# Transition Metals in Organic Synthesis

## A Practical Approach

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Edited by

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# Preface

The use of transition metals in organic synthesis has increased so dramatically in recent years that the importance and value of this area of chemistry is now beyond question. The teaching of the practical aspects of this topic, however, has lagged behind developments in the research laboratories, perhaps because some of the techniques associated with this area of chemistry have not traditionally been dealt with in organic chemistry undergraduate laboratories. It was with this omission in mind that this volume in the Practical Approach in Chemistry Series was compiled. Many of the protocols are suitable for advanced undergraduate experiments or short projects, whilst others are designed to provide guidance to more experienced research workers interested in applying a specific area of transition metal chemistry to their own particular research problem.

The coverage of the use of transition metals in organic synthesis in this volume is necessarily highly selective. The areas included, however, have been chosen to provide insight into the practical techniques associated with both catalytic and stoichiometric applications of transition metal complexes. Each chapter contains many valuable practical 'tips' on specific reagents, reactions, and techniques.

The chapters in this volume have been written by scientists with considerable expertise and experience in both laboratory practice and University teaching. I am indebted to all of them not only for their enthusiasm at the start of the project but also for their subsequent dedication to what at times seemed like a rather distant goal. The chapter authors and I are very grateful to the following people, all of whom provided invaluable advice and comments on the protocols described: Waldemar Adam, Howard Alper, Angela Brickwood, Ann Cotterill, Timothy N. Danks, Stephen G. Davies, Vittorio Farina, Alan Ford, Mike Harris, Laurence M. Harwood, Mark E. Howells, Eric N. Jacobsen, Richard F. W. Jackson, Russell James, Suresh Kapadia, Tsutomu Katsuki, Steven V. Ley, Robin Lord, Tim Luker, Jason Macro, David J. Miller, Norio Miyaura, Christopher J. Moody, Andy Mulvaney, Gareth Probert, Greg P. Roth, K. Barry Sharpless, Kenkichi Sonogashira, Lee Spence, Elizabeth Swann, Julie S. Torode, Barry M. Trost, Simon Tyler, Motokazu Uemura, Edwin Vedejs and Tohru Yamada. Finally, we also thank Domenico Albanese, Stephen A. Benyunes, Stefano C. G. Biagini, Miguel Gama Goicochea, Siân L. Griffiths, Nathalie Guillo, Gary R. Jefferson, Liang K. Ke, Stephen P. Keen, Patrick Metzner, Mark A. Peplow, Ellian Rahimian and Adam T. Wierzchleyski for proofreading the manuscript at various stages of production.

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*Andrew F. Browning and Nicholas Greeves*

# 1

# Transition metal-promoted oxidations

SIMON WOODWARD

## 1. Introduction

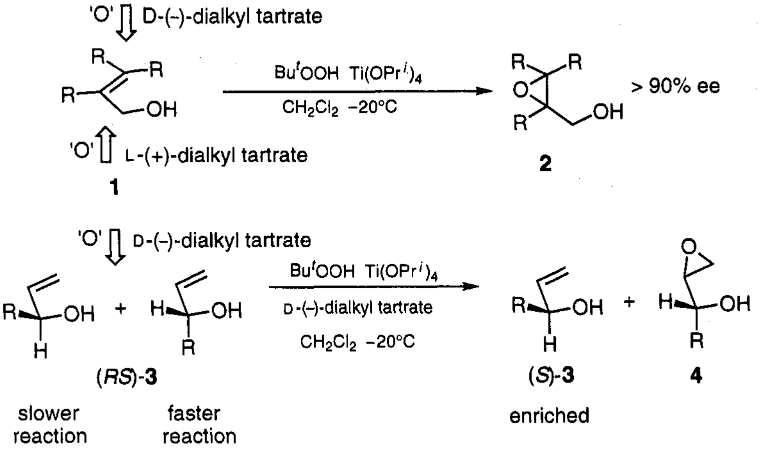
Few other areas of modern synthetic organic chemistry offer the diversity shown by homogeneous catalytic oxidation reactions. Practically all the transition metals have complexes showing oxidation activity; widely disparate mechanisms of action are standard.

It is the aim of this chapter to present in detail a few selected examples of useful organic transformations promoted by Group 4–11 (Ti–Cu) metals rather than to give a comprehensive listing of all possible transformations, as this information is available in several other excellent books.[1,2] The protocols are selected to demonstrate the most common oxygenation (addition of O atoms) or oxidation (removal of H atoms) pathways encountered in transition metal-promoted reactions of organic substrates.

**Caution!** As all oxidation reactions represent controlled highly exothermic reactions, and most involve the handling of toxic materials, all of the protocols in this chapter should be carried out in an efficient hood with explosion resistant sashes. Eye protection and disposable gloves must be worn. Clean reaction flasks are essential to avoid the accidental inclusion of materials known to bring about the rapid decomposition of high energy oxidants.

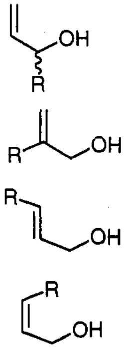
## 2. Group 4 metal-promoted oxidations: Sharpless–Katsuki asymmetric epoxidation

The generalised stereoselective epoxidation of allylic alcohols **1** by *t*-butyl hydroperoxide in the presence of titanium(IV) isopropoxide and tartrate esters to the epoxides **2** (Scheme 1.1) constitutes a seminal landmark in metal-mediated asymmetric oxidations. The catalytic version of this reaction is often the most effective procedure and is especially useful for the kinetic resolution of 1-substituted allylic alcohols, as in the transformation of **3** to **4**. The epoxidation of (*E*)-2-hexen-1-ol is demonstrated here to allow comparison with a stoichiometric protocol described in *Organic Synthesis*.[3]



**Scheme 1.1**

Full mechanistic details of asymmetric epoxidation (AE) reactions can be found in a comprehensive review.[4] The features of the transition state which leads to high enantioselectivities over such a wide range of allyl functions have been intensively studied,[5,6] but it is arguably more instructive from a practical point of view to indicate the behaviour of some commonly encountered substrates with this catalyst. Tri- and tetra-substituted allylic alcohols with their electron-rich double bonds react rapidly, even at −35 °C. 3-(*E*)-Monosubstituted allylic alcohols also react rapidly (1–4 h, as in Protocol 1) while other mono-substitution patterns dramatically slow down the reaction (10–50 h), necessitating the use of cryostatic cooling units. These reactivity patterns are summarised in Scheme 1.2.



1-substitution - kinetic resolution candidate, dicyclohexyl or dicyclododecyl tartrates preferred for highest ee

2-substitution - slow (10 h), catalytic reaction avoids epoxide ring opening, ee suffers (~85%) if R branched

(3*E*)-substitution - fast (1-4 h), very tolerant of R 1°, 2°, and 3° substituents all give high ee (>95%)

(3*Z*)-substitution - slow (24-48 h), ee suffers (25-95%) if R branched

**Scheme 1.2**

Although the AE reaction tolerates many functional groups, it is incompatible with $RCO_2H$, RSH, ArOH, $PR_3$, and most amines. If the substrate is free of these functions and the procedure fails, moisture contamination of the dialkyl tartrate or Bu$^t$OOH solution is usually to blame. The former should be distilled quickly below 100 °C (higher temperatures lead to tartrate polymerisation, resulting in lower product optical yields). The latter should be dried over a fresh supply of molecular sieves just before use. Cumene hydroperoxide may be substituted for Bu$^t$OOH in most AE reactions. Although its removal can complicate workup of the reaction mixture, its use normally results in slightly improved enantioselectivities.

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## Protocol 1.
## Preparation of (2*S*,3*S*)-3-propyloxiranemethanol. Catalytic Sharpless–Katsuki asymmetric epoxidation (AE) (Scheme 1.1)

**Caution!** Employ the standard precautions outlined in the introduction to this chapter for this reaction. Strong acids, transition metal salts, or metal syringe needles should **never** be added to concentrated Bu$^t$OOH stock solutions. Aliquots of Bu$^t$OOH remaining after use in reactions should **not** be returned to the stock solutions. 1,2-Dichloroethane should **not** be used as a solvent with Bu$^t$OOH, despite early recommendations.[7]

### *Equipment*

- Three-necked, round-bottomed flask (250 mL)
- Teflon-bladed overhead mechanical stirrer and Ŧ 24/40 sleeve adapter
- Low temperature thermometer and Ŧ 19/22 cone/screw thread adapter
- Ŧ 19/22 socket/cone adapter with T connection
- Well-insulated low-temperature bath
- Septa
- All-glass Luer syringes (2 mL and 20 mL)
- Needles (10 cm, 20 or 22 gauge)
- Pressure-equalising addition funnel (50 mL)
- Glass funnel
- Beaker (50 mL)
- Erlenmeyer flasks (3 × 50 mL)
- Source of dry inert gas (nitrogen or argon)
- Separating funnel (1 L)

### *Materials*

| | |
|---|---|
| • Dry dichloromethane,[a] *ca.* 120 mL total | **volatile, toxic at high concentrations** |
| • Activated powdered 4 Å molecular sieves, 4.0 g | **hydroscopic** |
| • Activated pelleted 4 Å molecular sieves, *ca.* 10 g | **hydroscopic** |
| • Titanium(IV) isopropoxide (tetraisopropyl orthotitanate) (FW 284.3), 1.5 mL, 1.45 g, 5.09 mmol (12.7 mol%) | **corrosive, moisture sensitive** |
| • Diethyl L-(+)-(*R*,*R*)-tartrate (FW 206.2), 1.27 g, 6.11 mmol (15.3 mol%) | **harmful** |
| • Anhydrous *t*-butyl hydroperoxide, 5.5 M in nonane,[b] 25 mL, 138 mmol | **oxidising agent, flammable** |
| • (*E*)-2-Hexen-1-ol (FW 100.2), 4.0 g, 40.0 mmol | **harmful** |
| • Iron(II) sulfate heptahydrate (FW 278.0), 29.9 g, 0.11 mol | |
| • L-(+)-(*R*,*R*)-Tartaric acid (FW 150.1), 9.9 g, 0.05 mol | |
| • Technical diethyl ether for extraction | **flammable** |

1. Clean all glassware, syringes, and needles sequentially in soap solution, water, and acetone. Allow the acetone to evaporate[c] and then dry every-

**Protocol 1.** *Continued*

thing in an electric oven (105°C) for at least 1 h. **Caution!** – Thoroughly dry the thermometer with paper tissues and a hair dryer just before use; do not over-heat it.

2. Rapidly assemble the glassware as in Fig. 1.1 and start the inert gas flow. Apply one drop of liquid paraffin to the sleeve adapter of the paddle stirrer, to ensure an air-tight fit. Rapidly weigh activated powdered 4 Å molecular sieves (4.0 g) into a small glass beaker. Add the molecular sieves to the flask using a funnel (lift it slightly to avoid air locks). Rinse in the residual amounts of molecular sieves left in the beaker with three 25 mL portions of dichloromethane.
3. Cap the remaining Ŧ 19/22 joint with a septum and cool the reaction mixture to about −20°C using an acetone/dry ice bath (the bath temperature will be about −23 to −25°C). If necessary increase the inert gas flow to avoid 'suck back' of the bubbler. From now on monitor the reaction periodically to ensure it is stirring at about −15 to −20°C, adding more dry ice if necessary.
4. Add 25 mL of stock 5.5 M *t*-butyl hydroperoxide to a 50 mL Erlenmeyer flask and add *ca.* 5 g of pelleted 4 Å molecular sieves to the solution. Cap the flask loosely with a septum or bung and set it aside to pre-dry the Bu$^t$OOH.
5. Using a Pasteur pipette, put diethyl L-(+)-(*R*,*R*)-tartrate (0.62 g, 3.01 mmol) into a 50 mL Erlenmeyer flask. Dilute it with 5 mL of dichloromethane and cap the flask with an air-tight stopper or bung.
6. Draw up 1.5 mL of titanium(IV) isopropoxide into a 2 mL syringe as shown in Fig. 1.2. Inject this into the reaction flask through the septum.
7. Using the 20 mL syringe transfer the L-(+)-(*R*,*R*)-tartrate solution to the reaction flask (keep the reaction temperature below −15°C). Wash any residual tartrate into the reaction mixture with a further 5 mL of dichloromethane using the syringe.
8. Using the 20 mL syringe, slowly add 20 mL of the pre-dried Bu$^t$OOH solution carefully keeping the reaction temperature in the range −20 ± 3°C. Allow the mixture to stir for 30 min at −20°C.[d] During this period weigh (*E*)-2-hexen-1-ol (4.0 g, 40.0 mmol) into a 50 mL Erlenmeyer flask. Add dichloromethane (20 mL) and some pelleted 4 Å molecular sieves to pre-dry the substrate. Cap the flask.
9. Change the septum for a 50 mL pressure-equalising dropping funnel (tap shut) and, using a Pasteur pipette, charge it with the (*E*)-2-hexen-1-ol solution. Rinse the Erlenmeyer flask with a further 5 mL of dichloromethane and pipette this into the dropping funnel.
10. Add the (*E*)-2-hexene-1-ol solution to the reaction mixture dropwise over a period of 20 min ensuring that the reaction mixture remains in the range −15 to −20°C.
11. Let the reaction stir at −15 to −20°C for 2 h, adding dry ice as required.

Completion of the reaction may be confirmed by TLC analysis if appropriate [Merck Kieselgel 60 $F_{254}$ plates, 7:3 hexane:ethyl acetate eluent, visualisation by $KMnO_4$ spray].

**12.** Let the mixture come to −10 °C. Meanwhile prepare a solution of 29.9 g of iron(II) sulfate heptahydrate and 9.9 g L-(+)-(*R,R*)-tartaric acid in water (90 mL) and chill this solution using an ice bath.

**13.** Add the chilled iron(II) solution to the reaction mixture once its temperature has reached −10 °C (**care!**).[e] Stir for 5 min at −10 °C and then continue stirring at room temperature until two layers are formed.

**14.** Transfer the mixture to a 1 L separating funnel, run off the lower dichloromethane layer, and retain it.[f] Extract the aqueous layer with two 50 mL portions of diethyl ether and combine these with the dichloromethane fraction. Remove the solvents with a rotary evaporator to give the crude wet product. This may be stored overnight in a freezer if necessary.

**15.** Wash out the reaction flask (it may be left wet) and add to it sodium chloride (5 g), sodium hydroxide (15 g), and water (50 mL). Set up the flask as in Fig. 1.1 but neglecting the low temperature thermometer and inert gas supply. Replace the acetone in the cooling bath with ice and some water. Stopper the remaining open joints.

**16.** Once the sodium hydroxide solution has cooled, add the crude epoxide dissolved in 50 mL of diethyl ether to the hydrolysis mixture and rinse any remaining epoxide left in the flask in with two 30 mL portions of diethyl ether. Let the reaction stir vigorously for 1 h.

**17.** Transfer the mixture to a 1 L separatory funnel and add water (50 mL). Separate the phases[f] (retaining both), and extract the aqueous phase with two 50 mL portions of diethyl ether. Combine the organic fractions and dry them with sodium sulfate.

**18.** Filtration and rotary evaporation of the filtrate yields (2*S*,3*S*)-3-propyloxiranemethanol as a pale oil contaminated with nonane (about 8.5 g). The nonane is removed by careful Kugelröhr distillation (25–60 °C, 8 mmHg), followed by the product as a colourless oil (b.p. 100–110 °C, 8 mmHg). About 3.5 g (75%) {$[\alpha]^{25}_{D}$ −46.6° (c 1.0, $CHCl_3$)} is obtained. A procedure is available for determining the optical purity of the product via its α-methoxy-α-(trifluoromethyl)phenylacetic acid ester (Mosher's ester).[3]

[a] Distilled from calcium hydride; each portion should be collected just before use.

[b] If the Aldrich product (41,806-4) is not available, this reagent may be prepared from aqueous 70% Bu$^t$OOH by known procedures;[8] toluene solutions can also be used. Commercial solutions of 3.0 M Bu$^t$OOH are available but can lead to inferior results[9] and therefore should be avoided. Similarly, Bu$^t$OOH solutions in decane may lead to a problematic distillation in the final step. Methods for determining the purity of *t*-butyl hydroperoxide are outlined in Protocol 2.

[c] Evaporation may be promoted by careful use of a hair dryer.

[d] This ageing of the catalyst is vital for high enantioselectivities and cannot be eliminated.

[e] **Caution!** For larger scale reactions the reaction mixture should be added to the stirred cold iron(II) sulfate solution to avoid the possibility of violent catalytic decomposition of the Bu$^t$OOH.

[f] If an emulsion forms, phase separation is promoted by filtration through Celite.

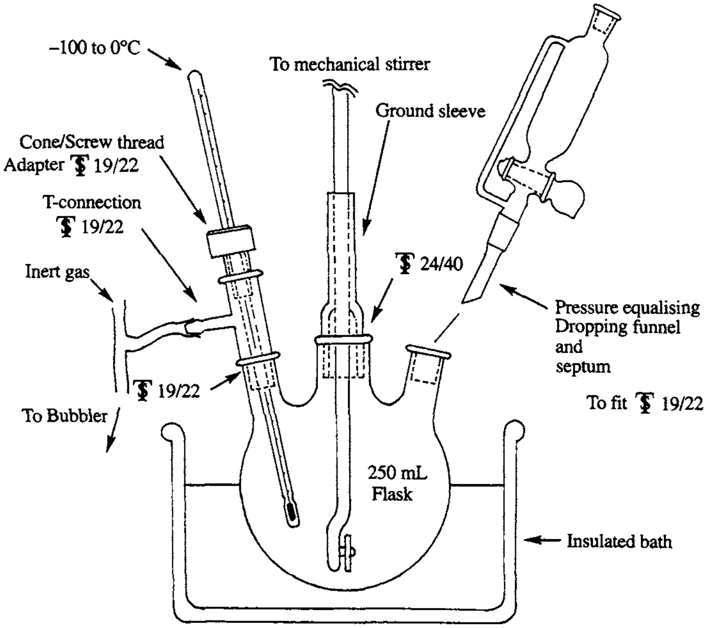

**Fig. 1.1** Assembled reaction apparatus for Protocols 1 and 3.

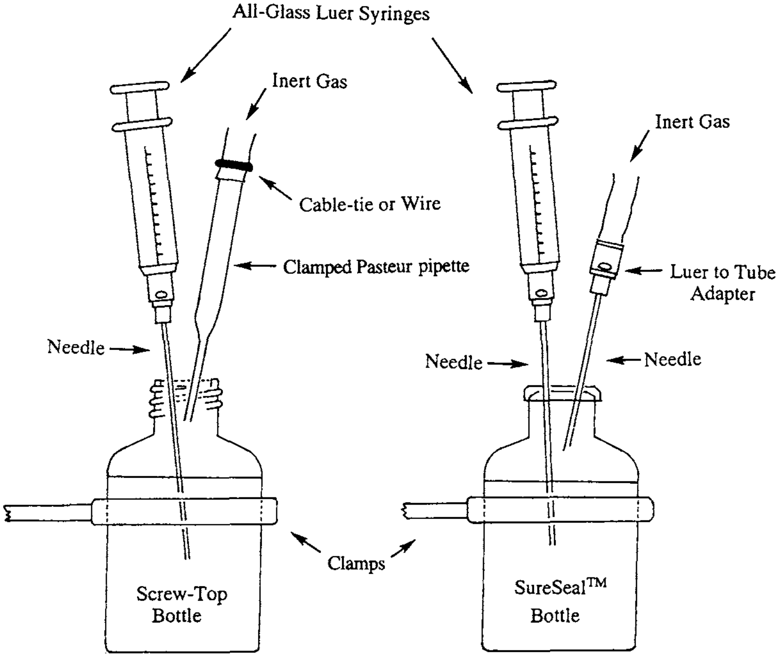

**Fig. 1.2** Collecting air- and moisture-sensitive liquids.

## Protocol 2.
## Determination of the molarity of *t*-butyl hydroperoxide samples[a][7]

**Caution!** Employ the standard precautions outlined in the introduction to this chapter for this reaction.

*Equipment*

- Erlenmeyer flasks (1 × 250 mL and 2 × 100 mL)
- Glass funnel
- Measuring cylinders (1 × 5 mL, 1 × 10 mL, and 1 × 100 mL)
- Electric hot air gun (paint stripper)
- An appropriate sized analytical pipette (0.25 mL for *ca.* 5 M $Bu^tOOH$)
- Appropriate sized volumetric flasks
- Graduated burette for titration

*Materials*

| | |
|---|---|
| • Sodium iodide, 11 g | **toxic** |
| • Isopropanol, *ca.* 300 mL | **toxic** |
| • Glacial acetic acid | **corrosive, malodorous** |
| • 0.1 M sodium thiosulfate | **toxic** |
| • Starch solution | |

1. Clean all glassware sequentially in soap solution, water, and acetone. Totally evaporate the acetone using a commercial hot air gun.
2. Dissolve 11 g of sodium iodide in 50 mL of isopropanol in a 100 mL Erlenmeyer flask by swirling the mixture and heating with the hot air gun.[b] Filter the solution into a fresh 100 mL Erlenmeyer flask. Put 10 mL of this solution in a 250 mL Erlenmeyer flask, and add glacial acetic acid (2 mL), and isopropanol (25 mL).
3. Accurately measure out a sample of *tert*-butyl hydroperoxide, containing no more than 2.5 mmol of active oxygen, using an analytical pipette and add this to the sodium iodide/acetic acid mixture. Bring the dark solution to reflux using the hot air gun until a constant colouration is attained (*ca* 30 sec).
4. Dilute the sample with 100 mL of distilled water and immediately titrate the liberated iodine with 0.1 M sodium thiosulfate. The endpoint is most easily visualised by addition of starch indicator (~ 1 mL) once a pale yellow colour is obtained. The blue colour disappears at the end point.
5. The concentration is calculated according to the equation: $[S \times M]/[2 \times (\text{mL of the sample})]$ = molarity of the $Bu^tOOH$ solution, where $S$ = mL of thiosulfate for the titration and $M$ = molarity of the thiosulfate solution.

[a] For *t*-butyl hydroperoxide solutions in toluene, an approximate molarity may be obtained from the $^1H$ NMR spectrum of the neat solution using the equation:

$$X/(0.1X + 0.32Y) = \text{molarity of the Bu}^t\text{OOH solution}$$

where $X$ = integration of *t*-butyl resonance and $Y$ = integration of toluene methyl resonance. However, this method is not as accurate as titration assays.

[b] Improved rates of dissolution may be attained by addition of small amounts of water; this does not affect the subsequent analysis.

## 3. Group 4 metal-promoted oxidations: asymmetric oxidation of sulfides

The original Katsuki–Sharpless system, with a titanium:tartrate ratio of ~1:1, is rather poor at the asymmetric conversion of sulfides to sulfoxides (enantiodifferential oxidation of one of the sulfur lone pairs in $R_2S$). Modification of the reaction procedure by addition of 1 equiv. of water and addition of extra tartrate ligands leads to an effective reagent for the stoichiometric oxidation of ArSMe species, although the structure of the active reagent is not known.[10,11] The sulfide $4\text{-MeC}_6H_4SMe$ **5** is a popular test substrate as its oxidation to (*R*)-**6** (Scheme 1.3) proceeds with high optical induction using natural tartrates; this is described in Protocol 3.[12] The strong binding of the product sulfoxides to the titanium oxidant precludes the development of catalytic protocols for these tartrate-mediated sulfide oxidations. However, switching to binaphthol-based ligands may offer a solution to this problem.[13,14]

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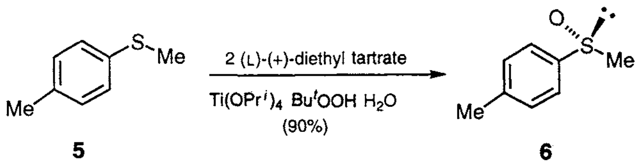
### Protocol 3.
### Preparation of (*R*)-methyl 4-tolyl sulfoxide (Structure 6). The modified Sharpless–Katsuki oxidation reagent (Scheme 1.3)

**Caution!** Employ the standard precautions outlined in the introduction to this chapter for this reaction. Strong acids, transition metal salts, or metal syringe needles should **never** be added to concentrated Bu$^t$OOH stock solutions. Aliquots of Bu$^t$OOH remaining after use in reactions should **not** be returned to stock solutions. 1,2-Dichloroethane should **not** be used as a solvent for Bu$^t$OOH, despite early recommendations.[7]



**5** **6**

**Scheme 1.3**

*Equipment*

- Three-necked, round-bottomed flask (250 mL)
- Teflon-bladed overhead mechanical stirrer and ₸ 24/40 sleeve adapter
- Low-temperature thermometer and ₸ 19/22 cone/screw thread adapter
- ₸ 19/22 socket/cone adapter with T connection
- Well-insulated low-temperature bath
- Septa
- All-glass Luer syringes (5 mL and 10 mL)
- Needles (10 cm, 20 or 22 gauge)
- Syringe (250 μL)
- Glass funnel
- Erlenmeyer flask (50 mL)
- Separating funnel (500 mL)
- Source of dry inert gas (nitrogen or argon)

## *Materials*

| | |
|---|---|
| • Dry dichloromethane,[a] *ca.* 100 mL total | **volatile, toxic at high concentrations** |
| • Titanium(IV) isopropoxide (tetraisopropyl orthotitanate) (FW 284.3), 1.8 mL, 1.7 g, 6.0 mmol | **corrosive, moisture sensitive** |
| • Diethyl L-(+)-(*R*,*R*)-tartrate (FW 206.2), 2.5 g, 12.1 mmol | **harmful** |
| • Anhydrous *t*-butyl hydroperoxide, 3.0 M in isooctane,[b] 2.2 mL, 6.6 mmol | **oxidising agent, flammable** |
| • Methyl 4-tolyl sulfide **5** (FW 138.2), 0.84 g, 6.00 mmol | **toxic, malodorous** |
| • Technical diethyl ether, for extraction | **flammable** |

1. Clean all glassware, syringes, and needles sequentially in soap solution, water, and acetone. Allow the acetone to evaporate[c] and then dry everything in an electric oven (105 °C) for at least 1 h. **Caution!** Thoroughly dry the thermometer with paper tissues and a hair dryer just before use; do not over-heat it. Do not oven dry microlitre syringes as they are easily damaged by excessive heating.
2. Promptly assemble the glassware as in Fig. 1.1 and start the inert gas flow. Apply one drop of liquid paraffin to the sleeve adapter of the paddle stirrer to ensure an air-tight fit. Weigh diethyl L-(+)-(*R*,*R*)-tartrate (2.5 g, 12.1 mmol) into the 50 mL Erlenmeyer flask, dissolve it in 30 mL of dichloromethane and pour this solution into the reaction flask using the funnel (lift it slightly to avoid air locks). Rinse the Erlenmeyer flask with a further 50 mL of dichloromethane and add this to the reaction flask as well.
3. Cap the remaining ₮ 19/22 joint with a septum and commence stirring. Draw up 1.8 mL of titanium(IV) isopropoxide into a 5 mL syringe as shown in Fig. 1.2. Inject this into the reaction flask through the septum.
4. Measure 180 μL of water into the 250 μL syringe and add this to the reaction mixture through the septum (guide the fine needle with your thumb and forefinger to avoid bending it). Stir the very pale yellow solution for 20 min at room temperature.
5. Dissolve methyl 4-tolyl sulfide **5** (0.84 g, 6.00 mmol) in dichloromethane (5 mL) and add it to the reaction mixture by syringe.
6. Cool the reaction mixture to about −20 °C using the acetone/dry ice bath. If necessary increase the inert gas flow to avoid bubbler 'suck back'. From now on periodically monitor the reaction to ensure it is stirring close to −20 °C, adding more dry ice if necessary.
7. Add 2.2 mL of *t*-butyl hydroperoxide dropwise to the solution using a clean dry 5 mL syringe over 5 min. Stir the reaction for 4 h keeping the temperature close to −20 °C.[d]
8. Using a syringe, add water (1 mL) to the reaction mixture and remove the flask from the low-temperature bath. Stir the reaction at room temperature for 1.5 h.
9. Filter the white gel produced through a pad of Celite and wash the pad with three 10 mL portions of dichloromethane. The slow filtration can be

**Protocol 3.** *Continued*

promoted by gentle scratching of the Celite surface with a spatula. Retain the filtrate.

10. Wash out the reaction flask and add to it sodium chloride (5 g), sodium hydroxide (15 g), and water (50 mL). Set up the flask as in Fig. 1.1 but omitting the low-temperature thermometer and nitrogen supply. Replace the acetone in the cooling bath with ice and some water.
11. Once the sodium hydroxide solution has cooled, add the dichloromethane solution from step 9 to the hydrolysis mixture. Rinse in any remaining crude sulfoxide left in the flask with small additional amounts of dichloromethane. Allow the hydrolysis reaction to stir vigorously for 1 h.
12. Transfer the mixture to a 500 mL separatory funnel. Separate the phases (retaining both) and extract the aqueous phase with two 20 mL portions of dichloromethane. Combine the organic fractions and dry them over sodium sulfate.
13. Filtration and removal of the solvent from the filtrate by rotary evaporation yields crude (*R*)-methyl 4-tolyl sulfoxide **6** (about 0.8 g, 85%) which may be purified by chromatography on silica gel with 1:9 hexane:ethyl acetate. This produces a colourless solid (m.p. 76–77 °C). Optically pure **6** shows $[\alpha]_D + 146 \pm 1$ (c 1.0, acetone), while that produced by this protocol has an optical purity of *ca.* 90%.[12,e]

[a] Distilled from calcium hydride; each portion should be collected just before use.

[b] If the Fluka product (19998) is not available, this reagent may be prepared from aqueous 70% $Bu^tOOH$ by known procedures;[8] toluene solutions can also be used (Fluka 20000). Methods for assessing the purity of *t*-butyl hydroperoxide are outlined in Protocol 2.

[c] Evaporation may be promoted by careful use of a hair dryer.

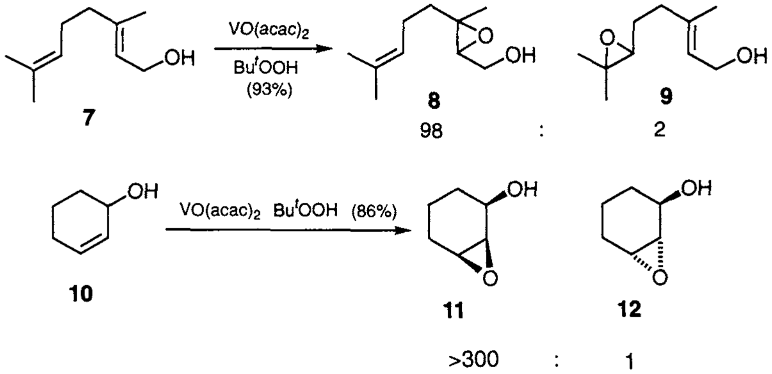
[d] Alternatively, the reaction mixture can be sealed under nitrogen or argon [using lightly greased stoppers and KECK clips (Aldrich Z15,043-6 and Z15,044-4)] and stored at −23 °C overnight in a domestic freezer to complete conversion to the sulfoxide.

[e] The enantioselectivity depends strongly on the reaction temperature and is greatest in the range −25 to −20 °C. Both higher and lower temperatures lead to lower optical yields.

## 4. Group 5 metal-promoted oxidations: epoxidations using vanadyl acetylacetonate

The complex $V(=O)(acac)_2$ is another highly useful catalyst for epoxidation of allylic alcohols using $Bu^tOOH$. Only double bonds proximal to the alcohol are epoxidised under high rate acceleration. For example, the less reactive double bond in geraniol **7** is epoxidised to generate the 2,3-epoxide **8** rather than the 6,7-epoxide **9** (Scheme 1.4),[15] suggesting that both the substrate and the $Bu^tOOH$ are bound to vanadium in the catalytic cycle. Supporting this notion, $V(=O)(acac)_2$-catalysed reactions often proceed with high levels of diastereoselectivity, as illustrated by the epoxidation of cyclohexenol **10** to the *syn* product **11** rather than the *anti* compound **12** (Scheme 1.4). The stereoselectivity in V(=O)(acac)$_2$-catalysed oxidations can be correlated to relief of strain between the 1,2- and 1,3-disposed substituents either within the substrate or between the substrate and catalyst, thus allowing the identity of the major stereoisomer to be predicted. These ideas are summarised in two excellent reviews.[7,16] The regioselective 2,3-epoxidation of geraniol **7** is presented in detail.

Although it is added to the reaction mixture, V(=O)(acac)$_2$ is not the actual catalyst in these reactions. The acetylacetone ligands are degraded to formic and acetic acid and V(=O)(OR)$_3$ species quickly form. The acidic by-products can cause problems in reactions leading to acid-sensitive epoxides. In these cases it is better to use isolated trialkyl vanadates as catalysts. The species V(=O)(OR)$_3$ (R = Et, Pr, Pr$^i$) work best.



Scheme 1.4

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## Protocol 4.
## Preparation of 2,3-epoxygeraniol. Regioselective epoxidation by V(=O)(acac)$_2$ (Scheme 1.4)

**Caution!** Employ the standard precautions outlined in the introduction to this chapter for this reaction. Strong acids, transition metal salts, or metal syringe needles should **never** be added to concentrated Bu$^t$OOH stock solutions. Aliquots of Bu$^t$OOH remaining after use in reactions should **not** be returned to stock solutions. 1,2-Dichloroethane should **not** be used as a solvent with Bu$^t$OOH despite early recommendations.[7]

*Equipment*

- Three-necked, round-bottomed flask (250 mL)
- Stirrer hot plates (× 2)
- Teflon-covered magnetic stirring bars, *ca.* 4 × 0.8 cm (× 2)
- Pressure-equalising dropping funnel (50 mL)
- Beaker (500 mL)
- Glass funnel
- Separating funnel (1 L)
- Sinter funnel
- Büchner flask (500 mL)
- Ŧ 19/22 cone to tube adapter
- Reduction adapter (Ŧ 24/40 to Ŧ 19/22)

## **Protocol 4.** *Continued*

- Septa
- Erlenmeyer flasks (50 mL) with stoppers (× 2)
- Source of dry inert gas (nitrogen or argon)
- Cooling bath

### *Materials*

| | |
|---|---|
| • Dry dichloromethane,[a] *ca.* 120 mL total | **volatile, toxic at high concentrations** |
| • Activated pelleted 4 Å molecular sieves | **hydroscopic** |
| • Vanadyl acetylacetonate, $V(=O)(acac)_2$ (FW 265.2), 0.66 g, 2.4 mmol, 4.8 mol% | **toxic** |
| • Anhydrous *t*-butyl hydroperoxide, 5.5 M in nonane,[b] 20 mL, 110 mmol | **oxidising agent, flammable** |
| • (*E*)-Geraniol **7** (FW 154.3), 8.2 g, 9.2 mL, 53 mmol | **toxic** |
| • Iron(II) sulfate heptahydrate (FW 278.0), 16.5 g, 0.06 mol | |
| • L-(+)-(*R,R*)-Tartaric acid (FW 150.1), 6.6 g, 0.04 mol | |
| • Technical diethyl ether, for extraction | **flammable** |
| • Silica gel | |
| • Hexane and ethylacetate for chromatography | **flammable** |

1. Clean all glassware sequentially in soap solution, water, and acetone. Allow the acetone to evaporate[c] and then dry everything in an electric oven (105 °C) for at least 1 h.
2. Put the (*E*)-geraniol **7** (8.2 g, 9.2 mL, 53 mmol) into a 50 mL Erlenmeyer flask along with 25 mL of dichloromethane and some 4 Å molecular sieves (2–4 g, mass unimportant). Stopper the flask and set it aside to pre-dry the substrate.
3. Put 20 mL of 5.5 M *t*-butyl hydroperoxide solution into a 50 mL Erlenmeyer flask along with some 4 Å molecular sieves (2–4 g, mass unimportant). Stopper the flask and set it aside to pre-dry the oxidant.
4. Set up the equipment as shown in Fig. 1.3 (with a stirrer hot plate under the apparatus) and fill the cooling bath with a mixture of ice and water. Using a glass funnel, add the solid vanadyl acetylacetonate (0.66 g) to the reaction flask. Wash any remaining catalyst adhered to the funnel into the reaction flask using the (*E*)-geraniol **7** solution prepared in step 2 (lift the funnel slightly to avoid any air locks). Be careful **not** to add the molecular sieves left in the Erlenmeyer flask to the reaction mixture as well. Rinse the geraniol flask with three 25 mL portions of dichloromethane, adding these to the reaction flask as well. Remove the funnel and insert the septum.
5. Ensure the stopcock on the dropping funnel is shut. Charge the dropping funnel with 5.5 M *t*-butyl hydroperoxide solution (15 mL).
6. Add the $Bu^tOOH$ solution to the reaction dropwise over about 10 min with stirring. The colour of the reaction mixture will change from blue to green to dark red.
7. Stir the reaction at room temperature for 1 h 45 min; completion of the reaction is best indicated by TLC (Merck Kieselgel 60 $F_{254}$ plates; 7:3 hexane:ethyl acetate eluent, visualisation by $KMnO_4$ spray).
8. Prepare a solution of 16.5 g of iron(II) sulfate heptahydrate and 6.6 g L-(+)-

(*R*,*R*)-tartaric acid in water (90 mL) in a 500 mL beaker. Stir and chill this solution to 0 °C using an ice bath on a stirrer hot plate.

9. Add the reaction mixture to the chilled iron(II) solution. Stir the mixture for 5 min at 0 °C and then continue stirring at room temperature until two layers are formed.
10. Transfer the mixture to a 1 L separating funnel, add 100 mL of water, and run off the lower pink dichloromethane layer and retain it. Extract the aqueous layer with two 50 mL portions of diethyl ether and combine these with the dichloromethane fraction. Dry the organic fractions ($Na_2SO_4$), filter the pale yellow solution, and remove the solvents with a rotary evaporator to give the crude product.
11. The product is purified by filtration chromatography. Place a 7 cm diameter by 5 cm high porosity 3 sinter funnel on a 500 mL Büchner flask (not connected to an aspirator). Fill the sinter with 40 g of chromatographic silica gel. Prepare 250 mL of a 10:1 mixture of hexane:ethyl acetate. Add 80 mL of this solution to the silica and stir the resulting slurry. Promptly dissolve the crude geraniol epoxide in 30 mL of eluent and carefully pour it onto the silica pad. Allow the solution to filter through the silica under gravity and then add another 30 mL of eluent. After this has filtered through under gravity apply suction to the Büchner flask and elute with the remaining 10:1 solution. Prepare 100 mL of a 4:1 mixture hexane:ethyl acetate and suck this through the silica pad as well.
12. Removal of the solvent on a rotory evaporator (water bath temperature 60 °C) yields 2,3-epoxygeraniol as a slightly coloured oil (about 7.9 g, 87%). The product may be further purified by formation of its acetate followed by vacuum distillation (0.025 mmHg, 104–106 °C) to yield 2,3-epoxygeranyl acetate as a colourless liquid containing only traces of its 6,7-isomer.[15]

[a] Distilled from calcium hydride.

[b] If the Aldrich product (41,806-4) is not available this reagent may be prepared from aqueous 70% $Bu^tOOH$ by known procedures;[8] toluene solutions can also be used. Methods for assessing the purity of *t*-butyl hydroperoxide are outlined in Protocol 2.

[c] Evaporation may be promoted by careful use of a hair dryer.

## 5. Group 6 metal-promoted oxidations: enolate oxygenation with MoOPH

Although molybdenum complexes are also potent activators of $Bu^tOOH$,[7] it seems appropriate here to consider instead the rather different behaviour of $[MoO_5(py)\{OP(NMe_2)_3\}]$ (MoOPH). This complex is one of the few reagents capable of direct oxygenation of enolate anions, leading to hydroxy ketones in moderate to good yields.[17] The behaviour of camphor **13** is exemplary,[18] resulting in the hydroxy ketone **14** (Scheme 1.5).

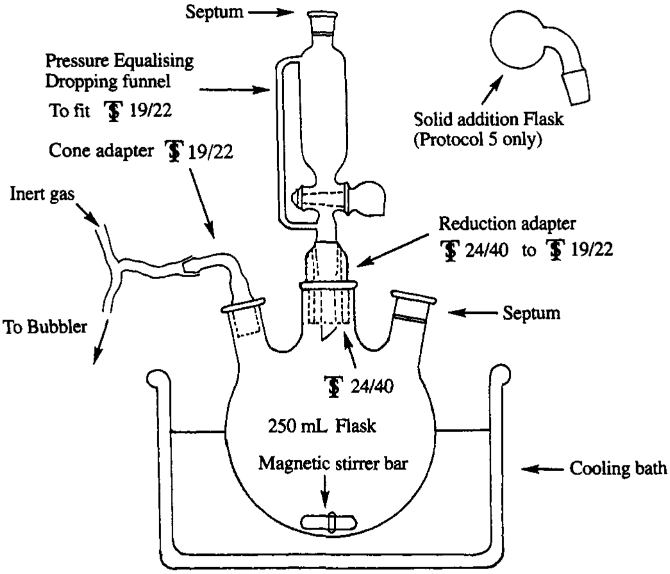

**Fig. 1.3** Assembled reaction apparatus for Protocols 4 and 5.

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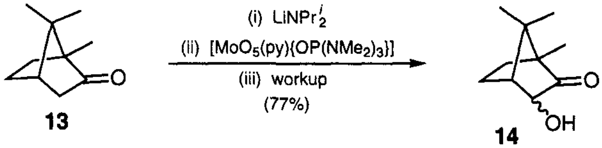
## Protocol 5.

## Preparation of 1,7,7-trimethyl-3-hydroxybicyclo[2.2.1]heptan-2-one (Structure 14). Hydroxylation of camphor (Structure 13) by [$MoO_5$(py){OP($Nme_3$)$_3$}] (MoOPH) (Scheme 1.5)

**Caution!** Employ the standard precautions outlined in the introduction to this chapter for this reaction. The MoOPH reagent should be treated as **potentially explosive;** a safety screen should be used. Complexes containing $OP(NMe_2)_3$ (HMPA) and other sources of this material should be treated with respect as HMPA is classed as a potent carcinogen. All operations should be conducted in an efficient hood using gloves. All residues should be bottled for appropriate disposable.



**Scheme 1.5**

### *Equipment*

- Three-necked, round-bottomed flask (250 mL)
- Electric heat gun (paint stripper)
- Magnetic stirrer
- Teflon-covered magnetic stirrer bar, *ca.* 4 × 0.8 cm
- Well-insulated low-temperature bath

- Low-temperature thermometer to monitor cooling bath temperatures
- All-glass Luer syringe with 10 cm needles (5 and 20 mL, gauge no: 20 or 22)
- Separating funnel (500 mL)
- Glass filtration frit
- Büchner flask
- Ŧ 19/22 cone to tube adapter
- Reduction adapter (Ŧ 24/40 to Ŧ 19/22)
- Pressure-equalising dropping funnel (200 mL)
- Septa
- Inert atmosphere solid addition flask[a]
- Source of dry inert gas (nitrogen or argon)

*Materials*

| | |
|---|---|
| • Dry THF,[b] 125 mL total | **flammable, hydroscopic** |
| • Dry diisopropylamine[c] (FW 101.2), 2.45 mL, 1.75 g, 17.5 mmol | **toxic, malodorous** |
| • 1.6 M $\mathrm{Bu^nLi}$ in hexane, 11.0 mL, 17.6 mmol | **air sensitive** |
| • $[\mathrm{MoO_5(py)\{OP(NMe_3)_3\}}]$ (MoOPH),[d] 10.45 g, 17.65 mmol | **toxic** |
| • Camphor **13** (FW 152.2), 2.44 g, 16.05 mmol | **toxic** |
| • Technical diethyl ether, for extraction | **flammable** |
| • Silica gel for filtration chromatography, 40 g | **irritant dust** |
| • 1:1 hexane:diethyl ether, 900 mL for chromatography | **flammable** |

1. Clean all glassware sequentially in soap solution, water, and acetone. Allow the acetone to evaporate[e] and then dry the glassware in an electric oven (105°C) for at least 1 h.
2. Set up the apparatus as in Fig. 1.3, but without the cooling bath in place, and with a stirrer hot plate under the apparatus. Start the inert gas flow. Heat the apparatus with an electric heat gun (>100°C), but avoid scorching the rubber septa. Leave the apparatus to cool.
3. Remove one septum and add to the flask diisopropylamine (2.45 mL, 17.5 mmol) and 50 mL of THF (collected from the still just before use). Replace the septum.
4. Cool the mixture to *ca.* −78°C using an acetone/dry ice cooling bath. Do **not** add excess dry ice to the bath as this will make raising the bath temperature later very difficult.
5. Rapidly assemble an oven-dried all-glass 20 mL syringe. Pierce the septum of the reaction flask and with the tip of the needle in the head-space, draw up about 15 mL of inert gas; pull out the syringe needle and expel the gas from the syringe. Repeat this twice more to remove traces of oxygen from the syringe.
6. Collect 11 mL of $\mathrm{Bu^nLi}$ (1.6 M) as indicated in Fig. 1.2 and add this to the reaction mixture. Allow the mixture to stir for 15 min generating the LDA *in situ.* The yield of LDA is near quantitative under these conditions.
7. Charge the dropping funnel (tap shut) with camphor **13** (2.44 g, 16.05 mmol) and 100 mL of freshly distilled THF. Ensure that the camphor has dissolved completely.
8. Add the camphor to the LDA solution dropwise over 30 min keeping the bath temperature at *ca.* −78°C. Allow the mixture to stir at this temperature for a further 10 min.

**Protocol 5.** *Continued*

9. Warm the bath temperature to −25 to −20°C by adding more acetone to the cooling bath.
10. Increase the inert gas flow to the reaction. Fill the solid addition flask with 10.45 g, 24.05 mmol of $[MoO_5(py)\{OP(NMe_3)_3\}]$ (MoOPH). Replace the septum with the solid addition flask and secure it in place with a KECK clip (Aldrich Z15,043-6). Reduce the gas flow to the reaction flask.
11. Add the MoOPH over 1–2 min by rotating the solid addition flask slowly and tapping it gently. After the addition, continue to stir the reaction mixture for a further 20 min at −25 to −20°C.
12. Add 50 mL of saturated sodium sulfite ($Na_2SO_3$) solution to the reaction mixture. Allow the solution to come to room temperature and then continue to stir it for a further 10 min.
13. Transfer the mixture to a 500 mL separating funnel and shake it with saturated brine (50 mL). Extract the mixture with two 50 mL portions of diethyl ether, combine the organic extracts and wash them once with a mixture of 10% aqueous hydrochloric acid (25 mL) and saturated brine (25 mL). Re-extract the acidic brine with more diethyl ether (50 mL) to ensure all the product is obtained.
14. Combine the diethyl ether fractions and dry them over magnesium sulfate, filter the solution and remove the solvent by rotary evaporation.
15. Suspend 40 g of silica gel in 100 mL of 1:1 hexane:diethyl ether and place the suspension in a 7 cm diameter 5 cm high glass filtration frit, mounted on a Büchner flask. Dissolve the blue-green oil in the minimum amount of the same solvent and apply the solution to the silica pad. Elute the product with 750 mL of the same solvent system using suction.
16. Remove the solvent by rotary evaporation and recrystallise the residue by dissolution in the minimum quantity of hexane (*ca.* 10 mL) followed by cooling to −20°C to give the pure material. The mother liquors contain appreciable amounts of product and should be evaporated and the crystallisation repeated with smaller volumes of hexane until an acceptable yield (*ca.* 1.9 g, 70%, m.p. 170–183°C) is obtained. The product **14** is obtained as a mixture of two stereoisomers whose ratio may be determined by $^1H$ NMR spectroscopy.[18]

[a] Shown in Fig. 1.3. The bulb has a volume of *ca.* 50 mL, the L bend should suit the reaction flask and end in a Ŧ 19/22 joint.

[b] Distilled from sodium benzophenone ketyl under an inert atmosphere immediately prior to use.

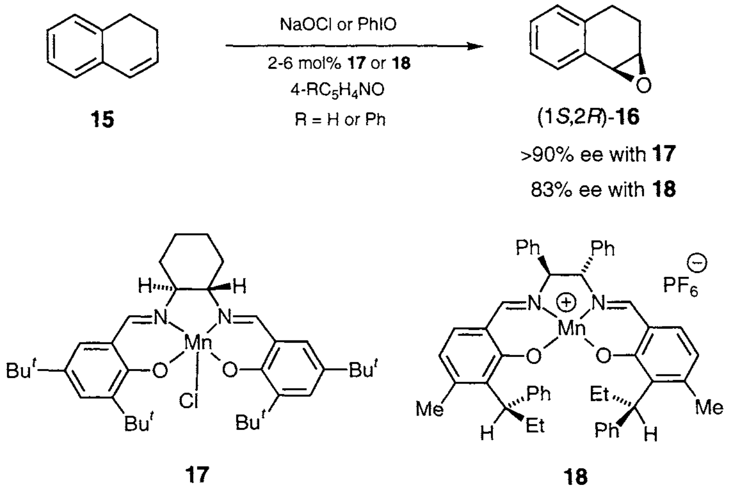
[c] Dried over 4 Å molecular sieves for at least 24 h prior to use.

[d] Prepared as described in *Organic Synthesis.*[18] **Caution!** In the two hundred or so uses of this reagent reported in the literature no explosions are noted. Prof. Vedejs has informed us, however, of two exothermic decompositions which lead to cracked glassware. Appropriate safety screens should be used. Although the DMPU analogue of MoOPH, $[MoO_5(py)(DMPU)]$, is undoubtedly less toxic than MoOPH and readily prepared[19] it is explosive under some conditions.[20]

[e] Evaporation may be promoted by careful use of a hair dryer.

## 6. Group 7 metal-promoted oxidations: epoxidation by salen manganese complexes

The ability of manganese(III) salen complexes to catalyse alkene epoxidation using appropriate oxygen atom sources was first systematically studied by Kochi.[21] Jacobsen and Katsuki have developed these reactions into highly efficient asymmetric processes for the epoxidation of *cis*-disubstituted alkenes such as the epoxidation of dihydronaphthalene **15** (Scheme 1.6).[22–24] The pyridine *N*-oxides added to these reactions do not act as terminal oxidants; rather they serve to ligate the active [Mn(=O)(salen)] intermediates formed in the reaction, thus improving their stability and enantioselectivity.[24] The most effective pre-catalysts are based on structures (*S*,*S*)-**17** and (*S*,*S*,*R*,*R*)-**18** (Scheme 1.6); the former is particularly attractive as it is readily prepared from commercial materials in two simple highly reproducible preparations.[25] One particularly useful oxygen atom source for these reactions is a buffered solution of bleach (NaOCl, Clorox) and this is used here in the epoxidation of dihydronaphthalene.



**Scheme 1.6**

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### Protocol 6.
### Preparation of (1*S*,2*R*)-1,2-epoxy-1,2,3,4-tetrahydronaphthalene (Structure 16). Asymmetric epoxidation using NaOCl catalysed by Jacobsen's chiral manganese salen complex (Structure 17), (Scheme 1.6)

**Caution!** Employ the standard precautions outlined in the introduction to this chapter for this reaction.

## **Protocol 6.** *Continued*

### *Equipment*

- Erlenmeyer flasks (2 × 50 mL)
- Magnetic stirrer
- All-glass Luer syringe (1 mL)
- Needle (5 cm, 20 or 22 gauge)
- Thermometer
- Teflon-covered magnetic stirrer bar (*ca.* 2.5 × 0.5 cm)
- Measuring cylinder (20 mL)
- Chromatography column (1.5 cm OD)
- Separating funnel (100 mL)

### *Materials*

| | |
|---|---|
| • Commercial undiluted household bleach (NaOCl, Clorox, *ca.* 0.8 M) 13 mL, *ca.* 10 mmol | **oxidising agent, strongly basic, toxic** |
| • 0.05 M sodium phosphate ($Na_2HPO_4$) solution 10 mL | **toxic** |
| • Dichloromethane, *ca.* 30 mL | **volatile, toxic at high concentrations** |
| • 1,2-Dihydronaphthalene **15** (FW 130.2), 0.65 mL, 0.65 g, 5.0 mmol | **toxic** |
| • 4-Phenylpyridine *N*-oxide (FW 171.2), 0.19 g, 1.25 mmol, 25 mol% | **toxic** |
| • *Complex* **17**[a] *(FW 546.8), 0.19 g, 0.25 mmol, 5 mol%* | **toxic** |
| • Silica gel for chromatography 25 g | **irritant dust** |
| • Sand for chromatography | |
| • 30:1 hexane:diethyl ether for flash chromatography | **flammable, toxic** |

1. Clean all glassware sequentially in soap solution, water, and acetone. Allow the acetone to evaporate[b] and then dry the glassware in an electric oven (105°C) for at least 1 h.
2. Place 13 mL of sodium hypochlorite solution (NaOCl, *ca.* 0.8 M) in a 50 mL Erlenmeyer flask. Buffer this by adding 5 mL of sodium phosphate ($Na_2HPO_4$) solution (0.05 M) and adjust the pH of the solution to about 11 using a few drops of 1 M NaOH.[c] Cool the solution in an ice–water bath.
3. Dissolve the 1,2-dihydronaphthalene **15** (0.65 mL, 5.0 mmol), 4-phenylpyridine *N*-oxide (0.19 g, 1.25 mmol), and the complex **17** (0.16 g, 0.25 mmol) in dichloromethane (10 mL) in a second 100 mL Erlenmeyer flask containing a magnetic stirrer bar. Stir the mixture in an ice–water bath at about 4°C for 5 min.
4. Promptly add the cold buffered NaOCl solution to the stirring reaction mixture and allow the reaction to stir vigorously for about 4 h at *ca.* 4°C. The reaction is best monitored by TLC analysis (4:1 hexane:diethyl ether) of the organic layer (visualisation is best achieved by $KMnO_4$ staining and heating).
5. Transfer the reaction mixture to a 100 mL separating funnel and rinse the reaction flask with two 10 mL portions of dichloromethane adding these to the funnel. Separate the phases and wash the organic layer once with 40 mL of saturated brine. Dry the organic layer ($Na_2SO_4$), filter, and evaporate the filtrate to yield a crude oil.
6. Slurry silica gel (25 g) in 50 mL of 30:1 hexane:diethyl ether. Pour the slurry in to a 2 cm diameter chromatography column half filled with the same eluent and containing a 1 cm high plug of sand at its base. Allow the solvent to

flow out of the column while firmly tapping with a short (10 cm) piece of thick rubber tube. Once the silica has compacted, protect the column top with more fine sand (*ca.* 1 cm). Run the eluent down until it is just level with the sand and then stop the solvent flow.

7. Dissolve most of the crude oil in a small amount of eluent and apply this to the top of the column using a Pasteur pipette. Open the column tap and allow the surface of the solvent to just come level with the sand again. Repeat this operation twice more.
8. Carefully load the top of the column with uncontaminated eluent, open the column stopcock, and start collecting fractions in test tubes. The presence of the epoxide (1*S*,2*R*)-**16** may be ascertained by TLC analysis of the fractions. The order of elution is: **15**, naphthalene (an impurity in commercial dihydronaphthalene), followed by (1*S*,2*R*)-**16**. If the epoxide does not elute pure, diethyl ether should be applied to the column.
9. Evaporation of the (1*S*,2*R*)-1,2-epoxy-1,2,3,4-tetrahydronaphthalene **16** fractions yields about 0.6 g (82%) of a low melting point solid. The optical purity is determined to be *ca.* 90% ee by $^1$H NMR analysis in the presence of the chiral shift reagent Eu(hfc)$_3$.

[a] Aldrich (40,443-8), or Fluka (14717); alternatively reliable preparations of complex **17** are available.[25,26]

[b] Evaporation may be promoted by careful use of a hair dryer.

[c] The exact quantities of sodium phosphate ($Na_2HPO_4$) and sodium hydroxide used depend somewhat on the source of bleach used; adjustment of these volumes may be necessary.

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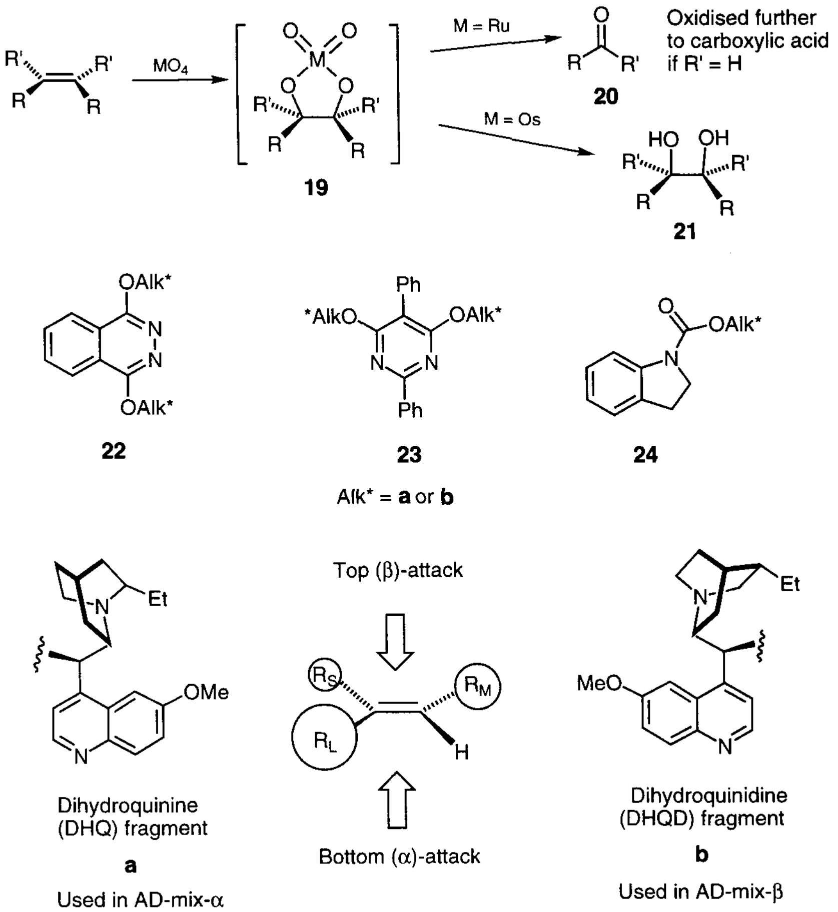
## 7. Group 8 metal-promoted oxidations: alkene cleavage and asymmetric dihydroxylation

In the presence of relatively strong oxidising agents, most ruthenium and osmium salts are smoothly converted to their highest oxidation state; solutions of the tetraoxides $MO_4$ (M = Ru, Os) are therefore rather easily prepared.[27] Both complexes react with alkenes to generate new organic products and the metals in lower oxidation states. Only catalytic amounts of metal are needed in these reactions providing that a sacrificial oxidant is available to provide a continuous supply of $MO_4$. Ruthenium tetraoxide and its osmium counterpart react with alkenes rather differently. Although both are known to yield a common cyclic diester intermediate **19**,[28,29] ruthenium leads to the C–C bond cleavage product **20**, while $OsO_4$ generates the dihydroxylated product **21** on workup. If the initial C-C cleavage product **20** is an aldehyde, rapid further oxidation to the carboxylic acid takes place (Scheme 1.7).

Ligation of the metal centres can have profound effects on the chemistry of $MO_4$ oxidations. For example, while the use of acetonitrile/water/$CCl_4$ solvents dramatically improves the efficiency of $RuO_4$-catalysed C-C cleavage,



**Scheme 1.7**

as demonstrated in Protocol 7,[30] the addition of other ligands, particularly bipyridyl or phenanthroline derivatives, changes the reaction pathway to epoxidation.[31] The origin of this change in chemoselectivity is the instability of [$RuO_4L$] adducts, leading to decomposition to catalysts of lower oxidation state and different behaviour.[27] In contrast, the species [$OsO_4L$] are stable, well-behaved, and generally result in faster dihydroxylation reactions than $OsO_4$ alone. In the cases where L is a phthalazine **22**,[32] pyrimidine **23**,[33] or indoline **24**[34] derivative, quite remarkable degrees of asymmetric induction are observed if pendant dihydroquinine (DHQ) **a** or dihydroquinidine (DHQD) **b** alkaloids are used. Although DHQD and DHQ are diastereoisomers, they differ only in the chirality of the 4- and 5-stereocentres and behave as enantiomeric ligands in asymmetric dihydroxylation (AD). These AD reactions are very simple to carry out as demonstrated in Protocol 8. The phthalazine ligands **22a/b** give excellent results (typically 80–99% ee) with most substrates. However, for most terminal alkenes the pyrimidine **23** is preferred, and for *cis*-disubstituted alkenes even specially designed **24** gives inferior optical yields. Suggestions on ligand choice for particular alkenes have been summarised.[35] The asymmetric dihydroxylation reaction is demonstrated here for styrene, which has the advantage of reacting quite quickly in the presence of **22** and 1 mol% $OsO_4$.

## Protocol 7.
## Preparation of pentanoic (valeric) acid. C=C bond cleavage by catalytically generated $RuO_4$

**Caution!** Employ the standard precautions outlined in the introduction to this chapter for this reaction. Ruthenium tetraoxide is volatile and toxic so an efficient hood **must** be used. Carbon tetrachloride and sodium periodate residues are environmentally unacceptable and so every attempt should be made to recover these materials. Carbon tetrachloride should be redistilled and stored for reuse while aqueous sodium periodate residues (mostly $NaIO_3$) should be bottled for appropriate disposal.

### *Equipment*

- Erlenmeyer flask (25 mL)
- Magnetic stirrer
- Teflon-covered magnetic stirring bar (*ca.* 1 × 0.5 cm)
- Measuring cylinder (5 mL)
- Syringe (250 μL)
- Separating funnel (50 mL)
- Glass filtration frit
- Single-necked, round-bottomed flasks (2 × 100 mL)

### *Materials*

| | |
|---|---|
| • Carbon tetrachloride (tetrachloromethane), 2 mL | **highly toxic** |
| • Acetonitrile, 2 mL | **flammable, toxic** |
| • (*E*)-5-Decene (FW 140.3), 189 μL, 140 mg, 1 mmol | **flammable, toxic** |
| • Sodium periodate[a] (FW 213.9), 875 mg, 4.1 mmol | **toxic, oxidising agent** |
| • Ruthenium trichloride hydrate[b] (FW 207.4), 13 mg, 0.04 mmol, 5 mol% | **highly staining, toxic** |
| • Dichloromethane for extraction | **volatile, toxic at high concentrations** |
| • Diethyl ether for extraction | **flammable** |
| • Celite | |

1. Clean all glassware sequentially in soap solution, water, and acetone. Allow the acetone to evaporate[c] and then dry everything in an electric oven (105°C) for at least 1 h.
2. Introduce into the Erlenmeyer flask carbon tetrachloride (2 mL), acetonitrile (2 mL), (*E*)-5-decene (189 μL, 140 mg, 1 mmol), a solution of sodium metaperiodate (875 mg, 4.1 mmol) in distilled water (8 mL), and the magnetic stirrer bar.
3. Add 13 mg of ruthenium trichloride hydrate to the reaction mixture, stopper the flask, and stir the two-phase reaction vigorously for 2 h at room temperature.

**Protocol 7.** *Continued*

4. Transfer the reaction mixture to a 50 mL separating funnel, rinse the Erlenmeyer flask with 5 mL of dichloromethane and add the washings to the separating funnel as well. Repeat this operation with a further 5 mL of dichloromethane.
5. Separate the lower organic phase and then re-extract the aqueous layer three times with 10 mL of dichloromethane. Combine all the organic extracts and dry them with $Na_2SO_4$. Filter the dried solution into a 100 mL round-bottomed flask, washing the $Na_2SO_4$ twice with small portions of dichloromethane.
6. Remove nearly all of the solvent by rotary evaporation and treat the oily residue with 20 mL of diethyl ether. Filter the resulting suspension through about 1 cm of Celite packed on a small glass filtration frit into a fresh weighed round-bottomed flask. Wash the Celite through with two *ca.* 7 mL portions of diethyl ether.
7. Evaporation of the diethyl ether yields about 180 mg (88%) of pentanoic acid (valeric acid), which may be further purified by microdistillation at reduced pressure (23 mmHg, 96°C) to yield a colourless oil with expected spectroscopic properties.

[a] The protocol may also be carried out using $H_5IO_6$ instead of $NaIO_4$; in many cases its use results in faster and cleaner reactions.

[b] Ruthenium trichloride hydrate is an ill-defined mixture of ruthenium(III) and (IV) compounds which may be approximated to the formula $[RuCl_3 \cdot H_2O]$. The compound should be a free flowing dark solid which becomes 'sticky' with increased water contamination.

[c] Evaporation may be promoted by careful use of a hair dryer.

## Protocol 8.
## Preparation of (1*R*)-1,2-dihydroxy-1-phenylethane. Catalytic asymmetric dihydroxylation (AD)

**Caution!** Employ the standard precautions outlined in the introduction to this chapter for this reaction. Osmium tetraoxide, formed *in situ* in this reaction, is volatile and highly toxic and so an efficient hood **must** be used.

