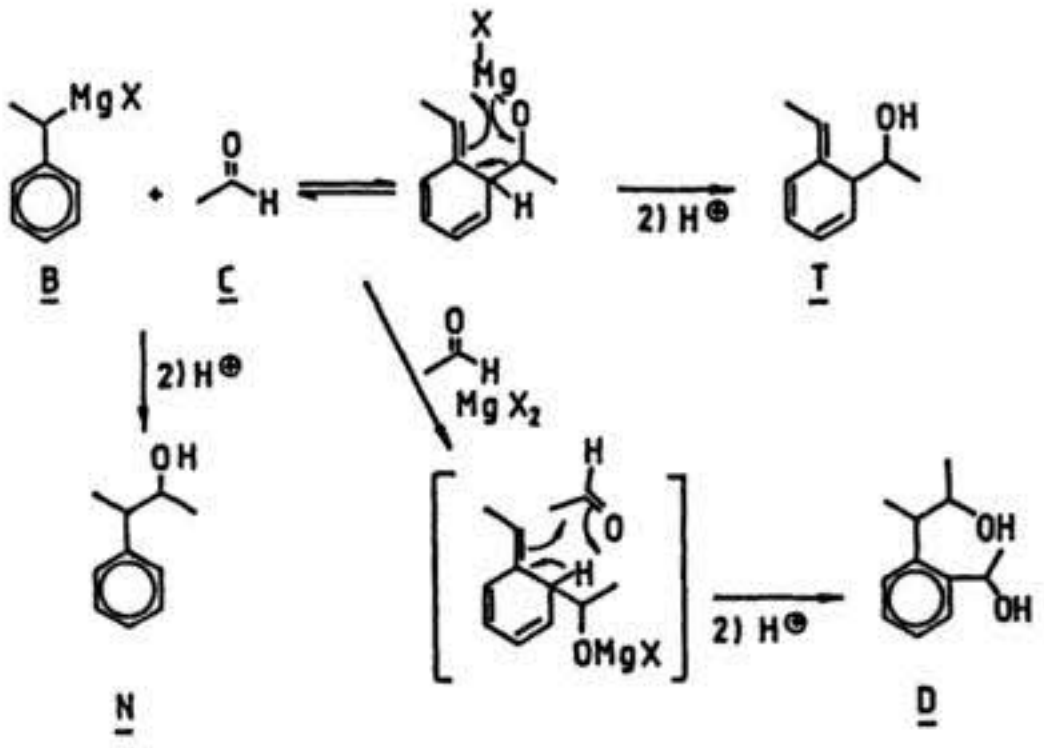
reaction product, **II**, the so-called abnormal *o*-tolylcarbinol, and **III**, the abnormal diol. The normal product **I** is a consistently minor component of the final product composition; **II** appears as the major product when low concentrations of formaldehyde were used, whereas the amount of the diol **III** increases at high formaldehyde concentrations.

In a detailed mechanism, proposed much earlier in 1933 [75], a six-center transition state (Scheme 27) was suggested to account for the formation of **II** (the *o*-toylcarbinol), whereas (probably) a four-center transition state is involved in the formation of the normal product.



Scheme 27

More recent investigations [73, 74, 76–78] have revealed the formation of **III**-type products in reactions of benzylic Grignard reagents *B* with carbonyl compounds *C*. When, for example (Scheme 28), the secondary benzylic Grignard reagent, 1-chloromagnesio-1-phenylethane, *B*, was reacted for 1 hr at 0°C with ethanal *C*, 52% of the trienic alcohol *T* was formed together with 41% of the diol *D*, and 7% of the normal product *N*. However, when the reaction was carried out at 20°C for 4 days, no *T* could be detected among the reaction products, whereas the yield of *D* had increased to 72% [78]. No more than 10% of the normal alcohol *N* was formed.



Scheme 28

The reaction of 1-chloromagnesio-1-phenylethane with benzophenone was the only one among the reactions investigated (nine carbonyl compounds were used) that gave a reasonable yield of the normal product: 55%. Of the benzophenone, 36% could be recovered from the reaction mixture. None of the products *D* or *T* were detected. Therefore, it is

Material chroniony prawem autorskim

probable that the reaction with benzophenone proceeds by an electron-transfer mechanism [see also pp. 225 and 240 and Refs. 21,46].

The author of Ref. [46] commented on his results in the following manner:

> This would not mean that free radicals are actual intermediates, but only that the alkyl assumes a significant amount of radical character in the transition state. The stability of the radical type transition state may be increased by pairing between benzophenone ketyl radical and the alkyl radical [46].

Therefore, it can also be concluded that, for reactions of allylic and benzylic Grignard reagents, a concerted mechanism can be in competition with an electron-transfer mechanism.

D. Reactivity of Various Magnesium Species

Rather early in the history of organomagnesium chemistry the suggestion was forwarded that RMgX was not the only species in solutions of Grignard reagents. In 1904, the existence of its dimer $(RMgX)_2$ was suggested [79]. In 1905, it was stated [80] that it would be of importance to try to verify the existence of the following equilibrium (Scheme 29):

$$2\ R\text{-}MgHlg \;=\; MgHlg_2 \;+\; MgR_2$$

Scheme 29

Several years later [81], the existence of the complex $Et_2Mg^{\bullet}MgI_2$ was made likely on the grounds of several observations, such as the easy solubility of diethylmagnesium in a solution of magnesium iodide and the deposition of magnesium in the anode compartment on electrolysis of a solution of ethylmagnesium iodide (for a more detailed discussion of the composition of solutions of Grignard reagents see Chapter 13).

When considering the structures of the different magnesium species in solution, it is obvious that each one of these will have its specific reactivity toward various substrates. Therefore, it comes as no surprise that, from the very beginning of the study of the mechanisms of reaction of Grignard reagents, the discussion of their composition was included. In the formulation of such reactions, the Grignard compound was often referred to as "RMgX," leaving unspecified its actual structure.

As early as in 1930, it was found—with the aid of the organomagnesium color tests—that phenylmagnesium bromide was 20 times faster than diphenylmagnesium in its reaction with 1-cyanobutane [82]. Such observations made it clear that knowledge of the composition of the Grignard reagent solutions under investigation is of vital importance for a correct understanding of the mechanism of their reactions. The first report on the (quantitative) kinetics of reactions of organomagnesium compounds with ketones [83], 20 years later, showed the reverse order of reactivity for a Grignard reagent and the related diorganomagnesium species: dimethylmagnesium reacted much faster with acetone than did methylmagnesium iodide. The same order of reactivity was found for reactions of these two organomagnesium compounds with benzophenone [38].

Inconclusive results were obtained for reactive species in solution (see Schemes 7 and 8 [37]). Indeed "RMgBr" was used in Scheme 8 in the reaction sequence that included a preliminary complexation of the ketone (pinacolone) with magnesium bromide.

A few years earlier, the kinetics of a much slower reaction (Scheme 30), the metal–hydrogen exchange reaction, was studied [84]; gas evolution was followed over time for the lower alkylmagnesium halides in their reactions with 1-hexyne (Scheme 30).

Material chroniony prawem autorskim



Scheme 30

The rates of the reactions of equimolar quantities in 1 *N* diethyl ether solutions of ethylmagnesium bromide and 1-hexyne, at the reflux temperature of the mixture, were measured. Assigning the value of 100 to the rate of reaction of ethylmagnesium bromide (based on the half-life of the reaction) the relative rates of reaction of other organomagnesium compounds could be determined. The relative rates of reaction of methylmagnesium iodide and methylmagnesium bromide, for example, were both 6, and that of allylmagnesium bromide was 435.

Halogen-free diethylmagnesium reacted with 1-hexyne three times as fast as ethylmagnesium bromide [85]. By (partial) removal of magnesium bromide from such a solution, through the addition of various amounts of 1,4-dioxane and measuring the relative rate of reaction of that solution with 1-hexyne, it was expected that information could be obtained about the position of the Schlenk equilibrium. Dioxane itself had no influence on the rate of reaction of diethylmagnesium in diethyl ether. The results were rather inconclusive.

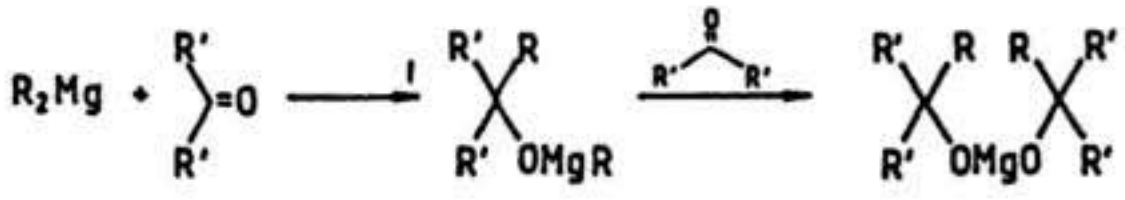
The interpretation of such rate measurements repeatedly encountered difficulties related to the structure of the organomagnesium species present in the solutions, in particular, when solvents, such as tertiary amines or when magnesium bromide, were added [86].

Triethyl amine has no effect on the rate of reaction of diethylmagnesium with 1-hexyne, but it has a significant effect on this reaction of ethylmagnesium bromide (relative rate increased from 100 to 493). It was suggested that the amine influenced the bridging between two magnesium species in complexes formed in solution and, by so doing, influenced the reactivity.

It became clear in that period that a better knowledge of the composition of the Grignard reagent was required. It was also in that period that erroneous results of investigations led to the conclusion that the Schlenk equilibrium was essentially nonexistent [87] (see also Chapter 13). In reports of kinetic investigations of the reaction of methylmagnesium bromide with benzophenone, as mentioned earlier in this chapter [see Ref. 40], consistent use was made of the mixed Grignard structure $R_2Mg^{\bullet}MgX_2$ to describe the transition states for the rate-determining steps, referring to others [88, 89].

An obvious way to obtain a better insight into the importance of the Schlenk equilibrium on the mechanistic aspects of the reactions of Grignard reagents with a wide variety of substrates is to first study these reactions for the simpler dialkyl- (or for that matter diaryl-) magnesium species.

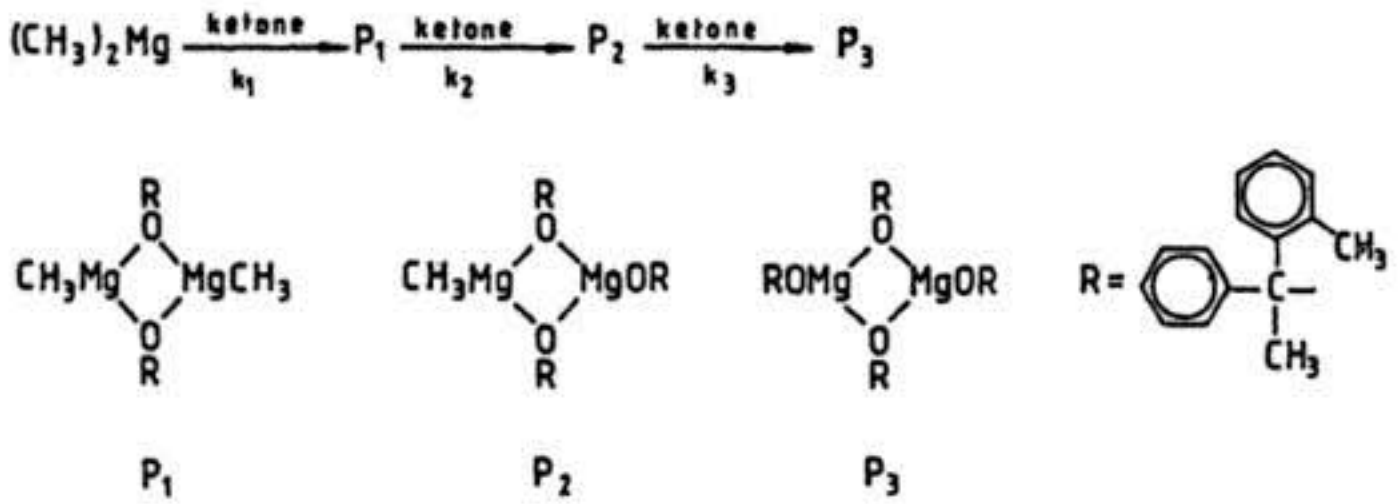
One of the interesting and important aspects of the reaction of dialkylmagnesium compounds with ketones concerns the nature and reactivity of one of the intermediates formed, which contains both a magnesium–oxygen and a magnesium–carbon bond as presented in Scheme 31:



Scheme 31

Material chroniony prawem autorskim

These compounds were also proposed as intermediates, formed in reactions of Grignard compounds with ketones [90,91]. Several complexed organomagnesium reagents were observed in the reaction of dimethylmagnesium with an excess of 2-methylbenzophenone [92] in diethyl ether (Scheme 32). With the reaction of both methyl groups in the organomagnesium reagent, yields of the product were quantitative.



Scheme 32

The reaction of dimethylmagnesium with excess ketone consists of a series of pseudo–first-order reactions involving the formation of two intermediate products, P_1 and P_2 before the formation of the final product P_3. Interpretation of the kinetic data did not necessarily lead to the conclusion that a complex between the ketone and the organomagnesium species was required to bring about a reaction (case II); a bimolecular collision not involving a complex (case I) also fit the data. Nevertheless, in the abstract of the paper the authors showed the three equations that did involve complex formation, which may reflect their preference for the traditional concept of the preliminary formation of a "Meisenheimer complex." The paper continued as follows: "Inability to distinguish between case I and case II is relatively minor compared to the more essential features of the reaction path which have been clearly established." A four-center concerted mechanism was presented in each of the carbon–carbon bond formation steps in the detailed mechanism depicted in the final scheme.

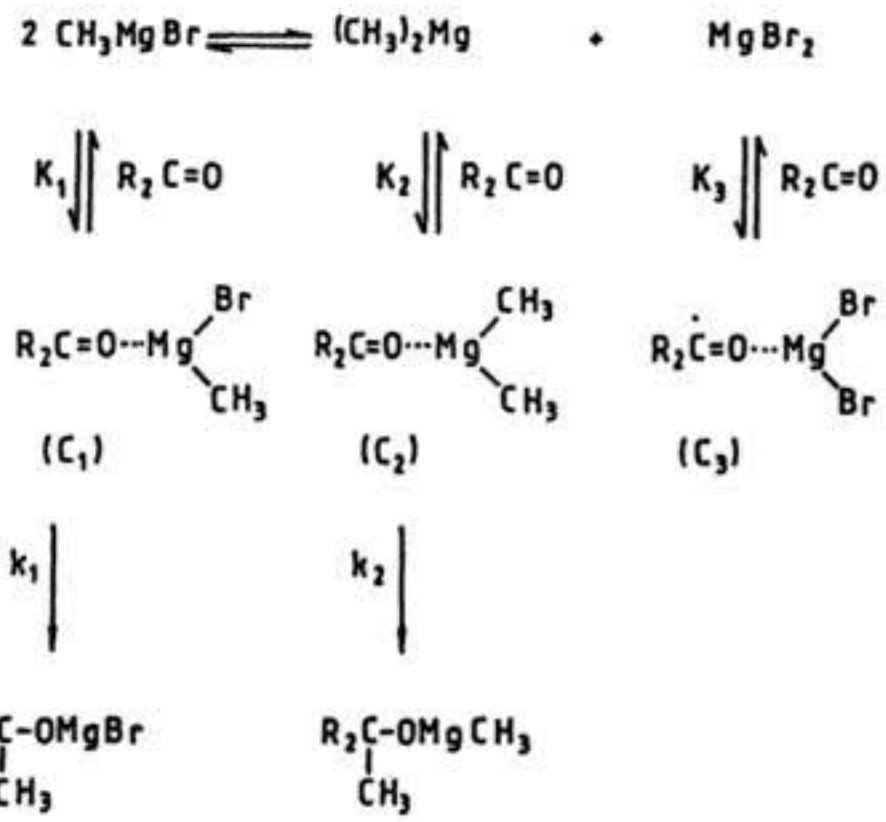
To conclude this section, the mechanistic aspects of the reaction of methylmagnesium bromide with (a substituted) benzophenone will be discussed in detail, as it was investigated in the same period [18,19,93].

Kinetic studies were carried out in excess ketone. It was important to keep the Grignard concentration below 0.1 *M* so that associated species would not present a problem in the interpretation of the kinetic data. It was also important to prepare the Grignard reagent from unusually pure magnesium, since even parts per million of certain transition metal impurities in Grignard reagents cause the formation of by-products in significant amounts.

The results of these investigations led to the following scheme of reactions (Scheme 33) in which complexes C_1, C_2, and C_3 are supposed to be formed, the first two of which

Material chroniony prawem autorskim

will lead to a product in which a new carbon–carbon bond has been formed:



Scheme 33

The values of (the initial rate constants) k_1 that were found for reactions of 0.0124 *M* CH_3MgBr with 2-methylbenzophenone in concentration ranges between 0.0128 and 0.668 *M* were reasonably constant (ranging from 0.0213 to 0.0284 L mol^{-1} sec^{-1}), indicating that the proposed model was correct and that all the parameters substituted in the rate expression were also correct.

When magnesium bromide was added to the Grignard solution of methylmagnesium bromide, much to the surprise of the author, the first-order plot, indicating the disappearance of the reagent, was linear over a large part of the progress of the reaction.

This result was most fortunate.

> the author concluded: in that it indicated that the reason for the observed curvature in the pseudo 1st order plot involving only the Grignard reagent (no extra added $MgBr_2$) is due to the fact that the Grignard reagent is disappearing in a more complex way ... whereas when excess $MgBr_2$ is added, the $MgBr_2$ serves to eliminate this complication. The suggestion at this point is that the Grignard reagent disappears in a 1st order fashion in its reaction with ketone but it also disappears by complexation with the product to form $RMgX^{\bullet}ROMgX$; however, when excess $MgBr_2$ is present, the product can complex the stronger Lewis acid ($MgBr_2$) and hence the Grignard reagent disappears in a true 1st order fashion [19].

A rather detailed scheme was presented of complexes formed between products and organomagnesium species as well as magnesium bromide.

These kinetic studies resolved two questions:

1. The controversy concerning the integral behavior of the Grignard reagent: the reaction is first-order in organomagnesium compounds.
2. The question concerning the nature of the reactive species: in diethyl ether the reaction proceeds by reaction of both RMgX and R_2Mg to about the same extent.

Although the reaction of dimethylmagnesium with ketone in diethyl ether is approximately ten times faster than the reaction of methylmagnesium bromide, there is

Material chroniony prawem autorskim

about ten times more methylmagnesium bromide than dimethylmagnesium in an ether solution of the Grignard reagent prepared from bromomethane and magnesium.

III. CONCLUSION

It becomes evident in this chapter that considerable progress has been made in the past 25 years in the understanding of the mechanisms of reactions of Grignard reagents (and, for that matter, of other organomagnesium species) with ketones, the main substrates in the synthetic procedures in which organomagnesium compounds are used. The rather negative remark, quoted from a very recent publication [15] that, "few positive results have been obtained," demonstrates the impatience of the modern scientist for an even better understanding of each one of the complicated reaction steps of each one of the possible reactive species. In the wide spectrum of reactivities, the extremes are to be found in the *electron-transfer reaction*, on the one hand, and the *polar or concerted mechanism*, on the other hand. Reduction and oxidation potentials of both the substrates and the organomagnesium species, respectively, determine to what extent the reactions observed belong to the electron-transfer or the polar or concerted groups of mechanisms.

An additional complicating factor in the unraveling of mechanisms of reactions of Grignard reagents is related to the composition of the solution of the organometallic reagent as well as the reactivity of each one of the reactive species present.

In view of the rapid developments in this field, it is appropriate to end this chapter with paraphrasing a statement published in 1980 [19], by one of the researchers who has—to a considerable extent—been responsible for a better understanding of the problems in this field.

> It is a fortunate fact that "we" have at the moment arrived at what is believed to be the beginning of a much better understanding of the mechanisms of reactions of Grignard reagents.

That was said more than a decade ago.

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12

Structure–Reactivity Relationships

CORNELIS BLOMBERG
Free University, Amsterdam, The Netherlands

I. INTRODUCTION

It has been made clear, in Chapter 11, that the nature of the Grignard reagent has a great influence on the mechanism of its reactions. The extremes in the reactivity spectrum of organomagnesium compounds in their interaction with ketones, for example, are (1) reactions in which a single electron transfer occurs as the first step, or (2) reactions in which a concerted bond-breaking–bond-making takes place within a cyclic transition state.

This chapter will deal with the predictability of the results of reactions of organomagnesium compounds, in general, and of Grignard reagents, in particular, with substrates of different kinds. It is evident that such a predictability requires a clear understanding of the mechanisms of the reactions involved. For the single-electron transfer reactions (see Chapter 11 for the discussion of the mechanism of such reactions), encouraging results have recently been obtained.

A rather successful *structure–reactivity* scheme [1] was introduced for reactions of a variety of reagents, such as ArMgBr, ArSMgBr, ArNHMgBr, $ArN(MgBr)_2$, and ArOMgBr, with substrates, such as benzophenone, substituted nitrobenzenes, benzoquinones, and many others. In this structure–reactivity scheme the values of differences between oxidation peaks and reduction potentials were taken as an estimate of the relative efficiency of electron transfer, the "ΔE-approach."

The prototype of this approach was reported in 1974 [2] when relative amounts of evolved heats of reaction of RMgBr with benzophenone were related to the overvoltages required for electrolytic oxidation of the (alkyl) Grignard reagents. The results presented by the authors and guided by the ΔE-approach will, as the authors stated,

> contribute to a comprehensive understanding of reaction behaviour and reactivity of magnesium reagents. The unified structure–reactivity and modification factors are useful as guidelines in

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> view of **selection of reaction conditions** and of **novel use of large DN compounds** (polar aprotic solvents) **in calculated small amounts** [2].

Many reactions of N–Mg and C–Mg (Grignard) reagents were classified in terms of "efficiency of single-electron transfer" (SET). From the detailed study of product distribution, minor factors arising from "the aggregation of excess reagent molecules" and from "σ-complexation of reactants" were disclosed.

Long before any insight into the mechanistic aspects of reactions of Grignard reagents was attained, studies had begun in which the reactivity of these reagents was investigated to acquire some understanding of a structure–reactivity relationship in Grignard chemistry. Among the first reports of such studies were those by Ivanoff and co-workers in the early 1930s [3]. These authors reasoned that the rate of the reactions of Grignard reagents was a measure of the strength of the carbon–magnesium bond. A further discussion of their results will follow in Section II.A.

Since that time, considerable progress has been made in the elucidation of the mechanisms of reactions of Grignard reagents. Still, the total number of kinetic investigations of such reactions is very limited, compared with, for example, reactions of solvolytically generated carbonium ions with nucleophiles. *Reactivity–selectivity relationships*, therefore, have been under study in this field for a considerable length of time, although more recent studies seem to be critical of the general validity of such relationships [4].

The application of the concept of reactivity in such structure–reactivity relationships has not yet been firmly established in Grignard chemistry. Only rather recently have successful and reliable kinetic measurements been published, and their application in attempts to elucidate mechanisms of reactions of organomagnesium compounds has just begun (see Chapter 11). Detailed mechanistic studies, such as structures of transition states, entropies of reactions, and so on, are still scarce; furthermore, such information is rather haphazard.

It may be illustrative for the present situation to quote from one of the most recent papers on the reactivity–selectivity principle [4] in which—as a final paragraph—"All experimental workers [were acknowledged] who have participated in measuring the 1600 rate constants used in this work."

Nevertheless, after having discussed this wealth of mechanistic information, the paper's conclusion was that the reactivity–selectivity principle had to be rejected as a general rule. The results of the study were not considered by the author, one of the leading researchers in this field, to be completely negative. The last two lines of the Conclusion were:

> ... investigations of selectivity and its relation to reactivity should be continued and used possibly to characterize a certain type of reaction or a certain mechanism. Particular attention should be given to reactions with a well known mechanism [4].

This chapter will present results of investigations in which some specific features, in the widest sense, of structures of Grignard reagents are brought into relation with the outcome of their reactions. It is hoped and expected that such a presentation will be helpful in obtaining a clearer insight into the structure–reactivity relationships that are gradually becoming more evident in organomagnesium chemistry.

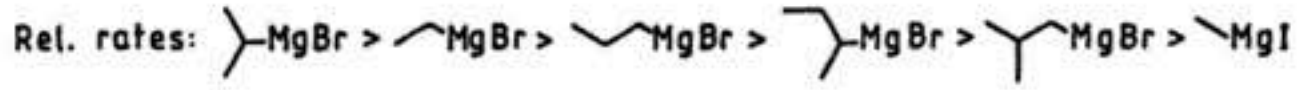
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II. SPECIFIC FEATURES OF REACTIVITY

A. Reactivity in General

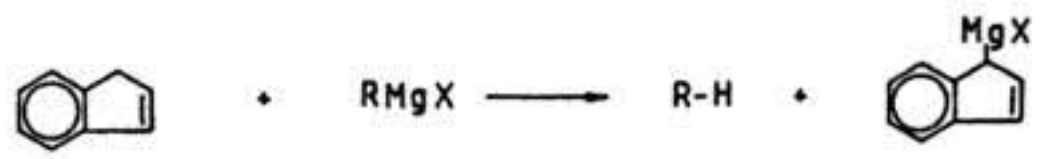
Among the earliest publications in the field of reactivity studies of Grignard reagents are those by Ivanoff [3] in the beginning of the 1930s. The relative rates of the following reactions (Scheme 1) with six different Grignard reagents (RMgBr, except that of the methylmagnesium Grignard reagent, for which the iodide was used) were determined to investigate the relative strengths of the carbon–magnesium bond involved [3a].

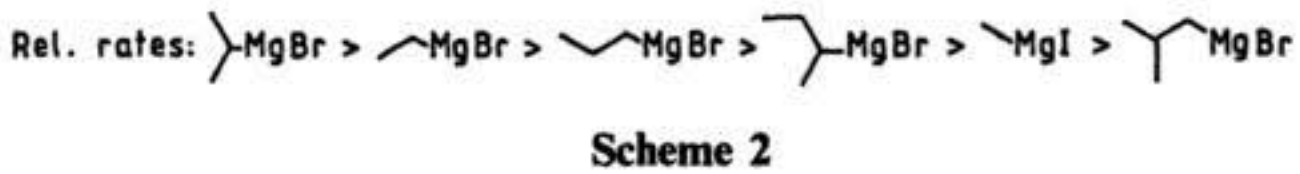




Scheme 1

The reaction with the sterically most-hindered Grignard reagent, isopropylmagnesium bromide, was the fastest, whereas the reaction with the least-hindered Grignard reagent, methylmagnesum iodide, was the slowest. For the reactions of various Grignard reagents (again all RMgBr, except the methyl Grignard) with indene (Scheme 2), the same order of reactivities was found, with a minor change: the methyl Grignard reagent was faster here than the isobutyl reagent [3b]:





Scheme 2

One year later, in 1934, Vavon and co-workers [5] determined the relative reactivities of Grignard reagents with a different type of substrates: benzoic acid esters. Steric requirements played a role when the alcohol component of the ester was changed from primary, to secondary, to tertiary; the relative rates of reactions of ethylmagnesium bromide were 400:40:1, respectively. The relative rates of reaction of ethyl-, isopropyl-, *n*-butyl-, and phenylmagnesium bromide with ethyl benzoate decreased in this order. The reaction with *tert*-butylmagnesium chloride was reported to be "extremely slow."

Changes in the steric requirements of the benzoic acid component of the ester did suggest a strong influence on the reactivity; the reactions of ethylmagnesium bromide with the ethylesters of benzoic acid, *o*-methylbenzoic acid, and 2,4,6-trimethylbenzoic acid had relative rates of 1000:30:1. An interesting series studied in the same paper consisted of the

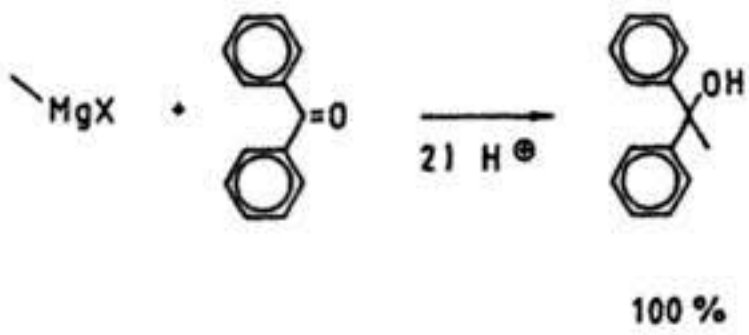
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reactions of *n*-butylmagnesium chloride, bromide, and iodide, with butyl benzoate. The relative rates were chloride:bromide:iodide = 17:4.5:1.

As was demonstrated in Chapter 11, considerably more knowledge on the mechanisms of reactions of Grignard reagents has been obtained since the Ivanoff and Vavon period. The predictability of relative reaction rates as well as of the products formed has improved. The next sections will discuss the following aspects of the structure and properties of Grignard reagents in relation to their reactivities: steric requirements, the halides, β-hydrogen atoms, Schlenk equilibrium, and solvent effects.

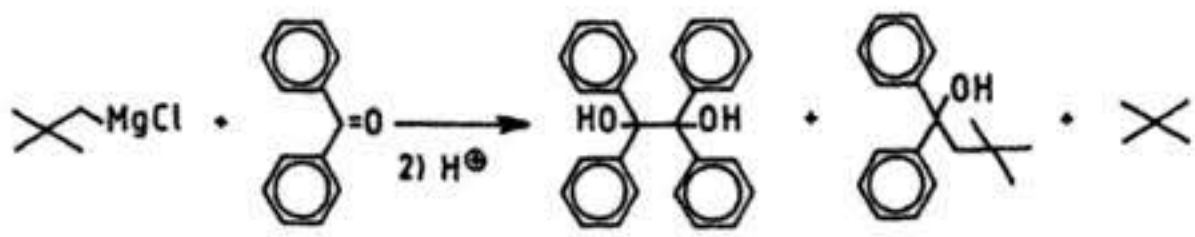
1. Steric Requirements

Among the most obvious properties of an organomagnesium compound that influence its reactivity are its steric requirements: the bulkier the reagent the more hindrance there will be in the approach of the substrate, and this may cause a considerable change in its chemical behavior. Whereas methylmagnesium bromide reacts with benzophenone (Scheme 3) to yield, on hydrolysis, the expected tertiary alcohol, 1,1-diphenyl-1-ethanol, in 100% yield,



Scheme 3

the comparable reaction of neopentylmagnesium chloride, also a primary Grignard reagent [6], leads to the formation of 20% benzopinacol (besides the expected tertiary alcohol) together with neopentane (Scheme 4).

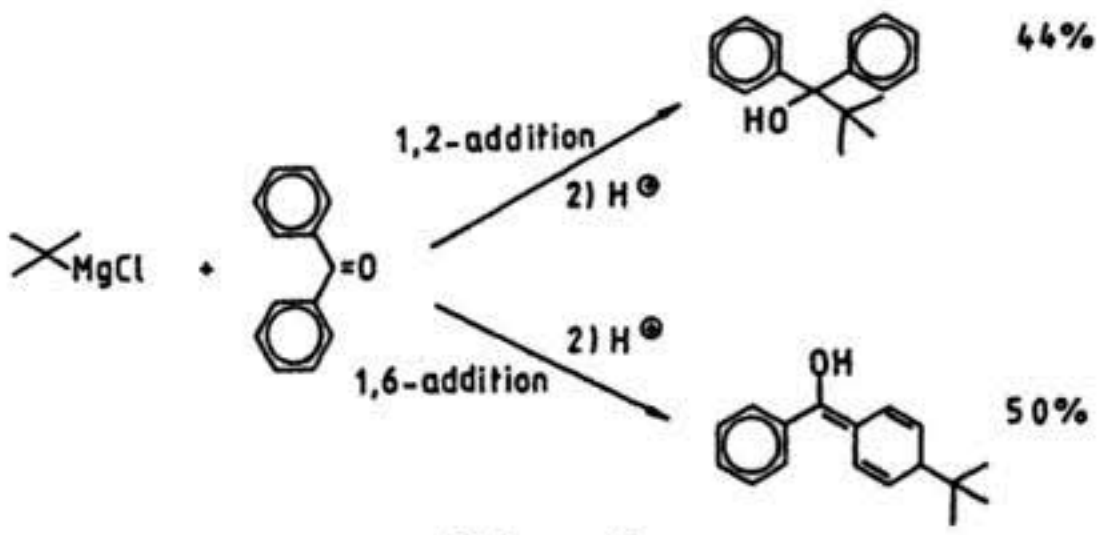


Scheme 4

Since the side product, benzopinacol, usually originates from a radical-type reaction [7,8], it seems that the "normal," nonradical, carbonyl addition reaction through a concerted mechanism is in competition with the reaction that is induced by a single-electron transfer. The slowing down of the first reaction must be ascribed to the steric requirements of the neopentyl group.

The even more sterically hindered Grignard reagent, *tert*-butylmagnesium bromide, reacts with benzophenone (Scheme 5) to give a ring-substituted product in high yields [2b,9] in a very fast reaction.

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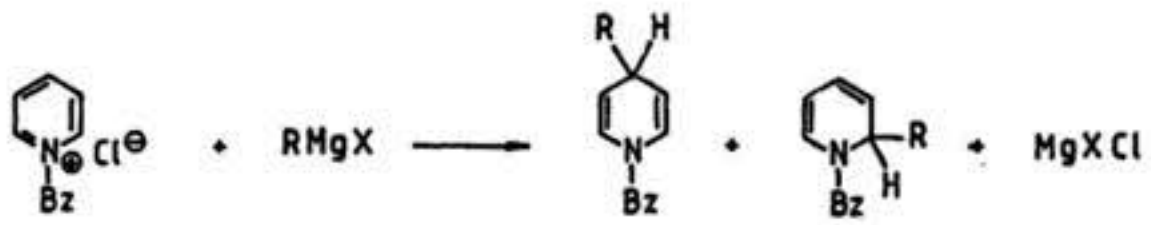
Scheme 5

Later reports on the rate of reactions of *tert*-butyl Grignard reagents with benzophenone indeed indicated that such reactions are much faster than those of methyl Grignard reagents: When a fivefold excess of the Grignard reagent was used in reaction with benzophenone (0.10 *M* and 0.02 *M*, respectively) in diethyl ether at 20°C, *tert*-butylmagnesium bromide was more than 130 times faster than the corresponding methyl Grignard reagent [10]. However, when benzophenone was in excess (0.25 *M* of the ketone and 0.02 *M* of the Grignard reagent in diethyl ether at 20°C), *tert*-butylmagnesium bromide was more than 1200 times faster in its reaction than methylmagnesium bromide [11]. It is relevant that Vavon and co-workers [5], when measuring relative rates of reactions of Grignard compounds with esters, found that the *tert*-butyl Grignard reagent reacted "extremely slowly" compared with the reactivity of ethyl-, isopropyl- and *n*-butylmagnesium bromide. Evidently, the two types of reactions—with benzophenone, on the one hand, and esters, on the other hand—follow two completely different mechanistic paths.

Such differences in mechanisms can also be derived from the results of rate measurements (Table 1) of reactions of various Grignard reagents with benzophenone, carbon dioxide, and acetone, respectively. The reactivity series of Grignard reagents toward carbon dioxide [12] is comparable with the series for acetone [13], which led to the conclusion that both types of reactions follow the same mechanistic path: a concerted mechanism. Steric requirements, therefore, are not the only parameter in the predictability of results of reactions of Grignard reagents and, in fact, are of little help when no other information on the reaction mechanism is available.

Other interesting conclusions can be drawn from the data presented in Table 1, among which are the extremely great reactivity of benzylmagnesium chloride toward benzophenone and an even greater, and actually immeasurable, reactivity of allylmagnesium bromide toward both benzophenone and acetone.

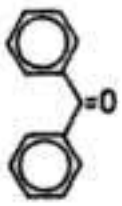
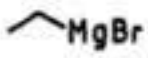
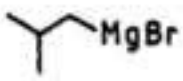
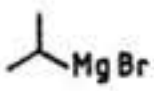
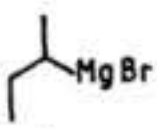
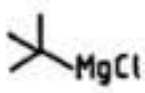
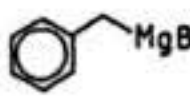
An interesting series of reactions were published in 1991 in which the steric requirements of the Grignard reagents involved are also very clearly made manifest [14]. When a Grignard reagent was added to a suspension of benzylpyridinium chloride in tetrahydrofuran (THF), heat was evolved, and a clear solution was obtained. The reaction is presented in Scheme 6: either a 1,2- or a 1,4-addition reaction occurs:



Scheme 6

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Table 1 Rate Constants for Reactions of Various Grignard Reagents with Benzophenone and Acetone (k_{obs}/sec^{-1}) [2b] (0.50 *M* RMgX with 0.05 *M* Ketone in Diethyl Ether at 20°C) and with Carbon Dioxide (k_{obs}/L mol^{-1} sec^{-1}) [12] (0.0022–0.0036 *M* CO_2 with 12-Fold Excess of RMgX) in THF at 0°C

		CO_2	
	0,30	9,23	3,8
	7,2	7,67	7,5
	3,2	6,49	-
	3,2	6,59	2,2 (36)
	-	4,25	-
	22	6,97	1,6
	27	3,26	0,1
	94	-	-
	0,3	-	44
	91 (350)	-	150
	momentary	-	momentary

The results of the reactions of seven different RMgX reagents with benzylpyridinium chloride are presented in Table 2. It is most likely that the large amounts of the 1,2-addition products formed in the reaction with methyl and phenyl Grignard reagents are, indeed, due to the decreased steric bulk of these reagents.

2. *The Halides in the Grignard Reagent*

The greater electronegativity of the earlier halides in the periodic table is expected to cause an increase in the polarity of the carbon–magnesium bond and, hence, to increase its reactivity.

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Table 2 Relative Product Distribution (%), from the Reaction of RMgX with Benzylpyridinium Chloride in THF [14]

Grignard reagent	1,2-Adduct	1,4-Adduct
CH_3MgBr	99	1
$(CH_3)_2CHMgBr$	5	95
C_4H_9MgBr	60	40
$(CH_3)_2CHCH_2MgBr$	67	33
$(CH_3)_3CMgCl$	36	64
C_6H_5MgBr	91	9
$C_6H_5CH_2MgBr$	45	55

In 1934, Vavon had already found that *n*-butylmagnesium chloride reacted four times faster with *n*-butyl benzoate than did the corresponding bromide which, in turn, showed the same increase in reactivity when compared with the iodide [5]. Large differences in reactivities for chloride and bromide reagents are also shown in Table 1 in reactions with both acetone and benzophenone. Even more striking differences were found for reactions of *p*-tolyl and *p*-chlorophenyl Grignard reagents with benzophenone [2b]: *p*-tolylmagnesium chloride reacted 700 times faster with benzophenone than did the corresponding bromide; and *p*-chlorophenylmagnesium chloride was 1200 times faster than the corresponding bromide in its reaction with benzophenone.

Apart from differences in polarity of the carbon–magnesium bond, there may be other reasons why organomagnesium chlorides react faster than the other organomagnesium halides. This, then, may also cause a change in the composition of the reaction products, since slower reactions have no chance to develop, as in the reaction of neopentylmagnesium chloride with benzophenone in Scheme 4.

In Chapter 11, mention was made of a mechanistic proposal [15], in which participation of a "neutral" Grignard reagent molecule was required for an alkyl radical transfer process within the stable anion-radical aggregate that was originally formed (see Scheme 16, in Chapter 11). According to the authors of this mechanistic proposal, a higher degree of association of Grignard reagents in solution promotes the formation of addition reaction products. The degree of association of organomagnesium halides is strongly influenced by the nature of the halide [16], with the earlier halides in the periodic table being more strongly associated. If the proposed mechanism is correct, a stronger association of the Grignard reagent promotes an easier and, hence, faster reaction. This seems to be supported by the relatively few results available.

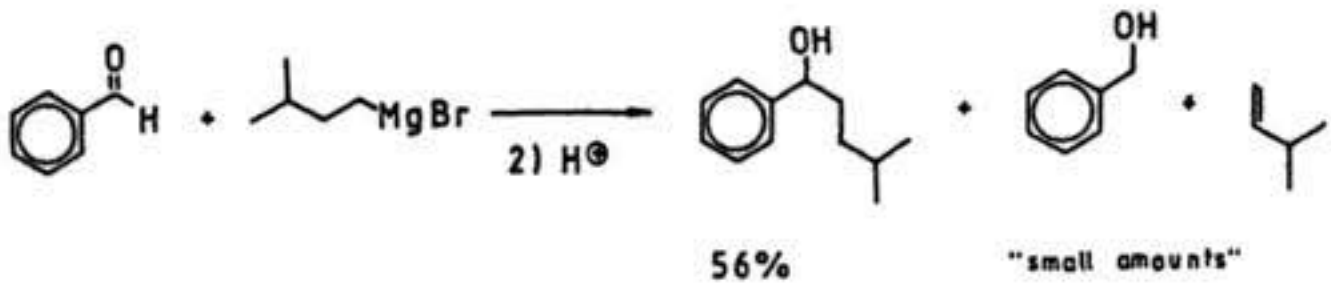
More detailed information on rates and mechanisms of reactions would be of great value to develop a more precise formulation of the mechanism just discussed. Originally it was applied to account for the differences in yields of products of addition and reduction reactions. However, as repeatedly stated already, the mechanisms involved in both types of reactions (reduction vs. addition) should then have to be firmly established, since mechanistic changes may well lead to different results.

3. *β-Hydrogen Atoms in Grignard Reagents*

Among the best known "abnormal" reactions of Grignard reagents is the one in which reduction of the substrate occurs.

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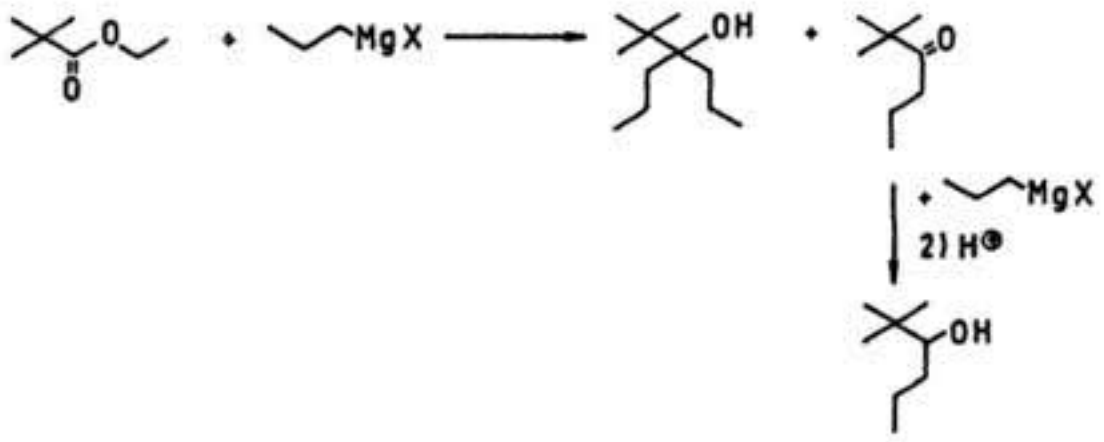
Grignard, in his pioneer paper on reactions of organomagnesium compounds [17], reported the formation of a small amount of benzyl alcohol (beside 56% of the expected main product, the secondary alcohol) in the reaction of benzaldehyde with isoamylmagnesium bromide (Scheme 7):



Scheme 7

Although this type of reduction is most frequently observed in reactions with carbonyl compounds, several different types of organic substrates have been reported to undergo reduction by a Grignard reagent.

In their paper on the reducing action of Grignard reagents Kharasch and Weinhouse [18], in 1936, reviewing previous reports on reduction by Grignard reagents, referred to the reduction of the ethyl ester of trimethylacetic acid ("ethyl pivalate") as studied by Leroide, in 1921 [19]. Indeed, a secondary alcohol was found among the reaction products, in addition to the expected tertiary alcohol (Scheme 8). This secondary alcohol must have been formed, however, in a reaction in which a ketone is reduced by the Grignard reagent; ketone formation is the first step in reactions of Grignard reagents with esters. Most likely, the addition reaction of another Grignard molecule with an intermediately formed ketone is retarded for steric reasons, which then permits the reduction reaction to take place.



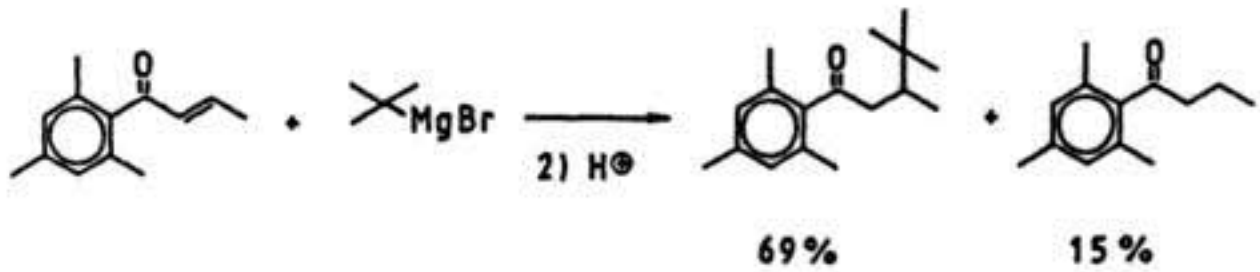
Scheme 8

In view of what has been discussed in the previous section (see Section II.A.2) on the influence of the halide in Grignard reagents, it is of interest to mention that Leroide reported the formation of considerably more of the reduction reaction product when the iodide was used, when compared with the results obtained with the chloride and the bromide. The yield ratios of secondary alcohol versus tertiary alcohol were (sec. alcohol/tert. alcohol) 1.2, 2.1, and 10, respectively, for the chloride, bromide, and iodide Grignard reagent.

The reduction of a carbon–carbon double bond was observed in 1991 [20] in the

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reaction of a sterically hindered enone with an organomagnesium halide (Scheme 9):



Scheme 9

The reduction of azobenzene by Grignard reagents will be discussed at the end of this section.

"Reduction by Grignard reagents is a very common reaction," was a statement by Kharasch and Weinhouse in their paper [18]. However, Whitmore and George, a few years later, in 1942 [21], in their classic paper on this subject used the following title: *Abnormal Grignard Reactions.* Among others, they reported:

> It has been definitely established that in the reaction of a ketone with an aliphatic Grignard reagent a beta-hydrogen in the latter is necessary for reduction. The extent of the reduction depends on the number and character of such beta-hydrogen atoms.

Table 3 presents the results of reactions of diisopropyl ketone with Grignard reagents, as studied by Whitmore and George [21]. In these reactions, not only addition and reduction occurs, but also enolization, which finally leads to the recovery of the starting ketone.

There is no β-hydrogen atom present in methyl- and neopentylmagnesium halide; therefore, no reduction reaction products are observed in their reactions. The highest yield of reduction reaction product was obtained with 2-methyl-1-propylmagnesium bromide, which has one tertiary hydrogen atom on the β-position. In a footnote, the authors made mention of an unpublished result in which the reaction of diisopropyl ketone with *tert*-butylmagnesium halide, which has nine primary hydrogens in the β-position, yielded 65% of the reduction reaction product.

The low yield of addition reaction product, obtained with the neopentyl Grignard reagent is most likely due to the bulkiness of this reagent (see Section II.A.1). Although

Table 3 Results of Reactions of Grignard Reagents with Diisopropyl Ketone [21]

	Yields (%)		
Grignard reagent	Enolization	Reduction	Addition
CH_3MgBr	0	0	95
C_2H_5MgBr	2	21	77
n-C_3H_7MgBr	2	60	36
$(CH_3)_2CHMgBr$	29	65	0
$(CH_3)_2CHCH_2MgBr$	11	78	8
$(CH_3)_3CCH_2MgCl$	90	0	4

Source: Ref. 21.

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Table 4 Comparison of the Properties of *n*-Propyl- and Isopropylmagnesium Bromide [15b]

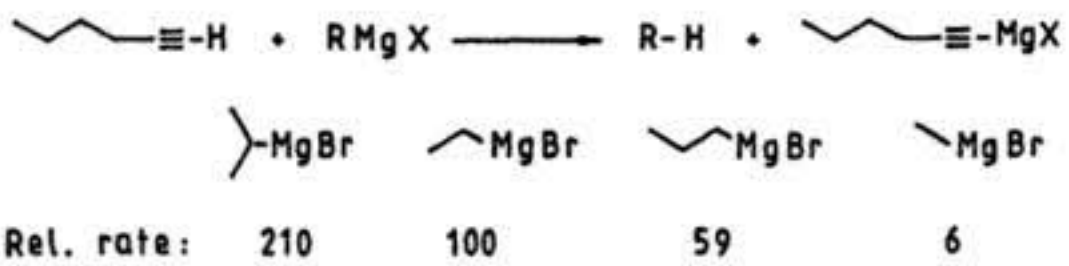
Reagent	Reducing ability	Strength of C–Mg bond	Strength of β-C–H bond
n-C_3H_7MgBr	Low	Strong	Weak
i-C_3H_7MgBr	High	Weak	Strong

the total yield of products obtained with the *n*-propyl Grignard reagent is almost equal to the total yield obtained with the ethyl Grignard reagent, the latter reagent gave mainly the addition reaction product (77%), whereas the former reagent yielded mainly the reduction reaction product (60%). The increase in the yield of this product was attributed to the secondary character of the hydrogens [21].

In the previous section (II.A.2), mention was made of proposals [15] for a reaction mechanism in which participation of a "neutral" Grignard reagent molecule was required to account for an alkyl radical transfer process within the stable anion-radical aggregate that was originally formed (see also Scheme 16 in Chapter 11). In these publications the authors studied the change in the addition/reduction product ratios in reactions of various alkylmagnesium bromides with substituted benzophenones. This ratio was 1.55 for the reaction of C_2H_5MgBr (0.159 *M*) with benzophenone (0.079 *M*) in Et_2O and 0.214 for the same reaction, under the same conditions, in THF. The increase of reduction reaction products in diethyl ether was attributed to the higher degree of association of the Grignard reagent in this solvent. This makes a second neutral Grignard molecule immediately available for the alkyl radical transfer within the anion-radical aggregate. When the excess of the Grignard reagent in THF was reduced (0.157 *M* C_2H_5MgBr and 0.314 *M* benzophenone), the addition/reduction ratio decreased from 0.214 to 0.139. This decrease, again, was attributed to the shortage of neutral Grignard molecules within the aggregate to assist in the transfer of an alkyl radical. There was an even more dramatic change in the addition/reduction ratio (decrease from 3.38 to 1,14 [15a]) for the reaction of *n*-butylmagnesium bromide with fluorenone.

A comparison of the results of reactions of *n*-propylmagnesium bromide and isopropylmagnesium bromide with (substituted) benzophenones [15b] led the authors to some conclusions that are presented in Table 4.

Another effect caused by the presence of β-hydrogen atoms in Grignard reagents is the change in rates of their reactions. When the rates of reactions of various Grignard reagents with 1-hexyne were compared (see Scheme 10; see also Scheme 30 in Chapter 11, Section II.C), the authors came to the conclusion that "there appears to be a simple correlation between the number of β-hydrogens and the reactivity, i.e., isopropyl > ethyl > *n*-propyl > methyl."



Scheme 10

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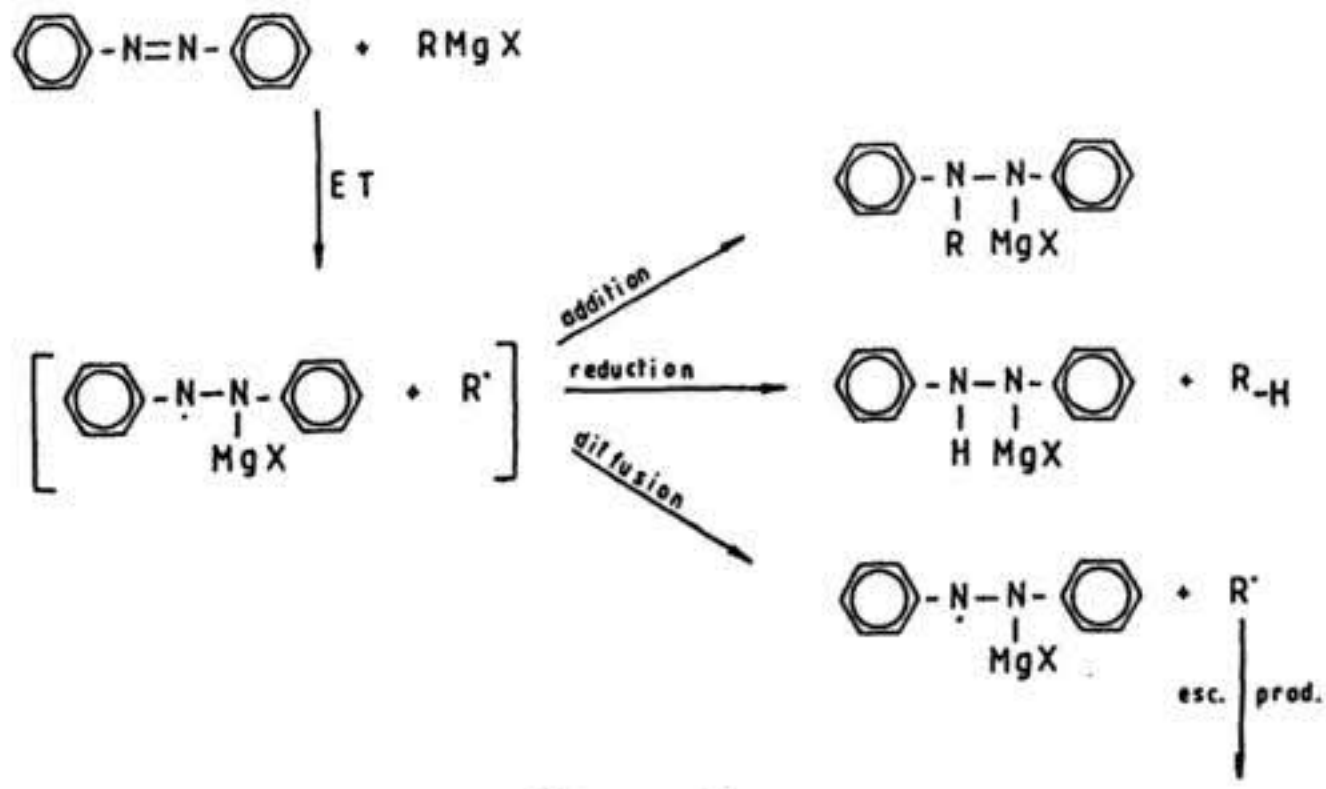
This could, in the authors' opinion, possibly reflect a "hyperconjugation" effect of the sort suggested by Polanyi [23], which is illustrated for the ethyl molecule [22a] in Scheme 11a; "A stabilization of the incipient carbanion $R:^{\ominus}$ by anionic hyperconjugation," as it was described 2 years later is presented in Scheme 11b [22b].



Scheme 11

The secondary β-deuterium kinetic isotope effects in reactions of β-perdeuterated ethyl-, isopropyl- and *tert*-butylmagnesium halides with four different ketones were described [24] and were found to be small (within $\pm 5\%$). There, too, hyperconjugative stabilization was supposed to play a role, but this effect was opposed by the steric effects. The role of hyperconjugation in reactions of Grignard reagents, therefore, seems complicated and requires further studies.

The reaction of azobenzene leads to several different products (Scheme 12) [25]



Scheme 12

Primary and secondary Grignard reagents all gave addition reaction products in yields between 10 and 20%, but the rates of reaction increased by a factor of 10 for each hydrogen in the β-position. Table 5 presents some of the results obtained. A six-center transition state seems indicated in which the β-hydrogen atom is very close to an azo-nitrogen. Comparison of the results obtained with benzophenone as the substrate did not lead to satisfactory answers for the exact mechanisms involved.

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Table 5 Pseudo–First-Order Rate Constants for the Reactions 0.1 *M* Azobenzene with 0.5 *M* Alkylmagnesium Bromide in Diethyl Ether at 20°C [25]

	k_{obs} ($sec^{-1} \times 10^5$)
CH_3MgBr	0.5
C_2H_5MgBr	1,000
n-C_4H_9MgBr	200
$(CH_3)_2CHMgBr$	100,000
$(CH_3)_2CHCH_2MgBr$	10
$(CH_3)_3CMgBr$	5,000
$C_6H_5CH_2MgBr$	30
C_3H_5MgBr (allyl)	12 million

4. *Schlenk Equilibrium*

The Schlenk equilibrium, and any equilibria involving association among the various species in solution, are complicating factors in organomagnesium chemistry (Scheme 13).

$$\text{associated species} \rightleftharpoons 2\,RMgX \rightleftharpoons R_2Mg + MgX_2 \rightleftharpoons \text{associated species}$$

Scheme 13

Mechanistic studies have been frustrated in the past by the possible differences in some of the aspects of the mechanism of their reactions and, furthermore, additional complications were caused by the presence of each one of the reactive magnesium species in solution. Some of these problems were discussed in Chapter 11. A detailed discussion of the Schlenk equilibrium of organomagnesium halides in solution is presented in Chapter 13.

The influence of the Schlenk equilibrium on the reactivity of Grignard reagents is seldom clearly traced in mechanistic studies. The different reagents involved in the equilibrium have different reactivities toward various substrates. Generally speaking, the symmetric organomagnesum compound, R_2Mg, is much more reactive than the Grignard reagent. In one of the earlier reports on reactivities of organomagnesum compounds [26], however, Gilman and co-workers reported that phenylmagnesium bromide was 20 times faster in its reaction with 1-cyanobutane than was diphenylmagnesium. In this particular case, a question can be raised concerning the reliability of the method used to monitor the disappearance of the organomagnesium reactant during the progress of the reaction; the color test that was applied for that purpose has never been fully accepted as a reliable instrument for these measurements.

At the end of Chapter 11 the reactivity of methylmagnesium compounds towards ketones was discussed, in view of the position of the Schlenk equilibrium [27]. Although the reaction of dimethylmagnesium with 2-methylbenzophenone in diethyl ether is approximately ten times faster than the reaction of methylmagnesium bromide, there is about ten times more methylmagnesium bromide than dimethylmagnesium in a diethyl ether solution of a Grignard reagent prepared from bromomethane and magnesium.

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Table 6 Pseudo–First-Order Rate Constants [k_1 (sec^{-1})] of the Overall Reaction of 0.05 *M* of Ketone with 0.5 *M* Alkylmagnesium Bromide in Diethyl Ether at 20°C [25b]

Reagent	Acetone	Benzophenone
CH_3MgBr	3.8	0.30
$(CH_3)_2Mg$	15	1.9
C_2H_5MgBr	7.5	7.2
$(C_2H_5)_2Mg$	15	–
n-C_4H_9MgBr	2.2	3.2
$(n$-$C_4H_9)_2Mg$	15	64

Therefore, there is roughly as much reaction taking place by methylmagnesium bromide as by dimethylmagnesium species. Although this has no further consequences for the overall outcome of the reaction, it does have consequences for the elucidation of the reaction mechanisms involved. In case R_2Mg reacts diferently from RMgX with a given substrate, such differences then lead to a different product composition.

Several quantitative values of absolute reactivities of alkylmagnesium halides and of dialkylmagnesium compounds toward ketones have been published. The values listed in Table 6 are quoted from Ref. 25b. In general, the symmetric organomagnesium compounds react faster than the corresponding Grignard reagent.

The Schlenk equilibrium, as represented by Scheme 13 can be shifted to the right by the addition of 1,4-dioxane to an ethereal solution of a Grignard reagent. A precipitate is formed of a complex of the dioxane with the magnesium halide. When enough dioxane is added most, if not all, of the halide is removed from the solution.

In the late 1950s, a study was undertaken of the differences in reactivity of diethylmagnesium and ethylmagnesium bromide toward 1-hexyne (see Scheme 10 for the reaction with the Grignard reagent) [28]. Halide-free diethylmagnesium reacts three times as fast as ethylmagnesium bromide (the value of 100 was assigned to the reactivity of this reagent) [23]. When portions of 1,4-dioxane were added to a solution of ethylmagnesium bromide, the relative reactivity of this solution toward 1-hexyne increased. After the addition of 1.00 molEq of the dioxane and several hours reflux of the reaction mixture (to complete the formation of the magnesium bromide–dioxane precipitate), the relative rate of reaction of the solution toward 1-hexyne had increased from 210 to 260, indicating that it contained mainly the symmetric organomagnesium compound. Figure 1 shows the results of these investigations. It was not clear, from this publication, why the value of 300 for the halide-free diethylmagnesium was not reached, even after the reaction mixture had been refluxed for 12 hr.

A striking exaple of the influence of the Schlenk equilibrium on the progress of reactions of organomagnesium compounds was observed in, what was named, a ligand-assisted nucleophilic addition reaction (LANA), in which the substrate was a lithium quinol alkoxide [29]. In a typical LANA reaction (Scheme 14) the lithium quinol alkoxide is first prepared in situ, after which follows the sequential addition of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (DPMU) and a Grignard reagent.

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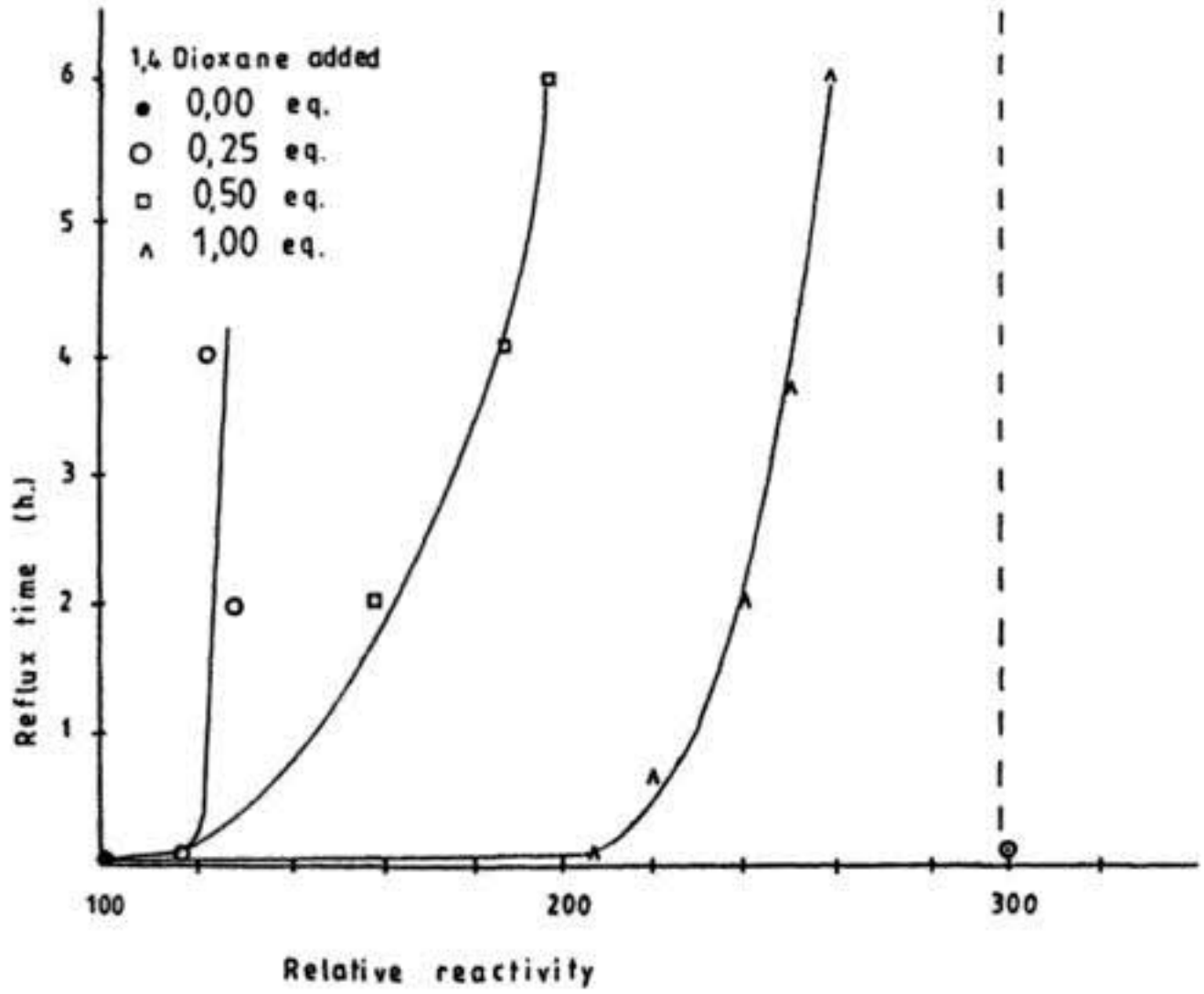
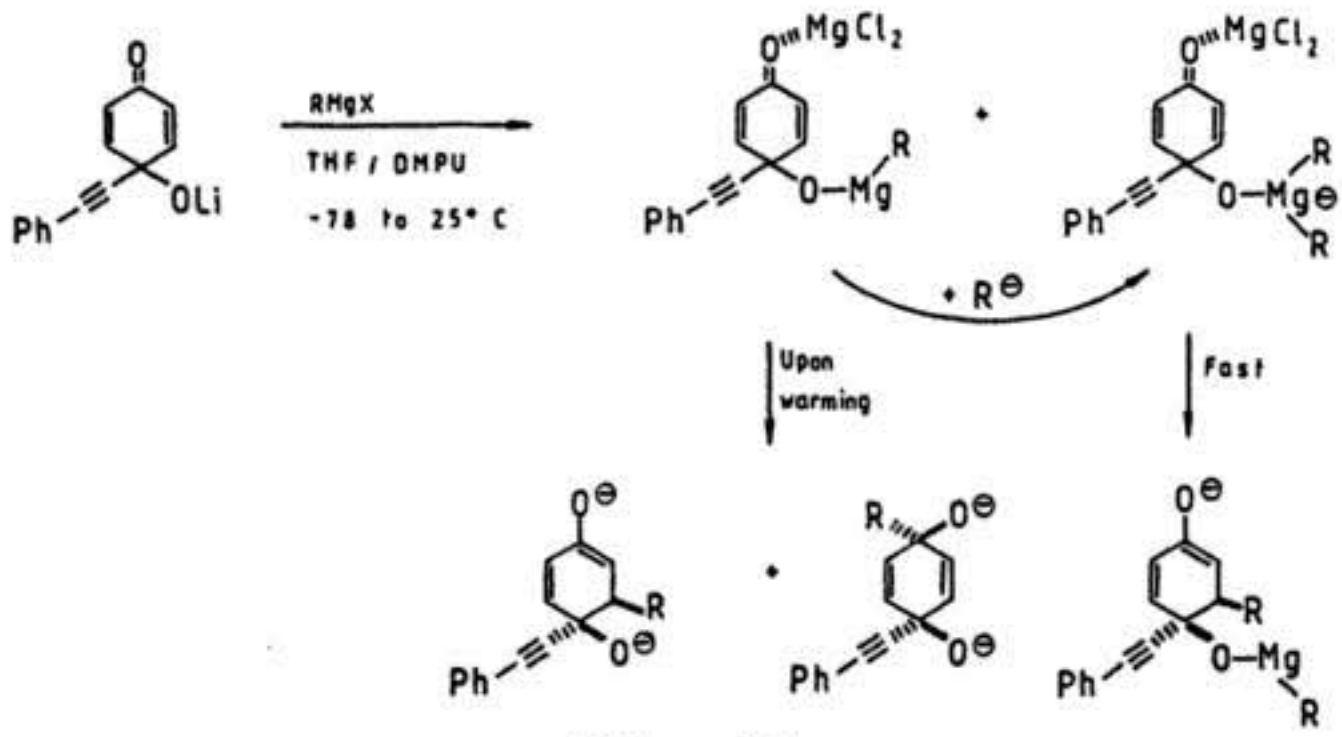


Figure 1 Relative reactivity of ethylmagnesium compounds toward 1-hexyne in diethyl ether on addition of 1,4-dioxane to a solution of C_2H_5MgBr. (From Ref. 28.)



Scheme 14

Both 1,2- and 1,4-addition take place in this reaction and the selectivity of the reaction seemed to "hinge primarily on how the various reaction constituents affect the position of the Schlenk equilibrium," as the authors put it.

The progress of the reaction of the quinol alkoxide and methylmagnesium chloride at −78°C was followed over several hours. Within 5 min the reaction had proceeded to 40–50% completion, with extremely high selectivity (1,4 addition/1,2 addition = 95:1). No

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further change was observed over a period of 24 hr. After the solution was warmed to approximately 25°C, further reaction occurred at a much slower rate and with much lower selectivity (1,4 add./1,2 add. = 5.5:1).

On grounds of additional evidence, the authors concluded that the reactive intermediate is not the complex of a quinol alkoxide and a Grignard reagent. Instead, a ternary complex was proposed that consisted of the quinol alkoxide, a dialkylmagnesium, and a Lewis acid (such as the magnesium halide). By, what the authors named "manipulation of the Schlenk equilibrium," a confirmation of their conclusion was obtained.

Methylmagnesium chloride gave a 13.0:1 selectivity ratio, whereas pure dimethylmagnesium, although much more reactive, exhibited only modest selectivity 4:1 to 6:1). When a solution of dimethylmagnesium was employed that contained 10% magnesium chloride, both a high reaction rate and high selectivity (30:1) were observed. When more magnesium chloride was added the Schlenk equilibrium was shifted to that of the normal Grignard solution and a normal selectivity was attained.

Contrary to what had been observed for the reaction of the two methylmagnesium species in the reaction of the Grignard solution prepared from bromomethane and magnesium with 2-methylbenzophenone [27], the LANA reactions of the two methylmagnesium species do, indeed, have different results, such that the overall outcome of the reaction is determined by the position of the Schlenk equilibrium.

A more systematic search for such differences in reactivities of both the symmetric organomagnesum species and the Grignard reagent would lead to interesting information about the influence of the Schlenk equilibrium on the course of reactions of Grignard compounds.

5. *Solvent and Reactivity*

The solvent in which reactions of Grignard compounds are performed may have a considerable effect on the progress and the outcome of such reactions. This should not come as a great surprise, since the organomagnesium compounds generally are strongly solvated. Before reaction with a substrate molecule can take place, probably one (or more) solvent molecules must be replaced from the complex with the organomagnesium compound. Changes in the properties of the solvent may then cause a change in the rate of the reaction which, in turn, may cause secondary reactions to occur that otherwise would not take place, leading to different products. Furthermore, among other parameters, the degrees of association of the different magnesium species in solution as well as the Schlenk equilibrium are also determined by the solvent, and changes in association may influence the progress of the reaction.

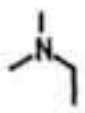
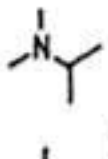
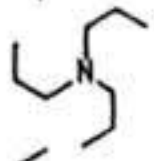
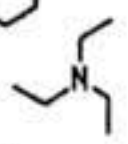
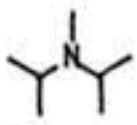
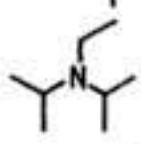
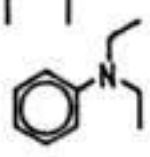
The variation in solvents that are available for synthesis with the aid of organomagnesium compounds is rather limited; most of the research in this field is done in ethereal solvents, such as diethyl ether, di-*n*-butyl ether, tetrahydrofuran, furan, anisole, and 1,2-dimethoxyethane. Some amines, such as triethylamine, dimethylaniline, and a few others of that type, have also been applied.

In this section some of the changes in the rates of reaction, as well as in the product composition, will be discussed and, when possible, the theoretical implications of these changes will be clarified.

Solvent effects were studied in the late 1950s for reactions of alkylmagnesium compounds with 1-hexyne in diethyl ether. These reactions have already been discussed several times in this and in Chapter 11 (see Scheme 10) [22a]. When 1.0 molEq triethylamine was added to the reaction mixture, the relative reactivity of methylmagnesium iodide toward 1-hexyne, which is 7 (the reactivity of ethylmagnesium bromide was arbitrarily set

Materiał chroniony prawem autorskim

Table 7 Relative Reactivities of Ethyl Grignard Reagents with 1-Hexyne in Diethyl Ether in the Presence of Tertiary Amines [31]

Amine	C_2H_5MgBr	C_2H_5MgI
	100	91
	144	269
	457	938
	243	-
	460	901
	493	1.010
	606	1.400
	314	466
	145	152
	125	-

on 100) increased with a factor of almost 200 (the relative rate became 1350). On the addition of the same amount of triethylamine to a reaction mixture containing ethylmagnesium bromide, the relative reactivity increased much less dramatically (from 100 to 840). There was no change in the reactivity of diethylmagnesium (relative reactivity 300) on addition of triethylamine. Further work on this reaction with various amines [31] showed that the increase in relative rates of reaction of 1-hexyne with ethyl Grignard reagents (bromide as well as iodide) increased with decreasing numbers of α-hydrogen atoms (Table 7).

This, according to the authors,

> may be attributed to an increase in the inductive effect (electron release) resulting from the substitution of alkyl groups in the α-carbon atom. Another possible explanation is that it may be caused by anionic hyperconjugation, "hydrization." [31].

In Scheme 11 this hyperconjugation has been shown for a carbanion.

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Table 8 Rates of Reactions of Grignard Reagents (RMgBr) with Phenylacetylene (Phenac) in Diethyl Ether (Et_2O) and in Tetrahydrofuran (THF) [32]

Reagent	Solvent	[RMgBr]	[Phenac]	T (°C)	$k_2 \times 10^4$ (L mol^{-1} sec^{-1})
PhMgBr	Et_2O	0.19	0.19	25	0.35
		0.21	0.20	25	0.40
		0.16	0.34	25	0.30
		0.20	0.12	25	0.38
	THF	0.24	0.23	15	172
		0.23	0.23	15	140
EtMgBr	Et_2O	0.21	0.21	25	2.92
		0.21	0.21	25	3.14
		0.20	0.39	25	2.84
		0.20	0.10	25	2.87
		0.20	0.40	25	2.87
		0.20	0.10	25	2.98

Source: Ref. 32.

> When applied to tertiary amines, as the number of α-hydrogens decreases in a series of amines, the number of hydrization possibilities would decrease and the electron pair on the nitrogen would become more available for reaction coordination. The reactivity toward a Lewis acid, magnesium in a Grignard reagent, would therefore increase until the alkyl groups introduce a steric factor [31].

According to the results presented in Table 7 this steric factor becomes important in methyldiisopropylamine. Further substitution of methyl groups, as in ethyldiisopropylamine, causes a significant reduction of the reactivity (for ethylmagnesium bromide from 314 to 145). Also, the small change in the relative reactivity of ethylmagnesium bromide after the addition of an aromatic amine is due to the weak basicities of such amines.

Interesting publications of work undertaken in this field of reactivity by a research group in (what at that time was part of) the USSR, unfortunately, was published mainly in rather inaccessible journals. The rates of reaction of phenylacetylene with ethyl- and phenylmagnesium bromide were measured in diethyl ether and in tetrahydrofuran, respectively [32]. The results, presented in Table 8, clearly show the dramatic change in the second-order rate constants, when diethyl ether is replaced by tetrahydrofuran as the solvent. The same effect had been found in 1968 by others [33] for the reaction of benzylmagnesium chloride with phenylacetylene: at 0°C the second-order rate constant ($k_2 \times 10^4$; L mol^{-1} sec^{-1}) was 0.008 in diethyl ether and 84 in tetrahydrofuran, a change by a factor of (more than) 10 thousand.

The reactions of diarylmagnesium compounds with 1-alkynes are about 10 thousand times faster than those of the corresponding Grignard reagents [34]. The following rates (L mol^{-1} sec^{-1}) were found for the reaction of diphenylmagnesium with 1-hexyne: 13.4 in tetrahydrofuran, 11.6 in diethyl ether, and 8.8 in di-*n*-butyl ether. The authors did not comment on this phenomenon.

Another striking result of this work was that, on going from one solvent to the other, only minor changes were found in the reaction rates. The authors concluded that

> Apparently, the increasing influence of the donor molecule, coordinated with the magnesium atom, on the nucleophilicity of the phenyl radical is compensated to a large extent by its

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Table 9 Percentages of Radical Anions Formed in Reactions of Dibenzylmagnesium (0.375 *M*) with Fluorenone (0.345 *M*) in Various Solvents [35]

Solvent	Signals	Radical anions (%)
$(C_2H_5)_2O$	Very weak and unstable	–
THF	Weak but stable	<0.1
DME	Rather stable	0.5
$(C_2H_5)_3N$	Unstable	>0.2
HMPA[a]	Strong and stable	36

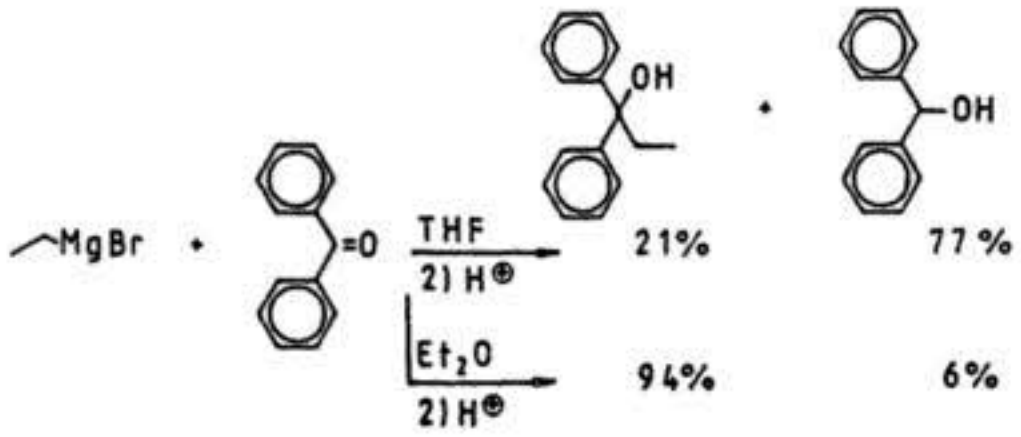
[a]HMPA, hexamethylphosphoric acid triamide.

influence on the electrophilicity of the magnesium atom, i.e., by preventing coordination of the latter with the acetylenic compound.

After some comments on what was named "the medium polarity effect" and "the medium dielectric constant" the authors came to the following conclusions: such nucleophilic addition reactions of diphenylmagnesium compounds with ketones and metallation reactions of 1-alkynes have some common features. Apparently, they can both be considered as a special case of aromatic electrophilic substitution, differing from (what the authors named) "the classical examples of this reaction," in that the latter one has a more pronounced reagent-like transition state.

A strong solvent effect in a completely different reaction was observed in 1968 [35] in a study of single-electron transfer (SET) reactions of organomagnesium compounds with ketones (see also Chapter 11, Section II.A). In some instances the formation of stable radical anions was observed in the reaction of dibenzylmagnesium with fluorenone. Table 9 presents the results. The authors concluded: "One notes that those solvents that strengthen the ionic character of magnesium, promote the formation of the ketyl radical anions." Furthermore, from the results obtained with other organomagnesium compounds, methyl < ethyl < *i*-propyl < *t*-butyl < benzyl, the authors concluded that the increasing charge on the carbon atom bearing the magnesium favors the radical formation.

Apart from these SET reactions, solvent effects in reactions of organomagnesium reagents with carbonyl compounds have been studied rather extensively. The reaction of ethylmagnesium bromide with benzophenone (Scheme 15) in diethyl ether yields 94% of the expected addition reaction product, 1,1-diphenyl-1-propanol, and 6% benzhydrol, resulting from a reduction reaction of the Grignard reagent [36]. In tetrahydrofuran this reaction yields 21 and 77%, respectively, of both products.



Scheme 15

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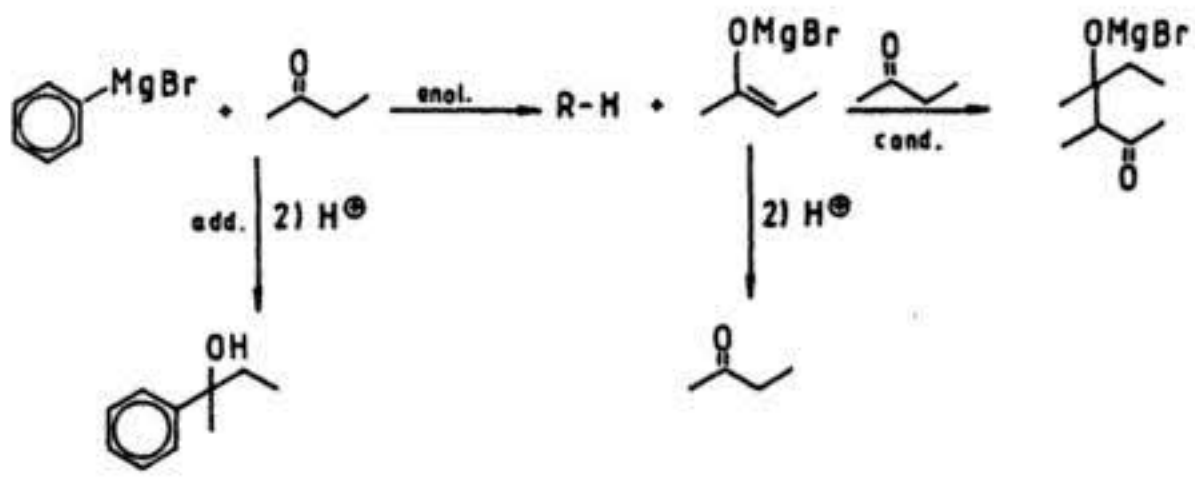
Table 10 Results of Reactions (% Yield) of *n*-Propyl- and *Iso*propylmagnesium Bromide with Benzophenone in Tetrahydrofuran (THF), Diethyl Ether (DEE), and 1,2-Dimethoxyethane (DME) [15b]

	n-PropMgBr		*iso*PropMgBr		
Solvent	Add.	Red.	Add.	Red.	Subst.
THF	17	83	58	19	18
DEE	32	68	40	26	30
DME	22	78	50	30	15

The reactions of *n*-propyl- and isopropylmagnesium bromide with (substituted) benzophenone(s) in diethyl ether, tetrahydrofuran, and 1,2-dimethoxyethane were carefully studied in 1991 [15b]. Several products were obtained. With *n*-propyl Grignard reagent, these were the products of the addition as well as of the reduction reaction, both taking place at the carbonyl group. With the isopropyl Grignard reagent, besides these two products, a third one was observed: the aromatic ring-substitution reaction product (see Scheme 5 [9]). The results, presented in Table 10, show that the ratios of these products were solvent-dependent.

As mentioned in Section II.A.2, the authors attributed these results to the degree of association of the various magnesium species in solution (see also Chapter 11 for the mechanistic aspects of this reaction).

Another side reaction, caused by changes in the solvent composition, was studied in 1980 (in the former USSR) and, unfortunately, was also published in rather inaccessible journals [37]. The reactions of phenylmagnesium bromide with the aliphatic ketones, 2-butanone and 3,3-dimethyl-2-butanone (methyl-*tert*-butyl ketone), were studied. Besides the carbonyl addition reaction, leading to a tertiary alcohol, enolization also takes place with this type of ketones. The enolate, on hydrolysis, yields the starting ketone; however, before hydrolysis, in the reaction mixture of the Grignard reagent and the ketone, the enolate can react further with the ketone to form a condensation product (Scheme 16).

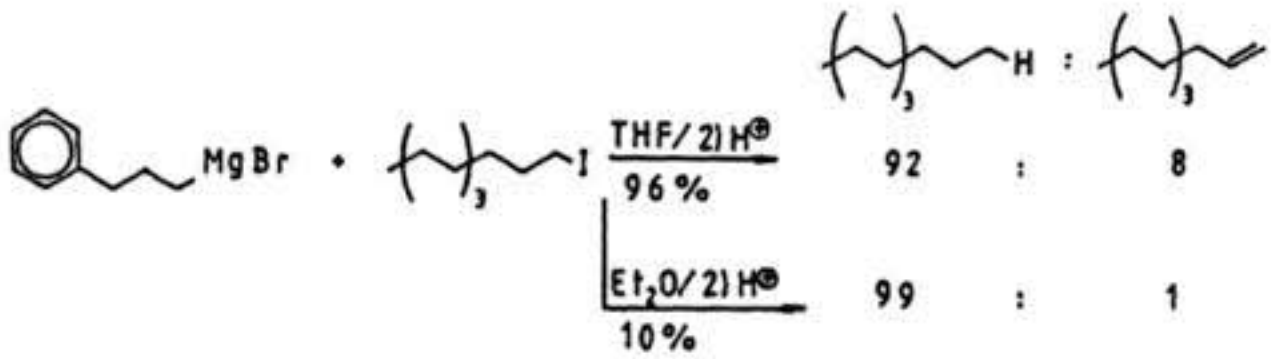


Scheme 16

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The rates k_{enol}/k_{add} were 7 and 8, respectively, for the reactions of phenylmagnesium bromide with 2-butanone and 3,3-dimethyl-2-butanone, but on the addition of large amounts of triethylamine (150 and 90%, respectively, for the two reactions) these rates were almost doubled: from 7 to 16 and from 8 to 14. The general conclusion from this work was that triethylamine did not change the rate of the addition reaction, but doubled the rate of the enolization reaction. Still, the influence of the amine on the rates of reactions were much smaller than for the reactions with 1-hexyne, as listed in Table 7.

Another reaction with a strong solvent effect is the reduction of primary halides with the aid of Grignard reagents. The reaction of 3-phenyl-1-propylmagnesium bromide with iododecane [38] (in the absence of catalysts) yielded 96% of R–H and R(–H) in tetrahydrofuran as the solvent, but only 10% of the same products in diethyl ether (Scheme 17). Although an extensive study of the mechanistic aspects of this reaction (including the effect of palladium catalysts) was made, no comments were given on the origin of the significant solvent effect.



Scheme 17

The following conclusions can be drawn from this section on solvent effects.

During the last three decades, extensive and systematic studies have been published on the composition in solution of organomagnesium compounds, in general, and of Grignard reagents, in particular. Various solvents were used in such studies. Furthermore, studies were made of the effects of solvents on the course of the reactions of these reactive species. In Chapter 11, it was made clear that the mechanistic aspects of such reactions are still not fully understood and, as a consequence, this implies that many aspects of the role of the solvent on the course of these reactions still require further study. In fact, in only one specific case was a relation suggested between the structure of the organomagnesium species in solution and the outcome of its reactions: monomeric species tend to yield less addition reaction products with ketones and more reduction reaction products than do di- or (perhaps) even polymeric species. The reaction mechanism requires the presence of a second magnesium species (see Table 10).

It is hoped that more systematic studies of both the composition of the solutions and the outcome of the reactions will ultimately lead to a better understanding of the effects that solvents play in these processes.

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13

The Composition of Grignard Reagents in Solution: The Schlenk Equilibrium and Its Effect on Reactivity

KEVIN C. CANNON

Elf Atochem North America, Inc., King of Prussia, Pennsylvania

GRANT R. KROW

Temple University, Philadelphia, Pennsylvania

I. INTRODUCTION

The composition of the Grignard reagent has intrigued researchers since its discovery in 1900. Both Ashby [1] and Wakefield [2] have written excellent reviews about the early history concerning the determination of Grignard reagent composition. Abegg, in 1905, suggested the possibility of an equilibrium to describe the composition of the Grignard reagent in an ether solution, with R representing the alkyl group and X representing a halide [3].

$$2RMgX \leftrightarrows R_2Mg + MgX_2$$

This equilibrium was later expanded by Schlenk and Schlenk to include molecular association of the Grignard reagent, and this equilibrium is now commonly referred to as the Schlenk equilibrium [4].

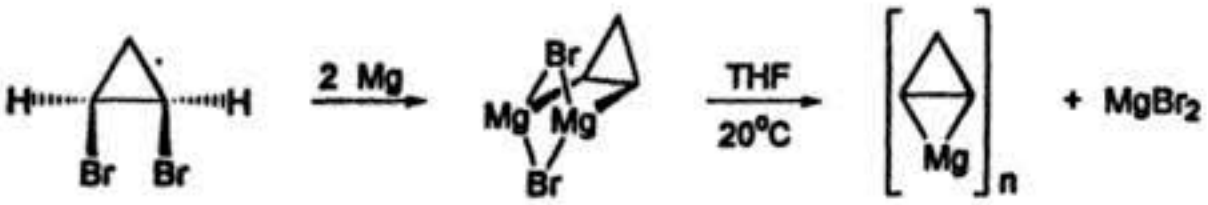
$$2RMgX \leftrightarrows R_2Mg + MgX_2$$

$$R_2Mg + MgX_2 \leftrightarrows R_2MgMgX_2$$

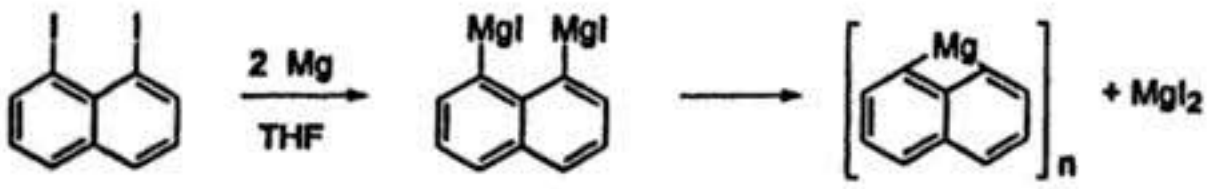
The addition of 1,4-dioxane to certain Grignard reagents results in the precipitation of an MgX_2 complex, resulting in essentially all of the halogen being removed from solution

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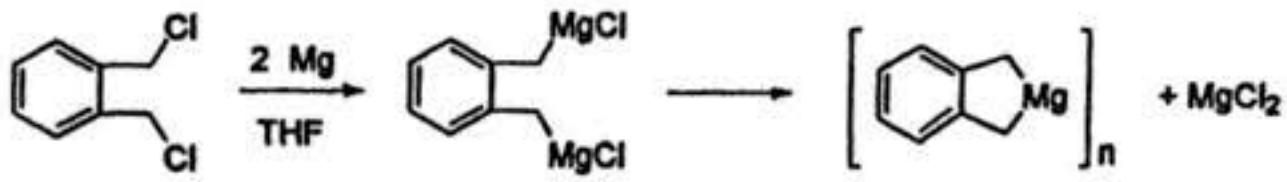
[4]. The authors believed that the addition of 1,4-dioxane and the subsequent precipitation of MgX_2 could be used to determine the equilibrium composition, implying that the rate of exchange among components in solution was slow. However, later investigations demonstrated that the equilibrium was dynamic, by showing that the amount of MgX_2 precipitated was a function of time and mode of addition [5,6]. The MgX_2 precipitates from solution as a bis-dioxane complex, resulting in a shift of the equilibrium and the formation of R_2Mg. This precipitation technique is often employed to selectively synthesize dialkyl Grignard reagents R_2Mg [7–9]. The reactivity of isolated R_2Mg may differ significantly from the reactivity of the equilibrium composition of a Grignard reagent; some differences in reactivity are discussed later in Section III. Alternatively, precipitation of the dialkyl Grignard reagent while MgX_2 remains in solution can also shift the equilibrium. For example, 1,2-, 1,3-, and 1,4-di-Grignard reagents, synthesized from the reaction of the corresponding dihalide compound and magnesium, form cyclic bifunctional organomagnesium compounds that are insoluble in tetrahydrofuran (THF) [10–13]. These cyclic bifunctional organomagnesium compounds (**1–3**) are assumed to be polymeric.



1



2



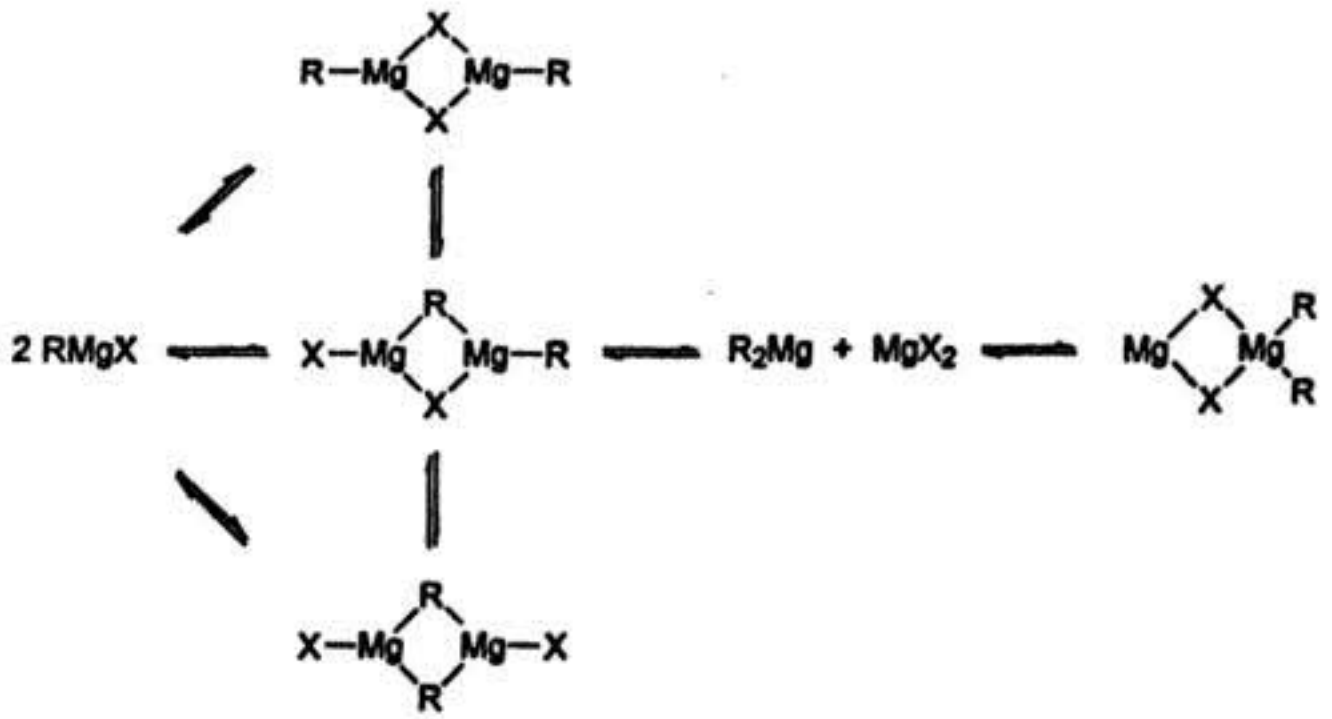
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A more comprehensive representation of the Schlenk equilibrium is shown in Scheme 1. *Ab initio* molecular orbital calculations for R = Me and X = Cl and Br were performed to determine which species in Scheme 1 were thermodynamically preferred [14]. In the absence of solvents, the various $(MeMgCl)_2$-bridged dimers were all significantly more stable than the corresponding monomers. For the reaction

$$2MeMgCl \leftrightarrows (MeMgCl)_2$$

the ΔH^0 ranged from -24.8 to -37.1 kcal/mol, and ΔG° ranged from -15.8 to -33.0 kcal/mol. On the other hand, in the presence of the solvent dimethyl ether, calculations showed that the dimerization process was nearly thermoneutral; ΔG^0 was -5.1 kcal/mol. The authors suggested that the relatively small negative ΔG^0 value indicated that the position of the equilibrium could easily be shifted in Scheme 1 to favor the presence of monomers by altering the halide, the alkyl group, or the solvent. The ΔH^0 and ΔG^0 for

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Scheme 1

the reaction

$$2MeMgCl \leftrightarrows (Me)_2Mg + MgCl_2$$

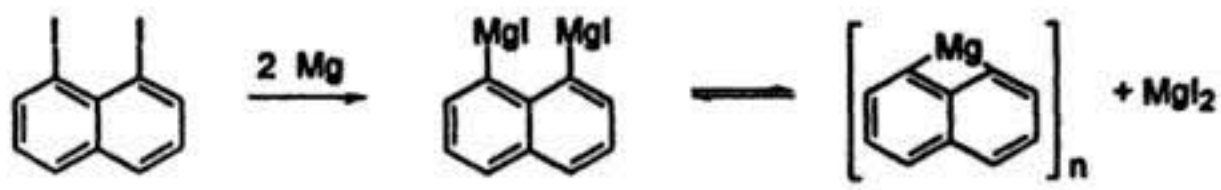
was calculated to be +5.7 and +4.5 kcal/mol, respectively. Substitution of Br for Cl yielded corresponding ΔH^0 and ΔG^0 values 1.3 kcal/mol less endothermic. Calculations that included dimethyl ether solvation also indicated a slightly more favorable reaction.

The results of the *ab initio* calculations corroborate some of the experimental results from preceding investigations of Grignard reagent composition. These investigations have shown that, in addition to the solvent, the alkyl group (R), and halide (X), the equilibrium in Scheme 1 is affected by concentration and temperature as well. Experimental results that exemplify the factors that affect Grignard reagent composition and reactivity are discussed in the following.

II. FACTORS AFFECTING THE COMPOSITION OF GRIGNARD REAGENTS IN SOLUTION

A. Solvent and Concentration Effects

The equilibrium in Scheme 1 and, therefore, the composition of Grignard reagents in solution, is a function of the solvent and concentration. In some instances, the composition may vary between solvents because of a solubility effect. An insoluble constituent of the equilibrium may precipitate, shifting the equilibrium to a composition different from that observed if all constituents were soluble. Such is the case with di-Grignard reagent **5** [12]. When 1,8-diiodonaphthalene **4** was reacted with magnesium in 2-methyltetrahydrofuran (2-MeTHF) at room temperature, a homogeneous solution of **5** was formed in 90% yield. However, when the reaction was performed in THF, sparingly soluble MgI_2 precipitated immediately. As a result, the THF solution contained **2** and unreacted **4**.

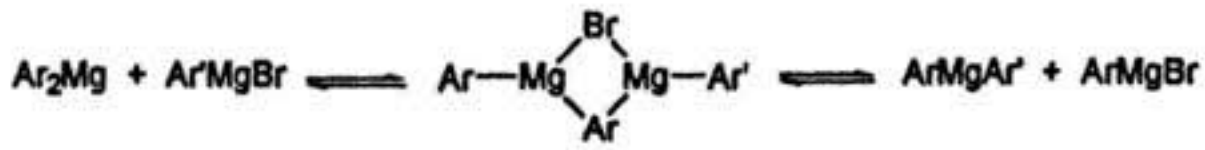


4 **5** **2**

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Solvent may also alter the composition of Grignard reagents in the absence of a solubility effect. A comprehensive ebullioscopic investigation of a variety of Grignard reagents (methyl, ethyl, *i*-propyl-, *t*-butyl-, and phenylmagnesium halides) showed that the degree of association is profoundly affected by several factors, including solvent [15]. All alkyl- and arylmagnesium chlorides, bromides, and iodides were determined to be monomeric complexes in THF over a wide concentration range (0.1–3.5 *M*). In diethyl ether, however, the alkyl- and arylmagnesium bromides and iodides were monomeric at concentrations less than 0.1 *M*. A general increase in association was observed with concentration; at 0.3 *M*, solutions are approximately half monomeric and half dimeric [16]. Between concentrations of 0.5 and 1.0 *M*, complexes are dimeric. Alkylmagnesium chlorides in diethyl ether form stable dimers, with the association being insensitive to concentration changes. The nature of the associated Grignard reagent in diethyl ether was characterized by ^{1}H-NMR studies of methylmagnesium bromide and iodide [17,18]. Bridging methyl signals were not observed at ambient temperatures, leading the authors to conclude that halogen is the predominant bridging group in the associated complexes. Bridging methyl signals were observed in trace quantities only after cooling to $-100°C$ for methylmagnesium bromide and to $-40°C$ for methylmagnesium iodide [18].

The difference in Grignard reagent association behavior in THF and diethyl ether is attributed to the relative Lewis basicities of the two solvents. Solvent–metal bonding competes with the bridging characteristics of the halide, and THF competes more favorably than diethyl ether. The relative donicities of THF and diethyl ether are 20.0 and 19.2 kcal mol^{-1}, respectively [19]. However, methylmagnesium fluoride and methylmagnesium *n*-butoxide are dimeric in THF, owing to the stronger bridging characteristics of fluoride and alkoxide groups compared with the larger halides [20,21]. The relation between solvent basicity and association was further demonstrated by ^{1}H/^{19}F-NMR studies of the rates of exchange of aryl groups between bisarylmagnesium complexes **6**, **6′** and the corresponding arylmagnesium bromide complexes **7**, **7′** [22]. The equilibration of these complexes requires the intermediacy of an associated complex, depicted as structure **8**:



6 **7** **8** **6′** **7′**

Rapid exchange of the aryl groups was observed spectroscopically in both benzene and diethyl ether. The addition of *NNN′N′*-tetraethylethylenediamine (TEED) considerably reduces the rate of aryl group exchange. This observation was attributed to strong coordination of TEED to the monomeric complexes, thereby inhibiting formation of the associated intermediate **8** [1]. The donicity of TEED exceeds 55 kcal mol^{-1} [19].

The equilibrium between monomeric complexes in solution,

$$R_2Mg + MgX_2 \leftrightarrows 2RMgX$$

is also a function of the solvent. Equilibrium constants of this reaction for a variety of Grignard reagents have been reviewed [23]. Equilibrium constants for selected alkyl- and arylmagnesium bromides in THF and diethyl ether are presented in Table 1. The numerical values were determined by several authors, with varying degrees of accuracy, using calorimetric, kinetic, and spectroscopic methods. Even with these limitations, the data suggest some clear trends. In THF, equilibrium constants range from 3.5 to ~9, whereas

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Table 1 Effect of Solvent on the Equilibrium Constant (K) and Enthalpy (ΔH) for the Interconversion of Monomeric Complexes, $R_2Mg + MgX_2 \leftrightarrows 2RMgX$

Grignard reagent	Solvent	K	ΔH (kcal mol^{-1})	Method of analysis	Ref.
MeMgBr	THF	3.5–4.0		IR, NMR	18, 24
	Et_2O	~320		Calorimetric	25
EtMgBr	THF	5.09	6.10	Calorimetric	26
	Et_2O	~480	−3.74	Calorimetric	27
BuMgBr	THF	~9	3.4	Calorimetric	28
	Et_2O	~10^3	−3.2	Calorimetric	28
PhMgBr	THF	3.77–4.0	2.82–3.2	Cal., NMR	22, 26
	Et_2O	55–62	−2.02	Calorimetric	27

in diethyl ether, they range from 55 to ~10^3. The values of ΔH in THF are positive, whereas the values in diethyl ether are negative. It was suggested that the difference in the equilibrium in THF and diethyl ether is due to the increased coordination number of the magnesium species in THF; the dominant effect was associated with the solvation of magnesium dibromide [23]. The alternative equilibria, shown as follows, were suggested by the authors to emphasize the solvent dependency of the interconversion of monomeric magnesium complexes.

$$R_2Mg(THF)_2 + MgX_2(THF)_4 \leftrightarrows RMgX(THF)_2 + RMgX(THF)_3 + THF$$

$$R_2Mg(Et_2O)_2 + MgX_2(Et_2O)_2 \leftrightarrows 2RMgX(Et_2O)_2$$

According to the equilibrium constants in Table 1, and others that were reviewed, all three monomeric complexes (R_2Mg, MgX_2, and RMgX) are present in appreciable concentration in THF. The simultaneous existence of R_2Mg and MgX_2 in solution has been challenged, based on the reactivity of magnesium dichloride in THF [29]. An alternative equilibrium in THF proposed by the authors (shown below) requires the presence of dimeric complexes, which have not yet been detected in association investigations.

$$4RMgX(THF)_n \leftrightarrows [(THF)_4Mg(\mu\text{-}Cl)_2MgR_2] + [RMg_2(\mu\text{-}Cl)_3(THF)_5]$$

An alternative ionic equilibrium has been more recently proposed, based on the reactivity of magnesium dichloride in THF [30].

$$6RMgCl(THF)_x \leftrightarrows 3R_2Mg(THF)_2 + [MgCl_4]^{2-} + 2[MgCl(THF)_5]^+$$

However, conductance experiments have demonstrated that the concentration of ionic species cannot be very significant, owing to the low conductivities reported for Grignard reagents in ether solutions [1].

Solvent effects were more dramatic for the 1,5-di-Grignard reagent **9** [31]. In THF, the equilibrium constant for conversion of 1,5-di(bromomagnesio)pentane **9** to magnesiacyclohexane **10** and magnesium dibromide was determined as 299 ± 31 ($\Delta H = +2$ kcal mol^{-1}, $\Delta S = +17$ eu). In diethyl ether, the equilibrium lies completely toward 1,5-di(bromomagnesio)pentane **9**.

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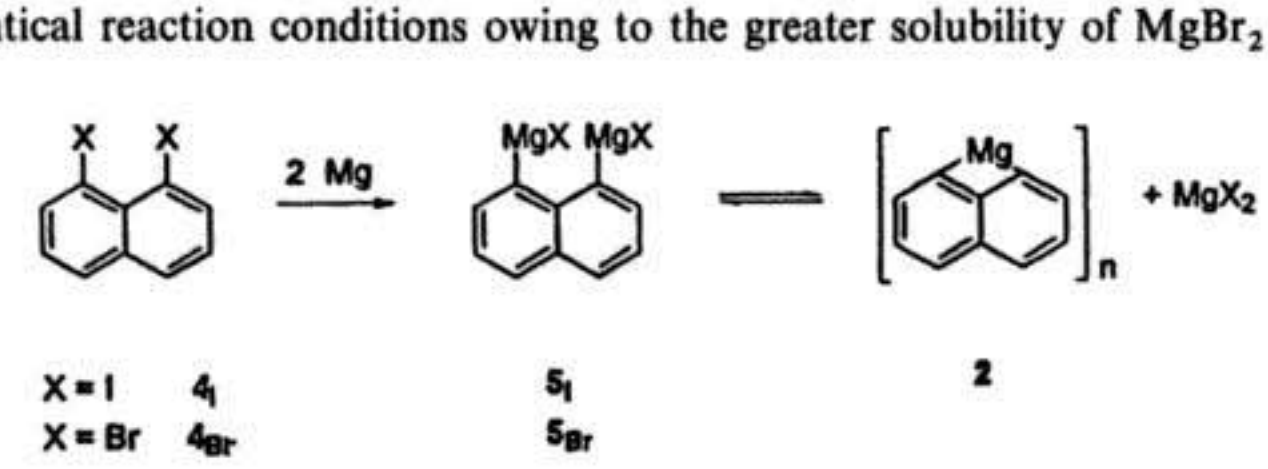
9 **10**

Effects of nonether solvent on the equilibrium between monomeric complexes have received little attention. An ^{1}H-NMR investigation of the effect of *N,N,N′,N′*-tetramethylethylenediamine (TMED) on THF solutions of ethylmagnesium bromide demonstrated little effect on the equilibrium constant at −50°C [32]; however, TMED may inhibit complex association required for reequilibration in the same manner that TEED inhibited the formation of **8** in aryl group exchange (see foregoing).

No conclusive data exist concerning the effect of Grignard reagent concentration on the equilibrium between monomeric complexes. An ^{1}H-NMR study of *t*-butyl chloride Grignard reagent in THF showed no detectable changes in equilibrium between 0.12 and 3.1 *M* [18]. Changes in the NMR spectra of more concentrated solutions from the same investigation were interpreted by the authors as resulting from preferential formation of *t*-butylmagnesium chloride (the RMgX component), but no subsequent investigations have addressed this hypothesis.

B. Anionic Nonalkyl Ligand Effects

The composition of Grignard reagents in solution is influenced significantly by the anionic, nonalkyl ligand (ANAL) coordinated to magnesium. The ANALs discussed in this section include halide (X^-), alkoxide (RO^-), and tris(pyrazolyl)hydroborato (η^3-$HB(pz)_3^-$) ligands. Solution composition may be affected by the low solubility of one of the components in Scheme 1, including the low solubility of $Mg(ANAL)_2$. Precipitation of an insoluble complex perturbs the equilibrium, and the composition will change in response to the perturbation. A solubility effect relating to $Mg(ANAL)_2$ can be illustrated by expanding on the previously discussed synthesis of di-Grignard reagent **5** in Section II.A. The halide-free di-Grignard reagent **2** was synthesized in THF from 1,8-di(iodomagnesio)naphthalene $\mathbf{4_I}$ as a result of the precipitation of MgI_2 at room temperature [12]. In contrast, the halide-free di-Grignard reagent could not be synthesized from 1,8-di(bromomagnesio)naphthalene $\mathbf{4_{Br}}$ under identical reaction conditions owing to the greater solubility of $MgBr_2$ in THF.



X = I 4_I 5_I
X = Br 4_{Br} 5_{Br}

2

The effect of ANAL substitution on Grignard reagent association was also mentioned in Section II.A. Associated complexes are believed to bridge predominantly through halide and alkoxide substitutents, based on ^{1}H-NMR studies of methylmagnesium bromide and iodide [17,18]. The degree of Grignard reagent association is determined by competing factors of solvent coordination (donicity) versus bridging characteristics of the ANAL. Fluoride and alkoxide bridging prevails over solvent coordination in both THF and diethyl ether and, as a result, alkylmagnesium complexes with these substituents are dimeric

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Table 2 Effect of Halide on the Equilibrium Constant (K) for the Interconversion of Monomeric Complexes, $R_2Mg + MgX_2 \leftrightarrows 2RMgX$

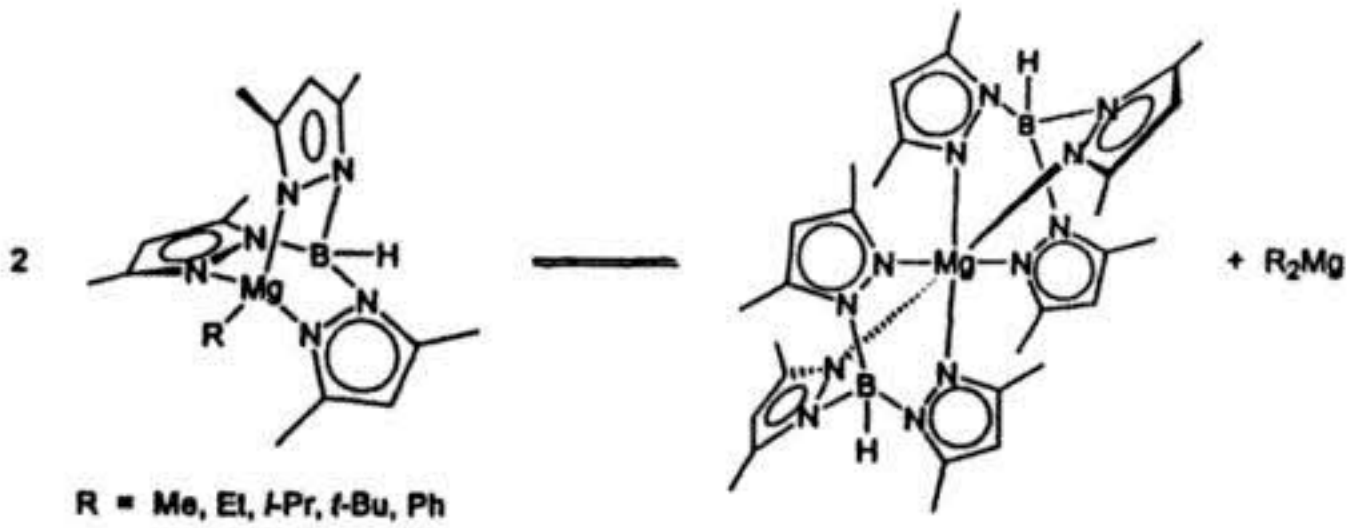
Grignard reagent	Solvent	K	Method of analysis	Ref.
MeMgCl	THF	4.5	IR	24
MeMgBr	THF	3.5–4.0	IR, NMR	18, 24
EtMgCl	THF	5.52	Calorimetric	26
EtMgBr	THF	5.09	Calorimetric	26
PhMgCl	THF	1.66	Calorimetric	26
PhMgBr	THF	3.77–4.0	Cal., NMR	22, 26
EtMgI	Et_2O	$\geqslant 630$	Calorimetric	27
EtMgBr	Et_2O	~480	Calorimetric	27
PhMgI	Et_2O	$\geqslant 15$	Calorimetric	27
PhMgBr	Et_2O	55–62	Calorimetric	27

[20,21]. Alkyl- and arylmagnesium chlorides behave differently in THF and diethyl ether. These Grignard reagents are monomeric in THF and dimeric in diethyl ether [15]. This difference in solution composition is attributed to the greater donicity of THF, compared with that of diethyl ether. The THF coordination competes favorably with chloride bridging, whereas diethyl ether coordination does not. Bromide and iodide bridging are weaker still. Alkyl- and arylmagnesium bromides and iodides are monomeric in THF and, at concentrations lower than 0.1 M, in diethyl ether. As concentration of the Grignard reagent increases from 0.1 to 0.5 M, uniform increases in association factors (i) indicate the gradual increase in dimer concentration [16].

The effect of the halide substituent on the equilibrium between monomeric magnesium complexes is small compared with the previously discussed solvent effects, but the magnitude of this halide effect may itself be solvent-dependent. Table 2 lists equilibrium constants (K) for methyl-, ethyl-, and phenylmagnesium halides in THF and diethyl ether [23]. Comparison of chloride versus bromide substitution of Grignard reagents in THF shows little difference in the equilibrium constants for the reaction, especially when the limitations of comparing numerical values, determined by several authors using different methods of analysis, are considered. In contrast, comparison of bromide versus iodide substitution for ethylmagnesum halide and phenylmagnesium halide in diethyl ether shows a significant difference in the calorimetrically calculated equilibrium constants [27]. However, according to the authors, the equilibrium constants for the iodide-substituted reagents are uncertain, owing to a observed concentration dependence in the analyses. Further investigation is required to quantify the solvent dependency, if any, that exists for the halide effect.

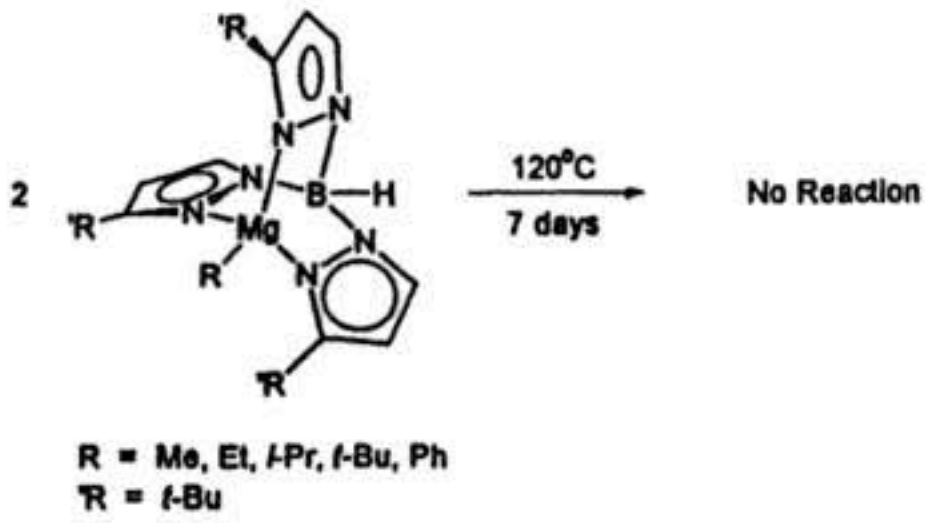
Tris(pyrazolyl)hydroborato (η^3-$HB(pz)_3^-$) ligands have been used to show that sterically demanding ligands can affect the equilibrium between monomeric magnesium complexes [33,34]. The monomeric tris(3,5-dimethylpyrazoyl)hydroboratomagnesium alkyl derivatives **11** are stable complexes at room temperature. When heated to 80–120°C in benzene, these derivatives undergo ligand redistribution to form R_2Mg and the six-coordinate sandwich complex **12**, which was followed by ^{1}H-NMR spectroscopy.

Material chroniony prawem autorskim



11 12

The reactions usually proceeded to approximately 90% completion over a period of days, at which point the authors believe the redistribution reached equilibrium. However, substitution of the tris(3,5-dimethylpyrazolyl)hydroborato (η^3-HB(3,5-Me_2pz)$_3^-$) by the more sterically demanding tris(*t*-butylpyrazoyl)hydroborato ligand (η^3-HB(3-*t*-Bupz)$_3^-$) in magnesium complexes **13** prevents ligand redistribution after 7 days at 120°C.

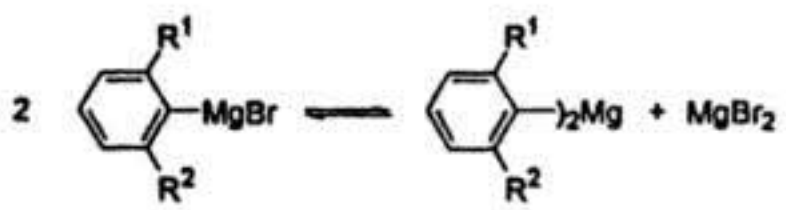


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The η^3-HB(3-*t*-Bupz)$_3^-$ ligand restricts a metal center to a maximum of four coordination sites, whereas the coordination of two η^3-HB(3,5-Me_2pz)$_3^-$ ligands to magnesium does not result in particularly excessive steric interactions [34].

C. Alkyl and Aryl Ligand Effects

Equilibrium constants estimated for the Schlenk equilibria of ethylmagnesium bromide (iodide) and phenylmagnesium bromide (iodide) in diethyl ether are shown in Table 3. Equilibria lie strongly to the side of the alkyl- and arylmagnesium halides for both substituents [27].



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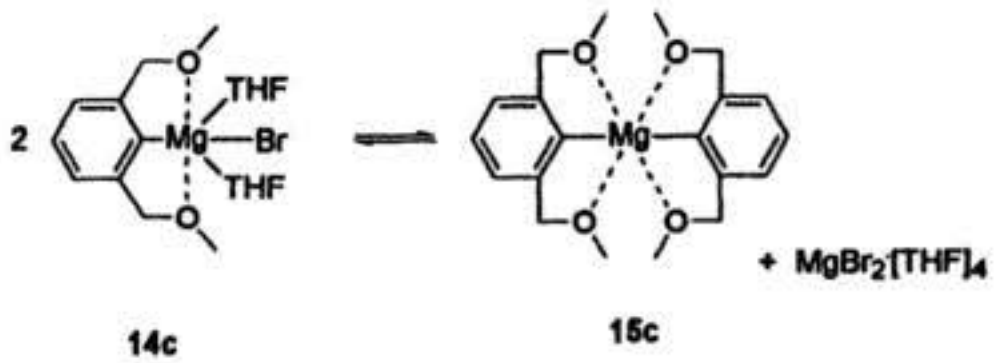
Table 3 Equilibrium Constants (K) for the Reaction $2RMgX \leftrightarrows R_2Mg + MgBr_2$ in Diethyl Ether

R	X	Molarity (M)	K
Et	Br	0.10	0.002
Ph	Br	0.10	0.018
Et	I	0.30	<0.016
Ph	I	0.30	<0.067

Table 4 Equilibrium Constants (K) for the Reaction of **14** $\leftrightarrows$ **15** + $MgBr_2$ in THF

Structure	R^1	R^2	K (298 K)
14a	H	H	0.134
14b	CH_2OMe	H	0.01
14c	CH_2OMe	CH_2OMe	1.061
14d	CH_2CH_2OMe	H	0.10
14e	CH_2NMe_2	H	8.57×10^{-3}
14f	CH_2NMe_2	CH_2NMe_2	6.06×10^{-4}
14g	*p*-CH_2OMe	H	0.352

Equilibrium constants for the Schlenk equilibria of arylmagnesium bromides in THF are shown in Table 4 [35]. Equilibria lie predominantly on the side of the arylmagnesium bromide, except for **14c**, in which there are chelating ether substituents at both the 2- and 6-positions. If we assume a six-coordinate ArMgX species **14c** in the conversion of two molecules of ArMgX into six-coordinate Ar_2Mg **15c** and $MgBr_2[THF]_4$, the number of Mg–O bonds and the number of THF molecules coordinated is the same on both sides of the balanced equilibrium. The 2,6-bis(dimethylaminomethyl)phenylmagnesium bromide **14f** is probably a four-coordinate structure. The steric bulk of the amine function, as well as the ability of the amine functions to satisfy the Lewis acidity of the magnesium atom, precludes further coordination by THF. Since four molecules of THF are needed to solvate the $MgBr_2$, entropy considerations favor the arylmagnesium halide at equilibrium.

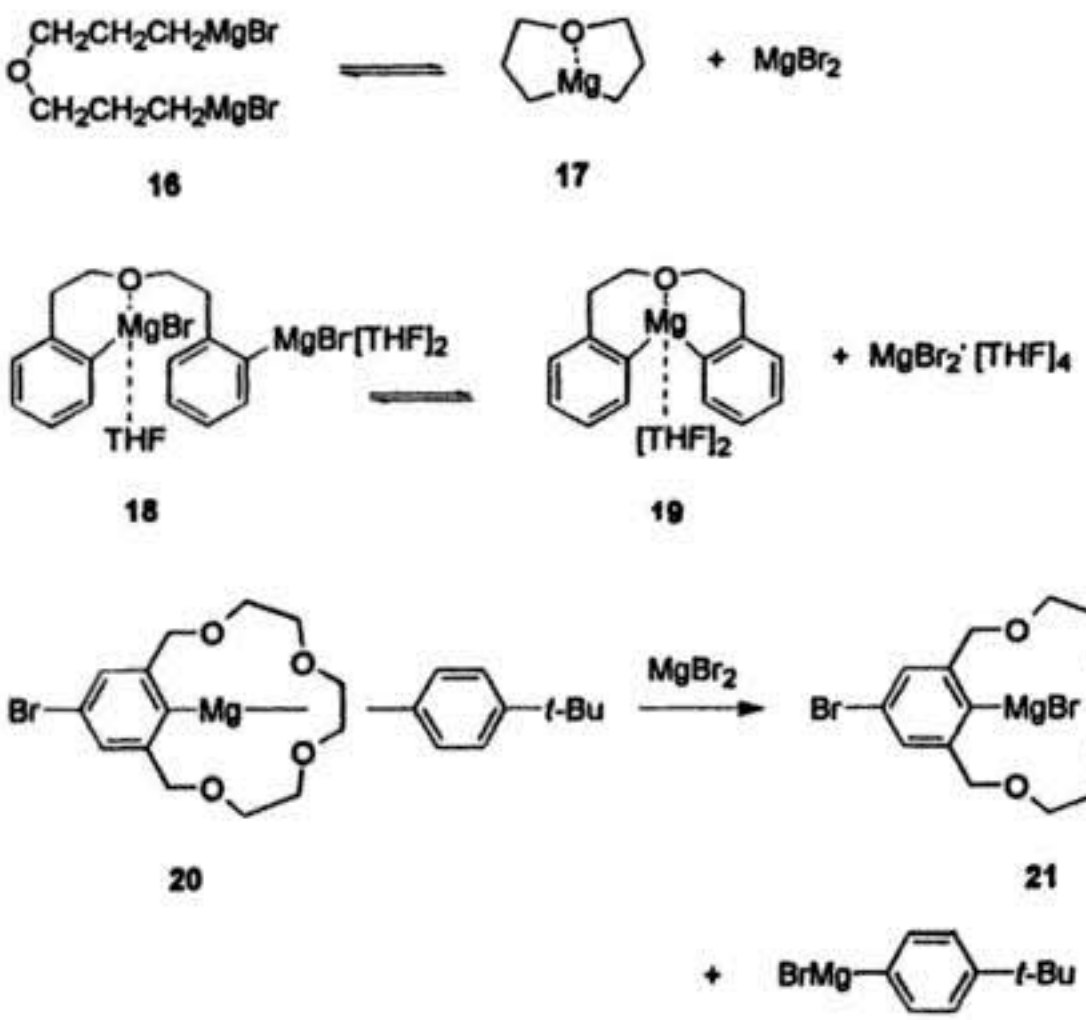


14c **15c**

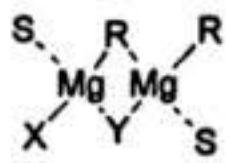
The Schlenk equilibrium of the di-Grignard reagent **16**, is driven completely to the magnesiacycle **17** by the bridging oxygen ligand [36]. The diaryl di-Grignard species **18**

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also exists completely as the magnesiacycle **19** [35]. When the stable nonsymmetric diarylmagnesium species **20** was admixed with magnesium bromide, a quantitative conversion to the crown ether Grignard species **21** and *p*-*t*-butylmagnesium bromide was observed. Coordination of the more positive magnesium is favored, and steric crowding is reduced in **21** [37].



For alkyl Grignard reagents, solvent is the most important factor in determining the position of the Schlenk equilibrium. However, variable-temperature NMR studies indicate that the rate of alkyl exchange is primarily a function of the structure of the alkyl group and is only secondarily a function of solvent [18]. Dilute diethyl ether solutions (0.1–0.3 *M*) of R_2Mg and MgX_2 (R = Et or Ph) react almost instantaneously on mixing to give RMgX and associated species [27]. In a comparison of alkyl groups, methyl group exchange is much faster than *t*-butyl group exchange, and the exchange is faster in diethyl ether than in the higher donicity solvent THF. In the mixed bridged species **22**, considered to be important in alkyl group exchange, branching in the alkyl group (R) would be expected to inhibit formation of the bridge bond. Further consistent with this postulate is the observation that when bis[tris(trimethylsilyl)methyl]magnesium **23** was sealed in an NMR tube with $MgBr_2$ in diethyl ether/benzene (9:1) for 5 hr at 25°C, no change was observed [38].



R = Alkyl
X = Halide
S = Solvent
Y = Halide, Alkoxide, etc.

22

$(SiMe_3)_3C\text{-}Mg\text{-}C(SiMe_3)_3$

23

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D. Temperature Effects

Temperature effects on the composition of Grignard reagents in solution can be either kinetic or thermodynamic. Increasing temperatures usually result in a faster exchange of ligands among magnesium complexes, which translates to faster equilibration rates. An extraordinary example of this kinetic effect is the equilibration of the

Table 6 Equilibrium Constants (K) as a Function of Temperature (T) for the Equilibrium $(t\text{-Bu})_2Mg + MgCl_2 \leftrightarrows 2t\text{-BuMgCl}$ in THF

T(°C)	K
⩾65	7.54
~59	5.00
51	2.36
42	1.74
33	1.12

Source: Ref. 18.

sites of the associated species was absent at 20°C. Therefore, it appears that low temperature shifts the monomer–dimer equilibrium toward the dimeric dimethylmagnesium complex in THF.

The equilibrium between monomeric magnesiacyclohexane **10** and its dimeric complex **24** was shown to be a function of temperature [31].



10 **24**

The mean value for the equilibrium at 28.25°C was 531 ± 81, whereas the mean value at 48.50°C was 223 ± 41. As with dimethylmagnesium, low temperature shifts the equilibrium toward the dimeric complex.

Temperature effects on the equilibrium between monomeric complexes have also been documented. An ^{1}H-NMR investigation of *t*-butylmagnesium chloride in either THF or diethyl ether showed that low temperature shifts the equilibrium toward the dialkyl complex [18].

$$(t\text{-Bu})_2Mg + MgCl_2 \leftrightarrows 2t\text{-BuMgCl}$$

Quantitative results concerning the position of the equilibrium in THF at various temperatures are shown in Table 6. With methyl halide Grignard reagents in THF and diethyl ether attempts to quantify temperature effects by the same technique were frustrated by precipitation of MgX_2 [18]. The interpretation of qualitative effects in diethyl ether were complicated by the existence of additional monomer–dimer equilibria. However, in THF solutions that contain only monomeric complexes, it was postulated that the formation of dimethylmagnesium was partly due to the precipitation of MgX_2 (solubility effect) and partly to a temperature-related shift in equilibrium, based on analyses of the precipitate. The reactivity of methyl chloride Grignard reagent, discussed later in Section III.B, corroborates this interpretation of the temperature effect [40].

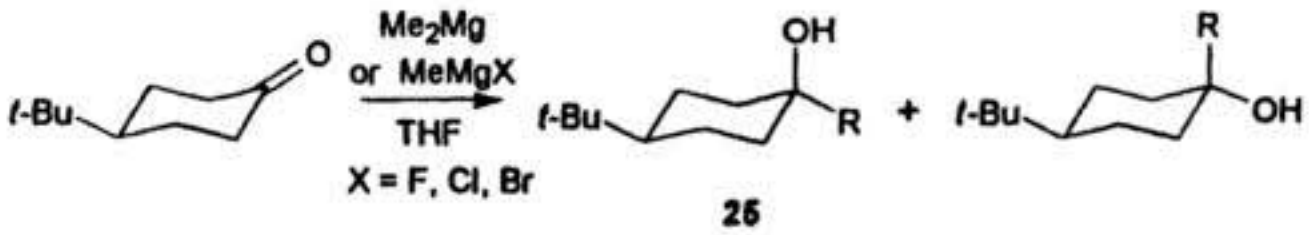
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III. SYNTHETIC USEFULNESS OF SCHLENK EQUILIBRIA MANIPULATIONS

The Schlenk equilibrium of dialkylmagnesium and alkylmagnesium halides, as well as their corresponding associated and solvent-coordinated species, are functions of the substrate, halide, solvent, concentration, and temperature. In this section, examples of manipulating these variables to influence the Schlenk equilibrium to control reaction stereochemistry, regiochemistry, and reactivity are described.

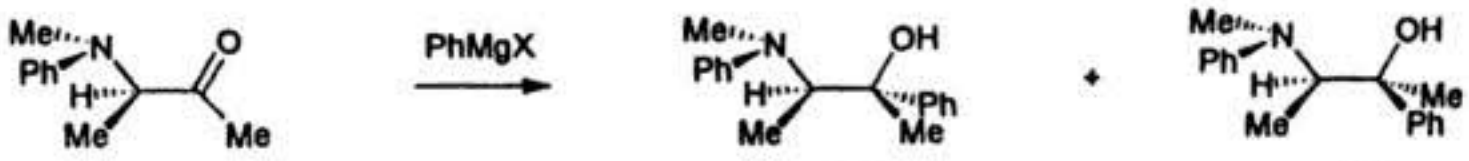
A. 1,2-Carbonyl Additions

The stereochemistry of Me_2Mg or MeMgX (X = F, Cl, or Br) additions to 4-*t*-butylcyclohexanone in THF was independent of reagent and resulted in predominantly equatorial attack to form mainly the axial alcohol product **25** (71–75%) [41]. All magnesium species were monomeric except MeMgF, which is dimeric in THF. A separate stereochemical study in diethyl ether, carried out at concentrations at which Me_2Mg, MeMgBr, and MeMgI exist in equilibrium between monomeric and dimeric species, gave 65, 61, and 54%, respectively, of axial alcohol **25**. Monomeric species MeMgX (0.1 *M*) in diethyl ether give more axial alcohol **25** than the dimeric species (0.8 *M*) [42]; for example, MeMgBr gave a 68:32 preference favoring axial alcohol **25** in diethyl ether under conditions during which the Grignard reagent was associated as the monomer, whereas when MeMgBr was present as the dimeric species, a 62:38 preference for the axial alcohol **25** was observed.



25

In studies of Grignard reagent additions to α-heteroatom-substituted ketones and aldehydes the choice of solvent and the halogen atom of the Grignard reagent have influenced stereochemical outcomes [43–47]. An example is the reaction of the α-aminoketone **26** with phenylmagnesium halides in THF and in benzene. In THF reaction selectivity is relatively independent of halide. In benzene phenylmagnesium bromide and iodide reactions have reversed selectivity. The stereochemical results can be rationalized by considerations of the Schlenk equilibrium of various magnesium species. Grignard reagent additions to **26** are controlled by steric factors and are considered to occur by reaction through either a cyclic model **27** or a dipolar structure **28** [48]. In THF, magnesium complexes are monomeric; the magnesium atoms are coordinated primarily with solvent, and the cyclic model is disfavored. In benzene, which does not coordinate magnesium



26 R*R* R*S*

Solvent	X	R*R*	R*S*	Solvent	X	R*R*	R*S*
THF	Cl	8	92	Benzene	Cl	45	55
	Br	14	86		Br	73	27
	I	8	92		I	85	15

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Cyclic Model

27

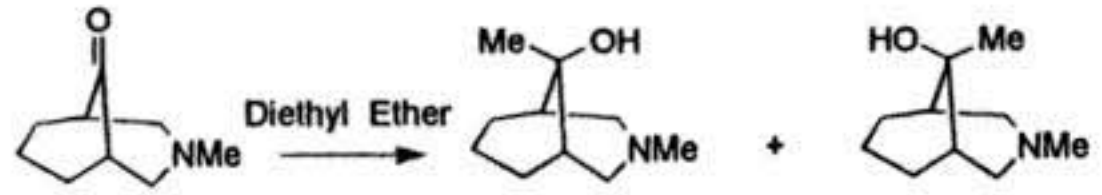
Dipolar Model

28

complexes, the substrate interacts more strongly with the magnesium metal center, and there is a greater percentage of products from the cyclic model.

The concentration of Grignard reagent could also be a factor in the stereochemical outcome. The addition of ethylmagnesium chloride to **26** in diethyl ether was highly selective for the R*R* stereoisomer at concentrations of 0.09–0.72 *M* (81–83%). The chloromagnesium compound is associated even at low concentrations. The stereoselectivity of addition to **26** by ethylmagnesium bromide, which is monomeric at low concentration, is concentration-dependent. Selectivity for the R*R* isomer varied from 74% at 0.70 *M*, where the dipolar model **28** should dominate, to 55% at 0.044 *M*, at which the cyclic model **27** should be more important. The stereoselectivity for reaction of **26** with ethylmagnesium iodide is also concentration-dependent.

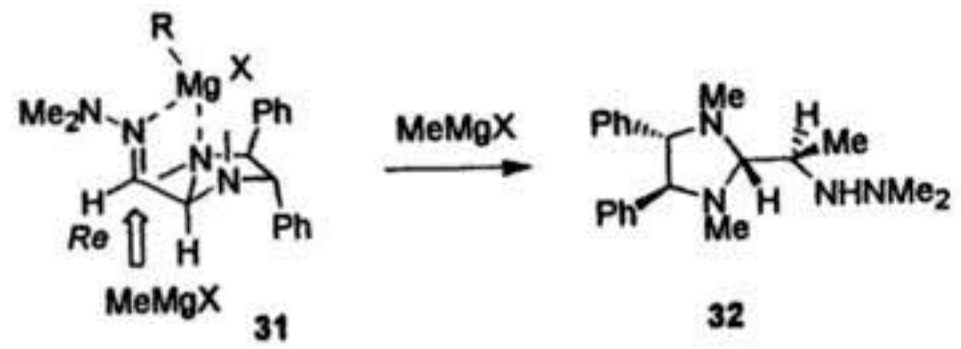
An attempt was made to exploit the propensity for coordination of the magnesium atom of a Grignard reagent with an amine functionality to control the stereochemistry of addition of Me_2Mg or MeMgBr to ketone **29** in diethyl ether. However, both dialkylmagnesium and alkyl halide Grignard reagents gave similar results; amine participation had little effect on the stereochemical outcome. The major product **30** resulted from addition to the less-hindered face of the ketone [49]. The geometry of **29** does not appear favorable for simultaneous coordination of nitrogen and carbonyl oxygen with a magnesium atom.



29 30

Me_2Mg	66 : 34
MeMgBr	61 : 39

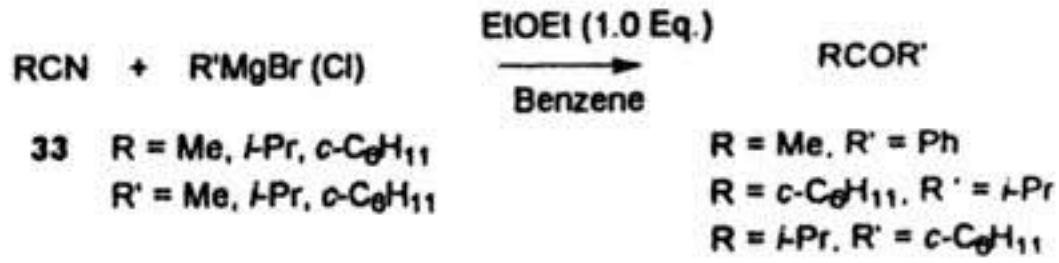
A successful approach to exploit the chelating ability of MeMgBr to control addition to the hydrazone **31** was discovered when the Grignard reaction was carried out in toluene solvent. Since toluene is a noncoordinating and nonpolar solvent, the magnesium coordinates with the substrate to activate the hydrazone and control the facial selectivity, as shown. A 94:6 selectivity for *Re* face attack to give **32** was observed after 1 hr at 20°C. There was no reaction after 48 hr at reflux temperature in THF [50].



31 32

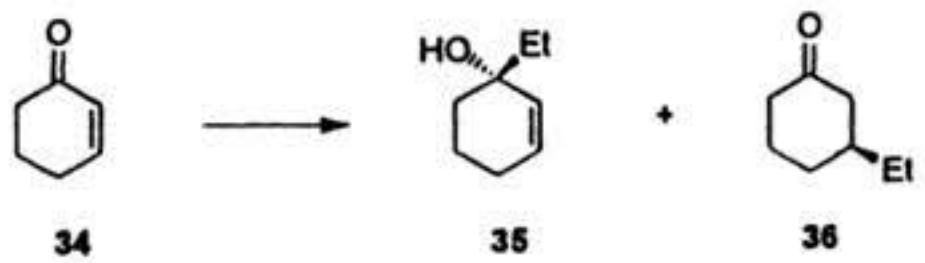
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Much improved yields of ketones, formed by reaction of Grignard reagents with nitriles **33**, have been obtained when reactions were performed in benzene containing 1 Eq of diethyl ether, rather than in diethyl ether alone [51]. Under the modified conditions, it is postulated that reaction occurs through a species in which the nitrile has displaced a diethyl ether solvent molecule from a dimeric Grignard species.

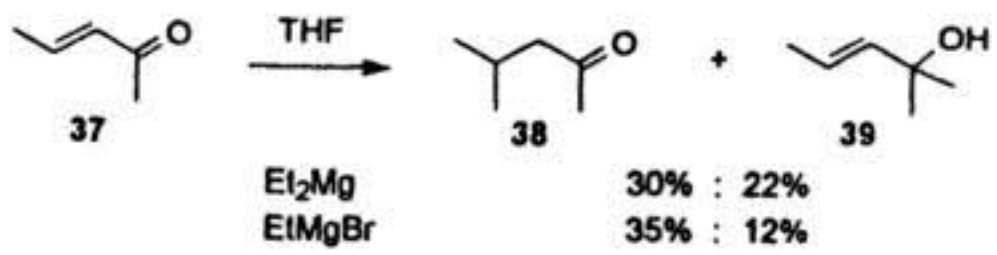


B. Conjugate Additions

The reaction of Et_2Mg or EtMgBr with 2-cyclohexenone **34** has been carried out in various solvents. The dialkylmagnesium reagent added to primarily the carbonyl group in all solvents studied. Dioxane afforded the best yield and greatest regioselectivity for **35**; the ratio of products was similar in THF. EtMgBr or $Et_2Mg/MgBr_2$ gave 53:39 and 54:35 ratios of 1,2-**35**/1,4-**36** addition product in THF, the solvent that provided the maximum amount of conjugate addition. With EtMgBr in hexane or benzene, only traces (2%) of 1,4-addition product **36** were observed [52].



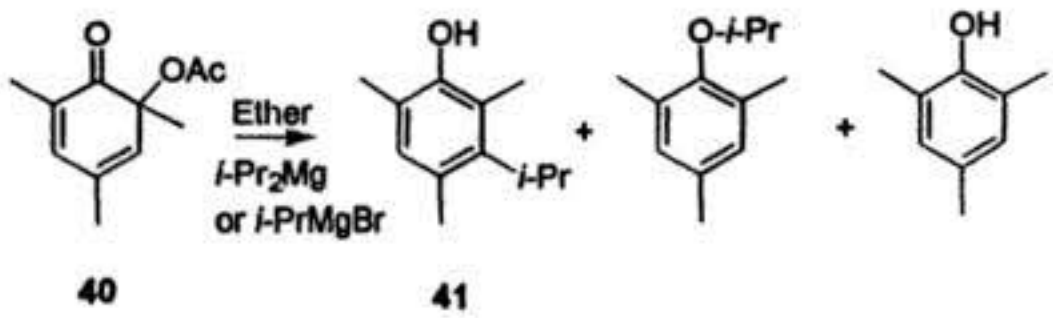
It is not possible to generalize about the propensity for 1,2- versus 1,4-addition from the results with cyclohexenone **34**, since *trans*-3-penten-2-one **37** reacts mainly by 1,4-addition to give **38**, with both diethylmagnesium and ethylmagnesium bromide in THF. The diethylmagnesium reactant give increased 1,2-addition product **39** [52].



A preference of 1,4-addition by the alkylmagnesium halide species rather than the dialkylmagnesium species, was observed during the reactions of di-*i*-propylmagnesium and *i*-propylmagnesium bromide in diethyl ether with the *o*-quinol acetate **40** [53]. Between concentrations of 0.06 and 0.24 *M* in diethyl ether, only 2% of 1,4-addition product **41** was observed with the dialkylmagnesium species. However, at 0.24 *M* concentration of

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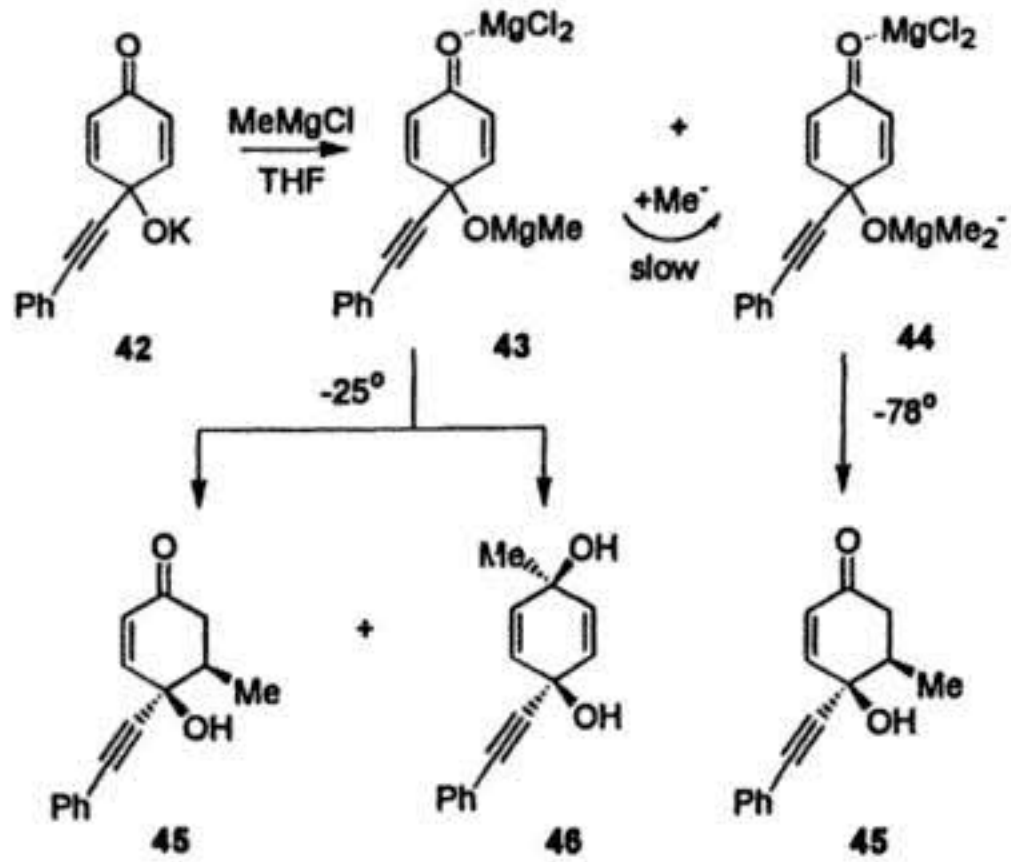
i-propylmagnesium bromide in diethyl ether, 19% of 1,4-addition product **41** was observed. At concentrations of *i*-propylmagnesium bromide below 0.5 *M*, the yield of 1,4-addition product **41** dropped sharply, and the results were similar to those of the di-*i*-propylmagnesium reagent at 0.06 *M* [53].



40 **41**

When the quinol alkoxide **42** was reacted with dimethylmagnesium and methylmagnesium halide reagents in diethyl ether, selectivities observed for 1,4/1,2-addition (**45**/**46**, respectively) were 5:1 with Me_2Mg, 7.7:1 with MeMgBr, and 13:1 with MeMgCl. More careful study indicated that temperature plays a major factor in the regiochemical outcome. When MeMgCl was added to **42** at −78°C, the reaction proceeded in 5 min to 40–50% completion, and then further reaction ceased. A 95:1 selectivity favoring 1,4-addition product **45** was observed. As the solution was warmed to −25°C, reaction resumed at a much slower rate and with lower selectivity (5.5:1). Although all of the organomagnesium reagents in the solution can coordinate with the alkoxide oxygen to give "ate" complex **43**, only the dialkylmagnesium species **44** can react at −78°C. At higher temperatures the remainder of the alkyl groups can react, but by a different reactive species [40].

By further experimentation, the 1,4-addition of the Me_2Mg reagent to the quinol alkoxide **42** was confirmed to be assisted by Lewis acid complexation of the ketone carbonyl with $MgCl_2$. The Me_2Mg in THF, with 10% $MgCl_2$ added, afforded 30:1 regio- and stereoselectivity for the 1,4-addition product **45** [40]. Reaction presumably occurs via the "ate" complex **44**. At higher concentrations of added $MgCl_2$, the Me_2Mg reaction stereoselectivity shifts to that observed for MeMgCl. As the salt shifts the Schlenk equilibrium, reaction occurs via the "ate" complex **43**.



42 **43** **44**

45 **46** **45**

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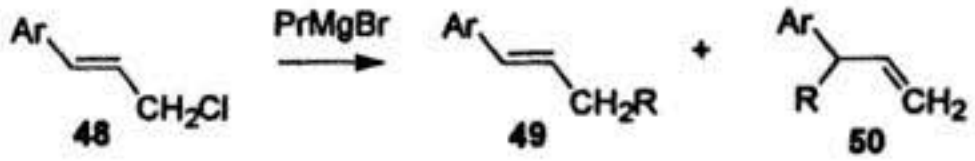
C. Displacement Reactions

Tetrabenzylvanadium **47** could be prepared by reaction of dibenzylmagnesium with vanadium tetrachloride in pentane at −20°C. Benzylmagnesium halide reagents fail in this reaction. It has been postulated that benzylmagnesium halides behave as Lewis acids and promote reduction in the oxidation state of vanadium [54].

$$(PhCH_2)_2Mg + VCl_4 \longrightarrow V(CH_2Ph)_4$$

47

Grignard reagents prepared from R′X (R′ = Me, Pr, Ph, *i*-Pr, *t*-Bu; X = Br, I) react in diethyl ether with 1-aryl-3-chloropropenes **48** to afford two alkylation products by competitive S_N2-S_N2' processes in addition to dimers formed by single-electron transfer (SET) processes. In diethyl ether RMgX is prevalent. This species can react by S_N2 or S_N2' pathways, which are facilitated by Lewis acid coordination of a magnesium species with the leaving chloride group. In THF, however, the S_N2 process dominates. In THF the more nucleophilic dialkylmagnesium R_2Mg is the major reactive species and favors an S_N2 process [55]. See Chapter 24 for discussion of S_N2 versus S_N2' addition.

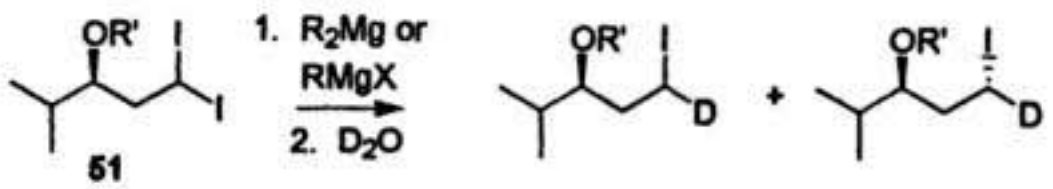


48 **49** **50**

4-OMe	THF	67 : 33
	Diethyl Ether	52 : 48
4-Me	THF	100 : 0
	Diethyl Ether	67 : 33
H	THF	100 : 0
	Diethyl Ether	87 : 13
4-Cl	THF	100 : 0
	Diethyl Ether	86 : 14
3-Cl	THF	100 : 0
	Diethyl Ether	94 : 6

D. Reductive Dehalogenation

Diastereoselective exchange of iodine for hydrogen has been effected by reaction of O-protected 1,1-diiodo-4-methyl-3-pentanol derivatives **51** with dialkylmagnesium or alkyl



51

R′ = Mem,	*i*-PrMgBr, THF	71 : 29
R′ = $SiMe_3$,	*i*-PrMgCl(Br), THF	40 : 60
	i-Pr_2Mg, THF	33 : 67
	i-Pr_2Mg, Ether	25 : 75

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halide Grignard reagents followed by aqueous quenching. Variation of reagents had little influence on the stereoselectivity compared with the choice of the protecting group [56].

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14

Effect of Tris(pyrazolyl)hydroborato Ligation

GERARD PARKIN
Columbia University, New York, New York

I. INTRODUCTION

Grignard reagent solutions comprise a complex distribution of magnesium alkyl and aryl derivatives [1]. In its simplest form, the composition of a Grignard reagent solution is described by the well-known Schlenk equilibrium [Eq. (1); 2].

$$2RMgX \leftrightarrows R_2Mg + MgX_2 \quad (1)$$

However, this simple model is complicated by a variety of other factors (e.g., solvation effects and oligomerization), as illustrated by X-ray diffraction studies on the species that crystallize from solution. For example, Figure 1 summarizes some of the complexes isolated from Grignard reagent solutions that have been characterized by X-ray diffraction. These complexes include both the four- and five-coordinate solvated monomers, $RMgBr(OEt_2)_2$ ($R = Et$ [3], Ph [4]) and $MeMgBr(THF)_3$ [5]; the halogen-bridged dimers $[EtMgBr(OPr^i_2)]_2$ [6] and $[EtMgBr(NEt_3)]_2$ [7]; and also the tetranuclear complex $[EtMg_2Cl_3(THF)_3]_2$ [8]. The tetranuclear complex may be considered as an adduct of the Grignard reagent EtMgCl and the $MgCl_2$ that is formed as a consqequence of the Schlenk equilibrium. Although these structural studies do indicate the complexity of Grignard reagent solutions, it should be recognized that the species that crystallize from such solutions are not necessarily representative of either the major, or the reactive, component. Nevertheless, despite the aforementioned complexity, and the uncertainty of the exact nature of the active species present in solution, Grignard reagents continue to be one of the most useful reagents in synthetic organic and organometallic chemistry. It is, therefore, of some interest to determine the reactivity of the magnesium alkyl moiety in well-defined coordination environments. In this section, the use of tris(pyrazolyl)hydroborato ligation [9] to provde a series of well-defined monomeric magnesium alkyl derivatives will be described, and the effect of such coordination on the reactivity of the magnesium carbon bond will be commented on.

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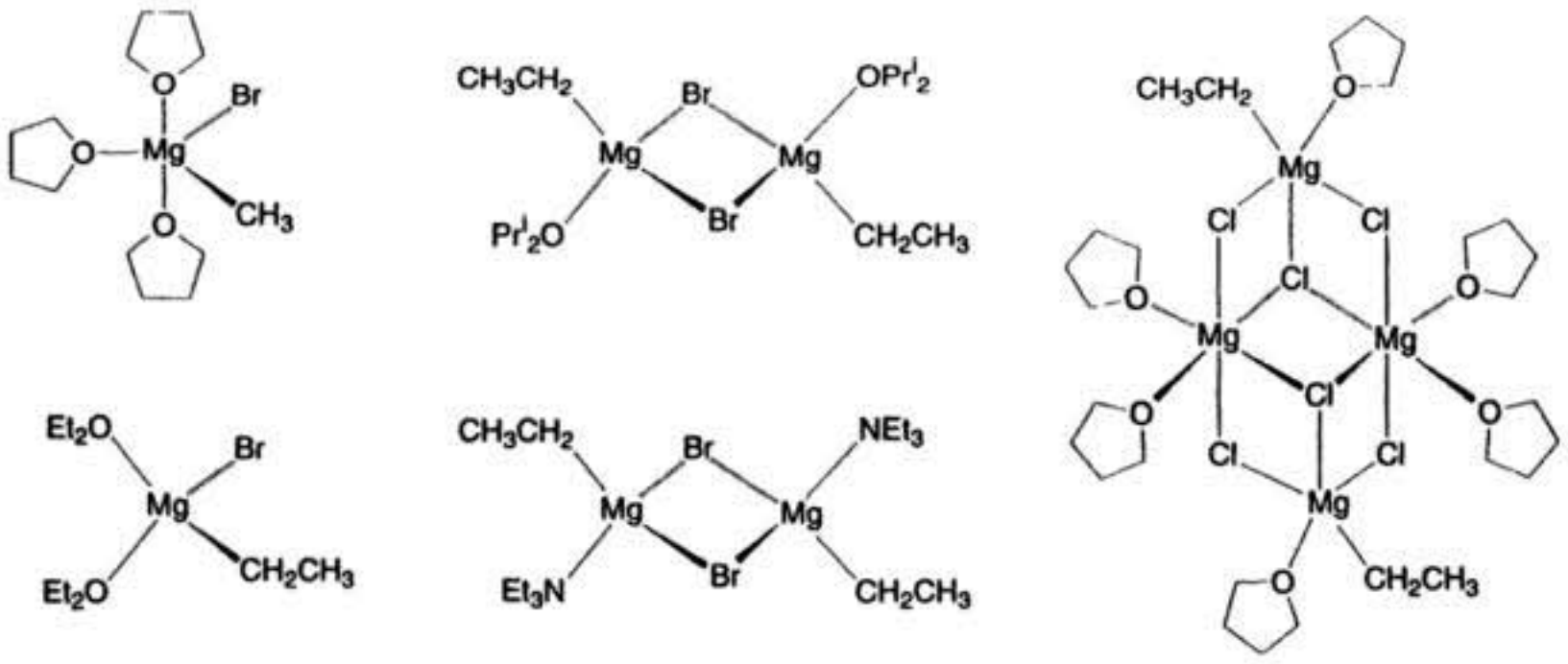
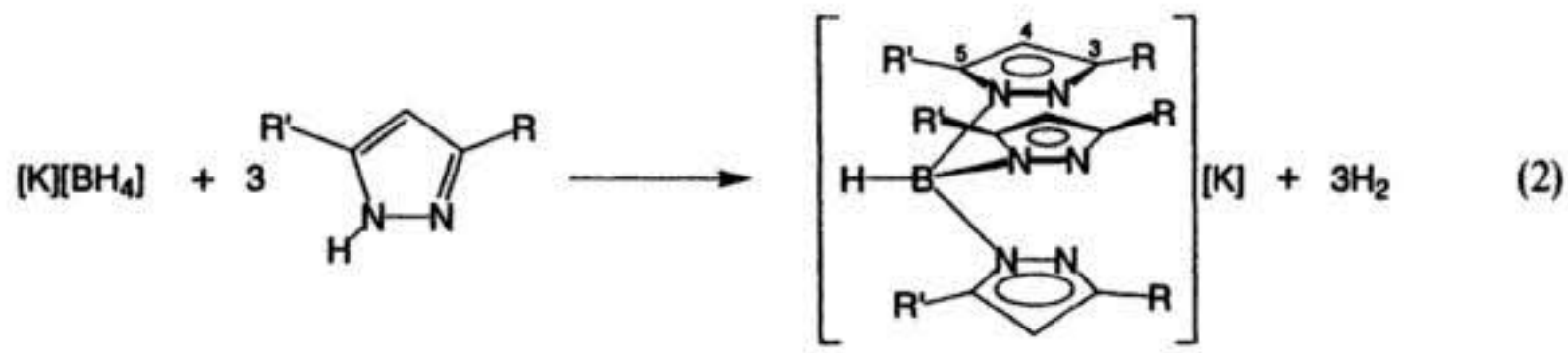


Figure 1 Structurally characterized complexes that crystallize from Grignard reagent solutions.

II. SYNTHESES AND STRUCTURES OF MONOMERIC FOUR-COORDINATE TRIS(PYRAZOLYL)HYDROBORATO MAGNESIUM ALKYL DERIVATIVES

A. Tris(pyrazolyl)hydroborato Ligands

Tris(pyrazolyl)hydroborato ligands $[HB(3,5\text{-}RR'pz)_3]^-$ ($RR'pz = C_3N_2RR'H$), which were introduced by Trofimenko in 1966 [10], are readily obtained as the potassium derivatives by the direct reaction of KBH_4 with the appropriate pyrazole RR'pzH [Eq. (2); 9].



Of particular significance, a wide variety of tris(pyrazolyl)hydroborato ligands are available; hence, the effects of both steric and electronic influences may be studied. For example, the steric demands of the tris(pyrazolyl)hydroborato ligands may be readily modified by substitution at the 3-position of the pyrazolyl group. Steric demands of ligands are often described in terms of their cone angles, Θ (Fig. 2) [11], which increase substantially from 184° to 244° upon substitution of the 3-H for a Bu^t substituent in the tris(pyrazolyl)hydroborato ligand system [12]. The nomenclature adopted here for tris(pyrazolyl)hydroborato ligands is based on that described by Trofimenko [9a]. Thus, the tris(pyrazolyl)hydroborato ligands are represented by the abbreviation Tp, with the alkyl substituents listed as superscripts. The tris(pyrazolyl)hydroborato ligands described in this section, namely, $[Tp^{Me_2}]$, $[Tp^{Bu^t}]$, and $[Tp^{Ar_2}]$ ($Ar = p\text{-}C_6H_4Bu^t$) [9,12a,13], are summarized in Figure 3, from which it can be seen that coordination of the three nitrogen donors to a magnesium center provides a well-defined coordination environment for investigating a series of monomeric four-coordinate magnesium alkyl derivatives.

