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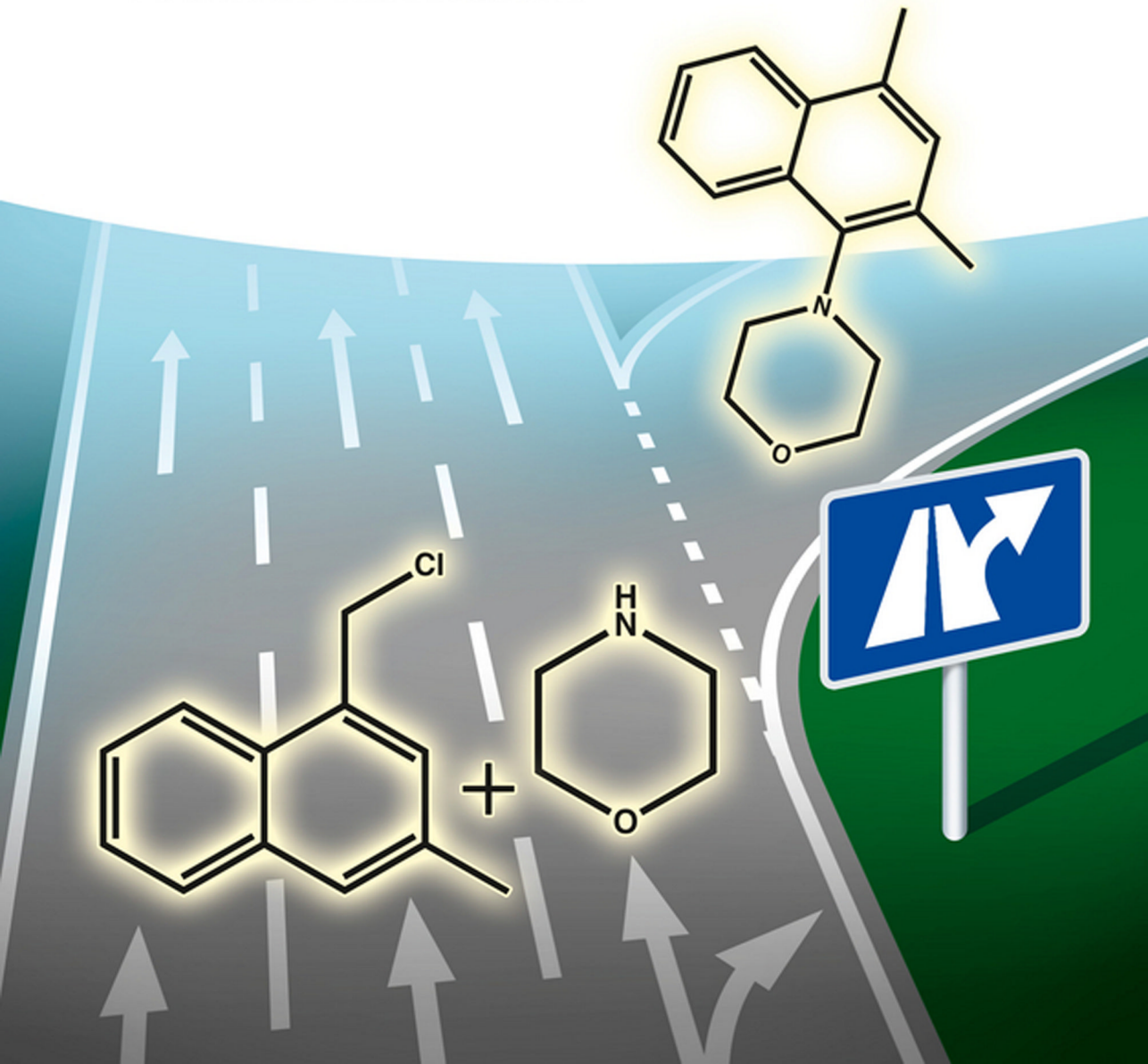

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Aromatic Substitutions

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Contents

Preface

Our job as chemists is mainly about problem solving. Therefore, the most interesting aspect of chemistry is not what works, but what does not work, and why. Difficult or ''impossible'' reactions, poor selectivities, low yields, expensive catalysts, or excessive waste generation are nothing to shrink away from, but great opportunities for relevant chemical research.

Ten years ago, I wrote ''Side Reactions in Organic Synthesis,'' with the aim of highlighting the competing processes and limitations of some of the most common reactions used in organic synthesis. Although some readers found the title confusing (and, yes, there are no side reactions), I also received a lot of positive feedback. For this reason I decided to write a second sequel.

In the first book of this series the focus had been alkylations, that is, substitutions at sp^3 carbon. An equally important area of organic synthesis is aromatic substitution, the main topic of the present book. Again, I try to show the main problems and limitations of popular synthetic transformations, hoping to help chemists to identify byproducts and plan better syntheses. As in my earlier titles, my main aim is to encourage bold experimentation, to inspire, challenge, and motivate.

Because time is a precious resource, I have kept the texts short (chemists can assimilate graphical information faster than text), and included in all equations a short code for the source. This code has the format year-journal-first page. For instance, 08joc4956 means *J. Org. Chem.* **2008**, 4956. The abbreviations used for the journals can be found in the ''Journal Abbreviation List.'' All patents can be downloaded at *worldwide.espacenet.com*.

I would like to thank Paul Hanselmann and Marcel Suhartono for proofreading and for the many instructive chemical discussions. I am also thankful for the help and support provided by the editors at Wiley-VCH, in particular by Anne Brennführer.

Visp, Switzerland
May 2014

Florencio Zaragoza Dörwald

Glossary and Abbreviations

Ac	Acetyl, MeCO
acac	Acetylacetone, pentane-2,4-dione
Ada	Adamantyl
AIBN	2,2′-Azobis(2-methylpropionitrile)
aq	Aqueous
Ar	Undefined aryl group
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
Boc	*tert*-Butyloxycarbonyl
bpy	2,2′-Bipyridine
CAN	Ceric ammonium nitrate, $(NH_4)_2Ce(NO_3)_6$
cat	Catalyst or catalytic amount
cod	1,5-Cyclooctadiene
coe	*cis*-Cyclooctene
concd	Concentrated
cot	1,3,5-Cyclooctatriene
Cp	Cyclopentadienyl
Cp*	Pentamethylcyclopentadienyl
Cy	Cyclohexyl
cym	Cymene, 4-isopropyltoluene
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	1,5-Diphenyl-1,4-pentadien-3-one
DBU	1,8-Diazabicyclo[5.4.0]undec-5-ene
DCE	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMA	*N,N*-Dimethylacetamide
DME	1,2-Dimethoxyethane
DMF	*N,N*-Dimethylformamide
DMI	1,3-Dimethylimidazolidin-2-one
DMPU	1,3-Dimethyltetrahydropyrimidin-2-one
DMSO	Dimethyl sulfoxide
DPEphos	Bis[(2-diphenylphosphino)phenyl] ether
dppb	1,4-Bis(diphenylphosphino)butane
dppf	1,1′-Bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane

dtbpy	2,6-Di(*tert*-butyl)pyridine
eq	Equivalent
Fmoc	9-Fluorenylmethyloxycarbonyl
GDP	Gross domestic product
Hal	Undefined halogen
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
HMPA	Hexamethylphosphoric triamide, $(Me_2N)_3PO$
L	Undefined ligand
LTMP	Li-TMP
Mes	Mesityl, 2,4,6-trimethylphenyl
Ms	Methanesulfonyl
MS	Molecular sieves
MW	Microwave
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NIS	*N*-Iodosuccinimide
NMP	*N*-Methylpyrrolidin-2-one
Nu	Undefined nucleophile
PEGDM	Poly(ethylene glycol) dimethacrylate
phen	Phenanthroline
pin	pinacolyl
Piv	Pivaloyl, 2,2-dimethylpropanoyl
PPA	Polyphosphoric acid
pyr	Pyridine
R	Undefined alkyl group
SET	Single electron transfer
S_NAr	Aromatic nucleophilic substitution
S_N1	Monomolecular nucleophilic substitution
S_N2	Bimolecular nucleophilic substitution
S-phos	2-(2′,6′-Dimethoxybiphenyl)dicyclohexylphosphine
st.mat.	Starting material
TBAB	Tetrabutylammonium bromide
TBAF	Tetrabutylammonium fluoride
TEMPO	(2,2,6,6-Tetramethyl-piperidin-1-yl)oxyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic acid anhydride
TfOH	Triflic acid, F_3CSO_3H
THF	Tetrahydrofuran
TMEDA	*N,N,N′,N′*-Tetramethyl-1,2-ethylenediamine
TMP	2,2,6,6-Tetramethylpiperidine
Tol	Tolyl
Ts	Tosyl, 4-toluenesulfonyl
wt	Weight
xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

Journal Abbreviation List

PLEASE NOTE:

Included in all equations is a short code for the source. This code has the format year-journal-first-page, for instance:

08joc4956 means *J. Org. Chem.* **2008**, 4956.

a	Arkivoc
ac	Acta Crystallographica
acr	Accounts of Chemical Research
ajc	Australian Journal of Chemistry
ang	Angewandte Chemie, International Edition in English
asc	Advanced Synthesis & Catalysis
bcsj	Bulletin of the Chemical Society of Japan
bj	Biochemical Journal
catc	Catalysis Communications
catl	Catalysis Letters
cb	Chemistry & Biology
cc	Chemical Communications
cej	Chemistry – A European Journal
cjc	Canadian Journal of Chemistry
cl	Chemistry Letters
coc	Current Organic Chemistry
cpb	Chemical & Pharmaceutical Bulletin
cr	Chemical Reviews
ejoc	European Journal of Organic Chemistry
hca	Helvetica Chimica Acta
iec	Industrial & Engineering Chemistry
ja	Journal of the American Chemical Society
jbcs	Journal of the Brazilian Chemical Society
jcat	Journal of Catalysis
jcs(p1)	Journal of the Chemical Society, Perkin Transactions 1
jmc	Journal of Medicinal Chemistry
joc	Journal of Organic Chemistry

jpc	Journal für Praktische Chemie
obmc	Organic & Biomolecular Chemistry
ol	Organic Letters
oprd	Organic Process Research & Development
oscv(1)	Organic Syntheses, Collective Volume 1
p	Pharmazie
pcs	Proceedings of the Chemical Society
rjoc	Russian Journal of Organic Chemistry
sc	Synthetic Communications
sl	Synlett
syn	Synthesis
tet	Tetrahedron
thl	Tetrahedron Letters
zok	Zhurnal Organicheskoi Khimii

1
Electrophilic Alkylation of Arenes

1.1
General Aspects

For large-scale industrial organic syntheses, electrophilic alkylations of arenes are essential (Scheme 1.1). Their attractive features include the absence of waste when alcohols or olefins are used as electrophiles, the large scope of available starting materials, and the high structural complexity attainable in a single step. The main issues are low regioselectivity, overalkylations, and isomerization of the intermediate carbocations. Important products resulting from this chemistry include isopropylbenzene (cumene – starting material for phenol and acetone), ethylbenzene (starting material for styrene), methylphenols, geminal diarylalkanes (monomers for polymer production), trityl chloride (from CCl_4 and benzene [1]), dichlorodiphenyltrichloroethane (DDT) (from chloral and chlorobenzene), and triarylmethane dyes.

To obtain acceptable yields, careful optimization of most reaction parameters is often required. Because the reactivity of an arene *increases* upon alkylation (around 2–3-fold for each new alkyl group), multiple alkylation can be a problem. This may be prevented by keeping the conversion low, or by modifying the reaction temperature, the concentration, the rate of stirring, or the solvent used (e.g., to provide for a homogeneous reaction mixture). In dedicated plants, processes are usually run at low conversion if the starting materials can be recycled. In the laboratory or when working with complex, high-boiling compounds, though, electrophilic alkylations of arenes can be more difficult to perform.

Typical electrophilic alkylating reagents for arenes include aliphatic alcohols, alkenes, halides, carboxylic and sulfonic esters, ethers, aldehydes, ketones, and imines. Examples of alkylations with carbonates [2], ureas [3], nitroalkanes [4], azides [5], diazoalkanes [6], aminoalcohols [7], cyclopropanes [8], and thioethers (Scheme 1.14) have also been reported. Amines can be used as alkylating agents either via intermediate conversion to *N*-alkylpyridinium salts [9] or by transient dehydrogenation to imines [10]. Some examples of Friedel–Crafts alkylation are given in Scheme 1.2.

In most instances, the electrophilic alkylation of arenes proceeds via carbocations, and complete racemization of chiral secondary halides or alcohols is usually observed. Only if neighboring groups are present and capable of forming

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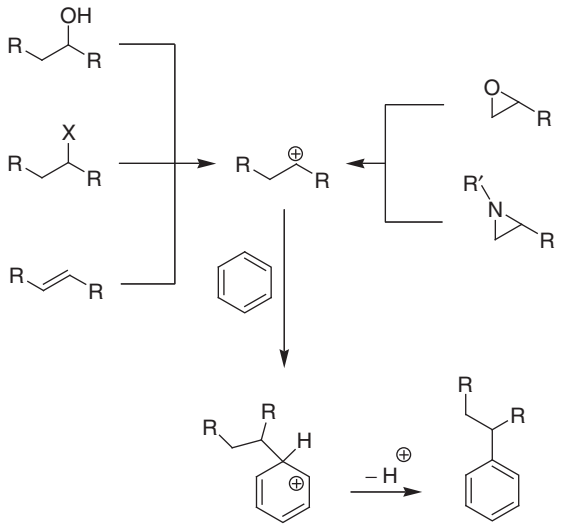


Scheme 1.1 Mechanism of the Friedel–Crafts alkylation.

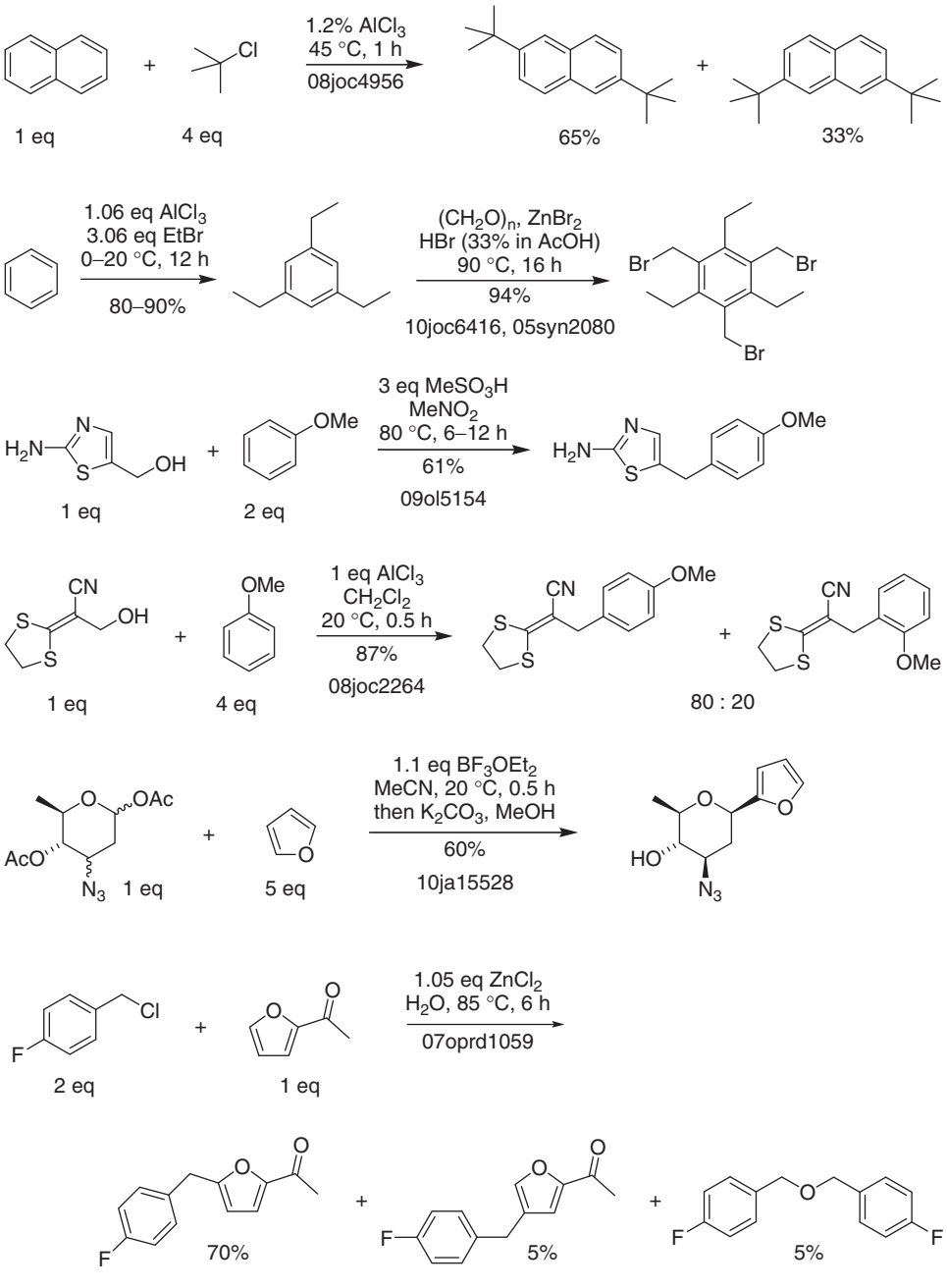
cyclic configurationally stable cations, arylations can occur with retention of configuration [18].

Stabilized carbocations (e.g., tertiary carbocations) are easy to generate, but they are less reactive (and more selective) than less stable cations. Thus, the trityl or tropylium ($C_7H_7^+$) cations react with anisole but not with benzene. On the other hand, carbocations destabilized by a further positively charged group in close proximity will show an increased reactivity [7, 19]. Highly stabilized cations may even be generated and arylated under almost neutral reaction conditions [20].

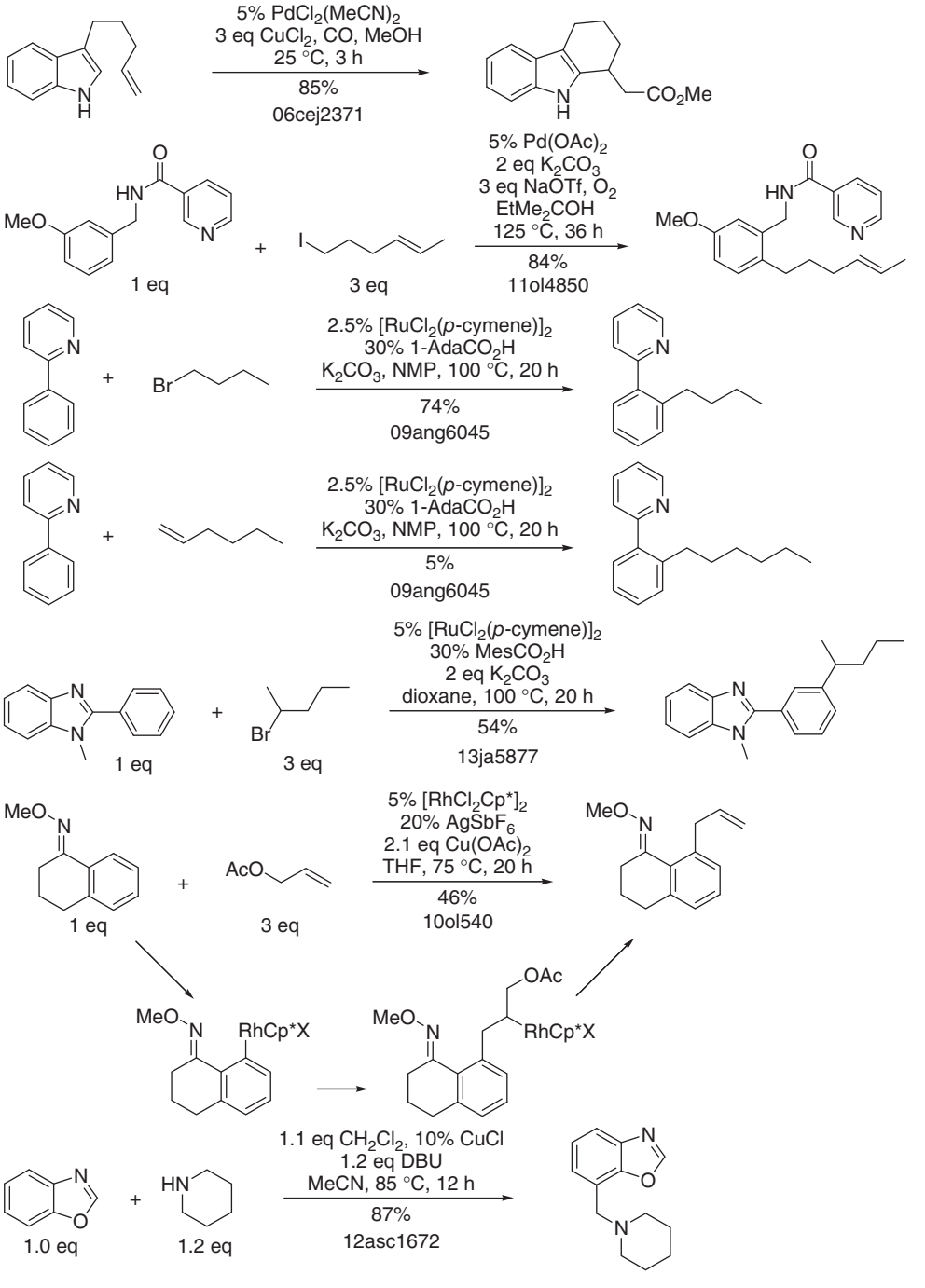
1.1.1 Catalysis by Transition-Metal Complexes

Electrophilic alkylations of arenes by olefins or alkyl halides can be catalyzed by soft electrophilic transition metals, for example, by Pd, Rh, or Ru complexes (Scheme 1.3). Most of the reported examples proceed via aromatic metallation through chelate formation. With Ru-based catalysts, selective meta-alkylation can be achieved when using sterically demanding electrophiles (fifth equation in Scheme 1.3).