*Equipment*

- Single-necked, round-bottomed flask (25 mL and 100 mL)
- Magnetic stirrer
- Teflon-covered magnetic stirrer bar, *ca.* 1 × 0.5 cm
- Separating funnel (50 mL)
- Glass filtration frit
- Büchner flask
- Cooling bath
- Syringe (250 μL)

*Materials*

| | |
|---|---|
| • Modified[a] AD-mix-β 1.4 g, enough for 1 mmol of alkene | **highly toxic** |
| • Styrene (FW 104.2), 114 μL, 104 mg, 1 mmol | **malodorous, toxic** |

| | |
|---|---|
| • *t*-Butyl alcohol 5 mL | **toxic** |
| • Sodium metabisulfite, 1.5 g, 7.9 mmol | **moisture sensitive** |
| • Dichloromethane for extraction | **volatile, toxic at high concentration** |
| • Silica gel for chromatography 10 g | **irritant dust** |
| • 7:3 ethyl acetate:hexane for chromatography, 100 mL | **flammable, toxic** |

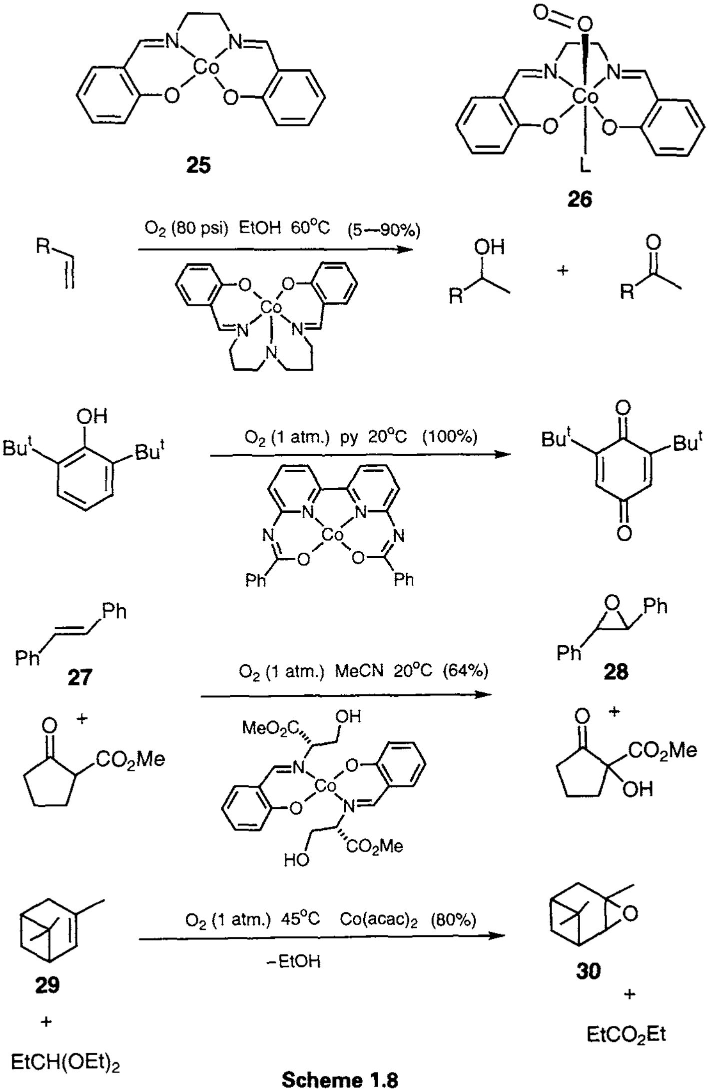
1. Clean all glassware sequentially in soap solution, water, and acetone. Allow the acetone to evaporate[b] and then dry the glassware in an electric oven (105 °C) for at least 1 h. **Caution!** Do not oven-dry microlitre syringes as they are easily damaged by overheating.
2. Load the 25 mL round-bottomed flask with modified[a] AD-mix-β (1.4 g) and the magnetic stirrer bar. Add 5 mL of *t*-butyl alcohol and 5 mL of distilled water.
3. Stir the mixture at room temperature until two clear phases are formed; the lower aqueous layer should be bright yellow.
4. Cool the reaction to 0 °C using an ice–water bath and ensure that the solution is still stirring. Add styrene (114 µL, 104 mg, 1 mmol) using a microlitre syringe and allow the heterogeneous slurry to stir vigorously at 0 °C for 3.5 h.
5. Slowly add 1.5 g of sodium metabisulfite ($Na_2S_2O_5$) to the reaction mixture, remove the flask from the ice bath, and allow the suspension to stir at room temperature for 30 min.
6. Transfer the reaction mixture to a 50 mL separating funnel, rinse the round-bottomed flask with 5 mL of dichloromethane and add this to the separating funnel as well. Repeat the rinsing operation with a further 5 mL of dichloromethane.
7. Separate the lower organic phase and then re-extract the aqueous layer three times with 10 mL of dichloromethane. Combine all the organic extracts and dry them with $Na_2SO_4$. Filter the drying mixture into a 100 mL round-bottomed flask, washing the $Na_2SO_4$ twice with small portions of dichloromethane. Evaporate the dichloromethane solution under reduced pressure to a yellow oil. Dissolve the oil in 7:3 ethyl acetate:hexane (5 mL).
8. Slurry silica gel (10 g) in 7:3 ethyl acetate:hexane (50 mL) and pour the slurry onto a suitable glass sintered filtration frit with a diameter of about 2 cm on top of a Büchner flask. When the solvent falls to the level of the silica gel, pipette on the crude yellow diol (already dissolved in ethyl acetate–hexane). Wash any residual diol in the flask onto the silica plug using fresh 7:3 ethyl acetate:hexane eluent until the added solution is clear. Elute the diol by passing 75 mL of 7:3 ethyl acetate:hexane through the plug of silica gel using suction.
9. Evaporation of the solvent mixture leads to about 110 mg (80%) of (1*R*)-1,2-dihydroxy-1-phenylethane with the expected spectroscopic properties.[33]

**Protocol 8.** *Continued*

The optical purity is determined to be at least 90% ee by preparation of the bis-α-methoxy-α-(trifluoromethyl)phenylacetic acid ester (Mosher's bis-ester).[33]

[a] Asymmetric dihydroxylation reactions using the commercial materials (AD-mix-α, Aldrich 39,275-8; AD-mix-β, Aldrich 39,276-6) result in typical reaction times of 16–24 h for most alkenes at 0 °C. For 1,2-disubstituted, trisubstituted, and tetrasubstituted alkenes further promotion by addition of methanesulfonamide is also required. The dihydroxylation rate is considerably improved by increasing the osmium concentration in the commercial product from 0.2 mol% to 1 mol% by adding 3.68 mg of finely ground $K_2[Os(=O)_2(OH)_4]$ per 1.4 g of AD-mix-α (or AD-mix-β) and mixing well.

[b] Evaporation may be promoted by careful use of a hair dryer.



**Scheme 1.8**

## 8. Group 9 metal-promoted oxidations: aerobic epoxidation of alkenes

Molecular oxygen is rather unreactive towards organic molecules under mild conditions as it has a triplet (paramagnetic) ground state which has the wrong symmetry for reaction with singlet ground state organics. These problems may be overcome by coordination of the molecular oxygen to transition metal centres. For example, in the presence of added amine ligands, the Co(salen) complex **25** reacts with $O_2$ to yield the adduct **26** (Scheme 1.8).[36,37] This behaviour has important consequences in that the bonding of the bound oxygen is modified, allowing reaction with singlet (diamagnetic) organic molecules. Many cobalt complexes other than **25** bind molecular oxygen and generally cobalt complexes are preferred for transition metal-catalysed reactions using this oxidant.

Cobalt species can be employed in oxidations of saturated hydrocarbons,[38] alkenes,[39–42] and phenols;[43,44] typical examples are shown in Scheme 1.8. These examples employ one of two reaction pathways; either $H^\bullet$ abstraction from RH followed by trapping of the $R^\bullet$ radical with a second molecule of $L_nCo—O_2$, or direct reaction of alkenes with $L_nCoOOH$. These radical reactions both result in the formation of hydroperoxide radicals ($ROO^\bullet$) which are stabilised by coordination to the cobalt centre. Under certain conditions these species may be isolated.[38,44] Developments in this area have involved the use of organic species that form stabilised hydroperoxides rather easily; these can be used *in situ* for the epoxidation of alkenes, as in the transformation of **27** to **28**[39] and α-pinene **29** to its epoxide **30** (Scheme 1.8).[40] The latter reaction is described in detail.

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### Protocol 9.
### Preparation of α-pinene oxide (Structure 30). Mukaiyama's catalytic aerobic epoxidation using propionaldehyde diethyl acetal and $Co(mac)_2$[a] (Scheme 1.8)

**Caution!** Employ the standard precautions outlined in the introduction to this chapter for this reaction.

*Equipment*

- Schlenk tube (40 mL capacity, internal diameter *ca.* 4 cm)
- ₸ 24/40 stopcock
- Magnetic stirrer
- Teflon-covered magnetic stirrer bars (2 × *ca.* 2 × 0.5 cm)
- All-glass Luer syringe (1 mL)
- Needle (5 cm, 20 or 22 gauge)
- Thermometer
- Single-necked, round-bottomed flask (100 mL)
- Oil bath
- Oxygen supply

*Materials*

| | |
|---|---|
| • (1*R*)-(+)-α-Pinene (FW 136.2), 0.5 mL, 0.43 g, 3.15 mmol | **flammable** |
| • Propionaldehyde diethyl acetal (FW 132.2), 20 mL, 16.3 g, 0.12 mol | **flammable, toxic** |

**Protocol 9.** *Continued*

| | |
|---|---|
| • $Co(mac)_2$[a] (FW 287.2), 65 mg, 0.22 mmol, 7.2 mol% | **toxic** |
| • Activated powdered 4 Å molecular sieves 1.0 g | **hydroscopic** |
| • Silica gel, 20 g | **irritant dust** |
| • Diethyl ether for chromatography | **flammable** |
| • Hexane for chromatography | **flammable** |

1. Clean all glassware sequentially in soap solution, water, and acetone. Allow the acetone to evaporate[b] and then dry the glassware in an electric oven (105 °C) for at least 1 h. **Caution!** Do not oven dry the thermometer.
2. Allow the oil bath to equilibrate at 50 °C for at least 0.5 h on the stirrer hot plate. Place the molecular sieves (1.0 g) in the Schlenk tube and stopper the flask with a greased stopper. Heat the molecular sieves vigorously with an electric heat gun while placing the Schlenk tube under high vacuum (<0.2 mmHg). Allow the apparatus to cool under vacuum. Set up the equipment as shown in Fig 1.4, but with the oxygen supply turned off. In the Schlenk tube place the magnetic stirrer bar, propionaldehyde diethyl acetal (20 mL), and (using a 1 mL syringe), α-pinene (0.5 mL, 3.15 mmol).
3. Promptly weigh out the $Co(mac)_2$ (65 mg, 0.22 mmol) into a small glass vial. Remove the stopcock from the Schlenk tube neck and add the catalyst to the reaction. Remove the stopcock and start the oxygen flow.
4. Stir the green reaction mixture at 50 °C for 10–17 h.
5. Transfer the reaction mixture to a 100 mL round-bottomed flask and then rinse the Schlenk tube with small amounts of diethyl ether to ensure complete transfer of the reaction mixture.
6. Remove most of the propionaldehyde diethyl acetal by rotary evaporation (keep the water bath at room temperature to avoid product loss).
7. Prepare a 10 cm high by 2 cm diameter chromatography column with 20 g of silica suspended in hexane (100 mL). Dissolve the crude reaction product in the minimal amount of hexane and apply it to the column. Residual α-pinene is eluted first followed by the epoxide on slowly changing over the eluent to a 4:1 mixture of hexane:diethyl ether (about 0.24 g, 50% is isolated).

[a] The complex $Co(mac)_2$ (macH = 3-methyl-2,4-pentanedione) is the best catalyst for this reaction but is not available commercially. It is prepared by treating a mixture of macH (2.40 g) and $CoCl_2{\cdot}6H_2O$ (2.50 g) in methanol (15 mL) and water (40 mL) with aqueous ammonia (*ca.* 2 M, 15 mL) under an inert atmosphere. The resulting orange solid must be filtered under an inert atmosphere and dried under high vacuum at 90 °C.

[b] Evaporation may be promoted by careful use of a hair dryer.

---

## 9. Group 10 metal-promoted oxidations: catalytic oxidative carbonylation

Perhaps the best-known example of oxidation by the Group 10 metals is the Wacker oxidation of ethene **31** (R = H) to ethanal **32** (R = H) (Scheme 1.9).

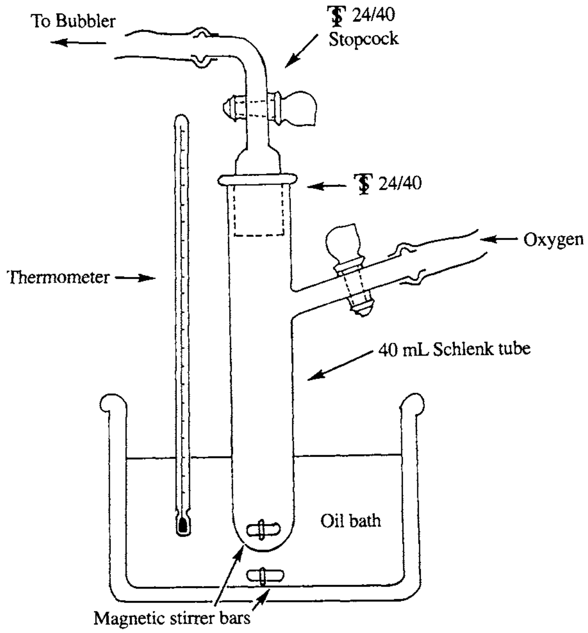
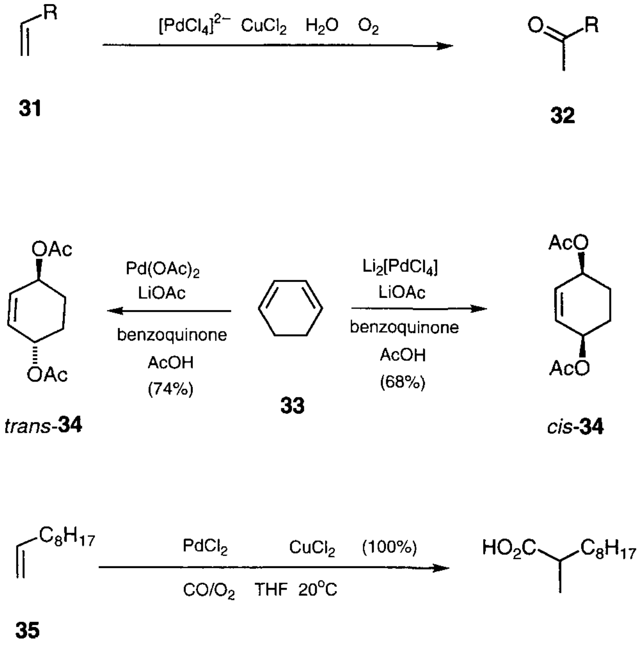


**Fig. 1.4** Assembled reaction apparatus for Protocol 9.

In this process palladium(II) is reduced to palladium(0) and a copper(II) promoter is added to allow oxidative recycling of the palladium to the active +2 state *via* aerial oxidation. While the reaction is highly successful for ethene, there are often selectivity problems when higher alkenes are used in the reaction (**31**, R $\neq$ H); isomeric ketones and partially halogenated products are normally formed. Given these problems, few organic workers have applied such approaches in their synthetic strategies. However, if appropriate conditions are employed these difficulties can be partially or fully overcome.[45,46] Also of note here are palladium-catalysed 1,3-diene oxidations developed by Bäckvall.[47,48] These reactions, in which benzoquinone is used as a reoxidant rather than oxygen, result in 1,4-diacetate structures. It is possible to control the relative stereochemistry to a high degree by modifying the reaction conditions: for example in the absence of chloride ions the diene **33** is converted to *trans*-**34** (>90%), but if $Li_2[PdCl_4]$ is used as the oxidant then *cis*-**34** is isolated (Scheme 1.9). The chloride plays a blocking role at the metal centre only allow *exo* delivery of the acetate groups. Another approach to oxidation with palladium is to carry out reactions under a mixed oxygen/carbon monoxide atmospheres, following chemistry developed by Alper.[49] Under these conditions α-substituted alkenes are selectively functionalised to secondary carboxylic acids. The oxidative carbonylation of 1-decene **35** is demonstrated here (Scheme 1.9). This reaction is of considerable interest for the preparation of anti-inflammatory pharmaceuticals. In the presence of suitable chiral ligands ibuprofen [2-(*p*-isobutylphenyl)propionic acid] and naproxen [2-(6-methoxy-2-naphthyl)propionic acid] can be prepared in high optical purities.[50]



**Scheme 1.9**

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## Protocol 10.
## Preparation of 2-methyldecanoic acid. Alper's oxidative carbonylation of terminal alkenes (Scheme 1.9)

**Caution!** Employ the standard precautions outlined in the introduction of this chapter for this reaction. Carbon monoxide is odourless and **highly toxic** even at low concentration; it **must** only be used in an efficient fume hood.

### *Equipment*

- Three-necked, round-bottomed flask (100 mL)
- Separating funnel (200 mL)
- Single-necked, round-bottomed flask
- Magnetic stirrer
- Teflon-covered magnetic stirrer bar (*ca.* 1 × 0.5 cm)
- ₮ 19/22 cone adapter
- Septa
- Needle-tubing connectors (Aldrich, Z10,116-8)
- All-glass Luer syringe (2 mL)
- Needles (5 cm and 10 cm, 20 or 22 gauge)
- Oxygen supply
- Carbon monoxide supply

### *Materials*

| | |
|---|---|
| • Tetrahydrofuran, 30 mL[a] | **flammable, peroxide risk** |
| • 1-Decene (FW 140.3), 1.45 mL, 1.07 g, 7.65 mmol | **toxic** |

| | |
|---|---|
| • Palladium(II) chloride (FW 177.3), 0.14 g, 0.78 mmol, 10 mol% | **toxic** |
| • Copper(II) chloride (FW 134.5), 0.20 g, 1.50 mmol | **toxic** |
| • Hydrochloric acid (37% w/v), 1 mL | **corrosive, toxic** |

1. Clean all glassware sequentially in soap solution, water, and acetone. Allow the acetone to evaporate[b] and then dry the apparatus in an electric oven (105°C) for at least 1 h.
2. Set up the apparatus as shown in Fig. 1.5. Put 30 mL of tetrahydrofuran, 1 mL of water, a magnetic stirrer bar, palladium(II) chloride (0.14 g, 0.78 mmol), copper(II) chloride (0.20 g, 1.50 mmol), and 1 mL of concentrated hydrochloric acid into the flask by temporarily removing the Ŧ 19/22 cone adapter.
3. Stir the mixture and adjust the carbon monoxide gas regulator so that the exit bubbler shows a flow of about two bubbles per second. Start the oxygen flow and adjust its rate until it is about half that of the carbon monoxide. The combined gas flow as measured by the exit bubbler should be about 2–3 bubbles per second. The flow rate of the carbon monoxide must be significantly greater than that of the oxygen or the regioselectivity of the reaction suffers.
4. Using a syringe measure out 1.45 mL of 1-decene (7.65 mmol) and inject this into the reaction mixture. Let the reaction stir for at least 4 h; the progress of the reaction may be monitored by the disappearance of the 1-decene as judged by TLC or GC.
5. Turn off both the oxygen and carbon monoxide gas flows and disassemble the apparatus ensuring any excess carbon monoxide has been vented into the hood. Transfer the reaction mixture to a 200 mL separating funnel. Rinse out the reaction flask with 50 mL of water and transfer these washings to the separatory funnel.
6. Extract the aqueous mixture with hexane (40 mL) and separate the layers (retaining both). Repeat the hexane extraction twice more. Combine the organic fractions and dry these with sodium sulfate. Filter the drying mixture into an appropriate round-bottomed flask and remove the hexane by rotary evaporation to give the crude product in essentially quantitative yield.
7. To purify the 2-methyldecanoic acid treat the crude product with 1 M NaOH (75 mL) and diethyl ether (75 mL) and transfer the mixture to a 200 mL separating funnel. Extract the acid into the aqueous layer as its sodium salt, discarding the diethyl ether layer. Reacidify the aqueous fraction to about pH 0–2 using concentrated HCl and extract the purified acid into 75 mL of fresh diethyl ether. After drying with sodium sulfate, removal of the diethyl ether, and drying under high vacuum, the 2-methyldecanoic acid, a clear oil (b.p. 137–139°C, 14 mmHg), shows the expected spectroscopic properties.

[a] Distilled from sodium benzophenone ketyl under an inert atmosphere.

[b] Evaporation may be promoted by careful use of a hair dryer.

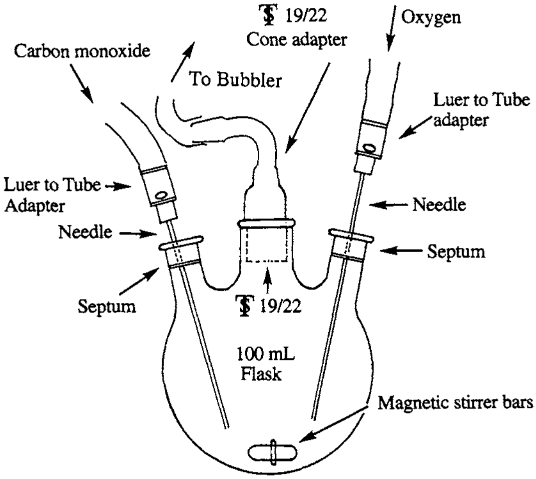


**Fig. 1.5** Assembled reaction apparatus for Protocol 10

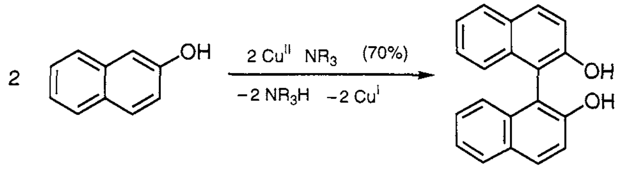
## 10. Group 11 metal-promoted oxidations: oxidative biaryl coupling

The ready accessibility of Cu(II) → Cu(I) → Cu(0) redox pathways together with the high insolubility of many copper(I) compounds causes simple copper(II) salts to be potent oxidants under appropriate conditions. One practical outcome is that copper(II) salts show facile C-H activation behaviour towards aromatic alcohols. Of particular interest is the ready formation of (±)-1,1′-bi-2-naphthol **36** from 2-naphthol (Scheme 1.10),[51] as enantiomerically enriched **36** is a popular ligand for many asymmetric transformations. The mechanism of this reaction is believed to involve oxidation of intermediate $[L_nCu_2(OC_{10}H_7)_2]$ complexes by internal and/or external redox processes. A number of attempts have been made to carry out this reaction in an asymmetric fashion, with varying degrees of success.[52–54] Nevertheless, the racemic version has its merits as a number of effective low cost resolutions of **36** have appeared.[55,56]

### Protocol 11.

### Preparation of (±)-1,1′-bi-2-naphthol (Structure 36). Oxidative dehydrogenation by copper(II) (Scheme 1.10)

**Caution!** Employ the standard precautions outlined in the introduction to this chapter for this reaction.



**36**

**Scheme 1.10**

*Equipment*

- Single-necked, round-bottomed flask with a Ŧ 24/40 joint (500 mL)
- Magnetic stirrer
- Teflon-covered magnetic stirrer bar approximately 4 cm × 0.8 cm
- All-glass Luer syringe
- Ground-glass Ŧ 24/40 stopper
- Measuring cylinders (25 mL and 250 mL)
- Erlenmeyer flask (500 mL)
- Reflux condenser
- Glass funnel

*Materials*

| | |
|---|---|
| • Technical methanol, 220 mL | **toxic** |
| • Copper(II) nitrate (FW 187.6), 9.4 g, 0.05 mol | **toxic** |
| • Benzylamine (FW 107.2), 13 mL, 12.75 g, 0.12 mol | **toxic** |
| • 2-Naphthol (FW 144.2), 5.66 g, 0.04 mol | **toxic** |

1. Clean all glassware, syringes, and needles sequentially in soap solution, water, and acetone. Allow the acetone to evaporate[a] and then dry everything in an electric oven (105 °C) for at least 1 h.
2. Put the copper(II) nitrate (9.4 g, 0.05 mol), and the magnetic stirrer bar into the round-bottomed flask and add methanol (120 mL). Stir the mixture until all of the solid has dissolved to give a bright blue solution.
3. Add 13 mL of benzylamine by syringe over a period of about 10 min.
4. Dissolve 2-naphthol (5.66 g, 0.04 mol) in methanol (100 mL). Add this solution to the reaction mixture to give a dark green solution. Stopper the flask sealing it with one or two wraps of Nesco film or Parafilm. Allow the reaction to stir at room temperature for 1 week.[b]
5. After 1 week a dark brown suspension should have formed. Acidify the mixture with 40 mL of concentrated hydrochloric acid (37% w/v) dissolved in 500 mL of distilled water. Filter the crude off-white product, wash it with copious quantities of water, and allow it to dry with suction.

**Protocol 11.** *Continued*

6. The crude product is dissolved in boiling methanol (about 100 mL is required) in a 500 mL Erlenmeyer flask equipped with a reflux condenser and magnetic stirring bar. Add three spatulas full of decolourising charcoal to the mixture and heat it under reflux (30 min). Filter the hot solution through fluted filter paper and allow it to cool to room temperature. Water (about 17 mL) is added slowly with occasional gentle swirling until crystallisation begins. Cooling the solution to *ca.* −15°C overnight yields about 3.9 g (70%) of (±)-1,1′-bi-2-naphthol as colourless crystals (m.p. 214–217°C) with the expected properties.[c] If less than the expected yield is realised, more water should be added to the mother liquors.

[a] May be promoted by use of a hair dryer.

[b] Shorter reaction times lead to contamination of the product with small and variable amounts of 2-naphthol.

[c] At scales much above the one presented in this protocol use of a mechanical stirrer is preferred over magnetic stirring. Under these conditions this protocol may be scaled up by at least a factor of ten (0.4–0.5 mol).

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# 2

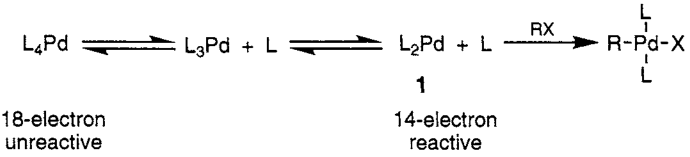
# Palladium-catalysed carbon–carbon bond formation

ANDREW F. BROWNING and NICHOLAS GREEVES

## 1. Introduction

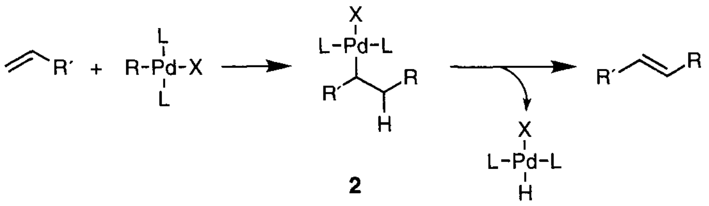
The use of palladium complexes as catalysts for a range of reactions has been one of the most remarkable developments in synthetic organic chemistry over the last 25 years.[1] The variety of reactions that can be catalysed, together with the range of functional groups tolerated and usually excellent chemo- and regioselectivity, has meant that an increasing amount of research has gone into this area of chemistry and that there are several important industrial applications.[2] Indeed, such is the widespread use of these compounds, there is seldom a total synthesis project that does not involve palladium chemistry in one or more key steps. For example, compounds containing an ene-diyne function, a class of molecules which has been under considerable scrutiny in recent years, have been targeted for total synthesis by a number of research groups. Frequently, the ene-diyne unit of these molecules is constructed using a Sonogashira coupling in excellent yield.

Palladium chemistry is dominated by two oxidation states. The lowest, palladium(0), present in tetrakis(triphenylphosphine)palladium, for example, is nominally electron rich, and will undergo oxidative addition with suitable substrates such as halides and triflates, resulting in a palladium(II) complex. Oxidative addition is thought to occur on the coordinatively unsaturated 14-electron species **1** present as a result of the ligands dissociating in solution.



The resulting σ-alkyl bond in such complexes is very reactive, especially towards carbon–carbon π-bonds. Thus the presence of an alkene in the reacting system will lead to coordination followed by insertion into the palladium–

carbon σ-bond to give **2**. Theoretically, it is possible for the process of alkene coordination and insertion to continue. However, more frequently, palladium is expelled from the system by a β-hydride elimination reaction.



**2**

The rate of this intramolecular β-hydride elimination is such that no polymeric species are ever observed. Indeed, this possible pathway means that the original substrate for the oxidative addition reaction must be chosen with care – the presence of a hydrogen at a sp$^3$ carbon in the β position must be avoided. Thus, substrates for oxidative addition reactions in palladium chemistry are frequently vinylic, allylic, or aromatic.

For the process described to be catalytic, a palladium(0) complex must be regenerated from the palladium(II) product of β-hydride elimination. This may be achieved by the presence of base in the system, which removes HX from the palladium species.

All the individual steps outlined above combine to make up the catalytic pathway in the Heck reaction (Fig 2.1).

Other than β-hydride elimination, another important pathway for palladium(II) intermediates is reductive elimination. This is the reverse of oxidative addition, and forms the basis of the mechanism for the Stille, Suzuki and other coupling reactions (Fig 2.2).[3] Once again, substrates must be chosen with care, as β-hydride elimination leads to undesired products and termination of the catalytic cycle.

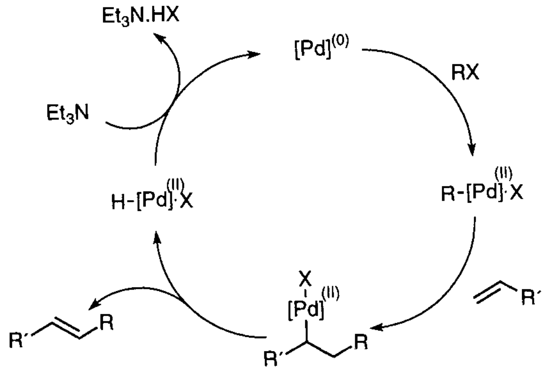


**Fig. 2.1** Catalytic cycle for the Heck reaction (ligands omitted for clarity).

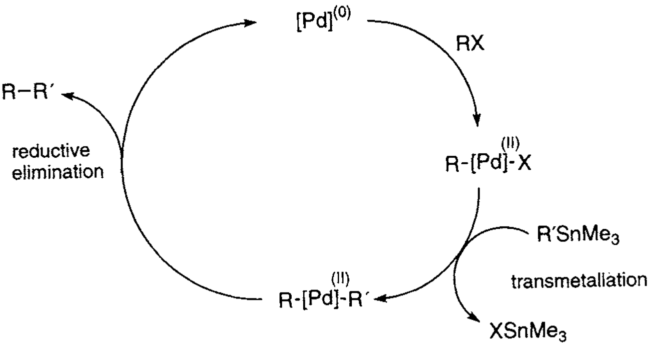
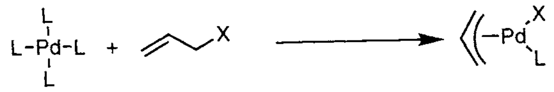


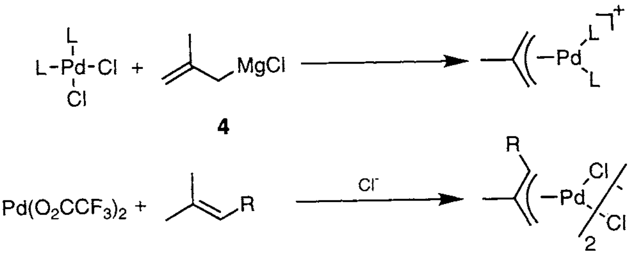
**Fig. 2.2** Catalytic cycle for the Stille coupling, showing the reductive elimination step (ligands omitted for clarity).

Another important class of palladium(II) complexes is that in which an $\eta^3$-$\pi$-allyl ligand is coordinated to the metal, as in **3**. It is possible to synthesise these types of complexes from both palladium(0) and palladium(II) starting materials. The most widely used method is the formation of an allyl complex from an allylic acetate, carbonate, sulfonate, or other suitable leaving group (X), and palladium(0).

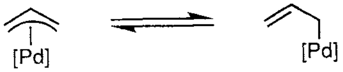


**3**

The synthesis of $\eta^3$-$\pi$-allyl complexes from palladium(II) may be achieved by transmetalation with an allylic Grignard such as **4** or directly from alkenes such as **5**.



π-Allyl complexes are generally more stable than σ-bonded ones due to the bidentate nature of the ligand, and because of the delocalised π system. The complexes are prone to nucleophilic attack by a wide range of nucleophiles. These nucleophiles may be delivered in an intramolecular fashion *via* the metal, or intermolecularly. In solution the π-allyl complex normally exists as a mixture of both π-allyl and σ-alkyl complexes, and it is possible for reactions to take place in either mode.



## 2. Sources of palladium complexes

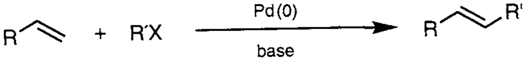
There are many readily available complexes of palladium(0) and palladium(II). Tetrakis(triphenylphosphine)palladium(0), $Pd(PPh_3)_4$, and tris(dibenzylideneacetone)dipalladium(0), $Pd_2(dba)_3$, or the chloroform complex, $Pd_2(dba)_3{\cdot}CHCl_3$, which is air stable, are the most common sources of palladium(0). $Pd(PPh_3)_4$ is bright yellow in colour when freshly synthesised, but is mildly air sensitive and is best stored under an inert atmosphere. The commercially obtained material is of variable quality, but generally good enough for most reactions.

Palladium(II) complexes are generally more stable than their palladium(0) counterparts. $PdCl_2$ exists as a polymer and is relatively insoluble in most organic solvents. However, $(PhCN)_2PdCl_2$ and $(MeCN)_2PdCl_2$ (both easily prepared from $PdCl_2$) can be thought of as soluble forms of $PdCl_2$, as the nitrile ligands are readily displaced in solution. Bis(phosphine) palladium(II) complexes are air stable and readily prepared from $PdCl_2$; many are commercially available.

In reactions where palladium(0) is required to start the catalytic process, formation of the active complex may be achieved *in situ* by the reduction of a suitable palladium(II) complex, e.g. $Pd(OAc)_2$. This process also has the advantage that any phosphine may be used in the reaction, without the need to synthesise and isolate the corresponding palladium(0) phosphine complex. Using this method, only 2–3 equiv of phosphine may be used, rendering the resulting palladium(0) complex coordinatively unsaturated and therefore very reactive. A good example of this is the use of $Pd(OAc)_2/P(o\text{-tolyl})_3$ in the protocol for the Heck reaction (Protocol 1 in this chapter). Another method for the *in situ* reduction of palladium(II) is the use of DIBAL-H as the reductant.[4] This has been used by Trost in trimethylenemethane (TMM) [3 + 2] cycloaddition reactions, an example of which is also given in this chapter (Protocol 7).

## 3. The Heck reaction

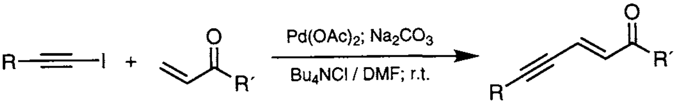
The palladium-catalysed addition of vinyl or substituted vinyl groups to organic halides or triflates, the Heck reaction, is one of the most synthetically useful palladium-catalysed reactions. The method is very efficient, and carries out a transformation on alkenes **6** that frequently cannot be accomplished in 'one pot' by more traditional techniques.



**6**

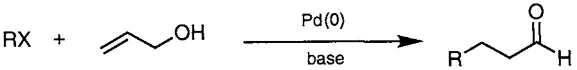
As outlined in the introduction to this chapter, the choice of substrates R'X is limited to aryl, heteroaryl, vinylic and benzylic halides, as the presence of a sp$^3$-carbon in the β-position carrying a hydrogen rapidly results in β-hydride elimination. The reaction tolerates a variety of functional groups, and works well with both electron withdrawing and electron donating groups on either substrate. The mechanism, as outlined in detail in the introduction (Fig. 2.1), involves the oxidative addition of the halide, insertion of the alkene, and elimination of the product by a β-hydride elimination process. The palladium(0) catalyst is then regenerated by a base. With alkenic substrates that are unsymmetrical, the alkyl group of the alkyl-palladium intermediate acts as the largest group, and therefore adds at the less hindered end of the double bond, providing there are no over-riding electronic factors. In the β-hydride elimination step, the palladium and hydride must be co-planar for reaction to take place, as this is a *syn*-elimination process. As a result of steric interactions, the R group will tend to eclipse the smallest group on the adjacent carbon as elimination occurs, leading predominantly to a *trans* double bond in the product.

The reaction has also been extended to alkynyl halides, although this is less well documented. For example, the reaction of 1-iodoalkynes **7** with α,β-unsaturated substrates may be carried out under very mild phase-transfer conditions, with moderate yields.[5]



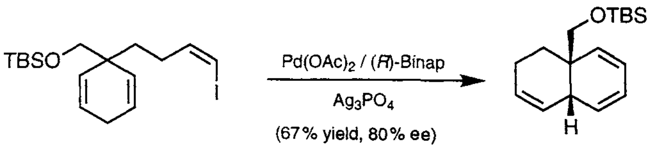
**7**

The reaction of allylic substrates frequently leads to a rearranged product resulting from double bond migration, as shown by the reaction of the allylic alcohol **8**.



**8**

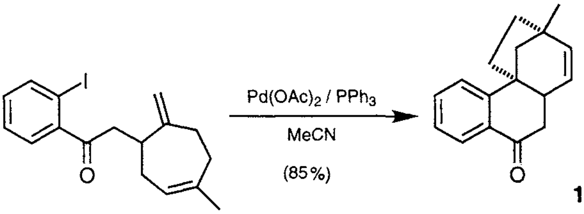
More recently, the Heck reaction has been used in cascade cyclisations, and under enantioselective conditions.[6] For example, the intramolecular synthesis of decalin derivative **9** has been achieved in good enantiomeric excess, using an optically pure phosphine (Binap) as part of the palladium catalyst.[7]



**9**

The presence of silver ions accelerates the reaction as well as preventing double bond isomerisation in the original substrate. The use of a non-coordinating counterion base was found to be essential, and it is thought that this prevents disruption of the ideal square planar transition state.

The use of palladium catalysts in the construction of complex ring systems, using the Heck reaction, has also generated widespread interest.[8] Grigg has shown that spiroindoles may be synthesised using this methodology, creating two or more new rings in one step.[9] Overman has also used an intramolecular Heck reaction to construct the ring system of scopadulcic acid B **10** as part of a total synthesis project.[10]



**10**

The protocol given for the Heck reaction, in which the aromatic bromide **11** is coupled with an α,β-unsaturated ester in excellent yield, is representative.

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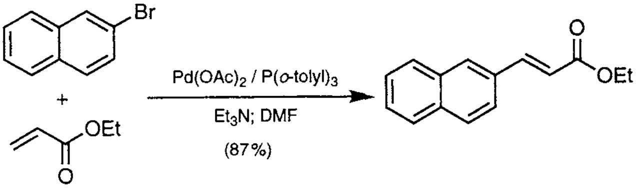
## Protocol 1.
## Heck reaction of 2-bromonaphthalene (Structure 11) and ethyl acrylate

**Caution!** All procedures should be carried out in a fume hood. Disposable vinyl or latex gloves and safety glasses should be worn.

**11**



### *Equipment*

- Stirrer hot plate
- Two-necked, round-bottomed flask (250 mL)
- Single-necked, round-bottomed flask (250 mL)
- Septum
- Needles (medium gauge)
- Source of dry argon

- Teflon-covered magnetic stirrer bar (2.5 cm long)
- All-glass syringes with needle-lock Luers (2 × 2 mL)
- Water-jacketed condenser
- Oil bath
- Chromatography column (45 cm × 4 cm)
- Source of vacuum (1 mmHg)

*Material*

| | |
|---|---|
| • Dry DMF,[a] 70 mL | **irritant** |
| • Palladium acetate (FW 224.5), 104 mg, 0.48 mmol | |
| • Tri(*o*-tolyl)phosphine (FW 304.4), 588 mg, 1.96 mmol | **irritant** |
| • Ethyl acrylate (FW 100.1), 1.2 mL, 11.1 mmol | **flammable liquid, cancer-suspect agent** |
| • Triethylamine[b] (FW 101.2), 1.6 mL, 11.5 mmol | **flammable liquid, corrosive** |
| • 2-Bromonaphthalene **11** (FW 207.1), 2.0 g, 9.64 mmol | |
| • Ethyl acetate technical grade | **flammable liquid, irritant** |
| • Petroleum ether (40-60) | **flammable liquid, toxic** |
| • Dichloromethane | **toxic, irritant** |
| • Silica gel (80 g) | **irritant** |

1. Clean all glassware, the stirrer bar and syringes and dry overnight in a hot oven before use.
2. Clamp the two-necked flask (containing the stirrer bar) fitted with the condenser, in the oil bath above the stirrer hot plate. Fit the argon source to the top of the condenser. Flush the assembly with argon by allowing the gas to flow through the flask for a few seconds before sealing the apparatus by fitting the septum.
3. Remove the septum and put palladium acetate (108 mg, 0.48 mmol), tri(*o*-tolyl)phosphine (588 mg, 1.96 mmol), and 2-bromonaphthalene (2 g, 9.64 mmol) into the flask. (Moderate the argon flow to facilitate this operation.)
4. Charge the flask with dry DMF (70 mL), flush the apparatus again with argon, and replace the septum.
5. Add triethylamine (1.6 mL, 11.5 mmol) and ethyl acrylate (1.2 mL, 11.1 mmol) through the septum using the 2 mL syringes.
6. Heat the mixture to reflux for 3 h, using the oil bath at *ca.* 160°C.
7. After cooling, transfer the mixture to a single-necked round-bottomed flask (250 mL) and remove the solvent and excess volatile reagents on a rotary evaporator, using a vacuum pump (1 mmHg).
8. Suspend 80 g of silica gel in a 9:1 mixture of petroleum ether (40-60)/ethyl acetate, and load into the chromatography column.[c]
9. Dissolve the crude product of the reaction in *ca.* 4 mL of dichloromethane and load onto the top of the column.
10. Elute the material with a 9:1 mixture of petroleum ether (40-60)/ethyl acetate.
11. Pool the appropriate fractions, remove the solvent under reduced pressure, and dry the product under high vacuum. The product is isolated as a white solid (1.9 g, 87%).

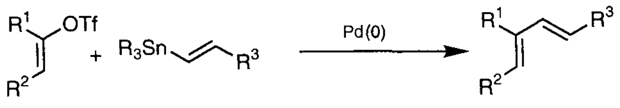
*Data*

M.p. 62–63°C. $\delta_H$(200 MHz, solvent $CDCl_3$, reference $SiMe_4$): 1.36 (3H, t, $J$ = 7.2 Hz), 4.29 (2H, q, $J$ = 7.2 Hz), 6.55 (1H, d, $J$ = 16.0 Hz), 7.47–7.96 (8H, m). $\delta_C$(63 MHz, $CDCl_3$, $SiMe_4$): δ 14.3, 60.4, 118.4, 123.4, 126.6, 127.1, 127.7, 128.5, 128.6, 129.8, 114.5, 131.9, 133.2, 134.1, 166.9.

[a] DMF was dried by distillation from $CaSO_4$ under reduced pressure and stored over molecular sieves.
[b] Triethylamine was dried by distillation from $CaH_2$.
[c] Solvents for chromatography were distilled before use.

## 4. The Stille coupling

Since the first reported use in the late 1970s, the Stille coupling has been widely used for the coupling of both aromatic and vinylic systems.[3,11]

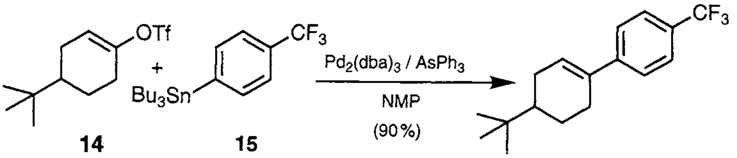


**12** **13**

The mechanism (see Fig. 2.2) involves the oxidative addition of the vinyl or aromatic triflate or halide **12** to give a palladium intermediate. This then undergoes a transmetalation reaction with the organostannane **13**, giving an organopalladium intermediate in which both components are σ-bound. This complex then undergoes a reductive elimination step, releasing the product and thereby regenerating the palladium(0) catalyst. The reaction will also occur if a vinyl or aryl halide is used in place of the analogous triflate. However, the triflates have been more widely used as they are readily prepared from phenols or enolisable aldehydes or ketones. In these reactions, the presence of a source of halide (typically LiCl) is generally (but not always) required. It is thought that this is because the triflate merely acts as a counterion to the palladium rather than a ligand, and that a ligand is required, giving the desired square planar geometry, for the transmetalation to occur.

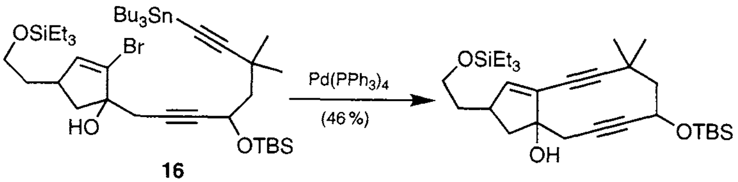
The phosphine or other ligand that is used to stabilise the palladium(0) catalyst can have a dramatic effect on the rate of the reaction. Both tri(2-furyl)phosphine and triphenylarsine can be used in place of the more normal triphenylphosphine in reactions where this ligand gives poor yields.[12] Indeed, the protocol for the Stille reaction between vinyl triflate **14** and organostannane **15** contained in this chapter (Protocol 2) is an excellent example of this. The reaction was originally reported not to proceed.[13] However, with triphenylarsine, Roth and co-workers have obtained excellent yields under mild conditions, without the need for added LiCl.[14]

The Stille reaction, which represents over 50% of all 1992 cross-coupling



**14** **15**

reactions[14] has been used in total synthesis with excellent results. Nicolaou's synthesis of rapamycin,[15] for example, uses the reaction in the macrocyclisation step, and the synthesis of indanomycin is also a good example of the Stille reaction at work.[16] The reaction may also be carried out intramolecularly and with alkynyl stannanes such as **16** instead of the more normal aryl or vinyl stannanes.[17]



**16**

Acid chlorides may also be used as substrates for the reaction leading to carbonylated products.[18] However, an atmosphere of carbon monoxide is frequently required to prevent decarbonylation after the oxidative addition step.[19] More recently, it has been shown that carbonylated products may also be accessed by performing the normal Stille reaction in the presence of carbon monoxide. Initially these reactions were performed under high pressures,[20] but recent developments have shown that the reaction can take place in a carbon monoxide saturated solution, under one atmosphere of pressure.[21] Using these conditions, excellent yields of the carbonylated product can be obtained, without any of the normal coupling product being present. An example of a carbonylative Stille coupling, which generates the unsaturated ketone **17**, is also given in this chapter (Protocol 3).

## Protocol 2
## Stille Coupling of 4-*t*-butyl-cyclohexen-1-yloxytriflate (Structure 14) with *p*-(trifluoromethyl)phenyltributyltin (Structure 15)

**Caution!** Triphenylarsine is very toxic. All procedures should be carried out in an efficient fume hood. Disposable vinyl or latex gloves and safety glasses should be worn.

*Equipment*

- Stirrer hotplate
- Oil bath
- Thermometer
- Two-necked, round-bottomed flask (25 mL)
- Pear-shaped flask (25 mL)
- Septa

## **Protocol 2** *Continued*

- All-glass syringe with a needle-lock Luer (10 mL)
- All-glass syringe with a needle-lock Luer (1 mL)
- Stainless steel needle (12", 20 gauge)
- Stainless steel needle (3", 22 gauge)
- Teflon-covered magnetic stirrer bar
- Large desiccator
- Vacuum/argon manifold (Figs 7.1 and 7.2)
- Büchner funnel with Whatman no. 1 filter paper 4.25 cm
- Glass wool
- Chromatography column (55 cm × 4 cm)
- Separating funnel (250 mL)

### *Material*

| | |
|---|---|
| • Triphenylarsine (FW 306.2), 92 mg, 0.3 mmol | **highly toxic** |
| • Tris(dibenzylideneacetone)dipalladium(0) (FW 915.7), 33.2 mg, 0.036 mmol | |
| • 4-*t*-Butyl-cyclohexen-1-yloxytriflate[a] (FW 435.1), 1.15 g, 4.0 mmol | |
| • *p*-(Trifluoromethyl)phenyltributyltin[a] (FW 435.1), 1.9 g, 4.4 mmol | **highly toxic** |
| • Anhydrous *N*-methylpyrrolidinone (NMP), *ca.* 10 mL | **irritant, hygroscopic** |
| • 1 M potassium fluoride solution | **toxic, corrosive** |
| • Ethyl acetate (HPLC grade), *ca.* 100 mL | **flammable liquid, irritant** |
| • Hexane (HPLC grade), *ca.* 1 L | **flammable liquid, irritant** |
| • Silica gel for chromatography | **irritant** |

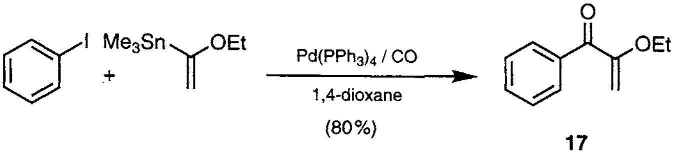
1. Place all glassware, syringes and needles in an electric oven for at least 2 h at 130°C. Before use, remove from the oven, and allow to cool to room temperature in the desiccator.
2. Clamp the two-necked flask over the stirrer hot plate, insert the stirrer bar, and cap with two septa.
3. Remove a septum and quickly put triphenylarsine (92 mg, 0.3 mmol), the triflate (1.15 g, 4.0 mmol), and the palladium catalyst (33.2 mg, 0.072 mmol) into the flask. Replace the septum, add NMP (5 mL) by syringe, and begin stirring.
4. Connect the flask to the vacuum/argon manifold by a flexible tubing connection equipped with a hypodermic needle, and saturate the solution with argon by applying three cycles of vacuum/argon (chapter 7, Protocol 2).
5. In the pear-shaped flask, dissolve the stannane (1.91 g, 4.4 mmol) in NMP (2 mL), and saturate the solution with argon as above.
6. Stir the flask containing the palladium complex until the deep red colour is discharged. When all the solids are dissolved, and the solution is a yellow or pale green colour, add the solution of the stannane using the dry 1 mL syringe. Rinse the flask with fresh aliquots of NMP (2 × 0.5 mL).
7. Heat the reaction mixture to *ca.* 55°C for 21 h. Monitoring of the reaction by TLC (hexane eluent) indicates all the triflate is consumed after this time.
8. Cool the reaction, and add 1 M aqueous potassium fluoride solution (5 mL). Stir for 30 min at room temperature, pour into ethyl acetate (50 mL), and then filter the resulting solution. Rinse the solids with a further portion of ethyl acetate (50 mL).
9. Dry the ethyl acetate solution over sodium sulfate, filter, and remove the solvent on a rotary evaporator.

10. Load the chromatography column with silica gel to reach a height of 19 cm. Pour on hexane and flush under pressure to remove trapped air.
11. Dissolve the crude product in hexane (*ca.* 3 mL), and load onto the top of the column. Elute the product with hexane.
12. Pool the appropriate fractions and remove the solvent under reduced pressure.
13. If necessary, the product may be recrystallised from methanol, giving colourless needles (90%, m.p. 84–85°C) which display the appropriate spectroscopic data.[14]

[a] 4-*t*-Butyl-cyclohexen-1-yloxytriflate[22] and *p*-(trifluoromethyl)phenyltributyltin[23] were prepared according to literature methods.

## Protocol 3.
## Carbonylative Stille coupling of iodobenzene and 1-ethoxy-(1-trimethylstannyl)ethene

**Caution!** Carbon monoxide is a highly toxic, flammable gas. All procedures should be carried out in an efficient fume hood. Disposable vinyl or latex gloves and safety glasses should be worn at all times.



**17**

### *Equipment*

- Stirrer hotplate
- Two-necked, round-bottomed flask (100 mL)
- Single-necked, round-bottomed flask (100 mL)
- Septum
- Teflon-covered magnetic stirrer bar (2.5 cm long)
- Syringe (500 μL)
- Source of dry argon
- Source of carbon monoxide
- Water-jacketed condenser
- Oil bath
- Chromatography column (35 cm × 3 cm)
- Dreschel bottle
- Needle (wide bore)
- Dry flexible tubing
- Oil bubbler

### *Material*

| | |
|---|---|
| • Iodobenzene (FW 204.0), 816 mg, 4 mmol | **irritant, light sensitive** |
| • 1-Ethoxy-(1-trimethylstannyl)ethene (FW 234.9), 940 mg, 4 mmol | **moisture sensitive, irritant** |
| • Tetrakis(triphenylphosphine)palladium(0) (FW 1155.6), 92 mg, 80 μmol | **air sensitive** |
| • Carbon monoxide | **highly toxic gas, flammable** |
| • 1,4-Dioxane,[a] 40 mL | **flammable, cancer-suspect agent** |
| • Ethyl acetate technical grade | **flammable liquid, irritant** |
| • Petroleum ether (40–60) | **flammable liquid, toxic** |
| • Silica gel for chromatography | **irritant** |

**Protocol 3** *Continued*

1. Clean all glassware, the stirrer bar, and syringe and dry overnight in a hot oven before use.
2. Clamp the two-necked flask (containing the stirrer bar) fitted with the condenser, in the oil bath above the stirrer hotplate. Fit the argon source to the top of the condenser. Flush the assembly with argon by allowing the gas to flow through the flask for a few seconds before sealing the apparatus by fitting the septum.
3. Remove the septum and put iodobenzene (816 mg, 4 mmol), 1-ethoxy-1-(trimethylstannyl)ethylene (753 μL, 940 mg, 4 mmol), tetrakis(triphenylphosphine)palladium (92 mg, 80 μmol), and 1,4-dioxane (40 mL) into the flask.
4. Attach the carbon monoxide cylinder, *via* the Dreschel bottle and flexible tubing, to the needle. Ensure the needle is securely attached to prevent the gas leaking.
5. Replace the argon source with an oil bubbler fitted to the top of the condenser. Pierce the septum with the needle and bubble carbon monoxide through the solution for 1 h whilst slowly warming the oil bath to 85°C. Ensure the gas is vented into the top of the fume hood *via* the oil bubbler.
6. Remove the needle from the flask. Replace the oil bubbler with a gas adapter fitted with a balloon of carbon monoxide gas, maintaining an atmosphere of carbon monoxide above the reaction mixture. Continue to heat the reaction mixture at 85°C for 18 h.
7. After cooling, transfer the mixture to a single-necked round-bottomed flask (200 mL) and remove the solvent on a rotary evaporator.
8. Suspend 50 g of silica gel in petroleum ether (40–60) and load into the chromatography column.[b]
9. Load the oily product directly onto the top of the column. Remove the tin residues from the material by eluting with 500 mL of petroleum ether. The product can then be eluted using a 9:1 mixture of petroleum ether (40–60)/ethyl acetate.
10. Remove the solvent under reduced pressure and dry the product under high vacuum. The product is isolated as a yellow oil (560 mg, 80%).

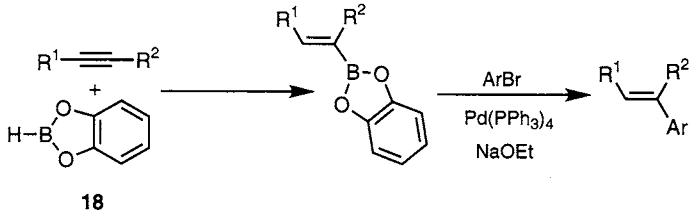
*Data*

$\delta_H$(250 MHz, solvent $CDCl_3$, reference $SiMe_4$): 1.38 (3H, t, $J$ = 7.0 Hz), 3.89 (2H, q, $J$ = 7.0 Hz), 4.75 (1H, d, $J$ = 2.8 Hz), 4.98 (1H, d, $J$ = 2.8 Hz), 7.35–7.57 (3H, m), 7.80–7.88 (2H, m). $\delta_C$(63 MHz, $CDCl_3$, $SiMe_4$): 14.0, 63.6, 94.5, 127.8, 129.5, 132.3, 136.5, 157.9, 191.2.

[a] 1,4-Dioxane was stored over molecular sieves before use. All other reagents were used as supplied.
[b] Solvents for chromatography were distilled before use.

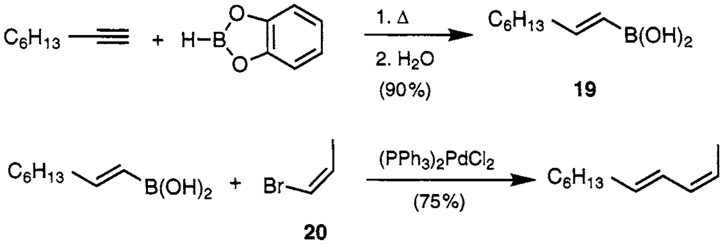
## 5. The Suzuki coupling

Since first being reported in 1979,[24] the Suzuki coupling has come to represent an important class of cross-coupling reactions, totalling 25% of all palladium-catalysed cross-coupling reactions in 1992.[14] The original report showed the reaction of an alkyl acetylene with catecholborane **18**, followed by coupling with an aromatic iodide or bromide.

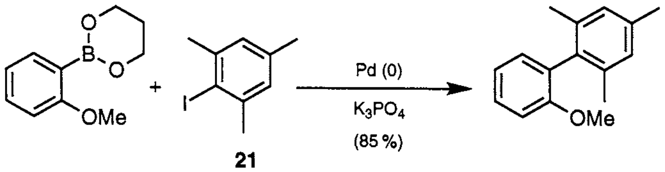


The mechanism is very similar to that of the Stille coupling. Oxidative addition of the vinylic or aromatic halide to the palladium(0) complex generates a palladium(II) intermediate. This then undergoes a transmetalation with the alkenylboronate, from which the product is expelled by reductive elimination, regenerating the palladium(0) catalyst.

The importance of the reaction stems from the ability to preserve alkene geometry in both starting materials. A good example of this forms the basis for Protocol 4. Thus, the (*E*)-alkenylboronate **19** synthesised from 1-octyne couples with the (*Z*)-alkenylbromide **20**, leading to (*E*) and (*Z*) double bonds in the product.

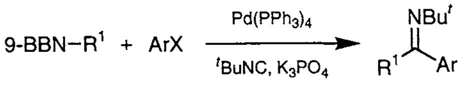


Sterically demanding substrates such as **21** are tolerated well,[25] and the methodology has been used in a wide range of aryl–aryl cross-couplings,



including the synthesis of hindered binaphthol derivatives, used as ligands in asymmetric synthesis.[26]

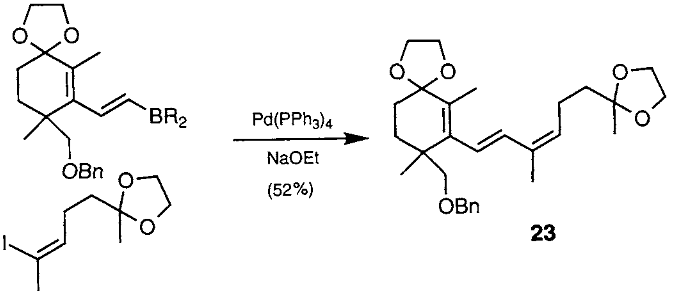
The Suzuki coupling may be used to prepare ketones by two methods. Firstly by performing the usual coupling in the presence of *t*-butylisonitrile, acidic hydrolysis of the resulting ketimine **22** gives the corresponding ketone in good yield.[27] The mechanism of the reaction is thought to involve the insertion of the isonitrile into the original oxidative addition product, forming an iminoacyl intermediate.



**22**

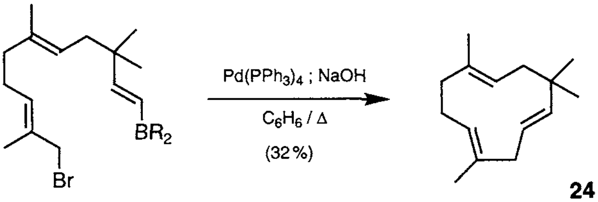
Similarly, the reaction of substrates under normal coupling conditions, but in the presence of an atmosphere of CO, gives excellent yields of the ketones directly, without the need for hydrolysis of an intermediate species.[28]

Due to the excellent stereoselectivity of the Suzuki coupling, the reaction has been used in the synthesis of the unsaturated units of a range of natural products. In an example drawn from the synthesis of trisporol B, a dienylic borane and a vinyl iodide are coupled to give the triene **23**.[29]



**23**

Macrocyclisations have also successfully been carried out using this methodology. The generation of the 11-membered ring of humulene **24** from an *allylic* bromide and vinylic borane in 32% yield is a good example.[30]



**24**

## Protocol 4.
## Synthesis of (2*Z*, 4*E*)-undecadiene

**Caution!** All procedures should be carried out in a fume hood. Disposable vinyl or latex gloves and safety glasses should be worn.

### *Equipment*

- Stirrer hotplate
- Two-necked, round-bottomed flask (200 mL)
- Teflon-covered magnetic stirrer bar
- Oil bath
- Reflux condenser
- All-glass syringes with a needle-lock Luer (volume appropriate for quantity of solution to be transferred)
- Needles (6", medium gauge)
- Source of dry nitrogen
- Büchner flask (100 mL)
- Büchner funnel
- Appropriately sized filter paper
- Water-jacketed semi-micro short-path distillation apparatus
- Septa
- Nitrogen adapter
- Separating funnel (100 mL)
- Beaker (50 mL)

### *Material*

| | |
|---|---|
| • 1-Octyne[a] (FW 110.2), 5.9 mL, 40 mmol | **flammable, irritant** |
| • Catecholborane[b] (FW 119.9), 4.9 mL, 44 mmol | **flammable, moisture sensitive** |
| • Bis(triphenylphosphine)palladium(II) chloride (FW 701.8), 0.42 g, 0.6 mmol | **hygroscopic** |
| • Dry toluene, 45 mL | **flammable, toxic** |
| • (*Z*)-1-Bromo-1-propene **20** (FW 120.9), 2.8 mL, 33 mmol | **flammable, irritant** |
| • Aqueous 3 M KOH solution, 26.7 mL, 80 mmol | **corrosive** |
| • Hexane for extraction, 40 mL | **flammable, irritant** |
| • Saturated brine | |
| • Magnesium sulfate | |

1. Clean all glassware, syringes, needles and the stirrer bar and dry in an oven (*ca.* 120°C) before use.
2. Clamp the two-necked flask (containing the stirrer bar) fitted with the condenser, in the oil bath above the stirrer hotplate. Fit the nitrogen source to the top of the condenser. Flush the assembly with nitrogen by allowing the gas to flow through the flask for a few seconds before sealing the apparatus by fitting the septum.
3. Assemble the syringes and allow to cool to room temperature in a desiccator.
4. Put 1-octyne (5.9 mL, 40 mmol) into the flask through the septum using a syringe. To this, add catecholborane (4.9 mL, 44 mmol) dropwise using a syringe through the septum over a period of 1 min whilst stirring the solution.
5. Stir the mixture for 30 min, and then warm the flask slowly to 70°C. Keep the mixture at this temperature for 2 h.
6. Cool the flask using an ice-water bath. Quench the excess borane by careful addition of water (1–2 mL).
7. After the evolution of hydrogen has ceased, disconnect the nitrogen

**Protocol 4** *Continued*

source, add a further amount of water (40 mL), stir for 1 h at room temperature, and then heat to 70–80°C for 1 h.

8. Cool the flask to 0°C, stand for 2 h, and then collect the precipitate by Büchner filtration through a filter paper, with suction. Wash the solid three times with ice-cold water (3 × 12 mL). Dry the solid overnight in a beaker. The octenylboronic acid obtained can be used for the coupling reaction without further purification (5.63 g, 90%).
9. Clean and dry the apparatus and assemble the flask and condenser as before in the oil bath placed on the stirrer hot plate.
10. Remove the septum and put bis(triphenylphosphine)palladium(II) chloride (0.42 g, 0.6 mmol) and 1-octenylboronic acid (4.7 g, 30 mmol) into the flask. Flush the apparatus with nitrogen and replace the septum.
11. Add toluene (45 mL), (*Z*)-1-bromo-1-propene (2.8 mL, 33 mmol), and aqueous KOH solution (26.7 mL, 80 mmol), using a syringe, through a septum. Stirring becomes difficult due to the precipitation of a light brown solid.
12. Heat the flask to 70°C for 3 h with stirring. After this time, most of the precipitate dissolves, resulting in a brown solution.
13. Cool the flask to room temperature and add hexane (30 mL) to dilute the reaction mixture.
14. Transfer the mixture to a separating funnel. Discard the basic aqueous layer, and wash the organic fraction with brine (2 × 30 mL). (If visualisation of the two layers proves difficult, add more water.) Dry the organic layer over magnesium sulfate, filter, and remove the solvent under reduced pressure.
15. Transfer the oily residue to the distillation apparatus. Distil the crude product under reduced pressure (84–86°C, 11 mmHg) to obtain (2*Z*,4*E*)-undecadiene (3.4 g, 75%).

*Data*

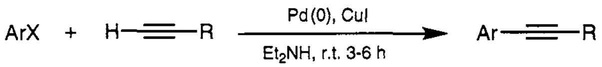
$\delta_H$(300 MHz, solvent $CDCl_3$, reference $SiMe_4$): 0.89 (3H, t, $J$ = 7.1 Hz), 1.23–1.43 (8H, m), 1.74 (3H, dd, $J$ = 7.1, 1.7 Hz), 2.11 (2H, td, $J$ = 7.2, 7.0 Hz), 5.37 (1H, dq, $J$ = 10.9, 7.1 Hz), 5.66 (1H, dt, $J$ = 15.1, 7.0 Hz), 5.97 (1H ddd, $J$ = 11.0, 10.9, 1.7 Hz), 6.33 (1H, ddd, $J$ = 15.1, 11.0, 1.2 Hz).

[a] 1-Octyne was purified by distillation prior to use.

[b] Catecholborane was distilled under nitrogen (58°C, 52 mmHg) and stored in a fridge under an inert atmosphere.

## 6. The Sonogashira coupling

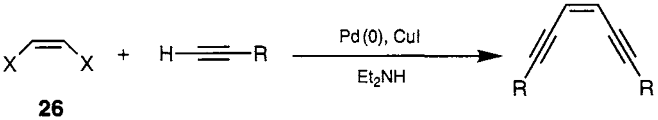
The coupling of terminal alkynes **25** with aryl or vinyl halides under palladium catalysis is known as the Sonogashira reaction. The catalytic process requires the use of a palladium(0) complex, is performed in the presence of base, and generally uses copper iodide as a co-catalyst.



**25**

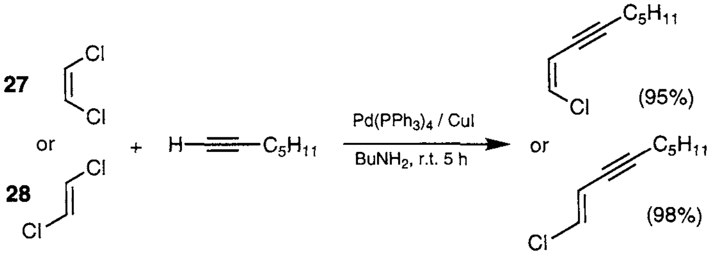
The reaction tolerates a wide range of substrates, including heteroaromatic halides, aryl and alkyl alkynes. The mild conditions usually employed (frequently room temperature) means that the reaction can be used with thermally sensitive substrates. The mechanism of the reaction is similar to that of the Stille and Suzuki couplings. Oxidative addition of the organic halide gives a palladium(II) intermediate which then undergoes a transmetalation reaction with the alkynylcuprate (generated from the terminal alkyne, base, and copper iodide). The resulting complex then undergoes reductive elimination giving the product and regenerating the palladium(0) catalyst. In many reactions, bis(triphenylphosphine)palladium(II) chloride is used as the source of palladium. This is rapidly reduced *in situ* to give a co-ordinatively unsaturated, catalytically active, palladium(0) species.

The reaction has received widespread current usage as a result of the huge interest generated by the potential of ene-diyne antibiotics. Symmetrical ene-diyne moieties of such molecules may be synthesised in one step from the appropriate alkyne and (*Z*)-dihaloethene **26**. More usually, however, the reaction is performed sequentially, thereby allowing different functionality on each of the alkyne units.



**26**

As is the case with the Suzuki coupling, the geometry of the alkene is generally preserved.[31] This is illustrated by the couplings of **27** and **28** with 1-heptyne.



both > 99 % isomeric purity

The protocol given for this reaction involves the coupling of acetylene with 2 equiv. of iodobenzene **29** and is representative of the reaction.

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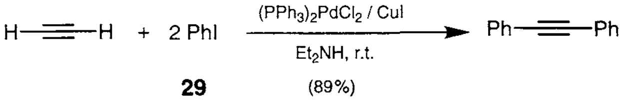
## Protocol 5. Synthesis of diphenylacetylene

**Caution!** All procedures should be carried out in a fume hood. Disposable vinyl or latex gloves and safety glasses should be worn.



**29**

### *Equipment*

- Magnetic stirrer
- Three-necked, round-bottomed flask (100 mL)
- Single-necked, round-bottomed flask (100 mL)
- Reflux condenser
- Teflon-covered magnetic stirring bar
- Source of nitrogen
- Nitrogen adapter
- Mercury bubbler
- Septum
- An empty 200 mL Dreschel bottle as a safety trap for acetylene cylinder
- Gas inlet tube
- Separating funnel (200 mL)
- Source of vacuum
- Chromatography column (10 cm × 2.7 cm)

### *Material*

| | |
|---|---|
| • Diethylamine,[a] 60 mL | **flammable, irritant** |
| • Copper(I) iodide (FW 190.4), 20 mg, 0.11 mmol | **irritant** |
| • Bis(triphenylphosphine)palladium(II) chloride (FW 701.89), 30 mg, 0.043 mmol | **irritant** |
| • Iodobenzene[a] **29** (FW 204.02), 2.40 g, 10 mmol | **light sensitive, irritant** |
| • Acetylene gas (cylinder) | **flammable** |
| • Toluene, *ca.* 400 mL | **flammable** |
| • Anhydrous calcium chloride (or sodium sulfate) | **irritant, hygroscopic** |
| • Technical hexane, *ca.* 500 mL | **flammable** |
| • Aluminium oxide, activated, neutral, 150 mesh for chromatography | **irritant** |

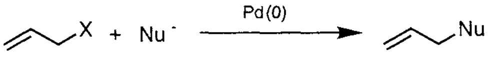
1. Clean all glassware and the magnetic stirrer bar, and dry in an oven before use.
2. Clamp the three-necked flask (containing the stirrer bar) fitted with the condenser above the magnetic stirrer. Attach the mercury bubbler to the top of the condenser. Fit the nitrogen adapter to the flask and flush the apparatus with nitrogen for a few seconds before sealing the system with the septum.
3. Remove the septum and put bis(triphenylphosphine)palladium(II) chloride (30 mg, 0.043 mmol), freshly distilled iodobenzene (2.40 g, 10 mmol) and diethylamine (60 mL) into the flask. (Moderate the flow of nitrogen to facilitate this.)