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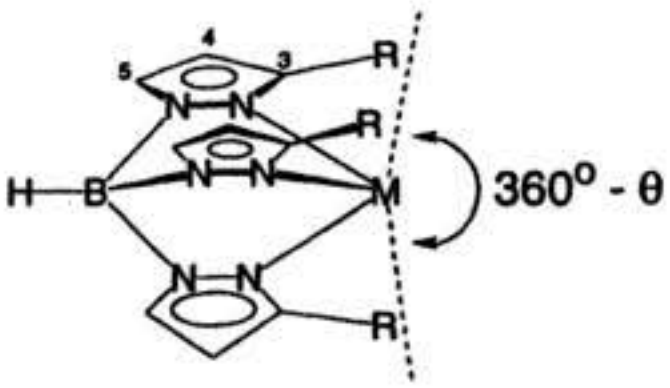


Figure 2 Cone angles of tris(pyrazolyl)hydroborato ligands.

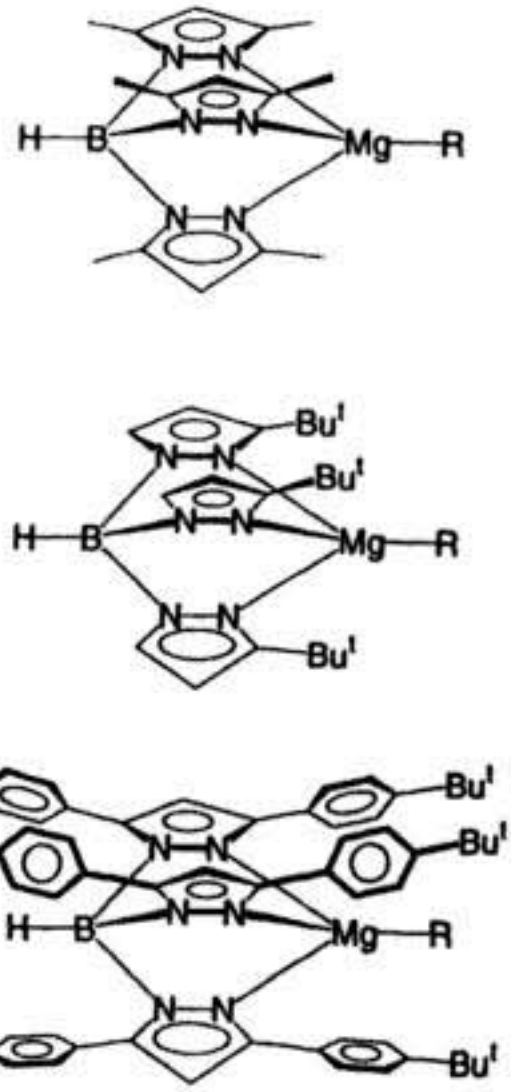


Figure 3 Tris(pyrazolyl)hydroborato magnesium alkyl derivarives.

In addition to providing a stable coordination environment, the alkyl substituents on the pyrazolyl group provide a useful and invaluable spectroscopic handle for monitoring the reactivity of these complexes.

B. Syntheses of $[Tp^{R,R'}]MgR$ Complexes

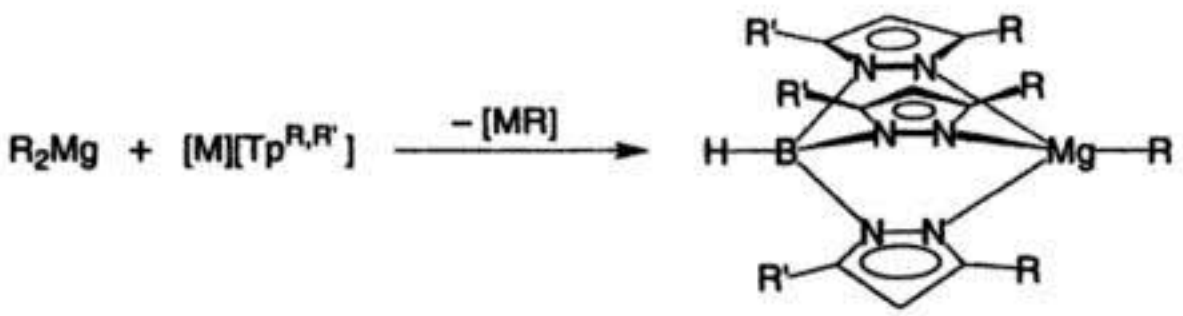
Tris(pyrazolyl)hydroborato magnesium alkyl derivatives $[Tp^{R,R'}]MgR$ are readily prepared by the reactions of $[M][Tp^{R,R'}]$ (M = K, Tl) with solutions of the appropriate dialkylmagnesium [Eq. (3); 14–17]. The reaction is very general and a series of primary, secondary tertiary, vinyl, and phenyl derivatives have been obtained, as illustrated in Table 1. The magnesium alkyl complexes $[Tp^{R,R'}]MgR$ are all white crystalline solids that are soluble

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Table 1 Isolated $[Tp^{R,R'}]MgR$ Complexes

	$[Tp^{Me_2}]MgR$	$[Tp^{Bu^t}]MgR$	$[Tp^{Ar_2}]MgR$
CH_3	●	●	●
CH_2CH_3	●	●	
$CH_2(CH_2)_3CH_3$	●	●	
$CH(CH_3)_2$	●	●	
$C(CH_3)_3$	●	●	
CH_2SiMe_3	●	●	
$CH{=}CH_2$	●	●	
C_6H_5	●	●	

in hydrocarbon solvents, such as benzene.



(3)

The reactions between R_2Mg and the thallium reagents $Tl[Tp^{R,R'}]$ are accompanied by the deposition of Tl metal owing to the decomposition of [TlR] [18], which thereby provides a very effective driving force for the reaction. In view of the effective driving force for the thallium reagent, the potassium derivative $[K][Tp^{R,R'}]$ may be preferred for the synthesis of magnesium alkyl derivatives of less sterically demanding ligands, for which disubstitution and the formation of the six-coordinate magnesium derivative $[Tp^{R,R'}]_2Mg$ may be facile. For example, the potassium derivative $[K][Tp^{Me_2}]$ is the reagent of choice for the synthesis of $[Tp^{Me_2}]MgR$, because the thallium reagent may result in disubstitution with the formation of $[Tp^{Me_2}]_2Mg$ [17]. In contrast, complexes of the more sterically demanding *t*-butyl-substituted ligand $[Tp^{Bu^t}]MgR$ are cleanly prepared using the thallium reagent, since the formation of $[Tp^{Bu^t}]_2Mg$ is not possible for this ligand system (see later discussion).

Finally, it is worth noting that although an appropriate method of synthesis of $[Tp^{R,R'}]MgR$ complexes would appear to involve the reaction of a Grignard reagent RMgX with $[M][Tp^{R,R'}]$, such a method is complicated by the formation of the corresponding magnesium halide derivative $[Tp^{R,R'}]MgX$ as a result of competition between Mg–X and Mg–R bond metathesis [17,19]. The products obtained depend upon the choice of Grignard reagent and reactant ratio, as summarized in Figures 4 and 5. Such a problem is obviously alleviated by using R_2Mg as the reagent, which cleanly gives the alkyl product $[Tp^{R,R'}]MgR$.

C. Structures and Spectroscopic Properties of $[Tp^{R,R'}]MgR$ Complexes

The molecular structures of several $[Tp^{R,R'}]MgR$ derivatives have been determined by single-crystal X-ray diffraction, which confirms that in each case the molecules are solvent-free monomers, and that the tris(pyrazolyl)hydroborato ligand is η^3-coordinated to magnesium. The coordination environment about the magnesium may be described as

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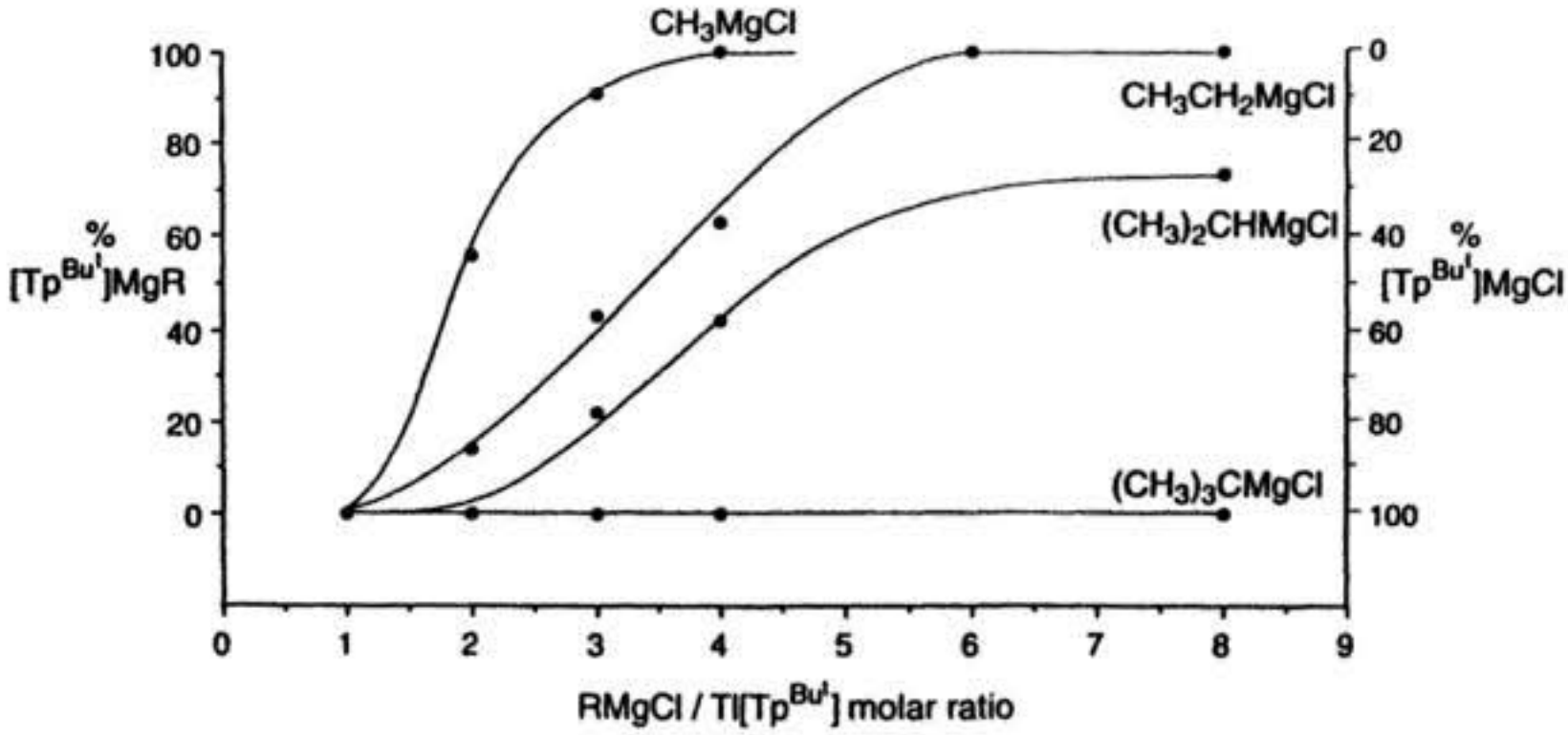


Figure 4 Product distribution of the reactions of RMgCl ($R = CH_3$, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$) with $Tl[Tp^{Bu'}]$ as a function of reactant molar ratio ($L = [Tp^{Bu'}]$). (Modified from Ref. 17.)

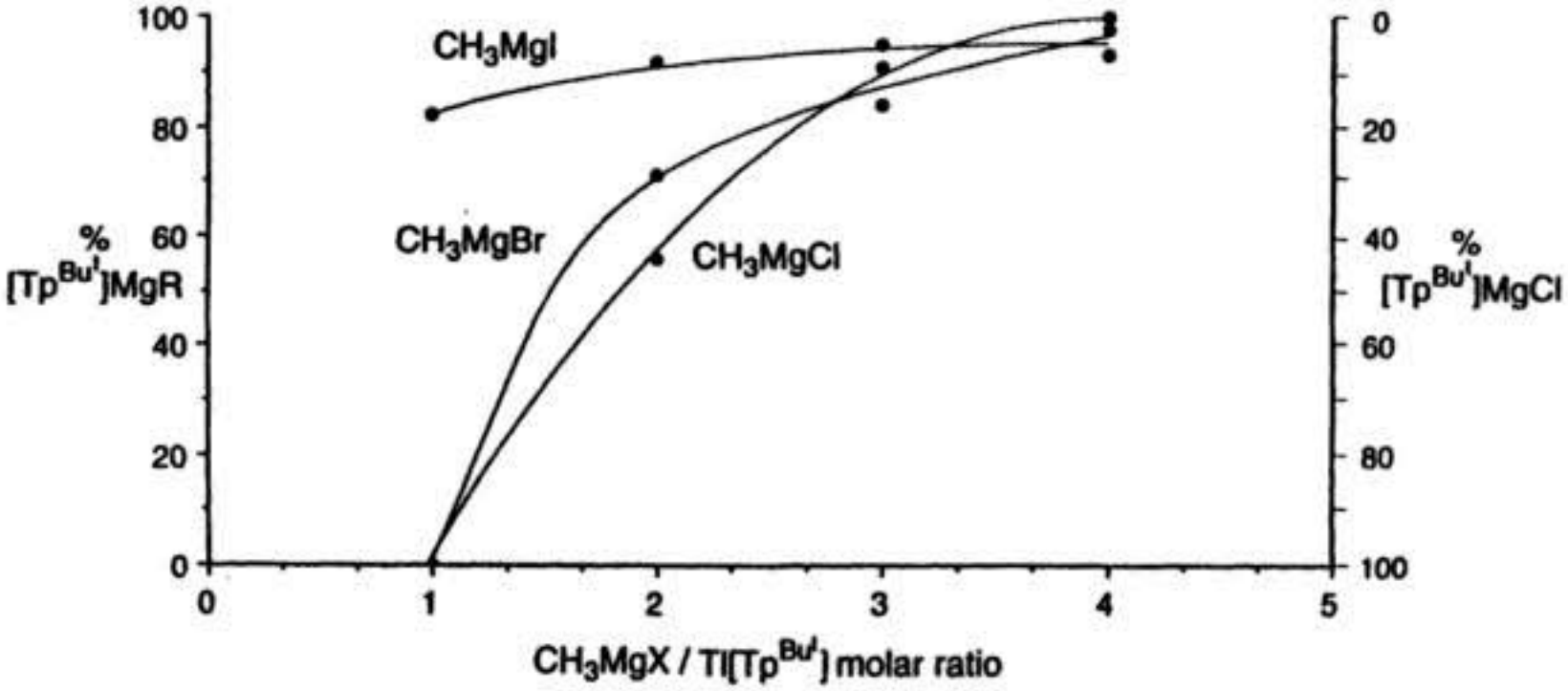


Figure 5 Product distribution of the reactions of CH_3MgX (X = Cl, Br, I) with $Tl[Tp^{Bu'}]$ as a function of reactant molar ratio ($L = [Tp^{Bu'}]$). (Modified from Ref. 17.)

trigonally distorted tetrahedral. ORTEP drawings for $[Tp^{Bu'}]MgCH_3$, $[Tp^{Bu'}]MgCH(CH_3)_2$, and $[Tp^{Me_2}]MgCH_2Si(CH_3)_3$ are shown in Figures 6–8, and selected bond lengths are presented in Table 2. The Mg–C bond lengths are in the range 2.096(9)–2.182(8) Å. For reference, other four-coordinate monomeric magnesium alkyl complexes of the type $RMgX(L)_2$ have Mg–C bond lengths in the range 2.15–2.23 Å [20].

The complexes $[Tp^{R,R'}]MgR$ have also been characterized by ^1H- and ^{13}C-nuclear magnetic resonance (NMR) spectroscopy. For example, the Mg–CH_3 groups of the methyl derivatives $[Tp^{Bu'}]MgCH_3$, $[Tp^{Ar_2}]MgCH_3$, and $[Tp^{Me_2}]MgCH_3$ exhibit ^1H-NMR signals at δ −0.05, −0.58, and −0.25 ppm, respectively, and ^{13}C-NMR signals at −5.2 ($^1J_{C-H} = 109$ Hz), −9.5 ($^1J_{C-H} = 109$ Hz) and −17.1 ($^1J_{C-H} = 109$ Hz) ppm, respectively. Furthermore, the resonances attributable to the tris(pyrazolyl)hydroborato ligand are also

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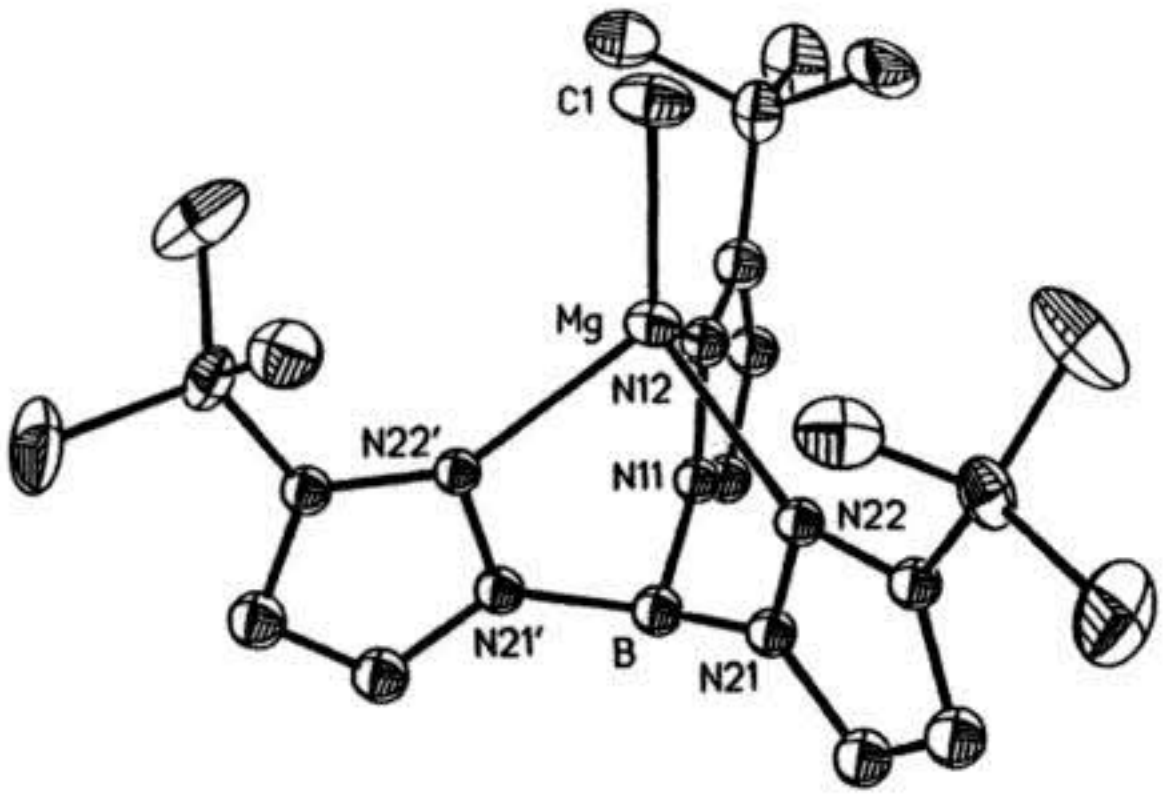


Figure 6 Molecular structure of $[Tp^{Bu'}]MgCH_3$. (From Ref. 17.)

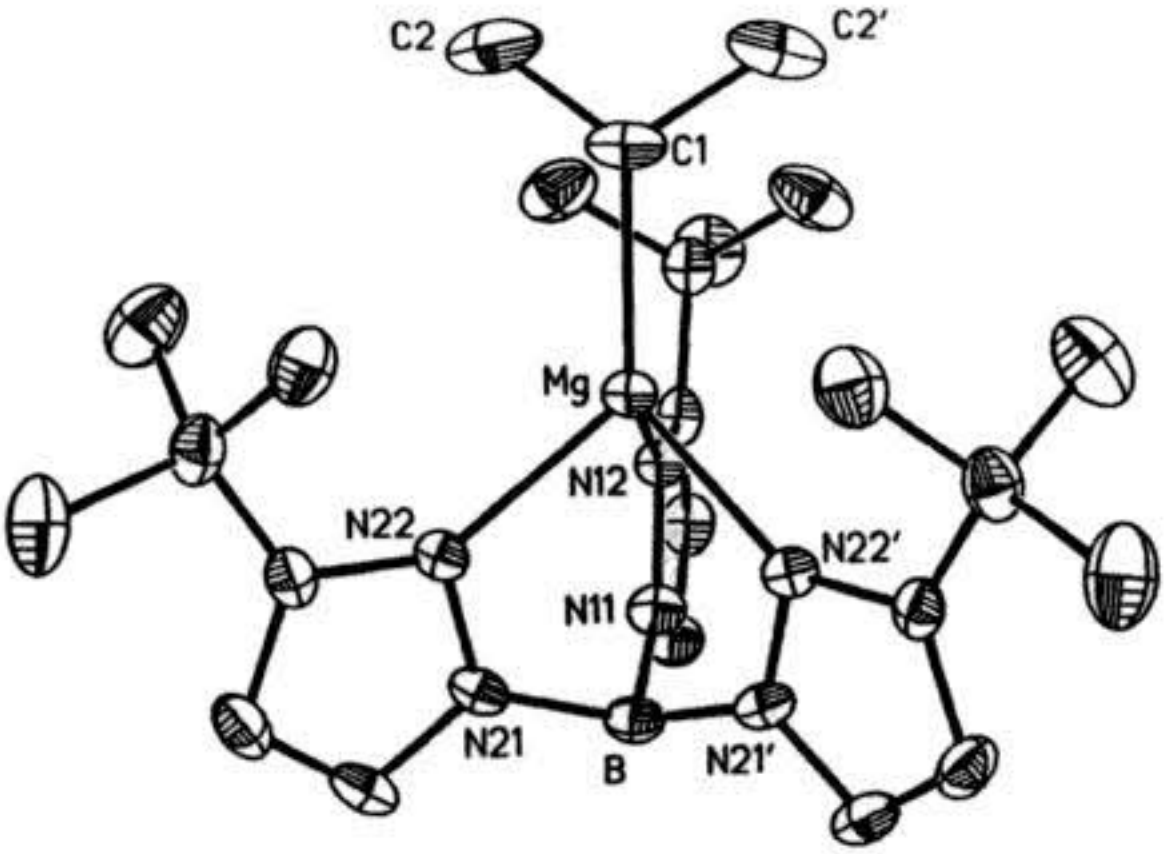


Figure 7 Molecular structure of $[Tp^{Bu'}]MgPr^i$. (From Ref. 17.)

Table 2 Selected Bond Lengths (Å) for $[Tp^{R,R'}]MgR$ Complexes

	$[Tp^{Bu'}]MgCH_3$	$[Tp^{Bu'}]MgCH(CH_3)_2$	$[Tp^{Me_2}]MgCH_2Si(CH_3)_3$
Mg–C	2.118(11)	2.182(8)	2.096(9)
Mg–N	2.130(10)	2.157(6)	2.012(6)
	2.137(7)	2.170(4)	2.097(5)
	2.137(7)	2.170(4)	2.119(6)

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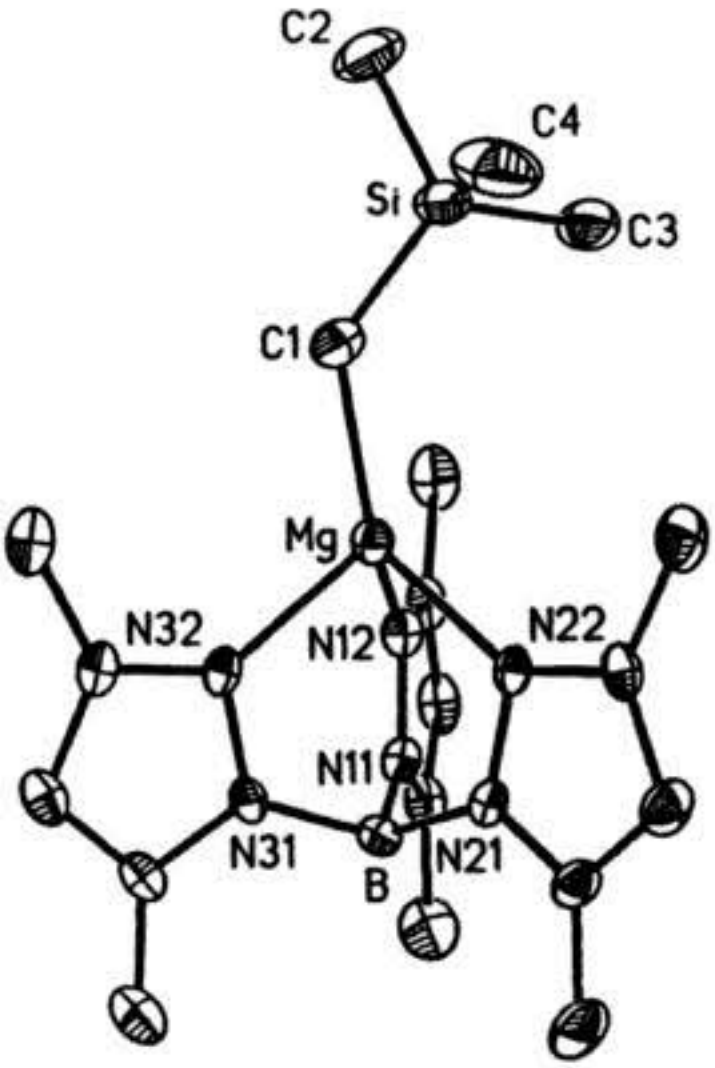


Figure 8 Molecular structure of $[Tp^{Me_2}]MgCH_3$. (From Ref. 17.)

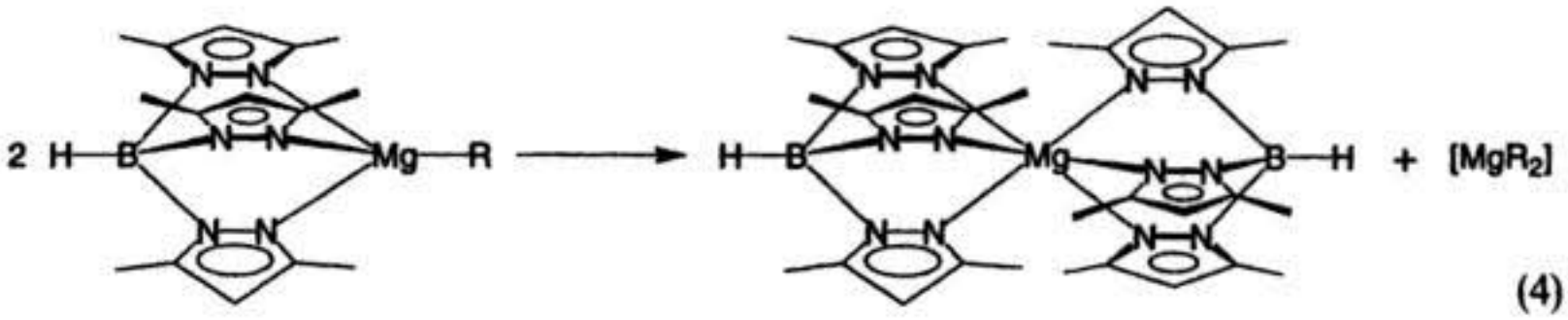
a valuable spectroscopic handle for monitoring reactivity. For example, each of the complexes $[Tp^{Bu'}]MgR$ exhibit a single characteristic resonance in the range δ 1.34–1.44 for the *t*-butyl substituents of the $[Tp^{Bu'}]$ ligand.

III. REACTIVITY STUDIES OF $[Tp^{R,R'}]MgR$ COMPLEXES

An investigation of the reactivity of the complexes $[Tp^{R,R'}]MgR$ is important both in terms of determining the reactivity of the Mg–C bond in a well-defined coordination environment, but also in terms of providing a comparison with the reactivity of Grignard reagents. Aspects of the reactivity of $[Tp^{R,R'}]MgR$ are considered in the following sections [21].

A. Ligand Redistribution

The complexes $[Tp^{R,R'}]MgR$ may be considered to be modifications of Grignard reagents. As such, these complexes may be expected to be subject to the facile ligand redistribution reactions of the Schlenk equilibrium. Indeed, although solutions of the tris(3,5-dimethylpyrazolyl)hydroborato derivatives $[Tp^{Me_2}]MgR$ are stable at room temperature, heating to 80–120°C does result in ligand redistribution and the formation of the six-coordinate sandwich complex $[Tp^{Me_2}]_2Mg$ [Eq. (4), 21,22]



(4)

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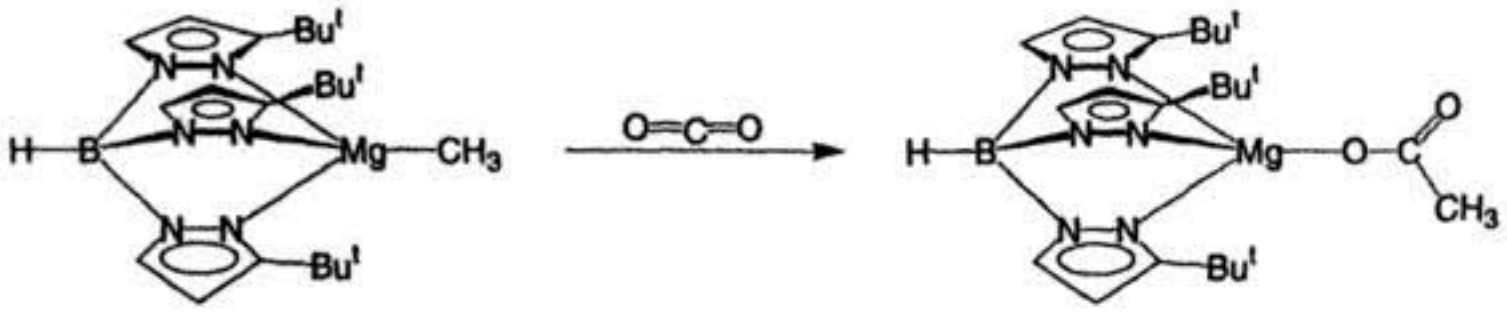
However, on increasing the steric demands of the tris(pyrazolyl)hydroborato ligand, the relative stability of the six-coordinate redistribution product $[Tp^{R,R'}]_2Mg$ decreases sufficiently so that ligand redistribution of $[Tp^{R,R'}]MgR$ is not observed. For example, solutions of $[Tp^{Bu^t}]MgCH_3$ show no evidence of decomposition after 7 days at 120°C. It is worth emphasizing that the $[Tp^{Bu^t}]$ ligand has been described as a "tetrahedral enforcer" owing to its ability to restrict a metal center to a maximum of four-coordination [12a]. For this reason, the sterically demanding $[Tp^{Bu^t}]MgR$ system is more appealing than less sterically demanding $[Tp^{R,R'}]MgR$ systems for defining the reactivity of the Mg–R group.

The foregoing redistribution reactions are, evidently, significantly slower than those involved in the Schlenk equilibrium of Grignard reagents. Consequently, a mixture of the alkyl derivatives $[Tp^{Bu^t}]MgCH_3$ and $[Tp^{Me_2}]MgC(CH_3)_3$ does not result in the formation of crossover products after heating at 80°C for 3 days [Eq. (5)].

$$[Tp^{Bu^t}]MgCH_3 + [Tp^{Me_2}]MgC(CH_3)_3 - X \rightarrow [Tp^{Bu^t}]MgC(CH_3)_3 + [Tp^{Me_2}]MgCH_3 \quad (5)$$

B. Reactions with Carbonyl Derivatives

Nucleophilic addition to carbonyl functionalities undoubtedly represents one of the most important reactions of Grignard reagents. One such reaction is the alkylation of carbon dioxide to give carboxylic acid derivatives. Analogous reactivity is also observed between $[Tp^{Bu^t}]MgCH_3$ and CO_2, which gives the acetate derivative $[Tp^{Bu^t}]Mg(\eta^1\text{-}O_2CCH_3)$ [Eq (6)].

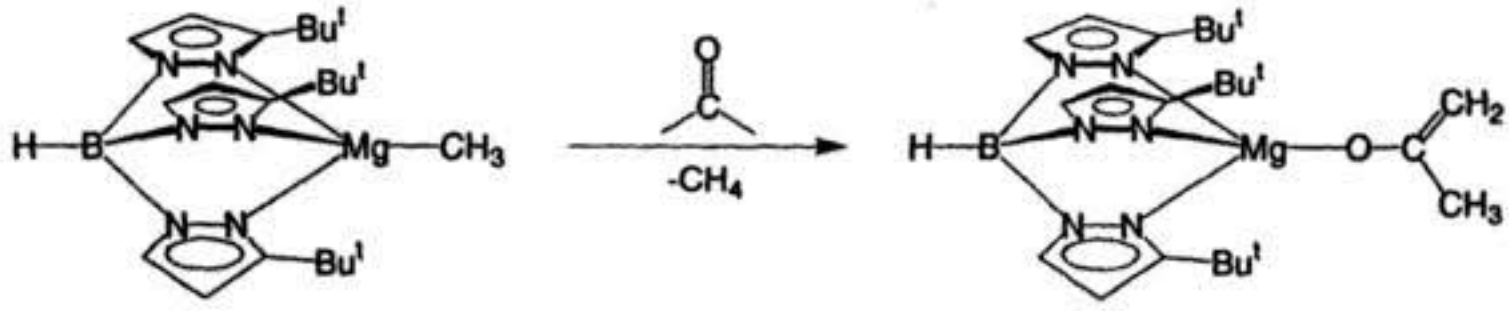


(6)

The corresponding reaction with $^{13}CO_2$ gives $[Tp^{Bu^t}]Mg(\eta^1\text{-}O_2{}^{13}CCH_3)$. Use of ^{13}C-NMR spectroscopy has identified that the magnitude of the $J_{C\text{-}C}$ coupling constant is 53 Hz, a value indicative of a one-bond coupling, thereby confirming the formation of the C–C bond in this reaction.

However, although the reaction between $[Tp^{Bu^t}]MgCH_3$ and CO_2 is similar to that of Grignard reagents, the reaction is significantly slower. The lower reactivity $[Tp^{Bu^t}]MgCH_3$ relative to that of Grignard reagents is presumably a consequence of both the sterically demanding nature and strong binding of the tris(pyrazolyl)hydroborato ligand to the magnesium center. Reduction of the steric demands of the 3-substitutent would be expected to promote reactivity, as is indicated by preliminary studies with $[Tp^{Ar_2}]MgCH_3$ ($Ar = p\text{-}C_6H_4Bu^t$) [13b].

In contrast to the addition of $[Tp^{Bu^t}]MgCH_3$ to CO_2, the reaction of $[Tp^{Bu^t}]MgCH_3$ with acetone is not typical of Grignard reactivity. Thus, rather than forming an alkoxide derivative $[Tp^{Bu^t}]MgOC(CH_3)_3$, the reaction between $[Tp^{Bu^t}]MgCH_3$ and $(CH_3)_2CO$ gives the enolate complex $[Tp^{Bu^t}]Mg\{\eta^1\text{-}OC(=CH_2)CH_3\}$ and CH_4 [Eq. (7)].



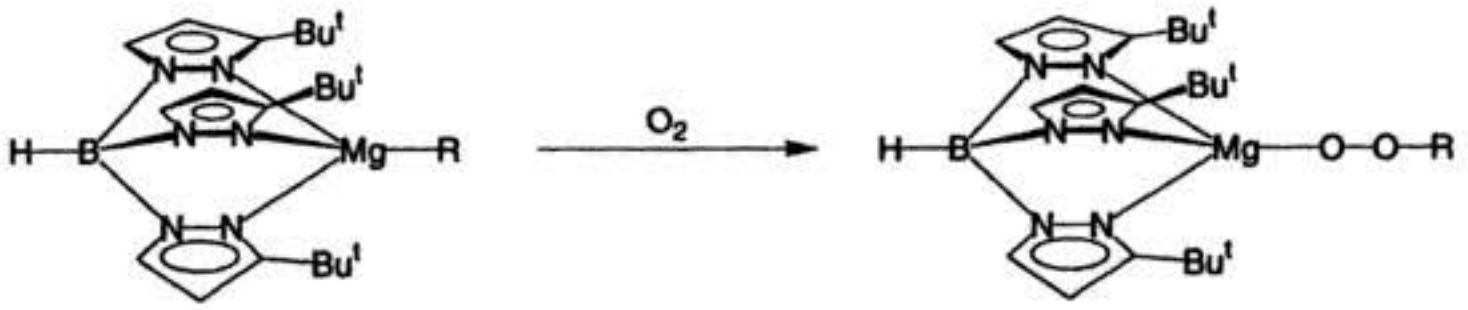
(7)

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Magnesium enolate complexes have previously been isolated only for ketones with sterically demanding substituents {e.g., Bu^{t}C(O)Et [23] and (1,3,5-Me$_3$C$_6$H$_2$)C(O)CH$_3$ [24]}, and the formation of [Tp$^{Bu^t}$]Mg{η1-OC(=CH$_2$)(CH$_3$)} represents an interesting example of a magnesium enolate derived from acetone. The reaction appears to be general for methyl ketones since CH$_3$C(O)Bu^t also reacts with [Tp$^{Bu^t}$]MgCH$_3$ to give the enolate derivative [Tp$^{Bu^t}$]Mg{η^1-OC(=CH$_2$)(Bu^t)}. The enolate derivatives [Tp$^{Bu^t}$]Mg[η^1-OC(=CH$_2$)(R)} are readily characterized by NMR and IR studies, as summarized in Table 3. For example, the triplet resonance ($^1J_{C-H}$ = 155 Hz) observed at δ 83.1 ppm in the ^{13}C-NMR spectrum of [Tp$^{Bu^t}$]Mg{η^1-OC(=CH$_2$)(CH$_3$)} is characteristic of a [OC(=$\underline{C}$H$_2$)(CH$_3$)] moiety, whereas the absorption at 1620 cm^{-1} in the IR spectrum is attributed to $\nu_{C=C}$.

C. Reactions with Oxygen

The alkyl complexes [Tp$^{Bu^t}$]MgR (R = Me, Et, Pr^i, Bu^t) react with excess O_2 at room temperature to give alkylperoxo complexes [Tp$^{Bu^t}$]MgOOR [Eq. (8); 15,21].



(8)

The reactions are instantaneous for the derivatives [Tp$^{Bu^t}$]MgR (R = Et, Pr^i, Bu^t), whereas the reaction of the methyl derivative [Tp$^{Bu^t}$]MgCH$_3$ is significantly slower, proceeding over a period of days at room temperature. Furthermore, the reaction of O_2 with [Tp$^{Bu^t}$]MgCH$_3$ is also accompanied by an approximate 30% decomposition, so that the product [Tp$^{Bu^t}$]MgOOCH$_3$ is not cleanly isolated [15,21].

The alkylperoxo complexes have been characterized by spectroscopic studies on isotopically labeled derivatives. Thus, the reaction of $^{17}O_2$ (41%) with [Tp$^{Bu^t}$]MgR gives the enriched alkylperoxo complexes [Tp$^{Bu^t}$]Mg^{17}O^{17}OR that have been investigated by ^{17}O-NMR spectroscopy. Each complex exhibits two ^{17}O-NMR resonances in the ranges δ 102–183 and δ 323–427 for the two distinct oxygen atoms of the alkylperoxo (Mg–O–O–R) moiety (Table 4 and Fig. 9) [15,21]. However, the ^{17}O-NMR chemical shifts of the two oxygen atoms of the alkylperoxo group exhibit different trends when varying the alkyl

Table 3 Selected Spectroscopic Data for the Enolate Complexes [Tp$^{Bu^t}$]Mg{η^1-OC(=CH$_2$)R} (R = Me, Bu^t) [Tp$^{Bu^t}$]Mg{η^1-OC(=CH$_2$)R}

		R = Me	R = Bu^t
^{1}H-NMR	δ (C$\underline{H}_2$)	4.29	3.84
		4.32	4.42
^{13}C-NMR	δ ($\underline{C}$H$_2$)	83.1[a]	82.1[b]
	δ ($\underline{C}$O)	161.9	172.4
IR	$c_{C=C}$ cm^{-1}	1620	1615

[a] *t*, $^1J_{C-H}$ = 155 H.
[b] *dd*, $^1J_{C-H}$ = 149 and 156 Hz.

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Table 4 ^{17}O=NMR Data for $[Tp^{Bu^t}]MgOOR$ (relative to $H_2{}^{17}O$)

	δ(MgOOR)	δ(MgOOR)
$[Tp^{Bu^t}]MgOOCH_3$	427	102
$[Tp^{Bu^t}]MgOOCH_2CH_3$	407	130
$[Tp^{Bu^t}]MgOOCH(CH_3)_2$	373	159
$[Tp^{Bu^t}]MgOOC(CH_3)_3$	323	183

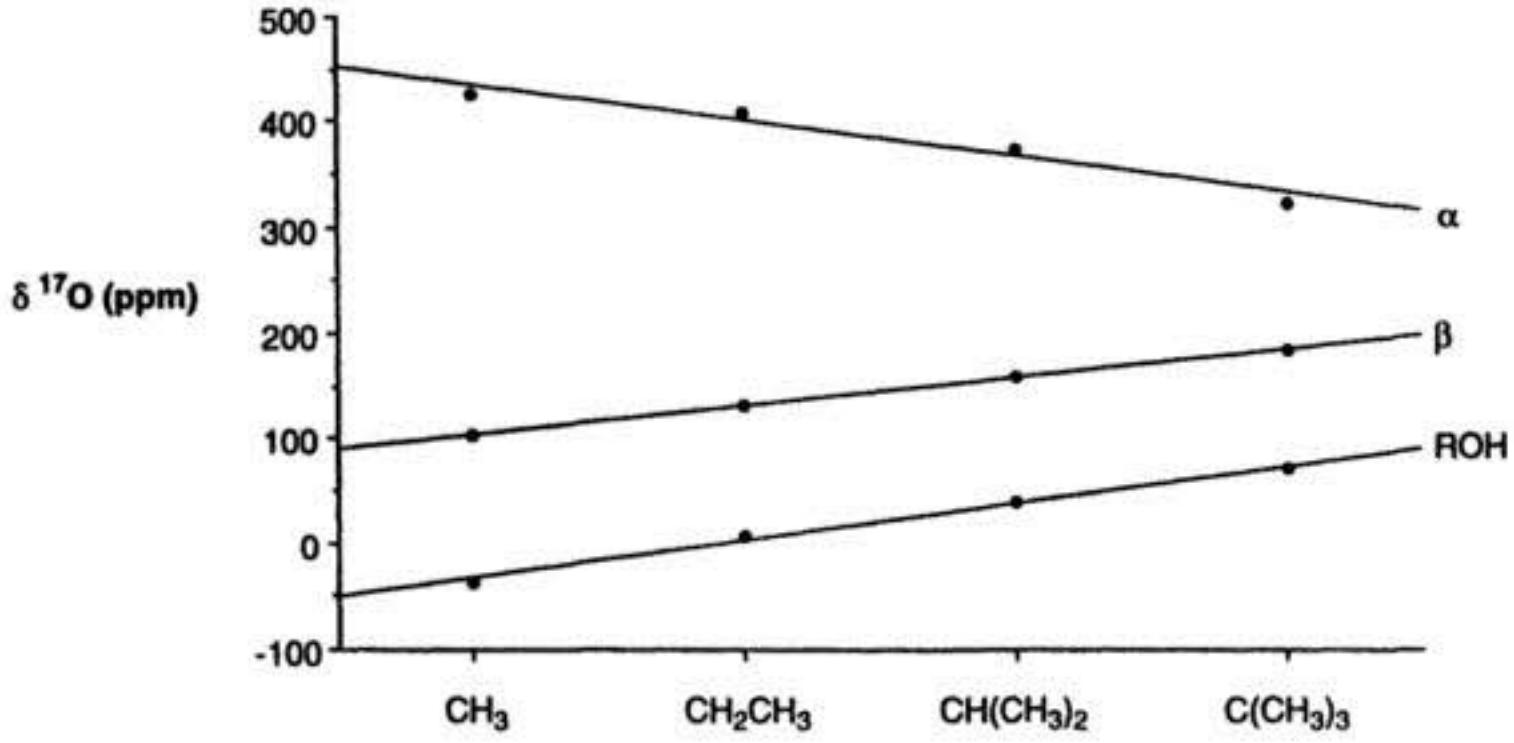


Figure 9 ^{17}O-NMR data for $[Tp^{Bu^t}]MgOOR$ and ROH.

substituent. On the basis of the observed trend for the ^{17}O-NMR chemical shifts of the corresponding alcohols, the set of resonances at higher field is suggested to correspond to the β-O atoms, and that the set of resonances at lower field correspond to the α-O atoms of the alkylperoxo moiety.

In general, the reactions of organometallic derivatives with oxygen often produce complex mixtures [25]. Typically, the isolated products of these reactions are alkoxo derivatives [L_nMOR], with relatively few examples involving isolation of aklylperoxo complexes [L_nMOOR] [26]. The successful isolation of magnesium alkylperoxo complexes $[Tp^{Bu^t}]MgOOR$ by the reactions of $[Tp^{Bu^t}]MgR$ with O_2 is presumably a consequence of the sterically demanding environment that is produced by the tris(pyrazolyl)hydroborato ligand (see later discussion). However, in contrast to the formation of the alkylperoxo complexes in the reactions of the alkyl derivatives $[Tp^{Bu^t}]MgR$ (R = Me, Et, Pr^i, Bu^t) with O_2, the analogous reaction of the trimethylsilylmethyl derivative $[Tp^{Bu^t}]MgCH_2SiMe_3$ with O_2 is accompanied by Si–C bond cleavage and the formation of the trimethylsiloxide derivative $[Tp^{Bu^t}]MgOSiMe_3$ [Eq. (9); 27].

$$[Tp^{Bu^t}]MgCH_2SiMe_3 \xrightarrow[-(CH_2O)_n]{O_2} [Tp^{Bu^t}]MgOSiMe_3 \qquad (9)$$

A precedent for this reaction is provided by the observation of organic products derived from Si–C bond cleavage after autooxidation of other trialkylsilyl metal derivatives. In

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particular, the Grignard reagent Me_3SiCH_2MgCl reacts with O_2 to give significant quantities of Me_3SiOH, $(Me_3Si)_2O$, and $(CH_2O)_n$ after hydrolysis [28].

The mechanisms of the reactions of oxygen with metal–alkyl derivatives have previously been suggested to involve radical intermediates (Scheme 1) on the basis of (1) alkly group rearrangement and racemization, and (2) inhibition of autooxidation by radical traps [29]

$$L_nM\text{-}R + O_2 \longrightarrow L_nMOO\bullet + R\bullet \quad \text{(initiation)}$$

$$R\bullet + O_2 \longrightarrow ROO\bullet$$

$$L_nM\text{-}R + ROO\bullet \longrightarrow L_nMOOR + R\bullet$$

Scheme 1 A mechanism for autoxidation of metal alkyls.

An analogous mechanism is also proposed for the reactions of $[Tp^{Bu'}]MgR$ with O_2, since (1) the reaction of $[Tp^{Bu'}]MgCH_3$ with O_2 is inhibited by small quantities of the radical trap galvinoxyl, and (2) crossover products are observed using two different tris(pyrazolyl)-hydroborato ligands. Specifically, the reaction of O_2 with a mixture of $[Tp^{Bu'}]MgCH_3$ and $[Tp^{Me_2}]MgC(CH_3)_3$ gives, among others, the crossover product $[Tp^{Bu'}]MgOOC(CH_3)_3$ [Eq. (10)].

$$[Tp^{Bu'}]MgCH_3 + [Tp^{Me_2}]MgC(CH_3)_3 \xrightarrow{O_2} [Tp^{Bu'}]MgOOC(CH_3)_3 + \ldots \qquad (10)$$

Notably, alkyl exchange between $[Tp^{Bu'}]MgCH_3$ and $[Tp^{Me_2}]MgC(CH_3)_3$ does *not* occur in the absence of O_2 over a period of more than a month at 80°C.

The formation of the trimethylsiloxide product $[Tp^{Bu'}]MgOSiMe_3$ in the reaction of $[Tp^{Bu'}]MgCH_2SiMe_3$ with O_2 is also proposed to occur by a radical process. Thus, elimination of formaldehyde from the radical intermediate $Me_3SiCH_2O_2^{\bullet}$ [Eq. (11)] would generate the trimethylsiloxide radical $Me_3SiO^{\bullet}$, a rearrangement that would be promoted by the formation of a strong Si–O bond.



(11)

The observation of crossover products in the reaction of a mixture of $[Tp^{Me_2}]MgCH_2SiMe_3$ and $[Tp^{Bu'}]MgC(CH_3)_3$ with O_2 supports the proposed radical mechanism.

The alkylperoxo derivatives $[Tp^{Bu'}]MgOOR$ are capable of transferring an oxygen atom to certain substrates, with the concomitant formation of the alkoxo complex $[Tp^{Bu'}]MgOR$. For example, oxygen atom transfer to a magnesium alkyl derivative occurs in the reaction of $[Tp^{Bu'}]MgOOPr^i$ with $[Tp^{Bu'}]MgPr^i$ at 80°C to give $[Tp^{Bu'}]MgOPr^i$ [Eq. (12)].

$$[Tp^{Bu'}]MgOOPr^i + [Tp^{Bu'}]MgPr^i \xrightarrow{80°C} 2[Tp^{Bu'}]MgOPr^i \qquad (12)$$

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However, it is noteworthy that oxygen atom transfer to the magnesium alkyl derivative does not occur rapidly at room temperature. This is presumably one of the factors that is responsible for the observation that the reactions of $[Tp^{Bu^t}]MgR$ with O_2 are selective in the formation of alkylperoxo complexes, rather than the alkoxo derivatives. It is likely that this is a consequence of the sterically encumbered nature of the magnesium centers in these complexes.

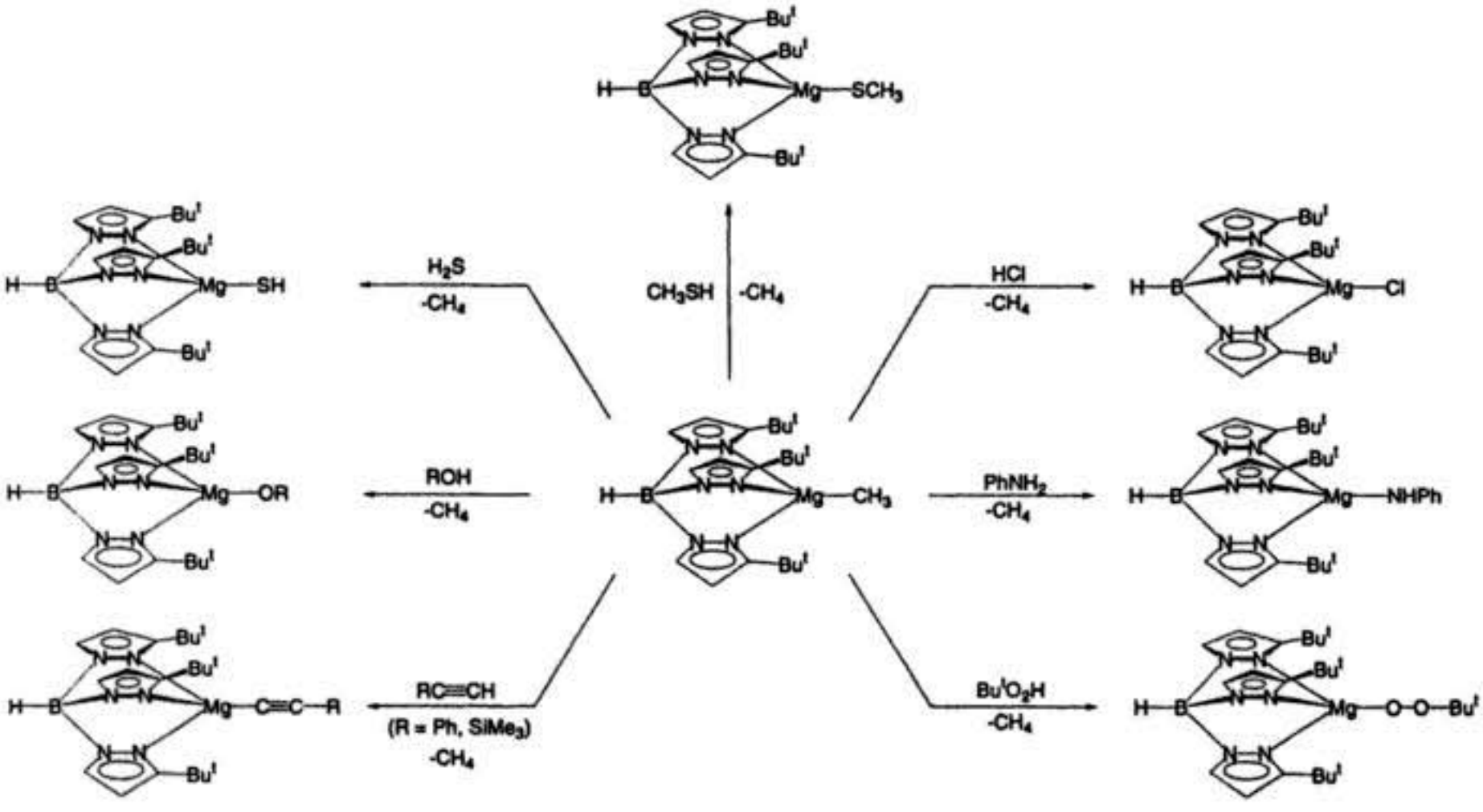
The alkylperoxo complexes $[Tp^{Bu^t}]MgOOR$ also effect oxygen atom transfer to PPh_3 at room temperature, giving $[Tp^{Bu^t}]MgOR$ and Ph_3PO [Eq. (13)].

$$[Tp^{Bu^t}]MgOOR + PPh_3 \rightarrow [Tp^{Bu^t}]MgOR + Ph_3PO \quad (13)$$

D. Reactions with HX and RX

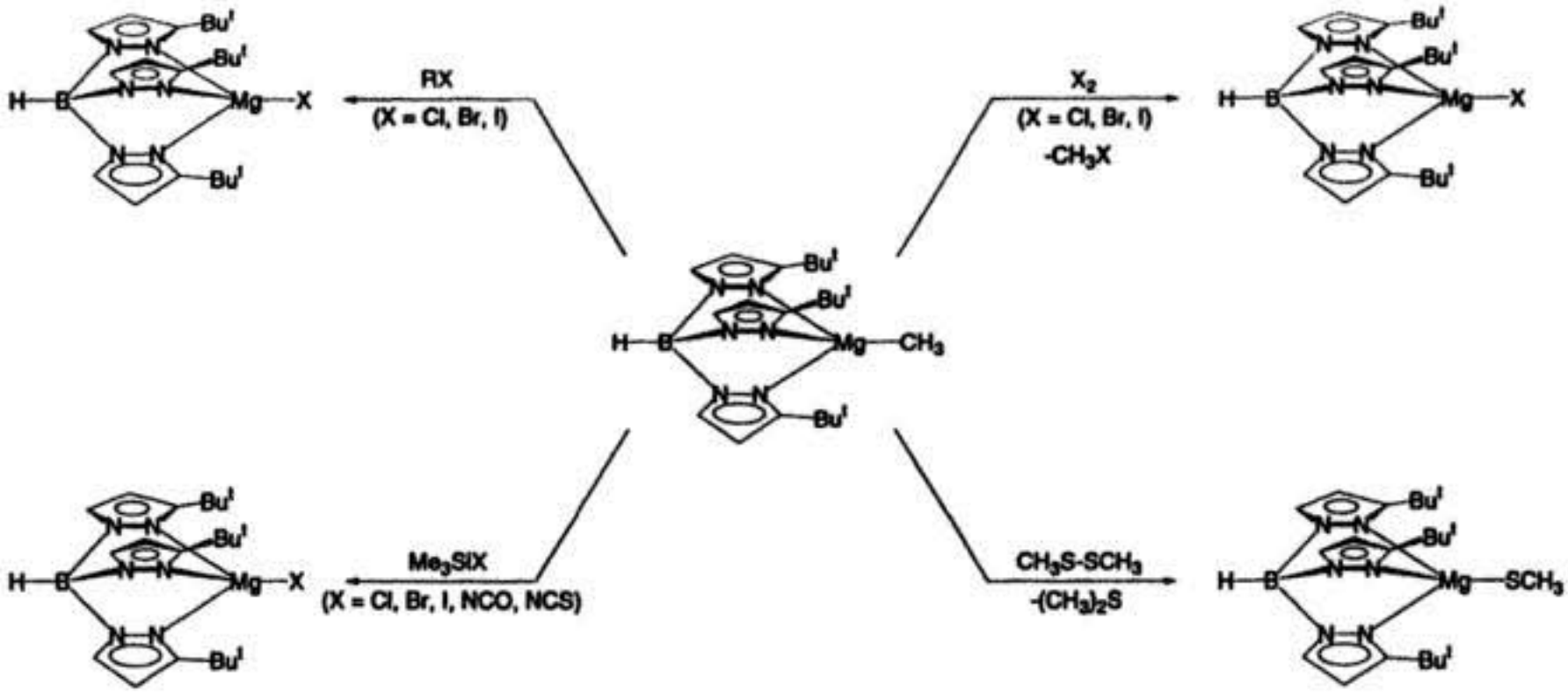
As would be anticipated, the magnesium–alkyl bonds in $[Tp^{Bu^t}]MgR$ are very susceptible toward reactions with protic reagents HX, which result in elimination of the alkane and formation of the corresponding $[Tp^{Bu^t}]MgX$ derivative. Although these reactions are not particularly useful from a synthetic organic chemistry perspective, they are of importance in terms of providing a wide variety of $[Tp^{Bu^t}]MgX$ derivatives, and also for defining the reactivity of the Mg–R bond in a controlled environment. Examples of protic reagents that react in this way include (1) $RC{\equiv}CH$ ($R = Ph$, $SiMe_3$); (2) ROH ($R = Et$, Pr^i, Bu^t, Ph, CH_2SiMe_3, $SiMe_3$); (3) Bu^tOOH; (4) $PhNH_2$; (5) CH_3SH; (6) H_2S; and (7) HCl, as summarized in Scheme 2.

A variety of nonprotic reagents, such as dimethyldisulfide, alkyl halides, trimethylsilyl derivatives, and halogens, also react with $[Tp^{Bu^t}]MgR$, and some of these reactions are summarized in Scheme 3.



Scheme 2 Reactivity of $[Tp^{Bu^t}]MgCH_3$ toward HX. (Modified from Ref. 21.)

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Scheme 3 Reactivity of $[Tp^{Bu'}]MgCH_3$ toward RX. (From Ref. 21.)



Scheme 4 Competitive alkyl exchange and coupling.

The reactions between $[Tp^{Bu'}]MgCH_3$ and a variety of alkyl and benzyl halides (RX) are not facile, and typically occur at about 100–140°C to give the halide derivative $[Tp^{Bu'}]MgX$. Similar derivatives are also obtained by the reactions of $[Tp^{Bu'}]MgCH_3$ with trimethylsilyl derivatives Me_3SiX (X = Cl, Br, I, NCS, NCO). The reactions of $[Tp^{Bu'}]MgCH_3$ with benzyl halides, $PhCH_2X$ (X = Cl, Br, I), cleanly give the halide derivative $[Tp^{Bu'}]MgX$. However, in addition to the formation of $PhCH_2CH_3$, significant quantities of bibenzyl ($PhCH_2CH_2Ph$) are also produced. The formation of bibenzyl is suggestive of radical processes in the reactions with RX, support for which is provided by the observation of ring opening in the reactions of cyclopropylmethyl halide derivatives [30]. Further support for a radical mechanism in these reactions is provided by the relative order of reactivities: for the alkyl iodides [CH_3I, CH_3CH_2I, $(CH_3)_2CHI$, $(CH_3)_3CI$] the increasing order of reactivity is primary < secondary < tertiary, and for the benzyl halides $C_6H_5CH_2X$ the order is chloride < bromide ≈ iodide. An alternative mechanism for formation of bibenzyl involves initial transmetallation to give the benzyl derivative $[Tp^{Bu'}]MgCH_2Ph$, followed by reaction with $PhCH_2X$. However, there is no evidence to support this pathway.

The reaction between $[Tp^{Bu'}]MgCH_3$ and labelled ${}^{13}CH_3I$ demonstrates that, in addition to alkylation (to give $[Tp^{Bu'}]MgI$ and ${}^{13}CH_3CH_3$), there is also a competitive metathesis process involving alkyl exchange (to give $[Tp^{Bu'}]Mg^{13}CH_3$ and CH_3I), as shown in Scheme 4. Similarly, the reaction between $[Tp^{Bu'}]MgCH_2CH_3$ and CH_3I also results in a degree of alkyl exchange, giving $[Tp^{Bu'}]MgCH_3$, concomitant with the irreversible formation of $[Tp^{Bu'}]MgI$. The exchange of alkyl groups between Grignard reagents and simply alklyl halides is not well documented. However, indirect evidence has

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been presented to support the occurrence of alkyl exchange with more complex derivatives [31,32]. Alkyl exchange between $[Tp^{Bu^t}]MgCH_3$ with $^{13}CH_3I$ is reminiscent of the sigma-bond metathesis exchange process reported for $(\eta^5\text{-}C_5Me_5)_2ScCH_3$ [33], but there is insufficient information available to identify whether there are any mechanistic similarities.

IV. COMPARISON OF $[Tp^{R,R'}]MgR$ WITH OTHER ALKYL AND HYDRIDE DERIVATIVES

The tris(pyrazolyl)hydroborato ligand system also provides a useful framework for stabilizing a series of other four-coordinate alkyl and hydride derivatives, such as $[Tp^{R,R'}]ZnR$ [34], $[Tp^{R,R'}]ZnH$ [35], $[Tp^{R,R'}]BeR$ [36], $[Tp^{R,R'}]BeH$ [37], $[Tp^{R,R'}]$ [38], $[Tp^{R,R'}]CdH$ [39], and $[Tp^{R,R'}]HgR$ [40]. The isostructural nature of these complexes is of importance in providing a means by which the intrinsic reactivities of M–R and M–H bonds may be assessed. For example, since dialkylzinc derivatives are two-coordinate monomers, whereas dialkylmagnesium derivatives are typically four-coordinate polymeric (or solvated) species, a comparison of the reactivities of these complexes does not necessarily provide a good indication of the intrinsic reactivity of the Mg–R versus Zn–R bond. In contrast, a comparison of the reactivities of the isostructural tris(pyrazolyl)hydroborato complexes $[Tp^{R,R'}]MgR$ and $[Tp^{R,R'}]ZnR$ provides a much better indication of the intrinsic reactivities of the respective M–R bonds. For example, $[Tp^{Bu^t}]MgCH_2CH_3$ reacts with $PhCH_2I$ approximately 10^4 times faster than the corresponding reaction between $[Tp^{Bu^t}]ZnCH_2CH_3$ and $PhCH_2I$. Similarly, $[Tp^{Bu^t}]MgCH_3$ reacts with CO_2 at room temperature, whereas no reaction is observed between $[Tp^{Bu^t}]ZnCH_3$ and CO_2 at 140°C [34].

V. SUMMARY

In summary, tris(pyrazolyl)hydroborato ligation provides a series of four-coordinate magnesium alkyl complexes, $[Tp^{R,R'}]MgR$, which are readily prepared by the reaction of R_2Mg with $[M][Tp^{R,R'}]$ (M = K, Tl). Although derivatives of the less sterically demanding tris(3,5-dimethylpyrazolyl)hydroborato ligand, $[Tp^{Me_2}]MgR$, are subject to thermal ligand redistribution reactions analogous to that of the Schlenk equilibrium (giving $[Tp^{Me_2}]_2Mg$), derivatives of the more sterically demanding tris(3-*t*-butylpyrazolyl)hydroborato ligand) $[Tp^{Bu^t}]MgR$ are thermally stable. The alkyl complexes $[Tp^{Bu^t}]MgR$, therefore, provide a means by which the reactivity of the Mg–R bond may be studied in a well-defined system. The reactivity of these complexes is typically lower than those of Grignard reagents, a factor that has aided isolation of complexes such as alkylperoxo derivatives. Furthermore, in some cases, such as reactions with methyl ketones, the enolate reaction products do not parallel the alkoxide products of the corresponding Grignard reaction.

ACKNOWLEDGMENT

I wish to acknowledge the National Science Foundation for support of the work that is described in this section, and also the students and postdoctoral associates who have worked on this project.

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15

Nucleophilic Substitution with Electrophilic Organic, Main Group, and Transition Metal Species

GARY S. SILVERMAN
Elf Atochem North America, Inc.
King of Prussia, Pennsylvania

I. INTRODUCTION

The chemistry described in Chapters 15–21 is categorized by the "net" synthetic product. In some instances this may be an oversimplification and the reader is encouraged to refer to the chapters in Part V for mechanistic details.

This chapter will cover the prototypical nucleophilic substitution reactions of Grignard reagents with organic, main group, and transition metal electrophiles. Because of the large volume of work, it is virtually impossible to be comprehensive. Therefore, the focus will be on the application of nucleophilic substitution reactions, what the competing reactions are and, if possible, how to minimize or take advantage of these competing reactions.

Allylic substitution reactions [1] will be discussed in the S_N2 versus S_N2' (see Chapter 24); cyclization reactions from di-Grignard reagents will be discussed in Chapter 25; metal-catalyzed reactions will be covered in Chapters 29 and 30; the chemistry of acetylenes and Si are covered in Chapters 31 and 32; and while some asymmetric reactions will be discussed, the reader is encouraged to peruse through Chapter 28.

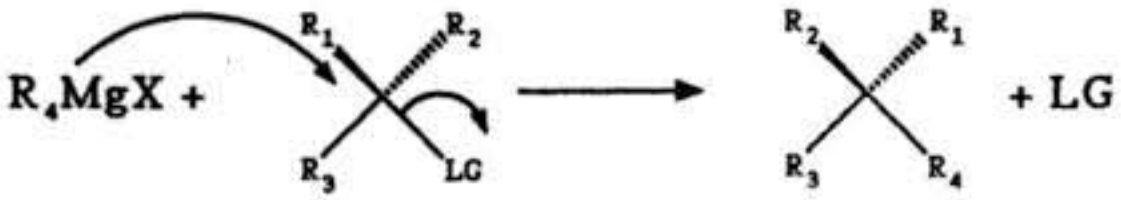
II. ELECTROPHILIC ORGANIC SPECIES

A. Potential Problems

Nucleophilic substitution reactions using Grignard reagents are ubiquitous throughout the literature and have important commercial applications [Eq. (1)]. These reactions are favored

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by a highly electrophilic carbon, good leaving groups, forcing conditions and, in specific cases, the relief of ring strain energy.

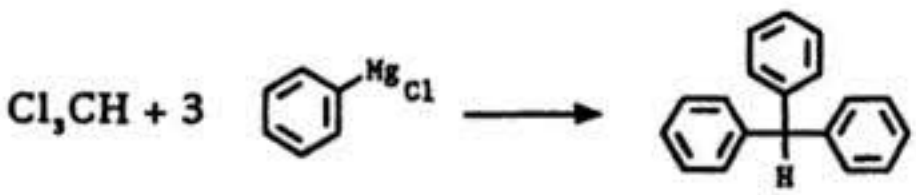


(1)

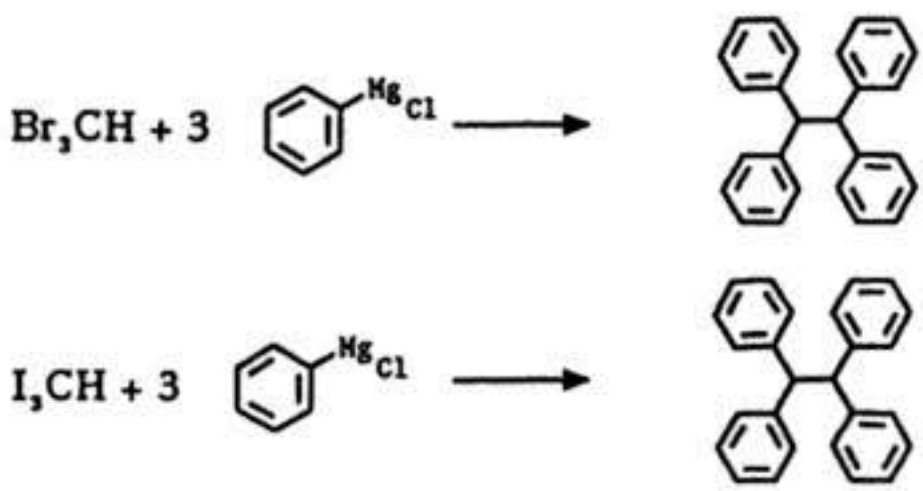
X = halogen
LG = leaving group such as: halogen, OR, SR, CN, etc.

One would expect these nucleophilic substitution reactions to proceed with inversion of configuration (S_N2), but occasionally, competitive reactions result in retention of configuration. Typically, the racemic product is observed; the stereochemical results are discussed in more detail in Chapters 10, 11, and 28. In addition to these stereochemical problems, there are other potential drawbacks for the nucleophilic substitution reaction, owing to competing reactions such as MgX–LG exchange, elimination, and to a smaller extent, electron-transfer reactions.

The MgX–LG exchange reaction was briefly discussed in Chapter 2 as an alternative method for the preparation of Grignard reagents. The same problem of forming two different Grignard reagents in solution also exists here, and polarization of R–LG bond enhances both the nucleophilic substitution as well as the MgX–LG reaction. A classic example of the MgX–LG exchange is the reaction of 3Eq of phenylmagnesium bromide with chloroform [2], bromoform [3], or iodoform [4]. The reaction with chloroform [Eq. (2)] proceeds as predicted, to give triphenylmethane in 70–80 wt% yield. The MgX–LG exchange is favored with the bromoform and iodoform to yield 1,1,2,2-tetraphenylethane as the final product [Eqs. (3) and (4)].



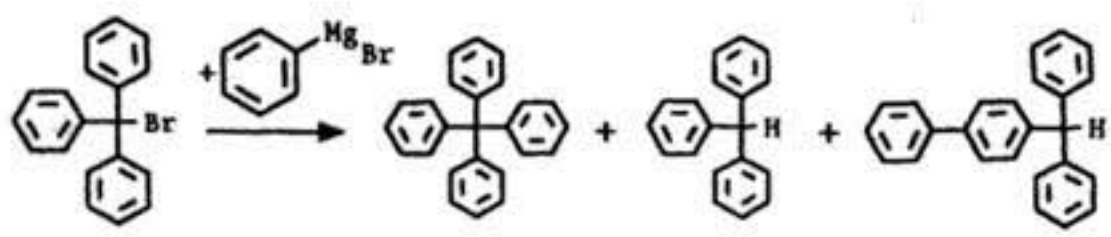
(2)



(3)

(4)

The exchange reaction becomes even more competitive when there are steric constraints and when there is the potential for resonance-stabilized ions, as in triphenylmethylbromide [Eq. (5); 5]. The presence of diphenylbiphenylmethane indicates

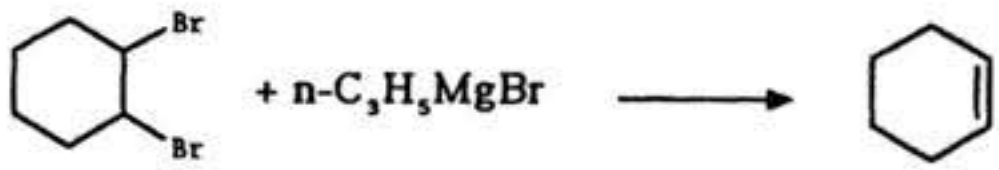


(5)

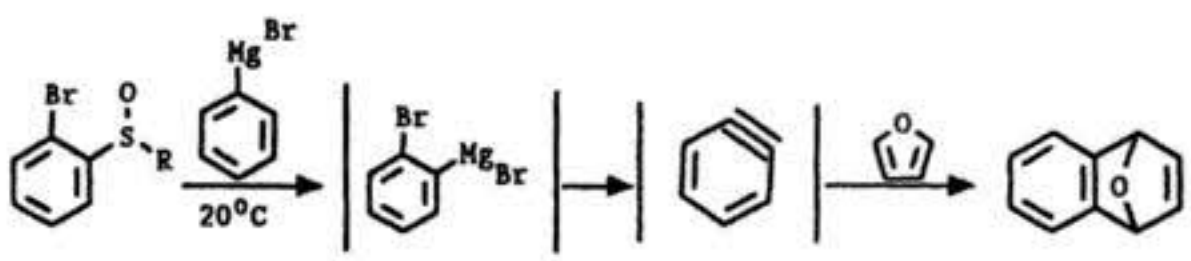
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that there is a resonance-stabilized intermediate that allows attack at the *para*-position, as well as the MgBr–Br exchange reaction that, after hydrolysis, yields the C–H bond. This indicates that there is a delicate balance between the exchange reaction versus nucleophilic substitution.

The second potential problem is elimination reactions [Eqs. (6) and (7); 6,7]. These reactions typically occur when there is a good leaving group at the β-position relative to an acidic proton, or a good leaving group that can undergo the MgX–Lg exchange (see Chapters 11, 12, and 23 for more details). When there are two good leaving groups at the α-position, a carbenoid is formed that typically results in a linear insertion of a carbon unit instead of the typical cyclopropyl ring formation [Eq. (8); 8].



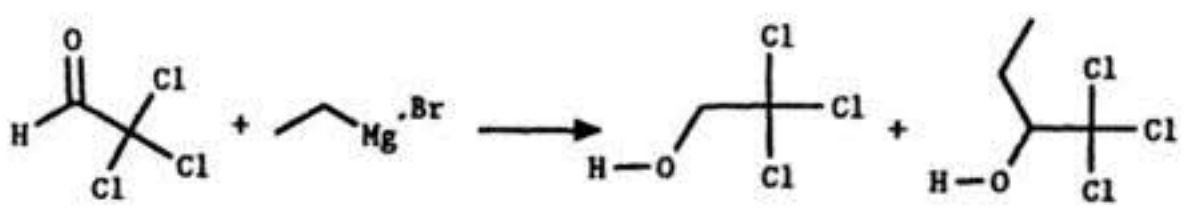
(6)



(7)

$$2RCH_2MgBr + CHBr_3 \rightarrow RCH{=}CH_2 + RCH_2Br + 2MgBr_2 \quad (8)$$

Electron transfer, the third type of competitive reaction, is not as significant in Grignard chemistry relative to organolithium chemistry. The reduction potentials of Grignard reagents are approximately -2.0 to -2.5 V (in ethereal solvents measured versus SCE) that can undergo reduction chemistry if the organic substrate can be reduced under the reaction conditions. This is particularly true with carbonyl derivatives, which are the focus for Chapters 17 and 20 [Eq. (9); 5]. Therefore, the substituents on the substrate need to be chosen carefully (i.e., the electrochemically sensitive groups needs to be masked or protected).



(9)

B. Effect of Leaving Groups

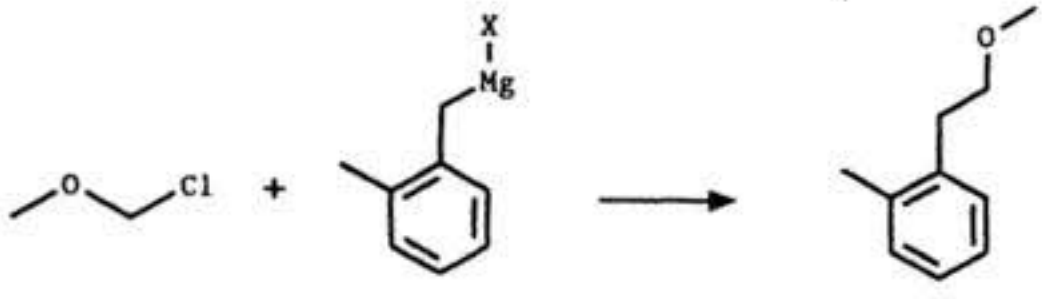
The general effect of the leaving groups relates to the polarization of the LG–C bond. Therefore, a general rate of reaction, based on the Grignard-compatible leaving groups is as follows: halogen > OR $\geqslant$ SR, CN, ... Another issue that was not discussed in the previous section is the prototypical addition reactions (see Chapters 11, 16–21). The leaving group and other functionality on the substrate must be compatible with the Grignard reagent, or the reaction rate of nucleophilic substitution must be much greater than the reaction rate of the addition reaction.

1. Halogens

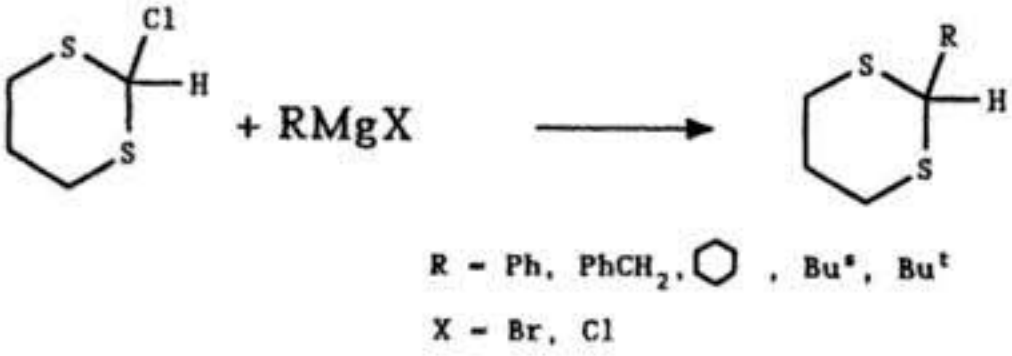
The halogens will polarize the R–X bond more than most leaving groups that are compatible with Grignard chemistry. Subsequently, the halogens tend to be the site of reactivity for

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substitution, MgX–X exchange, and so on. For example, chloromethylmethyl ether, an asymmetric ether, can be easily modified by simply adding a Grignard reagent that will displace the chloride instead of the methoxy group [Eq. (10); 9]. Competition of a halide versus a thioketyl is shown in Eq. (11) [10]. Again halide substitution is the predominant product.

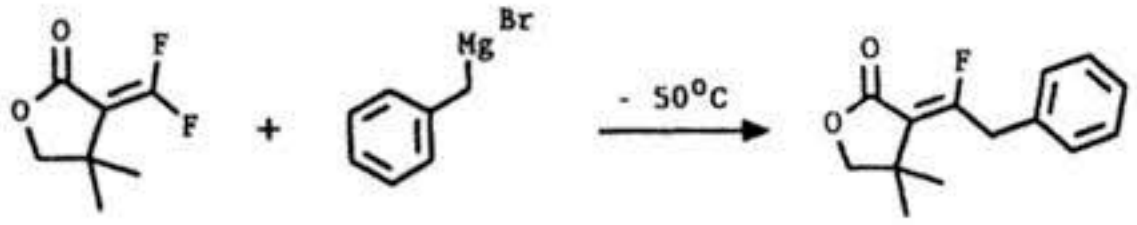


(10)



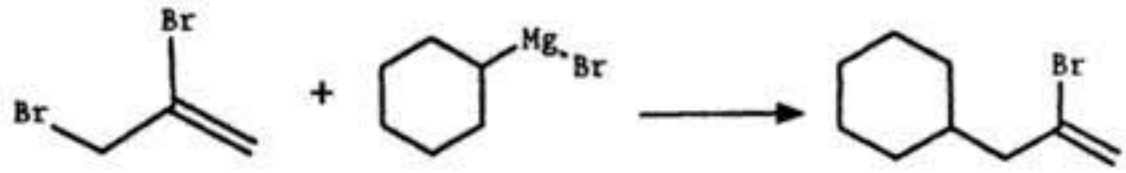
(11)

As expected, altering a reaction parameter, such as temperature, can facilitate nucleophilic substitution, over the other types of reactions [Eq. (12); 11]. In this example, at −50°C, nucleophilic substitution predominates, with the vinyl fluoride undergoing substitution with the benzylmagnesium bromide, instead of the competitive nucleophilic addition to the carbonyl or the olefin.

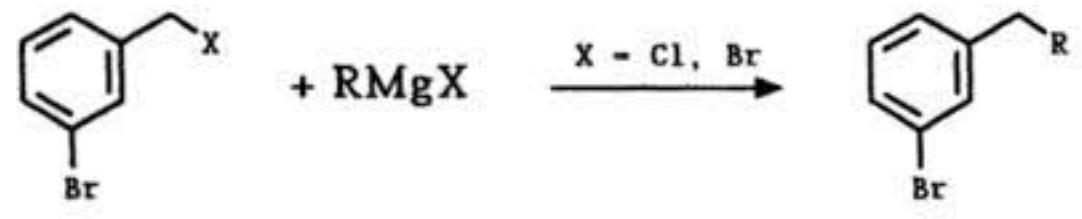


(12)

By taking advantage of the organic moiety, allylic (benzylic) versus vinylic (aromatic), regioselectivity can be accomplished with more than one halide present in the organic substrate [Eqs. (13) and (14); 12,13]. Not only are these reactions regioselective, but now there is a reactive halide in the product that can be converted into a Grignard reagent for subsequent reactions. Occasionally, the second halide is used for a intramolecular cyclization reaction (see Chapters 25–27).



(13)



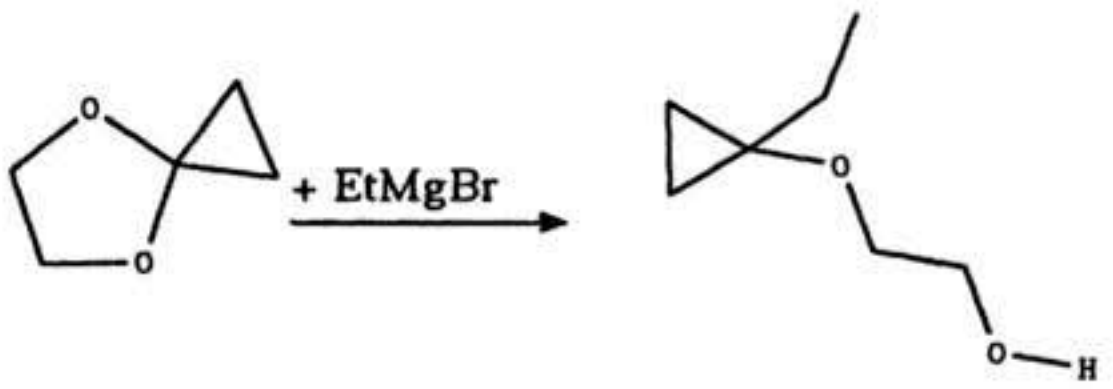
(14)

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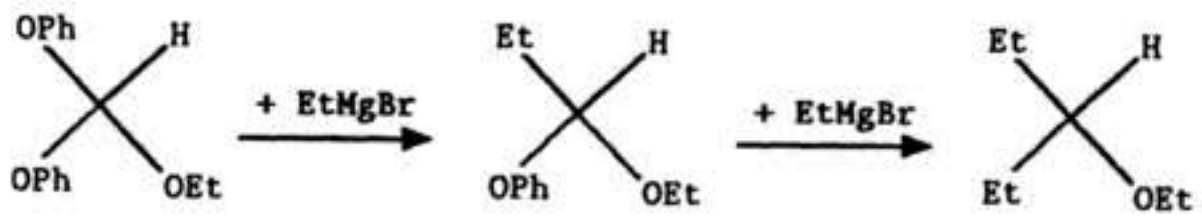
Some selected nucleophilic substitution reactions with halogens as the leaving group are shown in Table 1. Interestingly, few if any elimination products were formed in the example shown in Table 1, entry 2. This is in sharp contrast with the 1,2-dibromohexane example [see Eq. (6)], which can be attributed to the use of the less-reactive dichloride and the pyran ring.

2. *Alkoxy*

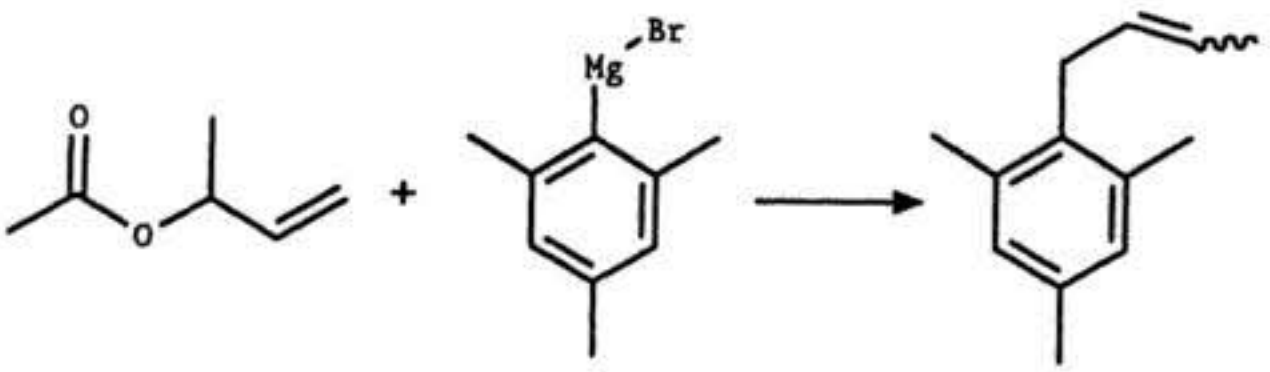
Another common leaving group is the alkoxy group (OR), which can be a cyclized leaving group, such as a ketal [Eq. (15); 24], lactone, or an epoxide (see Section II.D). Different alkoxy groups can be used for selective substitution, as shown in Eq. (16) [25]. In this example the phenoxy group is selectively displaced; rather than the ethoxy group. In fact, if there is a good leaving group, such as an acetate, substitution will prevail over addition to the carbonyl or an olefin [Eq. (17); 26].



(15)

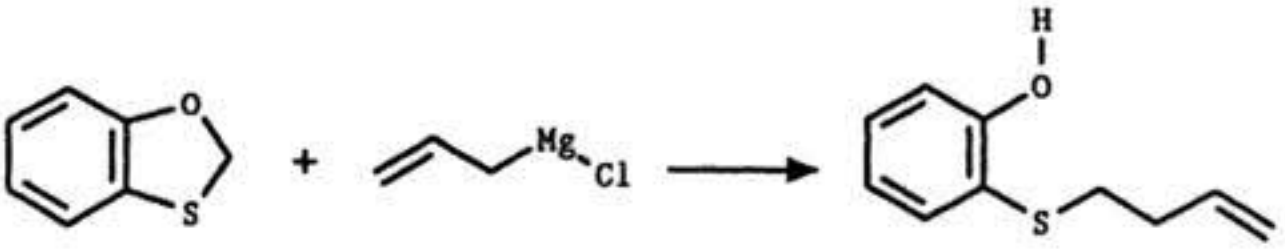


(16)



(17)

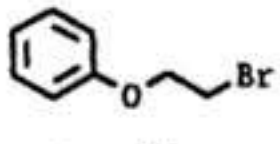
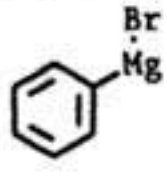
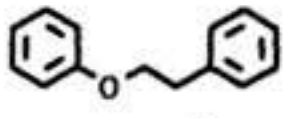
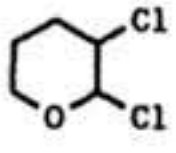
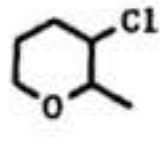
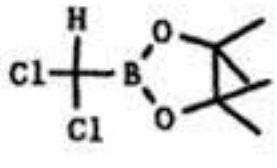
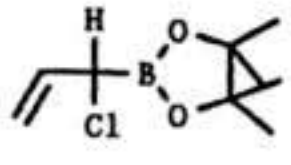
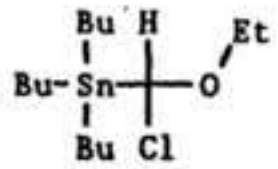
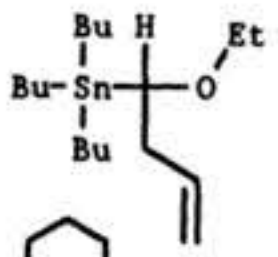
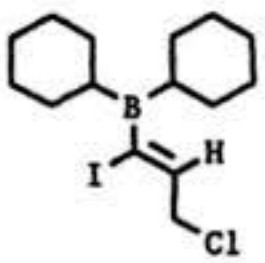
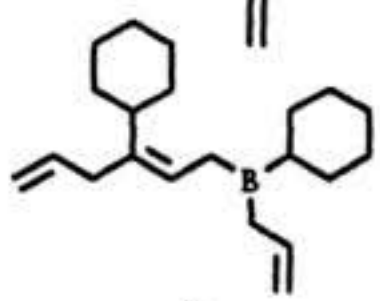
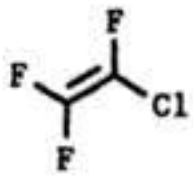
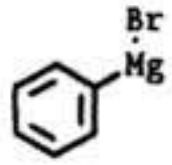
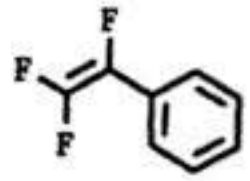
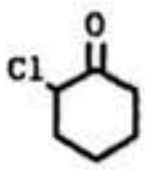
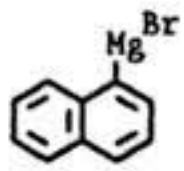
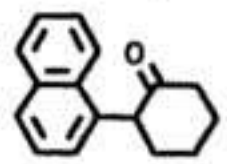
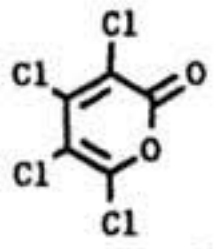
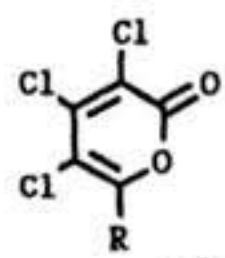
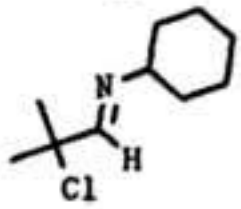
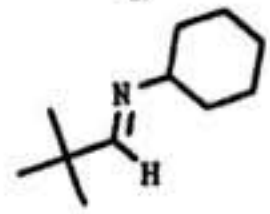
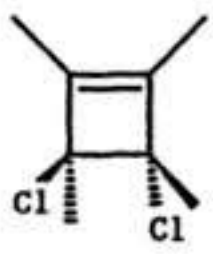
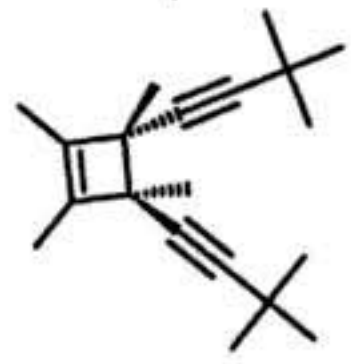
Typically the alkoxy leaving group is the better Grignard-compatible leaving group relative to other nonhalogen leaving groups [27–29]. In all three of the following reactions the OR is the preferred-leaving group versus the SR [Eq. (18)], NR_2 [Eq. (19)], and CN [Eq. (20)]. The reaction depicted in Eq. (20) is not a true competition between the CN and OR groups, but, as expected, the OR is displaced to yield the product (see Section II.B.3 and Table 3 for more information on the CN group). An interesting reaction resulting in the alkoxy displacement and retention of the CCl_3 substituent is shown in Eq. (21) [30]. Here the ring strain and the weak S–O bond facilitates OR as the leaving group. Some other selected examples of preferential OR substitution are listed in Table 2.



(18)

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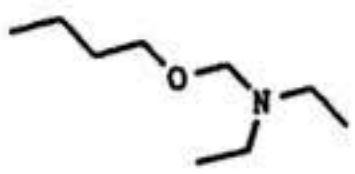
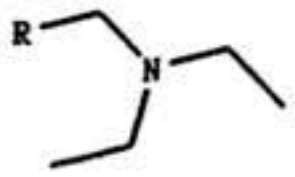
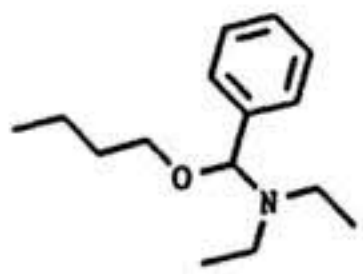
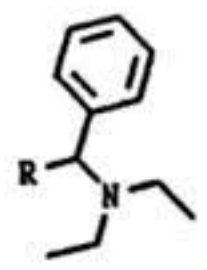
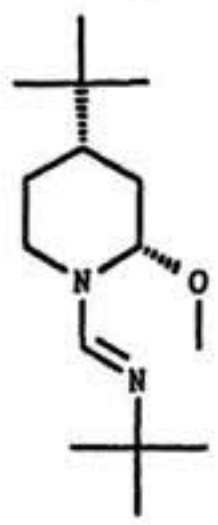
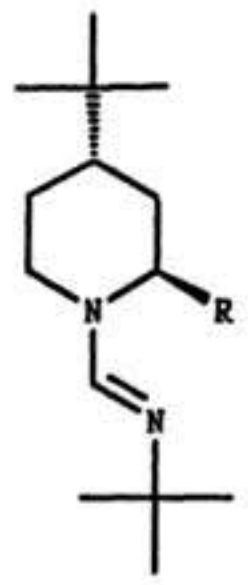
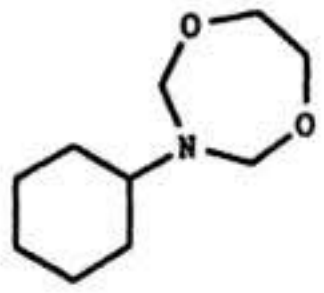
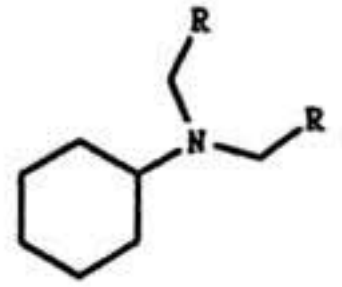
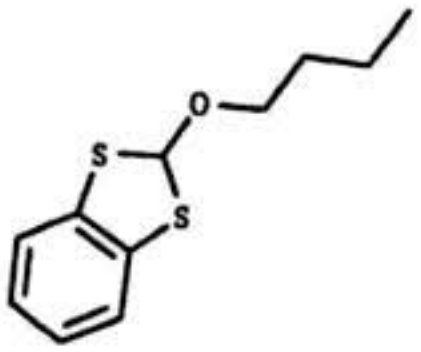
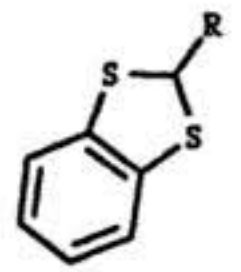
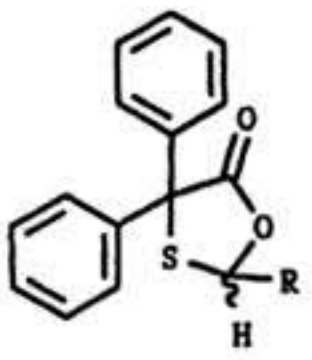
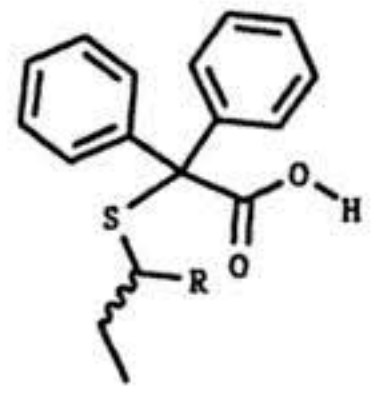
Table 1 Selected Examples of C–X Bond Cleavage

Entry	Substrate	RMgX	Product	Yield (%)
1[14]				83
2[15]		CH_3MgBr		65 - 72
3[16]		CH_2-CHMgCl		63 - 86
4[17]		CH_2-$CHCH_2MgBr$		80
5[18]		CH_2-$CHCH_2MgBr$[A]		71 - 75
6[19]				82
7[20]				62
8[21,B]		R = CH_3, Bu^t, Ph, 		20 - 57
9[22]		CH_3MgI		76[C]
10[23]		$(CH_3)_3CCCMgBr$[A]		29

A. 2 equivalents of Grignard reagent used for the reaction.
B. Reaction carried out at - 10°C.
C. Corrected yield based on 45% recovered starting material.

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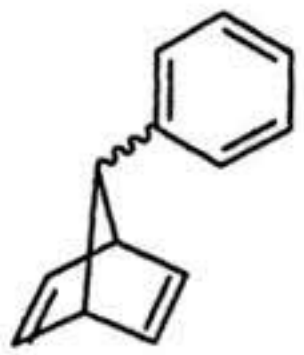
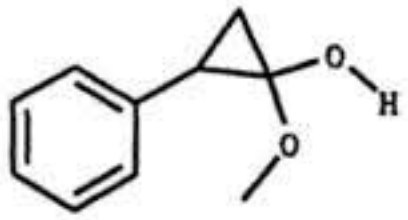
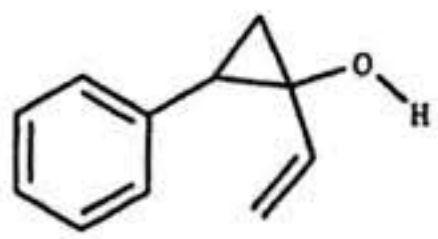
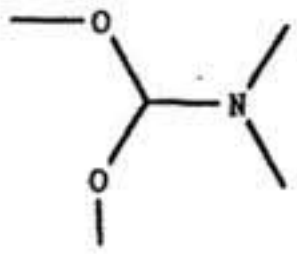
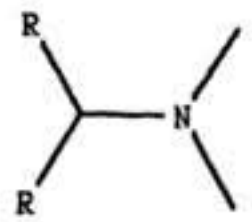
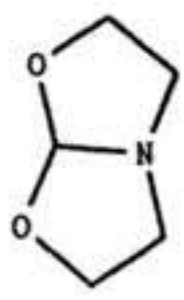
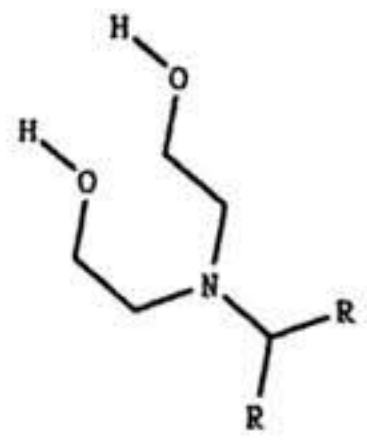
Table 2 Selected Examples of C–O Bond Cleavage

Entry	Substrate	RMgX	Product	Yield (%)
1[31]		R = $(CH_2)_4Cl$ $(CH_2)_4OCH_3$ $(CH_2)_4SCH_3$ $(CH_2)_4SiCH_3$		53 - 70
2[31]		R = $(CH_2)_4Cl$ $(CH_2)_4OCH_3$ $(CH_2)_4SCH_3$ $(CH_2)_4SiCH_3$		56 - 90
3[32]		R = CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, C_6H_5		76 - 98 (66 - 91 ee)
4[33,A]		R = CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, C_6H_5, $CH_2C_6H_5$		60 - 80
5[34]		R = $CH_2CH_2CH_3$, $CH(CH_3)_2$, C_6H_5, C_6H_{11}		68 - 89
6[35]		CH_3CH_2MgBr		50

Continued

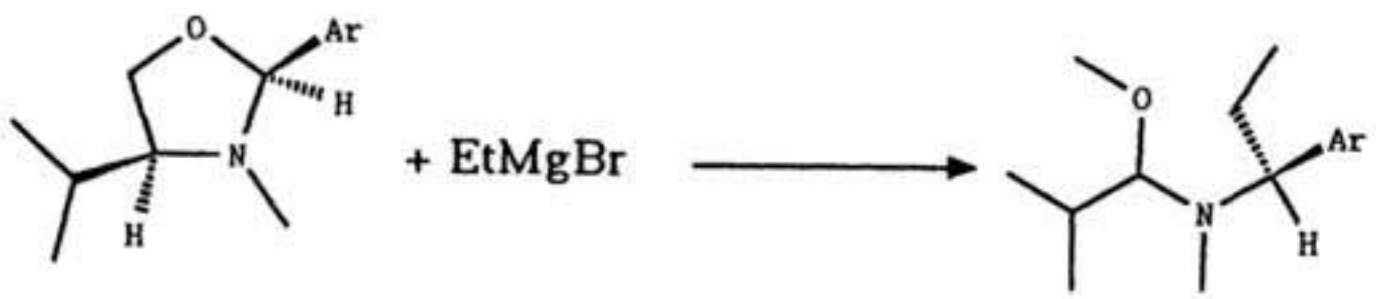
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Table 2 (Continued)

Entry	Substrate	RMgX	Product	Yield (%)
7[36]		C_6H_5MgCl		75
8[37,B]		CH_2-CHMgBr		50
9[38,A]		R - C_6H_5, $CH_2C_6H_5$, $CH_2CH_2CH_2CH_3$		50 - 90
10[38,A]		R - C_6H_5, $CH_2C_6H_5$, $CH_2CH_2CH_2CH_3$		41 - 84

A. 2 Equivalents of Grignard reagent

B. 1 Equivalent of Grignard is used to abstract the alcoholic H

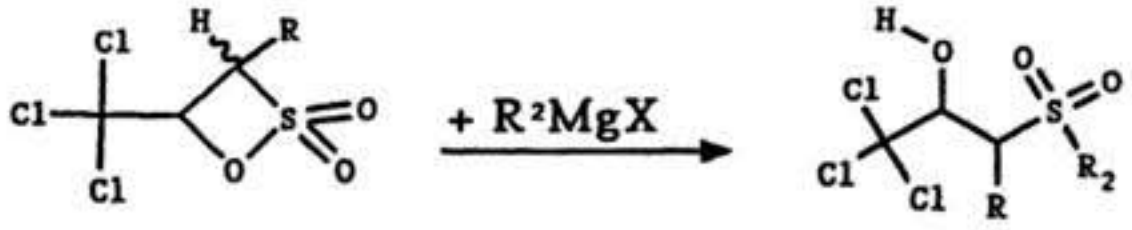


Ar - Ph, 4-ClPh, 4-CH_3Ph
58 -80 % ee

(19)

$$PhOCN + R^2MgX \xrightarrow[81 - 92\ \%\ yield]{R^2 = Me, {}^nBu, {}^tBu, Ph} PhOH + R^2CN \qquad (20)$$

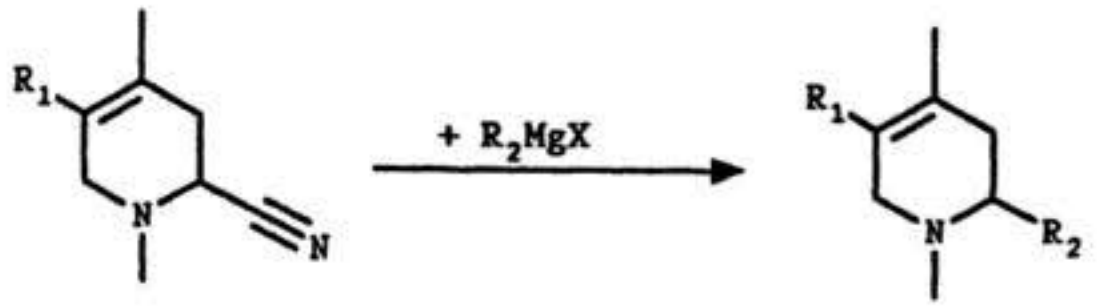
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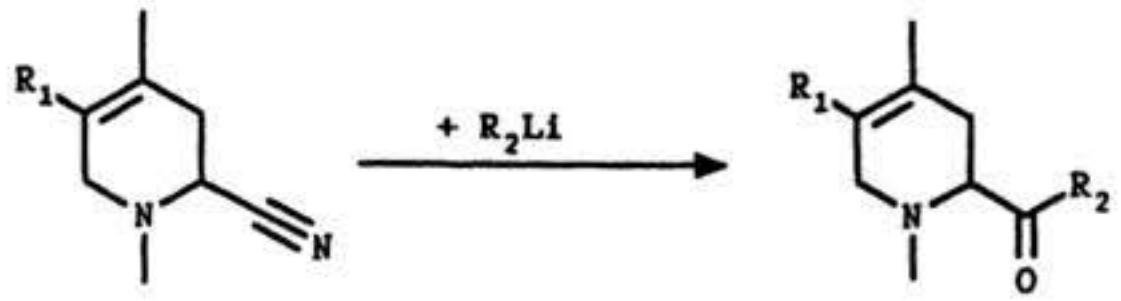
(21)

3. *Miscellaneous*

Other leaving groups are less successful, owing to insufficient polarization of the C–LG bond, or because competitive reactions predominate. A good example for competitive reactions is the cyanide (CN) leaving group which, under the right conditions, is an effective leaving group [Eq. (22); 39]. Use of the same substrate from Eq. (22) with the corresponding organolithium reagent (RLi) results in addition to the CN group [Eq. (23)].



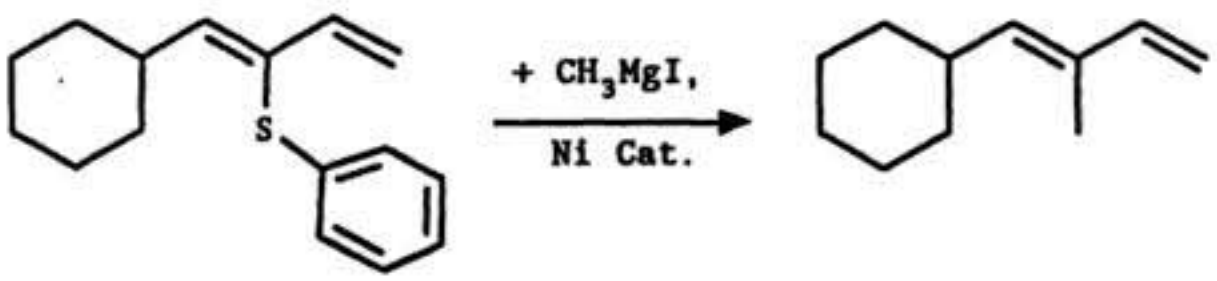
(22)



(23)

Other examples of the cyanide as a leaving group are shown in Table 3 (entries 1–3). The chemistry shown in Table 3, entry 3, indicates that not only does nucleophilic substitution of a thiocyanate group displace the cyanide to form a thioether, but an extra equivalent of CH_3MgI results in addition to the aldehyde and subsequent dehydrolysis to yield the final product. Typically addition to the cyanide group is competitive, with nucleophilic substitution resulting in a mixture of reaction products.

Mercapto leaving groups, such as SC_6H_5 or SCH_3, are effective, especially when a cross-coupling catalyst, such as $NiCl_2(PPh_3)_2$, is used [Eq. (24); 45]. As expected, an

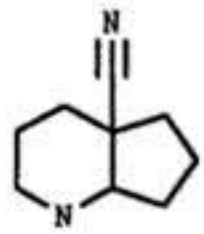
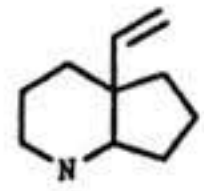
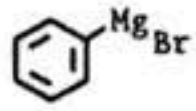
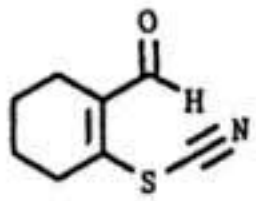
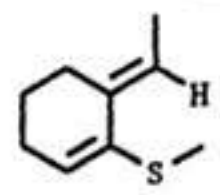
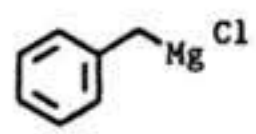
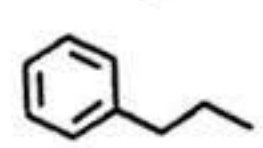
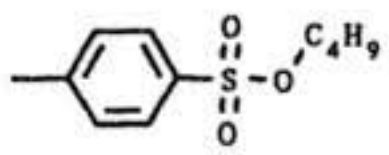
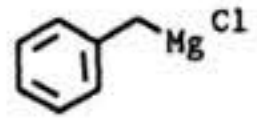
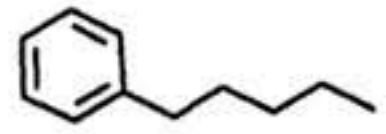
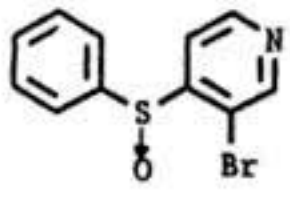
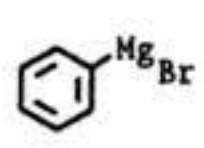
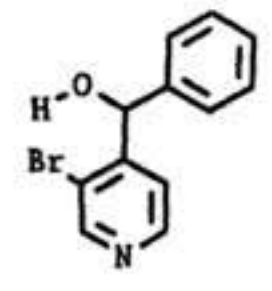
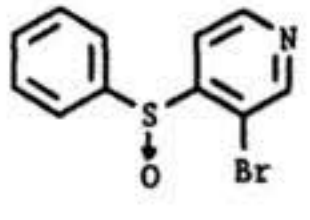
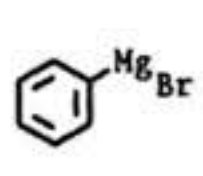
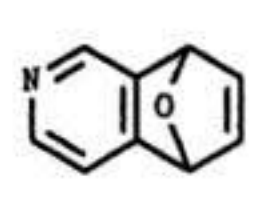


(24)

episulfide is susceptible to nucleophilic substitution because of the ring strain, as well as because of the polarization of the C–S bond [Eq. (25); 46]. Note that in this example [Eq. (25)] either the allylic anion has rearranged or there is a MgX–LC exchange followed by an S_N2' reaction (see Chapter 24). The S–S bond of disulfides can be reduced by Grignard reagents to give the expected thioethers [Eq. (26); 47]. Other examples of sulfoxides, sulfates, and arylsulfonic leaving groups are given in Table 3 (see entries 4–7). Entries 6 and 7 are

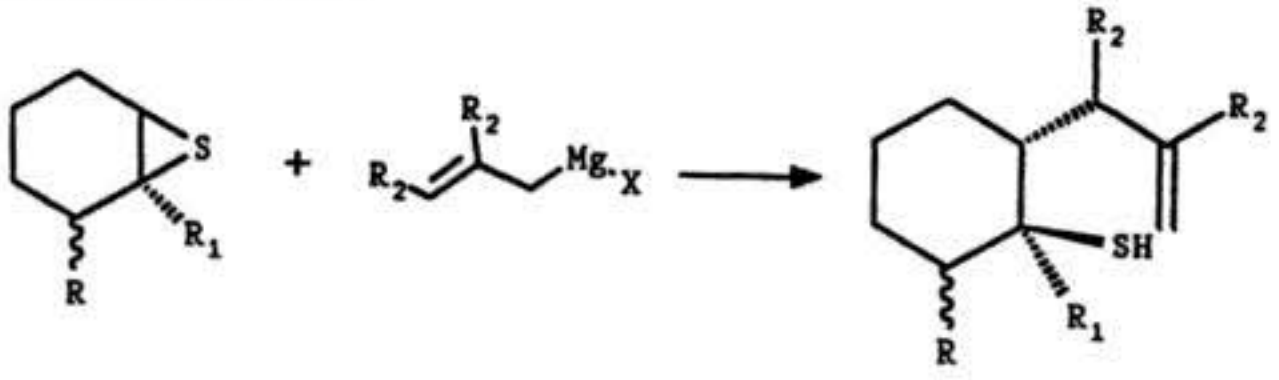
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Table 3 Selected Examples of C–LG Bond Cleavage

Entry	Substrate	RMgX	Product	Yield (%)
1[40]				94
2[41]	$(CH_3O)_3CCN$		$(CH_3O)_3C$ 	84
3[42]		CH_3MgI^A		75
4[43]	$(CH_3CH_2)_2SO_4$			70 - 75
5[44]				50 -57
6[7]				67
	+ PhCHO			
7[7]				42
	+ 			

A. 2 equivalents of Grignard reagent

particularly interesting because of the proposed pyridyne intermediate that forms after a MgX–S(O)Ph exchange.



(25)

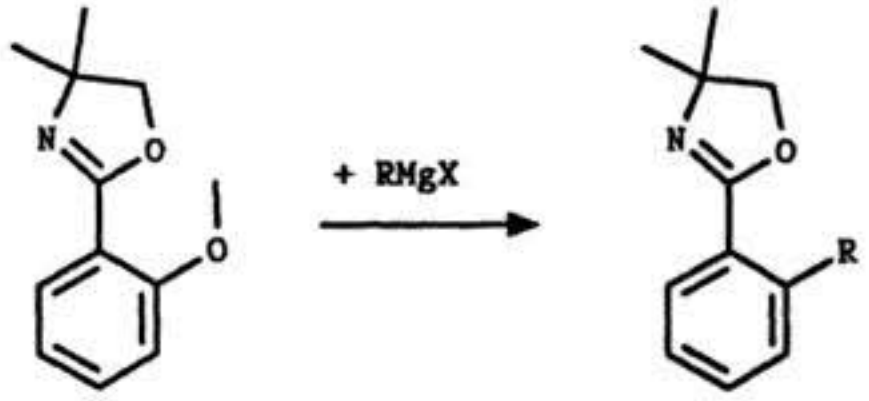
$$C_6F_5SSCl + C_6H_5MgBr \rightarrow C_6F_5SC_6H_5 + C_6H_5SC_6H_5 \quad (26)$$

Material chroniony prawem autorskim

C. Nucleophilic Aromatic Substitution

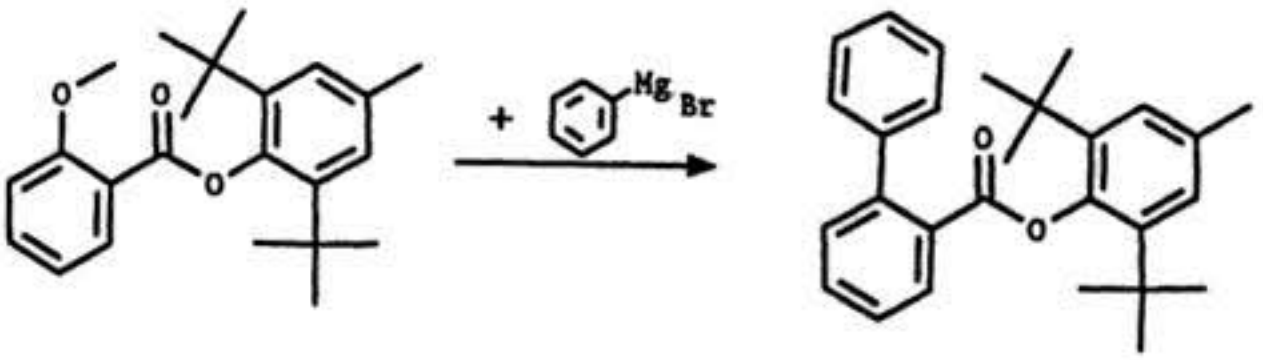
Aromatic substitution reactions are typically carried out in high yield using metal-catalyzed cross-coupling reactions (see Chapter 29) [48–50]. In particular, the biaryl reactions are difficult to obtain high yield without a metal catalyst. However, there are some non–metal-catalyzed coupling strategies that can result in high-yield reactions.

One of the more successful biaryl-coupling reactions was developed by the Myers group, using oxazoline to activate an *ortho*- or a *para*-leaving group, such as methoxy [51; Eq. (27)]. Recently, the Myers group has adapted this method to make chiral biaryl (Table 4, entry 1). This method is also effective with primary, secondary, and tertiary alkyl Grignard reagents (see Table 4, entries 4 and 6).



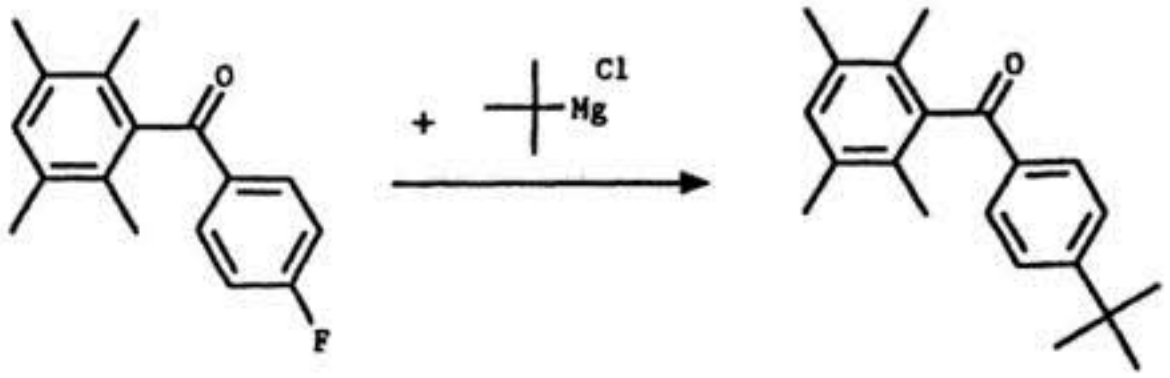
(27)

The Miyano group has modified the moderately successful ester activation of an *ortho*-leaving group by using a bulky 2,6-disubstituted phenol for the ester functionality [59; Eq. (28) and Table 5]. The problem encountered with the previous work [60,61] was the competitive addition reaction to the carbonyl of the ester, resulting in low to moderate yields (30–80%). Use of a (−)menthoxy as the leaving group, with an *ortho* bulky ester activating group, results in high yields (80–90%) of binaphthyls, with an optical yield of greater than 97% (see Table 5, entries 5 and 6).



(28)

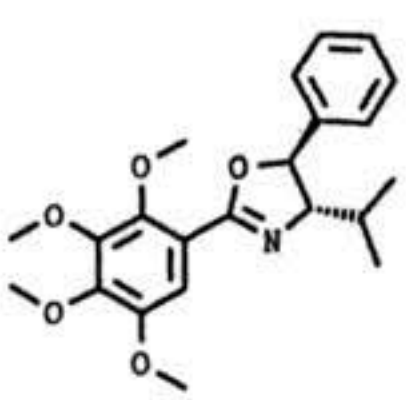
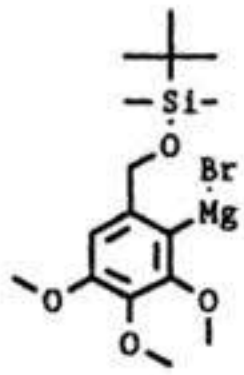
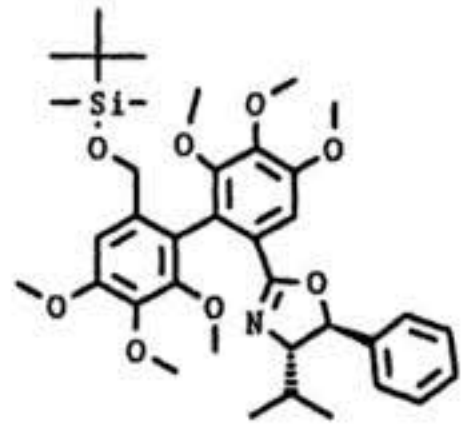
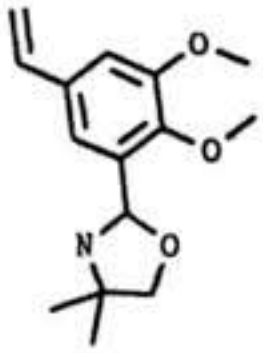
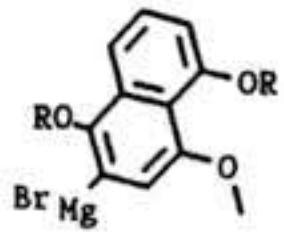
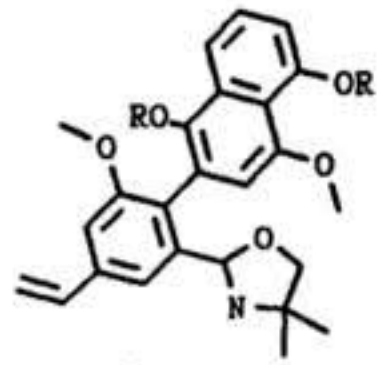
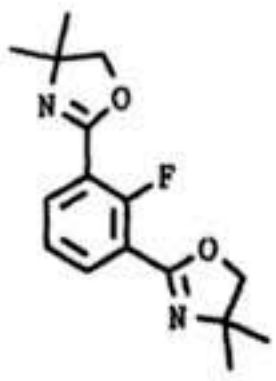
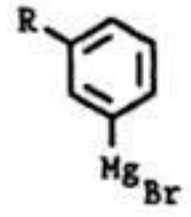
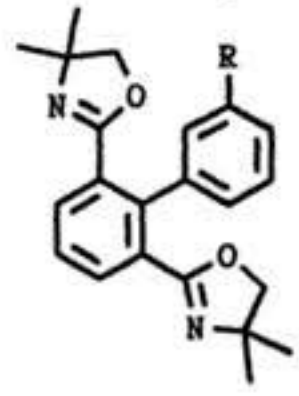
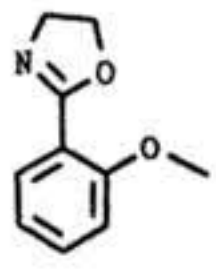
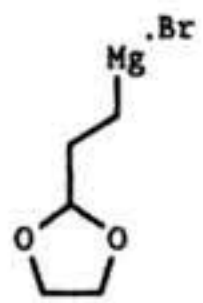
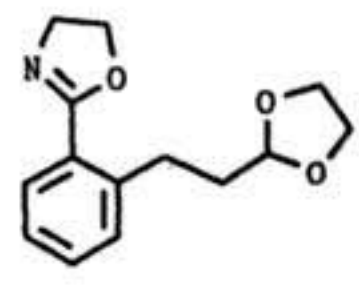
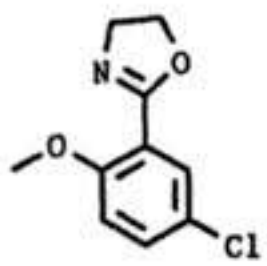
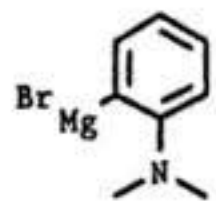
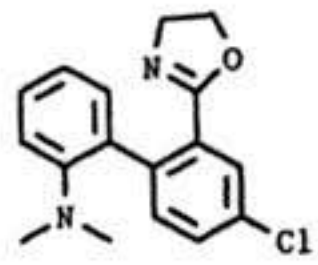
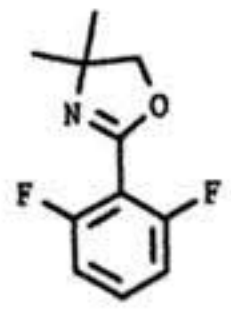
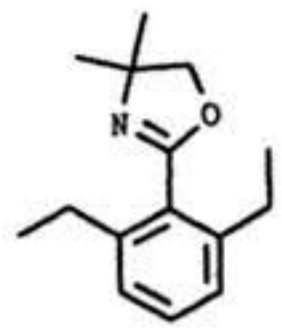
The same philosophy of using steric bulk has had some moderate success when a bulky ketone is used as an activating group (see Table 5, entires 9–13). The leaving group can have a dramatic effect on the yield, and Fuson's study indicates that $-OPh \geqslant -SO_2CH_3 > -SO_2Ph > -SPh > -SCH_3$. As expected, the *para*-position is also activated [Eq. (29)], with a similar dependency on the leaving group (see Table 5, entries 14 and 15).



(29)

Material chroniony prawem autorskim

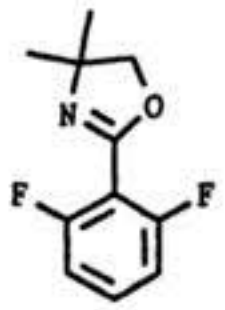
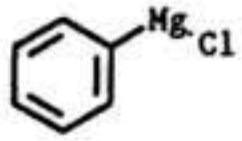
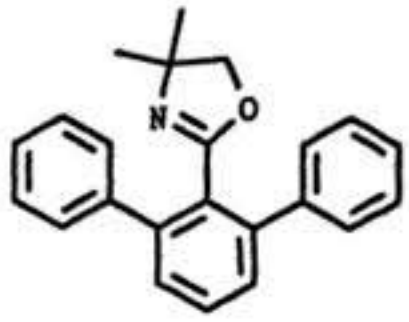
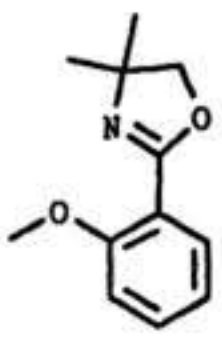
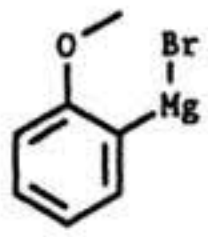
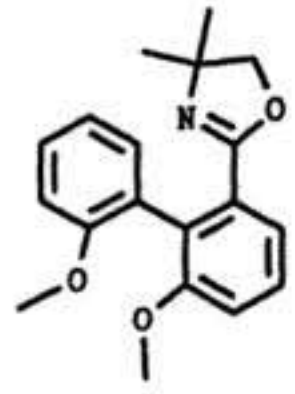
Table 4 Oxazoline Activation for Aromatic Substitution

Entry	Substrate	RMgX	Product	Yield (%)
1[52]				90
2[53]				50 - 60
3[54]				96
4[55]				95
5[56]				95
6[57,A]		CH_3CH_2MgCl		99

Continued

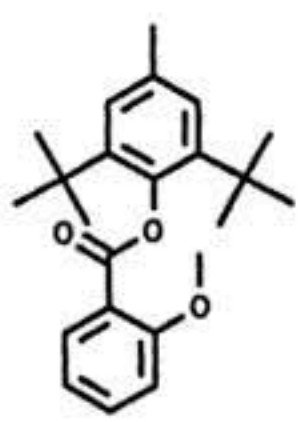
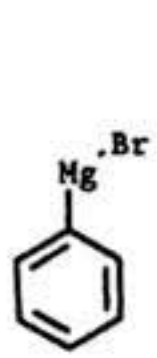
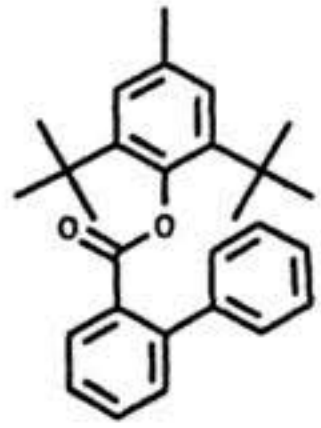
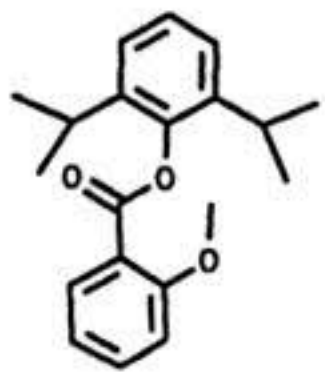
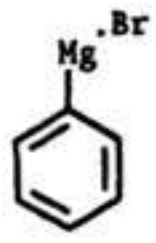
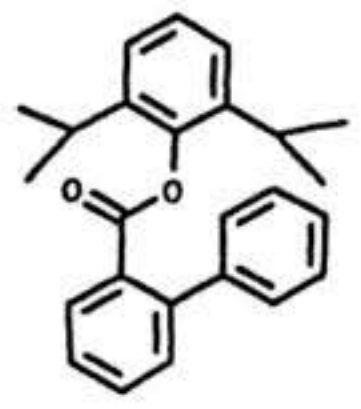
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Table 4 Continued

Entry	Substrate	RMgX	Product	Yield (%)
7[57,A]				80
8[58]				95 +

A. 2 equivalents of Grignard reagent

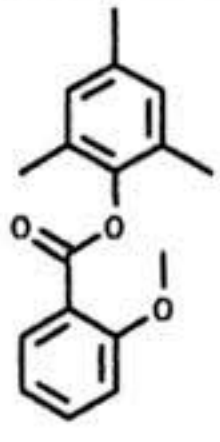
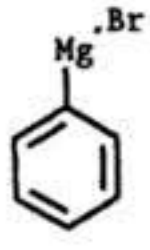
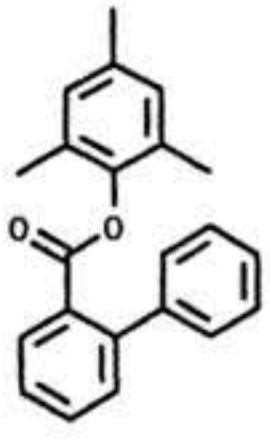
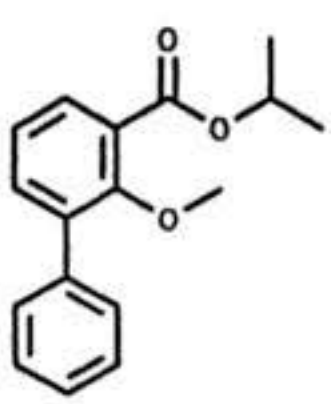
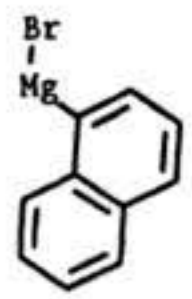
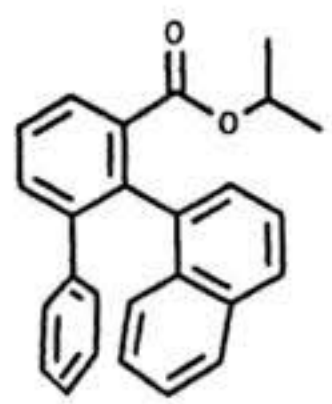
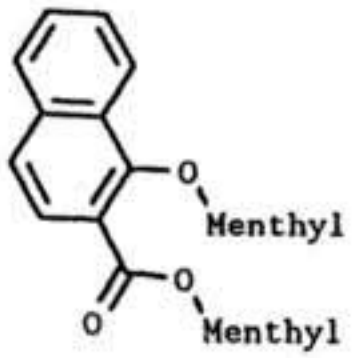
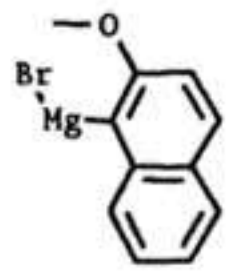
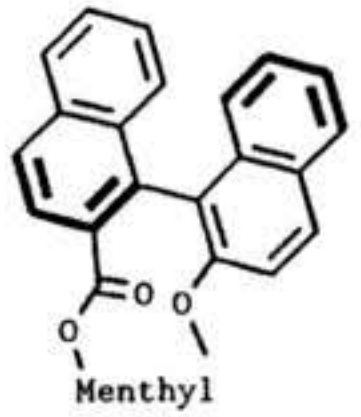
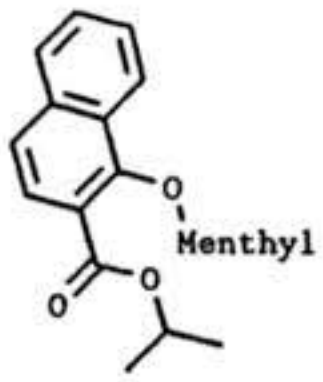
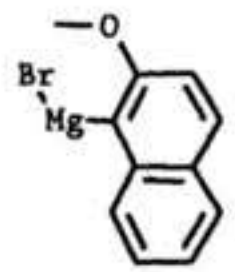
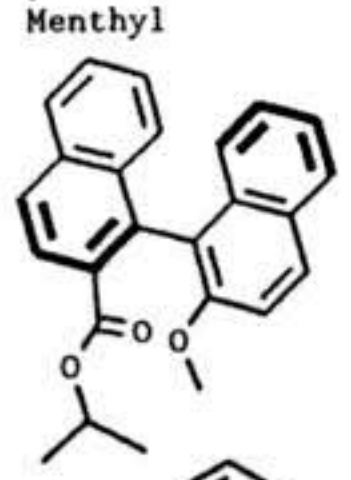
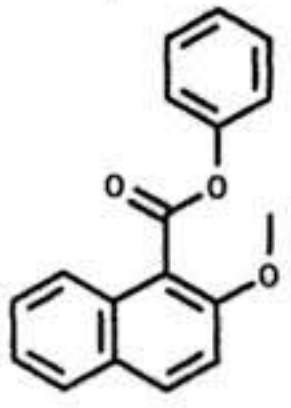
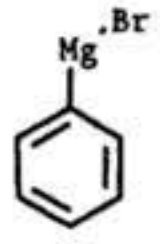
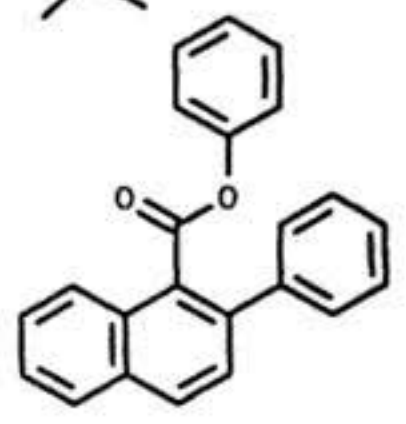
Table 5 Bulky Aromatic Ester or Ketone Activation

Entry	Substrate	RMgX	Product	Yield (%)
1[60]				96
2[60]				71

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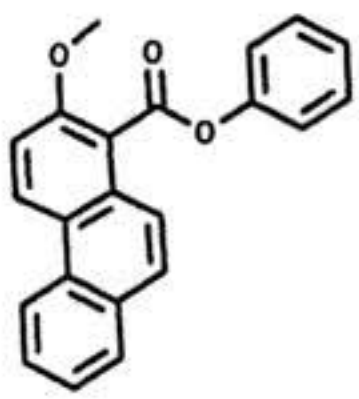
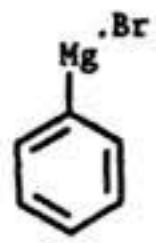
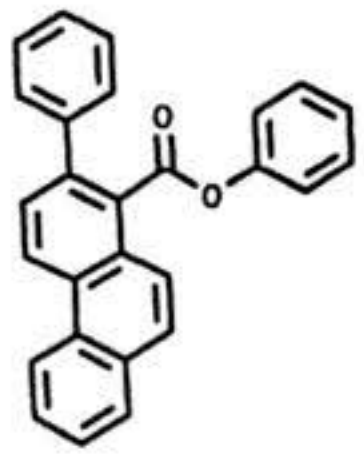
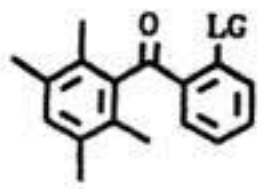
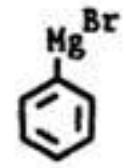
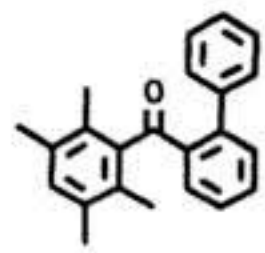
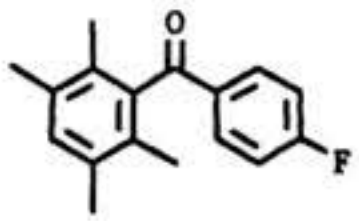
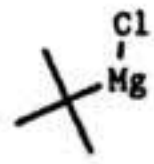
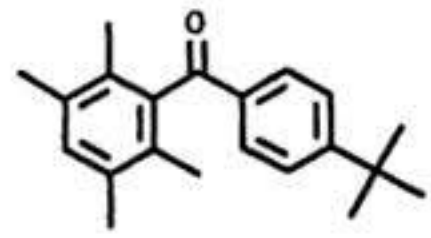
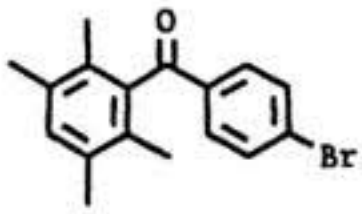
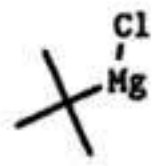
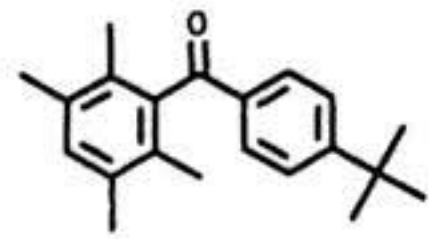
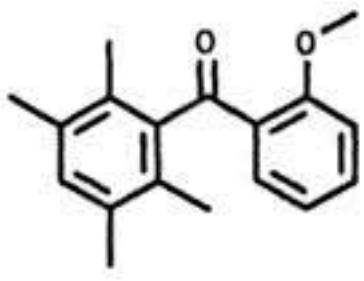
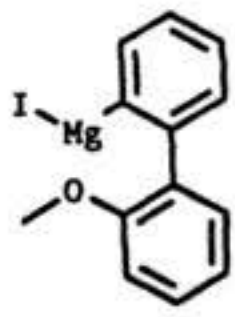
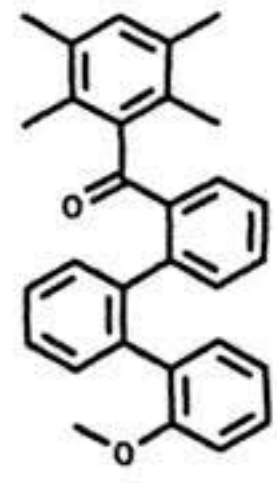
Table 5 (Continued)

Entry	Substrate	RMgX	Product	Yield (%)
3[60]				56
4[61]				93
5[62]				81 (98 ee)
6[62]				92 (97 ee)
7[63]				70

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Table 5 (Continued)

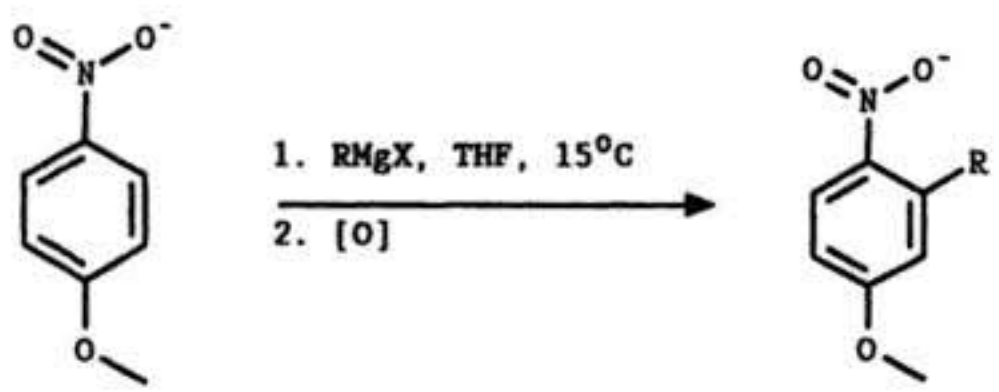
Entry	Substrate	RMgX	Product	Yield (%)
8[64]				80
				
9[65]	LG = C_6H_5O			99
10[65]	LG = CH_3SO_2			94
11[65]	LG = $C_6H_5SO_2$			68
12[65]	LG = C_6H_5S			61
13[65]	LG = CH_3S			37
14[66]				84
15[66]				50
16[67]				51

Materiał chroniony prawem autorskim

Use of CN or NO_2 as the *ortho*-activating group gives moderate yields (50–80%) of the desired product [Eqs. (30) and (31)], but does not work with aryl and tertiary Grignard reagents [67–71]. For the NO_2-activating group, the reaction is actually considered an addition reaction, and the isolable intermediate must be oxidized back to the aromatic product.



(30)

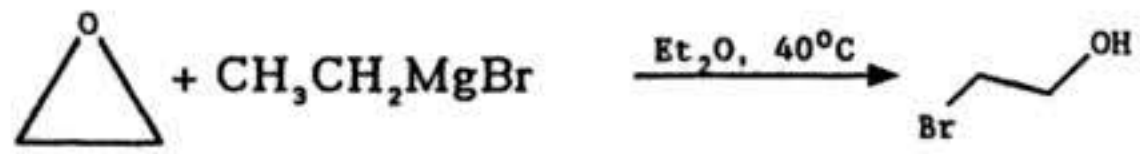


(31)

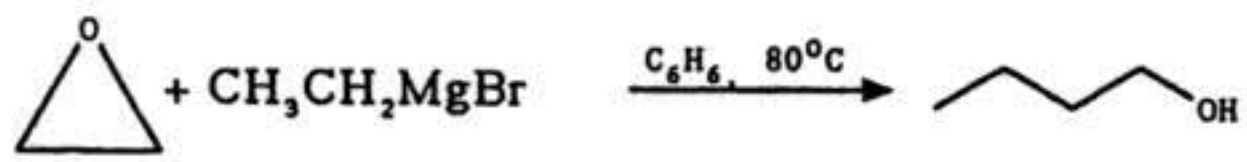
D. Epoxide (Oxirane) Ring Openings

The reaction of Grignard reagents with epoxides, at first glance, appears to be an effective method for a two-carbon homoligation. However, there are several competing reactions that limit the use of this method. These deleterious reactions are formation of halohydrins, rearrangements, polymerization of the epoxide, and in asymmetric epoxides, regioselectivity issues.

The formation of halohydrin was observed early on in Grignard reactions with epoxides [Eq. (32); 5,72]. Approaches to eliminate halohydrins as the final product include removing the diethyl ether and going to higher temperatures [Eq. (33)] or by adding greater than 2 Eq of Grignard reagent. The excess Grignard reagent should react with the halohydrin to give the desired product [Eq. (34)].



(32)



(33)

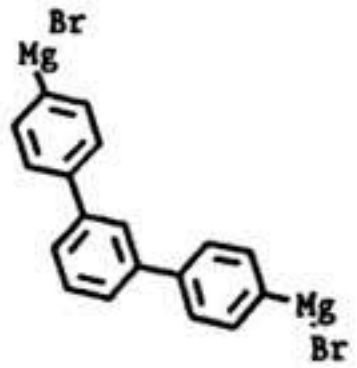
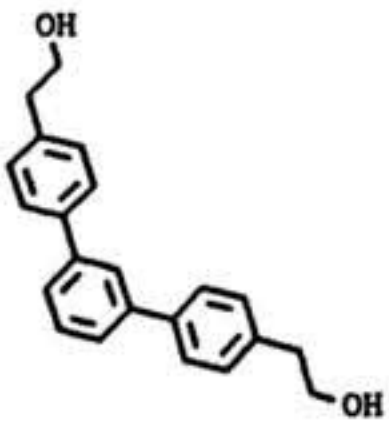
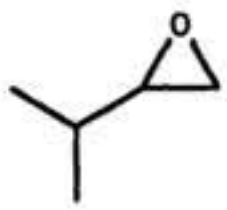
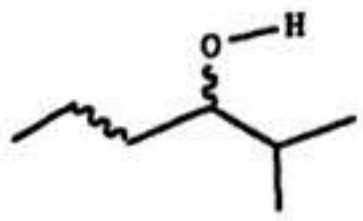
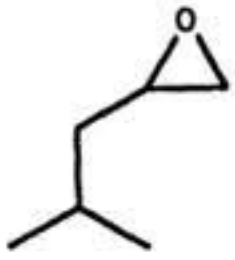
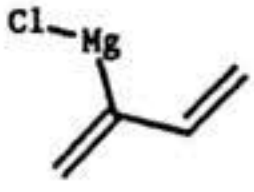
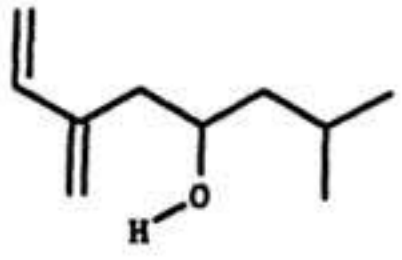
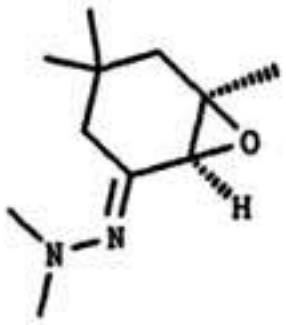
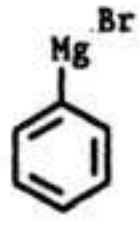
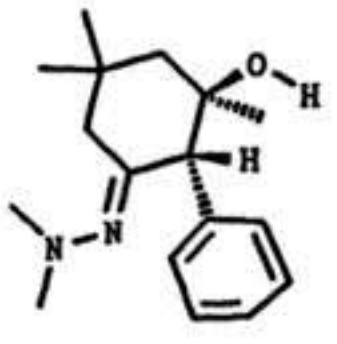
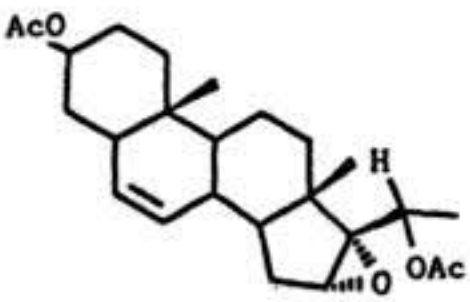
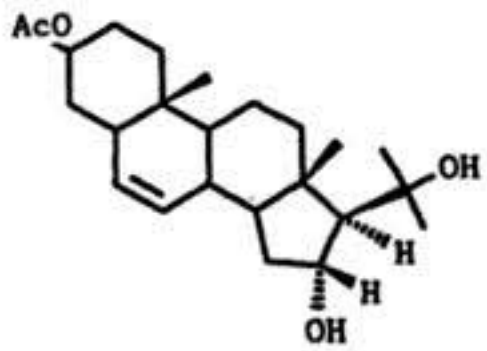
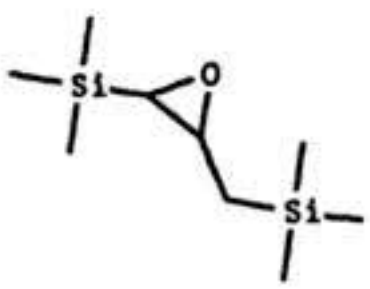
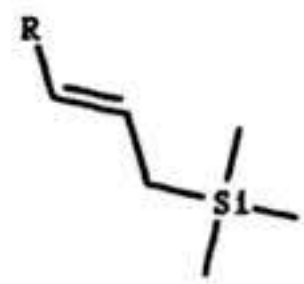


(34)

The rearrangement of an epoxide to an aldehyde or ketone is catalyzed by Lewis acids such as MgX_2 [Eq. (35); 5]. After the Grignard reagent addition to the carbonyl, this will result in the hydroxyl group and the R group of the Grignard being on the same

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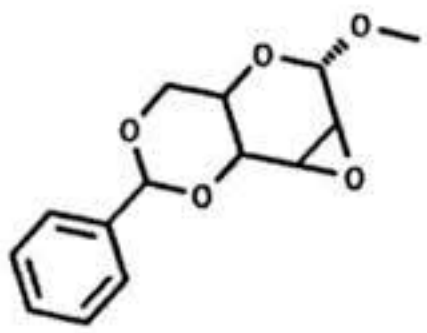
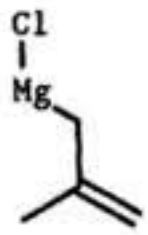
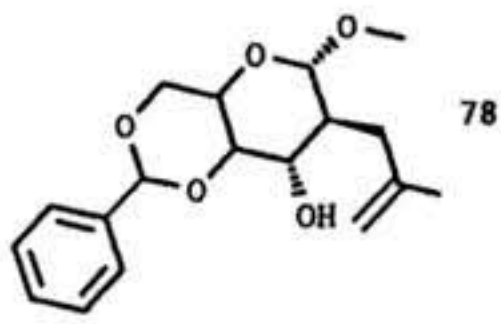
Table 6 Selected Examples of Oxirane Reactions

Entry	Oxirane	RMgX	Product	Yield (%)
1[76]		$CH_3(CH_2)_2CH_2MgBr$	$CH_3(CH_2)_4CH_2OH$	60 - 62
2[77,A]				
3[78]		CH_3CH_2MgBr		63
4[79]				72
5[80]				77
6[81,B]		CH_3MgI		76
7[82,C]		CH_3MgX, $n\text{-}C_4H_9MgX$, C_6H_5MgX		85 - 92

Continued

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Table 6 (Continued)

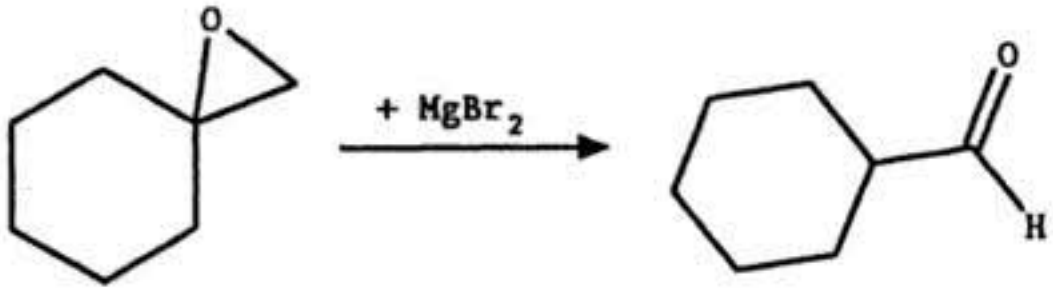
Entry	Oxirane	RMgX	Product	Yield (%)
8[83]				78

A. 2 equivalents of oxirane.

B. Reported as GC yield.

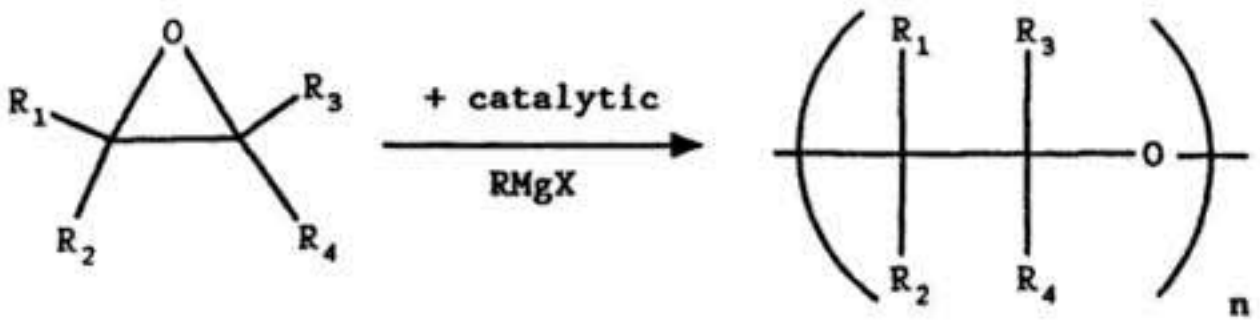
C. Peterson olefination for final product, BF_3 for *E*-isomer and KH for *Z*-isomer.

carbon. Alternatively, there can be a hydride, alkyl or aryl 1,2-shift that will yield the same product (Table 6, entry 6) [73.74].



(35)

Epoxides are used in numerous industrially important polymer and coating applications, whereas Grignard reagents have been used as anionic polymerization catalysts (see Chapter 34). Therefore, it is not surprising that polymerization can occur during the reaction of an epoxide with a Grignard reagent [75]. Obviously, this polymerization or oligomerization reaction is at the expense of the desired product [Eq. (36)].

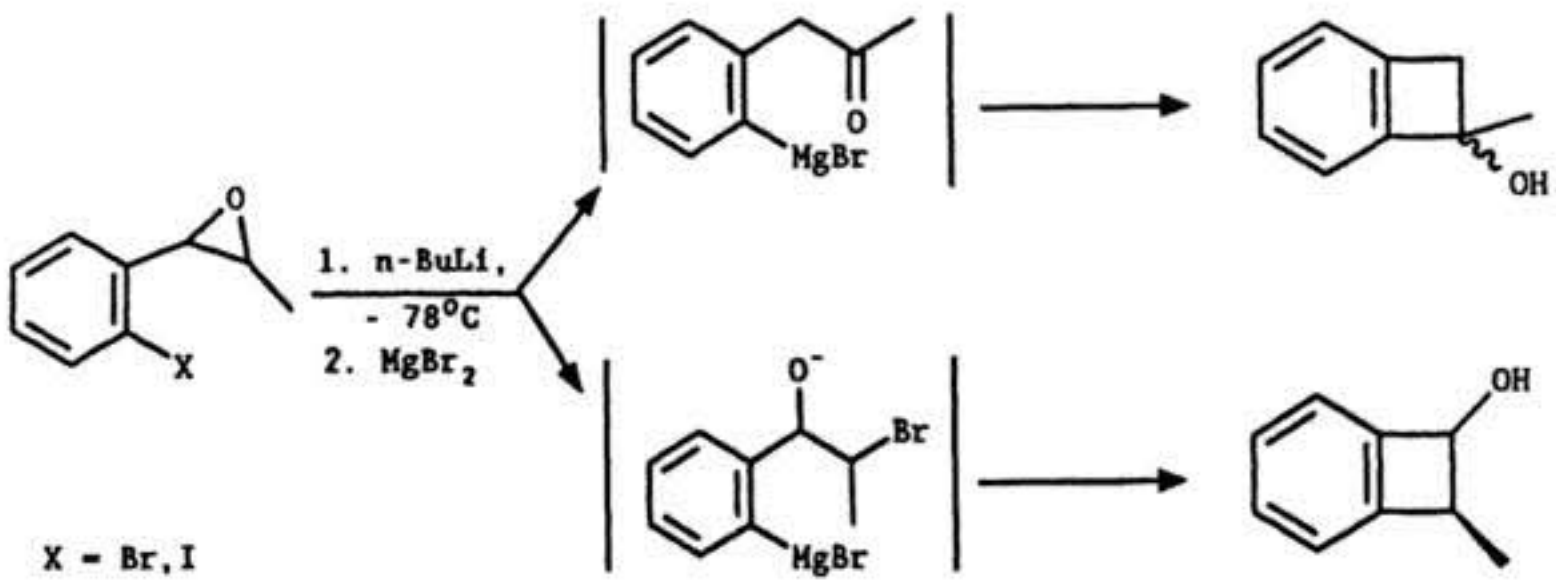


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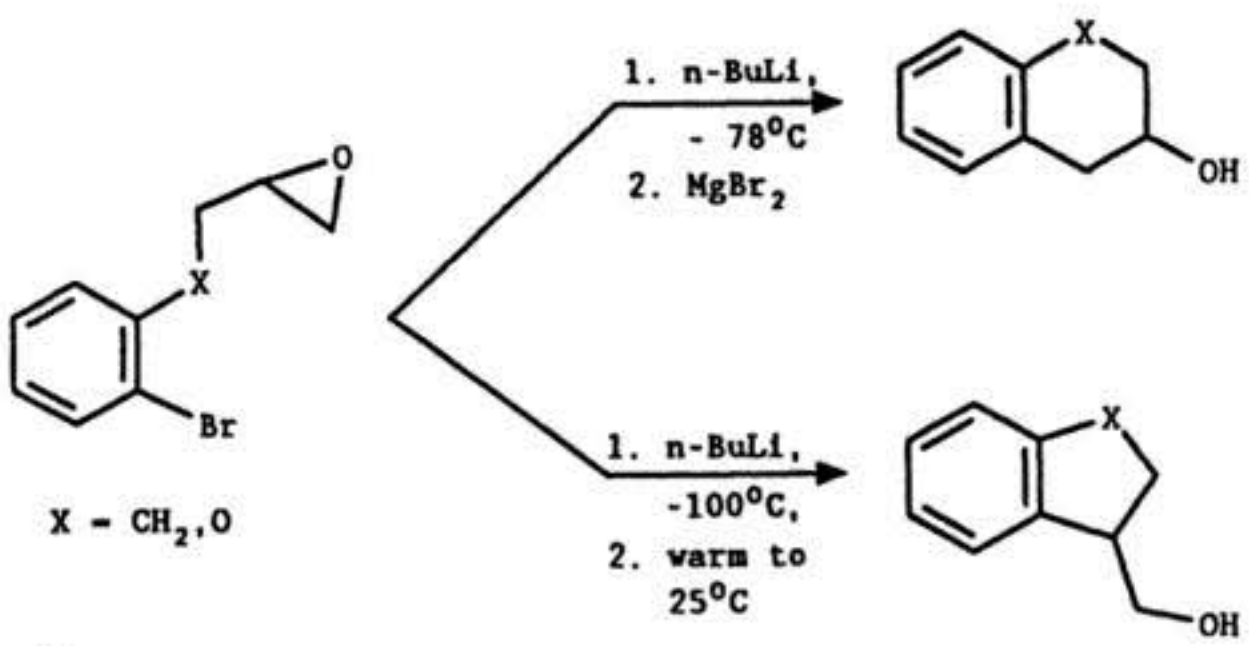
In general, the Grignard reagent will attack the most electrophilic carbon *trans* to the epoxide functionality confirmation (see Table 6, entries 3–6). However, the regioselectivity for asymmetric epoxides is not straightforward, because both steric and electronic effects are strong. In some instances, the steric effects preclude the Grignard reagent from approaching the electrophilic center. Some selected examples are shown in Table 6.

The Durst group has taken advantage of these competing reactions (halohydrin intermediate, Lewis acid-catalyzed rearrangement, and regioselectivity issues) to form

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Scheme 1



Scheme 2

benzocyloalkenols (Schemes 1 and 2). In Scheme 1 the regiochemistry of the eventual hydroxyl group is dependent on the reaction conditions [84,85]. Scheme 2 shows a drastic difference in regiochemistry between when $MgBr_2$ and an organolighium reagent are combined and use of only the organolithium reagent. Presumably, the difference is the proposed Grignard intermediate, which allows for complementary chemistry.