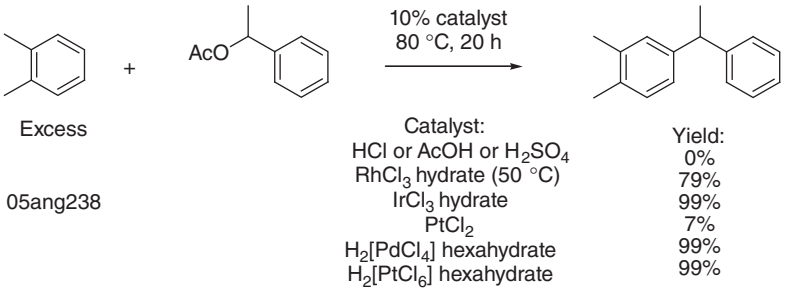
Reactions where carbocation formation is the slowest (rate-determining) step can be catalyzed by any compound capable of stabilizing the intermediate carbocation (and thereby promote its formation). This form of catalysis should be most pronounced in nonpolar solvents, in which free carbocations are only slightly stabilized by solvation. Some transition-metal complexes, for example, $IrCl_3$ and $H_2[PtCl_6]$, catalyze Friedel–Crafts alkylations with benzyl acetates, probably by

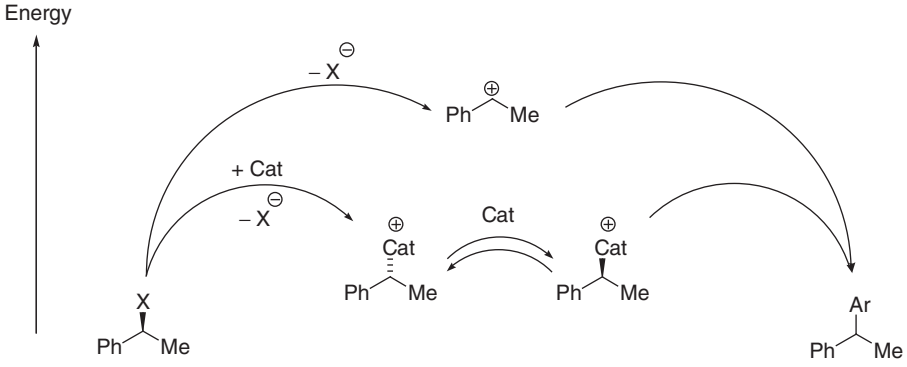


Scheme 1.2 Examples of Friedel–Crafts alkylations [11–17].



Scheme 1.3 Transitions-metal-catalyzed arene alkylations [21–26].





Scheme 1.4 Catalysis of Friedel–Crafts alkylations [28].

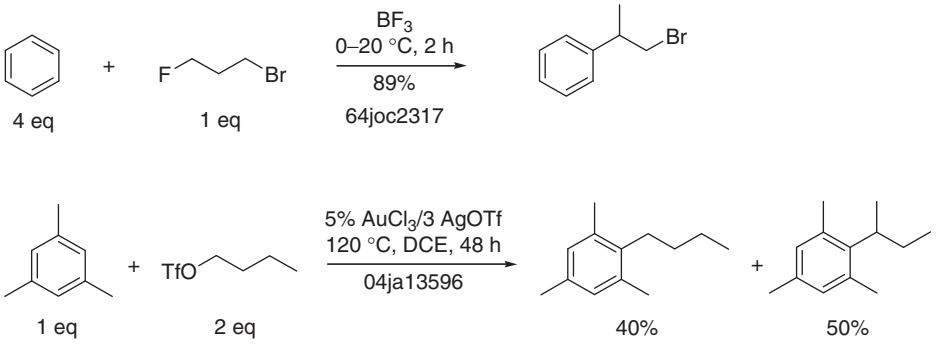
transient formation of benzylic metal complexes (Scheme 1.4). Because racemization is also observed in these instances, the intermediate complexes are likely to undergo fast transmetallation. Ru-based catalysts have been developed that enable the preparation of enantiomerically enriched alkylbenzenes and alkylated heteroarenes from racemic alcohols [27] (Scheme 1.18).

1.1.2
Typical Side Reactions

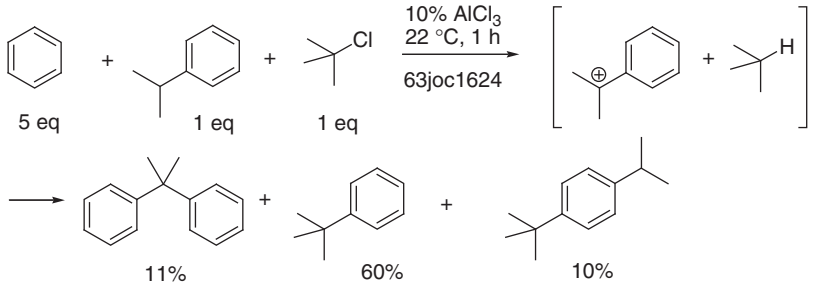
The rearrangement of intermediate carbocations is a common side reaction in Friedel–Crafts chemistry (Scheme 1.5). Rearrangements can sometimes be avoided with the aid of transition-metal-based catalysts, because the intermediate complexes are less reactive than uncomplexed carbocations.

Carbocations can also act as oxidants and abstract hydride from other molecules [31]. The newly formed carbocations may also alkylate arenes and lead to the formation of complex product mixtures (Scheme 1.6).

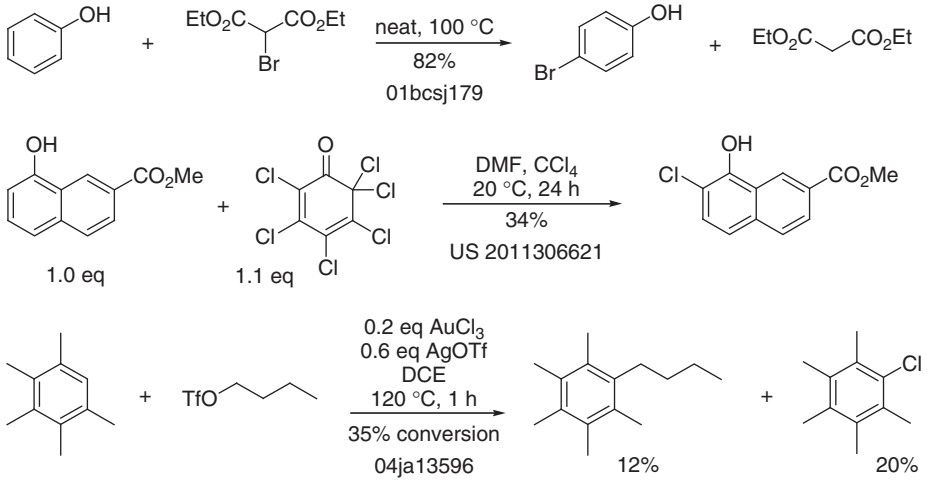
When using noble metal halides as catalysts, or α-haloketones, α-haloesters (Section 1.3.5), or perhaloalkanes as electrophiles, arenes may undergo halogenation instead of alkylation (Scheme 1.7). Alkyl halides with the halogen



Scheme 1.5 Rearrangement of carbocations during Friedel–Crafts alkylations [29, 30].



Scheme 1.6 Hydride abstraction by carbocations as side reaction during Friedel–Crafts alkylations [32].



Scheme 1.7 Halogenation of arenes by alkyl halides and by $AuCl_3$ [30, 33, 34].

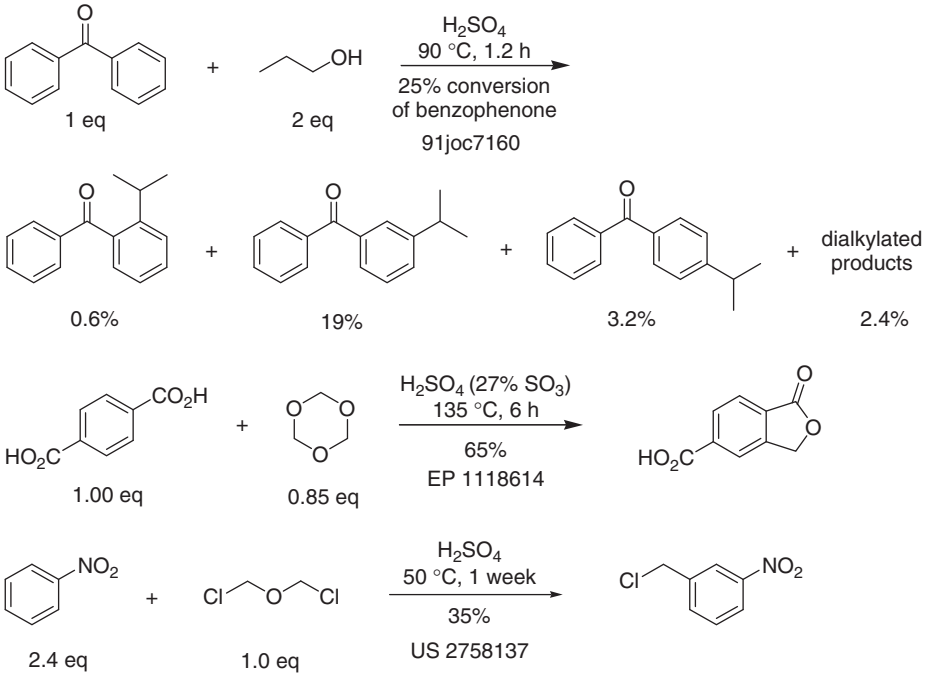
bound to good leaving groups (positions where a carbanion would be stabilized) are electrophilic halogenating reagents.

If the concentration of alkylating reagent is too low, arenes may undergo acid-catalyzed oxidative dimerization (Scholl reaction) [35]. This reaction occurs particularly easily with electron-rich arenes, such as phenols and anilines.

1.2 Problematic Arenes

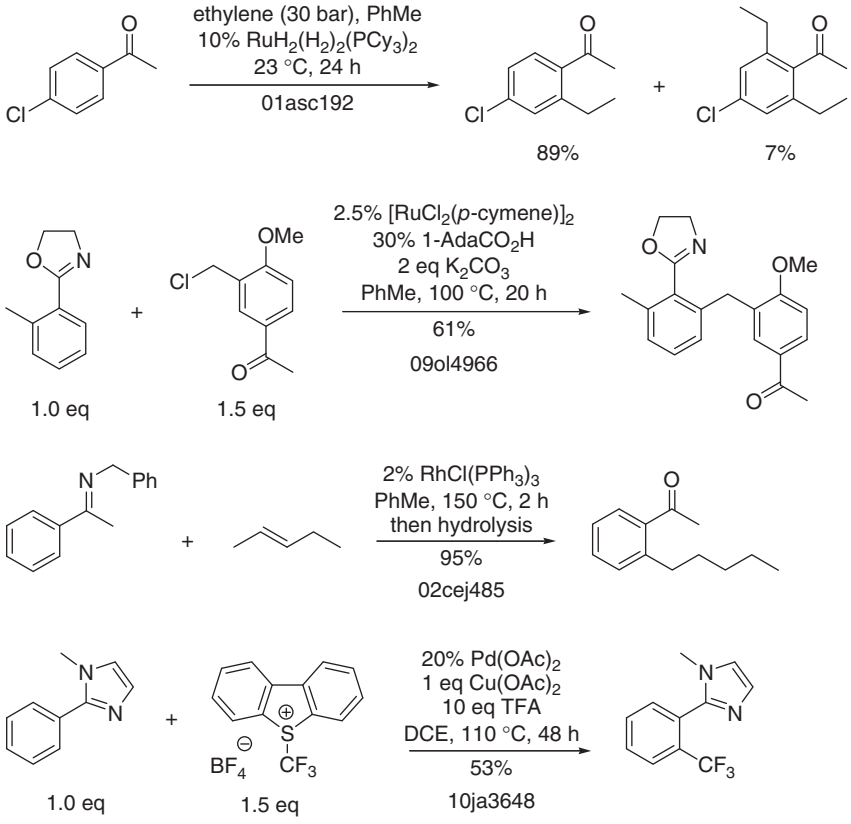
1.2.1 Electron-Deficient Arenes

Yields of alkylations of electron-deficient arenes by carbocations are usually low. This is mainly because the reaction is too slow, and the carbocation undergoes rearrangement and polymerization before attacking the arene. If no alternative reaction pathways are available for the carbocation, though, high-yielding Friedel–Crafts alkylations of electron-deficient arenes can be achieved (Scheme 1.8).



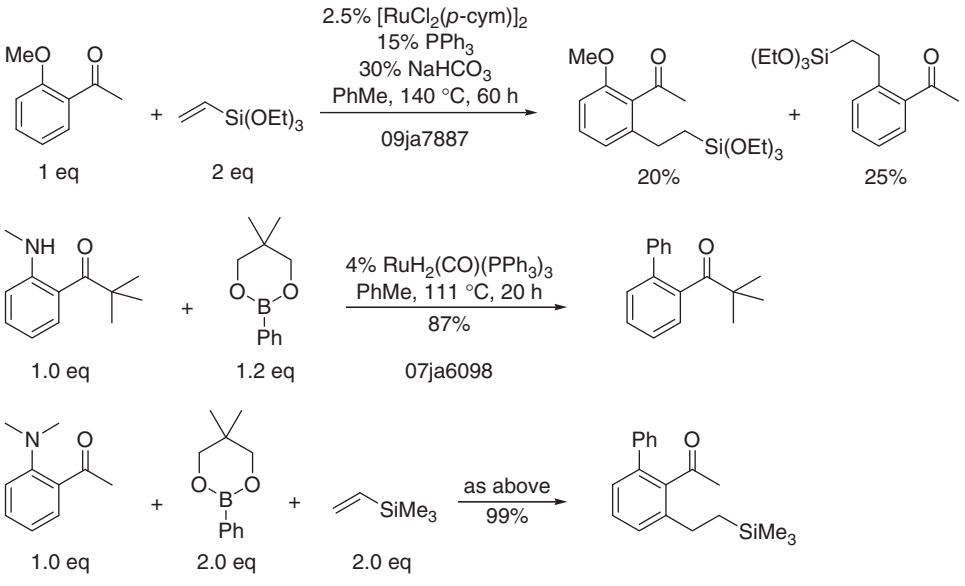
Scheme 1.8 Friedel–Crafts alkylation of electron-deficient arenes [36–38].

Electron-deficient arenes can be alkylated by olefins or alkyl halides via intermediate arene metallation. Chelate formation is usually required and crucial for the regioselectivity of transition-metal-catalyzed reactions (Scheme 1.9). The Ru- and Rh-catalyzed ortho-alkylation of acetophenones and acetophenone-imines by alkenes can even proceed at room temperature [39]. With sterically demanding alkyl halides, Ru complexes can mediate meta-alkylations [24]. When conducted in the presence of oxidants, these reactions can yield styrenes instead of alkylbenzenes [40–42] (see also Section 2.3).



Scheme 1.9 Ru-, Rh-, and Pd-catalyzed, chelate-mediated alkylation of electron-deficient arenes [43–46].

The metals used as catalysts for this ortho-alkylation of acetophenones insert not only into C–H bonds but also at similar rates into C–O and C–N bonds (Scheme 1.10). The selectivity can sometimes be improved by the precise choice of the catalyst [47]. Another potential side reaction of the alkylations described above



Scheme 1.10 Ru-catalyzed ortho-alkylation and -arylation of acetophenones [50, 51]. Further examples: [52, 53].

is aromatic hydroxylation, which can readily occur if oxidants are present in the reaction mixture [48, 49].

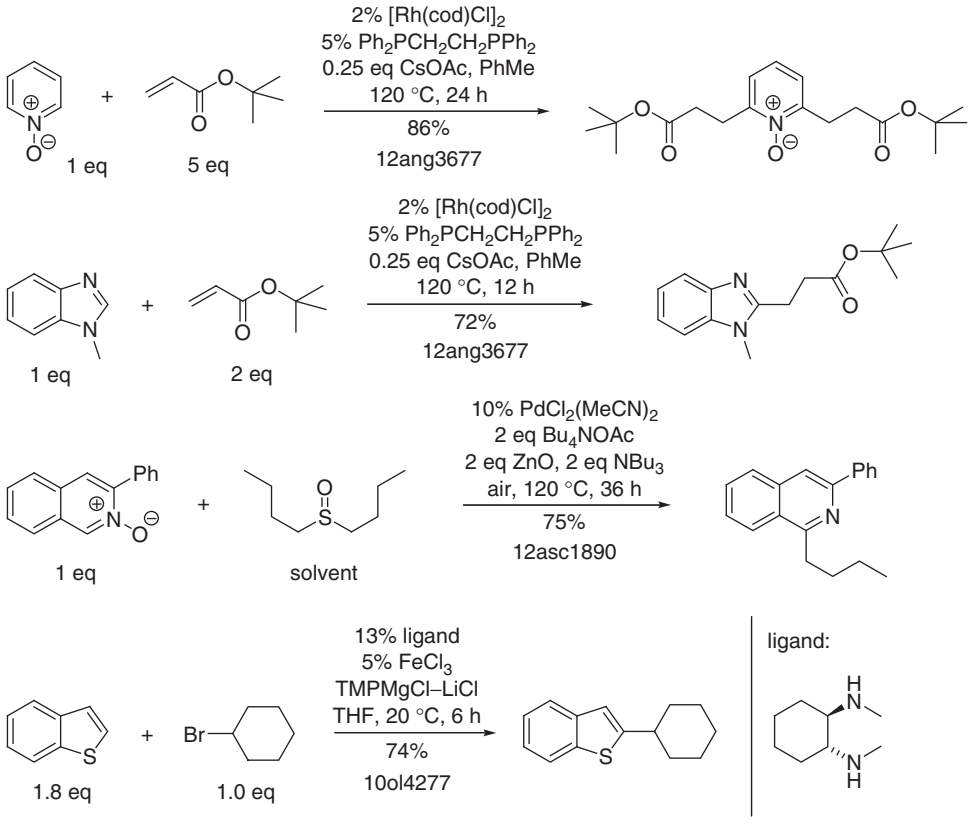
Some heteroarenes, such as pyridine *N*-oxides, thiazoles, or imidazoles, are strongly C–H acidic, and can be metallated catalytically even without chelate formation. In the examples in Scheme 1.11, the intermediates are, in fact, metal carbene complexes.

Under forcing conditions, fluoro- or nitrobenzenes can also be metallated without chelate formation, and trapped *in situ* with a number of electrophiles, including aldehydes and ketones (Scheme 1.12). Owing to the competing Cannizzaro reaction and the potential cleavage of ketones by strong nucleophiles (e.g., Haller–Bauer reaction), these reactions may require a large excess of electrophile and careful optimization.

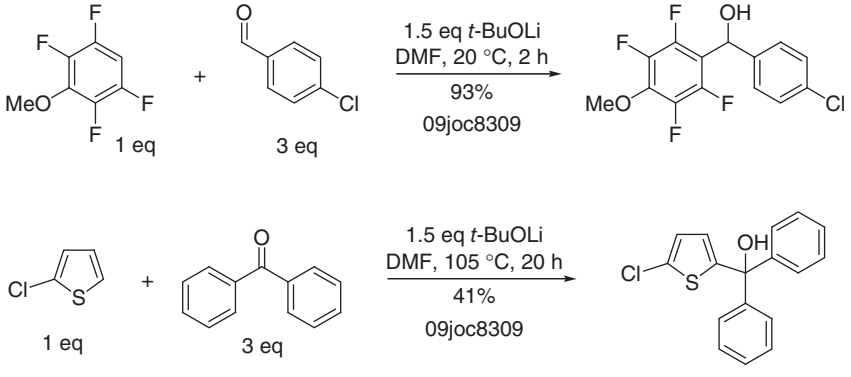
Electron-deficient arenes and heteroarenes, such as pyridinium salts, can react with carbon-centered, electron-rich radicals. These can be generated from alkanes, alkyl halides, carboxylic acids, and some diacylperoxides [58] (Scheme 1.13), or by oxidation of boranes [59]. The regioselectivity of such alkylations is, however, often poor.

1.2.2 Phenols

Phenols are inherently problematic nucleophiles in Friedel–Crafts type chemistry because the free hydroxyl group can deactivate Lewis acids and because phenols



Scheme 1.11 Metallation and alkylation of C–H acidic heteroarenes [54–56].

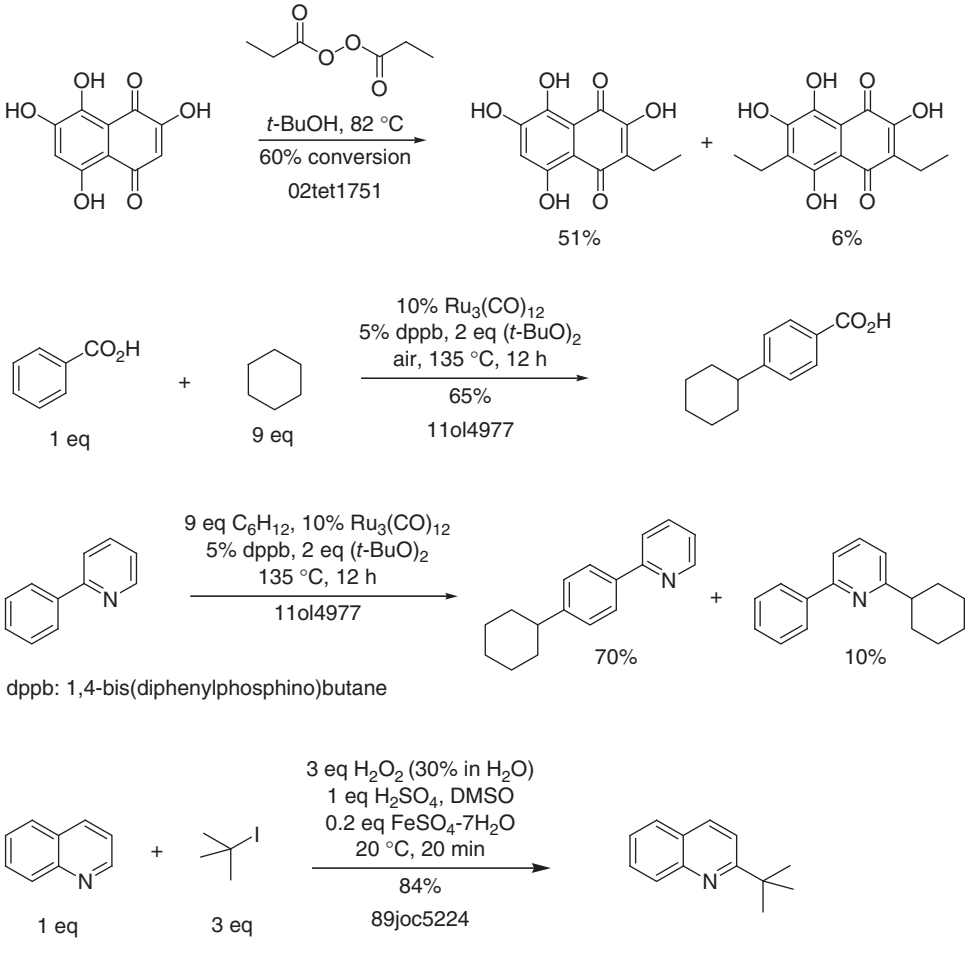


Scheme 1.12 Metallation and alkylation of C–H acidic arenes [57].