4. Flush the equipment with nitrogen, and add copper(I) iodide (20 mg, 0.11 mmol). Flush the equipment again, and replace the septum.
5. Replace the nitrogen adapter with a gas inlet tube linked to the acetylene cylinder *via* a Dreschel bottle. Adjust the gas inlet tube to extend below the surface of the liquid.
6. Pass a slow stream of acetylene through the gas inlet tube (about 1–2 bubbles per second, otherwise appreciable evaporation of the diethylamine will occur). The reaction should begin immediately as indicated by formation of a white precipitate of diethylamine hydroiodide.
7. Bubble acetylene gas through the reaction mixture for 6 h at room temperature.
8. Transfer the mixture to a single-necked round-bottomed flask and remove the solvent under reduced pressure. Transfer the residue to a separating funnel containing water (50 mL). Extract the product with toluene (3 × 50 mL). Wash the combined organic fractions with water (2 × 20 mL), and dry them over calcium chloride or sodium sulfate.
9. Filter, remove the solvent under reduced pressure, and suspend the residue in a small amount of hexane.
10. Pack a chromatography column (10 cm × 2.7 cm) with neutral alumina in hexane. Load the product onto the column and elute with hexane until all the iodobenzene is removed and then elute with a 1:1 mixture of hexane/toluene.
11. Pool the appropriate fractions and remove the solvent under reduced pressure.
12. Recrystallisation from ethanol (*ca.* 10 mL) affords 1.58 g (89%) of white needles (m.p. 60–61°C).

[a] Diethylamine and iodobenzene were freshly distilled before use.

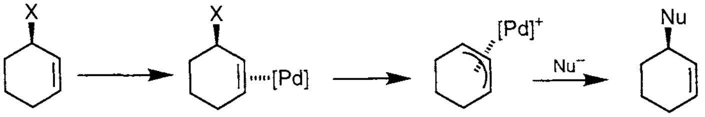
## 7. Allylic alkylations

The use of π-allyl complexes of palladium as intermediates in nucleophilic displacement reactions enables both the stereochemistry and regiochemistry of the reaction to be controlled.



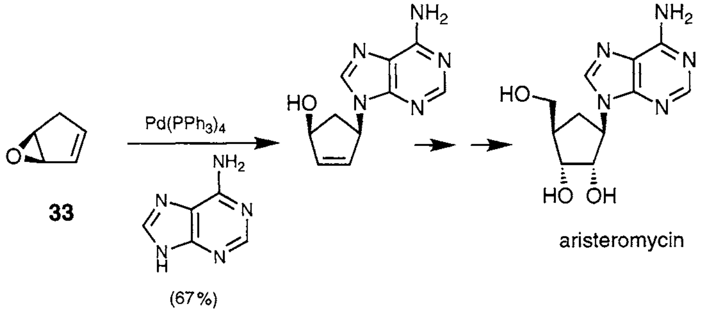
**30**

Whilst allylic acetates (**30**, X = OAc) are most commonly used, a wide range of other functionality (X = Cl, Br, OPh, $OCO_2R$) will perform a similar role. For carbon–carbon bond formation, stabilised enolates such as malonates may be used as nucleophiles, but the reaction is frequently equally successful with alkoxides, amines, and thioalkoxides. The reaction usually proceeds with *retention* of configuration at the reacting centre. At first, this might appear puzzling, as one would reasonably expect the oxidative addition/nucleophilic attack sequence to invert the stereocentre. However, the normal pathway of the reaction is coordination of the allylic acetate to give **31**, followed by an oxidative elimination step, which proceeds with inversion. Thereafter, the nucleophile attacks from the less-hindered face of the resulting π-allyl complex **32** (i.e. away from the metal) leading to overall *retention* of configuration.[32]



**31** **32**

The 'double inversion' process has been used in the synthesis of aristeromycin from epoxycyclopentadiene **33**.[33]



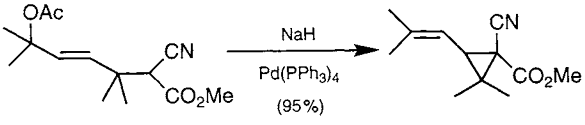
**33**

aristeromycin

It is noteworthy that the 1,4-*syn* stereochemistry of such carbocycles may be produced in one step using this methodology. Base is not required in this reaction, as the opening of the epoxide generates the required alkoxide *in situ*.

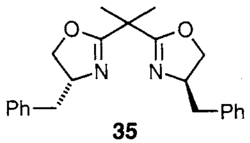
π-Allyl intermediates may also be used in cyclisation reactions,[34] including the synthesis of three-membered rings such as **34** using an intramolecular nucleophilic displacement.[35]

More recently, a number of research groups have shown that the use of



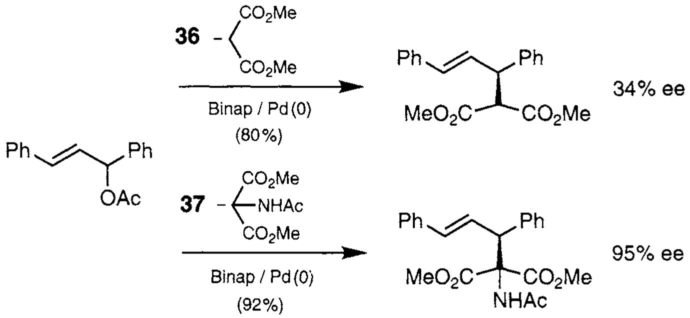
**34**

optically pure ligands enables the allylic alkylation reaction to be carried out on some substrates with good enantiomeric excess.[36] Initial studies of enantioselective allylic alkylations using readily available chiral phosphines as the ligand gave relatively low values.[37] Since these original studies however, improvements have been made by changing the ligand. Excellent enantioselectivity (up to 88% ee) may be obtained, for example, with optically pure bisoxazolines such as **35**.[38,39]



**35**

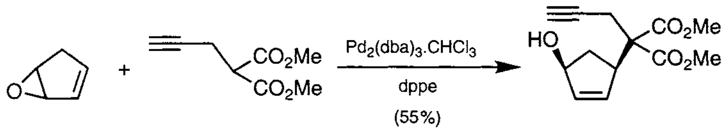
It has also been demonstrated that the choice of nucleophile can have a dramatic effect on the enantioselectivity of an allylic alkylation reaction, as indicated for the nucleophiles **36** and **37**.[40]



Williams has shown that the use of non $C_2$-symmetric ligands is equally effective. The regiochemical approach of the nucleophile is influenced by the relative *trans* effect of the two coordinating atoms in the optically pure ligand (i.e. approach *trans* to sulfur and phosphorus is favoured over nitrogen).[41,42] Protocol 6, which involves the reaction of epoxycyclopentadiene **33** with dimethyl propargylmalonate **38**, demonstrates the excellent stereochemical control that can be obtained using this reaction.

## Protocol 6.
## Allylic alkylation of epoxycyclopentadiene (Structure 33) with dimethyl propargylmalonate (Structure 38)

**Caution!** All procedures should be performed in a fume hood. Disposable vinyl or latex gloves and safety glasses should be worn.



**33** **38**

### *Equipment*

- Schlenk tube (25 mL) (Fig. 7.3)
- Single-necked, round-bottomed flask (25 mL)
- Magnetic stirrer
- Teflon-covered magnetic stirrer bar (1 cm × 3 mm)
- Source of dry nitrogen
- Septa
- All-glass syringe with a needle-lock Luer (10 mL)
- All-glass syringe with a needle-lock Luer (1 mL)
- Chromatography column (*ca.* 25 cm × 2 cm)

### *Material*

| | |
|---|---|
| • Epoxycyclopentadiene[a] (FW 82.1), 0.5 g, 6.1 mmol | **flammable** |
| • $Pd_2(dba)_3 \cdot CHCl_3$ (FW 1035.2), 158 mg 0.153 mmol | **irritant** |
| • 1,2-Bis(diphenylphosphino)ethane (dppe) (FW 398.4), 243 mg, 0.61 mmol | |
| • Dimethyl propargyl malonate[a] (FW 170.2), 1.24 g, 7.32 mmol | **flammable, irritant** |
| • THF (8 mL) | **flammable, irritant** |
| • Hexane | **flammable, irritant** |
| • Diethyl ether | **flammable, irritant** |
| • Silica gel for chromatography | **irritant** |

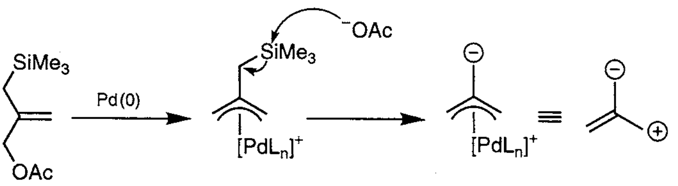
1. Clean all glassware, syringes and the magnetic stirrer bar, and dry in an oven before use.
2. Clamp the Schlenk tube containing the stirrer bar above the magnetic stirrer. Fit the nitrogen source to the side-arm of the Schlenk tube and flush the Schlenk tube with nitrogen by allowing the gas to flow through it for a few seconds before sealing the apparatus by fitting a septum.
3. Moderate the nitrogen flow, remove the septum, and put $Pd_2(dba)_3 \cdot CHCl_3$ (158 mg, 0.153 mmol), dppe (0.243 g, 0.61 mmol), and dimethyl propargyl malonate (1.24 g, 7.32 mmol) into the Schlenk tube.
4. Flush the Schlenk tube again with dry nitrogen, and replace the septum.
5. Using a syringe, add dry THF (8 mL), cool the Schlenk tube in an ice bath to 0°C and begin stirring.
6. Using a syringe, add epoxycyclopentadiene (0.5 g, 6.1 mmol), over a period of 2 h, maintaining the temperature at 0°C.

7. After addition is complete, maintain the temperature at 0°C for a further 3 h, and then allow the Schlenk tube to warm to room temperature overnight.
8. Transfer the mixture to the 25 mL single-necked round-bottomed flask, and remove the solvent under reduced pressure.
9. Suspend silica gel (*ca.* 40 g) in diethyl ether-hexane (3:2), and load into the chromatography column.
10. Dissolve the product in a little solvent and load onto the top of the column.
11. Elute the product using diethyl ether/hexane (3:2).
12. Pool the appropriate fractions and remove the solvent under reduced pressure, yielding the product as an oil (840 mg, 55%) which displays the appropriate spectroscopic data.[8]

[a] Epoxycyclopentadiene[43] and dimethylpropargyl malonate[44] were prepared using literature methods.

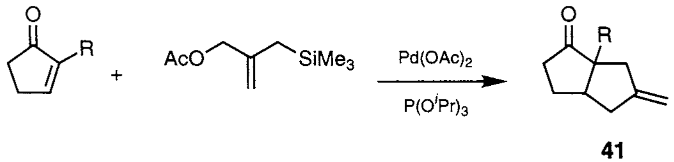
## 8. Trimethylenemethane [3 + 2] cycloaddition reactions

The presence of five-membered rings such as cyclopentanes, cyclopentenes, and dihydrofurans in a wide range of target molecules has led to a variety of methods for their preparation. One of the most successful of these is the use of the trimethylenemethane (TMM) [3 + 2] cycloaddition, catalysed by palladium(0) complexes. The TMM unit in these reactions is derived from 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate **39**. Formation of the palladium π-allyl complex is followed by removal of the trimethylsilyl group and nucleophilic attack of the resulting acetate ion, thus producing a zwitterionic palladium complex **40**.



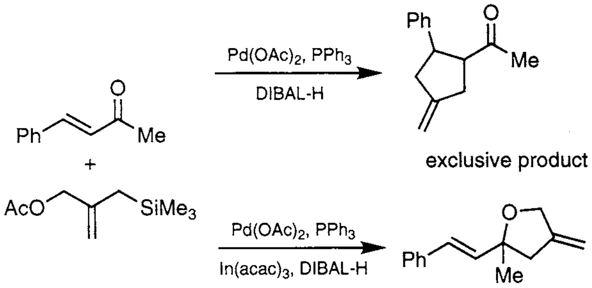
**39** **40**

Normally this is reacted with an alkene bearing electron withdrawing substituents, which make the substrate prone to Michael-type 1,4-addition. The resulting cyclisation product, exemplified by **41**, has an *exo* methylene functionality. The mechanism is thought to be stepwise, consisting of nucleophilic attack at carbon followed by attack of the resulting enolate on the π-allyl palladium unit.



**41**

The palladium(0) species required for the reaction is sometimes generated *in situ* by the reduction of palladium acetate with DIBAL-H.[4] The resulting palladium(0) intermediate is stabilised by phosphine or phosphite ligands. Whilst palladium(0), in the form of $Pd(PPh_3)_4$ for example, may be directly introduced, the work of Trost suggests that the best catalysts are prepared from $Pd(OAc)_2$ and $P(O^iPr)_3$.[45] Trost has shown that by using a small amount of a co-catalyst [most notably simple complexes of indium(III)], the reaction can be 'switched' to give a 1,2-reaction rather than the more normal 1,4-product, leading to substituted tetrahydrofurans such as **42**.[4]



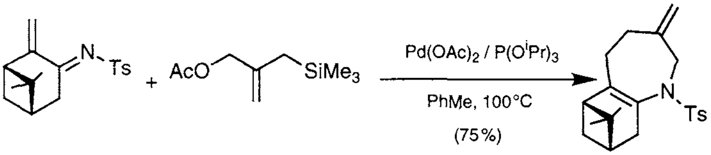
exclusive product

**42**

>96:4 selectivity

The cause of this remarkable selectivity switch is thought to be due to the relative stability of the two intermediates. Normal 1,4-addition leads to an enolate anion, the charge of which may be delocalised away from the oxygen centre. The presence of indium(III), however, stabilises the 1,2-addition product (an alkoxide), presumably forming an 'ate' complex. As the initial reaction of the TMM palladium complex with the α,β-unsaturated substrate is reversible, stabilisation of the 1,2-addition intermediate biases the equilibrium in favour of the eventual 1,2-cyclisation product.

The TMM [3 + 2] cycloaddition methodology may also be used in the preparation of nitrogen heterocycles by using imines as substrates.[46] The yields of the exomethylene pyrroles produced are generally excellent. Unlike their oxygenated analogues, α,β-unsaturated substrates were found to undergo exclusive 1,2-reaction to give the pyrrole, rather than 1,4-addition, to give the corresponding carbocycle. Interestingly, with the appropriate substrates, [4 + 3] cycloadditions which gave seven-membered ring products such as **43** were observed in preference to the [3 + 2] reaction.



**43**

Protocol 7, chosen for this reaction, is representative of the method described. Cycloaddition of the unsaturated diester gives the 1,4-cycloaddition product, with complete *exo* selectivity.

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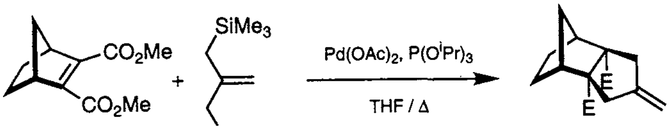
## Protocol 7.
## Preparation of *endo*-2,6-dimethoxy carbonyl-4-methylenetricyclo [5.2.1.0$^{2,6}$] decane (Structure 45)

**Caution!** All procedures should be performed in a fume hood. Disposable vinyl or latex gloves and safety glasses should be worn.



**44** **45**

E = $CO_2Me$

### *Equipment*

- Stirrer hot plate
- Two-necked, round-bottomed flask (100 mL)
- Water-jacketed condenser
- Oil bath
- Septum
- Teflon-covered magnetic stirrer bar
- Needles (medium gauge)
- All-glass syringes with a needle-lock Luer (volume appropriate for quantity of solution to be transferred)
- Bubbler
- Source of dry argon
- Chromatography column (10 cm × 25 cm)

### *Material*

| | |
|---|---|
| • Palladium acetate (FW 224.5), 0.2 g, 0.89 mmol | |
| • Tri(isopropyl)phosphite (FW 208.2), 1.11 g, 5.34 mmol | **toxic, moisture sensitive** |
| • Bicyclo[2.2.1]hept-2-ene dicarboxylic acid dimethyl ester[a] (FW 210.2), 6.27 g, 29.85 mmol | **irritant** |
| • 2-[(Trimethylsilyl)methyl]-2-propen-1-yl acetate (FW 186.3), 5.56 g, 29.85 mmol | **irritant** |
| • THF, 40 mL | **flammable, irritant** |
| • Hexane | **flammable, irritant** |
| • Diethyl ether | **flammable, irritant** |
| • Silica gel for chromatography | **irritant** |

1. Clean all glassware, syringes, needles, and the stirrer bar and dry overnight in an oven before use.
2. Clamp the two-necked flask (containing the stirrer bar) fitted with the condenser, in the oil bath above the stirrer hot plate. Fit the argon source to

**Protocol 7** *Continued*

the top of the condenser. Flush the assembly with argon by allowing the gas to flow through the flask for a few seconds before sealing the apparatus by fitting the septum.

3. Remove the septum, moderate the gas flow and put palladium acetate (0.2 g, 0.89 mmol) into the flask. Replace the septum and charge the flask with dry THF (20 mL) using a syringe by puncturing the septum on the reaction flask.
4. Put tri(isopropyl)phosphite (1.11 g, 5.34 mmol) into the flask using a syringe by puncturing the septum on the reaction flask. A yellow solution should form.
5. Add 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate (5.56 g, 29.85 mmol) and bicyclo[2.2.1]hept-2-ene dicarboxylic acid dimethyl ester (6.27 g, 29.85 mmol) in dry THF (20 mL) *via* syringe at room temperature with stirring.
6. Heat the mixture under reflux with stirring for 3.5 h.
7. On cooling, remove the solvent under reduced pressure using a rotary evaporator.
8. Load silica to a height of 16 cm into the chromatography column. Add a mixture of hexane/diethyl ether (4:1) onto the column and flush through under a positive pressure to remove any trapped air.
9. Transfer the crude oily product onto the top of the column, and elute with the above mentioned solvent system.
10. Pool the appropriate fractions, and remove the solvent under reduced pressure. The product is isolated as a colourless crystalline solid (63%, m.p. 52–53°C) which displays the appropriate spectroscopic data.[45]

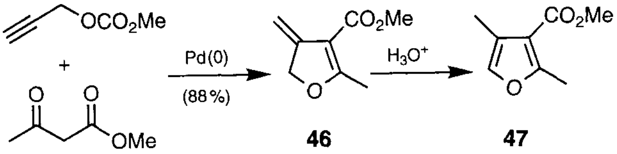
[a] Bicyclo[2.2.1]hept-2-ene dicarboxylic acid dimethyl ester[47] was prepared according to literature methods.

## 9. Furan annelation

The furan annelation reaction represents a new method for the preparation of this important class of compounds. Furans are widely found in nature, and highly functionalised furans are desirable targets in total synthesis work, either as products themselves, or as intermediates. Commercially available or readily accessible furans are usually limited to substitution at the more reactive 2- and 5-positions of the ring. The need for the preparation of furans with substitution at other positions on the ring, or with sensitive functional groups present, led to the development in 1987 of a palladium-catalysed method for their preparation.[48]

The original work used β-keto esters and propargyl carbonates as substrates. Under palladium(0) catalysis, these react to give *exo*-methylenefurans

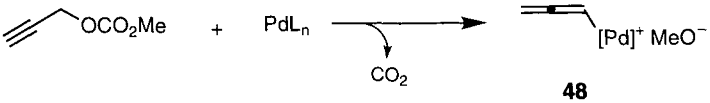
**46**, which isomerise readily under acidic conditions to give the corresponding furans **47**.



**46** **47**

Tsuji found that the β-keto esters could be replaced with acetylacetone derivatives, to give acetyl furans, and with 1,3-cyclohexanedione, to give a ring-fused furan system. A range of alkylated propargyl carbonates could also be used. In all cases the yields of the reaction were excellent.

The key intermediate in the mechanism of the reaction is the formation of a σ-allenylpalladium complex **48** together with methoxide which serves as an *in situ* base to deprotonate the nucleophile.



**48**

After nucleophilic attack on the central allenyl carbon, the resulting π-allyl intermediate is trapped by an intramolecular nucleophilic reaction, giving the initial 3-alkylidene-2,3-dihydrofuran product, and regenerating the palladium(0) catalyst. A mildly acidic work-up allows aromatisation, giving the final product.

This approach to highly substituted furans was used in the synthesis of a key intermediate in an approach to the synthesis of neoliacine.[49] The method used is described in the Protocol 8. The reaction proceeds very smoothly, giving high yields of furans such as **49** and has been performed on a large scale without complications.

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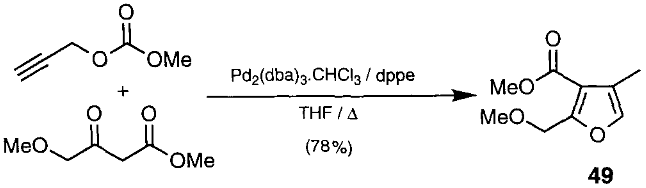
## Protocol 8.

## Synthesis of methyl 4-methyl 2-(methoxymethyl)-3-furoate (Structure 49)

**Caution!** All procedures should be carried out in a fume hood. Disposable vinyl or latex gloves and safety glasses should be worn.



**49**

## **Protocol 8** *Continued*

### *Equipment*

- Magnetic stirrer
- Oil bath
- Two-necked, round-bottomed flask (250 mL)
- Separating funnel
- Erlenmeyer flask (250 mL)
- Thermometer
- Septum
- Teflon-covered magnetic stirrer bar
- Needles (medium gauge)
- All-glass syringes with a needle-lock Luer (volume appropriate for quantity of solution to be transferred)
- Source of dry argon
- Water-jacketed condenser
- Water-jacketed short-path distillation apparatus
- Filter funnel with sinter

### *Material*

| | |
|---|---|
| • Dry THF, 120 mL | **flammable, irritant** |
| • Tris(dibenzylideneacetone)dipalladium(0) chloroform (FW 1035), 0.35 g, 0.34 mmol | |
| • 1,2-Bis(diphenylphosphino)ethane (dppe) (FW 398.4), 0.28 g, 0.70 mmol | |
| • Methyl 2-propynyl carbonate[a] (FW 114), 4.02 g, 35.2 mmol | **flammable, irritant** |
| • Methyl 4-methoxyacetoacetate[b] (FW 146.1), 4.56 mL, 35.2 mmol | **irritant** |
| • 2 N HCl, 20 mL | **corrosive** |
| • Technical grade diethyl ether, 150 mL | **flammable, irritant** |
| • Saturated aqueous sodium hydrogencarbonate solution, 60 mL | |
| • Saturated brine, 30 mL | |
| • Sodium sulfate | |

1. Clean all glassware, syringes, needles, and the stirrer bar and dry overnight in an oven before use.
2. Clamp the two-necked flask (containing the stirrer bar) fitted with the condenser, in the oil bath above the stirrer hotplate. Fit the argon source to the top of the condenser. Flush the assembly with argon by allowing the gas to flow through the flask for a few seconds before sealing the apparatus by fitting the septum.
3. Remove the septum, moderate the argon flow, and put the palladium catalyst (0.35 g, 0.34 mmol) and dppe (0.28 g, 0.70 mmol) into the flask. Flush with argon for a few seconds before replacing the septum.
4. Charge the flask with dry THF (80 mL) using a syringe by puncturing the septum on the reaction flask. A red solution should form.
5. Add methyl 2-propynyl carbonate (4.02 g, 35.2 mmol) in 20 mL of dry THF *via* a syringe at room temperature with stirring, followed by methyl 4-methoxyacetoacetate (4.56 mL, 35.2 mmol) in 20 mL of dry THF.
6. Warm the bath to 70°C and allow the reaction mixture to reflux for 3 h.
7. Allow to cool to room temperature, add 2 N HCl (20 mL) and stir for 10 min.
8. Using the filter funnel fitted with a sinter, filter the mixture through Celite

with suction to remove any inorganic material, and rinse the flask and filter cake with diethyl ether (3 × 25 mL).

9. Neutralise the filtrate by washing with sodium hydrogencarbonate (3 × 20 mL).
10. Transfer to a separating funnel and separate the two layers. Extract the aqueous layer with diethyl ether (3 × 25 mL). Combine the organic layers and wash with saturated brine (30 mL).
11. Transfer the diethyl ether layer to an Erlenmeyer flask. Dry the layer over anhydrous sodium sulfate and filter through a filter paper. Concentrate the filtrate under reduced pressure using a rotary evaporator.
12. Transfer the residue to a water-jacketed short-path distillation apparatus equipped with a thermometer. Distil the crude product under reduced pressure to obtain methyl 4-methyl-2-(methoxymethyl)-3-furoate (b.p. 165°C/0.8 mmHg) to give a yellow oil which displays appropriate spectroscopic data.[49]

[a] Methyl 2-propynyl carbonate was prepared using a literature method.[49]
[b] Methyl 4-methoxyacetoacetate was distilled prior to use.

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# 3

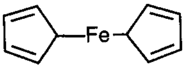
# Organoiron chemistry 1: ferrocene and dienyl iron tricarbonyl cation chemistry

CHRISTOPHER J. RICHARDS

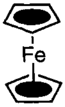
## 1. Introduction

This chapter deals with two differing applications of organoiron chemistry to organic synthesis. In the first section the chemistry of ferrocene is examined, in particular the reactions required for the construction of ferrocene-based ligands, which have found wide usage in asymmetric catalysis. In contrast, the cationic dienyl iron tricarbonyl complexes studied in the second section have been employed directly in many elegant total syntheses of complex organic structures.

The elucidation of the structure of ferrocene in 1952 was effectively the birth of a new area of research that has led to much of the fascinating chemistry described in this book. Ferrocene was first reported in 1951, isolated accidentally during the attempted synthesis of fulvalene by reaction of cyclopentadienyl magnesium bromide with iron(III) chloride.[1] Initially, the structure of the orange crystalline solid was believed to contain two cyclopentadienyl rings attached to an iron(II) centre by sigma bonds, as represented by **1**. However, there were a number of anomalies arising from this representation which resulted in two groups, led by G. Wilkinson and R. B. Woodward in the United States and E. O Fischer in Germany, independently proposing the novel sandwich structure **2** in which all of the carbon atoms are equidistant from the metal.[2]



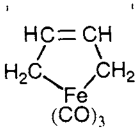
**1**



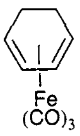
**2**

This type of structure, which arises as a result of the overlap of organic ligand π-orbitals with metal orbitals, had not previously been used to explain experimental observations. Its proposal, and the subsequent synthesis of further complexes containing π-bonded organic ligands, required a leap of imagination for which Fischer and Wilkinson were awarded the Nobel prize for chemistry in 1973. An account of this period of discovery was subsequently written by Wilkinson.[3]

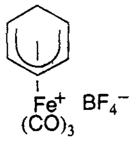
Interestingly, a π-bonded organometallic complex had been synthesised long before ferrocene. In 1930, Reihlen and fellow German co-workers reported that the reaction between $Fe(CO)_5$ and butadiene produced a yellow oil that analysed as $C_4H_6Fe(CO)_3$. Structure **3** was tentatively suggested for this compound.[4] However, it was not until 1958 that the true nature of this material was realised when Pauson and Hallam synthesised an iron tricarbonyl complex of cyclohexa- 1,3-diene and put forward evidence to favour the planar structure **4**, in which the π-orbitals are utilised in the bonding.[5]



**3**



**4**



**5**

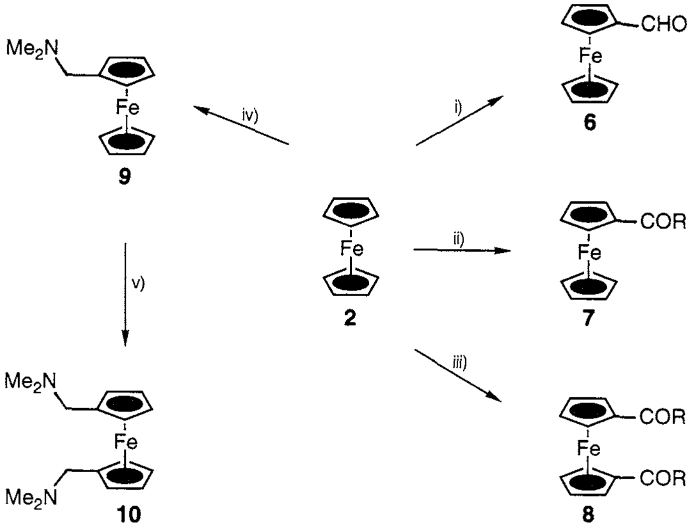
Shortly afterwards, in 1960, Fischer discovered that addition of triphenylcarbenium tetrafluoroborate to $\eta^4$-cyclohexa- 1,3-diene iron tricarbonyl **4** produced the novel $\eta^5$-cyclohexadienyl iron tricarbonyl cation **5** as a stable salt,[6] and the reactivity of such compounds towards C-C bond formation was soon being explored. The application of organometallic complexes to organic synthesis had begun.

# 2. Ferrocene chemistry

## 2.1 Electrophilic substitution

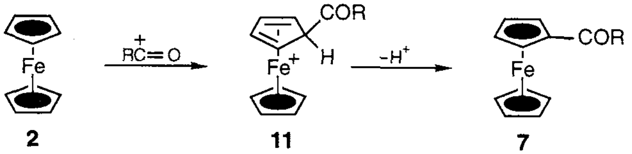
As ferrocene was readily available in large quantities, investigations into its chemistry began almost immediately after its discovery. The name ferrocene was coined as a consequence of the chemistry observed for the cyclopentadienyl rings of the molecule. They were found to undergo electrophilic substitution in the same manner as benzene itself, and thus gave the appearance of having aromatic character. Ferrocene results from the combination of two six-electron cyclopentadienyl anions with $Fe^{2+}$ to give a neutral species in which the aromatic character of the organic ligands is retained. The ligands donate electrons into empty metal orbitals, and back donation of electron density from the metal to the cyclopentadienyl groups results in a strong two-way bonding interaction that accounts for the stability of the system. Detailed molecular orbital calculations accounting for the bonding in ferrocene have been performed.[7]

A range of mild electrophilic reagents give substituted ferrocene derivatives. The reactions most frequently employed are formylation to ferrocenecarbaldehyde **6**, acylation to **7** and **8**, and aminomethylation to **9** and **10**. All of these reactions result in carbon–carbon bond formation and simple derivatives **6–10** have subsequently been employed in the synthesis of numerous ferrocene derivatives. The degree of substitution is readily controlled through the reaction conditions and the stoichiometry of the reagents. The second substituent is always introduced onto the second ring, resulting in a 1,1′-disubstituted product.



i) PhMeNCHO, $AlCl_3$ ii) 1 eq. RCOCl, 1 eq. $AlCl_3$ iii) 2 eq. RCOCl, 2 eq. $AlCl_3$ iv) $Me_2NCH_2CH_2NMe_2$, AcOH v) $EtNH_2$, Li, $FeCl_2$

The mechanism of Friedel–Crafts acylation is believed to involve rate-determining *exo* attack of the acylating species generating an intermediate **11**, analogous to the Wheland intermediates generated during electrophilic substitution of arenes. Rapid loss of a proton from **11** results in formation of the neutral product **7**.[8]



The five-membered cyclopentadienyl rings of ferrocene are relatively electron rich, such that acylation takes place at a rate $10^6$ times faster than for benzene, a factor that results in the rapid generation of substituted ferrocenes under mild conditions. Aluminium chloride-promoted Friedel–Crafts acetylation of ferrocene to give acetylferrocene **7a** is representative.

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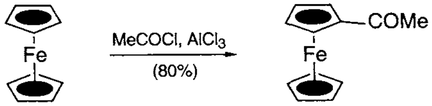
## Protocol 1.
## Electrophilic substitution. Preparation of acetylferrocene (Structure 7a)

**Caution!** All procedures should be carried out in an efficient fume hood. Eye protection must be worn at all times.



**2** **7a**

### *Equipment*

- Single-necked, round-bottomed flask (250 mL)
- Teflon-covered egg-shaped magnetic stirrer bar (3 cm length)
- Calcium chloride drying tube
- Magnetic stirrer
- Separating funnel (250 mL)
- Ice-water bath

### *Materials*

| | |
|---|---|
| • Ferrocene (FW 186.0), 20.0 g, 0.108 mol | |
| • Dry dichloromethane,[a] 90 mL | **toxic, irritant** |
| • Acetyl chloride (FW 78.5), 9.25 g, 0.118 mol | **corrosive, flammable** |
| • Anhydrous aluminium chloride | **corrosive** |
| (FW 133.3), 14.4 g, 0.108 mol | **moisture sensitive** |
| • Technical dichloromethane for work up, *ca.* 70 mL | **toxic, irritant** |

1. Ensure that the stirrer bar and glassware are clean, and that they have been dried thoroughly in an oven at 120 °C for 2 h.
2. Add ferrocene (20.0 g, 0.108 mol) to the 250 mL round-bottomed flask and dissolve with stirring in dry dichloromethane[a] (90 mL).
3. To the resultant dark orange/red solution add acetyl chloride (9.25 g, 0.118 mol); attach the drying tube to the flask and immerse the flask in an ice-water bath at 0–5 °C.
4. Weigh out anhydrous aluminium chloride (14.4 g, 0.108 mol) in a glass beaker. Add this in approximately 10 portions to the reaction mixture, allowing approximately 2 min between each addition for heat exchange. Replace the drying tube after each addition. The reaction begins on addition of the first portion of aluminium chloride and the reaction mixture darkens considerably.
5. Stir the reaction for 2 h during which time the ice-water bath is allowed to warm to room temperature.

6. Recool the solution by placing it in a fresh ice-water bath. Remove the drying tube and hydrolyse the reaction mixture by the **slow** addition of 4 × 5 mL portions of cold water. Then add a further 30 mL of cold water more rapidly.
7. Transfer the mixture to a 250 mL separating funnel and separate the organic (lower) phase. As both phases are very dark, take care to ensure a clean separation between the two. The divide between the two phases will become more apparent as it reaches the narrow bottom section of the separating funnel.
8. Extract the aqueous phase with two 25 mL portions of technical dichloromethane. Combine the organic extracts and wash with 25 mL of 5% sodium hydroxide solution followed by 25 mL of saturated aqueous sodium chloride solution. Dry the organic solution over sodium sulfate for 10 min, then filter off the drying agent. Wash the sodium sulfate with 5 mL portions of dichloromethane until it is no longer coloured red from the product. Remove the solvent on a rotary evaporator to give acetylferrocene (19.6 g, 80%) as a red/orange solid showing appropriate spectroscopic data [$\delta_H$ ($CDCl_3$), 2.40 (3 H, s, Me), 4.21 (5 H, s, FcH), 4.51 (2 H, brs, FcH), 4.78 (2H, brs, FcH)]. A small portion may be recrystallised from ethyl acetate/petroleum ether (40-60). Literature m.p. = 85–86°C.[9]

[a] Distil from calcium hydride under an atmosphere of nitrogen.

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The range of aromatic substitution reactions that may be performed on ferrocene is limited by the ease with which ferrocene is oxidised to the ferrocenium ion. For example, addition of $NO_2$+ and halogens results in formation of the ferrocenium ion, thus preventing direct formation of nitro- and halogen-substituted ferrocenes. However, such compounds may be generated from other substituted derivatives which are in turn synthesised from metalated ferrocenes.

## 2.2 Substitution reactions α to ferrocene. Generation of intermediate α-ferrocenylcarbenium ions from α-ferrocenyl alcohols

Much of the chemistry of ferrocene derivatives is concerned with carbon centres directly attached to a cyclopentadienyl ring. The proximity of the metal centre strongly influences both the rate and stereochemical outcome of reactions occurring at this position, which are characterised by the intermediacy of α-ferrocenylcarbenium ions. In order to generate such species, a leaving group must first be introduced at the α-position. This may be readily achieved by reduction of a carbonyl group, introduced during Friedel–Crafts acylation, to the corresponding alcohol.

The relatively high electron density associated with the cyclopentadienyl rings of ferrocene reduces the electrophilicity of an attached carbonyl group. As a result, reduction by sodium borohydride, normally an effective reagent for ketone reduction, is in this instance very sluggish. Instead, reduction may be more effectively achieved with lithium aluminium hydride. The following protocol describing the synthesis of α-ferrocenylethanol **12a** is representative.

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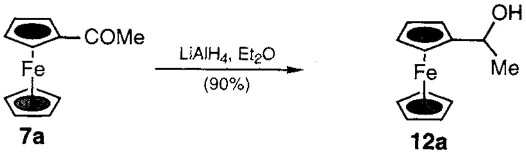
## Protocol 2.
## Lithium aluminium hydride reduction of acetylferrocene (Structure 7a) to α-ferrocenylethanol (Structure 12a)

**Caution!** All procedures should be carried out in an efficient fume hood. Eye protection must be worn at all times.



### *Equipment*

- Two-necked, round-bottomed flask (500 mL)
- Teflon-covered egg-shaped magnetic stirrer bar (4 cm length)
- Liebig condenser
- Pressure equalising dropping funnel (250 mL)
- Calcium chloride drying tubes (× 2)
- Erlenmeyer flask (250 mL)
- Glass funnel
- Magnetic stirrer
- Separating funnel (500 mL)
- Büchner funnel
- Büchner flask

### *Materials*

| | |
|---|---|
| • Acetylferrocene (FW 228.1), 15.0 g, 0.066 mol | **harmful** |
| • Lithium aluminium hydride (FW 38.0), 5 g, 0.132 mol | **flammable, caution! lithium aluminium hydride reacts violently with water evolving hydrogen** |
| • Dry diethyl ether,[a] 250 mL | **flammable, irritant** |
| • Ethyl acetate | **flammable, irritant** |
| • Petroleum ether (40-60) | **flammable** |

1. Ensure that the glassware is clean and that it has been dried thoroughly in an oven at 120°C for 2 h.
2. Fit the Liebig condenser and the pressure equalising dropping funnel (250 mL) to the 500 mL two-necked, round-bottomed flask containing the magnetic stirrer bar. Attach calcium chloride drying tubes to the condenser and dropping funnel and allow the apparatus to cool.
3. Add lithium aluminium hydride (5.0 g, 0.132 mol) to the round-bottomed flask followed by dry diethyl ether[a] (100 mL). Add acetylferrocene (15.0 g, 0.066 mol) to the 250 mL Erlenmeyer flask and dissolve in dry diethyl ether (140 mL). Pour this red solution into the dropping funnel and wash the Erlenmeyer flask with an additional 10 mL of dry diethyl ether.

4. Add the acetylferrocene solution to the grey suspension of lithium aluminium hydride at such a rate as to maintain gentle reflux. When the addition is complete stir at room temperature for an additional 10 min. The reaction is complete when the colour of the solution has changed from red to dark yellow.
5. Charge the dropping funnel with ethyl acetate (10 mL). Add this dropwise to the reaction mixture and stir at room temperature overnight.
6. **Cautiously** add water (10 mL) dropwise (if the ethyl acetate has completely destroyed the excess lithium aluminium hydride no reaction will be observed at this stage). Filter the resultant mixture with a Büchner funnel and flask, washing the collected aluminium salts with diethyl ether (2 × 20 mL). Transfer the filtrate to a separating funnel and wash with water (100 mL). Dry over magnesium sulfate, filter and remove the solvent on a rotary evaporator to give about 13.5 g of a dark yellow crystalline solid. Recrystallise from ethyl acetate/petroleum ether (40-60) to give pure α-ferrocenylethanol displaying the appropriate spectroscopic and microanalytical data [$\delta_H$ ($CDCl_3$) 1.44 (3 H, d, $J = 6$ Hz, Me), 1.84 (1 H, d, $J = 5$ Hz, OH), 4.16–4.18 (2 H, m, FcH), 4.20 (5 H, s, FcH), 4.21–4.23 (2 H, m, FcH), 4.55 (1 H, quintet, $J = 6$ Hz, C<u>H</u>MeOH)]. Literature m.p. = 73–75 °C.[10]

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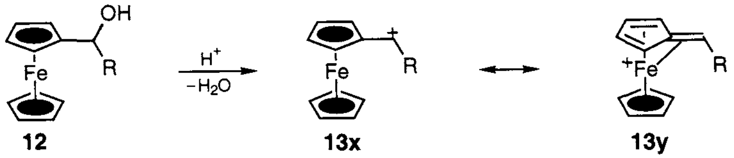
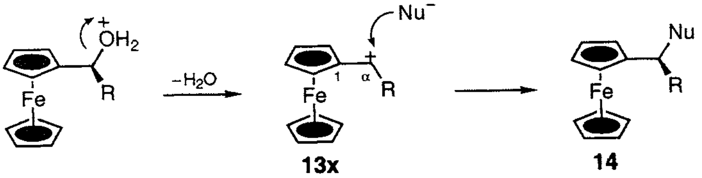
[a] Distil from sodium benzophenone ketyl under a nitrogen atmosphere.

The addition of strong acids to α-ferrocenyl alcohols **12** results in rapid formation of α-ferrocenylcarbenium ions **13**, *via* protonation of the alcohol oxygen and loss of water. Unlike the vast majority of purely organic carbenium ions, these species are easily isolated as stable tetrafluoroborate or hexafluorophosphate salts. Their stability stems from the delocalisation of positive charge over the ferrocenyl group, as a consequence of the overlap between the empty p-orbital of the α-$sp^2$ hybridised carbon and filled metal orbitals. This delocalisation is represented by the two canonical forms **13x** and **13y**, with the actual structure of α-ferrocenylcarbenium ions lying somewhere between the two.



Metal participation in stabilising these species dictates that during their formation, the leaving group departs away (*exo*) from the iron so as to maximise overlap between the metal orbitals and the rehybridising α-carbon (**12** to **13**). Nucleophilic addition to α-ferrocenylcarbenium ions proceeds *via* the reverse mechanism, the nucleophile attacking *exo* to the ferrocenyl group (**13** to **14**). Thus the overall process, **12** to **14**, proceeds with retention of configuration. Rotation about the $C_1$-$C_\alpha$ bond in **13** is largely prevented by its partial double bond character, but solutions of α-ferrocenylcarbenium ions do racemise very slowly at room temperature.



A wide range of heteroatomic nucleophiles such as amines, alcohols and thiols have been shown to add to α-ferrocenylcarbenium ions. Carbon–carbon bond formation can also be achieved by addition of silyl enol ethers.[11] The following protocol involving the generation of α-ferrocenylethylium tetrafluoroborate **13a** and its subsequent reaction with dimethylamine is representative.

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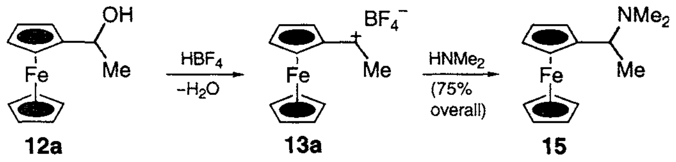
## Protocol 3.
## Synthesis of *N,N*-dimethyl-α-ferrocenylethylamine (Structure 15)

**Caution!** All procedures should be carried out in an efficient fume hood. Eye protection must be worn at all times.



### *Equipment*

- Two-necked, round-bottomed flask (250 mL)
- Cone/flexible tubing adapter
- Septum
- Teflon-covered egg-shaped magnetic stirrer bar (3 cm length)
- Magnetic stirrer
- Glass Luer-lock syringe (3 × 20 mL)
- Needle (3 × 15 cm, 18 gauge)
- Cannula with glass filtering attachment (30 cm, 16–18 gauge) (Fig. 3.1)
- Source of dry nitrogen
- Erlenmeyer flask (250 mL)

### *Materials*

| | |
|---|---|
| • α-Ferrocenylethanol (FW 230.1), 10.0 g, 0.043 mol | |
| • Dry diethyl ether,[a] 145 mL | **flammable, irritant** |
| • Tetrafluoroboric acid (FW 87.8)<br>54% solution in diethyl ether, 7.0 mL, 0.05 mol | **flammable corrosive** |
| • Dry dichloromethane,[b] 125 mL | **toxic, irritant** |
| • Dimethylamine (FW 45.1), 40 wt.% solution in water, 50 mL | **irritant** |

1. Ensure that the magnetic stirrer bar and all glassware to be used for the reaction is clean and has been in an oven at 120°C for at least 12 h prior to use.
2. Attach the cone/flexible tubing adapter to the 250 mL two-necked round-bottomed flask containing the magnetic stirrer, connect the nitrogen source and allow the apparatus to cool under a stream of nitrogen.
3. Add α-ferrocenylethanol (10.0 g, 0.043 mol) to the flask and dissolve this with stirring in dry diethyl ether[a] (125 mL). The diethyl ether may be added with a measuring cylinder **provided this is dry**. Attach the septum to the second neck of the two-necked flask.
4. Assemble the 20 mL syringe and needle while hot (**wear gloves!**). With the plunger of the syringe down, put the needle through the septum so that the end of the needle is in the nitrogen atmosphere of the flask. Draw up nitrogen into the syringe, remove the needle from the septum and empty the syringe. Repeat this flushing process once more, refill the syringe with nitrogen and allow to cool.
5. Place the needle into the container containing 54% tetrafluoroboric acid in diethyl ether. Gently draw up the plunger, filling the syringe until it contains 7.0 mL. Place the needle through the septum of the reaction flask. Whilst rapidly stirring the yellow solution of α-ferrocenylethanol in diethyl ether, add the solution of tetrafluoroboric acid at a rate of approximately 2 mL per min. The intermediate α-ferrocenylcarbenium ion will precipitate from the solution as a dark orange solid. If a dark oil is obtained at this stage, continue to rapidly stir the reaction mixture as this should promote formation of crystalline material.
6. After the addition is complete, dismantle the syringe and needle and rinse both thoroughly with water.
7. Attach a 5 cm circle of filter paper over the glass end of the filtering cannula with wire as shown in Fig. 3.1. Briefly remove the septum from the reaction flask and push the metal end of the cannula through the bottom of the septum. Pull the cannula through and replace the septum such that the filter paper-covered glass end of the filtering cannula is now inside the reaction flask.
8. Turn off the stirrer and allow the precipitate to settle. Gently bend the cannula such that the end that is outside the reaction flask lies within a 250 mL Erlenmeyer flask as illustrated in Fig. 3.2. Push the other end into the reaction mixture and provided there is a sufficient positive pressure of nitrogen (20 mbar is normally enough) the supernatant will bleed through the cannula into the Erlenmeyer flask. Remove as much of the solvent as possible to leave the desired α-ferrocenylcarbenium ion.
9. To wash the product, first pull the glass end of the filtering cannula back to

**Protocol 3.** *Continued*

the top of the flask. Using another 20 mL syringe with needle attached, dried and flushed with nitrogen as before, add 20 mL of dry diethyl ether to the reaction flask. Briefly stir the resulting suspension and filter by pushing the end of the cannula back into the solvent. Again remove as much of the solvent as possible before drying the product under a stream of nitrogen, created by removal of the septum. Remove the cannula from the septum and wash it through with acetone.

10. When the product is dry, replace the septum. Using a fresh syringe and needle, again dried and flushed as before, add dry dichloromethane[b] to the reaction flask. With stirring, dissolve the α-ferrocenylcarbenium ion to give a dark red solution, then place the flask in an ice-water bath. Remove the septum and add 50 mL of dimethylamine (40 wt.% solution in water). After the addition the flask should be disconnected from the nitrogen supply, as there is no further need to protect the reaction from oxygen and water. The reaction is complete when the colour of the reaction mixture has changed from a dark red colour to an orange/yellow colour.
11. Transfer the reaction mixture to a separating funnel. Remove the organic layer and wash the aqueous layer with a further 50 mL of dichloromethane. Combine the organic extracts and dry over sodium sulfate. Filter, washing the sodium sulfate with additional dichloromethane, and remove the solvent on a rotary evaporator. Distil the product under reduced pressure (b.p. 120°C/2 mmHg) to give a dark red-brown oil (8.4 g, 75%) displaying the appropriate spectroscopic data [$\delta_H$ ($CDCl_3$) 1.45 (3 H, d, $J$ = 7 Hz, $CH(NMe_2)\underline{Me}$), 2.08 (6 H, s, $CH(N\underline{Me_2})Me$), 3.59 (1 H, q, $J$ = 7 Hz, $C\underline{H}(NMe_2)Me$), 4.10–4.16 (4 H, m, FcH), 4.12 (5 H, s, FcH)]. The distillation should be done as rapidly as possible since prolonged heating of the amine results in a significant level of decomposition.

[a] Distil from sodium benzophenone ketyl under an atmosphere of nitrogen.

[b] Distil from calcium hydride under an atmosphere of nitrogen.

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The intermediate α-ferrocenylcarbenium ion need not be isolated in these substitution reactions. Alternatively, introduction of a good leaving group such as acetoxy (OAc) or an ammonium ion at the α-position enables substitution reactions to be carried out directly under mild conditions.

## 2.3 Routes to optically pure ferrocene derivatives

The presence of four different groups attached to the α-carbon obviously results in a tetrahedral chiral centre. When the compound containing such a centre is *N*,*N*-dimethyl-α-ferrocenylethylamine **15**, separation of the two enantiomers is readily achieved by a classical resolution with tartaric acid.

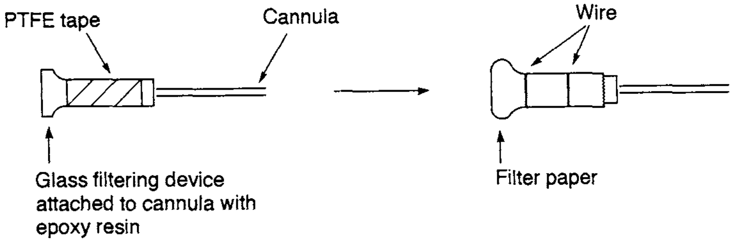


**Fig. 3.1** Assembly of the filtering cannula.

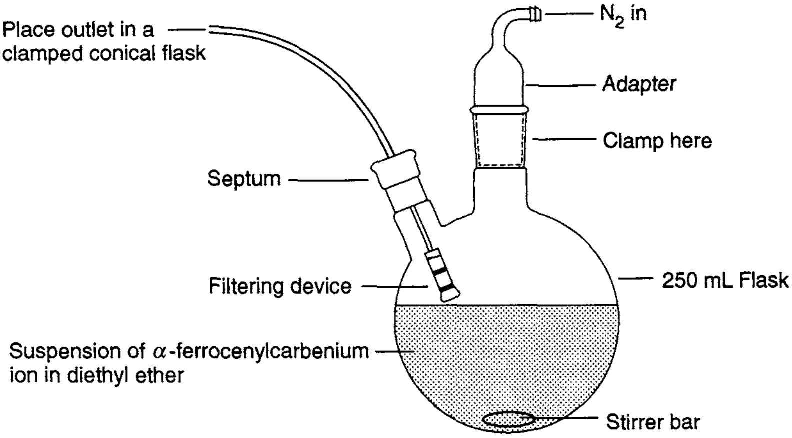
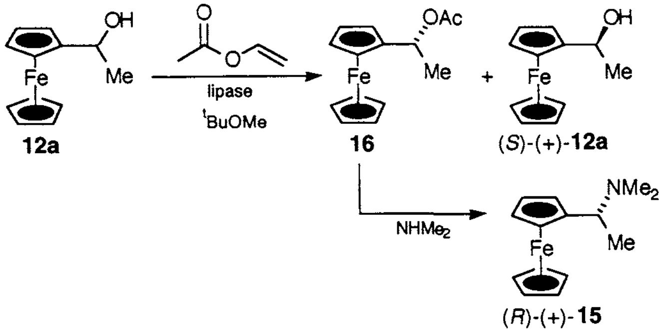


**Fig. 3.2** Reaction apparatus for Protocol 3, step 8.

The two diastereomeric tartrate salts of **15** have significantly differing solubilities, enabling them to be easily separated. Subsequent treatment with base releases optically pure (*S*)-(−)-**15** and (*R*)-(+)-**15**, $[\alpha]_D$ = −14.1 and +14.1 respectively.[12] Due to the ease of this resolution, *N*,*N*-dimethyl-α-ferrocenylethylamine **15** has become the key starting material for the synthesis of many optically active ferrocene derivatives.

The growing importance of **15** has lead to the development of alternative methodologies to obtain this compound enantiomerically pure. One of the most noteworthy uses the lipase from *Pseudomonas fluorescens* to effect a selective esterification of racemic 1-ferrocenylethanol **12a**. At 50% conversion the unreacted alcohol (*S*)-(+)-**12a** was isolated with an enantiomeric excess of 92% and the acetate **16** had an enantiomeric purity of 96%. Simply stirring this acetate with aqueous dimethylamine resulted in formation of (*R*)-(+)-*N*,*N*-dimethyl-α-ferrocenylethylamine with $[\alpha]_D$ + 12.8, corresponding to an optical purity of 91%.[13]



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## Protocol 4.
## Resolution of *N,N*-dimethyl-α-ferrocenylethylamine (Structure 15)

**Caution!** Eye protection must be worn at all times.

### *Equipment*

- Thermostatted water bath
- Erlenmeyer flask (2 × 100 mL)
- Single-necked, round-bottomed flask (50 mL)
- Polarimeter
- Separating funnel

### *Materials*

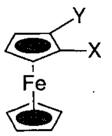
| | |
|---|---|
| • *N,N*-Dimethyl-α-ferrocenylethylamine (FW 257.2), 5 g, 0.019 mol | **corrosive, toxic** |
| • (*R*)-(+)-Tartaric acid (FW 150.1), 5 g, 0.033 mol | **irritant** |
| • Methanol, 100 mL | **flammable, toxic** |
| • 20% aqueous sodium hydroxide, 50 mL | **corrosive, toxic** |
| • Diethyl ether, 20 mL | **flammable, irritant** |
| • Acetone, 10 mL | **flammable, irritant** |

1. Place racemic *N,N*-dimethyl-α-ferrocenylethylamine (5 g, 0.019 mol) and (*R*)-(+)-tartaric acid (2.92 g, 0.019 mol) in separate Erlenmeyer flasks and dissolve each in 10 mL of methanol. Clamp both Erlenmeyer flasks into a thermostatted water bath, pre-set at a temperature of 55 °C.
2. When the solutions in both flasks have reached 55 °C, pour the tartaric acid solution into the amine solution with stirring. Turn off the waterbath and allow this to cool slowly overnight. The ideal rate of cooling is in the order of 2–5 °C per hour.
3. In the next laboratory session, collect the resultant amine tartrate salt by suction filtration and wash with a few mL of cold methanol. Retain and label the mother liquor from the filtration and keep for later use (see step 6).
4. Add the tartrate amine salt to 10 mL of 20% aqueous sodium hydroxide in a separating funnel, and extract the resulting free amine with 3 × 10 mL portions of dichloromethane. Combine the organic extracts, dry over

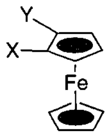
sodium sulfate, filter (washing the sodium sulfate with additional dichloromethane) and remove the solvent on a rotary evaporator.

5. Repeat steps 1 to 4 on all of the amine obtained at the end of step 4. The following ratio of materials is employed; 1 g amine, 0.58 g of (*R*)-(+)-tartaric acid, 2 × 2.6 mL of methanol. On converting back to the free amine, remove residual solvent by placing the material under vacuum (< 1 mmHg) at room temperature for a minimum of 1 h. If a Kugelrohr bulb-to-bulb distillation apparatus is available, quickly distil the amine (b.p. 120 °C/2 mmHg). Optically pure material should be obtained with $[\alpha]_D^{25} = -14.1$ (*c* 1.6, EtOH). If the optical rotation of the amine is lower, steps 1–4 must be repeated once more.
6. Transfer the mother liquor from the first crystallisation into a 50 mL round-bottomed flask and using a rotary evaporator reduce the volume of this material to *ca.* 5 mL. Slowly add diethyl ether until material just begins to precipitate from solution and stand the flask in a refrigerator overnight.
7. In the next laboratory session, filter off the resultant crystals, washing with a few mL of cold diethyl ether/methanol (1:1). Recrystallise from acetone/water (10:1), allowing 16 mL of solvent for every gram of salt. Wash the product with a few mL of cold acetone/water (10:1) and recrystallise once more from this same solvent mixture.
8. Release the amine from the amine tartrate salt as before. Dry under vacuum (< 1 mmHg) for a minimum of 1 h, or preferably Kugelrohr distil. This material should now be optically pure with $[\alpha]_D^{25} = +14.1$

In addition to being a component of tetrahedral chiral centres, ferrocene compounds with two different substituents on the same cyclopentadienyl ring display planar chirality. For example, the generalised structure **17** where X and Y represent two different substituents is non-superimposible upon its mirror image **ent-17** such that compounds of this sort may be separated into, or synthesised as, their constituent enantiomers. Separation may be achieved through classical resolution where X or Y is a suitable functionality, typically a carboxylic acid.



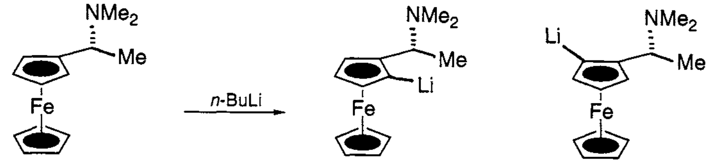
**17**



**ent-17**

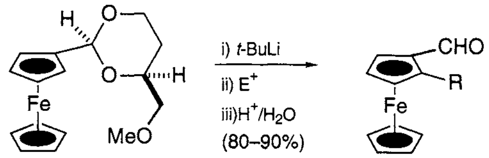
Generally though, planar chirality is introduced by means of an attached tetrahedral chiral centre in reactions that display high diastereoselectivity. The most frequently used examples proceed *via* tne *ortho*-lithiation of optically pure **15**, leading to the diastereoisomers **18** and **19** in a ratio of 96:4.[12]

Subsequent treatment with an electrophile and removal of the minor diastereoisomer by chromatography or recrystallisation has led to the synthesis of numerous optically pure ferrocene derivatives, displaying both planar and tetrahedral chirality. The only major disadvantage of this methodology is that all of the products contain a methyl substituent which cannot be easily removed or exchanged.



(*R*)-(+)-**15** **18** 96 : 4 **19**

To overcome this problem the ferrocenyl acetal **20** was developed, in which the acetal functionality directs the formation of a single diastereoisomer during the lithiation and electrophile quench sequence. Subsequent addition of aqueous acid then releases enantiomerically pure 2-substituted ferrocenealdehyes **21a–d**.[14] A further advantage of this method is that **20** and its corresponding enantiomer are synthesised from commercially available (*S*)- or (*R*)-1,2,4-butanetriol respectively, thus avoiding the need to perform a classical resolution.



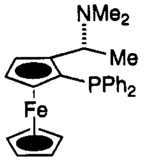
**20**

**21a** R = TMS
**b** R = $SnBu_3$
**c** R = $PPh_2$
**d** R = I

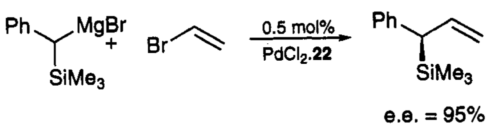
## 2.4 Ferrocene-based ligand systems

In addition to displaying both planar and tetrahedral chirality, ferrocene derivatives display a substituent geometry that is not available with conventional organic scaffolds. As a consequence, they have found widespread application as novel ligands in a number of transition metal-catalysed asymmetric reactions. For example, **22**, generated by addition of chlorodiphenylphosphine to **18** and **19** followed by recrystallisation, is a highly effective ligand for the palladium-catalysed Grignard cross-coupling of phenyl(trimethylsilyl)methylmagnesium bromide with vinyl bromide.[15]

More widely used are ferrocene derivatives in which both cyclopentadienyl rings are functionalised by diphenylphosphine. The parent to this series of



**22**

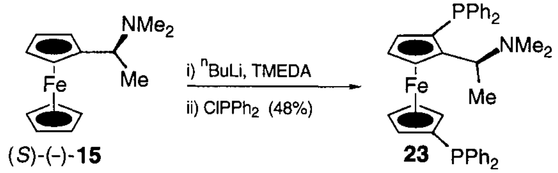


compounds is the 1′,2-bis(diphenylphosphino) derivative **23** and its enantiomer, which are also synthesised from optically pure (*S*)-(−)-**15** and (*R*)-(+)-**15**, respectively. The reaction with *n*-butyllithium is performed in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) which promotes additional lithiation of the unsubstituted ring, addition of chlorodiphenylphosphine then yielding the bidentate ligand **23**.[16]

---

## Protocol 5.
## Synthesis of (*S*)-*N*,*N*-dimethyl-1-[(*R*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethylamine (Structure 23)

**Caution!** All procedures should be carried out in an efficient fume hood. Eye protection must be worn at all times.



(*S*)-(-)-**15**

**23**

### *Equipment*

- Two-necked, round-bottomed flask (100 mL)
- Cone/flexible tubing adapter
- Septum
- Teflon-covered egg-shaped magnetic stirrer bar (1.5 cm length)
- Needles (5 × 10 cm, 20 gauge)
- Glass syringes with needle-luer lock (10 mL, 3 × 5 mL, 1 mL)
- Magnetic stirrer
- Source of dry nitrogen
- Separating funnel (100 mL)

### *Materials*

| | |
|---|---|
| • (*S*)-(−)-*N*,*N*-Dimethyl-1-ferrocenylethylamine[a] (FW 257.2), 1.0 g, 3.9 mmol | **irritant** |
| • Dry diethyl ether,[b] 6 mL | **flammable, irritant** |
| • *n*-Butyllithium, 1.4 M solution in hexanes,[c] 6.9 mL, 9.7 mmol | **flammable, moisture sensitive** |
| • *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine[d] (TMEDA) (FW 116.2), 0.53 g, 0.69 mL, 4.6 mmol | **flammable, irritant** |
| • Chlorodiphenylphosphine (FW 220.6, d 1.23), 2.1 mL, 11.7 mmol | **lachrymator** |

**Protocol 5.** *Continued*

1. Ensure that all the glassware, syringes, needles and the magnetic stirrer bar required for the reaction are clean, and dry them in an oven at 120°C for at least 12 h prior to use.
2. Place the cone/flexible tubing adapter in the two-necked round-bottomed flask containing the magnetic stirrer bar, attach the nitrogen supply and allow the apparatus to cool under a stream of nitrogen.
3. Add (*S*)-(−)-*N*,*N*-dimethyl-1-ferrocenylethylamine (1.0 g, 3.9 mmol) to the flask and place a septum in the remaining neck.
4. Flush a 10 mL syringe and needle with nitrogen as described in Protocol 3, step 4. Use this to transfer dry diethyl ether[b] (6 mL) to the reaction flask by pushing the needle through the septum. Wash down any of the starting amine that may be on the sides of the reaction vessel.
5. Securely clamp the bottle of 1.4 M *n*-butyllithium in hexanes with the bottom of the bottle placed on the retort stand. Attach a needle to a source of nitrogen and push this through the seal of the bottle containing the butyllithium. This is to ensure that the bottle is maintained under a positive pressure of nitrogen. Assemble a 5 mL syringe and needle, flush with nitrogen and allow to cool. Push the end of this needle through the seal, and into the solution of butyllithium. Gently draw-up the plunger, filling the syringe to the 3.3 mL graduation mark. Withdraw the end of the needle from the butyllithium, then pull up the syringe plunger a little further to draw nitrogen into the needle. Carefully remove from the bottle, push through the septum of the reaction flask and add 3.3 mL of butyllithium over a period of *ca.* 1 min to the stirred solution. Immediately after the addition, rinse the syringe and needle with water.
6. Stir the reaction mixture at room temperature for 1 h. With a dry, nitrogen-flushed 1 mL syringe and 10 cm needle assemblage, add 0.69 mL of TMEDA.[d] Follow this with the addition of a further 3.6 mL of *n*-butyllithium according to the procedure described in step 5, employing a thoroughly dried 5 mL syringe and needle. Stir the reaction mixture at room temperature for 5 h.
7. Cool the reaction mixture in an ice-water bath. With a 5 mL syringe and needle, once again dried and flushed with nitrogen as before, add chlorodiphenylphosphine (2.1 mL, 11.7 mmol) dropwise to the stirred solution. Wash the needle and syringe thoroughly with acetone after the addition. Leave the reaction mixture stirring overnight with the ice-water bath warming to room temperature.
8. Add 20 mL of saturated aqueous sodium hydrogencarbonate solution and stir for 5 min. Transfer to a separating funnel, and rinse the reaction flask with a further 10 mL of diethyl ether. Separate the organic (upper) layer and wash the aqueous layer with a further 20 mL of diethyl ether. Combine the

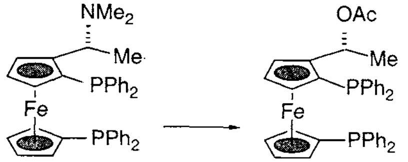
organic layers, dry over magnesium sulfate, filter and remove the solvent on a rotary evaporator.

9. Purify the product by flash chromatography on silica gel using a mixed solvent system of 30% ethyl acetate/petroleum ether (40-60). The product is the first major yellow/orange band to be eluted and has an $R_f$ of approximately 0.38. Combine those fractions containing only the desired product and evaporate the solvent to yield 1.16 g of an oil that crystallises on standing. Recrystallise from ethanol to yield pure (*S*)-*N*,*N*-dimethyl-1-[(*R*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethylamine **23** displaying the appropriate spectroscopic and rotational data.[16] Literature m.p. = 139–140°C.[16]

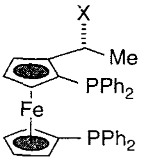
[a] Alternatively start with (*R*)-(+)-*N*,*N*-dimethyl-1-ferrocenylethylamine.
[b] Distil from sodium benzophenone ketyl under a nitrogen atmosphere and use immediately.
[c] Titrate against diphenylacetic acid in dry THF[17] and adjust the quantity of butyllithium employed as appropriate.
[d] Reflux with potassium hydroxide and distil under a nitrogen atmosphere. Store over 4 Å molecular sieves under nitrogen.

---

Further tuning of the ligand is achieved by stereospecific replacement of the dimethylamino group with other functionalised amines. This is readily carried out by heating, for example, **ent-23** with acetic anhydride, isolation of the acetate **24**, and addition of the appropriate amine in methanol.[16]

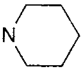


**ent-23** **24**

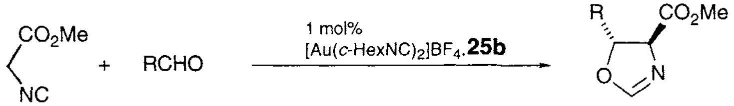


**25a** X = NMeCH(CH$_2$OH)$_2$

**25b** X = NMeCH$_2$CH$_2$–N



The exact nature of the replacing amine has been optimised for a number of metal-catalysed reactions. For example, **25a** directs palladium-catalysed allylic amination with up to 97% ee,[18] and **25b** is a very effective ligand for rhodium(I)-catalysed asymmetric hydrogenation (up to 97% ee).[19] In addition, **25b** is the controlling component of gold(I)-catalysed aldol reactions between isocyanoacetate and aldehydes, which generates oxazoline derivatives of general structure **26** with enantiomeric excesses typically greater than 95%.[20]



**26**

# 3. Dienyl iron tricarbonyl cation chemistry

## 3.1 Synthesis of $\eta^4$-cyclohexadiene iron tricarbonyl complexes

Fundamental to the development of dienyl iron tricarbonyl chemistry has been the availability of substituted cyclohexadiene precursors arising from the Birch reduction. In this process, a wide range of aromatic compounds are readily reduced to their corresponding unconjugated cyclohexa-1,4-dienes without further reduction to a cyclohexane.[21] The reaction is typically performed by adding sodium to a liquid ammonia solution of the substrate in the presence of an added alcohol.