III. ELECTROPHILIC MAIN GROUP SPECIES

A. Potential Problems

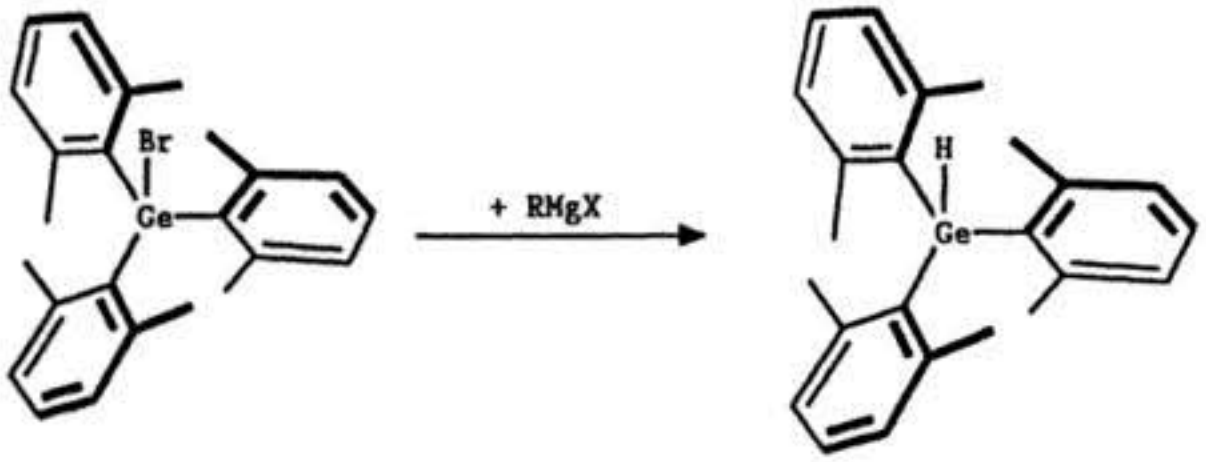
As mentioned earlier in Section II.A nucleophilic substitution reactions using Grignard reagents are favored by highly electrophilic centers, good leaving groups, and forcing conditions. The same competing reactions that were discussed earlier (see Section II.A)—MgX–LG exchange, elimination, and undesired electron transfer reactions—still apply. Another consideration for the main group (MG) electrophiles is whether the reaction is thermodynamically favorable. In general, the MG element must be more electronegative than Mg, which means that alkali (group I) and alkaline (group II) earth metals are not very effective electrophilic centers for nucleophilic substitution. An exception to this statement is Grignard reagent reactions with Be electrophilic centers, because Be is slightly more electronegative than Mg [Eq. (37); 86]. Interestingly, the insolubility of the by-product

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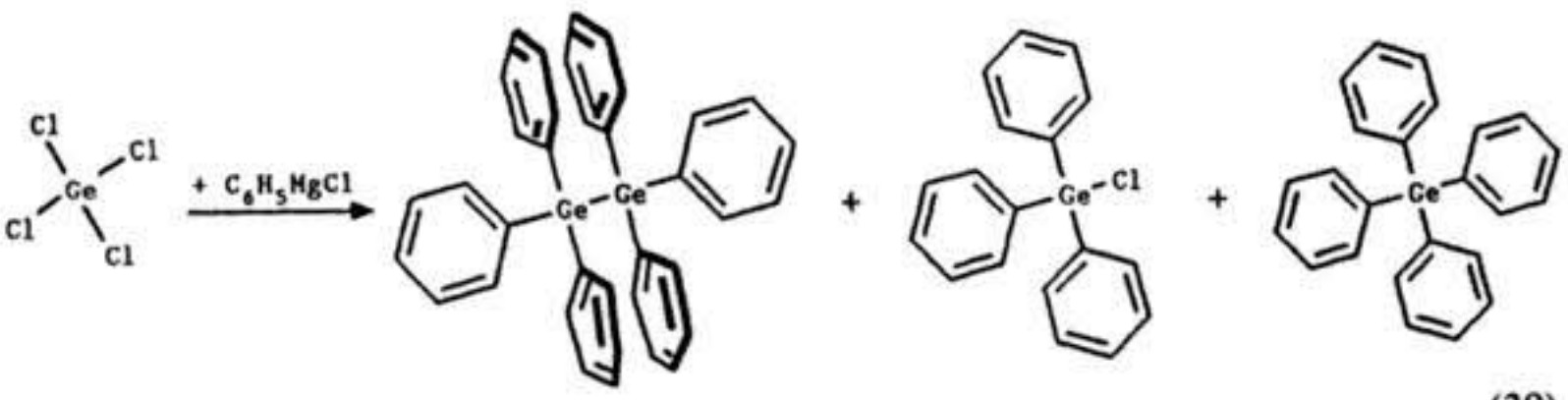
MgX_2 can shift an unfavorable equilibrium to the desired product, which implies that nonpolar solvents, such as heptane or toluene, may be advantageous to drive these reactions to completion.

$$BeCl_2 + 2RmMgX \rightarrow R_2Be + MgXCl_{(s)} \tag{37}$$

The MgX–LG exchange reactions are difficult to control, because greater polarization of the MG–LG bond favors both nucleophilic substitution as well as MgX–LG exchange. As expected, sterically demanding compounds will readily undergo the exchange reaction [Eq. (38); 87]. This typically leads to the formation of an MG–MG bond [Eq. (39); 88]. If the MG–MG bond is weak, then H_2O can add across this bond during the hydrolysis step, resulting in a complicated product distribution.

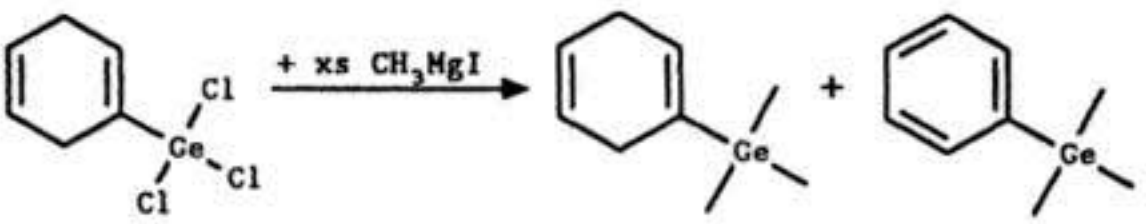


(38)



(39)

Reduction by electron transfer, the third type of competitive reaction, is more prevalent for main group chemistry relative to the previously discussed organic chemistry, but it is not as significant relative to transition metal chemistry. An example of a reduction reaction is shown in Eq. (40) [89].



(40)

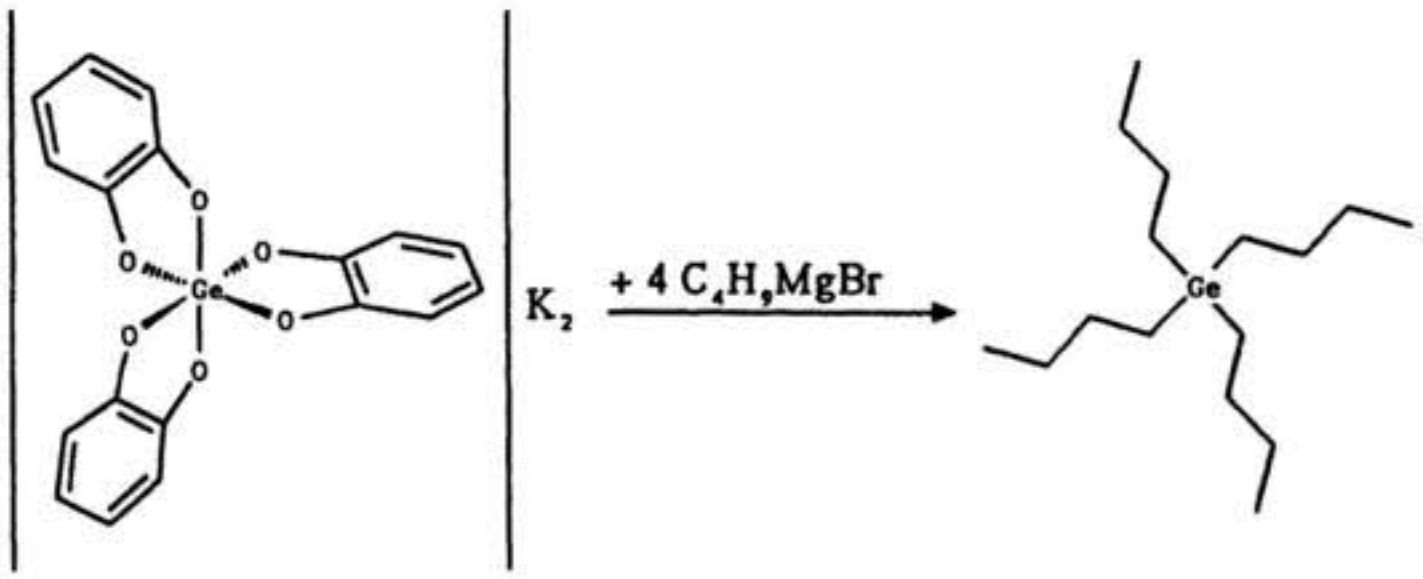
The leaving group also has a substantial effect on conversion to the desired product, and comments from Section I also apply to the main group elements. The difference in the reactivity of the leaving group(s) enables the chemist to rationally synthesize mixed aryl–alkyl derivatives.

B. Potential Solutions to Minimize Competing Reactions

As mentioned in the organic section (Section II), adjusting the electronegativity of the leaving group will affect the relative reaction rates of both nucleophilic substitution as well

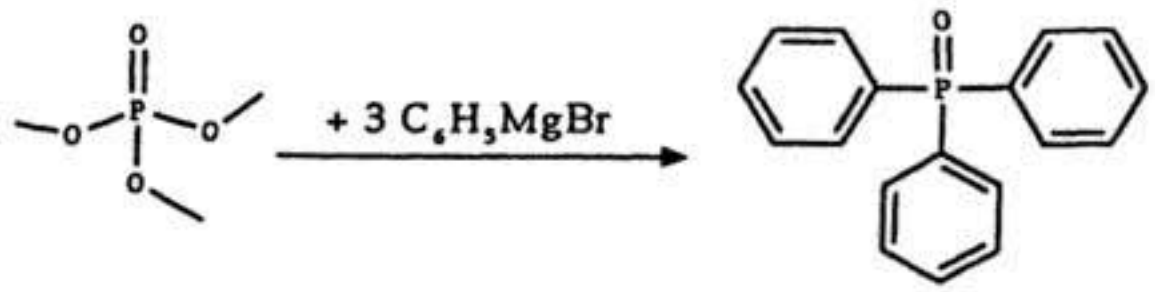
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as MgX–LG exchange. The MgX–LG exchange is a problem especially with group XIV and XV elements. Therefore, a significant amount of effort has been expended on selection of the leaving group(s). Corriu's group has taken advantage of catechol–germanium complexes to give high yields of tetraalkyl or tetraaryl germanium compounds [Eq. (41); 90] relative to $GeCl_4$ [see Eq. (39)], which gives significantly lower yields owing to the formation of digermanium compounds.

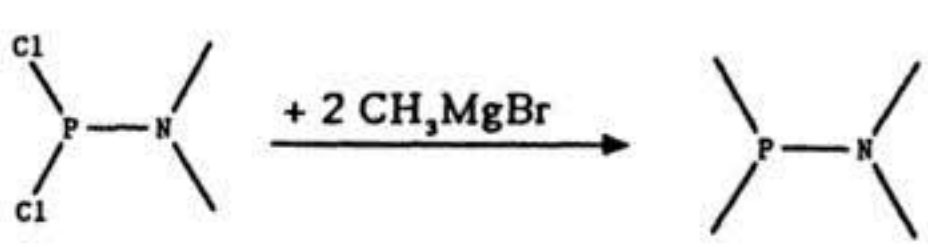


(41)

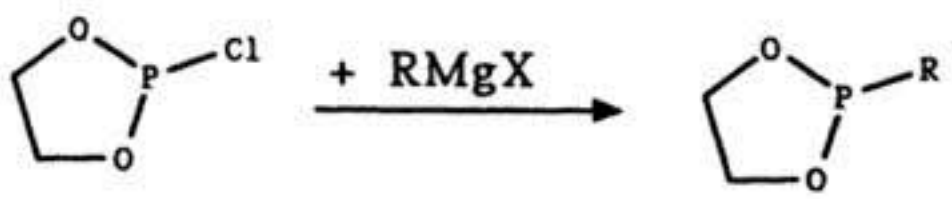
Alternative leaving groups, such as the general class of alkoxy groups [Eq. (42); 91] and mixed halogen–alkoxy or amino [Eqs. (43–45); 92], have also been used with similar results. If an excess of Grignard reagent is used, the final product is the trialkyl or triaryl phosphine. An electrophile with a chiral center and leaving groups with different reactivities allows for asymmetric synthesis [Eq. (46); 93]. (For general chiral phosphine synthesis see Ref. 94.)



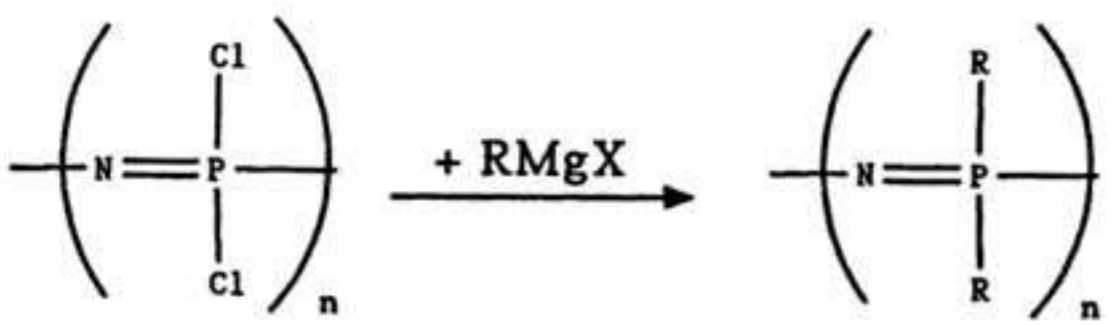
(42)



(43)

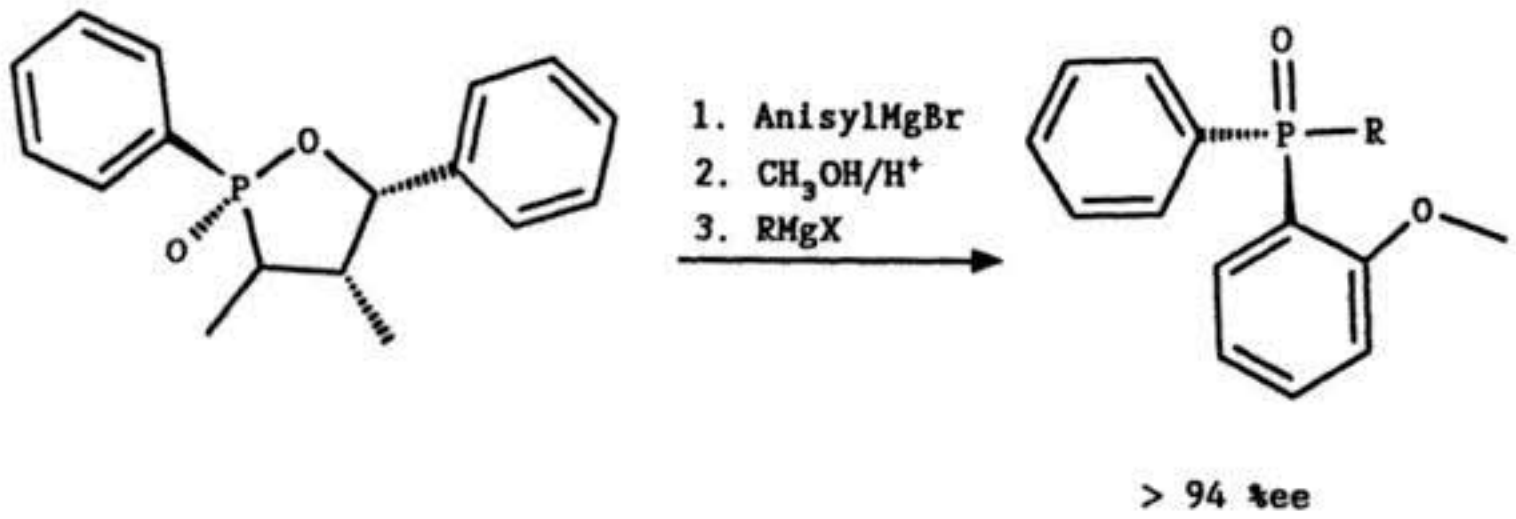


(44)



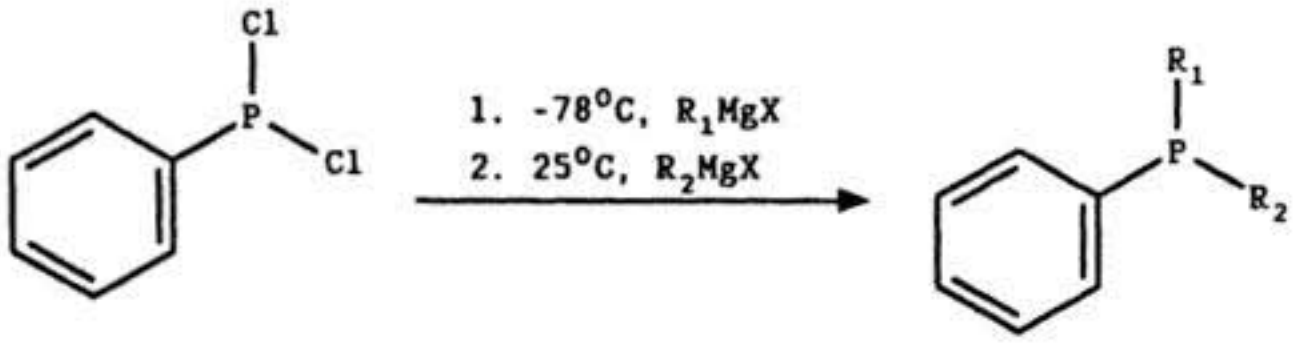
(45)

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(46)

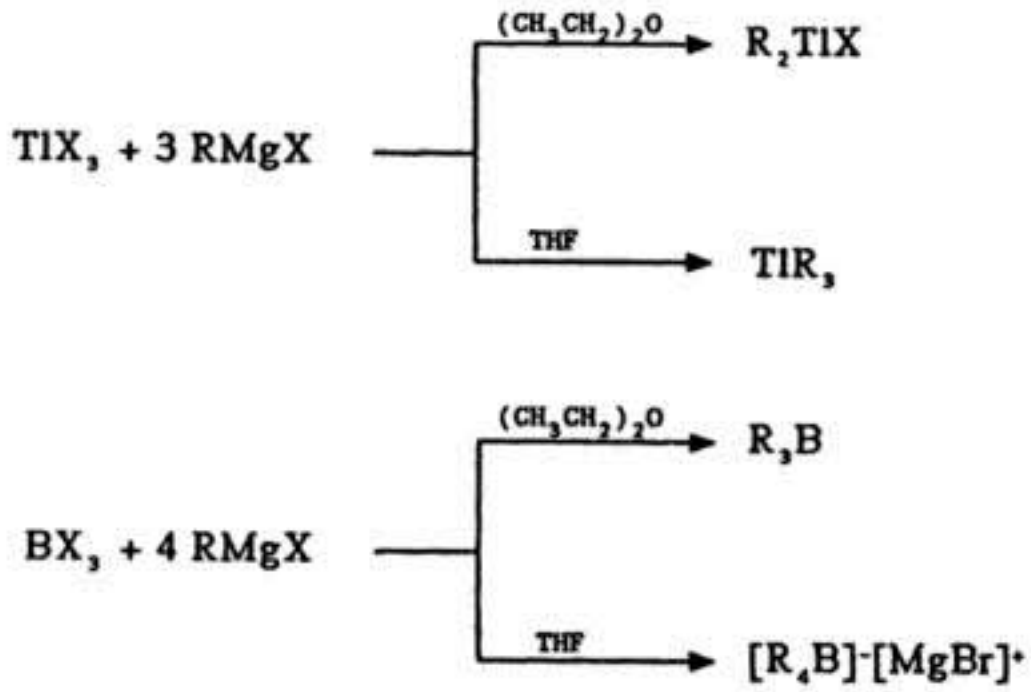
Temperature is another important parameter that can improve the yield of nucleophilic substitution by suppressing the competitive reactions. Interestingly, low temperature can be used to selectively make mixed alkyl or aryl compounds [Eq. (47); 95]. This can be an effective one-pot synthesis to make a chiral, albeit racemic, phosphine.



(47)

Solvent is another key parameter that can have an effect on the course of the reaction. Nonpolar solvents, such as toluene or heptane, facilitate nucleophilic substitution, and these are typically added to the etheral solutions [tetrahydrofuran (THF) or diethyl ether]. These solvents do not effectively solubilize $MgCl_2$, thereby minimizing the Lewis acid-catalyzed reactions as well as some exchange reactions. Note that these solvents were initially added to improve phase splits, especially with THF.

An interesting solvent effect (Scheme 3) was observed by Okhlobystin [96] and later by Brown [97]. In both cases the use of THF rather than diethyl ether allowed the complete alkylation of a group XIII substrate, whereas the diethyl ether reaction did not go to completion.



Scheme 3

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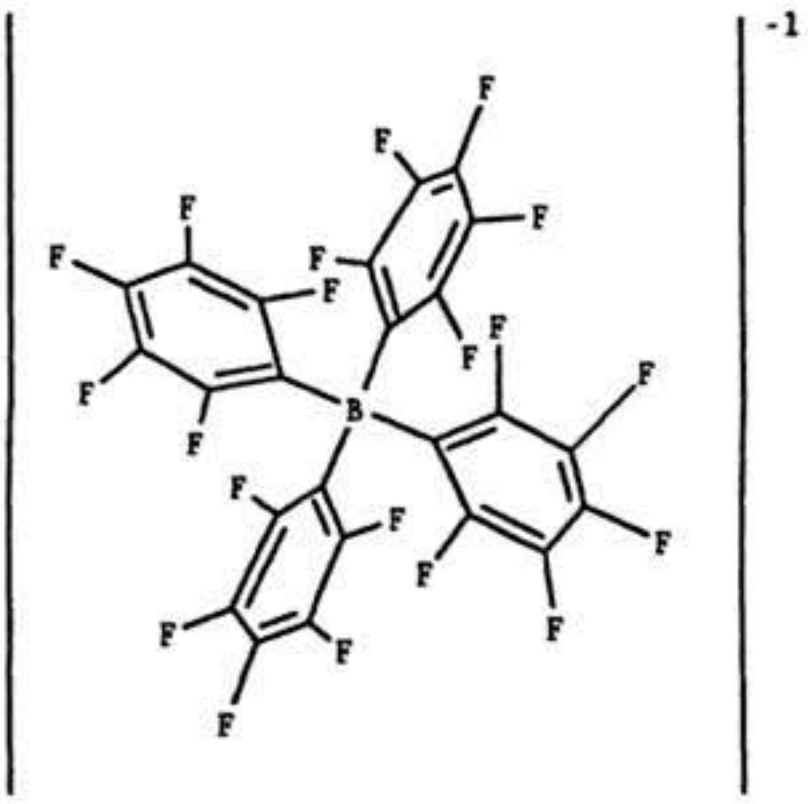
1. Examples and Applications

a. Group XIII

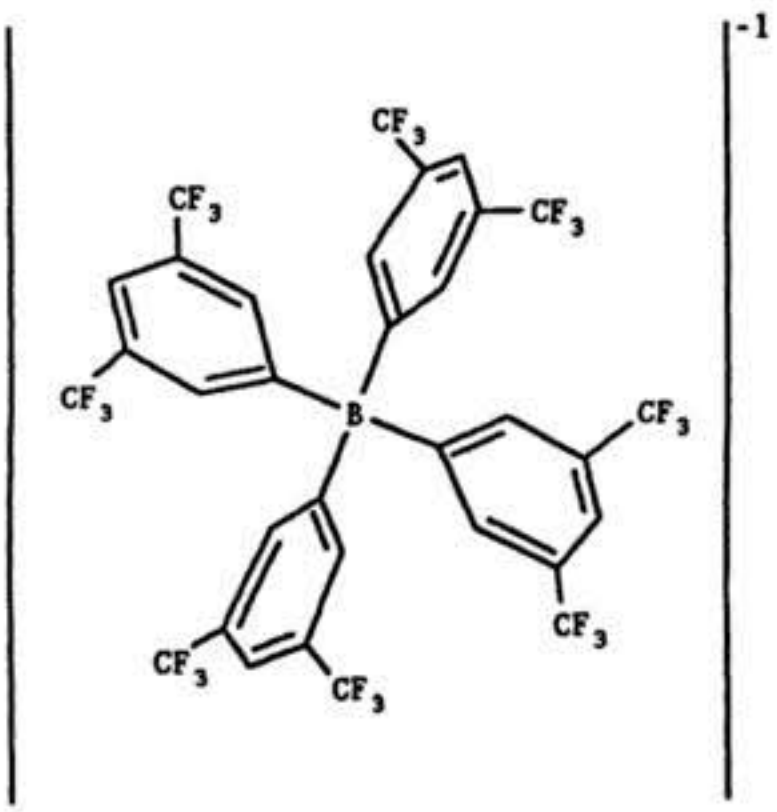
All of the elements within this group (i.e., B, Al, Ga, In, and Tl) undergo facile nucleophilic substitution with Grignard reagents in moderate to high yield. However, alternative, more economical, synthetic routes are typically used on a commercial scale, especially for alkylaluminum derivatives [98]. One major commercial use of Grignard reagents within this group is to make tetraarylborates [99].

Initially, sodium tetraphenylborate was used as a quantitative analytical reagent to precipitate group I elements [100]. This initial use was modified to precipitate group I elements [100]. This initial use was modified to precipitate and remove ^{137}Cs-radioactive waste [101].

The development of cationic catalysts necessitated the development of unreactive counteranions, which typically had been PF_6^- and BF_4^-. Unfortunately, a F^- can be transferred from either of these counteranions to a highly reactive cationic catalyst [102]. An initial response was to use the tetraphenylborate as a counterior, which eliminated the nucleophilic F^- problem, but had the problem of electrophilic addition to the aromatic ring [103]. A solution to these problems is fluorinated tetraarylborates that prevent nucleophilic attack of the F^- anion as well as electrophilic addition to the aromatic ring [104–107]. Structures **1** and **2** [105], are some examples of these counteranions.



1



2

Other uses for the arylborates are UV cationic cure [108,109], biological activity as fungicides (structure **3**) [110], and marine antifoulants for nylon fishing nets (structure **4**) [111]. In the UV cationic cure, the counteranion forms, after photolysis, a superacid intermediate that catalyzes an epoxide or vinyl ether polymerization.
Some examples of nucleophilic substitution of Grignard reagents with group XIII species are shown in Table 7.

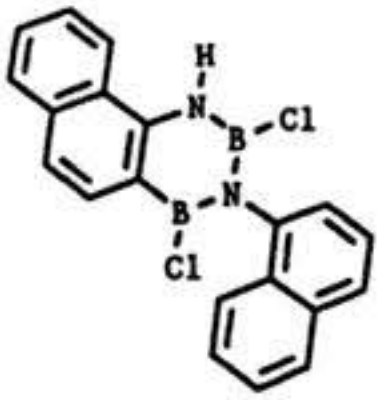
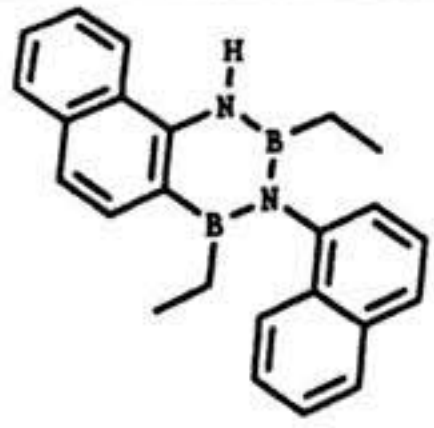
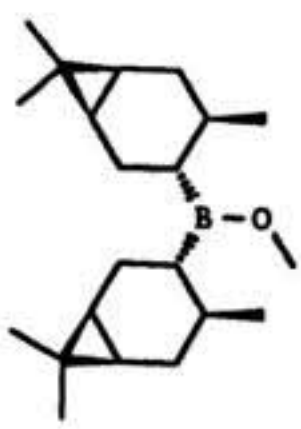
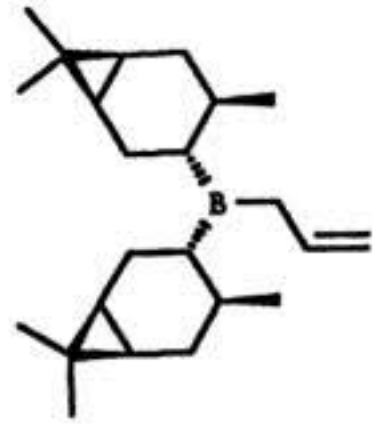
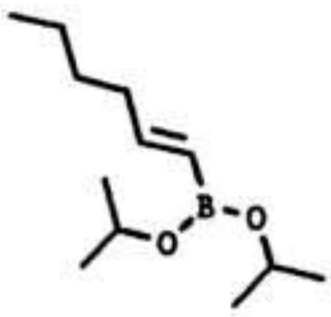
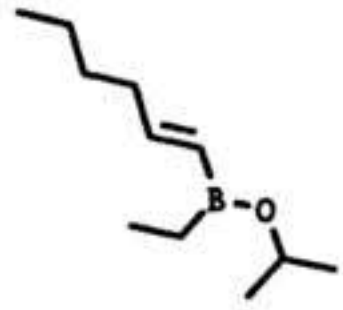
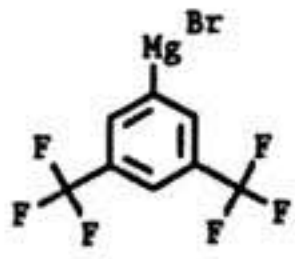
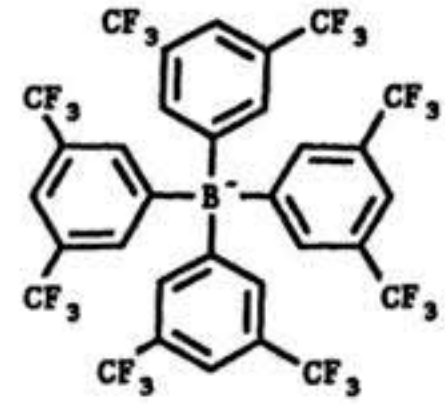
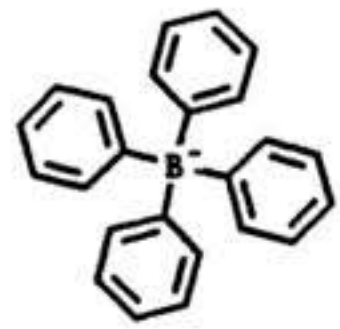
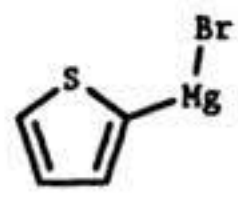
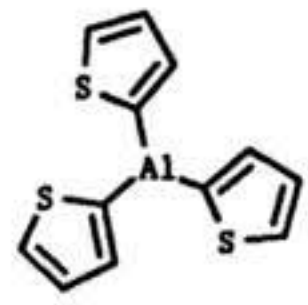
b. Group XIV

The organogroup XIV species (Ge, Sn, and Pb) are typically prepared from Grignard reagents in high yield and are arguably the largest synthetic commercial application for Grignard reagents. Both carbon (see Section II) and silicon (see Chapter 32) are discussed

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N+
B-
Na+
O
H
B-

Table 7 Selected Examples of Group XIII Electrophiles

Entry	Substrate	RMgX	Product	Yield (%)
1[A,112]		CH_3CH_2MgBr		46
2[113]		CH_2–$CHCH_2MgBr$		99
3[114]		CH_3CH_2MgBr		98
4[B,105]	$NaBF_4$			70
5[B,97]	BF_3	C_6H_5MgBr		96
6[C,115]	$AlCl_3$			85

Continued

Material chroniony prawem autorskim

Table 7 (Continued)

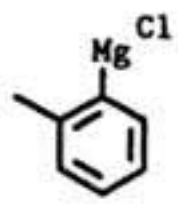
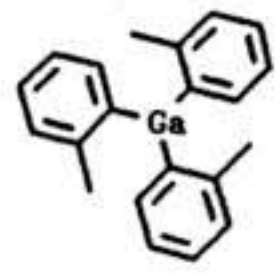
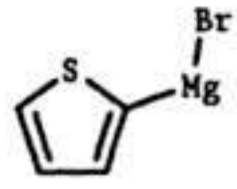
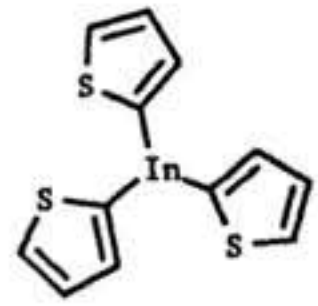
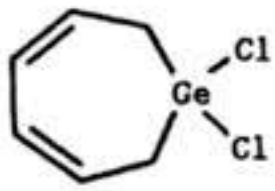
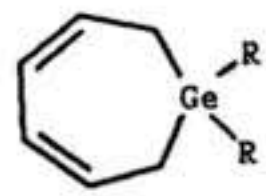
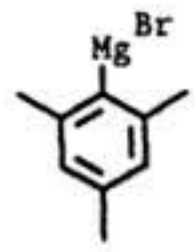
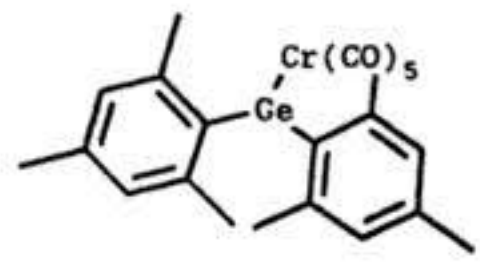
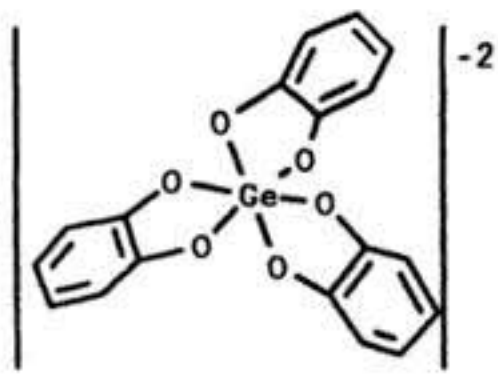
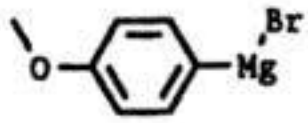
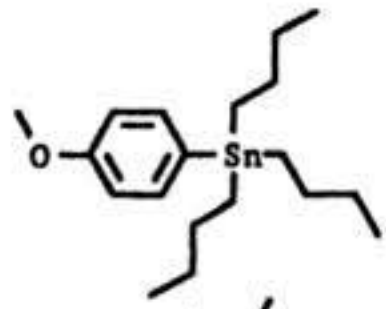
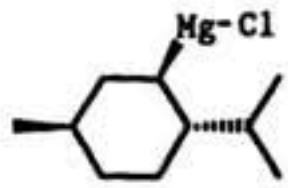
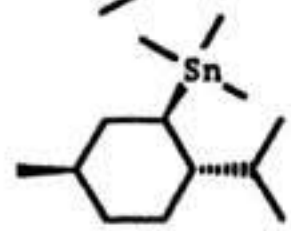
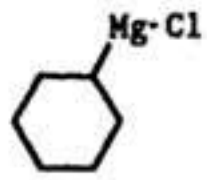
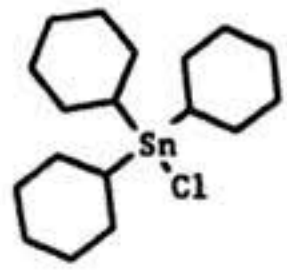
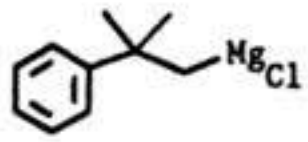
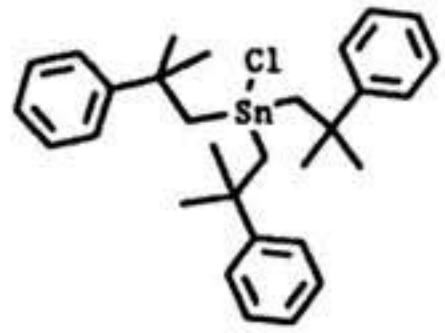
Entry	Substrate	RMgX	Product	Yield (%)
7[C,116]	$GaCl_3$			80
8[C,115]	$InCl_3$			85
9[C,96]	TlX_3	RMgX	TlR_3	"Good Yield"
	A. 2 equivalents of RMgX.			
	B. 4 equivalents of RMgX.			
	C. 3 equivalents of RMgX.			

Table 8 Selected Examples of Group XIV Electrophiles

Entry	Substrate	RMgX	Product	Yield (%)
1[A,120]		CH_3MgX, C_6H_5MgX		80 - 83
2[A,121]	$(CO)_5CrGeCl_2(THF)$			48
3[B,90]		CH_3MgX, CH_3CH_2MgX, C_4H_9MgX, C_6H_5MgX	GeR_4	69 - 87

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Table 8 (Continued)

Entry	Substrate	RMgX	Product	Yield (%)
4[122]	$[(C_4H_9)_3Sn]_2O$	$CH_2{-}CHCH_2MgBr$	$(C_4H_9)_3SnCH_2CH{-}CH_2$	94
5[123]	$(C_4H_9)_3SnCl$			92
6[124]	$(CH_3)_3SnCl$			94
7[C,125]	$SnCl_4$			"high yield"
8[126]	$SnCl_4$			"high yield"
9[A,D,127]	Pb	CH_3CH_2MgCl	$Pb(CH_2CH_3)_4$	70 - 80
10[C,128]	PbI_2	CH_3CH_2MgBr	$Pb(CH_2CH_3)_4$	85

A. 2 equivalents of Grignard reagent.
B. 4.5 equivalents of Grignard reagent.
C. 3 equivalents of Grignard reagent.
D. 2 equivalents of ethyl chloride.

and *trans*-esterification reactions. Organotin species are used for chemical vapor deposition (CVD) on window glass to achieve a low-emissivity that prevents reflected heat from leaving the house [119].

The major use of organolead was tetraethyllead, as an antiknock for gasoline (Table 8, entries 9 and 10). However, this additive has been banned for environmental reasons. Organogermanium has niche uses in the field of materials and, again, these compounds are typically made by the Grignard synthetic route. Some selected synthetic examples are shown in Table 8.

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c. Groups XV and XVI

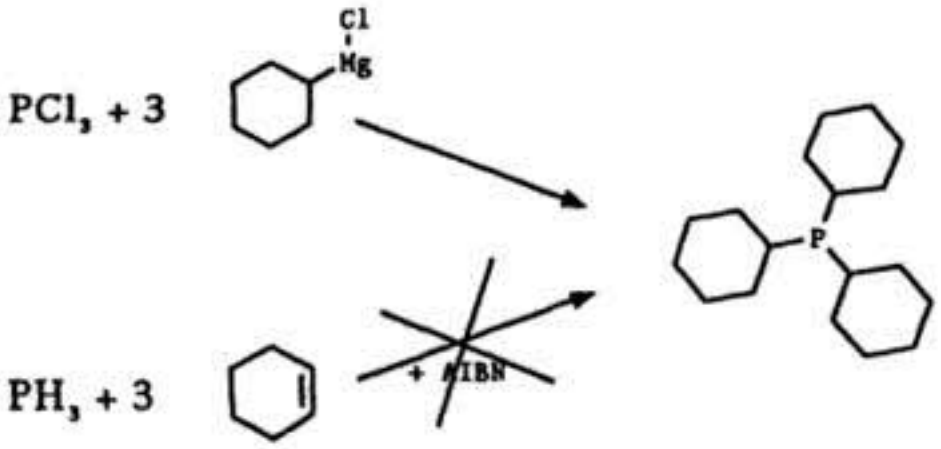
Nucleophilic substitution reactions proceed in moderate to good yields for the group XV, (N, P, As, Sb, and Bi) and XVI (O, S, Se, and Te) electrophiles. However, the competitive reaction of MgX–LG exchange is more prevalent relative to the group XIV elements. This exchange reaction typically leads to the formation of an MG–MG bond [see Eq. (39)]. Some examples of successful nucleophilic substitution reactions are shown in Tables 9 and 10 [see also Tables 2 (C–O cleavage) and 3 (C–S cleavage)].

From a commercial standpoint, the preparation of phosphorus species consumes the largest volume of Grignard reagents in this set of elements. Although there are alternative reactions for the preparation of phosphines, such as hydrophosphination [Eq. (48)], the Grignard reaction is still preferred when sterically hindered phosphines are desired (Scheme 4).

$$PH_3 + 3\ CH_2{=}CHR \xrightarrow{+\ AIBN} P(CH_2CH_2R)_3 \qquad (48)$$

These phosphines are typically used as ligands for catalytic reactions such as hydroformylation, hydrogenation, dimerization, and other metal-catalyzed reactions. Other uses for the phosphorus derivatives are Wittig chemistry (vitamin A and E), phase-transfer catalysis, epoxy curing, extractants, and agricultural and pharmaceutical intermediates.

An interesting example of an extractant is *n*-octylphenyl-*N*,*N*-diisobutylcarbomyl-methylphosphine oxide (Scheme 5) [48]. This nuclear extractant can concentrate nuclear waste by up to 10^4 and Dr. P. Horwitz from Argonne National Laboratories won a IR-100 award for the development of the TRUEX process [147]. Monitoring the reaction by ^{31}P-NMR indicates that nucleophilic substitution occurs first, followed by proton abstraction to form the anion [148].



Scheme 4

Although Grignard reagents are used to make other organo–MG species of group XV and XVI they are typically small-volume, value-added products, typically used in pharmaceuticals, CVD precursors, and other niche applications.

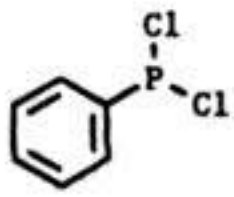
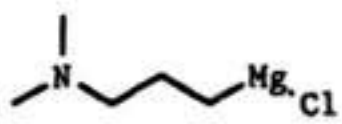
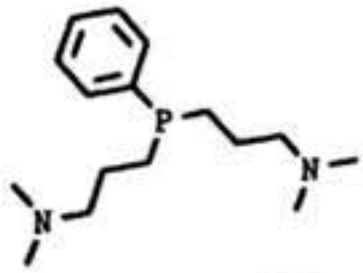
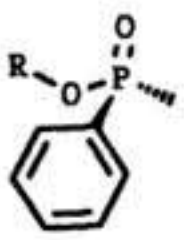
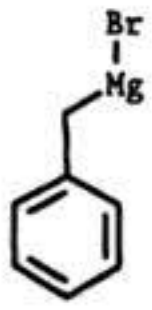
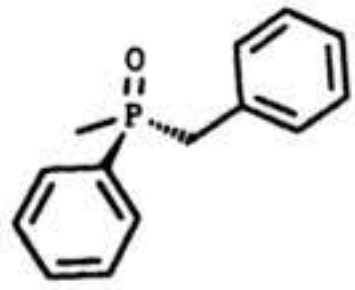
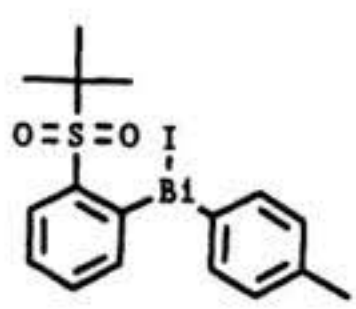
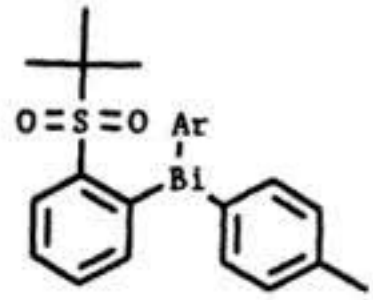
IV. ELECTROPHILIC TRANSITION METAL SPECIES

A. Potential Problems

In addition to the previous concerns that were discussed in Sections II and III (MgX–LG exchange, undesired electron-transfer reactions, and unfavorable electronegativity of the electrophilic element), transition metal aklyls can undergo α- and β-elimination reactions,

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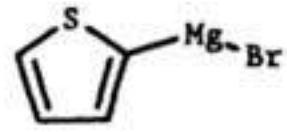
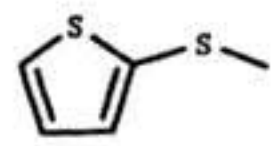
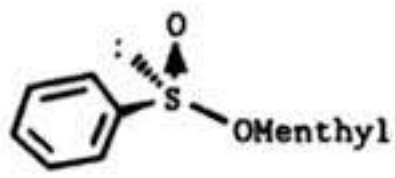
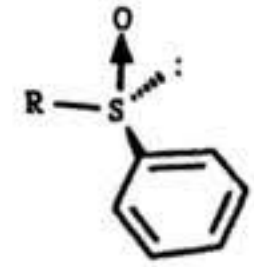
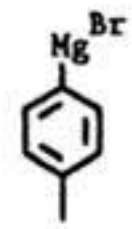
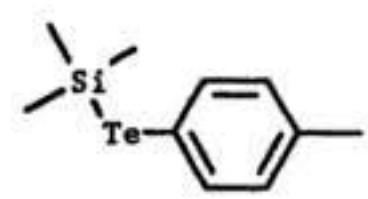
Table 9 Selected Examples of Group XV Electrophiles

Entry	Substrate	RMgX	Product	Yield (%)
1[129]	NH_2X	RMgX, R = C_6H_5, $C_6H_5CH_2$, C_4H_9, CH_3CH_2, CH_3	RNH_2	26 - 85
2[130]	$Br(CH_2)_nBr$ n = 3 - 9	$ArN(MgBr)_2$		50 - 90
3[A,131]	PCl_3	$C_6H_5CH_2MgX$	$P(CH_2C_6H_5)_3$	85
4[B,132]				87 - 91
5[133]				85
6[B,134]	$(CH_3CH_2)_2NPCl_2$	CH_2-CHMgBr	$CH_3CH_2)_2NP(CH$-$CH_2)_2$	50 - 60
7[A,135]	PCl_3	RMgX, R = alkyl, vinyl, aromatic, etc.	PR_3	"Good yield"
8[A,136]	$SbCl_3$	C_6H_5MgBr	$Sb(C_6H_5)_3$	82 - 90
9[137]	$SbCl_3$	1. $(CH_3)_3CMgCl$, -50°C 2. 2 CH_3MgBr, 0°C	$(CH_3)_2SbC(CH_3)_3$	64
10[C,138]		ArMgX		88 - 95

A. 3 equivalents of Grignard reagent.
B. 2 equivalents of Grignard reagent.
C. HMPA added to the reaction.

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Table 10 Selected Examples of Group XVI Electrophiles

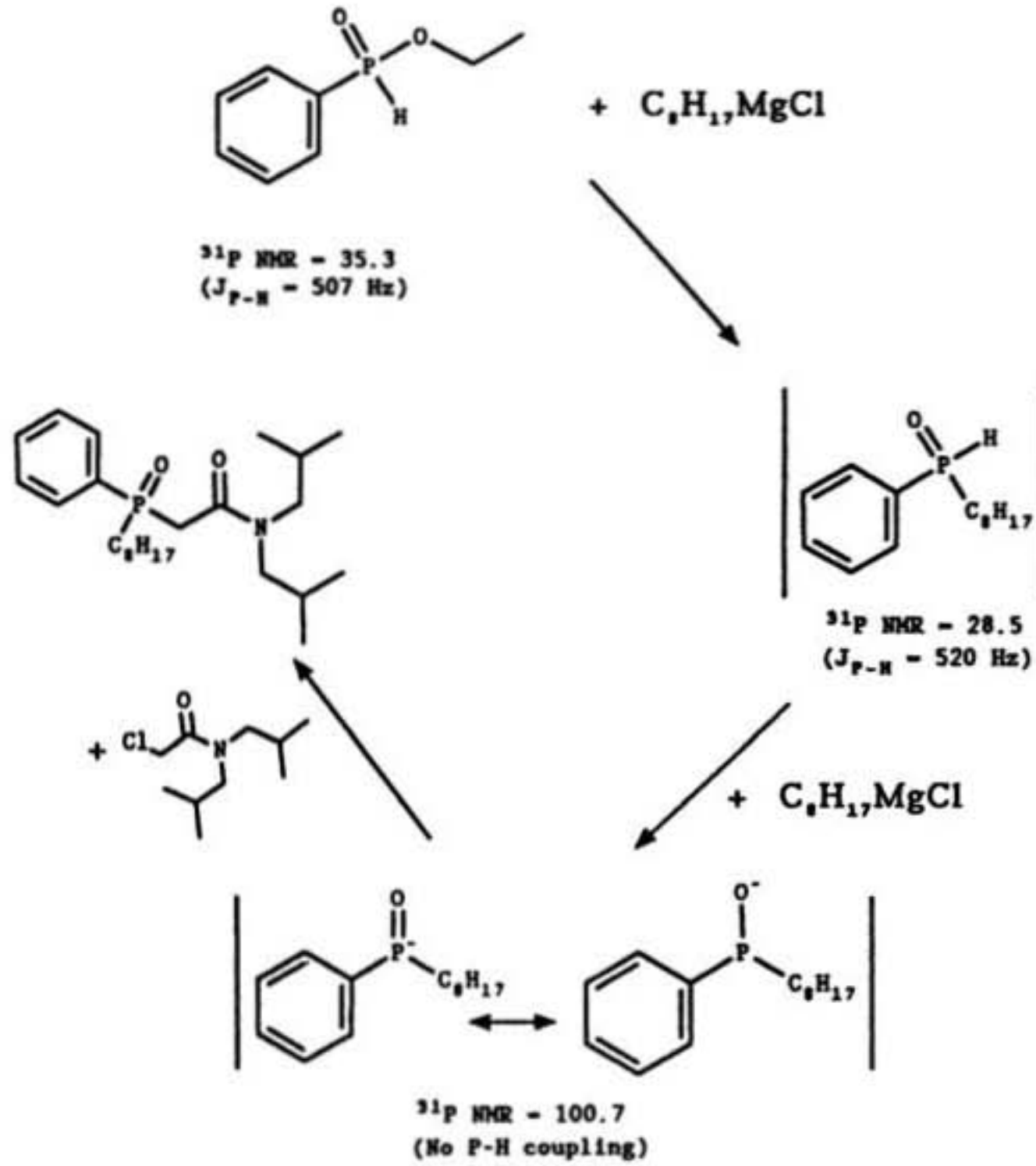
Entry	Substrate	RMgX	Product	Yield (%)
1[139]	S + CH_3I			53 - 60
2[140]	N_4S_4	C_6H_5MgBr	$[C_6H_5S]_2$	92
3[141]		RMgX		73 - 92
4[142]	2 $ClCH_2OCH_3$	$Se(MgBr)_2$	$Se(CH_2OCH_3)_2$	80 - 90
5[142]	Se + ArBr	ArMgBr	ArSAr	40
6[143]	Se, H^+	C_6H_5MgBr	PhSeH	55 - 71
7[143]	Se, Br_2	C_6H_5MgBr	$[C_6H_5Se]_2$	64 - 70
8[A,144]	$Se(O)Cl_2$	C_6H_5MgX	$(C_6H_5)_3Se^+Y^-$	50
9[145]	ArTeX	RMgX, R = C_4H_9, C_6H_5	ArTeR	> 90 %
10[146]	Te + $(CH_3)_3SiCl$			27

A. 3 equivalents of Grignard reagent.

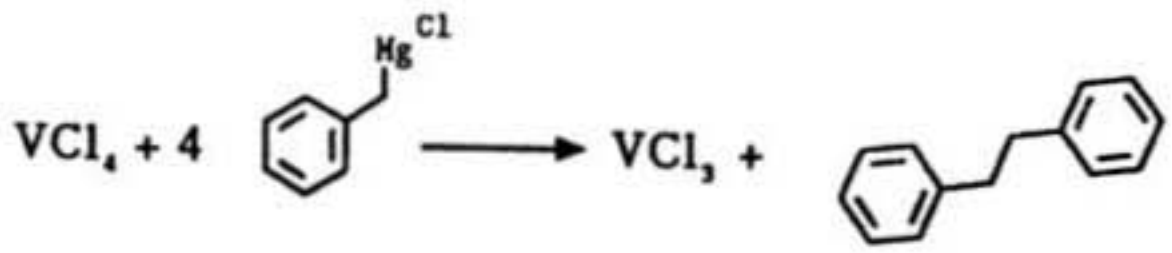
ortho-metallation with aryl groups, rearrangement, and ligand-exchange reactions. With all of these alternative reactions leading to "decomposition" products, it is no wonder that very few σ-alkyl and σ-aryl metal complexes were made before 1965 [149].

The exchange and reduction chemistry is particularly prevalent in the early transition metals (groups III–VII). Some examples are shown in Eqs. (49–51) [150–152]. Along with β-elimination, these deleterious reactions are the major reason for poor to moderate yields (20–60%) in early transition metal chemistry. It has been suggested that MgX_2 acts as a Lewis acid site that will promote the reduction of the transition metal's oxidation state

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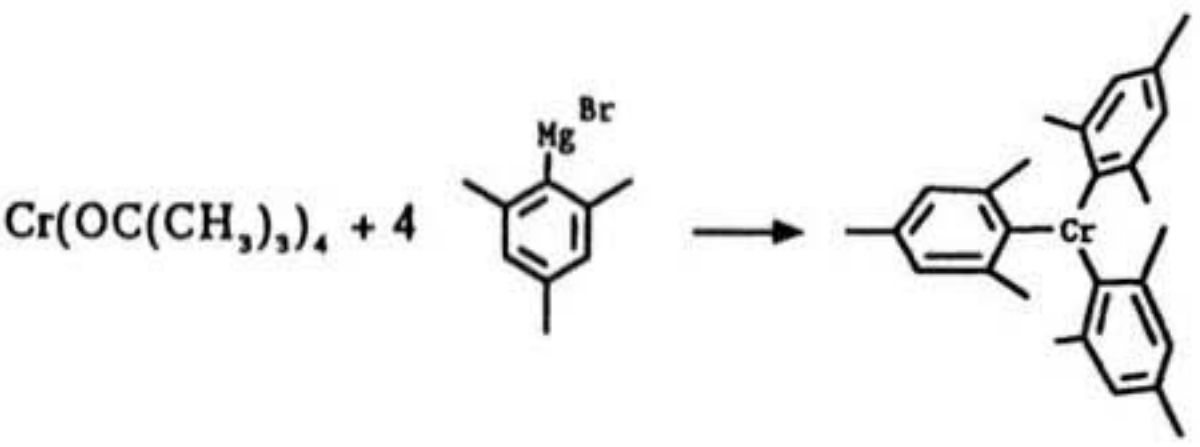
Scheme 5



(49)



(50)



(51)

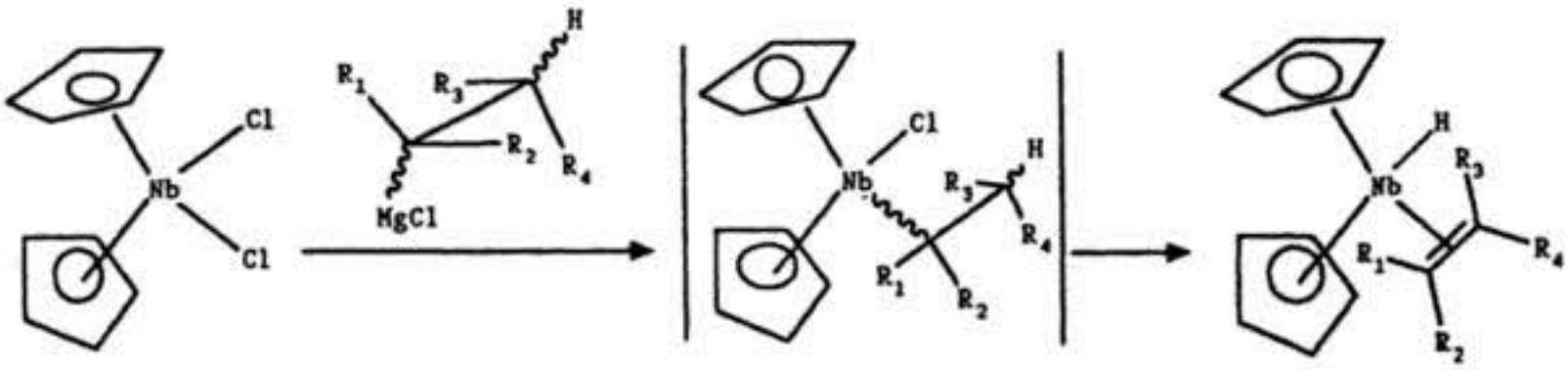
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$$4[Mg(R)Cl(THF)_x] + 2\,[ZrCl_4(THF)_2] \longrightarrow ZrR_4 + [Mg(THF)_6][ZrCl_6] + 3\,[MgCl_2(THF)_2] \quad (52)$$

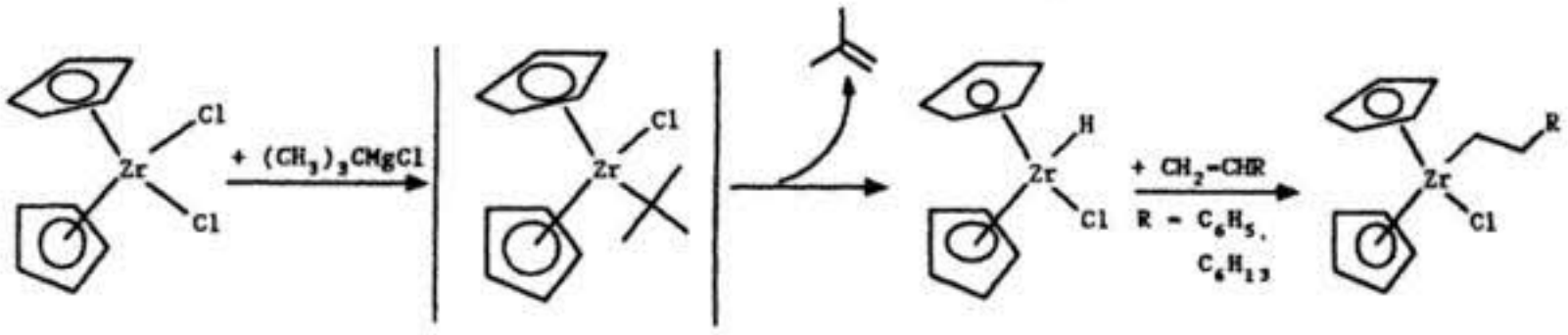
[150]. Recent work does indicate that MgX_2 will transfer a halide to a transition metal at the expense of tetraalkyl-M [Eq. (52); 153,154].

The unfavorable electronegativity issue refers specifically to the early transition metal elements, especially the group III (Sc, Y, actinides, and lanthinides) elements. The more electropositive elements form an equilibrium with Grignard reagents, giving the other alternative reactions a chance to occur, resulting in poor yields of the desired product.

β-Elimination is probably the most common decomposition pathway for transition metal alkyls and, again, is very common for the early transition metals, groups III–VII [Eq. (53); 149,155–157]. In fact, if the Grignard reagent is a precursor to a volatile olefin, such as 2-methylpropene, then an "olefin exchange" can be carried out to give an $Cp_2M(alkyl)(halide)$ derived from the nonvolatile olefin in high yield [Eq. (54); 158].

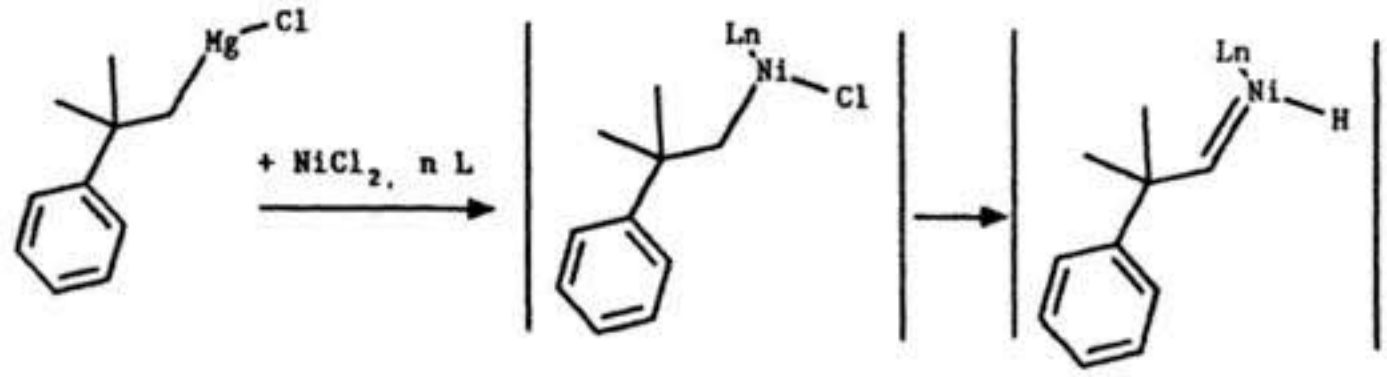


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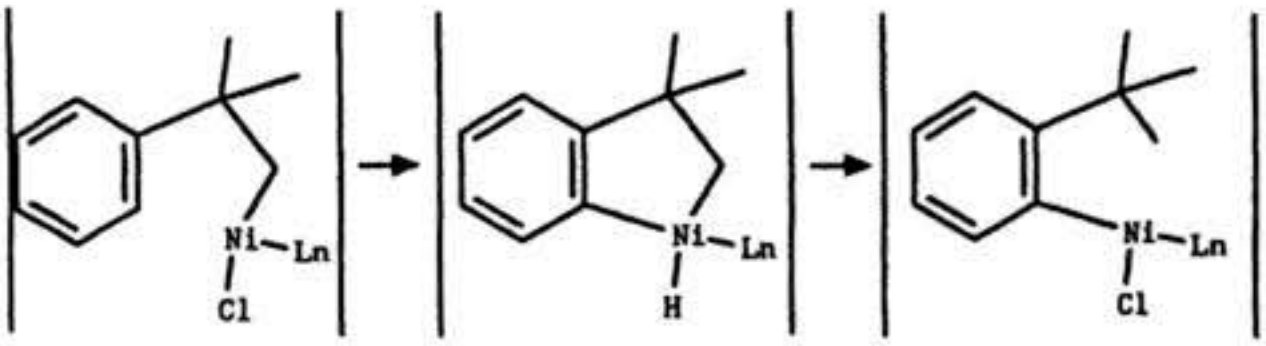
(54)

Although α-elimination is not as common as β-elimination, it will typically lead to a metal carbene that is highly reactive (see Chapters 18 and 21) [Eq. (55); 159]. Interestingly, in the same paper, products consistent with aromatic C–H activation, *ortho*-metallation, is observed [Eq. (56)] resulting in a low yield of the desired product.



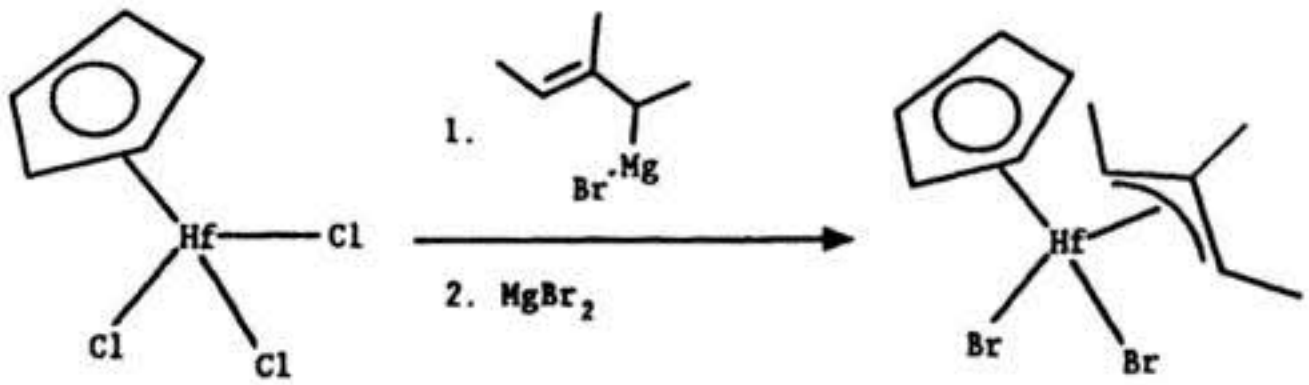
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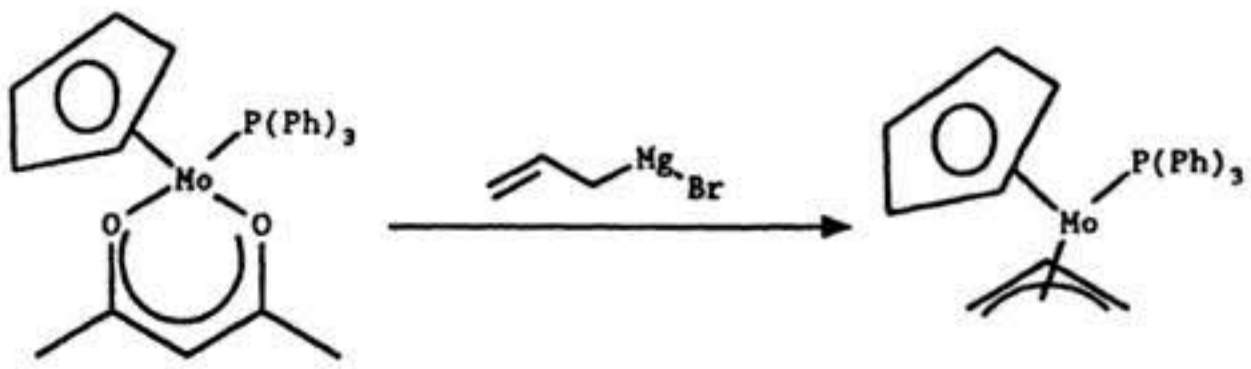


(56)

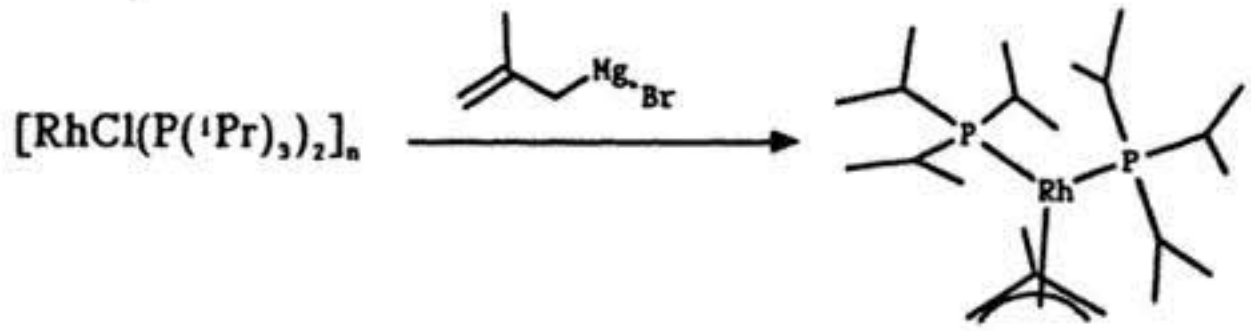
Rearrangements are common in transition metal chemistry, and it is not within the scope of this discussion to cover this topic. However, many of these rearrangements occur to increase the electron density on the metal center. An example of this concept is addition of allylic Grignard reagents to a metal-centered electrophile. Typically an η^3-complex is formed, presumably from the expected σ-bond, followed by coordination of the olefin as a π-bond, which is better represented as an η^3-complex [Eqs. (57–59); 160–162].



(57)



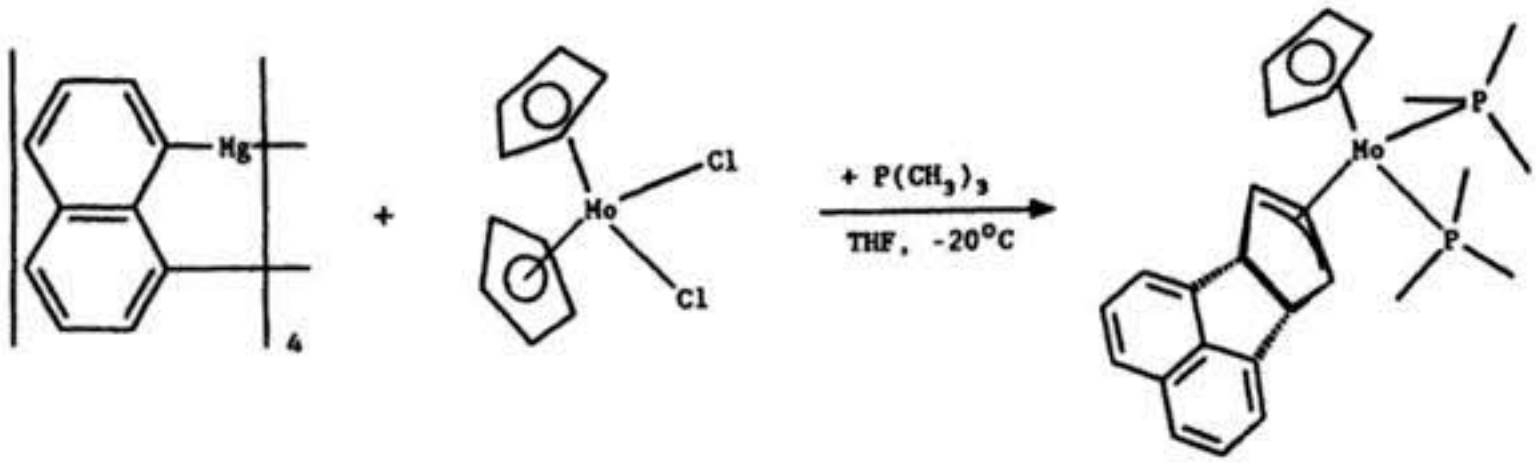
(58)



(59)

An interesting competing reaction (addition to a cyclopentadienyl ring) was recently reported by Bickelhaupt [Eq. (60); 163]. In this reaction, a bulky dication is formed, by the addition of phosphine ligands, that does not sterically allow the Grignard reagent to approach the Mo electrophilic center. Subsequently, a Cp ring slippage occurs as the Grignard reagent adds to the ring, forming an η^3-complex.

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(60)

B. Potential Solutions to Minimize Competing Reactions

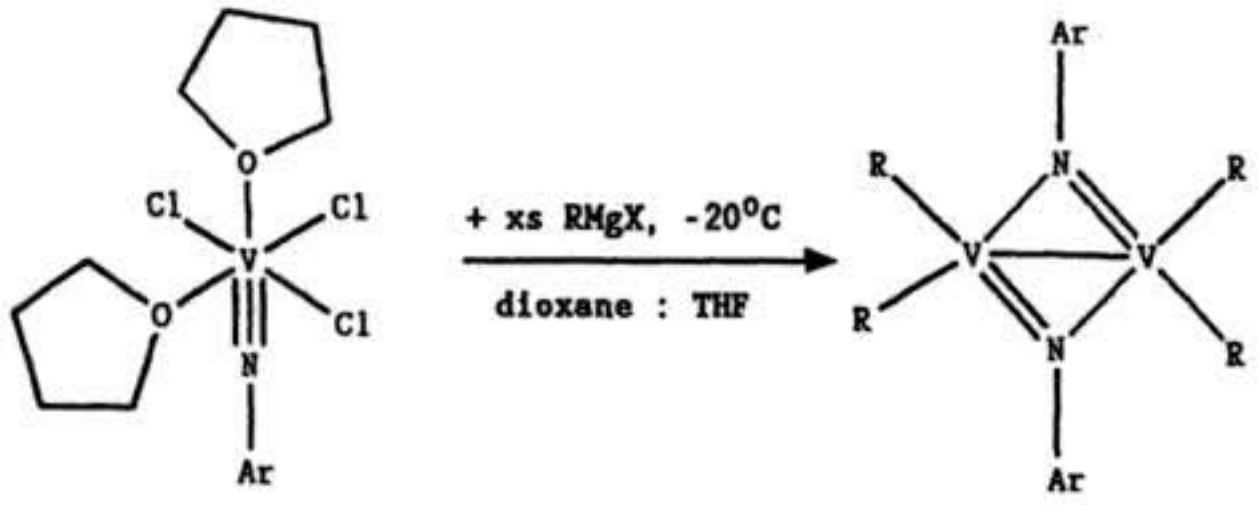
Decreasing the solvent polarity is an effective strategy to decrease the amount of MgX–LG exchange and reduction reactions. Two potential explanations are a decrease in the solubility of $MgX_2 \cdot THF_n$, or a shift in the Schlenk equilibrium (see Chapter 13). Subsequently, there are no Lewis acid sites in solution that could catalyze these competing reactions. For example the addition of toluene as a cosolvent can take a reaction that predominately undergoes reduction [80%, see Eq. (50)] to yield the nucleophilic substitution product [75%; Eq. (61); 151].

$$Nb(O)Cl_3 + CH_3MgI \xrightarrow[(CH_3CH_2)_2O]{C_6H_5CH_3\ +} CH_3Nb(O)Cl_2 \qquad (61)$$

The Schlenk equilibrium may play an important part in these reactions, as implied by the comparison of the reactions of $(C_6H_5CH_2)_2Mg$ [Eq. (62)] versus $C_6H_5CH_2MgCl$ [see Eq. (49)] with VCl_4 [150]. In fact, diorganomagnesium reagents are commonly used instead of Grignard reagents to control the exchange and reduction reactions [Eq. (63); 164]. Interestingly, some groups have made the diorganomagnesium reagent in situ by using a dioxane–THF solvent system that will form the diorganomagnesium reagent and precipitate $MgX_2 \cdot$ dioxane [Eq. (64); 165].

$$VCl_4 + 2\,(C_6H_5CH_2)_2Mg \longrightarrow (C_6H_5CH_2)_4V \qquad (62)$$

$$Ti(OC_4H_9)_4 + 2\,(C_6H_5)_2Mg \longrightarrow (C_6H_5)_4Ti \qquad (63)$$

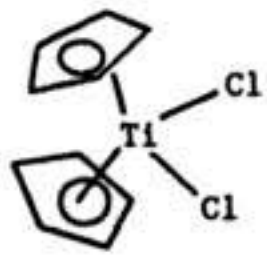
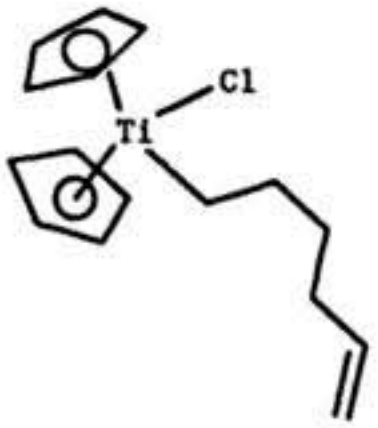
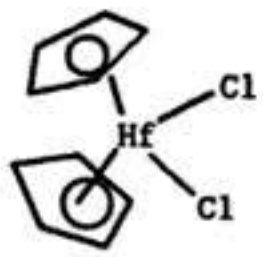
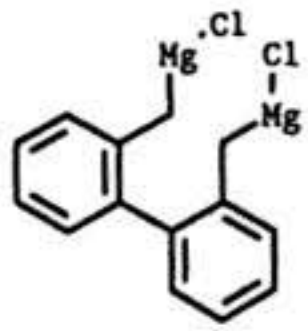
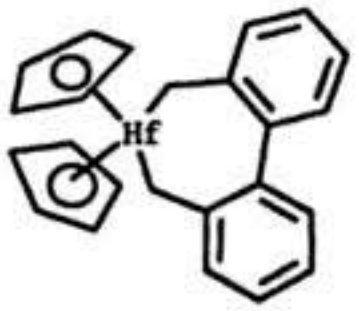


(64)

Burns and Buchwald take advantage of the fact that dioxane will precipitate MgX_2•dioxane to drive a group III nucleophilic substitution to completion in yields greater

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Table 11 (Continued)

Entry	Substrate	RMgX	Product	Yield (%)
7[A,D,173]	$(COT)ZrCl_2$	R = CH_3, CH_2CH_3, CH_2-$CHCH_2$	$R_2Zr(COT)$	60
8[174]				98
9[175]				55

A. 2 equivalents of Grignard reagent.
B. Reaction carried out in toluene, followed by dioxane addition.
C. 4 equivalents of Grignard reagent.
D. COT = cyclooctatetrene.

C. Examples of Applications

Some selected examples of nucleophilic substitution for the transition metals are listed in Tables 11–14.

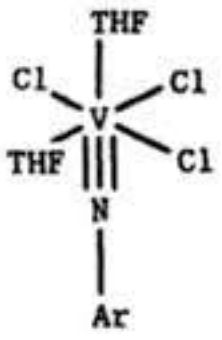
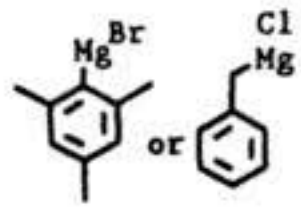
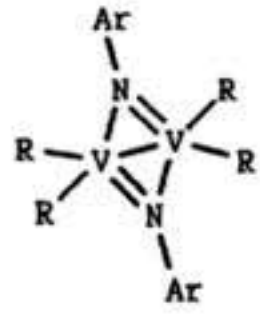
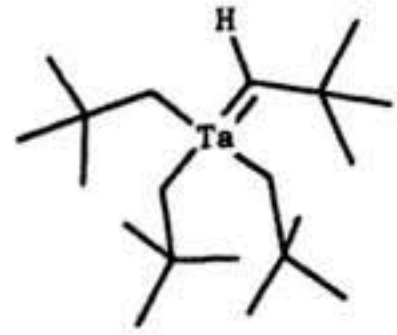
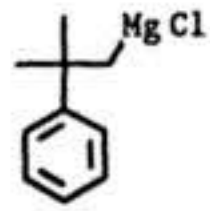
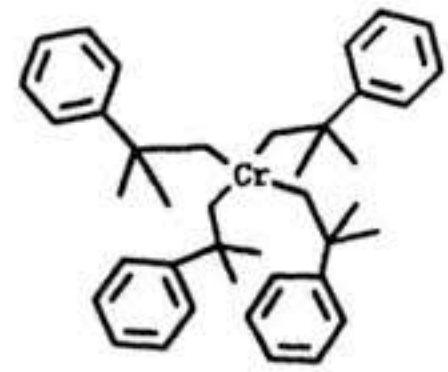
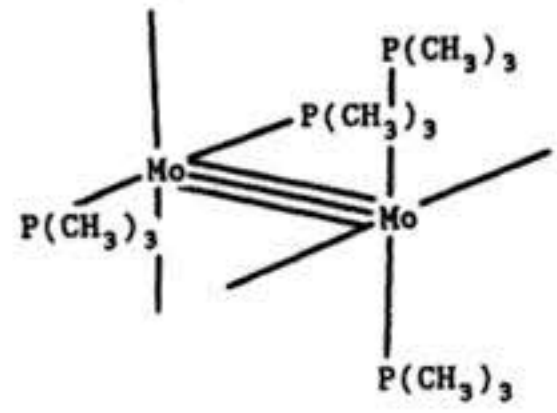
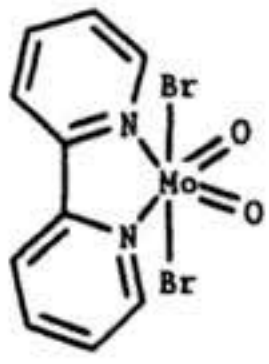
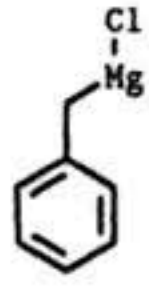
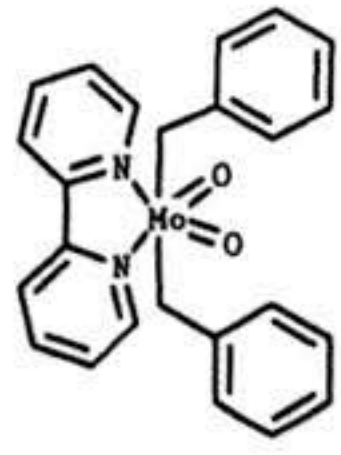
Interestingly, mixed alkyl or aromatic–halide complexes can be made in good yield for the early transition metal elements (see Table 11, entries 2, 3, and 8). However, as mentioned earlier, the fully alkylated or aromatic-substituted species typically give low to moderate yields (see Table 11, entries 1, 6, and 9). To obtain good yields of the fully alkylated or aromatic-substituted species, precipitation or removal of MgX_2 is required (see Table 11, entries 4 and 5).

The commercial applications of the organometallic species are typically in the area of catalysis (see Chapters 33 and 34) and preparation of precursors for chemical vapor deposition [201]. An example of the synthetic usefulness of Grignard reagents is demonstrated in the preparation of the new breed of metallocene catalyst that are used for polyolefin production (Scheme 7) [106,202,203].

Chemical vapor deposition applications range from the semiconductor–microelectronics industry, to the coatings industry for wear resistance. A significant portion of the precursors are made by nucleophilic substitution reactions with Grignard reagents. The organic

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Table 12 Selected Examples of Group V and VI Electrophiles

Entry	Substrate	RMgX	Product	Yield (%)
1[A,B,176]				37 - 48
2[C,151]	$Nb(O)Cl_3$	CH_3MgI	$CH_3Nb(O)Cl_2$	75
3[D,177]	$TaCl_5$	$(CH_3)_3CH_2MgCl$		54
4[A,178]	$CrCl_3$	C_6H_5MgBr	$Cr(C_6H_5)_3(THF)_3$	72
5[E,179]	$CrCl_3(THF)_3$			25
6[180]	$(C_5H_5)CrI(NO)_2$	CH_3MgI	$(C_5H_5)CrCH_3(NO)_2$	"Good yield"
7[F,181]	$Mo(O_2CCH_3)_4$	CH_3MgCl		"Not reported"
8[G,182]				50

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moieties modify the transition metal so it will have the desired properties, such as volatility, appropriate decomposition temperatures, and so forth [see Ref. 201 for more criteria].

V. SUMMARY

In general, nucleophilic substitution with Grignard reagents can be an effective synthetic tool. However, there are a multitude of competing reactions that need to be minimized to obtain satisfactory yields.

One of the key factors for yield improvement is to precipitate or remove MgX_2 from solution. This can be accomplished by going to less polar solvents, such as heptane, or by forming insoluble complexes, such as $MgX_2 \cdot$ dioxane. Potential explanations for this effect are removal of a Lewis acid, shift in the Schlenk equilibrium, or the change in solvent polarity that affects the nucleophilicity of the Grignard reagent.

Typical reaction parameters, such as temperature, addition rate, mass transfer, and such, can also help eliminate the competing reactions.

By making the electrophilic center more electropositive through modification of the leaving group(s), nucleophilic substition can be facilitated. However, sterically demanding electrophilic centers without an open coordination site should be avoided.

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16

Nucleophilic Addition to Unconjugated C–C Multiple Bonds

PHILIP E. RAKITA
Elf Atochem Agri, S.A., Plaisir, France

I. INTRODUCTION

This chapter is devoted to the general subject of nucleophilic addition reactions of Grignard reagents with unconjugated alkenes and alkynes (i.e., isolated carbon–carbon double and triple bonds). Reactions of this type involving metal catalysis are discussed in Chapter 29. The use of nucleophilic addition reactions to unconjugated olefins and alkynes for the synthesis of asymmetric products is reviewed in Chapter 28. Reactions of Grignard reagents with conjugated alkenes or alkynes (including conjugation with carbon–carbon double bonds, carbon–heteroatom multiple bonds, and aromatic systems) are discussed in Chapter 19. Not included are discussions of hydromagnesation (see Chapter 3) [1]. Also not included are "Barbier" (in situ) type reactions that may also involve an intramolecular magnesium–ene rearrangement.

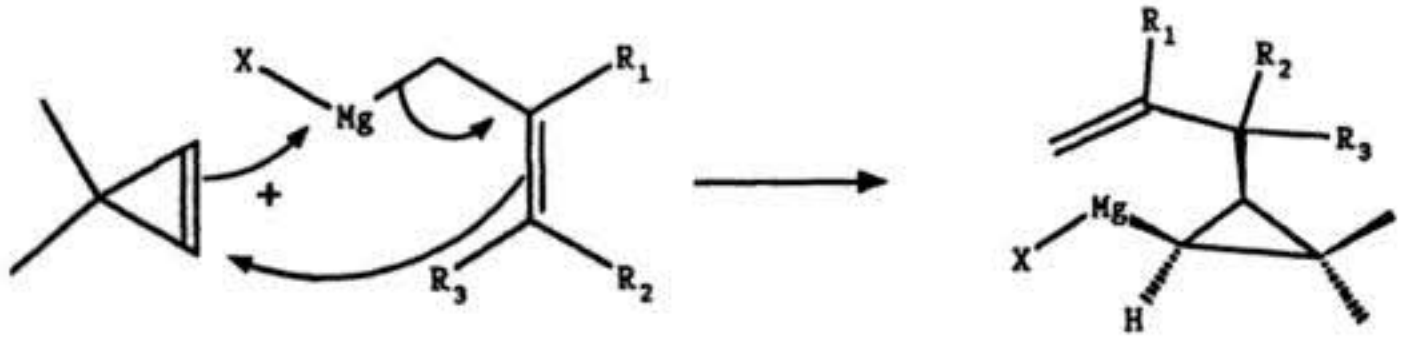
There are several reviews covering various aspects of the general topic of the addition of Grignard reagents to carbon–carbon multiple bonds. Hill [2] provides a mechanistic analysis of intramolecular rearrangements. Prasad and Pillai [3] focus on the synthetic possibilities of the addition of Grignard reagents to isolated multiple bonds in functionally substituted compounds. The addition of Grignard reagents to carbon–carbon multiple bonds has also been briefly reviewed by He [4].

II. FACTORS AFFECTING THE ADDITION OF RMgX TO UNCONJUGATED C–C MULTIPLE BONDS

Grignard reagents are generally not very reactive toward isolated carbon–carbon multiple bonds. There are, however, several factors, both steric and electronic, that can enhance the

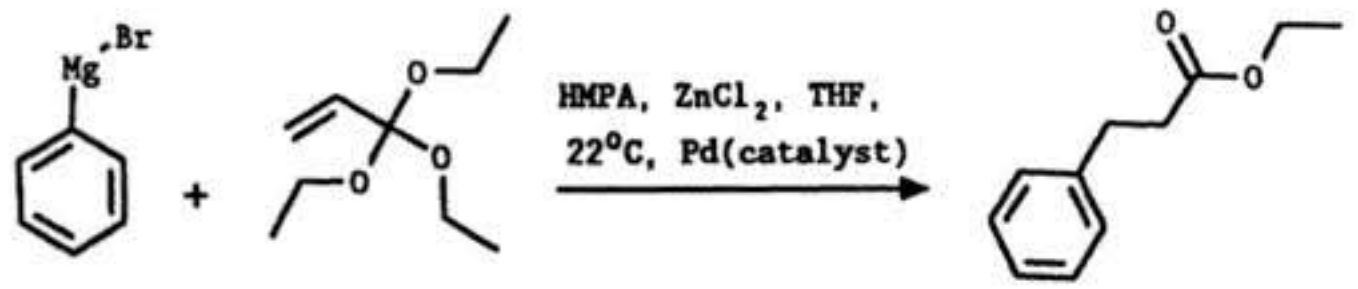
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precursors for chrysanthemic acid [22; Eq. (5)].



(5)

The presence of an electron-rich group (–OR or NR_2) in the allylic position contributes to the reactivity of the double bond toward Grignard reagents. Thus, allyl and benzyl Grignard reagents readily add to allyl alcohol [23,24]. Phenyl Grignard reagent reacts with 1,1,1-triethoxypropene to give, after workup, ethyl 3-phenyl propionate, in 74% yield [25; Eq. (6)].



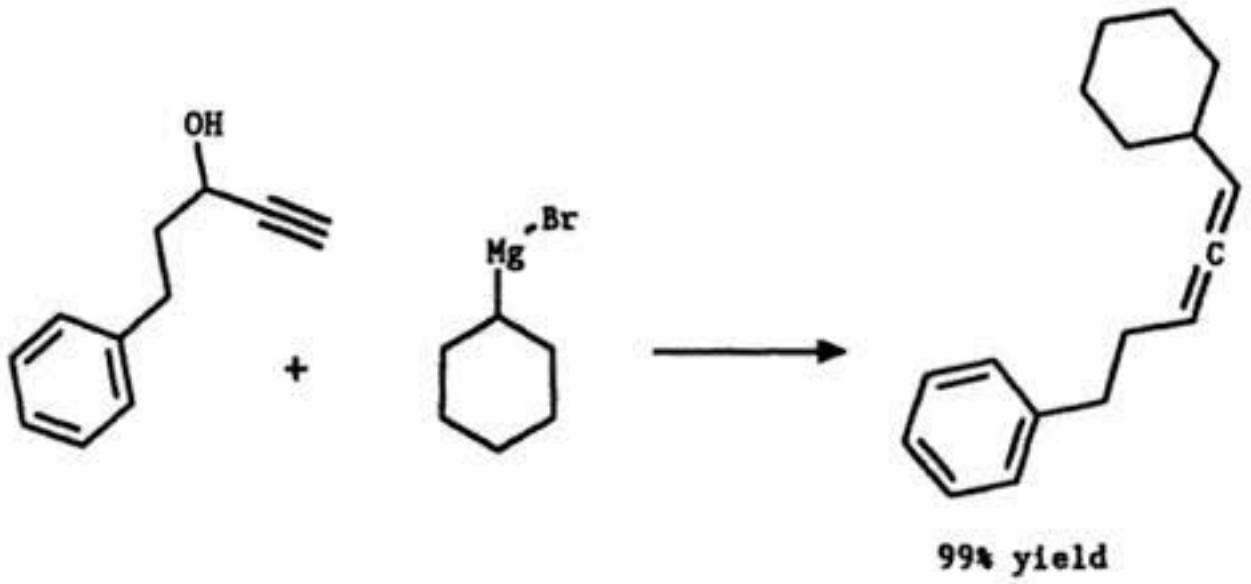
(6)

Allylic Grignard reagents also add to allylic and propargylic amines, but the metallated amine function is less effective that the comparable metallated hydroxy function in directing the course of the reaction [26].

VI. ADDITION TO ALKYNES

A. Terminal Alkynes

Reaction of simple terminal alkynes normally leads to transmetallation [27]. However, substituted propargly alcohol reacts with cyclohexylmagnesium bromide to give, after rearrangement, the substituted allene [Eq. (7); 28.29].



(7)

B. Internal Alkynes

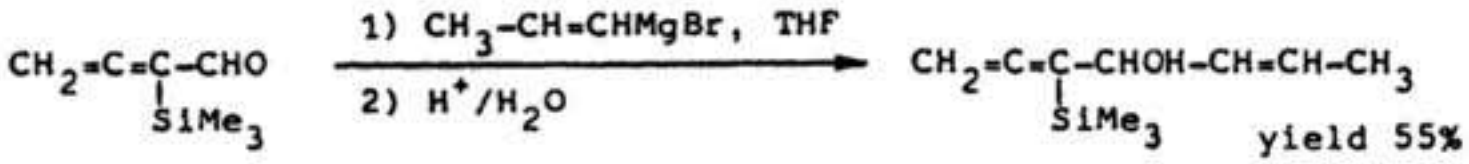
Intramolecular cyclization has been observed for the addition of a Grignard reagent across an internal alkyne [Eq. (8); 30].

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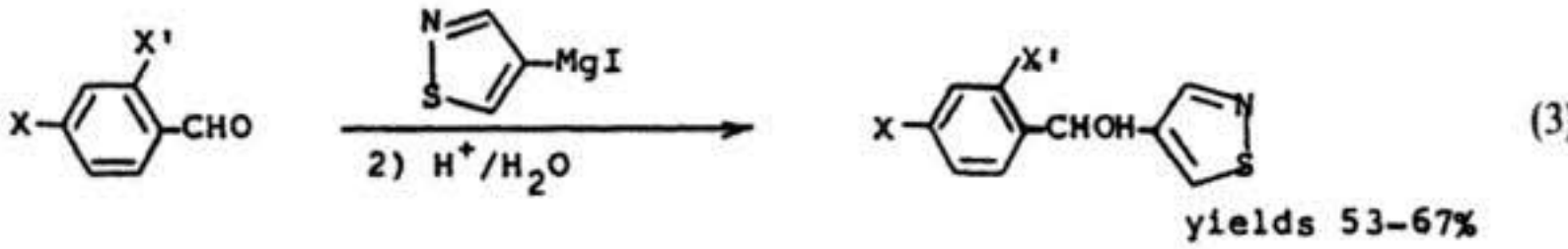
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5. B. J. Wakefield, Compounds of the alkali and alkaline earth metals in organic synthesis, *Comprehensive Organometallic Chemistry*, Pergamon Press, Oxford, 1982, Chap. 44.
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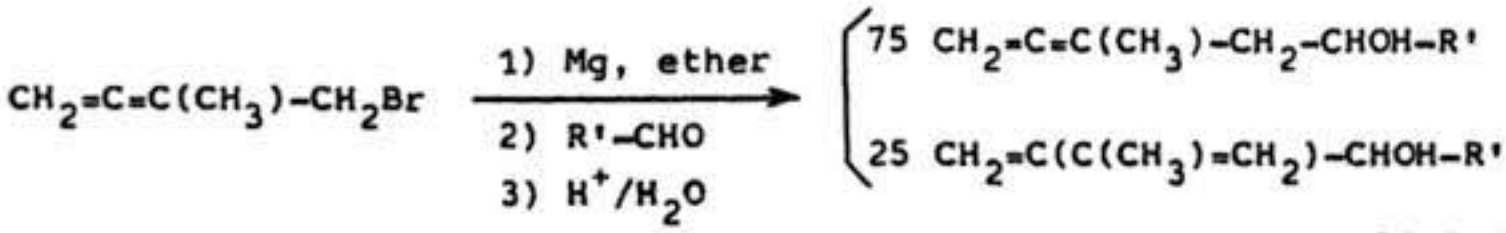
Recent research has dealt with new substrates [Eq. (2); 11] or new Grignard reagents [Eqs. (3) and (4); 12,13]:



(2)

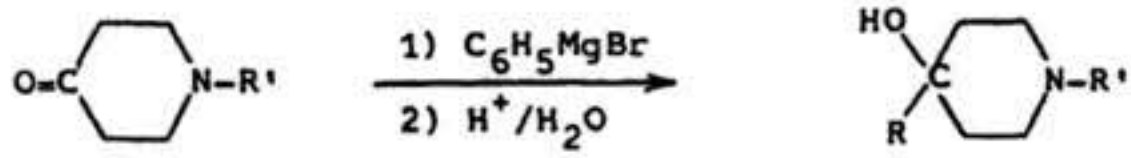


(3)

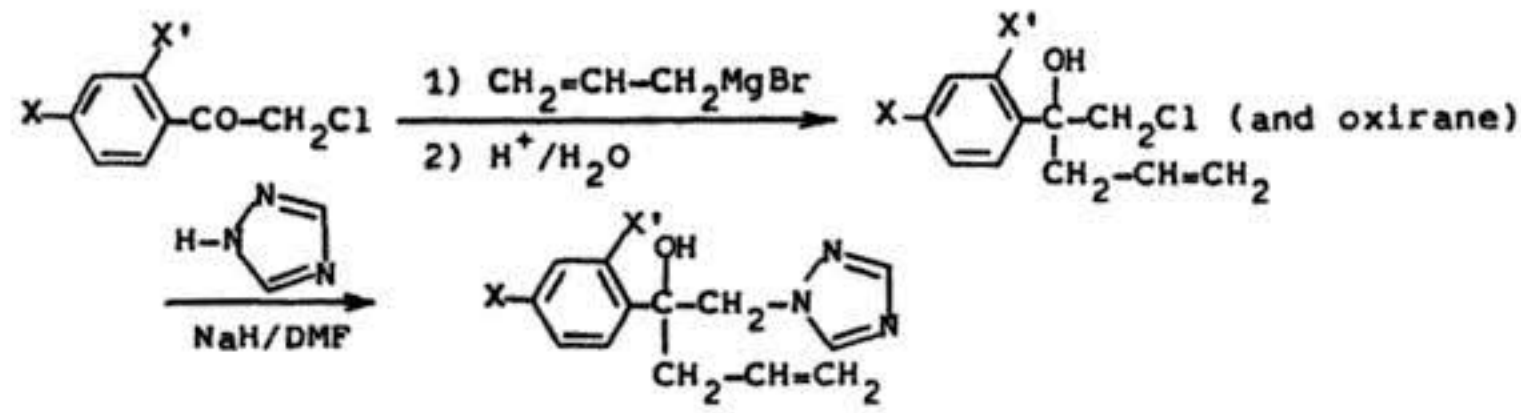


(4)

Applications were developed recently to address this problem for the fields of pharmaceutical [Eq. (5); 14] and pesticide chemistry [Eq. (6); 15].

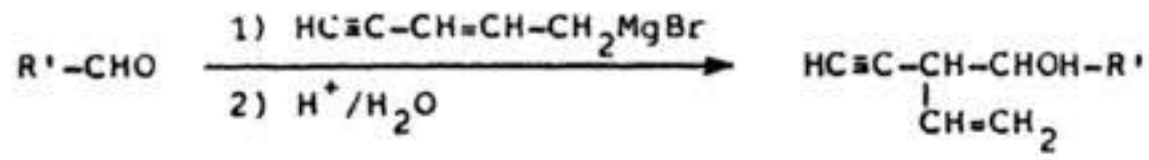


(5)

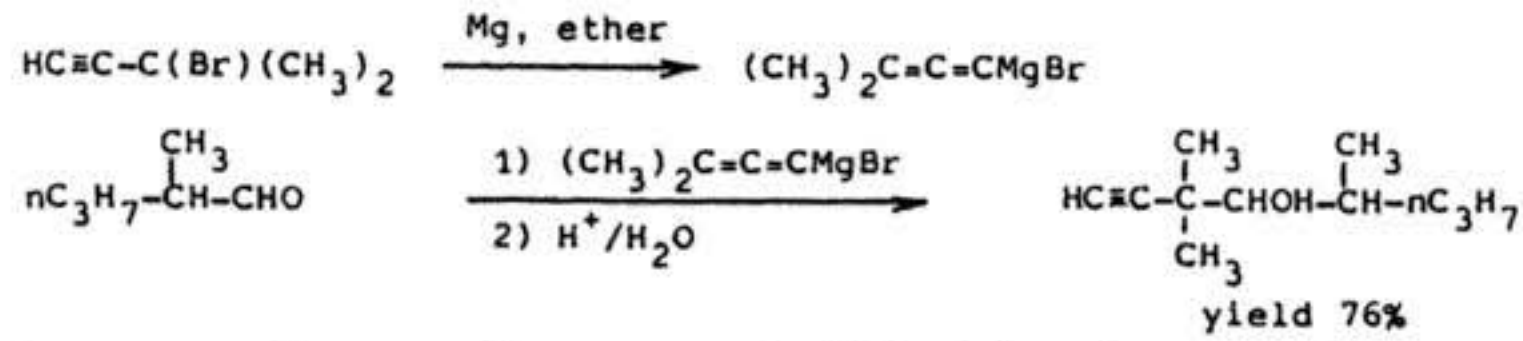


(6)

With organomagnesium compounds prepared from allylic or proparglyic halides, the reaction takes place readily and no enolization or reduction is observed [Eqs. (7) and (8); 16,17]:



(7)

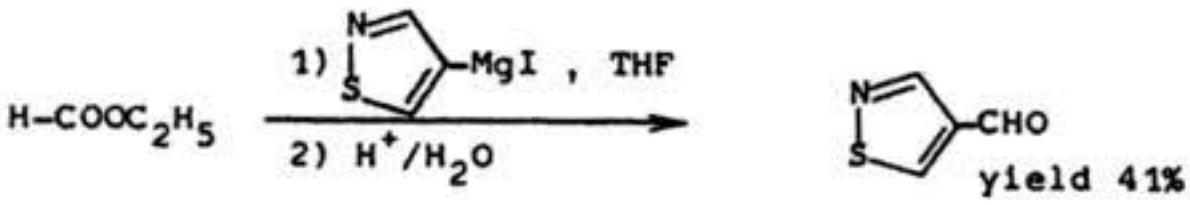


(8)

In contrast with organozinc compounds, allylic Grignard reagents often react with ketones in an irreversible manner [18]. The same results are obtained with organomagnesium

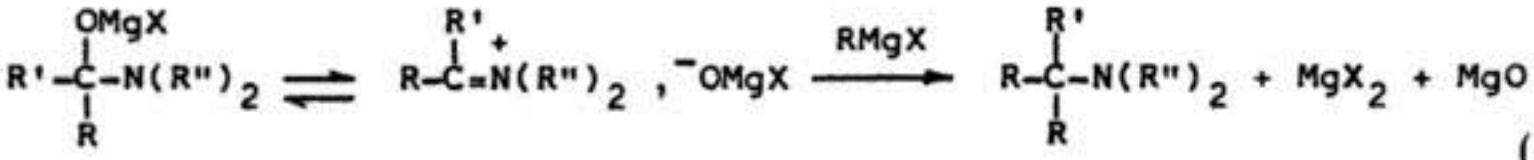
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For example [12]:



(16)

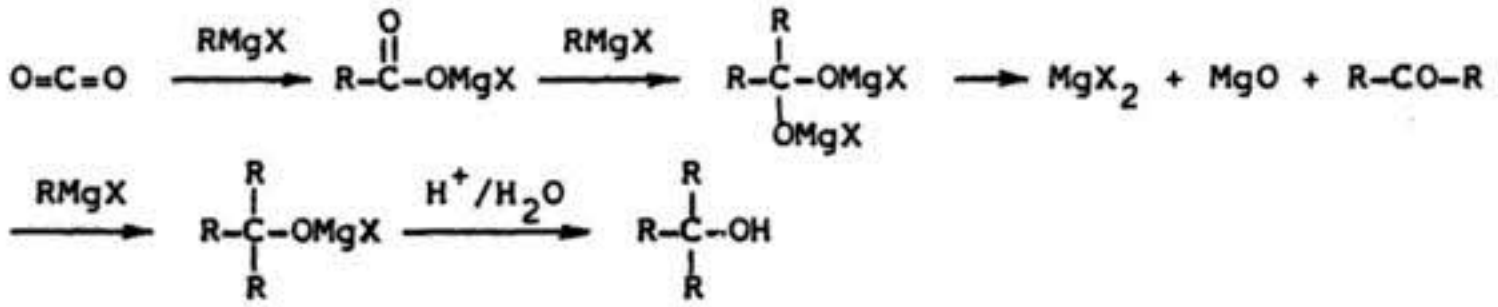
Occasionally, the reaction between an amide and a Grignard reagent may give a tertiary amine, resulting from the attack on the initial intermediate by a second mole of RMgX, Eq. (17).



(17)

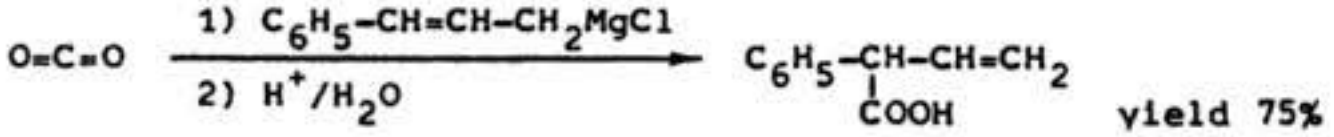
C. Carbon Dioxide and Derivatives

The reaction of carbon dioxide and Grignard reagents initially gives a salt of a carboxylic acid that is able to react further with the reagent [Eq. (18)]:

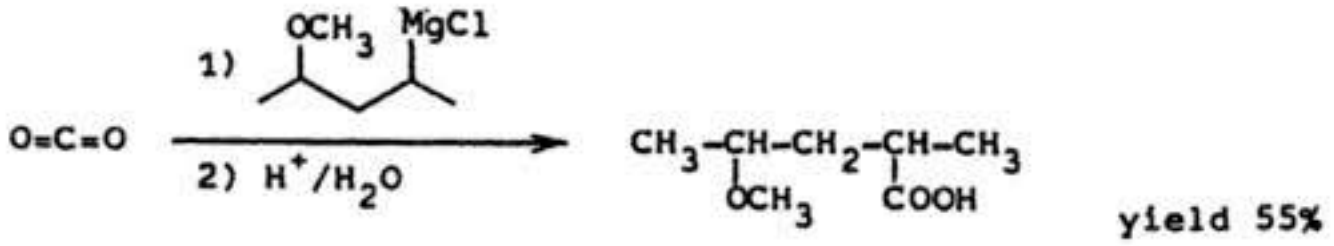


(18)

In practice, the second reaction is slow, even at room temperature, and can be essentially eliminated by pouring the Grignard solution onto finely powdered, stirred, solid carbon dioxide (dry ice). After hydrolysis, a carboxylic acid is obtained [27,28]:



(19)



(20)

When the reaction is realized with a large excess of RMgX and CO_2 gas, tertiary alcohols with three identical groups are isolated after hydrolysis. Such alcohols may also be obtained with dialkylcarbonates or phosgene.

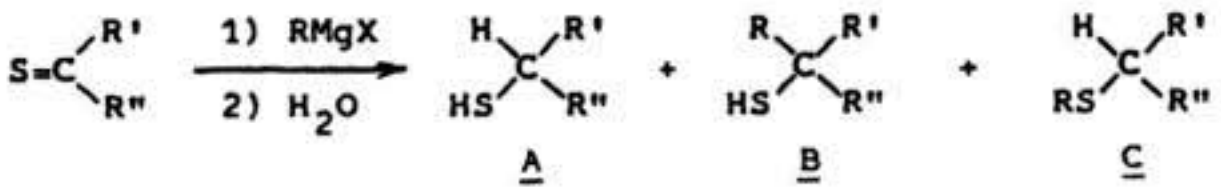
III. NUCLEOPHILIC ADDITION TO C=S BONDS

In addition to the general reviews already cited, the essential results obtained in this area before 1975 are summarized in a French review [29].

A. Thioketones

Usually, this reaction leads to a mixture of several products **A**, **B**, and **C** [Eq. 21); 29,30]:

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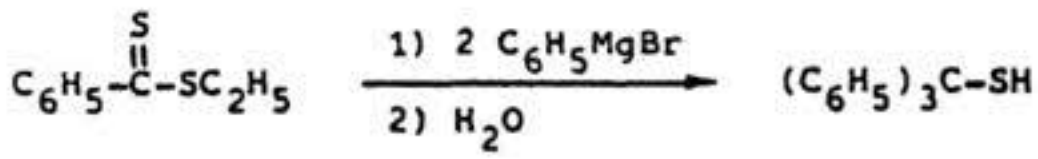


(21)

Saturated Grignard reagents, other than methyl, tend to give mostly reduction **A**, with a preference for thiophilic product **C** when addition occurs. Methyl magnesium bromide in THF gives thiophilic addition **C**, whereas the methyl magnesium iodide in ether gives carbophilic addition **B**. Vinylmagnesium chloride adds to sulfur or to carbon according to the thioketone; allylmagnesium bromide or allenylmagnesium bromide give only the carbophilic addition product **B**, which partially cyclizes under the reaction conditions.

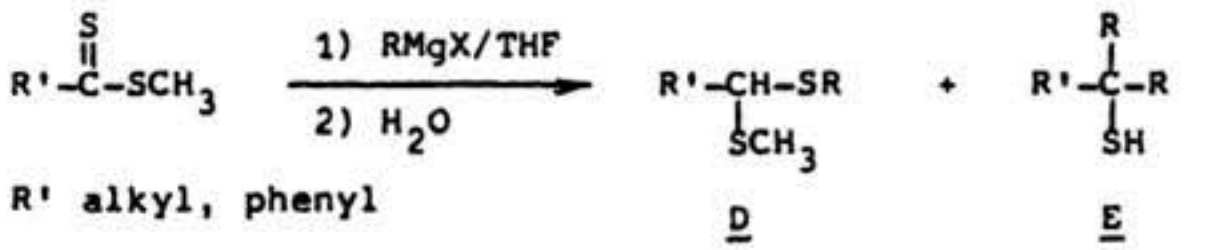
B. Dithioesters

Since 1926, it has been known that thiols could be formed by reaction of 2 mol of RMgX with 1 mol of dithioester [31]:



(22)

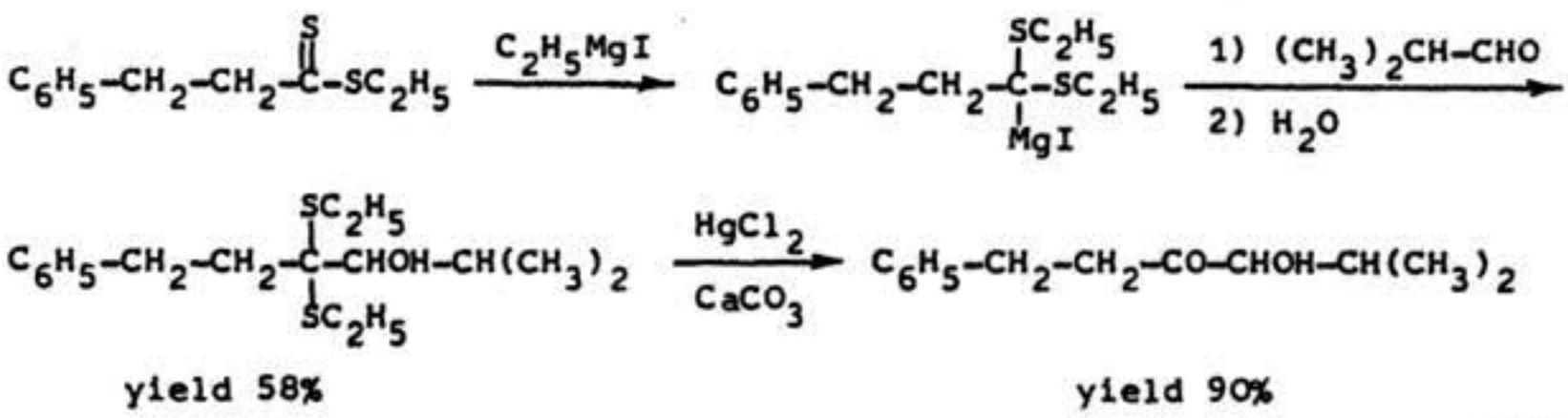
A detailed study of this reaction [Eq. (23); 32] has shown that two principal products, **D** and **E**, may appear, according to the R group of RMgX and the temperature of the reaction:



(23)

The thiophilic addition **D** is preferential when the temperature is less than $-17°C$ and when R is an ethyl or an isopropyl group; similar results are observed with other dithioesters [33]. With CH_3MgBr or CH_3MgI, carbophilic addition is preferential if the reaction is performed at 20°C or at reflux, leading to the thiol **E**.

Thiophilic addition of EtMgI to dithioesters leads to acyl anion equivalents that react with electrophilic reagents to yield to dithioacetals [34]. The latter compounds may be transformed into the corresponding carbonyl compounds on hydrolysis [Eq. (24)].

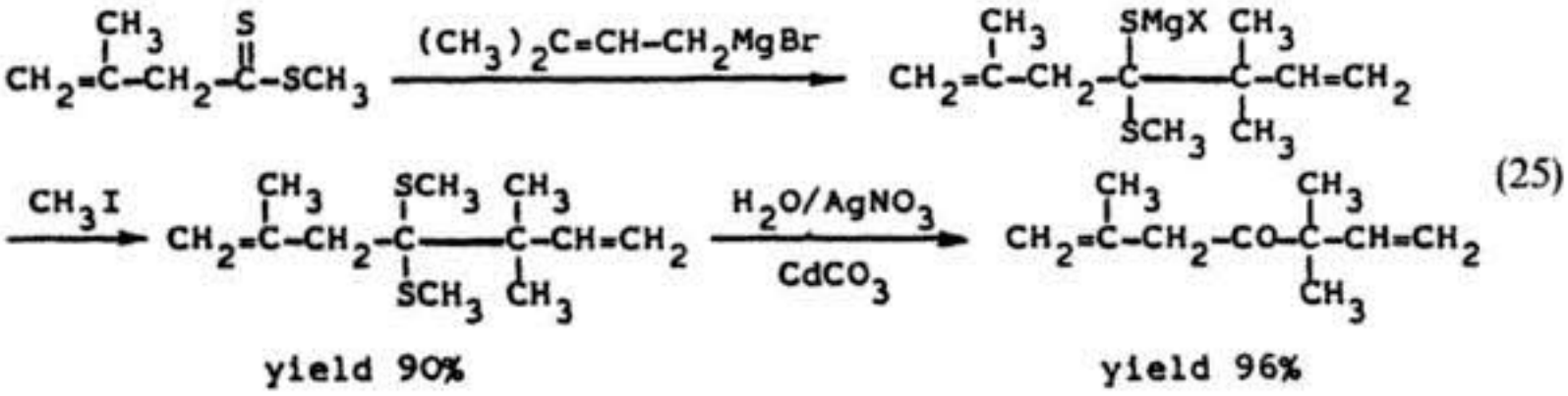


(24)

Carbophilic addition of prenylmagnesium bromide and other allylic Grignard reagents to the thiocarbonyl group of dithioesters occurs exclusively with rearrangement of the allylic

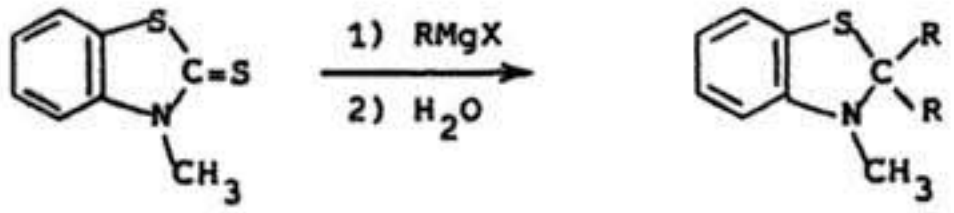
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chain [35]:



(25)

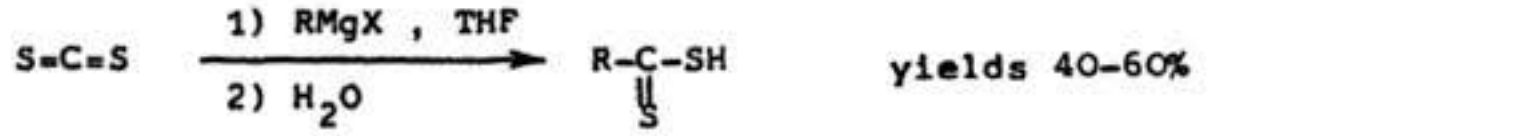
Finally, the reaction of Grignard reagents with a dithiocarbonate leads to gem-aminothioethers [36]:



(26)

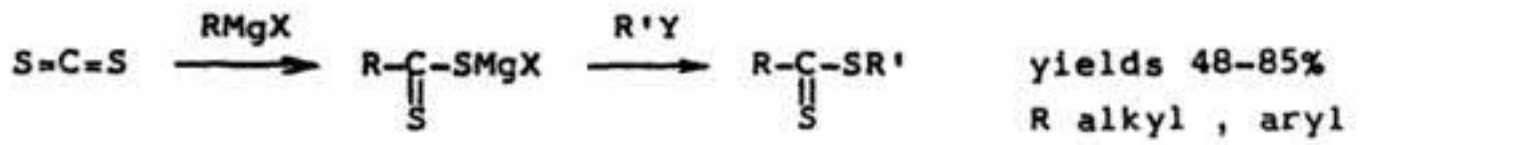
C. Carbon Disulfide and Carbon Sulfide

The reactions of carbon disulfide with Grignard reagents appear to be altogether similar to the corresponding reactions of carbon dioxide. Thus, it is possible to prepare dithioacids [37–39; Eq. (27)];



(27)

This method may be used to prepare dithioesters by the following scheme [40–44; Eq. (28)]:



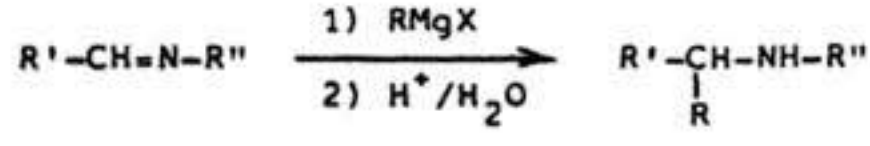
(28)

Successive reactions of Grignard reagents with carbon disulfide, 1-trifluoromethylsulfonyl-benzotriazole, and amines, afford the corresponding *N*-mono and *N*,*N*-disubstituted thioamides in good yields [45]. With carbonyl sulfide the reaction leads to a mixture of RCOSH and $(R)_3COH$ [30].

IV. NUCLEOPHILIC ADDITION TO C=N BONDS

A. Aldimines and Ketimines

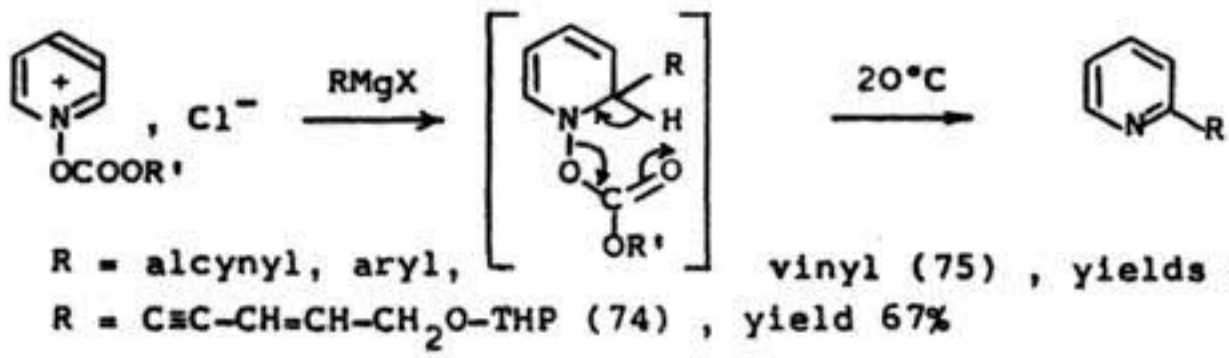
Imines are analogous to carbonyl compounds in their reactions with saturated Grignard reagents [46] (i.e., the addition reaction competes with enolization and reduction reactions). With imines that contain no α-hydrogens and with saturated Grignard reagents without a β-hydrogen, the reaction proceeds in the usual way [Eq. (29)], leading to secondary amines after hydrolysis:



(29)

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salts [72,73] and from *N*-alkoxycarboxylpyridinium salts [74,75].



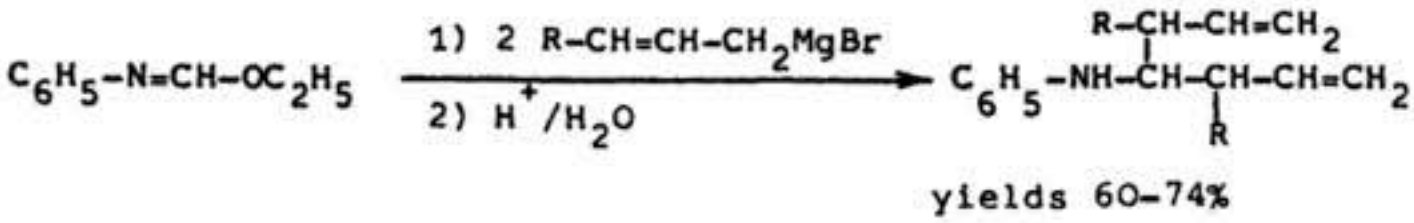
(35)

R = alcynyl, aryl, vinyl (75), yields 41–45%

R = C≡C–CH=CH–CH_2O–THP (74), yield 67%

C. Iminoethers and Iminothioethers

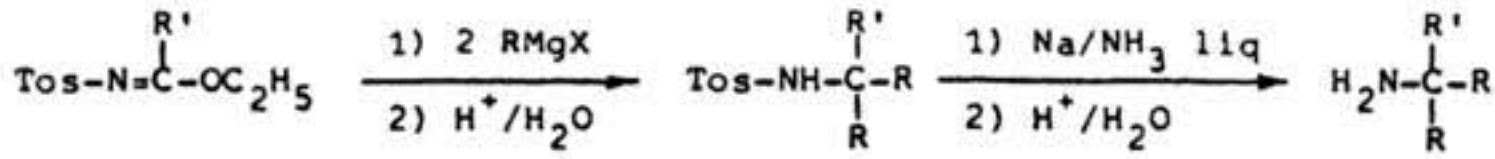
An *N*-aryliminoether undergoes a reaction with 2 mol of RMgX to lead directly to a secondary amine with two identical groups [76; Eq. (36)].



(36)

yields 60–74%

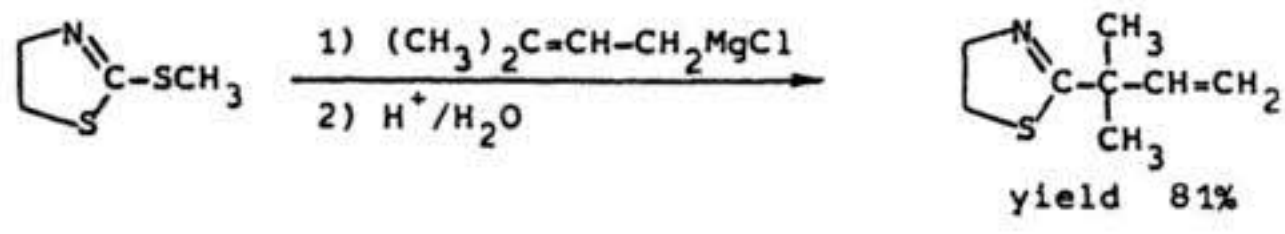
With an *N*-tosyliminoether [55], it is possible to obtain a primary amine [Eq. (37)]:



(37)

yields 40–44%

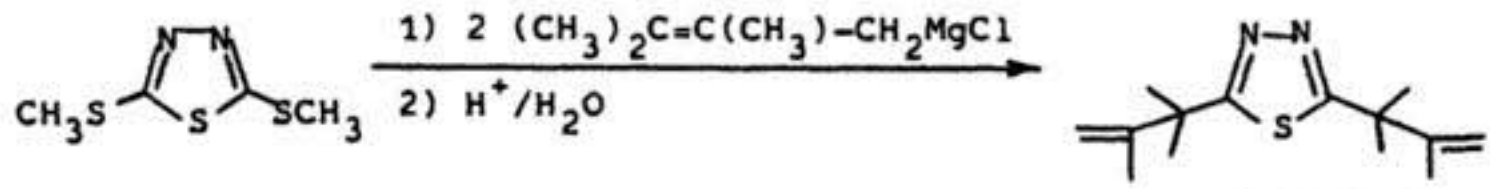
Reactions between substituted allylic Grignard reagents and cyclic iminothioethers or iminoethers have been tried with 2-methylthio-2-thiazolines or 2-oxazolines. Interestingly, only one addition–elimination reaction is observed [77; Eq. (38)]:



(38)

yield 81%

Similarly, symmetric or unsymmetric disubstituted derivatives of 1,3,4-thiadiazole are prepared [78] from 2,5-bis(methylthio)-1,3,4-thiadiazole or 5-methylthio-1,3,4-thiadiazol-2(3H)-thione [Eq. (39)]:



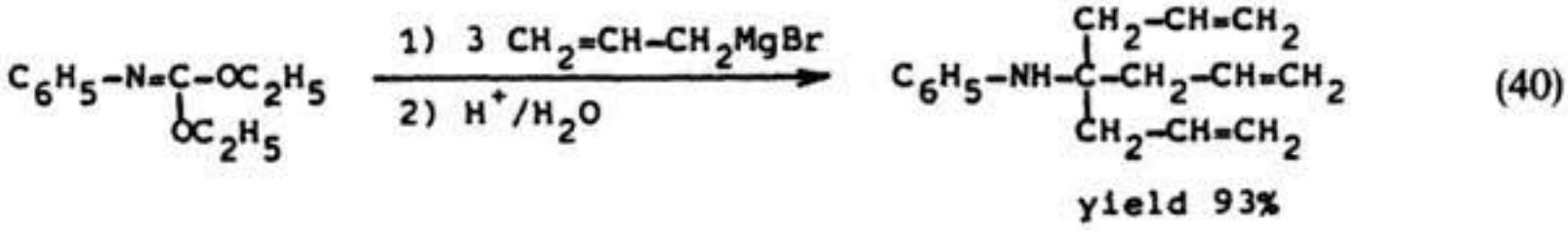
(39)

yield 85%

D. Iminocarbonates

With these compounds, Grignard reagents may react with the substrate three sequential times at the same carbon [79; Eq. (40)]:

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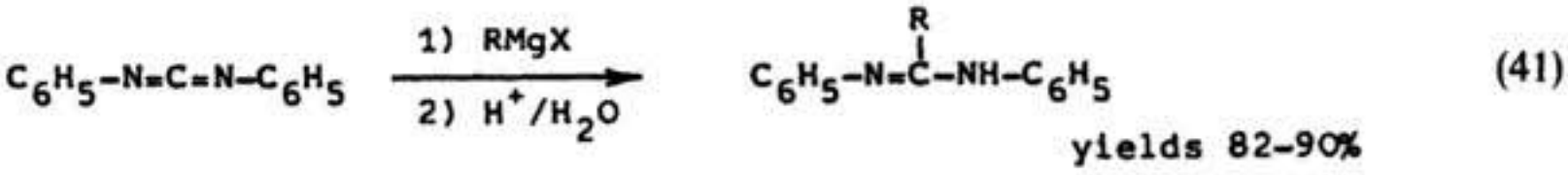


(40)

As expected, *N*-tosyliminocarbonates lead to *N*-tosylamines then to primary amines $H_2N\text{-}C(R)_3$ [55].

E. Carbodiimides

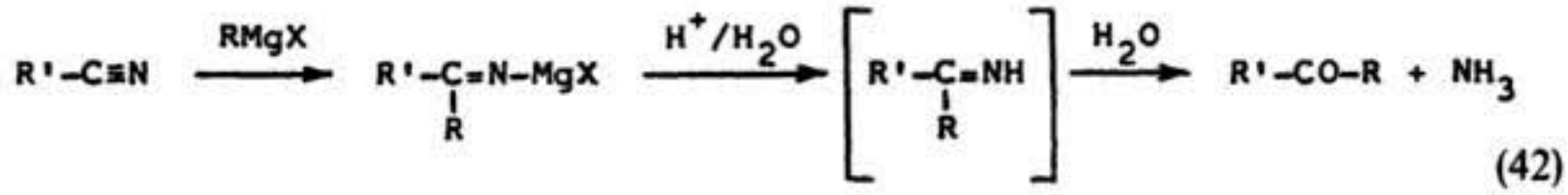
Even by using a large excess of RMgX (R = saturated, phenylic or allylic group), only 1 mol of RMgX adds, leading to amidines [80; Eq. (41)]:



(41)

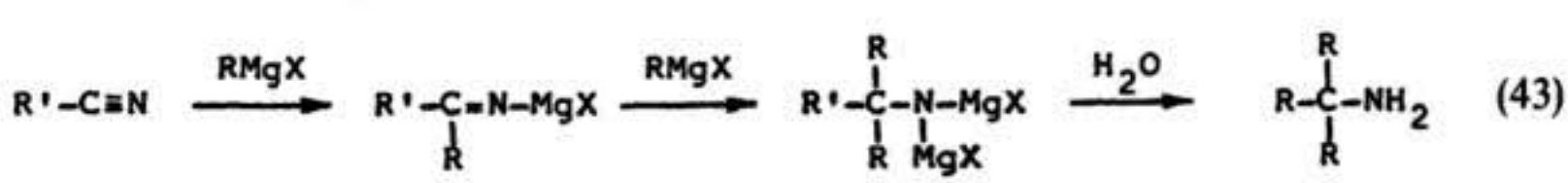
V. NUCLEOPHILIC ADDITION TO C≡N BONDS

Generally, Grignard reagents add once to a nitrile group [81–86]:



(42)

Hydrolysis of the adducts produces ketimines, which are instable under the reaction conditions and rapidly hydrolyze to ketones. The use of benzene, containing 1 eq. of ether as solvent, leads to increased yields of ketones, compared with results in diethyl ether [87]. Also, the addition of Grignard reagents to nitriles may be catalyzed by Cu^I salts [88]. Tandem alkylation–reduction of a series of nitriles, by alkylating with Grignard reagents, followed by reduction with lithium–ammonia affords the corresponding branched primary amines in reasonable isolated yields [89]. By use of a large excess of RMgX, a twofold reaction has occasionally been obtained, producing primary amines [90; Eq. (43)]:

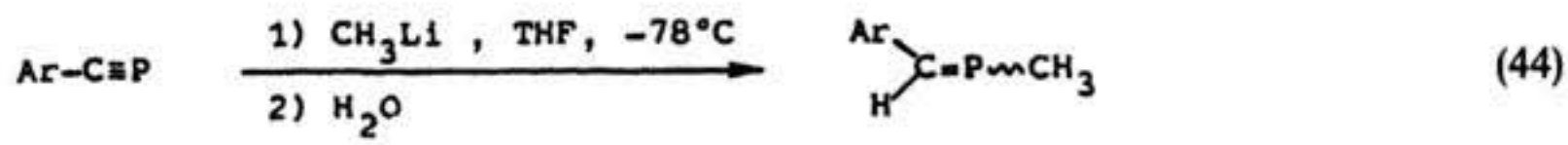


(43)

Similar results are observed with Grignard reagents and α-alkoxynitriles [91] and also with allylmagnesium bromide and various nitriles [83,92].

VI. NUCLEOPHILIC ADDITION TO C=P OR C≡P BONDS

Even in recent reviews, the addition of Grignard reagents to these functions has not been reported [93–95]. However, an example with an organolithium compound [94; Eq. (49)]:



(44)

allows a forecast of the possible behavior of organomagnesium derivatives.

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18

Nucleophilic Addition to Metal–Carbon Multiple Bonds

LISA A. MERCANDO

Air Products and Chemicals, Inc., Allentown, Pennsylvania

PAUL MERCANDO

Elf Atochem North America, Inc., King of Prussia, Pennsylvania

I. INTRODUCTION

This chapter will focus on the nucleophilic addition reactions of transiton metal carbene and carbyne complexes with Grignard reagents. The synthesis and some general reactions of these carbene and carbyne complexes will be presented. A more detailed description of the chemistry of these complexes can be found in the literature [1]. This chapter, although not exhaustive, is descriptive of the prototypical nucleophilic addition reactions of metal–carbon (M–C) multiple bonds with Grignard reagents.

II. TRANSITION METAL CARBENE COMPLEXES

Transition metal carbene complexes are described by the general formula $L_nM{=}CR_1R_2$, where the carbene ligand ($=CR_1R_2$) is bonded to the metal by a metal–carbon double bond. The first transition metal carbene complex was reported by Fischer and Maasböl in 1964 [2]. Subsequently, many other carbene complexes have been synthesized by the classic route of Fischer or by new synthetic methods.

Conventionally, carbene complexes are grouped into two classes: Fischer [2] and Schrock [3] carbenes. Fischer carbenes may be identified by their π-donor substituents on the carbene carbon and having π-acceptor ligands bonded to a low-oxidation state, late-transition metal. These ligands may be thought of as singlet carbenes that donate a

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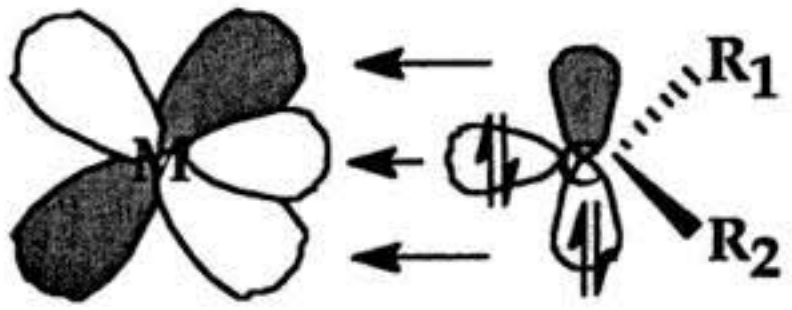
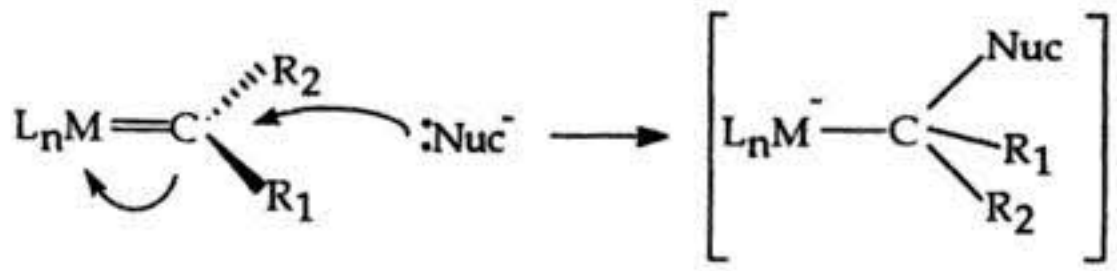


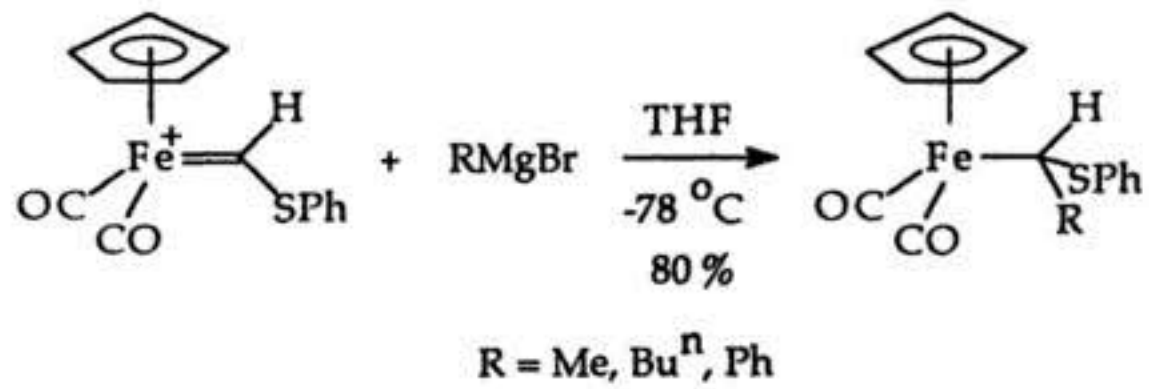
Figure 2

the Schrock carbene carbon, and is a typical reaction observed for these carbene complexes. In this specific example, an intermediate is formed that then rearranges to produce the final titanium enolate complex.

Typical reactivity of Fischer and Schrock carbene complexes with Grignard reagents (where the Grignard reagent is acting as a nucleophile) is illustrated in Eq. (4). This reactivity is based on the electronics and molecular orbital calculations for these types of complexes [10]. An example from the literature illustrating this type of reactivity between a Grignard reagent and a carbene complex was reported by Helquist and co-workers, as shown in Eq. (5) [11]. In these reactions, alkyl or phenyl magnesium bromide is added to the cationic carbene complex $[Cp(CO)_2Fe{=}CHSPh][PF_6]$. The resulting product is a neutral complex.

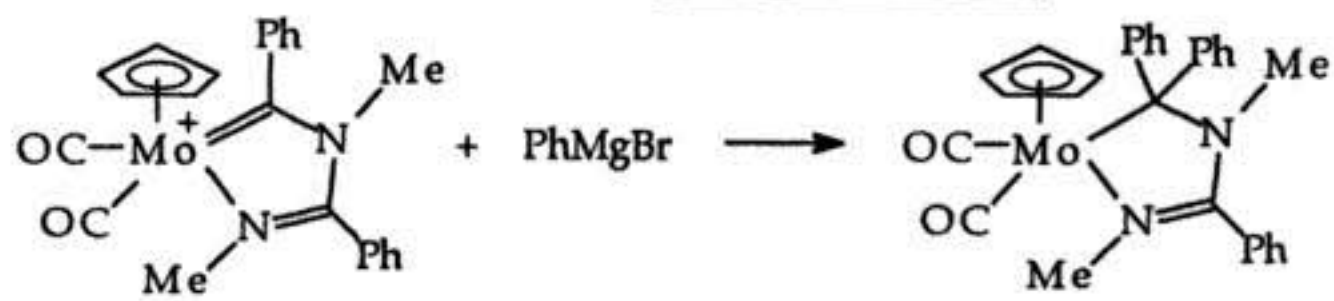


(4)



(5)

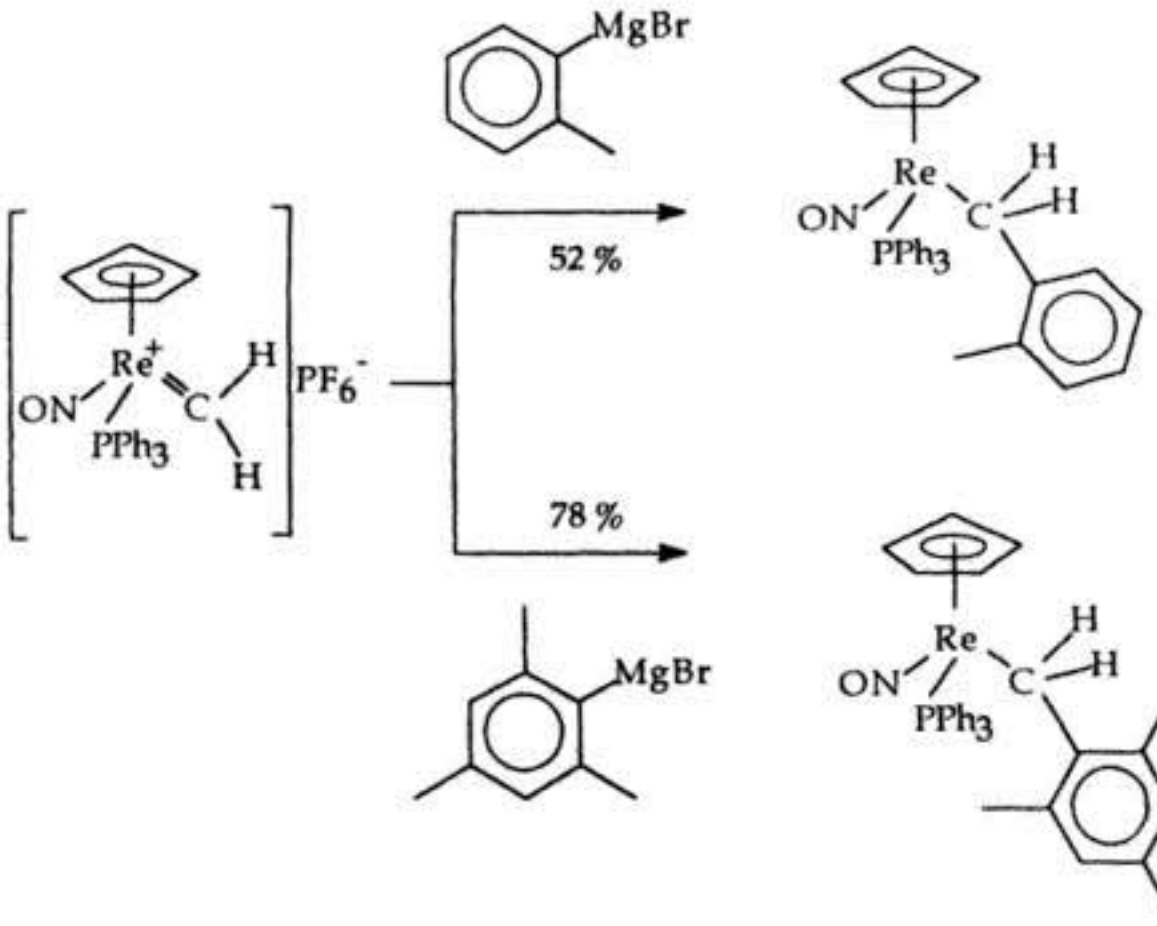
In addition, Gladysz and co-workers reported an example of a typical reaction involving a rhenium carbene complex and Grignard reagents, illustrated in Scheme I [12]. The addition of *o*-MeC_6H_4MgBr and mesityl Grignard reagent to $[CpRe(NO)(PPh_3)(=CH_2)][PF_6]$ produced rhenium alkyl complexes. The sterically crowded mesityl complex was observed to exhibit the presence of rotomers in the ^{1}H-nuclear magnetic resonance (NMR) as a result of a Re–C_α rotational barrier. Another example is the nucleophilic addition of phenyl Grignard reagent to $[Cp(CO)_2Mo{=}CPhNMeC{-}PhNMe]PF_6$ resulting in the neutral metallacycle $[Cp(CO)_2MoCPh_2N{-}MeCPhNMe]$, Eq. (6) [13].



(6)

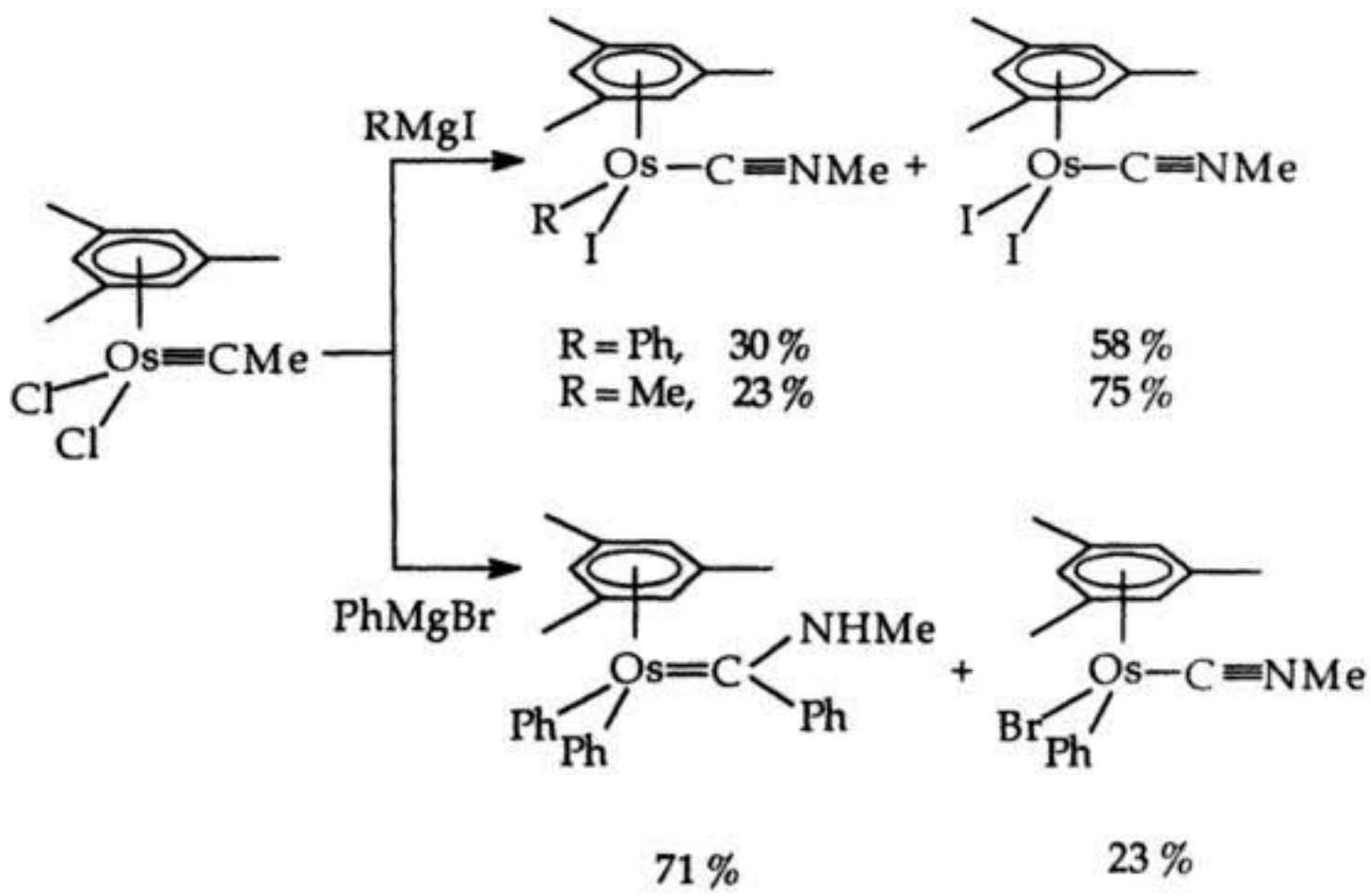
Grignard reagents have also been reported to be used in the synthesis of some carbene complexes. For example, Schrock and co-workers [14] reported the

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Scheme 1

use of $PhMe_2CCH_2MgCl$ to alkylate $Re(NAr)_2Cl_3$, resulting in the carbene complex, $Re(NAR)_2(CHCMe_2Ph)(CH_2CMe_2Ph)$, in near quantitative yield [Eq. (7)]. Another example of a carbene complex synthesized using a Grignard reagent was reported by Werner and co-workers [15]. In this reaction (Scheme 2), the osmium carbene complex, $[(mes)Os(=C(NHCH_3)(C_6H_5))C_6H_5)_2]$, probably results from nucleophilic attack of the Grignard reagent at the isocyanide carbon atom, followed by protonation of the nitrogen. In addition to the carbene complex, the bromophenyl compound, $[(mes)OsC_6H_5(CNCH_3)Br]$,



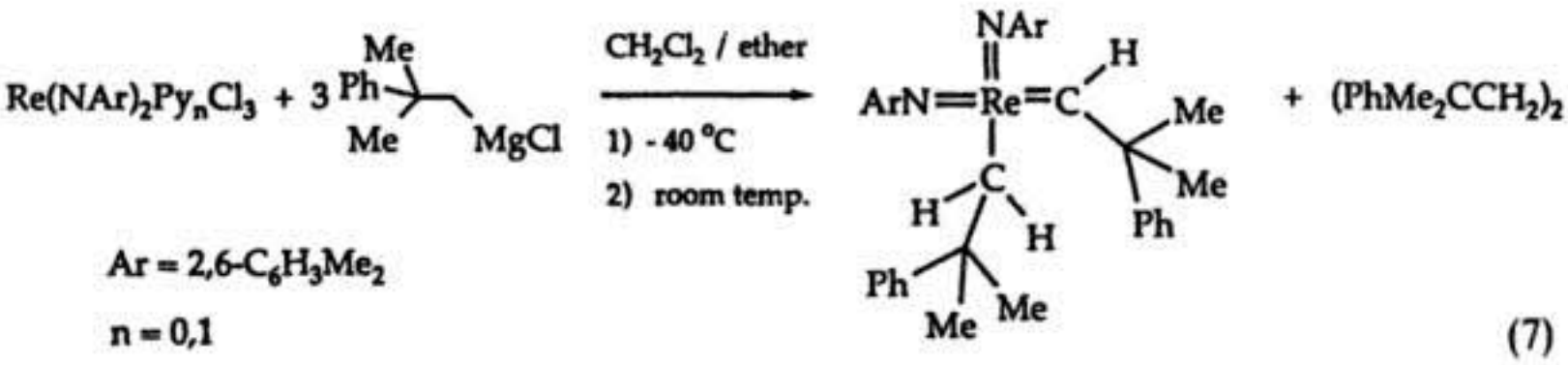
Scheme 2

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Table 1 Synthetic Routes to Carbene Complexes

Starting reagent	Grignard reagent	Metal carbene	Ref.
Cp_2TiCl_2	$CH_2(MgBr)_2$	$Cp_2TiCH_2Mg(Br)Cl$	16a
$Cp^*W(O)Cl_2R$	Me_3SiCH_2MgCl	$Cp^*W[=CHSiMe_3](O)R$	16b
$Cp^*W(O)Cl_2R$	$PhCH_2MgCl$	$Cp^*W[=CHPh](O)R$	16b

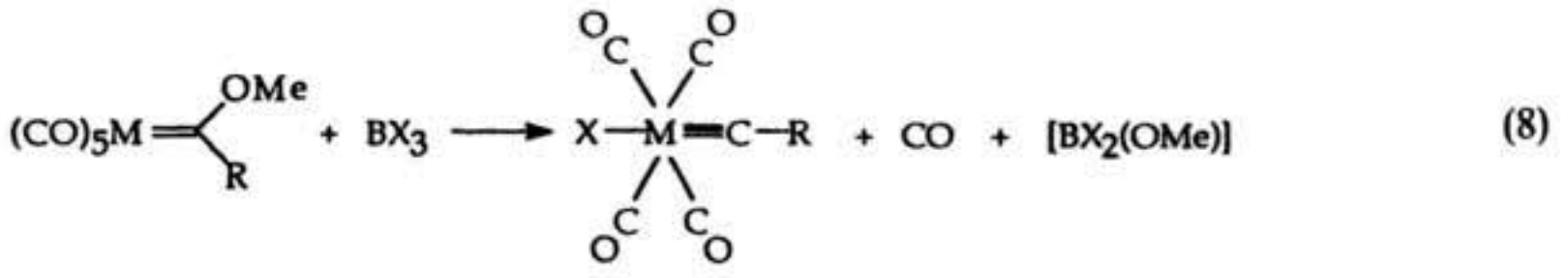
was isolated. Interestingly, also shown in this equation is the different activity observed, depending on the type of Grignard reagent used. The reaction of RMgI (R = Me, Ph) with the osmium isocyanide complex produces two products; however, the mixture of products is different when PhMgBr is used. Several synthetic routes to carbene complexes can be found in the literature involving Grignard reagents acting as metal alkylating agents (Table 1) [16].



(7)

III. TRANSITION METAL CARBYNE COMPLEXES

Transition metal carbyne complexes are described by the general formula $L_nM{\equiv}CR$ where the carbyne ligand ($\equiv$CR) is bonded to the metal by a metal–carbon triple bond. Transition metal carbene complexes have found numerous applications in synthetic organic chemistry through a variety of carbene transfer and cycloaddition reactions [17]. In contrast, carbyne ($L_nM{\equiv}CR$) and vinylidene ($L_nM{=}C{=}CRR'$) complexes have far fewer applications, in part because their overall chemistry is significantly less developed [18]. Addition reactions to transition metal vinylidene complexes will be discussed in Chapter 21. The first successful synthesis of a carbyne complex was reported by Fischer and co-workers in 1973 [Eq. (8); 19]. Subsequently, many other carbyne complexes have been synthesized by the classic route of Fischer or by new synthetic methods [20].



(8)

Carbyne ligands can also be grouped into two classes: Fischer and Schrock carbynes. The metal–carbyne carbon triple bond (Fig. 3) for a Fischer carbyne complex is formed

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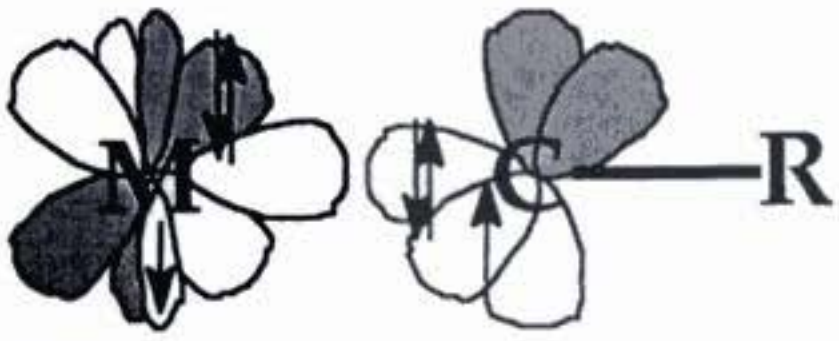
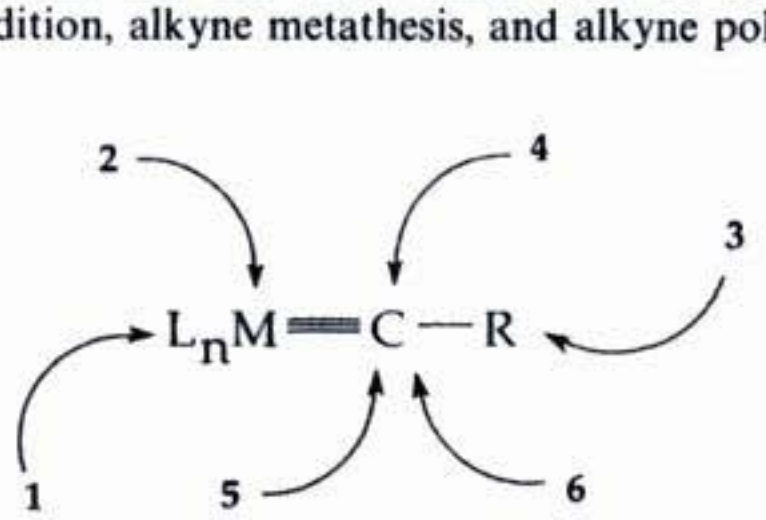


Figure 3

from the sp-hybridized lone pair electrons on the carbyne carbon, in conjunction with a π-bond from singly occupied metal-d and carbon-p orbitals and π-backbonding from a filled metal-d orbital into a vacant carbon-p orbital. The bonding scheme for Schrock carbynes can be drawn in two ways, depending on the oxidation state of the metal. The lone pair electrons that π-backbond from the metal in the Fischer carbyne can be moved to an empty p-orbital on the carbon atom. It may also be drawn such that all the electrons come from the carbyne carbon. Since the first report, research in the field of transition metal carbyne complexes has grown at a rapid rate [20]. However, there are still many gaps in the knowledge of the chemistry and properties of carbynes. Carbyne complexes can be synthesized in a variety of ways [18]. The interesting aspect of these complexes is that transition metal carbyne complexes may also react in a variety of different ways. The modes of reactivity of carbyne complexes are illustrated in Scheme 3 [21]. The first four modes of reactivity shown in Scheme 3 are (1) simple substitution of the ligands bound to the metal, (2) oxidation or reduction of the metal, (3) modification or exchange of the carbyne substituent, and (4) transfer of the carbyne ligand [18]. The last two modes of reactivity are nucleophilic and electrophilic addition at the carbyne carbon. These modes of reactivity are some of the most extensively studied. The types of nucleophiles that have been reported to react with carbyne complexes at the carbyne carbon include phosphines, isonitriles, amines, Grignards, pyridine, halogens, CN^-, OCN^-, SCN^-, OR^-, and SR^- [17]. In general, cationic carbyne complexes and neutral carbyne complexes, with electron-withdrawing ligands, have been the most reactive with nucleophiles. Neutral, electron-rich carbyne complexes react with such electrophiles as H^+ and Me^+ to give a variety of products, depending on the reactants involved and the conditions under which the reactions are run [18]. Other types of reactions not portrayed in Scheme 3 are cycloaddition, alkyne metathesis, and alkyne polymerization reactions [18].

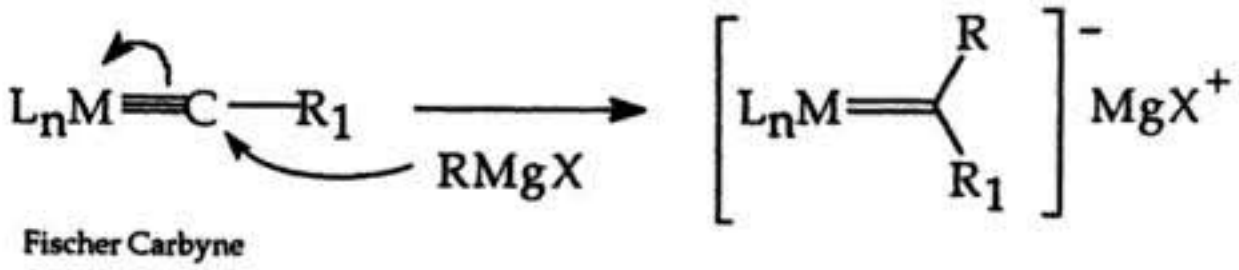


1) Substitution of ligands
2) Oxidation or reduction of the metal
3) Modification of the carbyne substituent
4) Transfer of the carbyne ligand
5) Addition of a nucleophile at the carbyne carbon
6) Addition of an electrophile at the carbyne carbon

Scheme 3

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The reactions of Fischer and Schrock carbyne complexes are of interest because they may act as intermediates in chemical synthesis. Typical reactivity of carbyne complexes with nucleophiles (i.e., alkyl lithium reagents and metal(I) alkoxides) are consistent with the electronics and molecular orbital calculations for these types of complexes [Eq. (9); 22]. The nucleophile adds to the carbyne–carbon, resulting in the formation of a carbene complex. The reaction of a Grignard reagent with a carbyne complex is expected to demonstrate similar reactivity.



(9)

Grignard reagents can be used in the synthesis of some carbyne complexes. For example, Chisholm and co-workers reported a convenient method for synthesizing trialkylalkylidyne tungsten compounds, based on the metathesis reaction between alkyl–Grignard reagents and $(^tBuO)_3W{\equiv}CR$ complexes, shown in Eq. (10) [23]. This type of synthesis allows the use of a wide variety of R groups; however, it is limited to alkyl ligands that lack β-hydrogen atoms owing to β-elimination reactions.

$$(^tBuO)_3W{\equiv}CR + 3\,R'MgCl \longrightarrow R'_3W{\equiv}CR + 3\,{}^tBuOMgCl$$

R =	R' =
^tBu	$PhCH_2$
SiMe3	Me_3CCH_2
Ph	Me_3SiCH_2
	$(Me_3CCH_2)_3WC$

(10)

IV. CONCLUSION

The reactions of Grignard reagents with transition metal carbene and carbyne complexes is certainly interesting chemistry. However, there is much more chemistry involving these reagents that needs to be explored. Grignard reagents have been used to prepare transition metal carbene and carbyne complexes [16,23]. Nucleophilic addition to transition metal carbene complexes has also been reported in the literature [12,13]. The chemistry of Grignard reagents and carbene and carbyne complexes remains a fertile ground for future investigation.