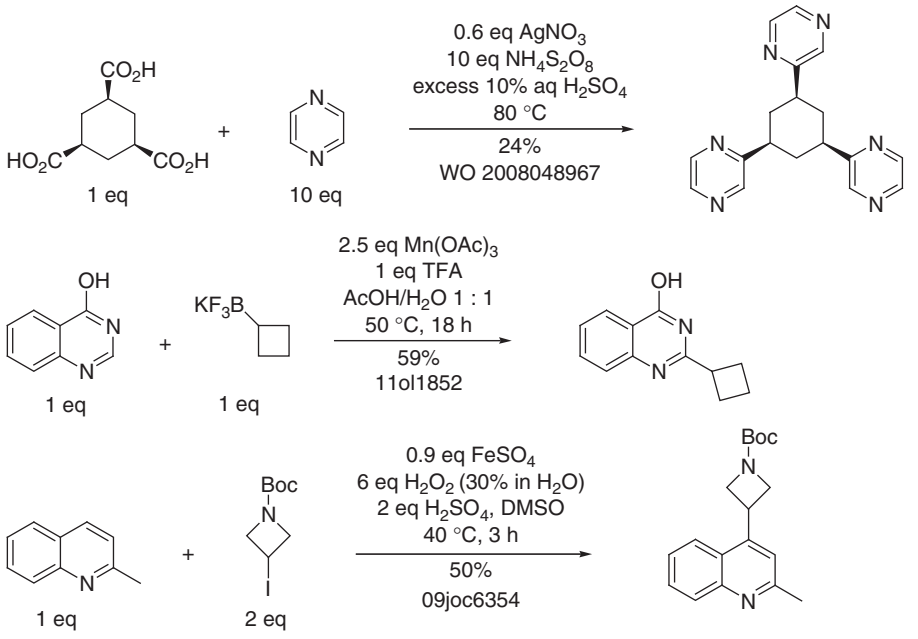
are tautomers of enones and may themselves act as electrophiles (see below). Moreover, phenols readily dimerize to biaryls in the presence of oxidants.

Under suitable reaction conditions, though, phenols can be alkylated at carbon, without extensive O-alkylation. Stabilized carbocations are soft electrophiles, and react preferentially with soft nucleophiles, such as arenes or olefins. Phenol O-alkylation under acidic conditions is observed only with hard alkylating reagents (diazomethane, dimethyl carbonate, methanol, methyl esters, alkoxyphosphonium salts (Mitsunobu reaction), or acetals). O-Alkylated phenols sometimes rearrange to C-alkylated phenols in the presence of acids [66] (Scheme 1.14).

At high temperatures, phenols and aluminum phenolates are C-alkylated by olefins (Scheme 1.15). This reaction proceeds less readily and has a narrower scope



Scheme 1.13 Alkylation of arenes with radicals [59–64]. Further examples: [65].

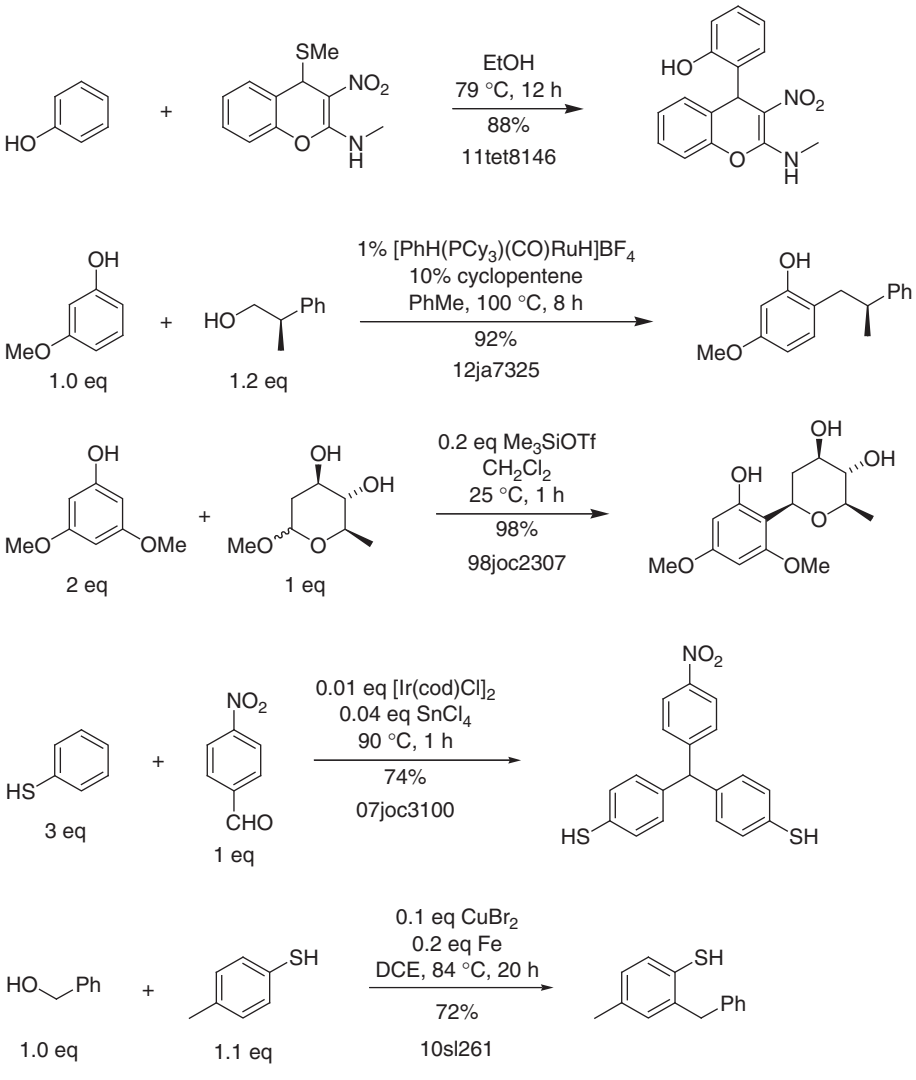


Scheme 1.13 (*Continued*)

than the corresponding reaction of aluminum anilides (see next section). Although ortho-alkylation occurs first, upon prolonged reaction with an excess of olefin, 2,4,6-trialkylated and higher alkylated phenols result [72, 73]. At high pressure, even Diels–Alder reactions with the olefin may occur [74]. Today, a number of important alkylphenols are prepared by high-temperature alkylations with olefins in the presence of heterogeneous catalysts [73, 75].

Some bis-electrophiles can alkylate phenols both at oxygen and at carbon. 1,3-Dienes, for instance, react with phenols in the presence of acids [78] or Rh complexes [79] to yield chromanes (Scheme 1.16).

Phenols are tautomers of cyclohexadienones, and may react as such. In particular, 1- or 2-naphthols, 1,3-dihydroxybenzenes, and 1,3,5-trihydroxybenzenes show strong cyclohexenone character. Phenols and arylethers react with arenes in the presence of aluminum halides or HF/SbF_5 to yield 3- or 4-arylcyclohexenones [81–83]. The precise outcome of these reactions is difficult to predict; depending on the amount of acid used and the basicity of the phenol, either conjugate arylation of an enone or arylation of a dication can occur (Scheme 1.17). Moreover, 4,4-disubstituted cyclohexenones, which also may be formed, undergo acid-mediated rearrangement to 3,4-disubstituted cyclohexanones. Phenols substituted with leaving groups (halides, hydroxyl groups) can undergo elimination after the arylation and yield 3- or 4-arylphenols.

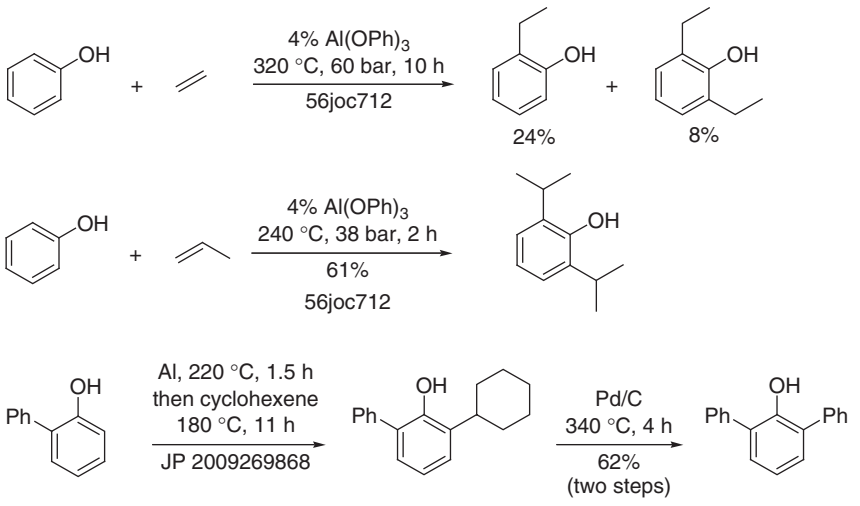


Scheme 1.14 C-Alkylation of phenols and thiophenols under acidic conditions [67–71].

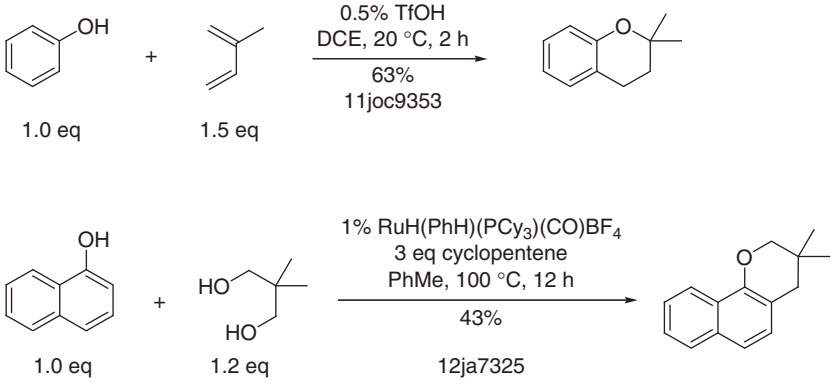
1.2.3 Anilines

Regardless of being N-protonated by acids, anilines can be alkylated at carbon *and* at nitrogen under acidic reaction conditions. Suitable alkylating reagents include alcohols, ethers, alkenes, aldehydes, ketones, and alkyl halides.

Despite the electron-withdrawing effect of ammonium groups, Friedel–Crafts alkylations of anilines usually proceed with ortho and para selectivity, and more



Scheme 1.15 Alkylation of aluminum phenolates with alkenes [76, 77].

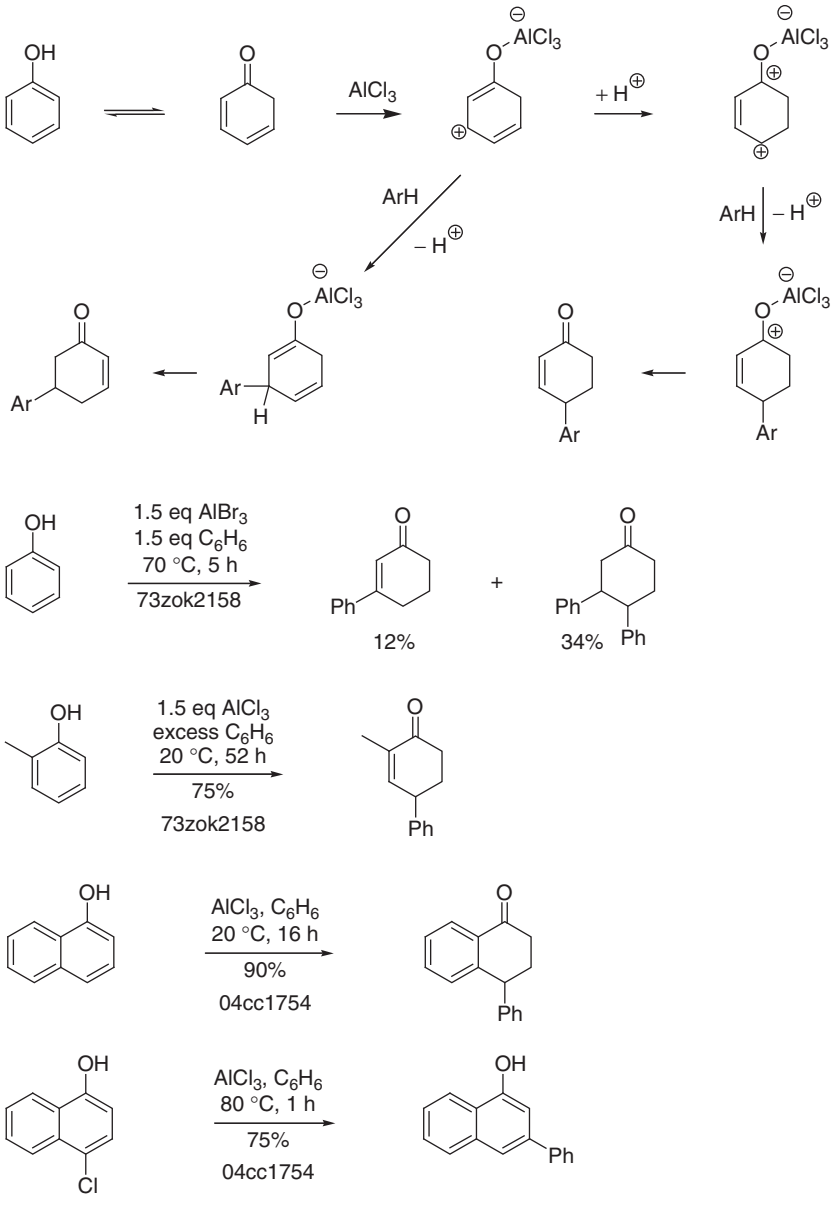


Scheme 1.16 Formation of chromanes from phenols [68, 80].

readily than Friedel–Crafts alkylations of the corresponding benzenes. Thus, although aniline hydrochloride can be para-tritylated in acetic acid (first example in Scheme 1.18), benzene does not react with the trityl cation.

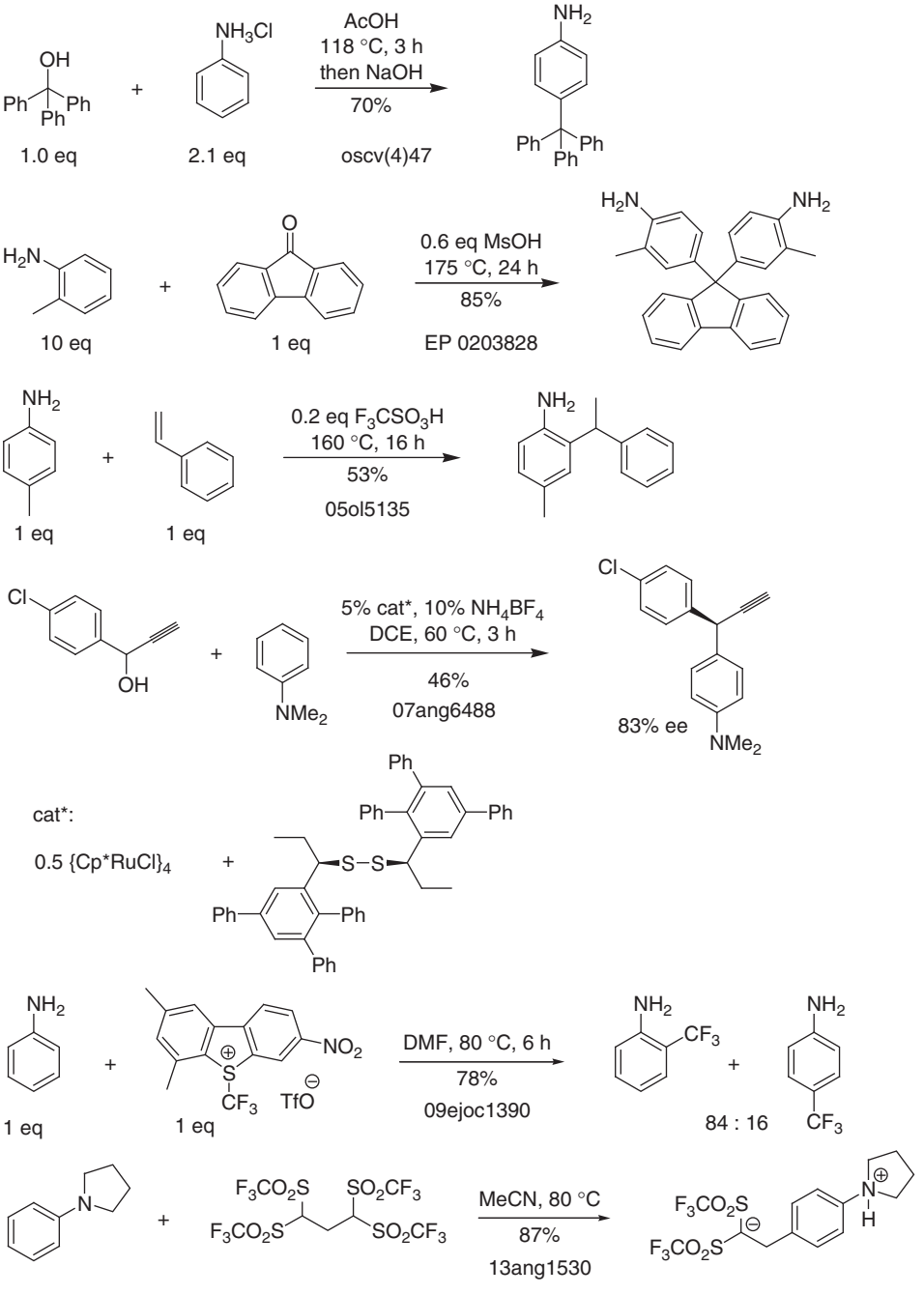
The precise outcome of the reaction of anilines with alkylating reagents can be difficult to predict. Stoichiometric amounts of strong acids usually favor C-alkylations. At high temperatures or in the presence of acids, *N*-alkylanilines may be dealkylated and act as alkylating agents themselves [91–93]. Occasionally, mixtures of N- and C-alkylated products are obtained (Scheme 1.19).

If anilines are treated with aldehydes or ketones in the presence of acids at room temperature, reversible aminal, imine, or enamine formation usually occurs. Upon heating, irreversible alkylation at carbon can take place. Thus, if aniline is

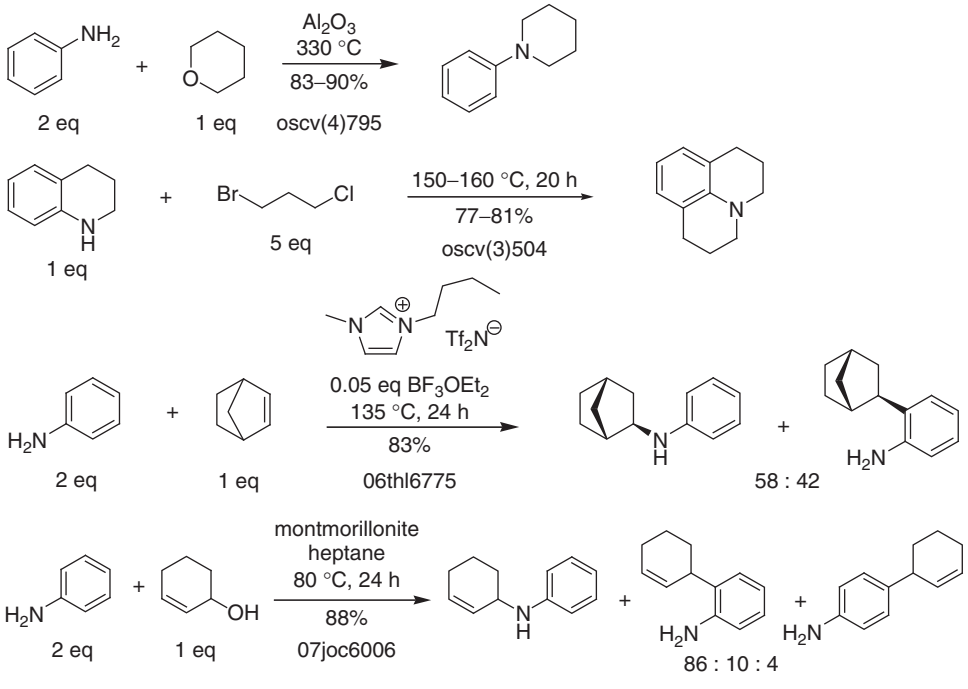


Scheme 1.17 Acid-mediated arylation of phenols [84, 85].