For aromatic compounds containing electron-donating alkoxy or alkyl groups, the substituent is found in a non-reduced position in the product. Thus, reduction of anisole results in the formation of 1-methoxycyclohexa-1,4-diene and not 3-methoxycyclohexa-1,4-diene. The following protocol for the synthesis of 1-methoxy-4-methylcyclohexa-1,4-diene **28** by Birch reduction of 4-methylanisole **27** is representative.

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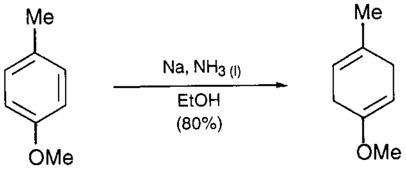
### Protocol 6.
### Birch reduction of 4-methylanisole (Structure 27)

**Caution!** All procedures should be carried out in an efficient fume hood. Eye protection must be worn at all times.



**27** **28**

*Equipment*

- Three-necked, round-bottomed flask (500 mL)
- Teflon-covered egg-shaped magnetic stirrer bar (4 cm length)
- Dry ice/acetone condenser
- Cone/flexible tubing adapter
- Stopper
- Source of dry nitrogen
- Magnetic stirrer
- Vermiculite insulation
- Drechsel bottle
- Beaker (200 mL)
- Separating funnel (1000 mL)

*Materials*

| | |
|---|---|
| • 4-Methylanisole[a] (FW 122.2), 24.4 g, 0.2 mol | **flammable, irritant** |
| • Absolute ethanol (FW 46.1), 46.1 g, 1.0 mol | **flammable, toxic** |
| • Sodium (FW 23.0), 11.5 g, 0.5 mol | **flammable** |
| • Liquid ammonia, *ca.* 200 mL | **corrosive, irritant** |
| • Dry hexane,[b] 50 mL | **flammable** |

| | |
|---|---|
| • Sodium benzoate | **irritant** |
| • Technical petroleum ether (40-60) 200 mL | **flammable** |

1. Ensure that all the glassware and the stirrer bar are clean, and dry them in an oven at 120°C for at least 12 h prior to use. Place the acetone–dry ice condenser in the central neck of the clamped three-necked flask containing the magnetic stirrer bar, attach the cone/flexible tubing adapter and stopper to the remaining necks of the flask, and allow the apparatus to cool under a stream of nitrogen.
2. Charge the round-bottomed flask with 4-methylanisole (24.4 g, 0.2 mol) followed by ethanol (46.1 g, 1 mol), ensuring that all of the 4-methylanisole is washed into the reaction vessel. Insulate the flask by placing it in a bowl containing vermiculite.
3. Pour acetone into the condenser until it is approximately one-quarter full.
4. To a thoroughly dry 200 mL beaker add 50 mL of dry hexane,[b] place on a top pan balance and tare. Ensure that the bench at which you are working is thoroughly dry. Wearing gloves, remove a stick of sodium from the oil in which it is stored. Cut into small portions (approximately 0.5 g) using a scalpel, wipe off excess oil with a tissue and add to the beaker of hexane. Continue until a total of 11.5 g of sodium has been transferred. Return the remaining stick of sodium to its container as quickly as possible.
5. Disconnect the nitrogen supply and connect the flask to an ammonia cylinder *via* a Drechsel bottle to protect against suck-back. Carefully open the valve of the ammonia cylinder and pass a slow stream of ammonia gas through the apparatus. Slowly add dry ice to the acetone in the condenser, waiting for the frothing to subside between each addition. Continue until the condenser is approximately two-thirds full of the acetone–dry ice mixture. When the condenser is sufficiently cold, ammonia liquid (b.p. −33°C) will begin to drop into the reaction vessel. When this is half full, that is when *ca.* 200 mL of ammonia liquid has condensed, close the valve of the cylinder and reconnect the nitrogen supply.
6. Stir the ammonia solution. Using tweezers, add the sodium in portions to the reaction vessel such that the slight frothing that occurs is given sufficient time to subside. Replace the stopper of the flask between each addition.
7. Stir the blue reaction mixture for a further 10 min after completion of the addition. Destroy the excess sodium by adding powdered sodium benzoate in small portions until the blue colour is discharged.
8. Remove the acetone–dry ice condenser and allow the ammonia solution to evaporate to approximately half the volume. Add water (200 mL) and transfer the resulting solution to a 1000 mL separating funnel. Extract the aqueous phase with petroleum ether (40-60) (2 × 100 mL), combine the organic phases, dry over magnesium sulfate and filter. Remove the solvent on a rotary evaporator to give the crude product. Distil under reduced pressure

## Protocol 6. *Continued*

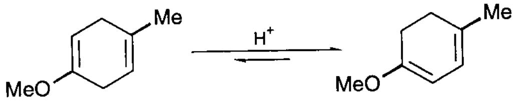
(b.p. 170–172 °C at atmospheric pressure) to give 1-methoxy-4-methylcyclohexa-1,4-diene (80%) as a colourless oil displaying the appropriate spectroscopic data [$\delta_H$ ($CDCl_3$) 1.69 (3 H, s, Me), 2.70 (4 H, brs, 2 × $CH_2$), 3.55 (3 H, s, OMe), 4.62 (1 H, brs, CH=), 5.36 (1 H, brs CH=)].

[a] Commercial 4-methylanisole may be used without further purification.
[b] A fresh bottle of hexanes (boiling fraction 68–69 °C) is sufficiently dry for this purpose.

Iron tricarbonyl complexes of diene ligands nearly always have their double bonds in conjugation with one another. Exceptions are only found with ligands such as norbornadiene where formation of a 1,3-diene would violate Bredt's rule by placing a double bond at a bridgehead position. The 1,4-unconjugated dienes from Birch reductions are often used directly in complexation reactions as iron carbonyl species promote double bond isomerisation prior to complexation. However, in some instances the yields obtained by this procedure are rather low and it pays to independently isomerise the diene prior to the addition of the iron carbonyl species. The following protocol describes how to isomerise the 1,4-diene **28** to an equilibrium mixture containing predominantly the 1,3-diene **29**.

## Protocol 7.
## Double bond isomerisation. Generation of equilibrium mixture of Structure 28 and Structure 29[22]

**Caution!** All procedures should be carried out in an efficient fume hood. Eye protection must be worn at all times.



**28** **29**

### *Equipment*

- Stirrer hotplate
- Oil bath
- Two-necked, round-bottomed flask (50 mL)
- Cone/flexible tubing adapter
- Teflon-covered egg-shaped magnetic stirrer bar (length 1.2 cm)
- Source of dry nitrogen
- Vacuum distillation apparatus

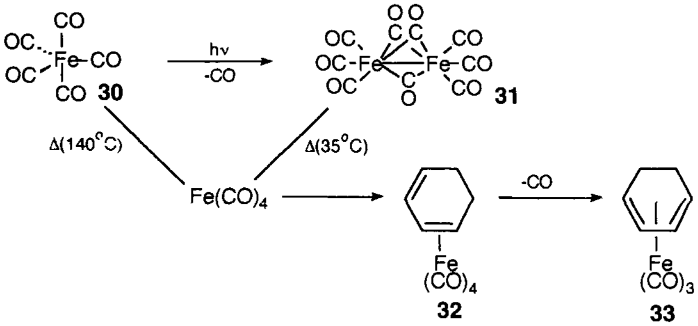
### *Materials*

| | |
|---|---|
| • 1-Methoxy-4-methylcyclohex-1,4-diene (FW 124.2), 15.0 g, 0.121 mol | **flammable** |
| • *p*-Toluenesulfonic acid monohydrate, 0.02 g | **corrosive, toxic** |

1. Using the stirrer hot plate, heat an oil bath until a constant temperature of 80 °C is maintained.
2. To the dry 50 mL two-necked round-bottomed flask containing the magnetic stirrer bar, add 1-methoxy-4-methylcyclohexa-1,4-diene (15.0 g, 0.121 mol) and *p*-toluenesulfonic acid monohydrate (0.02 g). Flush the system with nitrogen *via* the cone/flexible tubing adapter for 2 min and then place a stopper in the remaining neck of the flask.
3. Using the pre-equilibrated oil bath, heat the mixture with stirring at 80 °C for 2 h under a nitrogen atmosphere.
4. After cooling, vacuum distill (b.p. 78 °C, 30 mmHg) the resulting oil from the 50 mL flask to separate the 1:3 equilibrium mixture of unconjugated and conjugated dienes from *p*-toluenesulfonic acid. The product should be obtained in approximately 90% yield and confirmation that the isomerisation process has been successful may be obtained from its $^1$H NMR spectrum [$\delta_H$ ($CDCl_3$) 1.75 (3 H, s, Me), 2.29 (4 H, s, 2 × $CH_2$), 3.56 (3 H, s, OMe), 4.87 (1 H, d, $J$ = 6 Hz, CH=), 5.57 (1 H, d, $J$ = 6 Hz, CH=)].

---

Both iron pentacarbonyl **30** and diiron nonacarbonyl **31**, which are commercially available, are used as sources of iron tricarbonyl during complexation reactions. The former requires considerable thermal energy to bring about rate determining dissociation of a carbon monoxide ligand to form iron tetracarbonyl. This contains a vacant coordination site and adds to one of the double bonds of a diene generating an 18-electron $\eta^2$-adduct **32**. Further loss of a carbon monoxide ligand and coordination of the second double bond gives the $\eta^4$-diene iron tricarbonyl complex **33**. In contrast, diiron nonacarbonyl dissociates at much lower temperatures into iron pentacarbonyl and iron tetracarbonyl, and the 16-electron tetracarbonyl species then reacts in exactly the same way. The advantages of using iron pentacarbonyl are that it is considerably cheaper than diiron nonacarbonyl and that the relatively high temperatures required will additionally result in double bond isomerisations, as discussed above. Diiron nonacarbonyl is preferred for sensitive substrates, due to the much milder conditions used for complexation, and reactions are



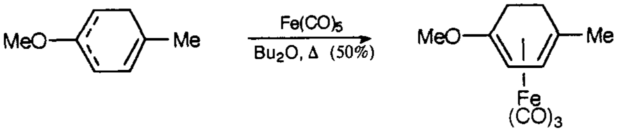
typically carried out in diethyl ether heated at reflux. Although relatively expensive to buy, diiron nonacarbonyl is easily synthesised by photolysis of the pentacarbonyl in glacial acetic acid.[23]

The following complexation protocol leading to the isolation of tricarbonyl(1-methoxy-4-methylcyclohexa-1,3-diene)iron **34** is representative.

---

## Protocol 8.
## Synthesis of tricarbonyl(1-methoxy-4-methylcyclohexa-1,3-diene)iron (Structure 34)[22]

**Caution!** All procedures must be carried out in an efficient fume hood. Eye protection must be worn at all times. Chemical resistant gloves must be worn when handling iron pentacarbonyl, tricarbonyl iron complexes and their solutions.



**28 + 29** **34**

### *Equipment*

- Two-necked, round-bottomed flask (250 mL)
- Liebig condenser
- Cone/flexible tubing adapter
- Stopper
- Teflon-covered egg-shaped magnetic stirrer bar (length 3 cm)
- Source of dry nitrogen
- Stirrer hot plate
- Measuring cylinder (50 mL)
- Glass funnel
- Single-necked round-bottomed flask (250 mL)
- 6.5 cm diameter glass sinter Büchner funnel with hose connection

### *Materials*

| | |
|---|---|
| • 3:1 mixture of 1-methoxy-4-methylcyclohexa-1,3-diene and 1-methoxy-4-methylcyclohexa-1,4-diene (FW 124.2), 10.0 g, 0.08 mol | **flammable** |
| • Iron pentacarbonyl[a] (FW 195.9), 27 g, 18 mL, 0.14 mol | **highly toxic** |
| • Dry di-*n*-butyl ether,[b] 85 mL | **flammable, irritant** |
| • Celite, *ca.* 25 g | |

1. Ensure that all glassware to be used for the reaction and the magnetic stirrer bar are clean and dry them in an oven at 120 °C for at least 12 h prior to use.
2. Assemble the glassware with the condenser in the central position of the two-necked round-bottomed flask. Attach the cone/flexible tubing adapter to a source of nitrogen, place in the top of the condenser and allow the apparatus to cool under a flow of nitrogen.
3. Charge the flask with the 3:1 mixture of 1,3- and 1,4-dienes (10.0 g, 0.08 mol) obtained in Protocol 7. **Wearing gloves** and exercising appropriate caution, transfer iron pentacarbonyl[a] (27 g, 18 mL, 0.14 mol) into the flask.

This is done with the aid of a 50 mL measuring cylinder and funnel containing a cotton wool plug, to remove any iron oxide residues that may be present in the iron pentacarbonyl. Use the funnel when pouring the iron pentacarbonyl into the measuring cylinder and again for transfer into the round-bottomed flask. Finally, add freshly distilled di-*n*-butyl ether[b] (75 mL) using the same measuring cylinder and funnel, so as to wash into the flask remaining traces of iron pentacarbonyl. Place the stopper into the neck of the flask and secure with a joint clip.

4. Using the stirrer hot plate and oil bath, heat the reaction mixture at reflux under a nitrogen atmosphere for 48 h. It is essential to ensure that the reaction mixture is efficiently stirred in order to ensure satisfactory yields. On completion of the reaction, allow the resultant very dark reaction mixture to cool to room temperature.
5. Attach the glass sintered Büchner funnel to a clamped, clean and dry 250 mL single-necked round-bottomed flask. Using a spoon, transfer celite into the sinter funnel to a depth of about 3–4 cm. Connect the side-arm of the sinter funnel to a water vacuum pump and carefully decant the reaction mixture onto the celite such that the mixture is filtered through the celite filtering aid. This should ensure an efficient filtration of the reaction mixture which contains pyrophoric particulate iron. It is important to ensure that the celite pad does not run dry, otherwise the iron may ignite.[c] Wash out the flask with an additional 10 mL of di-*n*-butyl ether.
6. Remove the solvent and excess iron pentacarbonyl on a rotary evaporator placed in a fume cupboard.[d] Remove traces of solvent by attaching the flask to a high vacuum pump for an hour, to give the crude tricarbonyl(1-methoxy-4-methylcyclohexa-1,3-diene)iron complex in approximately 50% yield, as a yellow oil displaying appropriate $^1$H NMR[e] and IR spectroscopic data.[24] This material is sufficiently pure for use in Protocol 9.

[a] Excess iron pentacarbonyl is readily destroyed on treatment with bromine water. This is prepared by shaking bromine (**care!**) (3 g) with water (100 mL) until a homogeneous solution is obtained. All glassware with which iron pentacarbonyl has been in contact should stand in a bromine water solution for an hour, prior to rinsing with water and removal from the fume cupboard.

[b] Distil from sodium benzophenone ketyl under a nitrogen atmosphere immediately prior to use.

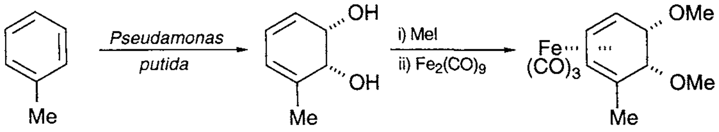
[c] Destroy the particulate iron residues with dilute hydrochloric acid.

[d] The iron pentacarbonyl and di-*n*-butyl ether distillate should be treated with bromine prior to disposal. After use, the rotary evaporator should be cleaned. This is best achieved by rotary evaporating a flask containing ethanol and then treating the distillate with bromine prior to disposal.

[e] The signals in the NMR spectrum of this compound may be significantly broadened due to the presence of paramagnetic iron salts. These can be removed by passing the $CDCl_3$ solution of the complex through a small plug of deactivated neutral alumina immediately before the recording of the spectrum. Deactivated neutral alumina is prepared by thoroughly shaking a 10:1 w/w ratio of Grade 1 neutral alumina and water.

---

Diols resulting from the microbal oxidation of arenes, such as toluene **35**, by *Pseudamonas putida* have recently been used as ligands for the iron tricarbonyl unit. These compounds, which are optically pure and of known absolute configuration, contain the cyclohexa-1,3-diene moiety, the two faces of which are diastereotopic as a consequence of the neighbouring tetrahedral chiral centres. After conversion of diol **36** to its corresponding dimethyl ether, complexation with diiron nonacarbonyl was found to give a single diastereoisomer **37**. The ether groups direct the iron carbonyl moiety to the same side of the cyclohexadiene ring.[25]

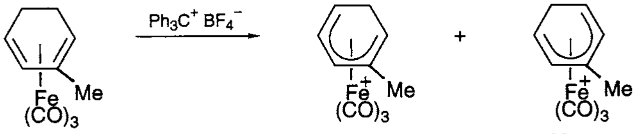


**35** **36** **37**

The attraction of this methodology is the rapid access it provides to optically pure diene complexes which have subsequently been converted to dienyl iron complexes. Using Birch substrates as starting materials for diene iron carbonyl synthesis requires a resolution step in order to obtain optically pure material, and to date no efficient method for performing this resolution has been devised.

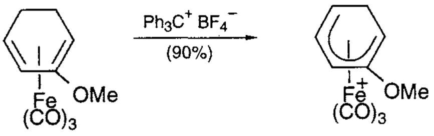
## 3.2 Synthesis of $\eta^5$-cyclohexadienyl iron tricarbonyl complexes

Triphenylcarbenium salts ($Ph_3C^+$) readily abstract a hydride from $\eta^4$-cyclohexadiene iron tricarbonyl complexes to form cationic $\eta^5$-cyclohexadienyl salts, the hydride being removed from one of the methylene groups adjacent to the $\eta^4$-diene unit. When the cyclohexadiene ligand is monosubstituted, or has two or more different functionalities attached, a mixture of regioisomers may potentially result. For example, hydride abstraction from **38** results in a 1.5:1 ratio of the two possible regioisomers **39** and **40**.



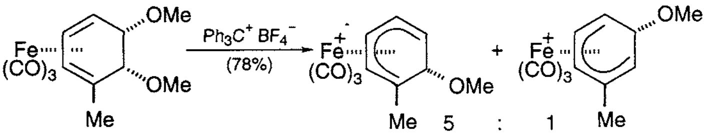
**38** **39** 56% **40** 38%

The regioselectivity may be accounted for by the relative HOMO and LUMO energies of the two dienyl cations, the preferred isomer having a stronger synergic two-way interaction with the iron tricarbonyl moiety. If the 2-methyl substituent is changed to a 2-methoxy group, the latter has a stronger pertubation on the relative HOMO and LUMO energies of the two possible dienyl cations. As a result, hydride abstraction from **41** yields almost exclusively the 2-methoxycyclohexadienyl complex **42**. Similarly, hydride abstraction from 1-methoxy-substituted cyclohexadiene ligands gives almost exclusively a single regioisomer.[24]



**41** **42**

In addition to hydride, other groups may be abstracted from neutral $\eta^4$-cyclohexadiene complexes. The reaction between the homochiral complex **37** and the triphenylcarbenium ion resulted in removal of a methoxide anion and formation of a 5:1 mixture of the two possible isomers **43** and **44**.[25] Trifluoroacetic acid (TFA) may also be used. For **37** this resulted in a lowering of the selectivity, but there are examples where regioisomers do not arise and TFA is the reagent of choice for the removal of methoxide.[26]



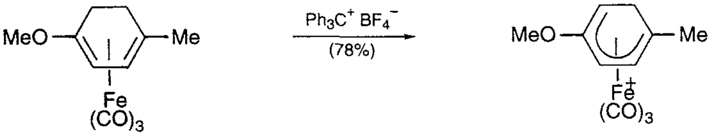
**37** **43** **44**

Cyclohexadienyl iron tricarbonyl cations are best isolated as their relatively stable hexafluorophosphate salts. These are easily formed by addition of a saturated aqueous solution of ammonium hexafluorophosphate to an aqueous solution containing the cationic complex arising from either hydride or methoxide abstraction. The following protocol for the hydride abstraction from tricarbonyl(1-methoxy-4-methylcyclohexa-1,3-diene)iron **34** is representative.

---

## Protocol 9.
## Synthesis of tricarbonyl(4-methoxy-1-methylcyclohexadienylium)iron hexafluorophosphate (Structure 45)[22]

**Caution!** All procedures should be carried out in an efficient fume hood. Eye protection must be worn at all times. Chemical resistant gloves must be worn when handling tricarbonyl iron complexes and their solutions.



**34** **45**

## **Protocol 9.** *Continued*

### *Equipment*

- Two-necked, round-bottomed flask (2 × 100 mL)
- Septum (× 2)
- Cone/flexible tubing adapter (× 2)
- Teflon-covered egg-shaped magnetic stirrer bar (2 × 1.5 cm length)
- Magnetic stirrer
- Glass syringe with needle-luer lock (20 mL)
- Needle (15 cm, 16–18 gauge)
- Single-necked, round-bottomed flask (250 mL)
- Glass funnel
- Beakers (100 mL, 250 mL)
- Büchner funnel
- Büchner flask

### *Materials*

| | |
|---|---|
| • Tricarbonyl(1-methoxy-4-methylcyclohexa-1,3-diene)iron (FW 264.1), 5.0 g, 0.019 mol | **toxic** |
| • Triphenylmethylium tetrafluoroborate (FW 330.1), 6.80 g, 0.021 mol | **hygroscopic, toxic** |
| • Dry dichloromethane,[a] 75 mL | **toxic, irritant** |
| • Wet diethyl ether,[b] 70 mL | **flammable, irritant** |
| • Ammonium hexafluorophosphate (FW 163.0), *ca.* 2.5 g, 0.015 mol | **hygroscopic, harmful** |

1. Ensure that all glassware to be used for the reaction and the magnetic stirrer bar are clean and have been in an oven at 120°C for at least 12 h prior to use.
2. Assemble both two-necked 100 mL round-bottomed flasks, each containing a magnetic stirrer bar and a cone/flexible tubing adapter connected to the nitrogen supply, and allow to cool under a stream of nitrogen.
3. Charge one of the flasks with the crude tricarbonyl(1-methoxy-4-methylcyclohexa-1,3-diene)iron (5.0 g, 0.019 mol) prepared in Protocol 8, add a septum to the open neck and label as flask A.
4. Disconnect the remaining two-necked round-bottomed flask from the nitrogen supply and weigh into this, as quickly as possible, triphenylmethylium tetrafluoroborate (6.80 g, 0.021 mol). Reconnect to the nitrogen supply, flush the flask through with nitrogen for a couple of minutes, then place a septum into the open neck. Label as flask B.
5. Assemble the 20 mL syringe and needle while hot and flush with nitrogen as described in Protocol 3, step 4. When cool, use the syringe to add dry dichloromethane[a] to flask A (15 mL) and flask B (40 mL). Stir the resulting mixtures to ensure the formation of homogeneous solutions.
6. Using the same syringe, transfer the solution of tricarbonyl(1-methoxy-4-methylcyclohexa-1,3-diene)iron from flask A to flask B, and stir the resulting mixture at room temperature for 1 h.
7. Disconnect the nitrogen supply and transfer the mixture to a clean single-necked round-bottomed flask (250 mL) with the aid of a funnel. Wash out the reaction flask with an additional 10 mL of dry dichloromethane. Reduce the volume of the solvent to about 10 mL on a rotary evaporator before adding wet diethyl ether[b] (50 mL) to precipitate tricarbonyl(4-methoxy-1-methylcyclohexadienylium)iron tetrafluoroborate. (If an oil is formed at this point, vigorous swirling and/or scratching the inside of the flask with a spatula

should produce the required solid.) Filter off this yellow solid with a Büchner funnel, wash with an additional 20 mL of wet diethyl ether and proceed immediately with step 8.

8. Transfer the tetrafluoroborate salt to a pre-weighed 250 mL beaker. Reweigh the beaker to determine the mass of the tetrafluoroborate salt (FW 349.9) before dissolving this salt in the minimum quantity of water to obtain a saturated aqueous solution. (Occasionally, a small amount of insoluble scum may form; if this is the case, it should be removed by gravity filtration.) In a 100 mL beaker, add 1.2 equiv. of ammonium hexafluorophosphate (FW 163.0), calculated with respect to the tetrafluoroborate salt, and dissolve in the minimum volume of water.
9. Add the solution of ammonium hexafluorophosphate to the saturated tetrafluoroborate solution, and leave standing at room temperature for 30 min. Filter the resultant precipitate, wash with water (2 × 5 mL) and dry under vacuum to give in the order of 6 g of tricarbonyl(4-methoxy-1-methylcyclohexadienylium)iron hexafluorophosphate as a yellow solid, displaying appropriate spectroscopic data.[24]

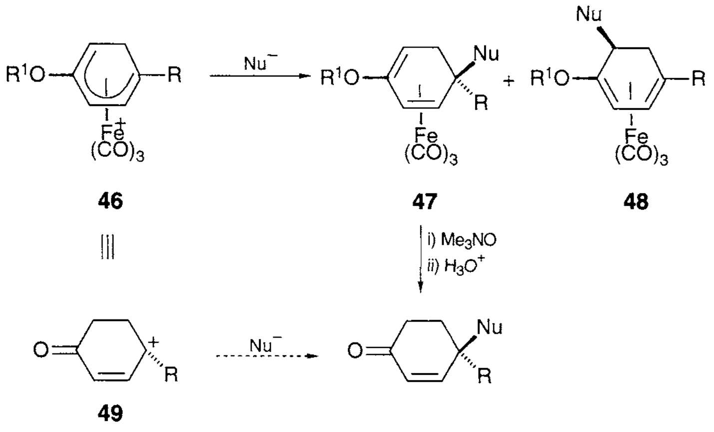
[a] Distil from calcium hydride under a nitrogen atmosphere.

[b] Saturate the diethyl ether by shaking with water in a separatory funnel and partitioning the layers.

---

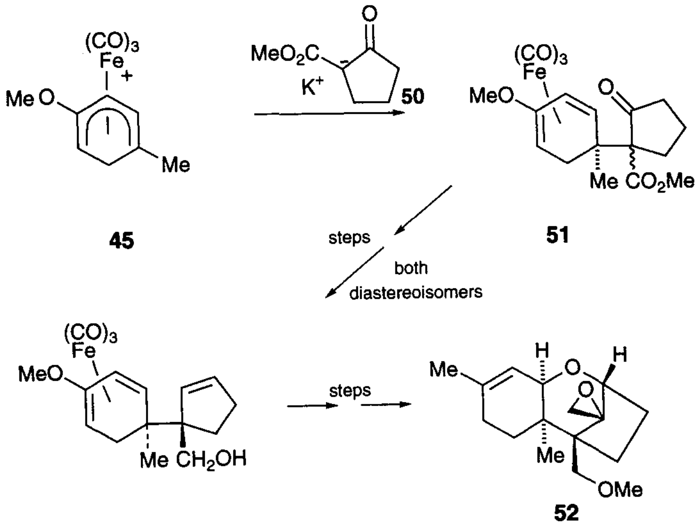
## 3.3 Nucleophilic addition to cyclohexadienyl iron tricarbonyl complexes. Applications to natural product synthesis

As detailed in the sections above, cyclohexadienyl iron complexes of general formula **46** are readily obtained by Birch reduction, complexation and highly regioselective hydride abstraction. Nucleophilic addition to these complexes occurs only at the terminal positions of the $\eta^5$-cyclohexadienyl unit such that two products **47** and **48** may be produced. In the vast majority of cases **47** is



the preferred product, the nucleophile attacking *exo* to the bulky iron carbonyl group to produce a single diastereoisomer.[27] The alternative product, which is also formed as a single diastereoisomer, is only produced in significant quantities for certain $R^1$ substituents (*e.g.* $-CH_2CH_2OAc$).[28]

Removal of the organic ligand of **47** followed by hydrolysis of the enol ether yields the 4,4-disubstituted cyclohexenone system and so **46** may be formally regarded as a synthetic equivalent of the cyclohexenone cation **49**. This methodology has been exploited in the synthesis of a number of natural products. For example, addition of the potassium enolate **50** to cyclohexadienyl complex **45** resulted in formation of a neutral complex **51** containing the two contiguous quaternary centres required for the synthesis of 12,13-epoxy-14-methoxytrichothecene **52**.[22]



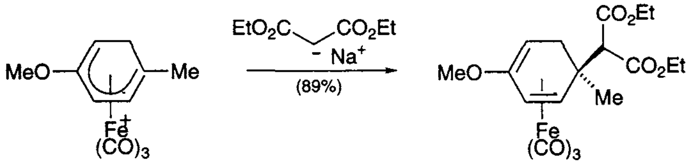
**45** **50** **51** **52**

Methodology of this type has also been applied to the synthesis of the related compounds trichodiene[29] and trichodermol,[30] and also to the alkaloid limaspermine.[31] The following protocol is representative of carbanion addition to cationic tricarbonyl($\eta^5$-cyclohexadienyl)iron complexes.

## Protocol 10.

## Synthesis of tricarbonyl(diethyl 4-methoxy-1-methylcyclohexa-2,4-dienylmalonate)iron (Structure 53)[27]

**Caution!** All procedures should be carried out in an efficient fume hood. Eye protection must be worn at all times. Chemical resistant gloves must be worn when handling tricarbonyl iron complexes and their solutions.



**45** **53**

*Equipment*

- Three-necked, round-bottomed flask (2 × 100 mL)
- Septum (× 2)
- Cone/flexible tubing adapter (× 2)
- Teflon-covered egg-shaped magnetic stirrer bar (2 × 1.5 cm length)
- Stopper (× 2)
- Magnetic stirrer
- Cannula with glass filtering attachment (30 cm, 16–18 gauge) (Fig. 3.1)
- Glass syringe with needle-luer lock (3 × 10 mL)
- Needle (3 × 15 cm, 16–18 gauge)

*Materials*

| | |
|---|---|
| • 60% dispersion of sodium hyride in mineral oil (FW 24.0), 0.12 g, 3 mmol | **flammable, moisture sensitive** |
| • Dry 40-60 petroleum ether,[a] 15 mL | **flammable** |
| • Dry tetrahydrofuran,[b] 25 mL | **flammable, irritant** |
| • Diethyl malonate (FW 160.2), 0.48 g, 3 mmol | **flammable** |
| • Tricarbonyl(4-methoxy-1-methylcyclohexadienylium)iron hexafluorophosphate (FW 408.0), 0.50 g, 1.22 mmol | **toxic** |
| • Petroleum ether 40–60 for extraction and flash chromatography | **flammable** |
| • Silica gel for flash chromatography (Merck 9385) | **irritant dust** |
| • Ethyl acetate for flash chromatography | **flammable, irritant** |

1. Ensure that all glassware to be used in the reaction and the magnetic stirrer bars are clean and have been in an oven at 120°C for at least 12 h prior to use.
2. Assemble a 100 mL three-necked round-bottomed flask, containing a magnetic stirrer bar, with a septum and a cone/flexible tubing adapter connected to the nitrogen supply, and allow to cool under a stream of nitrogen. Charge the flask with a 60% dispersion of sodium hydride in mineral oil (0.12 g, 3 mmol) and place a stopper in the remaining neck of the flask.
3. Attach a filter paper to the cannula filtering device as described in Protocol 3, step 7. Remove the septum from the flask, push the needle end of the

**Protocol 10.** *Continued*

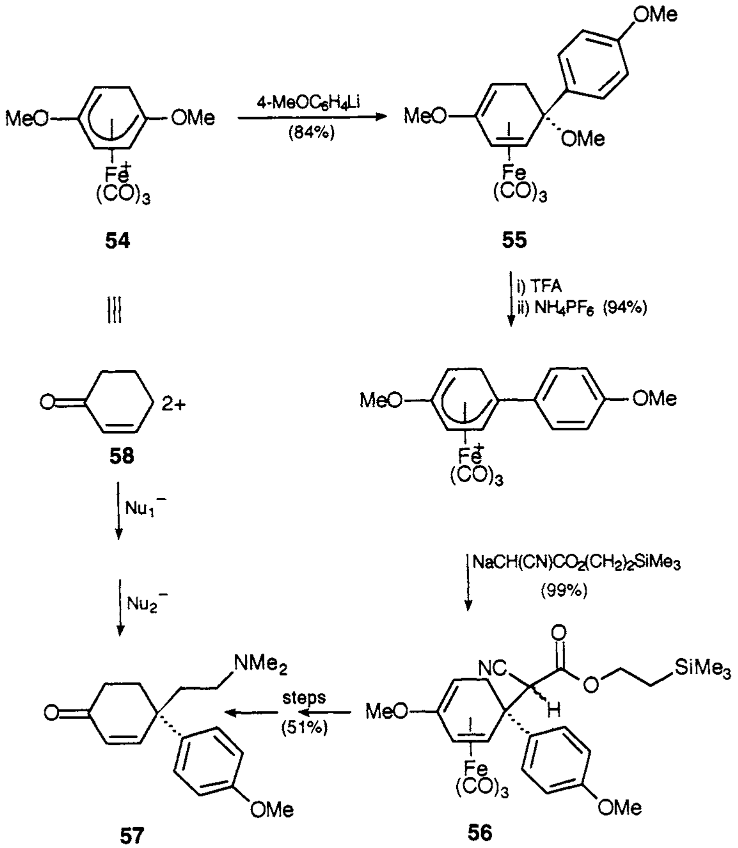
filtering cannula through the bottom of the septum and slide the septum down the cannula until it reaches the filtering end. Replace the septum in the neck of the flask such that the resulting apparatus is essentially as shown in Fig. 3.2.

4. Assemble a 10 mL syringe and needle while hot and flush with nitrogen as described in Protocol 3, step 4. Use to transfer 5 mL of dry petroleum ether (40-60)[a] into the flask. Stir the slurry briefly then allow the solid to settle. Remove the solvent by pushing the filtering end of the cannula into the slurry and placing the other end of the cannula into a small beaker to collect the filtrate. If no solvent is transferred, increase the flow rate of the nitrogen supply. Repeat this procedure for separating the sodium hydride from the mineral oil twice more. Knock off any solid that has accumulated on the filter paper, remove the cannula and replace the septum in the neck of the flask.
5. Use a fresh 10 mL syringe and needle, flushed with nitrogen as before, to transfer dry tetrahydrofuran[b] (10 mL) into the flask. Make a solution of diethyl malonate (0.48 g, 3 mmol) in tetrahydrofuran (5 mL) by weighing out the diethyl malonate into a clean, dry glass vial and adding the tetrahydrofuran from a syringe. Immediately draw the resulting solution back into the syringe, then add it dropwise to the sodium hydride/tetrahydrofuran mixture and stir for a further 15 min at room temperature to generate a clear solution of the diethyl malonate anion.
6. Assemble the remaining 100 mL three-necked round-bottomed flask, magnetic stirrer bar, septum and adapter, and cool under nitrogen as described in step 2. Charge this flask with tricarbonyl(4-methoxy-1-methylcyclohexadienylium)iron hexafluorophosphate (0.50 g, 1.22 mmol) and place a stopper into the remaining neck. Using a third 10 mL syringe and needle assembly, add dry tetrahydrofuran[b] (10 mL) and cool the resulting suspension to 0°C with stirring. Use this same syringe to transfer dropwise 7.5 mL of the diethyl malonate anion solution to the suspension of the hexafluorophosphate salt. The reaction is complete when a homogeneous solution is obtained. If this does not occur, add further 1 mL portions of the diethyl malonate anion solution until homogeneity occurs.
7. Pour the reaction mixture into water (20 mL) and extract with petroleum ether (40-60) (2 × 20 mL). Combine and dry the organic phase over magnesium sulfate, filter and remove the solvent on a rotary evaporator. Purify the product by flash column chromatography on silica gel using 10% ethyl acetate/petroleum ether (40-60) as eluent. Isolate the product as a yellow oil, 0.5 g (89%), displaying appropriate spectroscopic data.[27]

[a] Dry over magnesium sulfate and distil, discarding the first 10% which may contain water.

[b] Distil from sodium benzophenone ketyl under a nitrogen atmosphere and use immediately.

The product of addition to cyclohexadienyl complexes is a neutral $\eta^4$-cyclohexadiene species. If this contains a suitable leaving group, it may be used to synthesise a second cyclohexadienyl complex to which a second nucleophilic species may be added. In this way the iron carbonyl moiety may be employed to control the formation of two new C-C bonds. For example, addition of 4-lithioanisole to the dimethoxycyclohexadienyl complex **54** proceeds with high regioselectivity to give the neutral species **55**. Removal of the methoxide group with trifluoroacetic acid, precipitation of the hexafluorophosphate salt, followed by addition of a second nucleophilic species gives the product **56**. Further manipulation, removal of the iron and hydrolysis of the enol ether gives the 4,4-disubstituted cyclohexenone **57** such that the starting complex may be regarded as a synthetic equivalent for the cyclohexenone dication synthon **58**.[32]



This example illustrates an important extension of the use of iron cyclohexadienyl complexes in organic synthesis through multiple use of the metal.

The attraction of organometallic systems for the organic chemist is that they offer reactivity patterns that are not otherwise observed. However, as introduction of the metal centre does require some effort, it must be used to maximum effect, preferably to control two or more reactions with complete regio- and stereocontrol. This type of approach will continue to find use in organic synthesis, especially when utilising complexes that are readily generated in optically pure form.

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## 4

# Organoiron chemistry 2: iron acyl and π-allyltricarbonyliron lactone chemistry

MARTIN WILLS

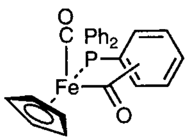
## 1. Introduction

Two classes of organoiron chemistry will be described in this chapter. The first part concerns the synthesis and applications of acyl derivatives of the enantiomerically pure chiral auxiliary $[(C_5H_5)Fe(CO)(PPh_3)]$. Such complexes may be elaborated through a variety of synthetic transformations with invariably high diastereoselectivity. Removal of the acyl group furnishes enantiomerically enriched or pure products. The second class of organoiron reagents featured in this chapter are iron tricarbonyl π-allyl complexes. These have been employed as intermediates in general methods for the synthesis of lactones and lactams and have been applied to a number of total syntheses of complex natural products.

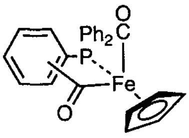
## 2. Iron acyl chemistry[1]

### 2.1 Introduction

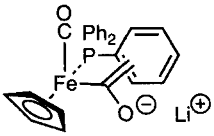
The chiral iron acyl complex $[(C_5H_5)Fe(CO)(PPh_3)COCH_3]$ **1** has an octahedral structure in which the acyl, triphenylphosphine and carbon monoxide ligands occupy three coordination sites and lie mutually at right angles to each other.[2] The remaining three sites are occupied by the cyclopentadienyl ligand. The preferred conformation of the acyl group is that in which the acetyl oxygen is *anti* to the carbon monoxide ligand, and this has been observed in all X-ray crystal structures of this class of iron acyl complex solved to date. Deprotonation of **1** with *n*-butyllithium generates the corresponding enolate **2** which may be alkylated cleanly on the carbon atom using a variety of electrophiles.[3] Complex **1** and its derivatives are generally air-stable crystalline solids, although they are prone to oxidation by air when kept in solution. Hence all manipulations of these compounds are routinely carried out under an inert atmosphere. Reactions are carried out in Schlenk tubes or round-bottomed flasks fitted with gas inlets and all manipulations are performed using the vacuum/inert manifold techniques described in Chapter 7 and elsewhere.[4] All solvents should be saturated with nitrogen or argon immediately prior to use and transferred by cannula tubing.



*R*-(–)-**1**



*S*-(+)-**1**



**2**

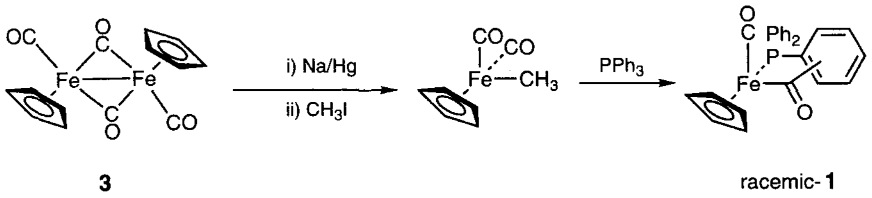
## 2.2 Preparation of iron acyl complex 1

Racemic **1** may be prepared in three steps from $[(C_5H_5)Fe(CO)_2]_2$ **3** in a high-yielding large-scale process (Scheme 4.1).[5] This method involves a one-pot reduction of **3** followed by reaction with iodomethane and subsequent treatment with triphenylphosphine. In the last step the methyl group migrates to the carbon monoxide ligand and triphenylphosphine fills the remaining coordination site. Purification of the product at the end of this sequence is achieved by recrystallisation; no chromatography is required.

---

### Protocol 1.
### Synthesis of racemic iron acyl complex (Structure 1) (Scheme 4.1)[5,a]

**Caution!** All procedures should be carried out in a well-ventilated hood, and disposable vinyl or latex gloves and chemical-resistant safety glasses should be worn.



**Scheme 4.1**

*Equipment*

- Three-necked, round-bottomed flasks (2 × 3 L, 2 × 2 L)
- Two-necked, round-bottomed flask (1 L)
- Gas inlets with stopcocks for round-bottomed flasks
- Septa
- Overhead mechanical stirrer apparatus (one motor, two paddles and adapters)
- Pre-trap assembly (see Fig. 4.1) (2 L)
- Pressure-equalising dropping funnel (100 mL)
- All-glass syringes of appropriate volumes with needle-lock luers
- Needles (6", 20 or 22 gauge)
- Vacuum/nitrogen manifold (Figs 7.1 and 7.2)
- Glass powder funnel
- Large frit (8 cm diameter, 25 cm high), (Fig. 4.2)
- Aluminium foil
- Long spatula (30 cm)
- Cannula or transfer tubing of appropriate size

*Materials*

| | |
|---|---|
| • Sodium metal (FW 23.0), 14.5 g, 0.63 mol | **flammable solid, pyrophoric, moisture sensitive** |
| • Mercury, 56 mL[b] | **highly toxic, irritant** |
| • $[(C_5H_5)Fe(CO)_2]_2$ (FW 353.7), 80 g, 0.225 mol | **toxic, irritant** |
| • Dry THF,[c] 600 mL and 20 mL | **flammable, irritant** |
| • Iodomethane (FW 141.9), 82.4 g, 36.1 mL, 0.58 mol | **highly toxic, irritant, corrosive** |
| • Triphenylphosphine (FW 262.3), 119 g, 0.45 mol | **toxic, irritant** |
| • Dry nitrogen-saturated petroleum ether (30-40), 600 mL | **flammable, irritant** |
| • Dry nitrogen-saturated acetonitrile, 400 mL | **flammable, lacrymator** |
| • Dry nitrogen-saturated hexane, 160 mL and 80 mL | **flammable, irritant** |
| • Dry nitrogen-saturated dichloromethane,[d] 600 mL and 2 × 100 mL | **toxic, irritant** |
| • Celite | **irritant** |
| • Alumina (Activated, Grade I) | **irritant** |
| • *Liquid nitrogen for pre-traps* | ***asphixiant*** |

1. Clean all glassware, syringes and needles and dry for at least 2 h in a hot oven (>100°C) before use.
2. Attach a 3 L three-necked flask to the overhead stirrer apparatus by the central inlet and insert a gas inlet and a septum into the remaining necks.
3. Support the flask using a clamp and stand with a heavy base.
4. Attach tubing from vacuum/nitrogen manifold to gas inlet.
5. Add the mercury (56 mL) to the flask and adjust the stirrer so that the paddle is just above its surface.
6. Add the sodium (14.5 g) in small pieces (*ca.* 1 g) to the mercury. The sodium should be kept under oil and each piece dried rapidly on a tissue before addition (it is not critical to remove all the oil). Mechanical agitation may be required before the first piece reacts. **CAUTION** – The reaction is highly exothermic and violent. Add the remaining pieces at intervals of *ca.* 5 min during which time the amalgam should remain hot and liquid. Fumes may be taken off at intervals by adjusting the vacuum/nitrogen manifold tap first to vacuum and then to nitrogen (Chapter 7, Protocol 1).
7. Allow the amalgam to cool to room temperature and solidify. This will usually take at least 1 h.
8. With the aid of a glass powder funnel, add the solid $[(C_5H_5)Fe(CO)_2]_2$ (80 g, 0.45 mol) against a steady stream of nitrogen after removal of the septum, which should be replaced immediately.
9. Assemble a syringe (50 mL) and needle and flush with nitrogen following the procedure given in Chapter 3, Protocol 3, step 4.
10. Add anhydrous THF (600 mL) by syringe (12 portions), taken directly from the still, and start the stirrer.
11. Place the system under vacuum carefully until the solvent just begins to boil, then carefully reintroduce nitrogen (Chapter 7, Protocol 2). Repeat the cycle three times.

**Protocol 1.** *Continued*

12. Stir the deep purple solution for 16 h at room temperature. After 10 min the amalgam may be a mobile liquid phase, although this may take longer in some cases. After 16 h the solution should be dark orange in colour.
13. Attach a 3 L three-necked flask to an overhead mechanical stirrer apparatus by the central inlet, and connect a gas inlet and a septum to the remaining necks.
14. Support the flask using a clamp and stand with a heavy base.
15. Attach a flexible tubing connection from the vacuum/nitrogen manifold to the gas inlet.
16. Carefully place the flask under vacuum, then slowly reintroduce nitrogen. Repeat two times.
17. Stop the stirrer on the first flask and decant the orange solution to the second flask using a cannula and the method described in Chapter 7, Protocol 4. All experimental details will now refer to the second flask.
18. Start the overhead stirrer.
19. Against a steady stream of nitrogen, replace the septum with the pressure-equalising dropping funnel fitted with a septum.
20. Place the system under vacuum carefully until the solvent just begins to boil and then carefully reintroduce nitrogen. Repeat the cycle three times.
21. Assemble a syringe and needle and flush the syringe with nitrogen.
22. Charge the pressure-equalising dropping funnel with iodomethane (82.4 g, 0.58 mol) and THF (20 mL) taken directly from a still.
23. Add the solution of iodomethane to the stirred orange solution slowly at room temperature. The addition should take around 40 min on this scale. The reaction is exothermic.
24. Stir at room temperature for 16 h. At the end of this time the solution should be an olive-green colour.
25. Replace the dropping funnel and overhead mechanical stirrer with septa and remove the solvent under reduced pressure to give a red-brown solid product. It will be necessary to use a 2 L pre-trap cooled in liquid nitrogen (Fig. 4.1).
26. Add dry nitrogen-saturated light petroleum ether (600 mL) and mechanically agitate the mixture so that a deep red solution over a white solid is formed.
27. Attach a large frit (8 cm diameter, 25 cm high) fitted with a septum and packed with a 10 cm depth of celite to a 2 L three-necked flask. A gas inlet and septum should also be fitted to the flask.
28. Support the flask using a clamp and stand with a heavy base.

29. Attach tubing from the vacuum/nitrogen manifold to the gas inlet.
30. With the use of a cannula, pass the deep red liquid through the frit and into the 2 L round-bottomed flask. Care should be taken not to transfer too much of the solid. The frit may become blocked by a build-up of sediment in which case mechanical clearance using a long spatula will be required. All experimental details will now refer to the second flask.
31. Use two further portions of nitrogen-saturated light petroleum ether (100 mL) to complete the transfer of product to the 2 L flask *via* the frit.
32. Remove the light petroleum ether under vacuum to give a red solid. It will be necessary to use a 2 L pre-trap cooled in liquid nitrogen.
33. Add dry nitrogen-saturated acetonitrile (400 mL) to the red solid.
34. Prepare a 1 L two-necked flask fitted with a condenser/gas inlet on one neck and a septum on the other. Dry the apparatus with an electric heat gun or a small Bunsen burner at reduced pressure (0.5–1 mmHg), allow to cool and refill with nitrogen.
35. Add triphenylphosphine (119 g, 0.45 mol) to the 1 L flask against a steady stream of nitrogen after removal of the septum, which should be replaced immediately.
36. Add the red acetonitrile solution to the 1 L flask by cannula.
37. Surround the flask with aluminium foil.
38. Place the system under vacuum carefully until the solvent just begins to boil, then carefully reintroduce nitrogen. Repeat the cycle three times.
39. Using an oil bath, heat the solution under reflux for *ca.* 55 h under nitrogen. The reaction may be followed by IR spectroscopy since the product and starting materials have characteristic carbonyl absorption bands (starting material at 2000 and 1945 $\text{cm}^{-1}$, product at 1900, 1600 $\text{cm}^{-1}$). During this time the solution changes to an orange colour.
40. Allow the solution to cool to room temperature and remove the acetonitrile under reduced pressure. It will be necessary to use a large pre-trap cooled in liquid nitrogen.
41. Add dry nitrogen-saturated dichloromethane (600 mL) to the solid mass and agitate the orange solution vigorously for 30 min.
42. Attach a large frit (8 cm diameter, 25 cm high) fitted with a septum and packed with a 10 cm depth of alumina to a 2 L three-necked flask. A gas inlet and septum should also be fitted to the flask.
43. Support the flask using a clamp and stand with a heavy base.
44. Attach tubing from the vacuum/nitrogen manifold to gas inlet.
45. With the aid of a cannula, pass the orange liquid through the frit into the 2 L round-bottomed flask. Care should be taken not to transfer too much

**Protocol 1.** *Continued*

of the solid. The frit may become blocked by a build-up of sediment in which case mechanical clearance using a long spatula will be required.

46. Add further portions of dry nitrogen-saturated dichloromethane (2 × 100 mL) to the first flask and transfer to the 2 L flask *via* the frit as described in step 45.
47. Reduce the volume of the dichloromethane solution to *ca.* 400 mL under vacuum. It will be necessary to use a large pre-trap cooled in liquid nitrogen.
48. Add dry degassed hexane (160 mL). A quantity of crystalline solid may appear by this time.
49. Reduce the volume of the solution to *ca.* 300 mL under vacuum.
50. Stand the solution overnight in a fridge. A large amount of orange crystalline solid should have formed by this stage.
51. Filter the solvent from the crystalline product using a filter cannula (Chapter 7, Protocol 4).
52. Wash the crystals of **1** with cold, dry nitrogen-saturated hexane (2 × 40 mL) injected by syringe, remove using a filter cannula, and dry under vacuum for 2 h. The yield of **1** is typically 120–140 g, 60–70% for the three steps and the material displays the appropriate spectroscopic data.[5] The dry solid is stable indefinitely in air. A further portion (5–10%) may be obtained by concentration of the filtrate.

[a] A three-step procedure without isolation and characterisation of intermediates.

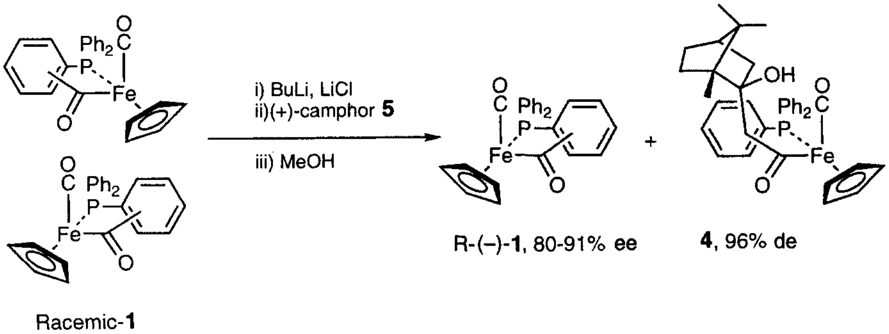
[b] Triple distilled (99.99%) grade.

[c] Freshly distilled from sodium benzophenone ketyl under an inert atmosphere.

[d] Freshly distilled from calcium hydride.

---

Although a number of methods for the preparation of enantiomerically pure **1** have been published,[6,7] resolution *via* the intermediacy of aldol adduct **4** has emerged as the most efficient (Scheme 4.2).[7] In this procedure racemic enolate **2** is treated with enantiomerically pure (+)-camphor **5** to give the aldol adduct. A significant kinetic resolution effect is observed which results in predominant formation of the product **4** (96% de) from addition of (*S*)-**2**



Racemic-**1**

R-(–)-**1**, 80-91% ee

**4**, 96% de

**Scheme 4.2**

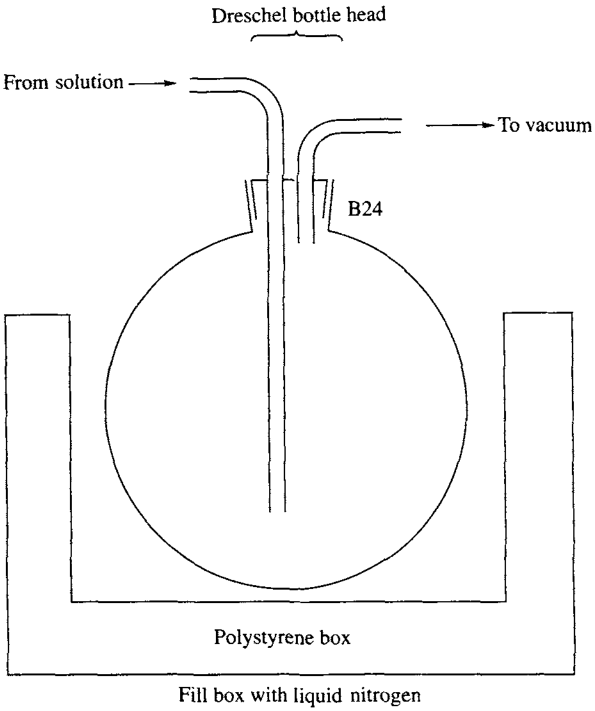
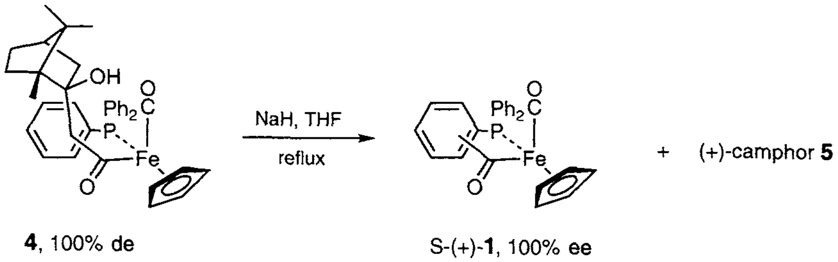


**Fig. 4.1** Pre-trap setup.

to (+)-**5**. Protonation of the reaction mixture reforms starting material which is enriched in (*R*)-**1** (80–91% ee). A single recrystallisation of this material gives enantiomerically pure (*R*)-**1** in 20–35% yield overall. It is essential to carry out this reaction in the presence of lithium chloride (1.5 equiv. is optimal) to achieve the highest levels of selectivity.

Recrystallisation of the aldol product **4** followed by treatment with sodium hydride at reflux results in a retro-aldol reaction to give (*S*)-**1** in 100% ee (Scheme 4.3).[7] Hence both enantiomers of **1** may be prepared in enantiomerically pure form by this method.



**Scheme 4.3**

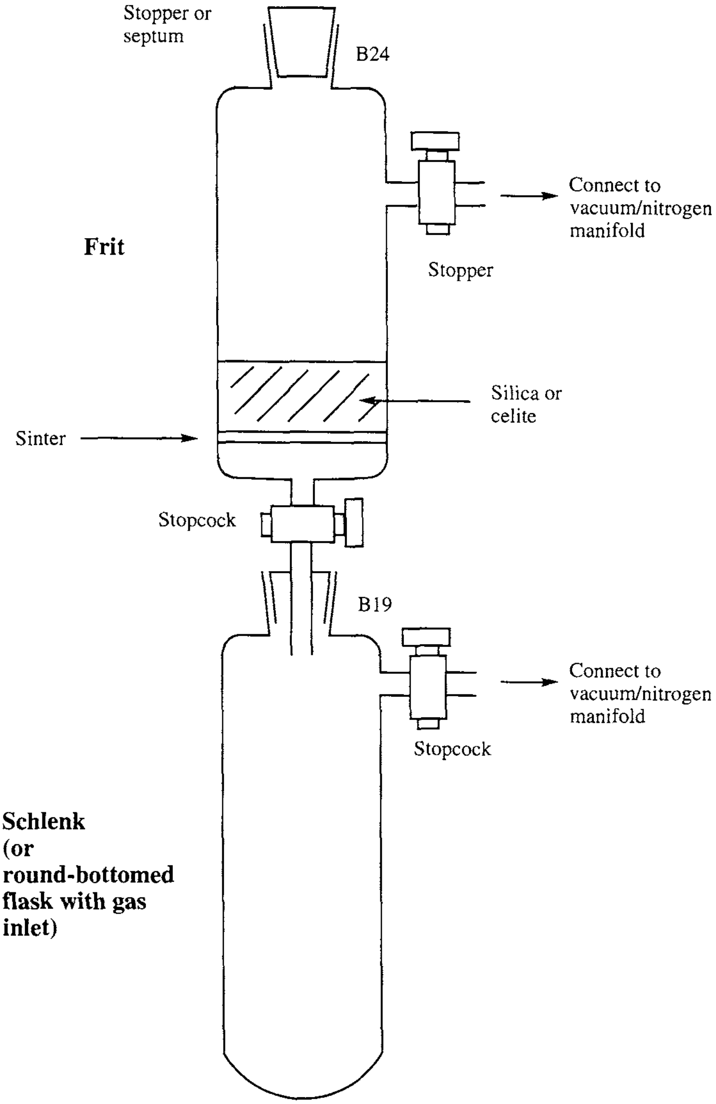


**Fig. 4.2** Frit/Schlenk arrangement for filtration.

## Protocol 2.
## Kinetic resolution of iron acyl complex (Structure 1) *via* aldol reaction with (+)-camphor 5 (Scheme 4.2)[7]

**Caution!** All procedures should be carried out in a well-ventilated hood, and disposable vinyl or latex gloves and chemical-resistant safety glasses should be worn.

### *Equipment*

- Magnetic stirrer
- Teflon-covered magnetic stirrer bar (5 mm × 5 mm × 15 mm, octagonal or egg-shaped)
- Two-necked, round-bottomed flasks (3 × 50 mL) or Schlenk tubes (3 × 100 mL)[a]
- Gas inlets with stopcocks if round-bottomed flasks are used
- Small frit (2.5 cm diameter, 15 cm high) (Fig. 4.2)
- Septa
- Glass syringes with needle-lock luers of appropriate volumes
- Needles (6″, 20 or 22 gauge)
- Vacuum/nitrogen manifold (Figs 7.1 and 7.2)
- Cannula or transfer tubing of appropriate lengths
- Column for chromatography

### *Materials*

| | |
|---|---|
| • Racemic iron acyl complex **1** (FW 454.2), 643 mg, 1.42 mmol (Protocol 1) | **toxic** |
| • *n*-Butyllithium,[b] 1.1 mL of a 1.6 M hexane solution, 1.7 mmol | **flammable, moisture sensitive** |
| • Lithium chloride (FW 42.4), 90 mg, 2.12 mmol | **toxic** |
| • (+)-Camphor (FW 152.2), 280 mg, 1.84 mmol[c] | **toxic** |
| • Dry THF, 15 + 5 mL[d] | **flammable, irritant** |
| • Dry diethyl ether, 20 mL[d] | **flammable, irritant** |
| • Methanol, 5 mL | **flammable, irritant** |
| • Petroleum ether (60-80) for chromatography | **flammable, irritant** |
| • Ethyl acetate for chromatography | **flammable, irritant** |
| • Dichloromethane[e] for recrystallisations | **toxic, irritant** |
| • Technical diethyl ether for extractions | **flammable, irritant** |
| • Solid carbon dioxide for cooling bath | **asphyxiant** |
| • Technical grade acetone for cooling bath | **flammable, toxic** |
| • Silica gel for chromatography (Merck Kieselgel 60) | **irritant** |

1. Clean all glassware, syringes, needles and the stirrer bar and dry for at least 2 h in a hot oven (>100°C) before use. Allow apparatus to cool in a desiccator.
2. Assemble a Schlenk tube or round-bottomed flask/gas inlet, place the stirrer bar in the flask or Schlenk and attach a septum to the remaining neck of the vessel.
3. Support the flask or Schlenk using a clamp and stand with a heavy base.
4. Attach a flexible tubing connection from the vacuum/nitrogen manifold to the gas inlet or side-arm.
5. Dry the apparatus with an electric heat gun or a small Bunsen burner at reduced pressure (0.5 – 1 mmHg), allow to cool and refill with nitrogen.

**Protocol 2.** *Continued*

6. Add anhydrous lithium chloride (90 mg, 2.12 mmol) and racemic iron acetyl complex **1** (643 mg, 1.42 mmol) to the flask or Schlenk. These compounds should be added rapidly against a gentle stream of nitrogen after removal of the septum, which should be replaced immediately.
7. Assemble a syringe and needle and flush with nitrogen following the procedure given in Chapter 3, Protocol 3, step 4.
8. Add anhydrous THF (15 mL) by syringe, taken directly from the still, and start the stirrer.
9. Place the system under vacuum carefully until the solvent just begins to boil, then carefully reintroduce nitrogen (Chapter 7, Protocol 2). Repeat the cycle three times.
10. Cool the solution to −78 °C in a carbon dioxide–acetone bath.
11. Add *n*-butyllithium[b] (1.1 mL of a 1.6 M hexane solution, 1.7 mmol) dropwise over 1 min by syringe. The colour of the solution changes from transparent orange to a deep and opaque red.
12. Stir the solution for 30 min at −78 °C.
13. While the solution is stirring, assemble the second Schlenk or flask and attach to the vacuum/nitrogen manifold. Place a septum in the neck of the vessel.
14. Treat the vessel following the procedure given in step 5.
15. Charge the vessel with (+)-camphor (280 mg, 1.80 mmol) by the method given in step 6.
16. Assemble a syringe and needle and flush with nitrogen.
17. Use this syringe to transfer THF (5 mL), taken directly from the still, into the flask or Schlenk containing the (+)-camphor.
18. Transfer the solution of (+)-camphor from this flask to the main reaction flask (still cooled to −78 °C) using the same syringe as in step 17. Add the solution dropwise over *ca.* 1 min.
19. Stir the main reaction flask for 90 min at −78 °C. The colour of the solution changes from deep red to transparent orange.
20. Assemble a syringe and needle and flush with nitrogen.
21. Add methanol (5 mL) to the reaction mixture dropwise at −78 °C. A further lightening of the orange colour may be observed during the addition.
22. Allow the reaction mixture to warm up to room temperature.
23. Remove the THF and methanol under vacuum.
24. Assemble a syringe and needle and flush the syringe with nitrogen.
25. Add dry diethyl ether (20 mL), taken directly from a still, by syringe.

26. Assemble a Schlenk or flask fitted with a gas inlet, and a small frit containing a plug of silica (2 cm depth) and a septum (Fig. 4.2).
27. With the aid of a cannula, filter the reaction solution through a plug of silica in the frit, following the procedure given in Chapter 7.
28. Remove the solvent and purify the products by flash chromatography on silica gel [EtOAc/petroleum ether (60-80), 1:15 → 1:3 v/v] following the procedure given in Chapter 7, Protocol 5. The aldol product **4** is eluted first (>60:1 mixture, 273 mg, 32%), followed by the enantiomerically enriched starting material (303 mg, 47%, 80% ee). Both materials display appropriate spectroscopic data.[7]

[a] Due to the design of a Schlenk tube, this must generally be of a larger volume than the corresponding round-bottomed flask for a reaction of a given scale.

[b] Titrate *n*-butyllithium using the Gilman double quench procedure[8] before use (1 mL quenched with 1,2-dibromoethane and 1 mL with water, each titrated with 1 M HCl using methyl orange indicator. Subtraction gives true alkyllithium concentration).

[c] Sublimed immediately prior to use.

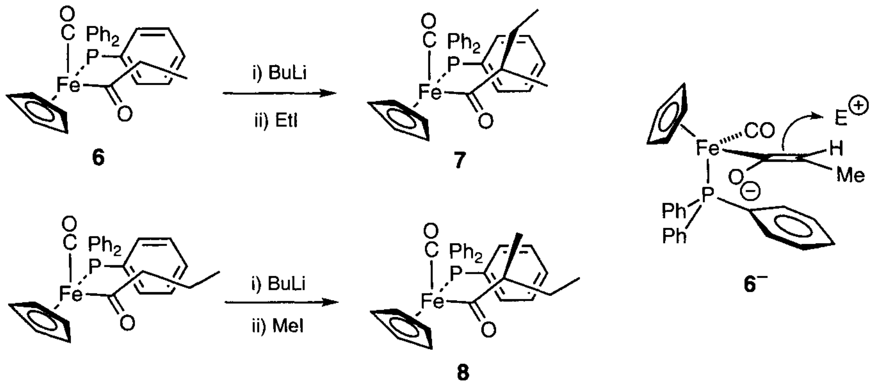
[d] Freshly distilled from sodium benzophenone ketyl under an inert atmosphere.

[e] Freshly distilled from calcium hydride.

---

## 2.3 Alkylation reactions

As stated above, enolate **2** may be cleanly monoalkylated on the carbon atom by a variety of electrophiles to give adducts such as **6**, in the case of iodomethane addition.[3] Subsequent deprotonation by *n*-butyllithium followed by addition of a second electrophile, such as iodoethane, results in a highly stereoselective alkylation to give **7** (Scheme 4.4), essentially as a single diastereoisomer.[9] Reversal of the order of electrophile addition results in the formation of the opposite diastereoisomer **8**.[9] The high selectivity is the result of the steric 'blocking' of one face of the exclusively (*E*)-enolate, which also exists in the *anti*-conformation of enolate and carbon monoxide C-O bonds,



**6** **7** **8** **6⁻**

**Scheme 4.4**

by one of the triphenylphosphine phenyl rings.[10] Approach of an electrophile is only possible from the upper face as shown in **$6^-$**.[10]

This remarkable alkylation stereocontrol has been exploited in a number of syntheses, including a concise synthesis of homochiral (*S*,*S*)-captopril and (*S*,*R*)-*epi*-captopril.[11] The example given in Protocol 3 is for the key step in the synthesis of (*S*)-(+)-2-methylhept-4-ynoate **9** (Scheme 4.5), the sidechain of prostacyclin.[9d]

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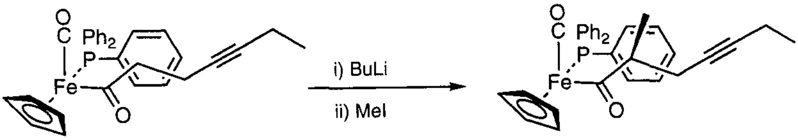
## Protocol 3.
## Stereoselective alkylation of an iron acyl complex (Scheme 4.5)[9d]

**Caution!** All procedures should be carried out in a well-ventilated hood, and disposable vinyl or latex gloves and chemical-resistant safety glasses should be worn.