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Nucleophilic Addition to Conjugated Carbon–Carbon Multiple Bonds

PHILIP E. RAKITA
Elf Atochem Agri, S.A., Plaisir, France

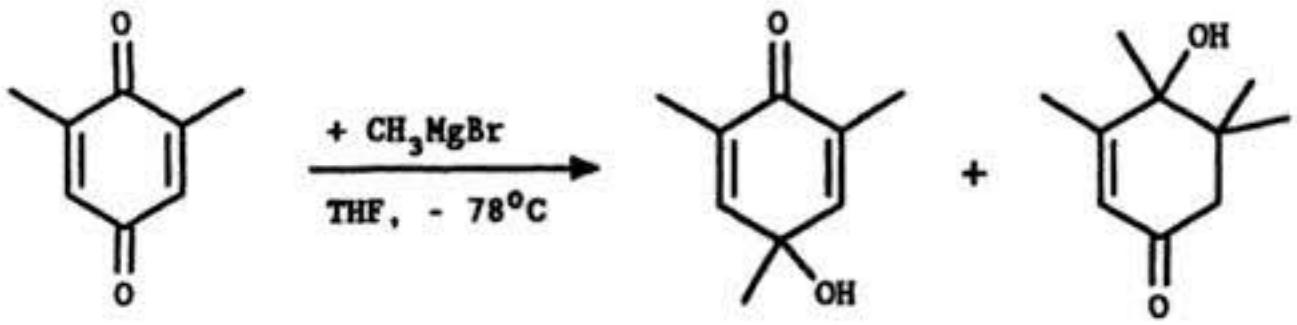
I. INTRODUCTION

This chapter deals with the nucleophilic addition of Grignard reagents to carbon–carbon multiple bonds (alkenes and alkynes) conjugated with other multiple bond systems (including other alkenes, alkynes, carbon–heteroatom multiple bonds, and aromatic systems). Also included for completeness are the nucleophilic addition reactions of organomagnesium halides with aromatic systems (arenes and arynes). Reactions for which the primary emphasis is on the effect of metal catalysis are discussed elsewhere (see Chapter 29). The use of these reactions for the synthesis of asymmetric products is covered in Chapter 28. A discussion of nucleophilic addition to *un*conjugated carbon–carbon multiple bonds is given in Chapter 16. The case of 1,2-addition to enones (carbonyl addition) is reviewed in Chapter 17. The reaction of magnesium metal with dienes and other conjugated olefins is discussed in Chapter 26. The use of Grignard reagents in the polymerization of olefins is presented in Chapter 34.

II. FACTORS AFFECTING THE ADDITION

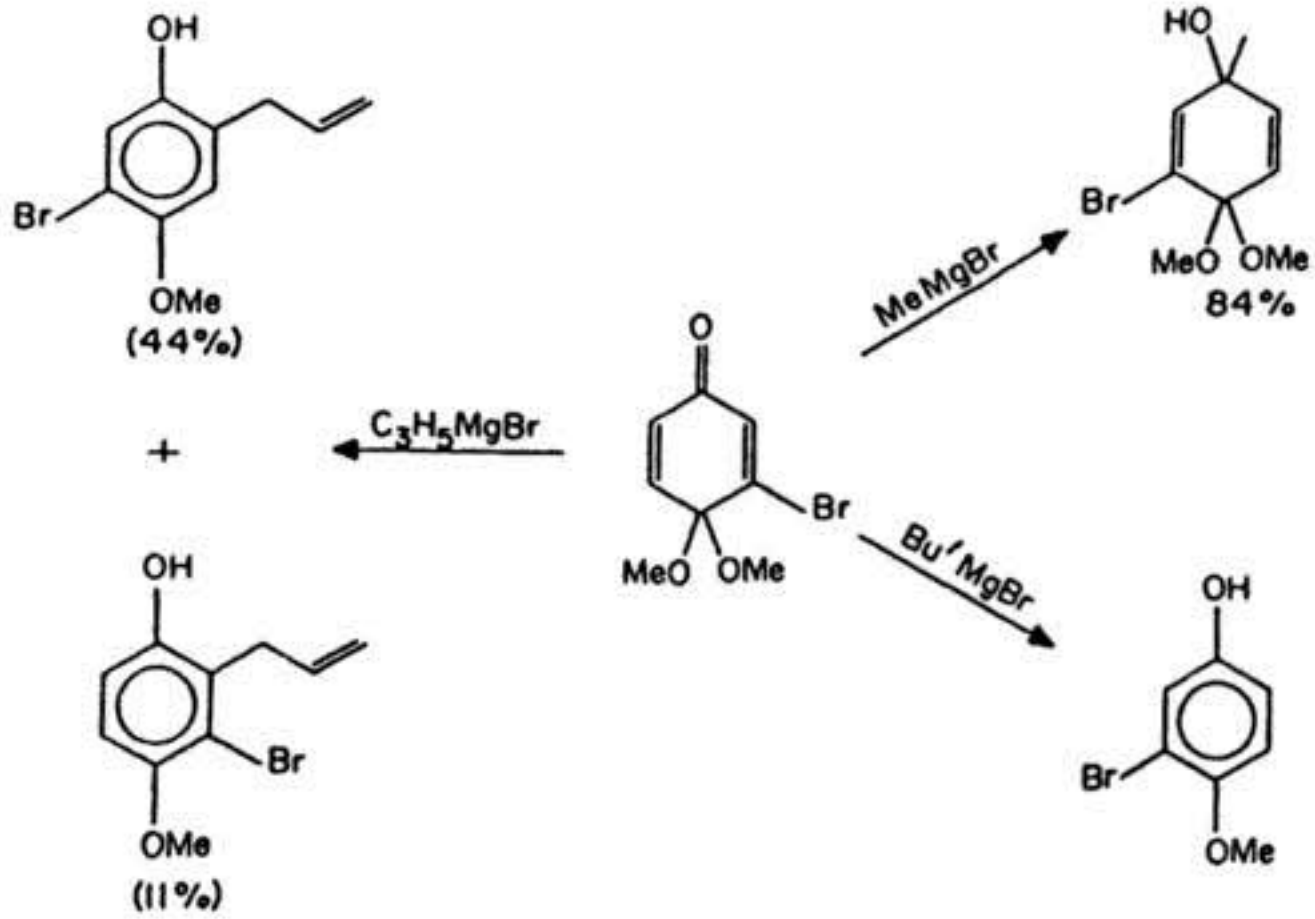
As noted in Chapter 16, Grignard reagents are generally unreactive toward isolated carbon–carbon multiple bonds. Conjugation with an adjacent π-system can enhance the degree of reactivity, sometimes enormously. Grignards add readily to enones (α,β-unsaturated carbonyls) and, less readily, to carbon–carbon multiple bonds conjugated with aromatic rings or other carbon–carbon multiple bonds [1]. Allylic Grignard regents give 1:1 adducts with conjugated dienes in the presence of titanium catalysts [2]. "Barbier"

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(4)

The reactions of quinone monoketals has also been reviewed (Scheme 1) [12].



Scheme 1

The theoretical study by Khan et al. [13] on the stereochemistry of nucleophilic addition of organometallics to unsaturated substrates can also be applied to conjugated systems. Of the three major factors affecting the orientation of the nucleophile to the substrate (see Chapter 16), the ability of the substrate to discriminate between the nucleophilic and electrophilic character of the Grignard reagent is the one most susceptible to influence by conjugation with an adjacent π-system. They concluded that the accessible electrophilic site (the metal) is the source of the stereochemical preference for the electron-rich olefin face.

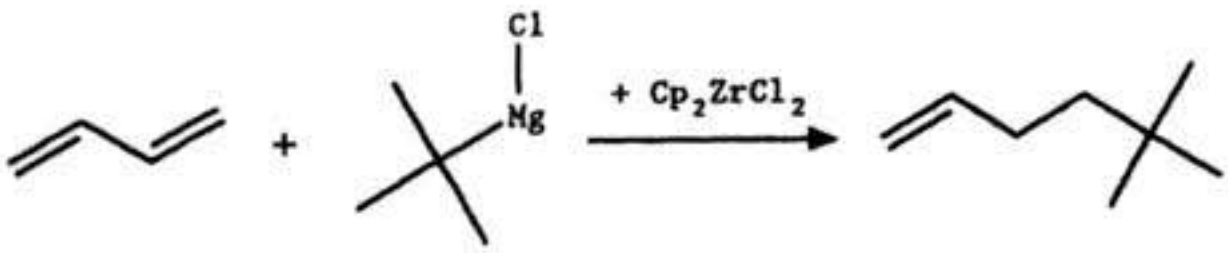
IV. ADDITION TO ALKENES

A. 1,3-Dienes

Grignard reagents exhibit widely divergent behavior toward 1,3-dienes, depending on the nature of the Grignard, the degree of substitution or steric crowding on the diene (or Grignard), the reaction conditions including solvent, presence of metal catalysts, and other substrates. For example, *t*-butylmagnesium chloride reacts with 1,3-butadiene (in the

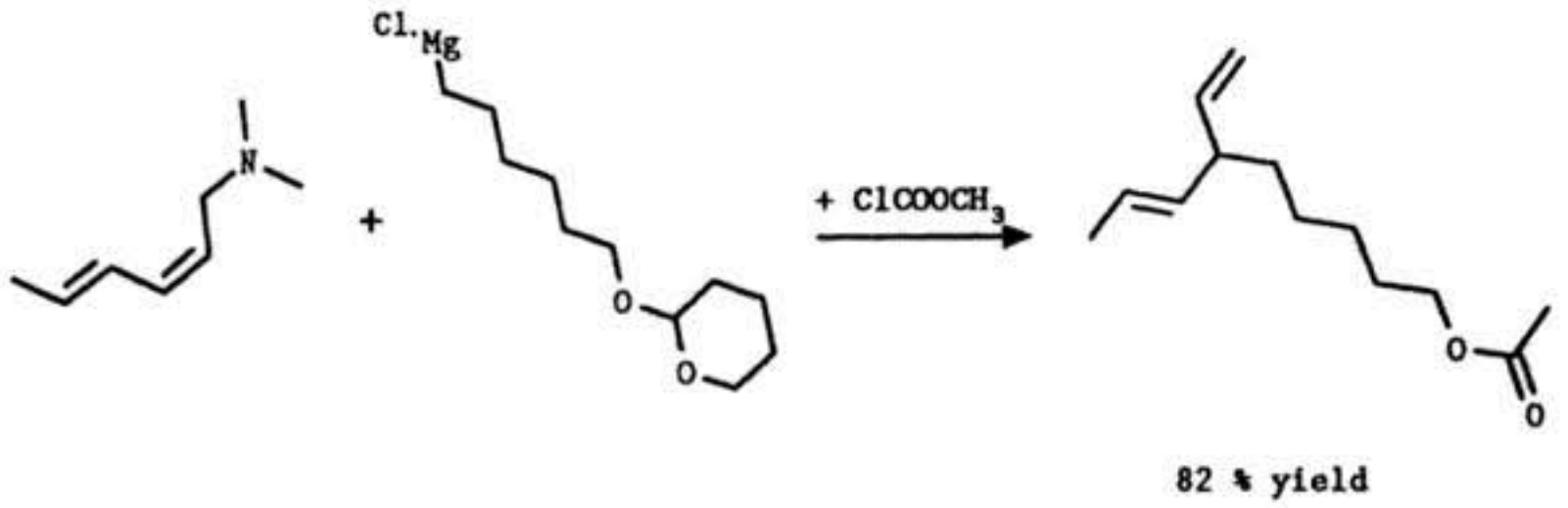
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presence of Cp_2ZrCl_2) to give 5,5-dimethyl-1-hexene (1,2-addition) in the 88% yield [Eq. (5); 14].



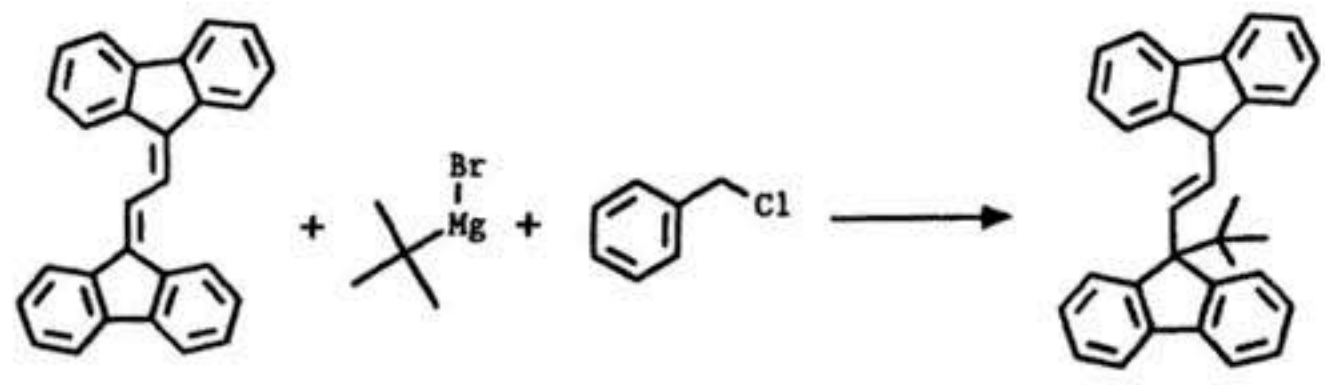
(5)

1,2-Addition accompanied by allylic rearrangement was observed by Langlois et al. [Eq. (6); 15].



(6)

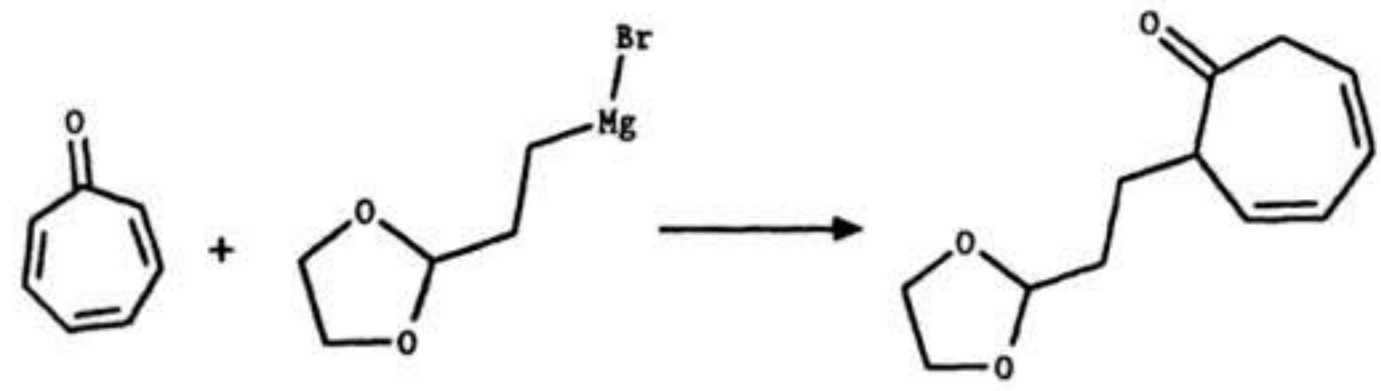
In contrast, 1,4-addition was obtained using *t*-butylmagnesium bromide and the highly hindered butadiene in Eq. (7) [16].



(7)

1,4-Addition was also observed for silyl-substituted 1,3-butadiene [17].

For the extended π-system of tropone, Rigby and Wilson observed a 1,6-addition across the hexatriene system [Eq. (8); 18].

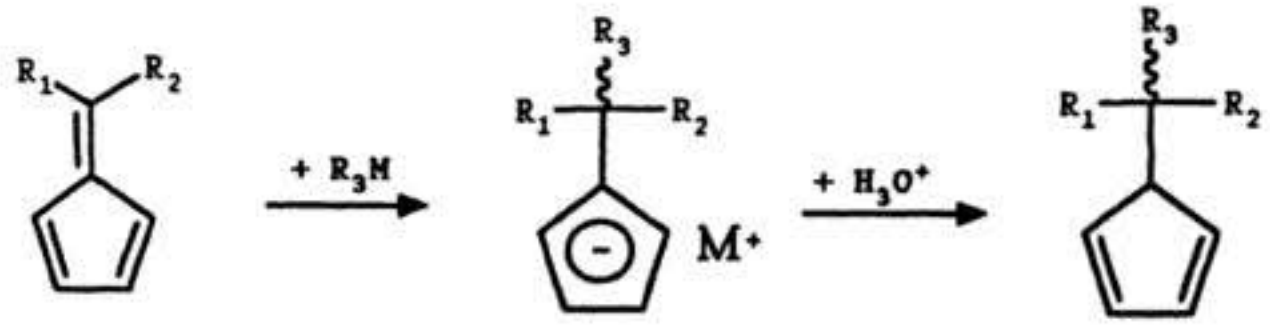


(8)

Fulvenes also add Grignard reagents. This represents a useful route to substituted cyclopentadiene derivatives, as the resulting Grignard reagent can reacted further to produce

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other metal cyclopentadienyl compounds [Eq. (9); 19].

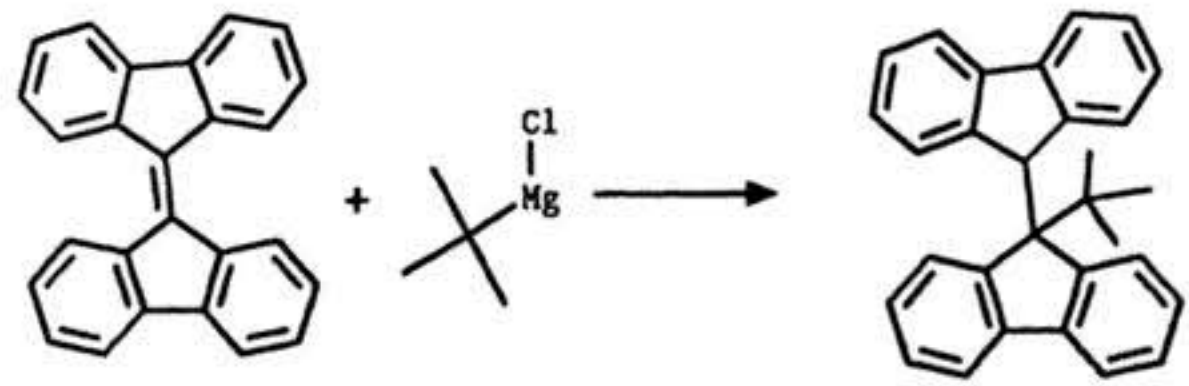


(9)

Mention should also be made of the extensive work of Calas and co-workers on the magnesium-induced silylation of olefins. Although this is not strictly "Grignard" chemistry, as defined for this volume, the reactions he has studied may be viewed conceptually as a "silico-Barbier reaction," namely, the addition of an in situ silicon analogue of a Grignard reagent Me_3SiMgX across a double bond [20].

B. Other Conjugated Olefins

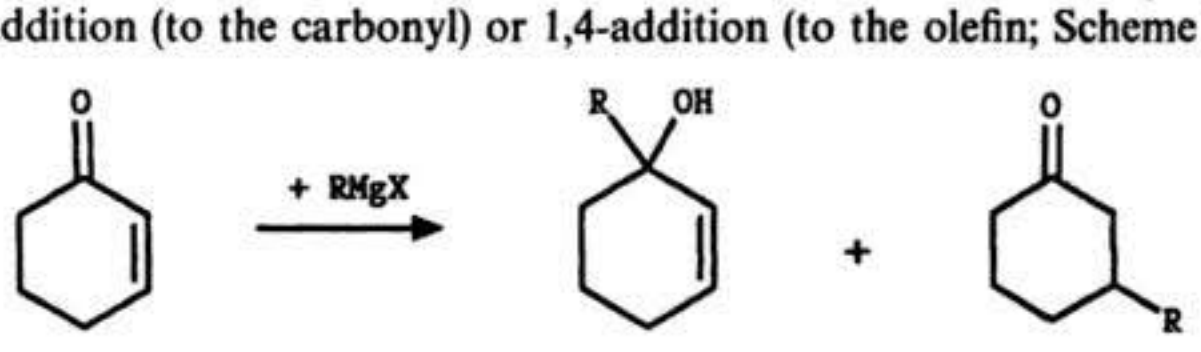
Grignard reagents add to enynes with electron-donor substituents in the allylic position. The highly hindered olefin in Eq. (10) gave simple addition of *t*-butylmagnesium chloride [21].



(10)

C. Enones

The addition of Grignard reagents to enones has been extensively studied and reviewed [6–12] (see also Chapter 16). Enones can react either as carbonyls or olefins, leading to 1,2-addition (to the carbonyl) or 1,4-addition (to the olefin; Scheme 2).



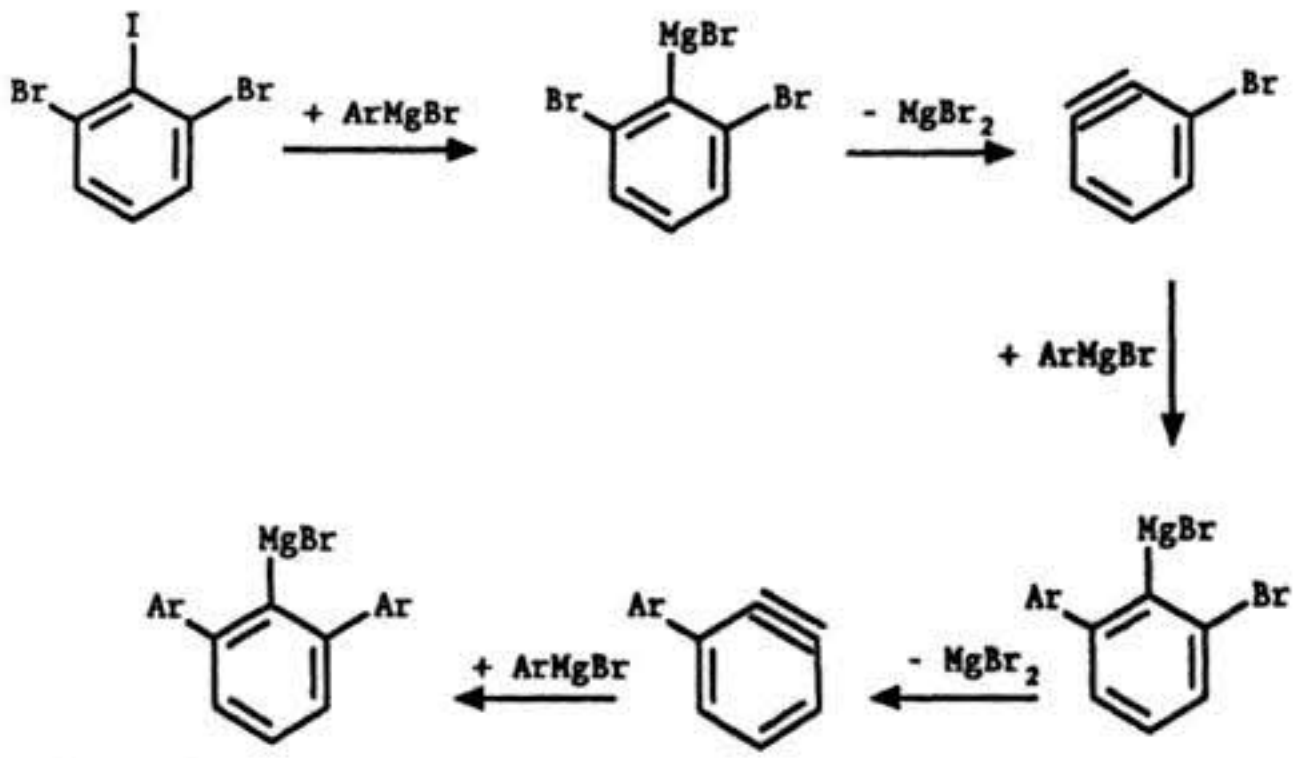
R	1,2 %	1,4%
CH_3	38	15
CH_2CH_3	52	24
$CH(CH_3)_2$	10	44
$C(CH_3)_3$	0	70

Scheme 2

Numerous studies have shown that multiple reaction mechanisms operate, and that a number of factors, both steric and electronic, influence the 1,2-/1,4- ratio [6,22].

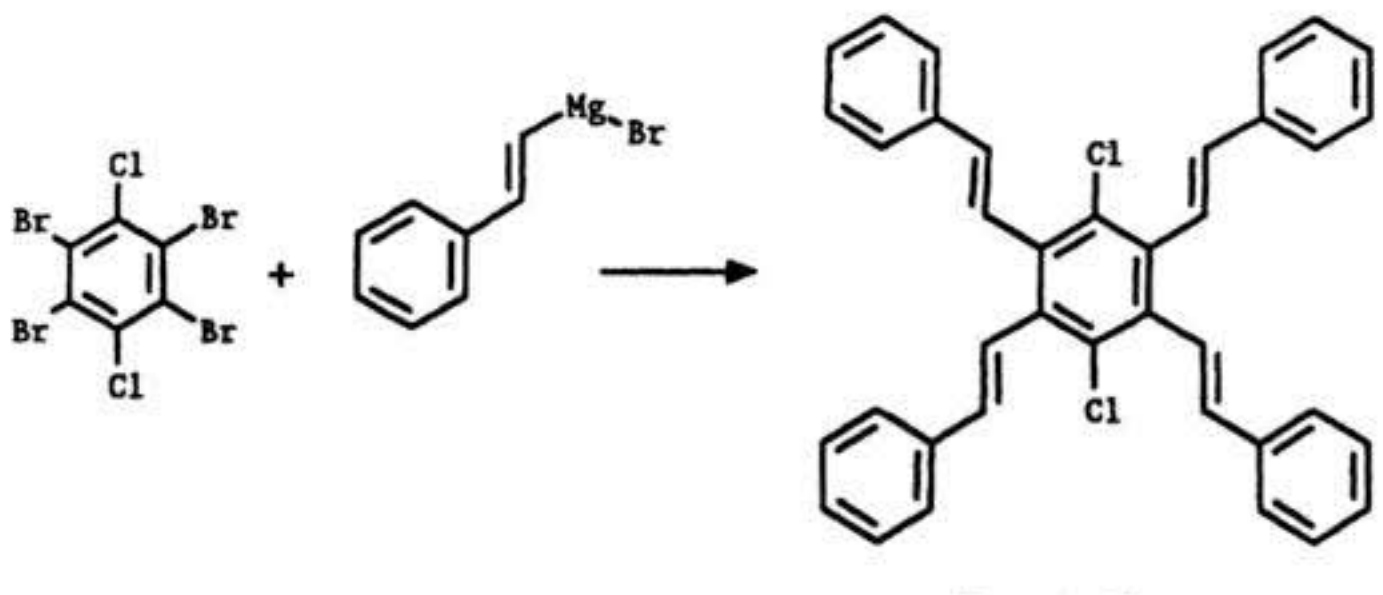
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reagents and polyhalo benzenes. Their method is based on the creation and subsequent capture of arynes with Grignard reagents (Scheme 3).



Scheme 3

The reaction proceeds by (1) organometallic exchange, followed by (2) aryne formation, and (3) a regiospecific nucleophilic addition of the aryl Grignard to the aryne. These steps can occur or recur in tandem fashion to form from one to six new carbon–carbon bonds in a single operation [33,34]. Subsequently, the method was extended to alkenyl and alkynyl Grignards [35; Eq. (13)] and trimethylsilylvinyl Grignards [36].



(13)

Trapping of the Grignard produced in step 3 (see foregoing) with allyl halide proved to be a useful route to allyl-, vinyl-, 1.2-disubstituted arenes [37].

VI. MISCELLANEOUS

Terminal alkynes typically undergo transmetallation with Grignard reagents to give the corresponding alkynyl Grignard (see Chapter 2). However, Kleijn and co-workers [38] reported that *t*-butylmagnesium chloride reacted with phenylbutadiyne (albeit in the presence of Ag ion) to give the products of 1,2-addition to the terminal triple bond [Eq. (14)].

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20

Nucleophilic Addition to Conjugated Carbon–Heteroatom Multiple Bonds: O, S, N

LÉONE MIGINIAC
Université de Poitiers, Poitiers, France

I. INTRODUCTION

Generally, Grignard reagents are not expected to add to carbon–carbon double or triple bonds; however, addition to these unsaturated bonds does occur, especially when the C=C or C≡C bond is activated by conjugation with a neighboring electron-withdrawing group such as C=O, C=N, or C≡N group [1–6].

II. NUCLEOPHILIC ADDITION TO CONJUGATED C=O BONDS

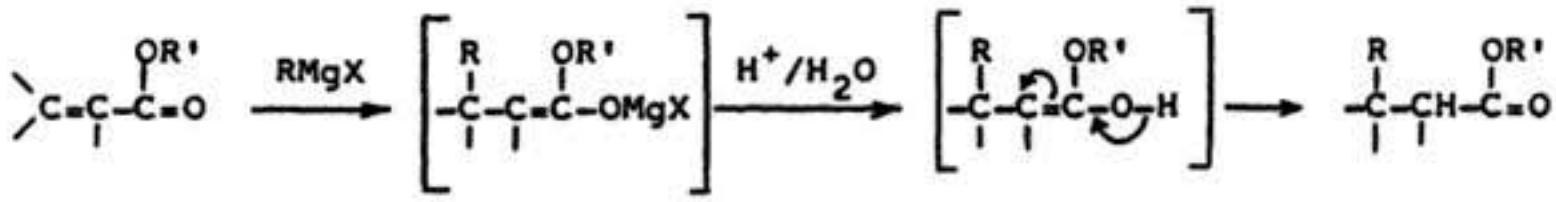
A. Conjugated Aldehydes and Ketones

1,4-Addition reactions (Michaël addition) can occur with α,β-unsaturated aldehydes and ketones, in competition with normal 1,2-addition [Eq. (1)]:



(1)

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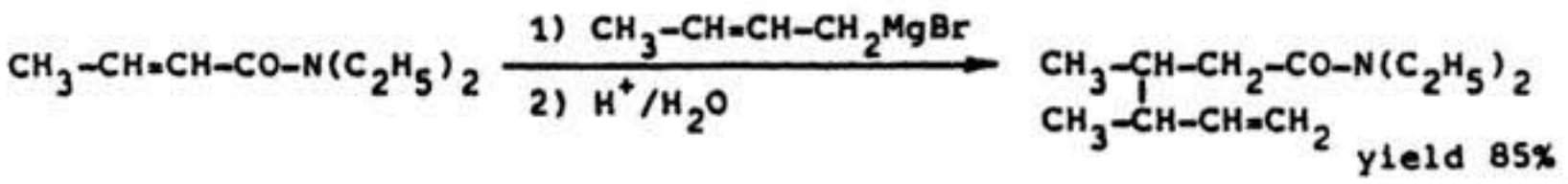


(6)

The yields are generally increased by proceeding in the presence of CuX [2,17] or CuCl and Me_3SiCl [18]. With a α,β-acetylenic ester, RMgX (R saturated, phenylic) gives 1,2-addition preferentially [19]. Also, allenylic [6] and allylic [2,20] Grignard reagents react with α,β-unsaturated esters to lead to 1,2-addition products exclusively.

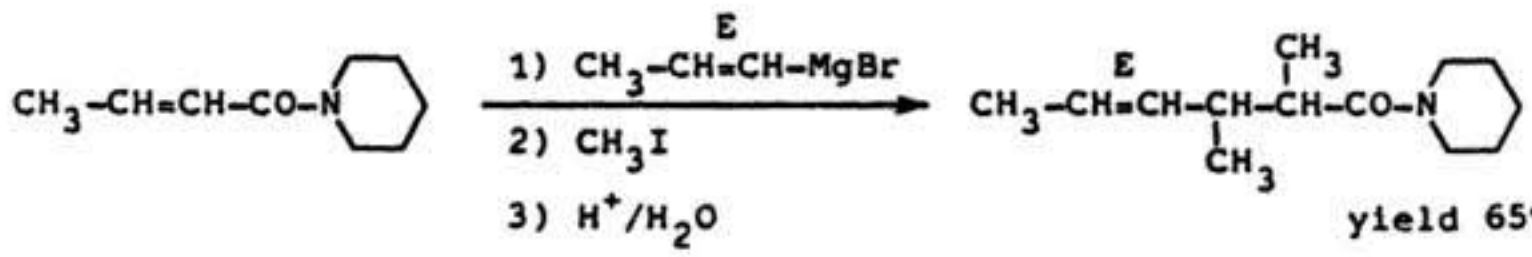
C. Conjugated Amides

In contrast with conjugated ketones and esters, the reaction between conjugated amides and all types of RMgX proceeds through a 1,4-addition [1–4], particularly with the allylic [21,22] and allenylic [6] organomagnesium derivatives [Eq. (7)]:



(7)

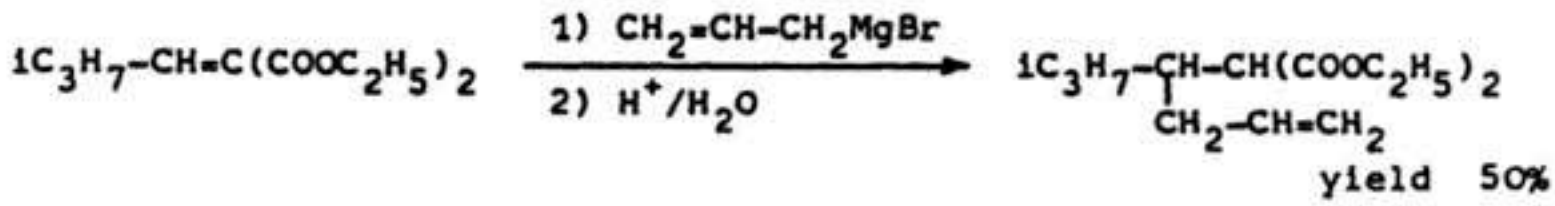
Also, 1,4-addition of RMgX to α,β-ethylenic amides followed by α-alkylation may constitute a general and efficient synthetic procedure for the formation of two C–C bonds in a single step [23; Eq. (8)]:



(8)

D. Alkylidene Malonates and Cyanacetates

Grignard reagents give 1,4-addition with these derivatives [1–6,24–27], especially with the allenylic and allylic organomagnesium derivatives:

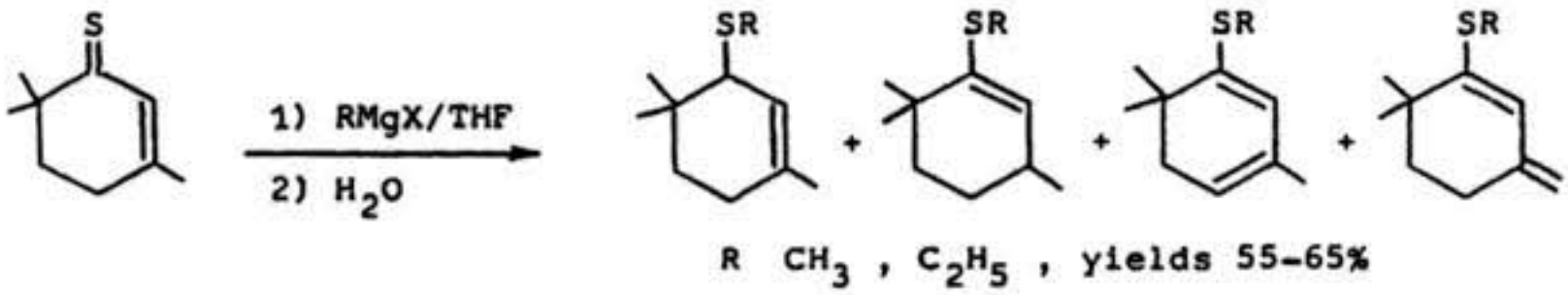


(9)

III. NUCLEOPHILIC ADDITION TO CONJUGATED C=S BONDS

Only a few studies have been made on this reaction. Saturated Grignard reagents react with α,β-ethylenic thioketones [28,29] to lead to a mixture of several products. They principally result from thiophilic 1,2-addition, thiophilic 1,4-addition, and *S*-alkylation [28,29].

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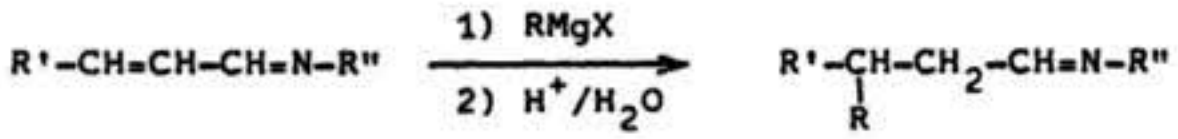


(10)

Under similar experimental conditions, no reaction is observed by using phenyl-, vinyl-, or ethynylmagnesium bromides [28,29].

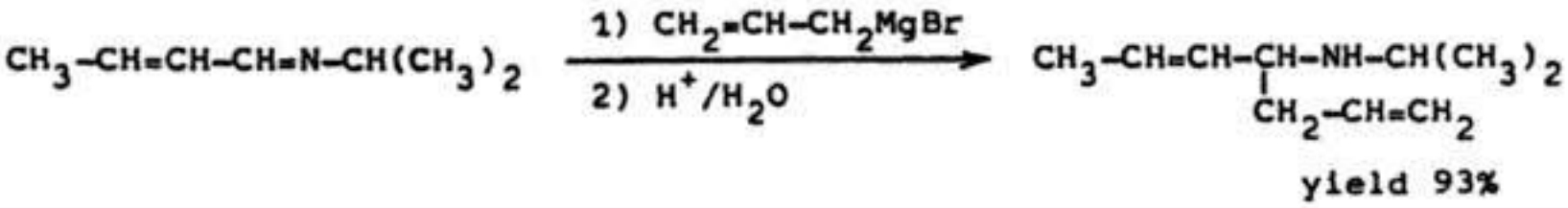
IV. NUCLEOPHILIC ADDITION TO CONJUGATED C=N BONDS

α,β-Ethylenic aldimines and ketimines readily react with saturated and vinylic organomagnesium derivatives to lead to 1,4-addition products [4,30]; Eq. (11)]:



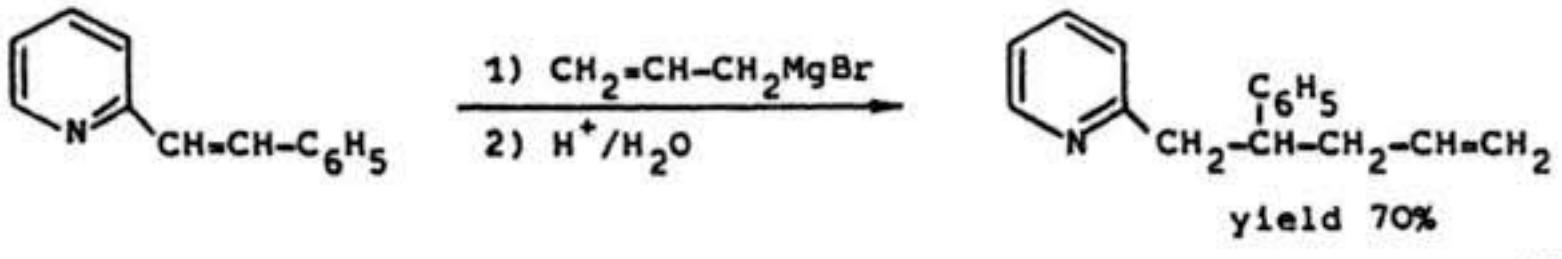
(11)

With allenylic [6] and allylic [31,32] Grignard reagents, α,β-unsaturated aldimines give secondary amines, resulting from a 1,2-addition [Eq. (12)]:



(12)

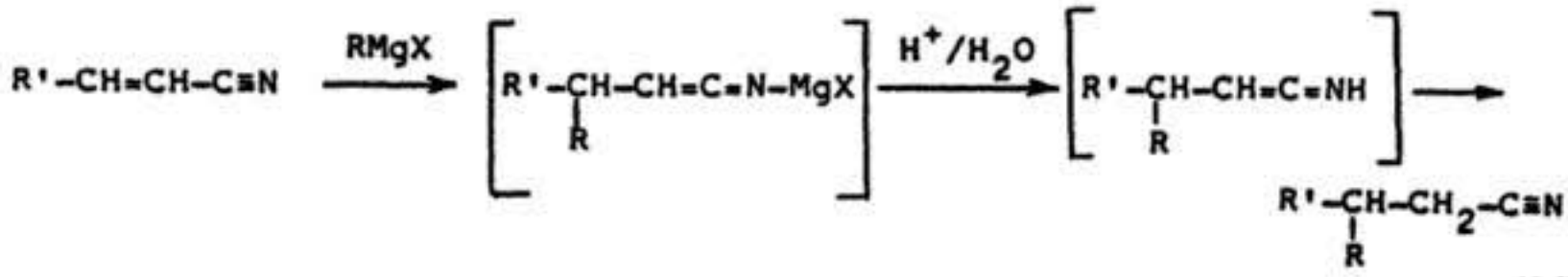
However, the 1,4-addition of allylmagnesium bromide to 2-styrylpyridine has been described [33; Eq. (13)]:



(13)

V. NUCLEOPHILIC ADDITION TO CONJUGATED C≡N BONDS

The reaction between α,β-unsaturated nitriles and Grignard reagents was studied in a few cases [4]. With α,β-ethylenic nitriles, saturated [4,34–36] and vinylic [37] Grignard reagents lead to 1,4-addition products:



(14)

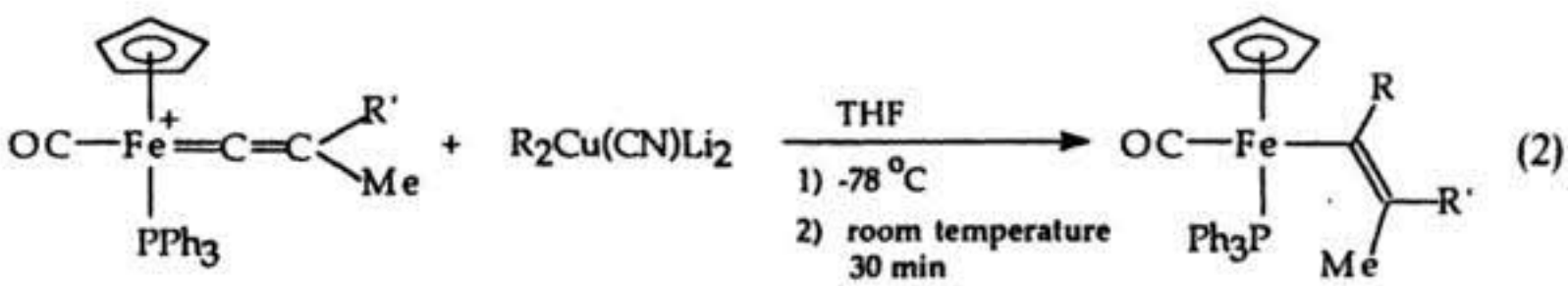
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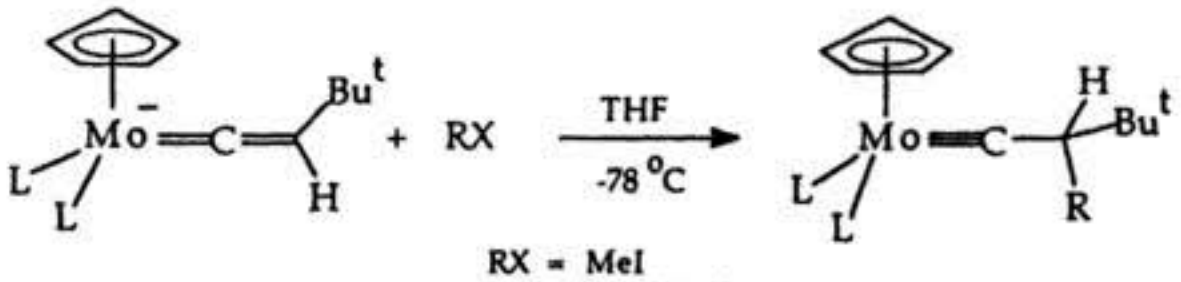
of reactivity are nucleophilic [9], and electrophilic [10] addition at the vinylidene α-carbon and β-carbon, respectively. These modes of reactivity are discussed in more detail because of the interesting reactivity of the vinylidene ligand. In general, cationic and neutral vinylidene complexes have been more reactive with nucleophiles; anionic and neutral, electron-rich, vinylidene complexes react with electrophiles. Other types of reactions not portrayed in Scheme 1 are cycloaddition reactions.

The vinylidene ligand is susceptible to both nucleophilic and electrophilic attack; therefore, these complexes may be useful precursors for stereospecific organic synthesis. Molecular orbital calculations for selected organometallic vinylidene complexes have shown that the HOMO is 25–30% localized on the vinylidene's β-carbon and the LUMO is 50–60% localized on the vinylidene's α-carbon [11]. These calculations have been supported by experimental data, in which the α-carbon is the site of nucleophilic attack and electrophiles add to the β-carbon [1]. Reger and Swift [Eq. (2)] reported that nucleophilic addition at the α-carbon atom of the cationic vinylidene $[Cp(CO)(PPh_3)Fe(=C=CMePh)]OSO_2CF_3$ produced $Cp(CO)(PPh_3)Fe(CMe=CMePh)$ in quantitative yield [12]. Reactivity between cationic vinylidene complexes and Grignard reagents is expected to be similar to Eq. (2); however, nucleophilic additions of Grignard reagent to vinylidene complexes were not found in the literature. The reaction of electrophiles with the vinylidene ligand, to form carbyne complexes, was reported by Green and co-workers [Eq. (3); 13]. Electrophiles (R = Me, CH_2CH_2OH, CH_2OEt, $COBu^t$, $SiMe_3$, SMe) added to the anionic vinylidene $Li[Cp(P(OMe)_3)_2Mo(=C=CHBu^t)]$ yielding the metal–carbyne $Cp(P(OMe)_3)_2Mo(\equiv CCHRBu^t)$.



(2)

R = Ph	R' = Me	yield = 45 %
R = CH_2=CH	R' = Me	yield = 54 %
R = Me	R' = Ph	yield = 100 %

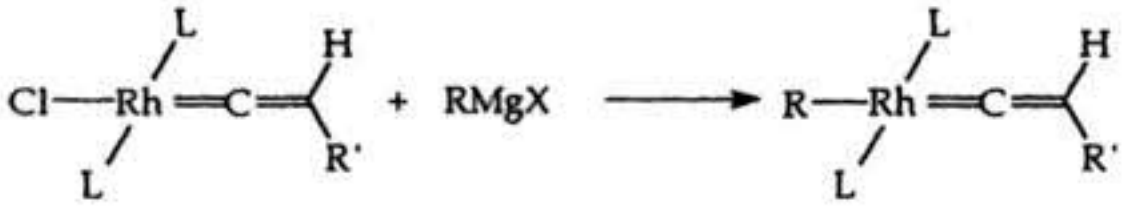


(3)

RX = MeI
$EtOCH_2Cl$
Bu^tCOCl
Me_3SiCl
MeSSMe

We found only one reported reaction between a Grignard reagent and a transition metal vinylidene complex. Wiedemann and co-workers [14] reacted neutral vinylidene complexes $ClL_2Rh(=C=CHR')$ ($L = P(Pr^i)_3$; $R' = Ph$, Bu^t) with Grignard reagents, and the substituted products were isolated in good yields [Eq. (4)]. The chloride ligand was the site of reactivity for this complex. This reaction illustrates the coupling of an alkyl, aryl, or vinyl group with a vinylidene unit, occurring in the coordination sphere of rhodium (I).

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(4)

L = $P(OPr^i)3$	R = Me	R' = Ph	yield = 87 %
	R = Ph	R' = Ph	yield = 81 %
	R = $CH{=}CH_2$	R' = Ph	yield = 85 %
	R= Ph	R' = Bu^t	yield = 87 %

III. TRANSITION METAL ALLYL COMPLEXES

The allyl group is an ubiquitous ligand, and a wide variety of allyl complexes are known [15]. The chemistry of allyl Grignard reagents with transition metal catalysts is thoroughly discussed in Chapter 29. The allyl group ($CH_2{=}CHCH_2^-$) can bind to a metal center in one of two ways: the monohapto form (Fig. 2a), in which the allyl is a X-type (1e) ligand, or the trihapto form (see Fig. 2b), in which the allyl is a LX-type (3e) ligand [16]. The trihapto form of the allyl ligand is best thought of in terms of the resonance forms indicated in Figure 3. The trihapto form [(η^3-C_3H_5)M] also contains *exo*-hydrogen atoms and *endo*-hydrogen atoms (Fig. 4). As defined by Crabtree, the carbon–carbon bonds in the metal η3-allyl complex are twisted, this places the *exo*-hydrogens farther away from the metal and the *endo*-hydrogens closer to the metal atom [16].



Figure 2a



Figure 2b

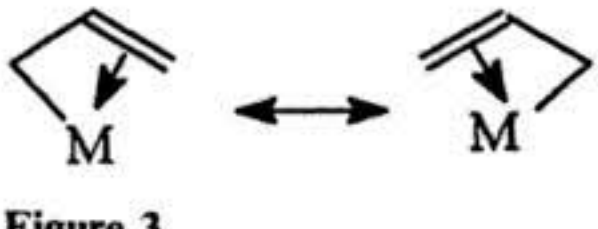


Figure 3

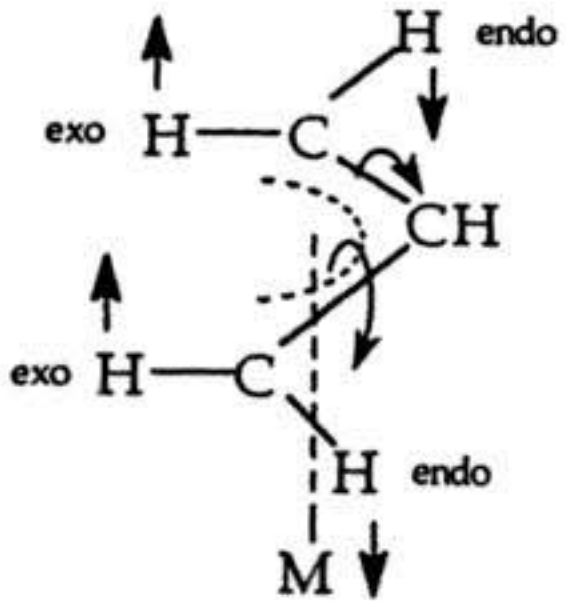


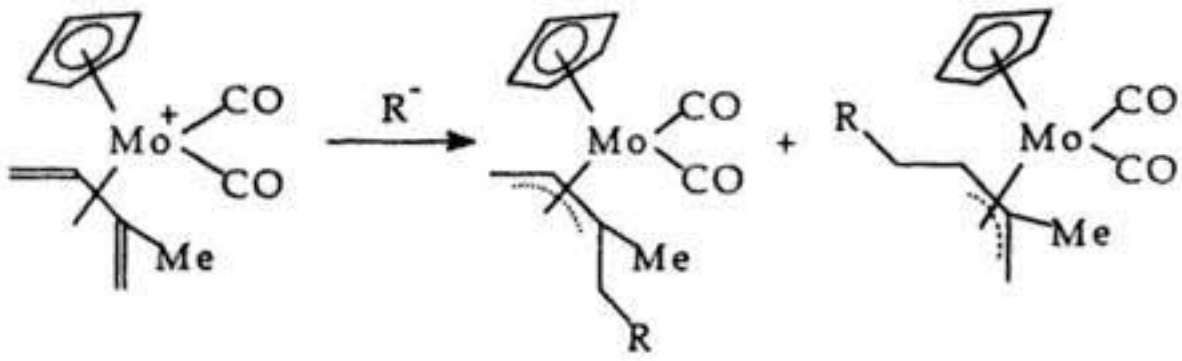
Figure 4

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Table 2 Solvent Dependent Results for Various Grignard Reagents

Nucleophile	Reaction conditions	Yield (%)	Ratio 2:3
PhMgBr	Et_2O, 0°C to RT, 1 hr	81	70:30
PhMgBr	CH_2Cl_2, 0°C to RT, 1 hr	74	55:45
MeMgBr	THF, 0°C to RT, 1 hr	87	30:70
MeMgBr	CH_2Cl_2, 0°C to RT, 1 hr	84	20:80
MeMgBr	Et_2O, 0°C to RT, 1 hr	90	70:30
(Vinyl)MgBr	CH_2Cl_2, 0°C to RT, 2 hr	94	55:45
(Vinyl)MgBr	Et_2O, 0°C to RT, 2 hr	96	75:25
(Allyl)MgBr	CH_2Cl_2, 0°C to RT, 2 hr	58	40:60

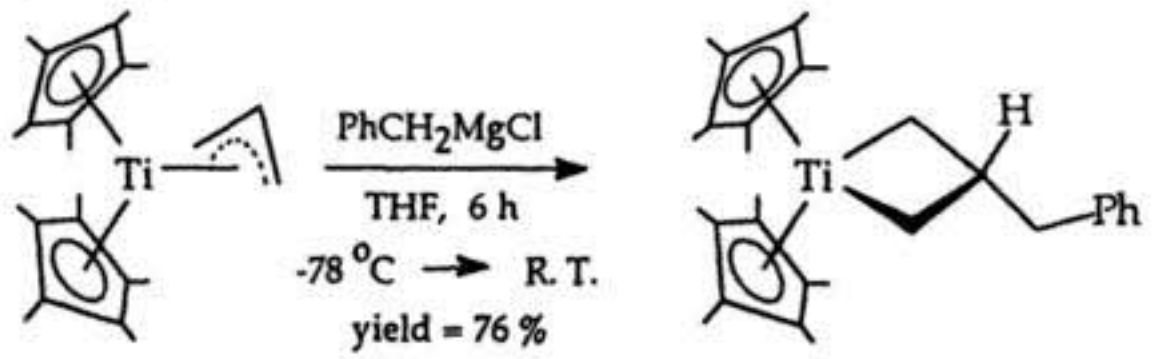
Table 2 lists the results found for the Grignard reagents investigated. In diethyl ether solution, the Grignard reagents preferentially add to C-1 [2], whereas in tetrahydrofuran (THF) and other solvents C-4 addition dominates [3]. It was also reported that the addition of complexing agents such as *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) or hexamethylphosphoramide (HMPA) in diethyl ether resulted in the reversal of selectivity.



(7)

R = Ph, Me, $CH{=}CH_2$, $CH_2CH{=}CH_2$

There are a variety of reactions reported in the literature demonstrating the reactivity of allyl complexes with Grignard reagents. A few of these are illustrated here. For example, the highly reactive unsaturated permethyltitanocene allyl cation, shown in Eq. (8), reacts with $PhCH_2MgCl$ regioselectively to add to the central allyl position by nucleophilic addition, producing a metallocycle complex in 76% yield [27]. Competitive addition to the allyl terminal position was not observed. In addition, competitive addition to the metal center was also not observed; most likely owing to the small ionic radius and the lower electrophilicity associated with titanium.

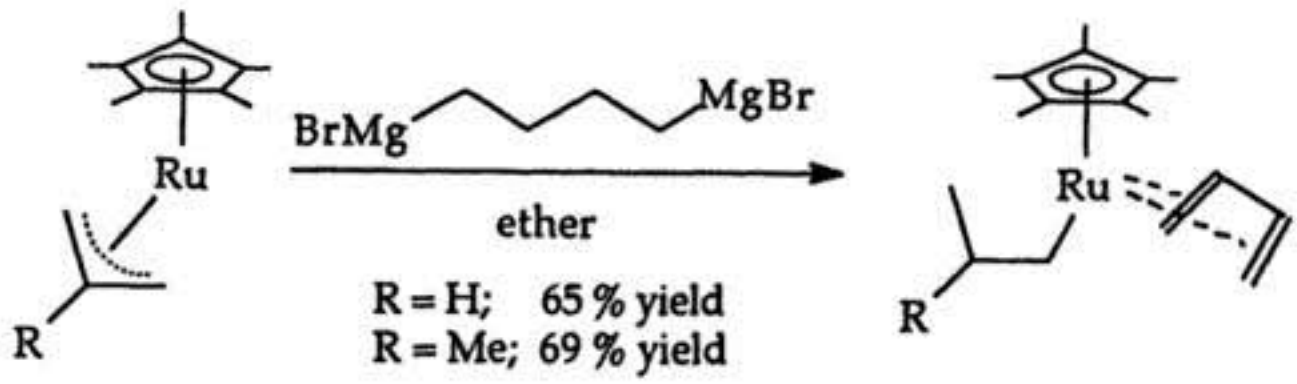


(8)

Another example of an allyl complex reacting with a Grignard reagent was reported by Itoh and co-workers [Eq. (9); 28]. $(C_5Me_5)RuBr_2(\eta^3\text{-}CH_2C(R)CH_2)$ [R = H, Me] was treated with $BrMg(CH_2)_4MgBr$ in ether to afford the Ru^{II}-alkyl-butadiene complexes $(C_5Me_5)Ru(\eta^4\text{-}CH_2CHRCH_3)$ [R = H, Me]. Labeling experiments have suggested that

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the reaction may proceed by an irreversible double β-hydrogen elimination from ruthena(IV)cyclopentane intermediates and stepwise transfer of the hydrogen atoms to hydrogenate the η^3-allyl ligand.



(9)

IV. CONCLUSION

The reactions of Grignard reagents with transition metal vinylidene and allyl complexes are certainly interesting chemistry. However, there is much more chemistry involving these reagents that needs to be explored. The chemistry of Grignard reagents with vinylidene and allyl complexes remains a fertile ground for future investigation.

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22

The Barbier Reaction

DAVID A. RUSSO
Elf Atochem North America, Inc.
King of Prussia, Pennsylvania

I. INTRODUCTION

The Barbier reaction has intrigued chemists from the time Barbier first reported the production of 2,6-dimethyl-6-hydroxy-2-heptene from the reaction of methyl iodide with 2-methyl-6-oxo-2-heptene and magensium metal in 1898 [1]. Although largely supplanted by the much more versatile Grignard reaction as a synthetic tool, this "one-step," "in situ Grignard," or "direct reaction," has found some unique applications and is still of interest to many researchers. Some large-scale industrial processes also employ the Barbier reaction for product synthesis. This section will try to convey the broad scope of the Barbier reaction and highlight some of the more useful applications. The reader is referred to major works on the Barbier reaction by Blomberg [188] and Hartog [189], review articles by Blomberg and Hartog [2] and Ralston and Salem [3] as well as the annual reviews on magnesium in the *Journal of Organometallic Chemistry* for additional information.

The *Barbier reaction* will be defined in the classic sense and will include any one of the following reaction sequences: (1) addition of an organic halide to a mixture of magnesium and an electrophilic coreactant such as a ketone, (2) addition of a mixture of an organic halide and coreactant, over time, to magnesium, or (3) the combination of all three reagents at once.

This is contrasted with the two-step Grignard reaction in which the first step entails the formation of an R–MgX specie followed by addition of, or addition to, a coreactant in a second step.

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reactions [10] is offered as proof for the postulated pathways. The authors propose that by knowing the electron affinities of the halides and carbonyls involved, one can predict the mechanism of the reaction.

Although the mechanism of the Barbier reaction is not completely resolved, the best evidence now indicates that radical anion or radical species, or both, are involved. These radical moieties most likely are formed by SET reactions on the metal surface and may involve the electrophile as well as the halide. The body of evidence indicates that a short-lived R–MgX species is not formed in most Barbier reactions.

III. ADDITION REACTIONS

A. With Aldehydes and Unsaturated Halides

Perhaps the widest use of the Barbier reaction has been in the production of alcohols and ketones from carbonyl electrophiles and alkenyl and benzylic halides. Usually, the Grignard reagents of the halides are too reactive, and unwanted side products, owing to Wurtz coupling, are formed. With Barbier conditions, iodides, bromides, and chlorides can be used, and some reactions can be conducted at room temperature. Aliphatic and cyclic ethers are generally used as solvents, but hydrocarbons are being used in increasing amounts, particularly in industrial applications. Electrophilic coreagents have ranged from aldehydes, ketones, and esters, to amides, silanes, and phosphonates. The major by-products are either dimers from Wurtz-type coupling of the halide, or diol formation from coupling of the "ketyl" radical anion.

The general scheme for the one-step Barbier addition reaction of alkenyl and benzylic halides with aliphatic or aromatic aldehydes is shown in Eq. (1).

$$\mathrm{R{-}CHO + R^1{-}X \xrightarrow[\text{solvent}]{\text{Mg}} R{-}\underset{\displaystyle H}{\overset{\displaystyle R^1}{\overset{|}{\underset{|}{C}}}}{-}OH} \qquad (1)$$

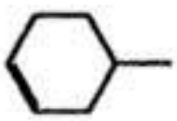
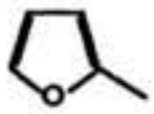
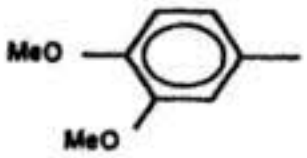
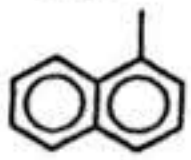
Several aldehyde and halide combinations have been studied and representative examples are shown in Table 1. The solvents of choice range from ethers, such as diethyl ether, tetrahydrofuran (THF) and furan, to hydrocarbons, such as benzene, toluene, and petroleum ether.

Yields of alcohols vary from 45 to 87%, irrespective of solvent or halogen type. However, when crotyl halides are used, 1-methylallyl products are isolated [20], along with occasional diaddition products [Eq. (2)].

$$\mathrm{CH_3{-}CH{=}CH{-}CH_2Cl + C_2H_5{-}CHO \longrightarrow CH_2{=}CH{-}CH(CH_3){-}\underset{\displaystyle OH}{\overset{|}{CH}}{-}C_2H_5} + \mathrm{(CH_2{=}CH{-}CH(CH_3))_2{-}\underset{\displaystyle OH}{\overset{|}{C}}{-}C_2H_5} \qquad (2)$$

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Table 1 Addition Reactions of Unsaturated Halides to Aldehydes

R	R'X	Yield ROH	Ref.
$CH_3CH_2CH_2$	CH_2=CH-CH_2Br	65	12,13
$CH_3(CH_2)_4CH_2$	"	47	11
CH_2=CH	"	66	14,15
CH_3-CH=CH_2	"	49,50	12,14,16
CH_3CH=$CHCH_2CH_2CH(CH_3)CH_2$	"	60	12
CH_3CH=$CHCH_2CH_2CH(CH_3)CH$=CH	"	50	12
	"	72	15
	"	78	17
C_6H_5	"	68	12
	CH_2=CH-CH_2Cl	87	18
	"	86	18,19
CH_3CH_2	CH_3CH=$CHCH_2Br$	-	2
CH_2=CH	CH_3CH=$CHCH_2Cl$	70	20
CH_3CH_2	$C_6H_5CH_2Cl$	-	21

B. With Aldehydes and Saturated Halides

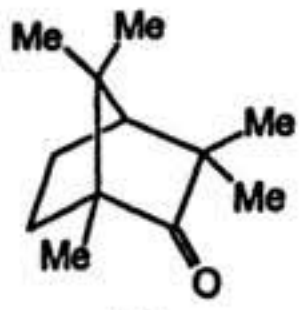
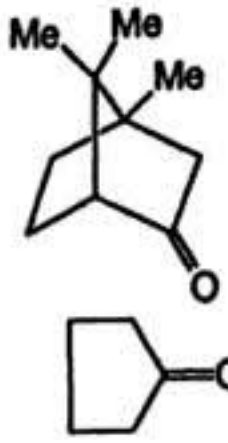
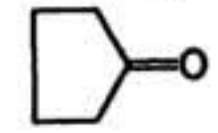
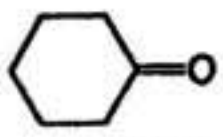
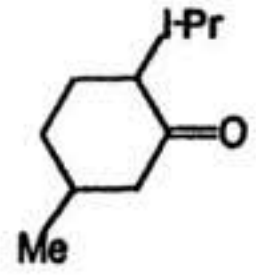
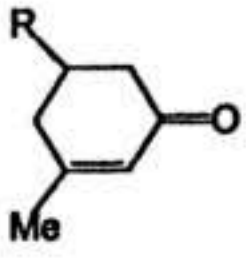
When an alkyl halide is used in the reaction with an aldehyde [2,21], both the halide and the solvent can influence the products that form in addition to the expected carbinol.

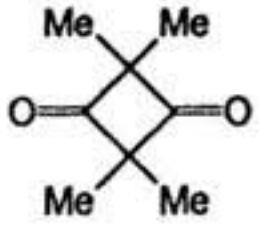
When ethyl iodide is reacted with benzaldehyde in ether, the expected ethyl phenyl carbinol is isolated in a lower yield (25%) than the by-products benzyl alcohol (35%) and ethyl phenyl ketone (35%). In THF, benzyl alcohol is the major product (50%) with the carbinol isolated in only a 10% yield. With ethyl bromide in ether, the major product is the ketone (55%). In THF, the carbinol is the predominant product, being isolated in a 70% yield [2].

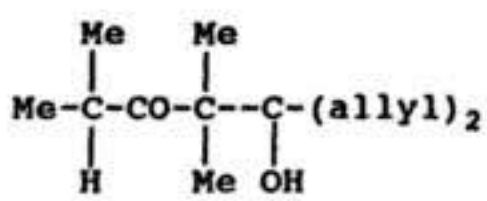
The reaction of a *t*-butyl halide with butanal yields the *t*-butyl propyl carbinol in a

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Table 2 (Continued)

R^1	R^2	R	Yield	Ref
		CH_2=CH-CH_2Br	50	21
		CH_2=CH-CH_2Br	96 (exo only)	31
		CH_2=CH-CH_2Br	80	25
		CH_2=CH-CH_2Br	95	15,25
		CH_2=CH-CH_2Br	<90	29
		CH_2=CH-CH_2Br	93	28





(7)

D. With Ketones and Saturated Halides

There are fewer reactions with saturated halides than with unsaturated halides. Generally, the ketones and halides range from C_1–C_4 alkyl and the expected alcohols are produced in 50–70% yields [21,35,36]. The same solvents and metal activation procedures used with the unsaturated halides are also applied in these reactions.

Some useful and interesting compounds are produced under Barbier conditions when the ketone or the halide is somewhat out of the ordinary.

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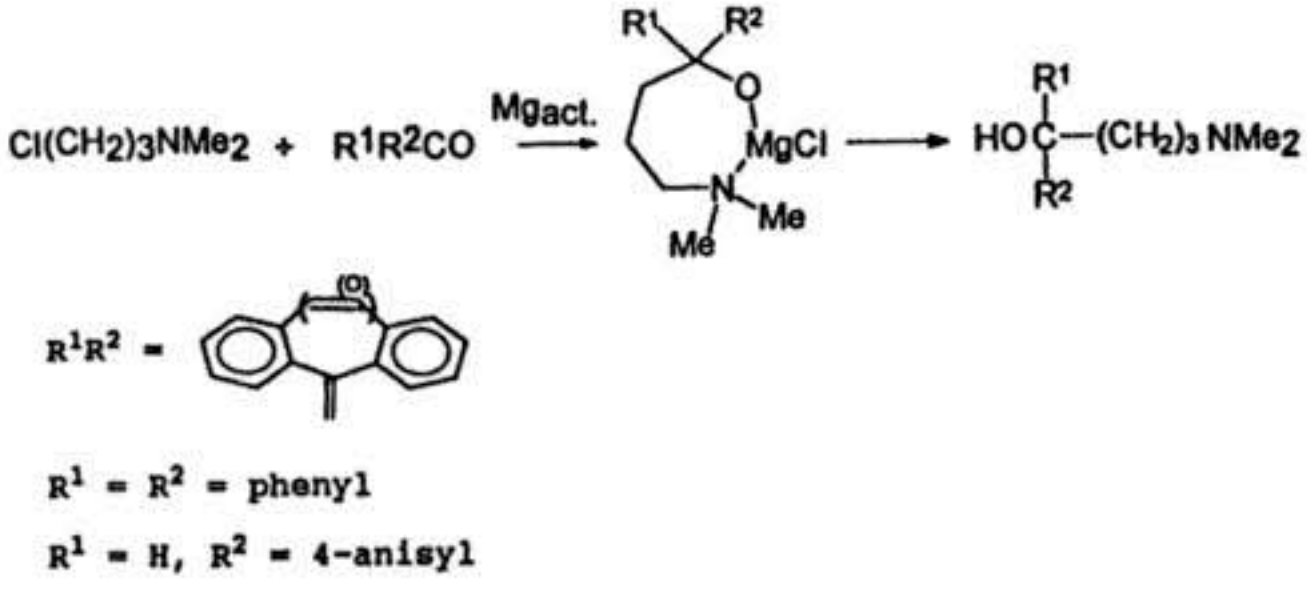


Figure 1 Reaction of haloalkylamine with a ketone under Barbier conditions. (From Ref. 38.)

When acetone, 1,1-diiodo-2-phenylcyclopropane, and magensium are reacted together, 2-phenylcyclopropyl dimethylcarbinol is produced [37].

Alkylamine moieties are integral components of many beneficial drugs. Normally, a Grignard reagent is formed from the haloalkyl amine as the first step in introducing this functional group into the rest of the molecule. However, the Grignard reagent is difficult to form and is somewhat unstable. With the in situ Barbier method, a very stable magnesium complex of the alkylamine and the ketone is formed and isolated (Fig. 1). Workup of the complex leads to some very pure products, in yields as high as 85% [38].

Spirolactone moieties are important components of some biologically active steroids that possess antitumor activity. A prelude to formation of the spiro unit is the introduction of an allyl side chain into a steroidal ketone. This reaction can be accomplished in good yield by the Barbier reaction of allyl bromide, ketone, and iodine-activated magnesium in ether. With 5α-cholestan-3-one, 51 and 48% of the epimeric allyl alcohols are isolated. With 3β-(tetrahydropyran-2-yloxy)-5α-androstan-17-one, 98% of the allyl alcohol is isolated [39].

Another interesting example of the Barbier reaction is that of 3-butylpyridine with aliphatic ketones in the presence of amalgamated magnesium [40]. With ethyl methyl ketone, 5-butyl-α-ethyl-α-methyl-2-pyridine methanol is isolated, in 70% yield. The corresponding α,α-dimethyl derivative is isolated when acetone is used as the ketone source. The ketyl-coupling products, R,R′C(OH)–C(OH)R,R′, are also produced in both reactions.

E. With Esters, Amides, Nitriles, Epoxides

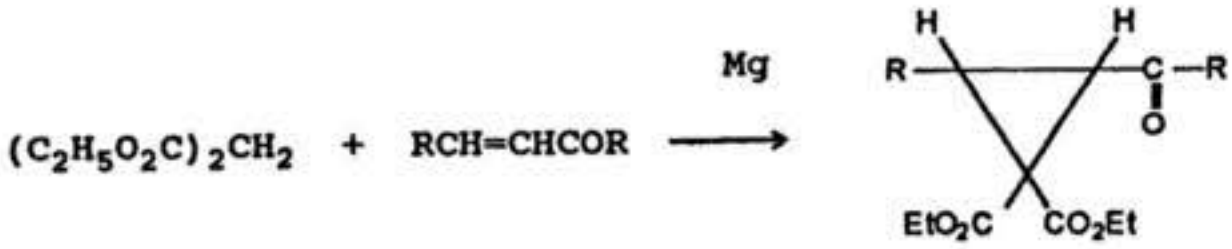
The reaction of esters, amides, nitriles, and the like, with alkyl or aryl halides under Barbier conditions generally produces alcohols and ketones, in much the same manner as the reactions with aldehydes and ketones [Eqs. (8–13)].

$$C_2H_5I + C_6H_5{-}CO_2{-}C_2H_5 \xrightarrow{Mg} C_6H_5{-}\underset{\displaystyle OH}{\overset{\displaystyle ET}{\overset{|}{\underset{|}{C}}}}{-}C_2H_5 \qquad 73\%\ [41] \tag{8}$$

$$C_3H_7I + C_3H_7CO_2{-}C_2H_5 \longrightarrow (C_3H_7)_2C{=}O \qquad 53\%\ [41] \tag{9}$$

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An interesting addition of a methylene moiety across a double bond of an unsaturated ketone under Barbier conditions has been reported by some French chemists [Eq. (16); 48].



(16)

No 1,2- or 1,4-addition products were isolated.

IV. CYCLIZATION REACTIONS

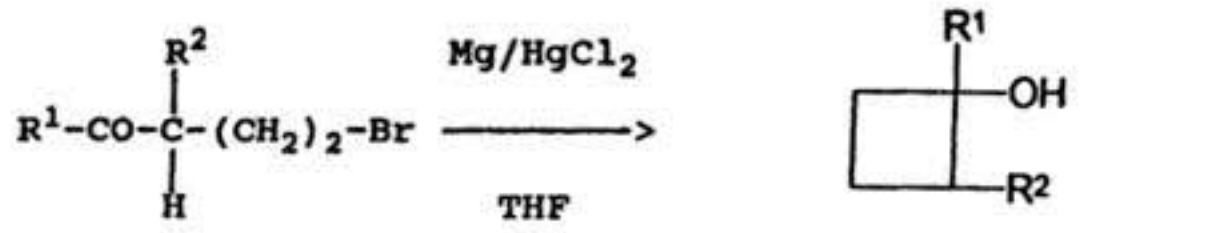
The Barbier reaction has been used for the synthesis of alcohols that were difficult to prepare by normal Grignard reagent techniques. This is particularly true for the preparation of cyclic alcohols from halogenated ketones. Several researchers [49–51] have shown that cyclobutanols and cyclopentanols can be prepared in good yields from δ- and γ-iodo- and bromoketones in either solvents with Mg or $Mg/HgCl_2$ [Eq. (17)].



(17)

The yield is only 20% in diethyl ether, but it improves to 65% when the bromo analogue or tetrahydrofuran is used.

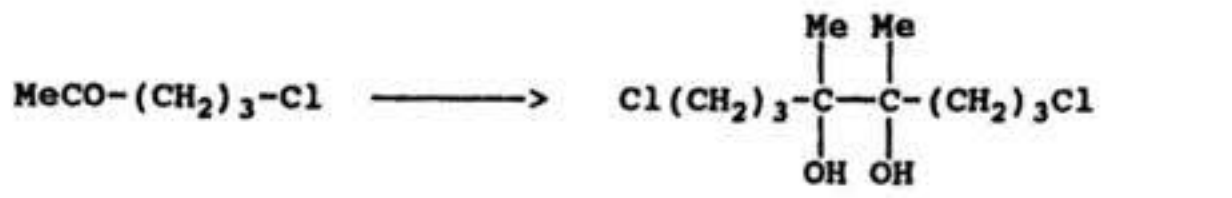
With the γ-bromo analogues, cyclobutanols are obtained in 25–60% yields [Eq. (18)].



(18)

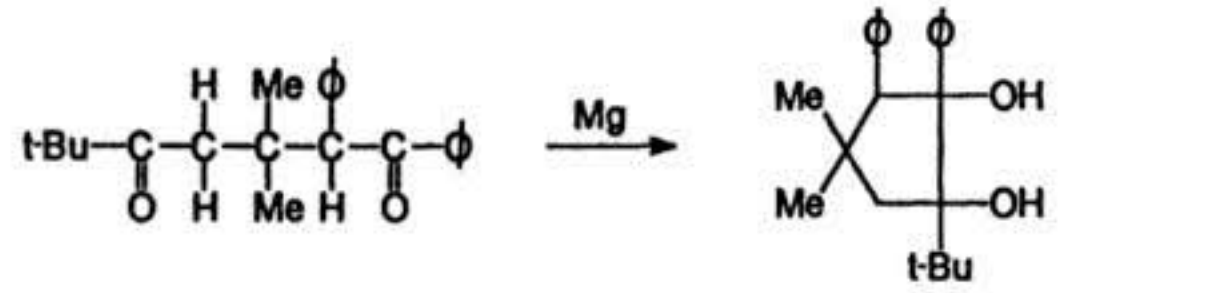
$R^1 = CH_3$ to C_5H_{11} and $R^2 = H$, CH_3, C_2H_5.

When R^1 = phenyl, or when the chloro analogue is used (R^1 = Me), only coupling products from a postulated ketyl radical anion are isolated [Eq. (19)].



(19)

Another interesting ketyl cyclization is that reported for a 1,5-pentanedione derivative on reaction with magnesium [Eq. (20); 52].



(20)

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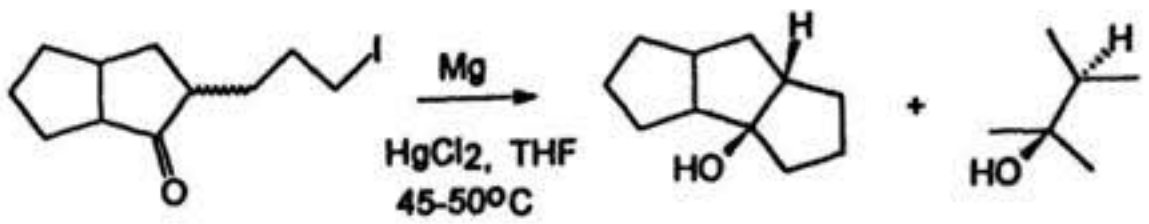


Figure 3 Preparation of a tricycloundecanol. (From Ref. 54.)

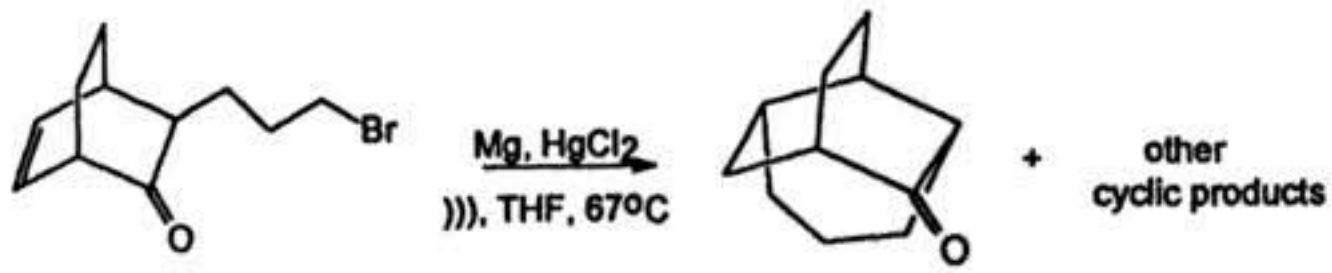
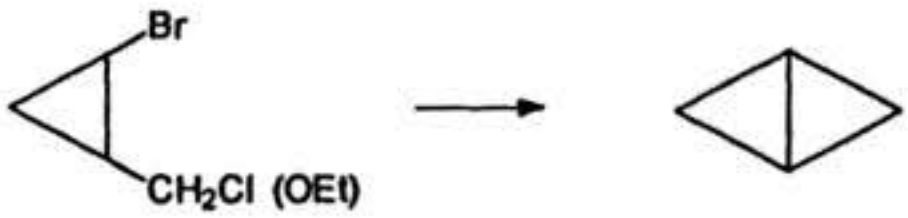


Figure 4 Preparation of a tricycloundecanone. (From Ref. 55.)

Stereoselective, fused-ring alicyclic alcohols are prepared in 10–77% yields from haloalkylalicyclic ketones. The cyclic ketones range from C_5 to C_7, with iodo-, bromopropyl-, or bromobutyl-substitution in the 2-position. Bicyclo[3.3.0]octan-1-ols, [4.3.0]nona-1-ols, [4.4.0]deca-1-ols, and [5.3.0]decan-1-ols are also prepared. When the side chain is extended to iodopentyl, no bicyclic products are obtained. Usually the ring fusion is cisoid [53].

Tricyclic compounds can also be prepared from haloalkyl bicyclic ketones under Barbier conditions (Figs. 3 and 4) [54]. Both the *trans*- and *cis*-derivatives are isolated in a combined yield of 43%. The reaction mechanisms for both products are explained by invoking SET and DET reactions [55].

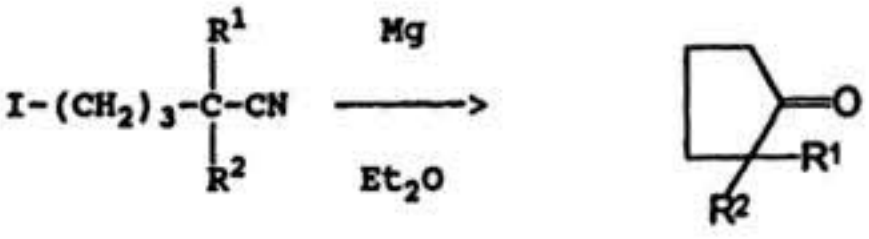
Bicyclobutanes can also be prepared under Barbier conditions from halocyclopropylmethyl ethers or chlorides in 32–45% yields [Eq. (21); 56].



(21)

Some cyclobutene and 1,3-butadiene are also isolated.

If cyano-haloalkanes are used instead of the halo-ketones, cyclization reactions take place under Barbier conditions to produce ketones [Eq. (22); 57]. However, the solvent and the halogen seem to have a greater effect on the product distribution.



(22)

R^1 = Me, i-Pr, i-Bu; R^2 = H, Me; R^1R^2 = cyclopropyl, cyclohexyl

Yields ranged from 61–79%, and no cyanoalkanes were isolated.

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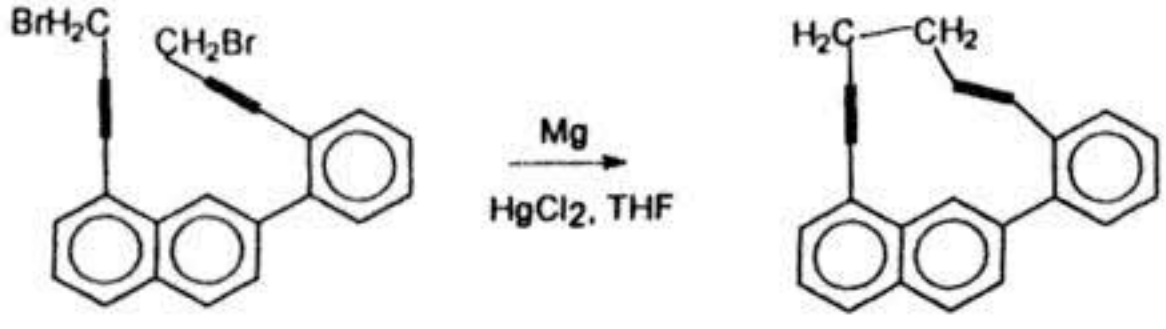
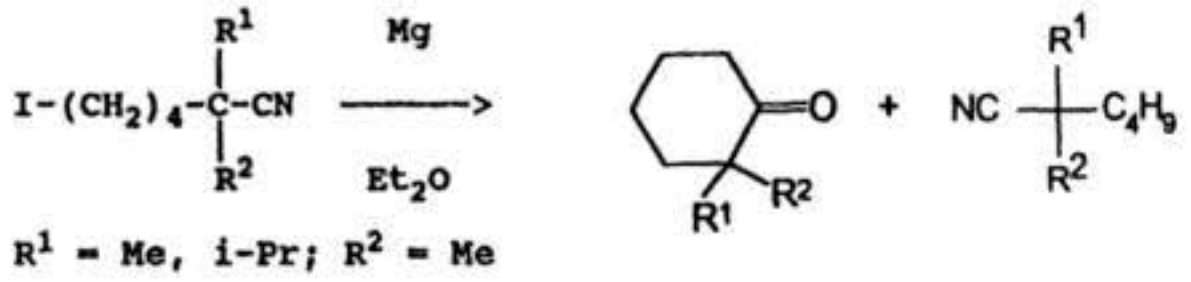


Figure 5 Cyclization of a reactive methylene halide. (From Ref. 60.)

When the alkyl chain is lengthened by one methylene unit, cyclohexanones are produced, along with some cyanoalkanes [Eq. (23)].



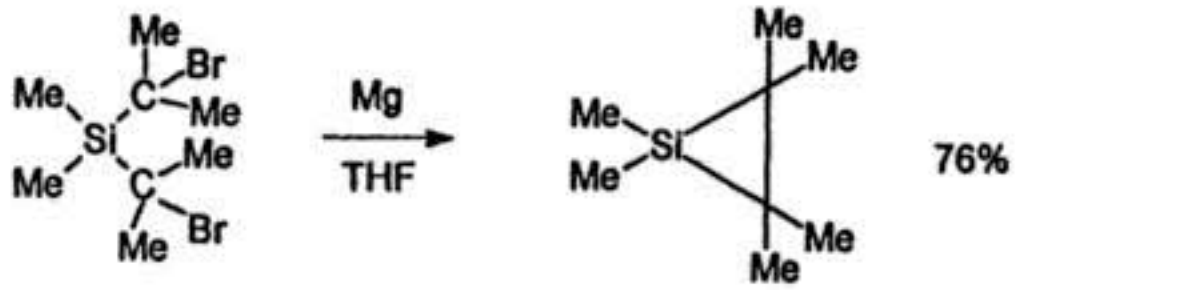
(23)

Yields as high as 75% for the ketones and 15% for the alkanes are obtained. When THF is used and both R groups are Me, ketone and alkane are isolated in only 10% yields, whereas the major product (70%) is the 1,1,10,10-tetramethyl-1,10-dicyanodecane.

When Br is substituted for I, the cyclohexanone product can be isolated in predominance only when HMPT is the solvent. If the methylene chain is lenghened by one unit, the cyanohexane and unreacted starting material are the major products. Only 2% of a cycloheptanone is isolated.

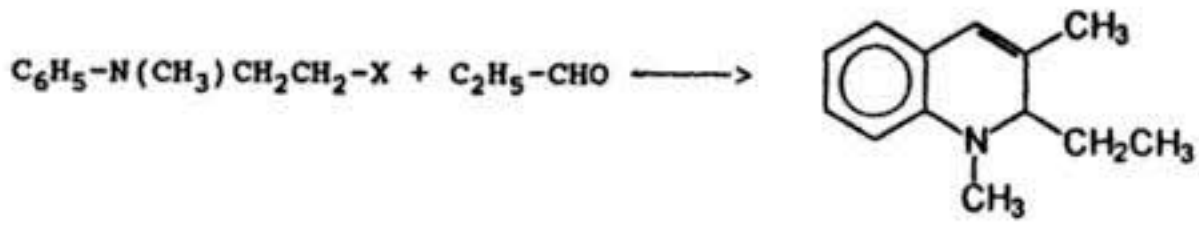
If Cl is substituted for I, no reaction occurs in ether or THF. The authors postulate that a surface-mediated reaction takes place, and because no positive Gilman test occurs, no intermediate Grignard reagent is formed.

Cyclization reactions under Barbier conditions can also occur with reactive methylene halides [Eq. (24) and Fig. 5; 58,59,60].



(24)

Heterocycles can also be prepared by cyclization reactions under Barbier conditions. An unexpected dihydroquinoline derivative is isolated from the reaction of a haloalkylaniline with an aldehyde [Eq. (25); 61].



(25)

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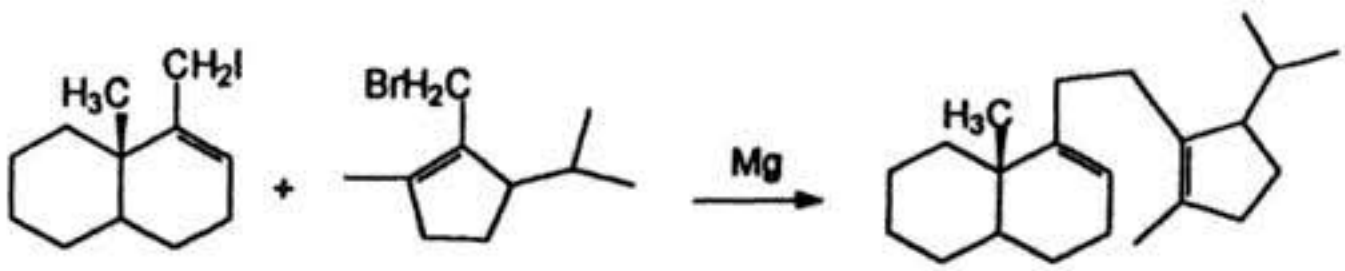


Figure 6 Coupling reaction of cyclic allylic halides. (From Ref. 63.)

V. COUPLING REACTIONS

In some instances, cross-coupling products are obtained under Barbier conditions [Eq. (26) and Fig. 6; 62,63].

$$RX + Cl\text{–}C{\equiv}C\text{–}C(CH_3)_2OH \longrightarrow R\text{–}C{\equiv}C\text{–}C(CH_3)_2OH \qquad (26)$$

R = C_4–C_{10} alkyl, phenyl, *o*- and *m*-tolyl, or *o*-anisyl

VI. DIMERIZATIONS

One of the benefits of the Barbier reaction over the Grignard reaction is generally the production of products with little or no R–R dimer formation. However, because of the radical nature of the reaction; Wurtz-type dimer formation can be the primary reaction in the absence of an electrophilic coreagent. Some Russian chemists have reported the dimerization of halogenated alkenes and alkanes using iodine-activated magnesium with silver bromide [Eqs. (27) and (28); 64].

$$Cl_2C{=}CH\text{–}(CH_2)_3\text{–}Br \longrightarrow Cl_2C{=}CH(CH_2)_6CHCl_2 \qquad 60\% \qquad (27)$$

$$Cl_2CH(CH_2)_6Br + BrCH_2CH_2Br \longrightarrow Cl_2CH(CH_2)_{14}CHCl_2 \qquad 56\% \qquad (28)$$

The ethylene bromide reaction presents an interesting way to extend the chain length of the dimer.

Vinyl bromide derivatives can be dimerized under slightly different Barbier conditions using magnesium and cuprous chloride in THF [Eq. (29); 65].

$$(CH_3)_2C{=}CHBr \longrightarrow (CH_3)_2C{=}CH\text{–}CH{=}C(CH_3)_2 \qquad 43\% \qquad (29)$$

Aromatic and benzylic halides can also be dimerized under Barbier conditions. 2-Bromofluorene dimerizes in a 52% yield with the magnesium–cuprous chloride combination [66].

p-Vinylbenzyl chloride dimerizes to the 1,2-bis(*p*-styryl)ethane when reacted with magnesium alone [67].

The following three reactions are not dimerizations in the same sense as the previous examples, but they show the range of the "dimeric"-like products that can be obtained from the in situ reaction [Eqs. (30) and (31) and Fig. 7; 68–70].

$$C_6H_5\text{–}CH_2\text{–}Cl + S \xrightarrow[NH_3(l)]{Mg} C_6H_5\text{–}CH_2\text{–}S\text{–}CH_2\text{–}C_6H_5 \qquad (30)$$

$$N{\equiv}C\text{–}CH{=}CH_2 \xrightarrow[CoCl_2]{Mg} \text{product} \xrightarrow{H_2O} NC(CH_2)_4CN \qquad (31)$$

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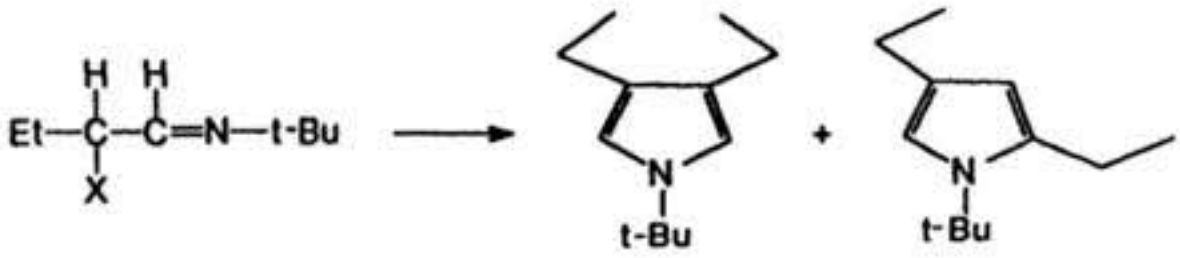


Figure 7 Cyclic dimers from the reaction of imines under Barbier conditions. (From Ref. 70.)

VII. WITTIG-TYPE REACTIONS

The reaction of *gem*-dihaloalkanes with alkyl or aryl aldehydes and ketones under Barbier conditions with Mg/Hg can be used to prepare unsaturated derivatives in a Wittig-type reaction. Some Japanese researchers [71] show that styrene and substituted styrenes, as well as octenes, can be prepared in yields as high as 75% using diiodomethane and the corresponding aldehydes [Eqs. (32) and (33)].

$$R\text{–}C_6H_4\text{–}CHO + CH_2I_2 \xrightarrow{Mg/Hg} R\text{–}C_6H_4\text{–}CH{=}CH_2 \quad (32)$$

$R = H,\ p\text{-}CH_3,\ p\text{-}Cl$

$$n\text{-}C_6H_{13}\text{–}CHO \longrightarrow n\text{-}C_7H_{14}{=}CH_2 \quad (33)$$

Similar reactions are reported with aliphatic and cycloaliphatic ketones and diiodomethane [Eqs. (34) and (35); 71,72].

$$C_2H_5\text{–}CO\text{–}C_2H_5 \longrightarrow (C_2H_5)_2CH{=}CH_2 \quad (34)$$

$$c\text{-}C_6H_{10}{=}O \longrightarrow c\text{-}C_6H_{10}{=}CH_2 \quad (35)$$

Other *gem*-dihalides are also used [Eq. (36); 73].

$$c\text{-}C_6H_{10}{=}O + (CH_3)_3SiCHBr_2 \longrightarrow c\text{-}C_6H_{10}{=}CHSi(CH_3)_3 \quad (36)$$

VIII. PHOSPHORUS AND OTHER METALS

A. Phosphorus

Organophosphorus compounds find wide use in the chemical industry as catalysts, intermediates, complexes, and end-use products. Arylphosphines and phosphine oxides are often produced by the reaction of a preformed Grignard reagent with a halophosphine or phosphine oxide. Yields are reduced by the production of unwanted side-reaction products such as biaryls. These unwanted products are reduced when the reaction is conducted under Barbier conditions. When alkyl and aryl halides are reacted with magnesium metal, a trihalophosphine or phosphine oxide, a metal halide or amine catalyst, in THF–benzene mixtures, at reflux, good yields of phosphines or phosphine oxides are obtained [74]. For example, triphenylphosphine can be prepared in a 97.2% yield from the reaction of bromobenzene, trichlorophosphine, magnesium metal, aluminum chloride, and sodium chloride in THF–benzene at 70–80°C.

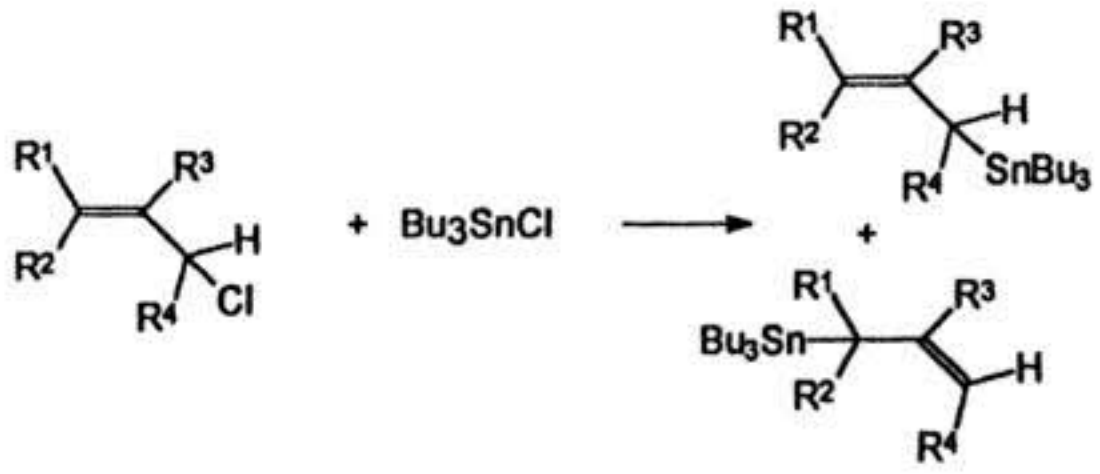
B. Tin

Grignards have often been used for the synthesis of many alkyl and aryl organotin compounds. However, certain derivatives, such as the perfluorinated alkyltins, cannot be

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made in this manner because the Grignard reagents are too reactive. Traditionally, they have been prepared by the cleavage reaction of ditins with perfluorinated alkyl iodides. However, perfluorinated alkyltins can be prepared by a Barbier reaction of a tin halide with perfluoroethyl iodide and magnesium metal in THF at room temperature. Dimethyl and dibutyl bis(perfluoroethyl)tins are prepared in this manner in 34 and 16% yields, respectively [75]. The diethyl and divinyl analogues, as well as the diethyl iodoperfluoroethyl and trivinyl perfluoroethyl tins can also prepared in 10% yields [76].

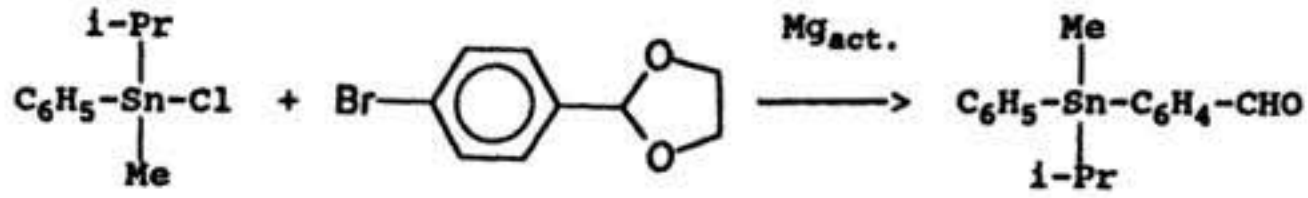
Tetraorganotins can be conveniently prepared from the coupling reaction of allyl halides with organotin halides under ultrasonic-assisted Barbier conditions [Eq. (37)].



(37)

R^1 = H, Me, Ph, vinyl, allyl; R^2 = H; R^3, R^4 = H, Me
Trans/cis-stereoisomer yield = 100:0–55:45
Yields range from 52 to 100%, with the α-isomer in predominance [77].

Another coupling reaction that produces an optically active tetraorganotin utilizes an aromatic halide and a triorganotin [Eq. (38); 78].



(38)

In their studies on the use of silyl-substituted ligands as thermal and oxidative stabilizers of transition metals, Pannell and collaborators [79] show that *trans*-1-trimethylsilyl-3-η^1-allyl(trimethyl)tin can be prepared in an approximate 50% yield by the Barbier reaction of a trialkyl or triarylmetal chloride with magnesium metal and 1-trimethylsilyl-3-chloroprop-1-ene. With nickel(II) chloride, magnesium, a trace of mercuric(II) chloride, and 2-trimethylsilyl-3-chloroprop-1-ene, the thermally and oxidatively stable bis(η^3-2-trimethylsilylallyl)nickel derivative is prepared in 36% yield. The unsubstituted derivative is thermally unstable and ignites in air.

C. Germanium

The Barbier reactions involving germanium derivatives are similar in many ways to those noted in the previous section. The work of Pannell [79] and collaborators also produced *trans*-1-trimethylsilyl-3-η^1-allyl(triphenyl)germane in a 50% yield.

The production of diphenylmethyl trimethylgermane in 44% yield is reported from the reductive germylation of benzhydrol with trimethylchlorogermane, magnesium, and HMPT [80].

Organogermanes can be prepared using a method similar to that used for the production of hypervalent silicon species. Hypervalent germanium species are reacted with

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magnesium and alkyl bromides to give tetra-alkylgermanes in yields from 28 to 78%. The hypervalent species are lithium or potassium tris(benzene-1,2-diolato)germanate, and the bromides range from methyl, ethyl, butyl, cyclohexyl, dibromobutane, and dibromopentane, to vinyl, allyl, and phenyl. The reactions are carried out in refluxing THF and, in some cases, the yields are better than those obtained from the traditional method of reacting tetrachlorogermane with Grignard reagents [81].

Di- and trigermanes have been synthesized in 73–75% yields by the Wurtz-type-coupling reactions of phenyl chlorogermane or phenyl dichlorogermane with amalgamated magnesium [82].

D. Lead and Gallium

Tetraorganolead derivatives, such as Et_4Pb are prepared from the reaction of Pb, Mg, and alkyl halides [83].

Trialkylgallium derivatives (R_3Ga) are prepared from the reaction of alkyl iodides with a magnesium–gallium alloy [84].

IX. ORGANOSILANE REACTIONS

Silylation reactions have been used for many years to prepare new and interesting organosilanes, ranging from thermally stable fluids and polymers, to biologically active materials.

Chlorotrimethylsilane (TMSCl) and other chlorosilanes are often used to prepare the organosilanes by the familiar two-step process employing a preformed Grignard or lithium reagent or the in situ process.

The in situ process occurs in the same manner as described earlier employing SET reactions from the magnesium surface to the reactants, forming radical and radical anion species. The question of whether or not a short-lived Grignard species exists in these reactions is still debatable, with evidence for and against still being offered. In addition to the ether solvents generally employed, the use of the highly polar solvent, hexamethyl-phosphorotriamide (HMPT), greatly enhances the in situ reaction. Reactions are generally run at reflux temperatures, with ether solvents, and at lower temperatures when HMPT is employed. Reaction times vary from a few minutes to hours.

A. Addition Reactions

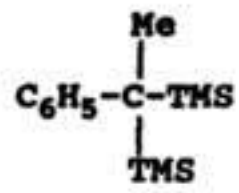
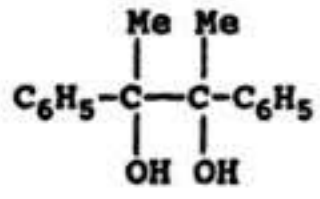
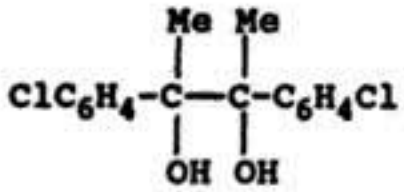
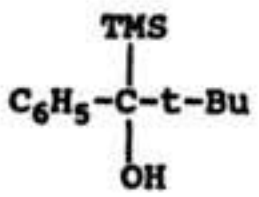
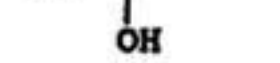
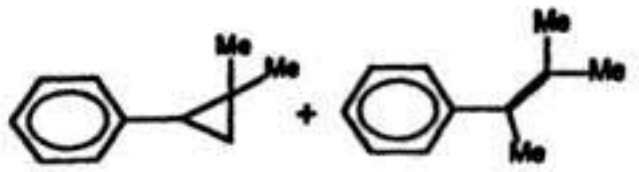
Functionally substituted benzylic, allylic, and vinylic compounds containing alkoxides, esters, ethers, nitriles, or amides can be reacted with halosilanes under Barbier conditions using HMPT to yield C- and O-silylated products, 1,2- or 1,4-addition products, as well as reductive dimers. Radical and anionic intermediates are postulated, based on SET reactions from the metal, and multiple silated species can be obtained. The use of the TMSCl–Mg–HMPT system has been extensively investigated by Calas' group [85] at the University of Bordeaux, and their work has greatly advanced the science of the Barbier reaction with silanes.

1. 1,2-Additions

The addition reactions of TMSCl to ketones under Barbier conditions, with HMPT as solvent, yield a variety of products, depending on the eqivalents of TMSCl used and the type of groups on the ketone. Table 3 illustrates the addition reactions for acetophenone and some of its analogues.

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Table 3 1,2-Addition Reactions of TMSCl (Mg–HMPT) with Ketones

Ketone	Equiv	Product	Yield
C_6H_5COMe	2		-
	0.5-1		88 (1:1 d:l/meso)
p-ClC_6H_4COMe	0.5-1		-
C_6H_5COt-Bu	2		-
	2 (TMU)	p-TMS-C_6H_5CO-t-Bu	-
	1		75
	1.5		60

TMU = tetramethylurea.
Source: Refs. 85–88.

Anion–radical species are postulated as reaction intermediates for the geminal TMS products [85]. However, for the glycol products, a silyl–Grignard intermediate is postulated. No radical anion species are required because the reaction does not occur in the absence of TMSCl [86,87].

When the ketone contains a bulky group, such as *t*-butyl, a TMS containing alcohol is obtained instead of a disubstituted hydrocarbon. If the solvent is changed from HMPT to tetramethylurea (TMU), the aryl ring is silylated and a ketone is isolated [88]. When less than 2 Eq of TMSCl are employed, the reaction products contain no silane species. The cyclopropyl and ethylenic benzene derivatives are postulated to arise from a carbene insertion into the *t*-Bu group and a Me group rearrangement [88].

Nitriles and imines are reduced in the presence of TMSCl–Mg–HMPT to yield silylated amines [Eq. (39); 87,89].

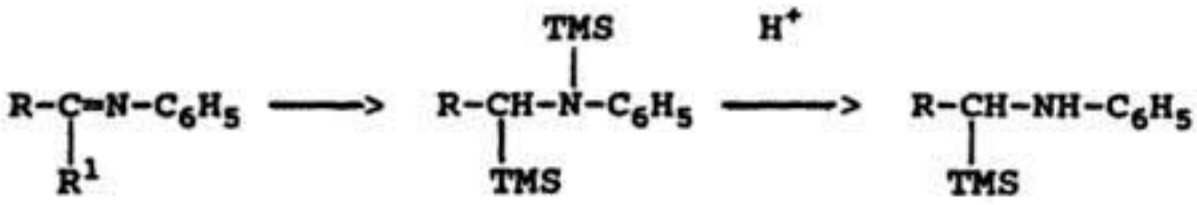
$$p\text{-R–}C_6H_5\text{–C}{\equiv}\text{N} \longrightarrow p\text{-TMS–}C_6H_5\text{–CH(TMS)–N(TMS)}_2 \xrightarrow[OH^-]{H^+} p\text{-TMS–}C_6H_5\text{–CH(TMS)–NH}_2 \quad (39)$$

R = H, Cl

Material chroniony prawem autorskim

When 1- or 2-cyanonaphthalene is silylated, the silylamine is prepared as well as various multiple silylated naphthalene species [90].

For amines, the addition follows a similar path [Eq. (40); 90,91].

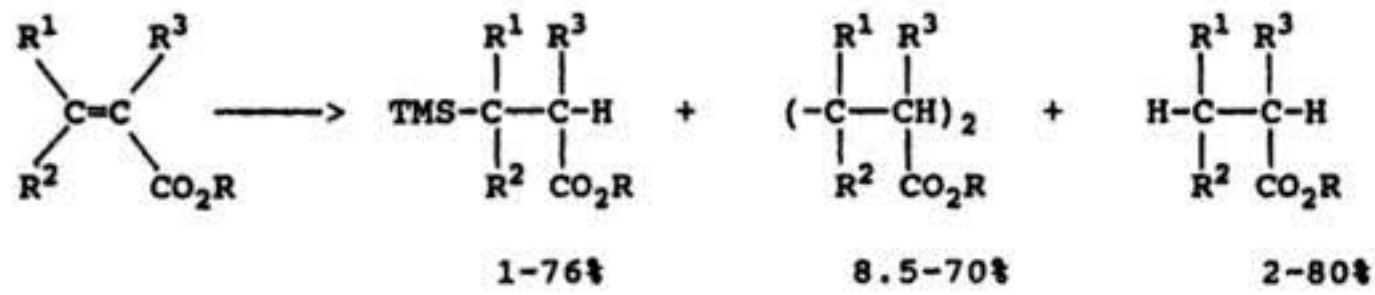


(40)

$R = t$-Bu, C_6H_5; R^1 = Cl, H, Me

When $R = C_6H_5$ and R^1 = Me, a TMS group also adds to the *para*-position of the aromatic ring [90].

Unsaturated esters yield a variety of products when reacted with TMSCl–Mg–HMPT [Eq. (41); 92].



(41)

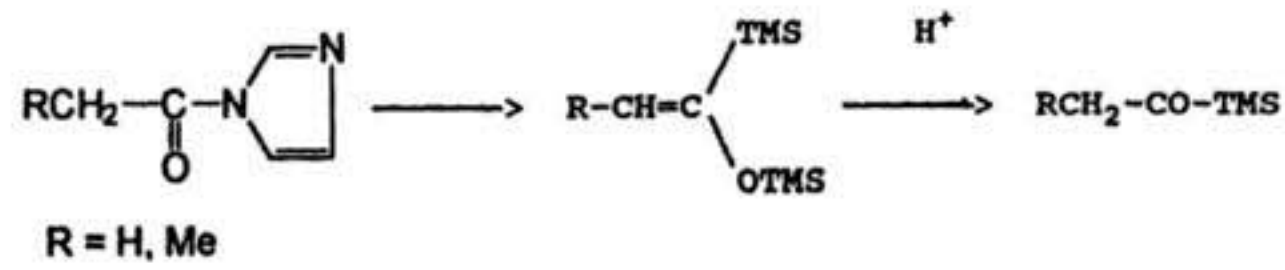
R^1 = H, Me, C_6H_5, CO_2Me
R^2 = H, Me, CO_2Me
R^3 = H, Br, Me, CO_2Et, C_6H_5
R = Me, Et, *n*-Bu, $CH_2C_6H_5$

The α- and β-trimethylsilyloxystyrenes will add more than 1 Eq of TMS during reaction with excess TMSCl–Mg–HMPT [Eq. (42); 93].



(42)

Acylimidazoles yield acylsilanes when the intermediates from the Barbier reaction are hydrolyzed [Eq. (43); 94].

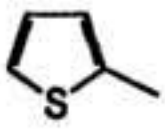


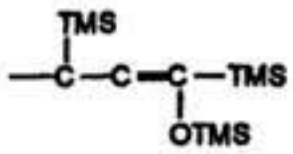
(43)

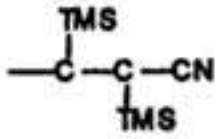
Phenacylamines yield silylamines, amides, and nonsilylated amines when reacted with TMSCl–Mg in THF [Eq. (44); 95].

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Table 4 (Continued)

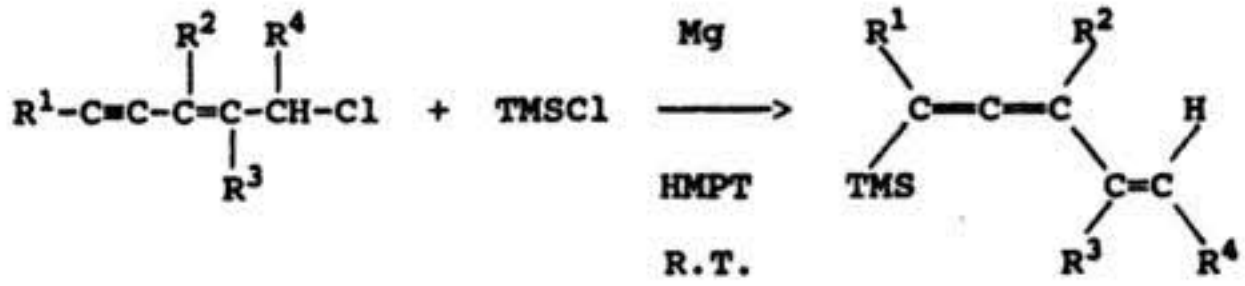
R^1	R^2	R^3	X	% Yield	
				Addition	4,4'-Dimer
	H	H	NR_2	-	-
MeCH=CH	H	H	NR_2	(1,6 add)	-

* = 

** = 

Source: Refs. 96–100.

Some interesting vinyl allenes are produced in 50–80% yields from the Barbier reaction of alkenylpentynes with TMSCl [Eq. (47); 102].



(47)

$R^1 = H$, TMS
$R^2 = R^3 = H$, Me, $-(CH_2)_4-$
$R^4 = H$, Me

A multiple-substituted 1,6-hexakis(TMS)but-2-yne is obtained from the reaction of 1,6-bis(TMS)buta-1,3-diyne with excess TMSCl under Barbier conditions [103].

The bicyclic 8,8-dimethyl-8-silyl-bicyclo[3.2.1]octa-2,6-diene is the only product isolated from the Barbier reaction of cylohepta-2,4,6-triene with dimethyldichlorosilane [104].

B. Carbon and Oxygen Silylation

Both C- and O-silylated compounds are isolated from the reaction of benzyl and allyl alcohols, ethers, and amines with TMSCl [Eq. (48); 105].

$$RR^1R^2COH + TMSCl \xrightarrow{Mg} RR^1R^2COTMS \qquad (48)$$

$R = H, C_6H_5$; $R^1 = H, CH_3, C_6H_5$; $R^2 = C_6H_5, SiMe_3$

When a second mole of TMSCl is used, the silane $RR^1R^2CSiMe_3$ is formed along with 1 mole of hexamethyldisiloxane, A Ti, Fe, or Ni catalyst is usually required for the second step.

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The general reaction can also occur with an ether or amine [Eq. (49)].

$$RR^1R^2CX + TMSCl \xrightarrow[HMPT]{Mg} RR^1R^2CSiMe_3 + XTMS \tag{49}$$

where $X = OTMS, OCH_3, OCH_2{-}CH{=}CH_2, NR^3R^4$. Yields range from 50 to 95% [105].

For allyl and substituted allyl alcohols and ethers, both S_N2 and S_N2' reaction products are formed [Eq. (50), 105].

$$R{-}CH{=}CH{-}CH_2OR' + TMSCl \xrightarrow[HMPT]{Mg} R{-}CH{=}CH{-}CH_2SiMe_3 + R{-}\underset{\displaystyle SiMe_3}{\underset{|}{CH}}{-}CH{=}CH_2 \tag{50}$$

55%

$(Z+E)$ 45%

$R = H, Me, C_6H_5$

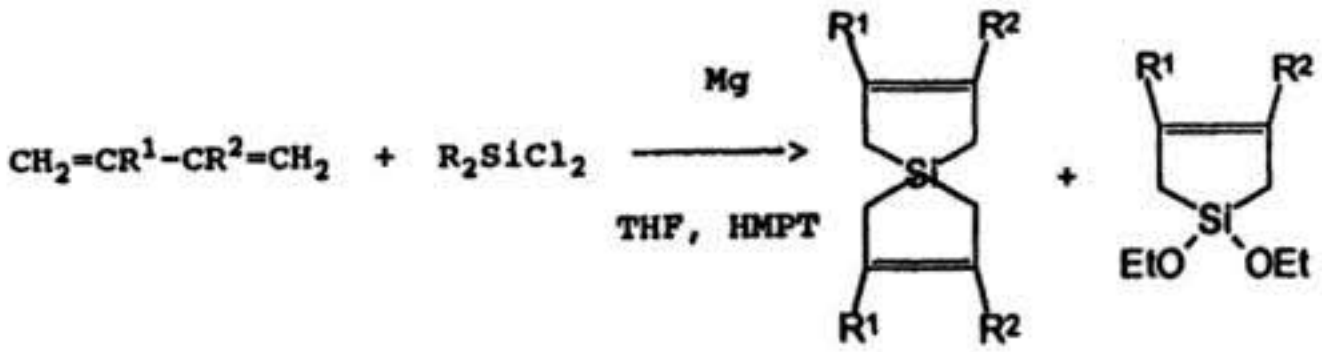
$R' = H$, alkyl, aryl

When $R = C_6H_5$, only the $Z+E$ isomers (S_N2 reaction) are produced. When $R = H$, a second mole of TMSCl will silylate the 3-position forming $Me_3SiCH{=}CH{-}CH_2SiMe_3$ in a 58% yield.

The C- and O-silylated products are obtained when the functional compound is highly halogenated [Eq. (51); 106].

$$\begin{array}{l} Cl_3C{-}\overset{\displaystyle Me}{\overset{|}{C}}{-}OH + TMSCl \longrightarrow Me_3Si{-}\overset{\displaystyle Cl}{\overset{|}{C}}{-}\overset{\displaystyle Me}{\overset{|}{C}}{-}OSiMe_3 + H{-}\overset{\displaystyle Cl}{\overset{|}{C}}{-}\overset{\displaystyle Me}{\overset{|}{C}}{-}OTMS + \\ \qquad\qquad\qquad\

1,3-Butadiene and substituted butadienes react with halosilanes in the presence of activated magnesium to yield silylspiroalkenes or cyclic silylalkenes in yields from 21 to 80% [Eq. (52); 107–109].



(52)

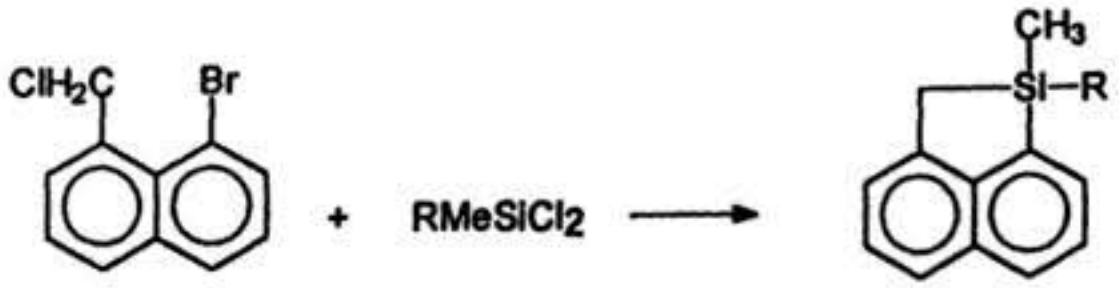
R^1 = H, Me

R^2 = H, Me

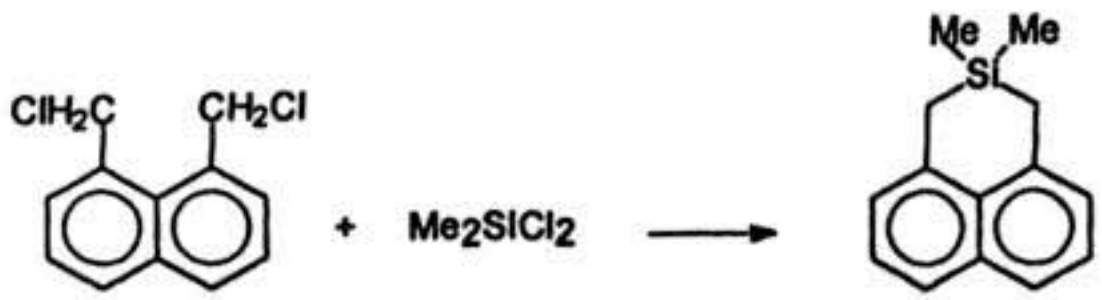
R = Cl, Me, OEt

A similar reaction with 1,3,5-hexatriene and dimethyldichlorosilane yields the 1,1-dimethyl-2-vinyl-1-silacyclopent-3-ene when THF and Cu_2Cl_2 are employed [110].

1-Silylacenaphthenes and 1-silylphenalenes are obtained in 54–71% yields from the reactions of 1,8-disubstituted naphthalenes with chlorosilanes and Mg in THF [Eqs. (53) and (54); 111–113].

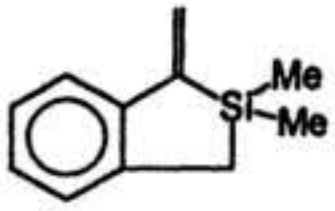


(53)

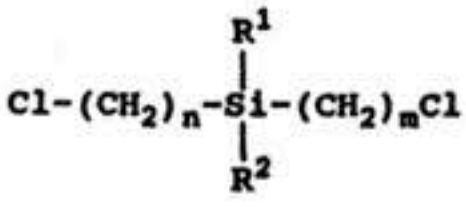


(54)

A unique silylindene results from the reaction of 1-(α-chlorovinyl)-2-bromomethyl-benzene with Me_2SiCl_2 and Mg in THF [114].



Silylcyclobutane derivatives are isolated from the reaction of certain dihalosilanes with Mg in ether or THF.



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with halosilanes under Barbier conditions yields several useful starting materials for other reactions [Eq. (57)].

$$R_{4-n}CCl_n + Me_2R'SiCl \xrightarrow[HMPT]{Mg} R_{4-n}CCl_{n-1}SiR'Me_2 \qquad (57)$$

30–60°C

$n = 2, 3, 4$
R = H, Me, C_6H_5, *p*-ClC_6H_5, $Cl_2C{=}$, and mixtures thereof
R′ = H, Me

Silanes such as Cl_3CTMS, HCl_2CTMS, $MeCl_2CTMS$, $C_6H_5CCl_2TMS$, $Cl_2C{=}C(Cl)TMS$, and $MeCl_2CSiMe_2H$ can be prepared in yields as high as 80% [120].

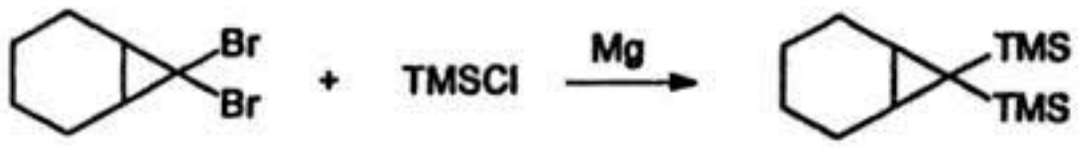
Some interesting multiple silylated species are prepared by this method [Eqs. (58–61); 121–123].

$$CBr_4 + Me_3SiCl \xrightarrow[THF]{Mg} \underset{28\%}{(Me_3Si)_4C} + \underset{40\%}{(Me_3Si)_3SiH} + \underset{5\%}{(Me_3Si)_2CH_2} \qquad (58)$$

$$CBr_4 + p\text{-}Me\text{–}C_6H_5\text{–}SiH_2Cl \longrightarrow (p\text{-}Me\text{–}C_6H_5\text{–}SiH_2)_4C \qquad (59)$$

$$Me_2CBr_2 + C_6H_5SiH_2Cl \longrightarrow (C_6H_5SiH_2)_2CMe_2 \qquad (60)$$

The H_3Si derivatives $(H_3Si)_4C$ and $(H_3Si)_2CMe_2$ can be prepared by treating the aryl silanes with acid, followed by reduction with LAH [122].



(61)

For the reaction of vinyl chloride with dichlorodimethylsilane, a disilane is isolated, not the expected divinyldimethylsilane [Eq. (62); 124].

$$CH_2{=}CH\text{–}Cl + Me_2SiCl_2 \longrightarrow CH_2{=}CH\text{–}Si(Me)_2\text{–}Si(Me)_2\text{–}CH{=}CH_2 \qquad (62)$$

Allyl halides react in the expected S_N2 manner [Eq. (63); 125,126].

$$CH_2{=}CH\text{–}CH_2\text{–}X + R^1R^2R^3SiCl \longrightarrow CH_2{=}CH\text{–}CH_2\text{–}SiR^1R^2R^3 \qquad (63)$$

X = Cl, Br
R^1 = H, Me, Et
R^2 = H, Me, Et, O
R^3 = H, Cp

Solvents can be ether and THF, and yields range from 51 to 81%.

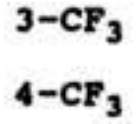
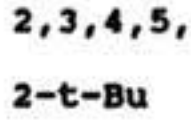
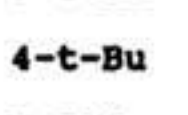
Cyclic allyl halides, such as 3-chlorocyclopent-1-ene, react with TMSCl under Barbier conditions to yield 3-trimethylsilyl derivatives in good yield [127].

Propynyl bromide gives both the trimethylsilyl propyne and allene derivatives (3:1) in a 71% yield on reaction with TMSCl [128], and 1,4-bis(trimethylsilyl)but-2-ene results from the TMSCl reaction with 1,4-dibromobut-2-ene [129].

The reaction of crotyl chloride with TMSCl under Barbier conditions yields the same ratio of products as the reaction of the preformed crotyl Grignard reagent with TMSCl in ether [Eq. (64); 130].

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Table 5 Coupling Reactions of Aryl Halides with TMSCl/Mg/HMPT

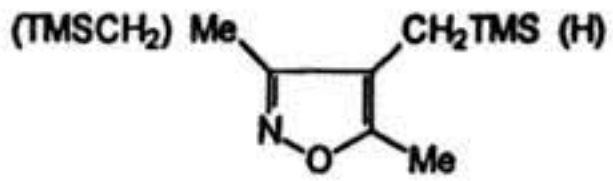
R	X	Yield
H	Cl	87
H	Br	88
4-F	Br	61
4-Cl	I	67
2-Me	Cl	80
3-Me	Cl	85
4-Me	Cl	81
3-CF_3	Br	76
4-CF_3	Cl	33
2,4-diMe	Br	85
3,5-diMe	Br	83
2,4,6-triMe	Br	62
2,3,4,5,6-pentaMe	Br	49
2-t-Bu	Br	58
3-t-Bu	Br	74
4-t-Bu	Br	80
2-OCH_3	Br	71
3-OCH_3	Br	73
4-OCH_3	Br	75
3-SCH_3	Br	74
4-SCH_3	Br	41
4-$N(Me)_2$	Br	75
4- 	Br	77
4-CN	Cl	44*
4-$CH=CH_2$	Cl	31
2-C_6H_5	Cl	68
4- 	Br	72
4- 	Br	76

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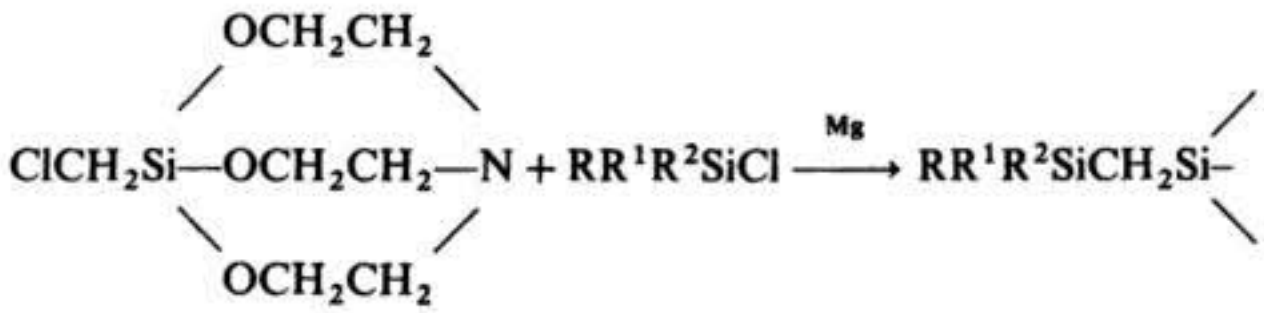
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However, in the absence of silane, MeOMgCl forms and reacts in a second step with the silane to yield the same products. These results give additional support for the intermediacy of a Grignard species in the Barbier reaction.

Chloromethyl heterocycles react with silanes under Barbier conditions to yield the silylmethyl derivatives in good yields. 3,5-Dimethyl-4-(chloromethyl)isoxazole and 5-methyl-3-(chloromethyl)isoxazole couple with TMSCl–Mg in THF to yield the corresponding 4- and 3-trimethylsilylmethyl analogues in yields of 60 and 40%, respectively [138].



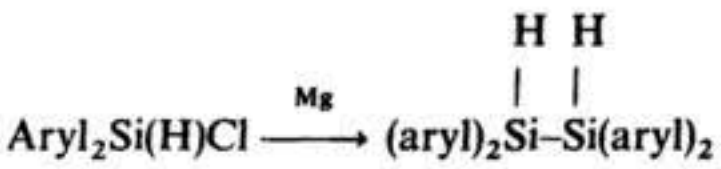
Silatranes are unstable in the presence of Grignard reagents, but under Barbier conditions, chloromethylsilatranes react with silyl halides to form silylmethylsilatranes in good yield (54–78%) [Eq. (71); 139].



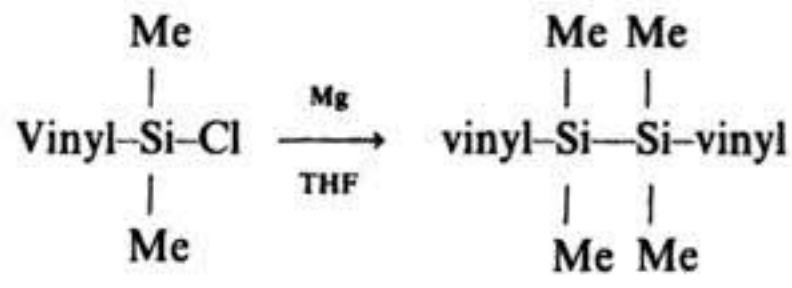
(71)

$R = Me$; $R^1 = Me, O$; $R^2 = H, Me, O$

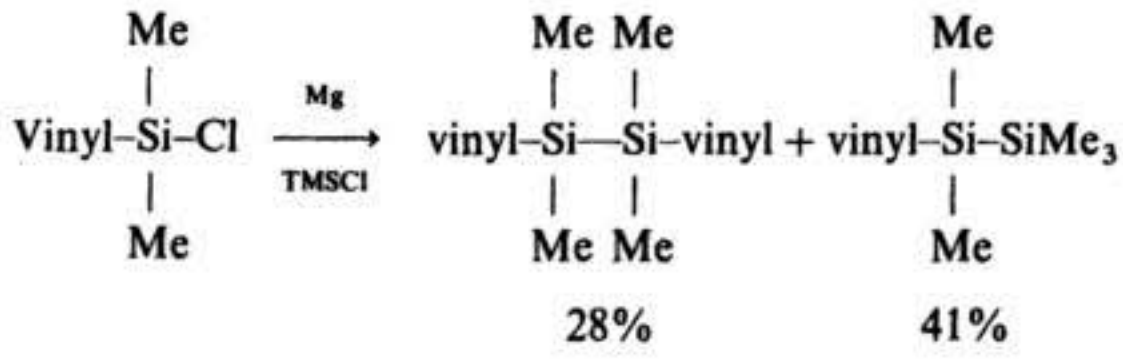
Disilane-coupling products are obtained from the reaction of some vinyl and aryl silyl chlorides with magnesium [Eqs. (72–76); 140,141].



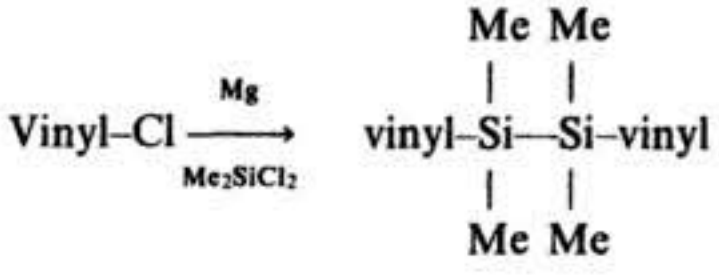
(72)



(73)

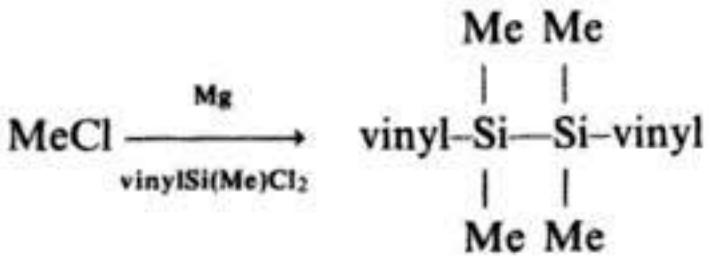


(74)



(75)

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(76)

X. ULTRASONIC REACTIONS

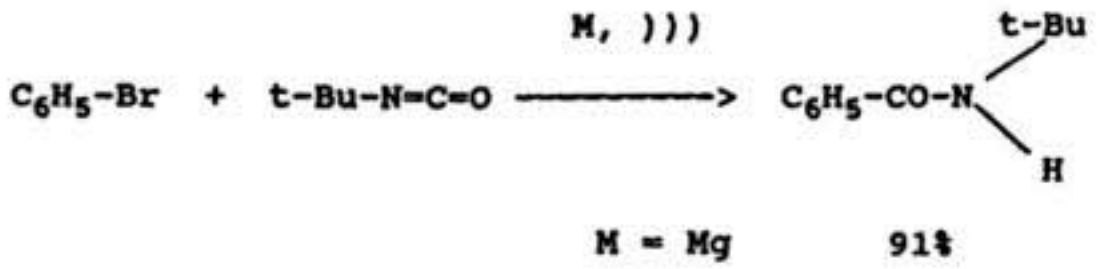
The use of ultrasonic techniques in virtually every field of chemistry has expanded greatly in recent years. Sonochemical methods have probably been most successful for heterogeneous reactions in general and, in particular, for organometallic synthesis. Ultrasonic synthesis allows the use of safer solvents that need not be anhydrous, cheaper chloride starting materials and, frequently, lower reaction temperatures. An excellent review on the use of sonochemistry in organic and organometallic chemistry is that of Einhorn and co-workers [141]. A second Einhorn publication on the ultrasonically assisted Barbier reaction is also very informative [142].

Sonochemical techniques have been used predominantely in the lithium–Barbier reaction [142–145].

Most of the work with magnesium has been aimed at preparing Grignard reagents that are normally difficult to synthesize. However, one recent publication has shown that the sonochemical Barbier reaction with magnesium can be useful on a large scale [Eq. (77); 146].

$$n\text{-}C_3H_7Br + C_6H_5\text{–}CHO \xrightarrow{Mg.)))} C_6H_5\text{–}CH(OH)\text{–}C_3H_7 \qquad (77)$$

Another example on the use of the ultrasonic technique with the magnesium–Barbier reaction is reported by Einhorn and Luche in their study of organometallic intermediates from isocyanates [Eq. (78); 147].

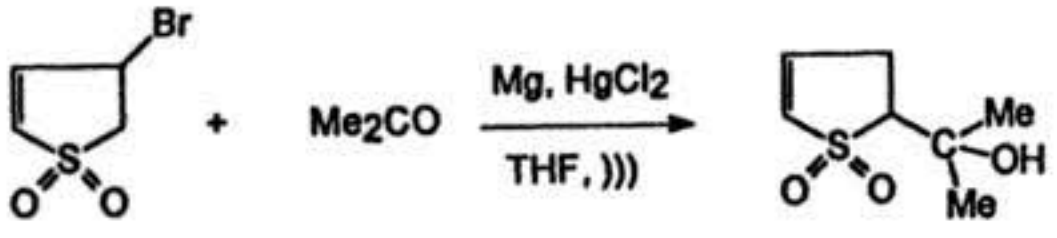


M = Mg 91%
= Li 51%
= Na 78%

(78)

The solvents can be ether or THF, and the reaction occurs at room temperature in as short a time as 15 min.

Ultrasonic assistance can also be effective in the Barbier reaction of certain heterocycles with ketones [Eq. (79); 148].



(79)

The yield of the 2-carbinol derivative is 31%, and none of the 3-carbinol is isolated.

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XI. REACTION WITH OTHER METALS AND METAL HALIDES

The Barbier reaction with other metals can occupy an entire volume on its own and, hence, will not be reviewed in this work. The interested reader should refer to the references cited at the beginning of this text and those noted in the following for additional information.

In the last 10 years, the Barbier reaction method has been utilized more with other metals than with magnesium. The number of papers published on the lithium–Barbier reaction is three to four times that of magnesium [149–157]. Reactions can be carried out at lower temperatures than possible with Mg–Barbier reactions and yields are often very high with fewer by-products. Other metals of note are samarium, in the form of its diiodide [158–165], and zine [166–169], the metal of choice for the pre-Barbier one-step reaction, and the classic Reformatsky reaction. In situ reactions have been reported for Al [170], Ce [171], Cd [172,173], Ga [174], Hg [175], In [176], Mn [177], Pb [178–180], Sb [181–183], Sn [184,185], and Ti [186]. An excellent paper by Li reviews the Barbier reactions of many metals in aqueous media [187].

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23

Grignard Reagents as Bases

WALTER KOSAR
Elf Atochem North America, Inc.
King of Prussia, Pennsylvania

I. INTRODUCTION

In addition to their well-known uses as alkylating agents, Grignard reagents have also been used as bases. There are two general classes of Grignard base reactions: metallation [Eq. (1)] and elimination [Eq. (2)]. Discrete metallated species may be used in intermolecular addition reactions, or allowed to undergo intramolecular rearrangement to the desired product. Elimination reactions involve loss of a stable magnesiate species, such as alkoxide or halide.

Metallation

$$RMgX + R'ZH \longrightarrow RH + R'ZMgX \tag{1}$$

Elimination

$$RMgX + R'CH(Z)CH_2R^2 \longrightarrow RH + ZMgX + R'HC{=}CHR^2 \tag{2}$$

Grignard reagents are very strong bases, comparable with lithium reagents, although not as widely reported. The most common example involves deprotonation of alkynes to give the acetylenic Grignard reagent [Eq. (3)].

$$RC{\equiv}CH + R'MgX \longrightarrow RC{\equiv}CMgX + RH \tag{3}$$

This class of compounds is reviewed in Chapter 32 and will not be discussed here. Physical studies of basicity will be reviewed, along with specific applications in metallation and elimination.

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II. BASICITY THEORY AND MEASUREMENT

Important parameters that determine base strength are solvent, structure, and electronegativity. Basicity is increased by polar solvents that can stabilize the anionic charge. The degree of association is also important, as monomeric organomagnesium species are more effective as bases. The ability of solvents, such as tetrahydrofuran (THF) and hexamethylphospharamide (HMPA), to stabilize monomer Grignard reagents is a major reason for the higher basicity in these solvents. Many deprotonation reactions are run in THF to take advantage of this increased basicity. The Grignard reagent may be prepared as a diethyl ether solution, but is then diluted with THF in the reaction medium to achieve the desired basicity.

Substitution on the organic moiety with electron-releasing groups also increases basicity. However, bulky groups, such as *t*-butyl, can introduce steric hindrance, thereby reducing reactivity. On the other hand, bulky groups can also introduce regioselectivity in deprotonations.

Base strength, expressed in pK_a units, has been determined electrochemically by the Chevrot group [1–4]. These studies correlate Grignard reagent basicity with the reduction potential at a hydrogen electrode. The initial study described electrochemical measurements of several Grignard reagents in THF. A dependence on partial pressure of hydrogen was noted with all compounds except *i*-PrMgCl and *t*-BuMgCl. The potentials of these Grignard reagents could not be determined with this particular method. A follow-up study showed that RMgCl compounds were stronger bases than RMgBr (Table 1). The ionic dissociation of RMgX was also proved.

These authors also compared basicities of other magnesium reagents (dialkyl, amidohalo, and alkoxyhalo) with Grignard reagents (Table 2). Excess halide ion was used to fully shift the Schlenk equilibrium to RMgX. As expected, the dialkyl magnesiums were dibasic. The dialkyl magnesiums had slightly higher pK_a values than the monoalkyl magnesium halides. The measured pK_a values different slightly from prior results [1], but fell within the ± 1 pK_a-unit variation.

Solvent coordination effects were demonstrated by addition of HMPA. Basicity increased when HMPA was added to THF Grignard solutions. This was rationalized as a complex formation between Grignard reagent and HMPA, increasing the reduction potential. A 2–5 pK_a-unit increase was observed when 1.5–2 mol HMPA was added per mole of Grignard reagent.

Table 1 Grignard Reagent pK_a Values

Grignard reagent	pK_a
CH_3MgCl	31.2
CH_3CH_2MgCl	30.1
CH_3MgBr	29.5
CH_3CH_2MgBr	29.3
$CH_3CH_2CH_2MgCl$	27.6
$CH_3CH_2CH_2CH_2MgCl$	26.8
$C_6H_5CH_2MgCl$	24.6
C_6H_5MgCl	23.9
C_6H_5MgBr	22.2

Source: Ref. 2.

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Table 2 pK_a Values of Other Magnesium Bases

Magnesium base	pK_a
$(Me)_2Mg$	30.8
$(Et)_2Mg$	30.5
PhNHMgCl	21.7
PhNHMgBr	20.7
n-BuOMgCl	15.7
n-BuOMgBr	14.1
$Mg(OH)_2$ [1]	11.0

Source: Ref. 2.

Table 3 Acidities of Grignard Base Conjugate Acids

Conjugate acid	pK_a
CH_4	≈40
CH_3CH_3	≈42
$(CH_3)_2CH$	≈44
$(CH_3CH_2CH_2)_2NH$	≈40
$(CH_3CH_2)_2NH$	≈35

III. METALLATION

The most common Grignard reagents for deprotonation are methyl, ethyl, and isopropyl. Magnesium dialkyl amides (similar to the lithium reagents) are another important class of reagents. These reagents may be easily prepared and are often commercially available. The lower alkyl derivatives form volatile by-products that are easily removed from the reaction. These simple alkyl- and amido-derivatives are also quite basic, as witnessed by the high pK_a values of the conjugate acids [5,6] (Table 3).

Alkoxymagnesium reagents are another popular basic reagent. These reagents themselves are derived by metallation of the appropriate alcohol [Eq. (4)].

$$ROH + R'MgX \longrightarrow ROMgX + R'H \tag{4}$$

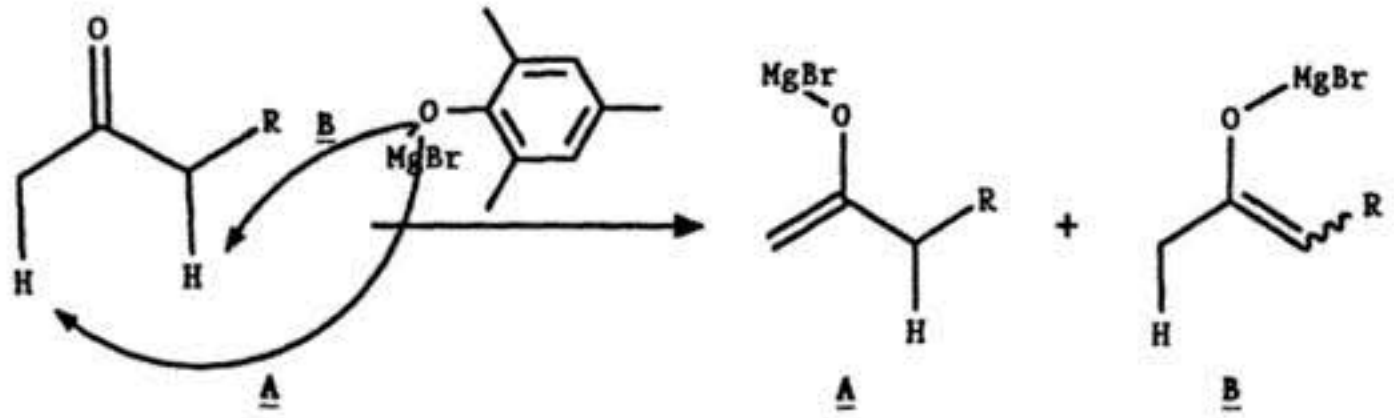
The following sections will discuss applications of Grignard reagents for metallation. The general categories are intramolecular rearrangements, enolates, and miscellaneous reactions. Eliminations are covered in a separate section.

A. Intramolecular Rearrangements

Equation (5) depicts an intramolecular Reformatsky reaction. The authors prepared the ester-substituted aziridines, then deprotonated at the α-keto- or N–H-position. The resulting anions then underwent rearrangement to open the aziridine and cyclize at the ester group, giving pyrolinone products. Use of the bulky mesityl Grignard reagent gave only products of deprotonation. Use of the less-hindered methyl Grignard reagent resulted in 45% yield of methylation at the ester position when the Grignard reagent was used in tenfold excess.

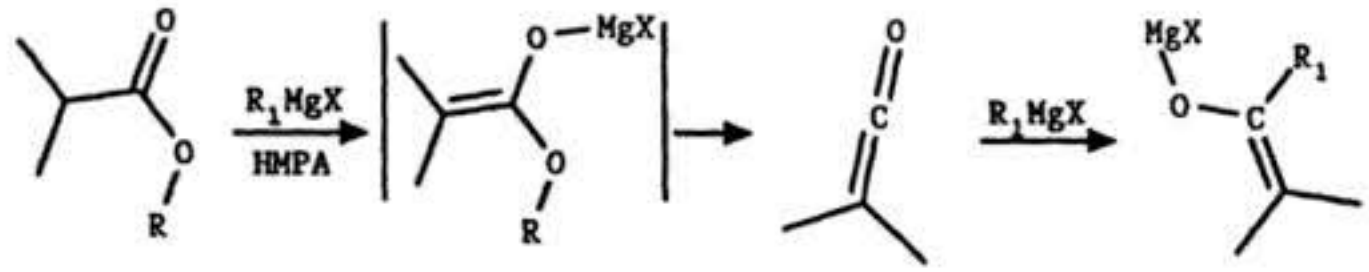
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2,4,6-Trimethylphenoxymagnesium bromide was used as the base to catalyze this aldol condensation [16; Eq. (12)]. Note that *H*-abstraction can occur at the methyl or methylene, permitting kinetic control.



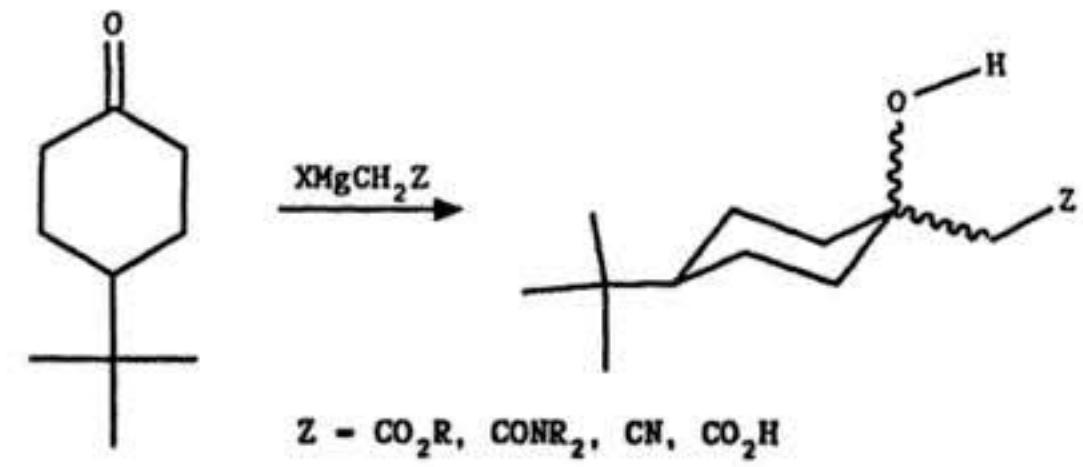
(12)

A series of Grignard reagents were reacted with aliphatic esters, and enolization occurred selectively at the less-hindered position. Interestingly, the ester enolate eliminates magnesium alkoxide, forming a ketene intermediate that reacts with a second equivalent of Grignard reagent to form keto-enolates [17; Eq. (13)].



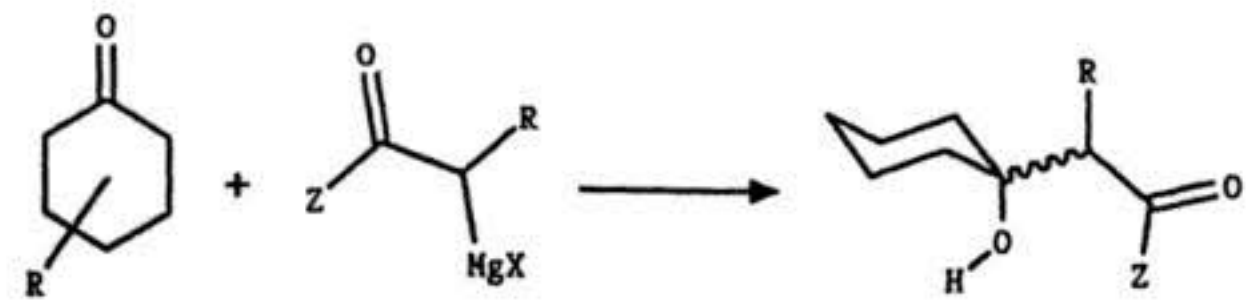
(13)

Axial versus equatorial attack of magnesium tertiary-enolates on substituted cyclohexanones is affected by solvent (i.e., HMPA increases axial substitution) [18]. Increased basicity favors axial attack. The enolates were generated by reaction of *i*-PrMgCl with *t*-butylacetate [Eq. (14)].



(14)

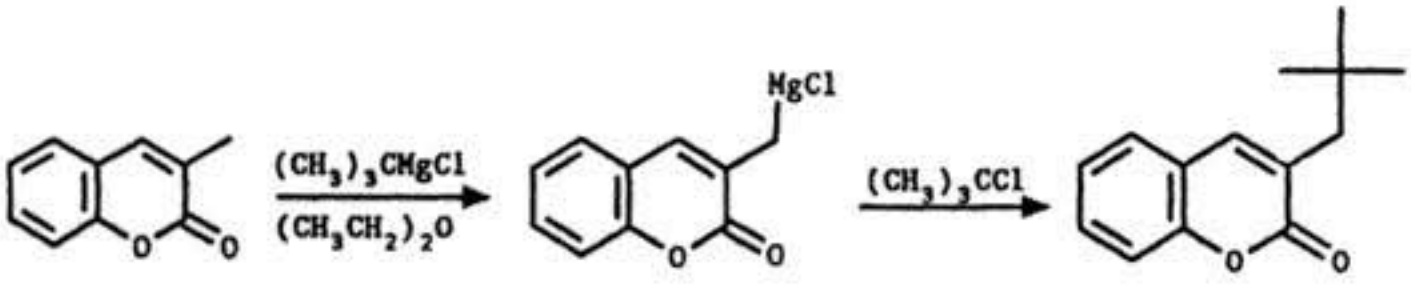
A more detailed study on selectivity of Grignard enolates reacting with *t*-butylcyclohexanone was conducted [19,20; Eq. (15)]. The enolates were acetic acid derivatives: ethyl



(15)

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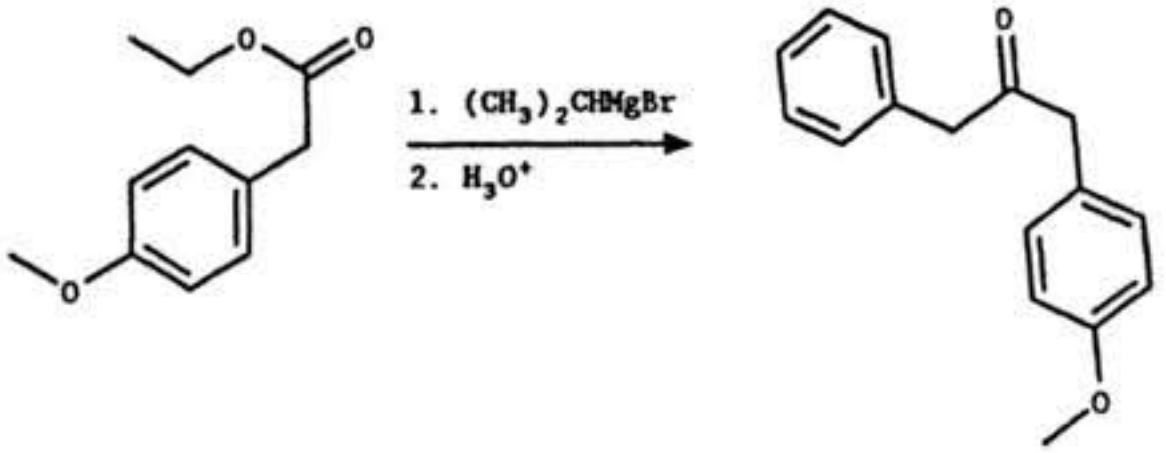
The regiochemistry of Grignard reagent attack on coumarins was evaluated using both theoretical and laboratory experiments [23; Eq. (16)]. The calculated nucleophilicity of the Grignard reagents, along with orbital energies of substituted coumarins, provided a theoretical basis to estimate points of reaction. Deprotonation occurred along with addition. Grignard reagents studied included *t*-BuMgCl, *i*-PrMgCl, diisopropyl magnesium, *s*-BuMgCl.



(16)

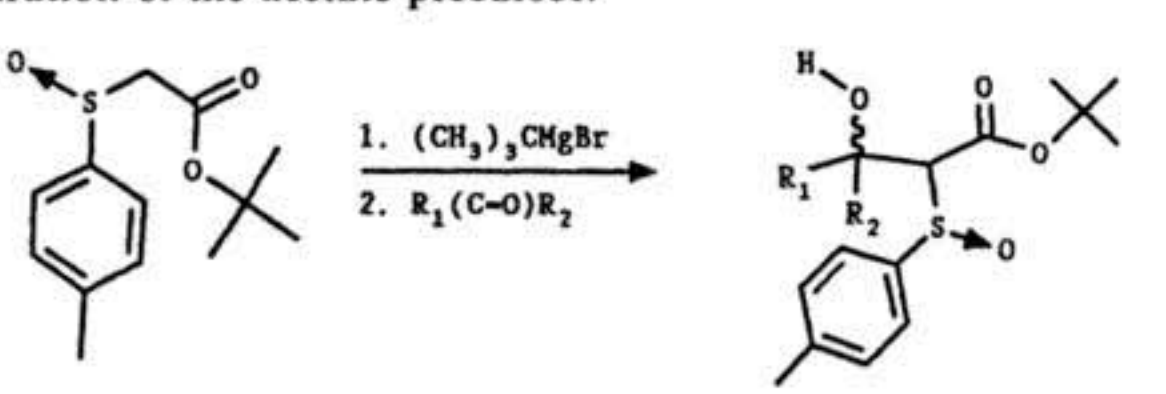
2. General Synthesis with Magnesium Enolates

Deprotonation of an ester led to a Claisen condensation, giving a bis-anisylketo ester intermediate [24]. Acidification and thermal decarboxylation led to the desired bis-anisylketone [Eq. (17)]. This product was an intermediate to a bicyclo[3.2.1]octadiene derivative used in a study of anionic homoaromaticity.



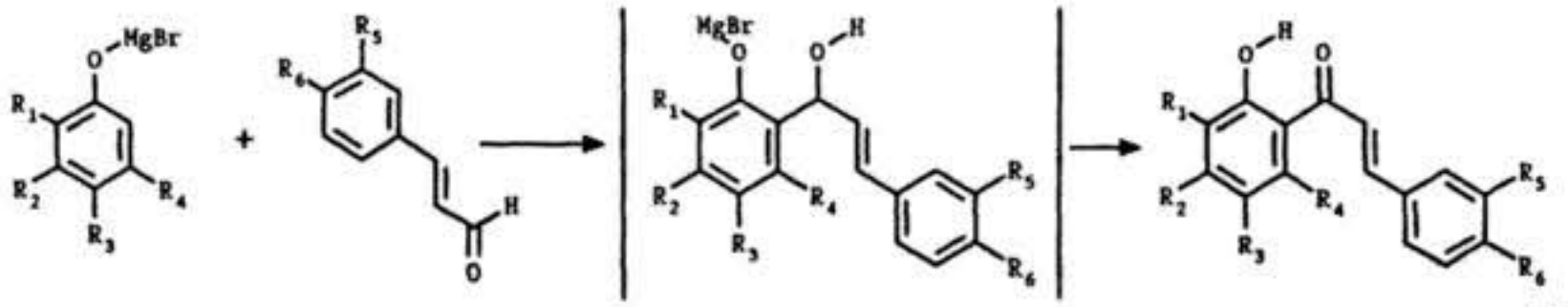
(17)

Stereospecific aldol synthesis of β-hydroxy acids derived from (*R*)−(+)-*t*-butyl-*p*-tolysulfinyl acetate has been reported [25; Eq. (18)]. The *t*-BuMgBr was crucial to the enolate generation without racemization. Magnesium diisopropylamide was used in preparation of the acetate precursor.



(18)

Equation (19) displays a regioselective route to 2′-hydroxychalcones by magensium phenoxides [26]. Selective 1,2-addition resulted from reaction of bromomagnesium

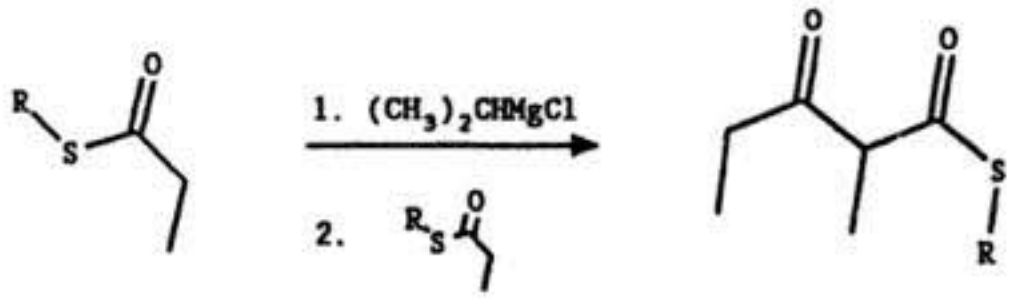


(19)

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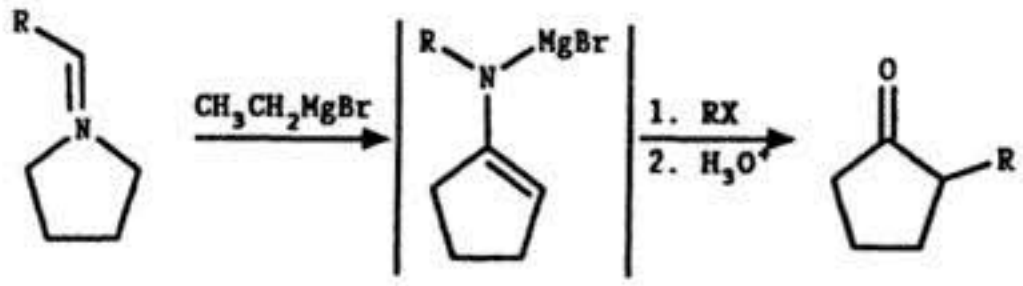
phenoxide on cinnamic aldehyde. The magnesium was critical in coordinating the phenoxide and aldehyde oxygens to direct regiochemistry. A tertiary amine was also required to obtain the desired selectivity. EtMgBr deprotonated the phenols to generate the phenoxides.

An example of a magnesium thioester enolate is shown in Eq. (20) [27]. These enolates were generated by reaction of thioesters with several bases, including *i*-PrMgCl, Et_2NMgBr, and EtSMgCl. The thioester enolates were used in subsequent Claisen condensations.