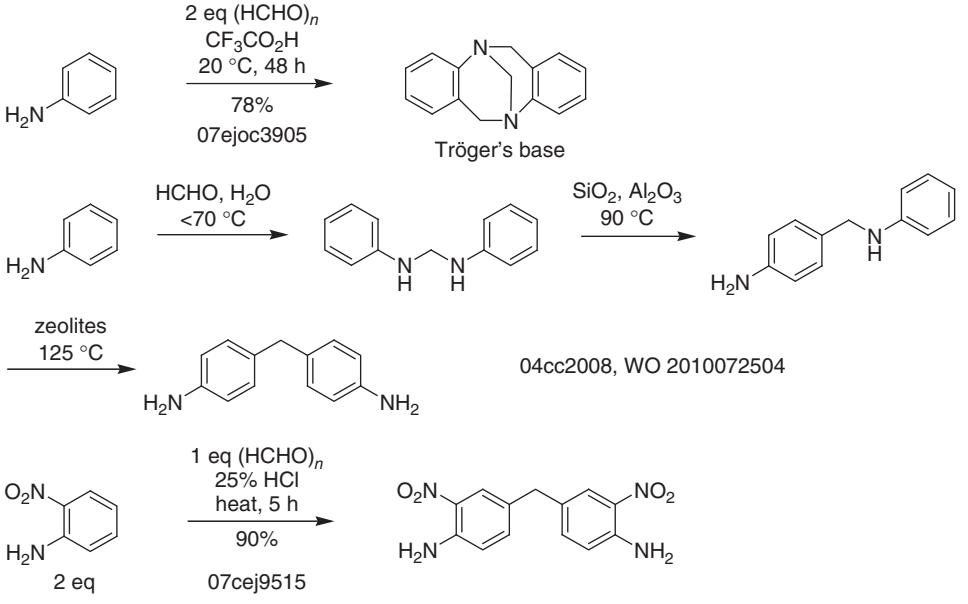
treated with formaldehyde at a low temperature, only aminals, benzylamines, or Tröger's base are formed. At higher temperatures, though, diarylmethanes are the main products (Scheme 1.20). Hydride transfer from aldehydes or anilines to intermediate iminium salts causes the formation of *N*-alkylanilines as byproducts.



Scheme 1.18 Examples of C-alkylations of anilines [27, 86–90].



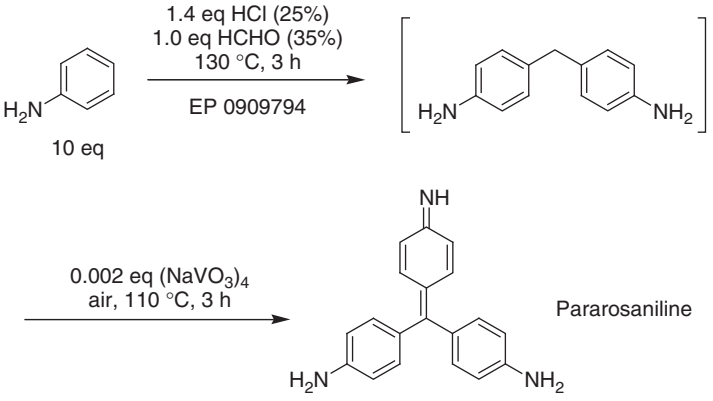
Scheme 1.19 Examples of C- and N-alkylations of anilines [94–97]. Further examples: [98, 99].



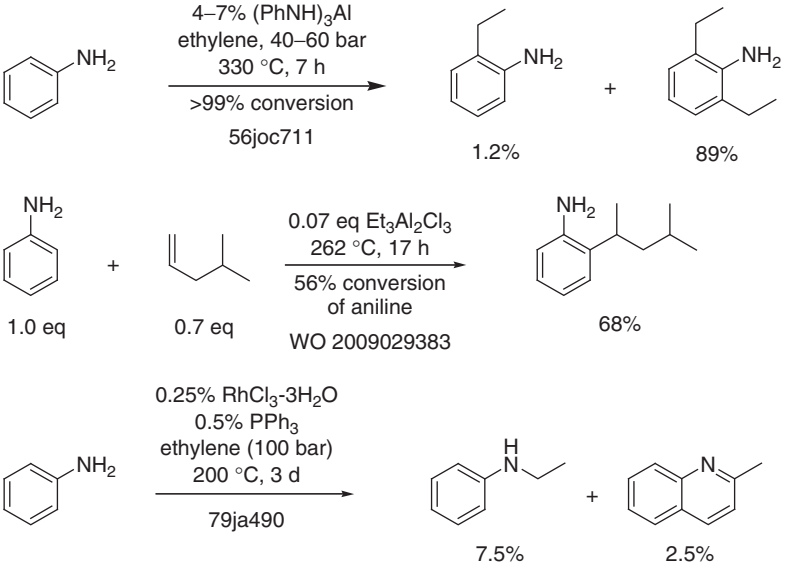
Scheme 1.20 Formation of diarylmethanes from anilines and formaldehyde [100–103].

One side reaction often observed during the preparation of diarylmethanes from anilines is the formation of triarylmethane dyes. A suitable oxidant is air, and the oxidation can be catalyzed by vanadates (Scheme 1.21). Even if oxygen is rigorously excluded, small amounts of these dyes will result from oxidation by the intermediate iminium salts.

Anilines can be selectively ortho-alkylated with olefins under basic reaction conditions. This requires conversion of the aniline into an aluminum anilide by treatment with $Al/AlCl_3$ (Scheme 1.22). This interesting reaction is, however, of little scope, and not well suited to alkylate phenols [76].



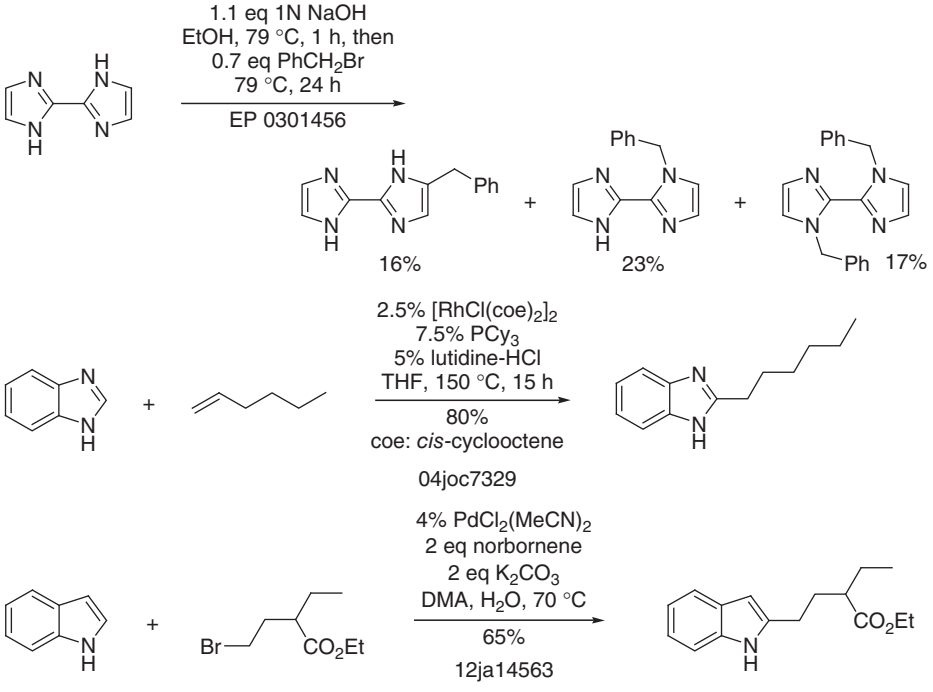
Scheme 1.21 Formation of triarylmethane dyes from diarylmethanes [104].



Scheme 1.22 Alkylation of anilines with olefins [105–107]. Further examples: [108].

1.2.4
Azoles

Azoles with a free NH group can be alkylated at nitrogen or at carbon. The outcome of such reactions is barely predictable, in particular for substrates containing arenes (e.g., indoles, benzimidazoles, etc.). Azoles may also be alkylated after stoichiometric metallation, which enhances the scope of regioselectivities even further. N-Alkylation is favored by hard electrophiles (e.g., methylating reagents), while soft electrophiles (e.g., olefins) lead sometimes to clean C-alkylations. Illustrative examples of the alkylation of non-metallated azoles are given in Scheme 1.23.

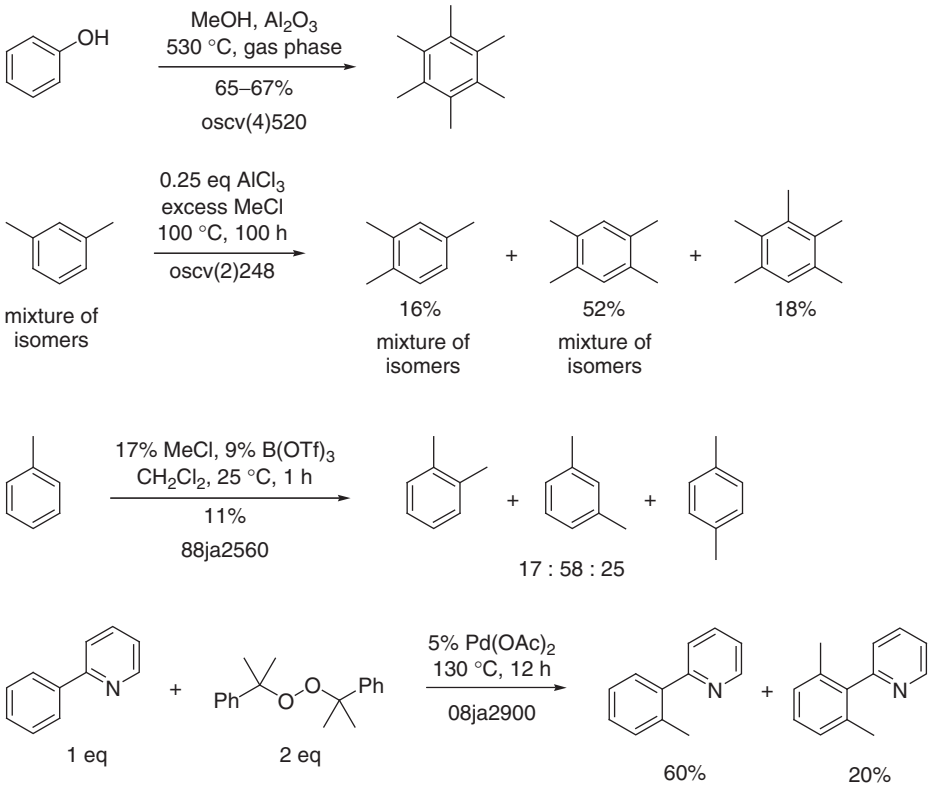


Scheme 1.23 Alkylation of azoles [109–111].

1.3
Problematic Electrophiles

1.3.1
Methylations

Because Friedel–Crafts alkylations require the formation of free carbocations or carbocation-like intermediates, methylations do not proceed readily. Phenols can



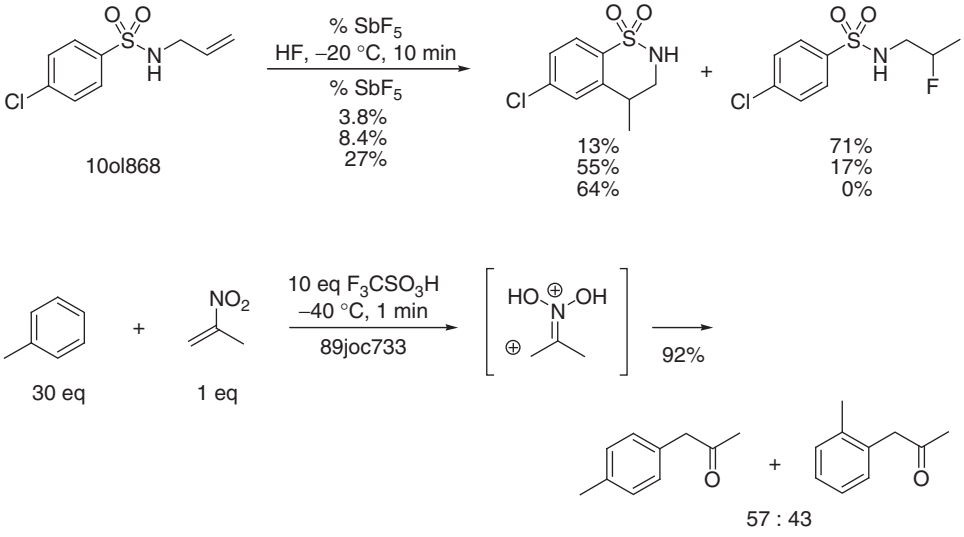
Scheme 1.24 Methylation of arenes with methanol, methyl chloride, and methyl radicals [112–115].

be C-methylated with MeOH, but high temperatures are required (Scheme 1.24). In acid-catalyzed methylations, free methyl cations are probably not formed, and a complex of catalyst with the methylating reagent is more likely to be the reactive intermediate [112].

1.3.2 Olefins

Upon reaction with an arene under acidic reaction conditions, unsymmetric olefins can yield two different products: the one resulting from the more stable carbocation (the Markovnikov product), or the one resulting from the less stable but more reactive carbocation (the anti-Markovnikov product). As with other acid-mediated additions to alkenes, arenes are usually alkylated by the predominant, more stable carbocation. This can also be the case for transition-metal-catalyzed alkylations [116]. Catalysts have been developed, however, that enable the preparation of linear alkylarenes from terminal olefins [117, 118] (Scheme 1.3).

Olefins substituted with electron-withdrawing groups (Michael acceptors) alkylate arenes with the more electrophilic β-carbon (e.g., [119]). Nitroalkenes do so, too, but may be hydrolyzed to ketones upon treatment with strong aqueous acids (Scheme 1.25).



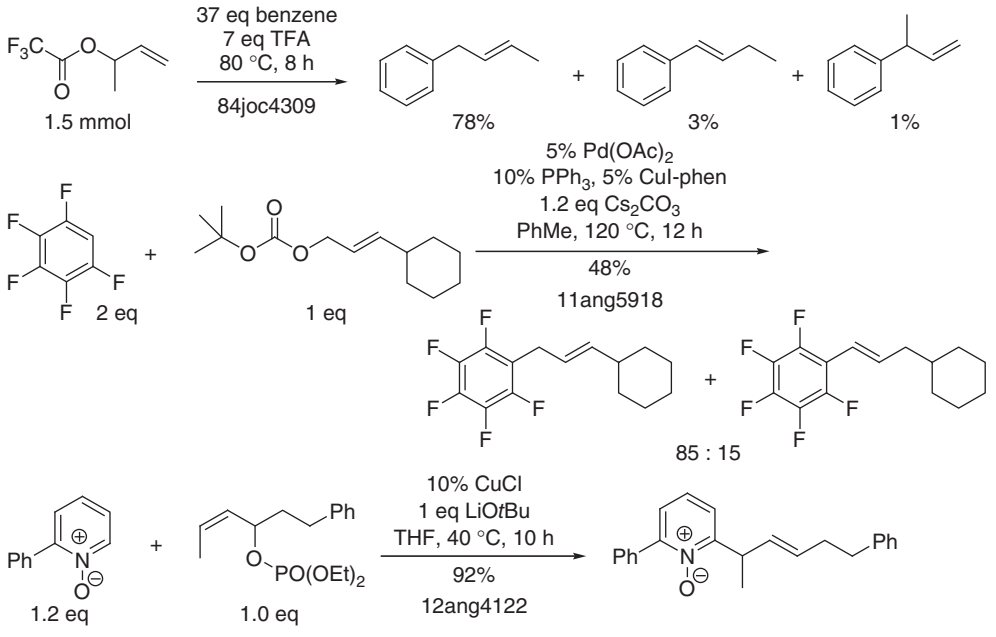
Scheme 1.25 Aromatic alkylations with olefins [120, 121].

A typical side reaction of acid-mediated alkylations with olefins is the oligomerization of the alkene. Styrenes and acrylates polymerize particularly easily. This can sometimes be avoided by keeping the concentration of alkene low, because olefins require a minimum concentration to polymerize. In the presence of oxidants or transition metals, the reaction of arenes with olefins can yield styrenes instead of alkylarenes (Section 2.3).

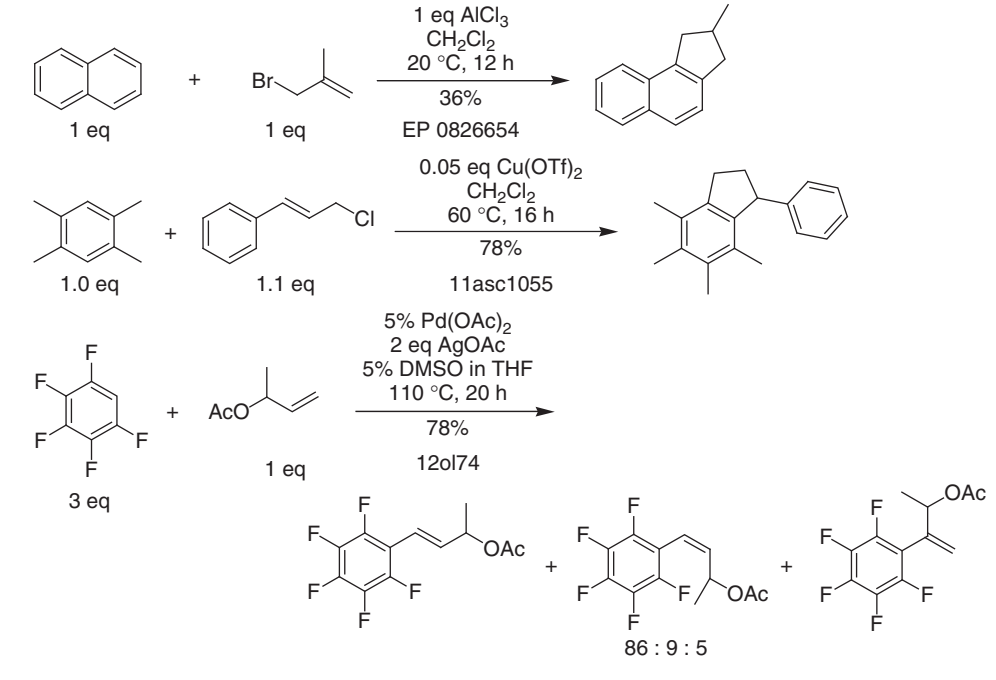
1.3.3 Allylic Electrophiles

The reaction of arenes with allylic electrophiles often yields mixtures of isomeric products. It is not always the dominant (more stable but less reactive) resonance formula that controls regioselectivity; steric effects also influence the course of the reaction (Scheme 1.26). The results may always be rationalized somehow, but the predictive value of such rationalizations is limited.

In the presence of acids, allylic electrophiles are synthetic equivalents of the 1,3-propylene dication. Accordingly, one potential side reaction is the cyclization of the product to yield indanes. Such cyclizations can sometimes be avoided by a large excess of arene. If Pd-based catalysts are used, Heck-type vinylations (instead of allylic substitution) are a further side reaction to be expected (Scheme 1.27).

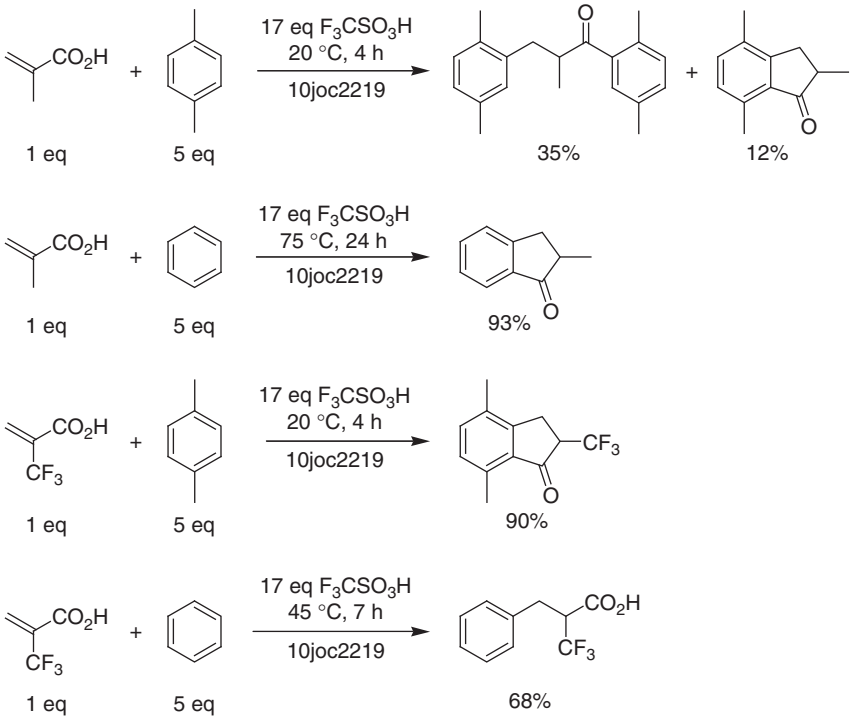


Scheme 1.26 Examples of the alkylation of arenes with allylic electrophiles [122–124]. Further examples: [125, 126].



Scheme 1.27 Cyclizations and Heck reaction of allylic electrophiles [126–128].

Acrylates are a further type of 1,3-dielectrophile that can cause the formation of bicyclic products upon acid-mediated reaction with arenes (Scheme 1.28).

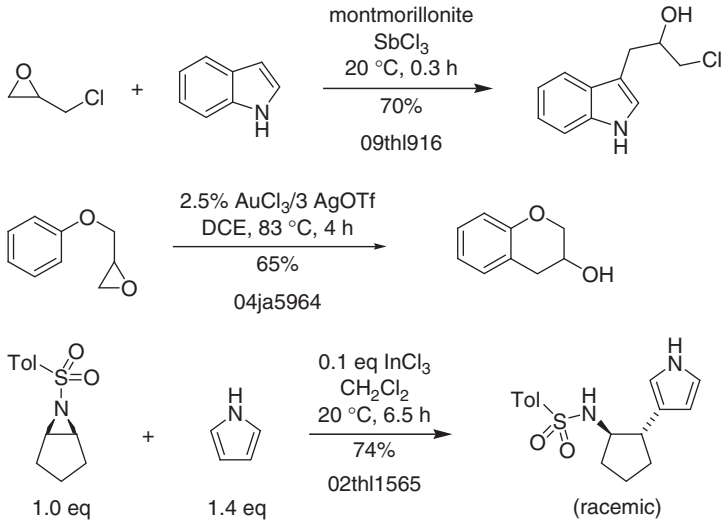


Scheme 1.28 Acid-mediated reactions of acrylic acids with arenes [129].