**9**

**Scheme 4.5**

### *Equipment*

- Magnetic stirrer
- Teflon-covered magnetic stirrer bar (5 mm × 5 mm × 25 mm, octagonal or egg-shaped)
- Two-necked, round-bottomed flask (250 mL) or a Schlenk tube (500 mL)[a]
- Gas inlets with stopcocks if round-bottomed flask is used
- Septa
- Glass syringes with needle-lock luers of appropriate volumes
- Needles (6", 20 or 22 gauge)
- Vacuum/nitrogen manifold (Figs 7.1 and 7.2)
- Cannulae or transfer tubing of appropriate lengths
- Chromatography column

### *Materials*

| | |
|---|---|
| • Homochiral iron complex [(*R*)-($\eta^5$-$C_5H_5$)Fe(CO)($PPh_3$) C(O)$CH_2CH_2CCCH_2CH_3$] (FW 520.3), 1.19 g, 2.29 mmol[9d] | **toxic** |
| • *n*-Butyllithium,[b] 1.56 mL of a 1.6 M hexane solution, 2.5 mmol | **flammable, moisture sensitive** |
| • Iodomethane, 1 mL, excess | **highly toxic, corrosive** |
| • Dry THF,[c] 50 mL | **flammable, irritant** |
| • Methanol, 5 mL | **flammable, irritant** |
| • Petroleum ether (60-80) for flash chromatography, 0.5 L | **flammable, irritant** |
| • Ethyl acetate for flash chromatography, 0.5 L | **flammable, irritant** |
| • Dichloromethane[d] for recrystallisations, 100 mL | **toxic, irritant** |
| • Solid carbon dioxide for cooling bath, 100 g | **asphyxiant** |
| • Technical grade acetone for cooling bath, 10 mL | **flammable, toxic** |
| • Silica gel for chromatography (Merck Kieselgel 60) | **irritant** |

1. Clean all glassware, syringes, needles and the stirrer bar and dry for at least 2 h in a hot oven (>100°C) before use. Allow apparatus to cool in a desiccator.
2. Assemble the Schlenk tube or round-bottomed flask/gas inlet, place the stirrer bar in the flask or Schlenk and attach the septum to the remaining neck of the vessel.
3. Support the flask or Schlenk using a clamp and stand with a heavy base.
4. Attach a flexible tubing connection from the vacuum/nitrogen manifold to the gas inlet or side-arm.
5. Dry the apparatus with an electric heat gun or a small Bunsen burner at reduced pressure (0.5–1 mmHg), allow to cool and refill with nitrogen.
6. Add iron complex $[(R)\text{-}(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)C(O)CH_2CH_2CCCH_2CH_3]$ (1.19 g, 2.29 mmol) to the flask or Schlenk. This should be added rapidly against a steady stream of nitrogen or argon after removal of the septum, which should be replaced immediately.
7. Assemble a syringe and needle and flush the syringe with nitrogen following the procedure given in Chapter 3, Protocol 3, step 4.
8. Add anhydrous THF (50 mL) by syringe, taken directly from the still, and start the stirrer.
9. Place the system under vacuum carefully until the solvent just begins to boil and then carefully reintroduce nitrogen (Chapter 7, Protocol 2). Repeat the cycle three times.
10. Cool the solution to −78°C in a carbon dioxide–acetone bath.
11. Add *n*-butyllithium (1.56 mL of a 1.6 M hexane solution, 2.5 mmol) dropwise over 1 min by syringe. The colour of the solution changes from transparent orange to a deep and opaque red.
12. Stir the solution for 60 min at −78°C.
13. Assemble a syringe and needle and flush the syringe with nitrogen.
14. Add neat iodomethane (1 mL, excess) dropwise by syringe, over 5 min at −78°C.
15. Stir for 15 min at −78°C. The colour of the solution changes from deep red to transparent orange.
16. Assemble a syringe and needle and flush the syringe with nitrogen.
17. Add methanol (5 mL) to the reaction mixture dropwise at −78°C. A further lightening of the orange colour may be observed during the addition.
18. Allow the reaction mixture to warm up to room temperature.
19. Remove the THF and methanol under vacuum (Chapter 7, Protocol 3).
20. Add silica gel (5 g) and dichloromethane (20 mL) to the orange residue. Swirl the flask until a suspension is obtained, and remove the solvent under vacuum to give a free-flowing solid.

**Protocol 3.** *Continued*

21. Purify the product (978 mg, 80%, m.p. 153–155 °C, 98% de) by flash chromatography on silica gel, eluting with dichloromethane petroleum ether (60-80) (4:1) (Chapter 7, Protocol 5). The product displays the appropriate spectroscopic data.[9d]

[a] Due to the design of a Schlenk tube, this must generally be of a larger volume than the corresponding round-bottomed flask for a reaction of a given scale.

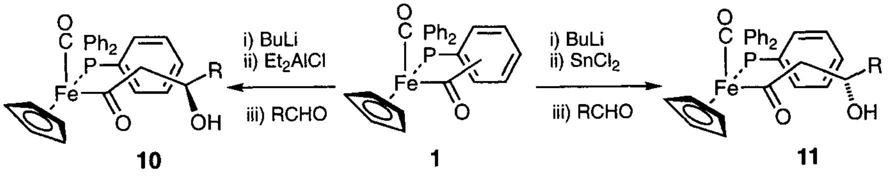
[b] Titrate *n*-butyllithium using the Gilman double quench procedure[8] before use (1 mL quenched with 1,2-dibromoethane and 1 mL with water, each titrated with 1 M HCl using methyl orange indicator. Subtraction gives true alkyllithium concentration).

[c] Freshly distilled from sodium benzophenone ketyl under an inert atmosphere.

[d] Freshly distilled from calcium hydride.

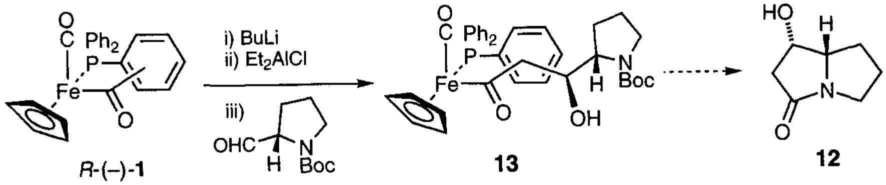
## 2.4 Aldol reactions

Enolates generated from iron acyl compounds such as **1** and **6** add readily to aldehydes.[12] In order to achieve high levels of selectivity in these reactions it is necessary to exchange the lithium for another metal, such as aluminium(III),[12a,b] (which gives diastereoisomer **10**) or tin(II)[12c] (which gives diastereoisomer **11**) prior to addition of the aldehyde (Scheme 4.6).



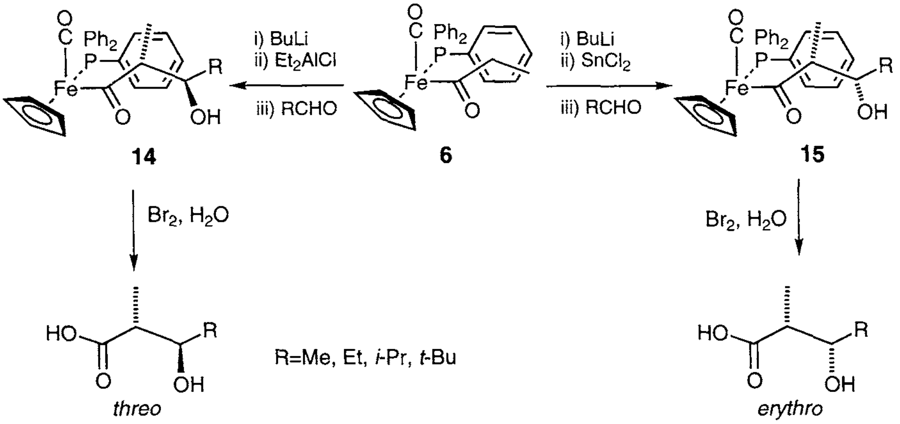
**Scheme 4.6**

This reaction has been successfully applied to the asymmetric syntheses of bicyclic lactams **12** *via* the intermediate aldol adduct **13** (Scheme 4.7).[13] Although only the reaction with (*R*)-**1** is illustrated, the same sequence using (*S*)-**1** generates the alternative diastereoisomer of pyrrolizidone alkaloid in essentially pure form, demonstrating that the iron acyl stereocontrol overwhelms the inherent stereocontrol of carbonyl addition dictated by the adjacent stereogenic centre in the aldehyde.



**Scheme 4.7**

Addition of aldehydes to the lithium enolate derived from propanoyl complex **6** requires prior transmetallation for optimum results.[14] In particular, the use of diethylaluminium chloride has proved to be most valuable when the *anti*-aldol adduct **14** is required, whilst copper cyanide is the transmetallation reagent of choice when the *syn*-aldol adduct **15** is the target (Scheme 4.8).[14] Oxidative cleavage and formation of the *threo* and *erythro* β-hydroxy acids, respectively, is easily achieved by treatment with aqueous bromine solution or CAN.[14] The aluminium(III)-mediated sequence has been employed in the synthesis of an enantiomerically pure degradation product of a marine cyclic peroxide, thereby proving its absolute configuration.[15]



**Scheme 4.8**

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## Protocol 4.
## Aluminium(III)-mediated aldol reaction of iron acyl complex (Structure 1) with propanal[12b]

**Caution!** All procedures should be carried out in a well-ventilated hood, and disposable vinyl or latex gloves and chemical-resistant safety glasses should be worn.

*Equipment*

- Magnetic stirrer
- Teflon-covered magnetic stirrer bar (6 mm × 6 mm × 30 mm, octagonal or egg-shaped)
- Two-necked, round-bottomed flask (250 mL) or Schlenk tube (500 mL)[a]
- Two-necked, round-bottomed flask (50 mL) or Schlenk tube (100 mL)[a]
- Gas inlets with stopcocks if round-bottomed flasks are used
- Septa
- Small frit (2.5 cm diameter, 15 cm high) (Fig. 4.2)
- Glass syringes with needle-lock luers of appropriate volumes
- Needles (6", 20 or 22 gauge)
- Vacuum/nitrogen manifold (Chapter 7, Figs 7.1 and 7.2)
- Cannulae or transfer tubing of appropriate lengths
- Chromatography column

## **Protocol 4.** *Continued*

### *Materials*

| | |
|---|---|
| • Iron acetyl complex **1** (FW 454.2), 310 mg, 0.68 mmol (Protocol 1) | **toxic** |
| • *n*-Butyllithium,[b] 0.9 mL of a 1.5 M hexane solution, 1.35 mmol | **flammable, moisture sensitive** |
| • Diethylaluminium chloride, 2.0 mL of a 1.8 M solution in toluene, 3.6 mmol | **toxic, moisture sensitive, flammable** |
| • Propanal (FW 58.1), 0.5 g, 8.62 mmol[c] | **flammable, toxic** |
| • Dry THF,[d] 80 + 10 mL | **flammable, irritant** |
| • Methanol, 1 mL | **flammable, irritant** |
| • Solid sodium hydrogencarbonate, 1.5 g | |
| • Saturated aqueous sodium hydrogencarbonate solution, 50 mL | **irritant** |
| • Petroleum ether (60-80) for flash chromatography, 0.5 L | **flammable, irritant** |
| • Ethyl acetate for flash chromatography, 0.5 L | **flammable, irritant** |
| • Hexane for recrystallisation, 50 mL | **flammable, irritant** |
| • Dichloromethane,[e] 3 × 40 mL | **toxic, irritant** |
| • Solid carbon dioxide for cooling bath, 100 g | **asphyxiant** |
| • Technical grade acetone for cooling bath, 100 mL | **flammable, toxic** |
| • Alumina (grade 5)[f] for chromatography and filtrations | **irritant** |

1. Clean all glassware, syringes, needles and the stirrer bar and dry for at least 2 h in a hot oven (>100 °C) before use. Allow apparatus to cool in a desiccator.
2. Assemble a 500 mL Schlenk tube or a 200 mL round-bottomed flask/nitrogen inlet, place the stirrer bar in the flask or Schlenk and attach a septum to the remaining neck of the vessel.
3. Support the flask or Schlenk using a clamp and stand with a heavy base.
4. Attach a flexible tubing connection from the vacuum/nitrogen manifold to the gas inlet.
5. Dry the apparatus with an electric heat gun or a small Bunsen burner at reduced pressure (0.5–1 mmHg), allow to cool and refill with nitrogen.
6. Add iron complex **1** (310 mg, 0.68 mmol) to the flask or Schlenk. This should be added rapidly against a gentle stream of nitrogen after removal of the septum, which should be replaced immediately.
7. Assemble a syringe and needle and flush the syringe with nitrogen following the procedure given in Chapter 3, Protocol 3, step 4.
8. Add anhydrous THF (80 mL) by syringe, taken directly from the still, and start the stirrer.
9. Place the system under vacuum carefully until the solvent just begins to boil and carefully reintroduce nitrogen (Chapter 7, Protocol 2). Repeat the cycle three times.
10. Cool the solution to −78 °C in a carbon dioxide–acetone bath.
11. Assemble a syringe and needle and flush the syringe with nitrogen.

12. Add *n*-butyllithium[b] (0.9 mL of a 1.5 M hexane solution, 1.35 mmol) dropwise over 1 min by syringe. The colour of the solution changes from transparent orange to a deep and opaque red.
13. Stir the solution for 30 min at −78 °C.
14. Assemble a syringe and needle and flush the syringe with nitrogen.
15. Add diethylaluminium chloride (2.0 mL of a 1.8 M solution in toluene, 3.6 mmol) dropwise over 1 min by syringe.
16. Allow the temperature of the reaction to rise to −40 °C and stir for 45 min. The reaction mixture changes to a transparent red colour.
17. Cool the reaction mixture to −100 °C (liquid nitrogen in acetone).
18. While the solution is stirring, assemble the second Schlenk or flask and attach to the vacuum/nitrogen manifold. Place septum in the remaining neck of the vessel.
19. Treat the vessel following the procedure given in step 5.
20. Charge the vessel with propanal (0.5 g, 8.62 mmol).
21. Assemble a syringe and needle and flush the syringe with nitrogen.
22. Use this syringe to transfer THF (10 mL), taken directly from the still, into the flask or Schlenk containing the propanal.[c]
23. Transfer the solution of propanal from this flask to the main reaction flask (still cooled to −100 °C) using the same syringe as in step 22. Add the solution dropwise over *ca.* 5 min.
24. Stir the main reaction flask for 2.5 h at −100 °C. The colour of the solution changes from deep red to transparent orange.
25. Assemble a syringe and needle and flush the syringe with nitrogen.
26. Add methanol (1 mL) to the reaction mixture dropwise at −100 °C. A further lightening of the orange colour may be observed during the addition.
27. Allow the reaction mixture to warm up to room temperature.
28. Remove the THF and methanol under vacuum (Chapter 7, Protocol 3).
29. Add nitrogen-saturated aqueous sodium hydrogencarbonate solution (50 mL) to the residue, followed by nitrogen-saturated dichloromethane (40 mL). Agitate well and separate the lower layer. Extract the aqueous layer with further dichloromethane (2 × 40 mL). The extraction should be carried out using a cannula following the method given in Chapter 7, Protocol 4.
30. Place a Schlenk or flask fitted with a gas inlet, under the small frit fitted with a septum containing a plug of alumina (grade 5; 2 cm depth) (Fig. 4.2).
31. With the aid of a cannula, filter the reaction solution through the plug of alumina in the frit into the Schlenk tube.
32. Reduce the solvent to *ca.* 10 mL under vacuum.

**Protocol 4.** *Continued*

**33.** Purify the product **10** (R = $CH_2CH_3$) (295 mg, 85%, >100:1 mixture of diastereoisomers) by chromatography on alumina[f] (deactivated, grade 5) following the procedure given in Chapter 7, Protocol 5. Further chromatography and recrystallisation from dichloromethane hexane gives pure (*R,R*[(*S,S*)]-**10** (R = $CH_2CH_3$) as an orange crystalline solid.[12b] The product displays the appropriate spectroscopic data.[12b]

[a] Due to the design of a Schlenk tube, this must generally be of a larger volume than the corresponding round-bottomed flask for a reaction of a given scale.

[b] Titrate *n*-butyllithium using the Gilman double quench procedure[8] before use (1 mL quenched with 1,2-dibromoethane and 1 mL with water, each titrated with 1 M HCl using methyl orange indicator. Subtraction gives true alkyllithium concentration).

[c] Freshly distilled.

[d] Freshly distilled from sodium benzophenone ketyl under an inert atmosphere.

[e] Freshly distilled from calcium hydride.

[f] Prepared by the combination of grade 1 (activated) alumina and water (4% v/w).

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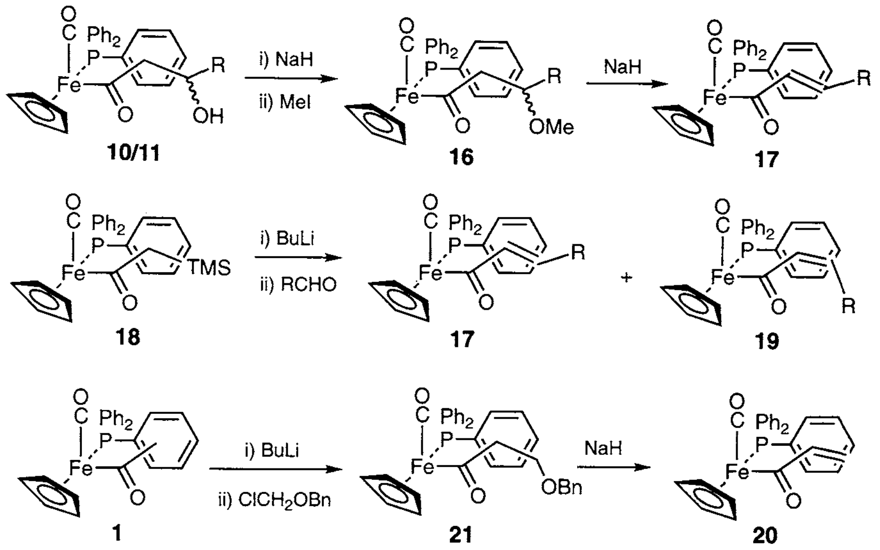
## 2.5 Preparation of α,β-unsaturated iron acyl complexes

Several methods have been developed for the preparation of α,β-unsaturated iron acyl complexes, a class of complex which is synthetically valuable because its members may be stereoselectively elaborated at two positions.[16] Methylation of the hydroxy group of an aldol reaction product to give **16** followed by sodium hydride-promoted elimination generates the (*E*)-unsaturated iron acyl complex **17**, in many cases exclusively (Scheme 4.9).[16] Since this selectivity is irrespective of the hydroxy group configuration, it is not



**Scheme 4.9**

necessary to employ a transmetalation strategy in the preparation of the precursor. Peterson elimination of the adduct formed from the enolate of α-trimethylsilyl acyl complex **18** and aldehydes furnishes a mixture of (*E*) and (*Z*) products, **17** and **19** (Scheme 4.9), which may be readily separated by chromatography.[16] The unsubstituted α,β-unsaturated acyl complex **20** may be prepared by sodium hydride-promoted elimination of the adduct **21** formed between the enolate of **1** and benzyl chloromethyl ether (Scheme 4.9).[16]

---

## Protocol 5.
## Preparation of (*E*)- (Structure 17) (R = Et) by elimination from the aldol precursor (Scheme 4.9)[16]

**Caution!** All procedures should be carried out in a well-ventilated hood, and disposable vinyl or latex gloves and chemical-resistant safety glasses should be worn.

### *Equipment*

- Magnetic stirrer
- Teflon-covered magnetic stirrer bars (6 mm × 6 mm × 30 mm, octagonal or egg-shaped)
- Two-necked, round-bottomed flask (100 mL) or Schlenk tube (250 mL)[a]
- Two-necked, round-bottomed flasks (3 × 50 mL) or Schlenk tubes (3 × 100 mL)[a]
- Gas inlets with stopcocks if round-bottomed flasks are used
- Septa
- Short frit (2.5 cm diameter, 15 cm high) (Fig. 4.2)
- Glass syringes with needle-lock luers of appropriate volumes
- Needles (6″, 20 or 22 gauge)
- Vacuum/nitrogen manifold (Figs 7.1 and 7.2)
- Cannulae or transfer tubing of appropriate lengths
- Chromatography column

### *Materials*

| | |
|---|---|
| • Racemic β-hydroxy, pentanoyl iron complex (FW 512.4), 2.97 g, 5.80 mmol (a 1.5:1 mixture of (*R*,R)[(S,*S*)]/(*R*,*S*)[(*S*,*R*)] isomers; Protocol 4, *via* Li enolate)[12b] | **toxic** |
| • Sodium hydride – 2 portions: 800 mg of a 50% suspension in oil, 400 mg, 16.7 mmol; 180 mg of a 50% suspension, 90 mg, 3.7 mmol | **toxic, irritant, pyrophoric solid, corrosive** |
| • Iodomethane (FW 141.9), 1 mL, 2.28 g, 16.1 mmol | **highly toxic, corrosive** |
| • Dry THF,[b] 2 × 50 + 15 mL | **flammable, irritant** |
| • Petroleum ether (60–80) for flash chromatography and washing NaH, 300 mL | **flammable, irritant** |
| • Ethyl acetate for chromatography, 0.5 L | **flammable, irritant** |
| • Dichloromethane for extractions,[c] 300 mL | **toxic, irritant** |
| • Alumina (active, grade 1) for chromatography | **irritant** |

1. Clean all glassware, syringes, needles and the stirrer bar and dry for at least 2 h in a hot oven (>100°C) before use. Allow apparatus to cool in a desiccator.
2. Assemble the Schlenk tube (250 mL) or the two-necked round-bottomed flask (100 mL)/nitrogen inlet, place the stirrer bar in the flask or Schlenk and attach a septum to the neck of the vessel.

**Protocol 5.** *Continued*

3. Support the flask or Schlenk using a clamp and stand with a heavy base.
4. Attach a flexible tubing connection from the vacuum/nitrogen manifold to the gas inlet or side-arm.
5. Dry the apparatus with an electric heat gun or a small Bunsen burner at reduced pressure (0.5–1 mmHg), allow to cool and refill with nitrogen.
6. Add sodium hydride (800 mg of a 50% suspension in oil, 400 mg, 16.7 mmol) to the flask or Schlenk. This should be added rapidly against a gentle stream of nitrogen after removal of the septum, which should be replaced immediately.
7. Assemble a syringe and needle and flush the syringe with nitrogen following the procedure given in Chapter 3, Protocol 3, step 4.
8. Add petroleum ether (20 mL) to the flask. Swirl the contents gently then filter off the solvent using a filter cannula following the procedure in Chapter 7, Protocol 4.
9. Remove the last trace of solvent under vacuum to leave a fine flowing powder. **CAUTION** – this is highly active sodium hydride. Gently reintroduce nitrogen into the flask.
10. Assemble a 100 mL Schlenk tube or 50 mL round-bottomed flask/gas inlet and attach to the vacuum/nitrogen manifold. Place a septum in the neck of the vessel.
11. Treat the flask following the procedure given in step 5.
12. Charge the flask with racemic β-hydroxy, pentanoyl iron complex (2.97 g, 5.80 mmol). This should be added rapidly against a gentle stream of nitrogen after removal of the septum, which should be replaced immediately.
13. Assemble a syringe and needle and flush the syringe with nitrogen.
14. Use this syringe to transfer THF (50 mL), taken directly from the still, into the flask or Schlenk containing the complex.
15. Transfer the solution of iron acyl complex from this flask to the main reaction flask, at room temperature, using the same syringe as in step 14. Add the solution dropwise over *ca.* 10 min.
16. Stir for 30 min at room temperature.
17. Assemble a syringe and needle and flush the syringe with nitrogen.
18. Add neat iodomethane (1 mL, 16.1 mmol) dropwise by syringe (1 min).
19. Stir for 30 min at room temperature.
20. Remove the solvent under vacuum (Chapter 7, Protocol 3).
21. Assemble a syringe and needle and flush the syringe with nitrogen.
22. Assemble a second small Schlenk and fit it with a small frit containing a plug of alumina and a septum. Attach the Schlenk to the vacuum/nitrogen manifold (Fig. 4.2).
23. Add nitrogen-saturated dichloromethane (20 mL) to the residue, agitate

briefly and then filter this solution through the short frit. Repeat this extraction twice.

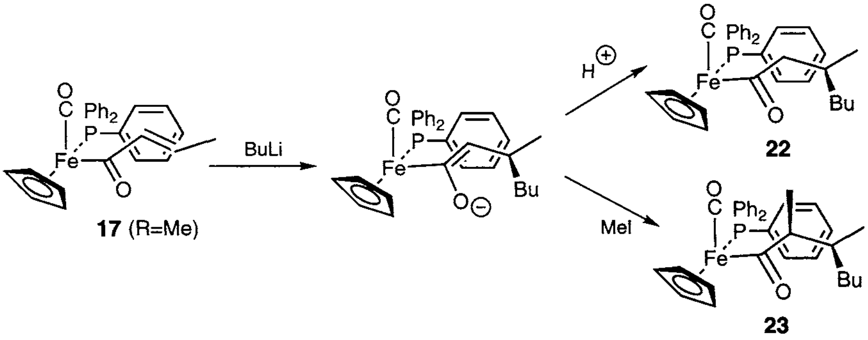
24. Remove solvent from the dichloromethane extracts to give the crude methylated product which may be purified by flash chromatography (Chapter 7, Protocol 5) to give 2.45 g, 80%, of an orange product. Alternatively this mixture may be taken directly on in the next step.
25. Assemble a syringe and needle and flush the syringe with nitrogen.
26. Assemble a third small Schlenk and add a magnetic stirrer bar. Attach the Schlenk to the vacuum/nitrogen manifold.
27. Treat the flask following the procedure given in step 5.
28. Add sodium hydride (180 mg of a 50% suspension, 90 mg, 3.7 mmol) to the flask or Schlenk. This should be added rapidly against a gentle stream of nitrogen after removal of the septum, which should be replaced immediately.
29. Repeat steps 7–9 above on this Schlenk.
30. Assemble a syringe and needle and flush the syringe with nitrogen.
31. Using the syringe from step 30, add THF (15 mL) to the flask containing the methylated β-hydroxy iron acyl complex.
32. Using the syringe from step 30, transfer the solution from step 31 into the Schlenk containing the sodium hydride.
33. Stir this solution at room temperature for 66 h.
34. Remove the solvent under vacuum.
35. Repeat steps 21–23 using three 10 mL portions of dichloromethane.
36. Reduce the solution to *ca.* 5 mL and purify the product, (*E*)-**17** (R = $CH_2CH_3$) (90 mg, 95%) by flash chromatography on alumina, following the procedure given in Chapter 7, Protocol 5. All materials in this protocol display the appropriate spectroscopic data.[16]

[a] Due to the design of a Schlenk tube, this must generally be of a larger volume than the corresponding round-bottomed flask for a reaction of a given scale.
[b] Freshly distilled from sodium benzophenone ketyl under an inert atmosphere.
[c] Freshly distilled from calcium hydride.

---

## 2.6 Conjugate addition reactions

Conjugate addition[17] of nucleophiles, such as alkyllithiums, to (*E*)-α,β-unsaturated iron acyl complexes takes place on the face opposite the phenyl ring of the triphenylphosphine group when the acryloyl group is in the *cisoid* conformation.[17] The intermediate enolates may be trapped by protonation to give **22** or with an electrophile to give the α,β-disubstituted product **23** in which the configuration of the new α-centre is dictated entirely by the iron complex (Scheme 4.10).[17] Such methodology has been successfully applied to the asymmetric synthesis of β-lactams *via* conjugate addition of a lithiated benzylamine.[17] In contrast (*Z*)-α,β-unsaturated acyl complexes are deprotonated by alkyllithiums to give dienolates which may be subsequently elaborated stereoselectively.[18]



**Scheme 4.10**

## 2.7 Other applications

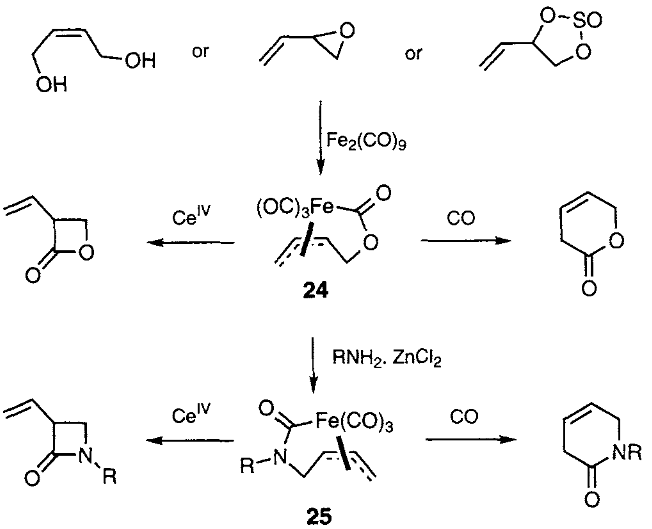
Chiral iron acyl complexes have been applied to the asymmetric synthesis of cyclopropane carboxylic acids,[19] sulfoxides[20] and β-amino acids.[21] Further details and applications may be found in the reviews given in the reference section.[1]

# 3. π-Allyltricarbonyliron lactone complexes[22]

## 3.1 Introduction

The reaction of vinyl epoxides with diiron nonacarbonyl in THF solution gives π-allyltricarbonyliron lactone complexes **24** in high yield (Scheme 4.11).[23,24] Alternatively butene-1,4-diols[25] and cyclic sulfites derived from 1,2-diols[26] may be employed as starting materials under appropriate conditions. The π-allyltricarbonyliron lactones may be converted into a number of products including β-lactones and unsaturated γ-lactones upon oxidative extrusion or carbonylation at high pressure, respectively.[22] The corresponding iron lactam complexes **25** may be prepared by treatment of **24** with an amine in the presence of a Lewis acid such as zinc dichloride and these can be converted to β- or γ-lactams in analogous ways (Scheme 4.11).[22]

The iron complexes **24** and **25** are invariably stable crystalline materials which may be purified by chromatography on silica gel, alumina or Florisil without significant decomposition. They are stable to certain oxidising agents including PCC, PDC, ozone, *t*-butyl peroxide, manganese dioxide and iron trichloride. They are unaffected by the reducing agent samarium diiodide and hydrogenation using palladium on a carbon support although they are decomposed by the more vigorous reducing agents sodium borohydride and lithium aluminium hydride. They are stable to water, isonitriles, Lewis acidic organometallics and Wittig reagents. Strongly basic or acidic conditions or

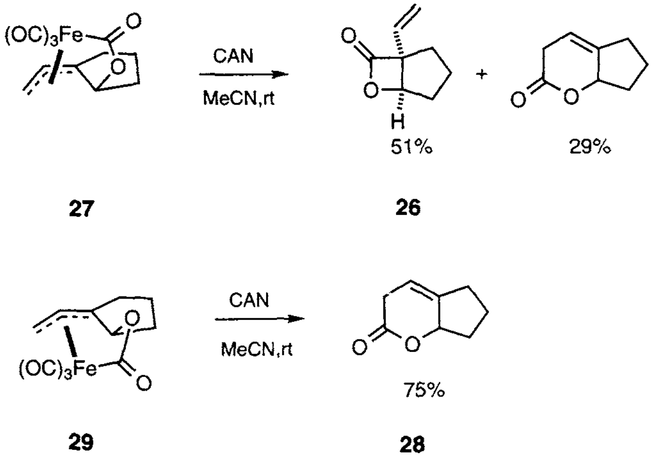


**Scheme 4.11**

temperatures above 60 °C cause decomposition, although synthetically valuable products may sometimes be formed in the process.[27]

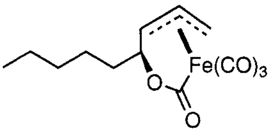
## 3.2 Synthesis of β-lactones[28]

Oxidative extrusion of β-lactones from the π-allyl complexes is most effectively achieved using ceric ammonium nitrate (CAN). It is essential that the structure of the complex does not preclude formation of the four-membered ring. Whilst the β-lactone **26** is readily formed as the major product from the *cis* complex **27**, the larger δ-lactone **28** is formed from the *trans* complex **29** (Scheme 4.12).

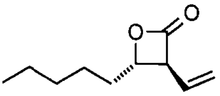


**Scheme 4.12**

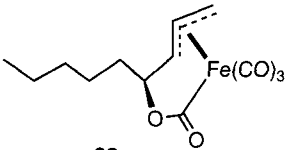
Stereochemical control is possible using this chemistry since the complexes are oxidatively degraded by a stereospecific pathway. Hence complex **30** is converted to lactone **31** and complex **32** to **33** upon decomplexation.[28] This has permitted the stereoselective synthesis of a number of natural products including Valilactone **34**.[29] In this synthesis the vinyl epoxide **35** was converted to a 4:1 mixture of complexes **36** and **37**, which could be separated by chromatography. Subsequent treatment of **36** with CAN gave the β-lactone **38** in 26% yield (Scheme 4.13).



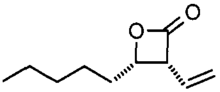
**30**



**31**



**32**



**33**

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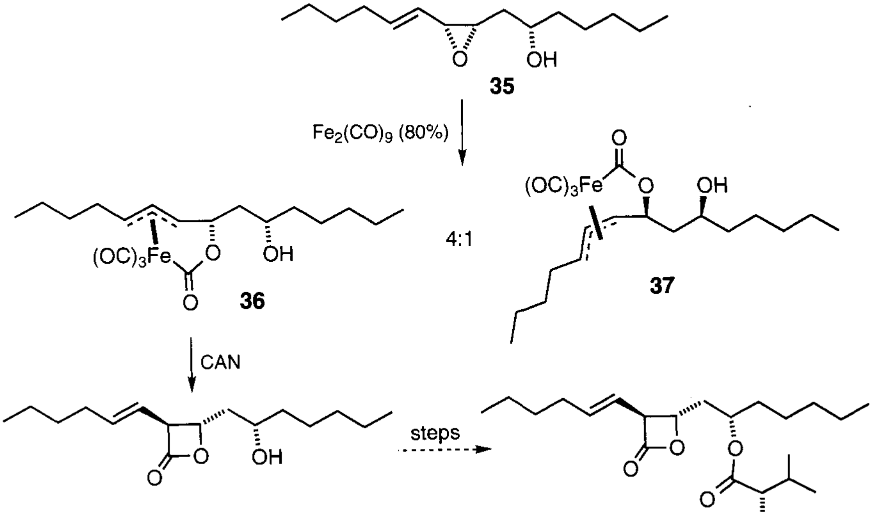
## Protocol 6.
## Synthesis of *trans*-β-lactone (Structure 38) from allylic epoxide (Structure 35) *via* intermediate π-allyl iron tricarbonyl complexes (Structures 36 and 37) (Scheme 4.13)[29]

**Caution!** All procedures should be carried out in a well-ventilated hood, and disposable vinyl or latex gloves and chemical-resistant safety glasses should be worn.



**Scheme 4.13**

### *Equipment*

- Magnetic stirrer box
- Teflon-covered magnetic stirrer bars (5 mm × 5 mm × 25 mm, octagonal or egg-shaped)
- Two-necked, round-bottomed flasks (50 mL) or Schlenk tubes (100 mL)[a]
- Gas inlets with stopcocks if round-bottomed flasks are used
- Septa
- Glass syringes with needle-lock luers of appropriate volumes
- Needles (6", 20 or 22 gauge)
- Vacuum/nitrogen manifold (Figs 7.1 and 7.2)
- Cannulae or transfer tubing of appropriate lengths
- Chromatography column

### *Materials*

| | |
|---|---|
| • Epoxide **35** (FW 240.1), 115 mg, 0.48 mmol[29] | **toxic** |
| • Di-iron nonacarbonyl (FW 363.8), 272 mg, 0.75 mmol | **highly toxic, irritant** |
| • Ceric ammonium nitrate (FW 548.2), 1.29 g, 2.4 mmol | **toxic, irritant** |
| • Phosphate buffer solution (pH 7), 50 mL | **irritant** |
| • Dry THF,[b] 5 mL | **flammable, irritant** |
| • Ethanol, 10 mL | **flammable, irritant** |
| • Petroleum ether (60-80) for chromatography, 0.5 L | **flammable, irritant** |
| • Diethyl ether for flash chromatography, 0.5 L | **flammable, irritant** |
| • Silica gel for chromatography (Merck Kieselgel 60) | **irritant** |

1. Clean all glassware, syringes, needles and stirrer bars and dry for at least 2 h in a hot oven (>100 °C) before use. Allow apparatus to cool in a desiccator.
2. Assemble a Schlenk tube or round-bottomed flask/nitrogen inlet, place the stirrer bar in the flask or Schlenk and attach a septum to the remaining neck of the vessel.
3. Support the flask or Schlenk using a clamp and stand with a heavy base.
4. Attach a flexible tubing connection from the vacuum/nitrogen manifold to the gas inlet.
5. Dry the apparatus with an electric heat gun or a small Bunsen burner at reduced pressure (0.5–1 mmHg), allow to cool and refill with nitrogen.
6. Assemble a syringe and needle and flush the syringe with nitrogen following the procedure given in Chapter 3, Protocol 3, step 4.
7. Add di-iron nonacarbonyl (272 mg, 0.75 mmol) to the flask or Schlenk.
8. Assemble a second Schlenk or flask and attach to the vacuum/nitrogen manifold. Place a septum in the remaining neck of the vessel.
9. Treat the flask following the procedure given in step 5.
10. Charge the flask with epoxide **35** (115 mg, 0.48 mmol).
11. Assemble a syringe and needle and flush the syringe with nitrogen.
12. Use this syringe to transfer THF (5 mL), taken directly from the still, into the flask or Schlenk containing the complex.
13. Transfer the solution of epoxide **35** from this flask to the main reaction flask, at room temperature, using the same syringe as in step 12.
14. Slowly reduce the pressure in the flask until the stirred solution begins to bubble, then slowly reintroduce nitrogen (Chapter 7, Protocol 2).

**Protocol 6.** *Continued*

15. *Stir for 2 h at room temperature.*
16. Remove the solvent under vacuum using a rotary evaporator.
17. Subject the mixture of ferrilactones **36** and **37** to flash chromatography on silica gel using petroleum ether/diethyl ether (1:1) as eluent (Chapter 7, Protocol 5). This gives **36** and **37** as a 4:1 mixture (153 mg, 80%).
18. Assemble a third Schlenk or flask and attach to the vacuum/nitrogen manifold. Place a septum in the remaining neck of the vessel.
19. Treat the flask following the procedure given in step 5.
20. Charge the flask with the 4:1 mixture of ferrilactones **36** and **37** (153 mg, 0.31 mmol) isolated in step 17.
21. Assemble a syringe and needle and flush the syringe with nitrogen.
22. Add ethanol (10 mL) to the flask by syringe.
23. Add solid ceric ammonium nitrate (1.29 g, 2.4 mmol) to the flask. This should be added rapidly against a gentle stream of nitrogen after removal of the septum, which should be replaced immediately.
24. Assemble a syringe and needle and flush the syringe with nitrogen.
25. Add buffer solution (3 drops) to the flask, using the syringe from step 24.
26. Slowly reduce the pressure in the flask until the stirred solution begins to bubble, then slowly reintroduce nitrogen.
27. Stir at room temperature for 2 h.
28. Remove the solvent under vacuum using a rotary evaporator.
29. Purify lactone **38** by flash chromatography on silica gel using petroleum ether/diethyl ether (4:1 to 1:1) as eluent (20 mg, 26% based on recovered starting material). Lactone **38** displays the appropriate spectroscopic data.[29]

[a] Due to the design of a Schlenk tube, this must generally be of a larger volume than the corresponding round-bottomed flask for a reaction of a given scale.
[b] Freshly distilled from sodium benzophenone ketyl under an inert atmosphere.

## 3.3 Synthesis of δ-lactones

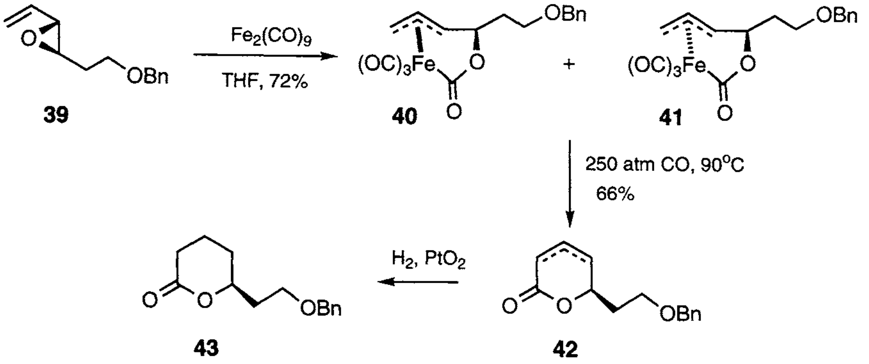
Exhaustive high-pressure carbonylation of π-allyl tricarbonylallyl complexes results in their conversion to unsaturated δ-lactones.[30] The products are usually unsaturated at the γ ,δ-position although the double bond can migrate into conjugation with the lactone carbonyl group in some cases. A particularly attractive feature of this chemistry is that certain functional groups, such as hydroxy groups, which would normally require protection can be left unprotected.[30] This chemistry has been applied to numerous synthetic projects including the total synthesis of the antibiotics Malyngolide[30] and Avermectin

Bla.[26b,31] The total synthesis of Routiennocin employed iron tricarbonyl chemistry for the synthesis of the spiroketal unit.[32] In this sequence the allylic epoxide **39** is converted to a mixture of allyl iron complexes **40** and **41** which is not separated but carbonylated together to give lactone **42** as a 9:1 (αβ:βγ) mixture (Scheme 4.14); this mixture is subsequently reduced to the saturated lactone **43**.[34]

---

## Protocol 7.
## Preparation of unsaturated γ-lactones (Structure 42) from epoxide (Structure 39) via intermediate π-allyl irontricarbonyl complexes (Structures 40 and 41) (Scheme 4.14)[32]

**Caution!** All procedures should be carried out in a well-ventilated hood, and disposable vinyl or latex gloves and chemical-resistant safety glasses should be worn.



**Scheme 4.14**

*Equipment*

- Magnetic stirrer
- Teflon-covered magnetic stirrer bars (6 mm × 6 mm × 30 mm, octagonal or egg-shaped)
- High-pressure (up to 250 atm) steel reaction vessel
- Two-necked, round-bottomed flasks (2 × 100 mL) or Schlenk tubes (2 × 200 mL)[a]
- Gas inlets with stopcocks if round-bottomed flasks are used
- Septa
- Glass syringes with needle-lock luers of appropriate volumes
- Needles (6", 20 or 22 gauge)
- Vacuum/nitrogen manifold (Figs 7.1 and 7.2)
- Cannulae or transfer tubing of appropriate lengths
- Chromatography column

*Materials*

| | |
|---|---|
| • Epoxide **39** (FW 190.1), 2.21 g, 10.8 mmol[32] | **toxic** |
| • Diiron nonacarbonyl (FW 363.8), 5.13 g, 14.1 mmol | **highly toxic, irritant** |
| • Ceric ammonium nitrate (FW 548.2), 2.96 g, 5.4 mmol | **toxic, irritant** |
| • Phosphate buffer solution (pH 7), 100 mL | **irritant** |
| • Dry THF,[b] 5 mL | **flammable, irritant** |

## Protocol 7. *Continued*

| | |
|---|---|
| • Dry benzene,[b] 50 mL | **carcinogenic, flammable, irritant** |
| • A supply of carbon monoxide of 250 atm pressure | |
| • Petroleum ether (60-80) for chromatography, 0.5 L | **flammable, irritant** |
| • Diethyl ether for flash chromatography, 0.5 L | **flammable, irritant** |
| • Silica gel for chromatography (Merck Kieselgel 60) | **irritant** |

1. Clean all glassware, syringes, needles and stirrer bars and dry for at least 2 h in a hot oven (>100 °C) before use. Allow apparatus to cool in a desiccator.
2. Assemble a 200 mL Schlenk tube or 100 mL flask with nitrogen inlet, place the stirrer bar in the flask or Schlenk and attach a septum to the remaining neck of the apparatus.
3. Support the flask or Schlenk using a clamp and stand with a heavy base.
4. Attach a flexible tubing connection from the vacuum/nitrogen manifold to the gas inlet.
5. Dry the apparatus with an electric heat gun or a small Bunsen burner at reduced pressure (0.5–1 mmHg), allow to cool and refill with nitrogen.
6. Assemble a syringe and needle and flush the syringe with nitrogen following the procedure given in Chapter 3, Protocol 3, step 4.
7. Add diiron nonacarbonyl (5.13 g, 14.1 mmol) to the flask or Schlenk.
8. Assemble the second Schlenk or flask and attach to the vacuum/nitrogen manifold. Place a septum in remaining neck of the vessel.
9. Treat the flask following the procedure given in step 5.
10. Charge the flask with epoxide **39** (2.21 g, 10.8 mmol).
11. Assemble a syringe and needle and flush the syringe with nitrogen.
12. Use this syringe to transfer THF (5 mL), taken directly from the still, into the flask or Schlenk containing the complex.
13. Transfer the solution of epoxide **39** from this flask to the main reaction flask, at room temperature, using the same syringe as in step 12.
14. Slowly reduce the pressure in the flask until the stirred solution begins to bubble, then slowly reintroduce nitrogen (Chapter 7, Protocol 2).
15. Stir for 6 h at room temperature.
16. Remove the solvent from the green solution under vacuum (Chapter 7, Protocol 3).
17. Purify the residue by flash chromatography on silica gel using petroleum ether/diethyl ether (7:3) as eluent (Chapter 7, Protocol 5). This gives a mixture of ferrilactones **40** and **41** as a yellow oil (2.7 g, 72%), which displays appropriate spectroscopic data.
18. Charge the high-pressure steel hydrogenation vessel with the purified 4:1 mixture of ferrilactones **40** and **41** (2.7 g, 7.5 mmol).
19. Assemble a syringe and needle and flush the syringe with nitrogen.

20. Add benzene (50 mL) to the high-pressure steel hydrogenation vessel, containing a stirrer bar, by syringe.
21. Seal the high-pressure steel hydrogenation vessel carefully.
22. Pressurise to 250 atm of carbon monoxide.
23. Heat the mixture, under pressure, at 90° C overnight with stirring.
24. Allow the mixture to cool down to room temperature and release the pressure carefully.
25. Remove the solvent under vacuum.
26. Purify the product by flash chromatography on silica gel using petroleum ether/diethyl ether (1:1) as eluent to afford a mixture of unsaturated lactones **42** (1.15 g, 66%, a 9:1 (αβ:βγ) mixture) as a colourless oil. Products **40–42** display appropriate spectroscopic data.[32]

[a] Due to the design of a Schlenk tube, this must generally be of a larger volume than the corresponding round-bottomed flask for a reaction of a given scale.

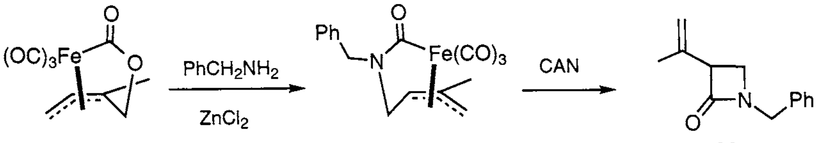
[b] Freshly distilled from sodium benzophenone ketyl under an inert atmosphere.

## 3.4 Synthesis of lactams[31–35]

As has been stated above, reaction of π-allyl tricarbonyliron lactone complexes with amines in the presence of Lewis acids such as $ZnCl_2$ results in the formation of the corresponding tricarbonyliron lactam complexes *via* an $S_N2'$ reaction.[24c,d,33] These complexes (e.g. **46**) may be converted by CAN to β-lactams such as **44** (Scheme 4.15) in an exactly analogous way to the method described above.[33] Since β-lactams occur in numerous physiologically important natural products this is a valuable reaction sequence which has been applied to the synthesis of nocardicins[34] and thienamycin.[35] Recently a synthesis of pyrrolizidine alkaloids has been developed using this methodology.[36]

### Protocol 8.
### Synthesis of π-allyl iron tricarbonyl lactam complex (Structure 46) from a π-allyl iron tricarbonyl lactone complex (Structure 45) (Scheme 4.15)

**Caution!** All procedures should be carried out in a well-ventilated hood, and disposable vinyl or latex gloves and chemical-resistant safety glasses should be worn.



**45** **46** **44**

Scheme 4.15

## **Protocol 8.** *Continued*

### *Equipment*

- Magnetic stirrer
- Teflon-covered magnetic stirrer bars (5 mm × 5 mm × 22 mm, octagonal or egg-shaped)
- Two-necked, round-bottomed flask (100 mL) or Schlenk tube (200 mL)[a]
- Gas inlet with stopcock if round-bottomed flask is used
- Septa
- Glass syringes with needle-lock luers of appropriate volumes
- Needles (6", 20 or 22 gauge)
- Vacuum/nitrogen manifold (Figs 7.1 and 7.2)
- Chromatography column

### *Materials*

| | |
|---|---|
| • Iron lactone complex **45** (FW 252.1), 100 mg, 0.4 mmol[33] | **toxic** |
| • Benzylamine (FW 107.2), 510 mg, 4.7 mmol | **toxic** |
| • Zinc dichloride (FW 136.3), 107 mg, 0.8 mmol | **irritant** |
| • Dry THF,[b] 1.5 mL | **flammable, irritant** |
| • Dry diethyl ether,[b] 3.5 mL | **flammable, irritant** |
| • Petroleum ether (60-80) for chromatography, 0.5 L | **flammable, irritant** |
| • Diethyl ether for chromatography, 0.5 L | **flammable, irritant** |
| • Silica gel for chromatography (Merck Kieselgel 60) | **irritant** |

1. Clean all glassware, syringes, needles and stirring bars and dry for at least 2 h in a hot oven (>100°C) before use. Allow apparatus to cool in a desiccator.
2. Assemble a 200 mL Schlenk tube or 100 mL round-bottomed flask and gas inlet, place the stirrer bar in the flask or Schlenk and attach the septum to the remaining neck of the apparatus.
3. Support the flask or Schlenk using a clamp and stand with a heavy base.
4. Attach a flexible tubing connection from the vacuum/nitrogen manifold to the gas inlet.
5. Dry the apparatus with an electric heat gun or a small Bunsen burner at reduced pressure (0.5–1 mmHg), allow to cool and refill with nitrogen.
6. Charge the flask with iron lactone complex **45** (100 mg, 0.4 mmol). This should be added rapidly against a steady stream of nitrogen after removal of the septum, which should be replaced immediately.
7. Assemble a syringe and needle and flush the syringe with nitrogen following the procedure given in Chapter 3, Protocol 3, step 4.
8. Add THF (1.5 mL), taken directly from the still, to the flask by syringe.
9. Assemble a syringe and needle and flush the syringe with nitrogen.
10. Add diethyl ether (3.5 mL), taken directly from the still, to the flask by syringe.
11. Start the stirrer.
12. Assemble a syringe and needle and flush the syringe with nitrogen.
13. Add the benzylamine (510 mg, 4.7 mmol) to the reaction mixture by syringe.

14. Add the zinc dichloride (107 mg, 0.8 mmol). This should be added rapidly against a gentle stream of nitrogen after removal of the septum, which should be replaced immediately.
15. Slowly reduce the pressure in the flask until the stirred solution begins to bubble, then slowly reintroduce nitrogen (Chapter 7, Protocol 2).
16. Stir the reaction mixture at room temperature until no more starting material can be detected by TLC (typically 0.5–3 h).
17. Remove the solvent under vacuum (Chapter 7, Protocol 3).
18. Flash chromatography on silica gel using petroleum ether/diethyl ether (1:2) as eluent (Chapter 7, Protocol 5) serves to purify the lactam complex **46** (128 mg, 95%) as a white crystalline solid. The β-lactam can be prepared from the complex by treatment with CAN following the method in Protocol 7. Complex **46** displays appropriate spectroscopic data.[33]

[a] *Due to the design of a Schlenk tube, this must generally be of a larger volume than the corresponding round-bottomed flask for a reaction of a given scale.*
[b] Freshly distilled from sodium benzophenone ketyl under an inert atmosphere.

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# 5

# Titanocene and zirconocene $\eta^2$-$\pi$ complexes

RICHARD J. WHITBY

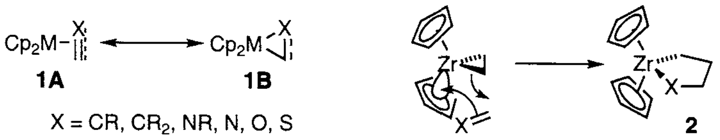
## 1. Introduction

Titanium and zirconium are Group 4 transition metals. Both are comparatively cheap and non-toxic and as a result stoichiometric applications are practical. The +4 oxidation state is most common, with the +2 oxidation state being important in many reactions. Titanium also has an extensive chemistry in the +3 oxidation state. The high oxidation state makes the +4 complexes strong Lewis acids, a property which has been widely used in synthesis.

Titanium and zirconium chemistry is conveniently divided between 'simple' complexes and those based on the metallocene unit '$Cp_2M$' ($Cp = C_5H_5$ = cyclopentadienyl). Most 'simple' complexes are oligomeric, insoluble, and difficult to characterise, although alkyl titanium complexes such as $X_3TiR$ have found some use as 'non-basic' Grignard equivalents.[1] The dicyclopentadienyl metal moiety, $Cp_2M$, renders complexes monomeric, soluble, and easily characterised by NMR spectroscopy, and thus many applications based on these systems have been devised. The most stable electronic configuration of titanocene and zirconocene complexes has only 16 electrons in the valence shell, not the 18 electrons common in most of the rest of the transition metal series. The empty orbital this leaves on the metal is crucial for reactivity.

Organotitanium and -zirconium chemistry already has an established place in organic synthesis and many reactions are covered elsewhere in the *Practical Approach* series. Examples include: reductive coupling of carbonyl compounds with low valent titanium to form 1,2-diols or alkenes;[2] methylenation of ester carbonyl groups with titanocene methylidene ($Cp_2Ti{=}CH_2$);[2] zirconium-catalysed methylalumination of alkynes;[2] and hydrozirconation of alkynes and alkenes with the Schwartz reagent, $Cp_2ZrHCl$.[3]

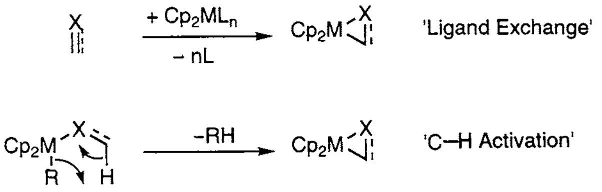
Described in this chapter is the stoichiometric chemistry of complexes in which a titanocene or zirconocene moiety is $\eta^2$-bound to an alkene, alkyne, heteroalkene, or heteroalkyne. These complexes may be viewed as a metallocene [M(II)] species (**1A**) or as the metallacyclopropane/ene [M(IV)] species (**1B**) (Scheme 5.1). Although the complexes have characteristics typical of both structures, the 'extreme back bonding' structure **1B** fits the physical data best and is generally the form drawn. The importance of complexes **1** is based on their ready insertion of unactivated alkenes or alkynes to give metallacyclopentanoids **2** as this makes them excellent carbometallating reagents.



**Scheme 5.1**

## 2. Formation of titanocene and zirconocene $\eta^2$-$\pi$ complexes

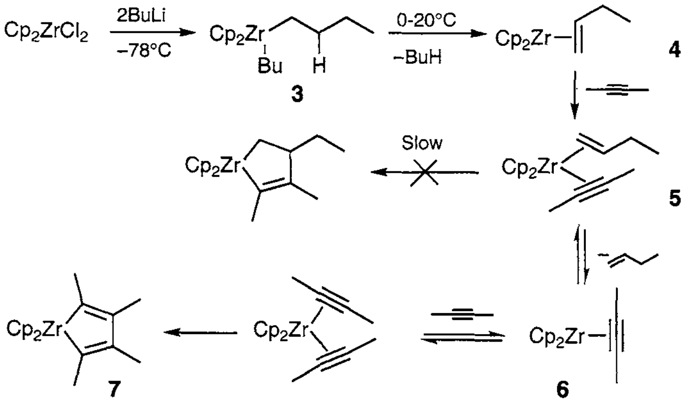
The two main routes to metallocene $\eta^2$-$\pi$ complexes are (i) direct complexation of the $\pi$-component to a metallocene equivalent (ligand exchange), and (ii) oxidation on the metal of the reduced $\pi$-component (C-H activation) (Scheme 5.2).



**Scheme 5.2**

### 2.1 Direct complexation/ligand exchange

Reaction between a $\pi$-component and '$Cp_2M$' should directly form the required $\eta^2$-$\pi$ complex **1**. The free metallocenes '$Cp_2M$' are very unstable but they may be generated *in situ* by reduction of $Cp_2MCl_2$ with a suitable metal (e.g. Na/Hg or Mg/Hg). Electronically saturated equivalents $Cp_2M(PMe_2R)_2$ and $Cp_2Zr(DMAP)_2$ (DMAP = *p*-dimethylaminopyridine) are relatively stable and are sometimes used as sources of '$Cp_2M$'. For zirconium it is more convenient to use ligand exchange from zirconocene 1-butene **4** (the 'Negishi reagent'[4]) which is generated *in situ* from dibutyl zirconocene **3**, which in turn is made by the addition of 2 equiv. of *n*-butyllithium to $Cp_2ZrCl_2$ (Scheme 5.3). The 1-butene ligand is only weakly bound to the '$Cp_2Zr$' moiety in **4** and may be readily displaced by other alkenes or alkynes to give **6**. Free zirconocene is probably not an intermediate in such displacements, transfer occurring *via* a di-$\pi$ complex such as **5**. The rate of co-cyclisation of **5** is much slower than dissociation of 1-butene leaving the more strongly bound alkyne ligand on the metal in **6**. The direct complexation method is not generally useful for the intermolecular cross-coupling of different components since the first formed $\eta^2$-$\pi$ complex **6** reacts rapidly with further uncomplexed component to give homocoupled products such as **7** (Scheme 5.3).



**Scheme 5.3**

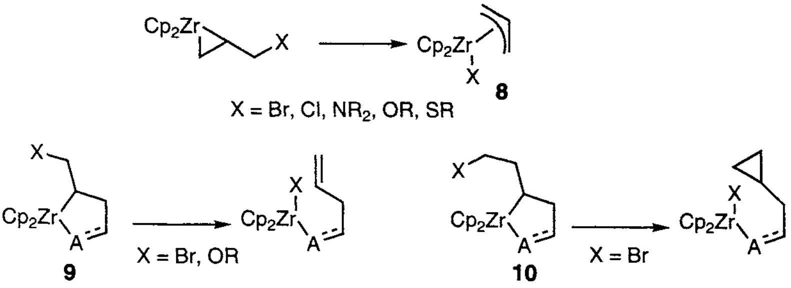
## 2.2 C-H activation

A valuable route to $\eta^2$-$\pi$ metallocene complexes is through a cyclometallation reaction with removal of a $\beta$-proton from the substrate and elimination of an alkane or arene. Typical of this approach is the formation of zirconocene 1-butene **4** (Scheme 5.3). The C-H activation method avoids the problem of dimerisation of the $\pi$-component since there is none of this initially free of the metal. The method also facilitates the formation of $\eta^2$-$\pi$ complexes of components which are unstable in the free state, such as benzyne, cycloalkynes, and thioaldehydes. It is normally successful for cross-couplings when the component generated on the metal is strongly bound. If this is not the case, exchange with the second $\pi$-component may take place, as described for zirconocene 1-butene (Scheme 5.3), giving the unwanted dimer or mixtures (see Section 5).

# 3. Practical considerations and known limitations

The main starting materials used in this area of chemistry are $Cp_2TiCl_2$ and $Cp_2ZrCl_2$, both of which are commercially available and may be handled in air. All the other metallocene complexes described are moisture and, in most cases, oxygen sensitive, and therefore all reactions must be carried out under anhydrous and oxygen-free conditions. Hydroxyl groups are not tolerated in the substrates but may be protected *in situ* as their lithium salts. Less acidic groups such as terminal alkynes and primary or secondary amines are tolerated in some cases. Ketones, aldehydes, and cyanides react rapidly with $\eta^2$-$\pi$ complexes of the metallocenes so are not compatible with the reactions described below. Esters and amides are sometimes tolerated, particularly by titanocene reagents.

A less obvious limitation is imposed by the facile rearrangement of zirconocene $\eta^2$-alkene complexes bearing adjacent leaving groups to allylzirconocene complexes **8** (Scheme 5.4) (a transformation which has provided access to allyl zirconocene reagents[5]). $\eta^2$-Alkyne complexes carrying adjacent leaving groups can undergo the same process,[6] but generally this is too slow to prevent co-cyclisation reactions. Zirconacyclopentanoids of types **9** and **10** also undergo facile elimination (Scheme 5.4), a reaction which has been used productively.[7,8]



**Scheme 5.4**

The use of titanocene and zirconocene $\eta^2$-$\pi$ complexes in organic synthesis will now be described in an order which reflects the first formed $\pi$-complex. As this is intended to be an illustrative rather than an exhaustive account of the field, the reader is directed towards several excellent reviews which provide access to much more of the primary literature.[9–13]

## 4. Coupling of $\eta^2$-alkyne complexes

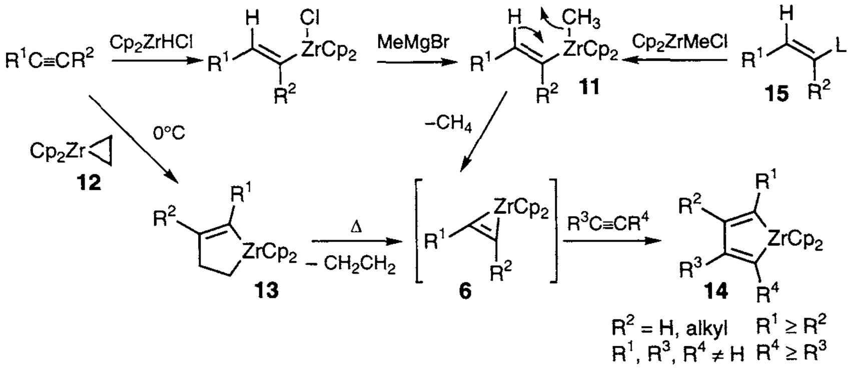
### 4.1 Coupling with alkynes

The intermolecular homocoupling of alkynes to afford metallacyclopentadienes such as **7** (Scheme 5.3) provides, on work-up, a useful synthesis of heavily substituted symmetric dienes.[14] Many sources of the metallocene fragment are used in this chemistry including $Cp_2TiCl_2/Na/Hg/PMe_2Ph$, $Cp_2ZrCl_2/Mg/Hg$, and $Cp_2ZrCl_2/2BuLi$. In certain special cases sequential addition of two different alkynes to the zirconocene equivalent $Cp_2Zr(DMAP)_2$ gives high yields of the cross-coupled products[15] but there are two more general methods that are commonly used to form the zirconacyclopentadiene.

(i) Hydrozirconation of an alkyne followed by addition of MeMgBr gives the methyl zirconocene complex **11**. Thermal elimination of methane then forms the zirconocene $\eta^2$-alkyne complex **6** which may be trapped with a second alkyne to form the mixed zirconacyclopentadiene **14** (Scheme 5.5).[16]

(ii)Reaction of an alkyne with zirconocene ethene **12** (generated *in situ* from diethyl zirconocene in the same fashion as zirconocene 1-butene **4**) forms the zirconoacyclopentene **13**. Thermal elimination of ethene in the presence of a second alkyne then gives the cross-coupled zirconacyclopentadiene **14** (Scheme 5.5).[17]

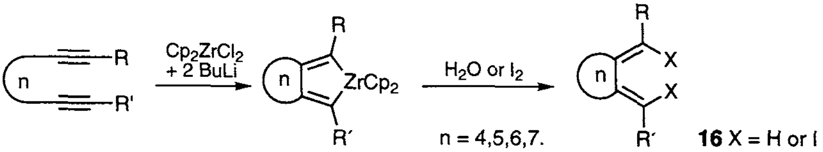
Both of these processes tolerate terminal alkynes as the first component.



**Scheme 5.5**

An alternative route to the methyl vinyl zirconocenes **11** is based on the reaction between a vinyllithium **15** and zirconocene methyl chloride. This approach has been used to form several $\eta^2$-alkyne complexes.[9,18]

The intramolecular 1,*n*-diyne coupling with 'MCp$_2$' equivalents is an efficient process which affords exocyclic dienes **16** (Scheme 5.6), valuable substrates for the Diels–Alder reaction. $Cp_2TiCl_2/Na/Hg/PPh_2Me$ and $Cp_2ZrCl_2/Mg$ reagents have been used but zirconocene 1-butene **4** is more convenient than either and gives excellent yields.[19,20] Using the zirconium reagents, ring sizes from four to seven may be made and very bulky groups on the alkynes are tolerated. Titanocene-induced cyclisations are limited to the formation of five- and six-membered rings, and do not tolerate bulky alkyne substituents. Terminal alkynes are not tolerated, but 1-trimethylsilyl or 1-trimethylstannyl

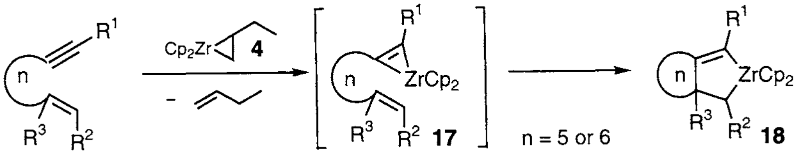


**Scheme 5.6**

alkynes may be used as masked forms of terminal alkynes. (Note that the stannyl groups are much easier to remove from the organic products.)

## 4.2 Coupling with alkenes

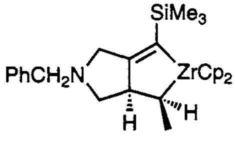
Intramolecular co-cyclisation of 1,6- and 1,7-enynes using the Negishi reagent **4** gives bicyclic zirconacyclopentenes **18** in excellent yields (Scheme 5.7).[20,21] An $\eta^2$-alkyne complex **17** is likely to be the first formed intermediate.



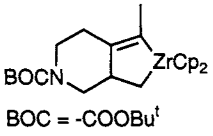
**Scheme 5.7**

The reaction will normally tolerate a di-substituted alkene group (1,1 or 1,2) although some failures have been noted, particularly when the alkyne carries a trimethylsilyl substituent. The most common problem is intermolecular dimerisation of the alkyne component, which may sometimes be overcome by slow addition of the enyne to a solution of $Cp_2Zr(DMAP)_2$ generated *in situ*. The stereochemistry of a 1,2-disubstituted alkene is retained in the cyclisation. Nitrogen-containing connecting chains work well to give, for example, **19** and **20**.

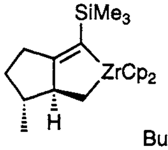
The co-cyclisation of substituted enynes is often highly diastereoselective. Substituents next to the alkene component exert complete control over the adjacent ring junction stereochemistry: for example, **21** and **22** are formed as single isomers.[22] In some cases the zirconacycles must be given time to equilibrate thermally to the more stable isomer in order to achieve high levels of diastereocontrol (the formation of zirconacyclopentenes is a reversible process).



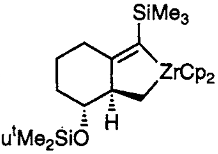
**19**



**20**



**21**

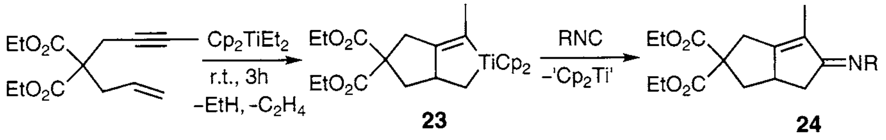


**22**

The co-cyclisation of enynes containing a terminal alkyne fails with zirconocene 1-butene **4**, but this process may be achieved using the two-step procedures shown in Scheme 5.5.

Cyclisations initiated by zirconocene 1-butene are incompatible with ester functionality, a limitation which has been overcome by the use of a diethyl titanocene reagent which gives titanocycles exemplified by **23** (Scheme 5.8).