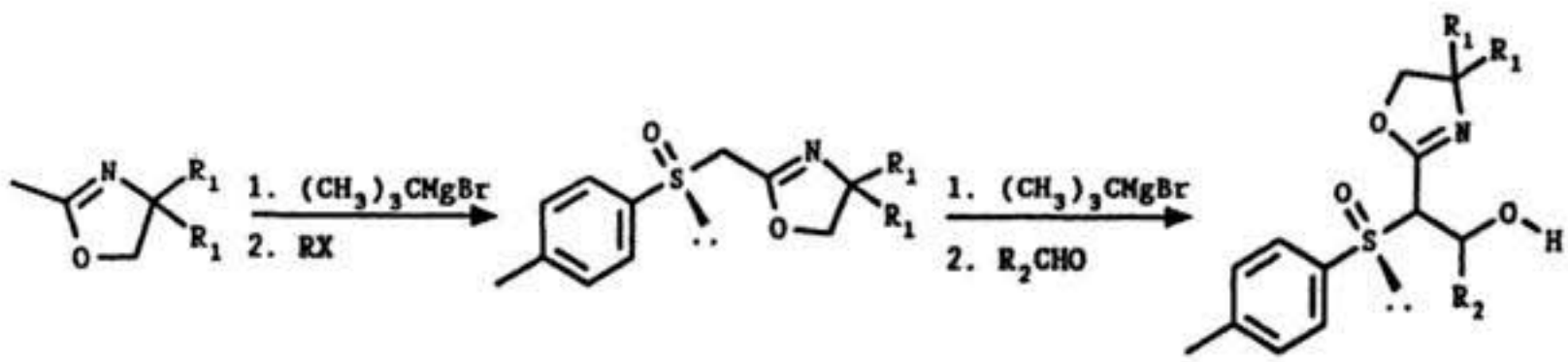
(20)

Eneamine chemistry, using Grignard reagents as bases, has been reviewed [28; Eq. (21)]. Included is the chemistry of eneamine anions generated from Grignard bases (usually EtMgBr and *i*-PrMgBr). These magnesium eneamine anions are effective in alkylations, although they require higher reaction temperatures than lithium anions.



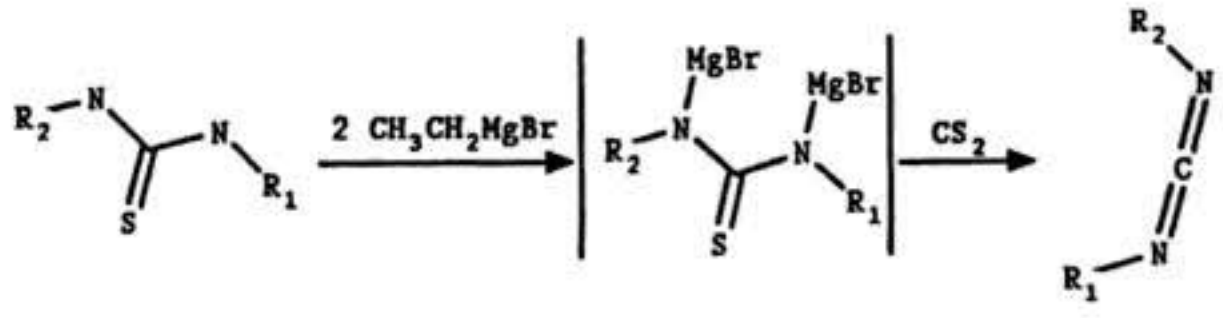
(21)

Magnesium-eneamides can be used in the synthesis of a chiral oxazoline [29; Eq. (22)]. *t*-Butylmagnesium bromide was used to deprotonate the starting eneamine. The chelating nature of the magnesium resulted in partial racemization, giving lower optical yields compared with lithium-eneamine.



(22)

Thioureas are metallated by ethylmagnesium bromide [30; Eq. (23)]. The magnesium-thiourea is then converted to a carbodiimide by reaction with carbon disulfide. Lithium-thioureas can also be used, but give good yields only with bulky substituents on the thiourea. Less hindered lithio-thioureas undergo reaction to give isothiocyanates, which the magnesio-derivatives do not.

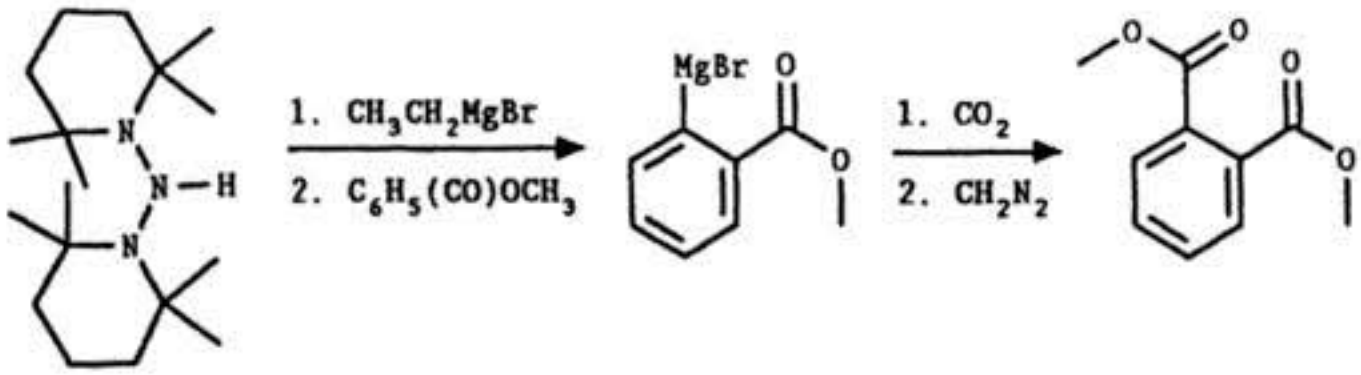


(23)

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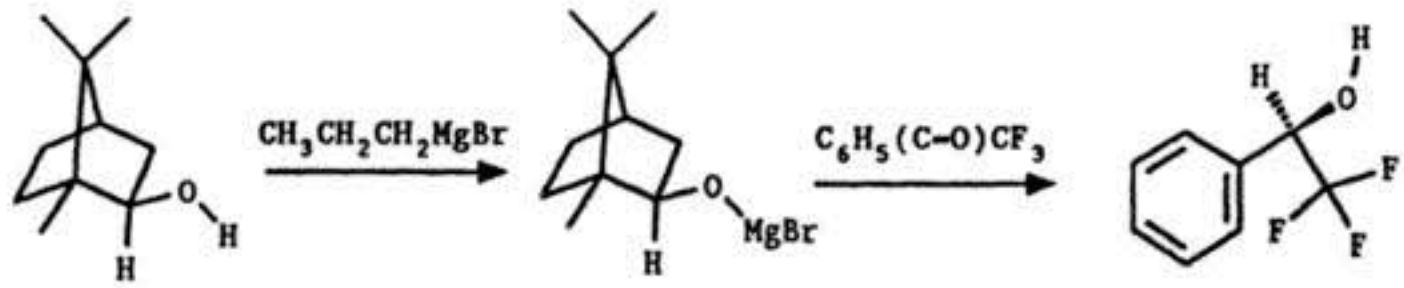
C. Miscellaneous Reactions

Magensium amides have been prepared and studied for use as bases [31; Eq. (24)]. Unlike lithium amides, these bases are much more thermally stable. The amine derivatives diisopropyl and tetramethylpiperidyl were deprotonated using either ethylmagnesium bromide or dibutylmagnesium.



(24)

Propylmagnesium bromide deprotonates several chiral alcohols (borneol, isoborneol, 1-phenylethanol, *p*-methan-3-ol). These chiral magnesium alkoxides are used for asymmetric reduction of phenyl-trifluoromethylketone [32; Eq. (25)]. The magnesium alkoxides generally give poorer asymmetric induction than aluminum derivatives.

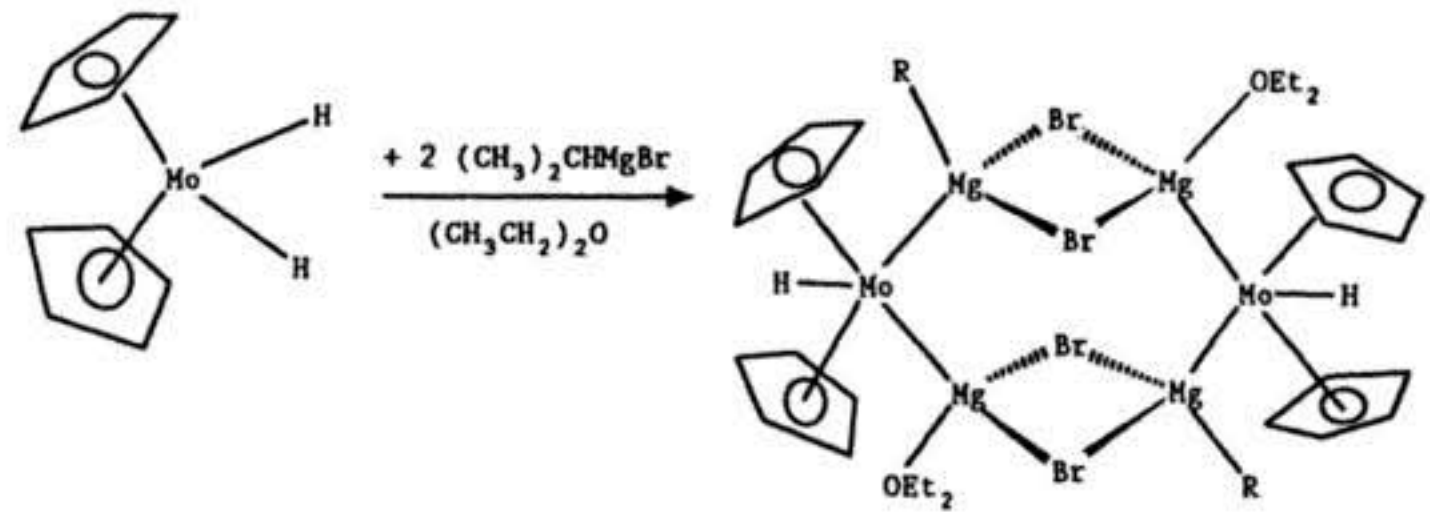


(25)

Alkoxy magnesium halides are prepared by either alcoholysis of Grignard reagents (MeMgI, BuMgCl, MeOH, EtOH, *n*-PrOH, *t*-BuOH) or pyrolysis of $Mg(OR)_2/MgX_2$ "cements." Alcoholysis proceeds by way of alkoxy–halide exchange, rather than simple 1:1 deprotonation [33; Eq. (26)]. Bulkier alcohols reacted more completely owing to lower solvation of magnesium salts.

$$2RMgCl + R'OH \longrightarrow R'OMgR + RH + MgCl_2 \qquad (26)$$

In diethyl ether, *i*-PrMgBr partially deprotonates a molybdenum dihydride complex, forming a dimagnesio–molybdenum dimer [34; Eq. (27)]. The complex contains *i*-PrMgBr coordinated through halogen bridges to another metal-bound magnesium. In THF, this complex breaks down into a much simpler Mo–MgBr complex.

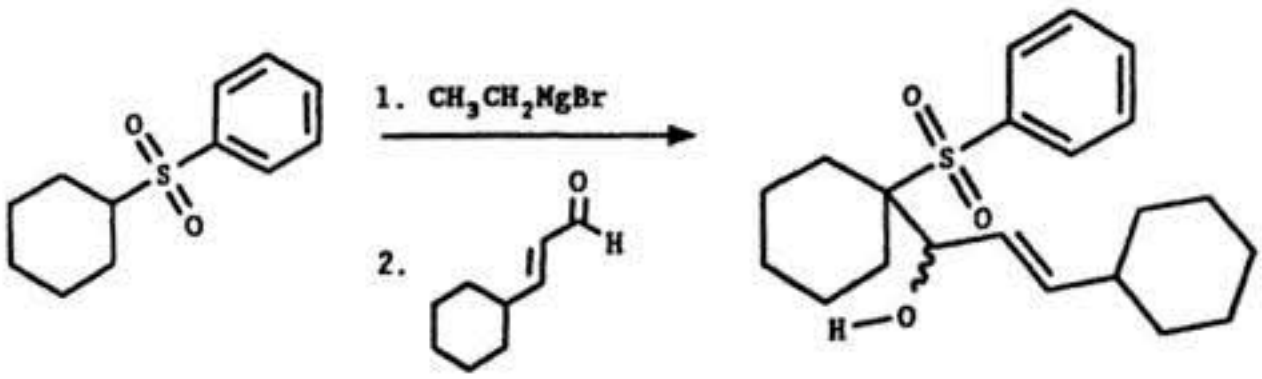


(27)

Olefins can be prepared from β-hydroxysulfones [35]. The hydroxyfulsones are prepared by alkylation of metallated sulfones using various aldehydes [Eq. (28)]. Both magnesium and lithium sulfones were evaluated, and the magnesium sulfones had the

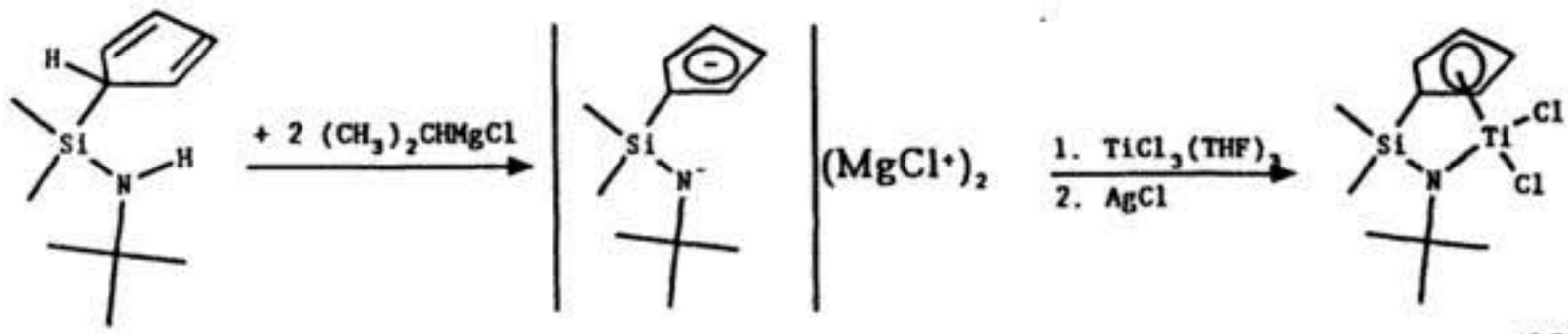
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advantage of suppressing enolization during reaction with the aldehyde. Ethylmagnesium bromide was used as the base.



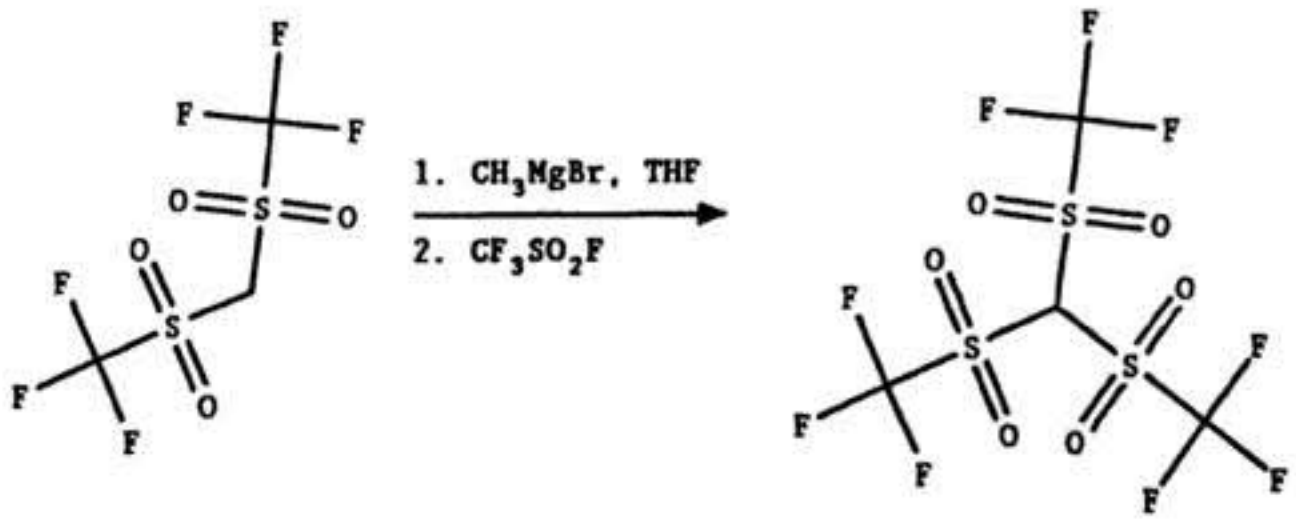
(28)

Isopropylmagnesium chloride is used to deprotonate the N–H and α-silyl ring proton of $Me_2Si(Me_4HC_5)$ (HN-*t*-Bu) [36]. This magnesium dianion is then reacted with $TiCl_3$ [Eq. (29)]. The product complex is used as an olefin polymerization catalyst.



(29)

Methylmagnesium chloride is used to deprotonate $CH_2(SO_2CF_3)_2$. The anion is then alkylated with CF_3SO_2F [37; Eq. (30)]. Subsequent treatment with LiOH gives the lithium salt that is used as an electrolyte in conducting polymer films.

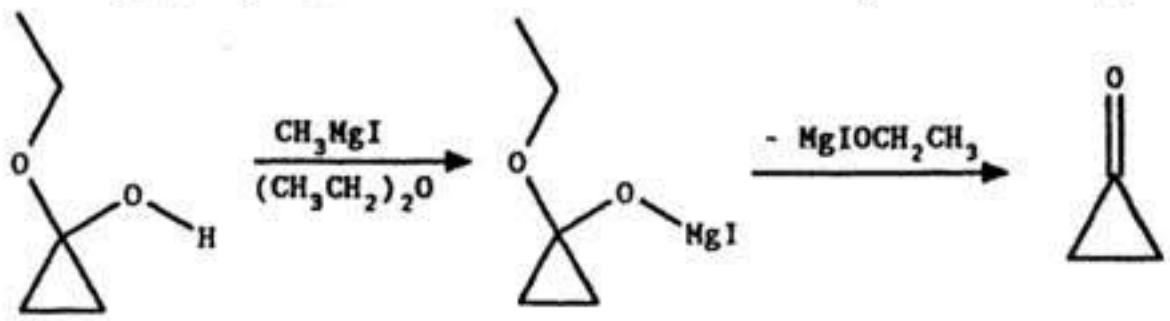


(30)

IV. ELIMINATIONS

The second major application for magnesium bases is elimination. The strong basicity of Grignard reagents allows a greater degree of elimination than do weaker bases,

1-Aryl-1-cyclopropanols are prepared by a Grignard base elimination process [38; Eq. (31)]. The key step is ethoxide elimination from the magnesium alkoxide intermediate. The resulting cyclopropanone is then reacted with aryl lithiums to give the final product.



(31)

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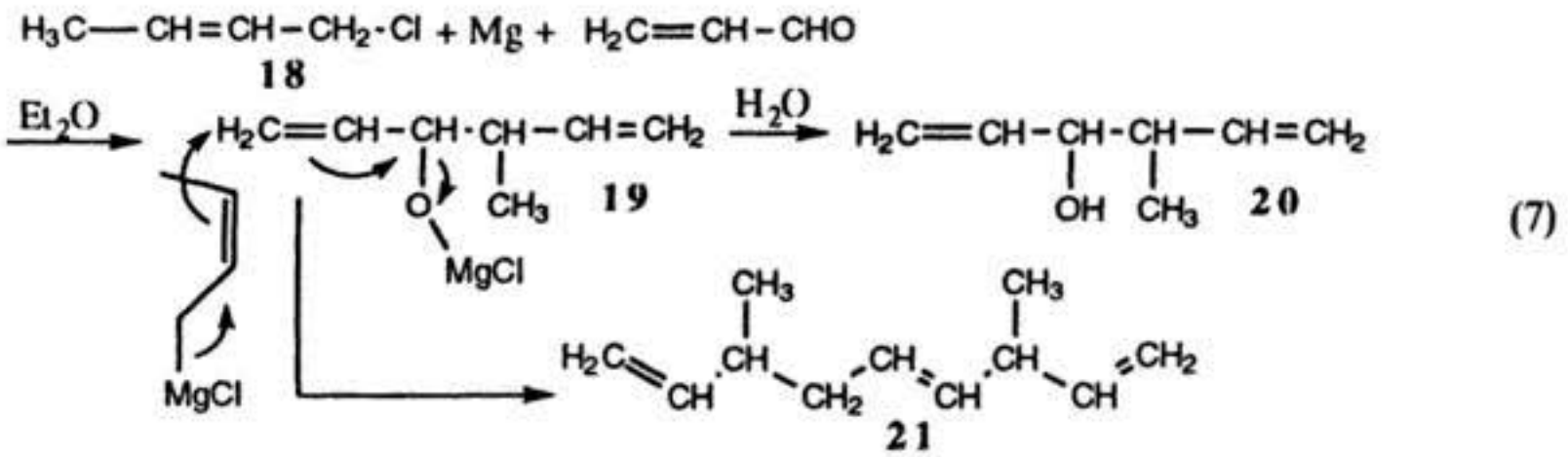
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Table 1

Diethyl phosphate	RMgX	Yield (%)	13	E/Z	14
Geranyl 11	n-$C_6H_{13}MgBr$	89	92	100/0	8
Geranyl 11	PhMgBr	97	99	99/1	1
Geranyl 11	CH_2=$CHCH_2MgBr$	80	100	100/0	0
Geranyl 11	$PhCH_2MgBr$	79	99	99/1	1
Geranyl 11	PhC≡CMgBr	72	100	99/1	0
Neryl 12	n-$C_6H_{13}MgBr$	87	89	0/100	11
Neryl 12	PhMgBr	92	99	4/96	1
Neryl 12	CH_2=$CHCH_2MgBr$	77	100	0/100	0
Neryl 12	$PhCH_2MgBr$	72	98	1/99	2
Neryl 12	PhC≡CMgBr	66	100	4/96	0

C. Allylic Ethers

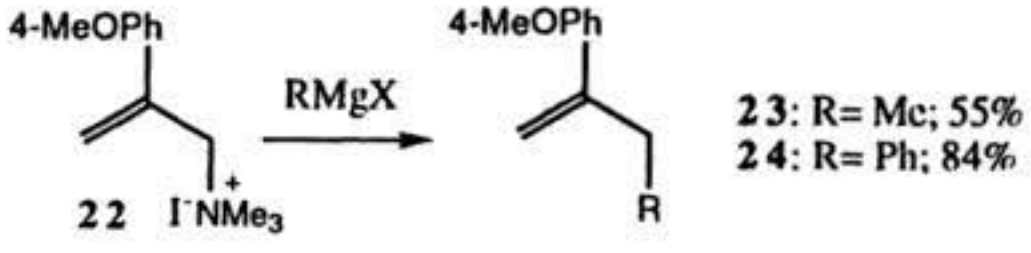
In the early 1940s, Luttringhaus [17] indicated that certain aryl allyl ethers and thioethers react with phenyl and alkyl Grignard reagents. Hill [18] has shown that n-heptylmagnesium bromide reacts with n-butyl γ-phenyl allyl ether to afford 52% of S_N2' product, namely 3-phenyl-1-decene. Richet and Pecque [19] observed that in Barbier conditions, crotyl chloride **18**, on reaction with magnesium and acrolein in diethyl ether, can afford either the expected alcohol **20** (in 70% yield) or a triene **21** (~15%) owing to the attack of the alkoxide **19** first formed by an allylic Grignard intermediate [Eq. (7)].



(7)

D. Allylic Ammonium Salts

Gupton [20] reported that allylic diethyl amines do not react with Grignard reagents, even in the presence of a catalytic amount of CuI. However, their corresponding quaternary ammonium salts **22** were effective reactants with methylmagnesium bromide and phenylmagnesium chloride, since the expected products **23** and **24** were obtained, after purification, in 55 and 84% yield, respectively [Eq. (8)]. Unfortunately, the regiochemistry was not studied because of the symetric nature of the starting material; therefore, the S_N2 or S_N2' mechanism by which the process does occur, cannot be certified.

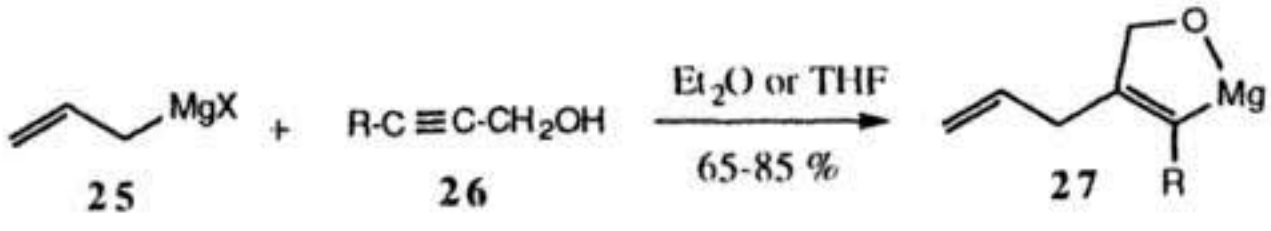


(8)

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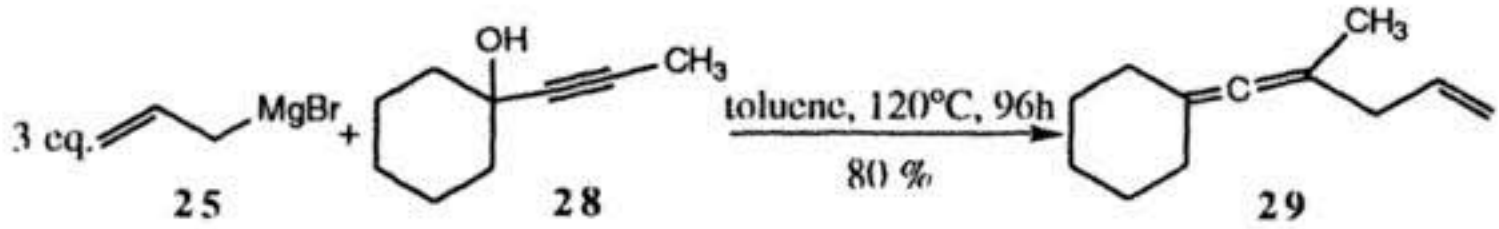
E. Propargyl Alcohols

The enhanced activity of allylic Grignard reagents enables them to react with acetylenic alcohols by an *anti*-addition [21]. In oxygenated solvents (Et_2O or THF), reactions occur regioselectively by oxygen assistance to give the desired carbometallation reaction product [Eq. (9)].



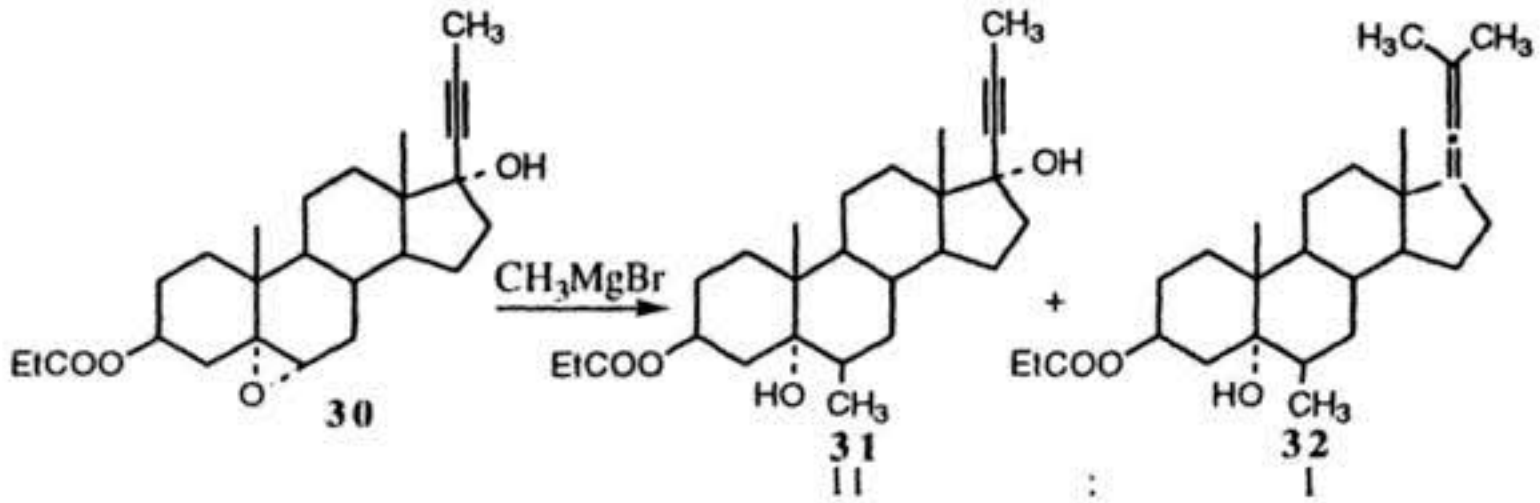
25 26 27 (9)

In toluene at 120°C, the reaction of allylmagnesium bromide **25** with propyn-1-cyclohexanol **28** lead to the S_N2' product **29** in 80% yield [22; Eq. (10)].



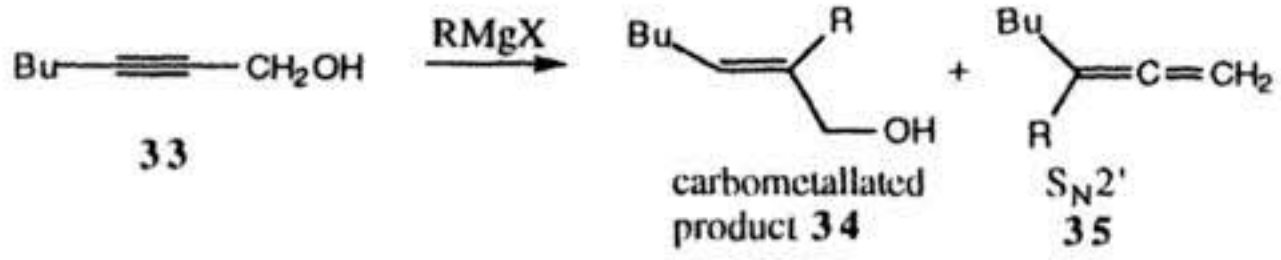
25 28 29 (10)

Van Dijck et al. [23] reported the formation of the S_N2' product **32** by reaction of methylmagnesium bromide with 5,6β-epoxy-17α-propynyl-androstane, 3β, 5α, 17β-triol **30** [Eq. (11)].



30 31 : 32 (11)

Gouin [24] also reported that alklymagnesium halides, after addition to heptyn-2-ol **33**, can to some extent give rise to the S_N2' products **35**; namely, the allenic derivatives, as by-products of the carbometallation reaction [Eq. (12)].



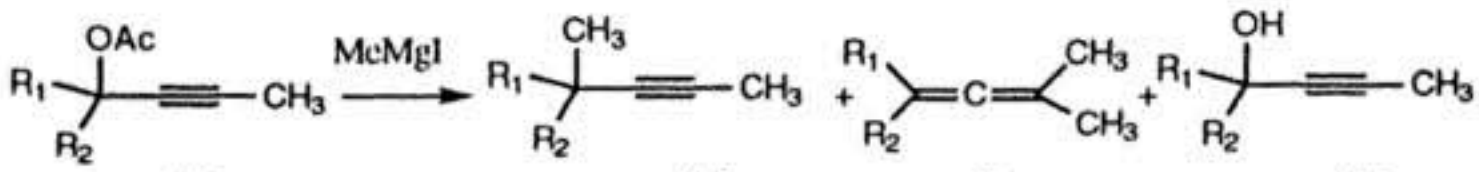
33 carbometallated product **34** S_N2' **35** (12)

F. Propargyl Halides

Propargyl halides have been used by Campbell [25] and by Banigan [26] to prepare acetylenic hydrocarbons. For example, Banigan prepared di-*t*-butylacetylene by reaction of methylmagnesium bromide with *t*-butyl-ethynyldimethylchloromethane [26]. However, 10% of the final product was an unidentified compound. Meyers [27] tentatively identified

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resulting from the attack of the acetate function [Eq. (15)].

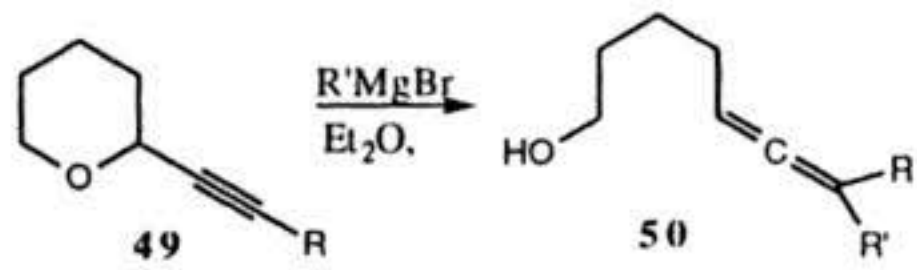


	45	46	47	48
$R_1=R_2=CH_3$		32	38	17
$R_1=R_2=-(CH_2)_4-$		24	35	22

(15)

H. Propargyl Ethers

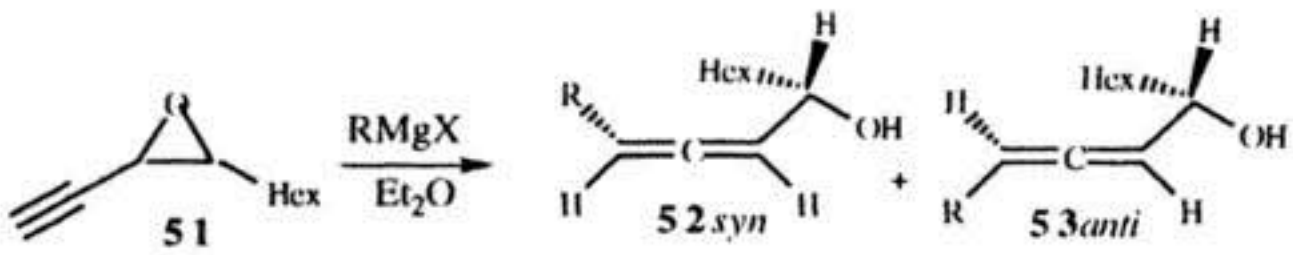
Nelson [31] reported that 2-alkylethynyl- or 2-arylethynyl tetrahydropyrans **49** treated, by Grignard reagents for 24 hr at room temperature in Et_2O, lead to high yields of S_N2'-coupled products **50**; namely, the 5,6-allenic alcohols [Eq. (16)].



(16)

I. Propargyl Oxiranes

Alexakis [32] reported that propargyl oxiranes **51** readily reacted with Grignard reagents to afford exclusively the S_N2' products; namely, the allenic derivatives **52** and **53** [Eq. (17) and Table 2].



(17)

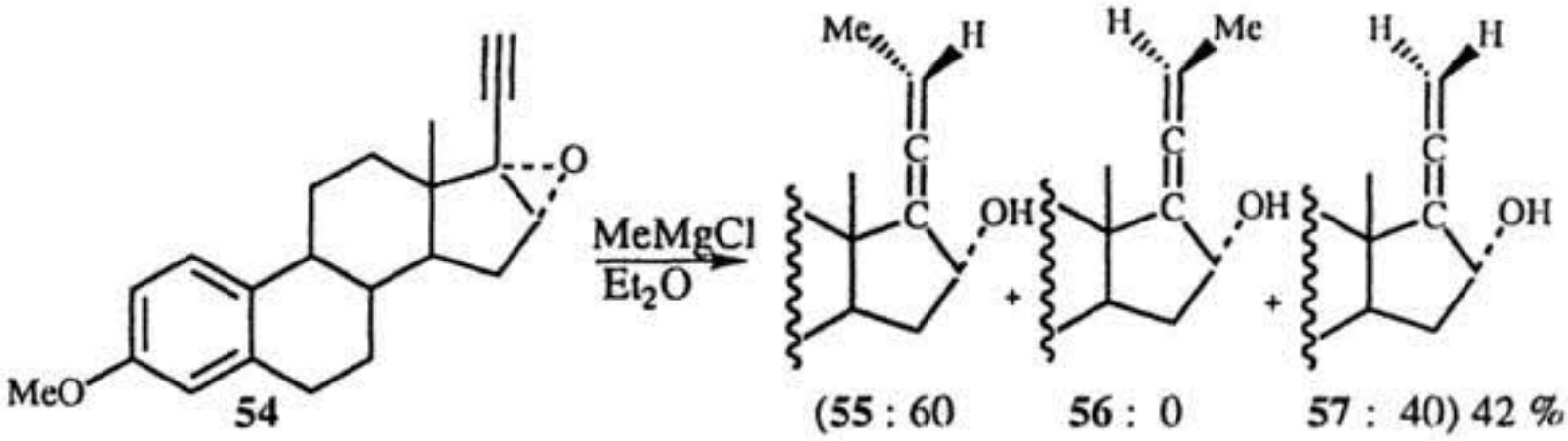
It is noteworthy that *cis*-epoxides lead to the *anti*-allenic product as the major compound, but the nature of the Grignard reagent halide can reverse the selectivity when bromide is used. For *trans*-epoxides, the *syn*-product is always the major compound, whatever the nature of the counterion. In the steroid series [33], the cross-coupling of a

Table 2

Epoxide	RMgX	Yield **52**+**63** (%)	*anti*/*syn*
cis	*n*-PentMgCl	92	81:19
cis	*n*-PentMgBr	91	38:62
cis	*t*-BuMgCl	93	83:17
trans	*n*-PentMgCl	94	4:96
trans	*n*-PentMgBr	93	14:86
trans	*t*-BuMgCl	92	6:94

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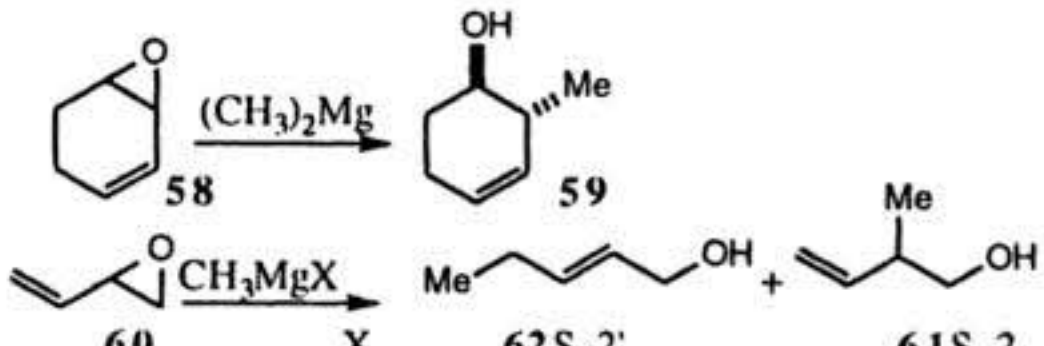
Grignard reagent with alkynyl oxiranes **54** is also very regioselective toward the S_N2' product **55**, and the *syn*-process is the sole process observed [Eq. (18)].



(18)

J. Vinyl Oxiranes

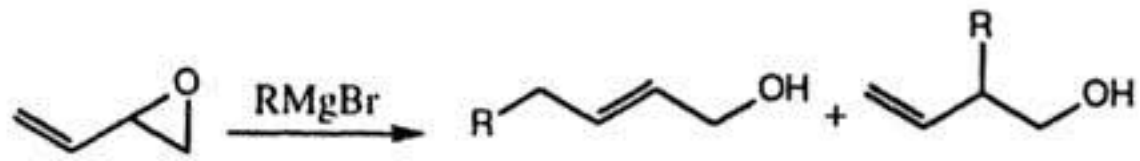
Rickborn [34] reported that 3,4-epoxycyclohexene **58**, on addition of Grignard reagent, gave only the S_N2 product **59** in 95% yield [see Eq. (11)]. Whereas Johnson [35] found that butadiene monoepoxide **60** reacted with methylmagnesium halides, affording the S_N2/S_N2' products **61** and **62**, respectively, with a ratio that strongly depended on the nature of the halide [Eq. (19)].



X	62 S_N2'	61 S_N2
I	68	22
Br	44	36
Cl	21	74

(19)

Anderson [36] reported that the product distributions of the reaction of butadiene monoepoxide **60** with Grignard reagents are also dependent on the nature of the Grignard reagent [Eq. (20)], which has been also observed by Rose et al. [37].



R	63 S_N2'	64 S_N2
Ethyl	30	35
n-Butyl	56	22
Phenyl	8	84

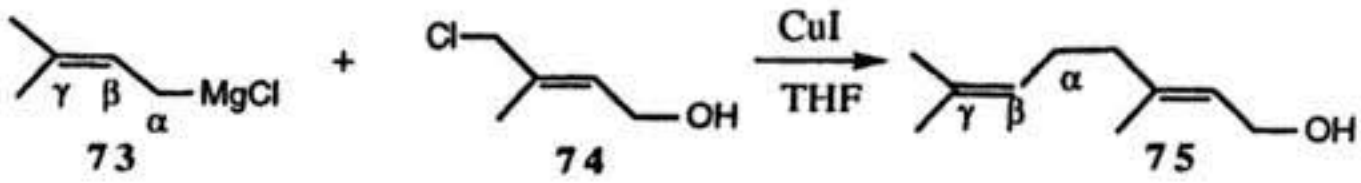
(20)

K. Intramolecular Reactions

Fischer and Howden [38] found that β,γ-unsaturated Grignard reagents bearing a δ-alkoxy group undergo an interesting organometallic rearrangement, with a carbon–carbon bond formation of a three-membered ring. In an acyclic example, halides **65** or **66**, when treated with magnesium turnings and ethyl bromide in anhydrous THF and heated to reflux of

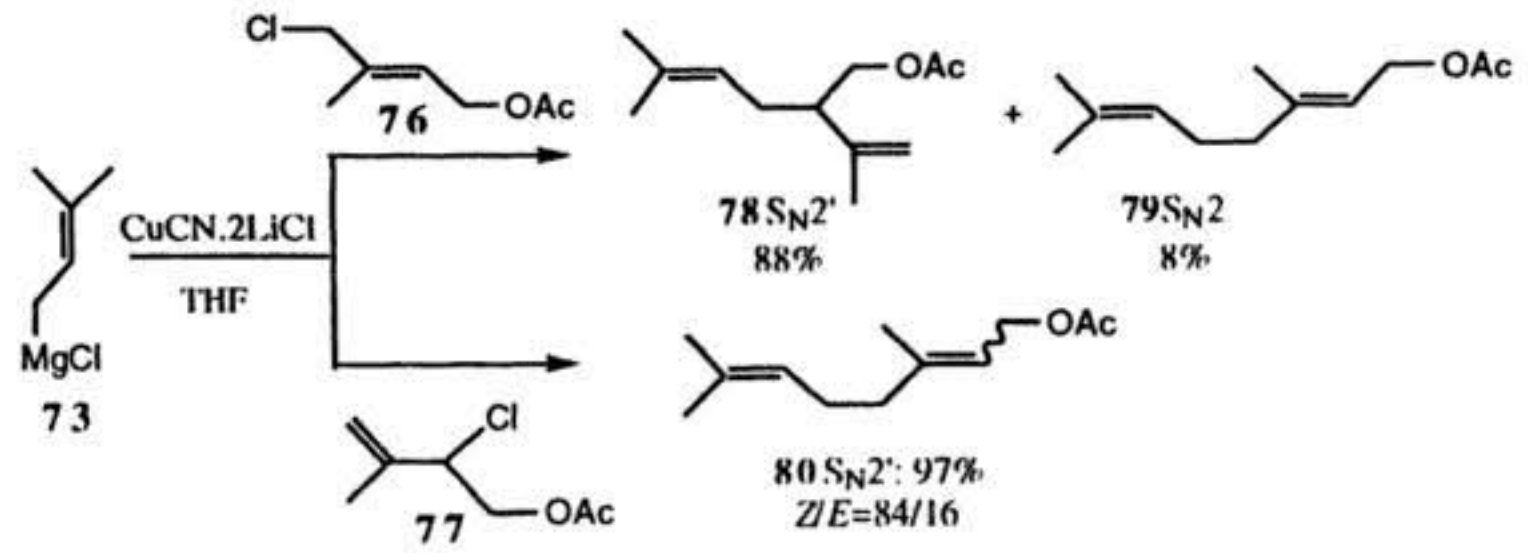
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[Eq. (23)].



(23)

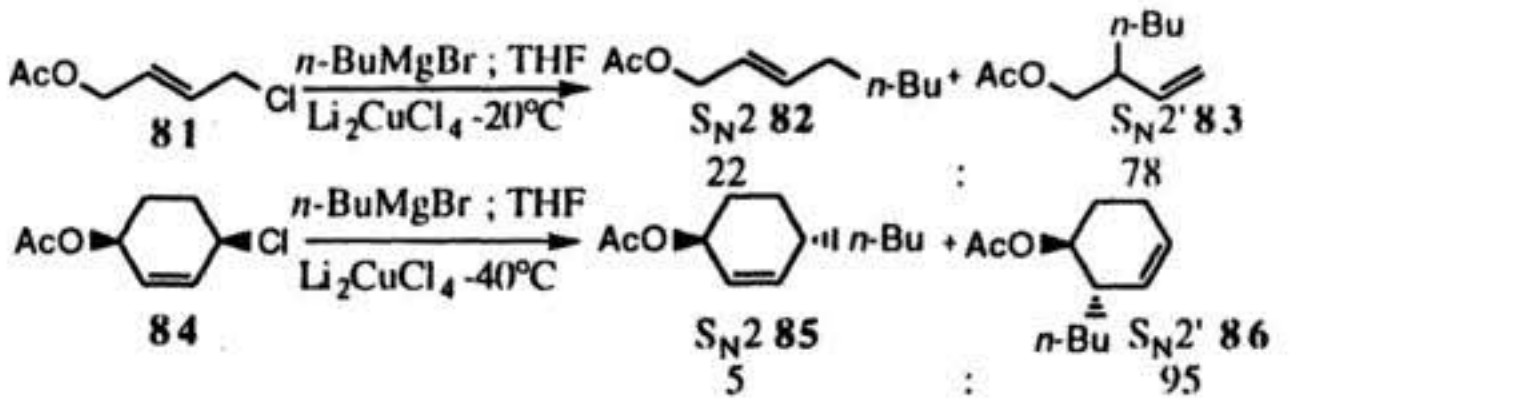
A complete reversed selectivity has been observed by Yamamoto [46] who, more recently, reported the chemoselective reaction of prenyl Grignard reagent **73** with primary allylic chlorides **76**, versus allylic acetates in the presence of CuCN·2LiCl at 0°C to give the S_N2' product **78** with high selectivity, as shown in Eq. (24).



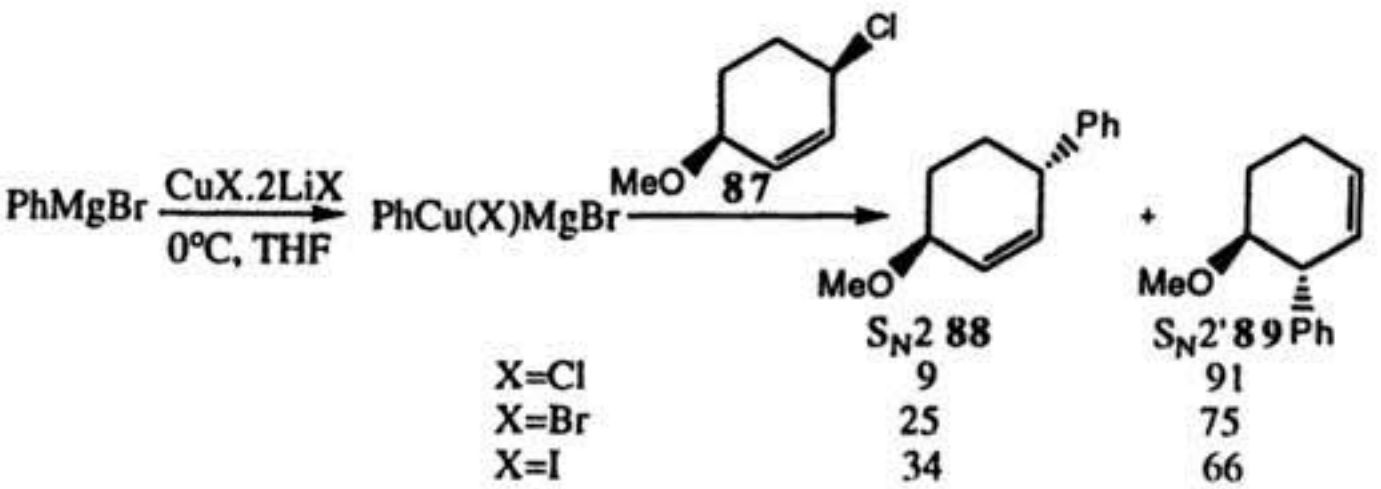
(24)

Furthermore, for secondary allylic chlorides **77**, addition of the same Grignard reagent **73** in the presence of a catalytic amount of CuCN·2LiCl, shows an even higher selectivity in favor of the S_N2' product **80**, but with a moderate stereoselectivity for the double bond ($Z/E = 84{:}16$) [see Eq. (24)].

Bäckvall [47] studied the chemo- and regioselectivity of the substitution of allylic chlorides in the presence of allylic acetates by Grignard reagents in the presence of a catalytic amount of Li_2CuCl_4 and showed that the reaction was chemoselective (the acetate function remains unchanged), and the regioselectivity was in favor of the S_N2' product. In the cyclic compound, the reaction was also *anti*-selective [Eq. (25)].



(25)



	S_N2 88	S_N2' 89 Ph
X=Cl	9	91
X=Br	25	75
X=I	34	66

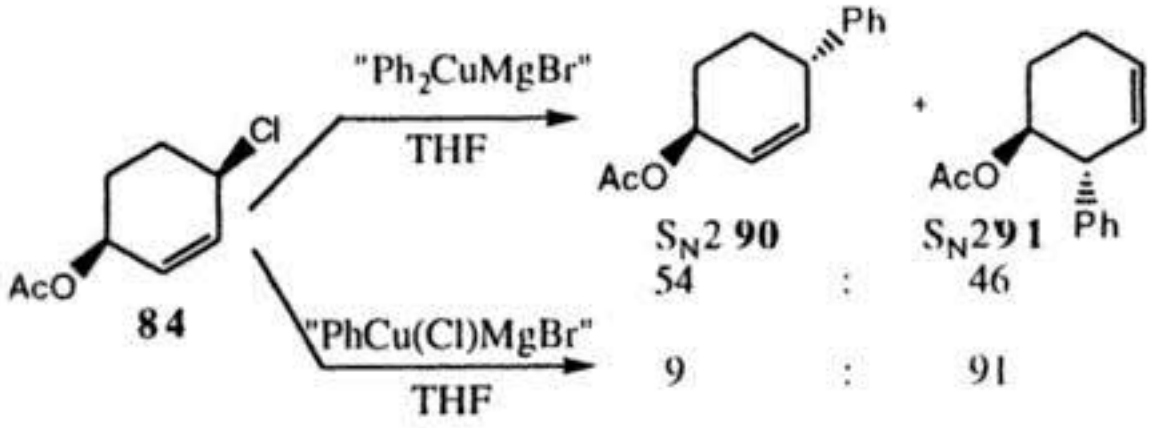
(26)

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Bäckvall [48] also studied the reactivity of ArCu(X)MgBr toward the allylation with acetoxy-4-chloro-1-cyclohexene-2 **87** as a function of the nature of the halide X in the initial copper salt used for the preparation of the organometallic species. This study shows the great influence of the halide on the product distributions of the reaction [Eq. (26)].

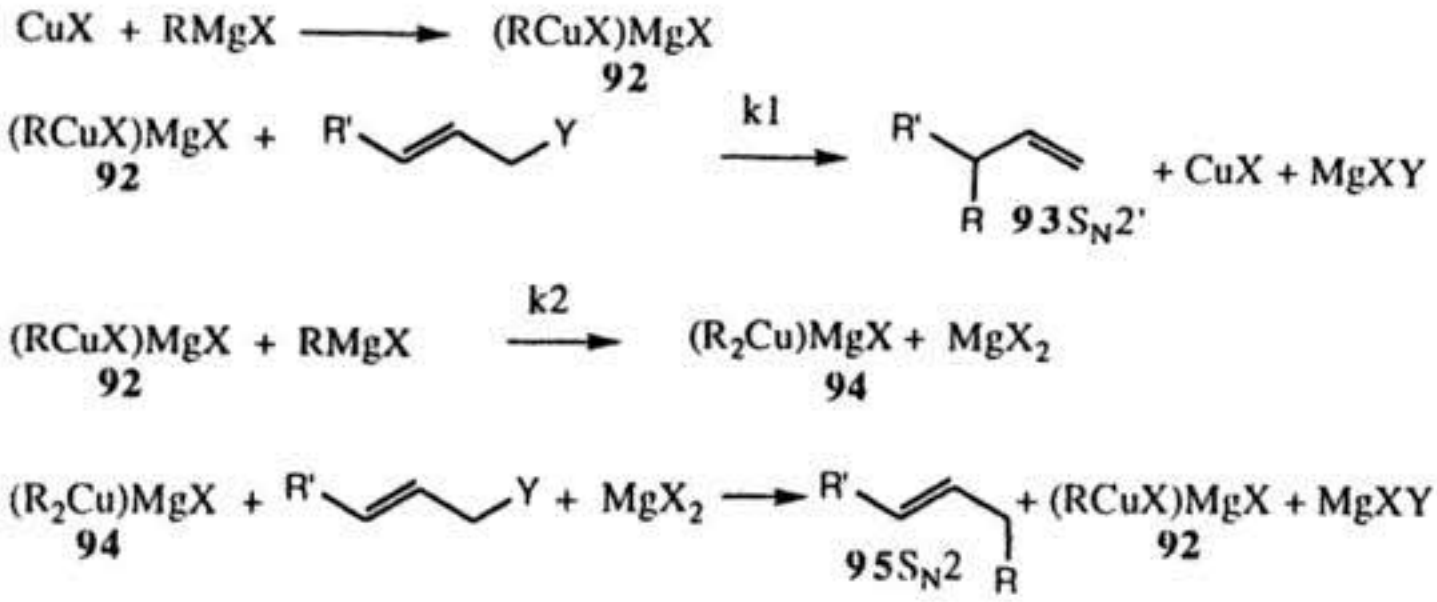
The formation of the S_N2' product **89** decreases with the electronegativity of the counterion of the copper species.

The regioselectivity of the alkylation of preformed organocopper species also depends on the nature of this organocopper species [48]. The organocopper complexes Ar_2CuMgX and ArCu(Cl)MgX were obtained by reaction of ArMgBr with CuCl·2LiCl in a 2:1 and 1:1 molar ratio, respectively. Reaction of $Ph_2CuMgBr$ with the cyclic allylic chloride **84** afforded a 54:46 mixture of S_N2 and S_N2' products **90** and **91**, whereas, with PhCu(Cl)MgBr, a regioselective S_N2' substitution (91%) occurred as shown in Eq. (27).



(27)

The regioselectivity of the reaction also seems to be strongly correlated to the addition time of the Grignard reagent [47], as shown in the following study [Eq. (28)]

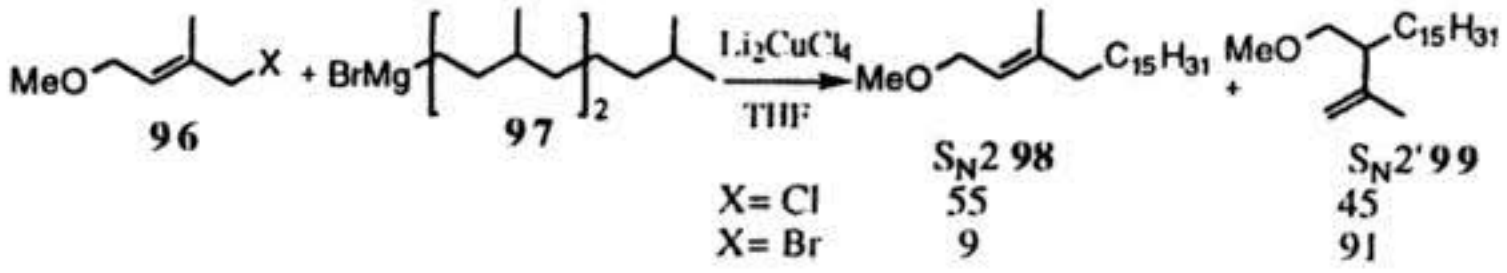


(28)

Monoalkylcopper complexes preferentially give S_N2' alkylation of allylic substrates [see Eq. (27)], whereas dialkylcuprates favor S_N2 with primary allylic substrates [47,48]. Consequently, if the Grignard reagent is added slowly or $k_1 > k_2$, the monoalkylcopper species **92** will predominate, and the major compound will be the S_N2' product (higher temperature, more catalyst, and a substrate reacting rapidly with **92** will increase the S_N2' product).

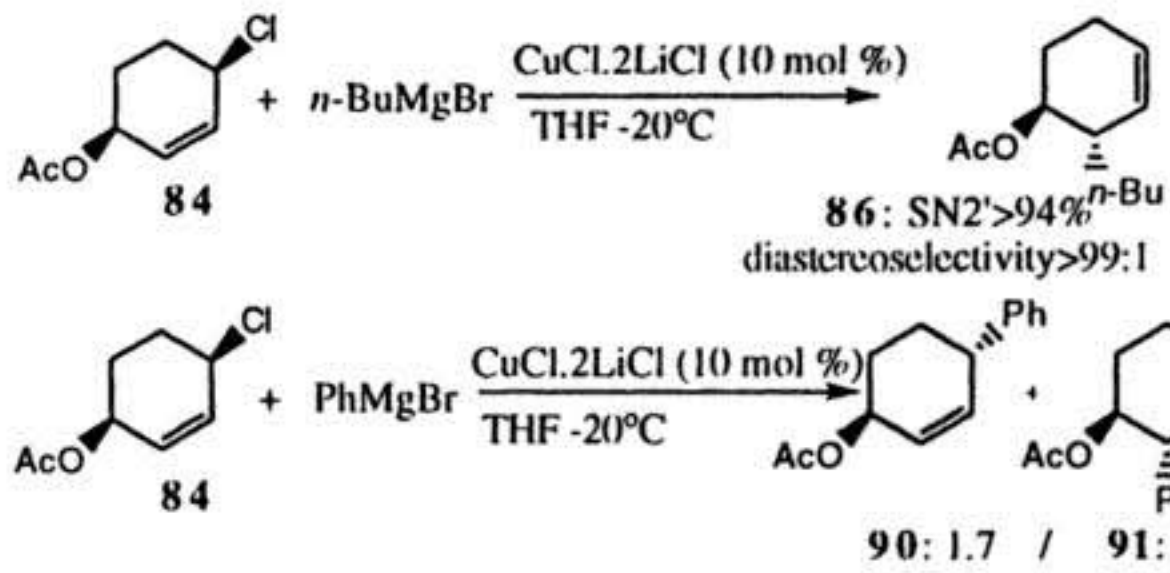
In the same manner, if the Grignard reagent is added rapidly or $k_2 > k_1$, the dialkylcopper species **94** will be in the majority, consequently, the S_N2 product will be enhanced. As an illustrative demonstration of such conclusions, a more reactive allylic halide should give a high degree of the S_N2' product, and by changing the nature of this halide from Cl to Br, the S_N2'/S_N2 ratio should be modified. That was previously observed by Schmid [49] in the following example [Eq. (29)].

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(29)

Bäckvall [48] also showed that the regioselectivity of the reaction of addition of a Grignard reagent on a cyclic allylic chloride in the presence of CuCl · 2LiCl, can be influenced by the nature of the organomagnesium species [Eq. (30)].



(30)

With phenylmagnesium bromide the reactions is less regioselective (1.7:1) in favor of the S_N2' product than with butylmagnesium bromide, but the attack is in both cases *anti*-selective.

The study of the addition time of aryl magnesium bromides on allyl chlorides shows that the addition time plays a significant role on the S_N2/S_N2' ratio [48] since a fast addition (1 min) gave a 60:40 ratio and a slow addition (10 hr) 27:73.

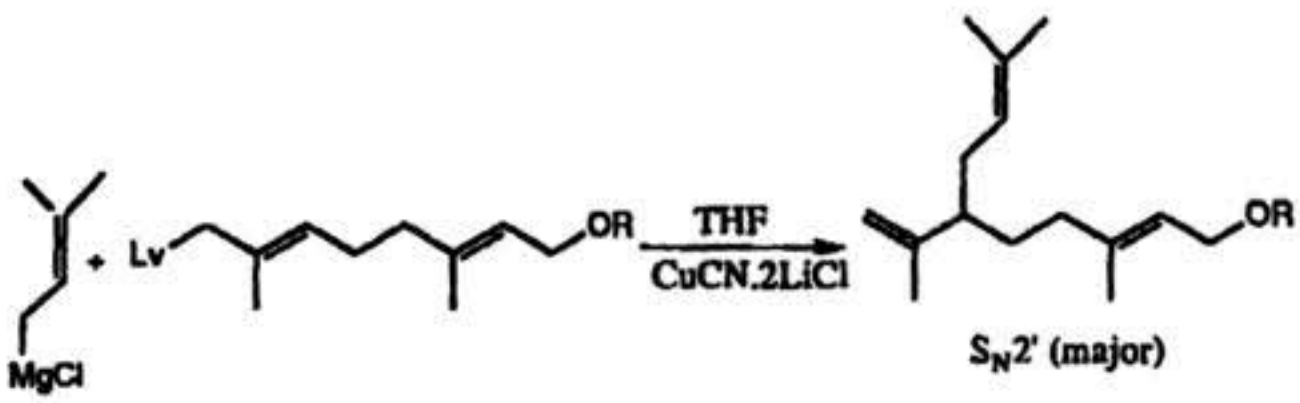
Temperature is also crucial [48] since the $S_N2:S_N2'$ distribution changed from 51:49 at $-43°C$ to 26:74 at 50°C.

For the same reaction, the variation of the amount of CuCl · 2LiCl was studied and shows a significant modification of the products distribution [48] since with 0.05 Eq. of CuCl · 2LiCl, the $S_N2:S_N2'$ ratio is 45:55 whereas for 1 Eq. of CuCl · 2LiCl, the same ratio is 26:74.

B. Allylic Phosphates

The use of the phosphate leaving group gives better results for both the stereoselectivity and the S_N2'/S_N2 ratio observed than the corresponding chloride [46].

The nature of the oxygenated groups on the phosphorus atom is crucial, since diphenyl phosphates afforded better S_N2'/S_N2 ratios than diisopropyl phosphates [(Eq. 31) and Table 3].

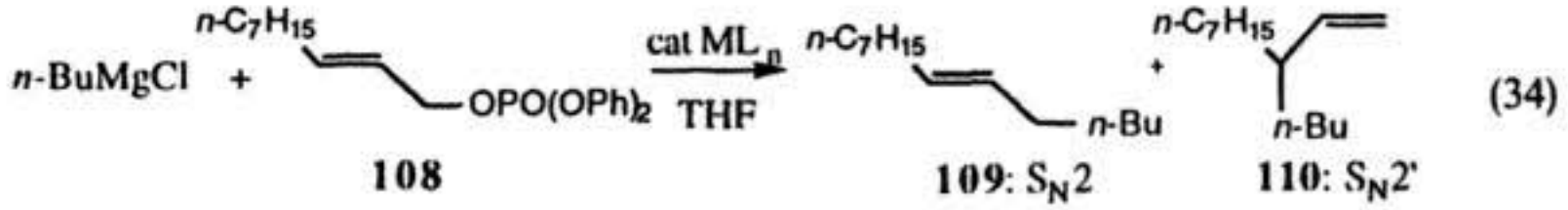


(31)

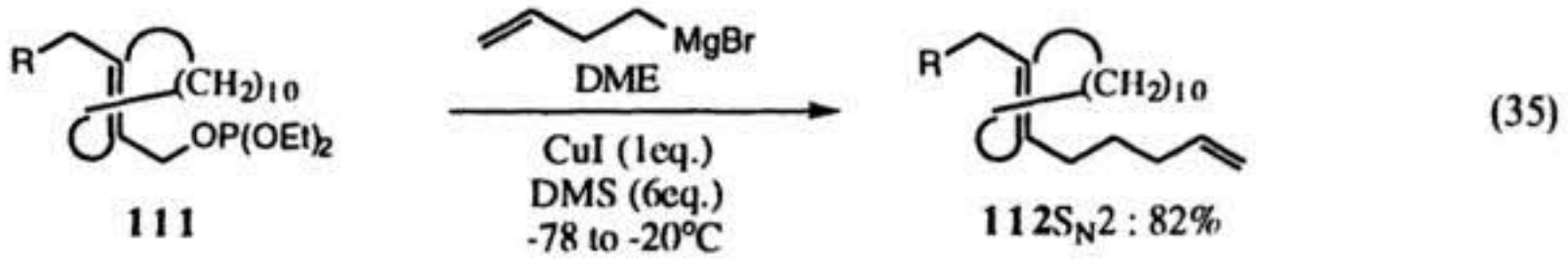
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Table 5

Catalyst (5–10%)	Conditions	Yield (%)	S_N2/S_N2'
CuCN·2LiCl	−78°C, 1 hr	98	1:99
n-BuC≡CCu	−75°C, 1 hr	95	14:86
CuI·2LiCl	−73°C, 1 hr	95	20:80
$CuBr_2$	−78°C, 1 hr	88	20:80
Li_2CuCl_4	−78°C, 1 hr	74	51:49
$CuBr \cdot Me_2S$	−78°C, 1 hr	65	66:34
CuOTf	−75°C, 1 hr	62	81:19
CuSCN	−43°C, 1 hr	94	91:9

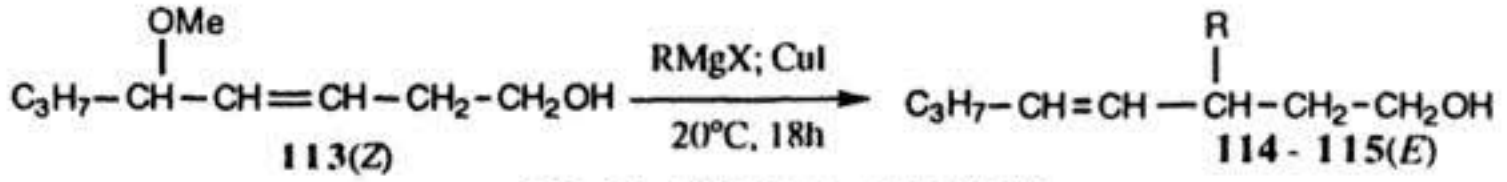


Interestingly, Marshall [50–52] found that on addition of a Grignard reagent to the tetrasubstituted allylic phosphate **111**, in the presence of 1 Eq of copper iodide in dimethoxyethane and dimethylsulfide, the sole product formed was the S_N2-coupled compound **112** in good yield (82%) [Eq. (35)].

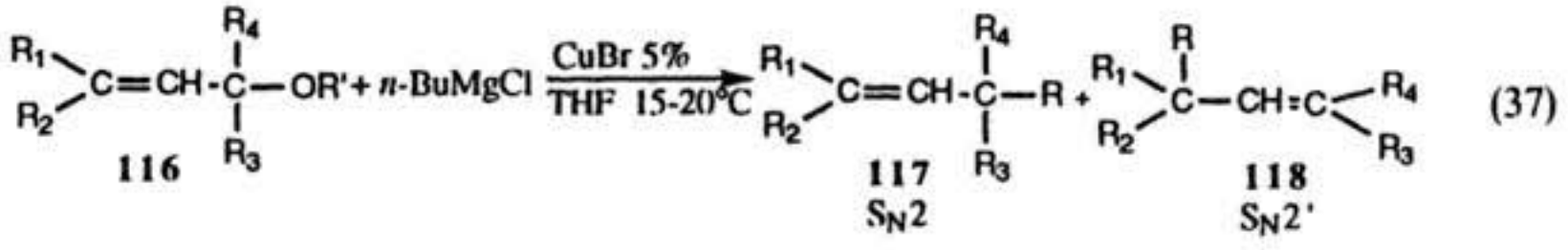


C. Allylic Ethers

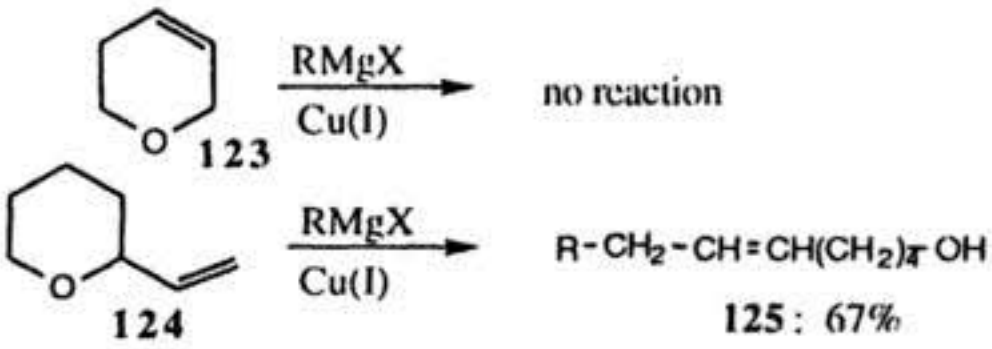
In the presence of Cu^I, allyl ethers can be coupled with Grignard reagents at room temperature in good yield and with high regioselectivity in favor of the S_N2' product, plus an excellent stereoselectivity toward the *E*-isomer [53], when using a 1:3 Et_2O/THF mixture [Eq. (36)].



The same year, it was noted by Commerçon [54] that the use of the Cu^IBr catalysis for the reaction of Grignard reagents with allyl methyl ethers lead to the mixture of S_N2 and S_N2' products, according to the steric hindrance of the substrate and the geometry of the double bond [Eq. (37) and Table 6].

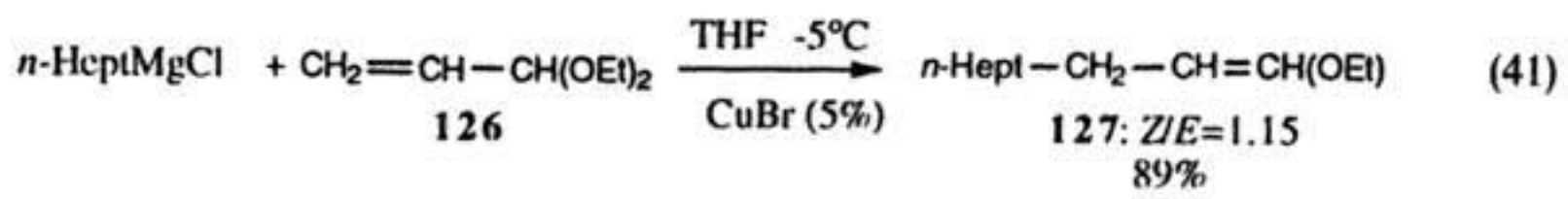


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(40)

With related compounds, such as allylic acetals, they react with total allylic transposition in good yields to afford the corresponding enol ethers [57; Eq. (41)].



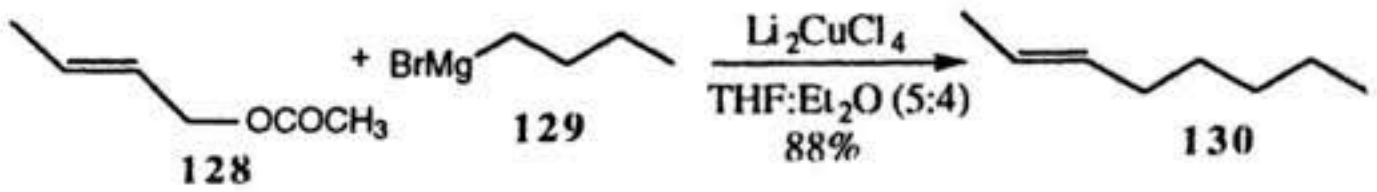
(41)

Acidic workup leads to the corresponding aldehyde. The addition of 2 Eq of $P(OEt)_3$ in relation with CuBr, allows the reaction to be performed at $+10°C$.

D. Allylic Carboxylates

1. *Allylic Acetates*

It is also possible to substitute allylic acetates by a Grignard reagent, but in the presence of copper catalyst. Fouquet [58] reported that *trans*-crotyl acetate **128** is converted regio- and stereoselectively by *n*-butylmagnesium bromide into *trans*-2-octene **130**, with 88% yield, by an S_N2 process [Eq. (42)].

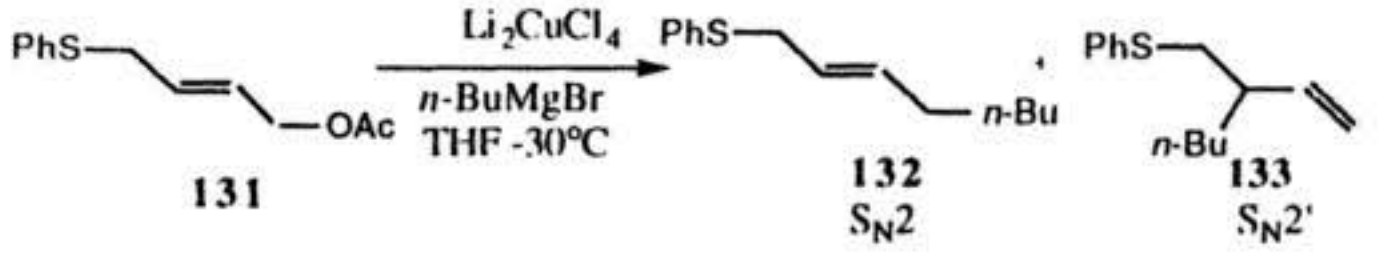


(42)

Schmid [49] made a similar observation, but noticed the formation of 9% of the product resulting from the attack of the carbonyl of the acetate function.

Allylic acetates can also give rise to the reduced products in the case of cinnamyl acetate. Indeed, treatment of cinnamyl acetate by ethylmagnesium bromide in the presence of a catalytic amount of CuBr in THF led to 16% of the reduced compounds and 84% of the S_N2 product in a 70% combined yield [55].

More recently, Bäckvall [47] showed that such reactions are very dependent on the nature of the solvent, temperature, catalyst, and addition time of the Grignard reagent. The catalyst Li_2CuCl_4 is convenient to use, since it is soluble in most solvents and is rapidly reduced in copper(I) by the Grignard reagent, even at $-78°C$. The influence of the addition time of the Grignard reagent on the regioselectivity of the reaction is proved by the following study [Eq. (43) and Table 7].



(43)

A slow addition of Grignard reagent gives a better S_N2'/S_N2 ratio in favor of the S_N2'

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Table 7

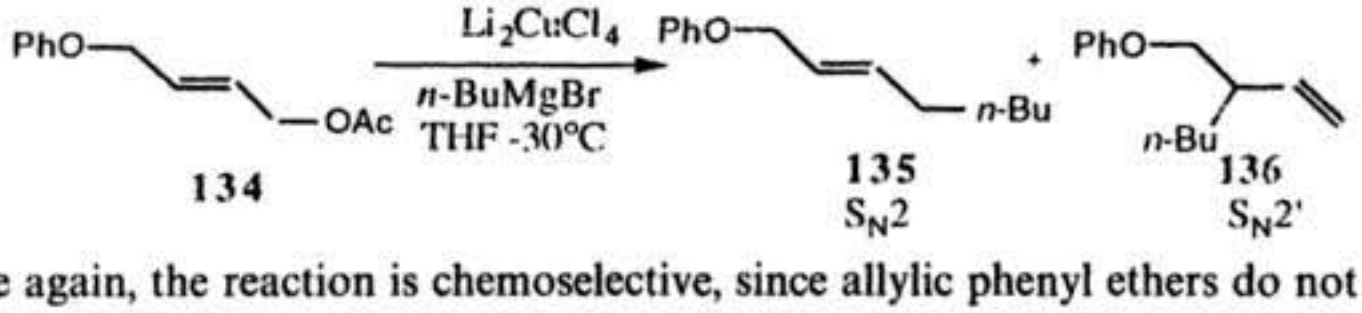
Addition time of *n*-BuMgBr (min)	mol% of Li_2CuCl_4	S_N2 **132**(%)	S_N2' **133**(%)
2	2	75	25
20	2	62	38
40	2	53	47
20	5	23	77
40	5	13	87

Table 8

Addition time of *n*-BuMgBr (min)	Temp.(°C)	Mol% of Li_2CuCl_4	S_N2 (%) **135**	S_N2' (%) **136**
1.5	−30	2	96	4
20	−30	2	82	18
40	−30	5	75	25
20	0	5	44	56
40	0	5	38	62
150	0	5	14	86

product. An increased amount of the catalyst favors the same S_N2' product. The reaction is also chemoselective, since an allylic phenyl sulfide does not react in these conditions.

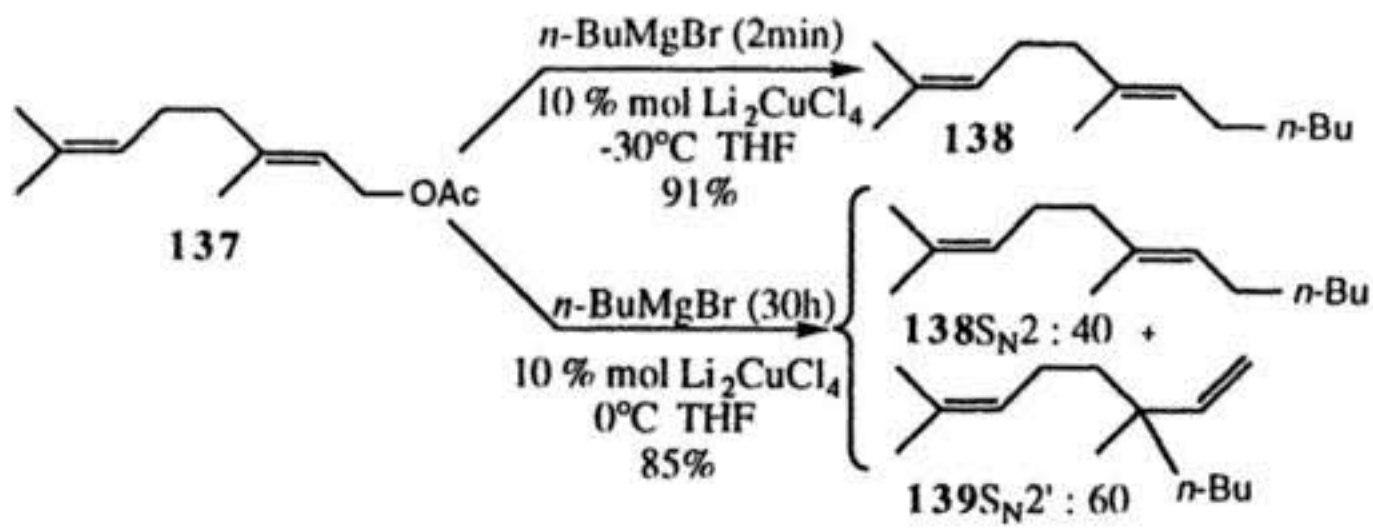
With less reactive substrates, the temperature has a dramatic effect on the selectivity: low temperature and fast addition favoring the S_N2 product, whereas higher temperature and slow addition give the S_N2' product as the major compound [47; Eq. (44) and Table 8].



(44)

Once again, the reaction is chemoselective, since allylic phenyl ethers do not react in such conditions.

Both effects, addition time and temperature, are illustrated [47] by the reaction of geranyl acetate with *n*-butylmagnesium bromide in THF in the presence of a catalytic amount of Li_2CuCl_4 [Eq. (45)].



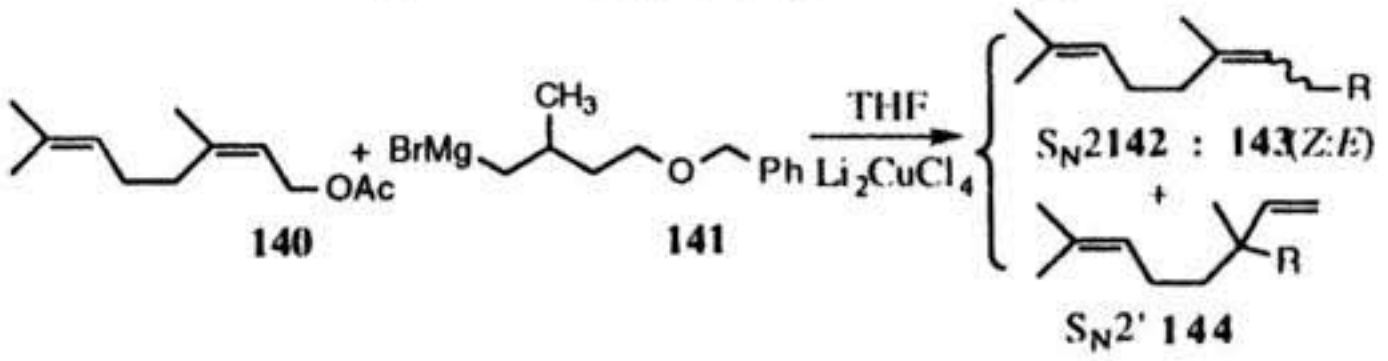
(45)

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Table 9

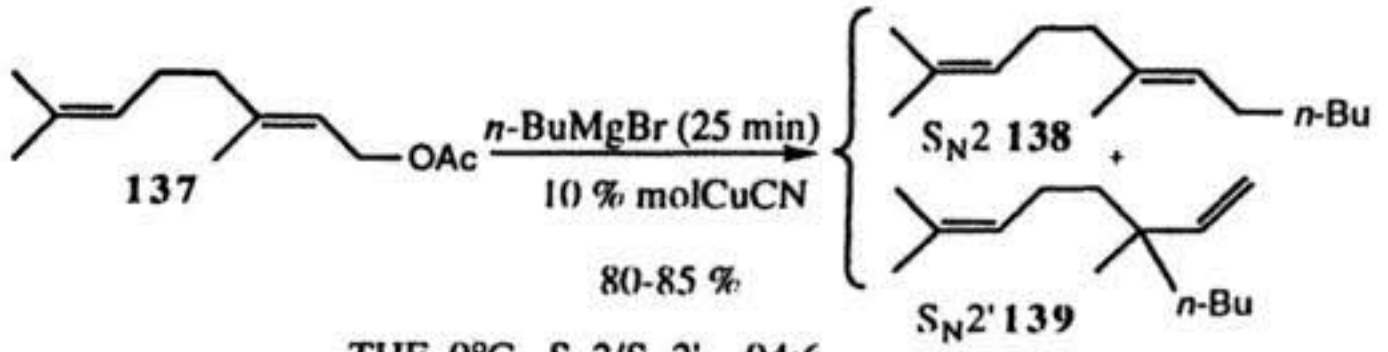
Molar ratio **141/140**	Li_2CuCl_4 (mol%)	Reaction Temp. (°C)	Solvent	Yield (%)	Distribution **142/143/144**
1.5	4	0	THF	62	100:0:0
2	16	0	THF	76	91:0:9
1.5	4	20	THF	74	95:1:4
2	4	0	Et_2O	75	80:0:20

Suzuki [59] also shows the high S_N2 selectivity of the reaction between allyl acetates and Grignard reagents by Li_2CuCl_4 catalysis in THF; but modification of the nature of the solvent, temperature, quantity of catalyst, and the Grignard reagent used, had a moderate effect on the regioselectivity [Eq. (46) and Table 9].



140 141 (46)

However, Bäckvall [47] reported a dramatic solvent effect, but used CuCN, rather than Li_2CuCl_4, as a catalyst. The reaction in THF at $-78°C$ gave only the S_N2 product, and by changing the solvent from THF to Et_2O, the selectivity can be totally reversed [Eq. (47)].

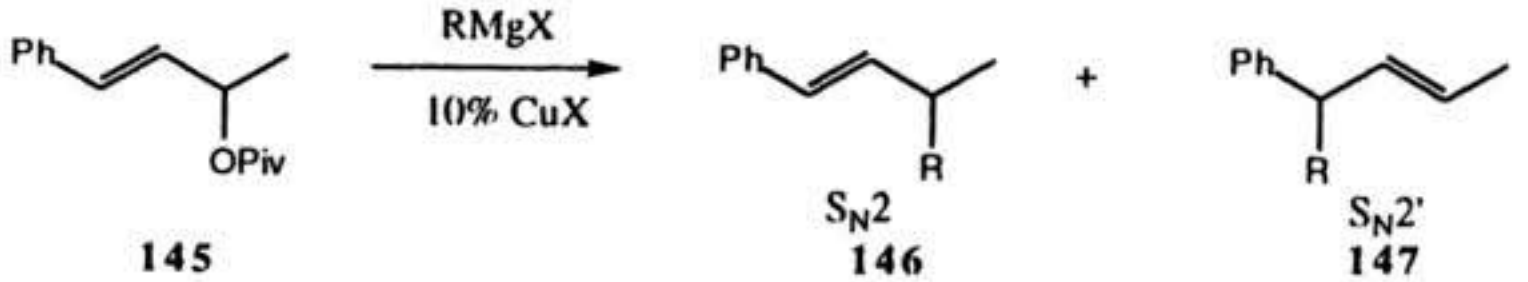


137 (47)

Very recently Bäckvall and van Koten [60] reported that *ortho*-aminoarenethiolato-copper compounds are excellent catalysts for the cross-coupling of Grignard reagents with acyclic allylic acetates. For example, with slow addition of *n*-butylmagnesium iodide to a solution of generanyl acetate containing *ortho*-thiodimethylaminomethyl benzene in catalytic amount, the S_N2-coupled product was exclusively obtained, whereas in THF at $-30°C$, a fast addition lead to the sole formation of the S_N2' product.

2. *Allylic Pivaloates*

Goering [61,62] undertook a study of alkylation of several Grignard reagents with allylic pivaloates in the presence of a copper catalyst, in Et_2O [Eq. (48) and Table 10].



145 146 147 (48)

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Table 10

RMgBr	CuX	S_N2 (**146**)	S_N2' (**147**)	Yield (%)
n-BuMgBr	CuCN	2–3	97–98	96–100
n-BuMgBr	CuCl	89	11	78–96
n-BuMgBr	CuBr	85	15	92
n-BuMgBr	CuI	86	14	86
n-BuMgBr	CuSCN	86	14	90
t-BuMgBr	CuCN	16–27	84–73	81–91
PhMgBr	CuCN	>99	<1	76

Table 11

Organocopper species	S_N2 (**146**)	S_N2' (**147**)	Yield (%)
BuCu(CN)MgBr	2.2	97.8	74
BuMgBr/CuCN (100:1)	2.6	97.4	99
$Bu_2CuMgBr$	85	15	78
BuMgBr/CuCl (100:1)	89	11	96

Acyclic allylic systems are sufficiently reactive that pivaloates can always be used without detectable carbonyl attack. With alkyl Grignard reagents, the CuCN-catalyzed reaction is highly regiospecific and gives either exclusively, or predominantly, the S_N2' products, whereas copper halides completely reversed the regioselectivity of the reaction in favor of the S_N2-coupled product (see Table 10).

Furthermore the CuCN catalyst is more regiospecific with the use of *n*-butylmagnesium bromide than with *t*-butylmagnesium bromide. The reaction with phenylmagnesium bromide also showed an excellent regioselectivity in favor of the S_N2 product.

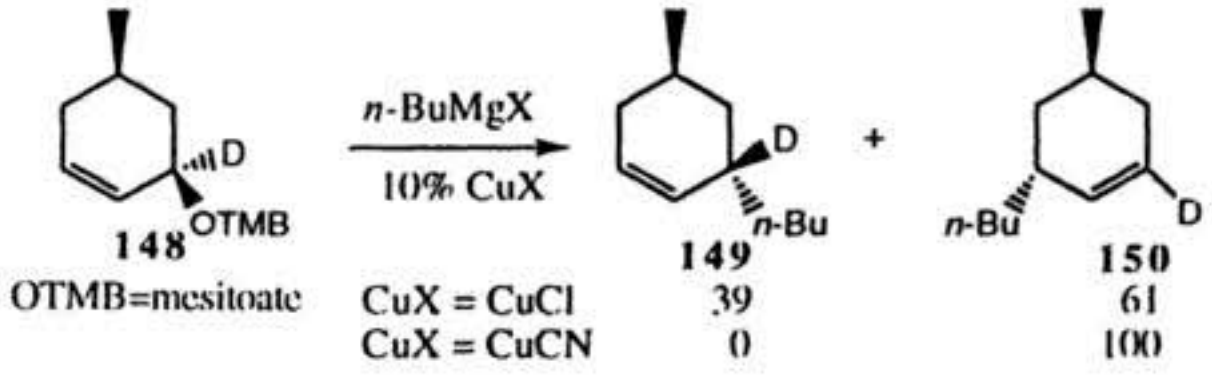
The distribution of S_N2/S_N2' products (**146/147**) for the reaction between *trans*-α-methyl-γ-phenyl allyl pivaloate **145** and *n*-butylmagnesium bromide in Et_2O [see Eq. (48], was studied as a function of the nature of the organocopper species [61] (Table 11). The regiochemistry of the stoichiometric alkylation (2.2:97.8) is the same as that for the catalyzed reaction with CuCN (2.6:97.4) and is in favor of the S_N2' product. No reaction occurs with *n*-BuMgBr/CuCl (1:1) because of the formation of the insoluble *n*-BuCu. Both regioselectivities observed for the alkylation with *n*-$Bu_2CuMgBr$ (85:15) and CuCl-catalyzed reaction (89:11) are in favor of the S_N2 product.

3. *Allylic Mesitoates*

In cyclic compounds, the influence of the catalyst is the same as already observed in acyclic cases with allylic pivaloates [61; Eq. (49)].

Although CuCl gives a partial regioselectivity (61:39) in favor of the S_N2' product, CuCN gives an exclusive S_N2' alkylation with, in both cases, an *anti*-addition.

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148 149 150

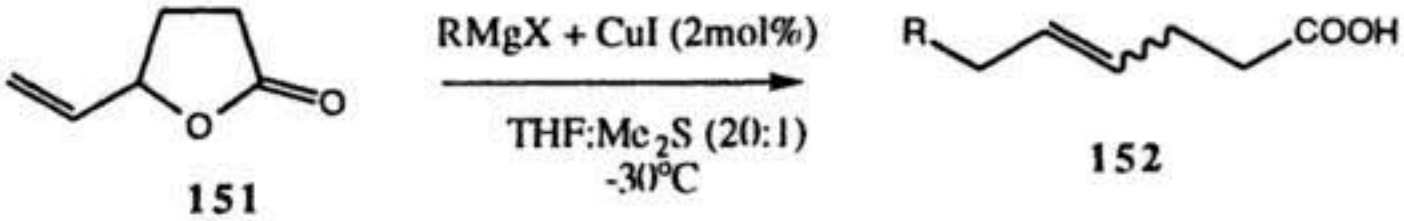
OTMB=mesitoate

	149	150
CuX = CuCl	39	61
CuX = CuCN	0	100

(49)

4. *Allylic Lactones*

Fujisawa [63] reported the nucleophilic ring-opening reaction of five- and six-membered lactones with Grignard reagents by a copper catalysis [Eq. (50) and Table 12].

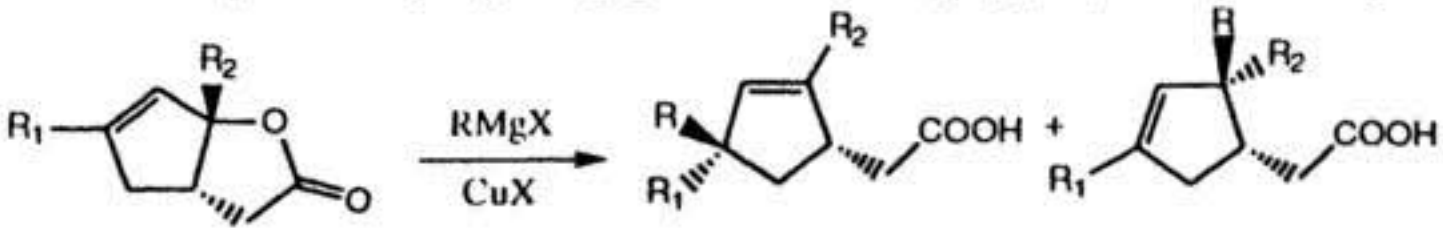


151 152

(50)

All reactions gave excellent regioselectivity in favor of the S_N2'-coupled products (since none S_N2-coupled product could be detected). Alkyl Grignard reagents led to the S_N2' product in high yields, whereas the vinyl-, allyl-, and phenyl Grignard reagents gave lower yields and a moderate stereoselectivity in favor of the *E*-compound. The same results were observed with δ-vinyl-δ-valerolactone [63].

More recently, Curran [64] reported that a Grignard reagent with copper catalysis could react and open 2*H*-cyclopenta[*b*]furanones **153** [Eq. (51) and Table 13].



153a-c a R_1=R_2=H; b R_1=H R_2=CH_3; c R_1=CH_3 R_2=H

S_N2' **154a-c** S_N2 **155a-c**

(51)

This study showed that $CuBr \cdot Me_2S$ must be employed in a stoichiometric quantity to obtain good selectivity in favor of the S_N2' product (>98:2), since a catalytic amount leads to a 50:50 mixture of the S_N2/S_N2'-coupled products.

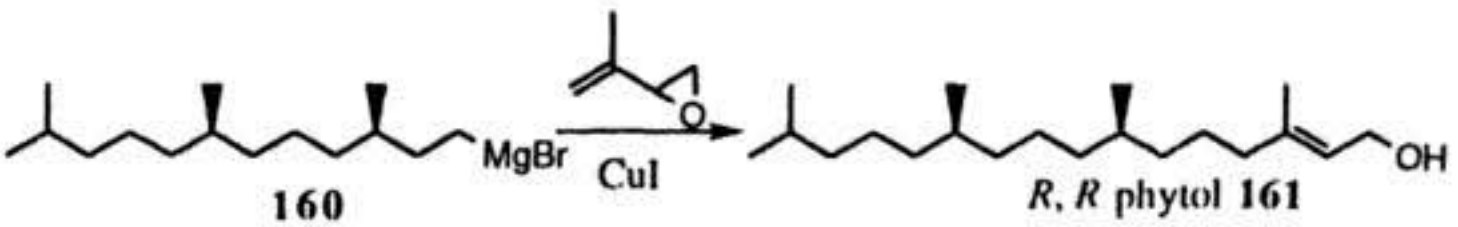
Table 12

Grignard reagent	Yield (%)	*E*/*Z*
MeMgBr	87	92:8
n-BuMgBr	93	86:14
s-BuMgBr	90	83:17
t-BuMgBr	91	78:22
PhMgBr	75	62:38
(Vinyl)MgBr	59	57:43
(Allyl)MgBr	9	92:8
$Ph_2CuMgBr$	91	82:18
$(Vinyl)_2CuMgBr$	70	82:18
$(Allyl)_2CuMgBr$	41	86:14

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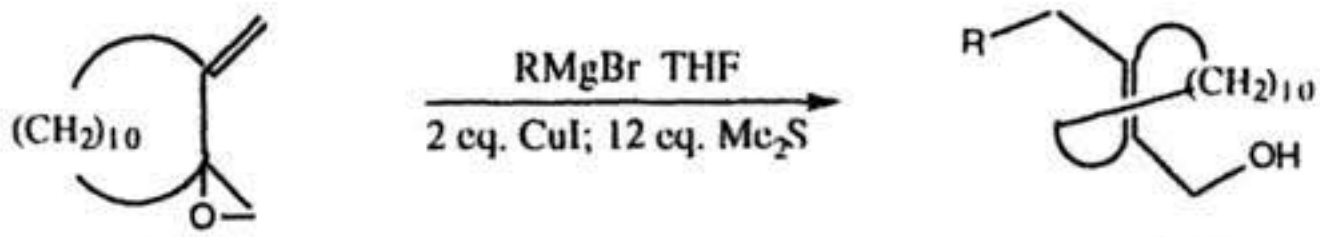
The reaction is stereoselective, as only the *anti*-product was formed.

Fujisawa [67] found that the stereoselective introduction of a prenyl alcohol moiety, with an *E*-configuration, into a vinyl oxirane was readily achieved by a copper-catalyzed S_N2' reaction. Thus, addition of a Grignard reagent **160** to a solution of isoprenyl oxirane and copper(I) iodide (5 mol%) in THF/Me_2S (20:1) at $-20°C$ afforded the allylic alcohol **161** in 95% yield in a 97:3 *E*/*Z* ratio [Eq. (54)].



160 *R, R* phytol **161** (54)

Such procedures were applied by Marshall [50–52] for the syntheses of large cycloalkanes [Eq. (55)].

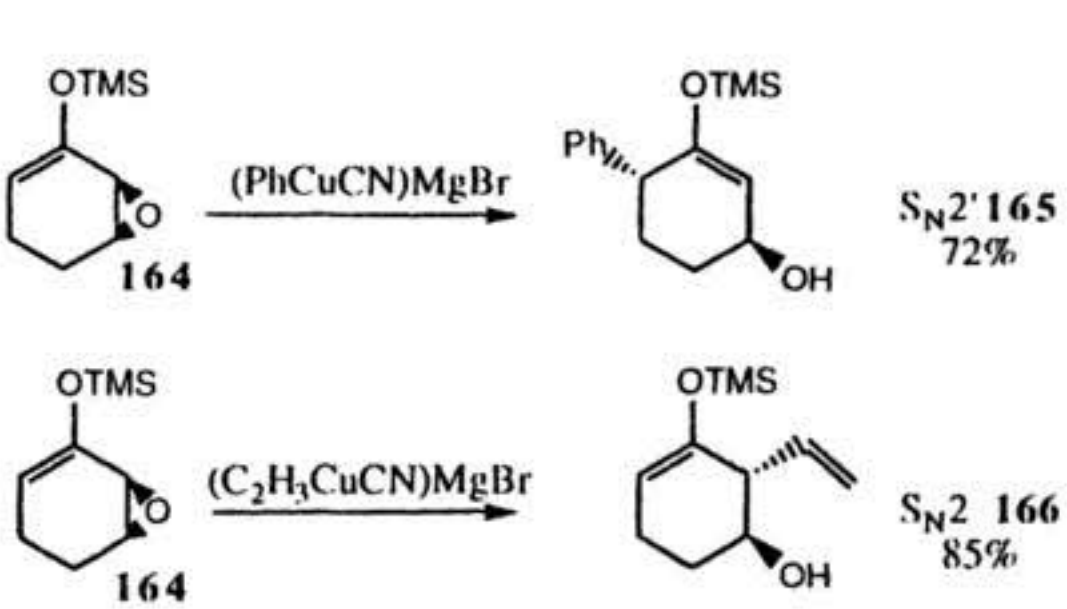


162 **163** (55)

RMgBr { $CH_2{=}CHCH_2CH_2MgBr$; $(i\text{-}Pr)_3SiC{\equiv}CCH_2MgBr$; BuMgBr

With addition of [(triisopropylsilyl)propargyl]magnesium bromide–copper(I) iodide to the vinyl oxirane **162** in THF–dimethylsulfide, the *trans*-allylic propargyl alcohol **163** is primarily formed, in 79% yield. Addition of the analogous trimethylsilyl reagent gave rise to considerable S_N2' allenic product, resulting from γ-attack of the propargyl reagent.

Marino [68] showed that the silyl enol ethers of substituted 2,3-epoxycyclohexanones react with (PhCuCN)MgBr and (C_2H_3CuCN)MgBr to give, respectively, the S_N2' and S_N2 products [Eq. (56)].

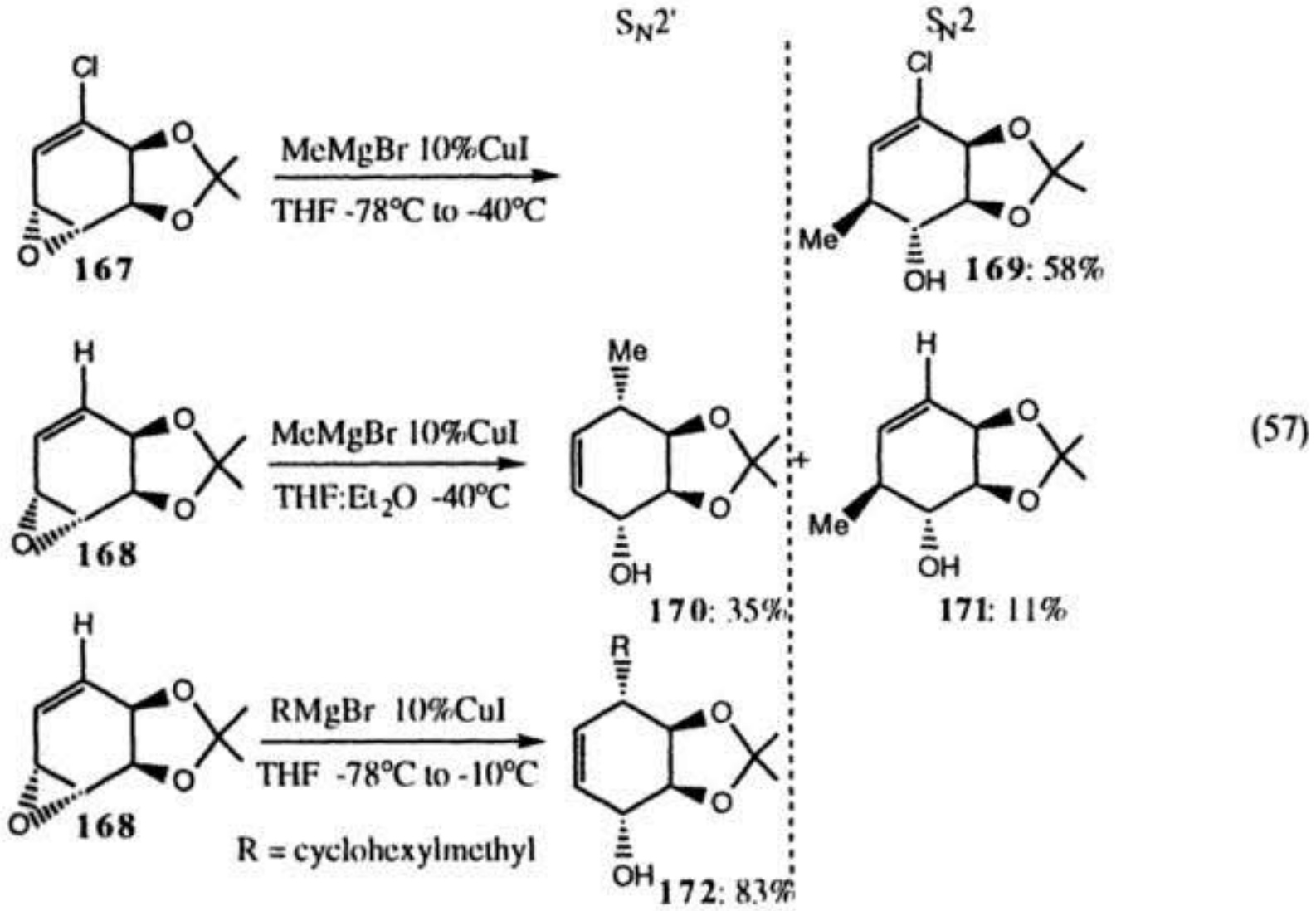


164 S_N2' **165** 72%

164 S_N2 **166** 85% (56)

More recently, Hudlicky [69] reported the regio- and chemoselectivity of the reaction between homochiral vinyloxiranes and Grignard reagents in the presence of a catalytic amount of copper iodide [Eq. (57)].

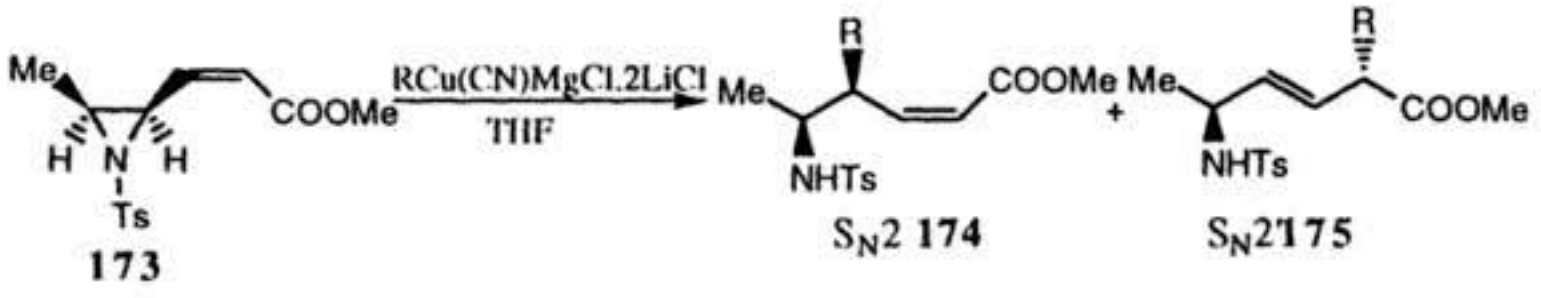
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The S_N2' product is predominantly formed by nonhalogenated compounds, which lack the bulky, electron-withdrawing halogen atom. The S_N2 product is *anti*, whereas the S_N2' product is *syn* (owing to the steric hindrance of the *anti*-face).

F. Allylic Aziridines

Allylic aziridines can be alkylated by Grignard reagents in the presence of stoichiometric quantities of copper cyanide [70] to give the *anti*-S_N2' product as the major compound [Eq. (58)].

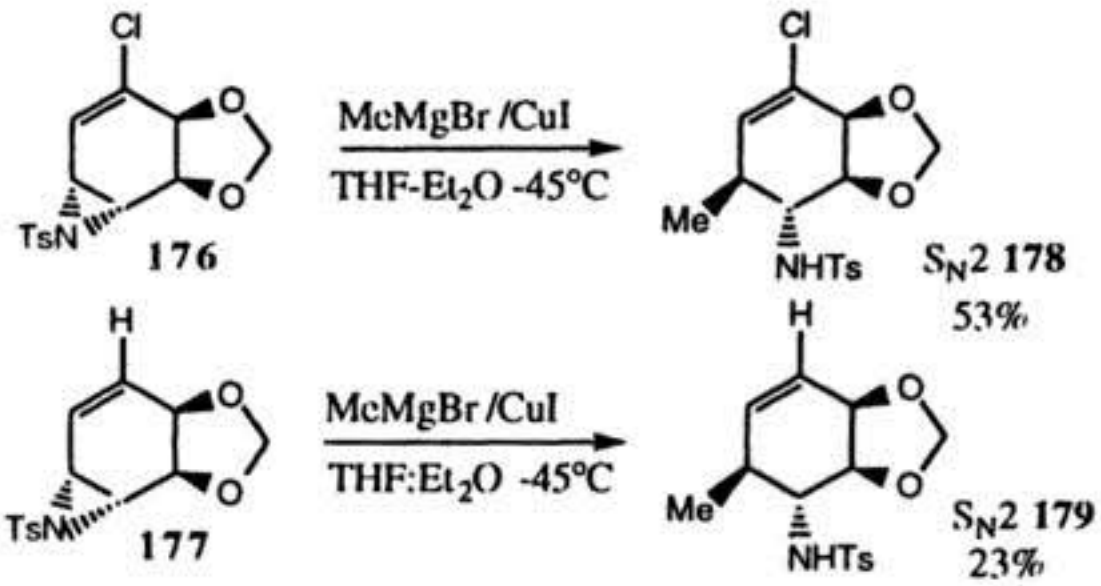


R=*i*-Pr	2	98
R=*i*-PrOSi(Me)$_2$CH$_2$	-	75
R=*p*F-C$_6$H$_4$CH$_2$	-	98

(58)

Hudlicky [69] reported the opening of vinyl aziridines in cyclic compounds that, as their corresponding epoxydes, gave rise to the S_N2 product in moderate yields [Eq. (59)]

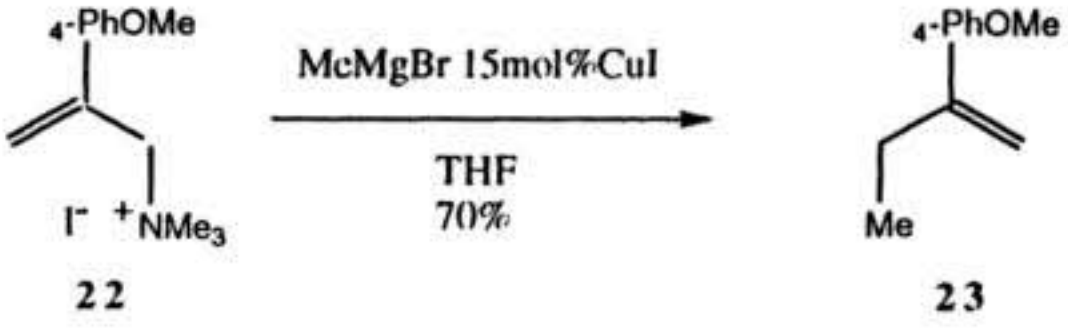
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(59)

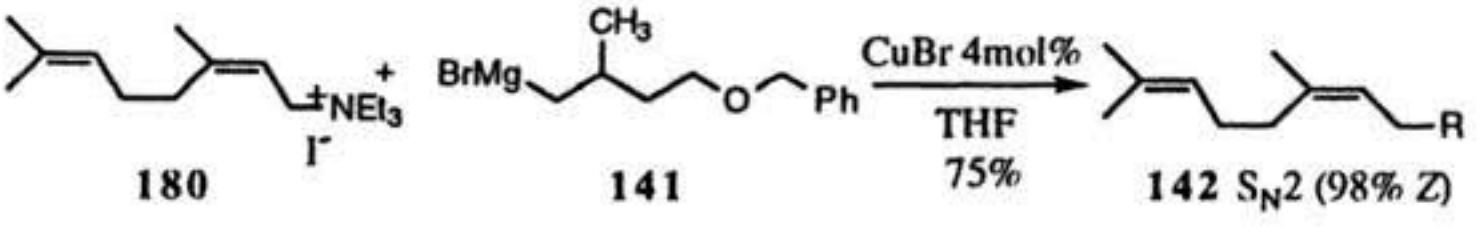
G. Allylic Ammonium Salts

Tertiary amines, when treating with Grignard reagents, with or without copper catalysis, do not react, whereas the corresponding quaternary ammonium salts can be displaced by organomagnesium reagents in the presence of a catalytic amount of CuI in THF [20; Eq. (60)].



(60)

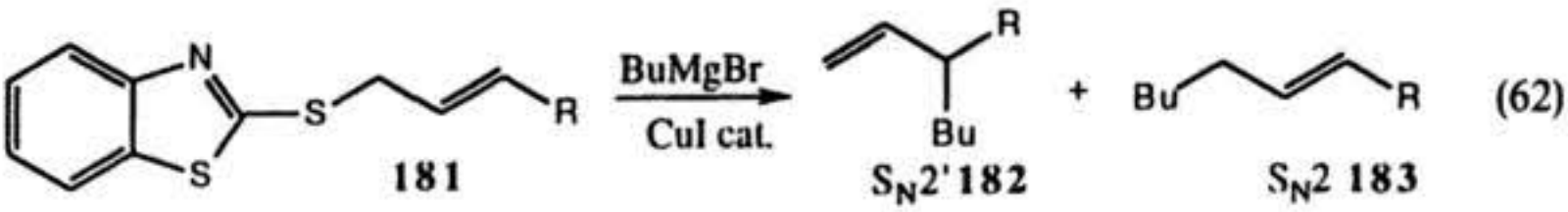
Suzuki [59] reported that alkylation of a Grignard reagent with geranyl triethylammonium iodide gave rise to the S_N2 product in excellent yields [Eq. (61)].



(61)

H. Allylic Sulfides

Primary allylic sulfides of derivatives of benzothiazole-2-thiol react with Grignard reagents in the presence of copper(I) iodide to yield olefins, with or without allylic rearrangement, depending on the nature of the solvent and the allylic sulfide [71; Eq. (62) and Table 14].



(62)

In ether, the S_N2' coupled product is formed predominantly, whereas in a mixture of THF and Et_2O, the S_N2 product is the major compound, with retention of the configuration of the double bond.

Calò [72] studied the effect of the ratio of Grignard reagent/CuBr on the regioselectivity in the cross-coupling of the 2-octa-2,6-dienylthiobenzothiazole with

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Table 14

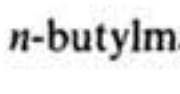
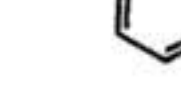
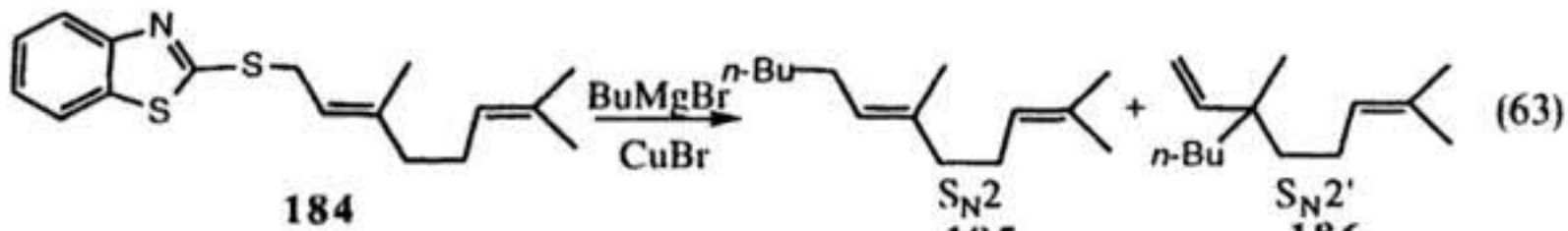
R	Solvent	S_N2' (182)	S_N2 (183)	Yield (182 + 183)
Ph	Ether	97	3	81
Ph	THF–ether (2:1)	5	95	83
	Ether	5	95	80
	THF–ether (2:1)	5	95	90
	THF	70	30	—

Table 15

n-BuMgBr/CuBr (Eq)	Product S_N2/S_N2'	Conversion after 15 min (%)
1:3	0.5:99.5	98
1:2	1:99	89
1:1	2:98	71
1:0.1	50:50	53
2:1	70:30	95
4:1	99:1	98

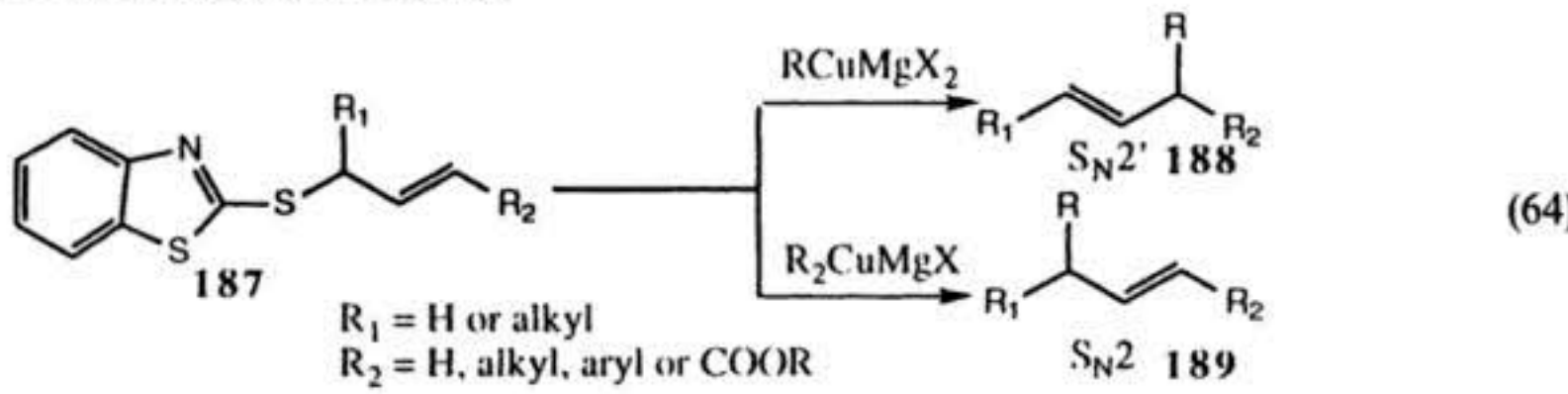
n-butylmagnesium bromide [Eq. (63)]; the results are summarized in Table 15.



184 S_N2 **185** S_N2' **186**

The S_N2/S_N2' ratio depends on the CuBr concentration. In a catalytic amount of CuBr (0.25 Eq), the product distribution is in favor of the S_N2 product (99:1), whereas an excess of CuBr (3 Eq) increases the S_N2' product (0.5:99.5).

Calò [72,73] also noted that the S_N2/S_N2' ratio depends on the nature of the organocopper species [Eq. (64)].



The S_N2' product is favored by a low ratio of Grignard reagent/CuBr and the S_N2 product by a higher one.

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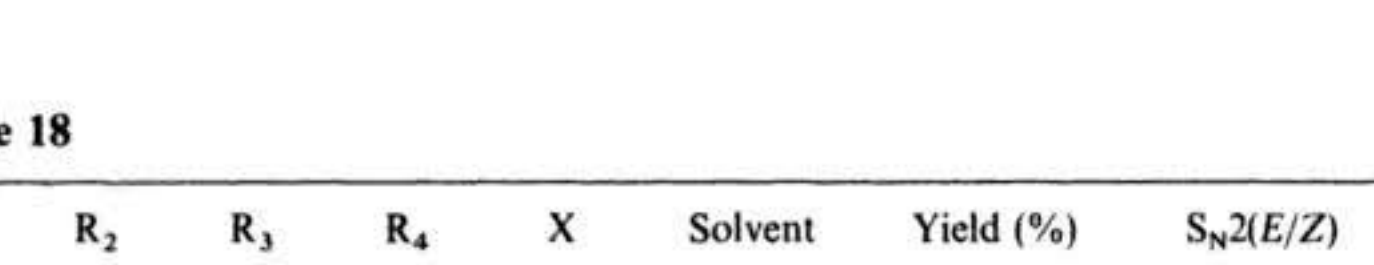
Table 17

R_1	R_2	R_3	R_4	R_5	RMgX	Yield (S_N2/S_N2')	S_N2 (E/Z)	S_N2' (E/Z)
H	H	H	H	H	*n*-HexMgBr	85	—	—
H	H	H	H	Me	*n*-HexMgBr	92	—	—
H	H	H	Me	H	*n*-HexMgBr	69	98(100:0)	2
H	H	H	Me	H	*n*-HexMgCl	91	100(100:0)	0
H	H	Me	H	H	*n*-HexMgBr	40	74(11:80)	26
H	H	Me	H	H	*n*-HexMgCl	42	75(13:87)	25
H	Me	H	H	H	*n*-HexMgBr	65	16	84(40:60)
H	Bu	H	H	Me	EtMgBr	60	20	80(50:50)
H	Bu	H	H	Me	EtMgBr(Et_2O)	40	4	96(70:30)
H	H	Me	Me	H	*n*-HexMgBr	2	100	0
H	H	Me	Me	H	*n*-HexMgCl	20	100	0
H	H	Me	C_6H_{11}	H	*n*-BuMgCl	30	100(100:0)	0
Me	Me	H	H	H	*n*-HexMgBr	90	0	100

Table 18

R_1	R_2	R_3	R_4	X	Solvent	Yield (%)	$S_N2(E/Z)$	$S_N2'(E/Z)$
H	H	H	Me	Br	THF	69	98(100:0)	2
H	H	H	Me	Cl	THF	91	100(100:0)	0
H	H	H	Me	Cl	Et_2O	10	90(100:0)	10
H	H	Me	H	Br	THF	40	74(11:89)	26
H	H	Me	H	Cl	THF	42	75(13:87)	25
Me	H	H	H	Br	THF	65	16	84(40:60)
Me	H	H	H	Br	Et_2O	20	2	98(50:50)
Me	H	H	H	Cl	Et_2O	51	8	94(61:39)

allylic sulfone has been studied and reported [75; Eq. (67) and Table 18].



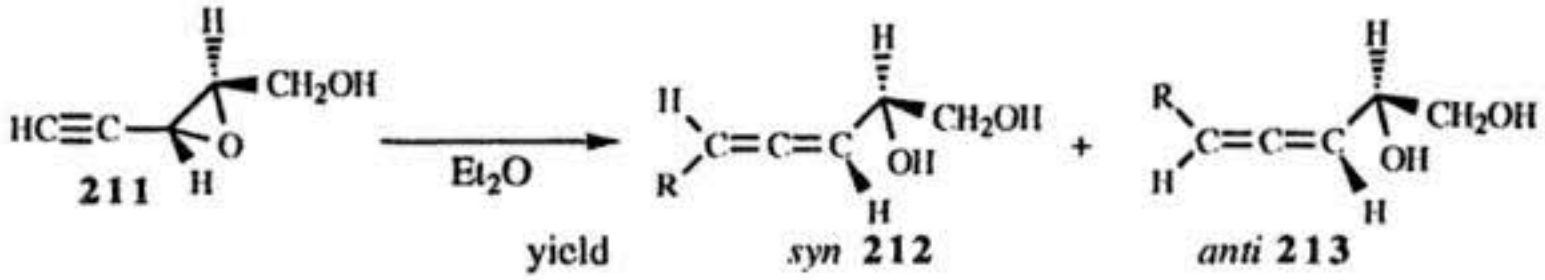
198 **199** S_N2 **200** S_N2' (67)

Organomagnesium chloride used in THF gave the best S_N2/S_N2' ratio in high yields, compared with the corresponding bromide. Secondary allylic sulfones led primarily to the S_N2' product in moderate yield in THF and in low yields in Et_2O.

Trost [76] reported the alkylation of allylic sulfones with Grignard reagents in the presence of a catalytic amount of CuCN in Et_2O, with high regio- and stereoselectivity in favor of the S_N2' product [Eq. (68)].

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product, when the reaction is performed at low temperature [77, Eq. (72)].

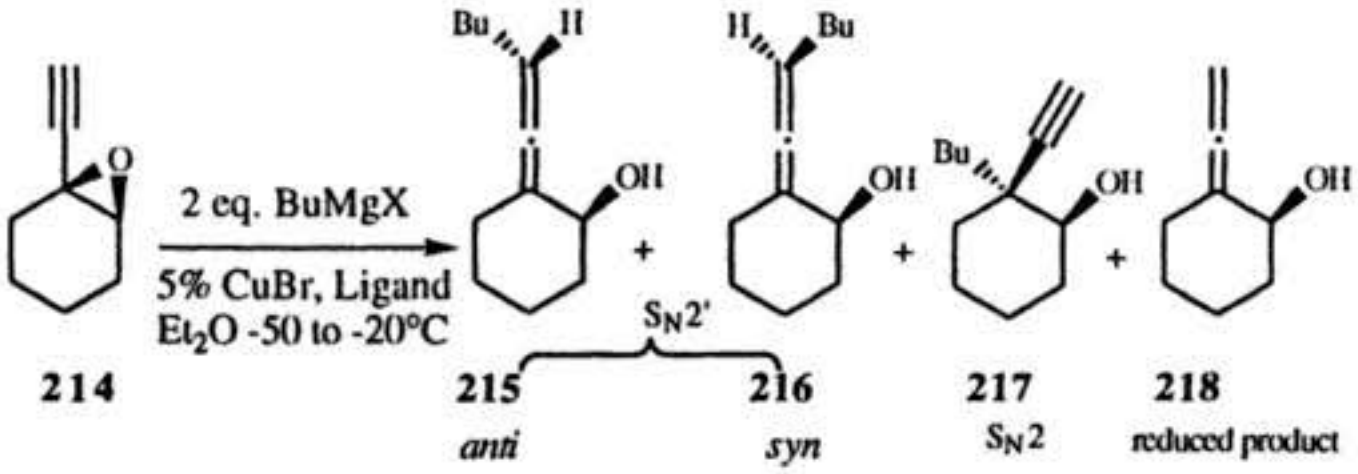


	yield	*syn* **212**	*anti* **213**
$(C_8H_{17})_2CuMgBr$; 30°C	50	60	40
$(C_4H_9)_2CuMgBr\ Me_2S$; -60°C	68	1	99
$(C_8H_{17})_2CuMgBr\ Me_2S$; -60°C	57	2	98
$(C_8H_{17})_2CuMgBr\ Me_2S$; -30°C	52	4	96

(72)

The reaction is completely regioselective in favor of the S_N2' product, and the cross-coupling of propargyl epoxides with organocuprates give nearly an exclusive *anti*-product when dimethyl sulfur is present, but give mixtures of *syn*- and *anti*-products in its absence.

More recently, Alexakis [32] reported the diastereoselective *syn*- or *anti*-opening of propargyl epoxides, with good to excellent S_N2' selectivity. Addition of two equivalents of phosphine as a ligand can influence the stereochemistry of the elimination step to afford either the *syn*- or *anti*-product, as shown in Eq. (73) and Table 19.



(73)

The best stereoisomeric *anti*/*syn* ratio was obtained with two equivalents of ligand (per Cu salt) and PBu_3 was preferred, because the reaction mixture remained homogeneous throughout the reaction. The nature of X in RMgX influences the stereochemistry, and the best results are obtained with X = Br.

Table 19

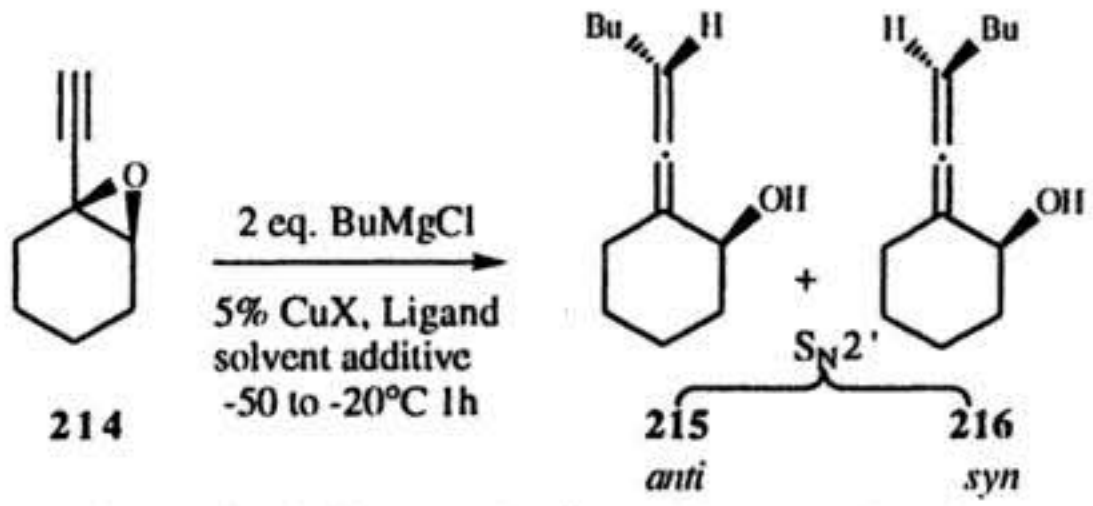
RMgX	Ligand	*anti*/*syn* (215/216)	Yield (%) 215+216	217(%)	218(%)
n-BuMgBr	$2P(OEt)_3$	46:54	95		
n-BuMgBr	$P(NMe_2)_3$	99:1	52	30	
n-BuMgBr	$2P(NMe_2)_3$	100:0	75	10	5
n-BuMgBr	PBu_3	88:12	50	25	10
n-BuMgBr	$2PBu_3$	100:0	74	18	
n-BuMgCl	$2PBu_3$	94:6	45		
n-BuMgI	$2PBu_3$	90:10	31		

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Table 20

CuX	Ligand	Solvent	Additive	*anti/syn*	Yield (%)
CuBr	$2(POEt_2)_3$	Et_2O	—	41:59	100
CuBr	—	Et_2O	—	35:65	72
CuBr	—	Benzene	—	20:80	48
CuBr	—	Et_2O	TMSCl	24:74	82
CuCl	—	Et_2O	TMSCl	29:71	100
CuCN	—	Et_2O	TMSCl	38:62	100
CuSPh	—	Et_2O	TMSCl	37:63	100
CuBr	—	Et_2O-pentane	TMSCl	12:88	100
CuBr	—	Et_2O (0°C)	—	10:90	84

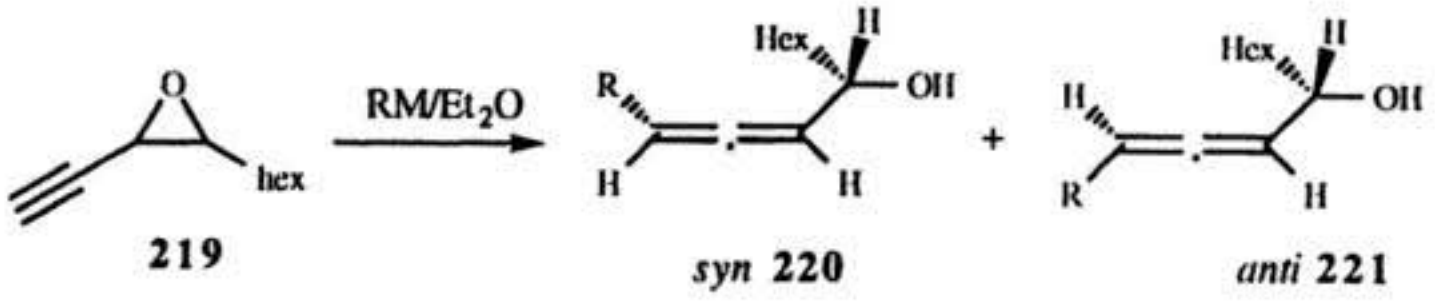
It is possible to increase the *syn/anti* ratio by addition of TMSCl or by changing the solvent [32; Eq. (74) and Table 20].



(74)

As shown in Table 20, the ligand has a deleterious effect on the amount of the *syn*-adduct, and the solvent plays a significant role on the stereoselectivity, since a reaction run in benzene gave a 20:80 *anti/syn* ratio, compared with Et_2O (35:65); however, the chemical yield is poorer (48 and 72, respectively). Addition of TMSCl improves both the *syn*-selectivity and the combined yield. With substituted alkynes, the same effects (ligand, additive, solvent) are observed [32].

Reaction of acyclic propargyl epoxides with Grignard reagents in the presence of Cu^I catalyst afforded the S_N2' products exclusively, with high stereoselectivity toward the *syn*-product. For the *trans*-epoxide, the selectivities are higher, particularly for the *syn*-process [32; Eq. (75) and Table 21].

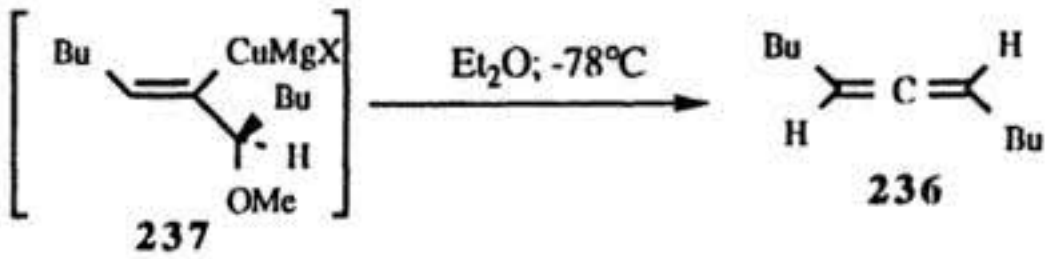


(75)

L. Propargyl Ethers

It was noted by several authors [53,78,79] that propargylic ethers react with Grignard reagents by a copper catalysis to afford a mixture of the S_N2 and S_N2' products, with an occasional elimination product [Eq. (76)].

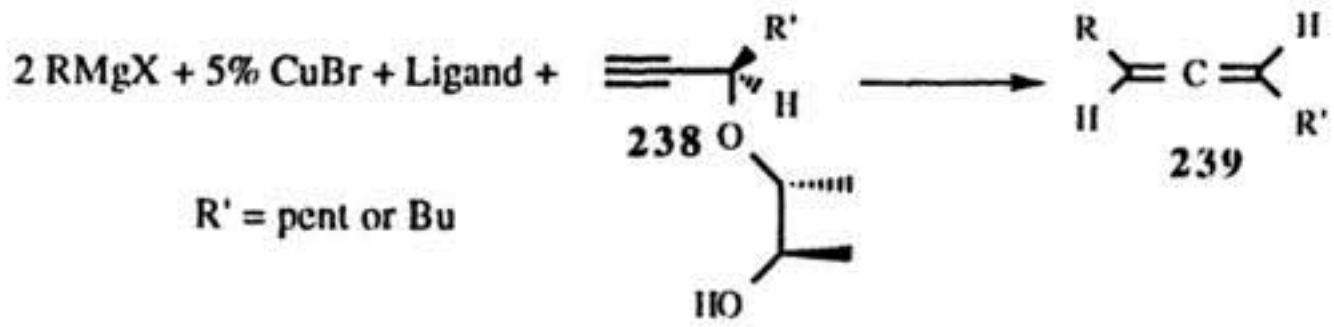
Material chroniony prawem autorskim



237 236 (78)

X=I *anti* product ee:65%
X=Cl *syn* product ee:35%

By using a homochiral ether, and controlling the *syn*- or *anti*-elimination conditions of the reaction, pure allenic derivatives can be obtained in high optical purity [80], as shown in Eq. (79) and Table 22.

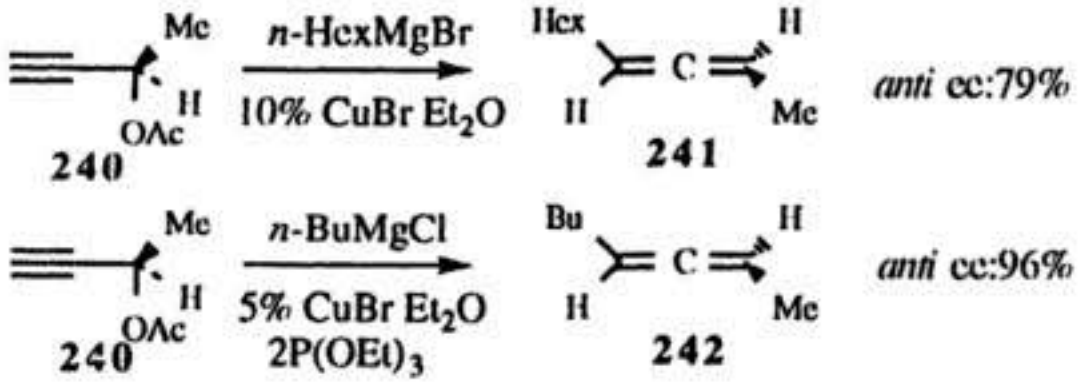


(79)

With primary alkyl Grignard reagents, the *syn*-process predominates, whatever the reaction conditions are. Under the best conditions (PentMgBr, $2P(OEt)_3$, Et_2O/pentane 1/1) the allene is obtained in up to 93% optical purity. With hindered Grignard reagents, the *anti*-process is predominant.

M. Propargyl Acetates

Propargyl acetates, on addition of alkyl Grignard reagents in the presence of a catalytic amount of Cu^I, afford exclusively the S_N2' product; namely, the allenic derivatives by an *anti*-process [80], as shown in Eq. (80).



(80)

Table 22

RMgX	Ligand	Solvent	Yield (%)	e.e. (%)	Allene config.	Overall process
n-PentMgCl	$2P(OEt)_3$	Et_2O	85	91	*R*	*syn*
n-PentMgBr	$2P(OEt)_3$	Et_2O	80	54	*R*	*syn*
n-PentMgBr	$2P(OEt)_3$	Et_2O/pentane, 1:1	80	93	*R*	*syn*
n-BuMgBr	$2P(OEt)_3$	Et_2O	66	89	*R*	*syn*
EtMgBr	$2P(OEt)_3$	Et_2O	60	72	*R*	*syn*
t-$BuOC_4H_8MgBr$	$2P(OEt)_3$	EtO	65		*R*	*syn*
t-BuMgBr	$2P(OEt)_3$	Et_2O/pentane, 1:1	60	64	*S*	*anti*
t-BuMgBr	$2PBu_3$	Et_2O	62	67	*S*	*anti*
t-BuMgBr	$2PBu_3$	Et_2O	65	70	*S*	*anti*

e.e., enantiomeric excess.

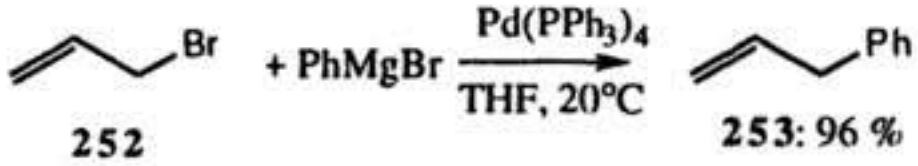
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IV. REACTIONS CATALYZED BY PALLADIUM

Palladium-catalyzed allylic alkylation by transmetallation with Grignard reagents is less frequently encountered than with aryl- and vinyltin reagents [85]. However, a few examples are known from the literature and reported herein. In some cases, if the reactivity of such allylic–ethers or amines have been reported, the regioselectivity was not studied because of the symmetric nature of the substrates.

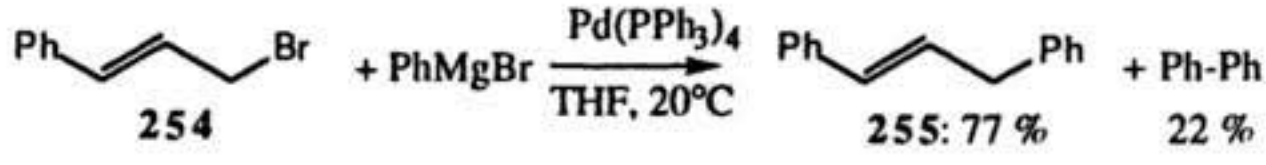
A. Allylic Halides

Bumagin et al. [86] noted that Grignard reagents reacted with allylic halides in THF in the presence of a catalytic amount of palladium triphenyl phosphine tetrakis [$Pd(PPh_3)_4$] at room temperature [Eq. (84)].



252 **253**: 96 % (84)

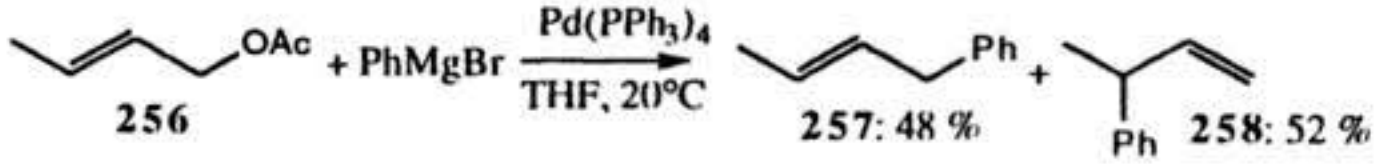
The same study showed that Pd^0 gives better results than Pd^{II} catalysis in the yields for formation of alkylated products. Unfortunately, except for a single report, the regioselectivity was not examined. Indeed, when cinnamyl bromide was reacted with phenylmagnesium bromide in the presence of $Pd(PPh_3)_4$, the S_N2 coupled product **255** was the only alkylated compound observed, in 77% yield with 22% of biphenyl [Eq. (85)].



254 **255**: 77 % 22 % (85)

B. Allylic Acetates

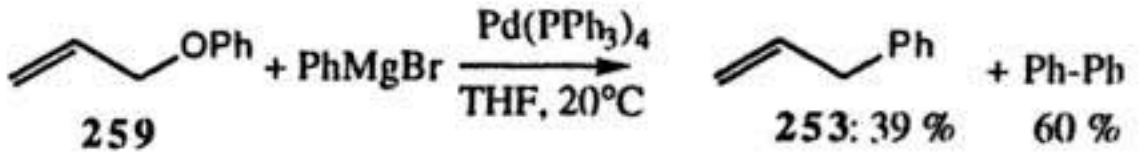
Negishi [87] found that phenylmagnesium bromide reacted with (*E*)-crotyl acetate in the presence of $Pd(PPh_3)_4$ to afford a nearly 1:1 mixture of S_N2 and S_N2' products [Eq. (86)].



256 **257**: 48 % **258**: 52 % (86)

C. Allylic Ethers

Bumagin et al. [86] also reported that allyl phenyl ethers can react with phenylmagnesium bromide in THF at room temperature in the presence of $Pd(PPh_3)_4$ to afford the desired phenyl-1-propene-2 in 39% yield. Unfortunately, the regiochemistry of such a reaction with other substrates was not studied [Eq. (87)].



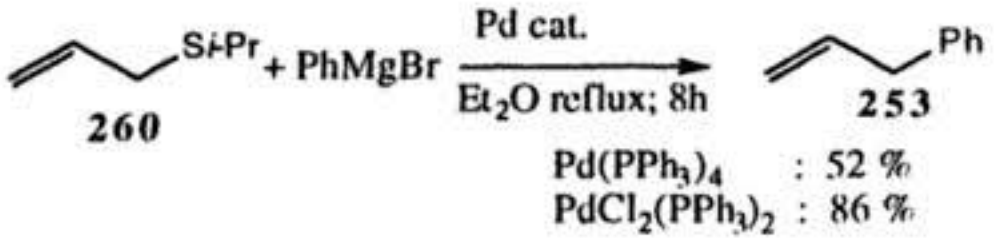
259 **253**: 39 % 60 % (87)

D. Allylic Sulfides

Takei [88] examined the catalytic activity of $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ on the reaction of phenylmagnesium bromide with allyl isopropyl sulfide; the alkylated products were

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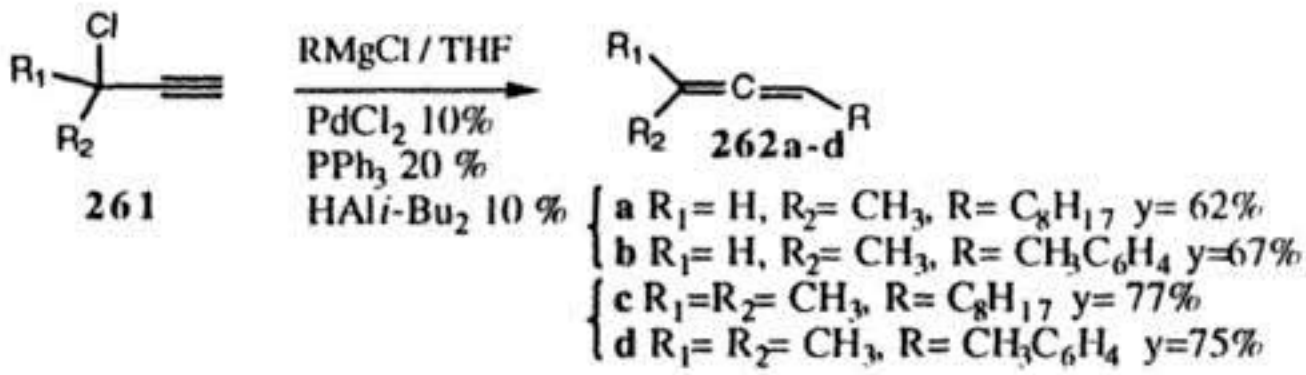
obtained in 52 and 86% yields, respectively. Unfortunately, the regiochemistry of the reaction was not studied [Eq. (88)].



(88)

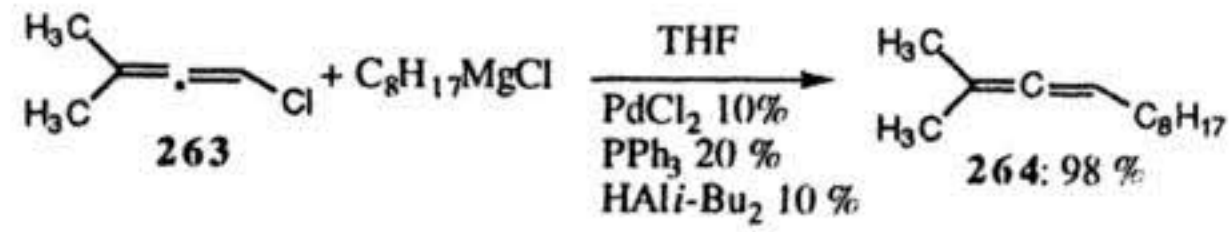
E. Propargyl Halides

Linstrumelle [89] reported that propargyl chlorides react with Grignard reagents to give, as the sole product of the reaction, the S_N2' compounds **262a–d**; namely, the allenic derivatives [Eq. (89)].



(89)

In the same report, the authors showed that allenic halides react with Grignard reagents to give the allenic compound, with fair to good yields [Eq. (90)].



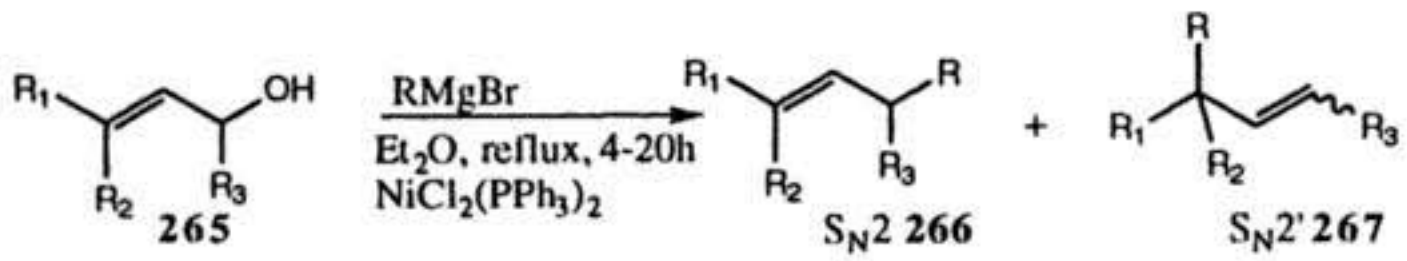
(90)

V. REACTIONS CATALYZED BY OTHER TRANSITION METALS (Ni, Fe, Co, Mn)

Copper-catalyzed substitution of allylic halides (and related cases) with Grignard reagents has been extensively studied (see Section III). To a lesser extent the use of other transition metal catalyst, such as Ni, Fe, Ti, Mn, Cr, remains anecdotally studied.

A. Allylic Alcohols

Allylic alcohols do not react with alkyl- and aryl-Grignard reagents [90]. However, Swierczewski [91] reported that methyl-, phenyl-, and benzylmagnesium bromides reacted with allylic alcohols in the presence of a catalytic amount of $NiCl_2(PPh_3)_2$ to give either a mixture of S_N2/S_N2'-coupled products, or when R_1 or R_2 is equal to phenyl, to the sole S_N2 compound [Eq. (91) and Table 23]. The same selectivity has been observed by Wenkert in similar conditions [92].



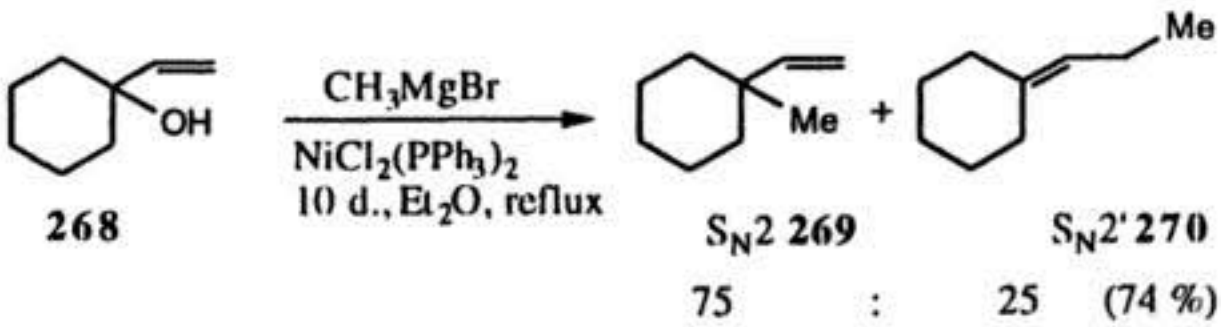
(91)

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Table 23

R_1	R_2	R_3	R	S_N2 (%)	S_N2' (%)	Yield (%)
CH_3	H	H	Me	54	46	87
CH_3	H	H	Ph	66	34	>73
H	CH_3	H	Me	9.8	90.2	80
H	CH_3	H	Ph	41.4	58.6	>64
H	H	CH_3	Me	31.2	68.2	82
H	H	CH_3	Ph	55.9	44.1	31
Ph	H	H	Me	100	0	81
H	Ph	H	Me	100	0	81
H	H	Ph	Me	100	0	75
Ph	H	CH_3	Me	100	0	74

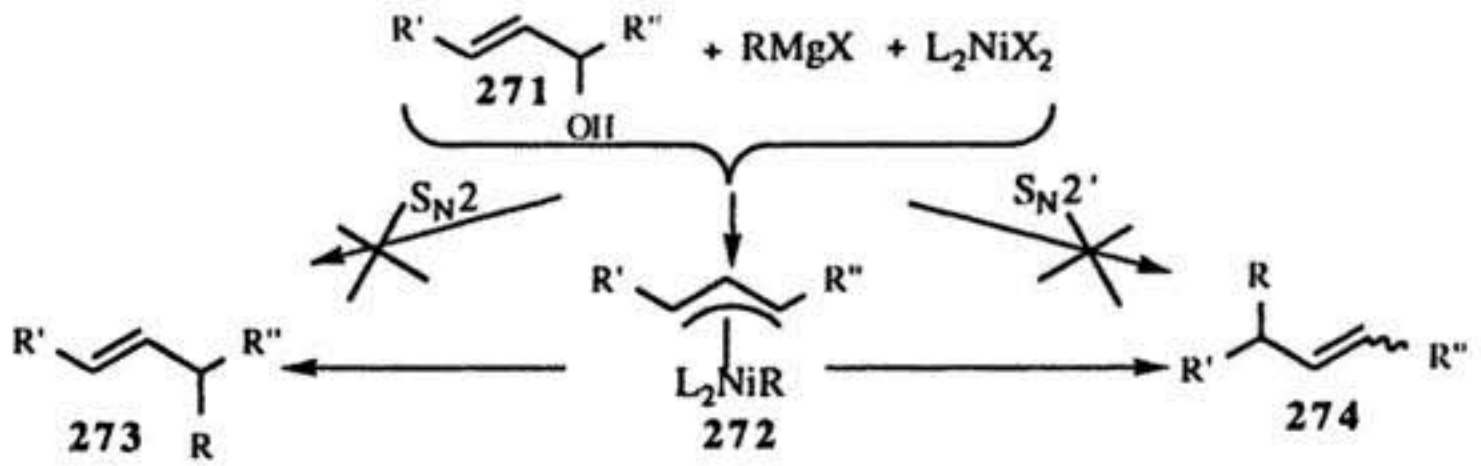
For a cyclic compound, when vinyl-1 cyclohexanol **268** is treated with methylmagnesium bromide, with 10 mol% of $NiCl_2(PPh_3)_2$, a 75:25 mixture of S_N2/S_N2', products **269** and **270** is obtained [Eq. (92)].



268 S_N2 **269** : S_N2' **270**

75 : 25 (74 %) (92)

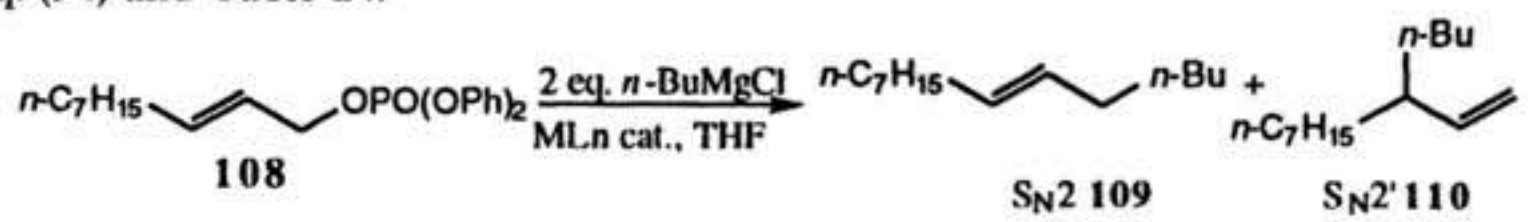
To rationalize these experimental results, the authors [91] proposed that the common intermediate is a π-allyl complex of nickel **272** that can give rise either to the S_N2-type coupled product **273**, or the S_N2'-type compound **274**, depending on the steric demands [Eq. (93)].



(93)

B. Allylic Phosphates

Yamamoto [16] examined the transition metal-catalyzed reactions of Grignard reagents with (*E*)-2-decenyl-1-diphenylphosphonate in THF. The results so observed are summarized in Eq. (94) and Table 24.



108 S_N2 **109** S_N2' **110** (94)

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Table 25

R_1	R_2	R_3	R	Ni catalyst	S_N2	S_N2'
CH_3	H	H	Ph	$NiCl_2[Ph_2P(CH_2)_3PPh_2]$	14	14
CH_3	H	H	Ph	$NiCl_2(PPh_3)_2$	66	34
H	H	CH_3	Ph	$NiCl_2[Ph_2P(CH_2)_3PPh_2]$	33	24
H	H	CH_3	Ph	$NiCl_2(PPh_3)_2$	55	38
CH_3	CH_3	H	Ph	$NiCl_2[Ph_2P(CH_2)_3PPh_2]$	7	7
CH_3	CH_3	H	Ph	$NiCl_2(PPh_3)_2$	62	35
Ph	H	H	Ph	$NiCl_2[Ph_2P(CH_2)_3PPh_2]$	96	0
Ph	H	H	$Ph(CH_2)_3$	$NiCl_2[Ph_2P(CH_2)_3PPh_2]$	83	0

Table 26

Entry	R_1	R_2	R_3	RMgX	Fe catalyst	S_N2'	S_N2
1	H	H	H	*n*-BuMgBr	$FeCl_3$	85	0
2	H	H	H	*sec*-BuMgBr	$FeCl_3$	70	0
3	CH_3	H	H	*n*-BuMgBr	$FeCl_3$	80	0
4	CH_3	CH_3	H	EtMgI	$FeCl_3$	80	0
5	CH_3	CH_3	H	*n*-BuMgBr	$FeCl_3$	80–90	0
6	CH_3	CH_3	H	*n*-BuMgBr	$Fe(acac)_3$	60	0
7	CH_3	CH_3	H	*sec*-BuMgBr	$FeCl_3$	75	0
8	CH_3	CH_3	CH_3	*n*-BuMgBr	$FeCl_3$	87	0
9	CH_3	CH_3	CH_3	*n*-BuMgBr	$FeBr_2$	80	0
10	CH_3	CH_3	CH_3	*i*-PrMgBr	$FeCl_3$	88	0
11	CH_3	CH_3	CH_3	MeMgI	$FeCl_3$	45	45
12	$-(CH_2)_5-$		CH_3	MeMgI	$FeCl_3$	45	45

Methylmagnesium iodide, in the presence of a catalytic amount of $FeCl_3$, reacted separately with two different propargyl chlorides (see Table 26, entries 11 and 12), to give a 1:1 mixture of S_N2 and S_N2' products. In the same study, Pasto also showed that $FeBr_2$ is an effective catalyst (see entry 9), whereas $Fe(acac)_3$ is not as effective as $FeCl_3$ (see entry 6).

VI. CONCLUSION

As we have seen, the S_N2/S_N2' ratio of the products formed by nucleophilic substitution of a Grignard reagent on allylic halides or related compounds is strongly dependent on several factors (e.g., the nature of the electrophilic substrate, solvent, counter-ion, Grignard reagent, and catalyst used). Therefore, for the preparation of a target molecule, by controlling all parameters of this high-yielding transformation, as shown in the foregoing, it is possible to obtain either compound with high chemo-, regio-, and stereoselectivity. But further new improvements are still to come.

ACKNOWLEDGMENT

We thank the CNRS for financial support, and Professor A. Cavé for his encouragement.

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25

Dihalide-Derived Di-Grignard Reagents: Preparation and Reactions

KEVIN C. CANNON
Elf Atochem North America, Inc.
King of Prussia, Pennsylvania

GRANT R. KROW
Temple University
Philadelphia, Pennsylvania

I. INTRODUCTION

The special utility of dihalide-derived di-Grignard reagents in the synthesis of cyclic metallocycles and carbocycles has required that a special section be devoted to the preparation and reaction of these species [1,2]. Reactions of magnesium, especially Rieke magnesium, with dienes to form magnesiacycloalkanes and spiroannelation reactions of di-Grignard reagents are covered specifically in Chapters 26 and 27, respectively. The ability to form di-Grignard reagents is largely a function of the positional relationship of 1,x (x=1, 2, $\cdots n$)-dihalide substituents on alkyl, alkenyl, alkynyl, aryl, and benzyl or allyl substrates; therefore, the discussion will be based on dihalide substrates. Di-Grignard reagent formation can be strongly dependent on choice of halogen, solvent, concentration, and type of activated magnesium.