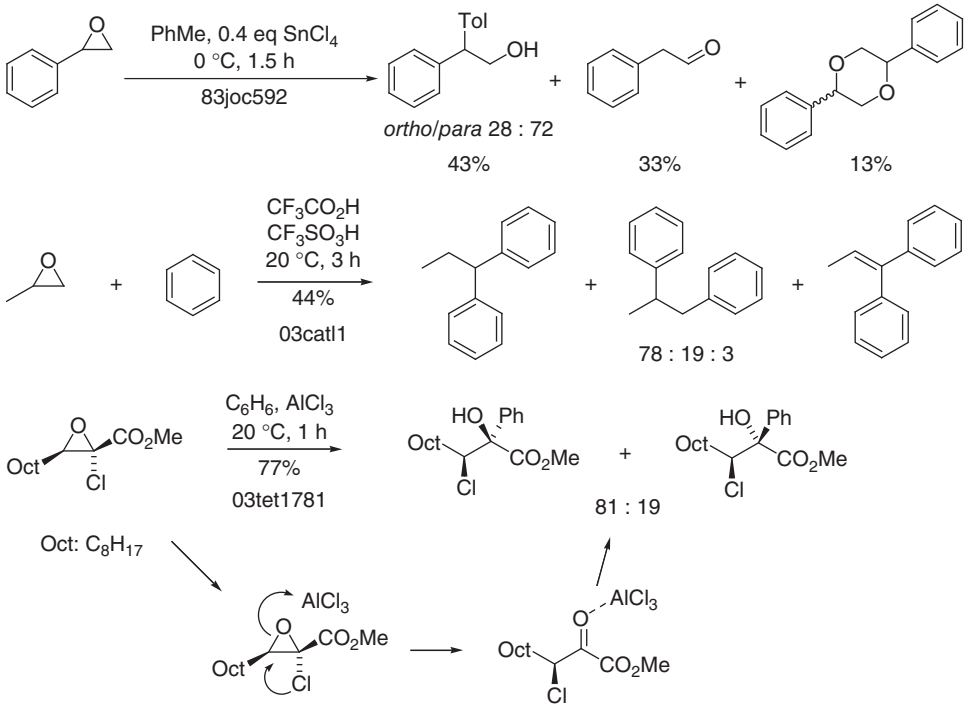
1.3.4 Epoxides

Arenes are usually alkylated by epoxides at the carbon atom that forms the more stable carbocation. Alkyl-, aryl-, or alkenylepoxides will therefore mostly yield primary alcohols, while epoxides substituted with electron-withdrawing groups will mostly yield secondary alcohols. Epichlorohydrin and glycidyl ethers also tend to yield secondary alcohols upon acid-mediated reaction with arenes (Scheme 1.29).

Epoxides are reactive intermediates and may lead to product mixtures if the reaction conditions are not carefully chosen. Typical side reactions include rearrangement of the oxiranes to aldehydes or ketones, dimerization or oligomerization of the oxirane, and alkylation of the arene by the newly formed alcohol (Scheme 1.30).



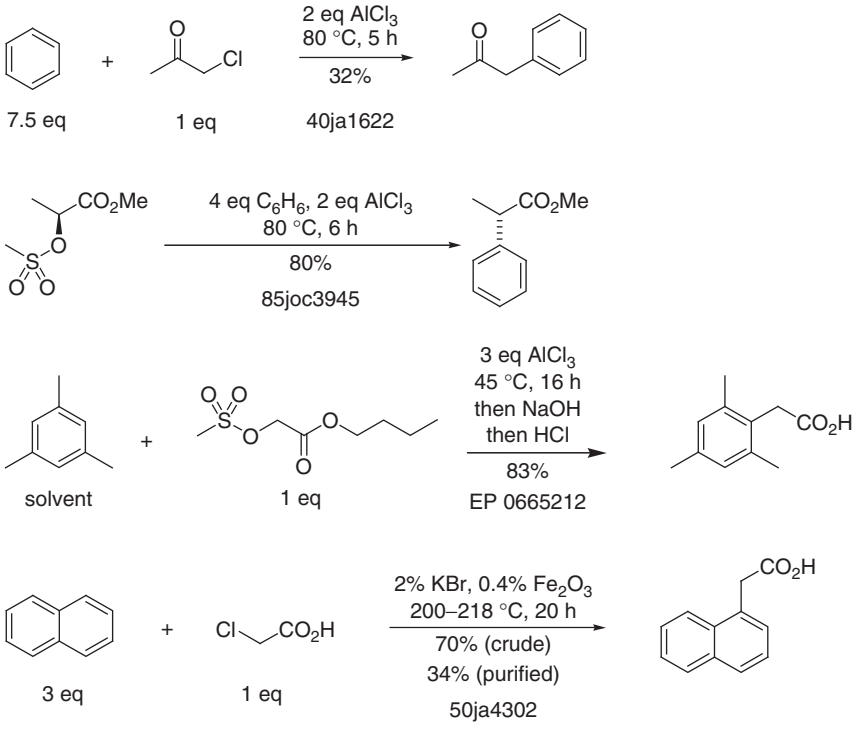
Scheme 1.29 Examples of the alkylation of arenes with epoxides and aziridines [130–132]. Further examples: [133].



Scheme 1.30 Side reactions during the alkylation of arenes by epoxides [134–136].

1.3.5
α-Haloketones and Related Electrophiles

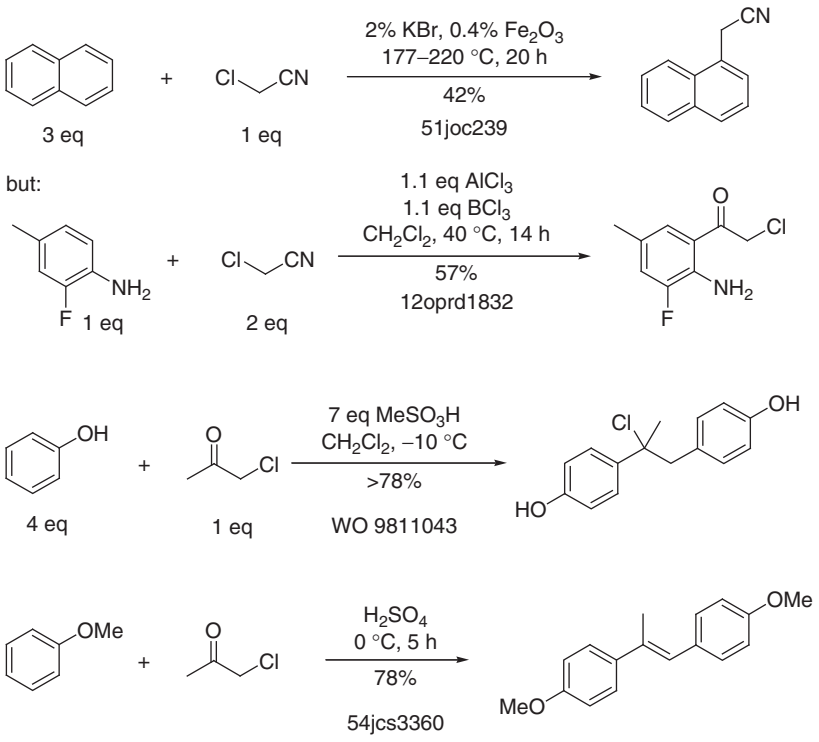
Alkylhalides with the halogen attached to a C–H acidic position (α-haloketones, α-haloesters, α-halonitriles, etc.) display a peculiar reactivity. Removal of the halide to produce a (destabilized) carbocation is difficult, and only a few examples of acid-catalyzed arene alkylations with such electrophiles have been reported [137, 138] (Scheme 1.31). Nucleophilic substitutions at such alkyl halides, however, can proceed with ease. Initial addition of the nucleophile to the carbonyl group is a possible reason for the enhanced reactivity of these electrophiles [139].



Scheme 1.31 Electrophilic alkylation of arenes with α-haloketones and related electrophiles [140–143].

Because arenes can also react with ketones, esters, and nitriles, this is a side reaction to be expected when alkylating arenes with α-haloketones and related electrophiles (Scheme 1.32). Moreover, α-haloketones may also act as halogenating reagents or oxidants [144], and can dimerize or trimerize in the presence of bases.

Ketones and esters may also be converted to radicals, which can then add to arenes or heteroarenes. The most common strategies to generate these radicals include the photolysis of α-haloketones or -esters, and the oxidation of ketones (Scheme 1.33). Because aliphatic α-haloesters absorb UV light of short wavelengths



Scheme 1.32 Arene alkylation or acylation with α-chloroketones and -nitriles [145–148].

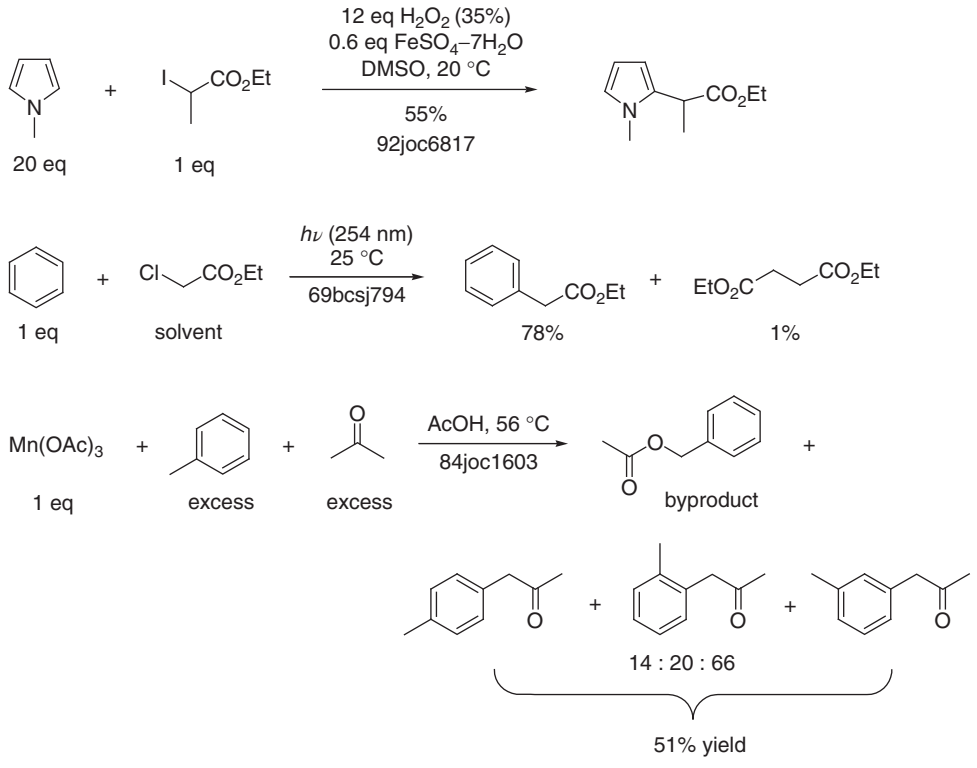
only, the arene cannot usually be used as solvent, because it would not allow the required UV light to reach the haloester (second example in Scheme 1.33).

α-Diazoketones or α-diazoesters are precursors to metal carbene complexes, which can undergo direct insertion into aromatic C–H bonds (Scheme 1.34). The intermediate carbene complexes, though, are highly reactive and electrophilic, and can alkylate many functional groups and abstract hydride and cyclopropanate alkenes, alkynes, and even arenes. For this reason, diazocarbonyl compounds (or diazoalkanes [6]) are only rarely used as electrophilic alkylating reagents for arenes.

The arylation of α-haloketones and related electrophiles via vicarious nucleophilic substitution is discussed in Section 8.2.3.

1.3.6 Nitroalkanes

A few examples have been reported of the alkylation of arenes with nitroalkanes, with the nitro group acting as leaving group [4] (Scheme 1.35). This reaction is complicated by numerous potential side reactions. Nitro groups can act as carbon electrophiles without loss of the nitro group. Moreover, in the presence



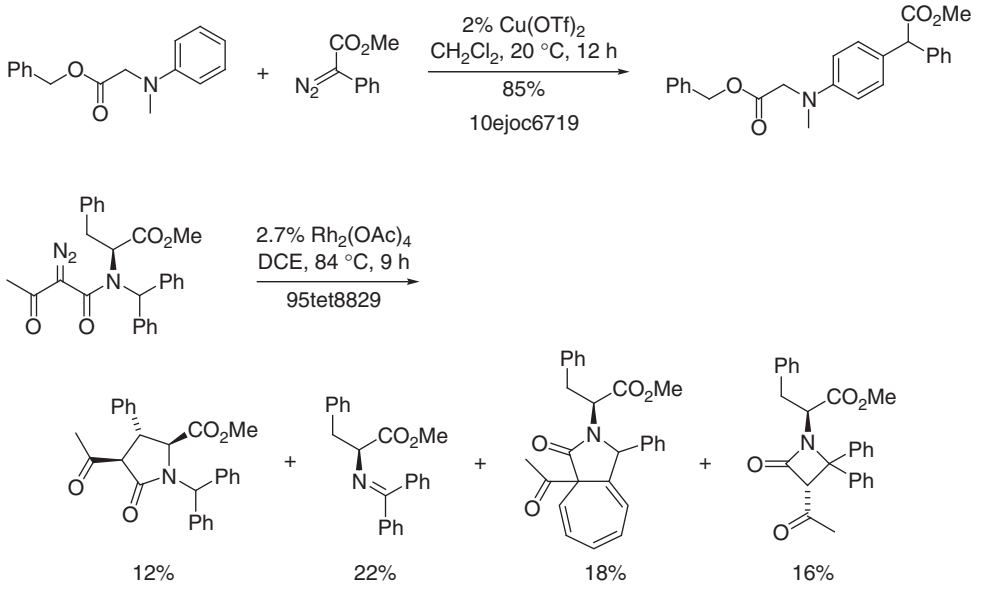
Scheme 1.33 Arylation of α-haloesters and ketones via radicals [149–151].

of strong acids, nitro groups can react with arenes at oxygen. For instance, 2-aryl-1-nitroethanes are converted to *O*-aryloximes when treated with triflic acid (Scheme 1.35). In this type of reactions, nitro groups become electrophilic at oxygen. Examples have also been reported of electrophilic aromatic aminations with nitro groups (last example, Scheme 1.35).

In the presence of dehydrating reagents, primary nitroalkanes (RCH_2NO_2) can be converted to nitrile oxides, which are highly reactive and readily dimerize, polymerize, rearrange to isocyanates, react with nucleophiles, or undergo 1,3-dipolar cycloadditions.

1.3.7 Ketones

Upon catalysis by acids, simple dialkylketones react cleanly with only electron-rich arenes, such as phenols, anilines, or pyrroles, but not with benzene or toluene. The resulting tertiary benzylic alcohols usually alkylate a second arene molecule, to yield geminal diaryl alkanes. Dehydratization of the intermediate alcohols and oligomerization of the resulting olefin are also occasionally observed. If the alcohol



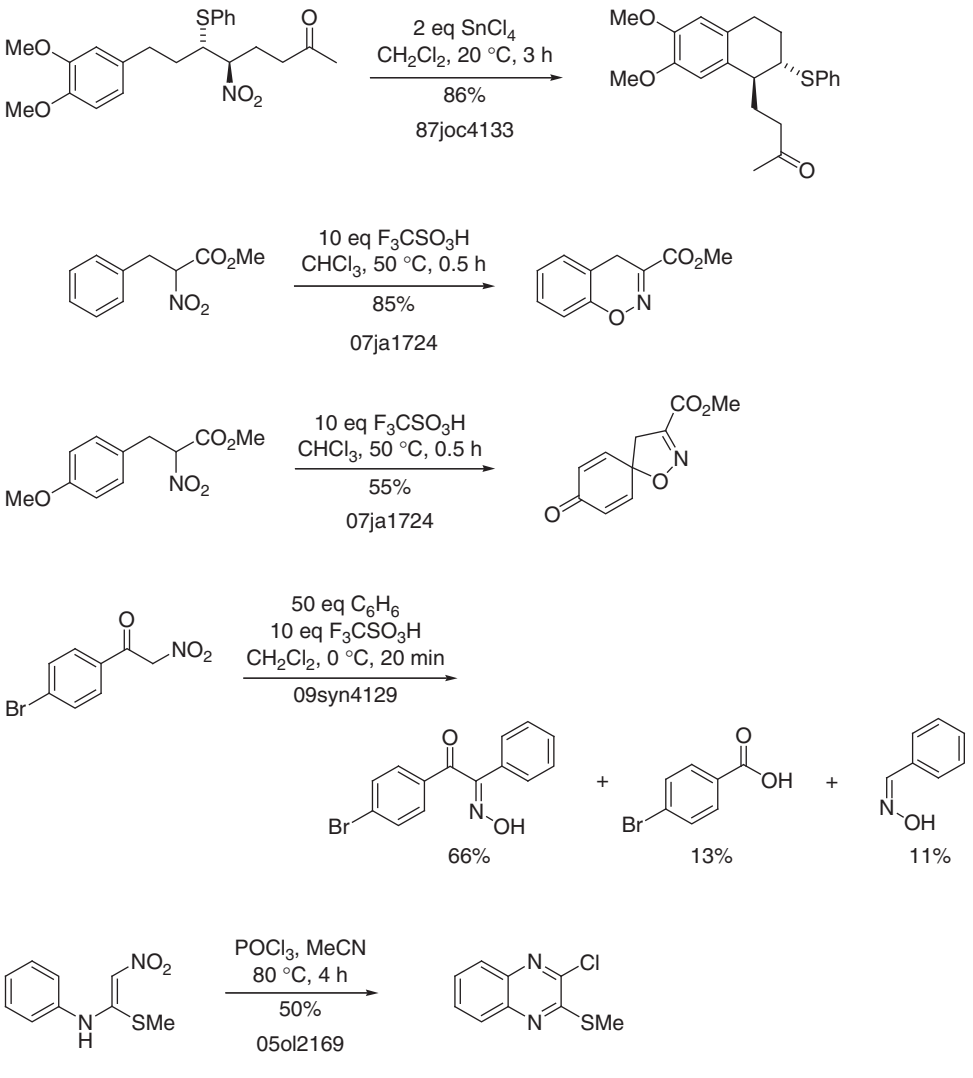
Scheme 1.34 Reaction of α-diazoesters with arenes [152, 153].

is the desired product, a mildly acidic catalyst and carefully optimized conditions will often be required.

Isopropenylbenzene, for instance, cannot be directly prepared from acetone and benzene (for recent research, see [159]) because the readily formed cumyl cation reacts with benzene [160]. The direct preparation of isopropenylbenzene from acetone would be valuable because, during the production of phenol from cumene hydroperoxide, one equivalent of acetone is formed, which cannot currently be used directly for the preparation of cumene. Processes have been developed in which acetone is hydrogenated to isopropanol, which is then converted to propene and used to alkylate benzene (Scheme 1.36). The direct alkylation of benzene with isopropyl alcohol is possible [161, 162], but most catalysts for Friedel–Crafts alkylations are deactivated by water, and isopropylations with propene are therefore more convenient than isopropylations with isopropanol.

Only ketones substituted with electron-withdrawing groups, such as trifluoromethylketones, 1,2-diketones, or α-ketocarboxylic esters, react with unactivated arenes. Fluorenones are also quite reactive because O-protonated fluorenones are antiaromatic. The initially formed alcohols do not form carbocations readily and can often be isolated (Scheme 1.37).

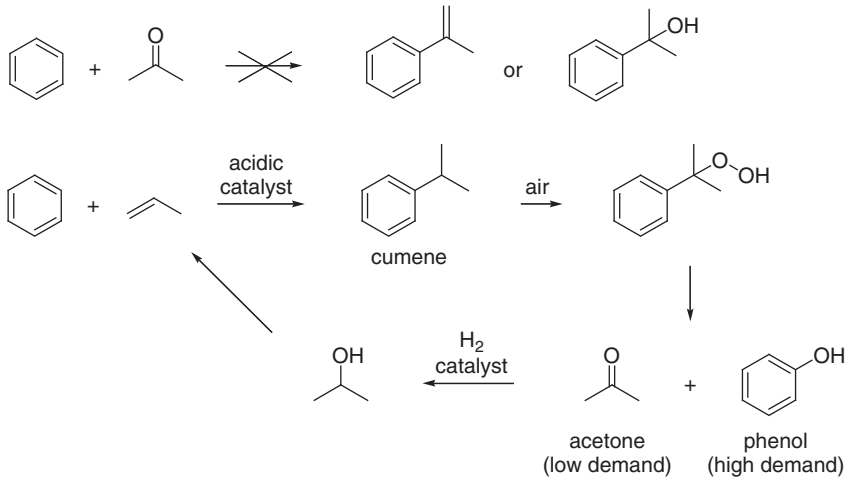
Potential side reactions of the Friedel–Crafts alkylation with ketones is the formation of diarylmethanes, the oligomerization of the products, and aldol condensation of the starting ketone. Moreover, in the presence of oxidants, ketones may be α-arylated via intermediate radical formation [151]. If Friedel–Crafts alkylations with ketones are conducted in the presence of hydride donors, a reductive alkylation of arenes can occur (Scheme 1.38).