Work-up of the titanacycles with isocyanides gives bicyclic imines **24**, a process which may be made catalytic in titanium since the 'titanocene' liberated from the imine may co-cyclise the enyne.[23,24]

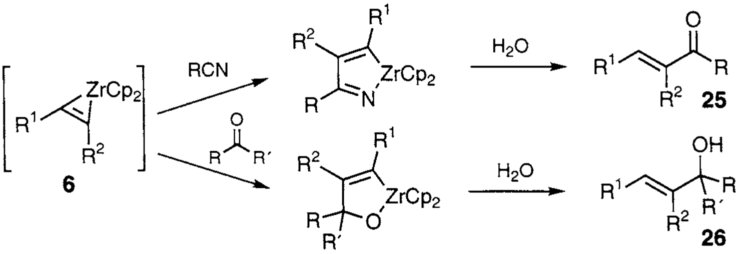


**Scheme 5.8**

Zirconocene $\eta^2$-alkyne complexes generated by the C-H activation method may be trapped intermolecularly with alkenes, but excepting ethene and norbornene the yields are generally low.[9,18]

## 4.3 Coupling with nitriles and carbonyl compounds

Zirconocene $\eta^2$-alkyne complexes generated by elimination of ethene ($\beta$–$\beta'$ C-C bond activation) or elimination of methane (C-H activation) as illustrated in Scheme 5.5 may be trapped with nitriles and aldehydes to provide enones and allylic alcohols **25** and **26** on hydrolysis (Scheme 5.9).[12,17]



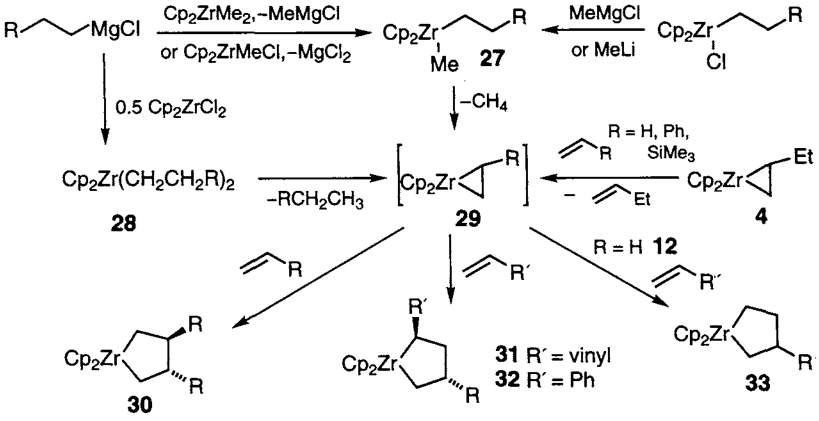
**Scheme 5.9**

# 5. Coupling of $\eta^2$-alkene complexes

## 5.1 Coupling with alkenes

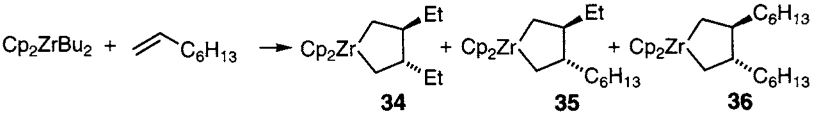
Zirconocene alkene complexes **29** are readily prepared by the $\beta$-hydride activation route from dialkyl zirconocenes **28** or methyl alkyl zirconocenes **27** (Scheme 5.10). It is also possible to prepare the zirconocene complexes of ethene, styrene, and, to a lesser extent, vinyltrimethylsilane by displacement of the weakly bound 1-butene ligand from **4**.[25]

When zirconocene alkene complexes are formed in the presence of an excess of the same alkene, symmetric dimers **30** are formed with high regio- and stereocontrol.[26] Cross-coupling of different alkenes is not generally successful because the rate of alkene exchange from the first formed $\eta^2$-alkene



Scheme 5.10

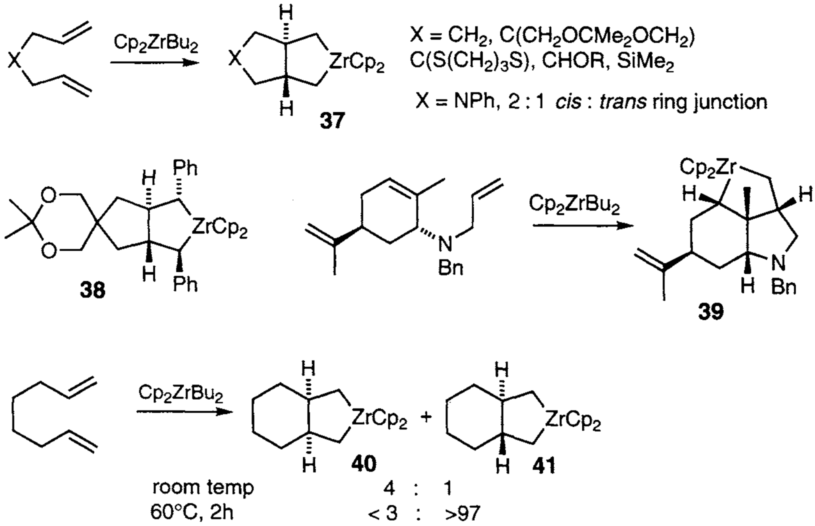
complex is faster than the rate of co-cyclisation to form the required zirconacyclopentane. The ready reversibility of the alkene addition reaction (i.e. β–β′ carbon–carbon bond cleavage)[27] may also contribute to the lack of selectivity, as illustrated by the reaction of zirconocene 1-butene with 1 equiv. of 1-octene to give a 1:2:1 statistical mixture of the three metallacycles **34**–**36** (Scheme 5.11).[26]



Scheme 5.11

Exceptions are trapping with styrene[26] and conjugated dienes[28] where pair selective products **31** and **32** are obtained (Scheme 5.10). In both these cases the added alkene substituent (phenyl or vinyl) ends up adjacent to the metal – quite different behaviour to other alkenes – and reflects stabilisation of the zirconacycle by phenyl – or vinyl–metal interactions. The most useful class of 'pair selective' couplings is between zirconocene ethene **12** and added alkenes where the ethene remains bound to the metal leading to a single product **33** (Scheme 5.10). The special reactivity of **12** has already been seen in the insertion of alkynes to afford zirconacyclopentenes **13** (Scheme 5.5).[17,29]

The intramolecular co-cyclisation of 1,6- and 1,7-dienes using zirconocene 1-butene **4** affords bicyclic zirconacyclopentanes **37** in high yield (Scheme 5.12). With simple 1,6-dienes the *trans*-fused bicyclo[3.3.0]octane is formed with good selectivity (90–97%). (It is important to leave the zirconacycles at room temperature for 2 h to ensure high stereocontrol.) Inclusion of a nitrogen atom in the ring gives 67% of the *cis*-fused product, although it has not yet been established whether thermal equilibration will improve the *trans* selectivity in this system. One disubstituted (1,1 or 1,2) double bond is tolerated, but not more,[30] with the exception of styryl systems such as that which leads to the efficient formation of **38**. Sometimes a trisubstituted double bond may be tolerated as in the formation of **39**.[31] A significant limitation to the co-cyclisation, however, is that an ether link in the connecting chain is not tolerated. 1,7-Dienes initially form *cis*-fused zirconacycles **40** (Scheme 5.12) with around 80% selectivity, but heating at 60 °C for a few hours isomerises this to the more stable *trans*-fused system **41** (>97%).[32]



**Scheme 5.12**

## 5.2 Other metallocene-mediated couplings

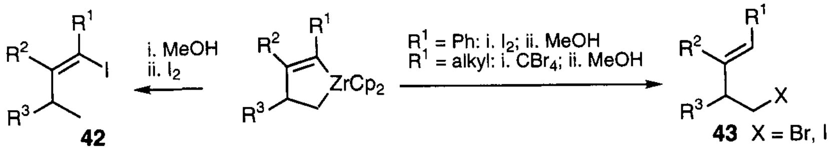
The intramolecular coupling of alkenes (and alkynes) with cyanides or hydrazones induced by zirconocene 1-butene has been reported,[33,34] and the intramolecular coupling between alkenes (and alkynes) and ketones or aldehydes induced by $Cp_2Ti(PMe_3)_2$ is also known.[35]

# 6. Functionalisation of zirconacyclopentanes and zirconacyclopentenes

Some of the methods available for elaborating zirconacycles are outlined below.

## 6.1 Halogenolysis

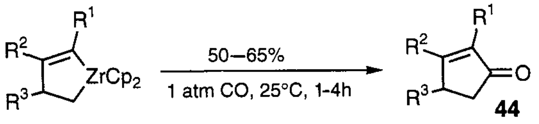
Treatment of zirconacyclopentanes with bromine, iodine, or *N*-bromosuccinimide (NBS) gives the 1,4-dihalide in good yield. Selective monohalogenation is achieved by initial protonolysis followed by halogenolysis.[36] Zirconacyclopentenes may be diiodinated or dibrominated in a similar way. Selective monohalogenation of the vinyl–zirconium bond to afford for example **42** (Scheme 5.13) is best achieved by protonolysis of the alkyl–zirconium bond followed by addition of iodine (or NBS). When the zirconacyclopentene has a 2-phenyl substituent ($R^1$), the alkyl halide **43** (Scheme 5.13) may be obtained by iodination or bromination (NBS is best) followed by protonolysis, but with a 2-alkyl substituent this method fails as the halogen attacks the vinyl–zirconium bond first. This problem has been overcome by the use of $CBr_4$ as the halogenating reagent.[37]



**Scheme 5.13**

## 6.2 Carbonylation and isocyanide insertion

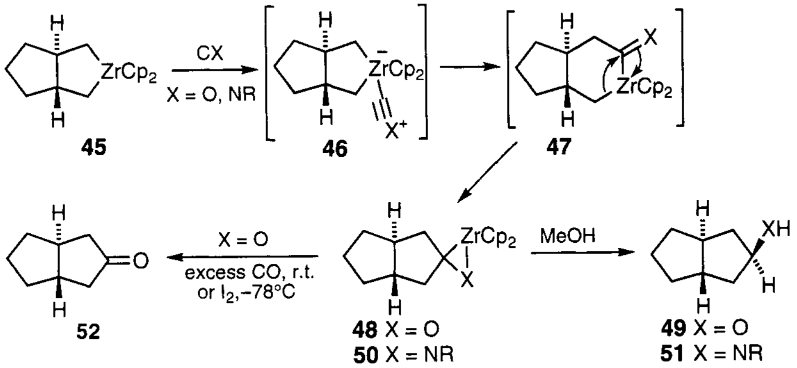
Carbonylation (1 atm CO, 25 °C, 1–4 h) of zirconacyclopentenes followed by acidic work-up gives cyclopentenones **44** in 50–65% yield (Scheme 5.14)[20] (*cf.* 80–95% for protonolysis). The reaction works best with $R^1 = SiMe_3$ or $SnMe_3$.



**Scheme 5.14**

Carbon monoxide insertion into zirconacyclopentanes such as **45** occurs rapidly at −78 °C. Work-up by protonolysis gives the alcohol **49** presumably *via* the $\eta^2$-ketone complex **48** (Scheme 5.15).[38] Carbonylation for longer periods at room temperature affords the cyclopentanones **52** but higher yields are obtained by work-up with iodine at low temperature.

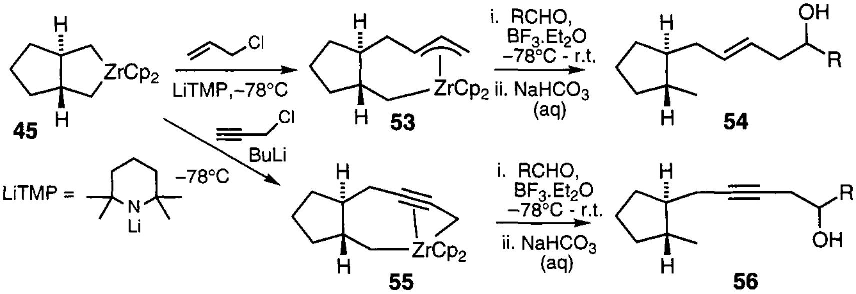
Insertion of isocyanides into zirconacyclopentanes and -enes is complete within a few minutes at room temperature to afford iminoacyl complexes such as **47** (Scheme 5.15). With most nitrogen substituents (especially $Me_3Si$ and Ph), these rearrange to the $\eta^2$-imine complexes **50** which can be trapped by protonolysis to afford **51**, or by the insertion of alkynes, alkenes, and ketones (see Section 8).[39–41] The rearrangement is induced by the addition of protic solvents, and so quenching the iminoacyl complexes **47** with methanol gives the amines **51** (in around 50% yield).



Scheme 5.15

## 6.3 Insertion of metal carbenoids

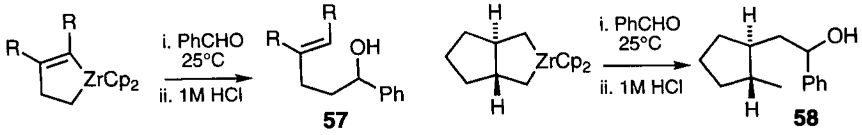
The facile insertion of carbenoid species such as carbon monoxide and isocyanides into zirconacycles, which contrasts strongly with the low reactivity of conventional electrophiles such as acetone and iodomethane towards these species, is due to their ability to donate a lone pair to the 16-electron zirconium centre to give an 18-electron 'ate' complex **46**. Migration of a carbon–zirconium bond returns the metal to the more stable 16-electron configuration. This type of reactivity is also shown by metal carbenoids ($R^1R^2CMX$):[42,43] indeed both lithiated propargyl chloride and lithiated allyl chloride insert extremely rapidly at −78 °C into zirconacyclopentanes to afford $\eta^3$-propargyl and $\eta^3$-allyl zirconacycles such as **55** and **53**, respectively (Scheme 5.16). These may be further elaborated, for example by insertion of $RCHO/BF_3$ to give **54** and **56**, in very high overall yields.[43] Zirconacyclopentenes may be elaborated in the same way, insertion only occurring into the alkyl–zirconium bond. The overall sequence is a good illustration of the way in which 'zirconocene' may act as a template upon which several carbon–carbon bonds may be formed in tandem processes.



Scheme 5.16

## 6.4 Insertion of aldehydes

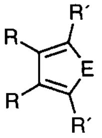
Zirconacyclopentanes and -enes react with aldehydes at room temperature to afford adducts such as **57** and **58** after aqueous work-up (Scheme 5.17).[29] With zirconacyclopentenes, insertion occurs only into the alkyl–zirconium bond.



**Scheme 5.17**

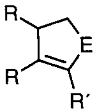
## 6.5 Metathesis reactions

Reaction of a variety of zirconacyclopentadienes, -enes, and -anes with main group element dihalides (or $E_2Cl_2$ for E = S, Se) gives the corresponding elementacycles **59–61**.[44]



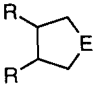
**59**

E = BPh, PPh, AsPh, SbCl, BiCl, GaCl, InCl GeCl$_2$, SnMe$_2$, SiBr$_2$, S, SO, Se



**60**

E = S, Se SnPh$_2$



**61** E = S, Se

The following protocols describe the synthesis of zirconacycle **45** from 1,6-heptadiene and its characterisation by NMR spectroscopy. Zirconacycle **45** is then elaborated into alcohol **49** by reaction with carbon monoxide, and alcohol **54** (R = Ph) by tandem insertion of lithium chloroallylide and benzaldehyde.

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### Protocol 1a.

### Co-cyclisation of 1,6-heptadiene to give zirconacycle (Structure 45) using *in situ* generated zirconocene 1-butene (Structure 4)

**Caution!** All procedures should be carried out in a well-ventilated fume hood. Disposable vinyl or latex gloves and safety glasses should be worn.

The following procedure may also be used for the co-cyclisation of 1,*n*-enynes and diynes.

*Equipment*

- Vacuum/argon manifold[a] (Figs 7.1 and 7.2)
- Magnetic stirrer[b]
- Round-bottomed flask with glass stopcock (B14, 25 mL) (Schlenk flask) (Fig. 5.1A)
- Stopcock unit (B14) (Fig. 5.1B)
- Small filter funnel
- Vent needle (Fig. 5.1C)
- Dewar bowl or other low-temperature bath
- Teflon-covered magnetic stirrer bar (≈1 cm long)

- All-glass tuberculin syringe[c] (1 mL)
- All glass syringes (1, 2, and 5 mL)
- Stainless steel needles (4 × 8″, 18 gauge)
- Silicone vacuum grease
- Single-necked, round-bottomed flask (B14, 10 mL)
- Septa[d] (3 × B14)

### Materials

- 1,6-Heptadiene (FW 96.2), 0.096 g, 1 mmol **flammable, irritant**
- Zirconocene dichloride (FW 292.3), 0.293 g, 1 mmol
- *n*-Butyllithium[e] in hexanes, 0.80 mL of a 2.5 M soln, 2 mmol **flammable, moisture sensitive**
- Dry and oxygen free THF, 10 mL[f] **flammable, may form explosive peroxides, irritant**

1. All glassware and the stirring bar should be dried overnight in a 150 °C oven and either assembled[g] while still warm, or allowed to cool in a desiccator before assembly. Syringes (not assembled) and needles should be dried at 150 °C in an oven overnight, allowed to cool in a desiccator then assembled using Teflon tape to ensure a gas-tight seal between the needle and syringe and to ease removal at the end of the experiment. All syringes should be flushed with argon before use by filling and emptying three times from a suitable source of pure argon.
2. Weigh the zirconocene dichloride into the 25 mL Schlenk flask (Fig. 5.1A), containing the stirrer bar through a small dry funnel, avoiding contamination of the B14 joint which should not be greased. Quickly insert the previously greased stopcock assembly (Fig. 5.1B) into the flask and attach the assembled apparatus to the vacuum/argon manifold as in Fig. 5.2. With stopcock **A** closed, evacuate the system (0.1–1 mmHg). Use an elastic band to ensure that the two parts of the apparatus stay together when a positive argon pressure is applied.
3. Carefully allow argon to enter the apparatus from the manifold, avoiding blowing the zirconocene dichloride around. Repeat the evacuate/refill cycle twice. The apparatus should be left with stopcock **B** open so that the manifold maintains a positive pressure of argon in the flask. Stopcock **A** should be kept closed except when adding reagents.
4. Place a B14 septum over the end of stopcock **A** and flush the space between the septum and the stopcock with argon by inserting a vent needle (Fig. 5.1C) and opening stopcock **A** slightly for a few seconds.
5. Add 5 mL of dry THF to the flask by syringe[h] through stopcock **A**. After the zirconocene dichloride has dissolved, cool the flask to −78 °C in an acetone bath cooled with liquid nitrogen or solid carbon dioxide.
6. After 5 min at the low temperature (ignore any precipitation of zirconocene dichloride), add the *n*-butyllithium solution[e] (Fig. 5.3) dropwise over 2 min using a 1 mL tuberculin syringe to give a pale yellow solution.
7. Weigh[i] the 1,6-heptadiene into a dry 10 mL B14 round-bottomed flask and fit the flask with a septum. Add dry THF (2 mL) and briefly flush the flask

**Protocol 1a.** *Continued*

with argon using a vent needle and an 'argon needle'[j] from the vacuum/argon manifold. Transfer the solution of 1,6-heptadiene to the reaction flask using the same syringe, and ensure complete transfer by adding and transferring another 1 mL of THF.

8. After at least 20 min at <−70 °C, remove the cooling bath, allow the reaction flask to warm to room temperature, and then stir at this temperature (>20 °C) for at least 2 h[k] (overnight is all right) to ensure high selectivity for the *trans*-ring junction in the product zirconacycle.

For footnotes, see the end of Protocol 1d.

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The above procedure provides a solution of the zirconacycle **45** in 80–100% yield for use in the following protocols.

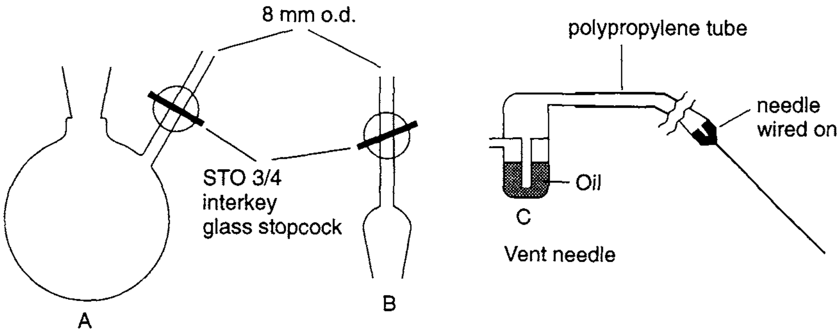

**Fig. 5.1** *Basic apparatus.*

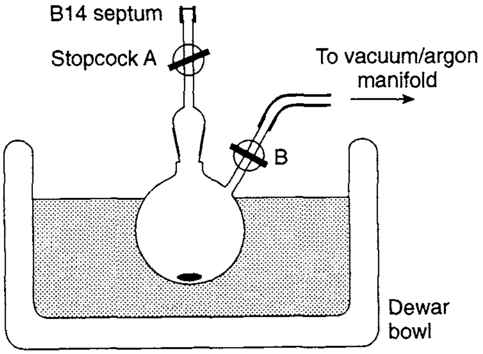

**Fig. 5.2**

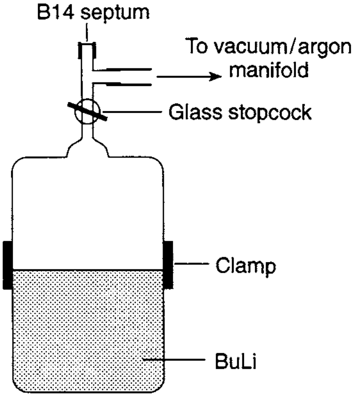

**Fig. 5.3**

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## Protocol 1b.
## NMR characterisation of the zirconacycle (Structure 45)

*Extra equipment required*

- All glass syringes (2 × 1 mL and 2 mL)
- Needles (3 × 8", 18 gauge)
- Single-necked, round-bottomed flask (B14, 10 mL)
- Two-stopcock assembly (Fig. 5.5)
- NMR tube (5 mm) and tight fitting plastic cap
- NMR tube filling apparatus (Fig. 5.4)[l]

*Extra materials required*

- Dry $d_6$-benzene, 0.7 mL[m] **flammable, may cause cancer, toxic – danger of serious damage to health by prolonged exposure**

1. Dry the NMR tube for at least 12 h at 100°C then, while it is still hot, place in the NMR tube filler[l] as in Fig. 5.4A and evacuate the system (the septum must be unpunctured). Admit argon and repeat the evacuation/refill cycle twice, leaving the system under argon.
2. Introduce by syringe approx. 2 mL of the zirconacycle solution into the 10 mL round-bottomed flask fitted with the joint carrying two stopcocks (Fig. 5.5) which has been flushed with argon using three evacuate/refill cycles. With stopcock **A** closed, open the vacuum side of the manifold to stopcock **B** and remove the solvent by *carefully* opening the stopcock **B** while swirling the apparatus. A warm water bath (≈40°C) should be used to help remove the last part of the solvent.
3. When all the solvent has been removed, allow argon back into the apparatus from the manifold. Flush the space above stopcock **A** with argon then add 0.7 mL of dry $d_6$-benzene by syringe. Allow the lithium chloride precipitate to settle and then take the supernatant back into the 1 mL syringe and transfer to the NMR tube held in the filler (Fig. 5.4A).

### **Protocol 1b.** *Continued*

4. Remove the NMR tube from the holder and fit a tight fitting plastic cap while keeping the tube opening in the stream of argon issuing from the hole previously occupied by the tube. A small piece of 'Labfilm' (2 mm × 5 mm is sufficient) may be wrapped around the cap/tube junction to complete the seal. Samples made up in this way survive for at least 24 h.

For footnotes, see the end of Protocol 1d

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The NMR sample prepared by the above method will contain lithium chloride,[n] but this does not usually prevent a satisfactory NMR spectrum being obtained.

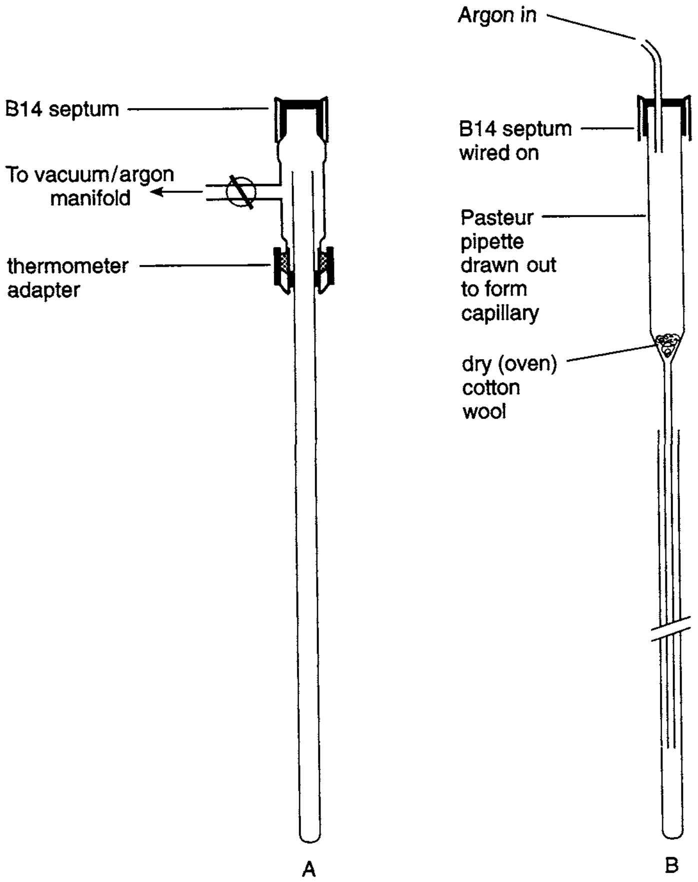

**Fig. 5.4**

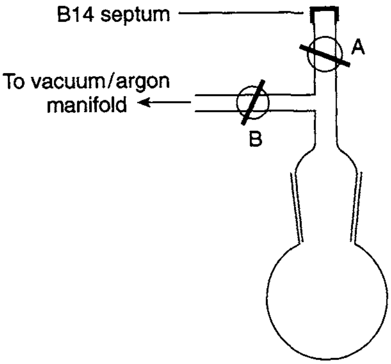

**Fig. 5.5**

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## Protocol 1c.
## Synthesis of *trans*-bicyclo[3.3.0]octan-3-ol (Structure 49) by insertion of carbon monoxide into 45

*N.B.* A similar procedure is used for carbonylation of zirconacyclopentenes, except that the reaction is allowed to warm to room temperature under carbon monoxide before quenching, and it produces the ketone rather than the alcohol.

*Extra equipment required*

- Glass T-piece
- Chromatography column
- Separating funnel

*Extra materials required*

| | |
|---|---|
| • Cylinder of carbon monoxide (technical grade is sufficient). | **Caution! This is a very toxic odourless gas. Ensure that the vacuum/argon manifold is vented high in the fume hood** |
| • Methanol, 3 mL | **flammable, toxic** |
| • Saturated aqueous sodium hydrogencarbonate solution | |
| • Brine | |
| • Anhydrous magnesium sulfate | |
| • Distilled petroleum ether (40-60) for chromatography | **flammable, very toxic** |
| • Diethyl ether for extraction and chromatography | **flammable, irritant** |
| • Silica gel (10 g) | **irritant dust** |

1. Attach a carbon monoxide cylinder with pressure reduction head and needle valve to the top of stopcock **A** (Fig. 5.2) using a piece of thick-walled flexible tubing containing a T-piece connected to the vacuum/argon manifold. The rubber tubing should be clamped in the fume hood so that if any of the glass connectors breaks the toxic carbon monoxide will be contained. All thick-walled flexible tubing should be of good quality and securely attached using hose connector clamps.
2. With stopcock **A** closed, evacuate the tubing using the vacuum manifold. Close the manifold stopcock and refill the tube with carbon monoxide from

**Protocol 1c.** *Continued*

the cylinder. It is important that the pressure head is set to no more than 0.5 p.s.i. Close the needle valve and evacuate the tubing again. Refill with carbon monoxide and leave the needle valve open.

3. Cool the zirconacycle solution prepared in Protocol 1a to −78°C and then evacuate the reaction flask through stopcock **B**. There will be some bubbling as gases are removed. Close stopcock **B** and open stopcock **A** to admit carbon monoxide. For larger scale reactions this evacuate/refill cycle should be repeated.
4. After 1 h (after which the temperature should be about −70°C, and the reaction mixture will have changed from golden brown to orange), close stopcock **A** and the carbon monoxide cylinder. Remove the flexible tubing from tap **A** and replace with a septum. Open stopcock **B** to the argon side of the manifold and then add methanol (3 mL) by syringe through stopcock **A**. Remove the cooling bath and allow the reaction mixture to warm to room temperature.
5. After 40 min (by which time there should be a yellow solution and a white precipitate), pour the reaction mixture into saturated sodium hydrogencarbonate solution and extract into diethyl ether (3 × 25 mL). Wash the combined organic layers with water (2 × 25 mL) and brine (2 × 25 mL) before drying over anhydrous magnesium sulfate.
6. Filter and then remove the solvent by rotary evaporation. Purify the crude product by chromatography on silica gel (10 g, 30% diethyl ether in petroleum ether as eluent) and Kugelrohr distillation (74°C, 1 torr) to afford *trans*-bicyclo[3.3.0]octan-3-ol **49** as a colourless oil (88 mg, 70%). TLC with 25% diethyl ether in petroleum ether as eluent produces a spot at an $R_f$ of about 0.15 which may be visualised by charring the plate with sulfuric acid[o] (it turns red and then dark brown on further heating).

For footnotes see the end of Protocol 1d.

## Protocol 1d.
## Tandem insertion of lithium chloroallylide and benzaldehyde into the zirconacycle (Structure 45) to give alcohol (Structure 54) (R = Ph)

*Extra equipment required*

- All glass syringes [5 × 1 mL tuberculin (250 μL gas-tight are better, but expensive), 3 × 2 mL, 5 mL, 20 mL]
- Luer lock needles (10 × 8″, 18 gauge)
- Schlenk flask (B14, 25 mL)
- Schlenk stopcock (B14)
- Small magnetic stirrer bar
- Magnetic stirrer
- Separating funnel (50 or 100 mL)
- Chromatography column

### *Extra materials required*

| | |
|---|---|
| • Allyl chloride (FW 76.5), 0.09 mL, 1.1 mmol | **flammable, very toxic** |
| • 2,2,6,6-Tetramethylpiperidine[p] (141.3), 0.19 mL, 1.1 mmol | |
| • *n*-Butyllithium in hexanes,[e] 0.44 mL of a 2.5 M soln, 1.1 mmol | **flammable, moisture sensitive** |
| • Benzaldehyde[q] (FW 106.1), 0.13 mL, 1.3 mmol | **irritant** |
| • Boron trifluoride etherate[p] (FW 141.9), 0.16 mL, 1.3 mmol | **corrosive, moisture sensitive** |
| • Dry THF, 2.5 mL | **flammable, may form explosive peroxides, irritant** |
| • Methanol, 3 mL | **flammable, toxic** |
| • Diethyl ether for extraction and chromatography | **flammable, irritant** |
| • Distilled petroleum ether (40–60) for chromatography | **flammable, very toxic** |
| • Silica gel for chromatography (30 mL) | **irritant dust** |
| • Saturated aqueous sodium hydrogensulfite solution | **corrosive** |
| • Saturated aqueous sodium hydrogencarbonate solution | |
| • Brine | |
| • Anhydrous magnesium sulfate | |

1. Assemble the 25 mL Schlenk flask and stopcock and insert a small stirrer bar. Attach this to the vacuum/argon manifold through the side-arm and fill with argon using three evacuate/refill cycles. Fit a septum to the upper stopcock (so that the apparatus resembles Fig. 5.2) and flush the gap between stopcock **A** and the septum with argon.
2. Through the septum, add tetramethylpiperidine (0.19 mL) *via* a tuberculin syringe and THF (1.5 mL) *via* a 2 mL syringe.
3. Cool the flask to 0°C and add the *n*-butyllithium solution (0.44 mL) dropwise through the septum using a tuberculin syringe to provide, after stirring for 30 min, a yellow solution of lithium tetramethylpiperidide.
4. Cool the solution of the zirconacycle **45** prepared in Protocol 1a to −85°C in an acetone/liquid nitrogen bath allowing 10 min for equilibration.
5. Add allyl chloride (0.09 mL) by tuberculin syringe and then add the solution of lithium tetramethylpiperidide prepared above dropwise by a 2 mL syringe. The addition should take ≈10 min. A small additional volume of THF is used to ensure complete transfer of the base.[r] For larger scale reactions an apparatus which allows the reaction mixture temperature to be monitored is required.
6. After 30 min, when the temperature has risen to ≈−60°C, add benzaldehyde (0.13 mL) followed by boron trifluoride etherate (0.16 mL) using 1 mL tuberculin syringes.
7. Remove the cooling bath and allow the reaction mixture to warm to room temperature over ≈1.5 h during which time the initially clear yellow/orange solution should become yellow and slightly cloudy.
8. Add methanol (3 mL) by syringe (slight effervescence, solution becomes

**Protocol 1d.** *Continued*

clear golden) followed immediately by saturated aqueous sodium hydrogencarbonate solution (15 mL). Vigorously stir the white suspension overnight.

9. Pour the reaction mixture into a separating funnel and remove the yellow organic phase. Extract the aqueous layer with diethyl ether (3 × 20 mL). Combine the organic layers and wash with saturated aqueous sodium hydrogensulfite solution (20 mL), brine (20 mL), and water (20 mL). Dry ($MgSO_4$), filter, and remove the solvent by rotary evaporation to afford a crude product, typically ≈90% pure by NMR spectroscopy. Purify by chromatography on silica gel (30 mL) eluting with 15–25% diethyl ether in petroleum ether to give **54** (R = Ph) as a colourless oil (0.220 g, 90%). The required compound has an $R_f$ of approximately 0.55 on TLC using a diethylether:light petroleum 1:1 as eluent and may be visualised by dipping the plate in a 10% solution of phosphomolybdic acid in ethanol and then heating.

[a] Dry 'oxygen-free' nitrogen can also be used.

[b] This must have a good enough magnet to stir the flask through the Dewar bowl used for the low-temperature stages.

[c] All glass tuberculin syringes (1 mL) may be difficult to obtain. Hamilton gas-tight syringes (1 mL) will work as well but are expensive. Normal syringes (1 mL) are not accurate enough.

[d] Septa are stored in a desiccator over silica gel containing an indicator.

[e] **Storage and dispensing of *n*-butyllithium.** It is important for this preparation that the *n*-butyllithium used is of good quality – cloudy samples give poor results even if the titre suggests that it is of reasonable quality. Aldrich sure-seal bottles do not provide sufficient protection once the septum is pierced by the 18-gauge needles used. We transfer the *n*-butyllithium into storage bottles of the design shown in Fig. 5.3 (similar are available from Aldrich: cat. No. Z10,733-6 for 125 mL capacity).

*Dispensing*: Use the set-up shown in Fig. 5.3. The space above the stopcock may be flushed with argon using evacuate/refill cycles provided that the septum has never been pierced. Flush the tuberculin syringe by filling/emptying with argon three times. Open the stopcock, lower the needle into the liquid, and allow the slight positive pressure of argon to force the *n*-butyllithium solution into the syringe. When ≈0.2 mL has entered the syringe it should be inverted and the gas bubble expelled before completing filling. The volume added to the reaction flask is measured between two marks on the syringe. This will leave a residue of *n*-butyllithium solution in the syringe (≈0.2 mL) which may be safely disposed of by squirting into running water in the fume cupboard (not in the open laboratory – the finely divided LiOH produced is very irritating).

[f] The THF is dried and maintained oxygen-free by heating under reflux over sodium benzophenone ketyl from which it is freshly distilled before use (preferably taken directly from the still).

[g] Stopcocks should be lightly greased lengthways, inserted into the socket and rotated. A clear film throughout the joint indicates that sufficient grease has been used. Air channels are easily seen as lighter streaks. After use the silicone vacuum grease should be removed from the stopcock using dichloromethane/tissue and pipe cleaners before the item is dried in the oven. Joints should likewise be greased and when assembled should be checked to ensure that a clear seal has been formed all around the joint. The bottom third of the joint (nearest the reaction flask) is often left ungreased to reduce contamination of the reaction mixture with silicone grease.

[h] It is economical to use the same syringe several times for handling solvent. This may be done, over short timespans, by inserting the needle into a solid rubber bung to protect from moisture between uses.

[i] It is much more convenient to add the appropriate volume of neat 1,6-heptadiene directly to the reaction mixture by syringe, but if reliable yields are required this is not accurate enough.

[j] Fix the Luer lock part from an old syringe into thick wall vacuum tubing from the manifold using a ring clip. Needles can then be fixed to this using teflon tape to ensure a good seal. Before use the tube and needle should be filled with argon using three evacuate/refill cycles after sealing the needle by insertion into a rubber bung. The bung should be used to seal the needle when not in use.

[k] The colour darkens to a golden yellow/brown. If left overnight a brown solution usually forms, but this seems no less pure by NMR spectroscopy than other samples.

[l] This is made from a 'thermometer adaptor' fused to a B14 socket and glass tap side arm. A less satisfactory, but workable, alternative can be made from a drawn out Pasteur pipette as shown in Fig. 5.4B. A constant flow of argon keeps the NMR tube oxygen-free and the solution of the zirconacycle is injected through the septum. The apparatus must be thoroughly flushed with argon before adding the zirconacycle.

[m] The $d_6$-benzene may be adequately dried by storage over 4 Å molecular sieves or calcium hydride. If the NMR spectrum of smaller quantities of the organometallic is required, the benzene should also be degassed.

[n] If a better NMR spectrum is required, a lithium chloride-free solution of the metallacycle must be prepared by either removing the THF by vacuum transfer (for apparatus and method see Protocol 2, step 7 and Fig. 5.7) and extracting the residue into toluene, or by carrying out the metallacycle preparation in toluene as solvent. In both these cases the lithium chloride is allowed to settle out before removal of the sample for NMR spectroscopy.

[o] Make up a solution of 5% concentrated sulfuric acid in methanol (**Care!** – add the acid very slowly to the methanol with stirring). The TLC plate (aluminium backed!) is then briefly dipped in this and then charred using a hot air gun. All operations should be done in a fume cupboard.

[p] Distilled from calcium hydride.

[q] Purified by washing with aqueous sodium hydroxide solution and then brine, and then drying over anhydrous magnesium sulfate, filtering, and distilling at water pump pressure (≈14 mmHg).

[r] The formation of the allyl zirconocene is immediate. To obtain an NMR sample the mixture may be warmed to room temperature and treated as in Protocol 1b.

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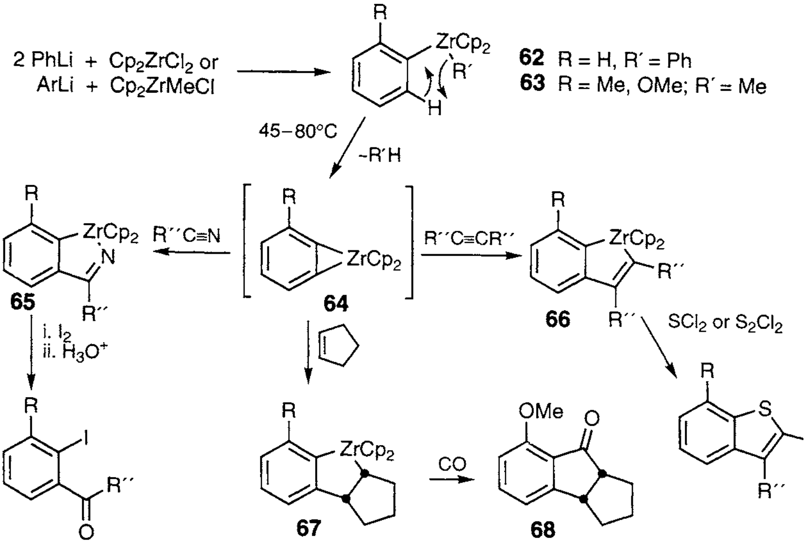
## 7. $\eta^2$-Benzyne zirconocene complexes

Thermolysis of diphenyl zirconocene **62** or an aryl methyl zirconocene **63** forms zirconocene benzyne complexes **64** *via* a C—H activation process (Scheme 5.18).[45,46] The benzyne complexes may be trapped in high yield with



**Scheme 5.18**

nitriles and alkynes, and in lower yield with alkenes, to form zirconacycles such as **65–67**. When the benzyne complex has an *ortho*-substituent, insertion occurs with good selectivity into the remote carbon–zirconium bond. Terminal alkenes give the 3-substituted zirconaindane whereas unsymmetric alkynes insert with the larger substituent adjacent to zirconium. The insertion of alkenes has not been well explored and only ethene and norbornene have been reported to give good yields. Terminal alkenes, cyclopentene, and cycloheptene do insert but the yields are typically around 50%.

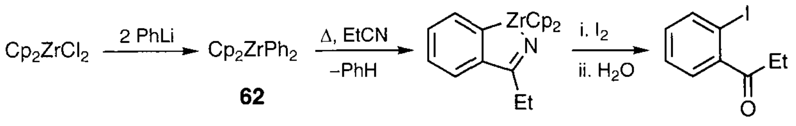
Nitrile adducts **65** undergo hydrolysis or iodinolysis to give *meta*-acylated aromatics thus providing products that are complemenetary to those generated by Friedel–Crafts methods. As well as hydrolysing to give styrenes, zirconaindenes **66** undergo metathesis with $S_2Cl_2$ or $SCl_2$ to afford benzothiophenes (Scheme 5.18).[47] Work-up of zirconaindanes by carbonylation gives indanones such as **68**.[48] Work-up with iodine affords 1,4-diiodides which may be cyclised to benzocyclobutanes on treatment with butyllithium.[45]

The need for $Cp_2ZrMeCl$ as a reagent in the above method may be avoided by using *in situ*-generated $Cp_2ZrBu^tCl$[49] although overall yields are lower.

The synthesis of diphenylzirconocene **62** and its transformation into an $\eta^2$-benzyne intermediate is described in Protocol 2 (Scheme 5.19). Subsequent trapping with a nitrile and iodinolysis give 2′-iodopropiophenone.

## Protocol 2.
## Preparation of diphenylzirconocene (Structure 62), thermolysis in the presence of propionitrile, and iodinolysis

**Caution!** All procedures should be carried out in an efficient fume hood. Disposable vinyl or latex gloves and safety glasses should be worn.



**Scheme 5.19**

*Equipment*

- Vacuum/argon manifold[a]
- Magnetic stirrer[b]
- Dewar bowl
- Round-bottomed flask with glass stopcock (B14, 50 mL) (Schlenk flask) (Fig. 5.1A)
- Small filter funnel
- Stopcock unit (B14) (3 × Fig. 5.1B)
- Liebig condenser (B14)
- Three-necked, round-bottomed flask (B14 side sockets, 100 mL)
- Vent needle (Fig. 5.1C)
- Teflon-covered magnetic stirrer bar (≈1 cm long)
- All glass syringes (2 × 1 mL, 5 mL, 4 × 10 mL)
- Stainless steel needles (7 × 8″, 18 gauge)
- Single-necked, round-bottomed flasks (10 mL and 25 mL)
- Silicone vacuum grease
- Septa[c] (4 × B14)
- Separating funnel (100 mL)
- Chromatography column

### *Materials*

| | |
|---|---|
| • Phenyllithium,$^{d}$ 2.56 mL of a 1.8 M solution, 4.6 mmol | **flammable, moisture sensitive** |
| • Zirconocene dichloride (FW 292.3), 0.584 g, 2 mmol | |
| • Dry and oxygen free THF,$^{e}$ 11 mL | **flammable, may form explosive peroxides, irritant** |
| • Dry oxygen-free benzene,$^{e,f}$ 25 mL | **flammable, toxic - danger of serious damage to health by prolonged exposure through inhalation, in contact with skin, and if swallowed, may cause cancer** |
| • Dry trimethylsilyl chloride$^{e}$ (FW 108.6), ≈0.13 mL, 1 mmol | **flammable, causes burns ≈ moisture sensitive, toxic** |
| • Dry propionitrile$^{e}$ (FW 55.1), 0.11 g, 0.14 mL, 2 mmol | **flammable, very toxic** |
| • Iodine (FW 253.8), 0.61 g, 2.4 mmol, 1.2 equiv | **harmful** |
| • Hydrochloric acid, 4 mL of a 1 M aqueous solution | |
| • Saturated sodium sulfite solution | |
| • Brine | |
| • Anydrous magnesium sulfate | |
| • Diethyl ether for chromatography | **flammable, irritant** |
| • Petroleum ether (40–60) for chromatography | **flammable, very toxic** |
| • Silica for chromatography | **irritant dust** |

1. All glassware and the stirrer bar should be dried overnight in a 150 °C oven and either assembled$^{g}$ while still warm, or allowed to cool in a desiccator before assembly. Syringes (not assembled) and needles should be dried at 150 °C in an oven overnight, allowed to cool in a desiccator and then assembled using Teflon tape to ensure a gas-tight seal between the needle and syringe and to ease removal at the end of the experiment. All syringes should be flushed with argon before use by filling and emptying three times from a suitable source of pure argon.
2. Weigh the zirconocene dichloride into the 50 mL Schlenk flask containing the stirrer bar through a small dry funnel, avoiding contamination of the B14 joint which should not be greased. Quickly insert the previously greased condenser and stopcock assembly (already attached to the manifold) into the flask (Fig. 5.6) and with stopcock **B** closed evacuate the system (0.1–1 mmHg) through stopcock **A**. Use elastic bands to keep the flasks together when a positive pressure of argon is applied.
3. Carefully allow argon to enter the apparatus from the manifold avoiding blowing the zirconocene dichloride around. Repeat the evacuate/refill cycle twice. The apparatus should be left with stopcock **A** open so that the manifold maintains a positive pressure of argon in the flask. Stopcock **B** should be kept closed except when adding reagents.
4. Place a B14 septum over the end of the side-arm of the 50 mL flask and flush the space between the septum and the stopcock with argon by inserting a vent needle (Fig. 5.1C) and opening stopcock **B** slightly for a few seconds.
5. Add 10 mL of dry THF to the flask by syringe$^{h}$ through stopcock **B** and, after the zirconocene dichloride has dissolved, cool the flask to −78 °C in an acetone bath cooled with liquid nitrogen or solid carbon dioxide.

**Protocol 2.** *Continued*

6. After 5 min at the low temperature add the phenyllithium solution by syringe over 2 min to give a dark brown solution. After a further 20 min add trimethylsilyl chloride (≈0.05 mL) and then remove the cooling bath.
7. Once the reaction mixture has reached room temperature, remove the THF by vacuum transfer. Remove the septum on the side-arm and connect to the vacuum/argon manifold. Evacuate/refill the flexible tubing connection three times then open stopcock **B** and close stopcock **A**. Remove the vacuum/argon manifold connection from stopcock **A** and replace with a 0.3–0.5 m length of vacuum tubing connected to a stopcock in the side-arm of a 100 mL three-necked flask. The other side-arm of the flask should contain a stopcock connected to the vacuum/argon manifold so that the whole set-up resembles Fig. 5.7.
8. With stopcocks **C** and **D** open, evacuate the three-necked flask and lower it into the liquid nitrogen. Close stopcocks **B** and **D** and, while stirring or swirling the flask slightly, open stopcock **A**. As the bubbling subsides open the stopcock more. When the bubbling stops, close stopcock **A**, open stopcock **D** and after a few seconds close stopcock **D** and then carefully open stopcock **A** as above. Repeat this process until bubbling persists and a rapid transfer of solvent to the cold trap is occurring (the liquid nitrogen is seen to boil as the vapour gives up its latent heat of vaporisation). This method is better than connecting the flask directly to the vacuum manifold since it ensures that all of the solvent is trapped in the 100 mL flask and it gives a more controllable transfer.
9. When all the solvent has been removed from the reaction flask, close stopcock **C** and open stopcock **B** to allow argon back into the apparatus. Close stopcock **A** and replace the vacuum tubing connecting to the three-necked flask with a connection to the argon manifold. Flush the vacuum tubing with three evacuate/refill cycles and then open stopcock **A**, close stopcock **B**, remove the vacuum tubing from stopcock **B** and replace with a septum (back to Fig. 5.6). The three-necked flask should be removed from the liquid nitrogen, stopcock **D** closed and stopcock **C** opened to prevent a pressure build-up.
10. Add benzene (10 mL) through stopcock **B**.
11. Weigh dry propionitrile[e] into a dry 10 mL round-bottomed flask and fit with a septum. Add benzene (1 mL) and flush the flask with argon. Add this solution to the reaction mixture, followed by another washing of benzene (1 mL) to ensure that all of the propionitrile has been transferred.[i]
12. With stopcock **B** closed and stopcock **A** open to the argon manifold, heat the reaction vessel in an oil bath at 80°C overnight. The reaction mixture should now be orange with a substantial amount of white precipitate present.

13. Weigh iodine into a dry 25 mL round-bottomed flask, fit a B14 septum and flush the air space with argon using a vent needle and a needle attached to the manifold. Add dry, oxygen-free benzene (10 mL) and swirl the flask to ensure that all the iodine has dissolved (gentle warming helps – if some is found not to have dissolved use more benzene to complete the transfer).
14. Cool the bath to 60 °C and then add the iodine solution by syringe to the orange reaction mixture.
15. After stirring at 60 °C for 20 min, remove the reaction flask from the oil bath. Once at room temperature remove the top stopcock unit, add hydrochloric acid (4 mL) and stir for 4 h.
16. Pour the reaction mixture into a 100 mL separating funnel and dilute with diethyl ether (30 mL). Wash the organic phase consecutively with saturated sodium sulfite solution (2 × 20 mL), water (2 × 20 mL), and brine (2 × 20 mL), and then dry over anhydrous magnesium sulfate. Filter and then concentrate by rotary evaporation to give a brown oil. Purify by column chromatography on silica gel (40 g, 5% diethyl ether/petroleum ether as eluent) to give 2′-iodopropiophenone as a yellow oil (0.39 g, 75%).

[a,b] See Protocol 1, footnotes a and b.

[c] Septa are stored in a desiccator over silica gel.

[d] Treat as for butyllithium (Protocol 1, footnote e).

[e] The benzene and THF are taken directly from a still (sodium benzophenone ketyl). Trimethylsilyl chloride and proprionitrile are distilled from calcium hydride under nitrogen.

[f] Toluene may be used if preferred for safety reasons. A carefully thermostatted oil-bath must be used to maintain the 80 °C temperature used in step 11.

[g, h] See Protocol 1, footnotes g and h.

[i] It is simpler to just add 0.13 mL of propionitrile to the reaction mixture provided that a good syringe is available and an accurate yield based on the nitrile is not required.

## 8. $\eta^2$-Imine zirconocene complexes

Zirconocene $\eta^2$-imine complexes **70** (Scheme 5.20) have been made by ligand exchange methods,[33,50] but the C—H activation route from amines provides the best access to these valuable intermediates.[51,52] The rate of the β-hydride activation depends mostly on the nitrogen substituent $R^1$ ($Me_3Si$ > Ar > alkyl) but is also influenced by how activated the hydrogen to be eliminated is (benzylic or not) and by steric constraints for cyclic amines (Table 5.1).[51] The *in situ* generated $\eta^2$-imine complexes are trapped in good yield by alkenes (terminal, 1,1- and 1,2-disubstituted), alkynes (including terminal alkynes), allenes and in lower yield by ketones. Good regio- and stereocontrol is usually found: alkynes insert with the larger group next to the metal, alkenes with it remote. Terminal alkenes insert into mono-substituted $\eta^2$-imine complexes ($R^3$ = H) with excellent selectivity (90 – >98%) for the *trans*-substituted zirconacycle **71** (Scheme 5.20). The problems of ligand ex-

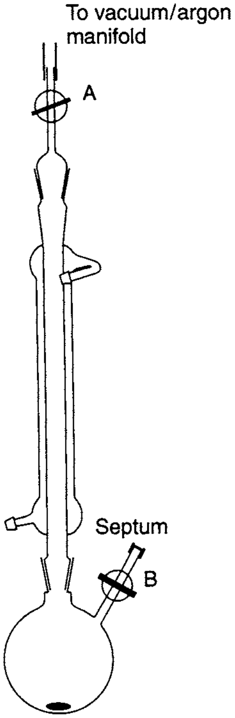
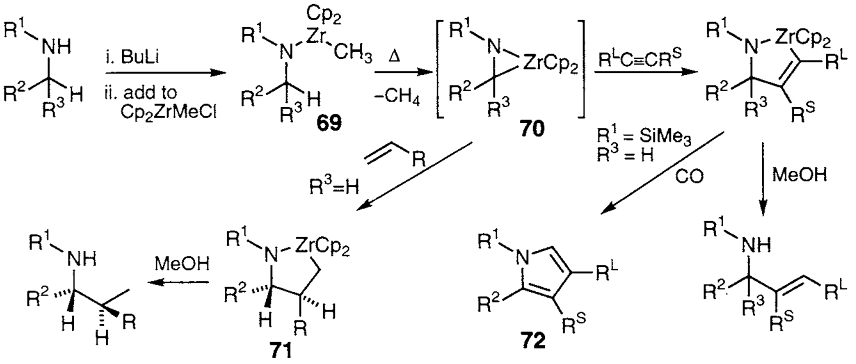


**Fig. 5.6**

change found with $\eta^2$-alkene complexes only rarely occur as the imine moiety is strongly bound to the metal.

The alkyne adducts derived from trimethylsilylamines and alkynes undergo high pressure carbonylation (1500 p.s.i. CO, $NH_4Cl$, r.t. 24 h or 90 p.s.i. CO, 80 °C, 24 h) to give pyrroles **72** in ≈50% overall yield (Scheme 5.20).[53]



**Scheme 5.20**

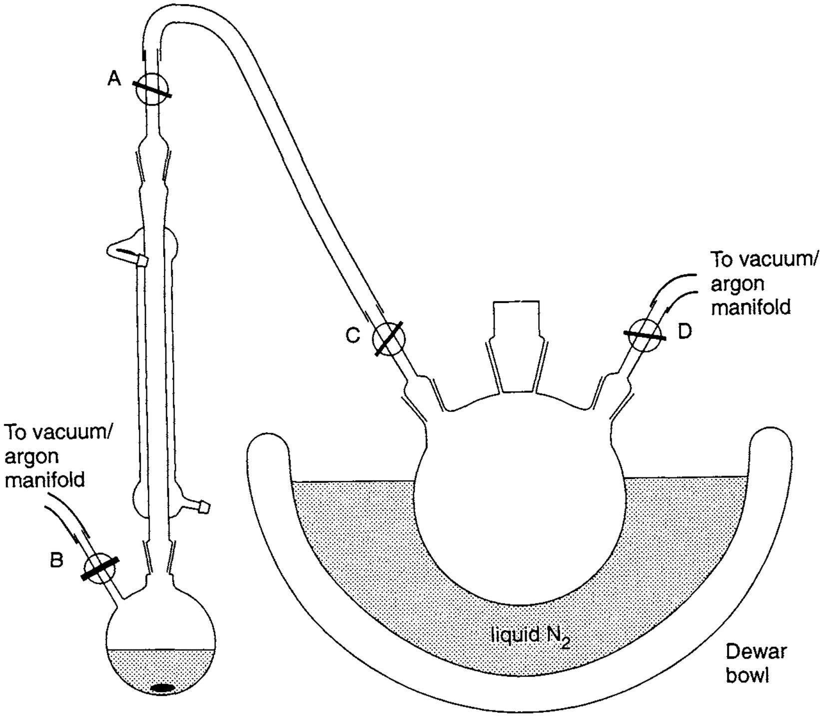
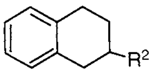


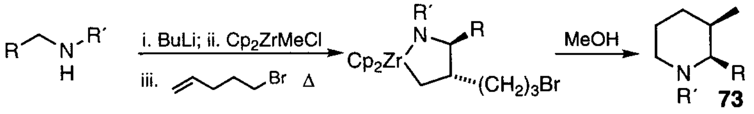
**Fig. 5.7**

**Table 5.1** Formation and trapping of zirconocene $\eta^2$-imine complexes.

| **$R^1$** | **$R^2$** | **$R^3$** | **Conditions (for trapping)** | **Comments** |
|---|---|---|---|---|
| $Me_3Si$ | Ar | H only | < 20°C (16 h, 20°C) | [a] |
| $Me_3Si$ | alkyl | H only | 20°C, 3 h (16 h, 40°C) | Alkynes only |
| Ar | Ar | H, (alkyl) | < 20°C (16 h, 20°C) | |
| Ar | alkyl | H, alkyl | 67°C, 5 h | |
| | | H, alkyl | 67°C, 16 h | |
|  | | | | |
| alkyl | Ar | H only | 67°C, 16 h | |
| alkyl | alkyl | H only | 100°C, 40 h | Alkynes only |

[a] Must not use THF as the solvent for alkene insertions – use benzene or toluene.

Otherwise only protonolysis of the azazirconacycles has been reported. The selective reaction of zirconocene $\eta^2$-imine complexes with alkynes or alkenes in the presence of alkyl halides allows a convergent synthesis of piperidines and pyrrolines such as **73** (Scheme 5.21).[55]



**73**

**Scheme 5.21**

The need to use $Cp_2ZrMeCl$ as a reagent has been avoided in two ways. $Cp_2Zr^tBuCl$, formed *in situ* from $Cp_2ZrCl_2$ and $^tBuLi$, acts as a reasonable replacement although yields are somewhat lower.[49] Alternatively, reaction between $Cp_2ZrCl_2$ and RR′NMgCl gives the chloroamide $Cp_2Zr(NRR')(Cl)$ which can be converted to the desired methyl amide complex **69** by addition of MeMgCl.[54]

Protocol 3 illustrates the generation of a zirconocene $\eta^2$-imine complex. Thus, reaction between chloromagnesium dibenzylamide and zirconocene dichloride followed by precipitation of magnesium chloride using dioxane/hexane gives chlorozirconocene dibenzylamide **74** (Scheme 5.22). Addition of methylmagnesium chloride gives methylzirconocene dibenzylamide which on thermolysis generates a zirconocene $\eta^2$-imine complex **75** which is then trapped *in situ* with 4-octyne to give **76**. Hydrolysis give the allylic amine **77** (Scheme 5.22).

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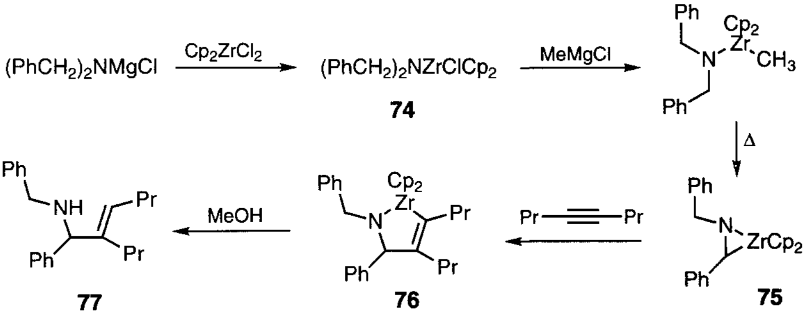
## Protocol 3.
## Generation and trapping of a zirconocene $\eta^2$-imine complex (Scheme 5.22)

**Caution!** All procedures should be carried out in an efficient fume hood. Disposable vinyl or latex gloves and safety glasses should be worn.



**Scheme 5.22**

### *Equipment*

- Vacuum/argon manifold[a]
- Magnetic stirrer[b]
- Cooling bath
- Round-bottomed flasks with glass stopcock (B14, 25 and 50 mL) (Schlenk flasks) (Fig. 5.1A)
- Stopcock unit (2 × B14) (Fig. 5.1B)
- Condenser (B14)
- Vent needle (Fig. 5.1C)
- All glass tuberculin syringe[c] (1 mL)
- Teflon-covered magnetic stirrer bars (2 × ≈1 cm long)
- All glass syringes (2 × 10 mL, 2 × 5 mL, 2 × 2 mL and 2 × 1 mL)
- Stainless steel needles (9 × 6″, medium gauge)
- Silicone vacuum grease
- Septa[d] (2 × B14)
- Separating funnel

### *Materials*

| | |
|---|---|
| • Dibenzylamine[e] (FW 96.2), 1.182 g, 6 mmol | **irritant** |
| • Zirconocene dichloride (FW 292.32), 1.752 g, 6 mmol | |
| • Methylmagnesium chloride,[f] 4 mL of a 3.0 M soln in THF 12 mmol | **moisture sensitive, flammable, causes burns** |
| • Dry and oxygen-free THF, 10 mL[e] | **flammable, may form explosive peroxides, irritant** |
| • Dry hexane,[e] 10 mL | **flammable, harmful** |
| • Dry dioxane,[e] 0.5 mL, 6 mmol | **flammable, may form explosive peroxides, irritant** |
| • 4-Octyne[e] (FW 110.2), 0.66 g, 0.88 mL, 6 mmol | **irritant** |
| • Ethyl acetate for chromatography | **flammable, irritant** |
| • Distilled petroleum ether (40-60) for chromatography | **flammable, very toxic** |
| • Diethyl ether for extraction | **flammable, irritant** |
| • Silica gel for chromatography | **irritant dust** |

1. All glassware and stirrer bars should be dried overnight in a 150°C oven and either assembled[g] while still warm, or allowed to cool in a desiccator before assembly. Syringes (not assembled) and needles should be dried at 150°C in an oven overnight, allowed to cool in a desiccator and then assembled using Teflon tape to ensure a gas-tight seal between the needle and syringe and to ease removal at the end of the experiment. All syringes should be flushed with argon before use by filling and emptying three times from a suitable source of pure argon. All liquids should be added by syringe.
2. Weigh the dibenzylamine into the 25 mL Schlenk flask containing the stirrer bar. Insert the greased stopcock assembly to give apparatus as depicted in Fig. 5.2. With stopcock **A** closed and stopcock **B** open, flush with argon using three evacuate/refill cycles (the vacuum should only be applied briefly to avoid loss of the amine – lower molecular weight amines should be frozen using a bath containing liquid nitrogen before the evacuate/refill cycles).
3. Place a B14 septum on the stopcock unit and flush the space between it and the stopcock by inserting a vent needle (Fig. 5.1C) and slightly opening stopcock **A**. Add 5 mL of dry THF by syringe followed by the dropwise addition of 2 mL of the 3.0 M MeMgCl solution. This should give a rapid evolution of methane and the solution should become warm. Allow to stir for 20 min at ambient temperature after addition is complete.

**Protocol 3.** *Continued*

4. Weigh the zirconocene dichloride into a 50 mL Schlenk flask (Fig. 5.1A), containing a stirrer bar through a small dry funnel, avoiding contamination of the B14 joint which should not be greased. Quickly insert the previously greased B14 condenser and stopcock assembly into the flask and attach the assembled apparatus to the vacuum/argon manifold as in Fig. 5.6. With stopcock **B** closed, evacuate the system (0.1–1 mmHg) through stopcock **A**. Use elastic bands to ensure that the apparatus stays together when a positive argon pressure is applied.
5. Carefully allow argon to enter the apparatus from the manifold avoiding blowing the zirconocene dichloride around. Repeat the evacuate/refill cycle twice. The apparatus should be left with stopcock **A** open so that the manifold maintains a positive pressure of argon in the flask. Stopcock **B** should be kept closed except when adding reagents.
6. Place a B14 septum over the end of the flask side-arm and flush the space between the septum and the stopcock with argon by inserting a vent needle (Fig. 5.1C) and opening stopcock **B** slightly for a few seconds.
7. Add 5 mL of dry THF to the flask by syringe[h] through stopcock **B** and after the zirconocene dichloride has dissolved cool the flask to −30°C in an acetone bath cooled with liquid nitrogen or solid carbon dioxide.
8. After 5 min at the low temperature add the magnesium amide solution prepared in steps 1 and 2 dropwise over 2 min using a 10 mL syringe. Use a further 1 mL of THF to ensure complete transfer. Remove the cooling bath and allow to stir at room temperature for 1 h to give a red solution (dibenzylamine is unusual in this respect – most amines give a yellow solution).
9. Add dry hexane (8 mL) followed by dioxane (0.5 mL, 6 mmol) to give a precipitate of $MgCl_2$·dioxane.
10. Cool the slurry to −30°C in an acetone/coolant bath and then add MeMgCl (2 mL of 3.0 M soln) dropwise over 2 min. Remove the bath and allow the reaction mixture to stir at room temperature for 4 h.
11. Add 4-octyne using a 1 mL tuberculin syringe and then heat the solution under reflux for 16 h using a thermostatted oil bath.
12. Allow to cool to room temperature and then add methanol (1 mL) and stir for 5 min to give a yellow solution.
13. Pour the reaction mixture into water (60 mL) and diethyl ether (40 mL) in a 250 mL separating funnel. Remove the organic layer and extract the aqueous solution with more diethyl ether (2 × 40 mL). Dry the combined organic layers over anhydrous magnesium sulfate, filter and remove the solvent *in vacuo* to give the crude product.
14. Purify by chromatography on silica gel (4 cm deep by 5 cm diameter col-

umn) using 2% ethyl acetate in petroleum ether (40-60) (450 mL) to give (*E*)-1-*N*-benzylamino-1-phenyl-2-propylhex-2-ene as a colourless or very pale yellow oil (1.43 g, 78%) [**Caution!** Allylic amines are often toxic.] On TLC the product has an $R_f$ of about 0.4 in 3% ethyl acetate/petroleum ether and stains black when charred with sulfuric acid.[i]

[a–d] See Protocol 1, footnotes a–d.

[e] 4-Octyne and dibenzylamine are distilled from calcium hydride. THF, dioxane, and hexane are taken directly from a still in which they are maintained at reflux over sodium benzophenone ketyl. In the last case, dimethyltetraglyme is added to the still to solubilise the blue ketyl radical.

[f] Treat as for *n*-butyllithium (Protocol 1, footnote e).

[g,h] See Protocol 1, footnotes g and h.

[i] See Protocol 1, footnote o.

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## Addendum

Great advances have been made in stoichiometric early transition metal induced reactions since this chapter was written. Chapters in Comprehensive Organometallic Chemistry II,[56] a recent Tetrahedron Symposium-in-Print,[57] and a review of the synthetic applications of acyclic organochlorozirconocene complexes[58] have appeared. The most significant advance is the introduction of $Ti(O^iPr)_4/2^iPrMgBr$ as a cheap reagent with much of the reactivity of '$Cp_2Zr$', and better functional group compatibility.[59] Elaboration of zirconacycles through copper catalysed reaction with acyl chlorides, aryl halides, allyl halides, and enones,[60] as well as development of the tandem allyl carbenoid/electrophile insertion methods[61] continue to enhance the synthetic utility of these intermediates. The range of zirconacycles which can be synthezised, as well as the diastereoselectivity in their formation have been further delineated.[57]

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# 6

# Arene chromium tricarbonyl chemistry

STÉPHANE PERRIO

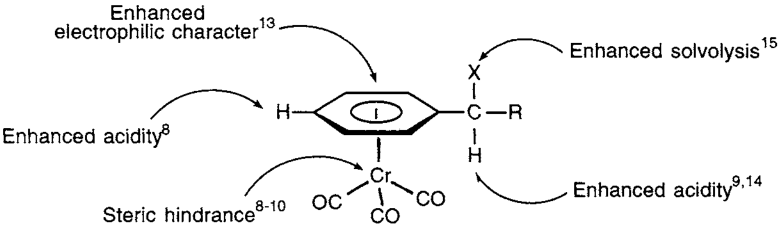
## 1. Introduction

Although a wide range of $\eta^6$-arene transition metal complexes are known,[1] it is only $\eta^6$-arene chromium tricarbonyl complexes that have found significant applications in synthetic organic chemistry.[2–10] These complexes have been investigated either as key intermediates in synthesis[6–10] or as efficient catalysts[11] in a variety of processes.

Chromium tricarbonyl complexes range in colour from bright yellow to red. They are air-stable, crystalline solids but are generally air sensitive in solution. The decomposition in solution, leading to chromium oxides, is autocatalytic in nature; as a consequence, when decomposition products are detected, at any stage of a synthesis, a filtration should be carried out. Purification is easily accomplished by chromatography on silica gel and/or recrystallisation from a nonpolar organic solvent.