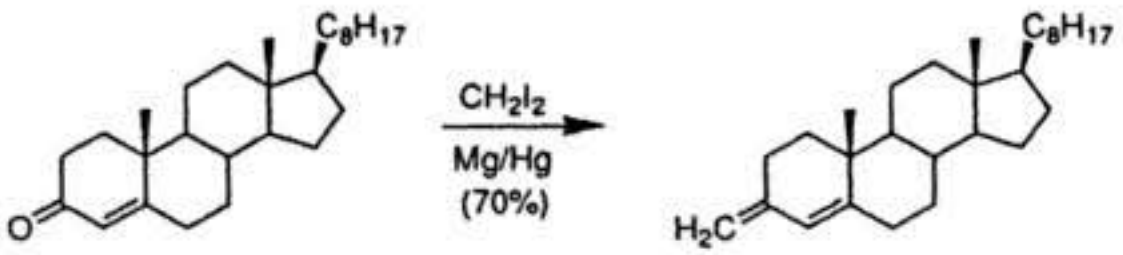
II. ALKYL DI-GRIGNARD REAGENTS

Stable geminal or methylene di-Grignard reagents $CH_2(MgX)_2$ have been prepared in 50–60% yields from CH_2X_2 (X=Br, I) and iodine-activated magnesium, or better with magnesium amalgam (0.5–3%) in 1:1 ether–benzene [3–5]. An alternative, higher-yielding synthesis of the methylene di-Grignard reagent involved the reaction of CH_2Br_2 and magnesium amalgam in isopropyl ether [6]. Yields of 60–80% are reported. The soluble

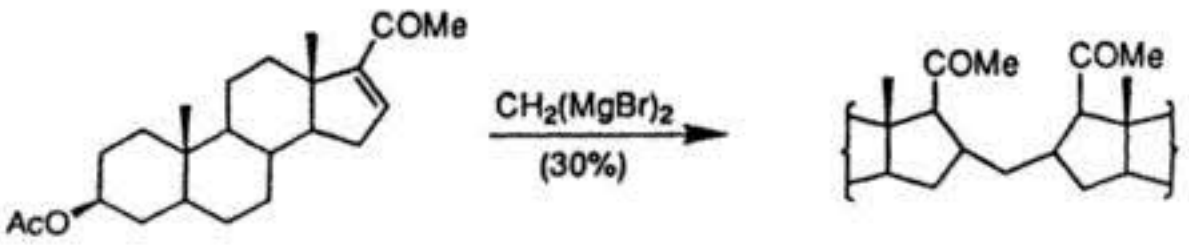
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by-product methylmagnesium bromide was separated from methylenedimagnesium dibromide by decantation, and the resultant slurry was subsequently dissolved in 1:1 diethyl ether–benzene. A mechanistic study of the reaction of 6,6-diiodo-5,5-dimethyl-1-hexene with magnesium in tetrahydrofuran (THF) with sonication showed rapid formation of mainly a *cis–trans* mixture of 1-iodomethyl-2-iodo-3,3-dimethylcyclopentane [7]. Reaction products were consistent with a single-electron radical chain mechanism.

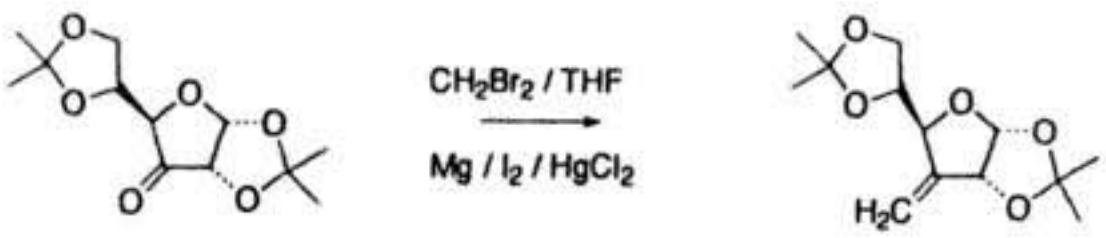
Methylene di-Grignard reagents methylenate alkyl and aryl aldehydes and ketones, in generally reasonable yields, at room temperature in a few minutes, in benzene–diethyl ether solutions. The reagents can be prepared in situ. The reagent is selective for reaction at the carbonyl group of cholest-4-en-3-one **1**, to give diene **2** [Eq. (1)] [3]. However, 3β-acetoxy-5α-pregn-16-en-20-one **3** affords a product **4**, formed by two successive conjugate additions in 30% yield, with only traces of methylenation product [Eq. (2)] [3]. Methylene dibromide has been converted to methylene dimagnesium bromide and reacted in situ with ulose sugars in THF. The magnesium is activated by catalytic amounts of iodine and mercuric chloride; this mixture serves as an alternative to the use of magnesium amalgam [8]. The yield in the methylenation of ketone **5** to afford alkene **6** [Eq. (3)] is superior to that of an alternative Wittig reaction.



1 2 (1)



3 4 (2)

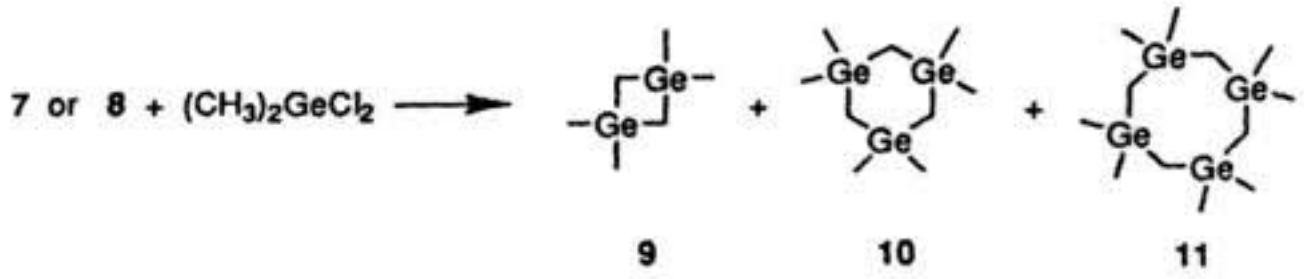


5 6 (3)

The conversion of the methylene di-Grignard reagent $CH_2(MgBr)_2$ **7** to a proposed methylenemagnesium–methylenedimagnesium dibromide reagent **8** [Eq. (4)] by repeated washing with fresh THF enhanced the reactivity of the di-Grignard reagent. This has been demonstrated in the synthesis of dimetallomethanes and polymetallocycloalkanes of main group XIV (IVA) elements [9]. The THF-washed reagent demonstrated superior yields in the synthesis of bis(trimethylsilyl)methane (55%) and bis(trimethylgermyl)methane (92%) compared with the unwashed reagent (low and 61%, respectively). Extraction of $MgBr_2$ from di-Grignard reagent **7** also altered the product distribution in the synthesis of the polygermacycloalkanes. The reagent **7** yielded the four-, six-, and eight-membered ring

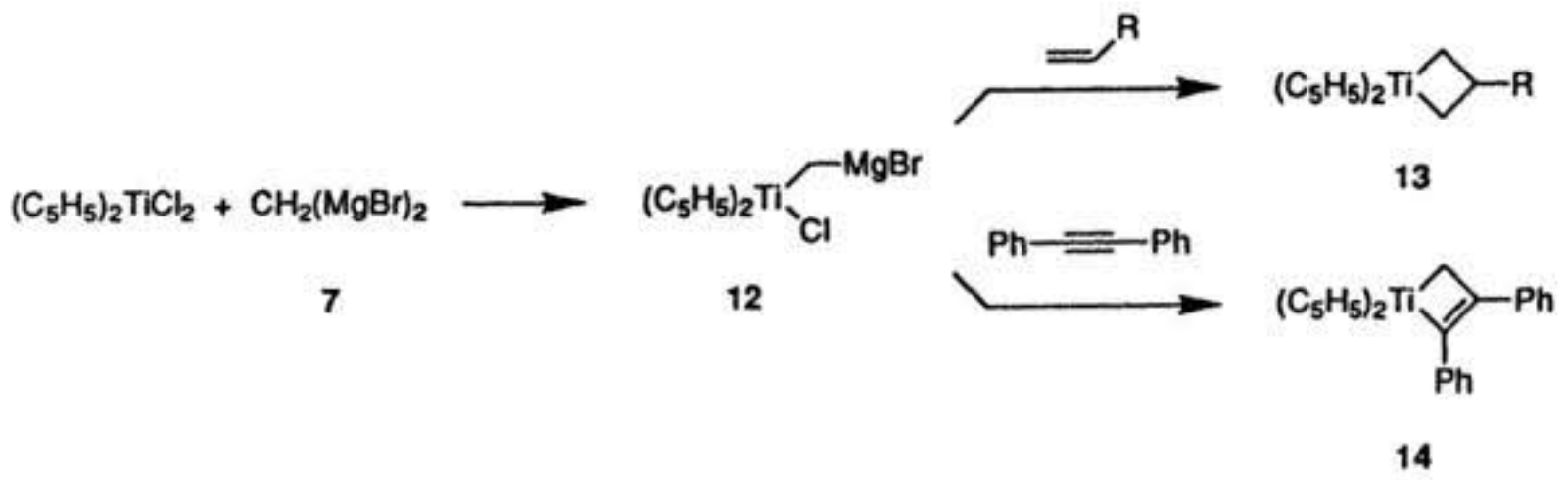
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compounds **9–11** in yields of 12, 36, and 2.3%, respectively; whereas reagent **8** yielded **9–11** in yields of 32, 17.5, and 1.8%.



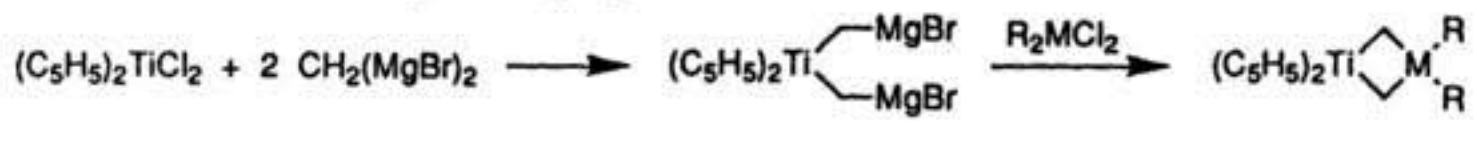
(4)

Titanacyclobutanes have also been synthesized using methylene di-Grignard reagent **7** [Eq. (5)]. The addition of 1 equivalent of **7** to Cp_2TiCl_2 yields **12** [10a]. Compound **12**, an analogue of Tebbe's reagent, $Cp_2TiCH_2[AlCl(CH_3)_2]$, was assigned as an open structure, based on ^{1}H-nuclear magnetic resonance (NMR) data. Reaction of complex **12** with alkenes and alkynes yielded titanacyclobutanes **13** and titanacyclobutenes **14**, respectively [5]. Attempts to reproduce this reaction sequence with zirconocene dichloride, however, were not successful.



(5)

The addition of two equivalents of the methylene di-Grignard reagent **7** with Cp_2TiCl_2 yields the titanocene di-Grignard reagent **15** (40%), which can be converted to a variety of 1,3-metallatitanacyclobutanes **16** by reaction with R_2MCl_2 [Eq. (6) and Table 1; 10b,11]. Competitive formation of 1,3-dititanacyclobutanes was observed in the synthesis of the germanium and tin complexes [11].

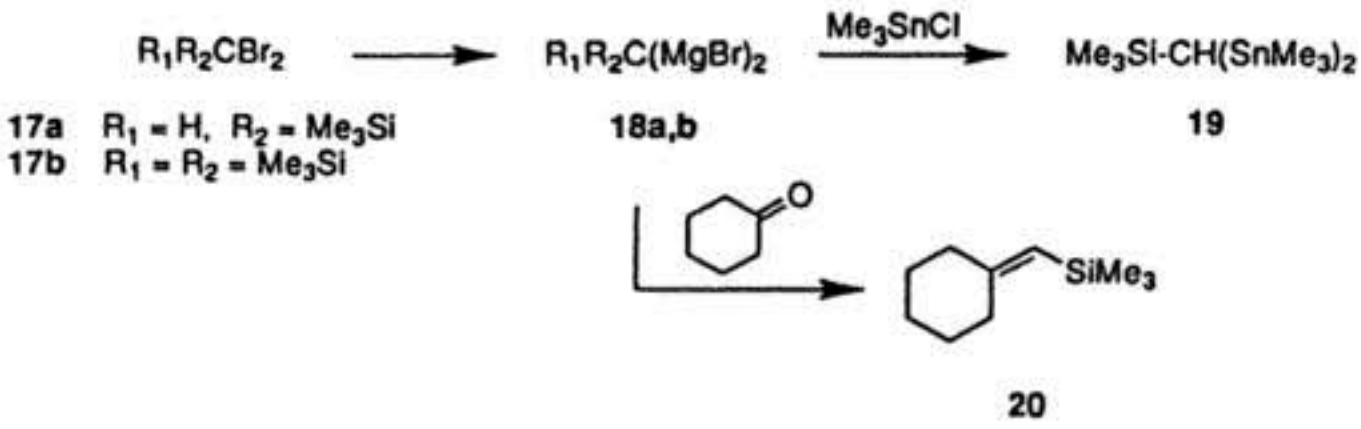


16a M = Si, R = CH_3 (100%)
16b M = Ge, R = CH_3 (75%)
16c M = Sn, R = CH_3 (15%)
16d M = Ti, R = C_5H_5 (33%)
16e M = Zr, R = C_5H_5 (31%)
16f M = Hf, R = C_5H_5 (36%)

(6)

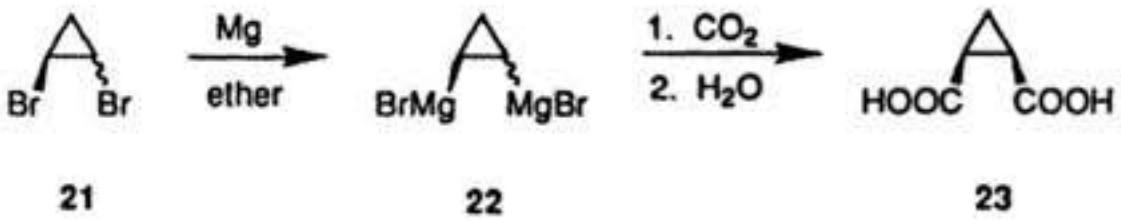
The trimethylsilyl-substituted methylene di-Grignard reagent **18** has been prepared by reaction of the geminal dibromide **17a** [Eq. (7)] with magnesium amalgam in isopropyl ether [12] or, alternatively, by treatment of dibromide **17a** with zinc(Cu) in THF, followed by heating of the resultant organozinc compound with magnesium for 2 days [13]. Reaction of dibromide **17a** in situ with magnesium amalgam in diethyl ether followed by addition

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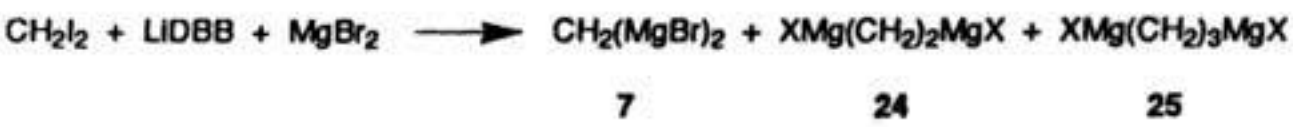
(7)

(8)], which has been obtained from both *cis*- and *trans*-1,2-dibromocyclopropane **21** with magnesium in diethyl ether in an evacuated, sealed glass apparatus. The reagent **22** reacts with carbon dioxide to afford the *cis*-diacid **23** [17]. The 1,2-di(bromomagnesio)cyclopropane reagent **22** can be precipitated from diethyl ether solution, but a dialkylmagnesium species precipitates from THF.



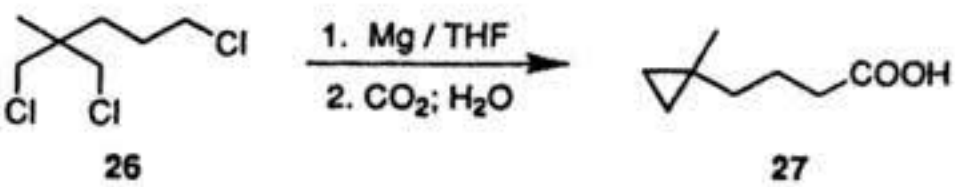
(8)

An acyclic 1,2-di-Grignard reagent, 1,2-di(bromomagnesio)ethane **24**, has been generated in situ at $-100°C$ by the reaction of CH_2I_2 with lithium-*p*,*p*'-di-*tert*-butylbiphenyl in the presence of $MgBr_2$ [18]. The yield of the 1,2-di-Grignard **24** was only 10%, as determined by reaction of the solution with trimethyltin chloride. The 1,1- and 1,3-di-Grignard reagent products **7** and **25** were formed in yields of 40 and 15%, respectively [Eq. (9)].



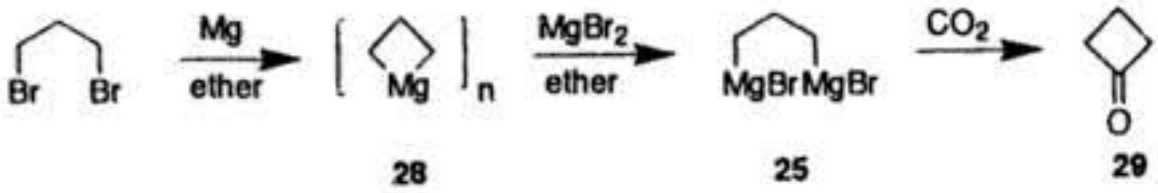
(9)

The reaction of 1,3-dihalopropanes with magnesium is a useful route to cyclopropanes, as can be seen in the reaction of trichloride **26** to afford acid **27** [Eq. (10); 19]. Whitesides et al. were first able to prepare 1,3-di(bromomagnesio)propane **25** from allene in five steps [20]. Purified **25** [Eq. (11)] has been prepared in 30% yield from 1,3-dibromopropane and triply sublimed magnesium in ether [21]. Removal of diethyl ether and addition of THF afforded a precipitate of an oligomer of magnesiacyclobutane **28**. Extraction of the precipitate with THF removed the side-product 1,6-di(bromomagnesio)hexane (15% yield). Addition of exactly 1 mol of magnesium bromide in diethyl ether to **28** re-forms the di-Grignard reagent **25**. Reaction of the di-Grignard reagent **25** with CO_2 is useful in the laboratory-scale preparation of cyclobutanone **29**; the straightforward synthesis is competitive in price with other routes to **29**. If addition of carbon dioxide is too rapid, glutaric acid is obtained [22].



(10)

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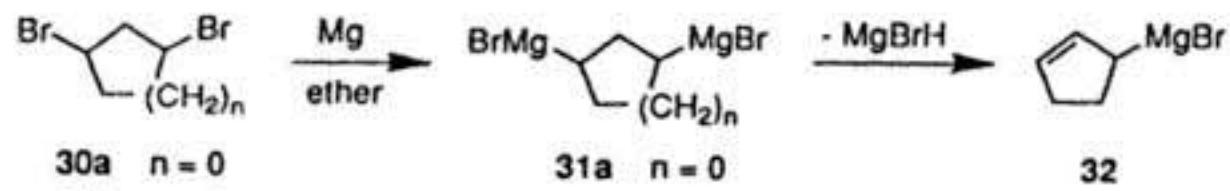


28 25 29 (11)

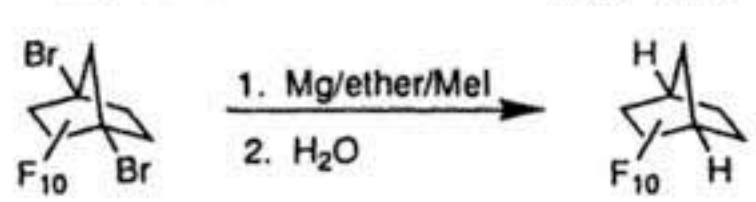
Application of the purified magnesium method to 1,3-dibromo-2,2-dimethylpropane affords 15–18% of 1,3-di-Grignard reagent [23], which has been reacted with two molecules of cyclohexanone to afford the expected 1,3-diol [24]. However, the substitution pattern of the 1,3-di-Grignard reagent is limited; one β-alkyl substituent resulted in low yields and high decomposition rates owing to increased β-hydride mobility [25].

The application of 1,3-di-Grignard reagents in the synthesis of metallacyclobutanes has been reviewed by Bickelhaupt [25]. Table 1 provides an updated listing of metallacyclobutanes and 4-metallaspiro[3.3]heptanes synthesized from 1,3-di-Grignard reagents. Facile oligomerization of observed stannacyclobutane derivatives made their isolation unsuccessful [25,29]. In contrast, reaction of $MeSbCl_2$ with 1,3-di-Grignard produced no stibacyclobutane, but directly produced distibacyclooctane [30]. There was no evidence for stibacyclobutane oligomerization. Low yields (1–5%) were also realized for unsubstituted transition metal derivatives owing to β-hydride elimination of the metallacyclobutanes, which occurred rapidly at $-20°C$.

It has been possible to prepare di-Grignard reagents **31a** and **31b** from 1,3-dibromocyclobutane **30a** and 1,3-dibromocyclopentane **30b** using doubly sublimed magnesium in deithyl ether [Eq. (12); 23]. Yields are 9 and 45%, respectively. The cyclopentyl di-Grignard reagent **30b** decomposes with loss of MgHBr to form an allyl Grignard reagent **32**. The di-Grignard reagents **31** can be reacted with carbon dioxide to form diacids and with trimethylsilyltin chloride to afford organotin compounds [23]. The bridgehead bromines of 1,4-dibromo-decafluoronorbornane **33** react in diethyl ether with magnesium-activated methyl iodide to form a di-Grignard reagent, which protonates on addition of water to give fluoronorbornane **34** [Eq. (13); 31].

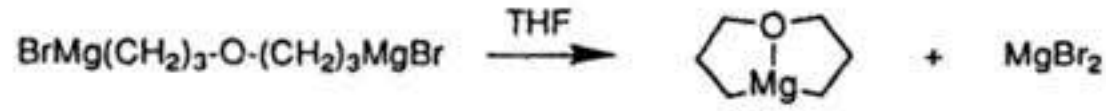


30a n = 0 31a n = 0 32
30b n = 1 31b n = 1 (12)



33 34 (13)

Di-Grignard reagents in which the magnesium halide functionalities are in a 1,*n*-relationship are easily prepared by reaction of the corresponding 1,*n*-dibromoalkane ($n>3$) with magnesium in diethyl ether or THF [32]. The di-Grignard reagent prepared from 1,5-dibromopentane is in equilibrium with the magnesiacyclohexane or related polymeric species [32], and an X-ray structural determination of the dimer isolated from THF has been reported [33]. After 1.5 hr, oxygen coordination drives the di-Grignard reagent **35** to form 1-oxa-5-magnesiacyclooctane **36** quantitatively [Eq. (14); 34].



35 36 (14)

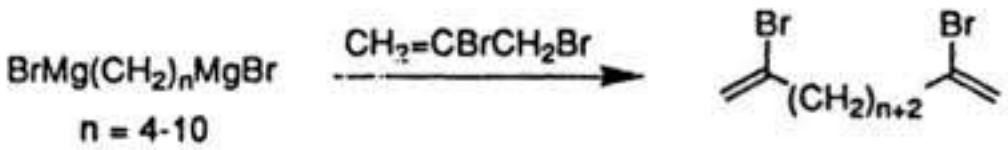
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Linear 1,*n*-di-Grignard reagents ($n=4$–10) have been prepared by addition of magnesium to the appropriate 1,*n*-dibromides in THF [35]. The di-Grignard reagent formed from 1,4-dibromobutane reacts with trimethylsilyl chloride in THF to form the disilane **37** [Eq. (15); 36] and the linear di-Grignard reagents **38** react with 2,3-dibromopropene to give products **39** by dialkylation at the allylic position [Eq. (16); 37,38].



(15)

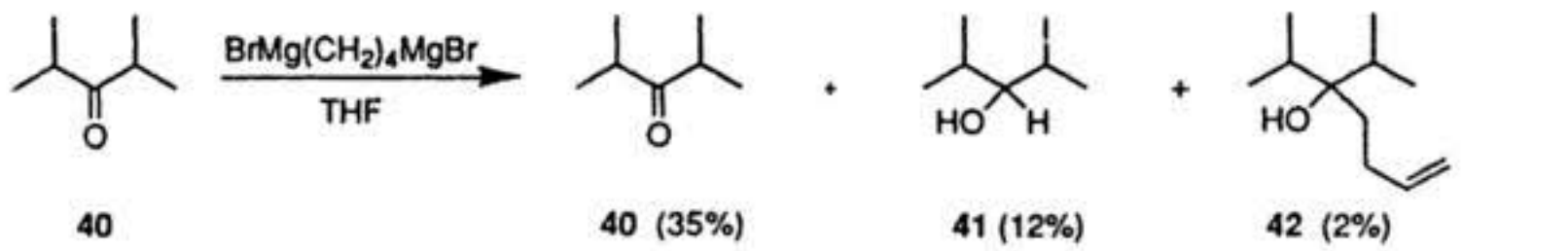
37



(16)

38 **39**

A study of the additions of 1,*n*-di-Grignard reagents ($n=4$–6) with diisopropyl ketone **40** reveals complex behavior, as is shown for the reaction with 1,4-di(bromomagnesio)butane [Eq. (17); 35]. A mixture was formed consisting of starting ketone **40** arising from Grignard reagent-induced enolate formation; alcohol **41** formed by hydride reduction of starting ketone; alcohols **42** and **43**, formed as products of di-Grignard reagent addition, followed by hydride expulsion or intramolecular enolate formation (protonation); and diaddition product **44**, formed by addition of ketone **40** to both ends of the di-Grignard reagent.



40 **40 (35%)** **41 (12%)** **42 (2%)**

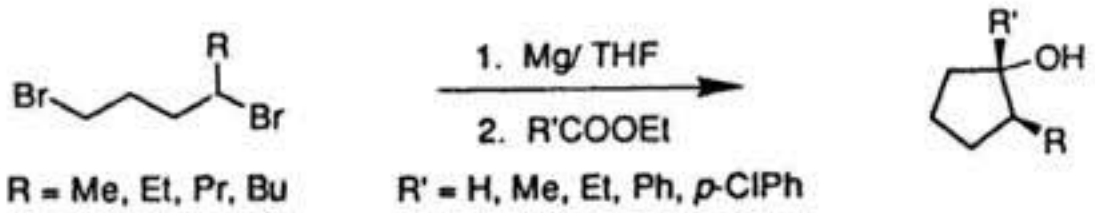
43 (26%) **44 (12%)**

(17)

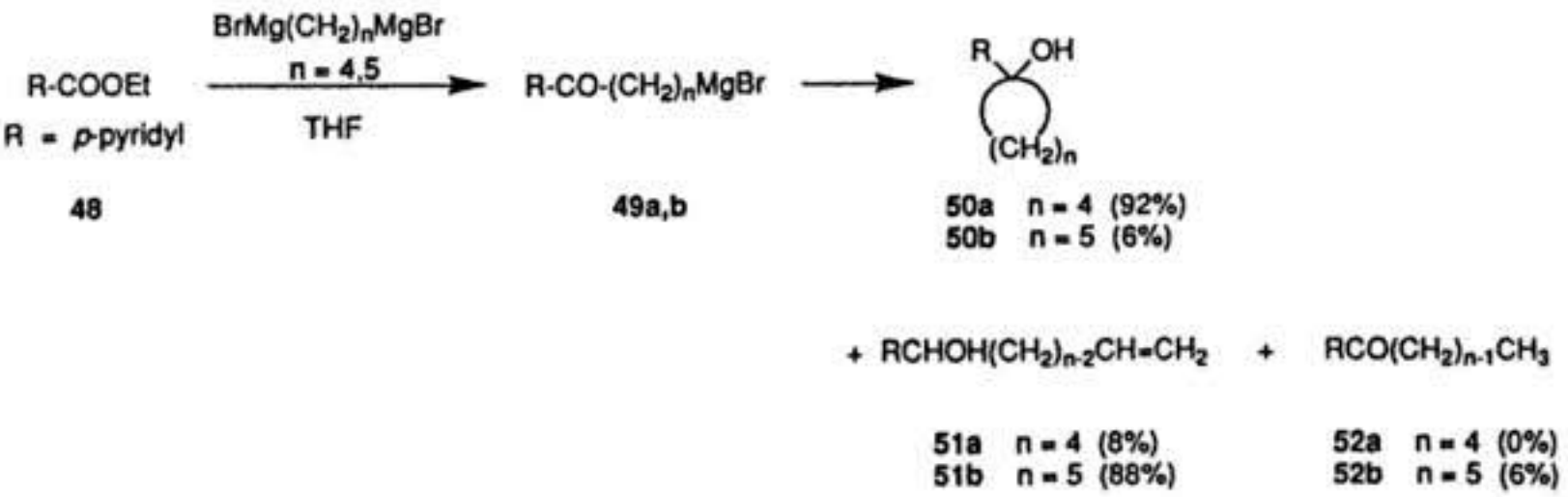
Of special interest to this account are the reactions of di-Grignard reagents with acid derivatives, since two Grignard reagent additions to the same atom can lead to the formation of cyclic alcohols. A stereochemical study of ring closures of di-Grignard reagents formed from 1,4-dibromoalkanes **45** with ethyl esters of aryl and alkyl acids **46** in THF, led to 68–88% yields of cyclopentanols **47** having mainly (77–96% stereoselectivity) *cis*-dialkyl substitution [Eq. (18); 39,49]. A specific example is the conversion of ethyl acetate (**46**, R′ = Me) and 1,4-di(bromomagnesio)pentane (**45**, R = Me) to a 96:4 mixture of *trans*-OH and *cis*-OH cyclopentanols **47** (R = Me) in 77% yield. Reactions were carried out at 25°C to avoid precipitation of magnesium bromide from the solution. The cyclization reaction is subject to a steric effect, as shown by comparison of the reaction of the 4-pyridyl ester **48** [Eq. (19)] with 1,4-di(bromomagnesio)butane and 1,5-di(bromomagnesio)pentane [41]. Addition of the di-Grignard reagents to the ester **48** forms keto-Grignard intermediates **49**, which undergo cyclization to cycloalkanols **50**, intramolecular reduction to alkenols

Material chroniony prawem autorskim

51, or enolization to ketones **52** in the ratios given in parentheses. Cyclication to **50a** is favored for the five-membered ring, but transfer of a hydride from a position β to the magnesium to give alkenol **51b** is favored over formation of a six-membered ring **50b** [41].

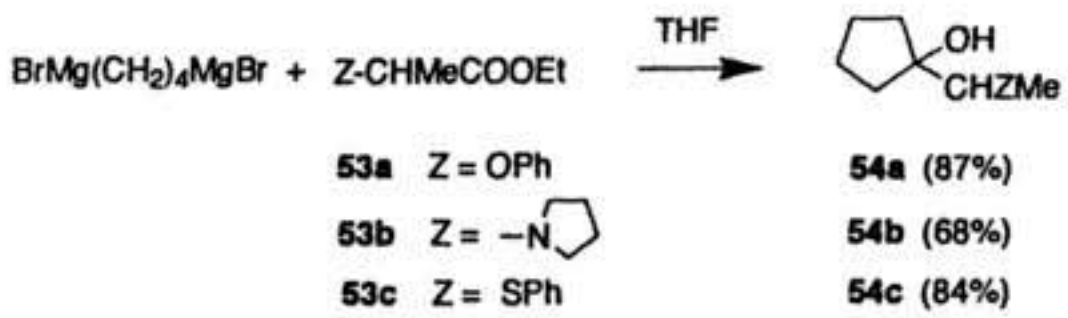


(18)

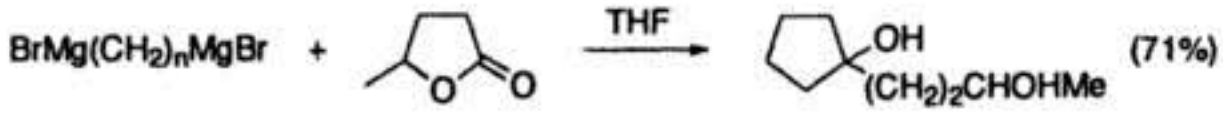


(19)

The di-Grignard method has also been applied to reactions of disubstituted amino [41,42], phenoxy, and phenylthio esters [42] to provide difunctional cycloalkanols; examples include the conversion of esters **53** to cyclopentanols **54** [Eq. (20); 42]. Similarly, lactones can be converted to diols as in the formation of cyclopentanol **56** from lactone **55** [Eq. (21); 43].

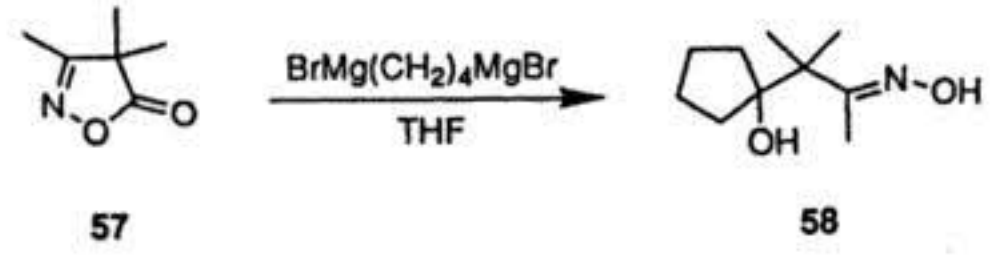


(20)



(21)

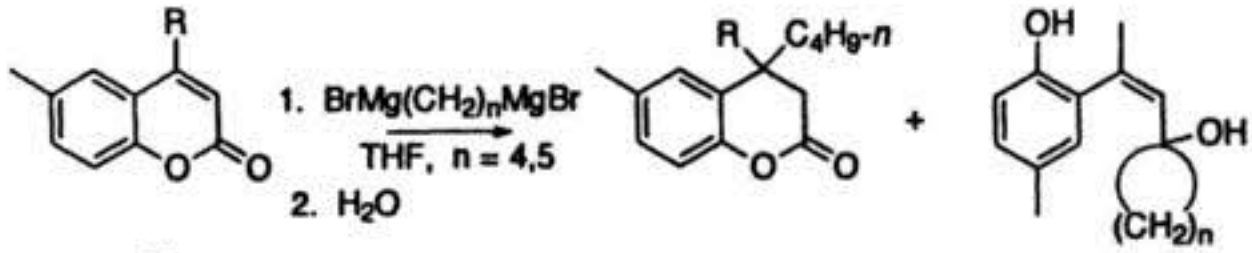
The conversion of 3,4,4-trialkylisoxazol-5-ones to oximes of 3-alkyl-3-(1-hydroxycyclopentyl)alkan-2-ones is evidenced by the reaction of **57** with 1,4-di(bromomagnesio) butane to afford oxime **58** [Eq. (22); 44]. The reaction can be contrasted with that of mono-Grignard reagents, which react only once at the carbonyl group of these substrates [44].



(22)

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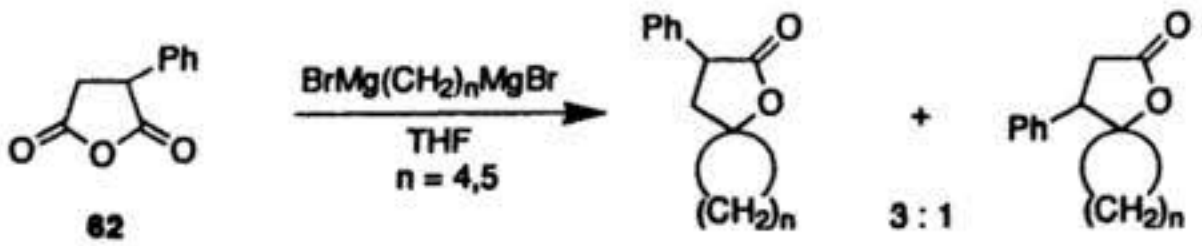
Coumarins **59**, which are conjugated lactones, react with 1,4-di(bromomagnesio)butane to give mixtures containing minor amounts of 4-alkyl-3,4-dihydrocoumarin **60**, formed by conjugate addition and hydrolysis, and major formation of 1-(*o*-hydroxystyryl)cyclopentanol **61**, formed by diaddition at the carbonyl group [Eq. (23); 45]. Reaction of coumarin **59c** with 1,5-di(bromomagnesio)pentane gave mainly conjugate addition product **60c**. The C-4 substituted coumarins **59b** and **59d** gave mainly cycloalkanol products **61b** and **61d** with either di-Grignard reagent.



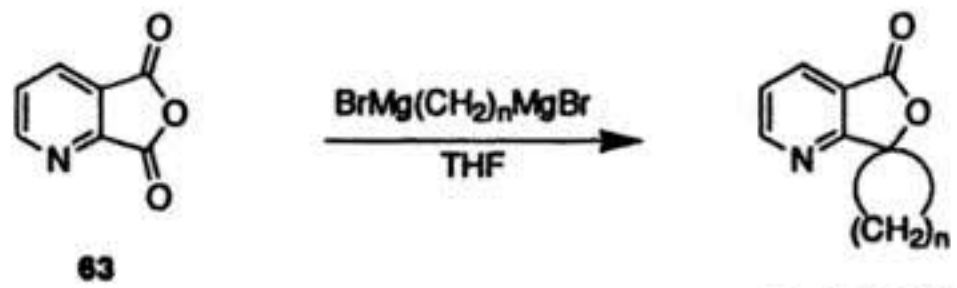
R = H, n = 4	(31%)	(47%)
R = Me, n = 4	(0%)	(65%)
R = H, n = 5	(43%)	(19%)
R = Me, n = 5	(10%)	(59%)

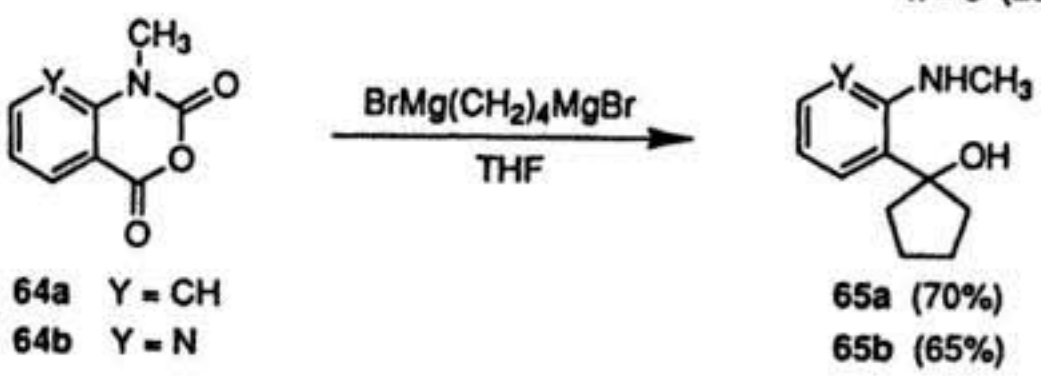
(23)

Anhydrides react with 1,4-di(bromomagnesio)butane and 1,5-di(bromomagnesio) pentane to form spirolactones [46–48]. Steric and electronic factors influence this reaction, as shown by the regioselectivity in the reaction of anhydrides **62** and **63** in Eq. (24). Unlike the reactions of esters, anhydrides react with 1,5-di(bromomagnesio)pentane to give generally useful yields of cyclohexane derivatives. Isotoic anhydride **64a** and azaisotoic anhydride **64b** react in the same way with 1,4- and 1,5-di(bromomagnesio)cycloalkanes to give substituted cycloalkanols **65a** and **65b** [Eq. (25)]; the 1-*o*-aminophenylcycloalkanols **65b** are difficult to prepare by other methods [49].



(24)

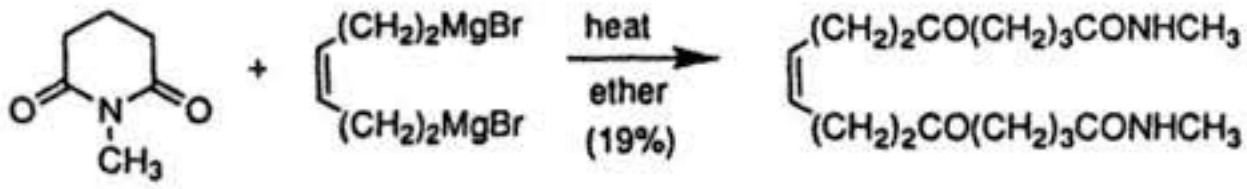




(25)

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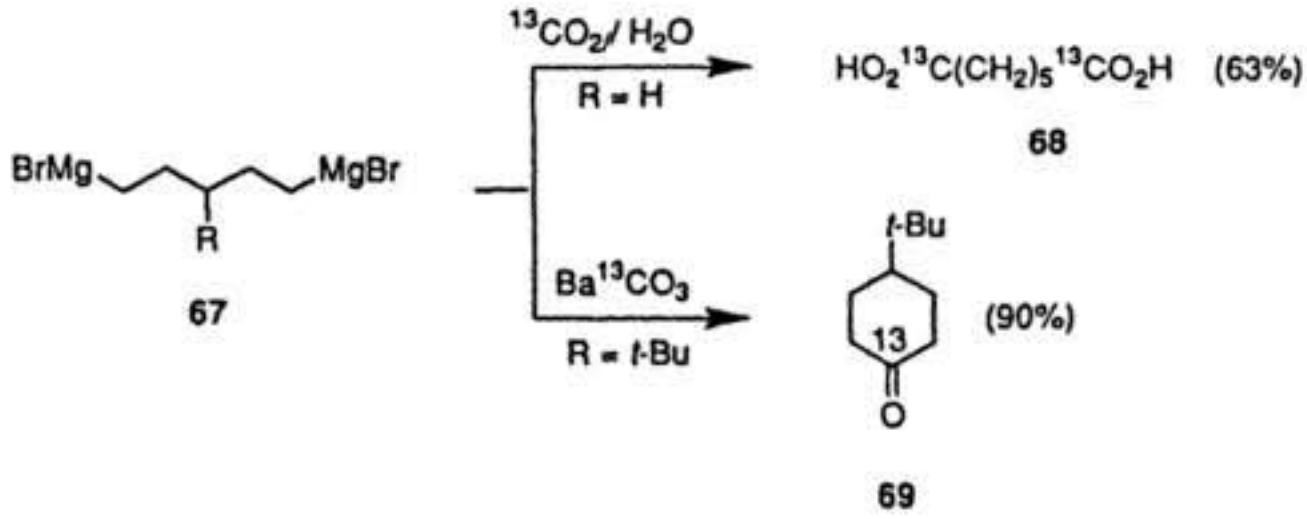
A method for formation of unsaturated ω,ω'-dicarboxylic acids by reaction of the di-Grignard reagents formed from 1,6-dibromohex-3-ene, or 1,8-dibromooct-4-ene, and *N*-methylglutarimide has been developed [50]. The formation of the diamide **66**, shown in Eq. 26, is an example. The chain extension method has also been applied to formation of diacids from long chain (C-9 and C-19) α,ω-dibromoalkanes.



(26)

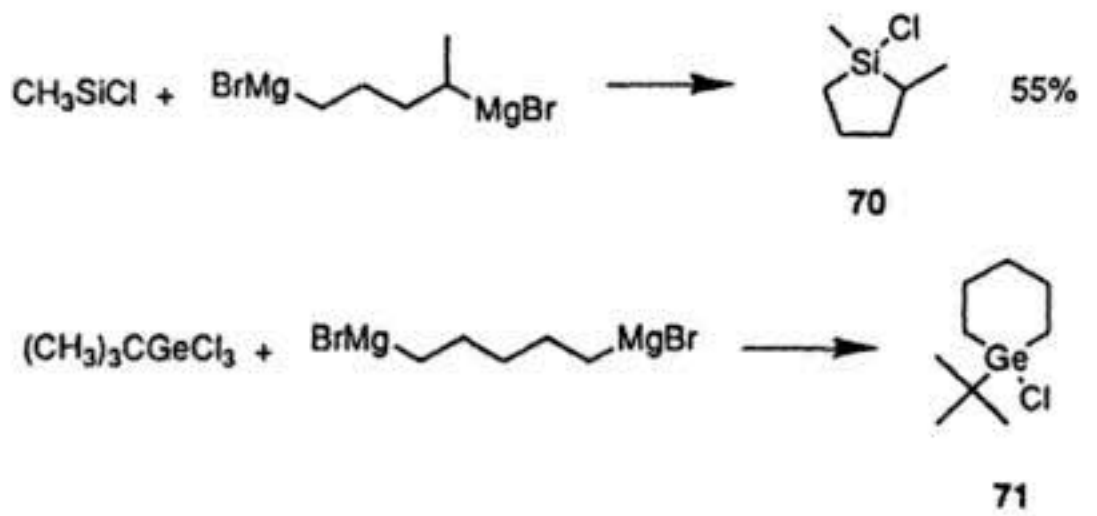
66

Carboxyl-labeled dicarboxylic acid **68** has been prepared from 1,5-di(bromomagnesio) pentane and labeled carbon dioxide [Eq. (27); 51]. However, when the di-Grignard reagent **67** was heated with isotopically labeled barium carbonate, labeled 4-*t*-butylcyclohexanone **69** was isolated [52].



(27)

Heterocyclopentane derivatives of Si [53,54], Ge [55], B [56], Ga [57], Al [57], and P [58] have been synthesized utilizing 1,4-di-Grignard reagents and aryl- or alkyl-substituted heteroatom dichlorides or dibromides. Similarly, heterocyclohexane derivatives of Si [59], Ge [60], As [61], Ga [57], and Al [57] have been realized using 1,5-di-Grignard reagents. Dihalides, such as $(Me_3Si)_2SiCl_2$ [53], $MeSiHCl_2$ [54], $(Et_2N)BCl_2$ [56], and $Cl_2P(O)OEt$ [58] have been successfully used to provide alternative substituents on the heteroatom. Alkyltrihalides, such as $MeSiCl_3$ [54] and *t*-$BuGeCl_3$ [60], have been successfully reacted with di-Grignards to produce the corresponding halogen-substituted heterocycles **70** and **71** in good yields, as shown in Eq. (28).

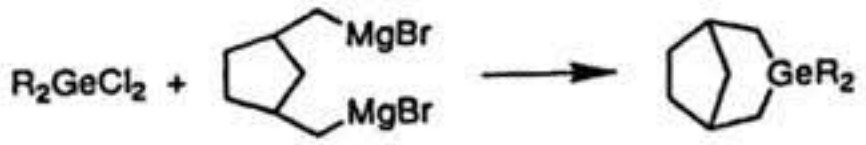


(28)

Bicyclic compounds can be synthesized from the appropriate di-Grignard reagent. 3-Germabicyclooctanes **73** have been synthesized from the di-Grignard reagent **72**

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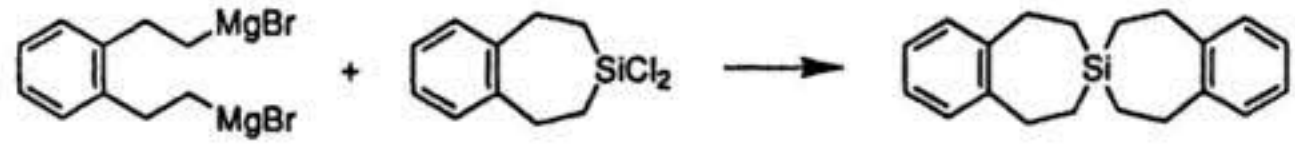
derived from *cis*-1,3-bis(bromomethyl)cyclopentane in diethyl ether [62]. The yield of the diphenyl compound **73a** was 41%, whereas that of the dimethyl compound **73b** was 21% [Eq. (29)].



(29)

72 **73a** R = Ph
73b R = Me

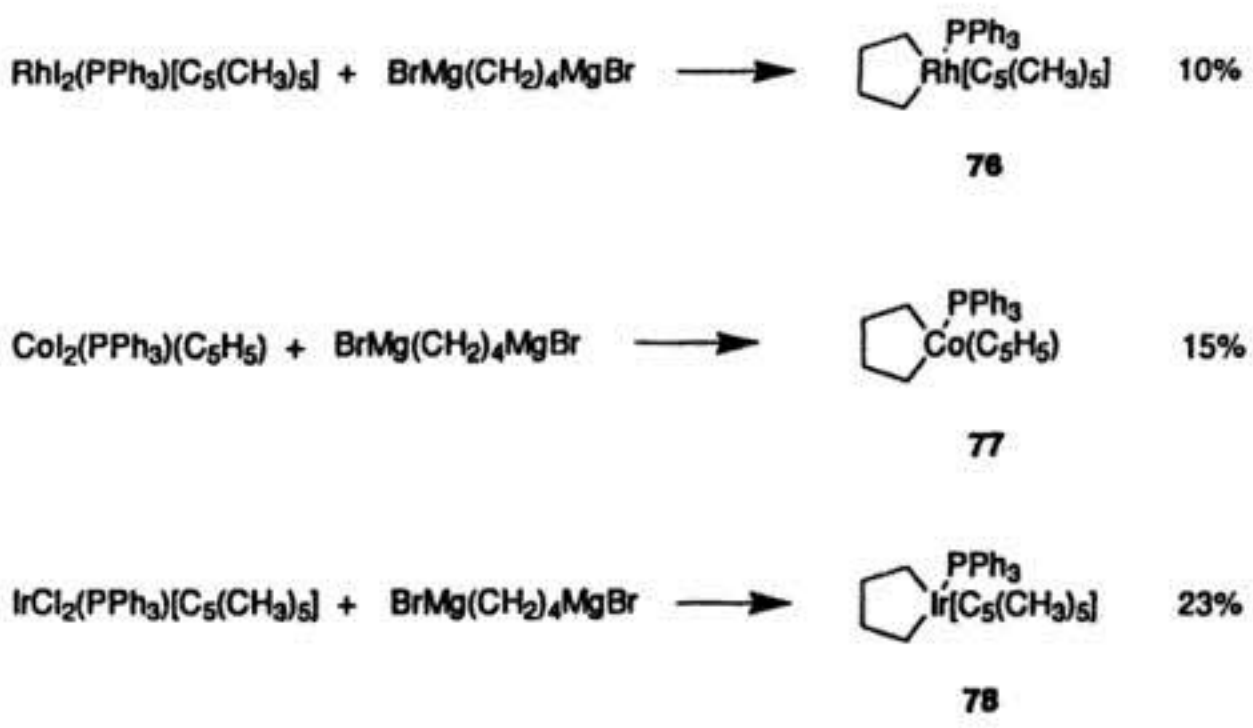
Spirobenzosilepines were prepared from the reaction of di-Grignard reagent **74** and dichlorobenzylsilepine derivatives in diethyl ether and THF [63]. Synthesis of spirocycle **75** was achieved with a yield of 31% [Eq. (30)].



(30)

74 **75**

Metallacyclopentane derivatives **76–78** of rhodium(III), iridium(III), and cobalt(III) have been synthesized by reacting 1,4-di(bromomagnesio)butane in THF at room temperature with dihalide complexes [Eq. (31); 64,65]. Use of a dioxane solution of magnesiocyclopentane did not affect the yield of the rhodacyclopentane **76** [64]. Several 3-alkyl- and 3,4-dialkyl-iridacyclopentane analogues of **78** were synthesized using 1,4-di-Grignard reagents prepared from the corresponding dichloroalkanes [66]. Yields ranged from 5% for the 3-isopropyl adduct to 45% for the 3,4-dimethyl adduct.



(31)

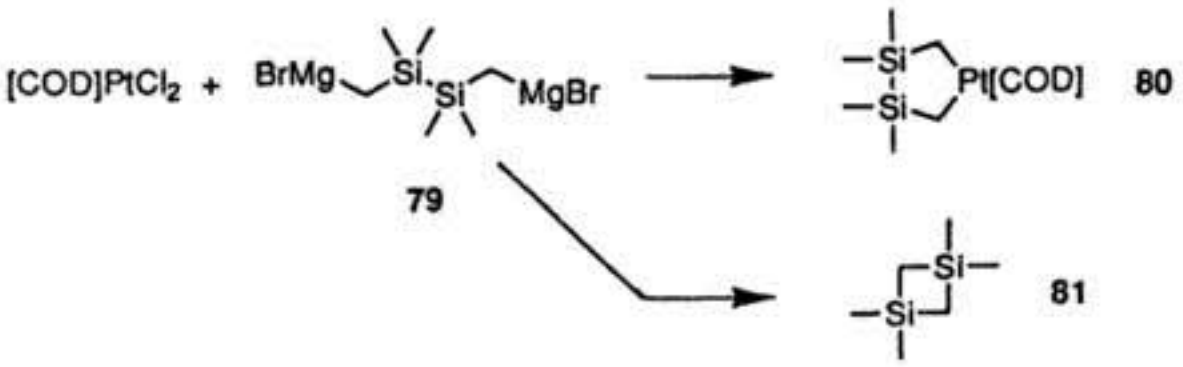
76

77

78

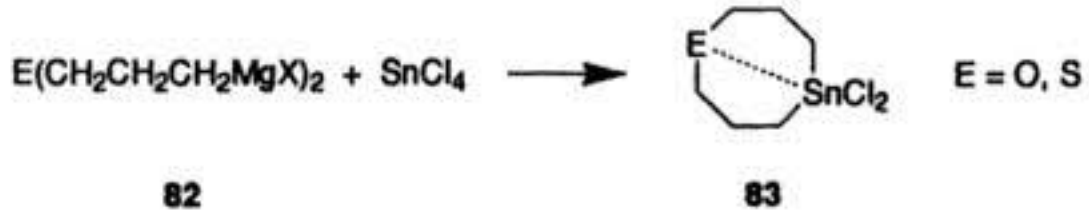
The di-Grignard reagent **79**, synthesized in a 60% yield from 1,2-di(bromomethyl) tetramethyldisilane and magnesium in diethyl ether, was successfully used in the synthesis of the platinadisilacyclopentane **80**, which was obtained in a 46% yield [Eq. (32); 67]. Similarly, a nickeladisilacyclopentane derivative was synthesized in 20% yield, but it was not isolated from the solution. In the formation of the di-Grignard reagent **79**, the novel 1,3-disilacyclobutane **81** was also isolated in 20% yield.

Material chroniony prawem autorskim



(32)

Di-Grignard reagents E-$(CH_2CH_2CH_2MgX)_2$ (E = O, S, NMe) have been used to synthesize a variety of metallaheterocyclooctanes. 1-Stanna-5-oxa- and 1-stanna-5-thiacyclooctane derivatives **83** were synthesized by reaction of the corresponding di-Grignard reagents **82** with $SnCl_4$ in yields of 35 and 10%, respectively [Eq. (33); 68].



(33)

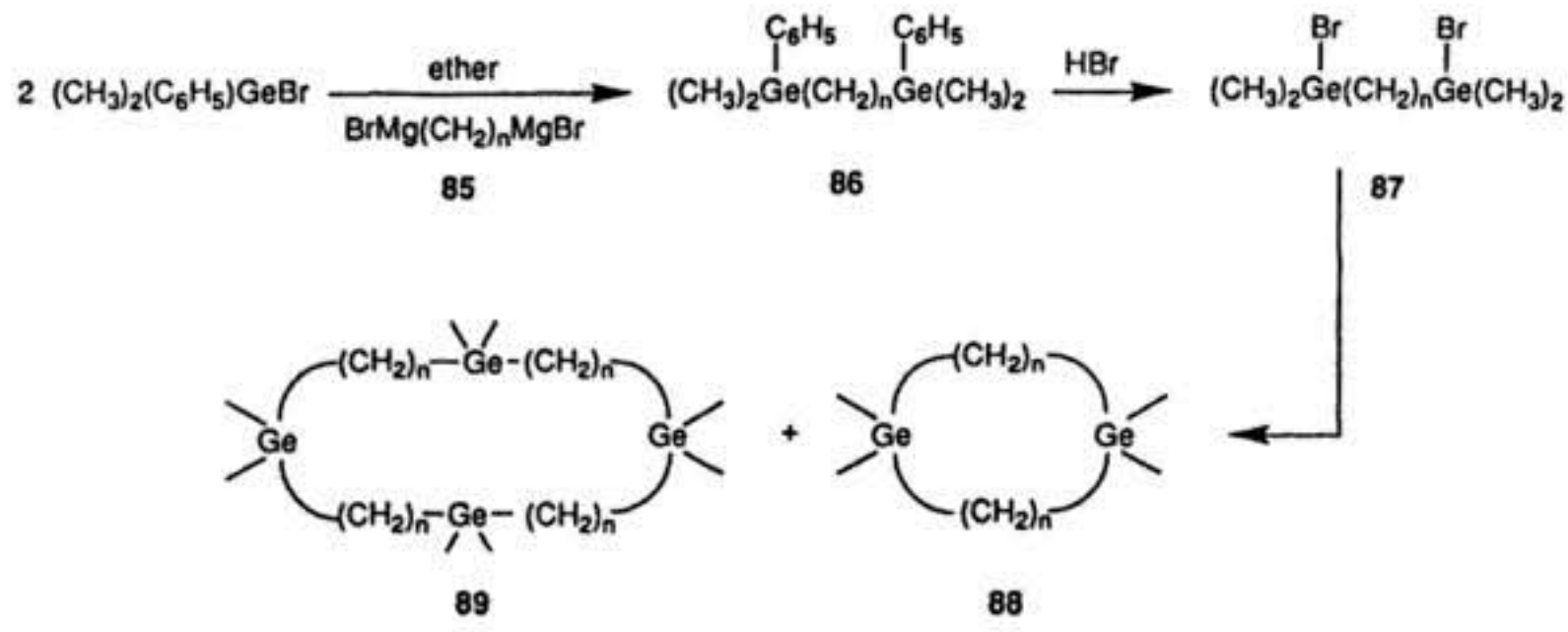
There have been reports of 1-metalla-5-aza-cyclooctanes of Al [57], Ga [57], In [57], Sn [68], P [69], and Si [70] from the reaction $MeN(CH_2CH_2CH_2MgX)_2$ and dihalide compounds. The tri-Grignard reagent $N(CH_2CH_2CH_2MgX)_3$ has been used to make 1-galla- and 1-aluma-5-azabicyclo[3.3.3]undecanes **84a–b** [Eq. (34)], in addition to 1-aza-5-sila-5-methyl-bicyclo[3.3.3]undecane **84c** [57,70].



84a M = Ga
84b M = Al
84c M = $SiCH_3$

(34)

Dimetallacycloalkanes have been prepared by reacting 1,*n*-di(bromomagnesio)alkanes ($n > 3$) with di(halometalla)alkanes, which also have been derived from di-Grignard reagents. Scheme 1 outlines the synthetic methodology for digermacycloalkanes **88** used by

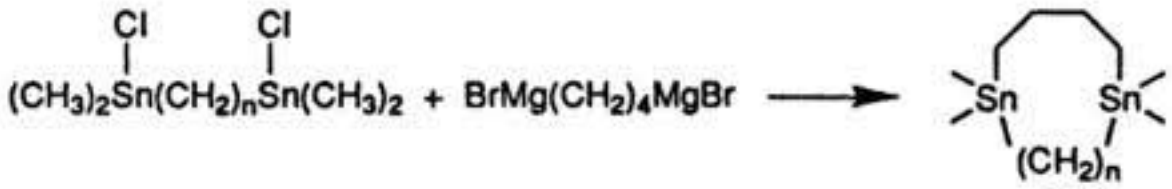


Scheme 1

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Takeuchi et al. [71]. Dimetallaalkanes **86**, produced in goods yields (70–92%) from the reaction of halide dimethylphenylgermanium bromide with di-Grignard reagent **85**, were converted to di(bromogerma)alkane **87** by reaction with HBr (83–89%). Compound **87** was then reacted with an equivalent of di-Grignard reagent **85** to produce digermacycloalkane **88**; yields ranged from 18% ($n=6$) to 9% ($n=8,10$). Yields of tetragermacycloalkane **89** ranged from 7% ($n=5$) to 2% ($n=8$).

Kuivila et al. synthesized distannacycloalkanes **91** by the reaction of di(chlorostanno) alkanes **90** ($n=1$–4) and 1,4-di(bromomagnesio)butane in THF at room temperature [Eq. (35); 72]. Yields of **91** decreased as ring size of the distannacycloalkanes increased: $n=1$, 38%; $n=2$, 27%; $n=3$, 28%; $n=4$, 20%.



(35)

90 **91**

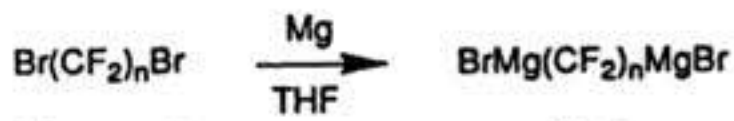
Distannacycloalkanes **92** and distannabicycloalkanes **93** [Eq. 36] were prepared using 1,*n*-di(bromomagnesio)alkanes, $n=6$, 7, 8, 10, and 12 [73,74]. The methodology was similar to that presented in Scheme 1. The reaction of triphenyltin chloride with a di-Grignard reagent yielded the corresponding distannoalkane. The selective cleavage of one phenyl group from each tin atom was accomplished by reaction with HCl or HBr. Distannacycloalkanes were then synthesized in a subsequent reaction with the same di-Grignard reagent. Repeating the sequence of selective cleavage and reaction with the di-Grignard reagent yielded the distannabicycloalkanes.



(36)

92 **93**

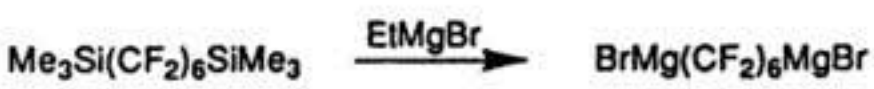
Magnesium activated by stirring in dry nitrogen converts α,ω-dibromoperfluorobutane (**94a**) and -hexane (**94b**) to the corresponding di-Grignard reagents (**95a,b**) in 45–50% yields [Eq. (37); 75]. The di-Grignard reagent **95b** has been prepared also from disilane **96** [Eq. (38)] by exchange of magnesium for silicon using ethylmagnesium bromide [76]. The formation of the halogenated diene **98** from 1,8-diiodoperfluorooctane and ethylmagnesium bromide probably occurs by thermal (−10°C) elimination of magnesium fluoride from a di-Grignard reagent **97** formed by an exchange reaction [Eq. (39); 76].



94a n = 4
94b n = 6

95a,b

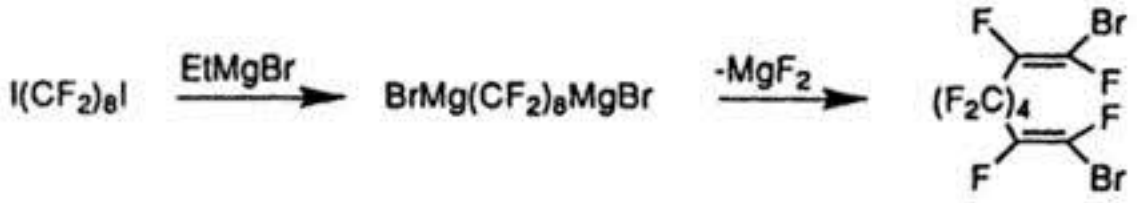
(37)



96 **95b**

(38)

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97 98 (39)

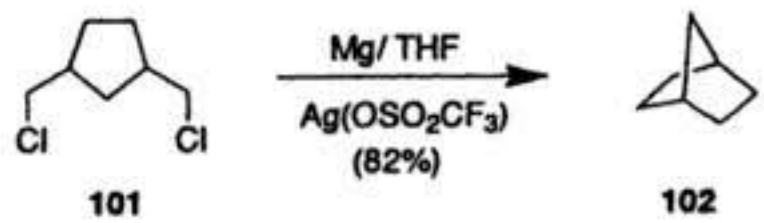
A 1,5-di-Grignard reagent **100** can be formed from disulfone **99** by removal of the protons α to the sulfonyl groups with ethylmagnesium bromide as base [Eq. (40); 77]. The reagent reacts with ketones or bromine to afford diadducts in low yields.



99 100 (40)

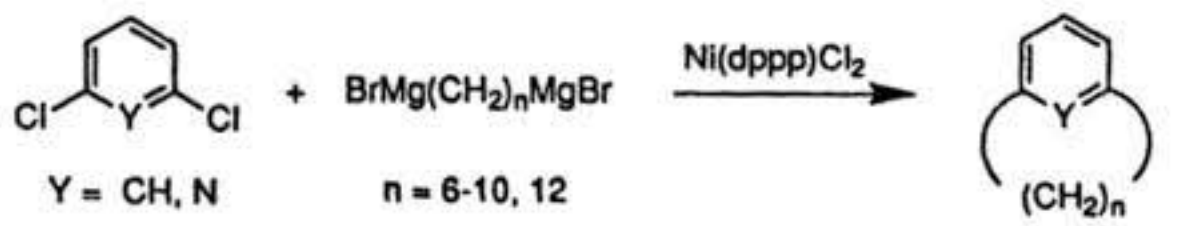
There have been unsuccessful attempts to isolate di-Grignard reagents from cyclic 1,4-dihaloalkanes. For example, 1,4-dibromocyclohexane, 1,4-dibromocyclooctane, and 1,4-dibromocyclononane give mixtures arising from ring cleavage, reduction, elimination, and cyclization processes [78,79].

The reactivity of di-Grignard reagents can be modified using a variety of metal catalysts. Primary α,ω-alkyl di-Grignard reagents, best prepared from alkyl dichlorides in THF, react with silver(I) triflate to form four, five, and six-membered rings in reasonable (40–90%) yields. The reaction is less effective for formation of medium-sized rings, but it is applicable to formation of norbornane **102** from the dichloride **101**, as shown in Eq. (41) [80].



101 102 (41)

Catalytic amounts of dichloro[1,3-bis(diphenylphosphino)propane]nickel(II) [$Ni(dppp)Cl_2$] enable di-Grignard reagents to selectively cyclocouple with aromatic 1,3-dichlorides in THF [81]. Yields are better for pyridinophanes **103a** (10–33%) than for metacyclophanes **103b** (best yield 22% for $n = 10$) [Eq. (42)]. The method has been applied to the synthesis of macrocyclic polyethers [81,82].



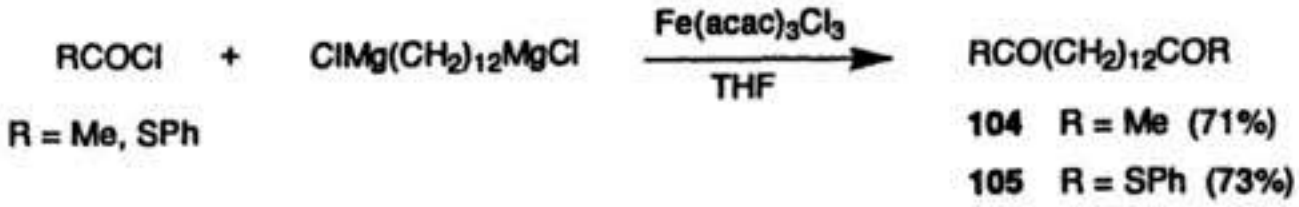
(42)

103a Y = N
103b Y = CH

Alkyl di-Grignard reagents can be reacted selectively with aliphatic and aromatic acid chlorides in the presence of tris(acetylacetonate)iron(III) [83]. The best conditions utilized alkyl chlorides in THF. Formation of alcohols is avoided in this one-step catalyzed

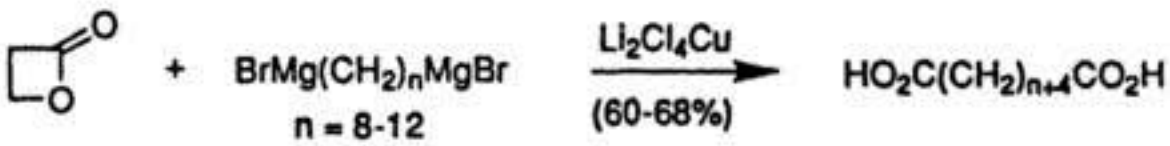
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synthesis of symmetric diketones **104** [Eq. (43)]. Phenylthiocarbonyl chloride also reacts selectively to afford long-chain diacid thiol esters **105**.

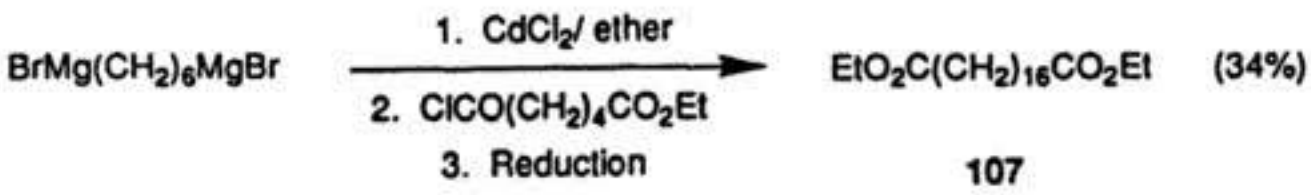


(43)

Long-chain dicarboxylic acids **106** have been prepared from β-propiolactone and alkyl di-Grignard reagents in the presence of catalytic dilithium copper tetrachloride [Eq. (44); 84]. The method extends the chain length of a 1,*n*-dihalide by six carbon atoms. The conversion of alkyl di-Grignard reagents ($n = 5, 6, 9, 10$) to dicadmium reagents, followed by reaction with half-ester acid chlorides has been used to prepare diketo C_{14}–C_{22} α,ω-dicarboxylic acid esters [85]. The dicarboxylic acid ester **107** was prepared using this method in concert with a Wolff-Kishner reduction to remove the ketone carbonyl groups [Eq. (45)].



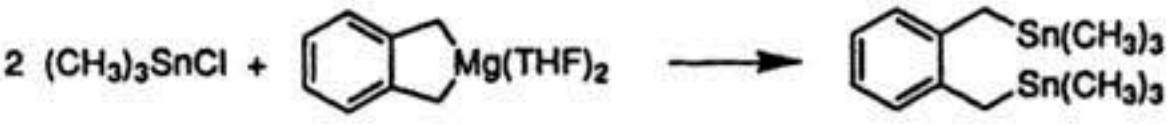
(44)



(45)

III. REACTIONS OF BENZYL AND MIXED BENZYL–ARYL DI-GRIGNARD REAGENTS

Benzyl di-Grignard reagents can be generated from halides located on the same or different rings. To obtain di-Grignard reagents from benzylic halides using magnesium powder, concentrations of the di-Grignard reagent cannot exceed 0.1*M* in THF, temperatures cannot exceed 35°C, and they must be prepared from benzylic chlorides [16,86,87]. A $MgCl_2$-free trimeric complex **108** [Eq. (46)] was reported to precipitate at room temperature (35% yield) when di-Grignard reagents exceeded concentrations of 0.1*M* [88]. The stoichiometry was reported as $Mg(CH_2C_6H_4CH_2\text{-}o)(THF)_2$. The usefulness of this precipitate was demonstrated by the formation of the bimetallic compound **109** in 52% yield from reaction with Me_3SnCl. On cooling a solution of $o\text{-}C_6H_4(CH_2MgCl)_2$ to -40°C, a colorless crystalline complex that analyzed as $Mg(CH_2C_6H_4CH_2\text{-}o)(THF)$ was obtained in a 50% yield; a crystal structure showed this complex to be trimeric [87].



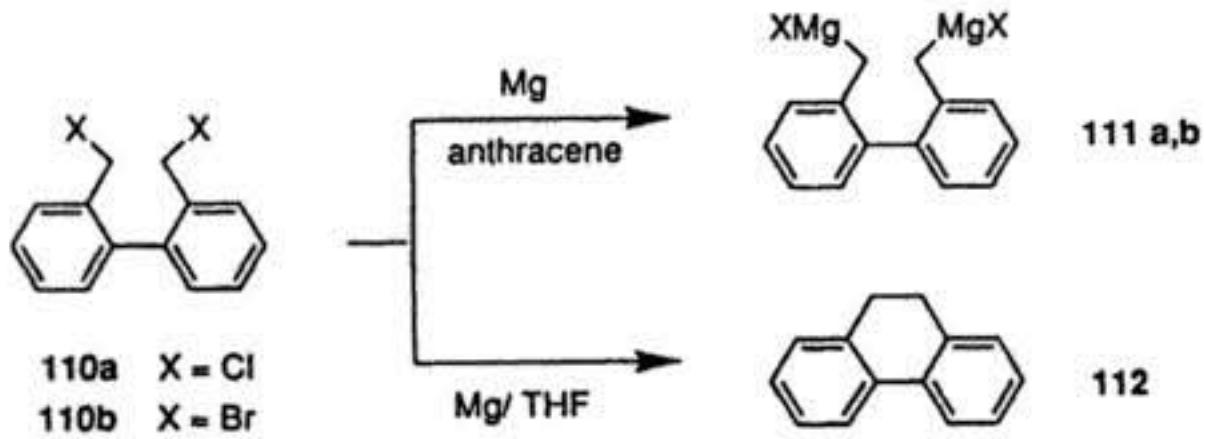
(46)

108 109

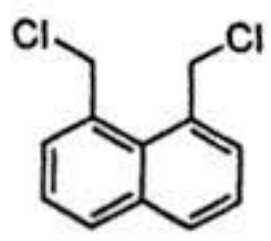
Although the dichloride **110a** can be converted to the corresponding di-Grignard reagent **111a** in 90–96% yields using magnesium in THF, the dibromide **111b** affords

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coupled product **112** [Eq. (47); 89,90]. If, however, magnesium anthracene is used as the magnesium source, benzylic di-Grignard reagents **111a,b** can be prepared in high yield from chlorides *and bromides*. The method is even successful with 1,8-dichloronaphthalene **113** [Eq. (48)], which fails to form a di-Grignard reagent with powdered magnesium [86].



(47)



113

(48)

The di-Grignard reagent **114**, synthesized from magnesium anthracene and $(o\text{-}ClCH_2C_6H_4)_2$, demonstrated an enhanced reactivity toward WCl_4O compared with the di-Grignard reagent prepared by the classic method using elemental magnesium [91]. The tungsten(V) complex **115** was synthesized in 45% yield using magnesium anthracene; the di-Grignard reagent prepared by the classic route gave $<10\%$ [92]. At higher reaction stoichiometries di-Grignard reagent **114** resulted in the formation of the oxo-free complex **116** [Eq. (49)]. This reaction could not be duplicated from the classically derived di-Grignard reagent, even under more forcing conditions.

$$\text{Mg(anthracene)(THF)}_3 + (2\text{-ClCH}_2\text{C}_6\text{H}_4)_2 \xrightarrow{\text{THF}} [\text{Mg(THF)}_n\text{Cl}]_2(2\text{-CH}_2\text{C}_6\text{H}_4)_2$$

114

$$WCl_4O \xrightarrow{\text{3.3 eq. 114}} [W\{(2\text{-CH}_2\text{C}_6\text{H}_4)_2\}_2O]_2Mg(THF)_4$$

115

$$WCl_4O \xrightarrow{\text{3.5 eq. 114}} W[(2\text{-CH}_2\text{C}_6\text{H}_4)_2]_3$$

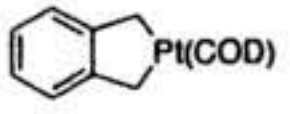
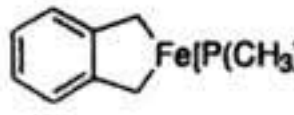
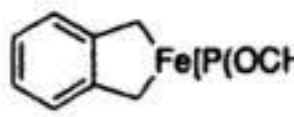
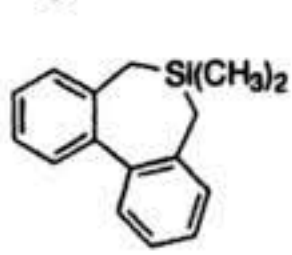
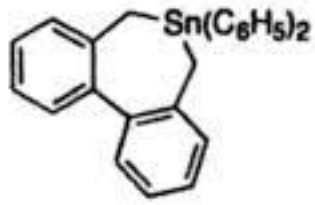
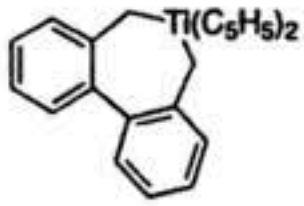
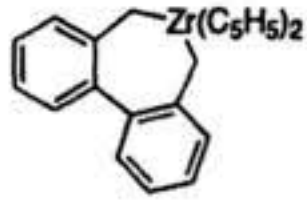
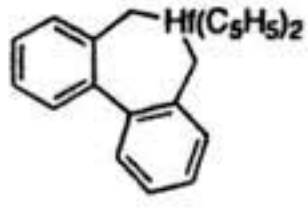
116

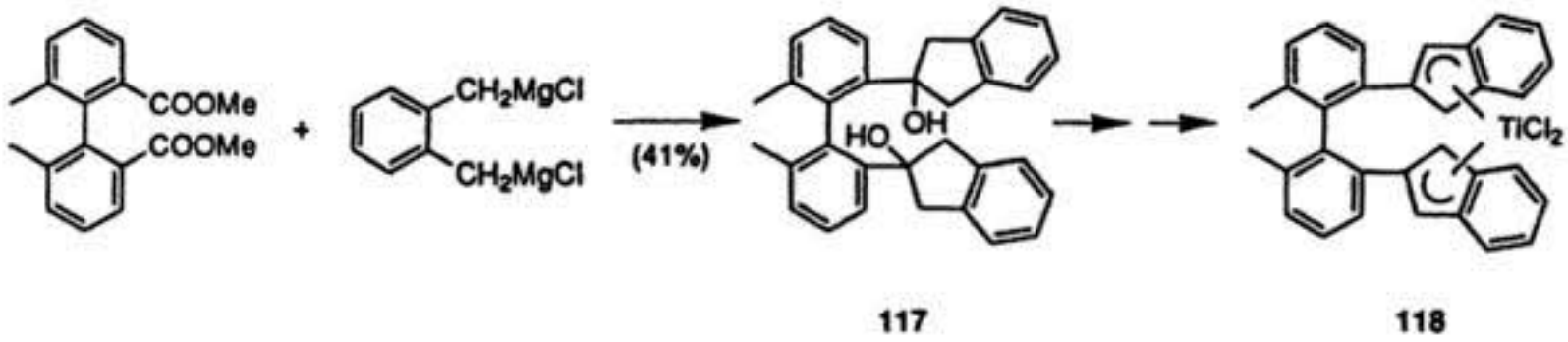
(49)

A variety of metallacycles have been synthesized using benzyl di-Grignard reagents prepared using elemental magnesium. Examples of metallacycles formed from the reaction of these di-Grignards with dihalide complexes are given in Table 2. Alternatively, the titanium bis(2-indenyl)-1,1′-biaryl metallocycle **118** was prepared from diol **117** [Eq. (50)], in which the cyclopentanol rings were formed by addition of *o*-di(chloromagnesiomethyl) benzene to a biphenyl diester [95].

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Table 2 Metallacycles Synthesized from Benzyl Di-Grignard Reagents and Dihalide Complexes

Dihalide Complex	Metallacycle	Yield	Ref.
$(COD)PtI_2$		51%	[87]
$FeCl_2[P(CH_3)_2C_6H_5]_2$		45%	[93]
$FeCl_2[P(OCH_3)_3]_3$		33%	[93]
$(CH_3)_2SiCl_2$		90%	[89]
$(C_6H_5)_2SnCl_2$		46%	[89]
$(C_5H_5)_2TlCl_2$		61%	[94]
$(C_5H_5)_2ZrCl_2$		70%	[94]
$(C_5H_5)_2HfCl_2$		55%	[94]



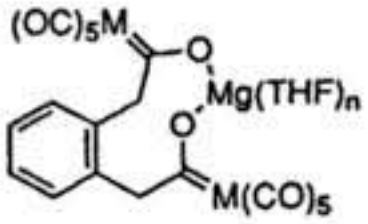
117 118

(50)

Benzyl di-Grignard reagents have been used in the synthesis of bridged bis(carbene)–dimetal complexes **119a–c** [Eq. (51); 96]. The di-Grignard reagent *o*-$C_6H_4(CH_2MgCl)_2$ was reacted with $W(CO)_6$ at room temperature in THF to synthesize the tungsten complex **119b** (51% yield), whereas $Mg(CH_2C_6H_4CH_2$-*o*$)(THF)$ was reacted with the appropriate

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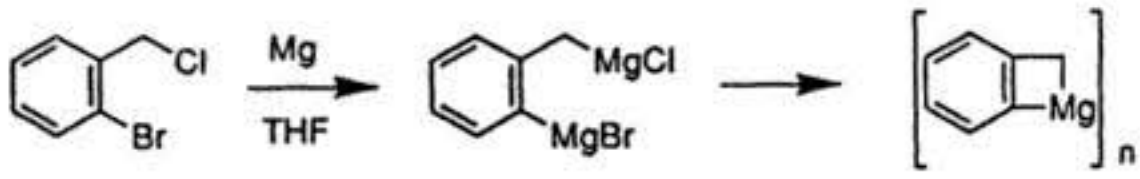
hexacarbonyl complexes under the same reaction conditions to produce the chromium (61%) and molybdenum (not determined) complexes **119a** and **119c**.



119a M = Cr, n = 3
119b M = W, n = 4
119c M = Mo, n = 4

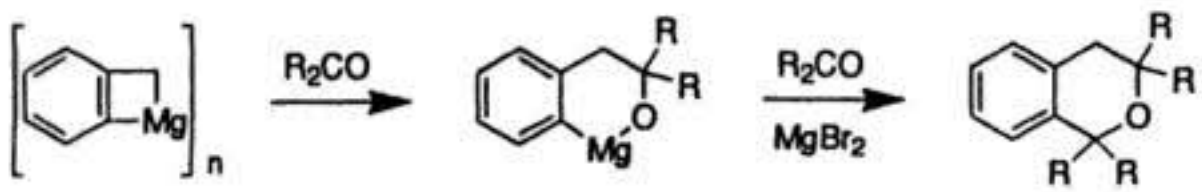
(51)

The synthesis of metallacyclobutabenzenes using di-Grignard reagents has been investigated by Bickelhaupt et al. The 1,2-dihydro-1-magnesiabenzocyclobutene reagent **122** was synthesized by the addition of 1-bromo-2-chloromethylbenzene **120** to sublimed magnesium powder in THF [Eq. (52); 97,98]. Di-Grignard reagent **121** was initially formed in >95% yield; precipitation, two THF washes, and decantation produced magnesiacycle **122** in 84–90% yield, based on the dihalide. The use of sublimed magnesium powder and dihalide **120** in THF was critical to avoid Wurtz coupling and other by-product formation [97]. The magnesiabenzocyclobutene **122** reacted with only a single molecule of ketone to form the chelate complex **123** [Eq. (53)]. Addition of $MgBr_2$ to the mixture opens the chelate and enables reaction with a second molecule of ketone to occur leading ultimately to the isochromane **124** [99].



120 **121** **122**

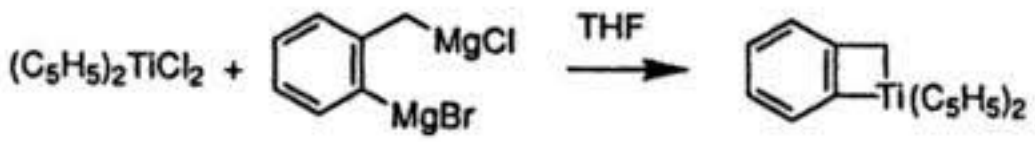
(52)



122 **123** **124**

(53)

Metallacyclobutabenzenes synthesized by reaction of reagent **122** and metal dihalides in THF are listed in Table 3. A profound effect of di-Grignard reagent purity on the product distribution was noted in the synthesis of the germabenzocyclobutene and attempted synthesis of the corresponding stannabenzocyclobutene; use of unpurified **122** dramatically increased unwanted dimer formation [97]. Di-Grignard reagent **121** has been applied to the synthesis of titanabenzocyclobutene **125** [Eq. (54)], which was obtained in a 93% yield [101].



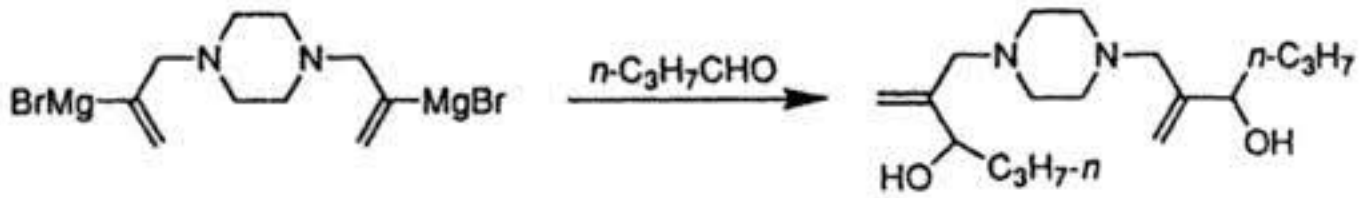
121 **125**

(54)

Preformed di-Grignard reagent **126** was utilized for the synthesis of 1-sila-acenaphthene **127** in 10% yield [Eq. (55); 102]. However, a yield of 71% of **127** was realized when 8-bromo-1-chloromethylnaphthalene and dimethyldichlorosilane were reacted in the presence of magnesium.

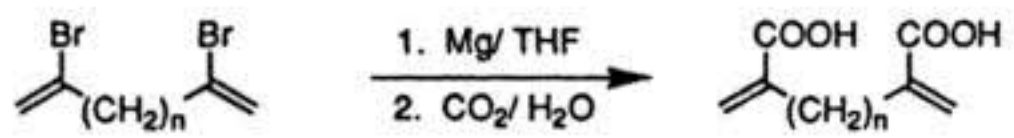
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Grignard reagents from molecules containing two vinyl bromide moieties have been prepared using magnesium in THF [37,38,104]. These di-Grignard reagents can be trapped with carbon dioxide, to give diacids; aldehydes, to give alcohols; or protons, to give alkenes. The β-aminovinyl di-Grignard reagent **132** [Eq. (57)] does not undergo elimination to give allene, but reacts with butanal to afford diol **133** [104]. The vinyl dihalides **134**, generated from reaction of a di-Grignard reagent with 2,3-dibromopropene, form vinyl di-Grignard reagents, which react with carbon dioxide to form unsaturated diacids **135** [Eq. (58)] in 50–66% yields [37.38].



(57)

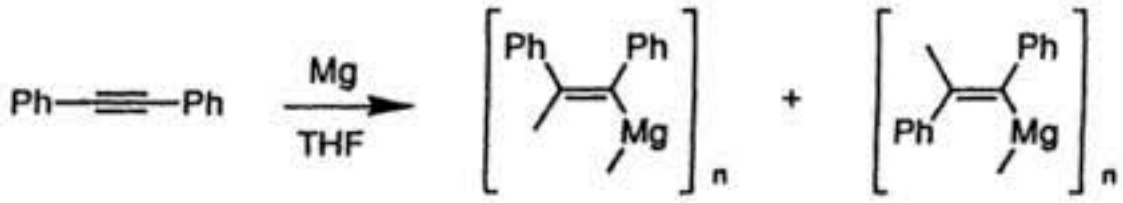
132 **133**



(58)

134 **135**

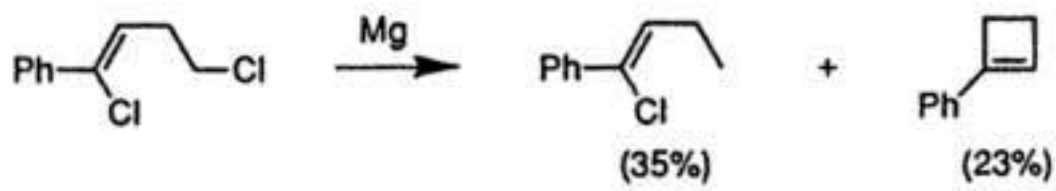
Geminal vinylic di-Grignard reagents can also be synthesized from halide-free reagents. The reaction of sublimed magnesium and diphenylacetylene in THF at $-100°C$ produced the di-Grignard reagents **136** and **137** [Eq. (59); 105]. A 3:2 ratio of **136** and **137** was formed according to product ratios from reaction with D_2O. Di-Grignard **136** was isolated exclusively by crystallization.



(59)

136 **137**

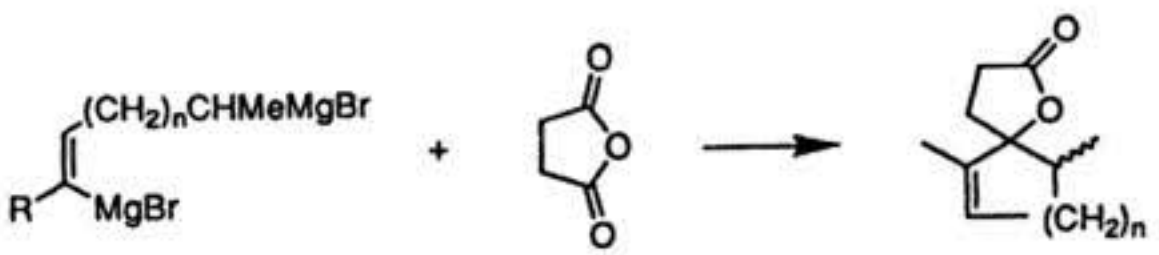
Newman and Kaugars reported a cyclobutene synthesis during the reaction of the vinyl alkyl dichloride **138** with magnesium in diethyl ether [106]. Quenching of the reaction with water gave alkene **139** (35%), formed by protonation of the mono-Grignard reagent from the primary chloride, and cyclobutene **140** (23%) [Eq. (60)]. Mixed alkyl vinyl di-Grignard reagents **141** have been formed, however, from the corresponding dibromides by reaction with magnesium in THF [107]. Reaction of di-Grignard reagent **141** with maleic anhydride provides five- and six-membered ring spirolactones **142**, by Eq. (61). A stereospecific reaction of di-Grignard reagent **143** with 1-chloro-cyclopenten-3-one affords spiroketone **144** [Eq. (62)], a suitable spirosesquiterpene precursor [107].



(60)

138 **139** **140**

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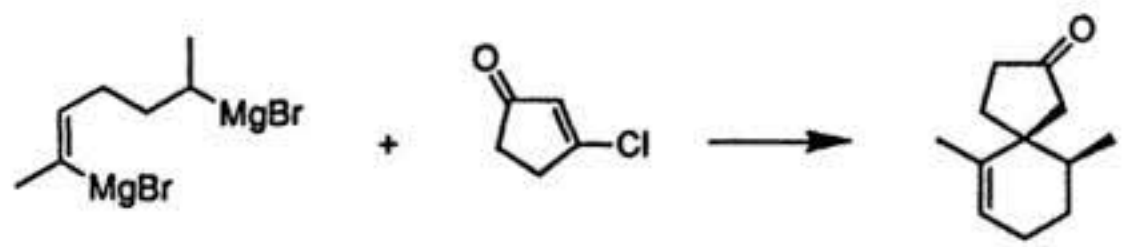


141

R = H, n = 2
R = Me, n = 2
R = *i*-Pr, n = 1

142

(61)



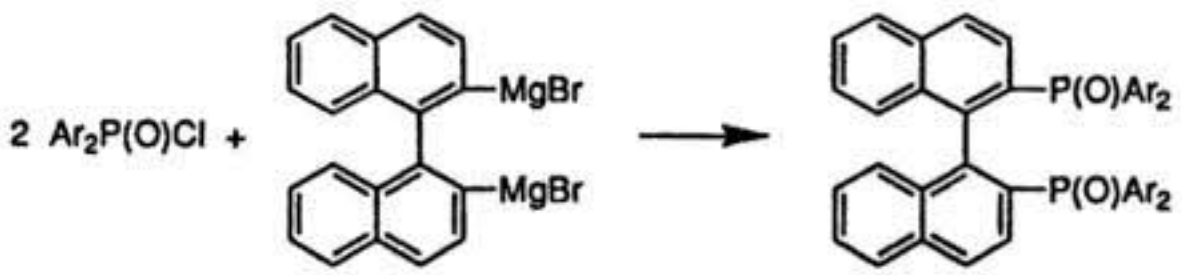
143 **144**

(62)

V. REACTION OF DIARYL DI-GRIGNARD REAGENTS

Aryl di-Grignard reagents are generally available from dihalides with powdered magnesium [16]. The halide atoms can be on the same or on different rings, and they can be substituents on heterocyclic rings [108]. Highly reactive Rieke magnesium, prepared from potassium, potassium iodide, and magnesium chloride, has been advantageous with less reactive aryl chlorides [109]. Proton exchange using ethylmagnesium bromide converts 1,2,4,5-tetrafluorobenzene to the corresponding *p*-substituted di-Grignard reagent [110]. Transmetallation of *o*-phenylenemercury with magnesium in THF produced *o*-phenylene-magnesium tetramer in 90% yield [105,111]. Halogen exchange between ethylmagnesium bromide and hexabromobenzene affords a mixture of *para* (6%) and *meta* (1%) di-Grignard reagents, but mainly a mono-Grignard reagent is formed [112].

A variety of applications of aryl di-Grignard reagents has been reported. For example, aryl di-Grignard reagents react with carbon dioxide to form diacids [110] and with ketones to give diols [109]. Low molecular weight poly-*p*-silaphenylenes have been synthesized with these di-Grignard reagents [113]. The 2,2′-bis(diarylphosphinyl)-1,1′-binaphthyl compounds **146** have been synthesized using the di-Grignard reagent **145** derived from 2,2′-dibromo-1,1′-binaphthyl and magnesium in THF [Eq. (63); 114,115]. Reaction yields varied according to the steric effects of the aryl groups of the diarylphosphinyl chloride. Yields ranged from 91 (Ar = phenyl) to 50% (Ar = 3,5-di-*tert*-butylphenyl).

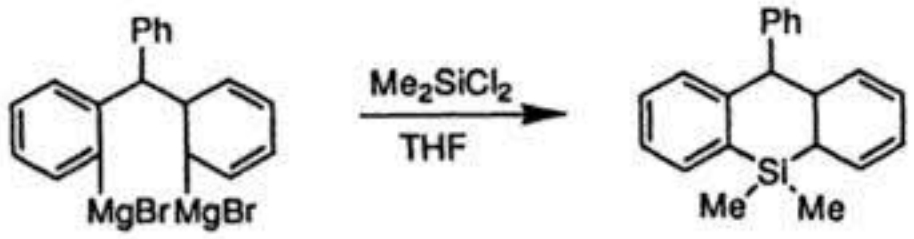


145 **146**

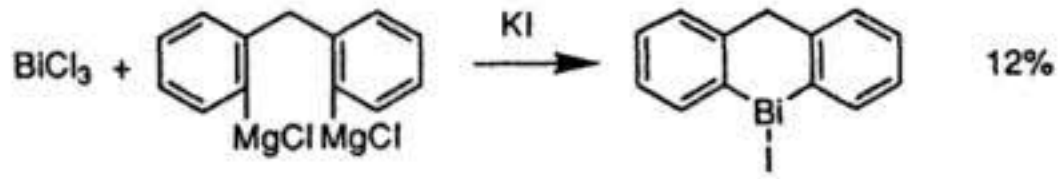
(63)

Aryl di-Grignard reagents have proved useful in the synthesis of heterocycles and metallacycles, as in the syntheses of the siladihydroanthracene **147** [Eq. (64); 116] and iododihydrobenzobismine **148** [Eq. (65); 117].

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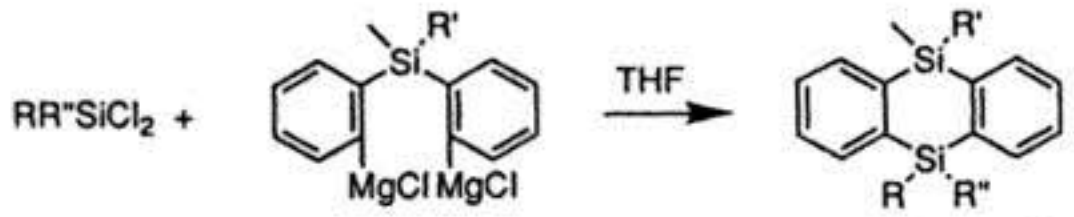
147 (64)



148 (65)

Germa- and stannadihydroanthracenes have also been synthesized by this procedure; the stannadihydroanthracene analogue of **148** may then serve as a precursor to other heterodihydroanthracenes by substitution reactions [118].

Dihydrodisilaanthracenes **150** [Eq. (66)] were successfully prepared from the aryl di-Grignard reagents **149** synthesized using Rieke magnesium and bis(*o*-chlorophenyl) methylsilane or bis(*o*-chlorophenyl)dimethylsilane [120,121]. These aryl chlorides were unreactive toward granular or powdered magnesium.

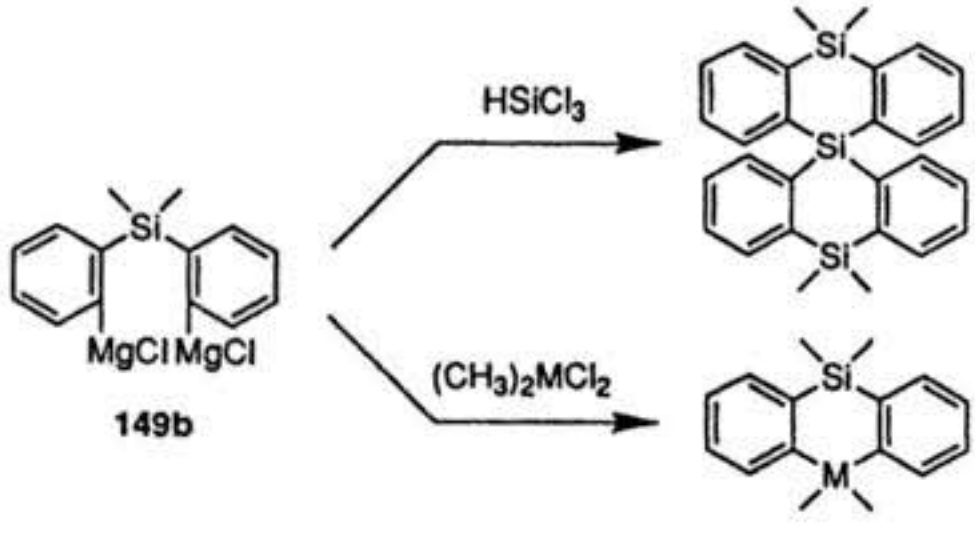


149

	R'	R	R''	Yield
150a	H	CH_3	H	70%
150b	CH_3	CH_3	H	61%
150c	CH_3	CH_3	CH_3	56%
150d	CH_3	CH_3	C_6H_5	44%
150e	CH_3	C_6H_5	C_6H_5	45%

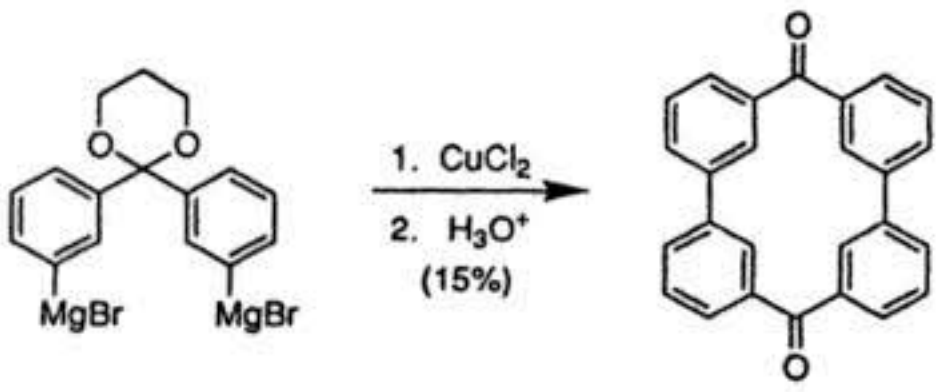
(66)

Reaction of the dimethylsilane di-Grignard reagent **149b** [Eq. (67)] with trichlorosilane resulted in the formation of the bis(dimethyl-*o*,*o'*-diphenylsilyl)spirosilane **151** in 47% yield [121]. The use of the dimethylsilane di-Grignard reagent **149b** was extended to the synthesis of dihydroheterosilaanthracenes [120]. The dihydrogermasilaanthracene **152a** and the dihydrostannasilaanthracene **152b** were prepared in yields of 33 and 56%, respectively. Attempts to prepare the lead derivative from Me_2PbCl_2 resulted in the formation of elemental lead.



(67)

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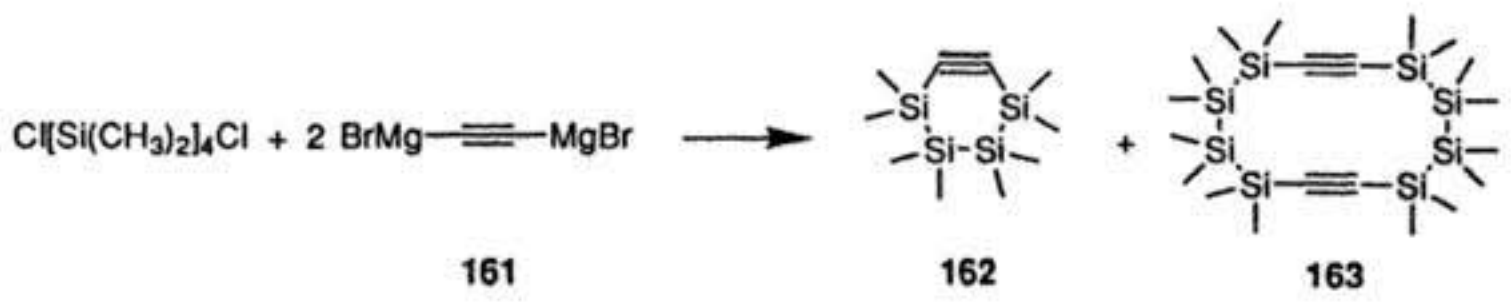


159 160 (71)

Examples of mixed aryl–benzyl di-Grignard reagents were covered in Section III.

VI. REACTIONS OF ACETYLENIC AND MIXED ARYL–ACETYLENIC DI-GRIGNARD REAGENTS

Acetylenic di-Grignard reagents have an advantage over disodium or dilithium reagents in that they are readily prepared in organic solvents. A precipitate of acetylene dimagnesium bromide separates quantitatively following an exchange reaction of ethyl magnesium bromide with acetylene in benzene–diethyl ether [130]. The most common application of this di-Grignard reagent has been in the synthesis of silacycloalkynes. Reaction of 1,4-dichlorooctamethyltetrasilane with di(bromomagnesio)acetylene **161** in THF yielded the tetrasilacyclohexyne **162** (52%) [Eq. (72); 131]. The octasilacyclododecyne **163** accounted for only 1% yield. The analogous pentasilacycloheptyne (22%) [132] and the hexasilacyclooctyne (46%) [132,133] were synthesized in a similar manner.



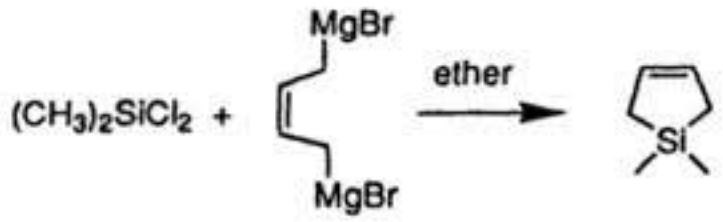
161 162 163 (72)

In contrast, cyclization of acetylenic di-Grignard reagent **161** and $(ClSiMe_2)_2(CH_2)_n$ ($n=0$–4) was reported to preferentially yield cyclocondensation adducts, resulting from multiple intermolecular reactions [134]. For example, the primary product resulting from the reaction of 3 Eq. of $(ClSiMe_2)_2(CH_2)_3$ with 3 Eq. of the di-Grignard reagent **161** was a 21-membered ring adduct (35%).

The di-Grignard reagent **164**, formed from 1,2-diethynyl-1,1,2,2-tetraalkyldisilane, has been prepared by reaction with either ethyl- or isopropylmagnesium bromide [Eq. (73); 135,136]. Reactions of di-Grignard reagent **164** with 1,2-dichlorotetraalkyldisilanes and 1,3-dichlorohexamethyltrisilane produced cyclic polysilanes **165** and **166**, respectively, in yields that were typically 37–73% [135–137].

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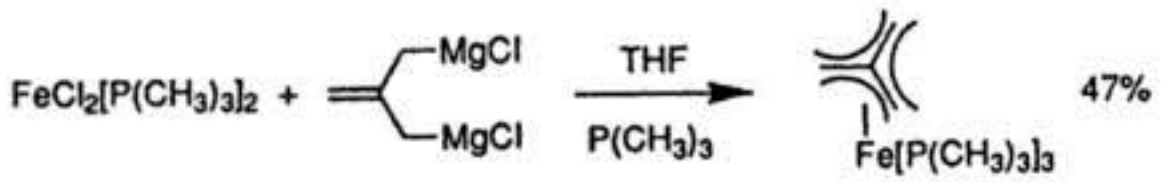
1,4-dibromobutane and magnesium in diethyl ether [142]. The reaction of the di-Grignard reagent **172** generated from butadiene using Rieke magnesium afforded a 20% yield of **173**.



(76)

172 **173**

Generation in situ of the di-Grignard reagent **175**, by reacting an excess of magnesium with $CH_2{=}C(CH_2Cl)_2$ in the presence of the iron complex **174** and PMe_3, afforded the novel iron complex **176** [Eq. (77); 93]. Di-Grignard reagent **175** is a cross-conjugated trimethylenemethane (TMM) dianion. Addition of the presynthesized di-Grignard reagent **175** to a THF solution of iron complex **174** resulted in low yield of iron complex **176**.



(77)

174 **175** **176**

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26

Formation and Reactions of Substituted (2-Butene-1,4-diyl)magnesium Complexes

REUBEN D. RIEKE

University of Nebraska and Rieke Metals, Inc., Lincoln , Nebraska

MATTHEW S. SELL

Rieke Metals, Inc., Lincoln, Nebraska

I. INTRODUCTION

In 1967, Ramsden demonstrated that, under forcing conditions, magnesium will react with 1,3-butadienes to generate a magnesium–diene complex [1]. The reactivity of the diene was not what one would have predicted for a bis-Grignard reagent. Although this appeared to be a promising new area of study in the 1970s, the chemistry advanced very little. The primary cause of this was the difficulty associated with the preparation of the diene–magnesium complexes [see 2, for review].

The reaction of ordinary magnesium with 1,3-dienes such as 1,3-butadiene or isoprene is usually accompanied by dimerization, trimerization, and oligomerization. This reaction may be catalyzed by alkyl halides or transition metal salts, but is generally accompanied by a variety of by-products and is very time-consuming. Consequently, the utilization of these reagents in organic synthesis has been quite limited [3], except for 1,3-butadiene–magnesium, which has found considerable application in organometallic synthesis [see Ref. 4 for relevant reviews].

In contrast, Rieke magnesium reacts with (*E*,*E*)-1,4-diphenyl-1,3-butadiene, 2,3-dimethyl-1,3-butadiene, isoprene, myrcene, or 2-phenyl-1,3-butadiene in tetrahydrofuran (THF) at ambient temperature to afford the corresponding substituted (2-butene-1,4-diyl)magnesium complexes in near quantitative yields. The structures of these complexes have not yet been determined except for (1,4-diphenyl-2-butene-1,4-diyl)magnesium, which has been shown to be a five-membered ring metallocycle [5]. Accordingly, the most likely structures for these complexes are five-membered metallocycles or oligomers. It is also possible that an equilibrium exists between these various forms.

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II. REACTIVITY

These magnesium–diene complexes exhibit unusual reactivity. Although one might expect the complexes to react as bis-Grignard reagents, it is clear that they are much more powerful nucleophiles. Remarkably, they react with alkyl bromides and chlorides at temperatures as low as −80°C. They appear to react by a standard S_N2 mechanism. However, they can serve as electron-transfer agents with certain reagents such as metal salts. With most electrophiles accommodating good leaving groups, clean S_N2 chemistry is observed.

As shown in Scheme 1, soft electrophiles such as organic halides demonstrate complete regioselectivity for the 2-position. The resulting primary organomagnesium intermediate can then be reacted with a wide range of second electrophiles.

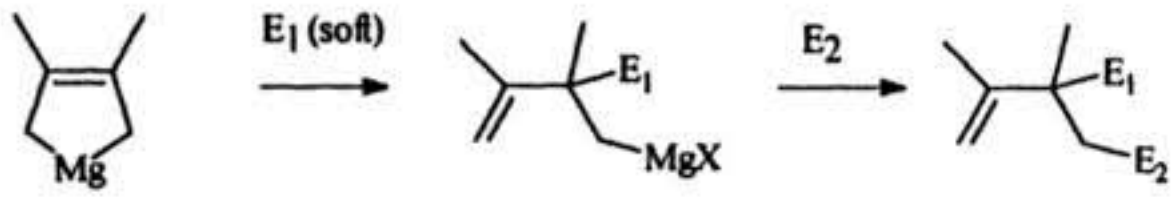
Harder electrophiles such as monohalosilanes, monohalostannanes, and such, react completely regioselectively in the 1-position, as shown in Scheme 2. Addition of a second electrophile occurs primarily in the 2-position.

The overall result is that one can effect a net 2,1-addition or a 1,2-addition by choosing appropriate electrophiles. Representative complex, highly functionalized molecules that have been prepared using this approach are shown in Table 1 [6].

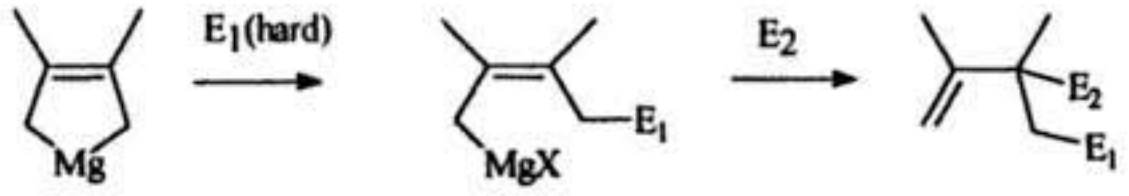
(*E*,*E*)-1,4-Diphenyl-1,3-butadiene has been one of the most reactive conjugated dienes towards metallic magnesium. Reaction of this diene with Rieke magnesium affords (1,4-diphenyl-2-butene-1,4-diyl)magnesium **2**, which can be treated with various electrophiles, as shown in Scheme 3.

However, reactions of **2** with 1,*n*-dibromoalkanes resulted in either cyclization or reduction of the electrophile, depending on the initial dibromides. For example, cyclization proceeded rapidly at −78°C in the reaction of **2** with 1,3-dibromopropane and 1,3-dichloropropane, yielding a single product, *trans*-1-phenyl-2-[(*E*)-2-phenylethenyl] cyclopentane **4**, in 65 and 81% isolated yield, respectively.

Similarly, reaction of 1,4-dichlorobutane or 1,4-dibromobutane with **2** gave *trans*-1-phenyl-2-[(*E*)-2-phenylethenyl]cyclohexane **3** as the only cyclized product in 51 and 40% isolated yield, respectively. Surprisingly, **2** cyclized with methylene dichloride to generate only a three-membered cyclic compound, *trans*-1-phenyl-2-[(*E*)-2-phenylethenyl] cyclopropane **6** in 76% isolated yield. Representative examples utilizing this approach are shown in Tables 2 and 3.



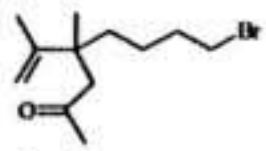
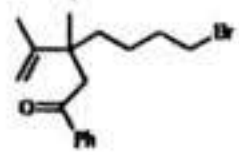
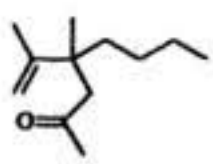
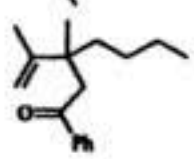
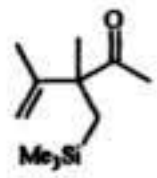
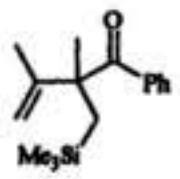
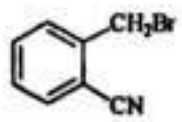
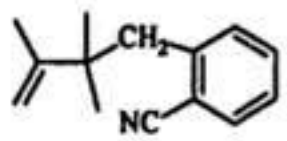
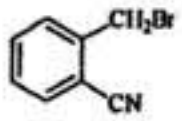
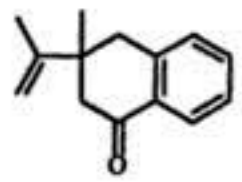
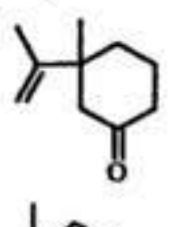
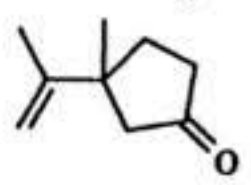
Scheme 1 Reaction of (2,3-dimethyl-2-butene-1,4-diyl)magnesium with a soft electrophile, followed by a second electrophile.



Scheme 2 Reaction of (2,3-dimethyl-2-butene-1,4-diyl)magnesium with a hard electrophile, followed by a second electrophile.

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Table 1 Stepwise Reactions of (2,3-Dimethyl-2-butene-1,4-diyl)magnesium

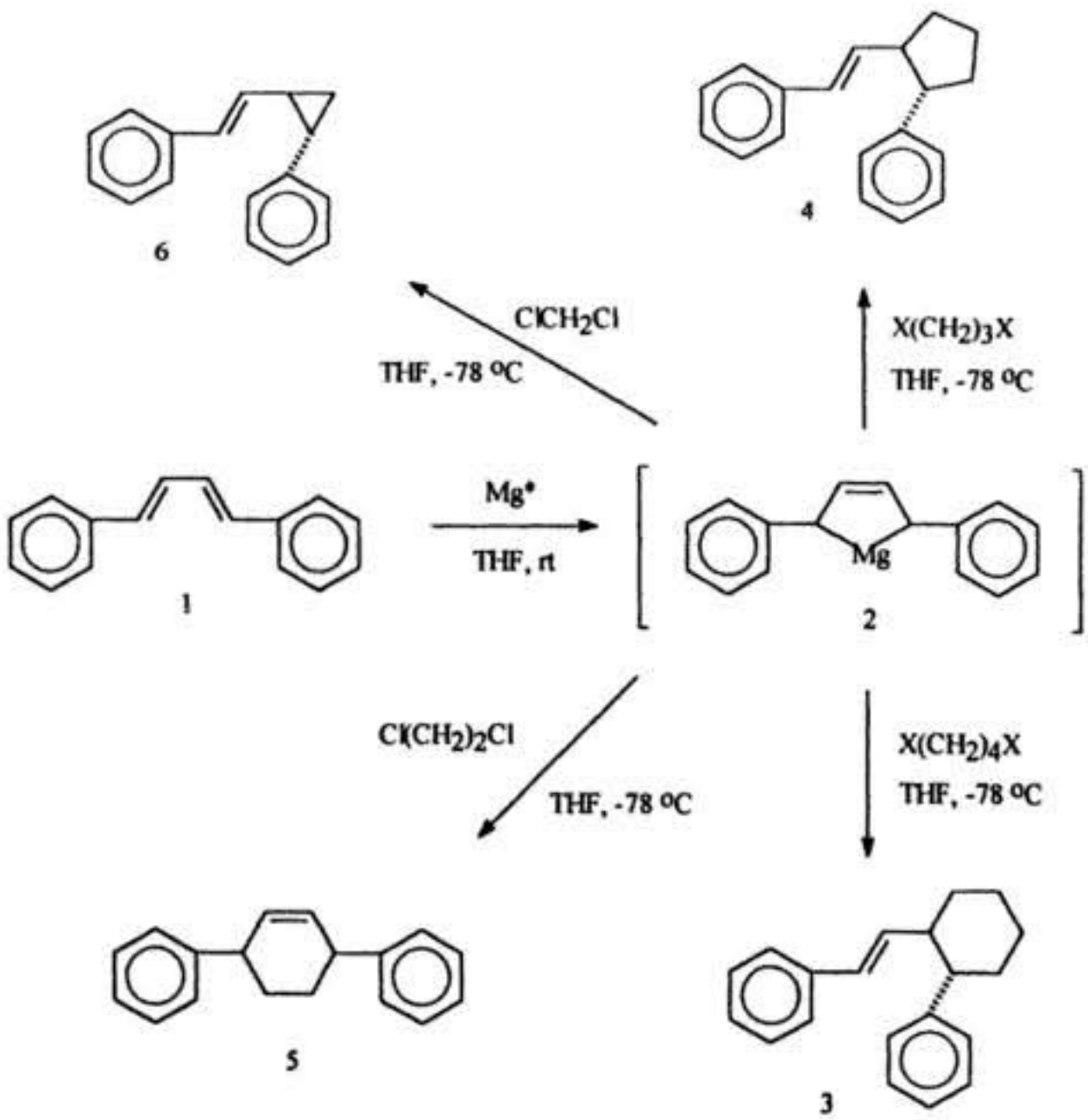
Entry	First Electrophile	Second Electrophile	Product	% Yield
1	$Br(CH_2)_4Br$	MeCOCl		62
2	$Br(CH_2)_4Br$	PhCOCl		60
3	$Me(CH_2)_3Br$	MeCOCl		61
4	$Me(CH_2)_3Br$	PhCOCl		82
5	Me_3SiCl	MeCOCl		73
6	Me_3SiCl	PhCOCl		79
7		H_3O^+		35
8		--		30
9	$Br(CH_2)_3CN$	H_3O^+		58
10	$Br(CH_2)_3CN$	--		31
11	$Br(CH_2)_2CN$	--		42

III. REGIOSELECTIVITY

Treatment of (1,4-diphenyl-2-butene-1,4-diyl)magnesium with 1,*n*-dihaloalkanes provides a convenient method for the generation of substituted three-, five-, and six-membered carbocycles. Significantly, the cyclizations are always stereospecific and completely regioselective.

It is particularly difficult to prepare asymmetric (2-butene-1,4-diyl)magnesium complexes from ordinary magnesium. The reaction is usually complicated by extensive

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Scheme 3 Cyclization of (1,4-diphenyl-2-butene-1,4-diyl)magnesium with 1,*n*-dihaloalkanes.

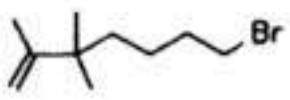
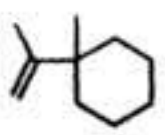
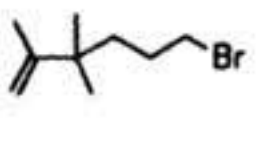
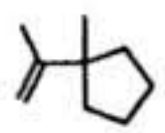
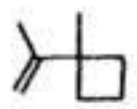
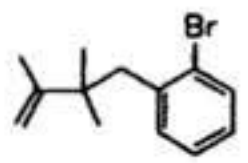
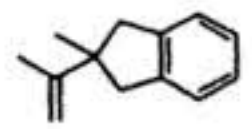
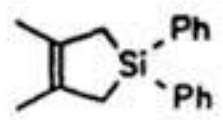
polymerization. It was reported that the use of Rieke magnesium circumvents this problem. For example, an excess of newly generated Rieke magnesium reacted with isoprene, myrcene, or 2-phenyl-1,3-butadiene in THF at room temperature in 2 hr to give the corresponding asymmetric (2-butene-1,4-diyl)magnesium complexes.

The basic difference in chemistry between asymmetric and symmetric (2-butene-1,4-diyl)magnesium originates from the fact that the former possesses four totally different reactive sites, and the latter has only two nonidentical nucleophilic centers. Accordingly, the regiochemistry of electrophilic attack is one of the essential problems associated with the reactions of these asymmetric (2-butene-1,4-diyl)magnesium complexes. It was reported that treatment of the magnesium complexes with triorganosilyl chloride in THF at $-78°C$, followed by cyclohexanone at 0°C, afforded a stepwise addition across a terminal double bond, with high regioselectivity, as shown in Scheme 4. The results of the regioselective reactions are summarized in Table 4.

It was suggested that the initial attack of the complex on the organosilicon reagent determined the selectivity, which was dependent on both the diene substrate and the initial electrophile. As shown in Scheme 4, reaction of (2-methyl-2-butene-1,4-diyl)magnesium with trimethylsilyl chloride resulted in initial attack at the 4- or 1-position, producing two isomers of allylic organomagnesium intermediates. Treatment of the intermediary allylic organomagnesium complexes with cyclohexanone led to overall additions across a terminal double bond. Workup gave a 77:23 mixture of products in 91% total yield (see Table 4, entry 1).

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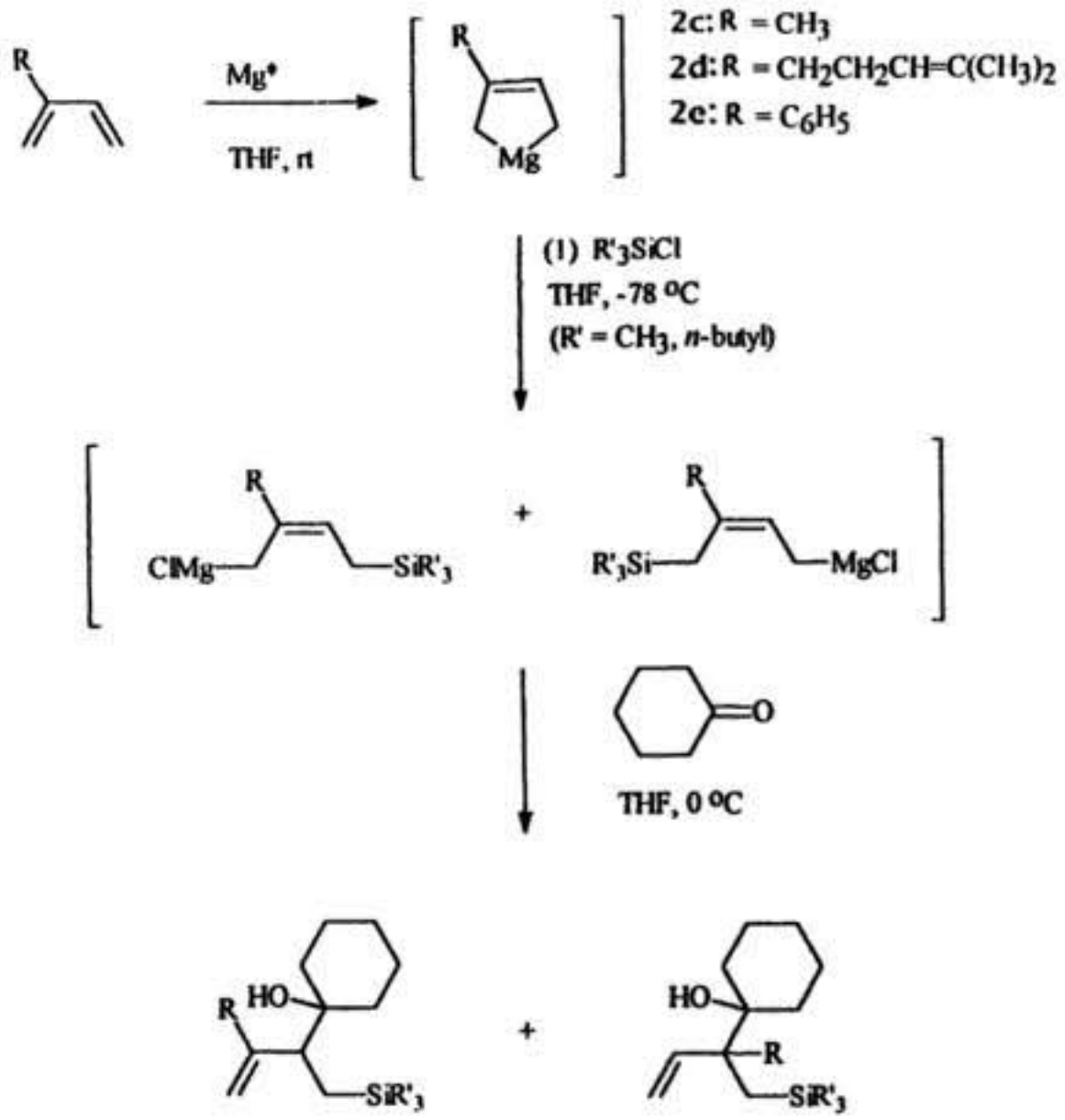
Table 3 Reactions of (2,3-Dimethyl-2-butene-1,4-diyl)magnesium with Organodihalides

Entry	Dihalide	Product	% Yield
1	$Br(CH_2)_4Br$		79
2	$Br(CH_2)_4Br$		53 (69)
3	$Br(CH_2)_3Br$		72
4	$Br(CH_2)_3Br$		-- (75)
5	$Cl(CH_2)_3Cl$		81
6	$Br(CH_2)_3Br$		-- (49)
7	$Cl(CH_2)_3Cl$		-- (61)
8	$o\text{-}BrC_6H_4CH_2Br$		62
9	$o\text{-}BrC_6H_4CH_2Br$		~30
10	Ph_2SiCl_2		65

Increasing the size of the organosilicon reagent resulted in increased regioselectivity. This was demonstrated by using tri-*n*-butylsilyl chloride as the initial electrophile.

Larger substituents at the 2-position of the diene were also demonstrated to increase selectivity. As shown in Scheme 4, the magnesium complex of myrcene reacted with trimethylsilyl chloride, followed by cyclohexanone, to yield the two compounds shown in

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Scheme 4 Regioselective reactions of asymmetric (2-butene-1,4-diyl)magnesium reagents with two different electrophiles.

Table 4, entry 3 in a 94:6 ratio. Furthermore, a single isomer was obtained in excellent yield by replacing the first electrophile with tri-*n*-butylsilyl chloride.

Remarkably, (2-phenyl-2-butene-1,4-diyl)magnesium reacted exclusively at the 4-position with either organosilicon electrophile, as shown in Scheme 4. The resulting allylic organomagnesium intermediate added to cyclohexanone exclusively in the 3-position.

Reaction of asymmetric (2-butene-1,4-diyl)magnesium with α,ω-alkylene dihalides usually gives two isomeric products. For example, treatment of (2-phenyl-2-butene-1,4-diyl)magnesium with 1,3-dibromopropane at $-78°C$, followed by warming to room temperature, resulted in the generation of two five-membered carbocycles, 1-phenyl-1-ethenylcyclopentane and α-cyclopentylstyrene, with a ratio of 77:23, in a 76% isolated yield.

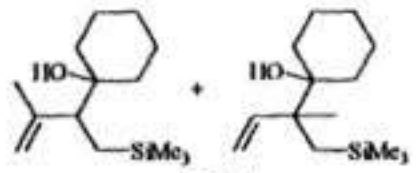
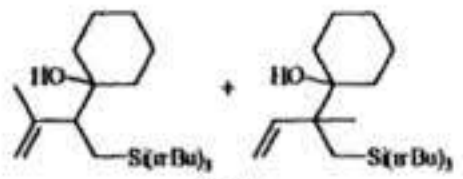
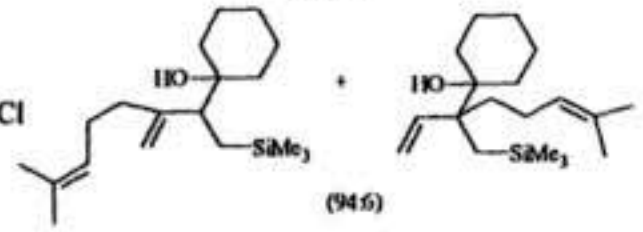
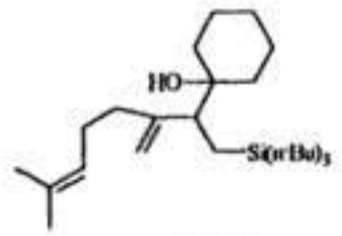
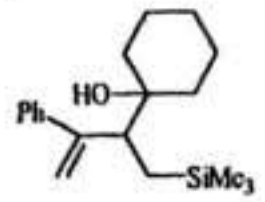
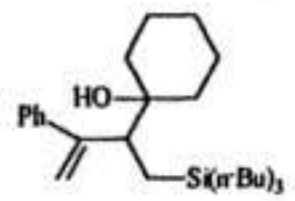
IV. PREPARATION OF HETEROCYCLES AND SPIRO COMPOUNDS

One of the useful applications of substituted (2-butene-1,4-diyl)magnesium complexes is the facile synthesis of silicon-containing five-membered cyclic compounds. This reaction has been reported earlier for the magnesium complex of 1,3-butadiene [7].

In contrast with the general 1,2-cyclizations of symmetric (2-butene-1,4-diyl)magnesium complexes with α,ω-alkylene dihalides, reactions of both symmetric and asymmetric (2-butene-1,4-diyl)magnesium complexes with diorganosilyl dichlorides yield exclusively overall 1,4-additions, generating silicon-containing five-membered rings. Some of these results are summarized in Table 5.

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Table 4 Regioselective Reactions of Asymmetric (2-Butene-1,4-diyl)magnesium Reagents with Two Different Electrophiles

Entry	Diene	R_3SiCl	Product(s)	% Yield
1	Isoprene	$(CH_3)_3SiCl$	 (77:23)	91
2	Isoprene	$(n\text{-Bu})_3SiCl$	 (92:8)	94
3	Myrcene	$(CH_3)_3SiCl$	 (94:6)	82
4	Myrcene	$(n\text{-Bu})_3SiCl$		94
5	2-Phenyl-butadiene	$(CH_3)_3SiCl$		95
6	2-Phenyl-butadiene	$(n\text{-Bu})_3SiCl$		92

For example, dichlorodimethylsilane reacted with (1,4-diphenyl-2-butene-1,4-diyl) magnesium at −78°C to give *cis*-1,1-dimethyl-2,5-diphenylsilacyclopent-3-ene in 66% isolated yield (Table 5, entry 1). Asymmetrically substituted silicon-containing heterocycles can also be prepared in this fashion (see Table 5, entries 3–5).

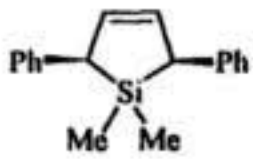
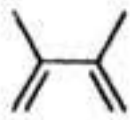
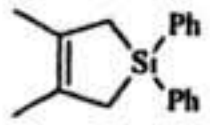
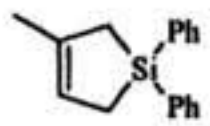
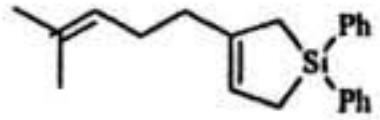
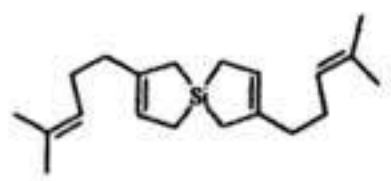
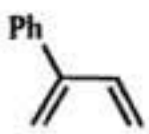
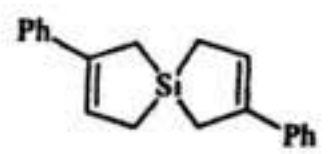
Significantly, double annelation can be accomplished in one step by treating the magnesium complex with $SiCl_4$ to form spiroheterocycles. Representative examples of this type of transformation can be seen in Scheme 5, as well as Table 5, entries 6–8. Addition of $SiCl_4$ to the THF solution of (2-methyl-2-butene-1,4-diyl)magnesium at −78°C caused an instantaneous disappearance of the pale orange color. Workup afforded 2,7-dimethyl-5-silaspiro[4.4]nona-2,7-diene in 75% isolated yield, as shown in Table 5, entry 6. This compound has been reported to be difficult to prepare [8]. Utilization of magnesium complexes of 1,3-dienes allows the preparation to be cleanly carried out under extremely mild conditions.

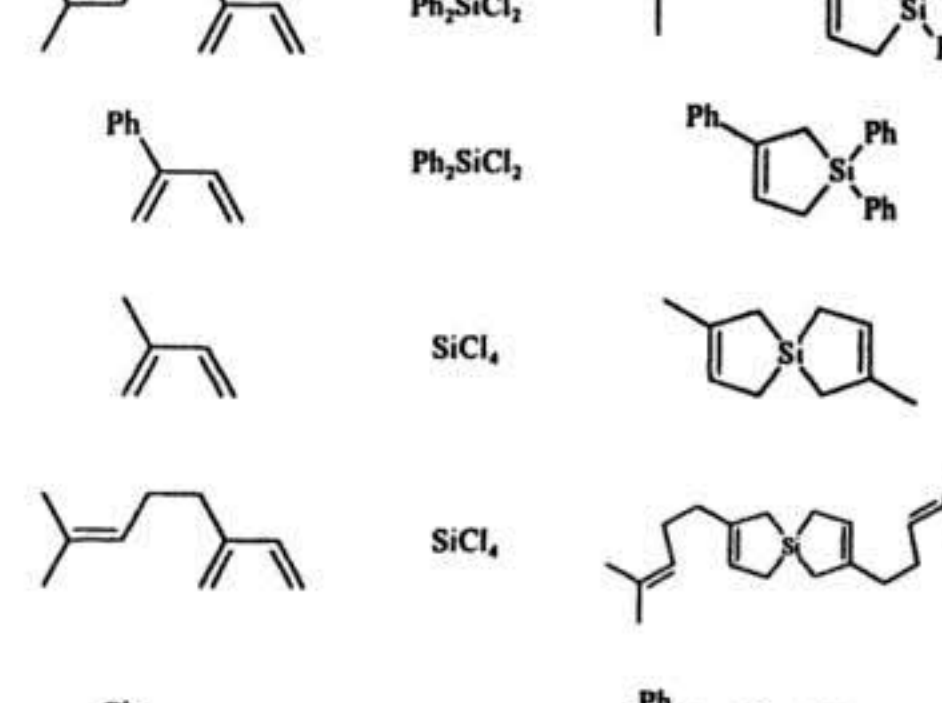
V. PREPARATION OF 1,3-DIENES

The reactivity of 1,3-dienes toward metallic magnesium varies greatly among individual 1,3-dienes. Dienes possessing extended conjugations through the connection with aromatic

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Table 5 Preparation of Silicon-Containing Heterocycles and Spiro Compounds from Asymmetric (2-Butene-1,4-diyl)magnesium

Entry	Diene	Electrophile	Product	% Yield
1		Me_2SiCl_2		66
2		Ph_2SiCl_2		65
3		Ph_2SiCl_2		96
4		Ph_2SiCl_2		91
5		Ph_2SiCl_2		93
6		$SiCl_4$		75
7		$SiCl_4$		62
8		$SiCl_4$		34



Scheme 5 Preparation of silicon-containing heterocycles and spiro compounds.

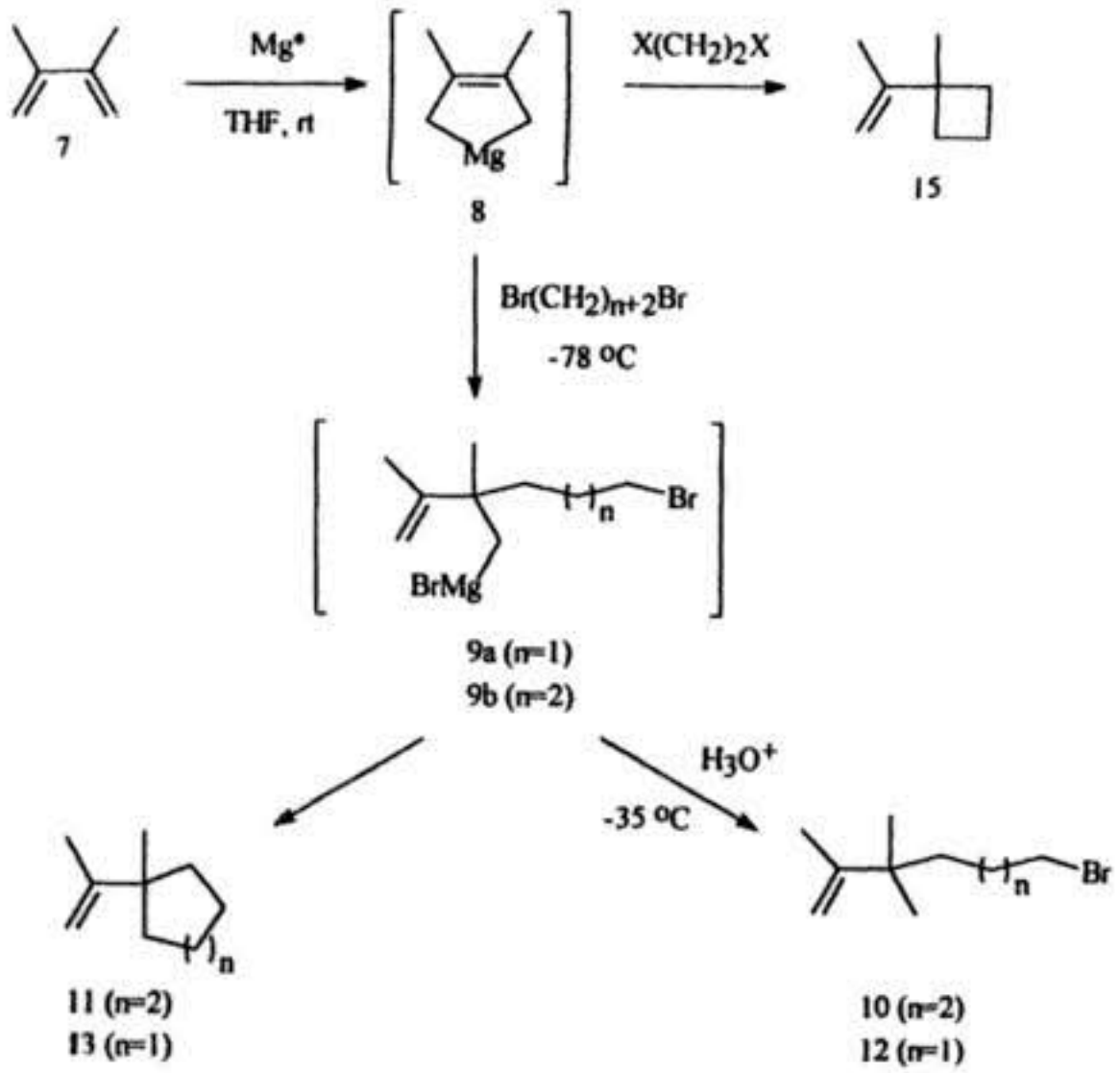
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groups, such as (*E*,*E*)-1,4-diphenyl-1,3-butadiene, display higher reactivity than aliphatic 1,3-dienes. Furthermore, 1,3-butadiene exhibits higher reactivity than substituted 1,3-dienes with nonaromatic groups. In particular, those 1,3-dienes accommodating more than one alkyl group about the double bonds react with ordinary magnesium only with great difficulty.

The nontrivial formation of a magnesium complex from activated magnesium and 2,3-dimethyl-1,3-butadiene has been achieved previously [9]. Complicated manipulations for activating commercial magnesium and long reaction times (5 days) are reportedly required for the preparation of the 2,3-dimethyl-1,3-butadiene-magnesium adduct.

The use of the preformed 2,3-dimethyl-1,3-butadiene–magnesium adduct as a reagent in organic synthesis has not been previously reported. The only case in which the diene–magnesium reagent was possible involved was the reactions between dichlorosilanes and 2,3-dimethyl-1,3-butadiene mediated by magnesium [10]. In this procedure, the diene, dichlorosilane, and metallic magnesium were refluxed in a THF–HMPT solvent mixture, producing a substituted 1-silacyclopent-3-ene.

In a typical preparation of (2,3-dimethyl-2-butene-1,4-diyl)magnesium **8**, freshly distilled 2,3-dimethyl-1,3-butadiene **7** is added to the newly generated Rieke magnesium in THF, as shown in Scheme 6. The mixture is stirred for 8 hr at ambient temperature to give **8** as a soluble complex in THF. The color of the solution is pale orange. The reactions of the resulting complex with 1,*n*-dihaloalkanes yield a number of highly useful transformations [6]. For example, cyclizations of (2,3-dimethyl-2-butene-1,4-diyl)magnesium **8** with a wide variety of organodihalides generate four-, five-, and six-membered carbocycles. Usually, the initial adducts can be trapped by protonation, furnishing monoalkylated products.



Scheme 6 Reactions of (2,3-dimethyl-2-butene-1,4-diyl)magnesium with organodibromides.

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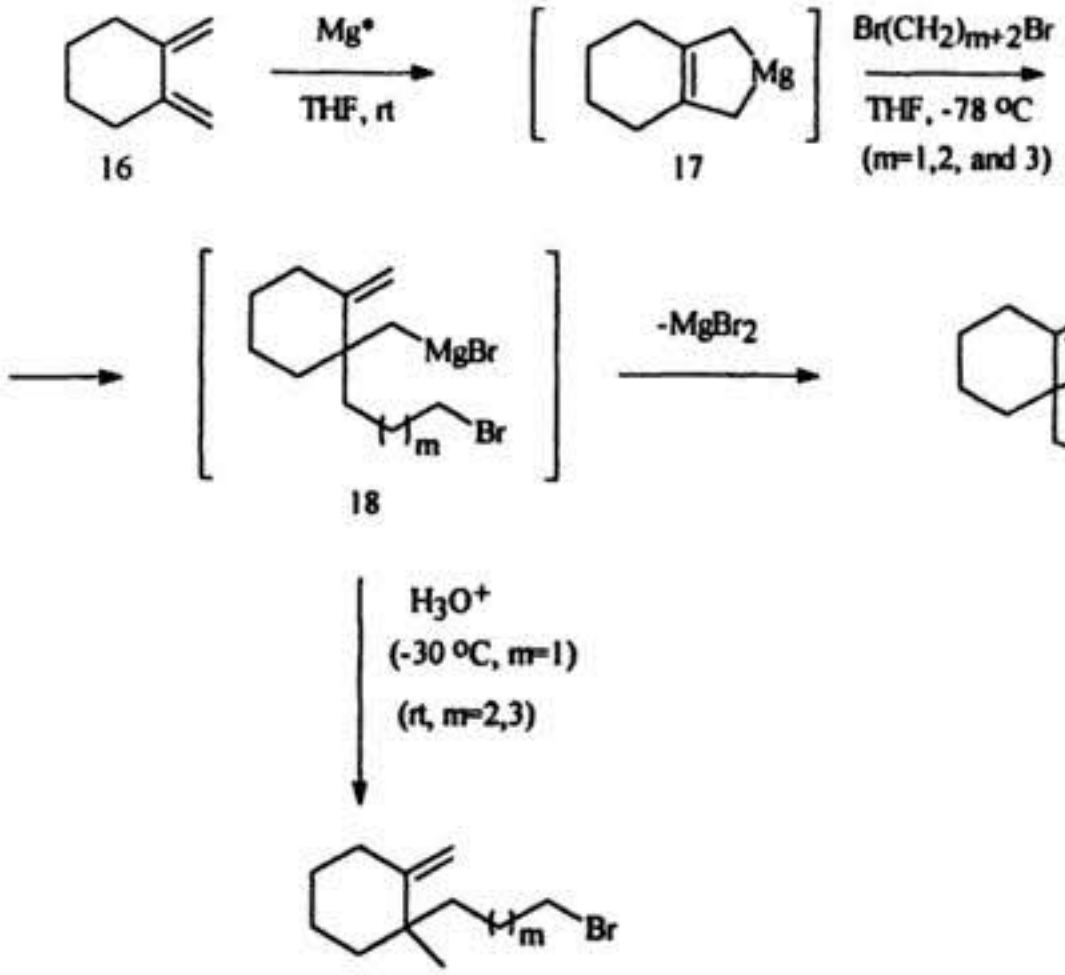
VI. PREPARATION OF CYCLIC DIENES

For example, addition of 1,3-dibromopropane to the THF solution of **8** at −78°C formed the intermediate **9a**, which cyclized, when warmed to room temperature, to yield 1-methyl-1-(1-methylethenyl)cyclopentane **13** [11]. On the other hand, an acidic workup of **9a** at −35°C gave a single monoalkylated product, 6-bromo-2,3,3-trimethyl-1-hexene **12**, in 72% isolated yield. Similar chemistry was observed with 1,4-dibromobutane, except that no cyclization would occur without refluxing conditions. Interestingly, the cyclization of **9a** to **13** represents a cross-coupling of an organomagnesium reagent with an alkyl bromide, which is normally observed only in the presence of certain transition metal salts or complexes [12].

It was recently discovered that Rieke magnesium reacts with 1,2-dimethylenecycloalkanes in THF at ambient temperature to afford the corresponding magnesium complexes in high yields. Significantly, treatment of these diene–magnesium reagents with bis-electrophiles provides a unique approach to commonly encountered spirocyclic systems [13].

Although 1,2-dimethylenecyclopentane and 1,2-dimethylenecycloheptane dienes have been used in combination with Rieke magnesium, most work has concentrated on the 1,2-dimethylenecyclohexane–magnesium complex. All three of these cyclic dienes have been synthesized by established procedures [14].

The preparation of the magnesium complex of 1,2-dimethylenecyclohexane was effected by using Rieke magnesium. In a typical reaction, 1,2-dimethylenecyclohexane was added to an excess of newly generated Rieke magnesium in THF (typical equivalent ratio of magnesium/diene = 1.5:1). After allowing the mixture to stir for 3 hr at ambient temperature, the corresponding diene–magnesium adduct **17** was formed as a soluble complex in THF, as shown in Scheme 7. The resulting yellowish gold THF solution of the complex was easily sequestered from the excess magnesium by transferring by cannula to



Scheme 7 Preparation of the magnesium complex of 1,2-dimethylenecyclohexane.

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another flask. The freshly prepared THF solution of diene–magnesium complex was subsequently treated with the appropriate electrophile(s). The structures of 1,2-dimethylenecyclohexane–magnesium reagents are presumably similar to those of magnesium complexes of open-chain 1,3-dienes. In THF solution, **17** exists most likely as five-membered metallocycle or organometallic oligomers.

Halide-free organomagnesium compounds prepared from the direct metallation of conjugated dienes with Rieke magnesium represents an important achievement in organomagnesium chemistry [reviewed in 2]. From the viewpoint of nucleophilic reactivity, these diene-magnesium reagents can be considered as magnesium 1,3-diene dianions that allow the formation of two bonds with electrophilic substrates in one synthetic operation. Depending on the nature of various electrophiles, both 1,2- and 1,4-additions to the original dienes have been observed [6,15]. When two electrophilic centers reside in one electrophile, the overall process provides easy access to cyclic molecules.

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11. The structure of (2,3-dimethyl-28butene-1,4-diyl)magnesium has not yet been determined. The most likely structures for aliphatic diene-magnesium complexes are five-membered metallocycles or organometallic oligomers.
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27

Spiroannulations Using Substituted (2-Butene-1,4-diyl)magnesium Complexes

REUBEN D. RIEKE

University of Nebraska and Rieke Metals, Inc., Lincoln , Nebraska

MATTHEW S. SELL

Rieke Metals, Inc., Lincoln, Nebraska

I. INTRODUCTION

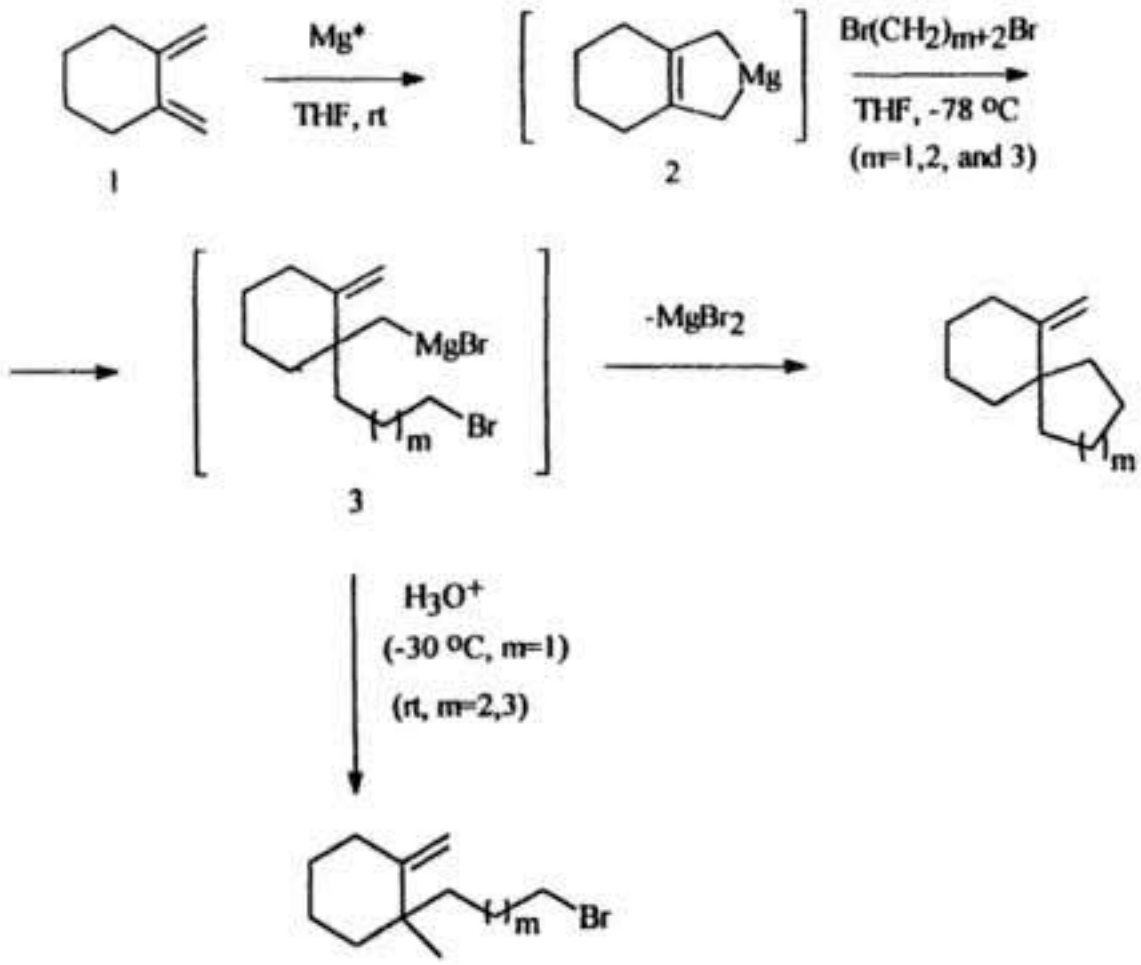
Spiro centers are found widely in natural products, such as sesquiterpenes. Several methods have been reported in the literature using spiroannulation as key steps in the synthesis of natural products. For example, (+)-acorenone B has recently been synthesized by a spiroannulation reaction using the [2,3]sigmatropic rearrangement through a cyclic allylsulfonium ylide [1]. Also, d'Angelo and Ferroud have reported an efficient spiroannulation process utilizing an intramolecular variant of asymmetric Michael alkylation [2]. Finally, Burnell and associates have recently reported the synthesis of pentalenene using a novel Lewis acid-catalyzed spiroannulation approach [3].

II. REACTIONS OF 1,2-DIMETHYLENE CYCLOHEXANE–MAGNESIUM COMPLEX

A. With Bis-electrophiles

As shown in Scheme 1, utilization of the unusual bis-nucleophilicity of 1,3-diene–magnesium complexes, reaction of **2** with bis-electrophiles can lead to spiro or fused bicyclic molecules, depending on the regioselectivity of the cyclization. Treatment of magnesium complexes of 1,2-dimethylenecyclohexane with 1,*n*-dibromoalkanes resulted in overall 1,2-cyclizations of the original dienes, affording spirocarbocycles in good excellent yields [4]. Scheme 1 depicts a general route for the spiro–olefin synthesis, emphasizing the reactions of **2** with 1,*n*-dibromoalkanes. Typically, 1,*n*-dibromoalkane was added to the tetrahydrofuran (THF) solution of **2** at $-78°C$, producing an organomagnesium intermediate accommodating a bromo group **3**. The intermediate cyclized when warmed, affording the corresponding spirocarbocycle containing an exocyclic double bond.

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Scheme 1 Reactions of the magnesium complex of 1,2-dimethylenecyclohexane with organodibromides.

The position of initial alkylation was established by protonation of the intermediate at the appropriate temperature. For the reaction of **2** with 1,3-dibromopropane, acidic hydrolysis at $-30°C$ resulted in monoalkylation, yielding the corresponding bromoolefin containing a quaternary center. On the other hand, the monoalkylated intermediates, derived from the treatment of 1,4-dibromobutane and 1,5-dibromopentane with **2**, were protonated at room temperature, affording the corresponding noncyclized products.

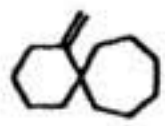
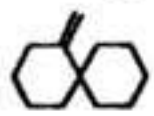
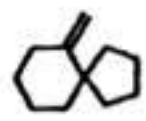
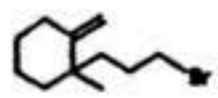
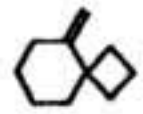
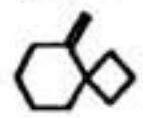
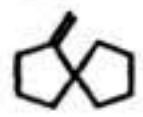
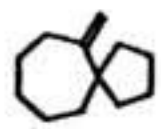
The spiroannulation approach described in Scheme 1 has been easily extended to analogous 1,2-dimethylenecycloalkanes. A wide variety of spirocycles have been synthesized from the reactions of magnesium complexes of 1,2-dimethylenecyclopentane and 1,2-dimethylenecycloheptane with 1,*n*-dibromoalkanes and are shown in Table 1. Therefore, the present spiroannulation method provides a very general approach to a large number of spirocarbocycles with different combinations of ring sizes.

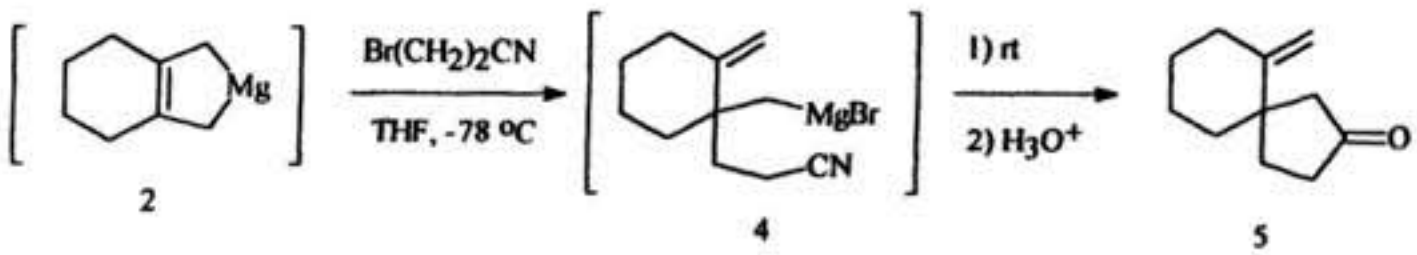
B. With Bromoalkylnitriles

Reaction of Grignard reagents with nitriles is a classic method of preparing ketones. A significant difference between an ordinary Grignard reagent and the 1,3-diene–magnesium intermediate is that the latter contains two formal magnesium–carbon bonds, providing a mode for ring annulation. Treatment of (2,3-dimethyl-2-butene-1,4-diyl)magnesium with bromoalkylnitriles has afforded cyclic ketones [5]. Studies have also demonstrated that the approach for the cyclic ketone formation can be extended to the 1,2-dimethylenecycloalkane–magnesium reagents. Thus, the reactions of **2** with bromoalkylnitriles resulted in the generation of keto-functionalized spirocycles as shown in Scheme 2. For example, addition of 3-bromopropionitrile to the magnesium complex of 1,2-dimethylenecyclohexane **2** at $-78°C$ yielded an organomagnesium intermediate containing a cyano group **4**. This intermediate began to cyclize even at $-78°C$, preventing the trapping of the monoalkylated adduct. Warming the reaction to room temperature, followed by hydrolysis; afforded

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Table 1 Reactions of Magnesium Complexes of 1,2-Dimethylenecycloalkanes with Bis-electrophiles

Entry	Diene	Electrophile	Conditions	Product	% yield
1	1a	$Br(CH_2)_3Br$	-78 °C to reflux		45
2	1a	$Br(CH_2)_4Br$	-78 °C to reflux		75 (81)
3	1a	$Br(CH_2)_5Br$	-78 °C to room temp.		75 (87)
4	1a	$Br(CH_2)_3Br$	-78 °C to -30 °C		78
5	1a	$Br(CH_2)_3Br$	-78 °C to room temp.		-- (15)
6	1a	$TsO(CH_2)_3OTs$	-78 °C to room temp.		52 (67)
7	1b	$Br(CH_2)_3Br$	-78 °C to room temp.		60 (70)
8	1c	$Br(CH_2)_3Br$	-78 °C to room temp.		77 (86)



Scheme 2 Reaction of the magnesium complex of 1,2-dimethylenecyclohexane with a bromoalkylnitrile.

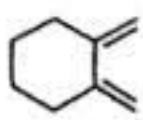
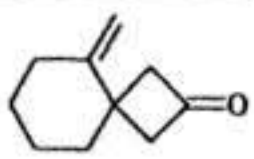
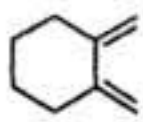
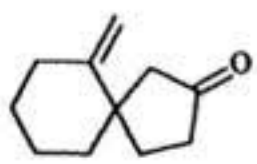
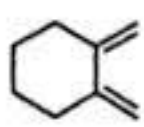
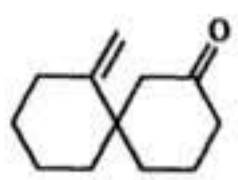
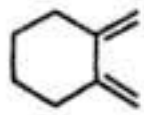
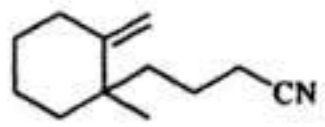
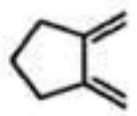
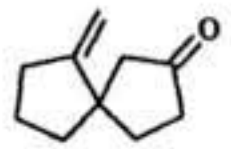
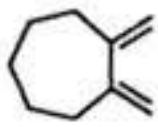
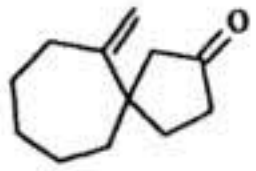
6-methylenespiro[4.5]decan-2-one **5** in 51% isolated yield (Table 2, entry 2). Representative examples of this reaction can be seen in this table.

In comparison with previous methods, the use of 1,2-dimethylenecycloalkane–magnesium reagents provides a simple approach for spiroannulation as well as access to a wide variety of spirocyclic systems. Furthermore, spirocarbocycles prepared by this method contain functional groups, such as the exocyclic double bond or a keto group in one of the rings which may be used for further elaboration of these molecules.