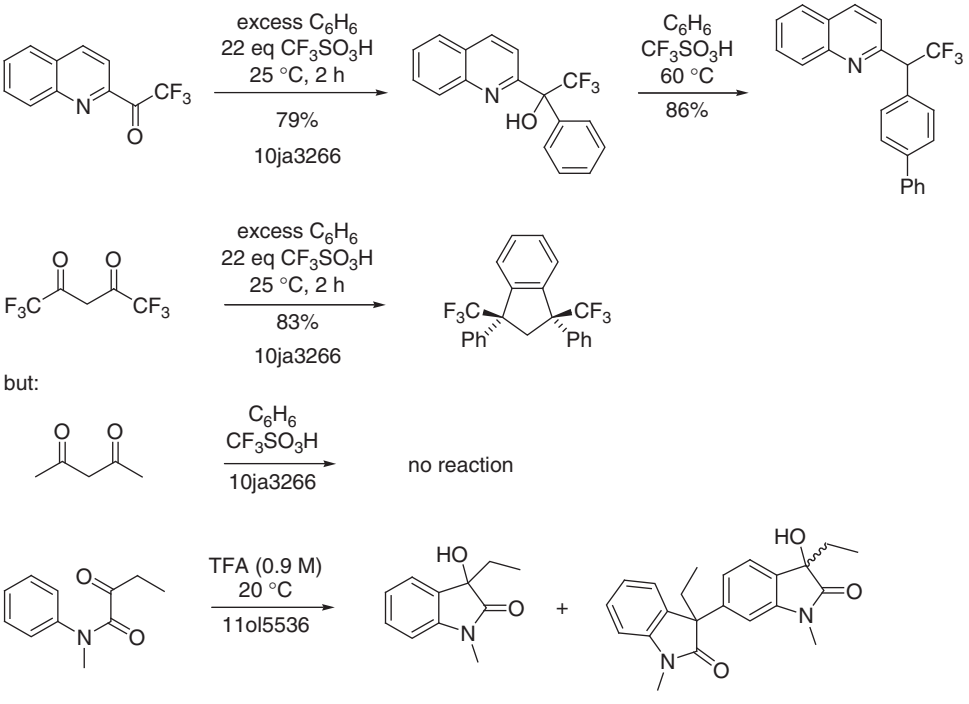
Scheme 1.35 Reactions of nitroalkanes with arenes [154–157]. Further examples: [158].

Strongly C–H acidic ketones, such as β-ketoesters, are readily palladated at carbon. The resulting intermediates can undergo β-hydride elimination to yield α,β-unsaturated ketones. The latter are Michael acceptors, capable of alkylating electron-rich arenes (Scheme 1.39).

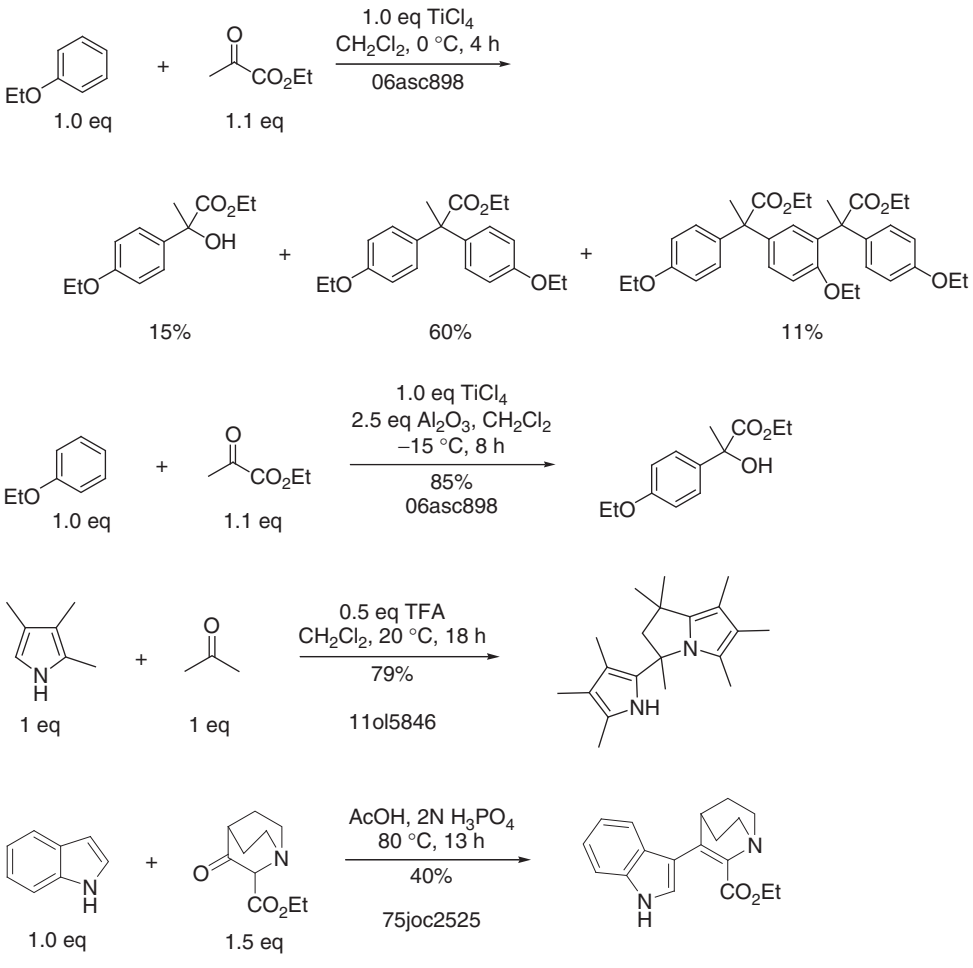
Occasionally, benzylic electrophiles are attacked by nucleophiles not at the benzylic position but at the arene (e.g., first equation in Scheme 1.37). Examples have been reported of the electrophilic arylation of unsubstituted arenes with tetralones and related aryl ketones (Scheme 1.40).



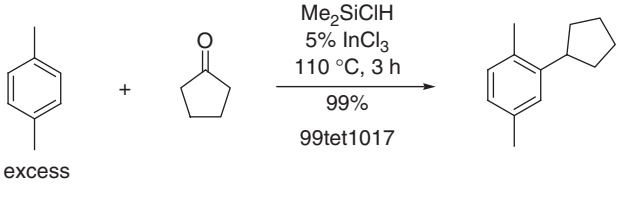
Scheme 1.36 Preparation of phenol and acetone from benzene.



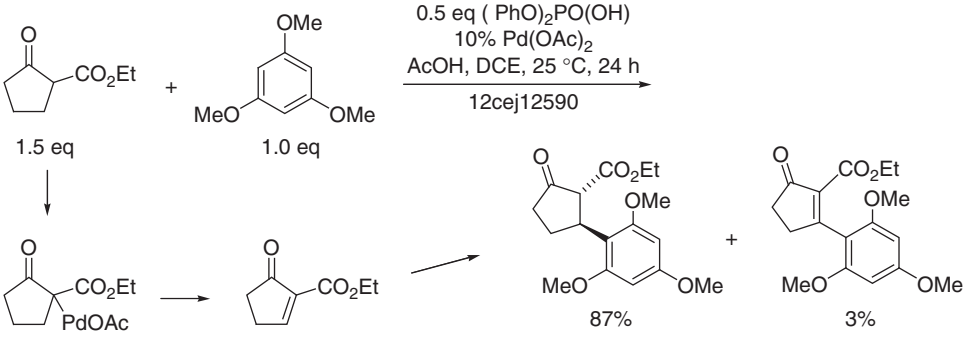
Scheme 1.37 Alkylation of arenes and heteroarenes by ketones [163–167].



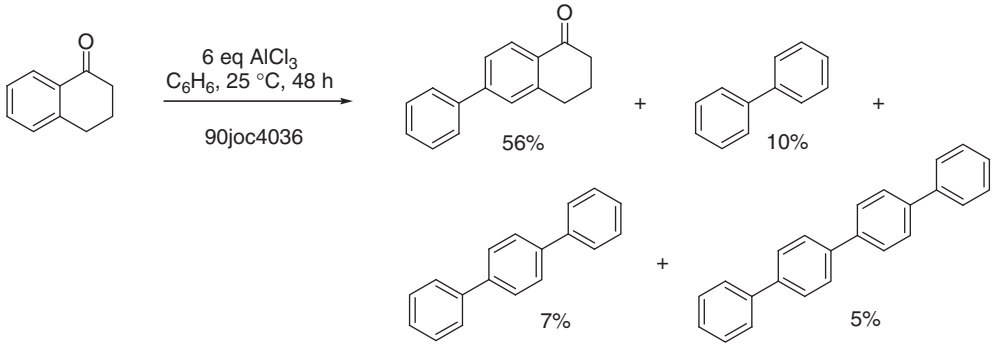
Scheme 1.37 (*Continued*)



Scheme 1.38 Reductive aromatic alkylation with ketones [168].



Scheme 1.39 Dehydrogenation as side reaction of the Pd-catalyzed arylation of ketones [169].



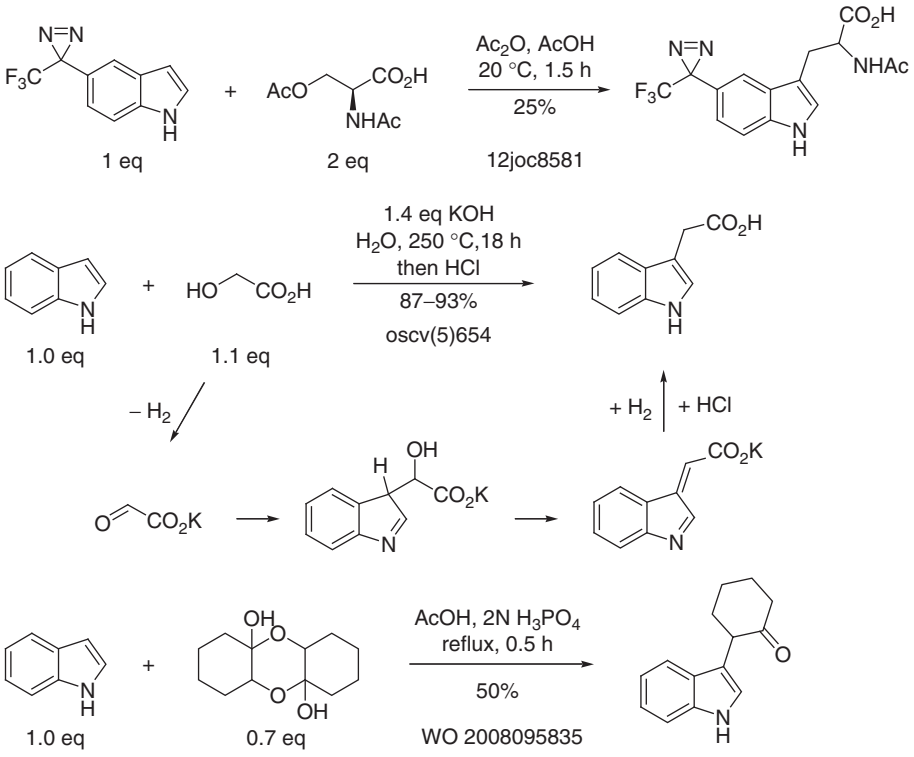
Scheme 1.40 Arylation of benzene with tetralone [83].

1.3.8 Alcohols

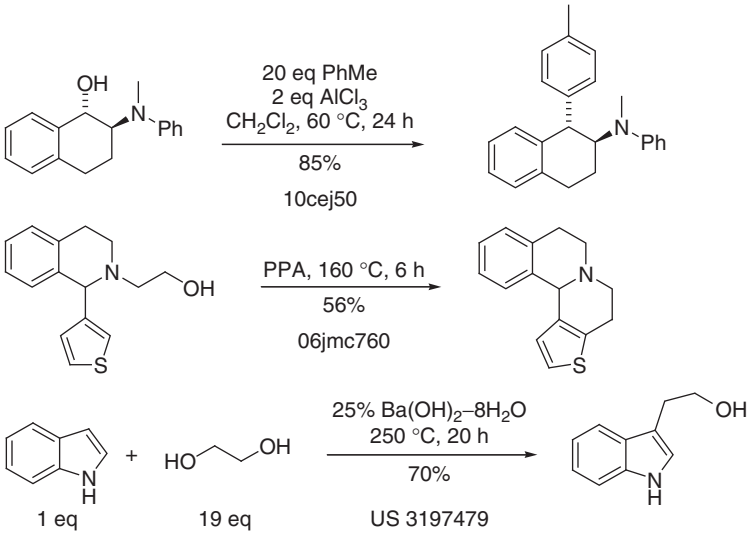
Alcohols are widely used electrophiles for Friedel–Crafts alkylations. Alcohols are often more reactive than alkyl halides, but require more acid to alkylate arenes. Primary, non-benzylic alcohols are rarely used as alkylating reagents, owing to their fast rearrangement to more stable secondary or tertiary cations.

As is the case with other electrophiles, alcohols that do not readily form carbocations are not well suited for arene alkylation. No examples for cationic arene alkylations with 2,2,2-trihaloethanols or cyanohydrins, for instance, could be found. Only a few examples have been reported of alkylations with α-hydroxycarboxylic acids or α-hydroxyketones, and most of these examples were alcohols with carbocation-stabilizing α-substituents (e.g., benzylic alcohols).

Under strongly basic conditions, indole can be alkylated at C-3 with glycolic acid, but this reaction proceeds by oxidation of the alcohol to an intermediate aldehyde (Scheme 1.41). A similar alkylation of fluorene with alcohols at the benzylic methylene group has also been reported [170, 171].



Scheme 1.41 Alkylation of indoles with alcohols and esters [172–174].



Scheme 1.42 Alkylation of arenes with 2-aminoalcohols and ethylene glycol [175–177].

Alcohols or esters thereof, which upon dehydratization yield Michael acceptors, react as soft electrophiles, and are well suited for the alkylation of electron-rich arenes (first equation, Scheme 1.41).

2-Amino- and 2-alkoxyethanols are further types of alcohol that do not readily alkylate arenes under acidic conditions. Oxygen and nitrogen are more electronegative than carbon, and the corresponding carbocations are destabilized by an inductive effect. Moreover, the acids will protonate amines and ethers, and thus further slow down the formation of the required dications. Otherwise, only activated alcohols (e.g., benzylic or allylic alcohols) or intramolecular alkylations proceed in acceptable yields (Scheme 1.42).

References

1. Bachmann, W.E. (1955) Triphenylchloromethane. *Org. Synth.*, Coll. Vol. **3**, 841–845.
2. Xu, X., Xu, X., Li, H., Xie, X., and Li, Y. (2010) Iron-catalyzed, microwave-promoted, one-pot synthesis of 9-substituted xanthenes by a cascade benzylation-cyclization process. *Org. Lett.*, **12**, 100–103.
3. Chung, K.H., Kim, J.N., and Ryu, E.K. (1994) Friedel–Crafts alkylation reactions of benzene with amide bond containing compounds. *Tetrahedron Lett.*, **35**, 2913–2914.
4. Bonvino, V., Casini, G., Ferappi, M., Cingolani, G.M., and Pietroni, B.R. (1981) Nitro compounds as alkylating reagents in Friedel–Crafts conditions: reaction of 2-nitropropane with benzene. *Tetrahedron*, **37**, 615–620.
5. Margosian, D., Speier, J., and Kovacic, P. (1981) Formation of (1-adamantylcarbinyl)arenes from 3-azidohomoadamantane–aluminum chloride–aromatic substrates. *J. Org. Chem.*, **46**, 1346–1350.
6. Zhao, X., Wu, G., Zhang, Y., and Wang, J. (2011) Copper-catalyzed direct benzylation or allylation of 1,3-azoles with *N*-tosylhydrazones. *J. Am. Chem. Soc.*, **133**, 3296–3299.
7. Klumpp, D.A., Aguirre, S.L., Sanchez, G.V. Jr., and de Leon, S.J. (2001) Reactions of amino alcohols in superacid: the direct observation of dicationic intermediates and their application in synthesis. *Org. Lett.*, **3**, 2781–2784.
8. Ohwada, T., Kasuga, M., and Shudo, K. (1990) Direct observation of an intermediate in the oxygen atom rearrangement of 2-cyclopropylnitrobenzene in a strong acid. *J. Org. Chem.*, **55**, 2717–2719.
9. Katritzky, A.R., Lopez Rodriguez, M.L., Keay, J.G., and King, R.W. (1985) Nucleophilic displacement with heterocycles as leaving groups. Part 16. Reactions of secondary alkyl primary amines with 5,6,8,9-tetrahydro-7-phenyldibenzo[*c*,*h*]xanthylium trifluoromethanesulfonate to give intermediates solvolysing without rearrangement. *J. Chem. Soc., Perkin Trans. 2*, 165–169.
10. Imm, S., Bähn, S., Tillack, A., Mevius, K., Neubert, L., and Beller, M. (2010) Selective ruthenium-catalyzed alkylation of indoles by using amines. *Chem. Eur. J.*, **16**, 2705–2709.
11. Quast, H., Nüdling, W., Klemm, G., Kirschfeld, A., Neuhaus, P., Sander, W., Hrovat, D.A., and Borden, W.T. (2008) A perimidine-derived non-Kekulé triplet diradical. *J. Org. Chem.*, **73**, 4956–4961.
12. Mazik, M. and Sonnenberg, C. (2010) Isopropylamino and isobutylamino groups as recognition sites for carbohydrates: acyclic receptors with enhanced binding affinity toward β-galactosides. *J. Org. Chem.*, **75**, 6416–6423.
13. Wallace, K.J., Hanes, R., Anslyn, E., Morey, J., Kilway, K.V., and Siegel, J. (2005) Preparation of

1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene from two versatile 1,3,5-tri(halosubstituted) 2,4,6-triethylbenzene derivatives. *Synthesis*, 2080–2083.

14. Saulnier, G., Dodier, M., Frennesson, D.B., Langley, D.R., and Vyas, D.M. (2009) Nucleophilic capture of the imino-quinone methide type intermediates generated from 2-aminothiazol-5-yl carbinols. *Org. Lett.*, **11**, 5154–5157.
15. Piao, C., Zhao, Y., Han, X., and Liu, Q. (2008) $AlCl_3$-mediated direct carbon–carbon bond-forming reaction of α-hydroxyketene-*S*,*S*-acetals with arenes and synthesis of 3,4-disubstituted dihydrocoumarin derivatives. *J. Org. Chem.*, **73**, 2264–2269.
16. O'Keefe, B.M., Mans, D.M., Kaelin, D.E., and Martin, S.F. (2010) Total synthesis of isokidamycin. *J. Am. Chem. Soc.*, **132**, 15528–15530.
17. Izumi, K., Kabaki, M., Uenaka, M., and Shimizu, S. (2007) One-step synthesis of 5-(4-fluorobenzyl)-2-furyl methyl ketone: a key intermediate of HIV-integrase inhibitor S-1360. *Org. Process Res. Dev.*, **11**, 1059–1061.
18. Piccolo, O., Azzena, U., Melloni, G., Delogu, G., and Valoti, E. (1991) Stereospecific Friedel–Crafts alkylation of aromatic compounds: synthesis of optically active 2- and 3-arylalkanoic esters. *J. Org. Chem.*, **56**, 183–187.
19. Klumpp, D.A., Garza, M., Jones, A., and Mendoza, S. (1999) Synthesis of aryl-substituted piperidines by superacid activation of piperidones. *J. Org. Chem.*, **64**, 6702–6705.
20. Hofmann, M., Hampel, N., Kanzian, T., and Mayr, H. (2004) Electrophilic alkylations in neutral aqueous or alcoholic solutions. *Angew. Chem. Int. Ed.*, **43**, 5402–5405.
21. Liu, C. and Widenhoefer, R.A. (2006) Scope and mechanism of the Pd^{II}-catalyzed arylation/carboalkoxylation of unactivated olefins with indoles. *Chem. Eur. J.*, **12**, 2371–2382.
22. Zhao, Y. and Chen, G. (2011) Palladium-catalyzed alkylation of *ortho*-C(sp^2)–H bonds of benzylamide substrates with alkyl halides. *Org. Lett.*, **13**, 4850–4853.
23. Ackermann, L., Novák, P., Vicente, R., and Hofmann, N. (2009) Ruthenium-catalyzed regioselective direct alkylation of arenes with unactivated alkyl halides through C–H bond cleavage. *Angew. Chem. Int. Ed.*, **48**, 6045–6048.
24. Hofmann, N. and Ackermann, L. (2013) *Meta*-selective C–H bond alkylation with secondary alkyl halides. *J. Am. Chem. Soc.*, **135**, 5877–5884.
25. Tsai, A.S., Brasse, M., Bergman, R.G., and Ellman, J.A. (2011) Rh(III)-catalyzed oxidative coupling of unactivated alkenes via C–H activation. *Org. Lett.*, **13**, 540–542.
26. Yu, D., Lee, S., Sum, Y.N., and Zhang, Y. (2012) Selective formation of formamidines or 7-aminomethylbenzoxazoles from unprecedented couplings between benzoxazoles and amines. *Adv. Synth. Catal.*, **354**, 1672–1678.
27. Matsuzawa, H., Miyake, Y., and Nishibayashi, Y. (2007) Ruthenium-catalyzed enantioselective propargylation of aromatic compounds with propargylic alcohols via allenylidene intermediates. *Angew. Chem. Int. Ed.*, **46**, 6488–6491.
28. Mertins, K., Iovel, I., Kischel, J., Zapf, A., and Beller, M. (2005) Transition-metal-catalyzed benzylation of arenes and heteroarenes. *Angew. Chem. Int. Ed.*, **44**, 238–242.
29. Olah, G.A. and Kuhn, S.J. (1964) Selective Friedel–Crafts reactions. I. Boron halide catalyzed haloalkylation of benzene and alkylbenzenes with fluorohaloalkanes. *J. Org. Chem.*, **29**, 2317–2320.
30. Shi, Z. and Chuan, H. (2004) Direct functionalization of arenes by primary alcohol sulfonate esters catalyzed by gold(III). *J. Am. Chem. Soc.*, **126**, 13596–13597.
31. Mayr, H., Lang, G., and Ofial, A.R. (2002) Reactions of carbocations with unsaturated hydrocarbons: electrophilic alkylation or hydride abstraction? *J. Am. Chem. Soc.*, **124**, 4076–4083.
32. Serres, C. and Fields, E.K. (1963) Synthesis of 2,2-diarylpropanes by hydride transfer. *J. Org. Chem.*, **28**, 1624–1627.