Characterisation is achieved by normal spectroscopic methods.[4,12] Complexation causes an upfield shift in the $^1$H NMR spectra of 1–2.5 ppm for the aryl hydrogens relative to the free arene whilst in the $^{13}$C NMR spectra, the metal-bound carbons show a 20–40 ppm shift to higher field. Infrared spectra of these complexes display a characteristic pair of carbonyl stretching frequencies in the region of 1940–2000 and 1850–1940 cm$^{-1}$, respectively. Mass spectrometry is also effective for the identification of such complexes: ions corresponding to the $M^+$, $(M\text{-}CO)^+$, $(M\text{-}2CO)^+$, $(M\text{-}3CO)^+$ and $(\text{arene})^+$ fragments are typically observed.

Due to the strong electron-withdrawing ability and the steric effect of the chromium tricarbonyl group, $\eta^6$-arene chromium tricarbonyl ('benchrotrenic') complexes have some important and characteristic properties.[8–10] The chemical modifications arising from complexation are summarised in Scheme 6.1. $\eta^6$-Arene chromium tricarbonyl complexes undergo a variety of efficient bond-forming reactions by both nucleophilic and electrophilic pathways, either at the aromatic nucleus (nucleophilic addition and deprotonation) or in a side-chain position (through the formation and reactivity of benzylic carbocations and carbanions).[8–10] It should be noted that many of these reactions are impossible to achieve with the corresponding free arene. In addition, most common synthetic transformations, such as acid or base hydrolysis, hydride reduction, carbanion additions to ketones, can be carried out on side chains without disturbing the arene–chromium bond.[8–10]



**Scheme 6.1**

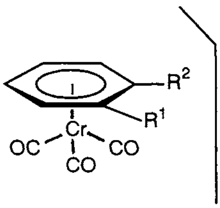
Replacement of one carbonyl ligand by a superior donor ligand, such as a phosphine or phosphite, can be accomplished by photoirradiation (Equation 6.1).[1] This results in a slight modification of the reactivity of the complex, due to an increase in electron density at the metal centre and hence on the ring.

$$\text{(Arene)Cr(CO)}_3 + \text{L} \xrightarrow{h\nu} \text{(Arene)Cr(CO)}_2\text{L} + \text{CO} \qquad (6.1)$$

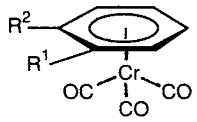
$$\text{L} = \text{PR}_3,\ \text{P(OR)}_3$$

Perhaps the most significant property inherent in these complexes is the elimination of the σ plane of the benzene ring.[10] As a result, *ortho*- and *meta*-disubstituted $\eta^6$-arene chromium tricarbonyl complexes (with different substituents) become chiral molecules and exist in two enantiomeric forms A and B. This feature, together with the stereofacial selectivity induced by the chromium tricarbonyl group, has led to a rapid development in the use of these species as chiral auxiliaries in synthesis.[10] It should be noted at this point that introduction of an additional stereogenic centre in a side chain leads to diastereoisomers.

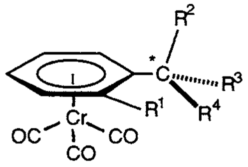
A variety of oxidative methods [cerium(IV) ammonium nitrate, $I_2$, $KMnO_4$, $MnO_2$, electrochemical oxidation] have been reported for the re-



Enantiomer A.



Enantiomer B



One diastereoisomer

moval of the chromium tricarbonyl unit.[3] In addition, decomplexation occurs readily upon exposure of an ethereal solution of the complex to atmospheric oxygen and sunlight (Equation 6.2). This is of central importance if the complex is to be used as a stoichiometric reagent for organic synthesis. Alternatively, the thermolysis of η$^6$-arene chromium tricarbonyl complexes in refluxing pyridine liberates the free arene ligand (Equation 6.3).[3]

$$\text{(Arene)Cr(CO)}_3 \xrightarrow{\text{Oxidant}} \text{Arene} + \text{Cr}_2\text{O}_3 \qquad (6.2)$$

$$\text{(Arene)Cr(CO)}_3 \xrightarrow{\text{Pyridine}} \text{Arene} + \text{(Pyridine)}_3\text{Cr(CO)}_3 \qquad (6.3)$$

This chapter will be divided into two distinct parts. Firstly, general methods for making η$^6$-arene chromium tricarbonyl complexes will be discussed. Particular attention will be paid to complexes bearing sulfinyl substituents[16] and protocols for their synthesis will be given. The second part will deal with enantiopure or enriched complexes. Examples of diastereoselective syntheses of optically pure 1,2-disubstituted complexes with amino and hydroxyl groups at the two benzylic positions[17] will be presented.

## 2. General methods for the synthesis of η$^6$-arene chromium tricarbonyl complexes

Arene chromium tricarbonyl complexes may be synthesised in a variety of ways. Two general approaches are available: direct complexation of the corresponding arene ligand or indirect routes involving the formation of an arene or a complex, previously identified as an appropriate precursor.

### 2.1 Direct complexation of an arene ligand

The simplest and most common procedure for generating η$^6$-arene chromium tricarbonyl species involves the direct heating of the free arene with chromium hexacarbonyl (Equation 6.4). The thermolysis is usually performed in a suitable solvent such as dioxane,[16] di-*n*-butyl ether[18] or decalin (decahydronaphthalene)[19] under refluxing conditions (the respective refluxing temperatures are 100–101°C, 141°C and 187–189°C). Addition of a small amount of a cosolvent, for example α-picoline,[19] THF[18] or *n*-butyl acetate[19] catalyses the reaction and results in a significant increase in the rate of complexation. The most effective and hence routinely used solvent medium for a wide range of high yielding syntheses is an approximately 10:1 mixture of di-*n*-butyl ether and THF.[18,20] Some practical problems can, however, be encountered with the use of di-*n*-butyl ether: depending on the supplier, it may be contaminated by *para*-xylene, thereby leading to unwanted side-products. Direct heating of the free arene with chromium hexacarbonyl requires special glassware to avoid loss of chromium hexacarbonyl *via* sublimation: use of a Strohmeier apparatus,[21] a modified water condenser[19] or an air condenser[16] is necessary in order to wash back into the reaction flask any sublimed chromium hexacarbonyl. Although a wide range of complexes may be formed in moderate to excellent yields with this direct method, the most serious drawbacks comprise long reaction times (up to several days) and relatively high reaction temperatures (in excess of 100°C). Both these problems may be circumvented by using alternative sources of the chromium tricarbonyl group.

$$\text{Arene} + \text{Cr(CO)}_6 \xrightarrow{\text{Heat}} \text{(Arene)Cr(CO)}_3 + 3\,\text{CO} \tag{6.4}$$

Complexes of structural type $L_3Cr(CO)_3$ undergo ligand exchange under milder conditions (Equations 6.5 and 6.6). The rate and the reaction temperature are dependent on the nature of the ligand L. The L unit can be donor ligands such as acetonitrile,[22] ammonia[23] or pyridine.[24] Use of the tris-pyridine derivative requires, however, the addition of boron trifluoride etherate. $\eta^6$-Naphthalene chromium tricarbonyl also undergoes arene exchange under mild conditions with many substituted arenes (Equation 6.7).[25,26] A wider range of reaction temperatures thereby becomes available and in some cases it may be as low as room temperature. As an alternative, photochemical routes may also be used, but these are usually lower yielding than the corresponding thermolytic procedures (Equation 6.8).[7]

$$\begin{gathered}\text{Arene} + \text{L}_3\text{Cr(CO)}_3 \xrightarrow{\text{Heat}} \text{(Arene)Cr(CO)}_3 + 3\,\text{L}\\ \text{L} = \text{CH}_3\text{CN, NH}_3\end{gathered} \tag{6.5}$$

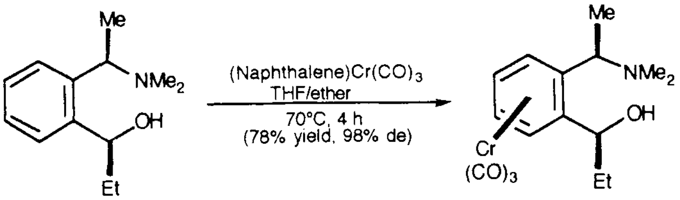
$$\text{Arene} + \text{(Pyridine)}_3\text{Cr(CO)}_3 \xrightarrow[\text{25°C}]{\text{BF}_3\text{.Et}_2\text{O}} \text{(Arene)Cr(CO)}_3 + 3\,\text{Pyridine} \tag{6.6}$$

$$\text{Arene} + \text{(Naphthalene)Cr(CO)}_3 \xrightarrow{\text{Heat}} \text{(Arene)Cr(CO)}_3 + \text{Naphthalene} \tag{6.7}$$

$$\text{Arene} + \text{Cr(CO)}_6 \xrightarrow[\text{25°C}]{h\nu} \text{(Arene)Cr(CO)}_3 + 3\,\text{CO} \tag{6.8}$$

If an *ortho*- or *meta*-disubstituted benzene derivative with a stereogenic centre on one of the side chains is used, complexation may occur with significant diastereoselectivity.[8] This results from delivery of the chromium tricarbonyl group to one of the diastereotopic faces of the arene unit; it is, in general, facilitated by lower temperature conditions for the complexation step. A spectacular example is represented in Scheme 6.2.[17]

Most arenes may, in principle, be coordinated to a chromium tricarbonyl centre. In practice, however, certain types of functional groups are incompatible. For example, arene complexes bearing nitro or nitrile substituents are unknown. π-Electron donating substituents accelerate the rate of complexation, whilst electron withdrawing substituents (e.g. CHO, $CO_2H$) retard com-



**Scheme 6.2**

plexation. The complexes are, in this case, best prepared by indirect methods. Table 6.1 indicates the best approach for a range of substituents.

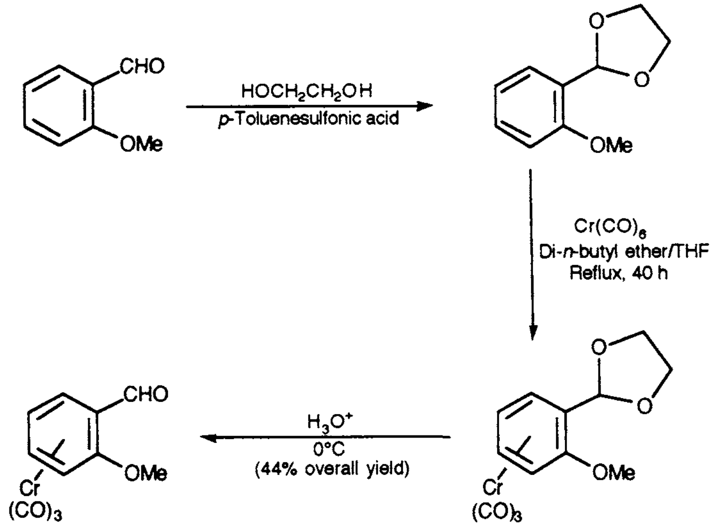
## 2.2 Indirect routes

In one indirect route to $\eta^6$-arene chromium tricarbonyl complexes, an incompatible or reactive functionality is protected in the free arene precursor.[10] Complexation of the protected ligand, followed by deprotection, gives the desired complex. This method is particularly effective, for example, for the synthesis of complexes with ketone or aldehyde functions where the carbonyl group is protected as an acetal. A typical example is represented in Scheme 6.3.[32] By comparison, the direct complexation reaction under standard conditions [$Cr(CO)_6$, *n*-$Bu_2O$/THF, reflux, 5 h] afforded the corresponding complex in 4% yield only.[32]

A second indirect method involves derivatisation of a preformed arene complex and is particularly useful with highly functionalised complexes. Included here are a wide range of reactions such as nucleophilic additions on the aromatic nucleus, electrophilic attacks on *in-situ*-generated carbanions (e.g. aldol condensation[34,35]) and the quenching of carbocations with nucleophiles.[8,10]

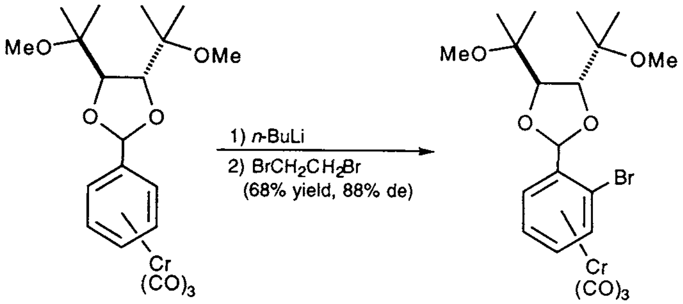
**Table 6.1** General synthetic procedures for the preparation of $\eta^6$-arene chromium tricarbonyl complexes.

| **Direct complexation** | | **Indirect complexation** | |
|---|---|---|---|
| **Substituent** | **Reference** | **Substituent** | **Reference** |
| $NR^1R^2$ | 27 | COR | 8,10 |
| OR | 28 | CHO | 10 |
| $CH_2OH$ | 8 | $CO_2H$ | 10,19 |
| Alkyl | 8 | S(O)R | 16 |
| F | 18 | Br | 33 |
| Cl | 29 | I | 33 |
| $SiR_3$ | 22 | | |
| SMe | 16 | | |
| $S(O_2)R$ | 30 | | |
| OH | 31 | | |



**Scheme 6.3**

As an example, reaction of a lithiated arene complex with dibromoethane or diiodoethane[33] permits the efficient introduction of bromo and iodo substituents (Scheme 6.4). The direct complexation of the parent free arene would be unsuccessful, giving rise instead to a dehalogenation reaction.[36]



**Scheme 6.4**

## 2.3 Synthesis of complexes bearing a sulfinyl substituent

Heating a sulfinyl substituted arene with an appropriate chromium tricarbonyl source does not afford the corresponding $\eta^6$-arene chromium tricarbonyl complex. Instead, a complex mixture of products is obtained, arising from an initial reduction of the sulfoxide functional group.[16]

An indirect route to these sulfinyl-substituted derivatives has however been devised. The method consists of a two-step synthesis, involving the formation of a sulfenyl-substituted chromium tricarbonyl complex, followed by oxidation of the sulfenyl substituent. As it has been known for many years that sulfenyl-substituted arenes readily form chromium tricarbonyl complexes,[36] the difficulty was to find an oxidising agent which would oxidise the sulfur centre without disturbing the chromium moiety. It was eventually discovered that dimethyldioxirane could achieve this transformation very efficiently. Protocols 1–4 describe how to synthesise chromium tricarbonyl complexes of sulfinyl substituted arenes using this approach. In applying this method to *ortho*-disubstituted derivatives, high diastereoselectivities were achieved.[16]

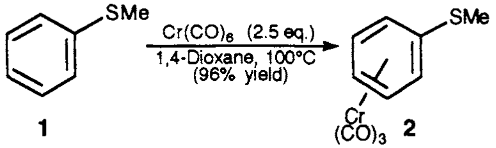
Protocol 1 describes the direct complexation of (methylsulfenyl)benzene **1** (Scheme 6.5).

---

## Protocol 1.

## Synthesis of tricarbonyl[$\eta^6$-(methylsulfenyl)benzene]chromium(0) (Structure 2). Complexation of (methylsulfenyl)benzene (Structure 1) by thermolysis with chromium hexacarbonyl (Scheme 6.5)

**Caution!** Due to the potential toxicity of chromium tricarbonyl complexes, all procedures should be carried out in a fume cupboard. Disposable nitrile or latex gloves and safety glasses should be worn. All procedures are performed with the exclusion of air by using standard nitrogen/vacuum line and Schlenk tube techniques. Although $\eta^6$-arene chromium tricarbonyl complexes are generally stable in air in a crystalline state for long periods, many have been found to decompose in solution on exposure to air under laboratory light. Consequently, all glassware used for complexation, filtration and crystallisation should always be protected from exposure to oxygen and light.



**Scheme 6.5**

*Equipment*

- Vacuum/nitrogen manifold (Figs 7.1 and 7.2)
- Stirrer- hot plate
- Single-necked, round-bottomed flask (B24, 50 mL)
- Liebig condenser, used as an air condenser
- Liebig condenser, used as a water condenser
- Side-arm adapter
- Cone/flexible tubing adapter
- Oil bath
- Contact thermometer (up to 200°C)
- Small magnetic stirrer bar (length 1.5 cm)
- Septum
- Aluminium foil
- All glass syringe (volume appropriate for quantity of solution to be transferred)
- Needle (6", gauge 20 or 22)
- Joint clips (× 3)
- Silicone vacuum grease
- Schlenk tubes for saturating solvents with nitrogen and recrystallisation (× 3)
- Single-necked, round-bottomed flask (B24, 250 mL) for filtration
- Filter column with filter frit (100 mL)

## **Protocol 1.** *Continued*

### *Materials*

| | |
|---|---|
| • Dry 1,4-dioxane,[a] 20 mL + 2 mL | **flammable, possible carcinogen, may form explosive peroxides** |
| • Chromium hexacarbonyl[b] (FW 220.1), 2.21 g, 10 mmol | **volatile, highly toxic** |
| • (Methylsulfenyl)benzene **1**[c] (FW 124.2), 0.5 g, 4 mmol | **harmful, stench** |
| • Diethyl ether for filtration | **flammable, irritant** |
| • Kieselguhr[d] for filtration | |
| • Dichloromethane for crystallisation | **harmful, irritant, toxic** |
| • Petroleum ether (60-80) for crystallisation | **flammable, harmful** |

1. Clean all glassware, syringes, needles and stirrer bar and dry for at least 2 h in a 100°C electric oven before use.
2. Prepare an oil bath at 115°C, controlling the temperature by a contact thermometer.
3. Equip the 50 mL round-bottomed flask with the stirrer bar and the side-arm adapter fitted with a septum. Assemble both pieces whilst still hot (Fig. 6.1).
4. Support the assembled flask using a clamp and a stand with a heavy base and connect the apparatus to the vacuum/nitrogen manifold. Apply the vacuum and then the nitrogen supply (Chapter 7, Protocol 1).
5. Remove the septum on the adapter, reduce the nitrogen to a gentle flow and introduce chromium hexacarbonyl (2.21 g, 10 mmol) with the aid of a rolled filter paper. Put the septum back on the adapter.
6. Protect the flask from light using foil.
7. Assemble the syringes and needles whilst hot and allow to cool to room temperature.
8. Fill a syringe with dioxane (20 mL) and charge the flask by injecting through the septum on the adapter.
9. Inject (methylsulfenyl)benzene **1** (0.5 g, 0.47 mL, 4 mmol) into the reaction flask through the septum on the adapter using a syringe.
10. Assemble both condensers and the cone/flexible tubing adapter whilst hot as shown in Fig. 6.2 (grease the joints carefully and use green clips to secure them), connect the cone/flexible tubing adapter to the vacuum/nitrogen manifold and turn on the flow of nitrogen.
11. Remove the side-arm adapter from the flask and replace by the assembled condensers (use a green clip to secure the joint) (Fig. 6.2).
12. Adjust the water condenser (the top one) to give a moderate flow and initiate stirring the suspension.
13. Apply vacuum till vigorous bubbling occurs and refill with nitrogen (Chapter 7, Protocol 2). Repeat a total of 10 times.

14. Immerse the mixture in the oil bath and generously wrap the apparatus with aluminium foil to minimize exposure to light.
15. After a few minutes, reflux will begin. Leave the solution refluxing for 64 h.[e] The solution gradually turns from pale yellow to dark orange.
16. Remove the oil bath and allow the solution to cool down in an ice-water bath (15 min). Unreacted chromium hexacarbonyl will precipitate out of the solution.[f]
17. During this time, pack the filter column with a short pad of Kieselguhr in diethyl ether[g] (Chapter 7, Protocol 5) and position a round-bottomed flask (250 mL), covered with foil, to collect the filtrate.
18. Disconnect the condensers from the water and nitrogen sources and remove the assembled condensers from the flask. Attach instead a side-arm adapter with a septum on top, already connected to the nitrogen source (Fig. 6.1).
19. Transfer the solution onto Kieselguhr *via* a cannula (Chapter 7, Protocol 3). Rinse the residue in the reaction flask with diethyl ether and transfer the resulting pale yellow solution to the filtration column.
20. Run the filtration column using a nitrogen pressure, collecting the yellow solution in the flask (Chapter 7, Protocol 5). Add diethyl ether until the yellow colour is flushed off the column.
21. Concentrate the resulting orange filtrate under reduced pressure (20 mmHg) by means of a rotary evaporator *located in a fume hood* [the use of a hot water bath (60°C) is necessary to remove the dioxane efficiently]. Store the resulting yellow solid, under an inert atmosphere.
22. Saturate dichloromethane and petroleum ether with nitrogen (Chapter 7, Protocol 2). Evacuate the Schlenk tube to be used for the crystallisation and refill with nitrogen (Chapter 7, Protocol 1).
23. Dissolve the crude yellow solid in the minimum amount of nitrogen-saturated dichloromethane.
24. Transfer the resulting yellow solution into the empty Schlenk tube *via* a filter cannula. If any decomposition is seen at this stage, the solution may be filtered through a small bed of Kieselguhr.
25. Rinse the flask with nitrogen-saturated dichloromethane and transfer to the Schlenk tube for crystallisation.
26. Use the vacuum manifold to remove a small portion of the dichloromethane and then add nitrogen-saturated petroleum ether.
27. Concentrate the solution using the vacuum manifold until the first solid appears.
28. In the sealed Schlenk tube, dissolve the crystals using a hot water bath, protect the Schlenk tube with foil and place it in a freezer (−20°C) for 2 days.

## **Protocol 1.** *Continued*

**29.** Separate the yellow crystals from the mother liquor by filtration using a filtering cannula and collect the mother liquor in a Schlenk tube.

**30.** Wash the crystals with cold nitrogen-saturated petroleum ether, shake gently, allow the solution to settle and withdraw the supernatant. Dry the yellow crystals at room temperature under reduced pressure and record the $^1H$ NMR spectrum in $CDCl_3$ under nitrogen, as described in Protocol 6 of Chapter 7.

**31.** Repeat the crystallisation procedure with the mother liquor.

**32.** Combine both crystallisation crops, which display appropriate spectroscopic data[16] (1.01 g, 3.88 mmol, 96% yield, m.p. 101–102°C), and keep in a vial protected from light with aluminium foil.

[a] 1,4-Dioxane is purified by distillation under nitrogen from calcium hydride and then stored under nitrogen over molecular sieves (4Å) in a bottle protected from light.

[b] Chromium hexacarbonyl is purchased from Strem Chemicals and is used as received. It can be weighed in air as it is relatively air stable and non-volatile. The usual precautions appropriate for a potentially toxic metal carbonyl should be employed, but the low volatility makes handling relatively easy.

[c] (Methylsulfenyl)benzene (thioanisole or methyl phenyl sulfide) is used as obtained from Aldrich. The smell of this sulfide is quite unpleasant. In order to destroy any trace of it, all contaminated glassware should be immersed in a bleach bath.

[d] Kieselguhr is supplied by BDH.

[e] During the complexation reaction, carbon monoxide is evolved slowly. Hence, gas evolution should be observed with the bubbler attached to the vacuum/nitrogen manifold.

If before 64 h of reflux, the reaction mixture develops a green colour, which is indicative of decomposition, stop heating and carry out the work-up. The decomposition is catalytic in nature.

[f] Unreacted chromium hexacarbonyl is destroyed in a well-ventilated hood by oxidation with bleach. If a green residue remains on the inside walls of the glassware, wash with nitric acid.

[g] Diethyl ether is used as obtained for the entire filtration sequence.

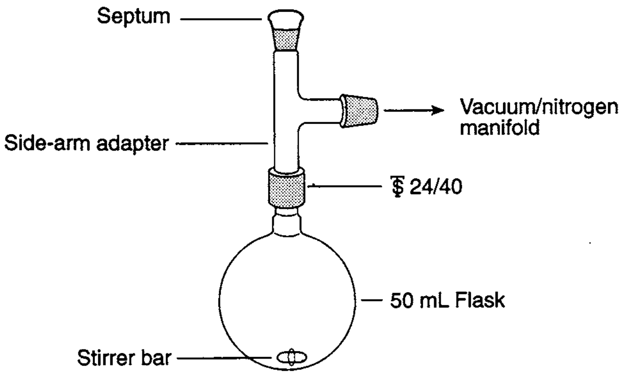


**Fig. 6.1** Assembled reaction apparatus.

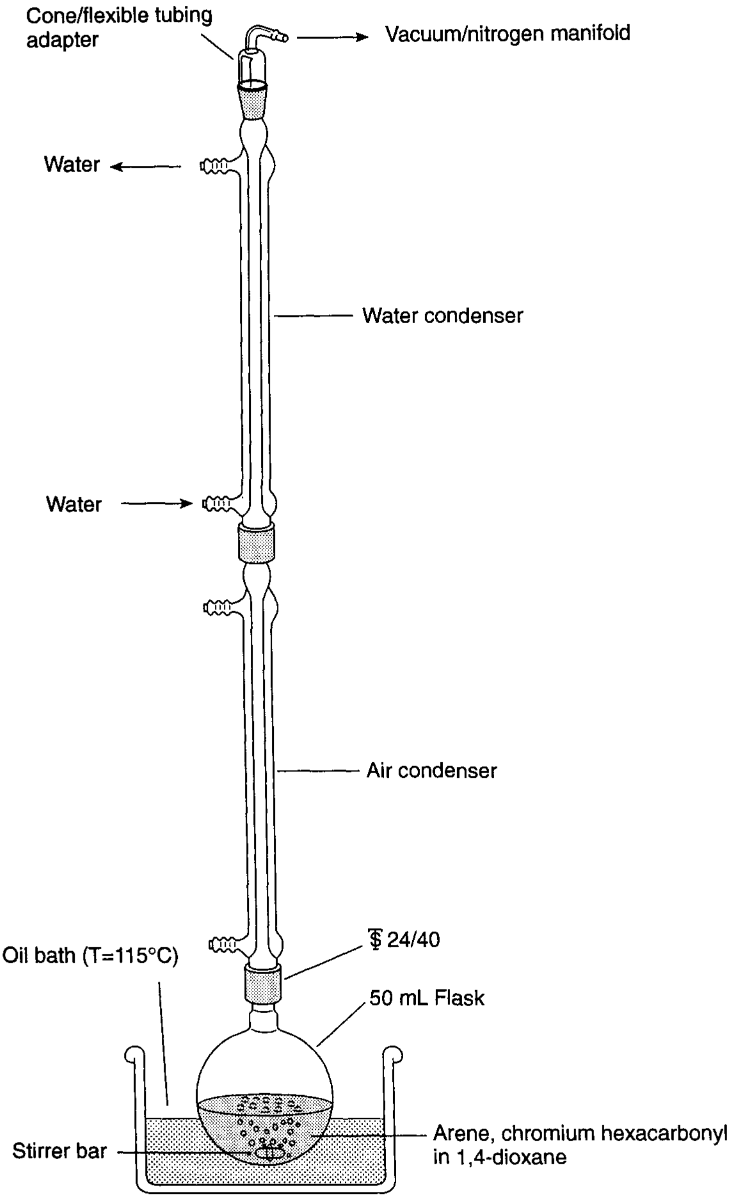
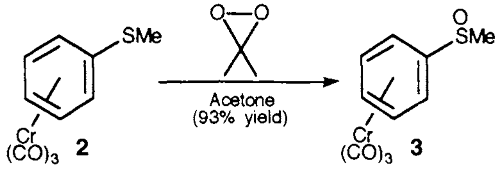


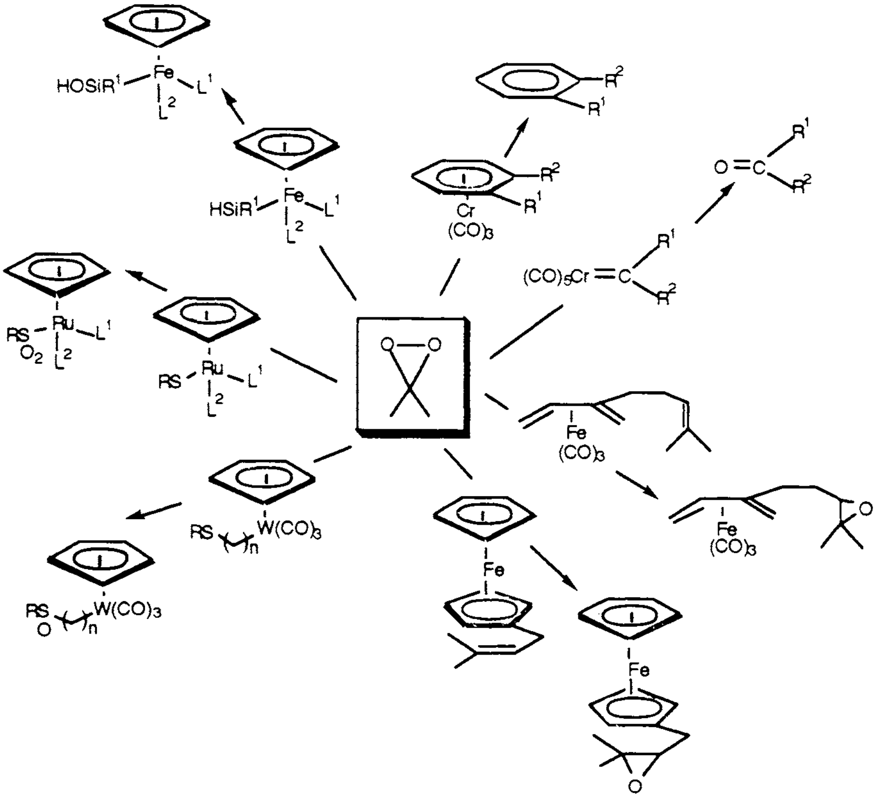
**Fig. 6.2** Apparatus used for the complexation reactions.

The chromium tricarbonyl complex **2** of (methylsulfenyl)benzene is then oxidised to its sulfinyl derivative **3** using dimethyldioxirane (Scheme 6.6).[37,38]

This cyclic peroxide, formed from potassium peroxymonosulfate and acetone[39] and isolated as a 0.09–0.11 M solution in acetone,[40] has undergone rapid development as a useful mild oxidant for a range of organic reactions, including the oxidation of sulfides to sulfoxides. In addition, it is beginning to prove useful for many oxidation reactions involving transition metal complexes, as depicted in Scheme 6.7.[37,38,41,42] An additional major advantage in the use of this reagent is that the only by-product is easily removable acetone.



**Scheme 6.6**



**Scheme 6.7**

## Protocol 2.
## Preparation of dimethyldioxirane solution in acetone[39]

**Caution!** All procedures should be carried out in a fume hood. Disposable vinyl or latex gloves and safety glasses should be worn.
As peroxides may be decomposed when brought in contact with metal utensils (e.g. spatulas), such practice should be avoided.

*Equipment*

- Overhead mechanical stirrer apparatus
- Three-necked, round-bottomed flask (4000 mL)
- Two-necked, round-bottomed flask (250 mL)
- Pyrex funnel
- Solid addition funnel
- U-Tube (i.d. 25 mm)
- Measuring cylinder (volume appropriate for quantity to be handled)
- Cone/flexible tubing adapter
- Thermometer adapter
- Thermometer (−20 to 110°C)
- Joint clips
- Silicone vacuum grease
- Source of nitrogen
- Septum
- Glass bottle (200 mL) for storage of the dioxirane solution

*Materials*

| | |
|---|---|
| • Distilled water, 254 mL | |
| • Acetone,[a] 192 mL | **flammable** |
| • Sodium hydrogencarbonate, 58 g | |
| • Potassium monoperoxysulfate (Oxone®)[b] (FW 614.8), 120 g, 0.195 mol | **oxidant, irritant** |
| • Molecular sieves[c] (4Å) | |
| • Dry ice | |

1. Clean and dry all glassware.
2. Set up the apparatus as depicted in Fig. 6.3 (grease all joints and use clips to secure them).
3. Equip the 'free' neck of the reaction flask with a Pyrex funnel and charge successively with water (254 mL) and acetone (192 mL), the volumes being measured in a measuring cylinder.
4. Remove the Pyrex funnel from the neck of the flask and replace with the solid addition funnel. Add the sodium hydrogencarbonate (58 g) and stir mechanically and vigorously the resulting white suspension.[d]
5. Cool the reaction flask to 0–5°C in an ice–water bath and control the temperature of the reaction mixture with the thermometer.
6. Cool the receiving flask with a dry ice–ethanol or dry ice–acetone bath to −78°C.
7. Keep stirring the suspension vigorously[d] and add in one aliquot of the Oxone® (120 g) through the neck of the reaction flask, which is still fitted with the solid addition funnel. Remove the solid addition funnel after the addition and replace with the thermometer adapter, fitted with the thermometer.

   **Important!** As the reaction is exothermic, it is important to maintain the reaction temperature at 0–5°C.
8. 15 min after the addition, connect the cone/flexible tubing adapter to a water pump and apply a moderate vacuum (80–100 mmHg).

**Protocol 2.** *Continued*

9. Remove the ice–water bath from the reaction flask and allow the temperature of the reaction mixture to rise to 30 °C by means of a warm water bath.
10. Keep stirring vigorously and collect the effluent pale yellow dimethyldioxirane–acetone solution (150 mL, 0.09–0.11 M, 5% yield) in the cooled receiving flask (−78°C). The distillation takes 2–4 h depending on the vacuum applied.
11. When the distillation is over, disconnect the cone/flexible tubing adapter from the water pump and connect it to the nitrogen source.
12. Remove the U-tube and the reaction flask, add molecular sieves to dry the dimethyldioxirane solution through the 'free' neck of the receiving flask, and stopper with a septum.
13. Pour the dimethyldioxirane solution in a small dry bottle, containing molecular sieves (4Å) and previously cooled in a dry ice–ethanol or dry ice–acetone bath at −20°C. Seal with a septum under a nitrogen atmosphere.
14. Store the bottle in a freezer (−20 °C).[e]

[a] Commercial-grade acetone was employed.

[b] Potassium monoperoxysulfate (the triple salt 2 $KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$) was purchased from Aldrich under the trade-name Oxone® and used as supplied. Other commercial sources sell the oxidant under the name Curox® or Caroate®.

[c] The molecular sieves were flame-dried under high vacuum just prior to use.

[d] **Care!** Over-vigorous stirring can cause the reaction mixture to splash up the neck of the flask.

[e] The reagent must be kept cold at all times to avoid decomposition. Once prepared, it can be stored at −20 °C under nitrogen for at least 2 months.

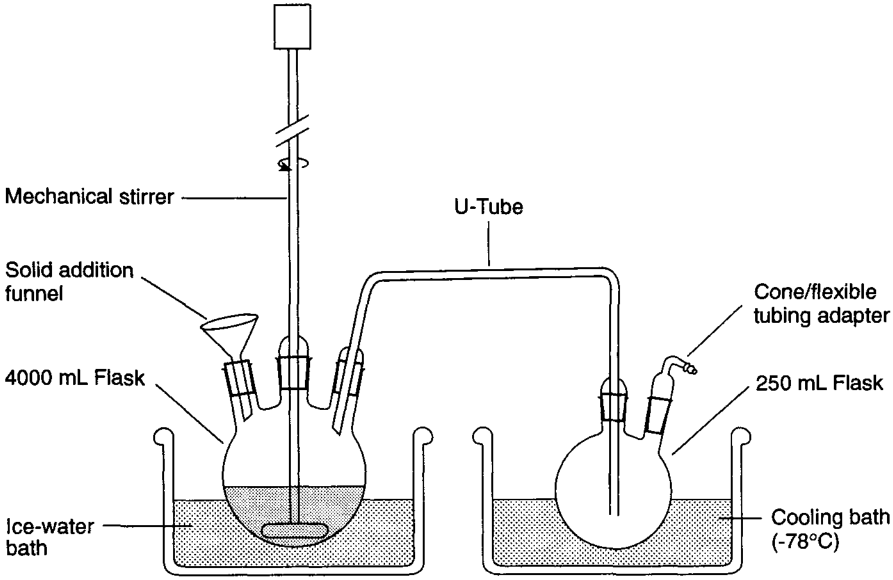


**Fig. 6.3** Apparatus used for the preparation of the dimethyldioxirane solution.

## Protocol 3.
## Iodometric titration of a dimethyldioxirane solution in acetone[40]

**Caution!** All procedures should be carried out in a well-ventilated hood. Disposable vinyl or latex gloves and safety glasses should be worn.

As peroxides are generally decomposed when brought in contact with metal utensils (e.g. spatulas), such practice should be avoided.

**Important!** Due to the slight instability of dimethyldioxirane, the concentration of the solution has to be determined before each experiment. The peroxide content is determined by titration with an aqueous sodium thiosulfate solution, *via* iodine.

(1) Dimethyldioxirane is first reacted with potassium iodide in an acidic medium. The oxidation–reduction reaction involved corresponds to the following half-reactions:

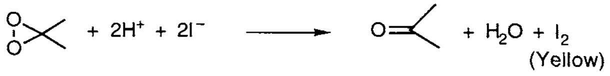
(a) Reduction of dimethyldioxirane to acetone:

(6.9)

(b) Oxidation of iodide to iodine:

$$2I^- \longrightarrow I_2 + 2e^- \qquad (6.10)$$

Adding both half-reactions gives the equation:



(6.11)

(2) The amount of iodine thereby liberated is subsequently titrated by an aqueous sodium thiosulfate solution according to the half-reactions:

(a) Oxidation of thiosulfate anion into tetrathionate anion:

$$2S_2O_3^{2-} \longrightarrow S_4O_6^{2-} + 2e^- \qquad (6.12)$$

(b) Reduction of iodine into iodide:

$$I_2 + 2e^- \longrightarrow 2I^- \qquad (6.13)$$

Adding both half-reactions gives the equation:

$$2S_2O_3^{2-} + \underset{\text{(Yellow)}}{I_2} \longrightarrow \underset{\text{(Colourless)}}{S_4O_6^{2-} + 2I^-} \qquad (6.14)$$

### Protocol 3. *Continued*

The end point is, therefore, indicated by the total disappearance of the characteristic yellow colour of iodine. The formula for calculating the dimethyldioxirane concentration is

$$M_{\text{Dioxirane}} = \frac{1}{2} \cdot \frac{M_{\text{Thiosulfate}} \cdot V_{\text{Thiosulfate}}}{V_{\text{Dioxirane}}} \qquad (6.15)$$

*Equipment*

- Erlenmeyer flask (50 mL)
- Measuring cylinder (volume appropriate for quantity to be handled)
- Graduated pipette (1 mL)
- Pipette filler
- Micro-burette (10 mL)
- Aluminium foil
- Dry ice
- Source of nitrogen

*Materials*

| | |
|---|---|
| • Dimethyldioxirane solution in acetone, 1 mL, *concentration to be determined* | |
| • Acetic acid/acetone solution 3:2, v/v, 2 mL | **corrosive, flammable** |
| • Saturated aqueous potassium iodide solution, 2 mL | **irritant, light sensitive** |
| • Distilled water, 5 mL | |
| • Aqueous $Na_2S_2O_3$ solution (0.01–0.05 M) | **irritant** |

1. Ensure that all glassware is thoroughly clean.
2. Charge the Erlenmeyer flask with a 3:2 mixture of acetic acid–acetone (2 mL).
3. Remove the septum of the bottle containing the dimethyldioxirane solution, cooled in a dry ice–ethanol or dry ice–acetone bath at −20°C. Fill the graduated pipette, equipped with the pipette filler, with the dioxirane solution (1 mL) and add it in one aliquot into the Erlenmeyer flask. Put the septum back on the bottle of dimethyldioxirane and fill it with $N_2$.
4. Add together a saturated aqueous potassium iodide solution (2 mL) and some dry ice to deaerate the mixture. The solution turns immediately dark yellow.
5. Protect the Erlenmeyer flask from light with aluminium foil and store the solution at room temperature for 10 min.
6. During this time, fill the burette with the thiosulfate solution.
7. Add the thiosulfate solution into the Erlenmeyer flask with frequent swirling of the contents of the flask until the yellow colour of iodine disappears. Repeat the same procedure with a second 1 mL aliquot of dimethyldioxirane.

## Protocol 4.
## Synthesis of tricarbonyl[$\eta^6$-(methylsulfinyl)benzene]chromium(0) (Structure 3). Oxidation of tricarbonyl[$\eta^6$-(methylsulfenyl)benzene]chromium(0) (Structure 2) with dimethyldioxirane (Scheme 6.6)

**Caution!** Due to potential toxicity of chromium carbonyl complexes, all procedures should be carried out in a well-ventilated hood. Disposable vinyl or latex gloves and safety glasses should be worn. All procedures are performed anaerobically by using standard vacuum/nitrogen manifold and Schlenk tube techniques. As chromium complexes are unstable in solution when exposed to air and light, the oxidation reaction and subsequent work-up are always carried out under nitrogen in glassware protected with foil.

*Equipment*

- Vacuum/nitrogen manifold (Figs 7.1 and 7.2)
- Magnetic stirrer
- Schlenk tubes (× 2)
- Magnetic stirrer bar (length 1.5 cm)
- Septum
- Pipette filler
- Graduated pipette (volume appropriate for quantity of solution to be used)
- Filter funnel with filter frit (100 mL)
- Schlenk tubes for filtration, saturating solvents with nitrogen and recrystallisation
- Aluminium foil

*Materials*

| | |
|---|---|
| • Chromium complex **2** (FW 260.2), 89 mg, 0.34 mmol | |
| • Dimethyldioxirane solution in acetone,[a] 4.3 mL of a 0.095 M solution, 0.41 mmol, 1.2 equiv | |
| • Acetone, 10 mL + 5 mL | **flammable** |
| • Kieselguhr for filtration | |
| • Dichloromethane for crystallisation | **harmful, irritant, toxic** |
| • Petroleum ether (60-80) for crystallisation | **flammable, harmful** |

1. Clean all glassware and stirrer bars and dry for at least 1 h in a 100°C electric oven before use.
2. Support a Schlenk tube, containing a magnetic stirrer bar, below its side-arm using a clamp and a stand with a heavy base. Attach it to the vacuum/nitrogen manifold *via* its side-arm.
3. Charge the Schlenk tube with sulfide complex **2** (89 mg, 0.34 mmol).
4. Equip the neck of the Schlenk tube with a septum, evacuate and refill with nitrogen (Chapter 7, Protocol 1).
5. Saturate acetone (10 mL) with nitrogen (Chapter 7, Protocol 2) and transfer it into the reaction Schlenk tube *via* a cannula (Chapter 7, Protocol 3).
6. Stir the resulting yellow solution magnetically, cool to −78°C (dry ice–acetone bath temperature) and protect from light using aluminium foil.
7. Saturate some more acetone (5 mL) with nitrogen and cool it in a dry ice–acetone bath at −78°C.

**Protocol 4.** *Continued*

8. Remove the septum of the bottle containing the dimethyldioxirane solution, cooled in a dry ice–ethanol or dry ice–acetone bath at −20°C. Fill the graduated pipette, equipped with the pipette filler, with the dioxirane solution and introduce the volume into the cooled Schlenk tube containing only acetone. Put the septum back on the bottle of dimethyldioxirane and fill it with nitrogen.
9. Transfer dropwise, *via* a narrow cannula, the diluted dimethyldioxirane solution to the solution of the chromium complex **2** cooled to −78°C as follows:
   (a) Interconnect both Schlenk tubes with the cannula, by insertion through septa. The ends should be above the solutions.
   (b) Hold the end of the cannula inserted in the Schlenk containing the chromium complex with a clamp. It should be placed so that the drops can fall directly into the solution.
   (c) Insert a short needle through the septum of the Schlenk containing the chromium complex to make a nitrogen bleed.
   (d) Dip the tip of the cannula into the dimethyldioxirane solution.
   (e) Slowly close the tap of the Schlenk tube containing the chromium complex until the appearance of the first drops. Regulate until the rate is approximately one drop per second.

   **Important!** The reaction is sensitive to the addition rate.
10. When the addition is complete, stir the reaction mixture for 15 min at −78°C.
11. Remove the cooling bath, allow the solution to warm up to room temperature and stir for a further hour. The solution will turn slightly green and cloudy.
12. Concentrate the reaction mixture using the vacuum manifold (Chapter 7, Protocol 2).
13. Prepare a filtration funnel packed with Kieselguhr and dichloromethane. Fill a Schlenk tube with nitrogen for collection of the filtrate and cover with foil.
14. Saturate a little dichloromethane with nitrogen.
15. Dissolve the green-yellow solid in the nitrogen-saturated dichloromethane.
16. Transfer the resulting green-yellow solution into the filtration column by cannula. Rinse the reaction Schlenk tube with nitrogen-saturated dichloromethane and transfer.
17. Flush the column with nitrogen-saturated dichloromethane, apply a nitrogen pressure and collect the yellow solution in the Schlenk tube.
18. Concentrate the yellow filtrate using the vacuum manifold. A yellow powder is obtained.

**19.** Saturate dichloromethane and petroleum ether with nitrogen (Chapter 7, Protocol 2).

**20.** Transfer the nitrogen-saturated dichloromethane *via* a cannula to dissolve the yellow solid.

**21.** Evaporate a small portion of dichloromethane using the vacuum manifold (Chapter 7, Protocol 2) and then add nitrogen-saturated petroleum ether *via* a cannula.

**22.** Concentrate the solution using the vacuum manifold until the appearance of the first crystals.

**23.** Dissolve the crystals using a warm water bath, protect the Schlenk tube with foil and place it in a freezer for 2 days.

**Caution!** Do not use any hot water. The sulfoxide complex is thermally unstable.

**24.** Separate the yellow crystals from the mother liquor by filtration using a filter cannula and collect the mother liquor in a Schlenk tube under nitrogen (Chapter 7, Protocol 3). Wash the crystals with cooled nitrogen-saturated petroleum ether and remove the supernatant solution.

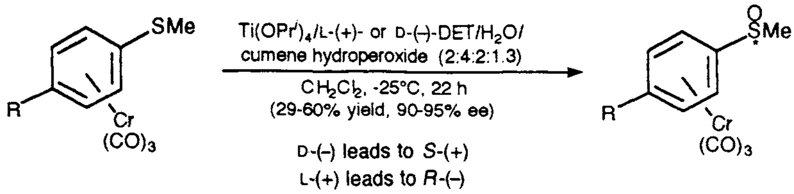
**25.** Dry the crystals at room temperature by applying vacuum for 30 min.

**26.** Repeat the crystallisation with the mother liquor.

**27.** Combine both crystallisation crops (87.5 mg, 0.32 mmol, 93% yield, m.p. = 82–83°C) and keep in a vial protected from light with foil. The product displays appropriate spectroscopic data.[16] The $^1$H NMR spectrum should be recorded on a sample prepared in $CDCl_3$ under nitrogen as described in Protocol 6 of Chapter 7.

[a] The concentration is assessed just before doing the reaction.

An enantioselective version of the reaction described in Protocol 4 has been recently investigated.[43] The asymmetric oxidation of the sulfur centre was performed with the Kagan's modified Sharpless system [1.3 equiv of cumene hydroperoxide in the presence of a $Ti(OPr^i)_4$/diethyl tartrate/$H_2O$ catalyst] and afforded the corresponding sulfinyl-substituted complexes with high enantiomeric purity (Scheme 6.8).

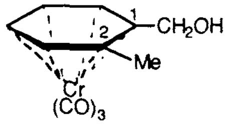


**Scheme 6.8**

## 3. Optically pure or enriched $\eta^6$-arene chromium tricarbonyl complexes

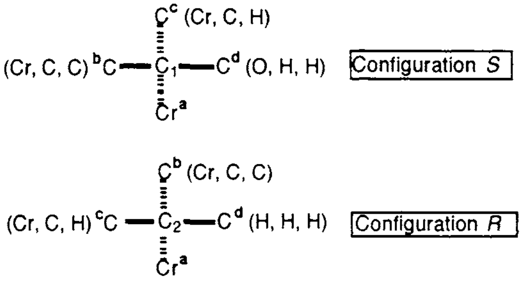
In the last decade a substantial proportion of research has been focussed on the design and implementation of efficient routes to optically active complexes possessing planar chirality.[10] This fact, in concert with both the ability of the chromium tricarbonyl unit to block effectively one face of the aromatic nucleus and its ease of removal, has led to a rapid increase in the use of chiral complexes as intermediates in asymmetric synthesis.[44]

Enantiomeric excesses of benchrotrenic complexes are generally assayed using classical methods such as NMR spectroscopy[10] in the presence of a chiral solvating or shift reagent or by HPLC with a chiral column.[43] Absolute configurations can only be determined unambiguously using X-ray methods or chemical correlations.[10,45] The (*R*) or (*S*) nomenclature used for planar chirality in benchrotrenic complexes derives from an extension of the Cahn–Ingold–Prelog system,[10] which was previously restricted to chiral centres with the classical tetrahedral geometry. The bonds proceeding from the chromium atom to the aromatic ring have to be regarded as single bonds and consequently, the six carbon atoms of the arene can be considered as $sp^3$ carbons. For example, the enantiomer **4** would be termed (1*S*) or (2*R*).



Enantiomer 1*S* (or 2*R*)

**4**

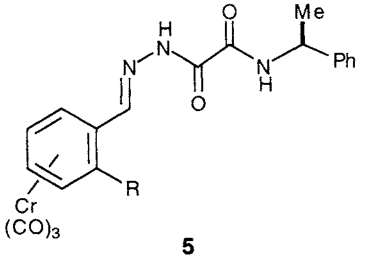


The preparation of enantiopure or enriched complexes possessing planar chirality has been accomplished either by resolution of racemic mixtures or by asymmetric syntheses. Reported methods for the resolution of planar chirality include both chemical and kinetic resolution procedures, whilst reported asymmetric syntheses of enantiomerically pure or enriched benchrotrenic complexes include enantioselective *ortho*-deprotonations with chiral lithium amide bases, and the transfer of side chain chirality onto the arene ring mediated by diastereoselective *ortho*-nucleophilic additions and *ortho*-metalations.

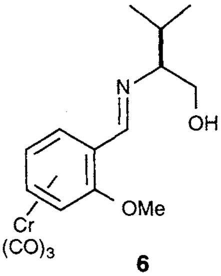
### 3.1 Chemical resolution

A wide range of racemic acid and amine complexes have been resolved through the crystallisation of diastereoisomeric ammonium salts obtained with optically pure chiral amines [brucine, quinidine, cinchonidine and (−)-α-methylbenzylamine] and optically pure chiral acids [(+)-camphorsulfonic acid], respectively.[10] From a practical point of view, this method is, however, rather unattractive, due to the lengthy and tedious nature of the crystallisation techniques involved.

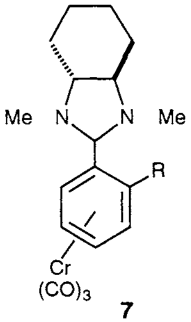
More versatile complexes such as aryl aldehyde complexes have been resolved by the chromatographic separation of diastereoisomeric derivatives such as semioxamazones (**5**) prepared with (*S*)-(−)-5-(α-phenylethyl) semioxamazide,[10] imines (**6**) prepared from L-valinol[32] or aminals (**7**) prepared from chiral diamines.[46] Separation is, in general, easy and efficient because the complexes involved are highly coloured; in addition, the subsequent hydrolysis to release the aldehyde functional group proceeds quantitatively.



**5**



**6**



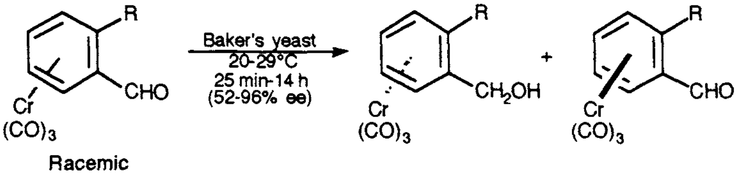
**7**

Finally, chromatography using chiral solid supports is showing considerable promise for the separation of racemic mixtures.[47]

## 3.2 Kinetic resolution

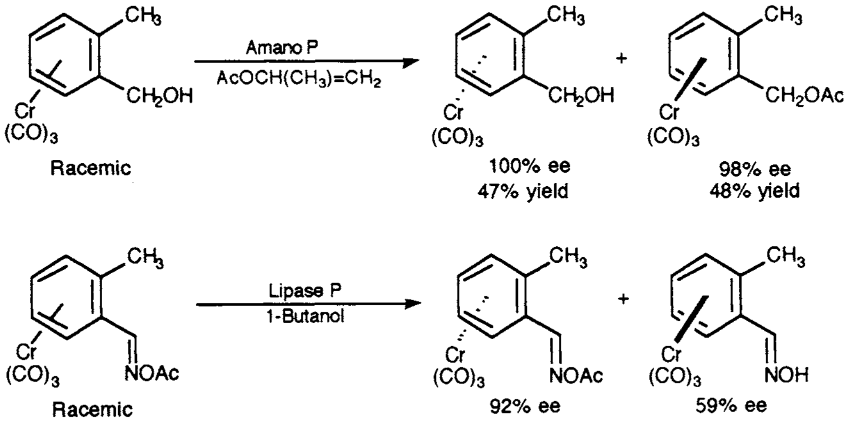
Since a 1,2- or 1,3-disubstituted arene complex possesses planar chirality and can exist in two enantiomeric forms, kinetic resolution may sometimes be achieved. Both enantiomers react at different rates, thereby allowing a total or partial resolution.[48,49] This technique does, however, require an effective method of monitoring the reaction.

Aromatic aldehyde complexes have been partially resolved by enantioselective reduction using baker's yeast in the presence of D-glucose (Scheme 6.9). The enantiomeric excesses for the alcohol obtained and the 'unchanged' aldehyde enantiomer ranged from moderate to high (52–96% ee).[50] It should be noted, however, that kinetic resolutions using baker's yeast are limited by the low water solubility of the substrates and the necessity for aerobic conditions. Better results were achieved using another reductive resolution procedure, mediated by the horse liver alcohol dehydrogenase (HLADH) and NADH system. Optical purities as good as 100% were obtained.[51]



**Scheme 6.9**

Lipases have been utilised for the resolution of benzyl alcohol derivatives[52,53] and (benzaldehyde oxime) complexes[54] (Scheme 6.10). The reverse reaction (transesterification of the corresponding esters with an alcohol) was also enantioselectively catalysed by these microorganisms.[53,54] These methods, involving lipases, have the advantage of being performed under anaerobic conditions, in an organic solvent (toluene, isopropenyl acetate, *n*-butanol) with the exclusion of light. In addition, the separation of the microbial catalyst is performed by a single filtration.



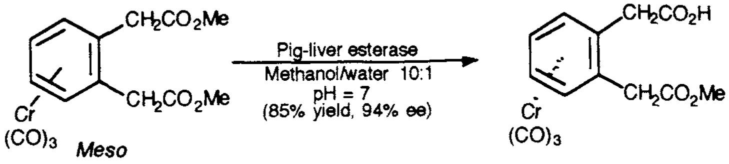
**Scheme 6.10**

## 3.3 Desymmetrisation of *meso*-complexes

Starting from *meso*-complexes (achiral species), benchrotrenic planar chirality can be generated. The differentiation of the enantiotopic substituents on the aromatic ring has been achieved using enzymes or a chiral palladium catalyst.

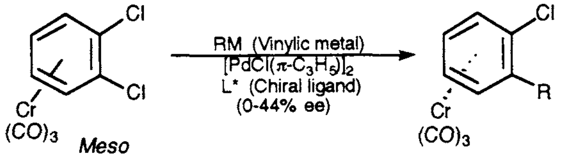
*Meso*-benzylic diester complexes have been hydrolysed using pig liver esterase to give rise to the corresponding mono-ester analogue with high enantiomeric purity (Scheme 6.11).[55]

The asymmetric cross-coupling of the *meso*-tricarbonyl (*ortho*-dichlorobenzene)chromium complex with a wide range of vinylic metals in the



**Scheme 6.11**

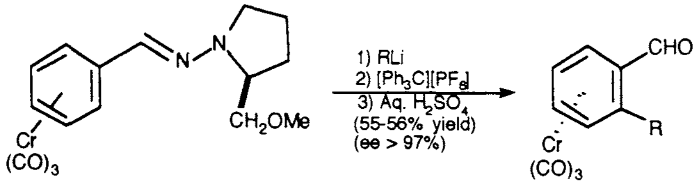
presence of a chiral palladium catalyst gave the corresponding mono-coupling products in up to 44% ee (Scheme 6.12).[56]



**Scheme 6.12**

## 3.4 Diastereoselective nucleophilic addition

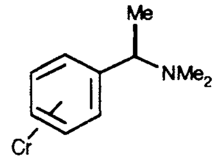
*Ortho*-substituted benzaldehyde complexes have been prepared in high enantiomeric purity (97% ee), and in a one-pot sequence, from an optically pure hydrazone derivative, readily available from $\eta^6$-benzaldehyde chromium tricarbonyl and SAMP [(*S*)-1-amino-2-(methoxymethyl)pyrrolidine].[57] The novelty derives from the combined use of a diastereoselective *ortho*-addition reaction of an organolithium nucleophile and a hydride abstraction with a triphenylmethyl cation. The subsequent acid hydrolysis serves to remove the hydrazone group, thus liberating the aldehyde functionality (Scheme 6.13).



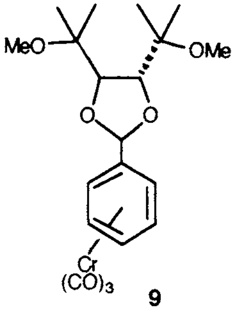
**Scheme 6.13**

## 3.5 Diastereo- or enantioselective *ortho*-metalations

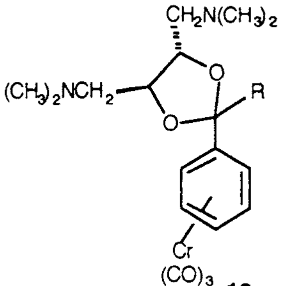
The directed *ortho*-lithiation of complexes substituted by an optically pure chiral side chain, followed by quenching with an electrophile, currently provides the best method for the preparation of enantiomerically enriched *ortho*-disubstituted benchrotrenic complexes. Examples of such chiral side chains are the (1-dimethylaminoethyl) group (**8**),[17] cyclic acetals (**9**)[33] and cyclic ketals (**10**).[58] In addition to being good substrates for *ortho*-lithiation, these chiral structural types are readily available in either optically active form from inexpensive and commercially available sources (α-phenethylamine and diethyl tartrate).



**8**

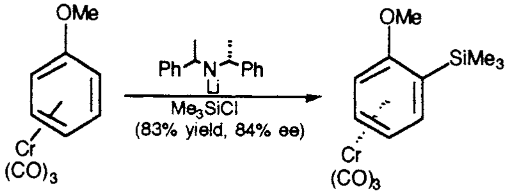


**9**



**10**

The very first results concerning the enantioselective *ortho*-lithiation of benchrotenic complexes mediated by chiral lithium bases have been reported by the groups of Simpkins[59] and Kündig.[60] Enantiomeric excesses of up to 84% were obtained (Scheme 6.14).



**Scheme 6.14**

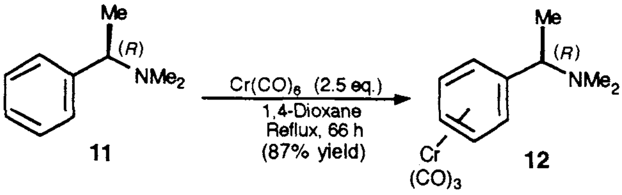
The next two protocols describe the use of the directed *ortho*-lithiation reaction for the stereoselective synthesis of an optically pure α-phenylethylamine derivative possessing planar chirality and stereogenic centres at both benzylic positions.

The conversion[61] of *N*,*N*-dimethyl-α(*R*)-phenylethylamine **11** into its chromium tricarbonyl derivative **12** was accomplished in 87% yield (Scheme 6.15) by thermolysis under standard conditions [$Cr(CO)_6$/1,4-dioxane/reflux/66 h].

## Protocol 5.

## Synthesis of tricarbonyl[*N,N*-dimethyl-α(*R*)-phenylethylamine] chromium(0) (Structure 12). Complexation of chiral complex 11 by thermolysis with chromium hexacarbonyl

**Caution!** Due to the potential toxicity of chromium carbonyl complexes, all procedures should be carried out in a fume hood. Disposable nitrile or latex gloves and safety glasses should be worn. All procedures are performed excluding air by using standard vacuum/nitrogen manifold and Schlenk tube techniques. Although chromium arene complexes are generally stable in air in a crystalline state for long periods, many have been found to decompose in solutions on exposure to air under laboratory light. Consequently, all glassware for complexation, filtration and crystallisation should be covered with aluminium foil.



**Scheme 6.15**

### *Equipment*

- Vacuum/nitrogen manifold (Figs 7.1 and 7.2)
- Stirrer hot plate
- Single-necked, round-bottomed flask (B24, 50 mL)
- Liebig condenser used as an air condenser
- Liebig condenser used as a water condenser
- Side-arm adapter
- Cone/flexible tubing adapter
- Oil bath
- Contact thermometer (up to 200°C)
- Magnetic stirrer bar (length 1.5 cm)
- Septum
- Aluminium foil
- All glass syringe (volume appropriate for quantity of solution to be transferred)
- Needle (6", 20 or 22 gauge)
- Joint clips (× 3)
- Silicone vacuum grease
- Schlenk tubes for saturating solvents with nitrogen and recrystallisation (× 3)
- Single-necked, round-bottomed flask (B24, 250 mL) for filtration
- Filter column with filter frit (100 mL)

### *Materials*

| | |
|---|---|
| • Dry 1,4-dioxane,[a] 60 mL + 2 mL | **flammable, toxic, possible carcinogen, may form explosive peroxides** |
| • Chromium hexacarbonyl[b] (FW 220.1), 5.5 g, 25 mmol | **volatile, highly toxic** |
| • Chiral amine[c] **11** (FW 149.2), 1.49 g, 10 mmol | **irritant, air sensitive** |
| • Diethyl ether for filtration | **flammable, irritant** |
| • Kieselguhr[d] for filtration | |
| • Diethyl ether for crystallisation | **flammable** |
| • *n*-Hexane for crystallisation | **flammable, irritant** |
| • $CDCl_3$ for NMR samples | **highly toxic, cancer-suspect agent** |

**Protocol 5.** *Continued*

1. Clean all glassware, syringes, needles and the stirrer bar and dry for at least 1 h in a 100°C electric oven before use.
2. Prepare an oil bath at 115°C, controlling the temperature using a contact thermometer.
3. Set up apparatus as in Fig. 6.1; whilst the glassware is still hot, evacuate it and refill it with nitrogen (Chapter 7, Protocol 1).
4. Remove the septum on the side-arm adapter, reduce the nitrogen to a gentle flow and introduce chromium hexacarbonyl (5.5 g, 25 mmol) into the flask through the adapter neck with the aid of a rolled filter paper. Put the septum back on the adapter.
5. Evacuate the flask and refill with nitrogen. Protect the flask from light using foil.
6. Assemble the syringes and needles and allow to cool to room temperature.
7. Fill the syringe with dioxane (60 mL) and charge the flask by injecting through the septum on the adapter.
8. Dissolve the chiral amine **11** (1.49 g, 10 mmol) in dioxane (2 mL) in a vial and inject the resulting colourless solution into the reaction flask.
9. Assemble both condensers and the cone/flexible tubing adapter whilst hot as shown in Fig. 6.2 (grease the joints carefully and use the green clips to secure them); then connect the cone/flexible tubing adapter to the vacuum/nitrogen manifold and turn on the flow of nitrogen.
10. Remove the side-arm adapter from the flask and replace with the assembled condensers (use a green clip to secure the joint) (see Fig. 6.2).
11. Pass a moderate flow of water through the top condenser, wire the rubber tubing and begin stirring.
12. Apply vacuum till vigorous bubbling occurs and refill the flask with nitrogen (Chapter 7, Protocol 2). Repeat a total of 10 times.
13. Immerse the mixture in the oil bath and generously wrap the apparatus with aluminium foil to minimise exposure to light.
14. After a few minutes, reflux will begin. Leave the solution refluxing for 66 h.[e] The solution turns gradually from pale yellow to orange.
15. Remove the oil bath and allow the solution to cool down in an ice-water bath (15 min). Unreacted chromium hexacarbonyl will precipitate out of the solution.[f]
16. During this time, pack the filter column with a short pad of Kieselguhr in diethyl ether.[g] Place a round-bottomed flask (250 mL), covered with foil, under the column for collection of the filtrate.

17. Disconnect the condensers from the water and nitrogen sources and replace the assembled condensers with a side-arm adapter with a septum on top, already connected to the nitrogen source (Fig. 6.1).
18. Transfer the solution into the filter column *via* a cannula (Chapter 7, Protocol 4), dissolve the residue in the reaction flask in diethyl ether and transfer.
19. Flush the column with diethyl ether, apply a nitrogen pressure and collect the yellow solution in the flask protected with foil (Chapter 7, Protocol 5).
20. Concentrate the resulting orange filtrate under reduced pressure (20 mmHg) by the means of a rotary evaporator *located in a fume hood* [the use of a hot water bath (60 °C) is necessary to remove efficiently the dioxane]. Store the resulting orange-yellow solid under an inert atmosphere.
21. Saturate some diethyl ether and *n*-hexane with nitrogen (Chapter 7, Protocol 2). Evacuate a Schlenk tube and refill with nitrogen.
22. Dissolve the crude yellow solid in the minimum amount of nitrogen-saturated diethyl ether and transfer the resulting yellow solution into the empty Schlenk tube *via* a filter cannula. If any decomposition is noticed at this stage, the solution may be filtered through a small bed of Kieselguhr.
23. Rinse the flask with nitrogen-saturated diethyl ether and transfer as in the previous step.
24. Use the vacuum manifold to remove a small amount of diethyl ether and add nitrogen-saturated *n*-hexane.
25. Concentrate the solution using the vacuum manifold until the first solid appears.
26. Dissolve the crystals using a hot water bath, protect the Schlenk tube with foil and place it in a freezer (−20 °C) for 2 days.
27. Separate the yellow crystals from the mother liquor by filtration using a filter cannula and collect the mother liquor in a Schlenk tube under nitrogen.
28. Wash the crystals with nitrogen-saturated *n*-hexane, withdraw the supernatant. Dry the yellow crystals under vacuum.
29. Repeat the crystallisation procedure with the mother liquor.
30. Combine both crystallisation crops [2.48 g, 8.7 mmol, 87% yield, m.p. 43 °C, $[\alpha]^{24}_{D}$ +14.4° ($c$ = 0.78, $CHCl_3$)] and keep in a vial covered with aluminium foil. The crystals display appropriate spectroscopic data.[17] The $^1$H NMR spectrum should be recorded on a sample prepared in $CDCl_3$ under nitrogen (Chapter 7, Protocol 6).

[a] 1,4-Dioxane is purified by distillation under nitrogen from calcium hydride and is then stored under nitrogen over molecular sieves (4Å) in a bottle protected from light.

[b] Chromium hexacarbonyl is purchased from Strem Chemical Company and is used as received. It can be weighed in air as it is relatively air-stable and non-volatile. The usual precautions appropriate for a potentially toxic metal carbonyl should be employed, but the low volatility makes handling relatively easy.

[c] The optically pure amine **11** is purchased from Fluka but is relatively expensive. It can be prepared[59] in a single step from α(*R*)-phenylethylamine, which is much cheaper.

**Protocol 5.** *Continued*

[d] Kieselguhr is supplied by BDH.

[e] During the complexation reaction, carbon monoxide is slowly evolved. Hence, gas evolution will be observed with the bubbler attached to the vacuum/nitrogen manifold.

If before 66 h of reflux, the reaction mixture develops a green colour, which signifies decomposition, stop the heating and carry out the work-up. The decomposition is catalytic in nature.

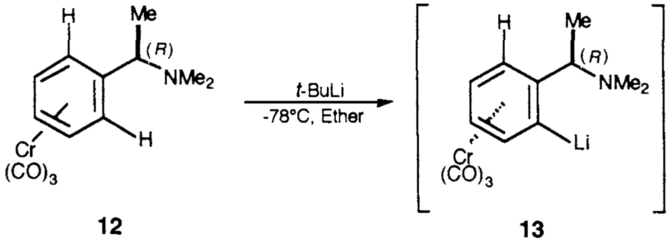
[f] Unreacted chromium hexacarbonyl is destroyed in a well-ventilated hood by oxidation with bleach. If a green residue remains on the inside walls of the glassware, wash with nitric acid.