The process for the conversion of conjugated dienes to five-membered rings is of great interest in synthetic organic chemistry. A common procedure to accomplish this transformation involves carbene addition to dienes and rearrangement of the resulting vinylcyclopropanes [reviewed in 6]. The usefulness of this approach is limited owing to the high-temperature thermolysis of the vinylcyclopropanes. To obviate this problem, Danheiser and co-workers have developed an efficient method for the synthesis of

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Table 2 Reactions of Magnesium Complexes of 1,2-Dimethylenecycloalkanes with Bromoalkylnitriles

Entry	Diene	Bromonitrile	Product	% Yield
1		$BrCH_2CN$		46
2		$Br(CH_2)_2CN$		51
3		$Br(CH_2)_3CN$		13
4		$Br(CH_2)_3CN$		61
5		$Br(CH_2)_2CN$		40
6		$Br(CH_2)_2CN$		54

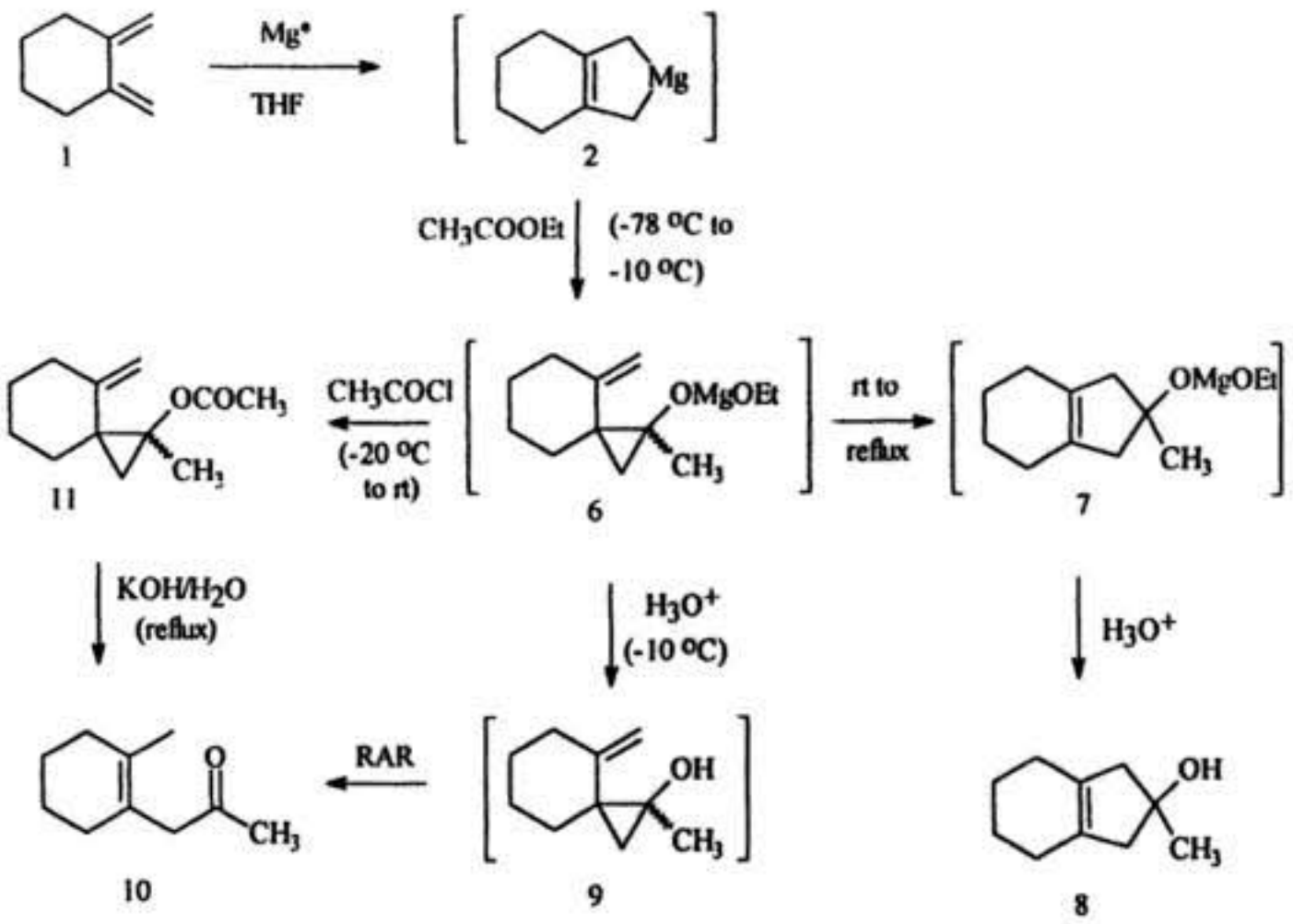
cyclopentene derivatives from conjugated dienes by alkoxy- or carbanion-accelerated vinylcyclopropane rearrangement [7].

In the course of the studies on the chemistry of 1,3-diene–magnesium reagents, the reactions of diene-magnesium reagents with bis-electrophiles have provided a simple approach to a wide variety of carbocycles [8]. These cyclizations occur generally at 1,2- or 3,4-positions of the original dienes. This chemistry has been extended to the corresponding exocyclic, conjugated dienes and has allowed a one-pot method to spirocarbocycles [9]. The further objective on the chemistry of 1,2-dimethylenecycloalkane–magnesium reagents **2** was the construction of fused rings. If overall 1,4-cyclizations of **2** could be effected by an appropriate one-carbon dielectrophile, fused carbocycles containing a five-membered ring would be easily accessed. A facile method for the synthesis of fused carbocyclic enols by the reactions of **2** with carboxylic esters has been described [10]. Interestingly, these reactions can also be used to prepare β,γ-unsaturated ketones, simply by controlling the reaction temperature. Application of the approach to (2-methyl-3-phenyl-2-butene-1,4-diyl)magnesium for the synthesis of substituted 3-cyclopentenols has also been presented.

C. Reaction with Ethyl Acetate

In early investigations, treatment of the magnesium complex of 1,2-dimethylenecyclohexane **2** with ethyl acetate at low temperature (-78 to $-10°C$), and then quenching the reaction at $-10°C$, resulted in the formation of (2-methyl-1-cyclohexenyl)propan-2-one in 72% isolated yield. On the other hand, warming the mixture to reflux, followed by workup, afforded a fused bicyclic enol, 2,3,4,5,6,7-hexahydro-2-methyl-1*H*-inden-2-ol in excellent

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Scheme 3 Reaction of the magnesium complex of 1,2-dimethylenecyclohexane with ethyl acetate.

yield. These results suggested that the adduct formed at low temperature was simply derived from the first attack by ethyl acetate at the 1-position of **2**, producing an allylic organomagnesium intermediate containing a carbonyl group. However, this suggestion was quickly ruled out by trapping the intermediate with acetyl chloride. A detailed rationalization for the reaction of **2** with ethyl acetate is given in Scheme 3.

III. SYNTHESIS OF FUSED CARBOCYCLES

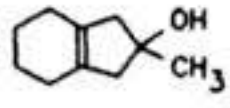
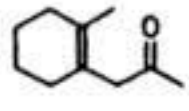
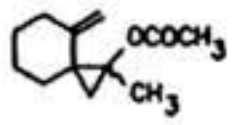
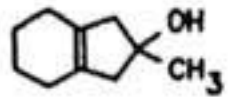
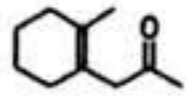
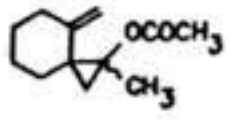
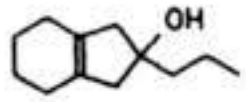
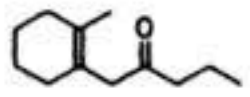
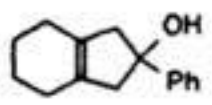
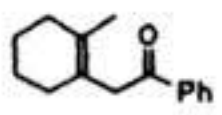
Treatment of the magnesium complex of 1,2-dimethylenecyclohexane with ethyl acetate at low temperature resulted in the formation of a magnesium salt of a spiroenol, containing a cyclopropane ring **6**. This intermediate underwent ring expansion when warmed, yielding the fused carbocyclic product **8**. Alternatively, protonation of **6** at $-10°C$ afforded the corresponding spiroenol **9**, which then rearranged *in situ* to the β,γ-unsaturated ketone **10**. Addition of acetyl chloride to **6** at $-20°C$ and workup afforded **11** as a mixture of two stereoisomers (*cis/trans* = 90:10), establishing the identity of the initial adduct. Significantly, a basic hydrolysis of **11** also afforded the enone **10**, again confirming that the β,γ-unsaturated ketone **10** was formed by rearrangement of the spiroenol **9**.

The ring enlargement from **6** to **7** involves a vinylcyclopropane–cyclopentene ring expansion, which has been observed for lithium salts of 2-vinylcyclopropanol systems [11]. On the other hand, the rearrangement of **9** to **10** is formally a 2-vinylcyclopropanol ring opening, with a proton transfer. This is the first report of such a rearrangement, although 1-vinylcyclopropanol–cyclobutanone rearrangements have been well documented [6].

Fused bicyclic systems, containing a substituted five-membered ring, can be conveniently prepared by the reactions of the magnesium complexes of 1,2-dimethylene-cycloalkanes with carboxylic esters. This reaction proceeds by a magnesium salt of a spiroenol that contains a cyclopropane ring. Quenching of the intermediate at an appropriate temperature creates an alternative pathway for the reaction, leading to a

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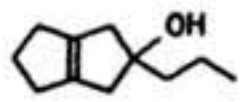
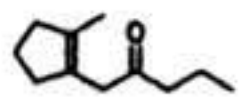
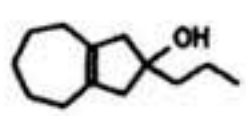
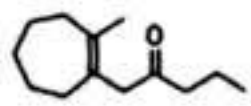
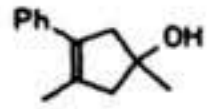
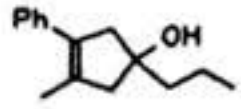
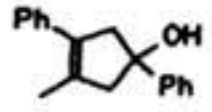
Table 3 Synthesis of Fused Carbocycles, β,γ-Unsaturated Ketones and 3-Cyclopentenols from Diene–Magnesium Reagents

Entry	Diene[a]	RCOX	Product[b]	Yield[c]	Note[d]
1	56a	CH_3COOEt		91	A
2	56a	CH_3COOEt		72	B
3	56a	(1) CH_3COOEt (2) CH_3COCl		75	C
			(*cis*/*trans*=90:10)		
4	56a	CH_3COCl		69	A
5	56a	CH_3COCl		58	B
6	56a	2 CH_3COCl		88	D
			(*cis*/*trans*=34:66)		
7	56a	$CH_3(CH_2)_2COOEt$		96	A
8	56a	$CH_3(CH_2)_2COOEt$		81	B
9	56a	PhCOOEt		55	A
10	56a	PhCOOEt		62	B

Continued

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Table 3 (*Continued*)

Entry	Diene[a]	RCOX	Product[b]	Yield[c]	Note[d]
11	**56b**	$CH_3(CH_2)_2COOEt$	 **98**	59	A
12	**56b**	$CH_3(CH_2)_2COOEt$		76	B
13	**56c**	$CH_3(CH_2)_2COOEt$		74	A
14	**56c**	$CH_3(CH_2)_2COOEt$		84	B
15	**102**	CH_3COOEt		68	E
16	**102**	$CH_3(CH_2)_2COOEt$		70	E
17	**102**	PhCOOEt		53	E

[a] **57a**: 1,2-Dimethylenecyclohexane; **57b**; 1,2-Dimethylenecyclopentane; **57c**: 1,2-Dimethylenecycloheptane; **102**: 2-Methyl-3-phenyl-1,3-butadiene.

[b] All new compounds have been fully characterized by ^{1}H-NMR, ^{13}C-NMR, FTIR, and mass spectra.

[c] Isolated yields.

[d] RCOX was added to the magnesium–diene complex at −78°C. After being stirred at −78°C for 30 min, the reaction mixture was gradually warmed to the specified temperature. **A**: Fused bicyclic product was obtained at reflux. **B**: Quenching the reaction at −10°C gave a β,γ-unsaturated ketone. **C**: Ethyl acetate was added to the magnesium complex of **57a** at −78°C. The mixture was stirred at −78°C for 30 min, then gradually warmed to −10°C as usual. Addition of acetyl chloride at −20°C afforded **93**. **D**: Addition of 2 Eq of acetyl chloride to **57a** at −78°C, followed by warming to room temperature, gave **93**. **E**: Esters were added to the magnesium complex of **102** at −78°C. The mixture was stirred at −78°C for 10 min and gradually warmed to room temperature followed by reflux.

regioselective synthesis of β,γ-unsaturated ketones. Representative reactions of this type are presented in Table 3.

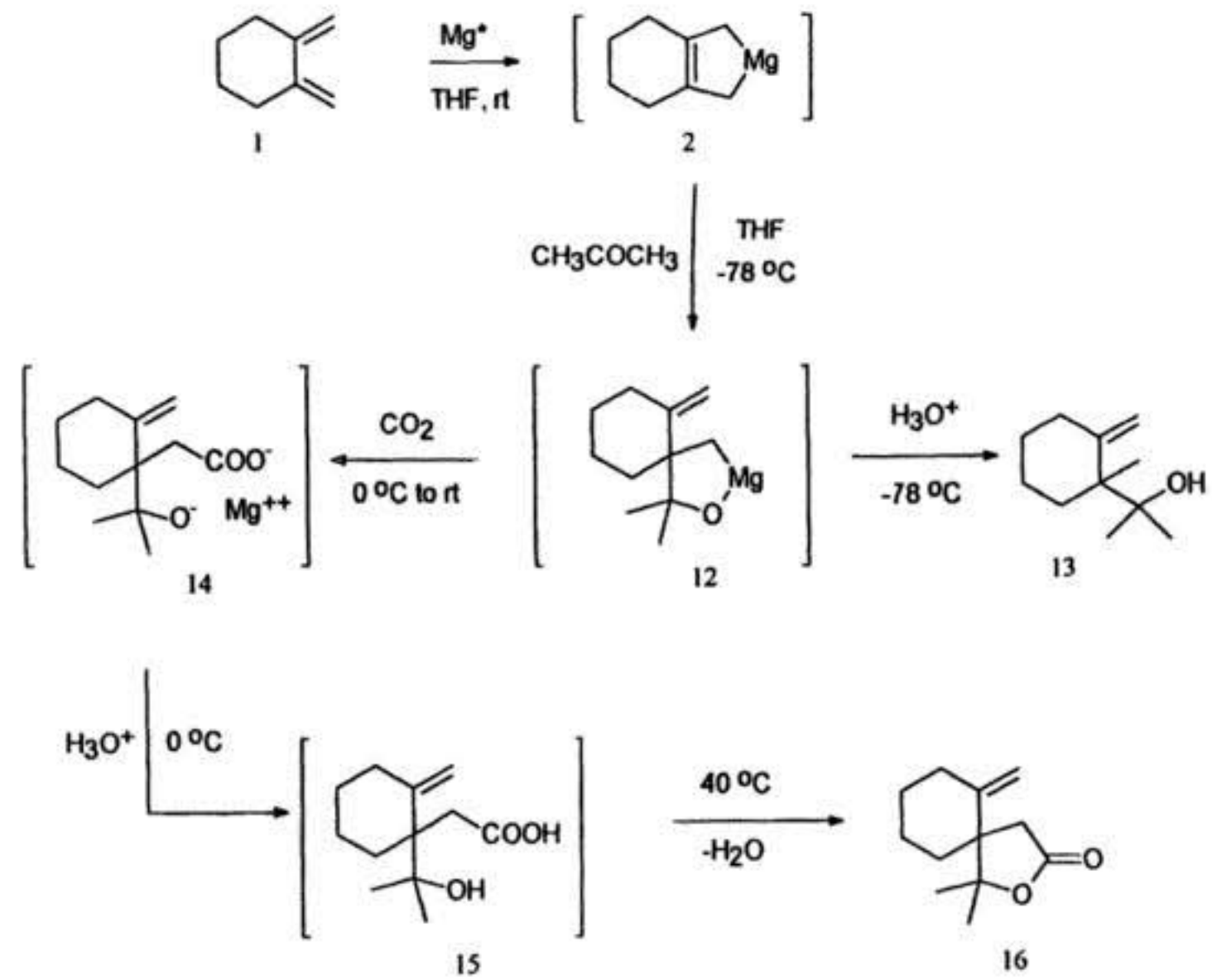
Recently, this method has been expanded to include reaction with lactones as well as the use of asymmetric dienes [12].

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A. Synthesis of Spiro γ-Lactones

The difficulties associated with the synthesis of spiro γ-lactones include the generation of a quaternary carbon center and the introduction of functionalities used for lactonization. Much work has been done in an effort to develop useful synthetic routes [13]. However, most methods require the use of complex reagents and multiple synthetic steps to accomplish the overall process.

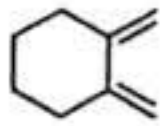
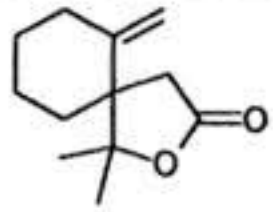
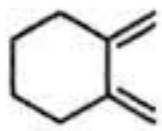
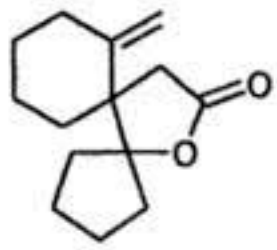
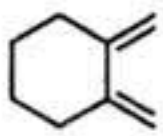
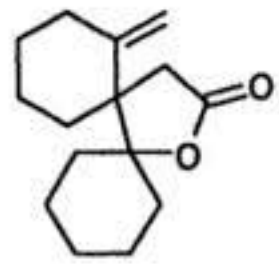
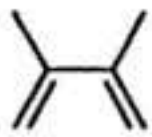
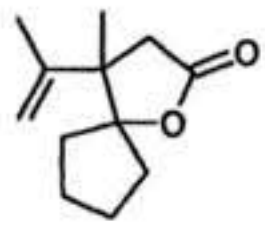
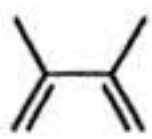
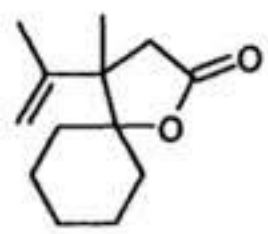
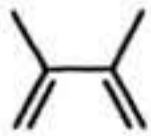
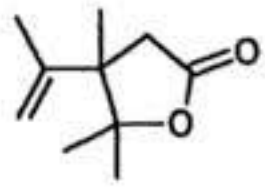
Recently, it was reported that spiro γ-lactones containing a vinyl group at the β-position can also be synthesized in a one-pot procedure, based on stepwise reaction of dienemagnesium reagents with ketones, followed by reaction with carbon dioxide [14]. Scheme 4 illustrates a route for spiro γ-lactone synthesis from the magnesium complex of 1,2-bis(methylene)cyclohexane **1**. Initially, it was observed that treatment of 1,2-bis(methylene)cyclohexane–magnesium **2** reagent with one equivalent of acetone at −78°C resulted in the formation of a 1,2-addition adduct **12**, derived from the incorporation of one molecule of acetone with the diene complex. Protonation of **12** at −78°C yielded a tertiary alcohol, containing a quaternary center **13**. It was considered that with warming, intermediate **12** should undergo nucleophilic addition to another electrophile. Thus, carbon dioxide was chosen as the second electrophile and introduced to the reaction mixture at 0°C to room temperature. As expected, the intermediate reacted quickly with carbon dioxide, presumably yielding a magnesium salt of a γ-hydroxy acid **14**. After acidic hydrolysis, followed by slight warming, a spiro γ-lactone, 4,4-dimethyl-6-methylene-3-oxaspiro [4.5]decan-2-one **16** was obtained in 68% isolated yield. The γ-hydroxycarboxylic



Scheme 4 Synthesis of a spiro γ-lactone from the magnesium complex of 1,2-dimethylenecyclohexane, acetone, and CO_2

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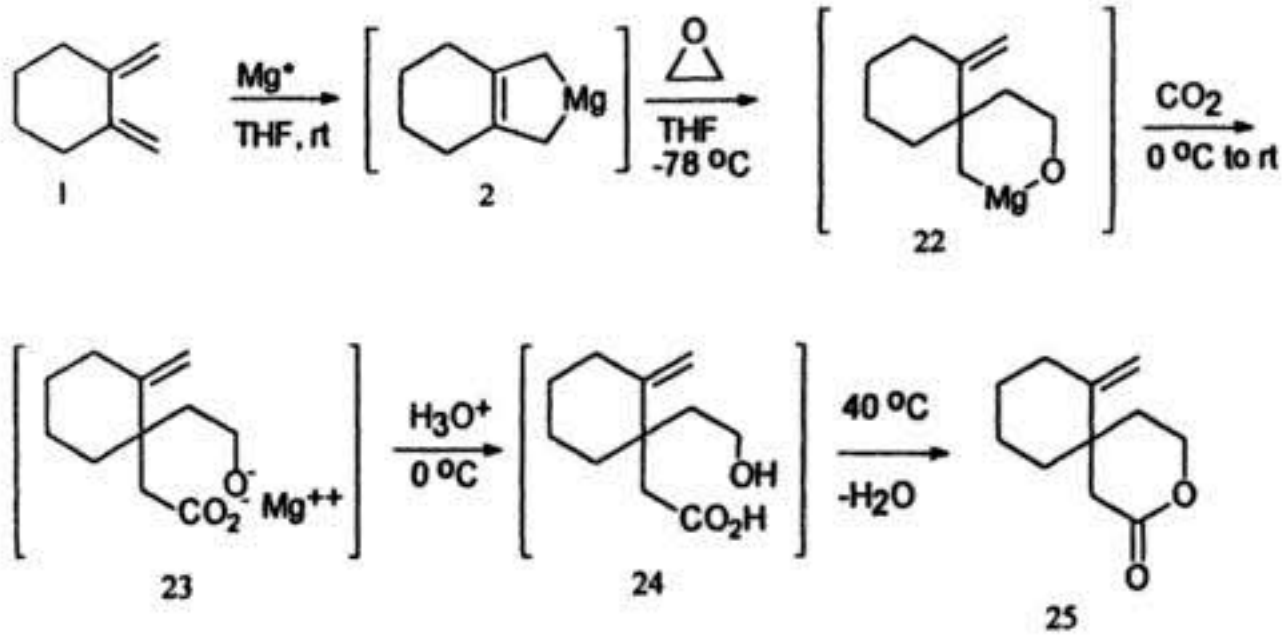
Table 4 Synthesis of Spiro γ-Lactones from Conjugated Dienes, Ketones, and CO_2

Entry	Diene	Ketone	Product	% Yield
1		Acetone		68
2		Cyclopentanone		66
3		Cyclohexanone		60
4		Cyclopentanone		68
5		Cyclohexanone		61
6		Acetone		59

B. Synthesis of Spiro δ-Lactones

The synthesis of spiro γ-lactones has been extended to the synthesis of spiro δ-lactones. This one-pot transformation of 1,3-dienes reacted with epoxides, mediated by Rieke magnesium to spiro δ-lactones in good isolated yields, was recently reported [15]. Much work has been done to elucidate novel synthetic routes for these types of molecules [16]. In particular, δ-substituted δ-lactones have recently attracted considerable attention, mainly because molecules of this class include many natural products that exhibit substantial biological activity [17]. However, most methods for the synthesis of these molecules require

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1 2 22 23 24 25

Scheme 6 Synthesis of a spiro δ-lactone from the magnesium complex of 1,2-dimethylenecyclohexane, ethylene oxide, and CO_2

the use of complex reagents and multiple synthetic steps to accomplish the overall process. One of the more adept methods involves the treatment of bis(bromomagnesium) alkanes with dicarboxylic anhydrides [18].

Scheme 6 illustrates a route for the spiro δ-lactone synthesis from the magnesium complex of 1,2-bis(methylene)cyclohexane **2**.

Initially, treatment of 1,2-bis(methylene)cyclohexane–magnesium reagent **2** with an excess of ethylene oxide at $-78°C$, resulted in the formation of the 1,2-adduct **22**, derived from the incorporation of 1 Eq of epoxide with the diene complex. Significantly, the bis-organomagnesium reagent **2** reacted with only 1 mol of epoxide, with 100% regioselectivity in the 2-position, to afford intermediate **22**. When warmed to 0°C, **22** reacted with carbon dioxide to yield presumably the magnesium salt of a δ-hydroxy carboxylic acid **23**. Acidic hydrolysis, followed by warming to 40°C generated the spiro δ-lactone, 7-methylene-3-oxaspiro[5.5]undecan-2-one **25**, in 69% isolated yield. Other examples of this type of reaction, are listed in Table 5.

When unsymmetrical epoxides were employed as the primary electrophile, good regioselectivity was observed. The attack of the unsymmetrical epoxide always occurred at the less sterically hindered carbon.

This convenient, one-pot process for the synthesis of spiro δ-lactones from 1,3-dienes and epoxides, mediated by Rieke magnesium, provides a proficient route to this class of complex organic molecules in good isolated yields.

IV. GENERATION OF QUATERNARY CARBON CENTERS

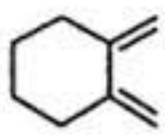
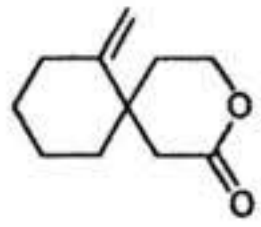
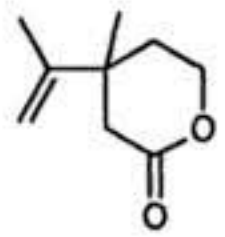
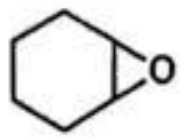
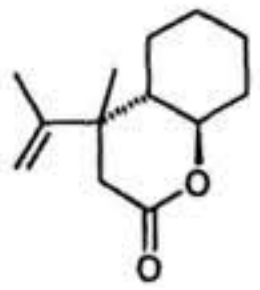
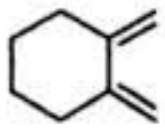
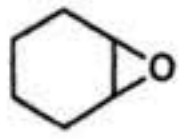
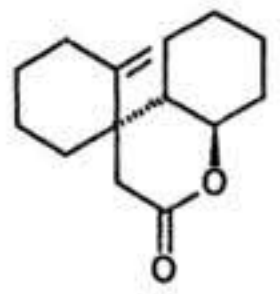
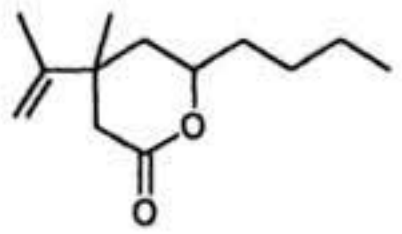
The generation of a quaternary carbon center is not a trivial undertaking in organic synthesis. Multiple synthetic steps are often required to generate a quaternary carbon. The high-yield formation of both alcohols and vicinal diols by a one-pot procedure with the concomitant formation of a quaternary carbon center was recently reported [19].

A. Synthesis of Alcohols

Scheme 7 outlines the general approach for the preparation of a primary alcohol that accommodates a quaternary carbon center. Significantly, the organomagnesium reagent **2** again reacted with only 1 mol of epoxide, with 100% regioselectivity. Again, if

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Table 5 Synthesis of Spiro δ-Lactones from Conjugated Diene–Magnesium Reagents, Epoxides, and CO_2

Entry	Diene	Epoxide	Product	% Yield
1				69
2				39
3				69
4				63
5				72

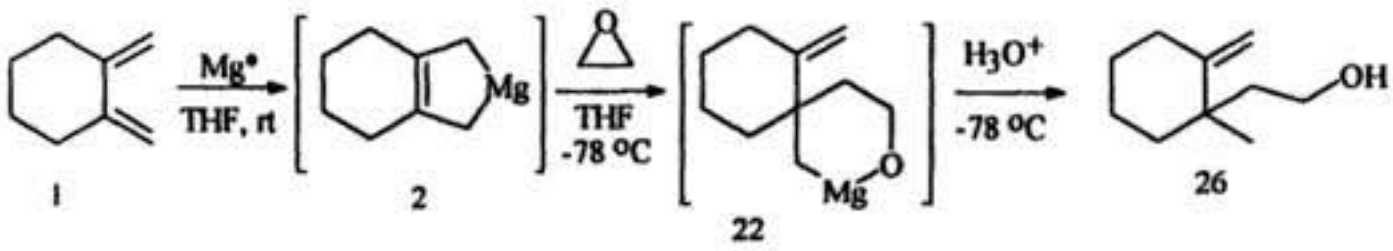
unsymmetrical epoxides were used the bis-organomagnesium reagent **2** was always completely regioselective for the less-hindered carbon atom. Representative examples of this reaction are shown in Table 6.

The process described here provides a facile preparation of alcohols and vicinal diols in one-pot in high yields.

B. Synthesis of γ-Lactams

γ-Lactams are important intermediates in routes to five-membered heterocyclic compounds. Moreover, tetramic acids and 3-pyrrolin-2-ones represent a diverse and profoundly important family of biologically active secondary metabolites, many of which have potential

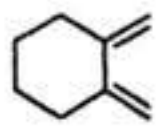
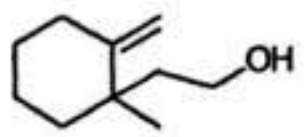
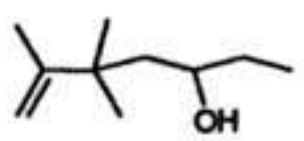
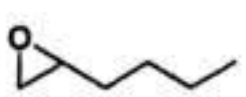
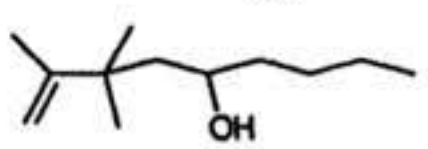
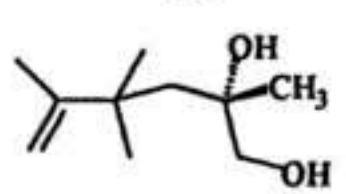
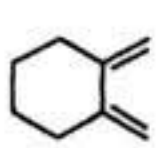
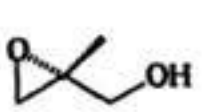
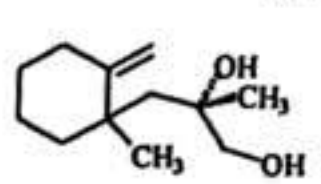
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Scheme 7 Reaction of the magnesium complex of 1,2-dimethylenecyclohexane and ethylene oxide followed by acidic hydrolysis

Table 6 Synthesis of Alcohols from Conjugated Diene–Magnesium Reagents and Epoxides, Followed by Acidic Hydrolysis

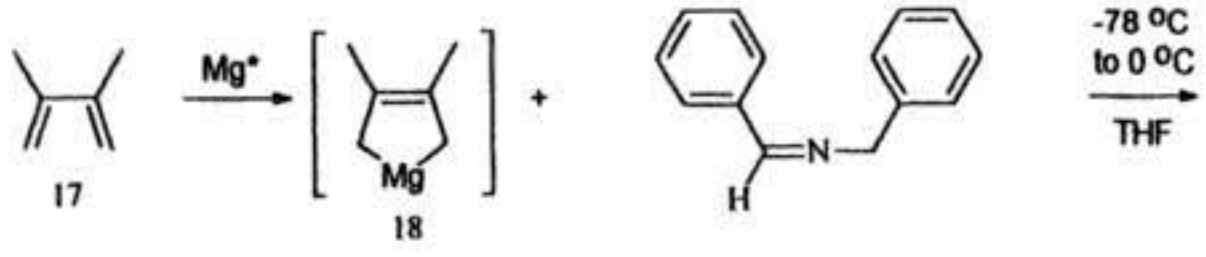
Entry	Diene	Epoxide	Product	% Yield
1				86
2				60
3				64
4				90
5				47
6				62

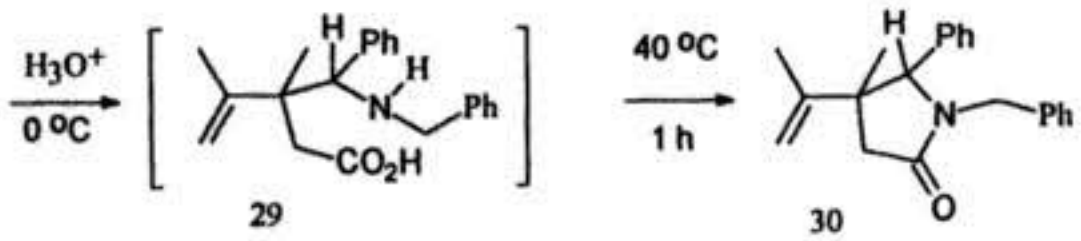
use in both medicine and agriculture [20]. Synthetic interest in this class of molecules has been intense, particularly in the past decade [21].

Many approaches to γ-lactams have been dependent on cyclization by acyl–nitrogen bond formation [22]. Cyclization involving carbon–carbon bond formation is an alternative route; however, until recently, this potential methodology has received little attention. Mori and co-workers reported a palladium-catalyzed cyclization of *N*-allyl iodoacetamides, in which the intramolecular addition reaction of the carbon–iodine bond to an olefinic linkage is a key step [23].

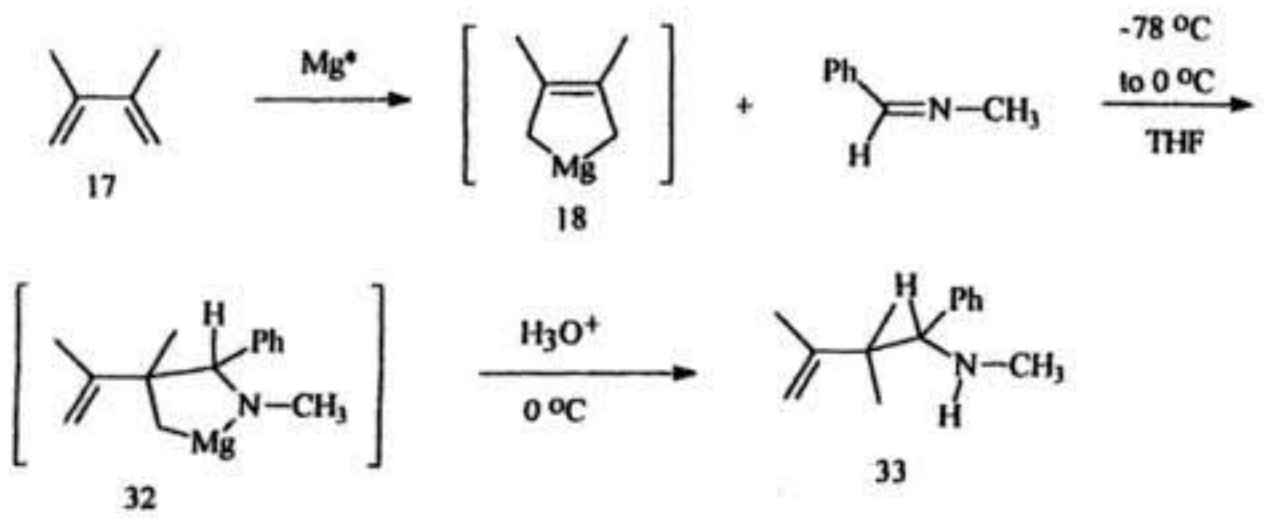
Recently, Nagashima and associates developed a new route to γ-lactams by the ruthenium-catalyzed cyclization of *N*-allyltrichloroacetamides [24]. Also, Stork and Mah reported the radical cyclization of *N*-protected haloacetamides to yield *N*-protected lactams. The protecting groups can then be easily removed under a range of different conditions [25]. This efficient radical cyclization route to *cis*-fused pyrrolidones and piperidones is interesting because of the widespread occurrence of related systems in natural products [26].

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Scheme 8 Reaction of (2,3-dimethyl-2-butene-1,4-diyl)magnesium with an imine and CO_2



Scheme 9 Reaction of (2,3-dimethyl-2-butene-1,4-diyl)magnesium with an imine, followed by acidic hydrolysis

Recently a convenient, one-pot preparation of γ-lactams by the reaction of a 1,3-diene and imine, mediated by Rieke magnesium, was accomplished [27].

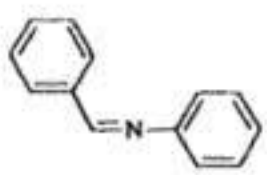
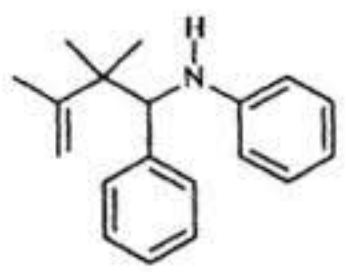
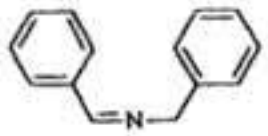
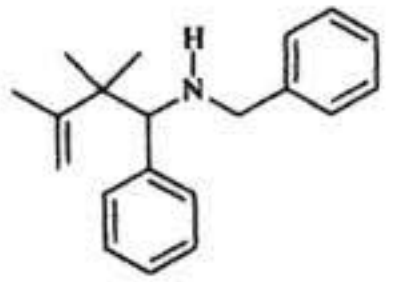
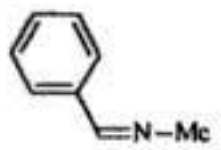
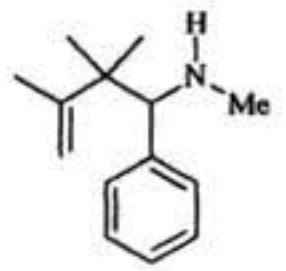
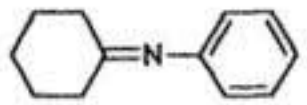
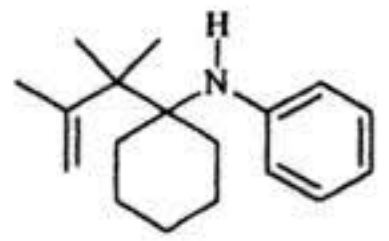
As shown in Scheme 8, reaction of (2,3-dimethyl-2-butene-1,4-diyl)magnesium **18** with an imine afforded the 1,2-addition adduct **27**, which after treatment with carbon dioxide, acidic hydrolysis, and subsequent heating afforded a γ-lactam **30** accommodating a quaternary carbon center in 62% isolated yield. For other examples of this type of transformation, see Table 7.

As shown in Scheme 9, when the initial adduct **32** (formed by the treatment of **18** with the imine) underwent acidic hydrolysis, the secondary amine **33** was afforded in 96% isolated yield. All of the amines formed by this procedure were isolated in excellent chemical yields and are shown in Table 8.

This facile one-pot transformation of a 1,3-diene-magnesium intermediate provides

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Table 8 Formation of Secondary Amines from Reactions of (2,3-Dimethyl-2-butene-1,4-diyl)magnesium with Imines, Followed by Acidic Hydrolysis

Entry	Diene	Imine	Product	%Yield
1				87
2				92
3				96
4				85

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28

Asymmetric Synthesis Using Grignard Reagents

JOHN T. ROBERTS
Elf Atochem North America, Inc.
King of Prussia, Pennsylvania

I. INTRODUCTION

The synthesis of optically pure materials has gained importance in recent years. As scientists have targeted synthetically challenging molecules that have biological activity, a keen interest has developed in the methods of producing, characterizing, and isolating chiral materials. The formation of chiral or optically active materials from nonoptically active precursors is titled *asymmetric induction.* Asymmetric induction can be easily accomplished using Grignard reagents and a nucleophilic acceptor.

A recent book details some catalyzed Grignard reactions for asymmetric induction. In *Asymmetric Catalysis in Organic Synthesis*, Noyori [1] reports the enantioselective addition of Grignard reagents to carbonyl compounds, catalyzed by chirally modified organometallic compounds. This book contains several interesting examples of asymmetric induction involving complexes from Grignard reagents and other chiral ligands, including amines and phosphines. For example, the formation of an alcohol from the reaction of BuMgCl with benzaldehyde can be catalyzed by a chiral tertiary amine to yield the *R*-enantiomer in 95% optical yield.

In this chapter, the details of selected syntheses of optically pure or enantiometrically enriched compounds using Grignard reagents will be presented. [For a fuller explanation of the concept of chirality and nomenclature, the readers are referred to Refs. 1–5.] However, as new terms are introduced, a brief explanation will be provided. The work is divided into three sections. The first section includes the major reactions to prepare pure or enriched materials by addition to a chiral or prochiral carbonyl with a Grignard reagent. These reactions are typically 1,2- or 1,4-additions. The second section include reactions of a suitable acceptor (e.g., an epoxide) and a Grignard. The third section is a miscellaneous section and covers the preparation of pure or enriched materials that contain heteroatoms, such as nitrogen, oxygen, silicon, and phosphorus and other reactions.

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II. ADDITION TO CARBONYL DERIVATIVES

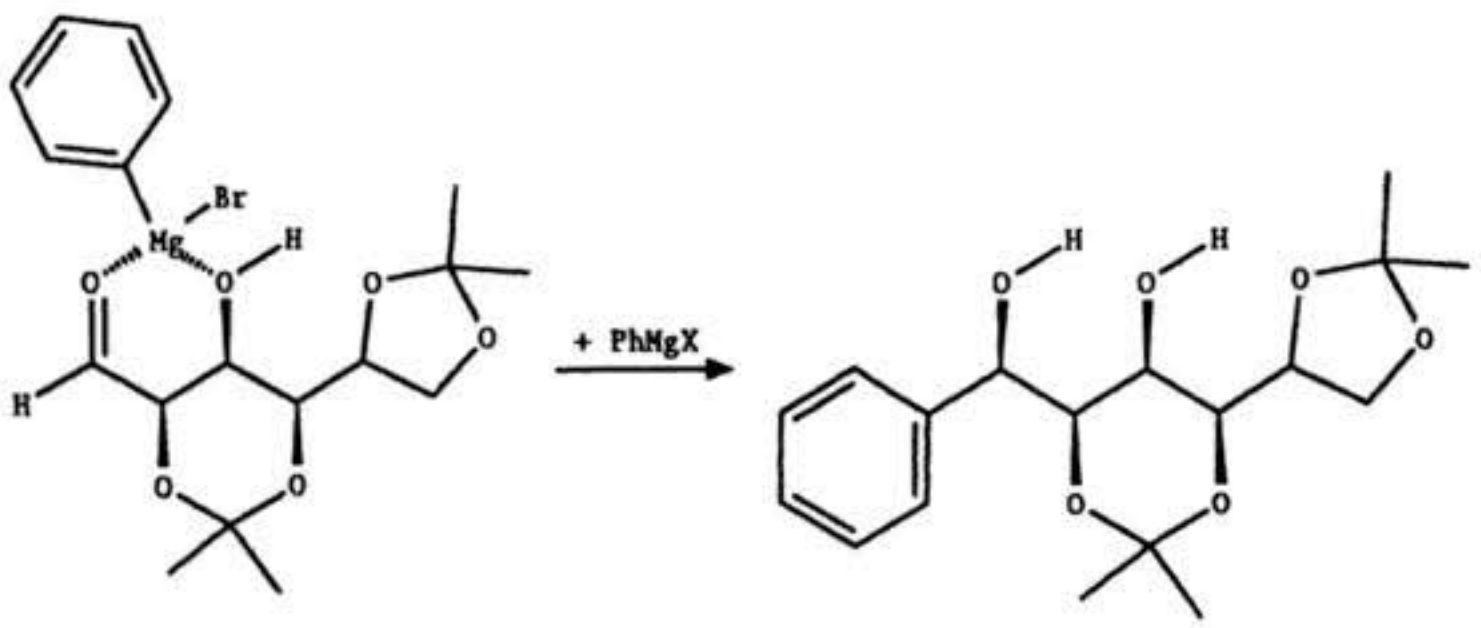
Typical addition of a Grignard reagent to a carbonyl compound leads to an alcohol. For example, reaction at the planar carbonyl carbon of an achiral (not optically active) aldehyde gives two possible stereoisomers, which are nonsuperimposable mirror images. Since two enantiomers or chiral compounds are formed, the carbon atom is described as a *stereogenic atom*. Before reaction, the carbonyl carbon is described as *prostereogenic* or *prochiral*, because it can lead to two different isomers or enantiomers. From a statistical point of view, one would predict that equal amounts of each enantiomer should be formed. However, if one isomer is formed in greater yield, the reaction mixture is described as *scalemic*, and the enantiomeric purity of the products is the enantiomeric excess (e.e.) of one isomer over the other. For example, if one enantiomer is formed in 75% and the second in 25%, the e.e. is 50% (75% − 25% = 50%). Most of the reactions in this chapter will present e.e. as the indication of asymmetric induction in a reaction. Certainly, for a reaction to be synthetically useful, the e.e. will be very high; an ideal example of asymmetric induction will have an e.e. of 100% (100% of one enantiomer and 0% of the second).

If one of the reactants has a stereogenic center, there then is a possibility of forming two pairs of diastereomers or two pairs of enantiomers, four different products. Depending on a variety of factors, we could distance e.e. or d.e. (diastereomeric excess, the predominance of pair of diastereomers over the second). A few authors will describe the ratio of their products.

A. 1,2-Additions

The results of Grignard additions to a variety of carbonyl compounds are shown in Table 1. The common theme for each example is the formation of a secondary alcohol from an aldehyde. The authors cited in Table 1 use a variety of conventions to indicate optical purity (op); however, if possible, these will be converted to the conventional percentage e.e., or to the configuration (*R*- or *S*-) of the isomer.

Shing and co-workers (see Table 1, entry 1) reported the stereoselective synthesis of the secondary alcohol from the aldehydo-D-glucose for use as an intermediate in the synthesis of goniopypyrones, cytotoxins to human tumor cells [6]. These intermediate products were the epimeric benzylic alcohols; the major product was the *R*-isomer, formed in 70% e.e. The authors propose an α-chelate transition state 1, a six-membered chelate ring, with the nucleophile attacking the carbonyl from the bottom face, relative to the coordinating hydroxyl and ketyl groups, as shown in Eq. (1).



(1)

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66:33 ratio. Gawley also identified a new oxazoline chiral auxiliary, a camphor derivative, that affords improved selectivity, up to 100% in one instance.

In contrast, Casiraghi et al. [10] (see Table 1, entry 5) reported the synthesis of α-pyrrylalditols as precursors to heteroatom nucleosides. Reaction of the pyrrol Grignard with 2,3-*O*-isopropylidene-D-glyceraldehyde gave a mixture of products, depending on the catalyst. When the reaction is assisted by a titanium salt, the major product is the D-*erythro*-glycerol (55% yield), with a small amount of the D-*threo*-isomer, 8%. With a cerium salt the major product has the opposite stereochemistry: the yield of D-*threo*-isomer is 65%, with only 7% of the D-*erythro*-isomer. This strategy will be discussed in subsequent sections.

Table 2 shows selected reactions of ketones with Grignard reagents. In the first entry, Miles and co-workers [11] used a chiral Grignard reagent as the nucleophile in the diastereoselective preparation of ether alcohols. Here, an optically active Grignard reagent gives both possible diastereomers in an approximate 70% yield, with an e.e. of 80% for the *S*-isomer. Reaction of the same Grignard with cyclopentanone gives similar yields (50%) and optical purity (80% e.e.).

Table 2, entry 2, shows an example of the work of Marco et al. [12]. They observed the diastereoselective addition to protected sugars as precursors to macrolide antibiotics. In general, the diastereomeric ratio of the tertiary alcohols depended on the reagent, the solvent, and the temperature. Pure enantiomeric erthrulose acetonides (either *R*- or *S*-isomer) gave a mixture of the two possible diastereomeric adducts in fair to excellent yield; the d.e. varied from 25:75 (*R* or *S*) *S*/*R* to 75:25 (*R* or *S*) *S*/*R* using the Grignard reagent at $-78°C$ in diethyl ether.

Nogano and co-workers [3] reported similar examples of asymmetric induction for natural product synthesis using protected sugars and a variety of R′MgX, where X = Cl, Br, or I. In Table 2, entries 3 and 4, the tetralose carbonyl can also contain in the R_1 position an ether, ester, urethane, alkyl, or aryl group [13]. The authors reported the diastereometer ratio from the *R* substrate and the labeled carbon-2 varied from 80:20 to 10:90 (2*S*/2*R*). The variability was controlled by the nature of the nucleophile, the solvent, and the temperature. The authors rationalized the product distribution based on chelation of the metal and steric bulk of the reactants, favoring the *R*-isomer.

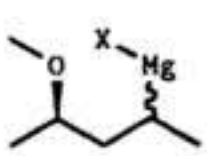
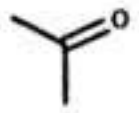
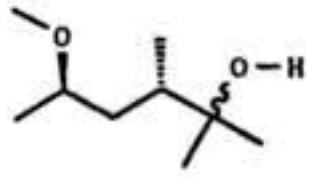
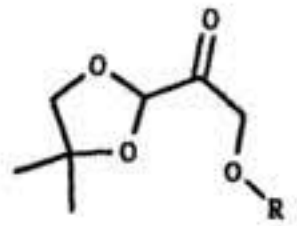
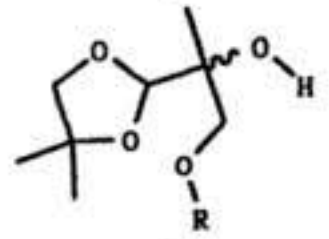
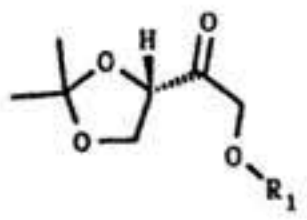
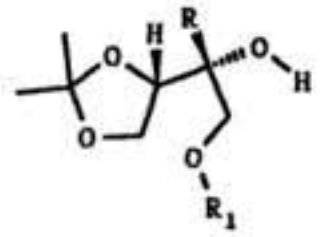
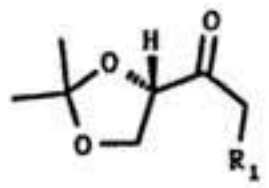
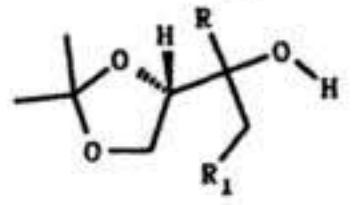
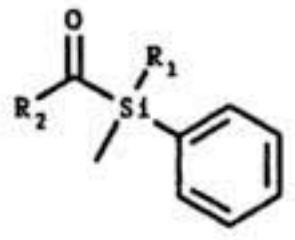
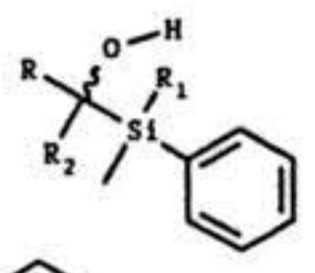
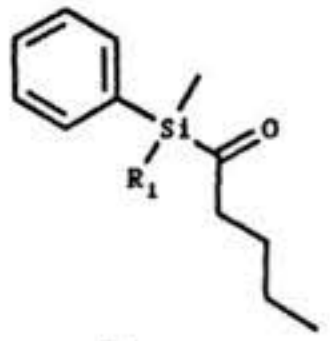
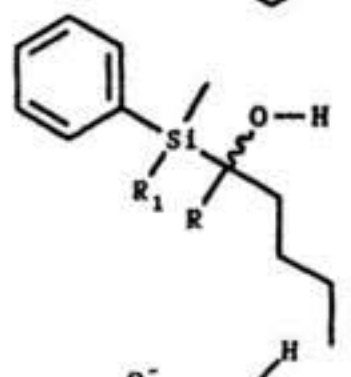
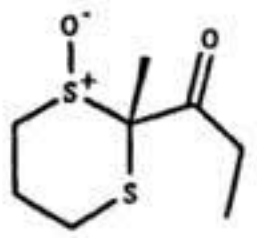
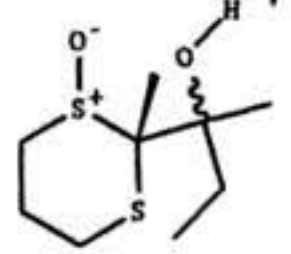
For their approach to optically active alcohols, Mazzanti and co-workers [14] used chiral acylsilanes (see Table 2, entries 5 and 6). Since the stereogenic silicon auxiliary could easily be removed by fluoride treatment [15], the authors hoped the alcohols had a high d.e. that would lead to a high e.e. They demonstrated the concept, but the overall e.e. was less than 30%. For example, use of either a phenyl or methyl Grignard with the chiral silane gave a range of d.e. (15–80%), but on hydrolytic workup the highest d.e. products gave an alcohol with a e.e. of 28%. Variation of the substituents on the silicon and adding steric bulk to the ketone gave mixed results.

Page and co-workers [16] used a diathiane oxide moiety because it allowed the stereocontrolled addition of nucleophiles without the loss of the protecting group (see Table 2, entry 7). These authors demonstrated high diastereoselectivities, depending on the solvent and the temperature. In tetrahydrofuran (THF), at $-20°C$, a 92% d.e. was obtained in almost quantitative yield; lower selectivities were obtained in diethyl ether or at higher temperatures.

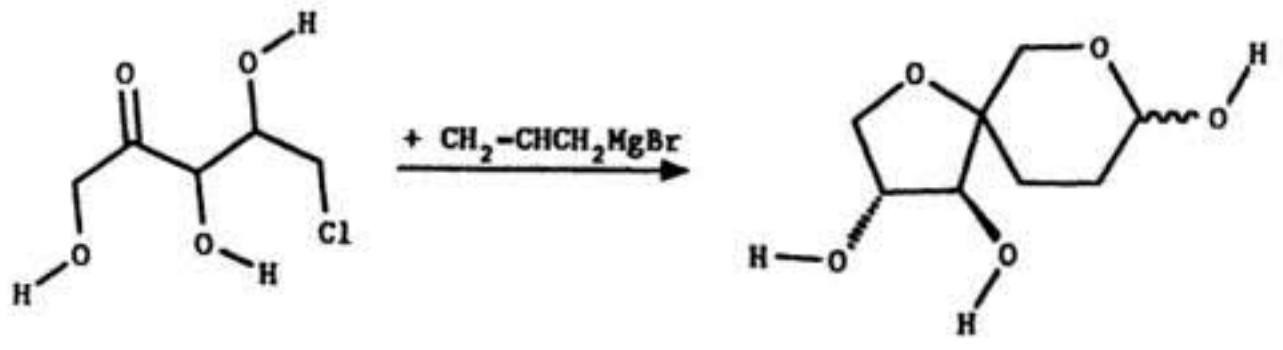
Schmid and Maliakel [17] reported diastereoselective Grignard reactions in their synthetic scheme to sphydrofurans, secondary metabolites from various strains of *Streptomycetes*. Although Eq. (2) depicts the desired sequence as a single equation, the actual scheme has four steps. The authors used the silyl-protected carbonyl with D-*threo*

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Table 2 Chiral Products from 1,2-Additions to Ketones

Entry (Reference)	RMgX	Substrate	Product	Configuration, Optical Yield
1 (11)				80 % ee
2 (12)	CH_3MgX			S:R 25:75 75:25
3 (13)	RMgX			R, 90% de
4 (13)	RMgX			S, 70% de
5 (14)	RMgX			72% de
6 (15)	RMgX			25 - 55% de
7 (16)	CH_3MgX			92% ee

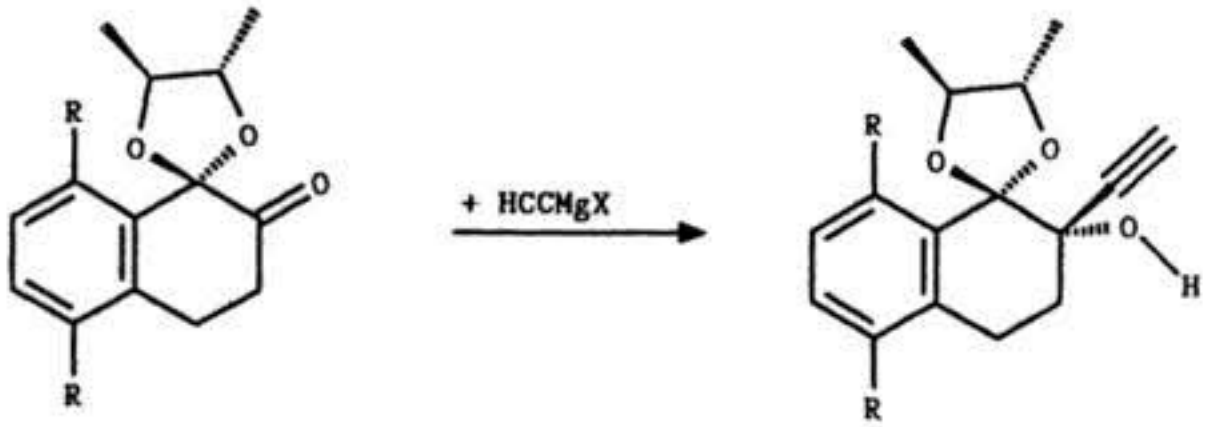
(3*S*, 4*R*) configuration and the allyl Grignard reagent to give a single, ring-closed furan, with a pendant allyl group, in 60% yield as the first step. Subsequent Wacker reaction gave the sphydrofuran.



(2)

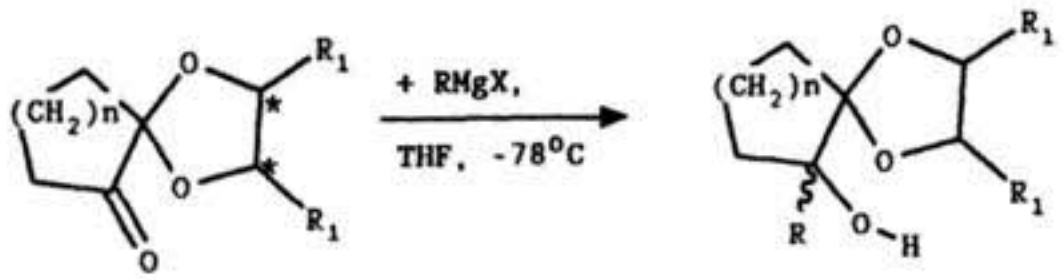
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Fujioka et al. [18] prepared a new chiral α,β-building block for use in the synthesis of optically active anthracyclinones [Eq. (3)]. Reaction of the propenyl Grignard reagent with the chiral β-tetralone gave the alkynylalcohol with an α,β-ring. The authors show one product with the indicated stereochemistry. Hydrolysis of the ketal gave the desired intermediate.



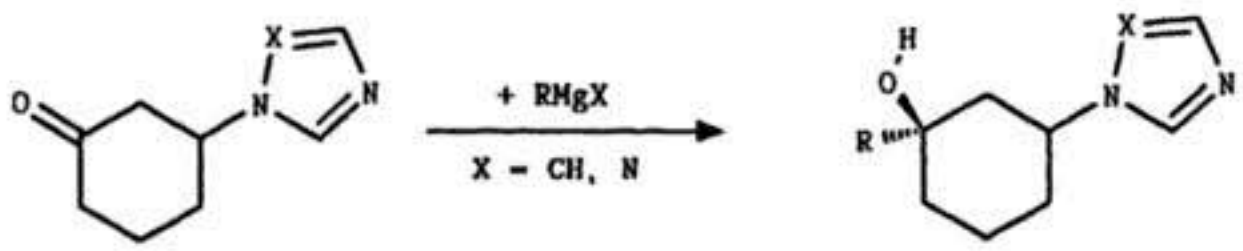
(3)

In related work, Tamura et al. [19] reported diastereoselective addition of Grignards to cyclic and acyclic α-ketoacetals to prepare mevalolactones. With high yields (>85%), the ratio of diastereomers varied from 60:40 to 100:0 [Eq. (4)]. Similar to the reaction in Eq. (2), the key step is the formation of the optically active ketoacetal, using (2*S*, 3*S*)-1,4-dimethoxy-2,3-butanediol.



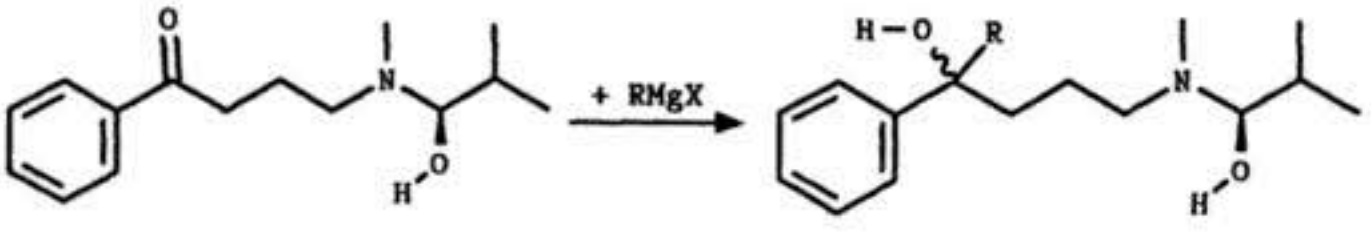
(4)

Murabayashi and Makisumi [20] prepared the antifungal azolylcyclohexanols [Eq. (5)] by the reaction of the corresponding cyclohexanone with aryl Grignard reagents. Yields were moderate to high, and the predominant isomer had the *cis*-configuration. For either the diaza- or triaza-substituents the *cis/trans* ratio was very high, more than 90:1. Only the *cis*-diastereomer was formed when the cycloheptanone was used.



(5)

Takahashi et al. [21] reported the synthesis of isomeric butanols from the tertiary amine, (*S*)-4-amino-1-phenylbutanone [Eq. (6)]. The stereochemistry formed at the new chiral center (2-*S*- or 2-*R*-) was dependent on the reaction conditions.



(6)

Addition of the Grignard reagent was catalyzed by a variety of organometallics in the work reported by Ukaji [22]. High diastereoselectivities were obtained in the reaction

Material chroniony prawem autorskim

major isomer was the *S*-isomer, usually formed in greater than 90% e.e. The authors rationalized the formation of the *S*-isomer by attack from the Si face of the imine, since the ester carbonyl and the imino group are held *syn* by the magnesium ion.

Addition of an allyl Grignard reagent to a β,γ-epoxyimine to give epoxyamines was accomplished by Beresford et al. [28] (see Table 3, entry 4). The authors suggested chelation control of the epoxide oxygen, and the electron pair on the nitrogen allowed backside attack on the imine, giving the *R*-configuration. Addition of a Lewis acid also contributed to the high stereoselectivities.

As part of a asymmetric synthesis of key precursors to various morphan or benzomorphan drugs, Marazano and co-workers [29] studied the formation of chiral tetrahydrapyridines with lipophilic counteranions from the corresponding pyridinium salts (see Table 3, entry 5). Addition of anisyl Grignard reagent followed by borohydride reduction gave the *R,S*-diastereomer in 80% d.e. Varying the *R*-group or the Grignard reagent still gave the *R,S*-isomer as the predominant product.

Alexakis and co-workers [30] developed a complementary method for the preparation of chiral α-amino aldehydes. Addition of the Grignard reagent to the imidazoline hydrazone gave a high selectivity for the *R*-isomer (see Table 3, entry 6). For a variety of Grignard reagents, the resulting isomer typically has the *R*-configuration. The authors suggested that formation of the preferred isomer was effected by chelation control by the lone pair of one of the two nitrogens of the imidazoline ring and the hydrazone functionality. Previously, the authors prepared the *S*-isomer from the alkyl lithium reagent.

Bartoli et al. [31] reported the formation of enantiomerically pure amines and hydroxylamines from optically active nitroalkanes with allylic and benzylic Grignard reagents. The intermediate nitrones (see Table 3, entry 7) were mixtures of *E*- and *Z*-isomers from the protected nitroalkanes. Although the regiochemistry is complicated, the stereochemistry of the double bond was affected by the nature of the Grignard reagent. The major isomer was always the *E*-isomer.

B. 1,4-Additions

Table 4 lists some examples of asymmetric 1,4-additions of Grignard reagents to enones. Spescha et al. [32] reported the conjugate addition of butyl Grignard to 2-cyclohexenone, catalyzed by a copper–thiosugar complex (see Table 4, entry 1). The chiral ligand was "HSSIG"—copper 1,2:5,6:di-*O*-isopropylidene-3-thio-α-D-glucofuran. The product, 3-butylcyclohexanone, was formed in greater than 98% yield, with an e.e. of 60%.

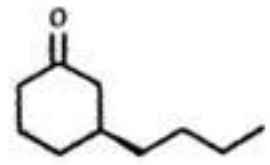
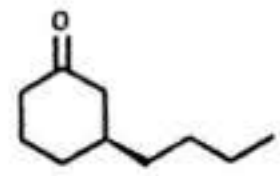
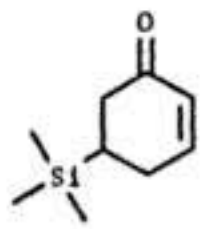
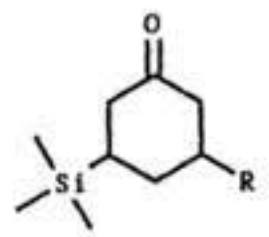
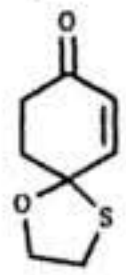
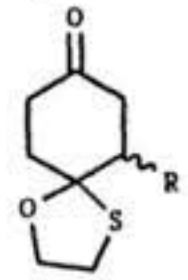
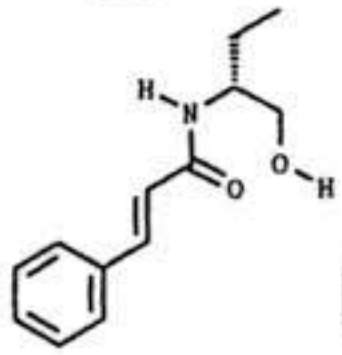
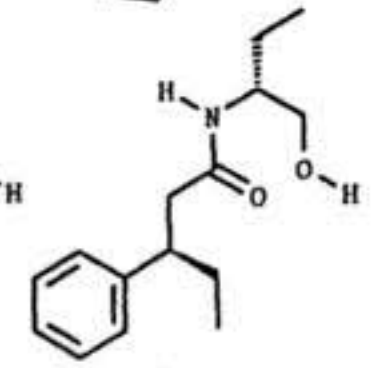
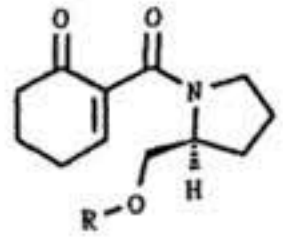
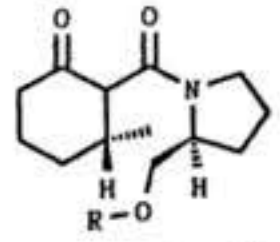
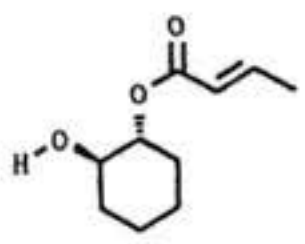
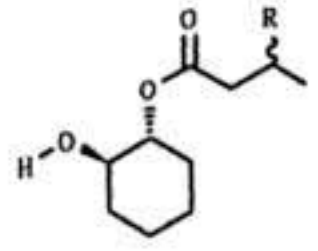
Lippard and co-workers [33] reported the same addition, but catalyzed by copperI(I) complexes with bidentate chiral auxiliary ligands (see Table 4, entry 2). The products, as precursors to prostaglandin synthesis, were formed in moderate yield and low e.e. when Cu(R-CHIRAMT), a chiral aminotropone imine, was used. However, higher enantiomeric excess purities ($>70\%$) were obtained when a silyl reagent and hexamethylphosphoramide (HMPA) were added. Not surprisingly, both catalysts gave similar products with similar enantiomeric purities.

A 5-silyl enone was reported to give a mixture of products from 1,2- and 1,4-addition [34]. The authors suggested that mixtures of diastereomers were obtained, but with uncharacterized stereochemistry at the 3- and 5-positions.

Takei and co-workers [35] also reported the copper-catalyzed addition to enones (see Table 4, entry 4), using an *R*-ethylenethioacetal as the potential building block, with a copper sulfide complex. Addition of the Grignard reagent gave the major product, with a (3*S*, 4*R*)-configuration, indicating that the addition occurred primarily *syn* to the thioacetal

Material chroniony prawem autorskim

Table 4 Chiral Products from 1,4-Additions

Entry (Reference)	RMgX	Substrate	Product	Configuration, Optical Yield
1 (32)	C_4H_9MgX			S, > 98%
2 (33)	C_4H_9MgX			S, 74%
3 (34)	RMgX			
4 (35)	RMgX			93:7
5 (36)	CH_3CH_2MgX			R, 85% ee
6 (37)	CH_3MgX			85 - 90% ee
7 (38)	RMgX			R, 56% ee

oxygen. Diastereoselectivities ranged from good to excellent (76:24–96:4). Interestingly, the use of bulky Grignard reagents led to lower ratios of *S*/*R* at the prochiral carbon.

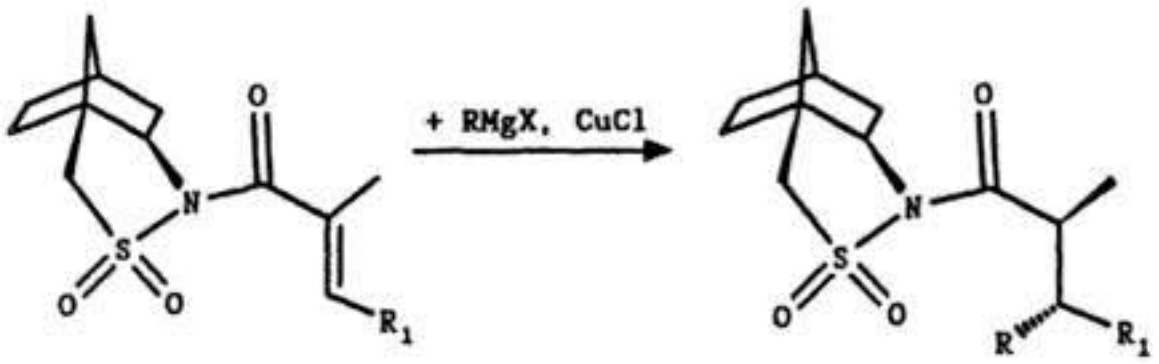
Touet et al. [36] prepared several β-methyl- and β-phenyl-alkanoic acids, with high enantiomeric purities. The Michael addition of ethyl Grignard reagent to β-hydroxy-cinnamamides in fair to excellent yields (see Table 4, entry 5). In each case, hydrolysis of the cinnamamide yielded the alkanoic acid with *R*-configuration in very high e.e. (>85%). The authors suggested that, because the magnesium binds both the carbonyl oxygen and the protected alcohol oxygen, the alkyl group is delivered to the double bond in a *trans*-fashion.

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Schultz and Harrington [37] added Grignards to α-amido enone (see Table 4, entry 6). They obtained high diasteromeric excesses with a variety of nucleophiles; for example, with methyl Grignard reagent, the d.e. ranged from 85 to 90%.

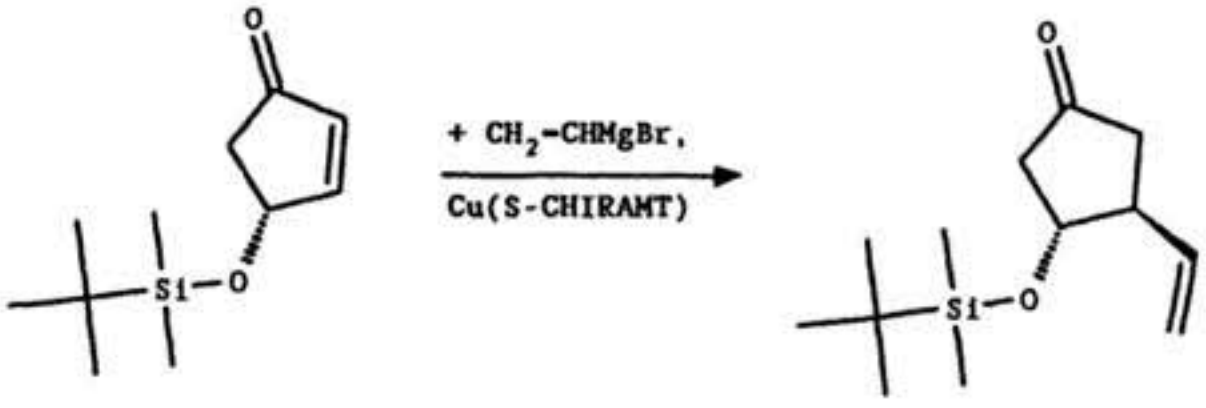
Sakai and co-workers [38] studied the additions to conjugate esters protected with a cyclic diol as a chiral auxiliary. The ester is protected with enantiomerically pure (1*R*,2*R*) *trans*-cyclohexane diol (see Table 4, entry 7). Addition of phenyl Grignard reagent, catalyzed by CuI, produced a moderate yield (50%) of a mixture of the two diastereomers (prochiral carbon $R/S = 78\%{:}22\%$) with a d.e. of 55%. In contrast, the authors also reported that addition of the phenyl lithium cuprate gave 94:6 ratio with the major product having the *S*-configuration for the prochiral carbon. Because of the differences in the structures of the complexes, attack from the lithium cuprate comes from the Re-face, whereas attack from the copper-Grignard comes from the Si-face.

A copper-catalyzed 1,4-addition was also described by Oppolzer and Kingma [39]. Addition of the Grignard to an enoylsultam [Eq. (10)] could possibly product four products because two stereogenic centers are formed. The authors found a high yield (90%) of a mixture of diastereomeric pairs, identified after in situ hydrolysis to recover the sultam auxiliary. The major products were the *S*,*S*- and the *R*,*R*-diastereomers (86:12). The authors rationalize the differences in the observed stereochemistries by coordination of the magnesium and copper with the carbonyl and the oxygens of the sultam, thereby permitting addition to the Re-face.



(10)

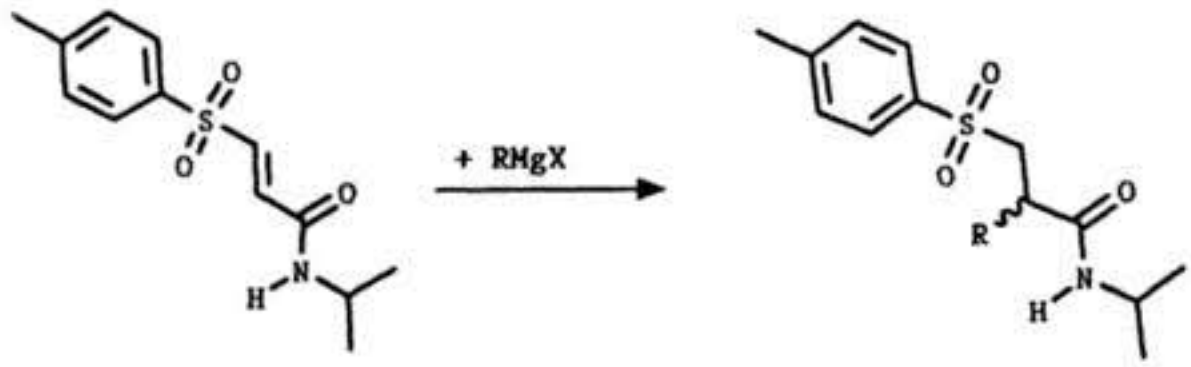
Lippard's work [33] on the conjugate addition, moderated by the addition of a copper catalyst and a silyl reagent, is described in Table 4, entry 2. Further reactions of an optically active 4-siloxy-2-cyclopentenone is depicted in Eq. (11). In this reaction—addition of the Grignard reagent with the copper catalyst, either Cu(*S*-CHIRAMT) or Cu(*R*-CHIRAMT)—gave the major product in which the alkyl group is delivered *trans* to the silyl group. The previous argument was used to rationalize the formation of the product.



(11)

Najera et al. [40,41] reported addition reactions to a variety of aryl sulfones. The Grignard reagent addition to an α,β-unsaturated sulfone (an enoyl sulfone) is depicted in Eq. (12). In this reaction, the major product is formed from conjugate addition to the

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(12)

sulfone, rather than to the carbonyl. Although the stereochemistry is not well controlled, the regiochemistry is.

III. NUCLEOPHILIC SUBSTITUTION REACTIONS WITH GRIGNARD REAGENTS

Table 5 lists several reactions in which the Grignard reagent is added to a system that allows ring-opening or displacement, rather than the typical addition reactions described previously. Umezawa [42] patented an approach to make long-chain alcohols from optically active epoxides (see Table 5, entry 1). In this example, they prepared optically pure 4-decyl alcohol in quantitative yield. The product was formed by the addition of a Grignard reagent to the epoxide; a catalyst, copper(I) iodide, was also used.

Bloch and Brillet [43] investigated the substitution reaction of Grignard reagents to tricyclic lactols. An example of 1,4-asymmetric induction to produce enantiomerically pure diols is shown in Table 5, entry 2. Addition of the Grignard reagent to a racemic lactol gave only one diastereomer in high yield (72–80%), which is consistent with other lactols. The authors suggested that attack of the nucleophile always occurs on the same face of the carbonyl, corresponding to the less-hindered face of the relatively rigid tridentate chelate.

Rollin and co-workers [44] treated 4-(2-pyridyl)thiomethyl-1,3-dioxolane with a variety of Grignard reagents to give branched propan-1-ols (see Table 5, entry 3). Although the yields were fair to moderate (20–70%), they depended on the chain length of the Grignard reagent: the longer the alkyl, the lower the yield. Surprisingly, the authors discovered that the regiochemistry is controlled by the remote pyridyl and the thiomethyl moieties. They argued that the mechanism is probably a remote-controlled substitution, with simultaneous acetone elimination from the more hindered nonketal carbon. They are currently evaluating the stereochemical consequences of the reaction.

Alberola et al. [45] reported the regioselective ring opening of tetrahydro-1,3-oxazines to give γ-amino alcohols (see Table 5, entry 4), with a wide variety of alkyl-, alkenyl-, and arylmagnesium halides. The major product was the ring-opened primary alcohol.

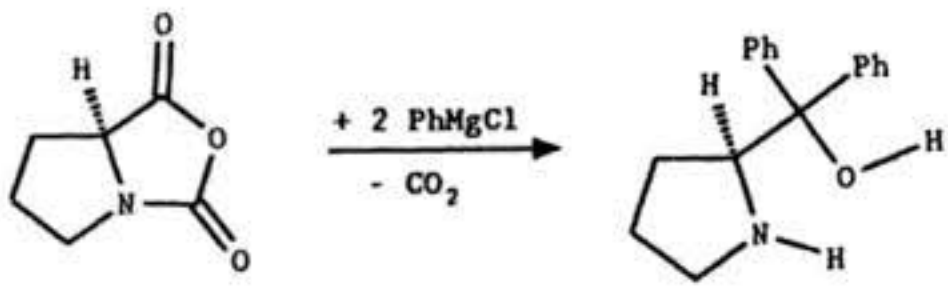
Wilcox and co-workers [46] investigated the reaction of Grignard reagents with dialkylaminofuranosides as a basis for their work on nucleosides and amino sugars. An example is the reaction of the ethynylmagnesium bromide with dibenzylaminoglycoside to give a 95% yield of a single diastereomer (see Table 5, entry 5). The product, the propargyl amine, has an *R*-configuration at the amine carbon. A range of gylcosides and furanosides reacted with a variety of Grignard reagents to give similar results. The authors propose that the C-2 center controls the displacement process, and the other two sterogenic carbons at C-3 and C-4 are not important in this process. These results provide products with stereochemistry opposite that of the products derived from the corresponding aldehydes.

As part of a synthetic campaign to prepare chiral precursors for biologically active

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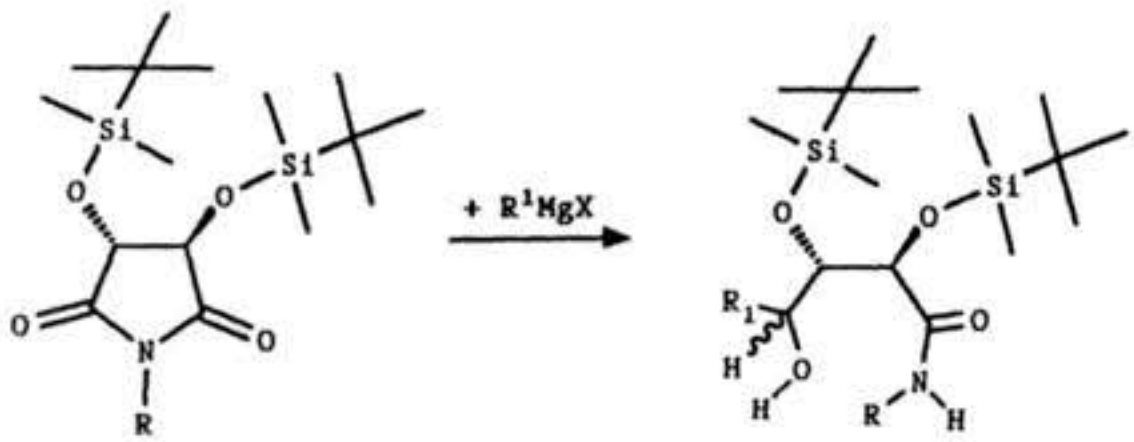
give pyrolidines. For example, reaction with 6-phenyl-4-oxa-7-diazahydroindan with a Grignard reagent gave chiral 1-[*N*-(2-hydroxy-1-phenylethyl)amino]pyrollidine in 60% yield (see Table 5, entry 7). Molecular models suggest that internal complexation of oxygen and the two nitrogens greatly enhances the yield of the *R*-isomer after attack at the ether.

Grabowski and co-workers [49] designed an enantioselective synthesis of α,α-diaryl-2-pyrrolidinemethanol that uses the addition of a Grignard reagent to proline-*N*-carboxanhydride, followed by substitution with the second equivalent of the Grignard reagent, to yield a tertiary alcohol, with 99% e.e., Eq. (13).



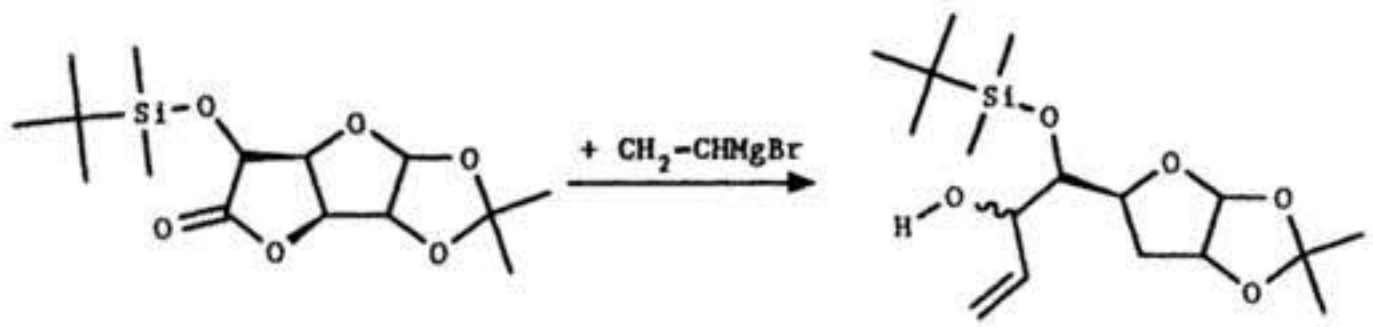
(13)

In Eq. (14), Yoda et al. [50] studied the preparation of optically active lactones, with three contiguous stereogenic centers, from imides with two stereogenic centers. The precursor chiral imide was easily prepared from tartaric acid. Silylation of the 2,3-diol and addition of lipophilic Grignard reagents to the imide gave the δ-hydroxy amide. The authors are investigating the stereochemical consequences of their work.



(14)

In the preparation of complex sugars, Dak et al. [51] reacted glycofuranuronolactones with allyl Grignard reagents. Addition to the carbonyl, followed by ring opening, gave the observed products, diastereomeric pairs of dideoxyoctenofuranoses [Eq. (15)].



(15)

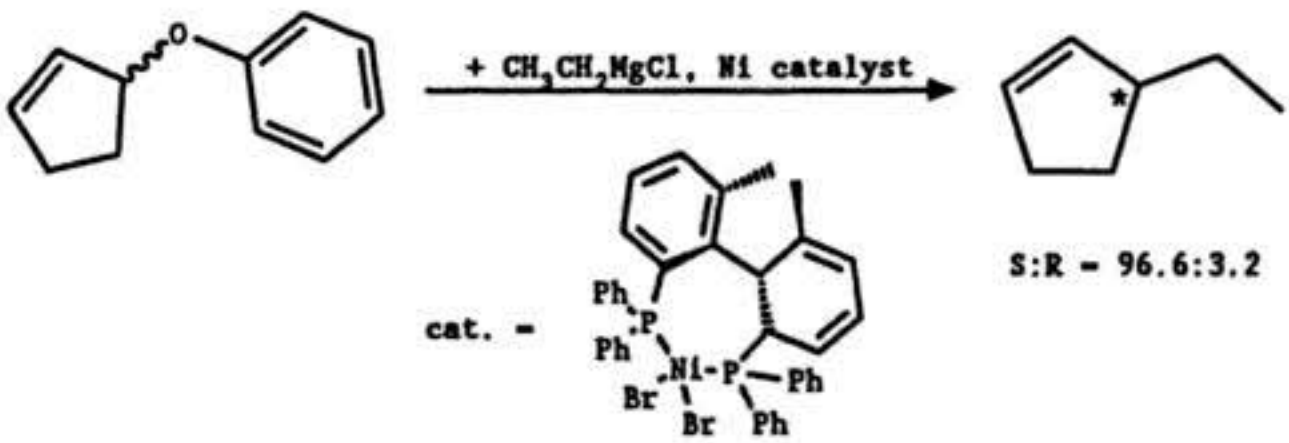
IV. MISCELLANEOUS REACTIONS

This section of the review covers the sundry reactions that Grignards undergo to effect a variety of molecular transformations.

Consiglio and Indolese [52] reported the allylation of Grignards with nickel–diphosphine catalysts, Eq. (16). The authors showed the excellent conversion of the allyl

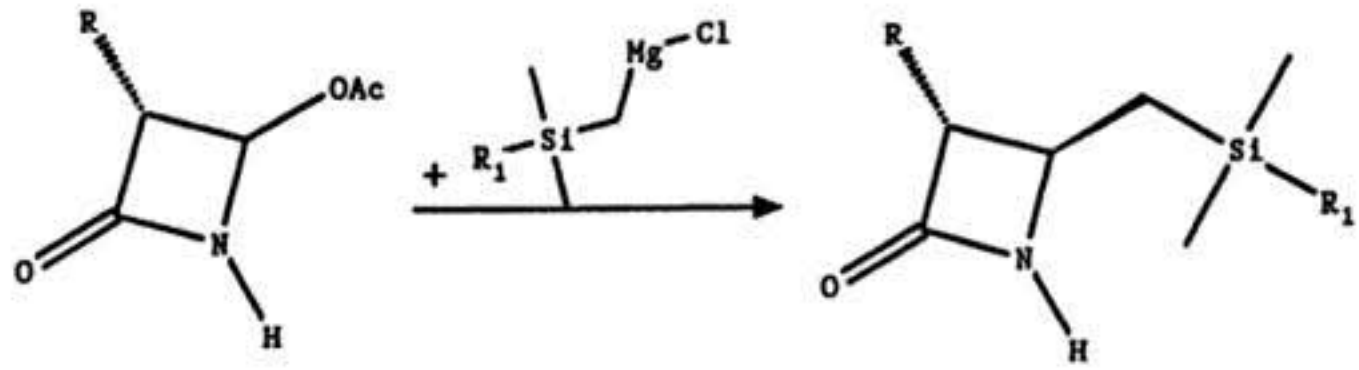
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ether to the alkylated cycloalkene; the conversions were usually greater than 90% for the five-membered ring and averaged more than 50% for the six-membered ring. The authors disclosed that the high enantioselectivity (optical yields up to 94%) depends more on steric factors than on electronic factors.



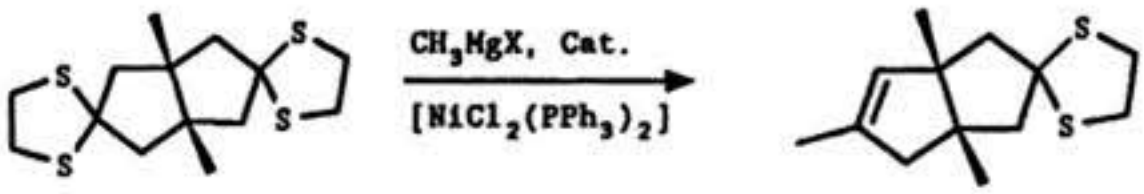
(16)

In a different displacement reaction, Nativi et al. [53] demonstrated the replacement of an acetoxy group in a β-lactam by a silylmethyl group. Reaction of 4-acetoxy-2-azatidinone with a variety of alkyl Grignard reagents gave complex mixtures and low yields of the desired product. However, reaction with trimethylsilylmethyl Grignard reagent gave the silylated β-lactam in greater than 50% yield, Eq. (17). The initial results do not look promising as a method for preparing substituted β-lactams.



(17)

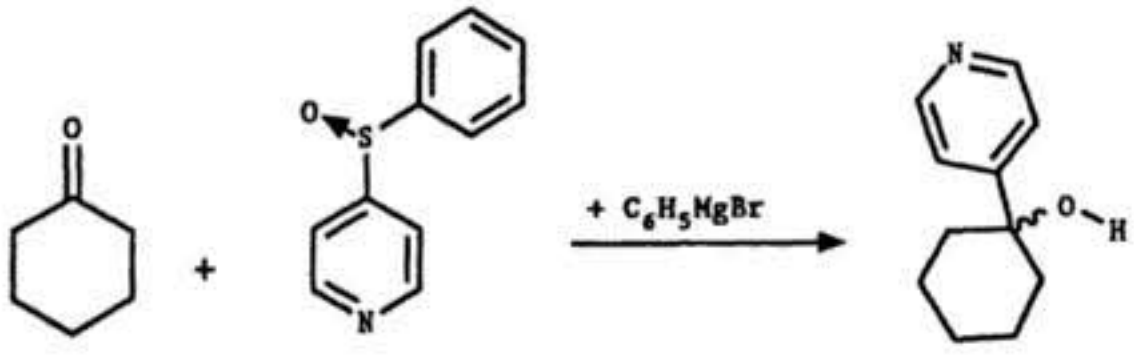
Wong et al. [54] described the regiocontrolled addition of methyl Grignard reagent and displacement, catalyzed by the Ni^{II} complex [Eq. (18)]. Addition to the bisthiane was catalyzed by Ni–bisphosphine complex. A chelation complex was proposed, giving a regioselective product by an *endo* double bond. Interestingly, only one of the dithio moieties reacts.



(18)

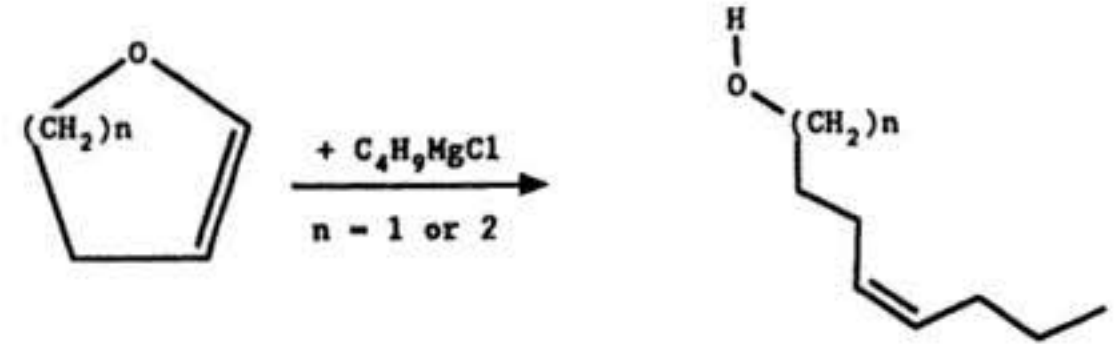
Furukawa and co-workers [55] describes their work as ligand-exchange reactions of arylpyridyl sulfoxides with Grignard reagents to generate a net pyridyl Grignard reagent. An example is the reaction of cyclohexanone with 2-pyridylphenyl sulfoxide in the presence of ethyl Grignard reagent to yield pyridylcyclohexanol, with unspecified stereochemistry [Eq. (19)]. However, when the authors used an optically active sulfoxide, they obtained the alkylpyridyl species, along with the *trans*-alkylated sulfoxide with the opposite configuration in 100% d.e. They proposed the formation of an intermediate in which only one diastereomer is formed.

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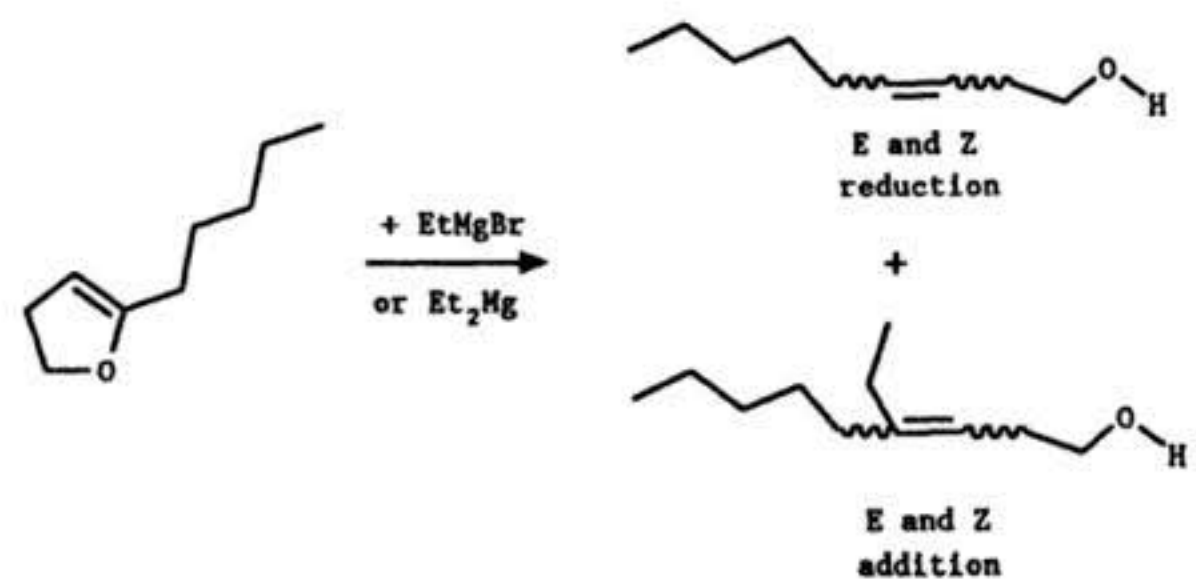
(19)

As part of a program to develop new methods of synthesis for the unsaturated backbone of *Z*-configured phermones, Kunesch et al. [56] converted cyclic enol ethers to the unsaturated acetate [Eq. (20)]. This nickel-assisted [$NiCl_2(Ph_3P)_2$] reaction produced stereoselectively (>95%) the *E,E*-diene. Here, the Grignard reagent adds to the vinylic carbon, with a ring opening to give the open-chain product.

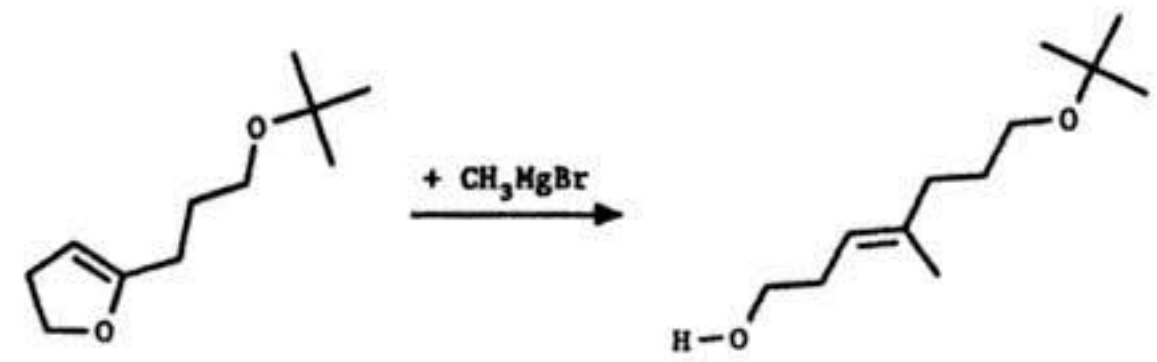


(20)

The purpose of the work reported by Kocienski and co-workers [57] was for the preparation of the typically inaccessible trisubstituted alkenes used as precursors for antifungal derivatives. They demonstrated the Ni^0-catalyzed cross-coupling of a Grignard reagent and 5-alkyl-2,3-dihydrofuran gave the addition or reduction products, depending on the workup. The least selective Grignard reagent gave a 5:1 ratio of addition/reduction, and the ratio of *Z/E* is dependent on the chain length of the Grignard reagent, Eq. (21). Kocienski also reported [58] the formation of the *E*-homoallyic alcohol in 82% yield [Eq. (22)]. In this case, *γ*-substitution of an ether allowed the chelation control required for the formation of the *E*-isomer.



(21)



(22)

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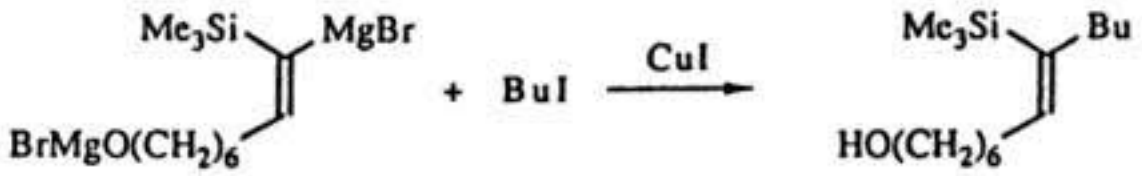
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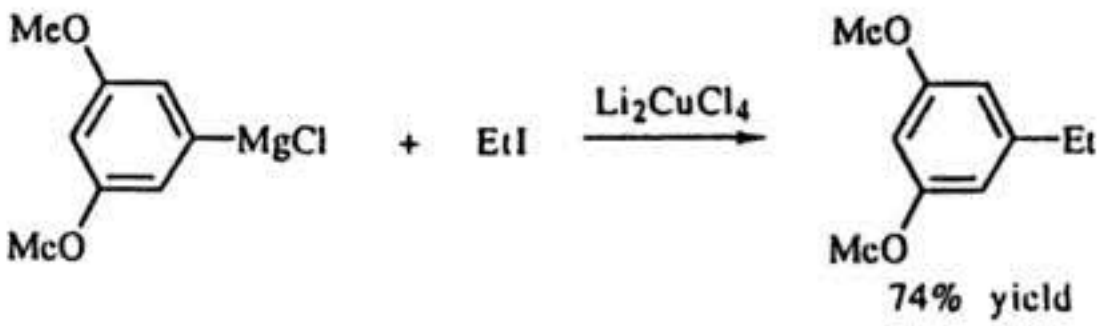
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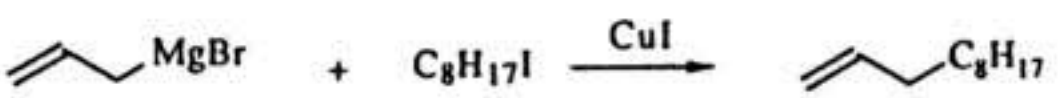
reagents selectively reacted with alkyl iodide and tosylate at the less-hindered terminus [38,46] in the presence of CuI [Eqs. (9) and (10); 38: see also Eqs. (15) and (30)].



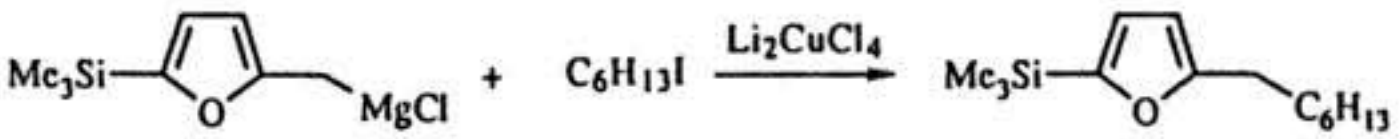
84% yield
Z/E = 96:4 (5)



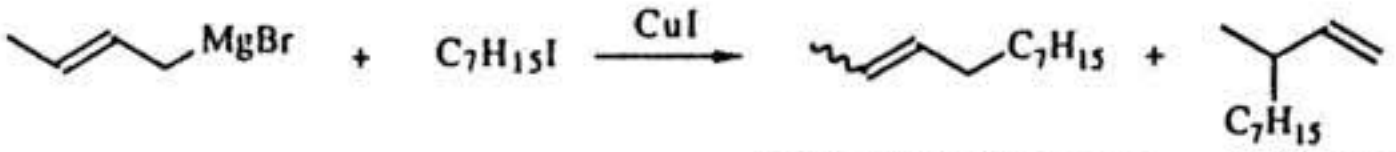
74% yield (6)



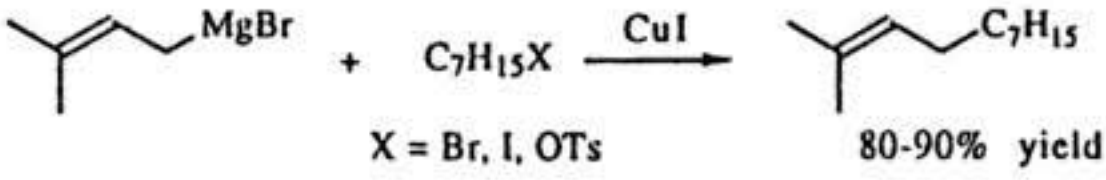
80% yield
(<20% yield without Cu) (7)



70% yield (8)

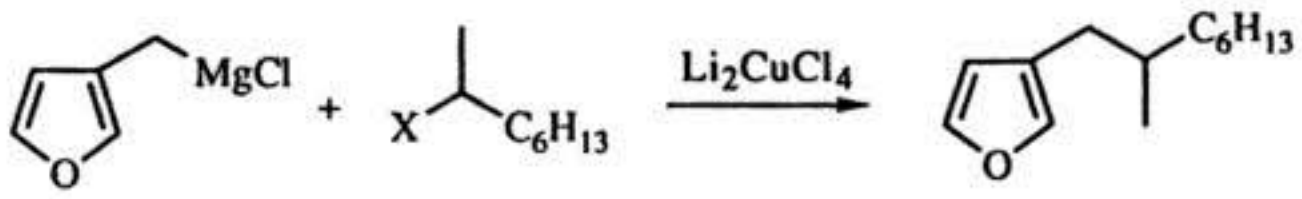


85% yield (*E*/*Z* = 1:1) < 5% yield
(83% yield 20 (*E*/*Z* = 1:1) : 80 without Cu) (9)



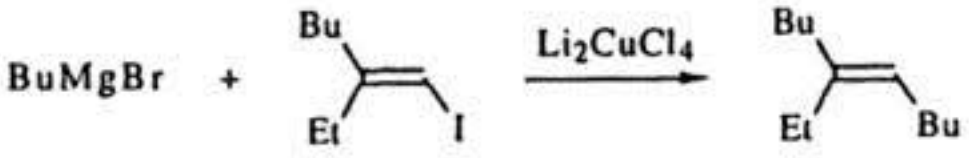
X = Br, I, OTs 80-90% yield (10)

The substrates are primary- [see Eqs. (2) and (5–9)] or secondary- [31,41] [Eq. (11); 41] alkyl, alkenyl [Eq. (12); 25], or aryl iodides [Eq. (13); 31]. Primary-alkyl bromides [22,27,43,47] [see Eq. (10) and Eq. (14); 22] and primary- and secondary-alkyl tosylates [23,32,33,48; see Eqs. (3) and 10)] still afforded the corresponding coupling products in good yields, but the use of chlorides—except allyl [38,40–43; Eq. (15); 38] and benzyl [29,37; Eq. (16); 37] chlorides—or tertiary alkyl substrates is usually discouraged [31].

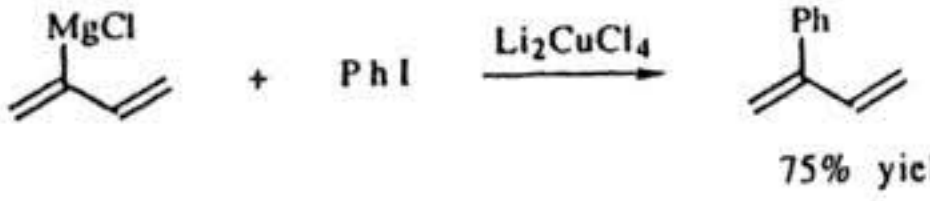


X = Br 0% yield
I 89% yield (11)

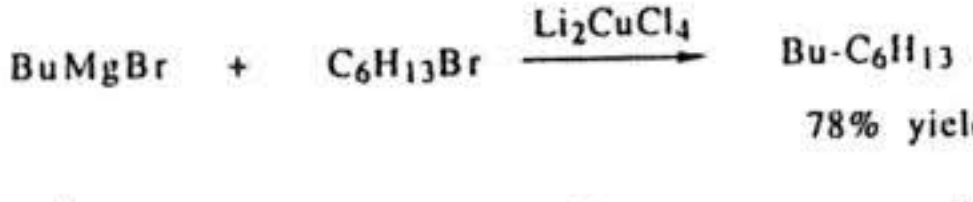
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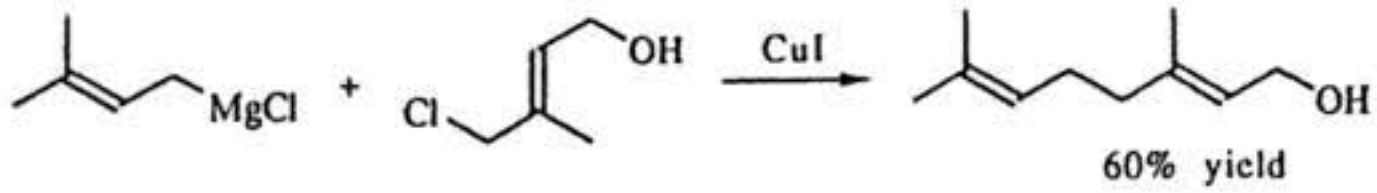
(12)



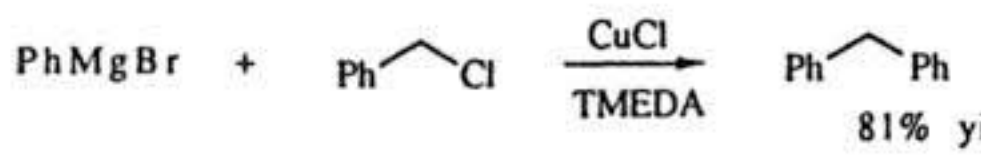
(13)



(14)

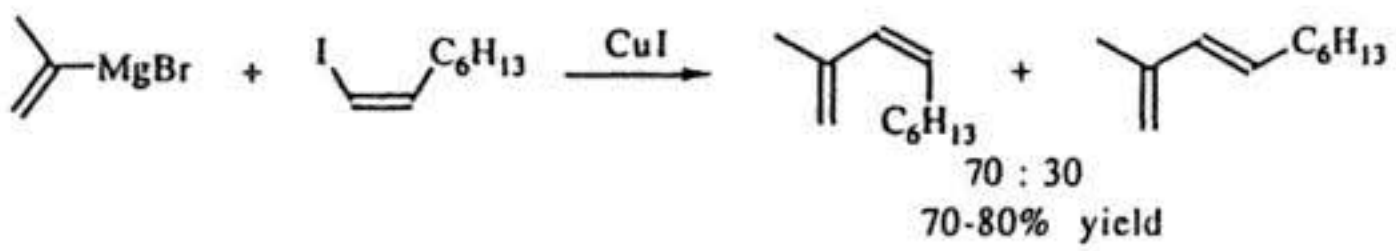


(15)

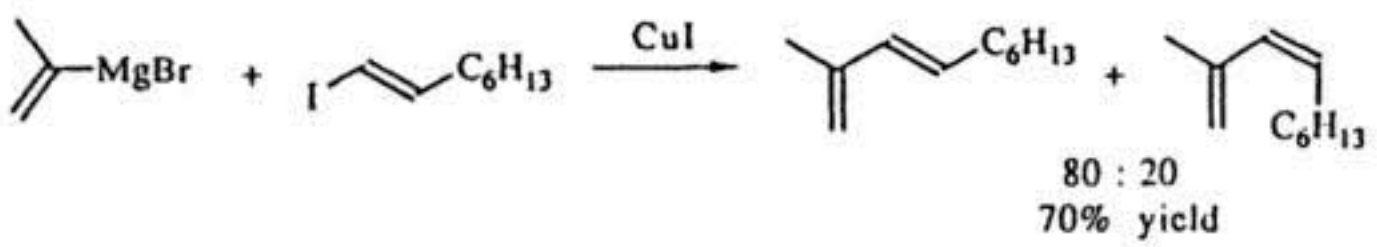


(16)

When alkenyl iodide was used as the substrate, its stereochemical integrity was retained in the product [see Eqs. (5) and (12); 25,35], but a decreased isomeric purity has also been mentioned [Eqs. (17) and (18); 49].

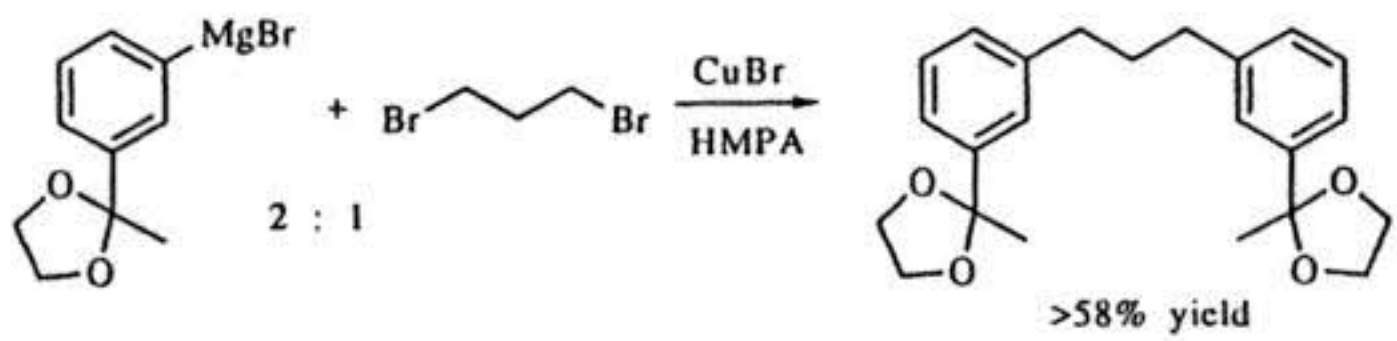


(17)



(18)

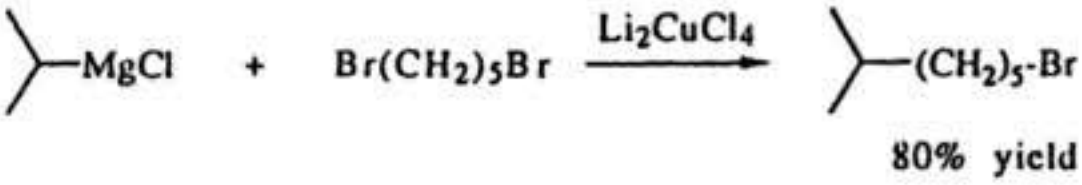
Among the foregoing substrates, primary-alkyl substrates are more reactive than are secondary ones [30,31,41], and iodides and tosylates are more reactive than bromides [31,32,48]. Alkenyl and aryl substrates seem to be less reactive compared with alkyl counterparts and, in the former type, Ni- and Pd-catalyzed reactions are much more popular (see the following discussions). Alkanes having 1,ω-leaving groups, when ω is three or more, underwent the displacement to give 1,ω-bis-substituted alkanes [Eq. (19);



(19)

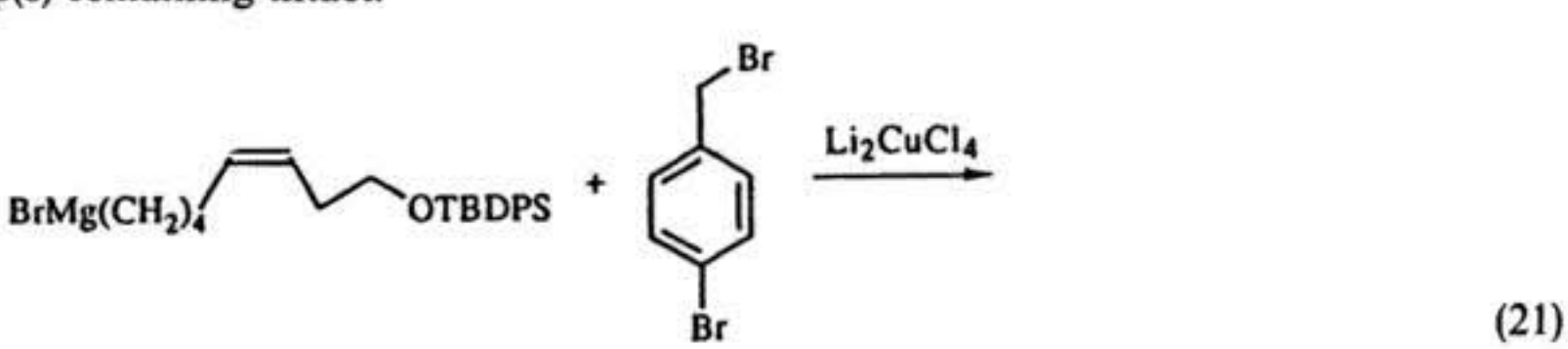
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50–52]. 1,2-Dihalides did not give the bis-alkylated compounds owing to elimination or reduction of the halide moiety [27]. A stepwise reaction was also possible [Eq. (20); 27,52,53].

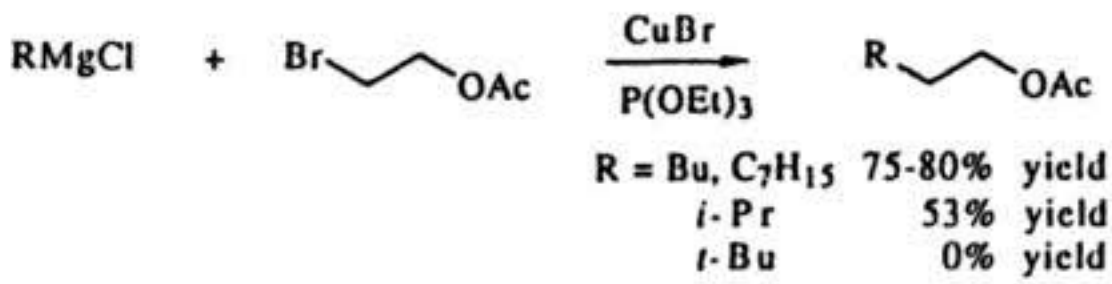


(20)

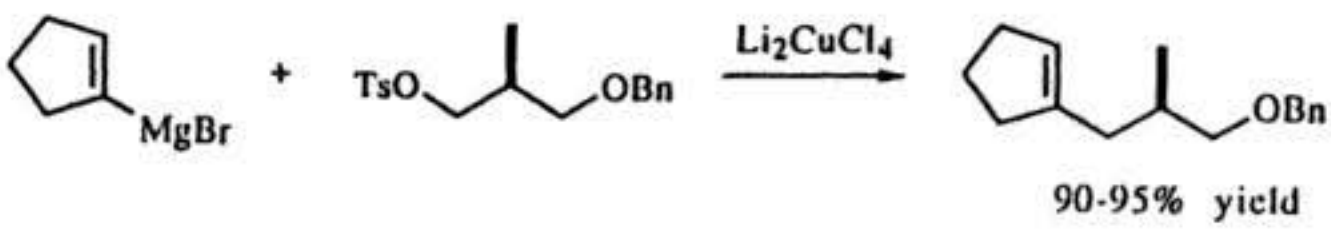
Many functionalized Grignard reagents as well as substrates that have halide [31,54; Eq. (21); 54]; ester [31,55; Eq. (22); 55]; nitrile [31]; ether, including acetal [24,26,47,50,52, 55–59; see Eqs. (2) and (23); 59]; hydroxyl [31,35,38,60,61; see Eqs. (5) and (15)]; or carboxyl groups [Eq. (24); 60] could participate in this reaction, with the additional functional group(s) remaining intact.



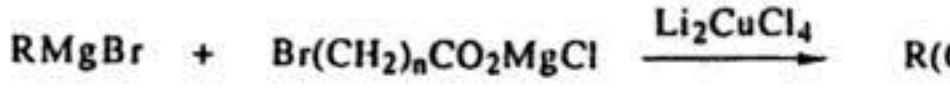
(21)



(22)

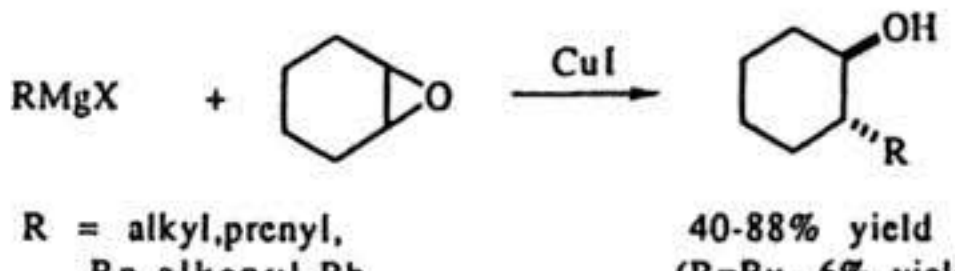


(23)



(24)

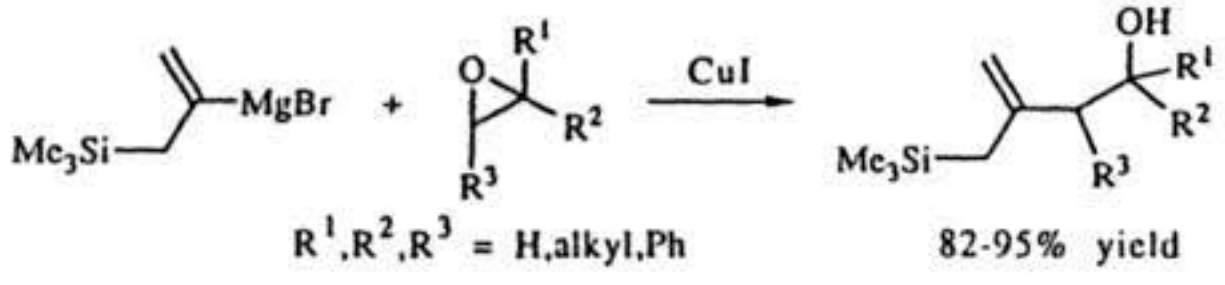
Uncatalyzed reactions of Grignard reagents with epoxides are not so straightforward that they give products resulting from ring opening with alkyl (R) as well as halide (X) of R-MgX or those from rearrangement promoted by the Lewis acidicity of the magnesium cation [62,70]. However, epoxides [62–71; Eqs. (25) and (26); 62,64], oxetane [Eq. (27);



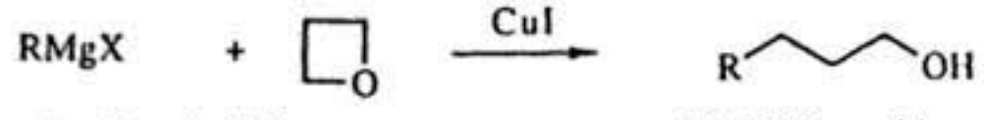
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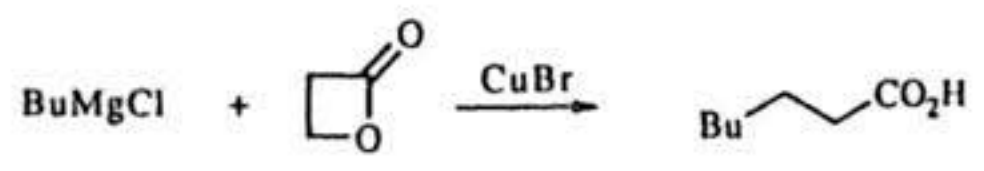
62], and small-ring lactones [Eqs. (28) and (29); 72,73] underwent clean-coupling reactions with Grignard reagents in the presence of a copper salt to give alcohols and carboxylic acids.



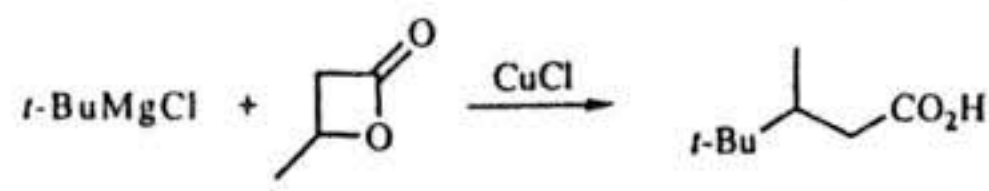
R^1, R^2, R^3 = H,alkyl,Ph 82-95% yield (26)



R: Bu,allyl,Ph 50-75% yield (R=Bu, 10% yield without Cu) (27)

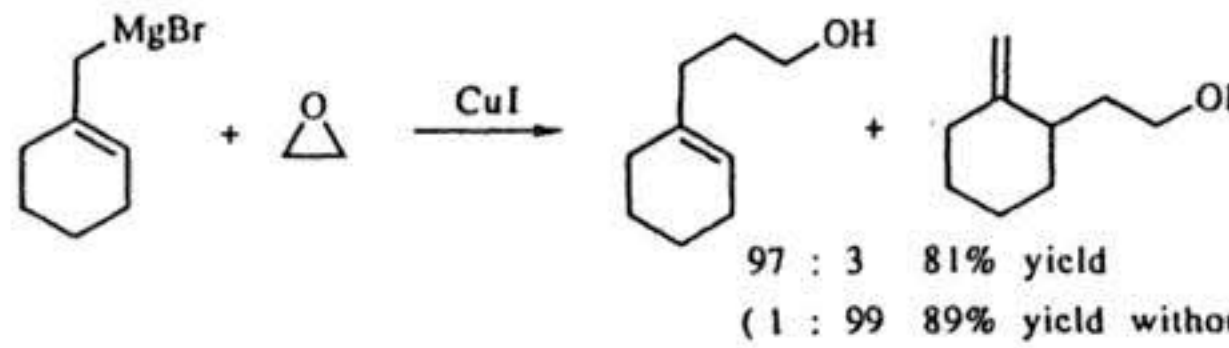


81% yield (61% yield with CuCl) (28)



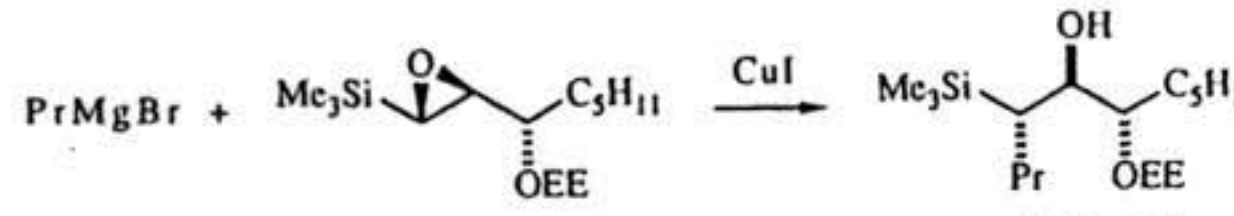
84% yield (29)

An allyl Grignard reagent coupled with epoxide at the less-substituted terminus of the Grignard in the presence of CuI, is exemplified in Eq. (30) [74,75]. This outcome is consistent with those appearing in Eqs. (9), (10), and (15).



97 : 3 81% yield
(1 : 99 89% yield without Cu) (30)

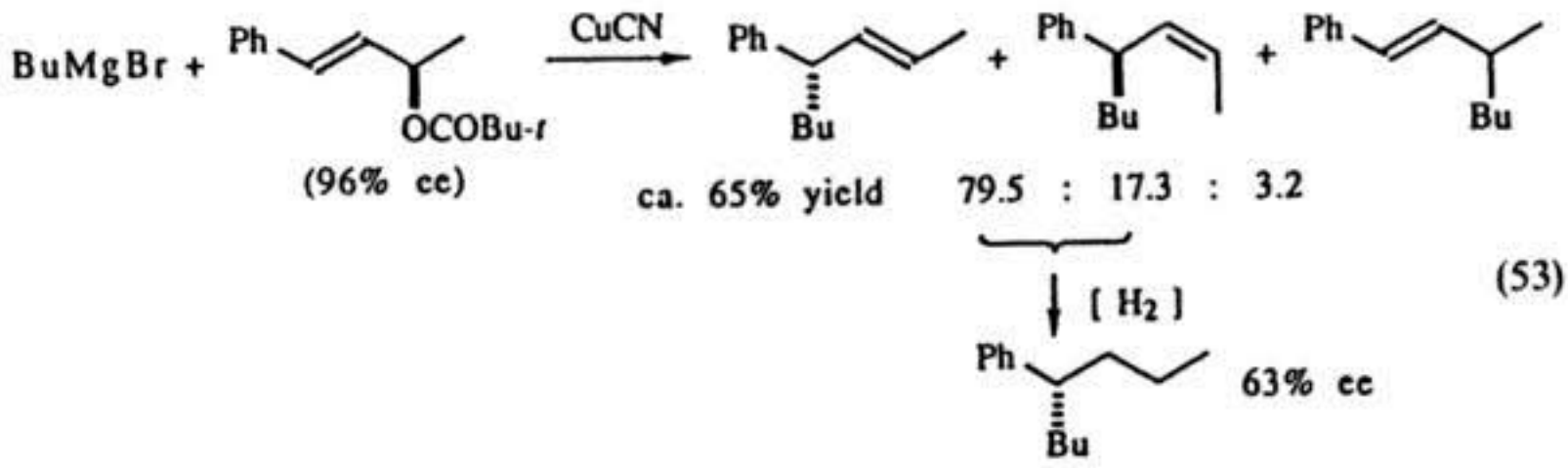
Regio- and chemoselective aspects of ring opening of epoxides have been studied. The ring-opening reactions usually tend to proceed at the less-substituted terminus of epoxides [63,64,67–69,71]. In other words, terminal epoxides are more reactive than internal ones [69]. An exception is the reaction of silylepoxides, for which the epoxide opening occurs selectively at the carbon bearing the silyl group, which is apparently bulkier than the alkyl group [Eq. (31); 65,76,77,78].



> 77% yield (31)

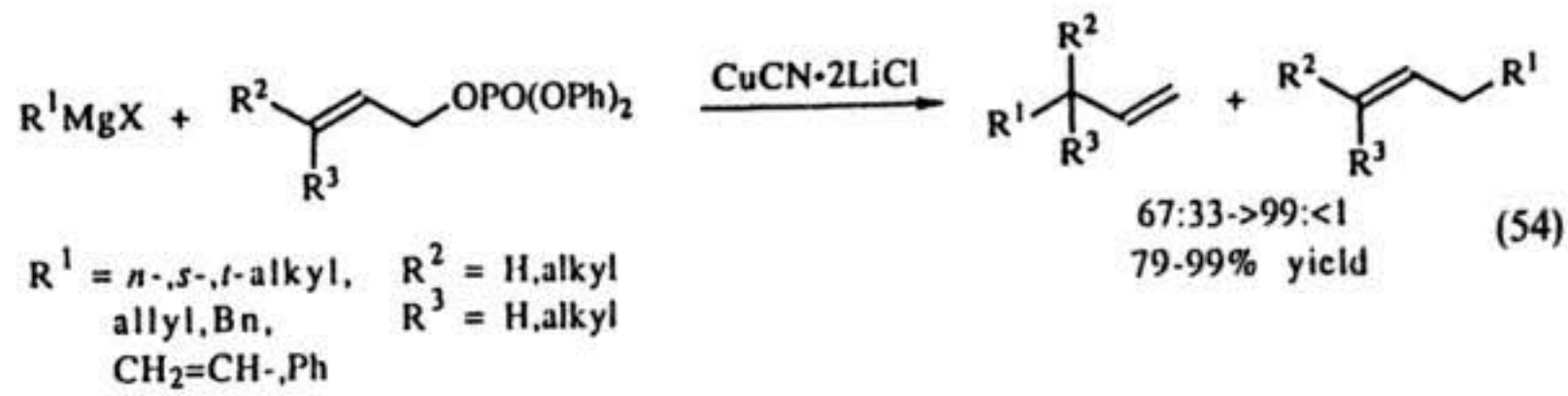
Reaction of tetra-substituted epoxide was sluggish and usually affords complex mixture of products.

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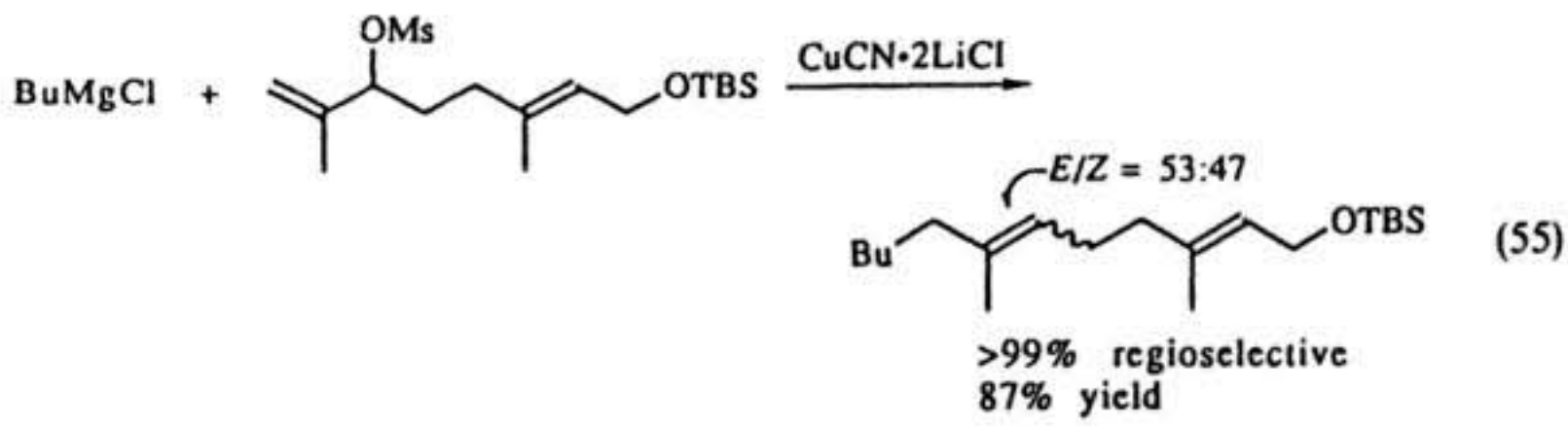


(53)

Excellent regio- and stereochemical control was recently more generally realized. Thus, the addition of a variety of Grignard reagents involving alkyl, benzyl, allyl, 1-alkenyl, and 1-alkynyl Grignard reagents to allyl chlorides, phosphates, acetates, or sulfonates was controlled to be γ to the leaving group (i.e., in S_N2' fashion) under the influence of a catalytic amount of CuCN–2LiCl complex [Eqs. (54) and (55); 118–121]. This observation indicates the position of the attack was determined by the location of the leaving group, rather than the steric hindrance of both allylic termini.

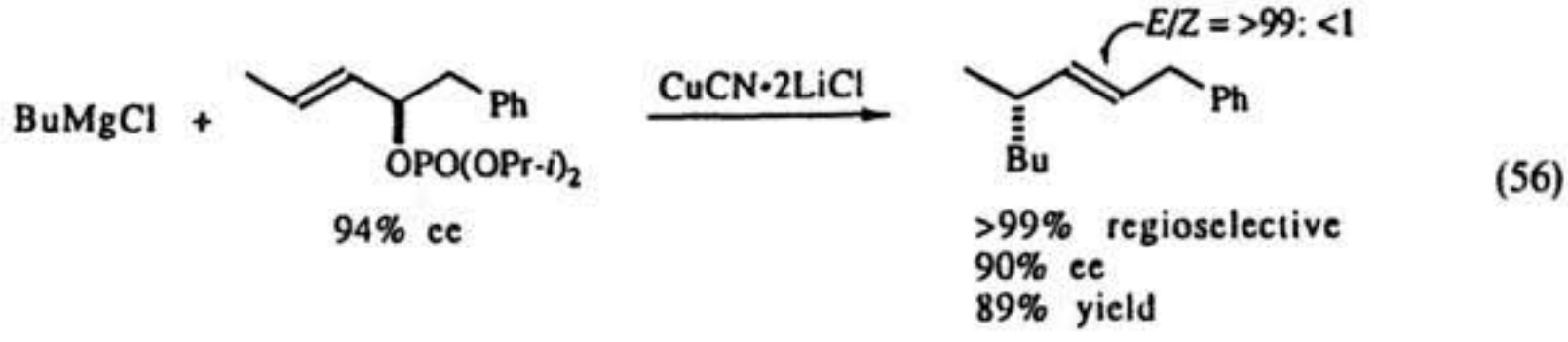


(54)



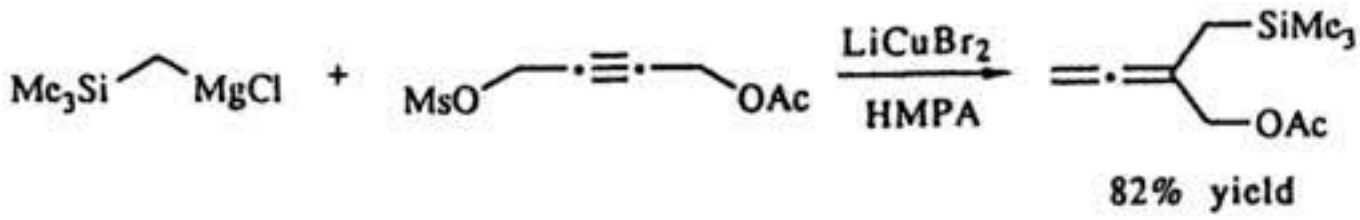
(55)

The substitution was also highly *anti*-stereoselective, which was verified with optically active starting materials, as illustrated in Eqs. (56) and (57) [119,120].



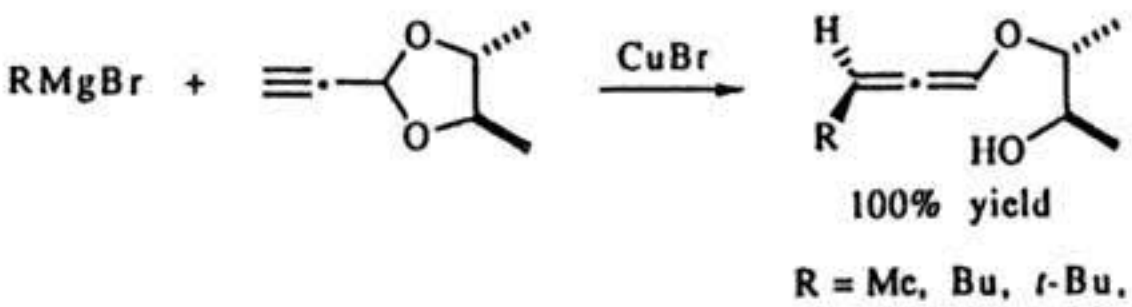
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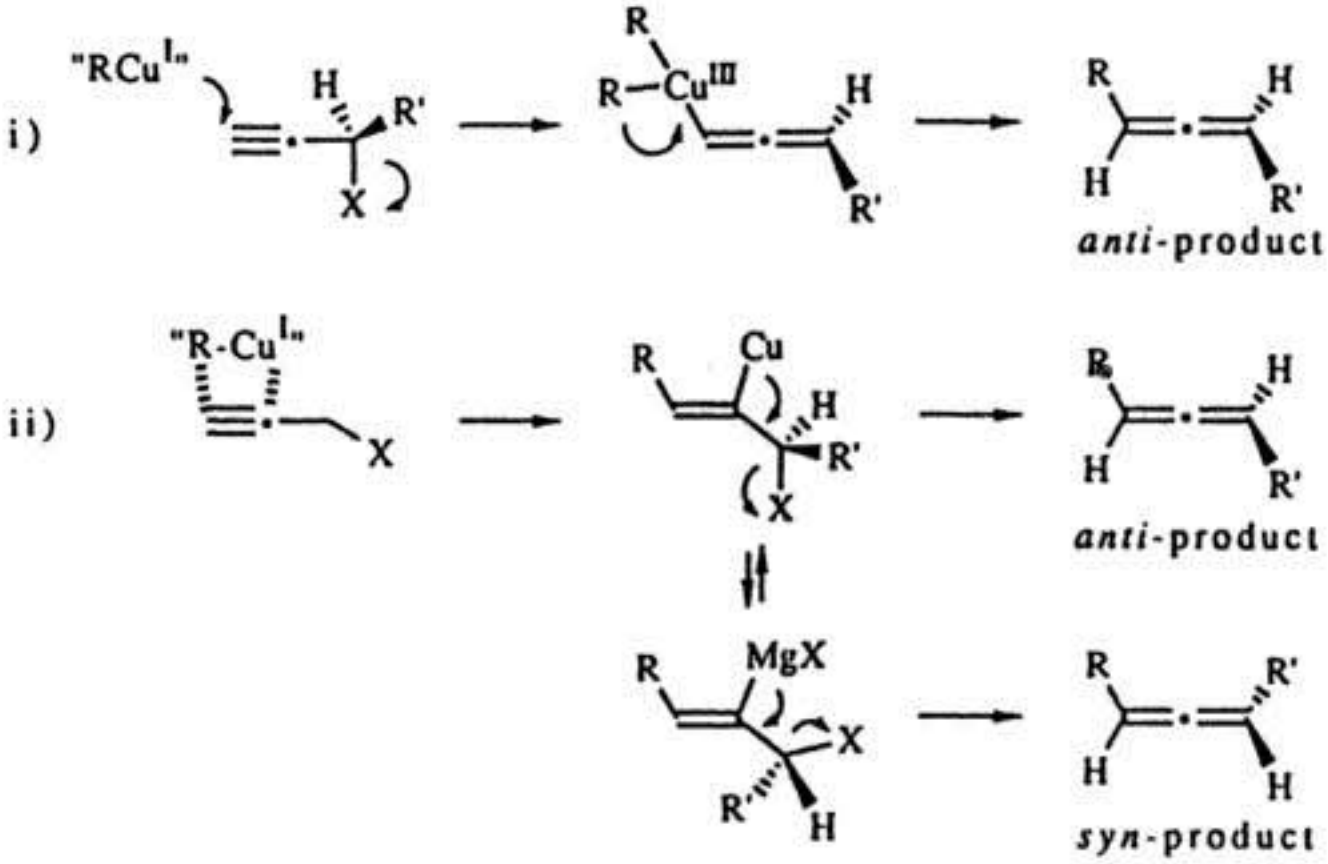
(71)

Diastereoselective, copper-catalyzed propargylic substitution by Grignard reagents to yield optically active allenes has been reported for substrates having a chiral acetal moiety [Eq. (72); 138] [10,148].



(72)

The degree and direction of enatio- or diastereoselectivity of the allene formation described in the foregoing cannot be discussed without understanding the exact mechanism of this reaction. Alexakis et al. carried out detailed studies in this area and presented two possibilities, which are summarized in Scheme 2. The first one, previously proposed by Vermeer et al. [130], involves *anti*-displacement of the propargyl-leaving group with RCu^I species, followed by delivery of the R group from copper to allene, with retention of configuration. The second consists of carbocupration of acetylene, followed by β-elimination of the metal and the leaving group in either *syn*- or *anti*-fashion. In fact, the stereochemical outcome of the allene formation by copper-catalyzed Grignard addition to propargyl substrates changes *syn* to *anti* by changing the organometallic species and the leaving group. Since the second mechanistic proposal can reasonably explain this observation, Alexakis et al. suggested that this one is the most likely for the copper-catalyzed Grignard additions. The detailed discussion has been reviewed [145,146].



Scheme 2

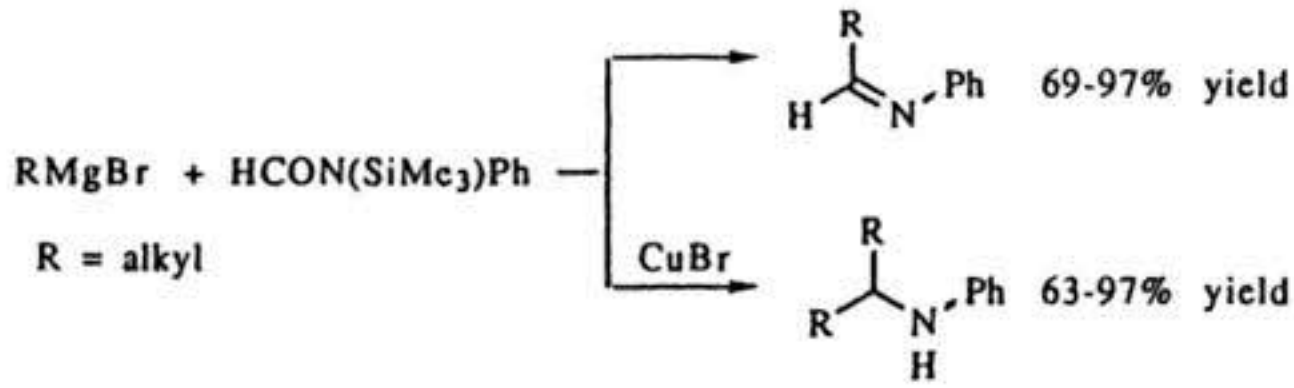
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B. 1,2-Addition Reactions to Carbonyl Compounds

Stoichiometric organocopper reagents prepared from RMgX and a copper salt are useful for the ketone synthesis from acyl halides [7]. The advantage of this reaction is that the formation of tertiary alcohols is usually negligible. The presence of a stoichiometric amount of CuCl was reported to facilitate the coupling of a hindered Grignard reagent and a hindered acyl halide to yield a ketone [149]. However, a catalytic version of this reaction was not examined, probably for the same reason described for reactions with aldehydes (see later).

Addition of Grignard reagents to aldehyde in the presence of a copper salt was examined in conjunction with the stereochemical outcome. Stoichiometric copper reagents prepared from Grignard reagents and copper salts often add to chiral aldehydes [150] and an imine [151] in a reversal sense when compared with Grignard reagent alone. However, copper-catalyzed addition of Grignard reagent to carbonyl compounds has not been examined. This presumably is because a Grignard reagent reacts much faster with aldehydes than the derived organocopper reagents and, thus, copper-catalyzed reactions show no characteristic advantage.

Although 1,2-addition of Grignard reagent to *N*-alkyl-*N*-silylformamide afforded the same type of product, imines, in the presence or absence of a copper salt, *N*-phenyl-*N*-silylformamide afforded a doubly alkylated amine in the reaction of Grignard reagent under copper catalysis [Eq. (73); 152].



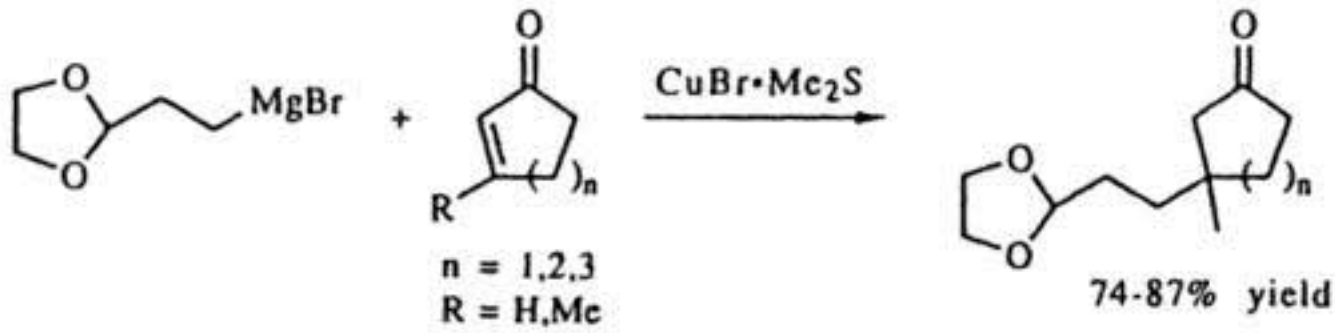
(73)

C. 1,4-Addition Reaction to α,β-Unsaturated Carbonyl Compounds

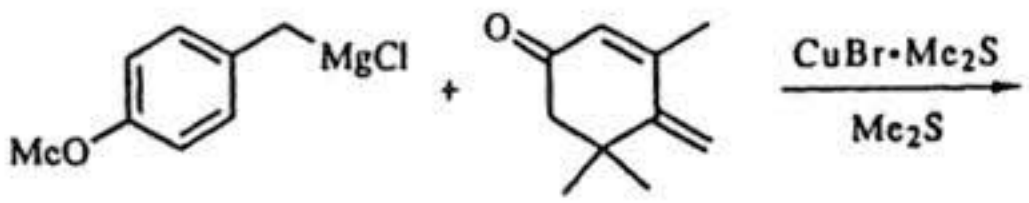
One of the most important features of organocopper reagents is their capability to undergo 1,4-addition to an α,β-unsaturated carbonyl compound, which was first reported by Kharasch and Tawney, in 1941 [153]. This reaction is now recognized as being quite general for a variety of substrates, including acyclic and cyclic, α,β-olefinic and α,β-acetylenic ketones and esters. Significant improvements in applicabilities as well as product yields have been brought about by many research chemists in these few decades. And, accordingly, this reaction is now one of the most important synthetic transformations, as amply demonstrated in several total syntheses of complex molecules. These reactions have been exhaustively surveyed by several reviews [7,8,15,154–156]. In addition, general aspects of 1,4-addition reactions with organocopper reagents have been reviewed in many articles and books [17–19,21,148,157–159], which may also be very helpful.

Copper salts vary from simple inorganic and organic salts, such as CuCl, CuBr, CuI, and $CuBr \cdot Me_2S$, to more sophisticated ones, which will be discussed in the following text. As described in the previous section, a Cu^{II} species is most likely to be reduced in the reaction medium to a Cu^{I} species, which catalyzes the 1,4-addition. This Cu^{II}–Cu^{I} issue was revisited recently and, in accord with the foregoing statement, Cu^{I} was reconfirmed to be an active catalyst, even though the added copper salt was divalent [160,161].

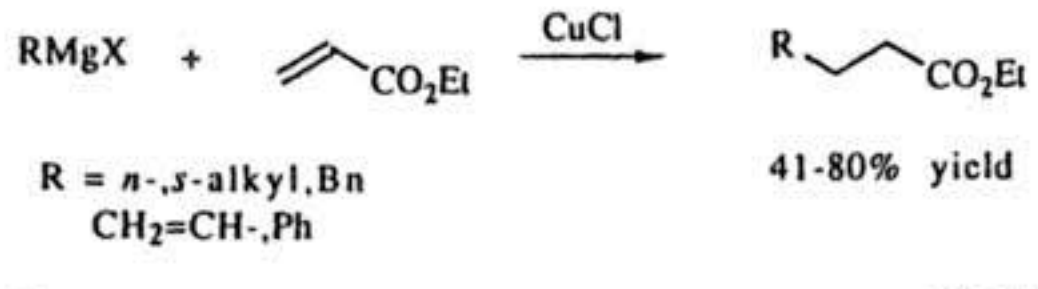
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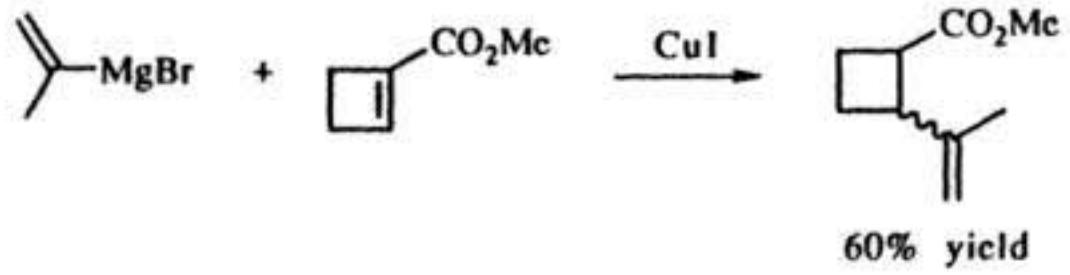
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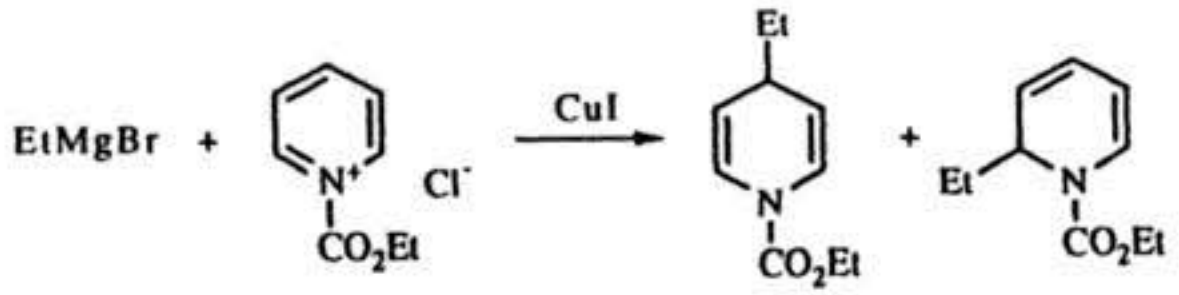
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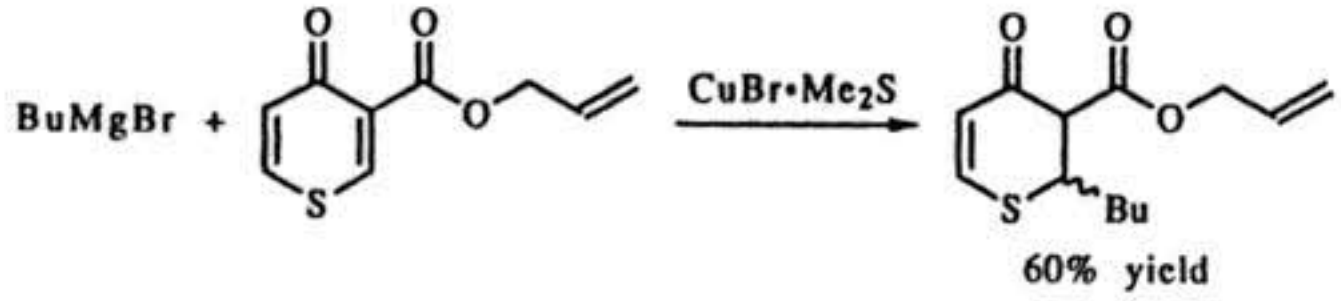
(81)



(82)



(83)

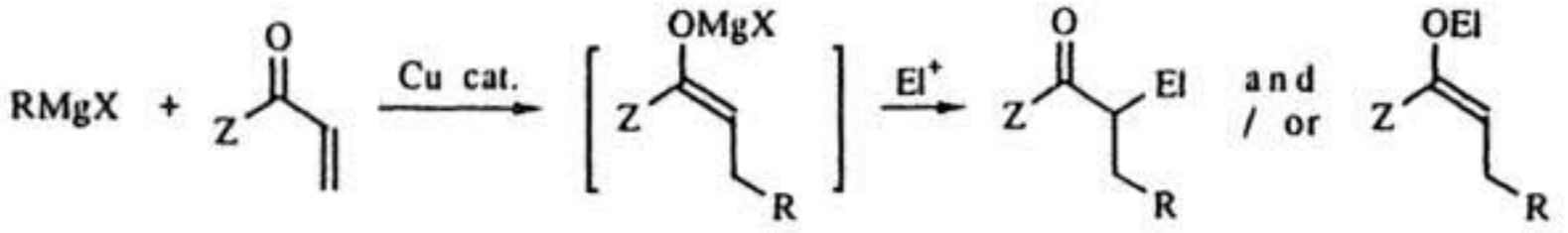


(84)

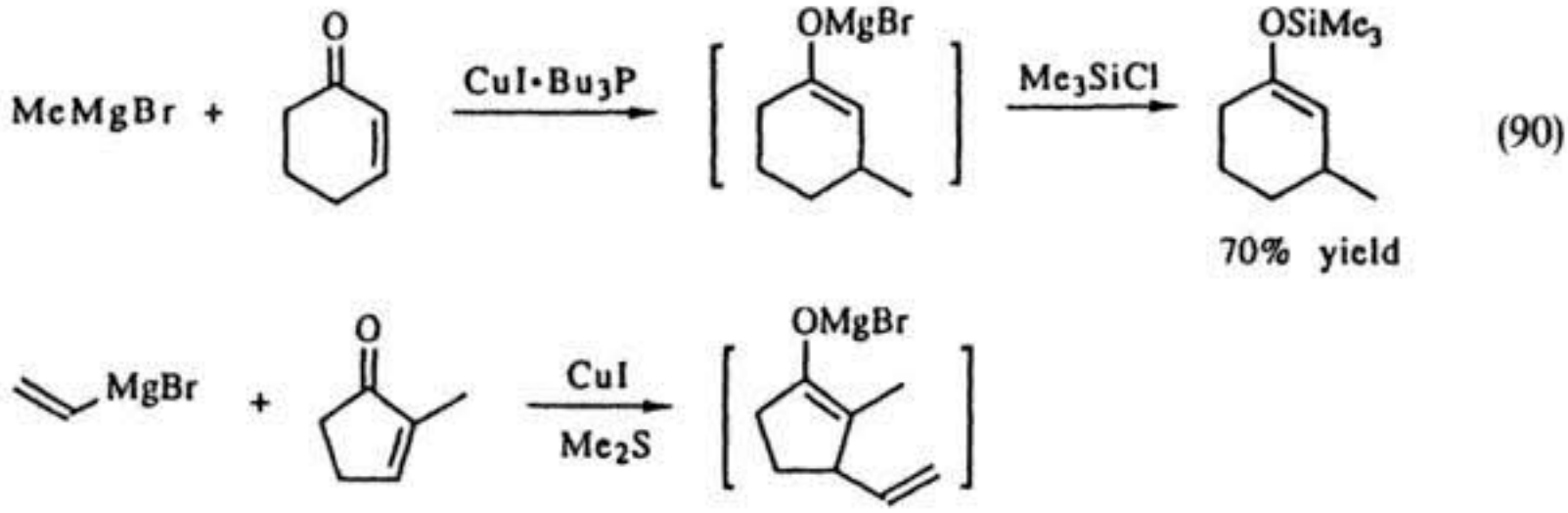
In general, the feasibility of the reactions depends on the reactivities of substrates and could be interpreted in terms of steric and electronic factors. Initially, in the history of organocopper reactions, substrates were limited to relatively unhindered, α,β-unsaturated ketones and esters. Since the β-substitution to α,β-unsaturated carbonyl compound retards

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The 1,4-addition of Grignard reagents under copper catalysis, followed by a trap of the resulting (magnesium) enolates with an appropriate electrophile, is a versatile method for double functionalization or double carbon–carbon bond formation at the α- and β-positions of an olefinic bond that bears a carbonyl group [Eq. (89)]. Recently, this topic has been extensively reviewed [155]. Examples [170,173,174] of this notion are presented in Eqs. (77), (90) [170], and (91) [174].



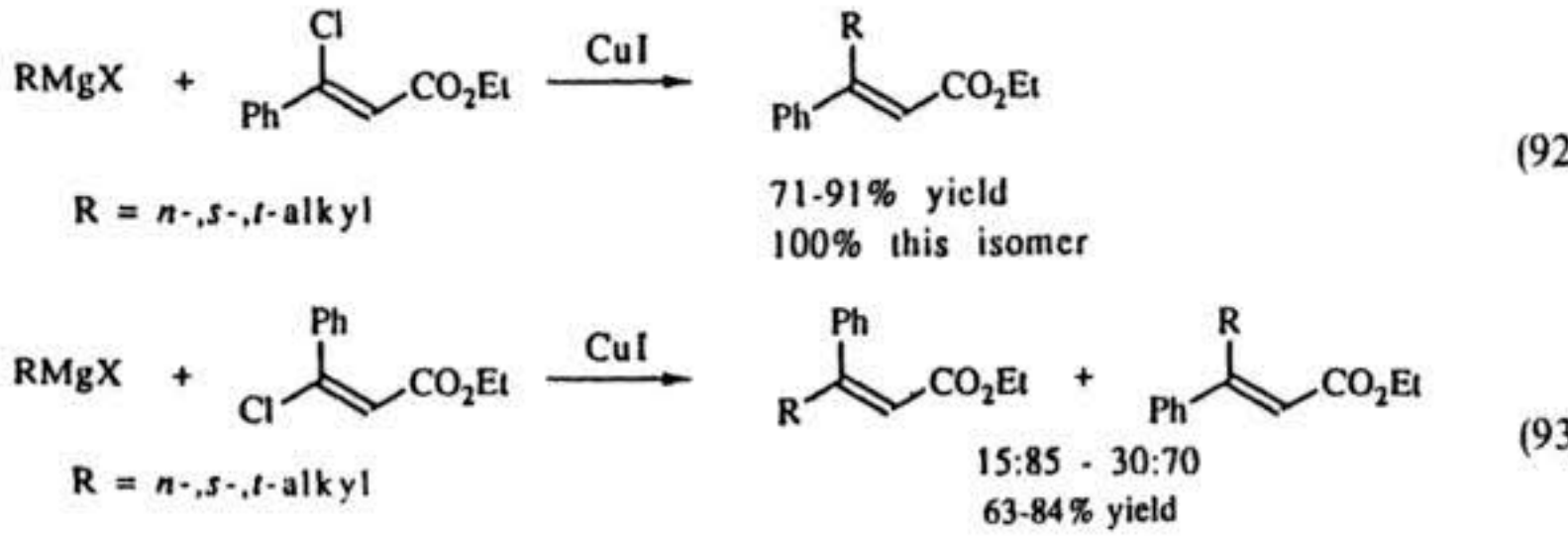
(89)



(90)

(91)

An addition–elimination sequence on an α,β-unsaturated ester having a β-leaving group was used for the preparation of a β-alkyl-α,β-unsaturated ester [Eqs. (92) and (93); 203]. However, the stereochemical integrity of the starting materials was not necessarily retained in the products. As far as the stereoselectivity is concerned, a stoichiometric copper reagent seems to afford a superior result [204,205]. Alternatively, a substrate having a β′-leaving group undergoes a similar addition–elimination sequence to give a β′-alkyl-α,β-unsaturated ester [Eq. (94); 98].