33. Coumbarides, G.S., Dingjan, M., Eames, J., and Weerasooriya, N. (2001) Investigations into the bromination of substituted phenols using diethyl bromomalonate and diethyl dibromomalonate. *Bull. Chem. Soc. Jpn.*, **74**, 179–180.
34. Kinoyama, I., Miyazaki, T., Koganemaru, Y., Shiraishi, N., Kawamoto, Y., and Washio, T. (2011) Acylguanidine derivatives. US Patent 2011306621.
35. Pradhan, A., Dechambenoit, P., Bock, H., and Durola, F. (2013) Twisted polycyclic arenes by intramolecular Scholl reactions of C3-symmetric precursors. *J. Org. Chem.*, **78**, 2266–2274.
36. Shen, Y., Liu, H., Wu, M., Du, W., Chen, Y., and Li, N. (1991) Friedel–Crafts alkylation of benzenes substituted with *meta*-directing groups. *J. Org. Chem.*, **56**, 7160–7162.
37. Dall'Asta, L., Casazza, U., and Cotticelli, G. (2001) Process for the preparation of 5-carboxyphthalide. EP Patent 1118614.
38. Buc, S.R. (1956) Preparation of *meta*-nitrobenzyl chlorides. US Patent 2758137.
39. Grellier, M., Vendier, L., Chaudret, B., Albinati, A., Rizzato, S., Mason, S., and Sabo-Etienne, S. (2005) Synthesis, neutron structure, and reactivity of the bis(dihydrogen) complex $RuH_2(\eta^2\text{-}H_2)_2(PCyp_3)_2$ stabilized by two tricyclopentylphosphines. *J. Am. Chem. Soc.*, **127**, 17592–17593.
40. Mochida, S., Hirano, K., Satoh, T., and Miura, M. (2011) Rhodium-catalyzed regioselective olefination directed by a carboxylic group. *J. Org. Chem.*, **76**, 3024–3033.
41. Park, S.H., Kim, J.Y., and Chang, S. (2011) Rhodium-catalyzed selective olefination of arene esters via C–H bond activation. *Org. Lett.*, **13**, 2372–2375.
42. Rakshit, S., Grohmann, C., Besset, T., and Glorius, F. (2011) Rh(III)-catalyzed directed C–H olefination using an oxidizing directing group: mild, efficient, and versatile. *J. Am. Chem. Soc.*, **133**, 2350–2353.
43. Busch, S. and Leitner, W. (2001) Ruthenium-catalysed Murai-type couplings at room temperature. *Adv. Synth. Catal.*, **343**, 192–195.
44. Ackermann, L. and Novák, P. (2009) Regioselective ruthenium-catalyzed direct benzylations of arenes through C–H bond cleavages. *Org. Lett.*, **11**, 4966–4969.
45. Jun, C., Moon, C.W., Hong, J., Lim, S., Chung, K., and Kim, Y. (2002) Chelation-assisted Rh^I-catalyzed *ortho*-alkylation of aromatic ketimines, or ketones with olefins. *Chem. Eur. J.*, **8**, 485–492.
46. Wang, X., Truesdale, L., and Yu, J. (2010) Pd(II)-catalyzed *ortho*-trifluoromethylation of arenes using TFA as a promoter. *J. Am. Chem. Soc.*, **132**, 3648–3649.
47. Ueno, S., Kochi, T., Chatani, N., and Kakiuchi, F. (2009) Unique effect of coordination of an alkene moiety in products on ruthenium-catalyzed chemoselective C–H alkenylation. *Org. Lett.*, **11**, 855–858.
48. Yang, Y., Lin, Y., and Rao, Y. (2012) Ruthenium(II)-catalyzed synthesis of hydroxylated arenes with ester as an effective directing group. *Org. Lett.*, **14**, 2874–2877.
49. Yadav, M.R., Rit, R.K., and Sahoo, A.K. (2012) Sulfoximines: a reusable directing group for chemo- and regioselective *ortho* C–H oxidation of arenes. *Chem. Eur. J.*, **18**, 5541–5545.
50. Martinez, R., Simon, M., Chevalier, R., Pautigny, C., Genet, J.-P., and Darses, S. (2009) C–C bond formation via C–H bond activation using an in situ-generated ruthenium catalyst. *J. Am. Chem. Soc.*, **131**, 7887–7895.
51. Ueno, S., Chatani, N., and Kakiuchi, F. (2007) Ruthenium-catalyzed C–C bond formation via the cleavage of an unreactive aryl C–N bond in aniline derivatives with organoboronates. *J. Am. Chem. Soc.*, **129**, 6098–6099.
52. Sonoda, M., Kakiuchi, F., Chatani, N., and Murai, S. (1997) Ruthenium-catalyzed addition of C–H bonds in aromatic ketones to olefins. The effect

of various substituents at the aromatic ring. *Bull. Chem. Soc. Jpn.*, **70**, 3117–3128.

53. Ueno, S., Mizushima, E., Chatani, N., and Kakiuchi, F. (2006) Direct observation of the oxidative addition of the aryl C–O bond to a ruthenium complex and elucidation of the relative reactivity between aryl C–O and aryl C–H bonds. *J. Am. Chem. Soc.*, **128**, 16516–16517.

54. Ryu, J., Cho, S.H., and Chang, S. (2012) A versatile rhodium(I) catalyst system for the addition of heteroarenes to both alkenes and alkynes by a C–H bond activation. *Angew. Chem. Int. Ed.*, **51**, 3677–3681.

55. Yao, B., Song, R., Liu, Y., Xie, Y., Li, J., Wang, M., Tang, R., Zhang, X., and Deng, C. (2012) Palladium-catalyzed C–H oxidation of isoquinoline *N*-oxides: selective alkylation with dialkyl sulfoxides and halogenation with dihalo sulfoxides. *Adv. Synth. Catal.*, **354**, 1890–1896.

56. Tran, L.D. and Daugulis, O. (2010) Iron-catalyzed heterocycle and arene deprotonative alkylation. *Org. Lett.*, **12**, 4277–4279.

57. Popov, I., Do, H., and Daugulis, O. (2009) In situ generation and trapping of aryllithium and arylpotassium species by halogen, sulfur, and carbon electrophiles. *J. Org. Chem.*, **74**, 8309–8313.

58. Linhardt, R.J., Montgomery, B.L.E., Osby, J., and Sherbine, J. (1982) Mechanism for diacyl peroxide decomposition. *J. Org. Chem.*, **47**, 2242–2251.

59. Molander, G.A., Colombel, V., and Braz, V.A. (2011) Direct alkylation of heteroaryls using potassium alkyl- and alkoxymethyltrifluoroborates. *Org. Lett.*, **13**, 1852–1855.

60. Glazunov, V.P., Tchizhova, A.Y., Pokhilo, N.D., Anufriev, V.P., and Elyakov, G.B. (2002) First direct observation of tautomerism of monohydroxynaphthazarins. *Tetrahedron*, **58**, 1751–1757.

61. Guo, X. and Li, C.-J. (2011) Ruthenium-catalyzed *para*-selective oxidative cross-coupling of arenes and cycloalkanes. *Org. Lett.*, **13**, 4977–4979.

62. Minisci, F., Vismara, E., and Fontana, F. (1989) Homolytic alkylation of protonated heteroaromatic bases by alkyl iodides, hydrogen peroxide, and dimethyl sulfoxide. *J. Org. Chem.*, **54**, 5224–5227.

63. Miller, B.L., Palde, P.B., and Gareiss, P.C. (2008) Tripodal cyclohexane derivatives and their use as carbohydrate receptors., WO Patent 2008048967.

64. Duncton, M.A.J., Estiarte, M.A., Johnson, R.J., Cox, M., O'Mahony, D.J.R., Edwards, W.T., and Kelly, M.G. (2009) Preparation of heteroaryloxetanes and heteroarylazetidines by use of a Minisci reaction. *J. Org. Chem.*, **74**, 6354–6357.

65. Yoshida, M., Amemiya, H., Kobayashi, M., Sawada, H., Hagii, H., and Aoshima, K. (1985) Perfluoropropylation of aromatic compounds with bis(heptafluorobutyryl) peroxide. *J. Chem. Soc., Chem. Commun*, 234–236.

66. Firth, B.E. and Rosen, T.J. (1985) Preparation of *ortho*-alkylated phenols. US Patent 4538008.

67. Rao, H.S.P., Geetha, K., and Kamalraj, M. (2011) Synthesis of 4-(2-hydroxyaryl)-3-nitro-4*H*-chromenes. *Tetrahedron*, **67**, 8146–8154.

68. Lee, D.-H., Kwon, K.-H., and Yi, C.S. (2012) Dehydrative C–H alkylation and alkenylation of phenols with alcohols: expedient synthesis for substituted phenols and benzofurans. *J. Am. Chem. Soc.*, **134**, 7325–7328.

69. Toshima, K., Matsuo, G., Ishizuka, T., Ushiki, Y., Nakata, M., and Matsumura, S. (1998) Aryl and allyl *C*-glycosidation methods using unprotected sugars. *J. Org. Chem.*, **63**, 2307–2313.

70. Podder, S., Choudhury, J., Roy, U.K., and Roy, S. (2007) Dual-reagent catalysis within Ir–Sn domain: highly selective alkylation of arenes and heteroarenes with aromatic aldehydes. *J. Org. Chem.*, **72**, 3100–3103.

71. Zhang, C., Gao, X., Zhang, J., and Peng, X. (2010) Fe/$CuBr_2$-catalyzed benzylation of arenes and thiophenes with benzyl alcohols. *Synlett*, 261–265.

72. Firth, B.E. (1981) Preparation of 2,4,6-triisopropylphenol. US Patent 4275248.
73. Klemm, L.H. and Taylor, D.R. (1980) Alumina-catalyzed reactions of hydroxyarenes and hydroaromatic ketones. 9. Reaction of phenol with l-propanol. *J. Org. Chem.*, **45**, 4320–4326.
74. Kealy, T.J. and Coffman, D.D. (1961) Thermal addition reactions of monocyclic phenols with ethylene. *J. Org. Chem.*, **26**, 987–992.
75. Zhao, C., Camaioni, D.M., and Lercher, J.A. (2012) Selective catalytic hydroalkylation and deoxygenation of substituted phenols to bicycloalkanes. *J. Catal.*, **288**, 92–103.
76. Kolka, J., Napolitano, J.P., and Ecke, G.G. (1956) The *ortho*-alkylation of phenols. *J. Org. Chem.*, **21**, 712–713.
77. Nakagawa, Y. and Sato, T. (2009) Preparation of 2,6-diphenylphenols. JP Patent 2009269868.
78. Youn, S.W. and Eom, J.I. (2006) Ag(I)-catalyzed sequential C–C and C–O bond formations between phenols and dienes with atom economy. *J. Org. Chem.*, **71**, 6705–6707.
79. Ancel, J.E., Bienayme, H., and Meilland, P. (1996) Procédé des préparations de phénols substitués. EP Patent 0742194.
80. Dang, T.T., Boeck, F., and Hintermann, L. (2011) Hidden Brønsted acid catalysis: pathways of accidental or deliberate generation of triflic acid from metal triflates. *J. Org. Chem.*, **76**, 9353–9361.
81. Repinskaya, I.B., Barkhutova, D.D., Makarova, Z.S., Alekseeva, A.V., and Koptyug, V.A. (1985) Condensation of phenols and their derivatives with aromatic compounds in the presence of acidic agents. VII. Comparison of the condensation of phenols with aromatic compounds in $HF–SbF_5$ and in the presence of aluminum halides. *Zh. Org. Khim.*, **21**, 836–845 (translation: 759–767).
82. Repinskaya, I.B. and Koptyug, V.A. (1980) Condensation of substituted resorcinols with benzene and chlorobenzene. *Zh. Org. Khim.*, **16**, 1508–1514 (translation: 1298–1303).
83. El-Zohry, M.F. and El-Khawaga, A.M. (1990) Nonconventional Friedel–Crafts chemistry. 1. Reaction of α-tetralone and anthrone with arenes under Friedel–Crafts conditions. *J. Org. Chem.*, **55**, 4036–4039.
84. Koptyug, V.A. and Golounin, A.V. (1973) Reaction of phenols with Lewis acids VIII. Reaction of phenol and its methylated derivatives with benzene and aluminum halides. *Zh. Org. Khim.*, **9**, 2158–2163 (translation: 2172–2176).
85. Koltunov, K.Y., Walspurger, S., and Sommer, J. (2004) Superelectrophilic activation of polyfunctional organic compounds using zeolites and other solid acids. *Chem. Commun.*, 1754–1755.
86. Witten, B. and Reid, E.E. (1963) p-Aminotetraphenylmethane. *Org. Synth.*, Coll. Vol. **4**, 47–48.
87. Schultz, W.J., Portelli, G.B., and Tane, J.P. (1986) Epoxy resin curing agent, curing process and composition containing it. EP Patent 0203828.
88. Cherian, A.E., Domski, G.J., Rose, J.M., Lobkovsky, E.B., and Coates, G.W. (2005) Acid-catalyzed *ortho*-alkylation of anilines with styrenes: an improved route to chiral anilines with bulky substituents. *Org. Lett.*, **7**, 5135–5137.
89. Macé, Y., Raymondeau, B., Pradet, C., Blazejewski, J.-C., and Magnier, E. (2009) Benchmark and solvent-free preparation of sulfonium salt based electrophilic trifluoromethylating reagents. *Eur. J. Org. Chem.*, **2009**, 1390–1397.
90. Yanai, H., Yoshino, T., Fujita, M., Fukaya, H., Kotani, A., Kusu, F., and Taguchi, T. (2013) Synthesis, characterization, and applications of zwitterions containing a carbanion moiety. *Angew. Chem. Int. Ed.*, **52**, 1560–1563.
91. Hickinbottom, W.J. (1933) The elimination of tertiary alkyl groups from alkylanilines by hydrolysis. *J. Chem. Soc.*, 1070–1073.
92. Pillai, R.B.C. (1999) Isomerisation of *N*-isopropylaniline and *N*-n-propylaniline over zeolites. *J. Indian Chem. Soc.*, **76**, 157–158.
93. Beyer, H., Gerencsérné, A., Palkovics, I., Gémes, I., Rátosi, E., Sebestyén,

B., Horváth, J., Czágler, I., Perger, J., Hegedüs, I., Arányi, P., Torkos, L., Hódossy, L., Borbéli, G., and Halász, I. (1992) Process for the Preparation of Ring-Alkylated Anilines by Isomerization of *N*-alkylanilines Over Acidic Zeolites as Catalysts. Ger. Offen. 4023652.

94. Bourns, A.N., Embleton, H.W., and Hansuld, M.K. (1963) 1-Phenylpiperidine. *Org. Synth.*, Coll. Vol. **4**, 795–798.

95. Glass, D.B. and Weissberger, A. (1955) Julolidine. *Org. Synth.*, Coll. Vol. **3**, 504–505.

96. Lapis, A.A.M., DaSilveira Neto, B.A., Scholten, J.D., Nachtigall, F.M., Eberlin, M.N., and Dupont, J. (2006) Intermolecular hydroamination and hydroarylation reactions of alkenes in ionic liquids. *Tetrahedron Lett.*, **47**, 6775–6779.

97. Motokura, K., Nakagiri, N., Mizugaki, T., Ebitani, K., and Kaneda, K. (2007) Nucleophilic substitution reactions of alcohols with use of montmorillonite catalysts as solid Brønsted acids. *J. Org. Chem.*, **72**, 6006–6015.

98. Tsuji, Y., Huh, K.-T., Ohsugi, Y., and Watanabe, Y. (1985) Ruthenium complex catalyzed *N*-heterocyclization. Syntheses of *N*-substituted piperidines, morpholines, and piperazines from amines and 1,5-diols. *J. Org. Chem.*, **50**, 1365–1370.

99. Wei, H., Qian, G., Xia, Y., Li, K., Li, Y., and Li, W. (2007) $BiCl_3$-catalyzed hydroamination of norbornene with aromatic amines. *Eur. J. Org. Chem.*, **2007**, 4471–4474.

100. Didier, D. and Sergeyev, S. (2007) Bromination and iodination of 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine: a convenient entry to unsymmetrical analogs of Tröger's base. *Eur. J. Org. Chem.*, **2007**, 3905–3910.

101. Corma, A., Botella, P., and Mitchell, C. (2004) Replacing HCl by solid acids in industrial processes: synthesis of diamino diphenyl methane (DADPM) for producing polyurethanes. *Chem. Commun.*, 2008–2010.

102. Mitchell, C.J., Corma Canos, A., Carr, R.H., and Botella Asunción, P. (2010) Process for production of methylene-bridged polyphenyl polyamines. WO Patent 2010072504.

103. Chauvin, A.-S., Comby, S., Song, B., Vandevyver, C.D.B., Thomas, F., and Bünzli, J.-C.G. (2007) A polyoxyethylene-substituted bimetallic europium helicate for luminescent staining of living cells. *Chem. Eur. J.*, **13**, 9515–9526.

104. Ellis, G.D., Dimarcello, B.J., and Bradshaw, D.J. (1999) Preparation of a dye for coloring protein-based fibers and cellulose-based materials from the oxidation byproducts of the manufacture of a triphenylmethane dye. EP Patent 0909794.

105. Ecke, G.G., Napolitano, J.P., and Kolka, A.J. (1956) The *ortho*-alkylation of aromatic amines. *J. Org. Chem.*, **21**, 711–712.

106. Chockalingam, K. (2009) Preparation of 2-(1,3-dimethylbutyl)aniline and other branched alkyl-substituted anilines. WO Patent 2009029383.

107. Diamond, S.E., Szalkiewicz, A., and Mares, F. (1979) Reactions of aniline with olefins catalyzed by group 8 metal complexes: *N*-alkylation and heterocycle formation. *J. Am. Chem. Soc.*, **101**, 490–491.

108. Ecke, G.G., Napolitano, J.P., Filbey, A.H., and Kolka, A.J. (1957) *Ortho*-alkylation of aromatic amines. *J. Org. Chem.*, **22**, 639–642.

109. Matthews, D.P., McCarthy, J.R., and Whitten, J.P. (1989) Novel (aryl or heteroaromatic methyl)-2,2′-bi-1*H*-imidazoles, EP Patent 0301456.

110. Tan, K.L., Park, S., Ellman, J.A., and Bergman, R.G. (2004) Intermolecular coupling of alkenes to heterocycles via C–H bond activation. *J. Org. Chem.*, **69**, 7329–7335.

111. Jiao, L., Herdtweck, E., and Bach, T. (2012) Pd(II)-catalyzed regioselective 2-alkylation of indoles via a norbornene-mediated C–H activation: mechanism and applications. *J. Am. Chem. Soc.*, **134**, 14563–14572.

112. Olah, G.A., Farooq, O., Farnia, S.M.F., and Olah, J.A. (1988)

Boron, aluminum, and gallium tris(trifluoromethanesulfonate) (triflate): effective new Friedel–Crafts catalysts. *J. Am. Chem. Soc.*, **110**, 2560–2565.

113. Cullinane, N.M., Chard, S.J., and Dawkins, C.W.C. (1963) Hexamethylbenzene. *Org. Synth.*, Coll. Vol. **4**, 520–521.

114. Smith, L.I. (1943) Durene. *Org. Synth.*, Coll. Vol. **2**, 248–253.

115. Zhang, Y., Feng, J., and Li, C.-J. (2008) Palladium-catalyzed methylation of aryl C–H bonds by using peroxides. *J. Am. Chem. Soc.*, **130**, 2900–2901.

116. Nakao, Y., Kashihara, N., Kanyiva, K.S., and Hiyama, T. (2010) Nickel-catalyzed hydroheteroarylation of vinylarenes. *Angew. Chem. Int. Ed.*, **49**, 4451–4454.

117. Watson, A.J.A., Maxwell, A.C., and Williams, J.M.J. (2010) Ruthenium-catalyzed aromatic C–H activation of benzylic alcohols via remote electronic activation. *Org. Lett.*, **12**, 3856–3859.

118. Matsumoto, T., Taube, D.J., Periana, R.A., Taube, H., and Yoshida, H. (2000) Anti-Markovnikov olefin arylation catalyzed by an iridium complex. *J. Am. Chem. Soc.*, **122**, 7414–7415.

119. Sun, Z.-M., Zhang, J., Manan, R.S., and Zhao, P. (2010) Rh(I)-catalyzed olefin hydroarylation with electron-deficient perfluoroarenes. *J. Am. Chem. Soc.*, **132**, 6935–6937.

120. Liu, F., Martin-Mingot, A., Jouannetaud, M., Zunino, F., and Thibaudeau, S. (2010) Superelectrophilic activation in superacid HF/SbF_5 and synthesis of benzofused sultams. *Org. Lett.*, **12**, 868–871.

121. Okabe, K., Ohwada, T., Ohta, T., and Shudo, K. (1989) Novel electrophilic species equivalent to α-keto cations. Reactions of *O,O*-diprotonated nitro olefins with benzenes yield arylmethyl ketones. *J. Org. Chem.*, **54**, 733–734.

122. Fujiwara, Y., Kuromaru, H., and Taniguchi, H. (1984) Trifluoroacetic acid catalyzed allylic phenylation of α-methylallyl acetate, α-methylallyl trifluoroacetate, and α-methylallyl alcohol with benzene. *J. Org. Chem.*, **49**, 4309–4310.

123. Fan, S., Chen, F., and Zhang, X. (2011) Direct palladium-catalyzed intermolecular allylation of highly electron-deficient polyfluoroarenes. *Angew. Chem. Int. Ed.*, **50**, 5918–5923.

124. Makida, Y., Ohmiya, H., and Sawamura, M. (2012) Regio- and stereocontrolled introduction of secondary alkyl groups to electron-deficient arenes through copper-catalyzed allylic alkylation. *Angew. Chem. Int. Ed.*, **51**, 4122–4127.

125. Yao, T., Hirano, K., Satoh, T., and Miura, M. (2011) Stereospecific copper-catalyzed C–H allylation of electron-deficient arenes with allyl phosphates. *Angew. Chem. Int. Ed.*, **50**, 2990–2994.