**Important!** Do not dispose of these washings in a sink.

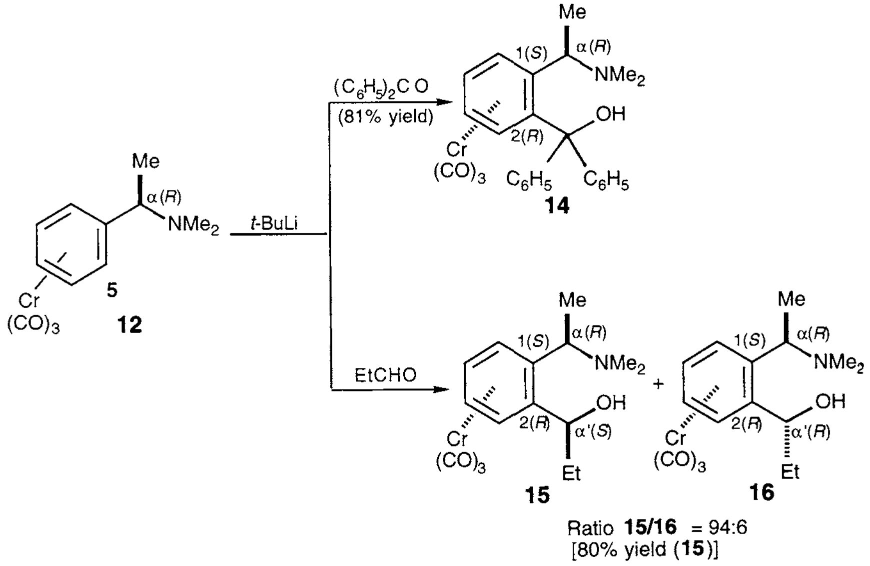
[g] Diethyl ether is used as obtained for the entire filtration sequence.

---

Treatment of complex **12** with *t*-butyllithium in ether at −78 °C led to the exclusive deprotonation at one of the two diastereotopic *ortho* positions and hence to the formation of the lithio compound **13** (Scheme 6.16).



**Scheme 6.16**



**Scheme 6.17**

Subsequent quenching with benzophenone afforded exclusively the Ar(1*S*, 2*R*)-α(*R*) diastereoisomeric complex **14** in 81% yield. A similar reaction with propanal introduces an additional stereogenic centre (in the α′ side-chain position) and thus a mixture of two epimers **15** and **16** was obtained, in a ratio of 94:6 (Scheme 6.17).[17] Their configurations were Ar(1*S*,2*R*)-α(*R*)-α′(*S*) and Ar(1*S*,2*R*)-α(*R*)-α′(*R*), respectively. Column chromatography on silica gel, followed by crystallisation led to the isolation of the major diastereoisomer **15** in 80% yield.

---

## Protocol 6.
## Synthesis of Ar(1*S*,2*R*)-tricarbonyl{1-[α(*R*)-(*N*,*N*-dimethylamino)ethyl]-2-[α′(*S*)-hydroxypropyl]benzene}chromium(0) (Structure 15). *Ortho*-lithiation of a chiral complex (Structure 12) followed by quench with propanal (Scheme 6.17)

**Caution!** When using chromium tricarbonyl complexes and *t*-BuLi, all procedures should be conducted in a well-ventilated hood, using standard vacuum/nitrogen line and Schlenk tube techniques. Disposable vinyl or latex gloves and safety glasses should be worn. As benchrotrenic complexes are unstable in solution when exposed to air and light, the deprotonation reaction and subsequent work-up are carried out in glassware covered with foil.

### *Equipment*

- Vacuum/nitrogen manifold (Figs 7.1 and 7.2)
- Magnetic stirrer
- Schlenk tube
- Magnetic stirrer bar (length 1.5 cm)
- Septum
- All glass syringe (volume appropriate for quantity of solution to be transferred)
- Needle (6″, 20 or 22 gauge)
- Filter column with filter frit (100 mL)
- Schlenk tubes for filtration, saturating solvents with nitrogen and recrystallisation
- Aluminium foil
- Dewar or cooling bath

### *Materials*

| | |
|---|---|
| • Chiral complex **12** (FW 285.2), 100 mg, 0.35 mmol | |
| • Dry diethyl ether,[a] 5 mL + 0.5 mL | **flammable, irritant** |
| • *t*-BuLi,[b] 0.18 mL, 2.3 M in pentane, 0.42 mmol | **air/moisture sensitive, corrosive** |
| • Propanal[c] (FW 58.1), 31 mg, 0.53 mmol | **flammable, irritant** |
| • Technical diethyl ether for extraction | **flammable, irritant** |
| • Saturated aqueous ammonium chloride solution | **irritant, toxic** |
| • Saturated brine | |
| • Anhydrous magnesium sulfate for drying | |
| • Silica gel for chromatography, 4 g | **irritant, dust** |
| • Diethyl ether for column chromatography and crystallisation | **flammable, irritant** |
| • *n*-Hexane for column chromatography and crystallisation | **flammable, irritant** |

1. Clean all glassware, syringes, needles and the stirrer bar and dry for at least 4 h in a 100 °C electric oven before use.
2. Support a Schlenk tube, containing a magnetic stirrer bar, below its side-

**Protocol 6.** *Continued*

arm, using a clamp and a stand with a heavy base; attach the Schlenk tube to the vacuum/nitrogen manifold *via* its side-arm.

3. Charge the Schlenk tube with chiral complex **12** (100 mg, 0.35 mmol) and fit the neck of the Schlenk tube with a septum.
4. Evacuate and refill with nitrogen (Chapter 7, Protocol 1).
5. Add nitrogen-saturated dry diethyl ether (5 mL) and begin stirring the resulting yellow solution.
6. Cool the solution in a dry ice–acetone bath at −78°C and protect from light using aluminium foil.
7. Assemble the syringes and needles whilst hot and allow to cool to room temperature in a desiccator.
8. Fill a syringe with *t*-butyllithium in pentane (0.18 mL, 2.3 M in pentane, 0.42 mmol) (Chapter 3, Protocol 5, step 5) and add dropwise to the solution of complex **12** over a period of 5 min, keeping the temperature of the cold bath at −78°C.
9. Allow the bath temperature to warm up to −40°C over 40 min.
10. While maintaining the bath temperature at −40°C, add *via* a syringe propanal (31 mg, 0.53 mmol), previously dissolved in dry diethyl ether (0.5 mL).
11. Allow the mixture to warm to −10°C over 40 min with stirring.
12. Quench with degassed aqueous ammonium chloride solution and add nitrogen-saturated diethyl ether.
13. Remove the aqueous layer *via* a cannula (Chapter 7, Protocol 4).
14. *Wash the ethereal layer with nitrogen-saturated brine, removing the resulting* aqueous layer *via* a cannula. Dry the organic layer over anhydrous magnesium sulfate.
15. Filter into a Schlenk tube *via* a filtering cannula and concentrate using the vacuum line to give an orange residue.
16. Apply the residue to a silica gel column using a 1:4 mixture of diethyl ether and *n*-hexane. Elute with the combination of solvents (Chapter 7, Protocol 5).
17. Concentrate using the vacuum line.
18. Saturate diethyl ether and *n*-hexane with nitrogen and dissolve the product in the minimum amount of nitrogen-saturated diethyl ether.
19. Add nitrogen-saturated *n*-hexane and concentrate the yellow solution using the vacuum manifold until the first solid appears.
20. Dissolve the crystals using a warm water bath, protect the Schlenk tube with foil and place it in a freezer (−20°C) for 2 days.
21. Separate the yellow crystals from the mother liquor by filtration using a filter cannula and collect the mother liquor in a Schlenk tube under nitrogen.

22. Wash the crystals with cold nitrogen-saturated *n*-hexane and withdraw the supernatant. Dry the yellow crystals under reduced pressure.
23. Repeat the crystallisation procedure with the mother liquor.
24. Combine both crystallisation crops [96 mg, 0.28 mmol, 80% yield, m.p. 62°C, $[\alpha]^{24}_{D}$ + 13.5° ($c$ = 0.66, $CHCl_3$)] and keep in a vial protected from light with aluminium foil. The product displays appropriate spectroscopic and chiroptical data.[17] The $^1H$ NMR spectrum should be recorded on a sample prepared in $CDCl_3$ under nitrogen (Chapter 7, Protocol 6).

[a] Distil diethyl ether from lithium aluminium hydride or sodium benzophenone ketyl under an inert atmosphere (nitrogen or argon) and use immediately.

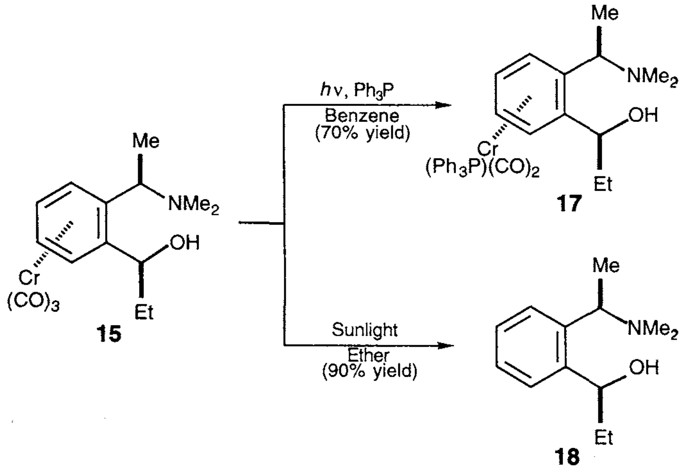
[b] **Be careful!** *t*-BuLi ignites in contact with air. Wash the syringe just after use with dilute hydrochloric acid, water and acetone, respectively.

[c] Propanal was purchased from Aldrich and distilled just prior to use.

---

The optically pure complex **15** (Scheme 6.17), generated in Protocol 6, may be subjected to additional further transformations.

Photoirradiation of complex **15** in benzene solution with a high-pressure mercury lamp in the presence of triphenylphosphine induces ligand exchange and leads to the formation of the dicarbonyltriphenylphosphine analogue **17** (Scheme 6.18) in 70% yield, as described in Protocol 7.



**Scheme 6.18**

Decomplexation of complex **15** by exposure to sunlight in ethereal solution affords the optically active free amino alcohol **18** in 90% yield, as described in Protocol 8. It is worth noting that recomplexation of this compound **18** by a ligand-transfer reaction with $\eta^6$-naphthalene chromium tricarbonyl did not give rise to the precursor **15** but to its diastereoisomeric complex in which the opposite face of the ring is coordinated to the chromium moiety.[17] In this case, the direct complexation reaction and deprotonation/alkylation sequence gave complementary results.

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## Protocol 7.
## Synthesis of Ar(1*S*,2*R*)-dicarbonyltriphenylphosphine{1-[α(*R*)-(*N*,*N*-dimethylamino)ethyl]-2-[α′(*S*)-hydroxypropyl]}benzene (Structure 17). Photoirradiation of chromium tricarbonyl complex (Structure 15) in the presence of triphenylphosphine (Scheme 6.18)

**Caution!** Ultraviolet light is extremely dangerous to the eyes and also harmful to the skin. The apparatus should be situated in a fume hood with aluminium foil wrapped around it (this additionally serves as a light reflector). Flexible tubing for cooling water should be wired on and a suitable cut-out device for the lamp incorporated into the circuit. Disposable vinyl or latex gloves and safety glasses should be worn. Benzene is toxic; contact with the liquid should be avoided.

### *Equipment*

- Vacuum/nitrogen manifold (Figs 7.1 and 7.2)
- Quartz vessel [Model UM-103B-B, Ushio electric inc. (Japan)]
- High-pressure mercury lamp[a]
- Aluminium foil
- Filter column with filter frit for filtration and column chromatography
- Schlenk tubes for filtration, saturating solvents with nitrogen and column chromatography
- Magnetic stirrer bar

### *Materials*

| | |
|---|---|
| • Chromium complex **15** (FW 343.2), 200 mg, 0.58 mmol | |
| • Triphenylphosphine[b] (FW 262.3), 224 mg, 0.86 mmol | **harmful, irritant** |
| • Benzene,[c] 15 mL | **highly flammable, cancer-suspect agent, highly toxic** |
| • Kieselguhr[d] | |
| • Silica gel for flash chromatography, 5 g | **irritant, dust** |
| • *n*-Hexane for flash chromatography | **flammable, irritant** |
| • Diethyl ether for flash chromatography | **flammable, irritant** |

1. Ensure that all glassware and the magnetic stirrer bar is thoroughly clean and dried.
2. Equip the reactor vessel with the magnetic stirrer bar and support it with a clamp and a stand with a heavy base.
3. Connect to water and insert the lamp.
4. Introduce triphenylphosphine (224 mg, 0.86 mmol), complex **15** (200 mg, 0.58 mmol) and benzene (15 mL) successively and surround the whole apparatus with aluminium foil (Fig. 6.4).
5. Remove dissolved oxygen by passing nitrogen through the reaction solution for about 1 h.

   **Caution!** A nitrogen atmosphere must be maintained throughout the experiment.

6. Switch the lamp on and irradiate for 30 min.
7. Switch the lamp off, remove the lamp from the vessel and disconnect from the water source.
8. Pack the filter column with a short pad of Kieselguhr in diethyl ether,[e] and fill a Schlenk tube, for collection of the filtrate, with nitrogen.
9. Pour the solution onto Kieselguhr and filter by applying a nitrogen pressure and washing through with diethyl ether.
10. Concentrate the resultant filtrate using the vacuum manifold.[c]
11. Apply the residue to a silica gel column using a 1:4 mixture of diethyl ether and *n*-hexane. Elute with the same combination of solvents (Chapter 7, Protocol 5). After concentration under reduced pressure, complex **17** is obtained as a yellow oil [211 mg, 0.3 mmol, 70% yield, $[\alpha]^{25}_{D}$ + 5.6° ($c$ = 0.86, $CHCl_3$)] which displays appropriate spectroscopic and chiroptical data.[17] The $^{1}H$ NMR spectrum should be recorded on a sample prepared in $CDCl_3$ under nitrogen as described in Protocol 6 of Chapter 7.

---

[a] The high-pressure mercury lamp [Model UM-102, Ushio Electric Inc. (Japan)] emits the UV spectrum from about 200 to 1400 nm.

[b] Triphenylphosphine was purchased from Wako Pure Chemical Industries (Osaka) and used as received.

[c] **Caution!** Keep solutions contaminated with benzene in closed bottles.

[d] Kieselguhr is supplied by BDH.

[e] Diethyl ether is used as obtained for the filtration step.

## Protocol 8.

## Synthesis of 1-[α(*R*)-(*N,N*-dimethylamino)ethyl]-2-[α′(*S*)-hydroxypropyl]benzene (Structure 18). Air-oxidation of complex (Structure 15) (Scheme 6.18)

**Caution!** All procedures involving chromium complexes should be carried out in a well-ventilated hood. Disposable vinyl or latex gloves and safety glasses should be worn.

### *Equipment*

- Magnetic stirrer
- Single-necked, round-bottomed flask (100 mL)
- Magnetic stirrer bar (length 1.5 cm)
- Condenser
- Chromatography column

### *Materials*

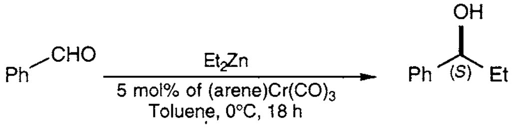
| | |
|---|---|
| • Chiral complex **15** (FW 343.2), 400 mg, 1.17 mmol | |
| • Diethyl ether, 50 mL | **flammable, irritant** |
| • Celite for filtration | |
| • Diethyl ether for filtration | |
| • *n*-Hexane for flash chromatography | **flammable, irritant** |
| • Diethyl ether for flash chromatography | **flammable, irritant** |
| • Silica gel for flash chromatography, 4 g | **irritant, dust** |

**Protocol 8.** *Continued*

1. Ensure that all glassware is clean and dried and support the flask using a clamp and a stand with a heavy base.
2. Charge the flask successively with the stirrer bar, complex **15** (400 mg, 1.17 mmol) and dry diethyl ether (50 mL).
3. Equip the neck of the flask with a water condenser and begin stirring the resulting yellow solution.
4. Stir the solution exposed to light under air for 3 h. The colour of the mixture fades to pale yellow. (Disappearance of the yellow colour signifies decomplexation. This is accompanied by the formation of a green precipitate of chromium oxides.)
5. Disassemble the flask and the condenser.
6. Filter the mixture through Celite under suction to remove the inorganic precipitate and rinse the flask and the filter cake with diethyl ether (3 × 15 mL).
7. Concentrate the filtrate under reduced pressure by means of a rotary evaporator (25 °C, 20 mmHg).
8. Load the residual oil onto a flash silica gel column using a 1:4 mixture of diethyl ether and *n*-hexane. Elute the column with the same combination of solvents to obtain pure ligand **18** (186 mg, 1.06 mmol, 90% yield) as a colourless oil, which displays appropriate spectroscopic data.[17]

---

Several reports of the use of complexes **14**, **15** and **16** or similar substrates as chiral catalysts or auxiliaries have been published. In one example, 5 mol% of the complex **16** catalysed the addition of diethylzinc to benzaldehyde to afford (*S*)-1-phenylpropan-1-ol in 97% yield and 96% ee (Scheme 6.19).[17] Using complexes **14** and **15**, samples of the same enantiomer were produced with an enantioexcess of 93% ee (the isolated yields were 83% and 87%, respectively). By comparison, the corresponding chromium-free derivative **18** resulted in only 24% ee to give the (*S*)-alcohol.



**Scheme 6.19**

In a second example, the conjugate addition of diethylzinc to chalcone in the presence of a catalyst generated from Ni(acac)$_2$ and a chromium complex was investigated.[62] Using 1 mol% of Ni(acac)$_2$ and 10 mol% of complex **14**, the (*R*)-conjugate addition ketone was obtained in 66% yield and in 36% ee (Scheme 6.20). The asymmetric induction is highly dependent on the amount

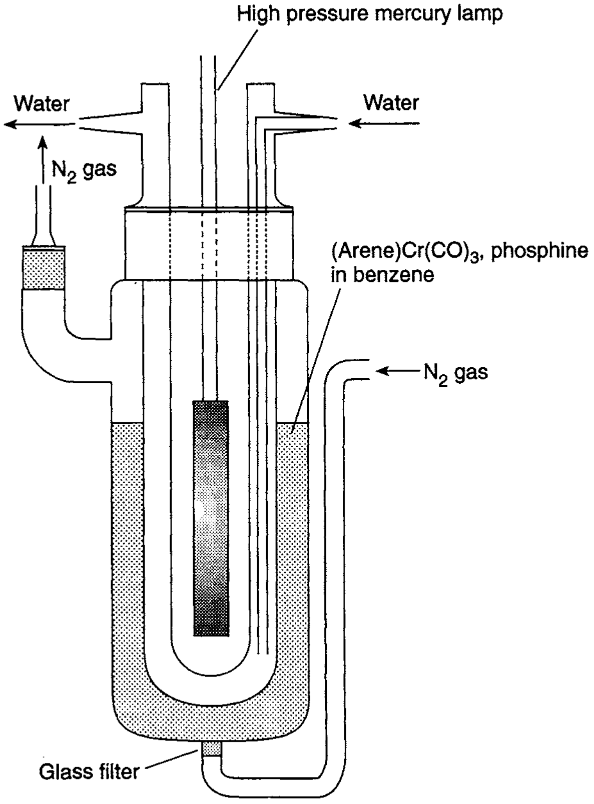
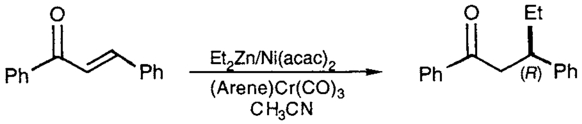
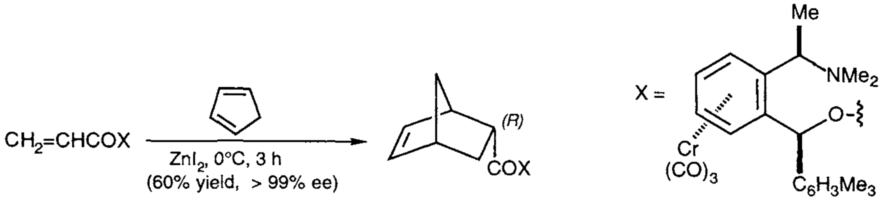


**Fig. 6.4** Apparatus used for the photo-irradiation reaction.

of the chiral catalyst used: the enantioselectivity increased to 62% ee with 5 mol% of the catalyst, and to 78% ee under stoichiometric conditions.



**Scheme 6.20**



**Scheme 6.21**

Finally, the corresponding acrylate derivatives have been reported to undergo stereoselective Lewis acid-catalysed Diels-Alder cycloadditions (Scheme 6.21).[63]

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# 7

# General techniques for handling air-sensitive compounds

NATHALIE GUILLO and STÉPHANE PERRIO

The manipulation and purification of many of the compounds described in this *Practical Approach* volume are best performed using a vacuum/inert gas manifold together with Schlenk tubes (or round-bottomed flasks fitted with a gas inlet adapter). The protocols in this chapter describe, in general terms, how a vacuum/inert gas manifold is used to fill Schlenk tubes with an inert gas (nitrogen or argon), how a solvent or solution is saturated with an inert gas using Schlenk techniques, and how solvents are removed from a Schlenk tube. The transfer of liquids from one Schlenk to another, either directly or *via* a filtration device, is also described, as is the column chromatography of air-sensitive materials. Finally, a technique for preparing samples for NMR spectroscopy under an inert atmosphere is detailed.

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## Protocol 1.
## Evacuating and filling a Schlenk tube with an inert gas using a vacuum/inert gas manifold

**Caution!** All procedures should be performed in a fume hood. Safety glasses should be worn.

*Equipment*

- Vacuum/inert gas manifold (Figs 7.1 and 7.2)
- Schlenk tube (Fig. 7.3)
- Septum

*Materials*

- Silicone vacuum grease

1. Ensure that the Schlenk tube is clean and has been dried for at least an hour in a 100°C oven before use.
2. Grease the stopcock[a] and then support the Schlenk tube under its side-arm using a clamp and a stand with a heavy base.

## **Protocol 1.** *Continued*

3. Immediately equip the neck of the Schlenk tube with the septum and attach the side-arm to the vacuum/inert gas manifold *via* one of the flexible tubing connections.
4. Open the Schlenk tube stopcock.
5. Adjust the vacuum/inert gas manifold to vacuum (Fig. 7.2b) and leave for 1 min.
6. Adjust the vacuum/inert gas manifold to gas (Fig. 7.2c) and fill the Schlenk tube with nitrogen/argon.
7. Repeat steps 5 and 6 a total of five times.

[a] Stopcocks should be lightly greased lengthways, inserted into the socket and rotated. A clear film throughout the joint indicates that sufficient grease has been used. Air channels are easily seen as lighter streaks. After use the vacuum grease should be removed from the stopcock using dichloromethane/tissue and pipe cleaners.

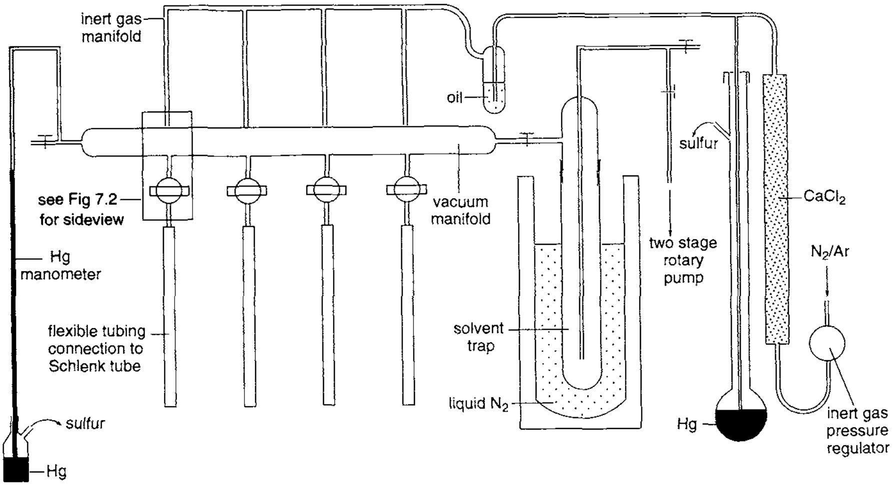

**Fig. 7.1** Vacuum/inert gas manifold

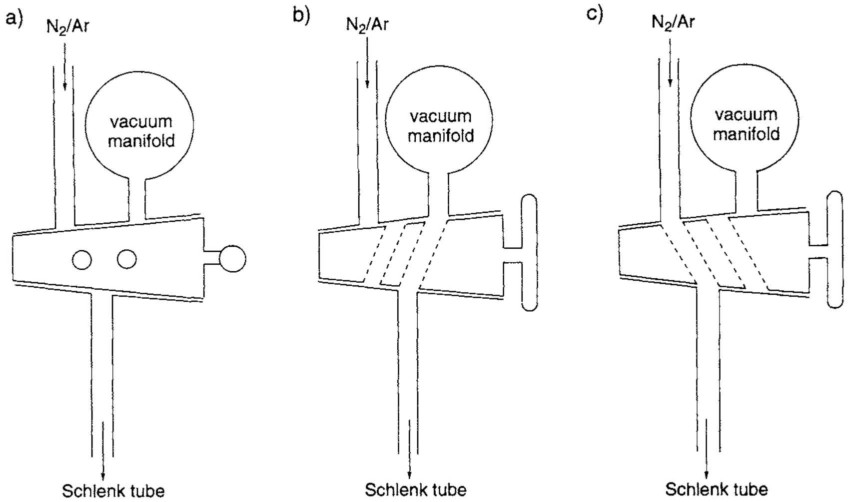

**Fig. 7.2** Sideview of manifold stopcock: (a) closed, (b) open to vacuum, (c) open to nitrogen/argon.

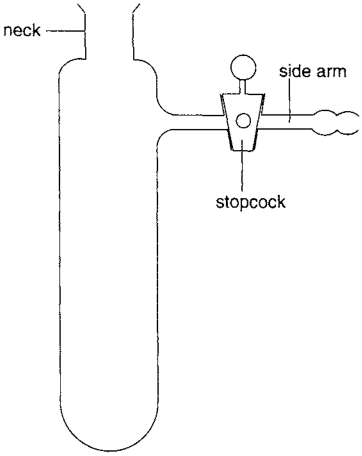

**Fig. 7.3** Schlenk tube.

## Protocol 2.
## Saturating solvents with an inert gas using a vacuum/inert gas manifold

**Caution!** All procedures should be performed in a fume hood. Disposable vinyl or latex gloves and safety glasses should be worn.

### *Equipment*

- Vacuum/inert gas manifold (Figs 7.1 and 7.2)
- Schlenk tube (Fig. 7.3)
- Pyrex funnel
- Septum

### *Materials*

- Silicone vacuum grease
- Solvent to be saturated with inert gas

1. Ensure that the Schlenk tube is clean and has been dried for at least an hour in a 100°C oven before use.
2. Grease the stopcock, and then support the Schlenk tube under its side-arm using a clamp and a stand with a heavy base.
3. Introduce the solvent into the Schlenk tube through its neck with the aid of a Pyrex funnel.
4. Equip the neck of the Schlenk tube with a septum and attach the side-arm to the vacuum/inert gas manifold *via* one of the flexible tubing connections.
5. Close the Schlenk tube stopcock. Adjust the vacuum/nitrogen manifold to vacuum and evacuate the flexible tubing connection between the manifold and the Schlenk tube stopcock.
6. Hold the Schlenk tube and while shaking it gently, apply the vacuum for 2–3 s by opening the Schlenk tube stopcock. Close the Schlenk tube stopcock.
7. Adjust the vacuum/inert gas manifold to nitrogen/argon and fill the flexible tubing connection between the manifold and the Schlenk tube stopcock with inert gas. Still shaking the Schlenk tube gently, open the Schlenk tube stopcock and refill the Schlenk tube with inert gas.
8. Repeat steps 5–7 a total of five times.

## Protocol 3.
## Removal of solvents using a vacuum/inert gas manifold

**Caution!** All procedures should be performed in a fume hood. Disposable vinyl or latex gloves and safety glasses should be worn.

*Equipment*

- Vacuum/inert gas manifold (Figs 7.1 and 7.2)
- Schlenk tube (Fig. 7.3)
- Septum

*Materials*

- Silicone vacuum grease
- Solution to be concentrated or evaporated to dryness

1. Attach the Schlenk tube containing the solution to be concentrated to the vacuum/inert gas manifold *via* one of the flexible tubing connections, equip the neck of the Schlenk tube with a septum and close the Schlenk tube stopcock.
2. Adjust the vacuum/inert gas manifold to vacuum and evacuate the flexible tubing connection between the manifold and the Schlenk tube stopcock.
3. Hold the Schlenk tube and while shaking it gently, apply the vacuum for 2–3 s by opening the Schlenk tube stopcock. Close the Schlenk tube stopcock. Repeat this sequence until no vigorous bubbling occurs.
4. Apply the vacuum continuously and while shaking the Schlenk tube gently, let the solvent evaporate. When necessary, use a water bath to avoid formation of ice on the outside of the Schlenk tube.
5. When the desired amount of solvent has been removed, close the Schlenk tube stopcock. Adjust the vacuum/inert gas manifold to nitrogen/argon and fill the flexible tubing connection between the manifold and the Schlenk tube stopcock with inert gas. Still shaking the Schlenk tube gently, open the Schlenk tube stopcock and refill the Schlenk tube with inert gas.

## Protocol 4.
## Transferring liquids from one Schlenk tube to another *via* a cannula or filtering cannula

**Caution!** All procedures should be performed in a fume hood. Disposable vinyl or latex gloves and safety glasses should be worn.

*Equipment*

- Vacuum/inert gas manifold (Figs 7.1 and 7.2)
- Schlenk tube containing the liquid to be transferred (Schlenk tube A)
- Schlenk tube for receiving the liquid (Schlenk tube B)
- Septum
- Stainless steel cannula or filtering cannula (Fig. 3.1)

## Protocol 4. *Continued*

*Materials*

- Solvent, solution or solid/liquid mixture to be transferred or filtered

1. Ensure that Schlenk tube B and the cannula (or filtering cannula) are clean and have been dried for at least an hour in a 100°C oven before use.
2. Support Schlenk tube B under its side-arm using a clamp and a stand with a heavy base. Fit it with a septum, attach it to the vacuum/inert gas manifold and evacuate it and refill it with inert gas (Protocol 1).
3. Allow the cannula (or filtering cannula) to cool to room temperature. If using a filtering cannula, place and wire a piece of filter paper around the glass filtering device as illustrated in Fig. 3.1.
4. Insert the cannula just through the septum of the Schlenk tube containing the liquid to be transferred (Schlenk tube A). (See Fig. 3.2 for a similar arrangement using a round-bottomed flask rather than a Schlenk. When using a filtering cannula, push the opposite end of the cannula to the filtering device through the bottom of a new septum and replace the septum on Schlenk tube A with this septum.) Purge by allowing inert gas to flow through for one minute.
5. The other end of the cannula (or filtering cannula) is then inserted through the septum of Schlenk tube B.
6. Insert a short needle through the septum of Schlenk tube B to make an inert gas bleed.
7. Lower the tip of the cannula (or filtering cannula) into Schlenk tube A until it is just below the level of the liquid to be transferred.
8. Slowly, close the tap of Schlenk tube B. Control the rate of the transfer of the solution by adjusting the flow of inert gas with the stopcock of Schlenk tube A.
9. Open the stopcock of Schlenk tube B to stop the transfer.
10. Remove the short needle and the end of the cannula.

## Protocol 5.
## Column chromatography of air-sensitive compounds

**Caution!** All procedures should be performed in a fume hood. Disposable vinyl or latex gloves and safety glasses should be worn.

*Equipment*

- Vacuum/inert gas manifold (Figs 7.1 and 7.2)
- Column with side-arm and filter frit (Aldrich Z17, 318-5)
- Septum
- Schlenk tubes for fraction collection
- Aluminium foil

*Materials*

- Crude sample to be purified
- Silica gel (approximately 5 g for 0.1 g of sample) **irritant dust**
- Sand (50–100 μm mesh)
- Eluent

1. Find a low viscosity solvent mixture (e.g. *n*-hexane/diethyl ether, petroleum ether/ethyl acetate) which separates the mixture and moves the desired compound on analytical TLC to an $R_f$ of 0.35. If several compounds are to be separated which run very close on TLC, adjust the solvent so that the midpoint between the components is at $R_f = 0.35$. If the compounds are widely separated, adjust the $R_f$ of the less mobile component to 0.35.
2. Clamp the column, prepare the solvent system selected previously, and furnish two or three Schlenk tubes with an inert gas atmosphere (Protocol 1).
3. Weigh out the required amount of silica gel in a fume hood and pour the silica gel into the column in a single portion. Ensure that the column is vertical and tap it gently to pack the gel. Close the stopcock on the side-arm of the column.
4. Carefully pour the solvent system selected above to fill the column completely and fit the top of the column with a septum. Attach the side-arm of the column to the vacuum/inert gas manifold and adjust the vacuum/inert gas manifold to nitrogen/argon. Open the stopcock and compress the gel. Maintain the pressure until all the air is expelled and the lower part of the column is cool. Note that the level of the solvent must always remain above that of the silica gel.
5. When the column is packed, remove the septum from the top of the column and maintain a gentle flow of inert gas over the silica gel using the side-arm stopcock. Place a 3 mm layer of 50–100 μm mesh sand on the flat top of the silica gel bed. Check the column. If there are air bubbles or cracks in the column, start again. Replace the septum on the top of the column.
6. Using Schlenk tube techniques, saturate the eluent with inert gas (Protocol 2), transfer some eluent to the top of the adsorbent bed *via* a cannula (Protocol 4) and allow the inert gas-saturated eluent to run through the column.
7. Place the sample to be purified in a Schlenk tube and dissolve it in the minimum amount of the inert gas-saturated eluent (see Protocol 4 for the transfer of a liquid from Schlenk to Schlenk *via* a cannula). Apply the resulting solution to the top of the sand *via* a cannula.
8. Wash down the walls of the column with a few millilitres of degassed eluent and push the washings into the silica gel as before.
9. Fill the column with inert gas saturated eluent taking care not to disturb the silica bed.

### Protocol 5. *Continued*

10. Allow eluent to run through the column until the first compound emerges. Adjust the flow rate with the aid of the side-arm stopcock.
    **Important!** At no time let the level of the solvent get below the top of the sand. If necessary, stop the flow by removing the septum, add more eluent and start the flow again.
11. Collect fractions in Schlenk tubes with inert gas flowing gently through them and concentrate using the vacuum/inert gas manifold (Protocol 3).

## Protocol 6.
## Preparation of an NMR sample of an air-sensitive complex under an inert gas

**Caution!** Due to the potential toxicity of transition metal complexes, prepare the NMR sample in a fume hood and wear disposable vinyl or latex gloves and safety glasses.
*NB* NMR samples of air-sensitive organometallics should be prepared just before being recorded.

### *Equipment*

- Vacuum/inert gas manifold (Figs 7.1 and 7.2)
- Enlarging adapter (B24 and B19 joints)
- Septum-inlet adapter (B24 and B14 joints)
- Septum
- Parafilm
- High vacuum one-way stopcock
- Vacuum tubing
- NMR tube (5 mm size)
- Septum for 5 mm NMR tube
- Teat pipettes
- Cotton wool
- Aluminium foil

### *Material*

- Complex to be analysed by NMR spectroscopy
- Kieselguhr for filtration
- Appropriate deuterated solvent

1. Prepare the apparatus depicted in Fig. 7.4 as follows: (a) assemble the septum-inlet adapter and the enlarging adapter and secure the joint with Parafilm; (b) carefully pierce a B14 septum in its centre with a hole borer [the NMR tube (5 mm size) must fit exactly into the resulting hole] and equip the bottom joint of the septum inlet adapter with it; (c) connect the septum-inlet adapter to a one-way stopcock using vacuum tubing.
2. Support the apparatus using a clamp and a stand with a heavy base.
3. Introduce the NMR tube into the apparatus through the hole in the septum. The top of the NMR tube should be approximately 5 cm below the top of the apparatus (see Fig. 7.4).
4. Equip the top of the septum-inlet adapter with a septum and attach the

apparatus to the vacuum/inert gas manifold *via* the one-way stopcock. Close the one-way stopcock.

5. Adjust the vacuum/inert gas manifold to vacuum and evacuate the flexible tubing connection between the manifold and the one-way stopcock. Open the one-way stopcock to apply vacuum to the apparatus.
6. Prepare a short Pasteur pipette for filtration of the NMR sample. (This filtration is necessary to remove any paramagnetic material which arises from decomposition. Running the NMR spectrum without filtration would lead to poor resolution and broad signals.) Push a small plug of cotton wool to the bottom of the pipette (use a second pipette), add enough Kieselguhr[a] to form a 2 cm layer over the cotton wool and level the surface by tapping.
7. Close the one-way stopcock. Adjust the vacuum/inert gas manifold to nitrogen/argon and fill the flexible tubing connection between the manifold and the one-way stopcock with inert gas. Open the one-way stopcock and fill the apparatus with inert gas. If necessary, refill the flask or Schlenk tube containing the sample with inert gas.
8. Remove the septum on the apparatus and carefully sit the filtration pipette in the top of the NMR tube.
9. Dissolve the complex ($\approx$10 mg) in a small amount of deuterated solvent (0.3 mL) and transfer the solution *via* a pipette onto the filtration pipette (if highly air-sensitive organometallics are involved, use inert gas-saturated deuterated solvent and transfer any solution *via* a cannula).
10. Equip the filtration pipette with a teat and press the teat. Remove the teat, add deuterated solvent (0.3 mL) and repeat as before.
11. Remove the filtration pipette and put the septum back on the apparatus.
12. Close the stopcock, adjust the vacuum/inert gas manifold to vacuum and evacuate the flexible tubing connection between the manifold and the one-way stopcock. Apply the vacuum momentarily (1–2 s) by opening the stopcock. Adjust the vacuum/inert gas manifold to inert gas and fill the flexible tubing connection between the manifold and the one-way stopcock with inert gas. Open the one-way stopcock and refill the apparatus with inert gas. Repeat this sequence a total of three times.
13. Push the tube up until the top of the tube is $\approx$1.5 cm below the top of the apparatus and insert a septum in the top of the NMR tube under a flow of inert gas. Free the tube from the apparatus.
14. Disconnect the apparatus from the inert gas source and protect the NMR tube with foil if using light-sensitive solutions.

[a] Kieselguhr is introduced dry, without being suspended in any solvent.

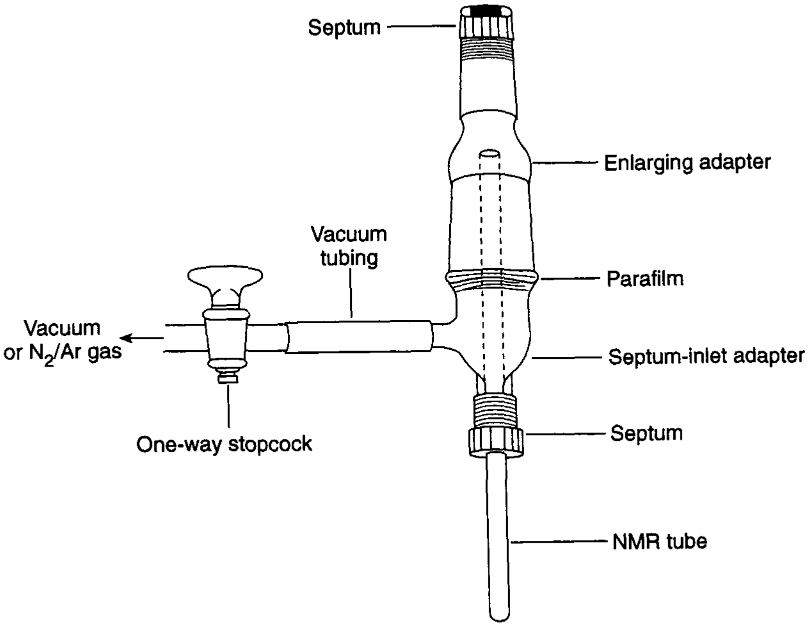

**Fig. 7.4** Apparatus used for the preparation of an NMR sample under an inert atmosphere.

# A1

# List of suppliers

**Aldrich Chemical Co. Ltd**
*France*: BP 701, L'Isle D'Abeau Chesnes, 38297 St. Quentin Fallavier Cedex. Tel. 74822800
*Germany*: Riedstrasse 2, D-89555 Steinheim. Tel. 7329-9702
*Japan*: JL Nihonbashi Bldg., 1-10-15 Nihonbashi Horidomecho, Chou-ku, Tokyo 103. Tel. 33258-0155
*UK*: The Old Brickyard, New Road, Gillingham, Dorset SP8 4JL. Tel. 0800-717181
*USA*: PO Box 355, Milwaukee, WI 53201. Tel. 414-2733850

**A.R. Walker Ltd** (inert gas pressure regulators)
*UK*: Unit 5, Overthorpe Road, Banbury, Oxon OX16 8SX. Tel. 01295-269880

**BDH**
*UK*: (Head Office and International Sales) Merck Ltd, Merck House, Poole, Dorset BH15 1TD. Tel. 01202-665599

**Fluka Chemika-BioChemika**
*France*: Fluka S.a.r.l., 38297 St. Quentin Fallavier Cedex. Tel. 74822800
*Germany*: Fluka Feinchemikalien GmbH, D-7910 Neu-Ulm. Tel. 0731-729670
*Japan*: Fluka Fine Chemical, Chiyoda-Ku, Tokyo. Tel. 03-32554787
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**Johnson Matthey Chemical Products**
*France*: Johnson Matthey SA, BP 50240, Rue de la Perdix, ZI Paris Nord LL, 95956 Roissy, Charles de Gaulle Cedex. Tel. 48632299
*Germany*: Johnson-Matthey GmbH, Zeppelinstrasse 7, D-7500 Karlsruhe-1. Tel. 0721-840070
*UK*: Catalogue Sales, Materials Technology Division, Orchard Road, Royston, Herts. SG8 5HE. Tel. 01763-253715
*USA*: Alfa-Johnson Matthey, PO Box 8247, Ward Hill MA 01835-0747. Tel. 0508-5216300

**Lancaster Synthesis**

*France*: Lancaster Synthesis Ltd, 15 Rue de l'Atome, Zone Industrielle, 67800 Bischheim, Strasbourg. Tel. 05035147

*Germany*: Lancaster Synthesis GmbH, Postfach 15 18, D-63155 Mülheim am Main. Tel. 0130-6562

*Japan*: Hydrus Chemical Inc., Kurihara Building, 2-12, Uchikanda 3-chome, Chiyoda-ku, Tokyo 101. Tel. 03-32585031

*UK*: Lancaster Synthesis, Eastgate, White Lund, Morecambe, Lancashire LA3 3DY. Tel. 0800-262336.

*USA*: Lancaster Synthesis Inc., PO Box 1000, Windham, NH 03087-9977. Tel. 0800-2382324

**Orme Scientific Equipment**

*UK*: PO Box 3, Stakehill Industrial Park, Middleton, Manchester M24 2RH. Tel. 0161-6534589

**Richardsons of Leicester Ltd.** (stainless steel cannulae)

*UK*: Evington Valley Road, Leicestershire LE5 5LJ. Tel. 01162-736571

**Strem**

*France*: Strem Chemicals, Inc., 15 Rue de l'Atome, Zone Industrielle, 67800 Bischheim. Tel. 88625260

*Germany*: Strem Chemicals GmbH, Postfach 1215, 77672 Kehl. Tel. 07851-75879

*UK*: Strem Chemicals, 48 High Street, Orwell, Royston, Hertfordshire SG8 5QN. Tel. 01223-207430

*USA*: Strem Chemicals, Inc., 7 Mulliken Way, Dexter Industrial Park, Newburyport, MA 01950-4098. Tel. 0508-4623191

**William Freeman and Co. Ltd.** (septa)

*UK*: Suba Seal Works, Staincross, Barnsley, Yorkshire S75 6DH. Tel. 01226-284081

**Wako**

*Japan*: 3-10 Dosho-Machi, Higashi-Ku, Osaka 541. Tel. 06-2033741

# A2

# Summary of protocols

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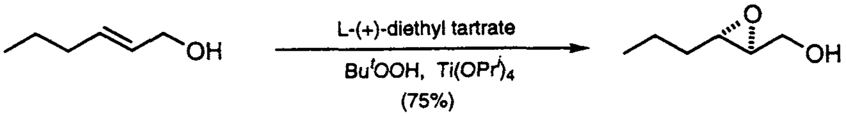
### Chapter 1, Protocol 1, p. 3–5



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Bu$^t$OOH—molarity determination

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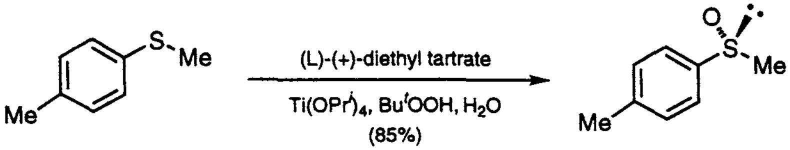

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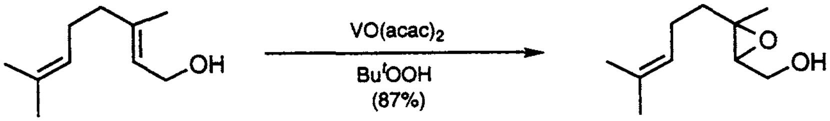

# *Summary of protocols*

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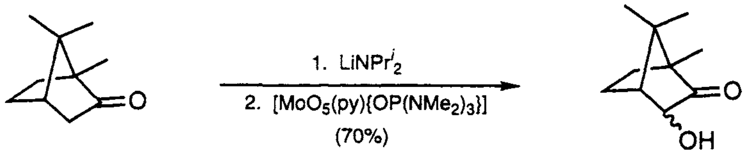

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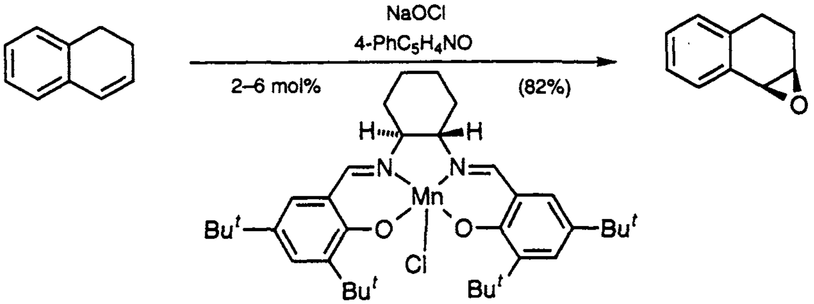

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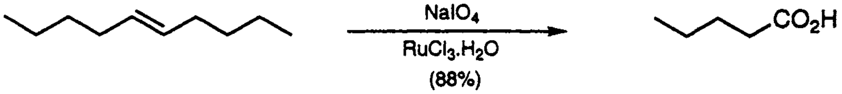
## Chapter 1, Protocol 7, p. 21–2



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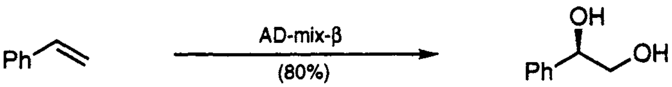

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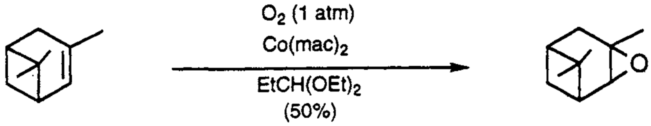
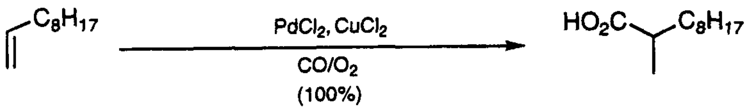
## Chapter 1, Protocol 9, p. 25–6



## Chapter 1, Protocol 10, p. 28–30



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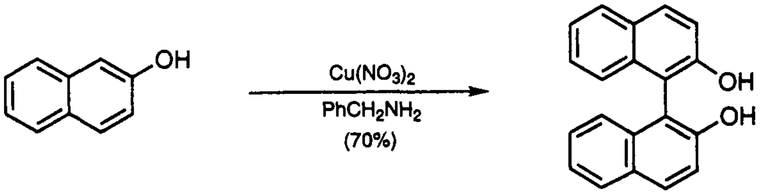

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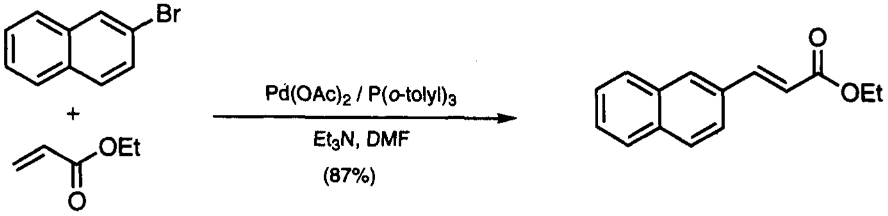

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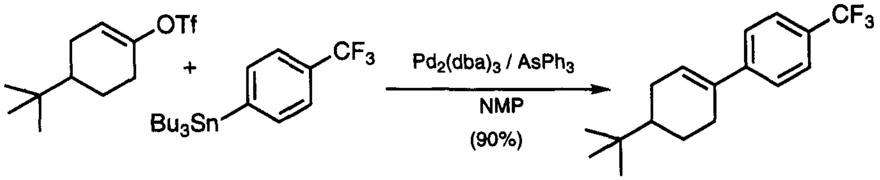

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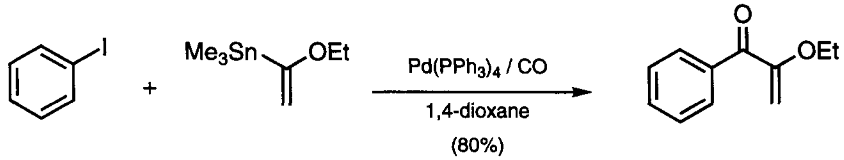

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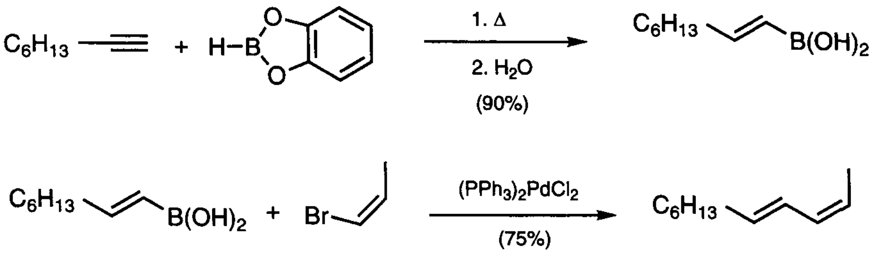

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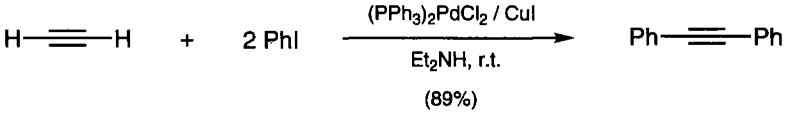

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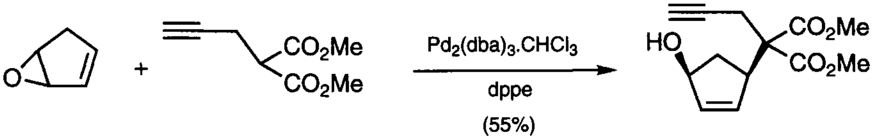

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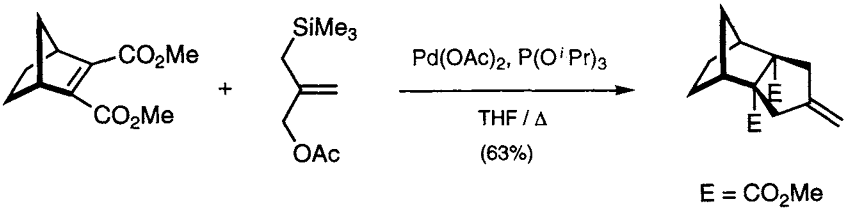

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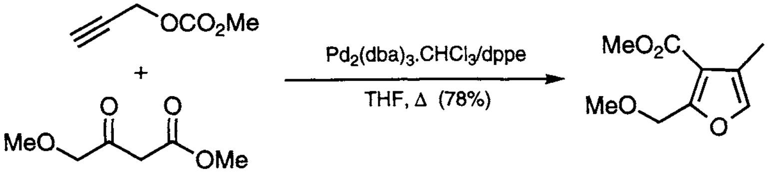

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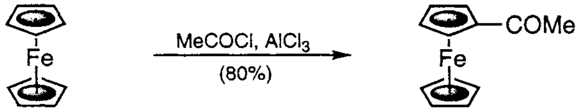
### Chapter 3, Protocol 1, p. 68–9



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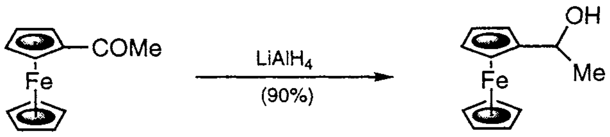
### Chapter 3, Protocol 2, p. 70–1



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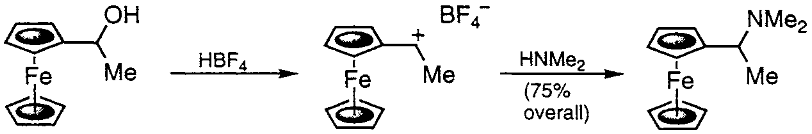

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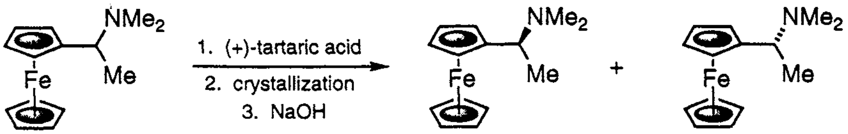

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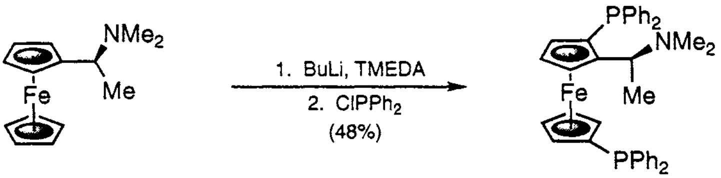
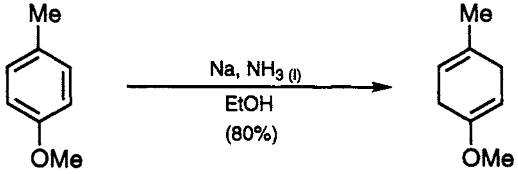


## Chapter 3, Protocol 6, p. 82–4



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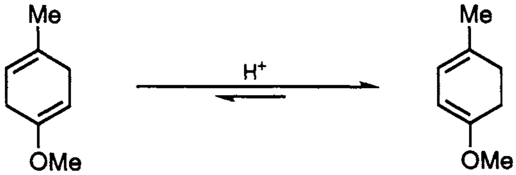

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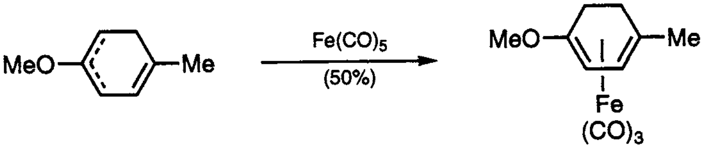

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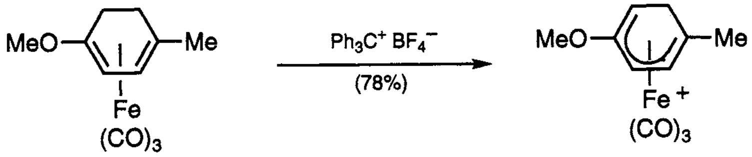

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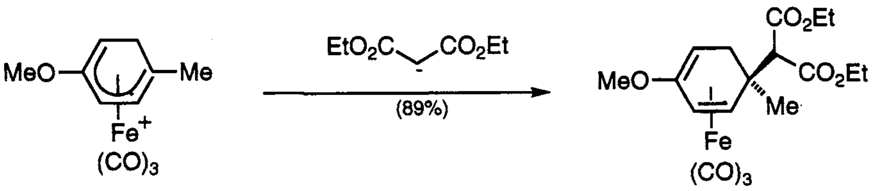

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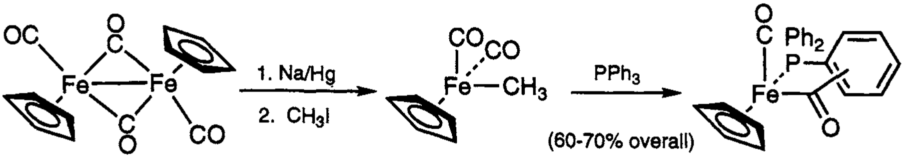

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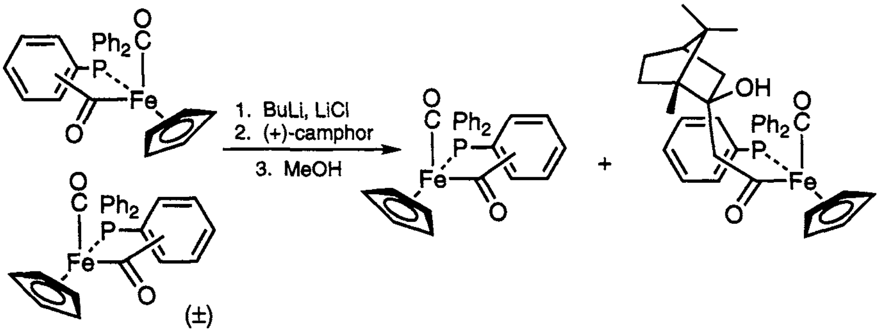

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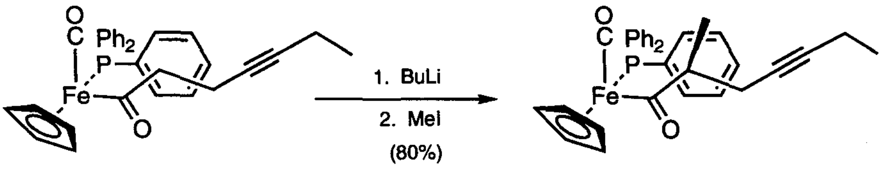

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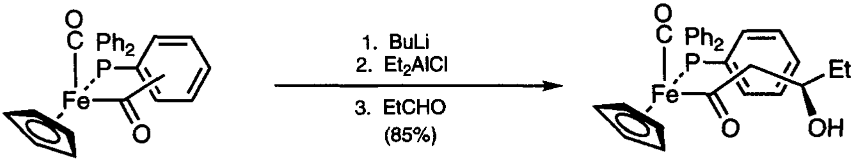

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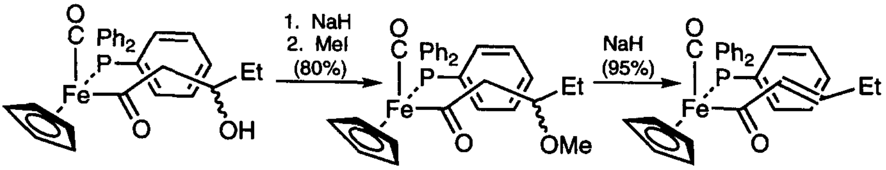

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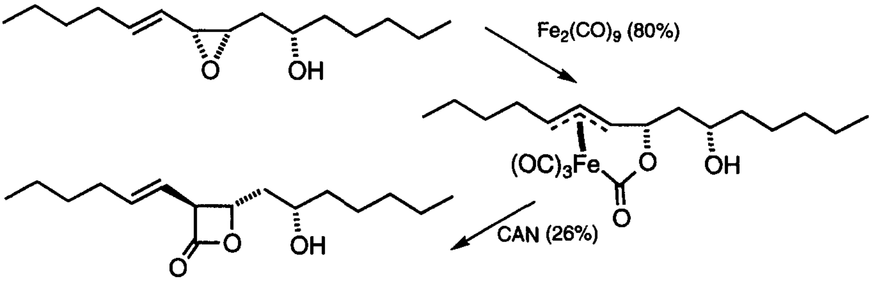

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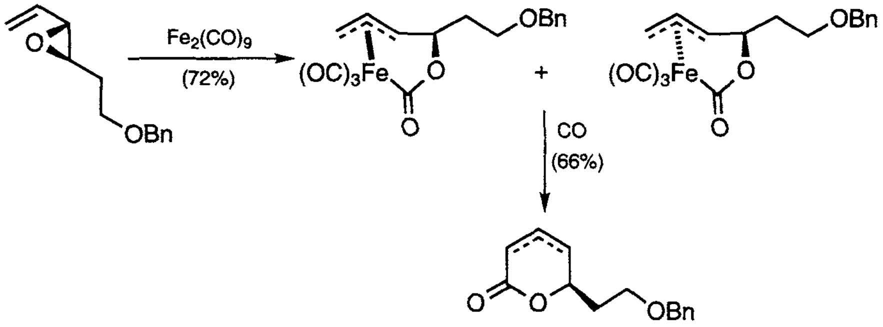

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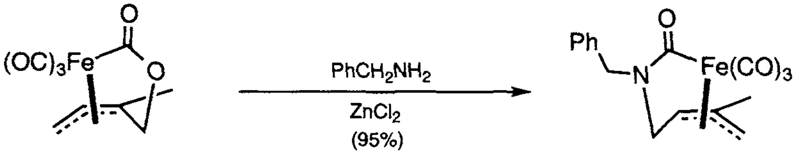

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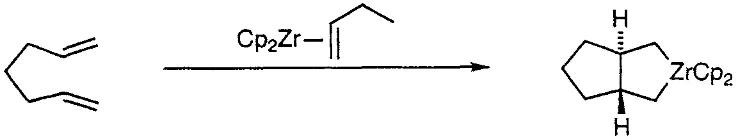

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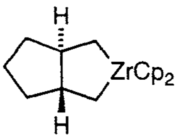
NMR characterization of



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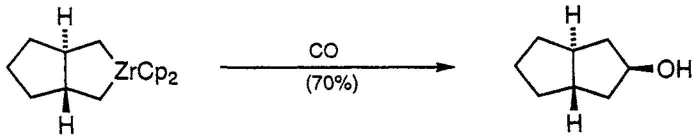

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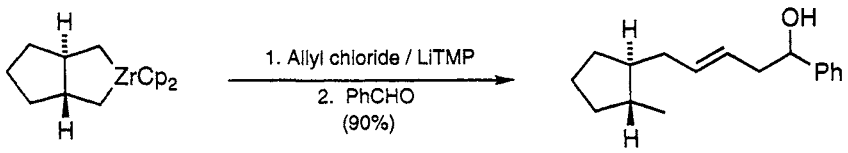

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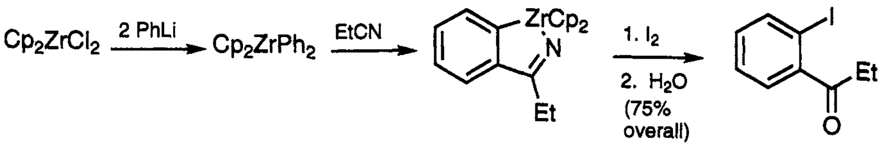

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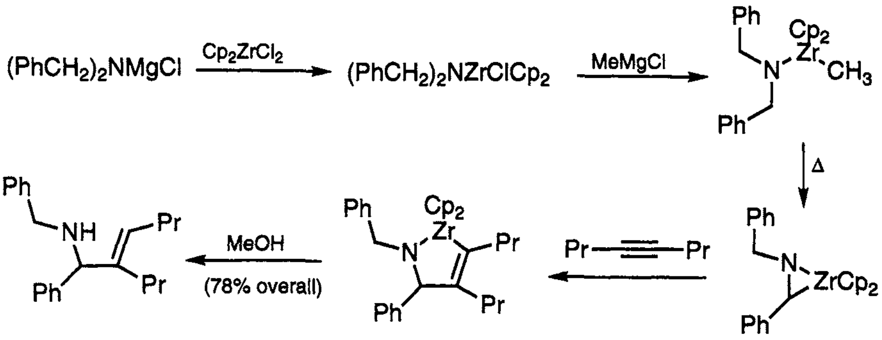

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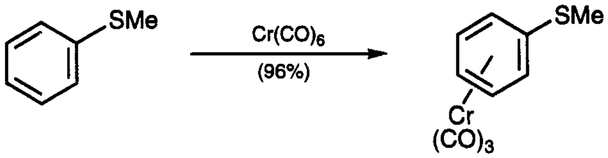

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— Molarity determination

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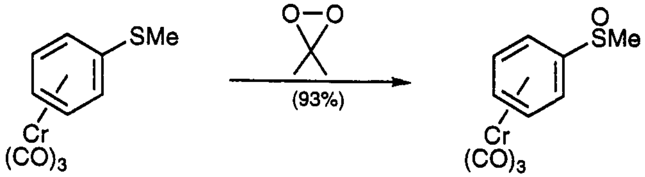

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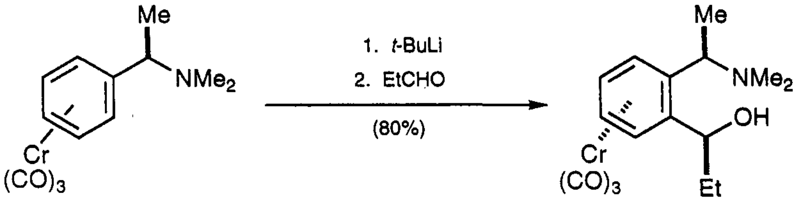

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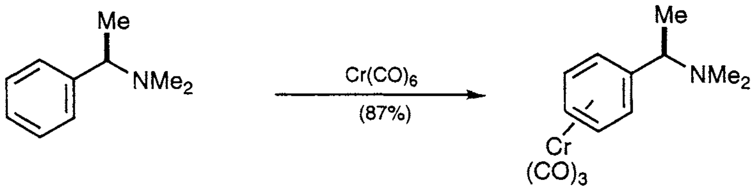

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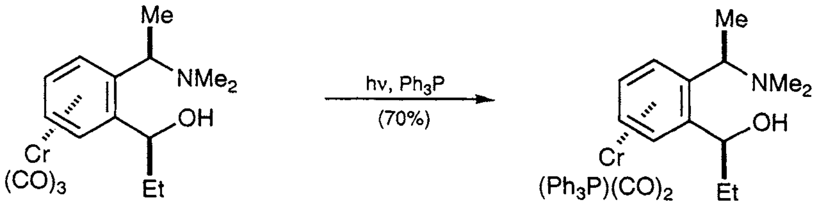

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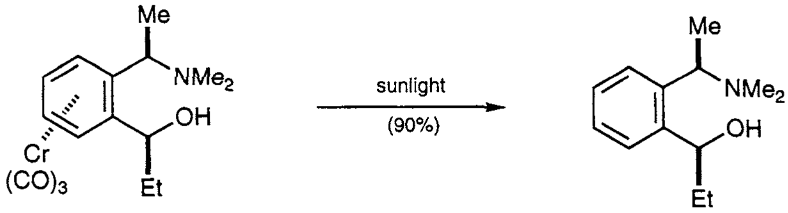

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### Chapter 7, Protocol 1, p. 205–6

Vacuum/inert gas manifold manipulation—Schlenk tube evacuation/filling

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### Chapter 7, Protocol 2, p. 208

Vacuum/inert gas manifold manipulation—inert gas saturation of solvents

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