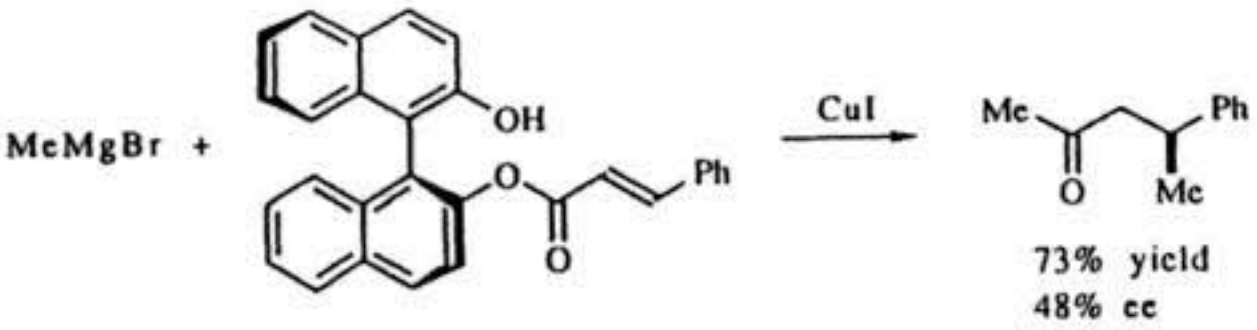


(92)

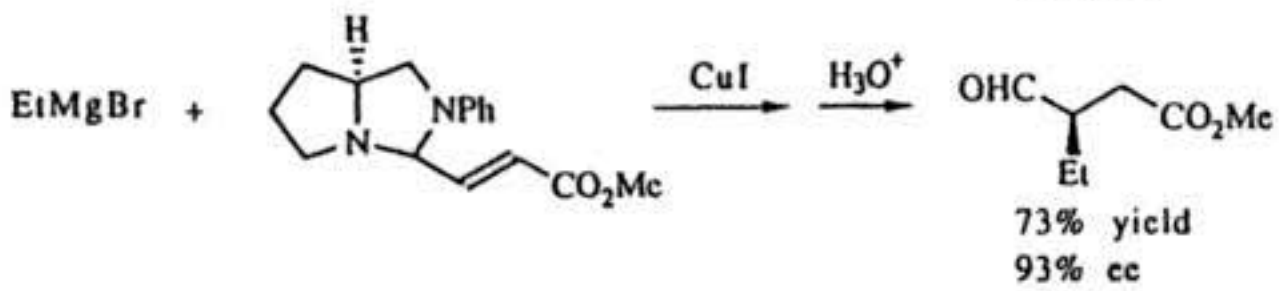
(93)

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the stereochemistry of the product was emphasized in the reaction shown in Eq. (97), because the similar reaction performed with Me_2CuLi afforded the product having the reversed absolute configuration.

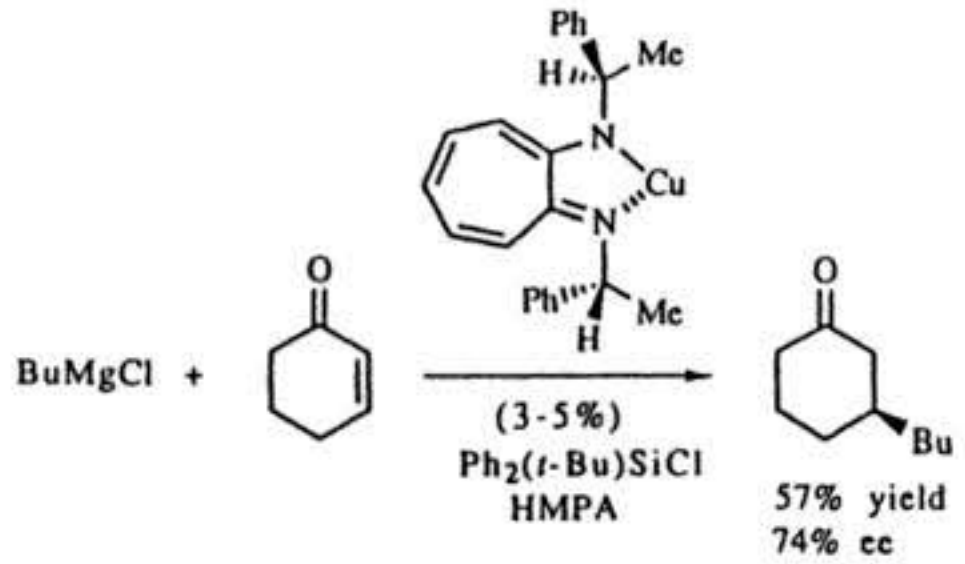


(97)

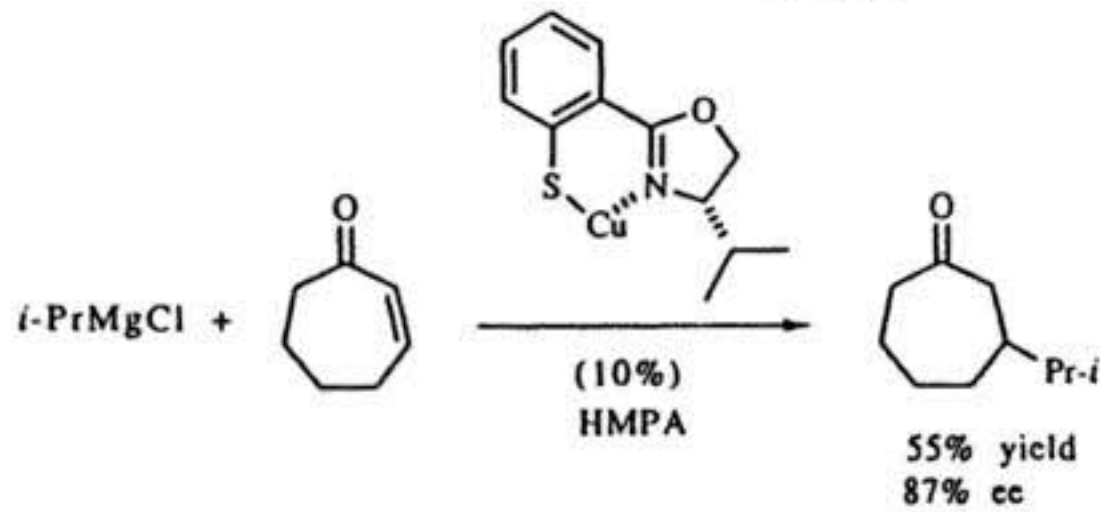


(98)

A (stoichiometric) organocopper reagent having a chiral ligand may promote an asymmetric 1,4-addition reaction. Ligands derived from chiral alkoxide, amide, amine, phosphine, and thiolate have been applied [148]. However, in contrast with the stoichiometric use of these chiral auxiliaries, a catalytic version of this reaction is still quite limited. A conjugate addition of RMgX to 2-cyclohexenone in the presence of a small amount of a chiral copper–diamine complex was investigated and afforded a product with up to 74% enantiomere excess (e.e.), provided a certain silyl chloride was added at the same time [Eq. (99); 217]. Alternatively, an optically active copper thiolate complex catalyzed asymmetric alkyl Grignard addition to α,β-unsaturated ketones [218–222]. The highest degree of chiral induction in copper-catalyzed 1,4-additions of Grignard reagents has been achieved with 2-cycloheptenone, in up to 87% e.e. by the use of a thiolate–copper complex shown in Eq. (100) [218,219].

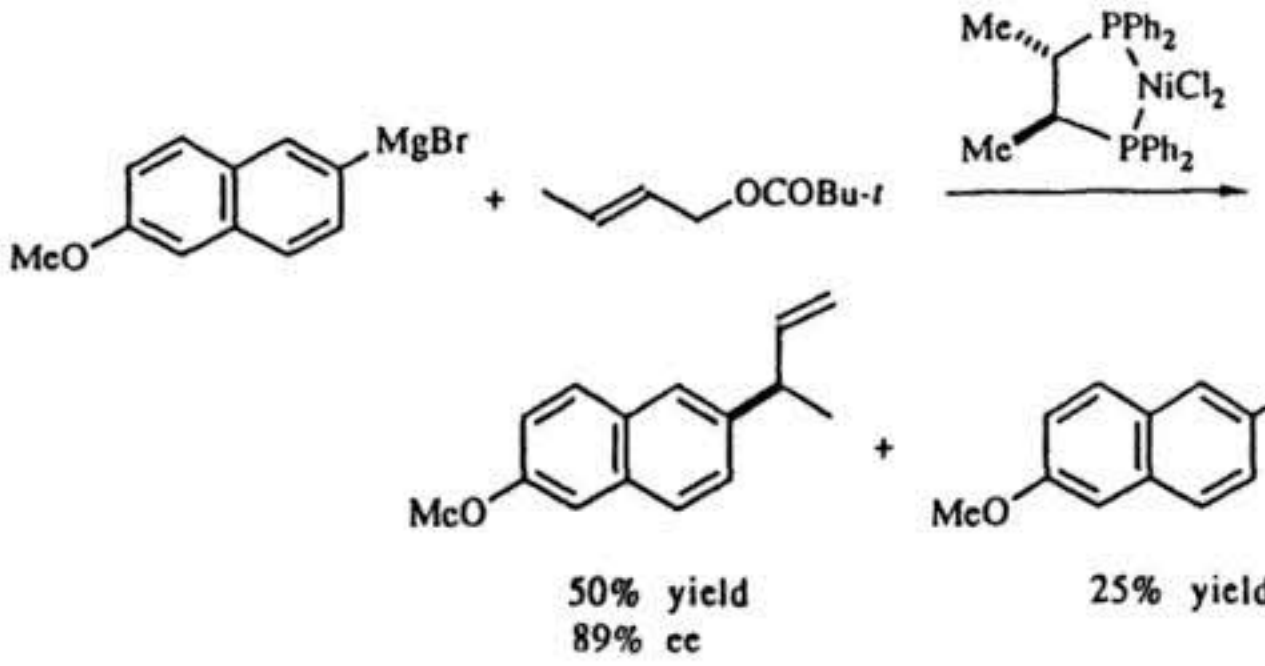


(99)

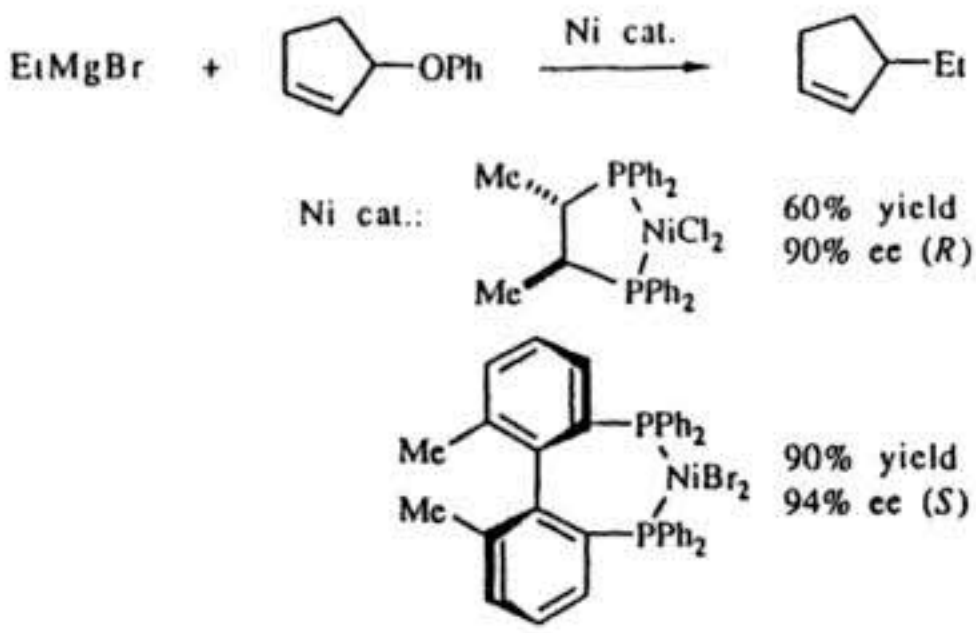


(100)

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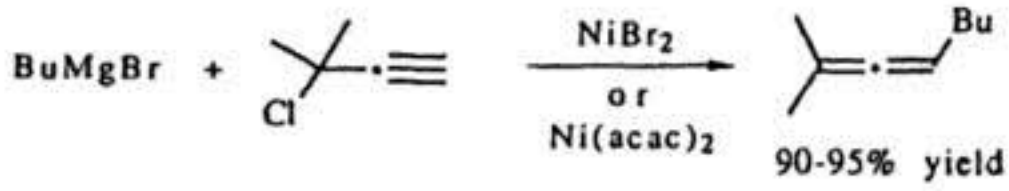


(112)



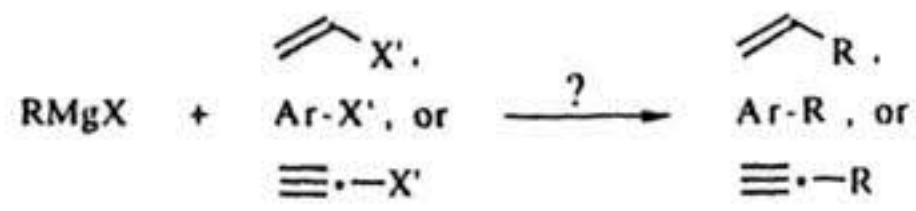
(113)

A propargyl chloride was converted to an allene with a Grignard reagent and a nickel catalyst such as $NiBr_2$ or $Ni(acac)_2$ [Eq. (114); 129].



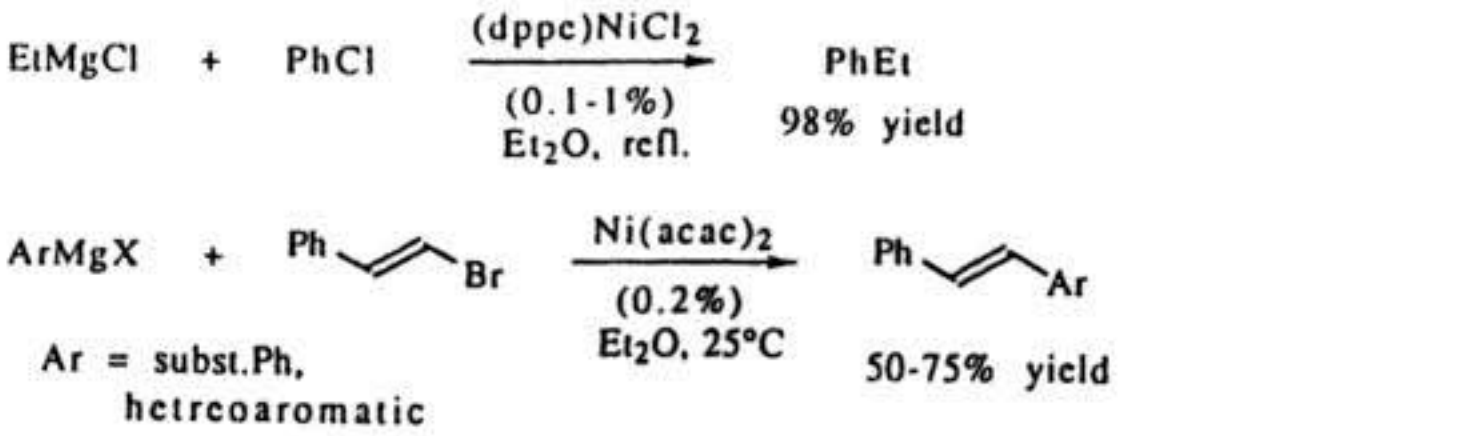
(114)

As both S_N2- and S_N1-type substitutions, which work well for alkyl halides and related compounds, are not applicable to sp^2 or sp carbon centers having a leaving group; introduction of an alkyl group to 1-alkenyl, aryl, or 1-alkynyl halides, and related compounds, as formulated in Eq. (115) is seldom achieved by Grignard reagents alone. Thus, another completely different mechanism has been required to effect these types of reactions. A breakthrough in this context was brought about by two independent groups located in Japan [Tamao et al., Eq. (116); 244] and in France [Corriu and Masse, Eq. (117); 245] in 1972. They described that the addition of a certain nickel salt, together with a Grignard reagent, dramatically facilitated the foregoing substitution reactions. Since then, the importance of this method has been repeatedly shown in many critical stages in organic syntheses and is extensively reviewed in many articles and books [2,3,11,12,14, 246–257].



(115)

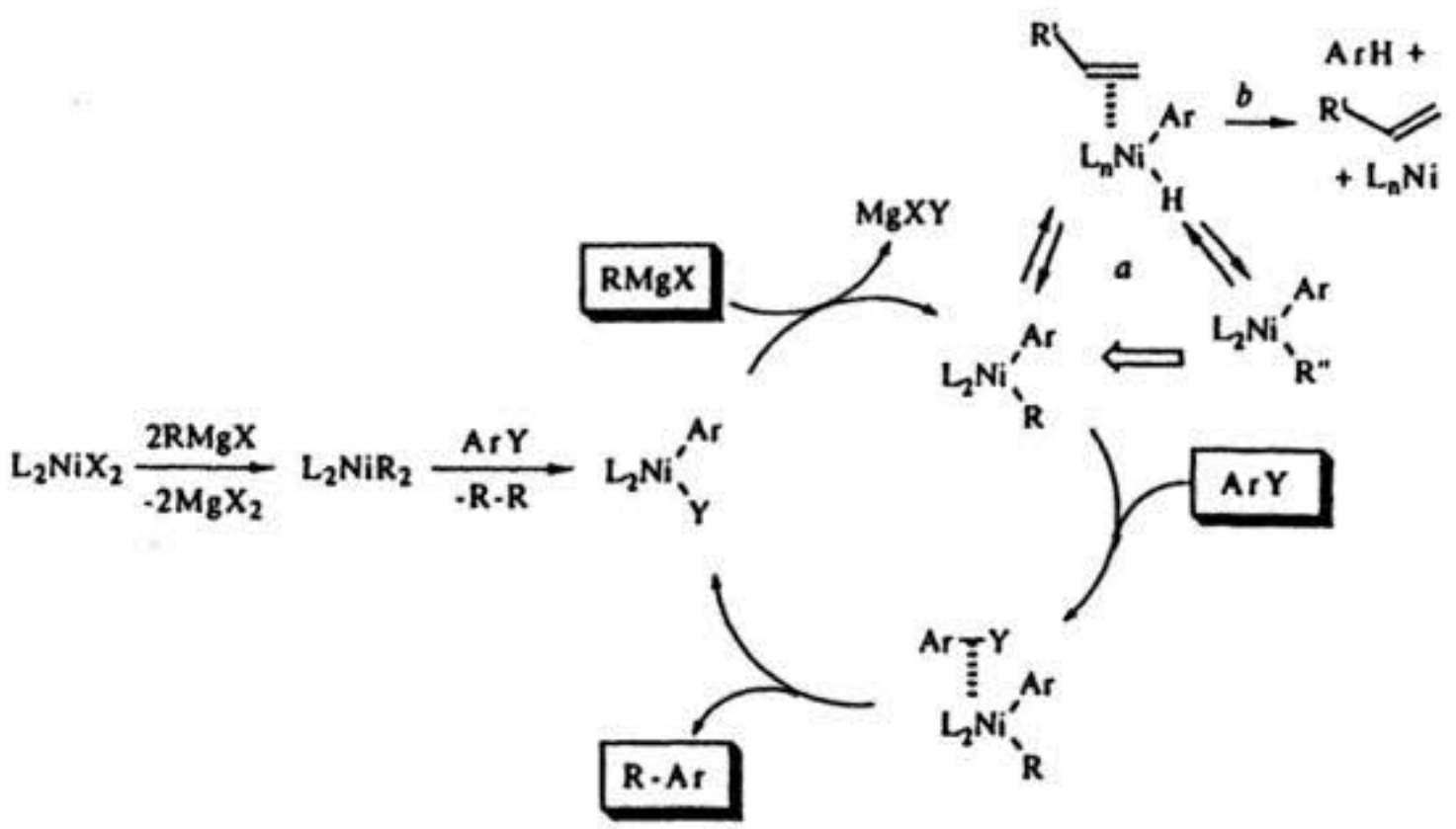
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The mechanism of this reaction was proposed by Kumada et al. and also by other research groups [2,3,246]. A simplified illustration, which is generally accepted and can rationalize other side reactions involving isomerization of the alkyl group of Grignard reagent (path *a*) and reduction of substrates (path *b*), is shown in Scheme 4.

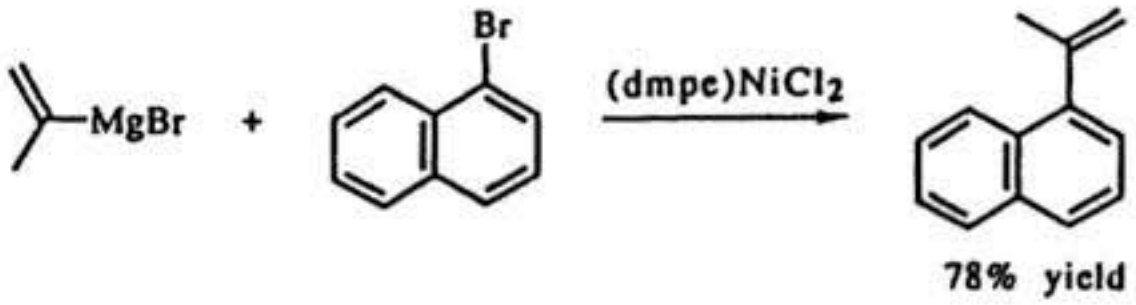
Reaction of L_2NiX_2 with 2 eq of RMgX affords L_2NiR_2, which then reacts with ArY to give $L_2Ni(Ar)Y$ species (oxidative addition), with extrusion of R-R. Sequential incorporation of RMgX (transmetallation) and ArY onto the nickel center induces the catalytic cycle to yield the cross-coupled product R–Ar. If β-hydride elimination occurs in the R group of intermediate $L_2Ni(Ar)R$, a new species, $L_nNi(Ar)H$ complexed by $R'CH{=}CH_2$, is generated (see Scheme 4, path *a*). This species may give back to the starting $L_2Ni(Ar)R$ or, alternatively, may proceed to another $L_2Ni(Ar)R''$ having the isomeric alkyl group R″, rather than original R. This path *a* accounts for isomerization of the alkyl group of Grignard reagent, which is one of the major side reactions. Another course of the side reaction (see Scheme 4, path *b*) is reductive elimination of Ar and H from $L_nNi(Ar)H$ to yield ArH plus olefin. Thus, this overall process is reduction of ArY.

The most common nickel catalysts are NiX_2, $Ni(acac)_2$, and much more frequently, a group of bis(phosphine)nickel$^{(II)}$ halides having $2PPh_3$, dppe, dppp, dppb, and dppf as the phosphine moiety, the reactivities of which were compared with each other [Eq. (118); 246]. More elaborate complexes, such as those having optically active phosphines followed later (discussed later). The foregoing divalent nickel salts are believed to be reduced by Grignard reagent to generate active Ni^0 species in situ. In fact, the zero-valent nickel

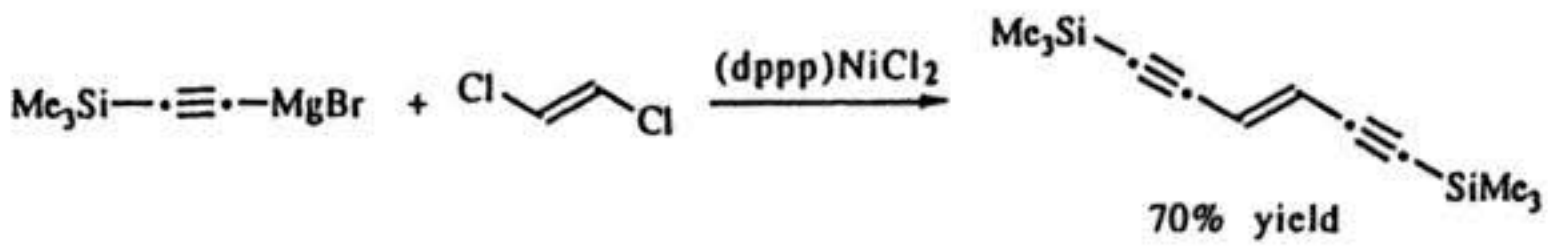


Scheme 4

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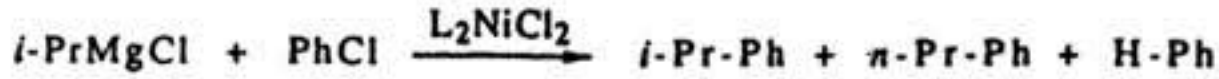


(122)



(123)

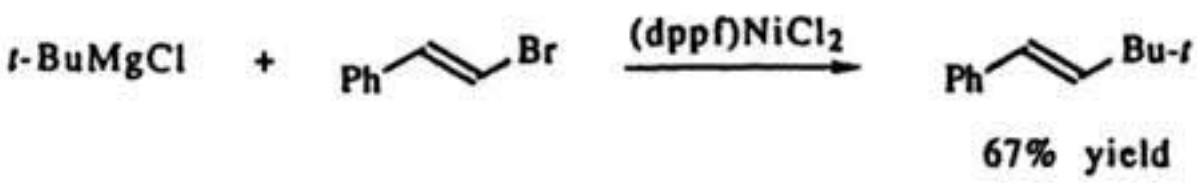
For example, the reaction of *i*-PrMgCl with PhCl afforded three products, *i*-PrPh, *n*-PrPh, and PhH, depending on a choice of the catalyst (see Scheme 4), which is summarized in Eq. (124) [246,285]. Bidentate low-electron–donating phosphine ligands such as dppp, dppe, and, in addition, dppf [271,292] are particularly useful to prepare desired isopropylbenzene.



L_2	Yield(%)	Ratio
dppp	89	96 : 4 : 0
dppe	74	96 : 4 : 0
dmpe	84	9 : 84 : 7
dmpf	48	8 : 74 : 18
$2PPh_3$	44	16 : 30 : 54
$2PBu_3$	8	2 : 16 : 82
$2PEt_3$	9	1 : 11 : 88

(124)

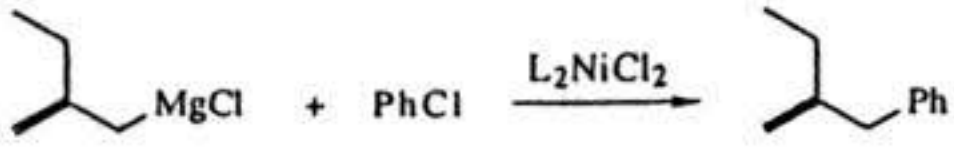
In the reaction of *tert*-butyl Grignard reagent and β-bromostyrene, $(dppf)NiCl_2$ was the most effective catalyst in allowing the reaction to proceed cleanly and give only the desired product. Other phosphine-nickel catalysts afforded a varying amount of the *iso*-butylated product [Eq. (125); 301].



(125)

The importance in the choice of nickel catalysts was also mentioned when optically active 2-methylbutyl Grignard reagent was allowed to react with PhCl. When $(dppp)NiCl_2$ was applied to the reaction, little racemization if any, of the optically active alkyl portion took place during the coupling reaction, whereas the use of $(Ph_3P)_2NiCl_2$ or $(dmpe)NiCl_2$ resulted in an appreciable decrease in the optical purity of the product [Eq. (126); 285].

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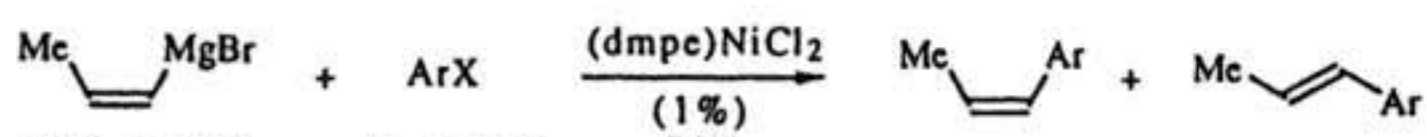


(98% op)

lit.	$[\alpha]^{25}$	10.7-11.6°	
L_2: dppp		10.5°	
dmpe		9.6°	

(126)

A decrease in stereochemical purity of a product when compared with a starting alkenyl Grignard reagent was also observed. Thus, care should be taken, since the *cis/trans* ratio of the alkenyl portion of Grignard reagents will not necessarily be reflected in the final products under certain reaction conditions [246]. Equation (127) illustrates such an example.

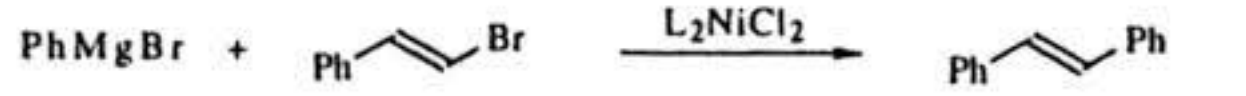


(1.2 equiv) (1 equiv)
Z/E = 96: 4

ArX	Yield(%)	Ratio
PhCl	15	0 : 100
PhBr	84	27 : 73
1-Br-$C_{10}H_7$	87	95 : 5

(127)

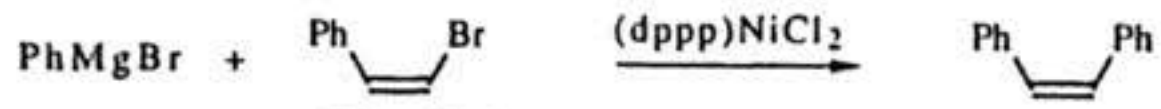
For the substrates, a variety of leaving groups, including all halides (I, Br, Cl, and even F [246]) [Eqs. (128) and (129); 296; and earlier discusion]), carboxylates in small-ring enol lactones [Eq. (130); 302,303], carbonates [Eq. (131); 304] alkoxides [292,305–312; Eqs. (132); 308,309 and (133); 292], sulfides [231,236,237,289,300,311,313–329; Eqs. (134); 236: (135); 236: and (136); 322], sulfoxide [Eq. (137); 237,272,322], sulfones [237,330,331; Eq. (138); 331], selenides [311,239; Eq. (139); 239], tellurides [251,311], phosphates [332–334; Eq. (140); 334], sulfonates [335; Eq. (141); 304], ammonium salt [Eq. (142); 336], and so on, bearing an sp^2 carbon, can be displaced by this method to accomplish the carbon–carbon bond formation. A 1-alkenyl halide, such as 1-bromo-2-(trimethylsilyl)acetylene, could be substituted with PhMgBr to yield phenyl(trimethylsilyl)acetylene [247].



E/Z = 92: 8
L_2 = dppp, dppe, dmpe, $2Ph_3P$

74-88% yield
E/Z = 90:10-93: 7

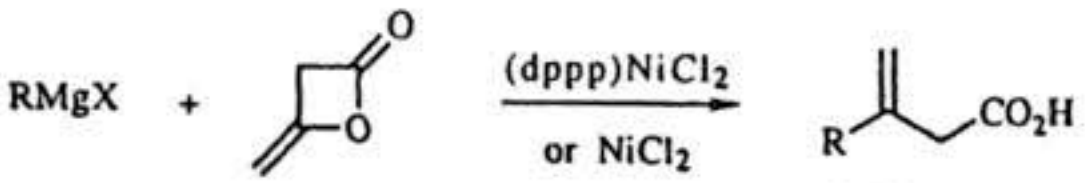
(128)



Z/E = 92: 8

100% yield
Z/E = 93: 7

(129)

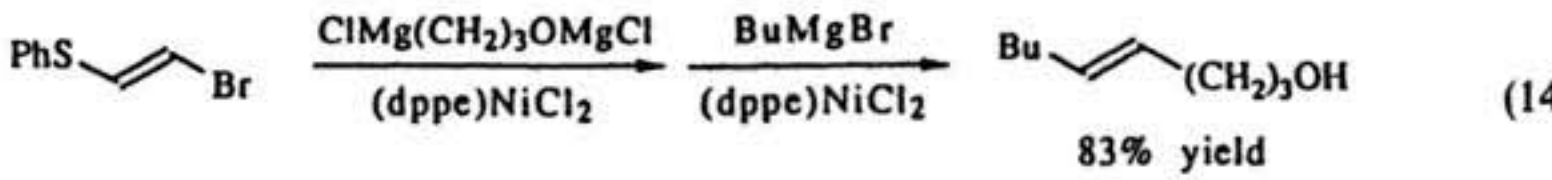


R = *n*-alkyl, Me_3SiCH_2-, Bn

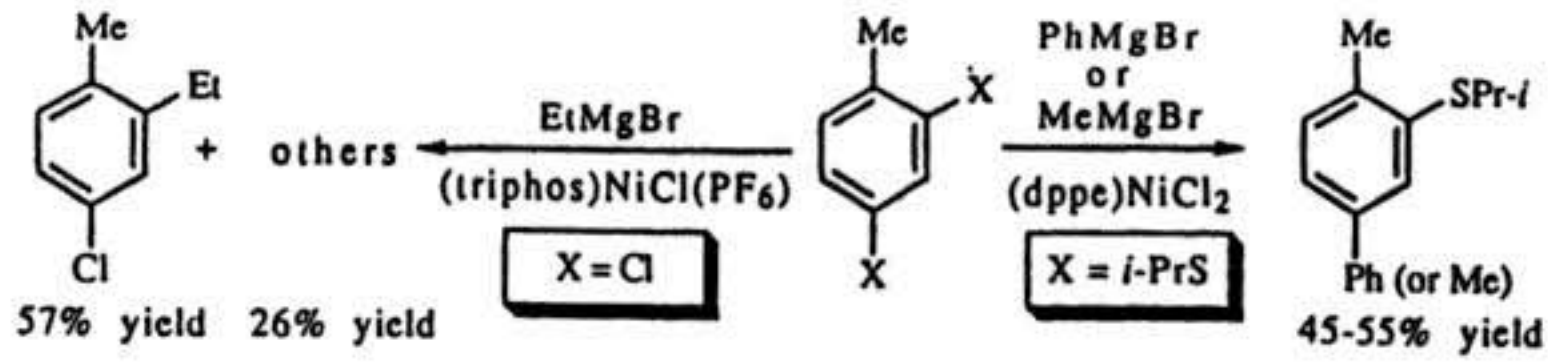
43-95% yield

(130)

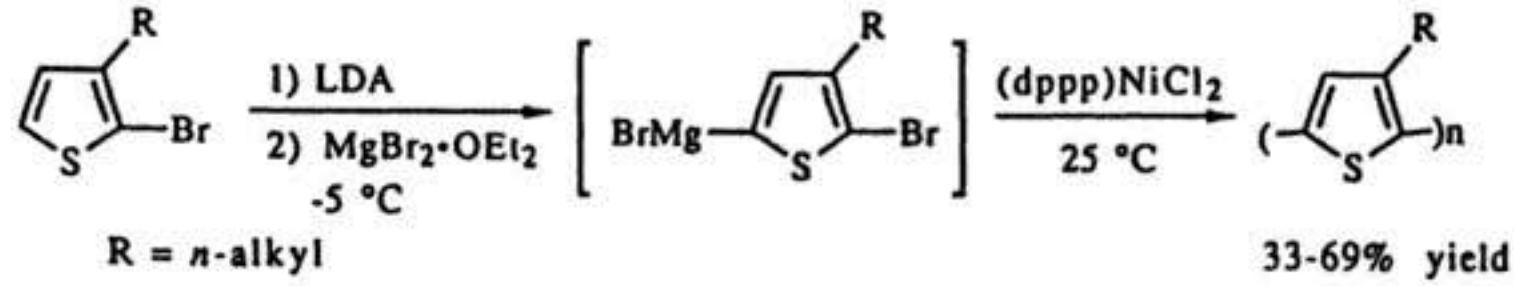
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(146)

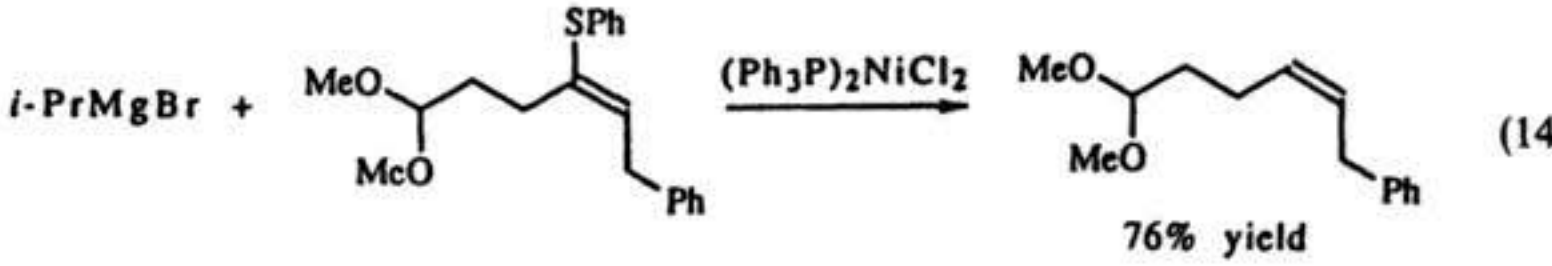


(147)



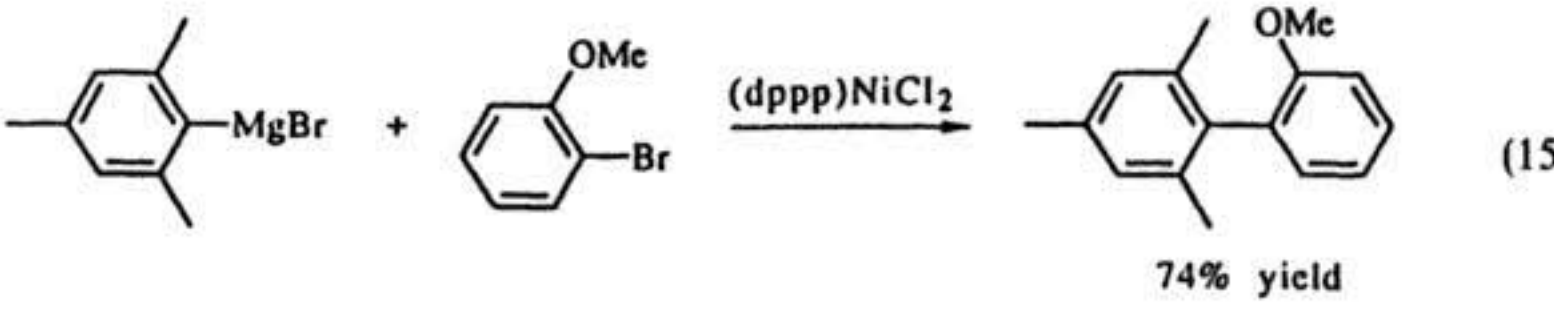
(148)

The mode of reduction by *i*-PrMgCl shown in Scheme 4 and Eq. (124) was employed in stereoselective desulfurization of alkenyl and aryl sulfides, sulfoxides, or sulfones [237,314,331; Eq. (149); 314].



(149)

The nickel-catalyzed coupling reaction is relatively unaffected by the steric congestion of the reaction partners, as exemplified in Eq. (150) [351]. In addition, it shows reasonable compatibility of functional groups that are susceptible to the Grignard addition. An example is shown in Eq. (151) [187].



(150)

(151)

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reagent was possibly consumed to give a product of high e.e. Some insight into the mechanisms of this reaction has been reported [353,370]. Another somewhat more straightforward example is asymmetric coupling of an aryl Grignard reagent with an aryl halide to form an optically active biaryl [Eq. (155); 371] [351,371–374].

B. Carbonyl Addition

Addition of Grignard reagents to carboxylic acids [Eq. (156); 375] or phenylthiochloroformate [Eq. (157); 376] cleanly stopped at the carbonyl stage in the presence of a nickel salt.

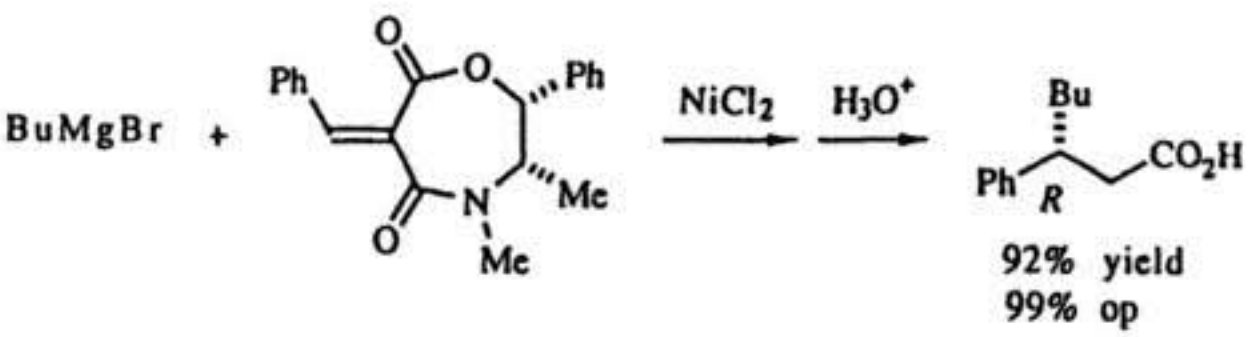
$$C_5H_{11}MgBr + PhCO_2H \xrightarrow{(dppe)NiCl_2} \underset{92\ (75\%\ yield)}{C_5H_{11}(C{=}O)Ph} + \underset{3}{C_5H_{11}CH(OH)Ph} + \underset{5}{C_5H_{11}C(OH)(C_5H_{11})Ph} \quad (156)$$

(16 : 8 : 76 without Ni)

$$RMgX + ClCOSPh \xrightarrow{(dppe)NiCl_2} RCOSPh \quad (157)$$

R = *n*-,*s*-alkyl, Ph — 78-87% yield

Diastereoselective 1,4-addition of Grignard reagent to a methylenemalonic acid derivative was promoted by $NiCl_2$ [Eq. (158); 182,183]. Other metallic salts such as $ZnCl_2$, $FeCl_3$, and CuI were less useful relative to the diastereoselectivity.



92% yield
99% op (158)

C. Hydro- and Carbomagnesation of Olefins and Acetylenes

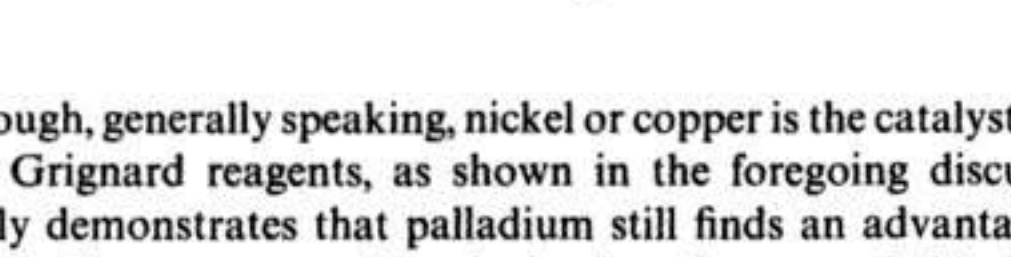
A certain nickel salt is known to catalyze hydro- or carbomagnesation of unsaturated bonds with Grignard reagents (see Chapter 3).

IV. PALLADIUM-CATALYZED REACTIONS

Action of alkyl Grignard reagents with a variety of alkyl halides (except MeI, which undergoes methylation [377]) in the presence of a palladium catalyst usually resulted in clean reduction of the halides, rather than alkylation or elimination [Eq. (159); 378,379].

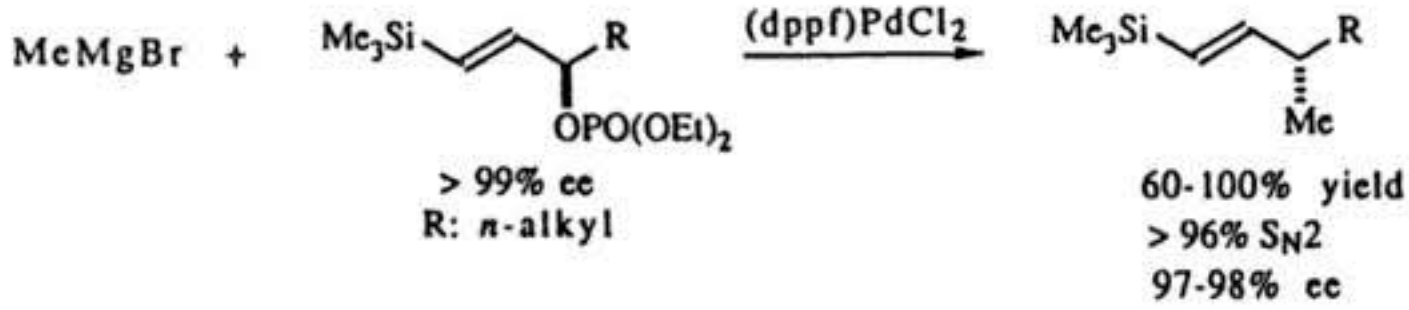
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In this palladium-catalyzed reaction, even a neopentyl iodide, which lacks β-hydrogens, did not afforded the alkylated products.



(159)

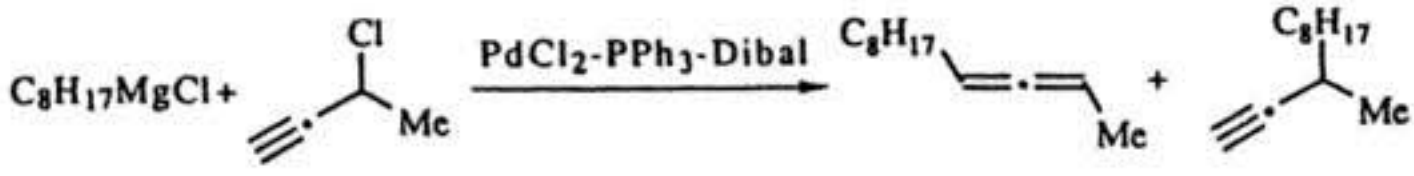
Palladium-catalyzed substitution at an allylic carbon having a leaving group with soft carbon nucleophiles, such as active methylene compounds, is well documented, and immeasurable data have been accumulated on its chemo-, regio-, and stereochemical aspects [241,380–387]. To the contrary, these reactions, in which Grignard reagents were used as the nucleophiles, are still rare [94,230,388,389] and are usually ignored. However, recently, a very high regio- and stereoselective allylic alkylation was reported by the use of palladium catalyst, rather than a nickel or copper catalyst [Eq. (160); 391]. The inversion of configuration observed here is consistent with the previous study using cyclic substrates and palladium catalysts [230; cf. Eqs. (109) and (110)].



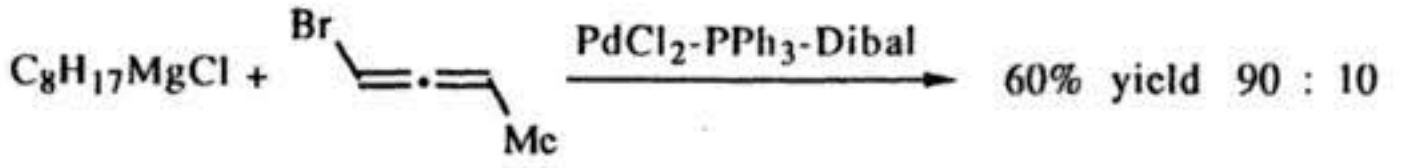
(160)

Although, generally speaking, nickel or copper is the catalyst of choice for allylic substitution with Grignard reagents, as shown in the foregoing discussions, the result of Eq. (160) clearly demonstrates that palladium still finds an advantage in allylic substitutions.

S_N2'-type propargylic substitution of propargyl chlorides with alkyl or aryl Grignard reagents could be carried out with the catalyst generated from $PdCl_2$-PPh_3-Dibal (1:2:1) [Eq. (161); 392]. Interestingly, the reaction starting from propargyl chloride showed a higher isomeric purity of the allene than that from the isomeric allenyl bromide [Eq. (162); 392].



(161)



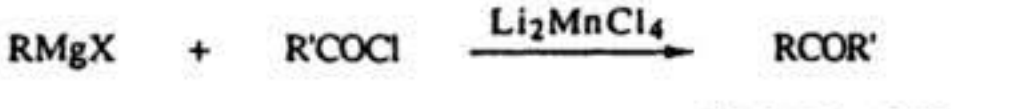
(162)

Palladium also catalyzes the substitution at sp^2 carbons having a leaving group with Grignard reagents [393,394]. Many review articles are available on this topic [11,12,14, 246,248–250,252–254,380,381,390].

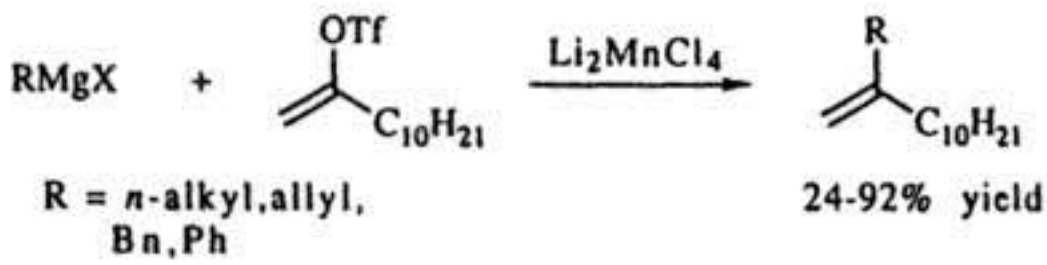
A variety of Grignard reagents involving primary [33,49,53,108,258,261,271,272,290, 341,377,393–400; Eqs. (163) and (164); 393,394] and secondary [49,261,271,272,284,399,401] alkyl [Eq. (165); 271], allyl [Eq. (166); 398], benzyl [272,290,397; Eq. (167); 290], alkenyl

Material chroniony prawem autorskim

Manganese [444], such as $MnCl_2$, was reported to facilitate ketone formation from acyl halides and Grignard reagent [Eq. (202); 445]. The actual salt added here is soluble Li_2MnCl_4. Another application is that enol triflates were substituted with Grignard reagents under Li_2MnCl_4 catalysis [Eq. (203); 446].

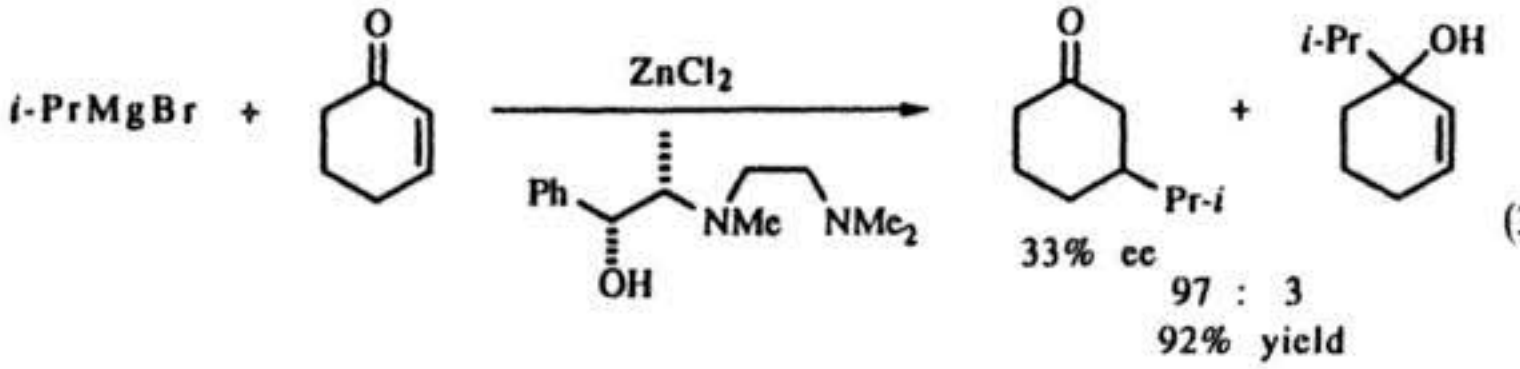


(202)



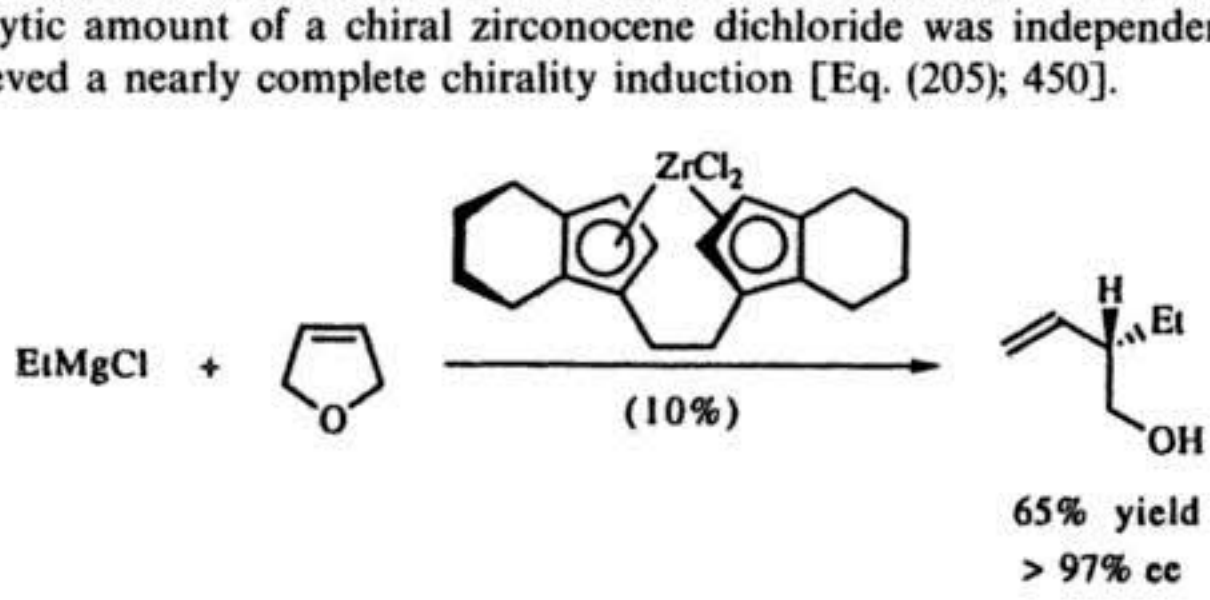
(203)

Zinc complexes, consisting of amine, amino alcohol, alcohol, sulfide, or phosphine as ligand, catalyzed 1,4-addition of Grignard reagents to α,β-unsaturated carbonyl compounds [447,448]. An optically active ligand on zinc achieved asymmetric 1,4-addition, the best result is presented in Eq. (204) [448].



(204)

Zirconocene dichloride was used as a catalyst for allylic displacement of allyl ethers with Grignard reagents [449]. An asymmetric version of this reaction by the use of a catalytic amount of a chiral zirconocene dichloride was independently reported, and it achieved a nearly complete chirality induction [Eq. (205); 450].

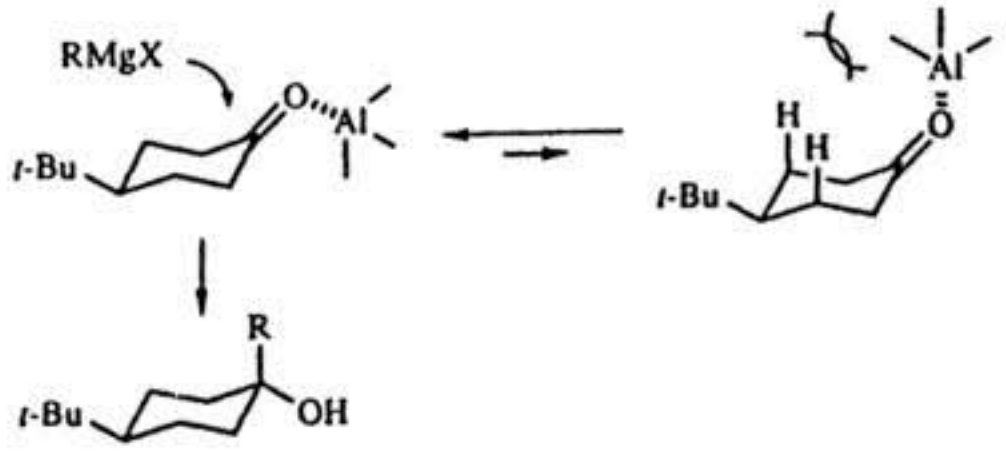


(205)

Other applications of zirconium catalysts in hydro- and carbomagnesation with Grignard reagents are described in Chapter 3.

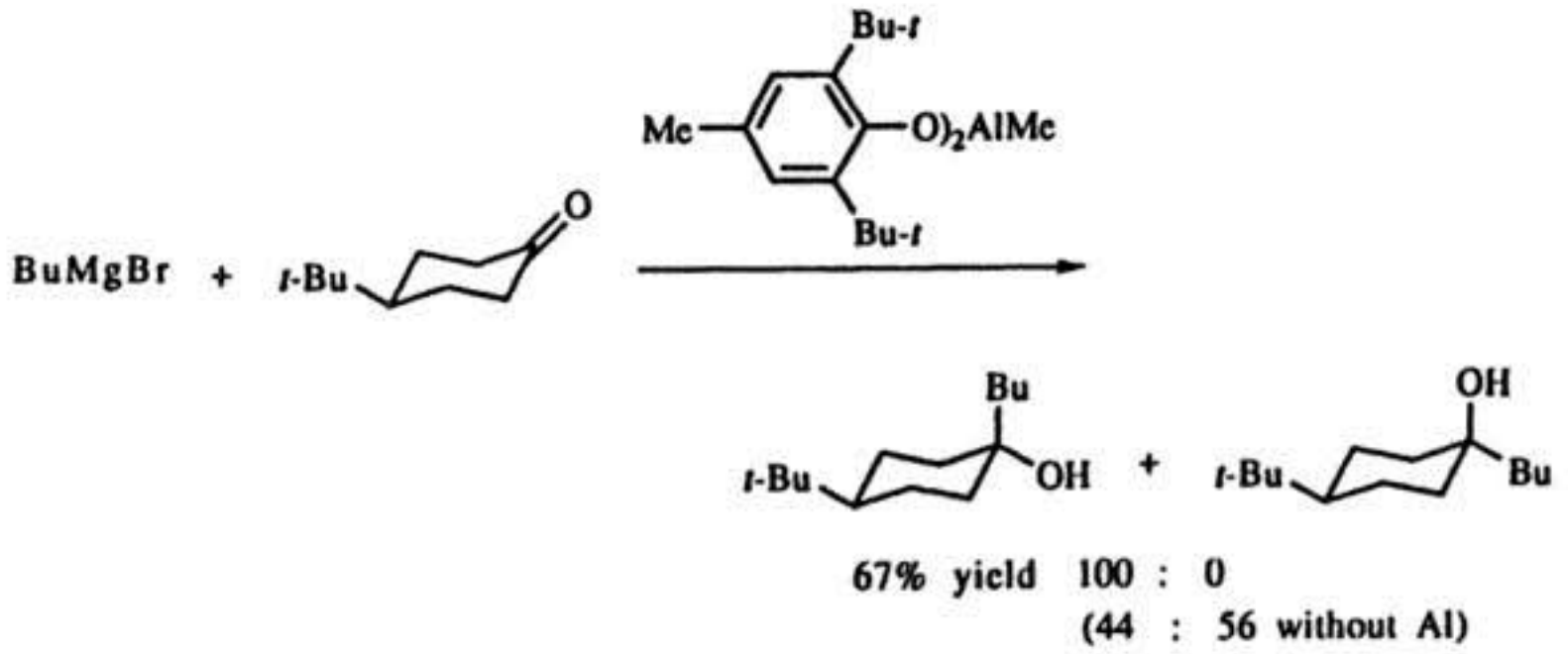
Addition of Grignard reagents to ketones to form alcohols is a class of the most fundamental reactions in organic synthesis. Much data on selectivities of this reaction are available. Yamamoto et al. utilized a highly bulky organoaluminum compounds as a

Material chroniony prawem autorskim



Scheme 5

sterically shielding element that controls and even reverses the stereochemical outcome of the addition of Grignard reagent to a cyclohexanone [451–453], which is exemplified in Eq. (206) [454].



(206)

Scheme 5 accounts for the observation in Eq. (206). At first, the bulky aluminum reagent occupies a less-hindered space of the substrate so that an incoming nucleophile should approach the ketone from its superficially more-hindered side (i.e., by axial attack). The change in selectivity here has been considered to arise from a steric control, rather than transmetallation of the Grignard reagent to an aluminumate complex before the addition. Other selective reactions based on the same notion have also been developed [451–453].

Other metal catalysts in Grignard reactions will enable a variety of unprecedented reactions or more drastic alternations in selectivities, which are future problems.

GLOSSARY

The following abbreviations are used throughout this chapter:

Et	ethyl
Pr	*n*-propyl, unless otherwise indexed
Bu	*n*-butyl, unless otherwise indexed
C_nH_{2n+1}	*n*-alkyl, unless otherwise indexed
Bn	$PhCH_2$
Ph	phenyl

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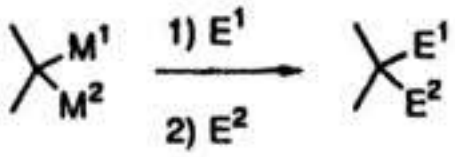
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The Preparation of 1,1-Bimetallics of Magnesium and Zinc

PAUL KNOCHEL
University of Marburg, Marburg, Germany

I. INTRODUCTION

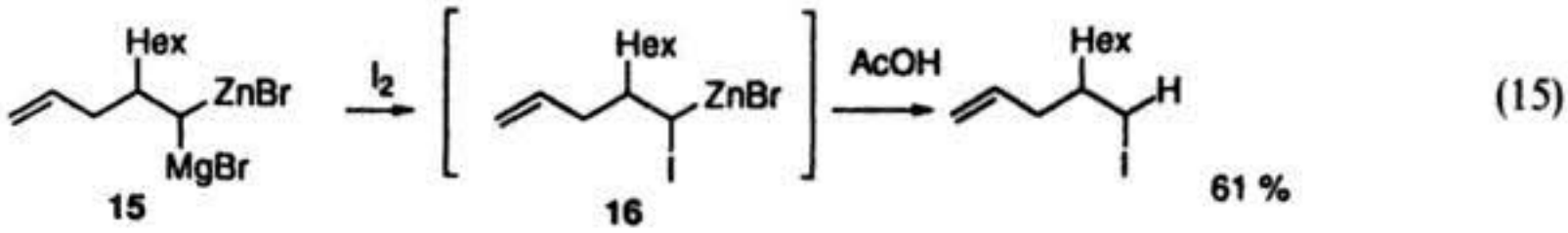
The preparation, structural and chemical properties of molecules having several metals attached to the same carbon atom have fascinated chemists for a long time. Theoretical predictions speculate that some of these molecules may have a planar tetracoordinated carbon atom [1,2]. Several polymetallated compounds such as CLi_4 [3] have been prepared and their properties were carefully investigated. Unfortunately, owing to their high reactivity, very few synthetic applications have been found, and sequential reactions of the four carbon–metal bonds with different electrophiles could not be realized [3]. On the other hand, mixed 1,1-bimetallics, in principle, should be able to react in a selective way with two different electrophiles (E^1 and E^2) as long as the reactivity of the first carbon–metal bond ($C–M^1$) is substantially different from the reactivity of the second carbon–metal bond [$C–M^2$; Eq. (1)]. In 1971, Gaudemar discovered a very general and practical preparation of mixed 1,1-bimetallics of zinc and magnesium by performing the addition of an allylic zinc halide to alkenylmagnesium halides [4–6]. This reaction allows the convenient study of the reactivity of mixed 1,1-bimetallics, and it was soon found by Knochel [7–14,19], that the sequential reaction of these organometallic reagents with various electrophiles can be realized. Furthermore, these compounds proved to be excellent olefination reagents, allowing the stereoselective preparation of polyfunctional (*E*)- and (*Z*)-disubstituted olefins [12–14; Eq. (2)]. This chapter describes the preparation and reactivity of mixed magnesium and zinc 1,1-bimetallics. The chemistry of some related reagents will also be covered.



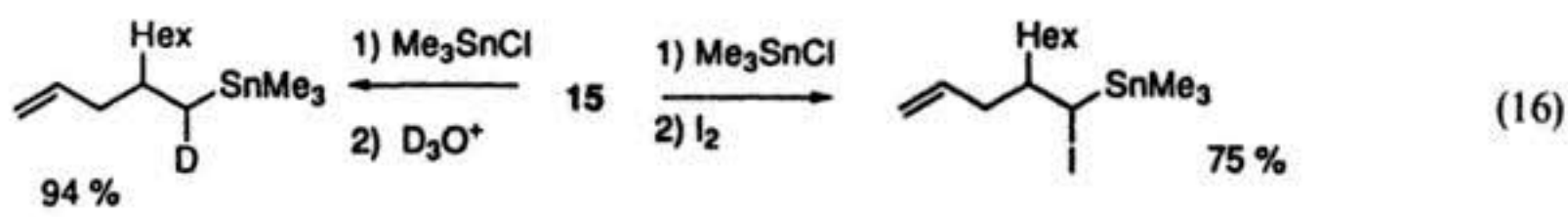
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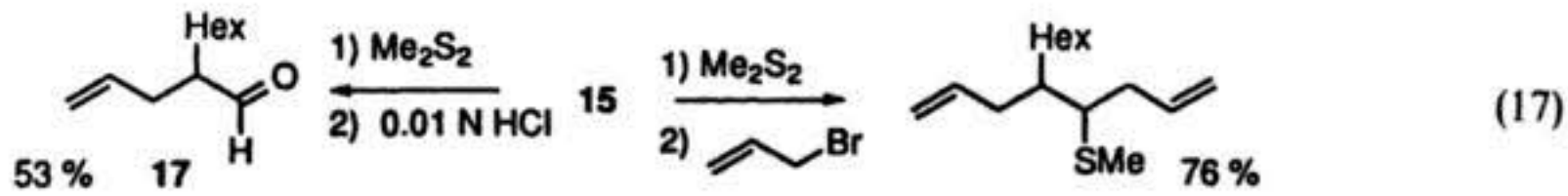
is isolated as the sole product [Eq. (18); 8]. In the presence of copper salts, such as copper cyanide [9] or, better, copper cyanide–lithium chloride complex [26], a higher reactivity of the zinc–lithium bimetallics is observed. Thus, the reaction of **18** with allyl bromide in the presence of CuCN·2LiCl (10 mol%) produces the bis-allylated product **20** in 85% yield, whereas the reaction with chlorotrimethylstannane produces the distannane **21** [85%; 9; Eq. (19)]. The selective quenching of a lithium zinc dimetallic with methanol produces an organozinc reagent that reacts in the presence of a copper, palladium, or titanium catalyst with a range of electrophiles, as shown in Scheme 1. The magnesium, zinc bimetallic **15** can also be converted selectively to the a zincated nitrile **22** by the reaction with tosyl cyanide [Eq. (20); 27]. A related reaction of a zinc 1,1-bimetallic compound with benzenesulfonyl chloride furnishes primary alkyl chlorides after hydrolysis [28].



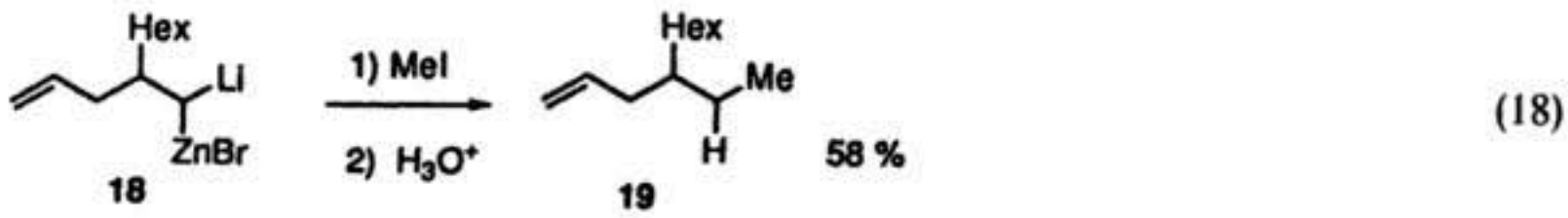
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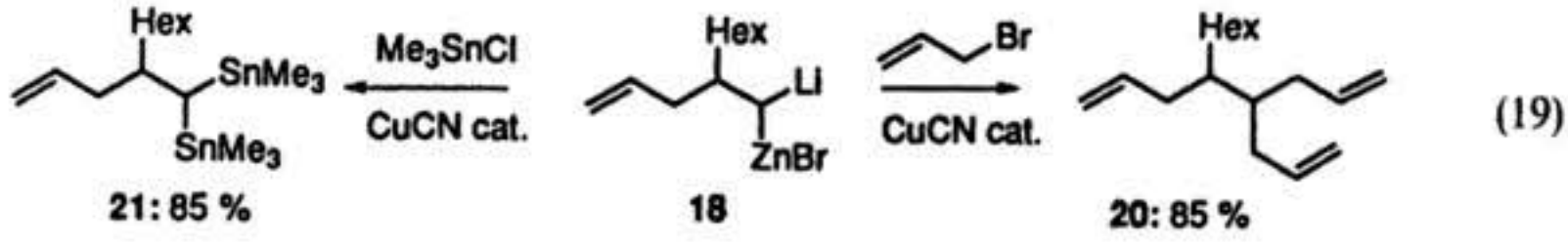
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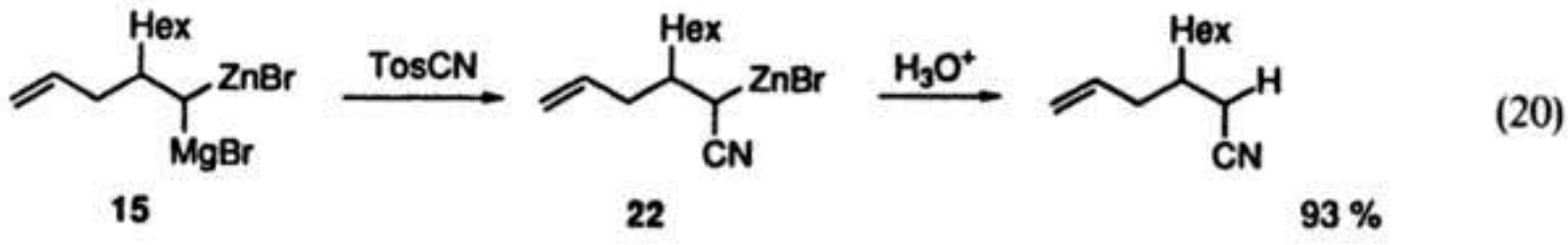
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(18)



(19)

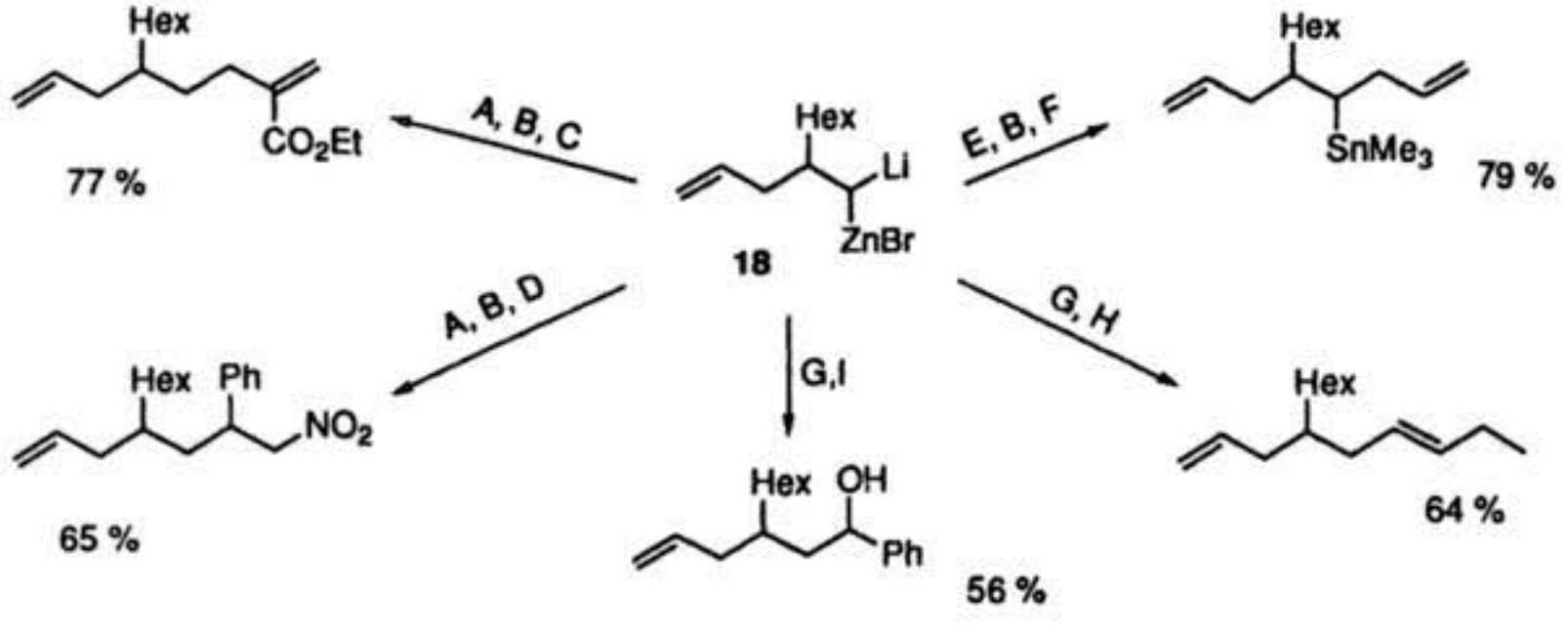


(20)

B. Olefination Reactions

Although the selective reaction with electrophiles [7–11,29] constitutes an interesting reactivity pattern, the most useful synthetic application of 1,1-bimetallics are olefination reactions [30–32]. First investigations have shown that magnesium–zinc 1,1-bimetallics react with a range of aldehydes in the presence of stoichiometric amounts of boron trifluoride etherate, leading to (*E*)-disubstituted olefins [Eq. (21); 7]. Ketones do not undergo

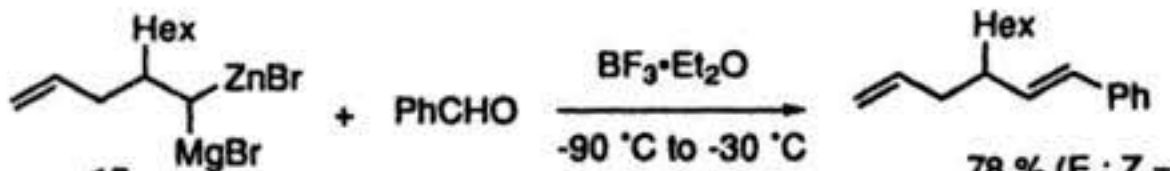
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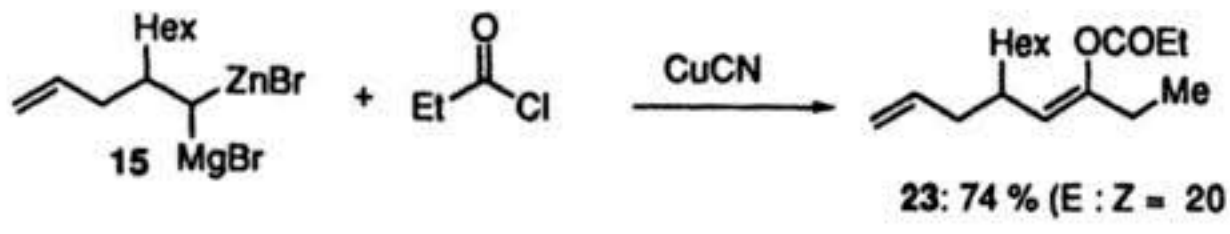
Reaction conditions: A: MeOH (1 equiv.); B: CuCN (1 equiv.); C: ethyl 2-(bromomethyl)acrylate; D: nitrostyrene; E: Me_3SnCl (1 equiv.); F: allyl bromide; G: i-BuOH (1 equiv); (E)-1-iodo-1-butene, $Pd(PPh_3)$ cat; I: $ClTi(OiPr)_3$ (2 equiv.), benzaldehyde (1.5 equiv.).

Scheme 1

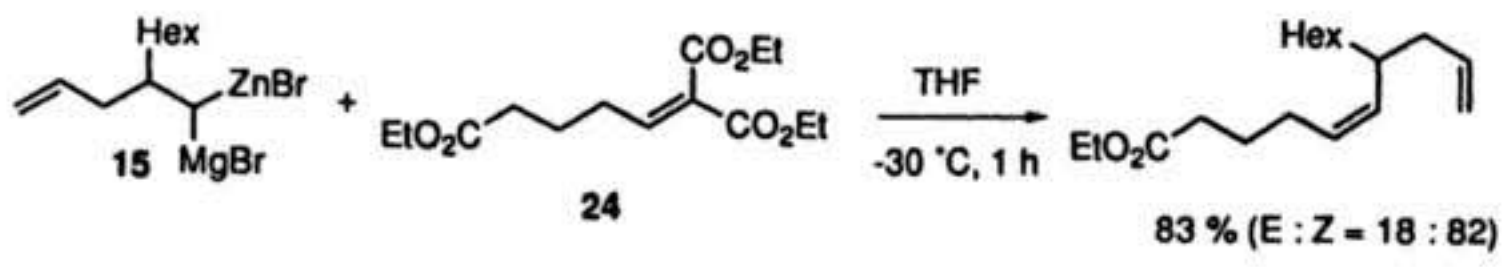
the olefination reaction, and a sterically hindered aldehyde, such as pivalaldehyde, reacts only at a higher temperature ($-20°C$), leading to the corresponding olefin in moderate yield [7]. The reaction of **15** with acid chlorides in the presence of copper(I) cyanide leads to enol esters, such as **23**, in good yields. The reaction proceeds less satisfactorily in the absence of copper salts [Eq. (22); 8,9]. The best olefination procedure of magnesium–zinc 1,1-bimetallics is realized by reacting them with alkylidenemalonates **24** [Eq. (23); 12,13]. This remarkable reaction products selectively (*Z*)-olefins. By using a *dimethyl* alkylidenemalonate, such as **25**, instead of the corresponding diethyl alkylidenemalonate, it is possible to obtain very high *Z*-selectivities [Eq. (24); 13].



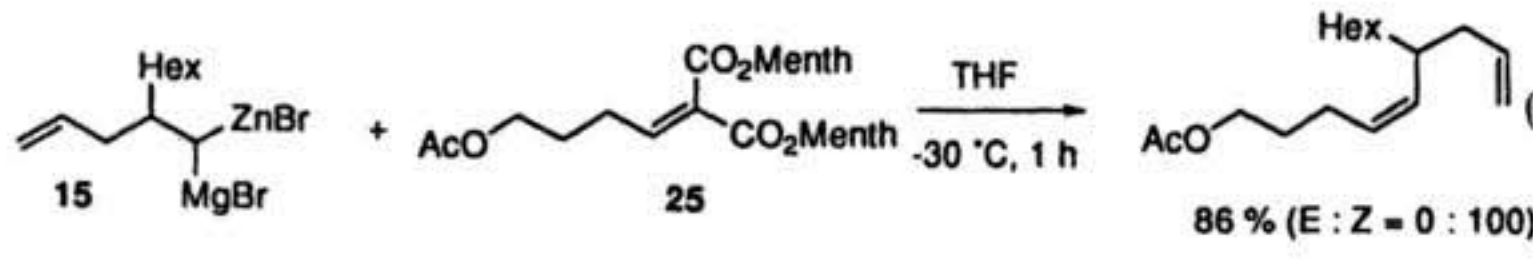
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(22)

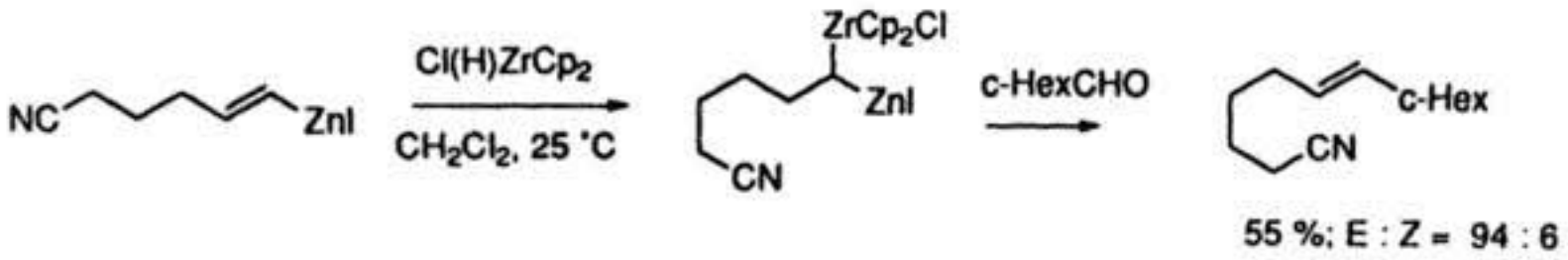


(23)



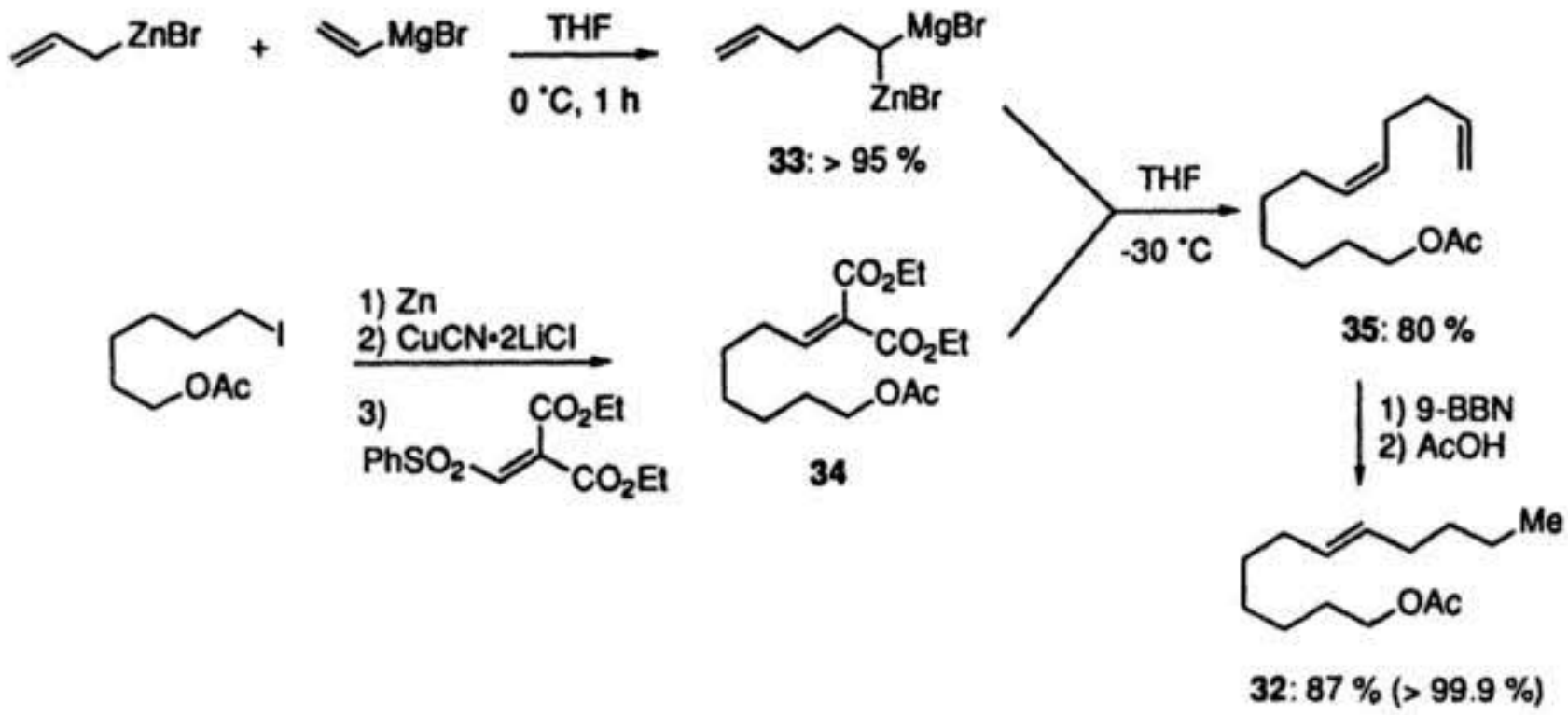
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(26)

Scheme 3



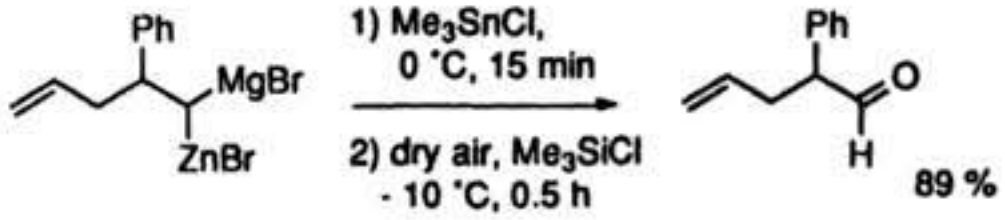
Scheme 3

C. Oxidation of 1,1-Bimetallics of Magnesium and Zinc

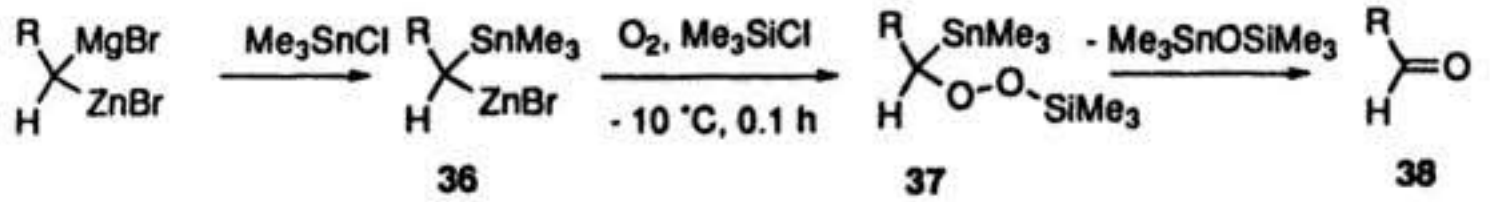
The presence of two metals attached to the same carbon allows the performance of novel reactions, and the controlled oxidation of 1,1-bimetallics with air provides an expeditive conversion of these organometallic compounds to aldehydes [19,21]. Carbon–zinc and carbon–magnesium bonds are readily oxidized by air. Whereas the direct oxidation of 1,1-bimetallics leads to complex mixtures, the treatment of the magnesium–zinc 1,1-bimetallic reagent with chlorotrimethylstannane (0°C, 15 min), followed by the addition of dry air in the presence of chlorotrimethylsilane, produces the corresponding aldehyde in excellent yields [Eq. (27); 21]. The reaction proceeds first through the formation of a trimethylstannyl–zinc 1,1-bimetallic reagent of type **36**, which readily inserts oxygen into the carbon–zinc bond, leading to the silylated hydroperoxide **37**, which undergoes a rearrangement, leading to the aldehyde **38** [Eq. (28); 21]. Interestingly, the reaction can be extended to α-silylated organozinc reagents and the addition of butyllithium to α-trimethylsilylstyrene furnishes, after transmetalation with zinc bromide, the benzylic zinc compound **39**, which is smoothly oxidized by dry air in the presence of chlorotrimethylsilane (−10°C, 5 min) and affords the ketone **40** in 84% yield [Eq. (29); 21]. This oxidation procedure allows the stereoselective preparation of aldol products. Thus, the addition of 3-ethoxyallylzinc bromide **41** [39,40] to 1-octenylmagnesium bromide ($E/Z = 12{:}88$) leads to a mixture of two diastereomeric bimetallic species **42** and **43** that are oxidized with

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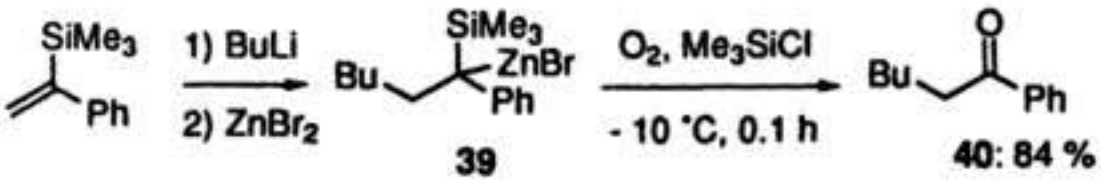
dry air, leading to the two diastereomeric aldehydes **44** and **45** (ratio 88:12) in 56% overall yield. There is a complete transfer of the stereochemical information of the alkenyl magnesium compound to aldehydes **44** and **45** [Eq. (30); 21]. The use of an alkoxy substituent for controlling the stereochemistry in the formation of 1,1-dimetallics has been elegantly developed by Marek, showing that the control of up to three stereocenters in an acyclic chain using the [3,3]-sigmatropic shift is possible [Eq. (31); 41–43].



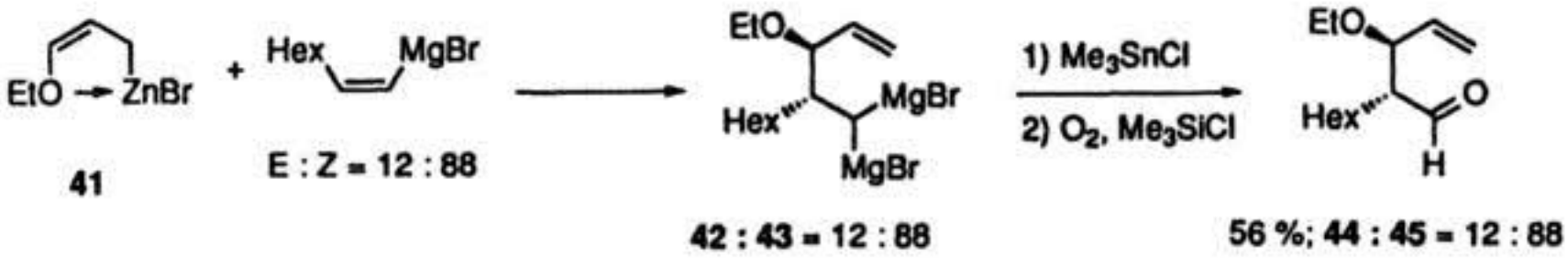
(27)



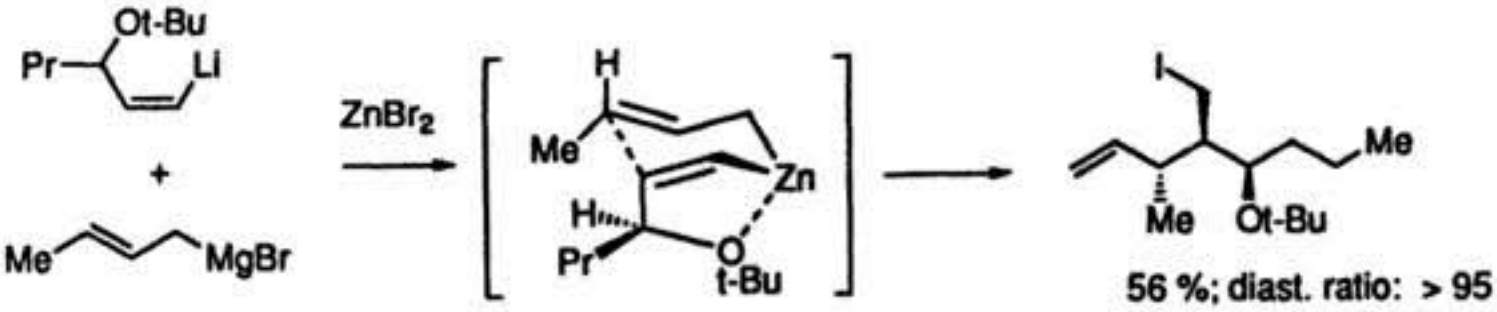
(28)



(29)



(30)



(31)

IV. RELATED REAGENTS

The interactions between the two carbon–metal bonds (carbon–magnesium and carbon–zinc) lead to new reactivity patterns that are not found either in organomagnesium or organozinc reagents. Such interactions between carbon–metal bonds are also possible for some other bimetallic magnesium reagents [44,45]. Labaudinière [46] has shown some interesting aspects of the chemistry of 1,3-bimetallic reagents and has found that these compounds are efficient multicoupling reagents [47,48]. Thus, the reaction of the lithium–zinc 1,1-allylic bimetallics **46**, prepared by the reaction of the allenyllithium **47** with allylzinc bromide, reacts selectively with two different electrophiles, affording polyfunctional molecules of type **48** in excellent yields [Eq. (32); 46]. Interestingly, the two carbon–metal bonds can also be separated by several carbon atoms without a lost of selectivity. Thus, the copper–zinc

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31

Alkynyl Grignard Reagents and Their Uses

MASAYUKI UMENO
Hokko Chemical Industry Co., Ltd., Atugi, Kanagawa, Japan

AKIO SUZUKI
Hokko Chemical Industry Co., Ltd., Tokyo, Japan

I. INTRODUCTION: FUTURE OF ACETYLENIC COMPOUNDS

The chemical and physical properties of acetylenic compounds are characterized by their strong acidic acetylenic hydrogen, unsaturated triplebond, and linear structures. The strong acidity of the hydrogen that is bount to the triple bond can be readily transformed to the corresponding organometallic compounds. These organometallic species can be used for generating a new carbon–carbon bond or converted to various functional groups by substitution or addition reactions. Some of the typical reactions of acetylenic compounds are

1. Replacement of metal acetylides -Li, -Na, -K, -MgX
2. Addition to the triple bond
3. Addition to other unsaturated positions
4. Polymerization

Acetylenic compounds readily undergo reduction, addition, or cyclization at the triple bond. The straight-chain structure, with the triple bond in the center, and a high degree of unsaturation, can be expected to provide a versatile tool for the synthesis of liquid crystals and organoelectric conductors. Acetylene has the simplest carbon–carbon triple bond structure and, historically, has been an important building block for the chemical industry. For example, commercial production of vinylchloride, acetaldehyde, acrylic acid, acrylonitrile, and perchloroethylene was first accomplished by the Reppe reaction, which used acetylene as the starting material. Acetylene was also employed conveniently for the production of acetone, its conversion to methyl rubber, and dimerized vinyl acetylene was converted to chloroprene rubber. At present, acetylene chemistry has been largely replaced by lower-cost olefin chemistry that uses ethylene and propylene for most of these processes. Its use has continued in limited fields such as the preparation of 1,4-butanediol, vinyl acetate, and acetylenic alcohols [1].

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II. GENERAL METHODS OF PREPARATION FOR ACETYLENIC COMPOUNDS

There are several review articles on the preparation methods for acetylenic compounds, either by the elimination of halogen compounds, or by the displacement of metal acetylides [2].

A. Elimination of Hydrogen Halogenide and Dehalogenation of Alkylhalogen Compounds

The elimination of 1,2- or 1,1-dihalogenoalkanes or that of halogenoalkenes by base is effective for preparing alkynes. This route is especially effective owing to a variety of halides that are commercially available for use as raw materials. Usually, caustic alkali, alkali alcoholate, alkali amide, or *n*-butyl lithium are used as the base. Under certain conditions side reactions occur, leading to isomerization or rearrangement to form more stable internal alkynes or allene derivatives.

For the preparation of aryl or heteroaryl acetylenic compounds, the reactions proceed in good yield, with little isomerization of the products. When a two-step process is used, a highly stable vinyl halogenide forms in the first step under mild conditions. Dehalogenation with a strong base in the second step yields the corresponding alkynes [Eqs. (1–8)].

$$RCH{=}CH_2 \xrightarrow{Br_2} RCHBr\text{-}CH_2Br \xrightarrow{KOH} RCH{=}CHBr \xrightarrow{NaNH_2} RC{\equiv}CH \quad (1)$$

$$R\text{-}CO\text{-}CH_2R^1 \xrightarrow{PCl_5} R\text{-}CCl_2\text{-}CH_2R^1 + R\text{-}CCl{=}CHR^1 \xrightarrow{Base} RC{\equiv}CR^1 \quad (2)$$

$$RCl \xrightarrow{CH_2=CHCl} RCH_2CHCl_2 \xrightarrow{Base} RC{\equiv}CH \quad (3)$$

$$RCHO \xrightarrow{Ph_3P=CHX} RCH{=}CHX \xrightarrow{Base} RC{\equiv}CH \quad (4)$$

$$RCHO \xrightarrow{CBr_4\ \ Ph_3P} RCH{=}CBr_2 \xrightarrow{Base} RC{\equiv}CH \quad (5)$$

$$RCHO \xrightarrow{LiCHCl_2} RCH{=}CCl_2 \xrightarrow{Base} RC{\equiv}CH \quad (6)$$

$$RCBr_2\text{-}CHBr_2 \xrightarrow{Zn} RC{\equiv}CH \quad (7)$$

$$RR^1CH{=}CHX \xrightarrow{Base\ (rearrangement)} RC{\equiv}CR^1 \quad (8)$$

B. Introduction to Acetylenic Group with Metal Acetylide and Acetylenic Compounds

Acetylenic Grignard reagents of the type RC═CMgX or alkalimetal acetylides of RC═CM, where M denotes Li, Na, or K, are widely used for the preparation of acetylenic compounds. Acetylenic Grignard reagents are normally prepared in ethereal solvents at ambient temperatures, or at reflux temperatures under atmospheric pressure, by replacement with other Grignard reagents. However, their reactivity is sometimes lower than their corresponding alkalimetal acetylides, subsequently their application is restricted in some cases. On the other hand, acetylenic Grignard reagents have an advantage for reaction

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The acidity of the acetylenic hydrogen varies with the R-group [10], and higher acidity facilitates the displacement reactions. The reaction is especially fast for alkoxy-acetylenes and slow for compounds with a side chain at a position close to an ethynyl group [11]. The relative pK_a for acetylenes has the following trend, with substitution [Eq. (14)].

$$\text{pKa: } RC{\equiv}CH > HC{\equiv}CH > RCH{=}CHC{\equiv}CH > RC{\equiv}C{-}C{\equiv}CH = ArC{\equiv}CH \quad (14)$$

The reaction between 1-hexyne and various Grignard reagents, RMgX, has been studied extensively, and the rate has been measured by using gas evolution and electrochemical methods at certain time intervals (Table 1). The rate of reaction decreases in the order of R: allyl- > iPr- > Et- > Pr- > Ph- > Me-, and X: Cl > Br > I [12].

The reaction with diethylmagnesium is accelerated, to a great extent, and the correlation to the decomposition potential of Grignard reagents has been pointed out [13]. The reaction rate tends to decrease with the higher basicity of solvents employed, but the difference is not large [14]. The difference in the solubility of acetylenic Grignard reagents formed by displacement frequently affects the subsequent reactions (Table 2). The addition of amines (such as triethylamine) accelerates these reactions considerably (Table 3) [15].

In fact, the solubility of certain acetylenic Grignard reagents in diethyl ether is low and, in some instances, oily matter separates from solution. In this case, diethyl ether may be replaced by another solvent with higher solubility, but oily or slurry-like Grignard reagents have little effect on the reaction processes. Tetrahydrofuran shows excellent solubility properties and is used extensively for the preparation of acetylenic Grignard reagents.

A similar displacement reaction can be conducted for acetylenic carbinol compounds by protecting the active hydroxyl group as tetrahydropyranyl ether or with addition of 2 Eq of ethylmagnesium bromide [Eq. (15); 17]. However, this reaction is often very slow

$$RR^1C(OH)C{\equiv}CH \xrightarrow{\text{Dihydropyran}} RR^1C(O\text{-THP})C{\equiv}CH \xrightarrow{\text{EtMgBr}} RR^1C(O\text{-THP})C{\equiv}C\text{-MgBr}$$
$$\xrightarrow{\text{2 EtMgBr}} RR^1C(OMgBr)C{\equiv}C\text{-MgBr} \quad (15)$$

Table 1 Relative Reactivity of 1-Hexyne with R-MgX (Reflux-Ether, 1-Hexyne/RMgX:1/1)

p-ClPhMgBr	6	EtMgI	71
MeMgI	6	EtMgBr	100
MeMgBr	6	EtMgCl	155
MeMgCl	16	*i*-PrMgBr	210
PhMgBr	25	(Et_2Mg)	300
PrMgBr	59	AllylMgBr	435
p-MePhMgBr	60		

Table 2 Relative Reactivity of 1-Hexyne with EtMgBr in Certain Ethers (1-Hexyne/EtMgBr, 10:1)

	i-Pr_2O	Bu_2O	Et_2O	THF	2-Me-THF
EtMgBr	155	130	110	105	37

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Table 3 Relative Reactivity of 1-Hexyne with RMgX in the Presence of Amines

	Addition Et_3N (mol)			
	0	0.25	0.5	1.0
EtMgBr (1 mol/L)	100	450	620	840
(0.5 mol/L)	48	210	340	520
EtMgI (1.0 mol/L)	(91)			
EtMgCl (1.0 mol/L)	160			240
MeMgBr (1.0 mol/L)	7	560	750	950
MeMgI (1.0 mol/L)	7	1000	1170	1350
Et_2Mg (0.5 mol/L)	300			300

	Amines (0.25 mol/RMgX)					
	t-$BuNMe_2$	(Et_3N)	Pr_3N	Me_2NEt	Py.	$PhNMe_2$
EtMgBr (1.0 mol/L)	606	(496)	243	144	126	124
EtMgI (1.0 mol/L)	1400	1010		269		

and, to accelerate it, cuprous chloride is added [18]. Highly active *i*-propylmagnesium bromide is occasionally used instead of ethylmagnesium bromide [19].

Although not accepted as general methods, the following direct or indirect methods of using halogeno acetylenes as starting materials have been proposed [20; Eqs. (16–22)].

$$\text{R-C}\equiv\text{C-X} \xrightarrow[\text{R : Alkyl, Aryl, Vinyl}\quad \text{X (reactivity) : I > Br > Cl}]{\text{Mg / THF (or Tetrahydropyran, Diethyleneglycol-dialkylether)}} \text{R-C}\equiv\text{C-MgX} \tag{16}$$

$$\text{Ph-C}\equiv\text{C-Cl} \xrightarrow[\text{X : Cl 27.6\%, Br 13.4\%, I 14.2\%}]{\text{MeMgX}} \text{Ph-C}\equiv\text{C-MgX} \xrightarrow{H_2O} \text{Ph-C}\equiv\text{CH} \tag{17}$$

$$\text{Ph-C}\equiv\text{C-Br} \xrightarrow{\text{MeMgBr / } Et_2O} \text{Ph-C}\equiv\text{C-MgBr} \xrightarrow{H_2O} \text{Ph-C}\equiv\text{CH (89\%)}$$
$$\xrightarrow{\text{MeMgBr / } CoCl_2\text{-}Et_2O} \text{Ph-C}\equiv\text{C-Me (62\%)} \tag{18}$$

$$\text{F-C}\equiv\text{CH} \xrightarrow{\text{2 R-MgBr}} \text{R-C}\equiv\text{C-MgBr} + \text{R-H} + \text{MgFBr} \tag{19}$$

$$\text{Br-C}\equiv\text{CH} \xrightarrow{\text{2 Et-MgBr}} \text{BrMg-C}\equiv\text{C-MgBr} + \text{Et-H} + \text{Et-Br} \tag{20}$$

$$\text{I-C}\equiv\text{C-I} \xrightarrow{\text{2 R-MgBr}} \text{BrMg-C}\equiv\text{C-MgBr} + \text{2 R-I} \tag{21}$$

$$\text{Na-C}\equiv\text{CH} \xrightarrow{\text{Et-MgBr / Nonane 85~95°C 2days}} \text{[Na-C}\equiv\text{CH : Et-MgBr]}$$
$$\xrightarrow{\text{Bu-MgBr / } Bu_2O\ 140°C} \text{Na-C}\equiv\text{C-MgBr} \tag{22}$$

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B. Ethynylmagnesium Halides, Bis(halogenomagnesium)-acetylene

Of all acetylenic Grignard reagents, ethynylmagnesium bromide HC≡CMgBr is the most important reagent. Ethynylmagnesium bromide is prepared by the reaction of acetylene with ethylmagnesium bromide in diethyl ether [21], or in diethyl ether–benzene, under 1.5 atm of acetylene with vigorous stirring [22]. However, formation of monosubstituted ethynylmagnesium bromide under these conditions has been rejected by many studies performed since then. In fact, this reaction yielded an insoluble oily product in diethyl ether that was later found to be acetylene dimagnesium bromide BrMgC≡CMgBr. These Grignard reagents were soluble in certain solvents, such as chloroform [23] and methylal [24], but they were not considered to be practical. However, acetylene dimagnesium bromide has been useful to prepare several disubstituted acetylene derivatives.

Today, tetrahydrofuran is used almost exclusively as a solvent for preparation of ethynylmagnesium bromide, because the Grignard reagent is highly soluble in this solvent. In practice, ethynylmagnesium bromide can be obtained by adding a tetrahydrofuran solution of ethylmagnesium bromide, dropwise, into a 30°C reaction vessel that bubbles in acetylene into tetrahydrofuran at the rate of consumption [25]. For the synthesis of acetylene dimagnesium bromide, the temperature must be raised to 40–50°C [26]. The tetrahydrofuran solution of ethynylmagnesium chloride can be prepared by the reaction of acetylene with methylmagnesium chloride or butylmagnesium chloride and is used successfully for the reaction involving trimethylchlorosilane [27]. When methylmagnesium chloride is employed as a reagent, gaseous acetylene can be introduced directly into the tetrahydrofuran solution of the Grignard reagent, by properly controlling the temperature [28]. Since acetylene has active hydrogens on both sites, disubstituted acetylene dimagnesium halides tend to increase by disproportionation in the course of the synthetic process or in the subsequent reactions involving the ethynyl Grignard reagents [Eqs. (23–26)].

$$HC{\equiv}CH \xrightarrow{EtMgBr} HC{\equiv}C\text{-}MgBr + Et\text{-}H \qquad HC{\equiv}C\text{-}MgBr \xrightarrow{EtMgBr} BrMg\text{-}C{\equiv}C\text{-}MgBr + Et\text{-}H \tag{23}$$

$$2\ HC{\equiv}C\text{-}MgBr \longrightarrow BrMg\text{-}C{\equiv}C\text{-}MgBr + HC{\equiv}CH \qquad BrMg\text{-}C{\equiv}C\text{-}MgBr \longrightarrow MgBr_2 + MgC_2 \tag{24}$$

$$HC{\equiv}C\text{-}MgBr \xrightarrow{RX} RC{\equiv}CH + MgXBr \qquad RC{\equiv}CH \xrightarrow{HC{\equiv}C\text{-}MgBr} RC{\equiv}C\text{-}MgBr + HC{\equiv}CH \tag{25}$$

$$BrMg\text{-}C{\equiv}C\text{-}MgBr \xrightarrow{2RX} RC{\equiv}CR + 2MgXBr \qquad RC{\equiv}C\text{-}MgBr \xrightarrow{RX} RC{\equiv}CR + MgXBr \tag{26}$$

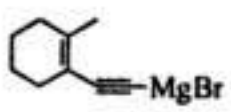
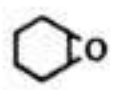
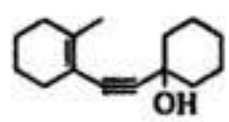
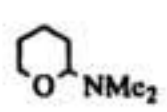
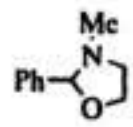
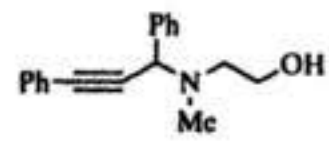
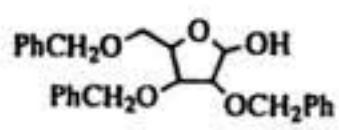
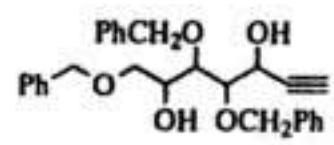
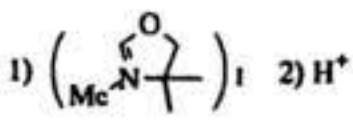
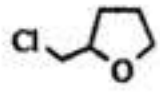
IV. REACTIONS OF ACETYLENIC GRIGNARD REAGENTS

In general, acetylenic Grignard reagents RC≡CMgBr are low in reactivity compared with other Grignard reagents. However, they are capable of participating in the usual Grignard reactions and are widely used for producing useful organic chemical substances (Table 4).

Some examples of the lower reactivity of acetylenic Grignard reagents are the 1,2-addition reactions involving benzonitrile [29], and nucleophilic substitution reactions with halogen compounds that are limited to those highly reactive compounds, such as

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Table 4 Reaction of Acetylenic Grignard Reagents

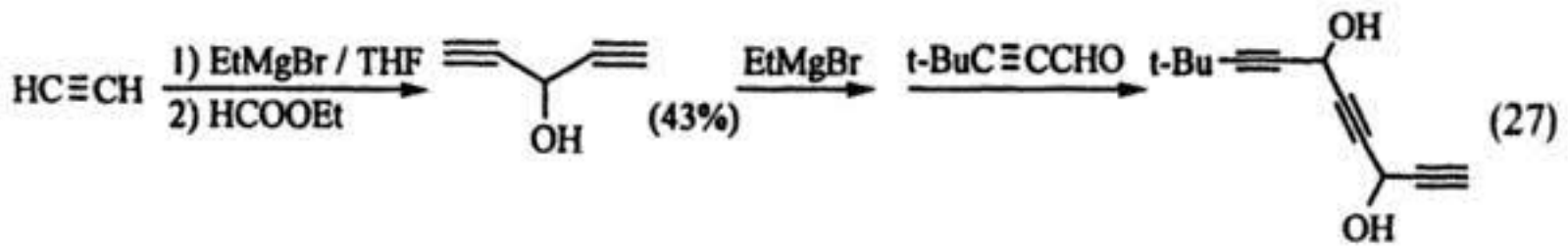
No.	Grignard reagents	Reactants	Products	Yield	Ref.
1	HC≡CMgBr	PhCH=CHCHO	PhCH=CHCH(OH)C≡CH	(69%)	[35]
2	t-BuC≡CMgBr	HCHO	t-BuC≡CCH$_2$OH	(70%)	[37]
3	CH$_2$=CHC≡CMgBr	Me$_2$CO	CH$_2$=CHC≡CC(OH)Me$_2$	(53%)	[38]
4	Me$_2$C(OMgBr)C≡CMgBr	HCOOEt	Me$_2$C(OH)C≡CCH(OH)C≡CC(OH)Me$_2$		[41]
5	BuC≡CMgBr		BuC≡CCH$_2$CH$_2$OH	(81%)	[53]
6				(75%)	[55]
7	HC≡CMgBr		HC≡CCH(NMe$_2$)C$_4$H$_8$OH	(96%)	[59]
8	PhC≡CMgBr			(53%)	[60]
9	HC≡CMgBr				[61]
10	BuC≡CMgBr	CH(OEt)$_3$	BuC≡C-CHO	(83%)	[62]
11	BrMg-C≡C-MgBr	CH(OEt)$_3$	(EtO)$_2$CHC≡CCH(OEt)$_2$		[66]
12	BuC≡CMgBr	Me$_2$NCHO	BuC≡C-CHO	(50%)	[68]
13	PhC≡CMgBr	 2) H$^+$	PhC≡C-CHO	(51%)	[69]
14	MeC≡CMgBr	PhOCMe(OEt)$_2$	MeC≡CCMe(OEt)$_2$	(71%)	[70]
15	BuC≡MgBr	CO$_2$	BuC≡C-COOH	(72%)	[72]
16	(BuC≡C)$_2$Mg	CO$_2$	BuC≡C-COOH	(73%)	[74]
17	BuC≡CMgCl	(MeCO)$_2$O	BuC≡C-COMe	(98%)	[75]
18	PhC≡CMgBr	Ph-NCO	PhC≡C-CONHPh	(90%)	[81]
19	PhC≡CMgBr	1) ClCH$_2$-CO-NCO 2) NaOH / MeOH	PhC≡C-CONH$_2$		[82]
20	PhC≡CMgBr	p-TsOC$_2$H$_4$Cl	PhC≡CCH$_2$H$_4$Cl	(46%)	[83]
21	BuC≡CMgBr	MeSO$_2$-OCH$_2$C≡CBu	BuC≡C-CH$_2$C≡CBu	(78%)	[86]
22	PhC≡CMgBr	Ph$_2$CHCl	PhC≡C-CHPh$_2$	(80%)	[88]
23	PhC≡CMgBr			(35%)	[89]

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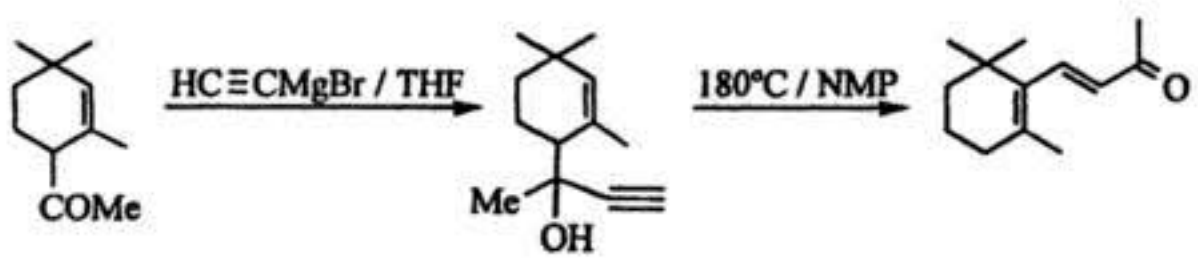
triphenylmethylchloride [30]. Although allylic halides or propargylic halides react with other common Grignard reagents without the addition of catalyst, they do not react with acetylenic Grignard reagents unless a catalyst, such as cuprous chloride, is present [31]. In a similar way, acetylenic Grignard reagents do not react with metal halides, such as cadmium chloride, to form cadmium acetylide. Nevertheless, they are useful reagents for reactions with highly reactive compounds, such as acid chlorides.

A. 1,2-Addition Reactions with Carbonyl Compounds

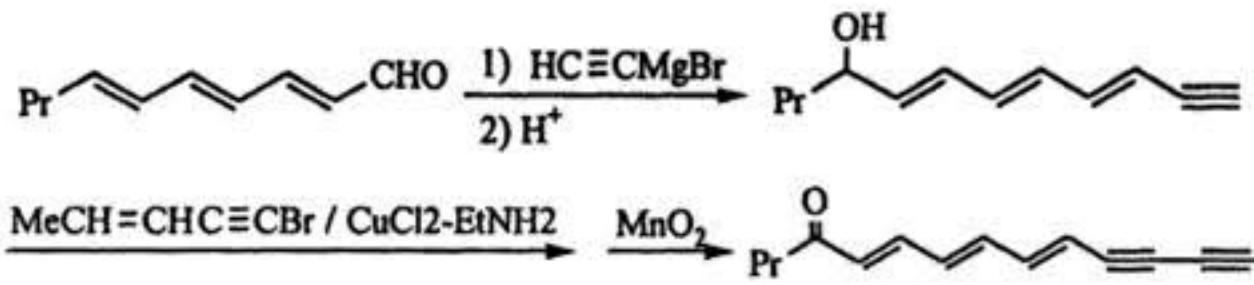
Acetylenic Grignard reagents react readily with aldehydes or ketones to form acetylenic alcohols (see Table 4, entries 1–4) [32–45]. This alcohol synthesis is one of the most important processes in the acetylenic Grignard reactions and is used for the production of various pharmaceutical and agrochemical compounds. The acetylenic alcohols formed are further converted to other functional groups and are used for the total synthesis of natural organic substances. Almost all carbonyl compounds, including alky, aryl, cycloalkyl, and heterocyclic compounds, can be employed without exception for this reaction. This Grignard process is particularly effective for carbonyl compounds that are unstable with base, for example, α-tetralones or α-halogenocarbonyl compounds [32,33]. The reaction of carbonyl compounds with acetylene dimagnesium bromide yields the corresponding symmetric acetylenic glycols in one step and is used for preparation of poly-ynes [Eqs. (27–29); 34,40,42,43].



(27)

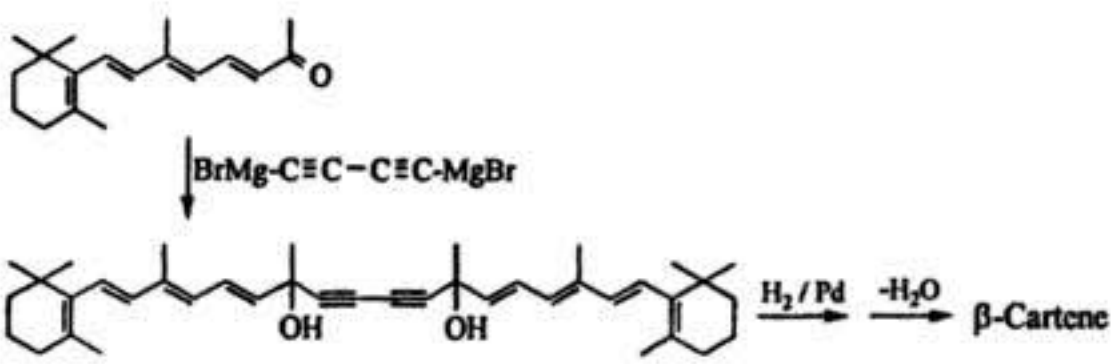


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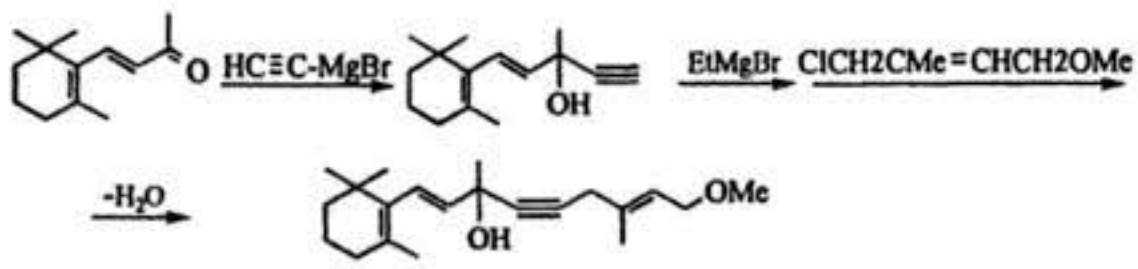
(29)

Acetylenic Grignard reagents are effective for reaction with conjugated compounds such as β-ionone, which is an important starting material for the preparation of carotenoids that readily undergoes enolation under basic conditions. Some examples of synthetic processes are given [Eqs. (30–33); 46–49].

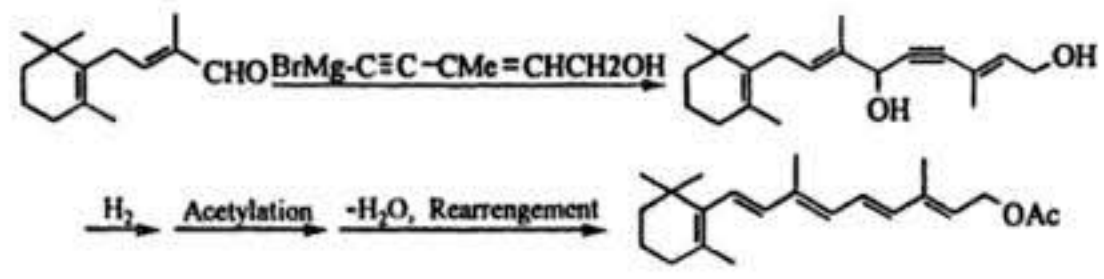


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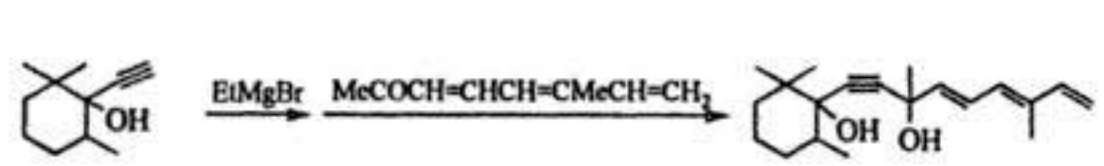
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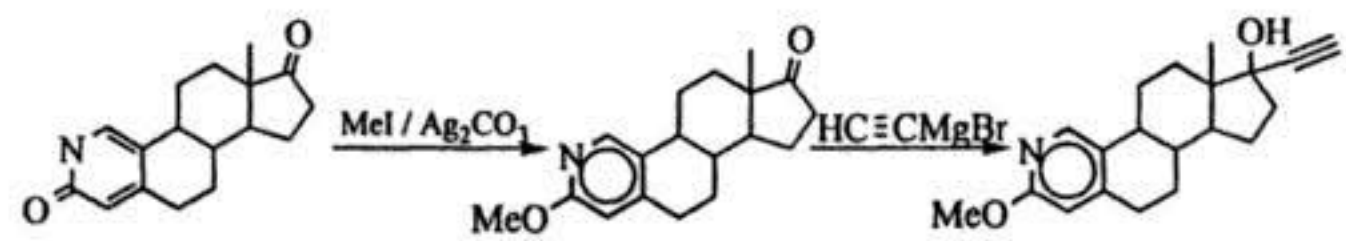


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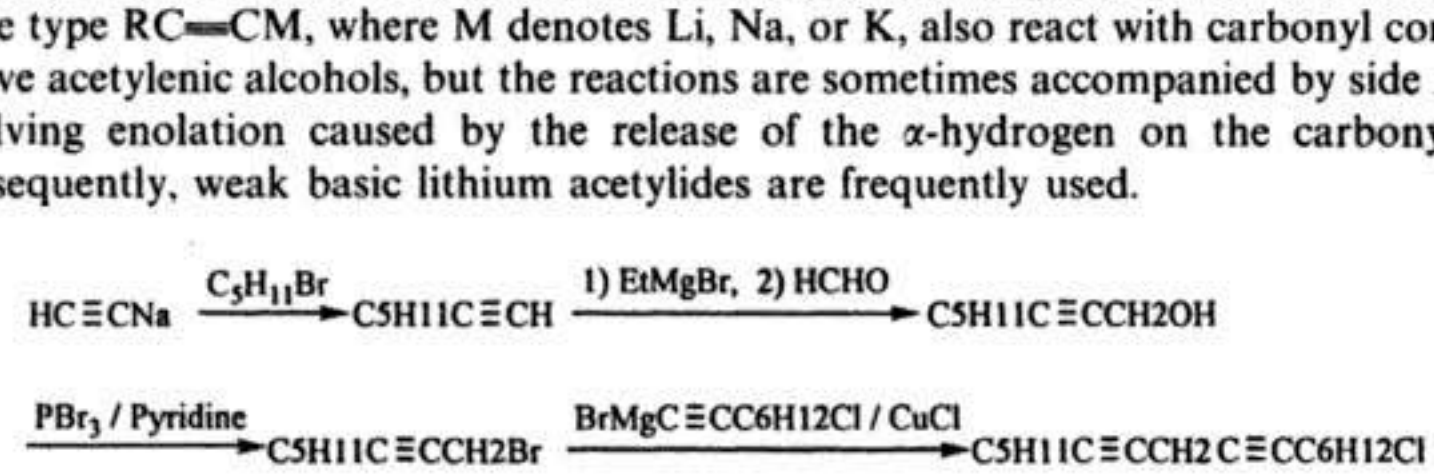
(33)

The Grignard ethynylation of a carbonyl group is frequently used as a simple method of preparation for steroids, as an alternative to processes involving sodium acetylide in liquid ammonia or acetylene in potassium *t*-butoxide [Eq. (34); 50].



(34)

Synthesis of asymmetric acetylenic compounds can be made by adding a functional group to a monosubstituted acetylenic compound and then converting to the disubstituted acetylenic compound by Grignard reactions [Eq. (35); 51,52]. Other alkali metal acetylides of the type RC≡CM, where M denotes Li, Na, or K, also react with carbonyl compounds to give acetylenic alcohols, but the reactions are sometimes accompanied by side reactions involving enolation caused by the release of the α-hydrogen on the carbonyl group. Consequently, weak basic lithium acetylides are frequently used.



(35)

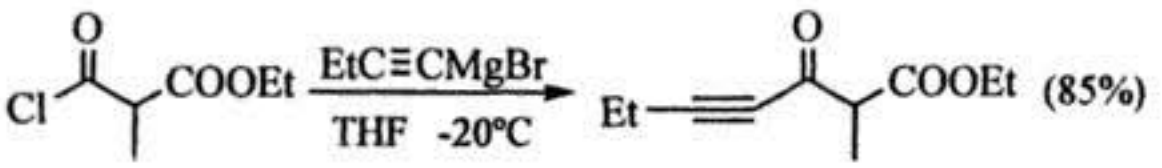
B. Nucleophilic Addition to Epoxy Compounds

As expected, the ring-opening addition of epoxy compounds with acetylenic Grignard reagents gives acetylenic alcohols. Ethylene oxide, having the simplest epoxy structure, reacts readily with acetylenic Grignard reagents to form β-hydroxyethyl acetylenic alcohols, in which the number of carbon atoms is increased by two [53,54]. This reaction has also been successfully applied to an epoxicyclohexane, or an epoxide on steroid rings (see Table 4, entries 5 and 6) [Eqs. (36) and (37); 55,57,58].

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formate (ClCOOEt) give carboxylic esters RC≡CCOOEt [71,72]. For these reactions, better results were obtained with lithium acetylides RC≡CLi [73]. Good product yields were also obtained with reactions of dialkynyl magnesium compounds in dioxane (see Table 4, entries 15 and 16) [74].

Acetylenic ketones can be prepared in moderate yield by the reaction of acetylenic Grignard reagents with acid chlorides or anhydrides [Eq. (41); 75–78]. Alkynyl magnesium chloride reacts with acetic anhydride to give acetylenic ketones in good yield (see Table 4, entry 17).



(41)

The oxidation of α-oxyacetylene, which results from the reaction between acetylenic Grignard reagents and carbonyl compounds, readily gives acetylenic ketones and has many applications [76]. Generally speaking, for the preparation of ketones from acid chlorides, zinc compounds may give better results. Trimethylsilyl acetylene compounds of the type $RC{=}CSiMe_3$, which are synthesized by the Grignard method, undergo a Friedel–Crafts reaction with acid chlorides to form acetylenic ketones in good yield, and this process is widely used as a simplified route to acetylenic ketones [Eq. (42); 79].

$$BuC{\equiv}CMgBr \xrightarrow{Me_3SiCl} BuC{\equiv}CSiMe3 \xrightarrow{MeCOCl - AlCl_3 / CS_2} BuC{\equiv}C\text{-}CO\text{-}Me\ (75\%) \quad (42)$$

Isocyanates (RNCO) and isothiocyanates (RNCS) also react with acetylenic Grignard reagents to give the corresponding substituted acid amides (RC≡CCONHR′) and thioamides (RC≡CCSNHR′) [80,81]. The reaction of chloroacetyl isocyanate ($ClCH_2CONCO$) and the Grignard reagents, followed by hydrolysis, yields acid amide compounds directly (see Table 4, entries 18 and 19) [82].

E. Nucleophilic Substitution Reactions

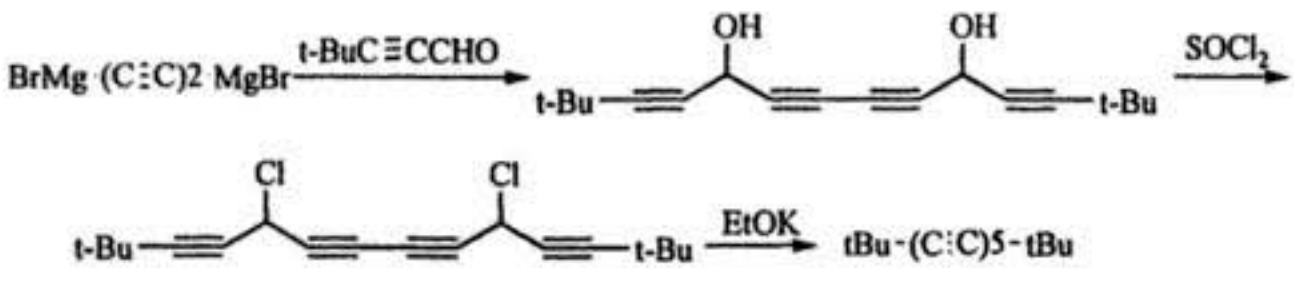
The reactivity of acetylenic Grignard reagents is lower than that of alkali metal acetylides for synthesis of acetylenic hydrocarbons by nucleophilic substitution reactions. However, good results were obtained when alkyl *p*-toluenesulfonates, alkylmethane sulfonates, or alkylsulfonates were used [83–87]. In general, coupling reactions do not occur between acetylenic Grignard reagents and alkyl halides, but if highly reactive halides, such as triphenylmethyl chloride, benzhydryl chloride, or 2-furfuryl chloride, are used, the corresponding coupling products are obtained [88,89]. For coupling of less reactive alkyl halides, alkalimetal acetylides that are prepared by metallation with *n*-butyllithium in tetrahydrofuran are used in place of the Grignard reagents (see Table 4, entries 20–23).

The reactions of acetylenic Grignard reagents with α-haloethers that have a highly reactive halogen, such as chloromethyl ethers [90–92], or 2-chlorotetrahydropyran [93], result in the expected coupling products (see Table 4, entries 24–26). Chloroformamidines [94], chlorotriazine [95], or chlorooximes [96] react with the acetylenic Grignard reagents readily. The reaction between dibromo derivatives of cyclooctatetraene by phenyl-acetylenicmagnesium bromide form the corresponding conjugated long-chain coupling products [Eqs. (43) and (44); see Table 4, entries 27, 28; 94,97].

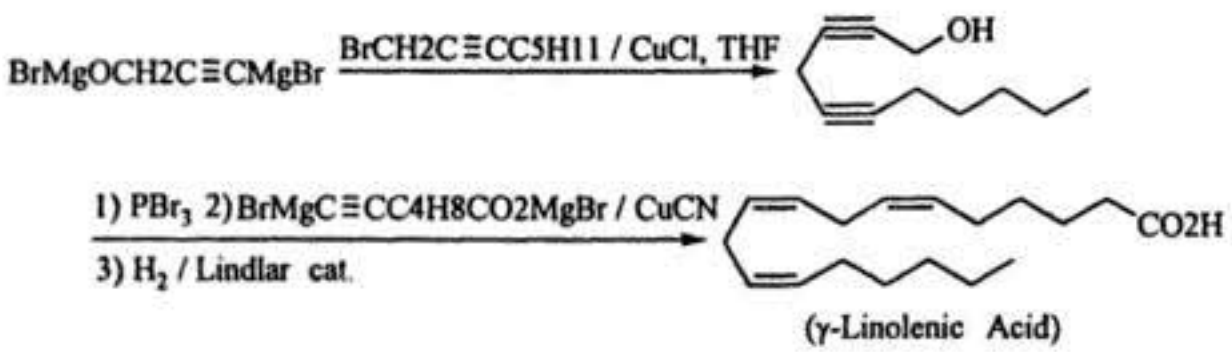
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For example, the treatment of 1,4-dichloro-2-butyne with sodium hydroxide results in diacetylene (HC≡C—C≡CH) in good yield (see Table 4, entry 39).

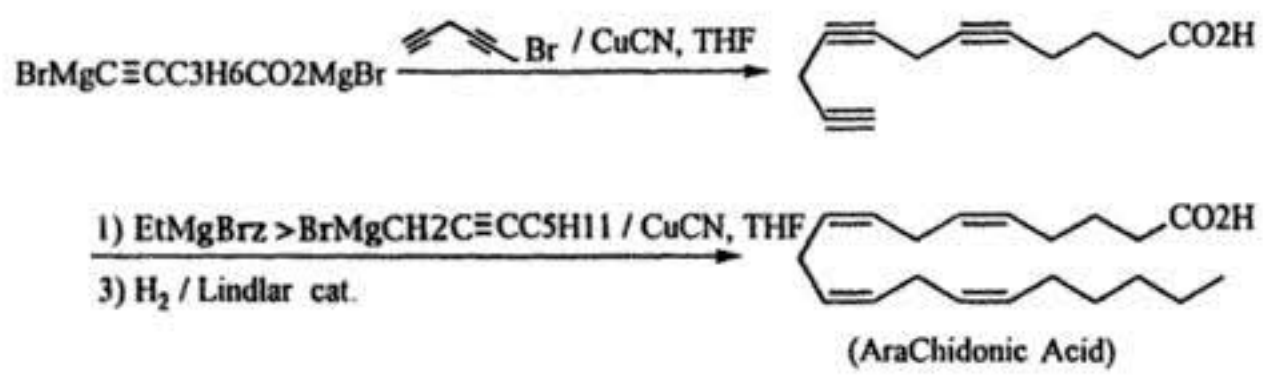
The reactions involving the generation of acetylenic bonds or extension of unsaturated bonds are extremely useful in chemical synthesis of unsaturated alcohols, carboxylic acids, and poly-yne acetals [Eq. (47); 125]. For the preparation of essential fatty acids, extension of propargyl units, followed by hydrogenation in the presence of Lindlar catalyst, will result in the efficient formation of all *cis*-type fatty acids [Eqs. (48) and (49); 126,127].



(47)



(48)



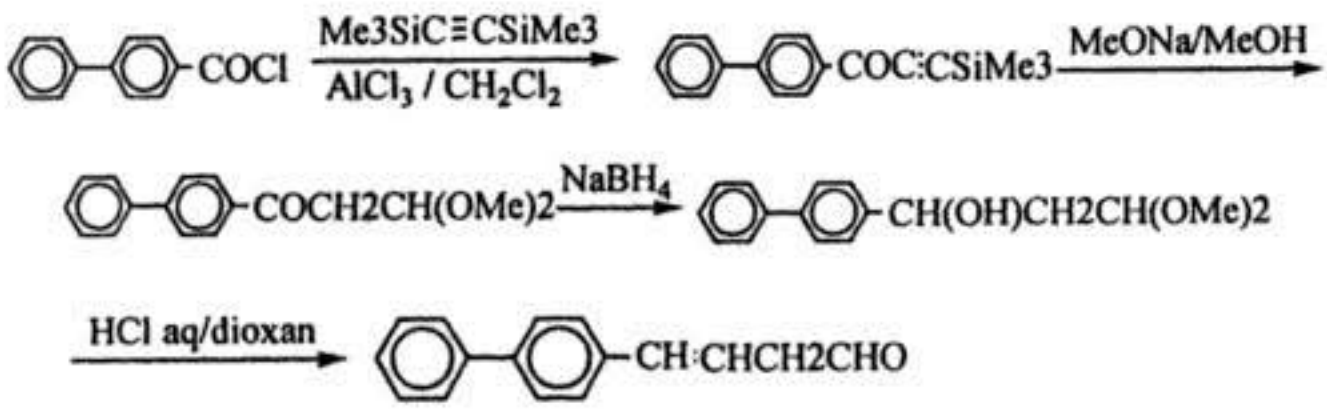
(49)

G. Organometallic Acetylene Compounds with Metal Halides

Several organometallic acetylene compounds are prepared by the replacement of acetylenic Grignard reagents or alkalimetal acetylides with metal halides (MX) where M is B, Al, Si, Ge, Sn, P, As, Sb, Cu, or Ag [128–131]. They are also synthesized by metallation of metal halides and R_3Al or R_2Hg (see Table 4, entries 40 and 41). Metal acetylides of the type $(RC{\equiv}C)_3B$ or $(RC{\equiv}C)_3Al$ are unstable and are isolated as complex with amines or ethers. Note that many of the precious metal acetylides are extremely explosive, and the appropriate precautions should be taken for their handling and storage.

Cuprous acetylide compounds, that are conveniently prepared from the corresponding Grignard reagent, are typically employed for various synthetic processes [Eq. (50); 132]. Alternatively, acetylenic silicone compounds are used for electronic applications, as well as for synthesis [Eq. (51); 133]. Trialkylsilyl acetylenic compounds ($RC{\equiv}CSiR'_3$), which are used frequently for introducing an acetylene group, are prepared by the reaction between trialkylsilyl halides and acetylenic Grignard reagents [Eqs. (52) and 53); 134,136–138] or alkalimetal acetylides (see Table 4, entry 42) [135]. They are also prepared by a one-step coupling reaction in the presence of catalytic amount of silver chloride and base [139].

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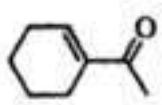
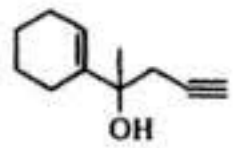
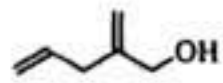
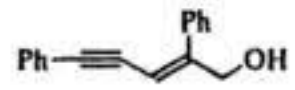
(57)

(58)

H. Reactions of Propargyl and Its Protected Grignard Reagents

Propargyl bromide ($HC{\equiv}CCH_2Br$) has three reactive sites—a primary bromide group, a triple bond, and an acetylenic hydrogen—making it an extremely versatile chemical intermediate. The bromine atom is highly reactive toward the formation of a Grignard reagent and is typically used in pheromone synthesis [Eq. (59); 148–151]. Propargyl alcohol ($HC{\equiv}CCH_2OH$) is also reactive; however, its hydroxyl group must be protected by either reacting the alcohol with 2.5-dihydro-2H-pyran or adding excess Grignard reagent to make the ether or Mg salt [Eq. (60); Table 5, entries 1 and 2; 152,153]. Propargyl alcohols of the type $RC{\equiv}CCH_2OH$ react with excess Grignard reagents in the presence of a cuprous halide catalyst to form, by addition, allylic alcohols $RR'C{=}CCH_2OH$ (see Table 5, entries 3 and 4) [154]. On the other hand, a Reformatsky reaction of propargyl bromide with carbonyl compounds in the presence of zinc gives acetylenic alcohols. For example, secondary acetylenic alcohols that are obtained by the reaction of propargyl bromide with aldehydes and zinc can be converted to acetylenic Grignard reagents which, after further

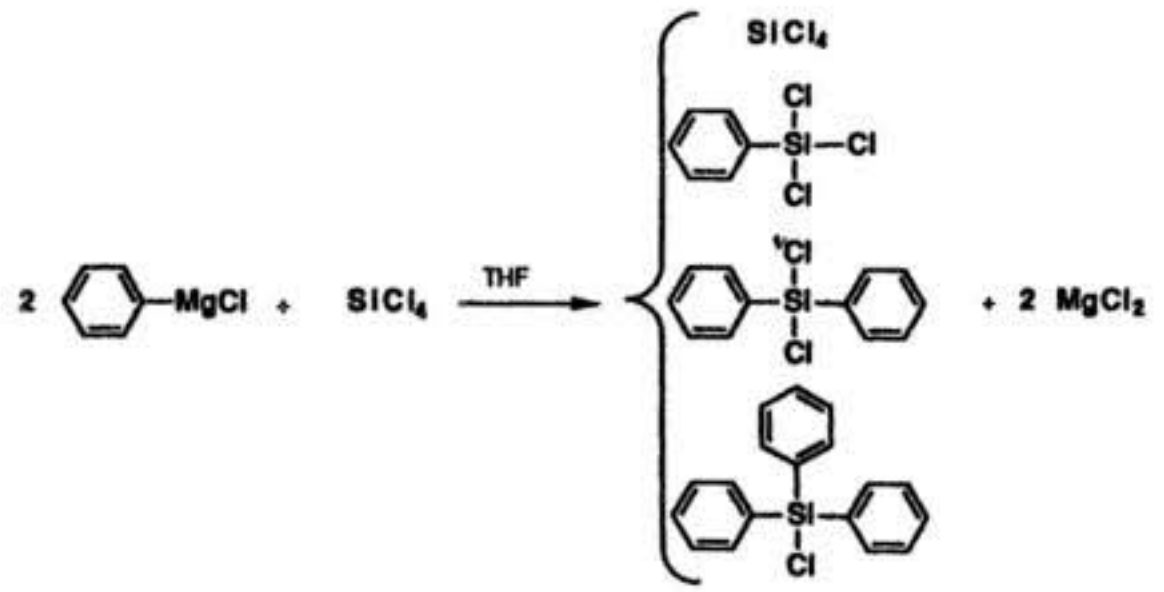
Table 5 Grignard Reaction of Propargylic Compounds

No.	Grignard Reagents	Reactants	Products	Yield	Ref.
1	$HC{\equiv}CCH_2MgBr$				[149]
2	$BrMg{-}C{\equiv}C{-}CH_2OMgBr$	$C_5H_{11}C{=}CCH_2Br/CuCl$		(83%)	[152]
3	$CH_2{=}CHCH_2MgCl$	$HC{\equiv}CCH_2OH/CuI$		(60%)	[154]
4	PhMgBr	$PhC{\equiv}CC{\equiv}CCH_2OH/CuI$		(69%)	[154]

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is to indicate where the Grignard reaction remains a viable technology for the preparation of silanes.

The generalized structure of an organosilane is $R_nSiX_{(4-n)}$, where X is an electron-withdrawing group, typically halide. In the simplest and earliest examples of the reaction chemistry, silicon tetrachloride was substituted by addition of Grignard reagents, such as ethylmagnesium bromide and phenylmagnesium chloride [1,3]. In addition, Grignard reagents substitute alkoxides (OR), siloxanes (O–Si), and nitriles (CN).



(1)

The general inability to accomplish clean, integral, partial substitution leading to organohalosilanes is the primary, but not the only, restriction of the Grignard process. The difficult separation of the corrosive, hydrolytically sensitive halosilanes from the reaction mixture, the relatively low product concentration, and the complex technology involved in removal of by-products, and the recycle of solvents pose significant design barriers in process scale-up and result in economic barriers for product acceptance [4]. If the target compound is tetraalkylsilane or equivalent, process control is not as critical, and water workup is allowed. Water workup is often facilitated by the addition of dilute hydrochloric acid, particularly when products are derived from alkoxysilanes.

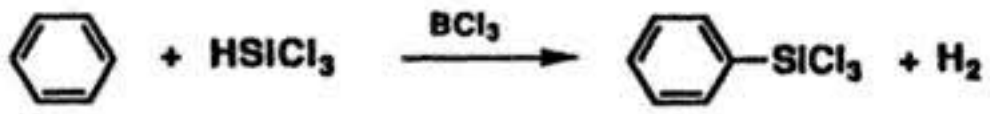
Alternative technologies that are used to generate organosilanes on a commercial scale are the Rochow-Müller direct process, which works best with low molecular weight alkyl and aryl halides [5]:

$$CH_3Cl + Si \xrightarrow[300\text{-}450^\circ]{Cu} \begin{matrix} MeSiCl_3 \\ + \\ Me_2SiCl_2 \\ + \\ Me_3SiCl \end{matrix} \qquad (2)$$

The hydrosilylation reaction, which is limited by the availability of hydridosilanes and olefins [6]:

$$RCH{=}CH_2 + HSiCl_3 \xrightarrow{Pt} RCH_2CH_2SiCl_3 \qquad (3)$$

The Barry process, which is generally limited by thermal stability of the aryl precursors [7,8]:



(4)

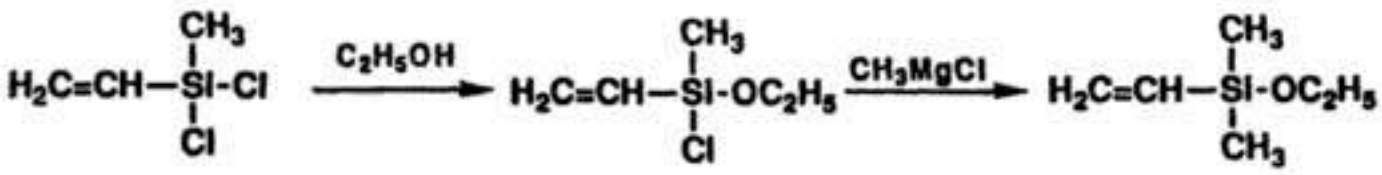
Although the production of organosilanes by non-Grignard processes is at least 1000 times greater than with Grignard processes, they remain essential for many of the specialty

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3. Substitution Versus Electron-Withdrawing Group

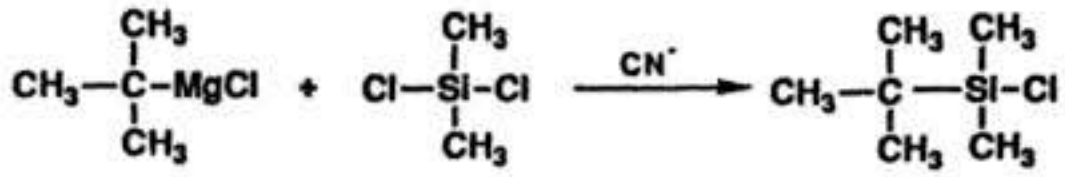
Si—CN > Si—Cl > Si—OR > Si—O—Si

For the substitution reaction, the alkoxy group of the silane is practically limited to linear radicals, notably methoxy and ethoxy. Although substitution of chlorides accounts for most transformations, the conversion of chlorides to other electron-withdrawing groups provides the ability to alter the degree of substitution in reactions [12,13]. In some reactions, the relatively slow reaction of an alkoxy group relative to a chlorine is exploited. For example, the target compound divinyltetramethyldisiloxane, an important endcapper in silicone chemistry, cannot be prepared in practical yield by the addition of 1 Eq of methyl Grignard to vinylmethyldichlorosilane, followed by hydrolysis. Alternatively, mono-alkoxylation of vinylmethyldichlorosilane increases the selectivity for substitution by only 1 mol of Grignard. (This process is utilized only when availability of dimethylchlorosilane for the alternate route of hydrosilyation of acetylene does not meet demand.)



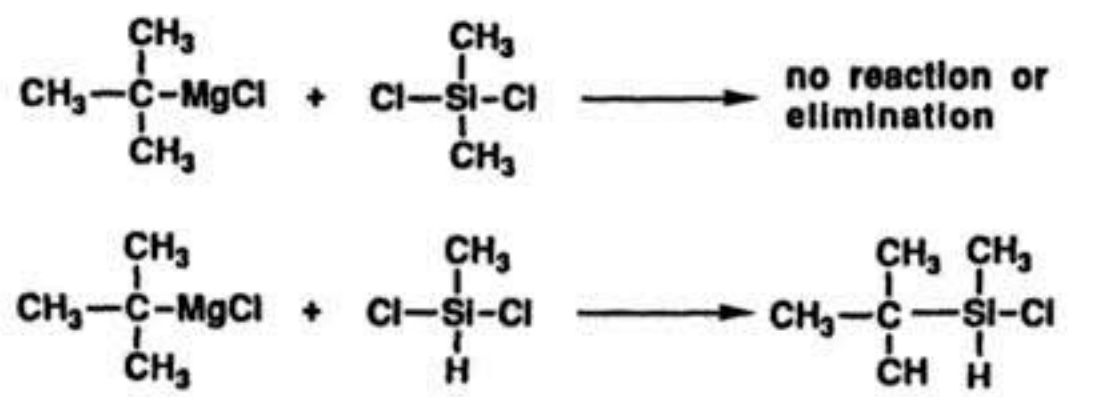
(6)

Control of substitution by partial alkoxylation is much less effective when an alkoxychlorosilane with a single organic substituent without steric bulk is involved. For methyldiisopropoxychlorosilane little selectivity between substitution of chloride versus isopropoxide was observed [14]. Although cyanosilanes are rarely used directly in Grignard reactions, the addition of 5 mol% of a cyanide salt often catalyzes Grignard substitution reactions [15–17]. Thiocyanate, another pseudohalogen, exerts a similar effect [18].



(7)

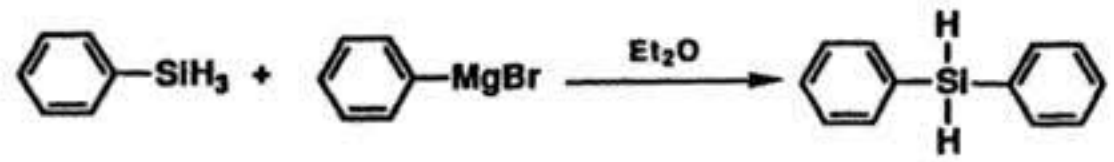
4. The Introduction of Si—H Facilitates Substitution of Halides



(8)

5. Reaction with Hydrides

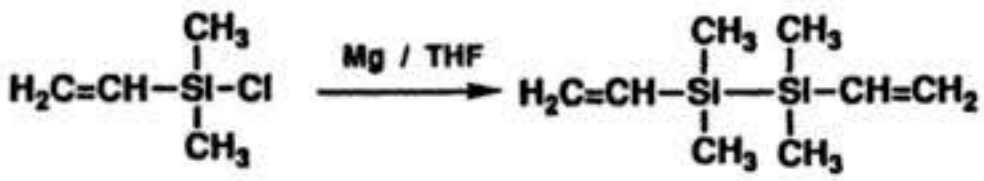
Despite their relative basicity, Grignard reagents do not generally react with hydrides. However, in tetrahydrofuran at elevated temperature and in the case of polyhydridosilanes in diethyl ether, the hydride can also be displaced [19].



(9)

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when partial substitution of the silane is required. An example of a product produced by the reverse addition is diphenylmethylmethoxysilane. In situ formation of the Grignard in the presence of silane is preferred when the Grignard has poor solution stability or poor solubility. An example of a product produced by the in situ process is allyltrimethylsilane. Some hydridosilanes and vinylic silanes are reactive in the presence of magnesium metal and diethyl ether, eliminating the in situ method as an option. After a brief induction period, trichlorosilane reacts violently with magnesium in ether and tetrahydrofuran. Phenylhydridochlorosilanes [23] and vinylmethylchlorosilanes [24] undergo reactions similar to Wurtz coupling with magnesium in tetrahydrofuran. For example, divinyltetramethyldisilane forms from vinyldimethylchlorosilane.



(14)

Commercially, continuous or continuous batch versions of these three protocols are generally employed [25].

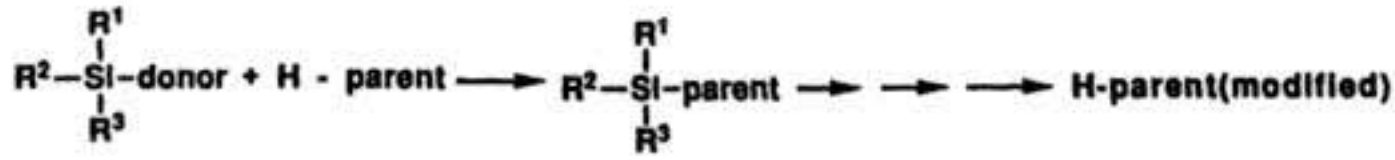
D. Process Chemistry Without Ethers

Chlorobenzene and bromobenzene can act both as reagents and solvents in the formation of multiply substituted phenylchlorosilanes such as triphenylchlorosilane [26,27]. The reactions run at elevated temperatures, 130–280°C, under atmospheric pressure.

Tetraethoxysilane and tetramethoxysilane can act as both solvents and reactants [28,29], or as cosolvents–catalysts in combination with benzene [30]. The use of tetraethoxysilane as a solvent–reactant has been important for a variety of continuous Grignard processes, since it allows an efficient recycle loop [31]. The continuous reactor portion of one such process disclosed in detail by Russian workers for diethyldiethoxysilane is depicted in Figure 1 [32] and may be contrasted with an earlier batch process [33]. Similarly, methylalkoxysilane and other alkylalkoxysilanes are reported as solvents–reactants in Grignard reactions, eliminating the need for ethereal solvents [34].

III. SILANE-BLOCKING AGENTS

Silane-blocking agents are employed to derivatize and protect various substrates during synthetic sequences. In a typical application, a silane-blocking group replaces an active hydrogen in a parent compound, a series of chemical transformations are performed on the modified parent compound, and finally, the blocking agent is removed.



(15)

The optimum blocking agent is one that derivatizes the parent readily, withstands the transforming reactions, is readily deblocked, and has reasonable economics. Grignard substitution is one of the reactions frequently performed on silane-blocked intermediates. The most common blocking group, the trimethylsiloxy group, is not resistant to attack from Grignard reagents. For example, blocked phenoxybromides react with themselves, forming none of the desired Grignard reagent.

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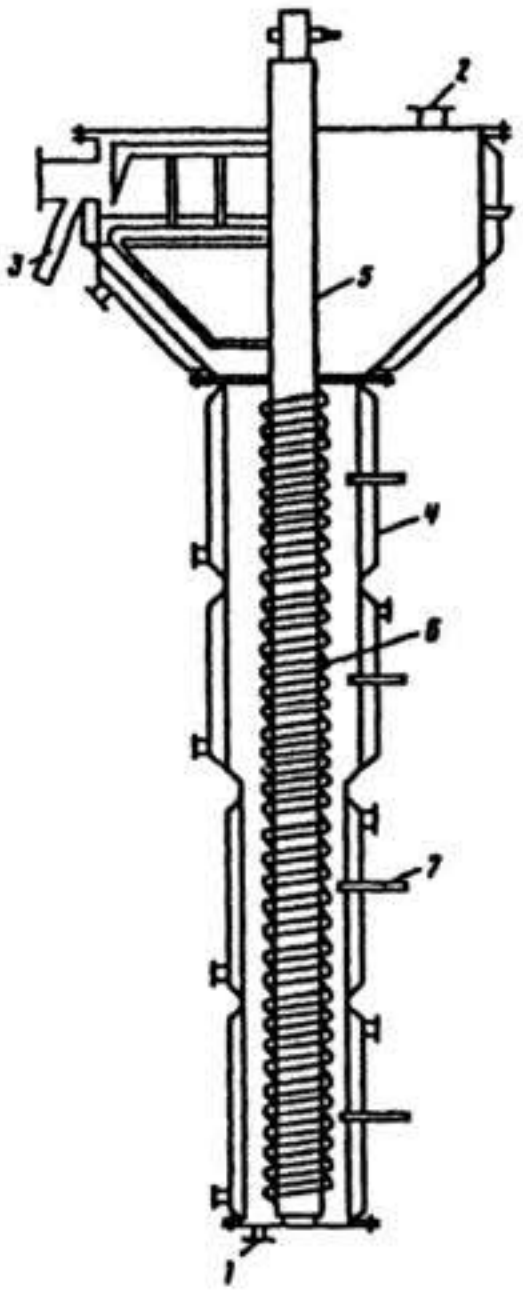
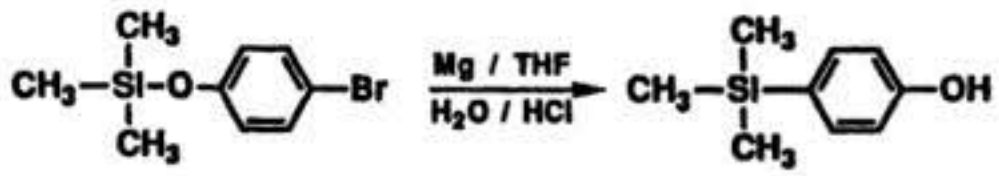


Figure 1 Continuous synthesis reactor for ethylalkoxysilanes: 1, input for reaction mixture; 2, input for magnesium; 3, output for product; 4, reactor body; 5, stirrer shaft; 6, spiral; 7, thermocouple well. (From Ref. 32)



(16)

The choice of proper blocking agent for Grignard chemistry depends on economics, reaction conditions, and acceptable conditions for deblocking the final product. As illustrated in Table 1, all but the least sterically hindered silane-blocking agents have reasonable resistance to attack by Grignards and alkyl lithiums [35]. However, the reactions are reported for mild conditions. For example, the $t^{1/2}$ for the reaction of trimethylsiloxy-*n*-butanol with methylmagnesium bromide at room temperature is 48 hr. In contrast, the reaction of trimethylsiloxy-*n*-butanol with methylmagnesium chloride in refluxing tetrahydrofuran is virtually complete within 30 min.

IV. CONCLUSION

Although it is no longer crucial to the silicone industry, Grignard chemistry remains a vital and versatile method for the production of organosilanes. The technology of organosilanes derived from Grignards has been refined to control degree of substitution,

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about the book . . .

This **useful** handbook provides the theoretical and **practical** information necessary to explore **new** applications for Grignard reagents on a day-to-day basis—presenting a **comprehensive** overview of current research activities in Grignard chemistry.

Surveying **specific** reactions and applications of Grignard chemistry, the ***Handbook of Grignard Reagents*** elucidates methods of Grignard reagent preparation from organic halides and olefins...examines both the formation and reaction mechanisms of Grignard reagents...summarizes the spectrum of reactions exhibited by Grignard reagents in one **convenient** source...defines general structure–reactivity relationships...considers the modification of Grignard reagent reactivity using catalysts...discusses **modern** instrumental methods of analysis, including infrared spectroscopy, magnetic resonance, and x-ray crystallography ...focuses on industrial-scale safe handling procedures...details topics of **special** interest such as the Barbier reaction, asymmetric synthesis using Grignard reagents, and Ziegler-Natta catalysis...and more.

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about the editors . . .

GARY S. SILVERMAN is Principal Scientist at Elf Atochem North America, Inc., King of Prussia, Pennsylvania. The major focus of his work for the past 10 years has been the modification of Grignard reagent reactivity. Dr. Silverman is the author or coauthor of numerous professional publications in his field of expertise. He received the B.Sc. degree (1979) in chemistry from the University of Florida, Gainesville, and the Ph.D. degree (1984) in organic chemistry from the University of South Carolina, Columbia.

PHILIP E. RAKITA is Business Manager at Elf Atochem Agri, S.A., Plaisir, France. The author or coauthor of over 35 research papers in the fields of organometallic chemistry, additives for plastics, and industrial chemistry, Dr. Rakita is a member of the American Chemical Society and the Association of Research Directors. He received the B.Sc. degree (1966) in chemistry from the Case Institute of Technology, Cleveland, Ohio, and the Ph.D. degree (1970) in organometallic chemistry from the Massachusetts Institute of Technology, Cambridge.

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