126. Zhang, Y., Chen, L., and Lu, T. (2011) A copper(II) triflate-catalyzed tandem Friedel–Crafts alkylation/cyclization process towards dihydroindenes. *Adv. Synth. Catal.*, **353**, 1055–1060.

127. Müller, H., Trübenbach, P., Rieger, B., Wagner, J.M., and Dietrich, U. (1998) Verfahren zur Herstellung von Indenderivaten. EP Patent 0826654.

128. Li, Z., Zhang, Y., and Liu, Z.-Q. (2012) Pd-catalyzed olefination of perfluoroarenes with allyl esters. *Org. Lett.*, **14**, 74–77.

129. Prakash, G.K.S., Paknia, F., Vaghoo, H., Rasul, G., Mathew, T., and Olah, G.A. (2010) Preparation of trifluoromethylated dihydrocoumarins, indanones, and arylpropanoic acids by tandem superacidic activation of 2-(trifluoromethyl)acrylic acid with arenes. *J. Org. Chem.*, **75**, 2219–2226.

130. Liu, Y.-H., Liu, Q.-S., and Zhang, Z.-H. (2009) An efficient Friedel–Crafts alkylation of nitrogen heterocycles catalyzed by antimony trichloride/montmorillonite K-10. *Tetrahedron Lett.*, **50**, 916–921.

131. Shi, Z. and He, C. (2004) An Au-catalyzed cyclialkylation of electron-rich arenes with epoxides to prepare 3-chromanols. *J. Am. Chem. Soc.*, **126**, 5964–5965.

132. Yadav, J.S., Reddy, B.V.S., Abraham, S., and Sabitha, G. (2002) $InCl_3$-catalyzed regioselective opening of aziridines

with heteroaromatics. *Tetrahedron Lett.*, **43**, 1565–1567.

133. Thirupathi, B., Srinivas, R., Prasad, A.N., Kumar, J.K.P., and Reddy, B.M. (2010) Green progression for synthesis of regioselective β-amino alcohols and chemoselective alkylated indoles. *Org. Process Res. Dev.*, **14**, 1457–1463.

134. Taylor, S.K., Clark, D.L., Heinz, K.L., Schramm, S.B., Westermann, C.D., and Barnell, K.K. (1983) Friedel–Crafts reactions of some conjugated epoxides. *J. Org. Chem.*, **48**, 592–596.

135. Molnar, A., Ledneczki, I., Bucsi, I., and Bartok, M. (2003) Alkylation of benzene with cyclic ethers in superacidic media. *Catal. Lett.*, **89**, 1–9.

136. Lin, J.-R., Gubaidullin, A.T., Mamedovb, V.A., and Tsuboi, S. (2003) Nucleophilic addition reaction of aromatic compounds with α-chloroglycidates in the presence of Lewis acid. *Tetrahedron*, **59**, 1781–1790.

137. Schultz, E.M. and Mickey, S. (1955) α,α-Diphenylacetone. *Org. Synth.*, Coll. Vol. **3**, 343–346.

138. Robb, C.M. and Schultz, E.M. (1955) Diphenylacetonitrile. *Org. Synth.*, Coll. Vol. **3**, 347–349.

139. Itoh, S., Yoshimura, N., Sato, M., and Yamataka, H. (2011) Computational study on the reaction pathway of α-bromoacetophenones with hydroxide ion: possible path bifurcation in the addition/substitution mechanism. *J. Org. Chem.*, **76**, 8294–8299.

140. Mason, J.P. and Terry, L.I. (1940) Preparation of phenylacetone. *J. Am. Chem. Soc.*, **62**, 1622.

141. Piccolo, O., Spreafico, F., Visentin, G., and Valoti, E. (1985) Alkylation of aromatic compounds with optically active lactic acid derivatives: synthesis of optically pure 2-arylpropionic acid and esters. *J. Org. Chem.*, **50**, 3945–3946.

142. Stelzer, U. (1995) Verfahren zur Herstellung von substituierten Phenylessigsäurederivaten und Zwischenprodukten. EP Patent 0665212.

143. Ogata, Y. and Ishiguro, J. (1950) Preparation of α-naphthaleneacetic acid by the condensation of naphthalene with chloroacetic acid. *J. Am. Chem. Soc.*, **72**, 4302.

144. Kawai, D., Kawasumi, K., Miyahara, T., Hirashita, T., and Araki, S. (2009) Cyclopropanation of electron-deficient alkenes with activated dibromomethylene compounds mediated by lithium iodide or tetrabutylammonium salts. *Tetrahedron*, **65**, 10390–10394.

145. Ogata, Y., Ishiguro, J., and Kitamura, Y. (1951) Condensation of naphthalenes with α-halo fatty acids and related reactions. *J. Org. Chem.*, **21**, 239–242.

146. Chung, J.Y.L., Steinhübel, D., Krska, S.W., Hartner, F.W., Cai, C., Rosen, J., Mancheno, D.E., Pei, T., DiMichele, L., Ball, R.G., Chen, C., Tan, L., Alorati, A.D., Brewer, S.E., and Scott, J.P. (2012) Asymmetric synthesis of a glucagon receptor antagonist via Friedel–Crafts alkylation of indole with chiral α-phenyl benzyl cation. *Org. Process Res. Dev.*, **16**, 1832–1845.

147. Clement, K., Tasset, E.L., and Walker, L.L. (1998) Process for the preparation of stilbene diols. WO Patent 9811043.

148. Zaheer, S.H., Singh, B., Bhushan, B., Bhargava, P.M., Kacker, I.K., Ramachandran, K., Sastri, V.D.N., and Rao, N.S. (1954) Reactions of α-halogeno-ketones with aromatic compounds. Part I. Reactions of chloroacetone and 3-chlorobutanone with phenol and its ethers. *J. Chem. Soc.*, 3360–3362.

149. Baciocchi, E., Muraglia, E., and Sleiter, G. (1992) Homolytic substitution reactions of electron-rich pentatomic heteroaromatics by electrophilic carbon-centered radicals. Synthesis of α-heteroarylacetic acids. *J. Org. Chem.*, **57**, 6817–6820.

150. Ogata, Y., Itoh, T., and Izawa, Y. (1969) Photochemical ethoxycarbonylmethylation of benzene with ethyl haloacetates. *Bull. Chem. Soc. Jpn.*, **42**, 794–797.

151. Kurz, M.E., Baru, V., and Nguyen, P.-N. (1984) Aromatic acetonylation promoted by manganese(III) and cerium(IV) salts. *J. Org. Chem.*, **49**, 1603–1607.

152. Tayama, E., Yanaki, T., Iwamoto, H., and Hasegawa, E. (2010) Copper(II) triflate catalyzed intermolecular aromatic substitution of *N,N*-disubstituted

anilines with diazo esters. *Eur. J. Org. Chem.*, **2010**, 6719–6721.
153. Zaragoza, F. (1995) Remarkable substituent effects on the chemoselectivity of rhodium(II) carbenoids derived from *N*-(2-diazo-3-oxobutyryl)-L-phenylalanine esters. *Tetrahedron*, **51**, 8829–8834.
154. Ono, N., Kamimura, A., Sasatani, H., and Kaji, A. (1987) Lewis acid induced nucleophilic substitution reactions of β-nitro sulfides via episulfonium ions. *J. Org. Chem.*, **52**, 4133–4135.
155. Nakamura, S., Sugimoto, H., and Ohwada, T. (2007) Formation of 4*H*-1,2-benzoxazines by intramolecular cyclization of nitroalkanes. Scope of aromatic oxygen-functionalization reaction involving a nitro oxygen atom and mechanistic insights. *J. Am. Chem. Soc.*, **129**, 1724–1732.
156. Takamoto, M., Kurouchi, H., Otani, Y., and Ohwada, T. (2009) Phenylation reaction of α-acylnitromethanes to give 1,2-diketone monooximes: involvement of carbon electrophile at the position α to the nitro group. *Synthesis*, 4129–4136.
157. Venkatesh, C., Singh, B., Mahata, P.K., Ila, H., and Junjappa, H. (2005) Heteroannulation of nitroketene *N*,*S*-arylaminoacetals with $POCl_3$: a novel highly regioselective synthesis of unsymmetrical 2,3-substituted quinoxalines. *Org. Lett.*, **7**, 2169–2172.
158. Yao, C.-F., Kao, K.-H., Liu, J.-T., Chu, C.-M., Wang, Y., Chen, W.-C., Lin, Y.-M., Lin, W.-W., Yan, M.-C., Liu, J.-Y., Chuang, M.-C., and Shiue, J.-L. (1998) Generation of nitroalkanes, hydroximoyl halides and nitrile oxides from the reactions of β-nitrostyrenes with Grignard or organolithium reagents. *Tetrahedron*, **54**, 791–822.
159. Shutkina, O.V., Ponomareva, O.A., and Ivanova, I.I. (2013) Catalytic synthesis of cumene from benzene and acetone. *Pet. Chem.*, **53**, 20–26.
160. Zimmerman, H.E. and Zweig, A. (1961) Carbanion rearrangements. II. *J. Am. Chem. Soc.*, **83**, 1196–1213.
161. Girotti, G., Rivetti, F., Ramello, S., and Carnelli, L. (2003) Alkylation of benzene with isopropanol on β-zeolite: influence of physical state and water concentration on catalyst performances. *J. Mol. Catal. A*, **204–205**, 571–579.
162. Ohkubo, T., Aoki, S., Ishibashi, M., Imai, M., Fujita, T., and Fujiwara, K. (2012) Process for producing alkylated aromatic compounds and process for producing phenols. US Patent 2012004471.
163. O'Connor, M.J., Boblak, K.N., Topinka, M.J., Kindelin, P.J., Briski, J.M., Zheng, C., and Klumpp, D.A. (2010) Superelectrophiles and the effects of trifluoromethyl substituents. *J. Am. Chem. Soc.*, **132**, 3266–3267.
164. Gorokhovik, I., Neuville, L., and Zhu, J. (2011) Trifluoroacetic acid-promoted synthesis of 3-hydroxy, 3-amino and spirooxindoles from α-keto-*N*-anilides. *Org. Lett.*, **13**, 5536–5539.
165. Si, Y.-G., Chen, J., Li, F., Li, J.-H., Qin, Y.-J., and Jiang, B. (2006) Highly regioselective Friedel–Crafts reactions of electron-rich aromatic compounds with pyruvate catalyzed by Lewis acid-base: efficient synthesis of pesticide cycloprothrin. *Adv. Synth. Catal.*, **348**, 898–904.
166. Smithen, D.A., Cameron, T.S., and Thompson, A. (2011) One-pot synthesis of asymmetric annulated bis(pyrrole)s. *Org. Lett.*, **13**, 5846–5849.
167. Freter, K. (1975) 3-Cycloalkenylindoles. *J. Org. Chem.*, **40**, 2525–2529.
168. Miyai, T., Onishi, Y., and Baba, A. (1999) Novel reductive Friedel–Crafts alkylation of aromatics catalyzed by indium compounds: chemoselective utilization of carbonyl moieties as alkylating reagents. *Tetrahedron*, **55**, 1017–1026.
169. Yip, K.-T., Nimje, R.Y., Leskinen, M.V., and Pihko, P.M. (2012) Palladium-catalyzed dehydrogenative β′-arylation of β-keto esters under aerobic conditions: interplay of metal and Brønsted acids. *Chem. Eur. J.*, **18**, 12590–12594.
170. Schoen, K.L. and Becker, E.I. (1963) 9-Methylfluorene. *Org. Synth.*, Coll. Vol. **4**, 623–626.
171. Fleckenstein, C.A., Kadyrov, R., and Plenio, H. (2008) Efficient large-scale synthesis of 9-alkylfluorenyl phosphines for Pd-catalyzed cross-coupling

reactions. *Org. Process Res. Dev.*, **12**, 475–479.

172. Murai, Y., Masuda, K., Sakihama, Y., Hashidoko, Y., Hatanaka, Y., and Hashimoto, M. (2012) Comprehensive synthesis of photoreactive (3-trifluoromethyl)diazirinyl indole derivatives from 5- and 6-trifluoroacetylindoles for photoaffinity labeling. *J. Org. Chem.*, **77**, 8581–8587.

173. Johnson, H.E. and Crosby, D.G. (1973) Indole-3-acetic acid. *Org. Synth.*, Coll. Vol. **5**, 654–656.

174. Weinbrenner, S., Dunkern, T., Marx, D., Schmidt, B., Stengel, T., Flockerzi, D., Kautz, U., Hauser, D., Diefenbach, J., Christiaans, J.A.M., and Menge, W.M.P.B. (2008) 6-Benzyl-2,3,4,7-tetrahydroindolo[2,3-*c*]quinoline compounds useful as PDE5 inhibitors. WO Patent 2008095835.

175. Davoust, M., Kitching, J.A., Fleming, M.J., and Lautens, M. (2010) Diastereoselective benzylic arylation of tetralins. *Chem. Eur. J.*, **16**, 50–54.

176. Hoefgen, B., Decker, M., Mohr, P., Schramm, A.M., Rostom, S.A.F., El-Subbagh, H., Schweikert, P.M., Rudolf, D.R., Kassack, M.U., and Lehmann, J. (2006) Dopamine/serotonin receptor ligands. 10: SAR studies on azecine-type dopamine receptor ligands by functional screening at human cloned D_1, D_{2L}, and D_5 receptors with a microplate reader based calcium assay lead to a novel potent D_1/D_5 selective antagonist. *J. Med. Chem.*, **49**, 760–769.

177. Johnson, H.E. (1965) Process for producing 3-substituted indoles. US Patent 3197479.

2
Electrophilic Olefination of Arenes

2.1
General Aspects

This chapter will focus on reactions that enable the attachment of alkenyl groups to unfunctionalized aromatic C–H groups. Most known instances of such reactions are electrophilic olefinations of electron-rich arenes and olefinations via *in situ* metallation of the arene (Scheme 2.1). In principle, an electron-deficient arene may also be olefinated by reaction with electron-rich alkenes or alkynes, but few instances of such reactions have been reported.

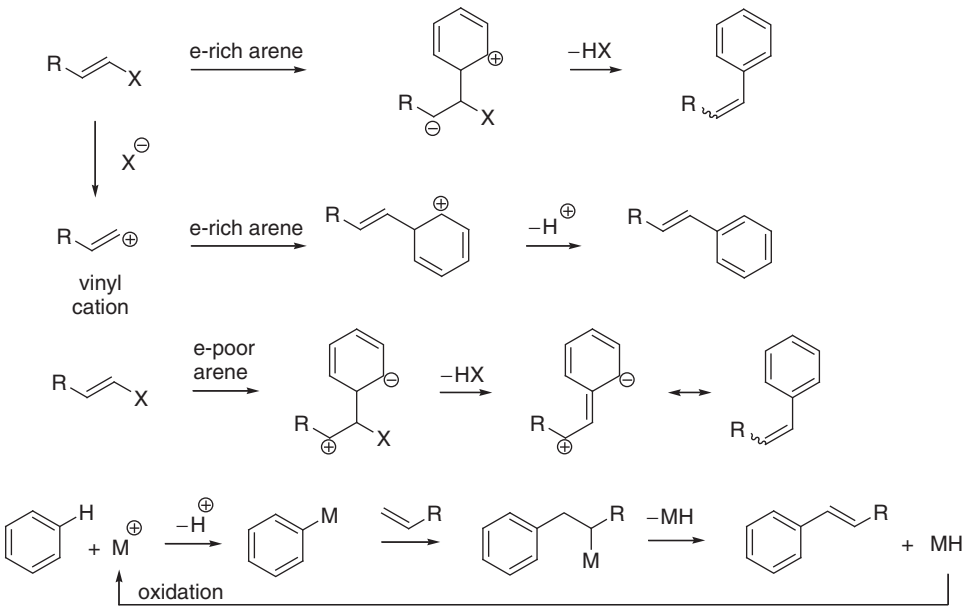
2.2
Olefinations with Leaving-Group-Substituted Olefins

The electrophilic olefination of electron-rich arenes with vinyl halides or related electrophiles is of little scope. Vinylic carbocations are highly reactive intermediates, prone to rearrangements, reduction, and unselective electrophilic attack. A large excess of nucleophile is usually required to attain acceptable yields (Scheme 2.2).

C–H acidic arenes or heteroarenes ($pK_a < 27$) can be olefinated with vinyl halides in the presence of Cu(I) salts. This reaction proceeds via formation of an arylcopper intermediate, which is olefinated by the vinyl halide (Scheme 2.3). The olefination of the arylcopper intermediate is analogous to the arylation of arylcopper intermediates by aryl halides in the Ullmann reaction [5–8], and probably proceeds via nucleophilic addition of the arylcopper intermediate to the olefin, followed by elimination of a copper halide.

Arenes may also be metallated by chelate formation, and the resulting intermediates can react with leaving-group-substituted olefins (Scheme 2.4). Most reported examples are ruthenium-, rhodium-, and palladium-catalyzed olefinations. Suitable olefinating reagents include vinyl acetates, vinylboronic esters, alkenylcarboxylic anhydrides, and β-haloacrylates [11, 12]. The mechanism of these reactions has not been elucidated in all instances, but probably proceeds via aryl(vinyl)metal complexes, which are formed in two steps from the starting materials. As illustrated by the penultimate example in Scheme 2.4, groups other than hydrogen may be replaced by a metal during chelate formation.

Side Reactions in Organic Synthesis II: Aromatic Substitutions, First Edition. Florencio Zaragoza Dörwald.



Scheme 2.1 Mechanisms of the olefination of unfunctionalized arenes. X, leaving group for nucleophilic displacement; M, metal, typically Pd.

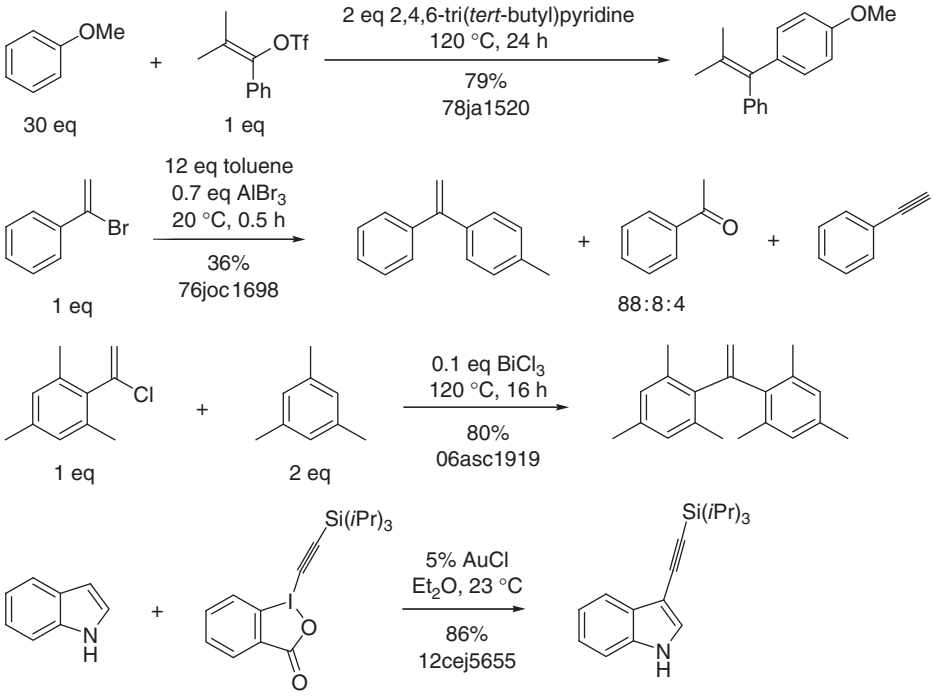
2.3
Olefinations with Unsubstituted Olefins

Aryl halides can be olefinated with unsubstituted alkenes by the Heck reaction [16]. The olefination of arenes without leaving group at the arene or the olefin is formally an oxidation, and stoichiometric amounts of an oxidant will be required to regenerate the catalyst (e.g., Pd(II) from Pd(0)). Common oxidants are oxygen, Cu(II) salts, benzoquinones, peroxides, or prohibitively expensive Ag(I) salts [17] (Schemes 2.5 and 2.6).

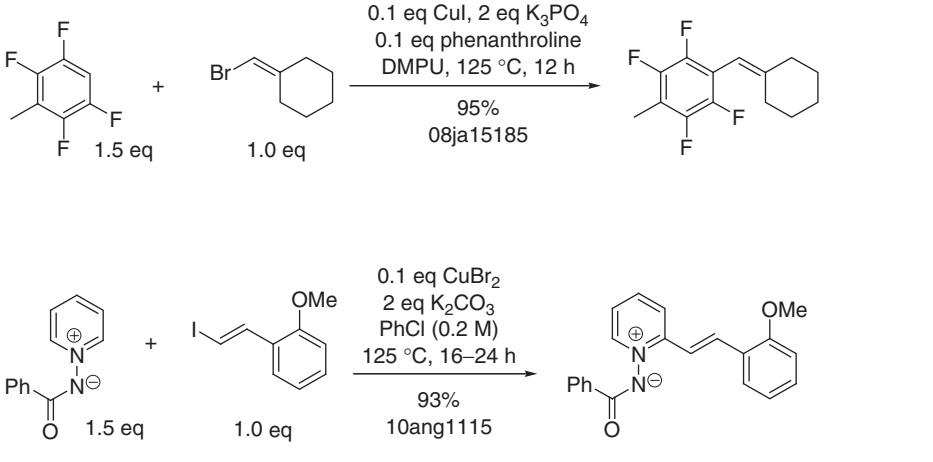
The regioselectivity of the metallation of an arene is controlled by the acidity of the aromatic C–H group, by chelate formation, or by steric repulsion. A large number of functional groups can direct the metallation into their ortho positions. These chelate-forming groups include carbonyl groups, azoles, pyridines, pyrimidines, pyrazines, tertiary amines, sulfonamides, amides, alcohols, silanols, and triazenes [37].

As alternative to an external oxidant, one of the starting materials may also contain a reducible functional group, which can act as oxidant (e.g., last example in Scheme 2.6).

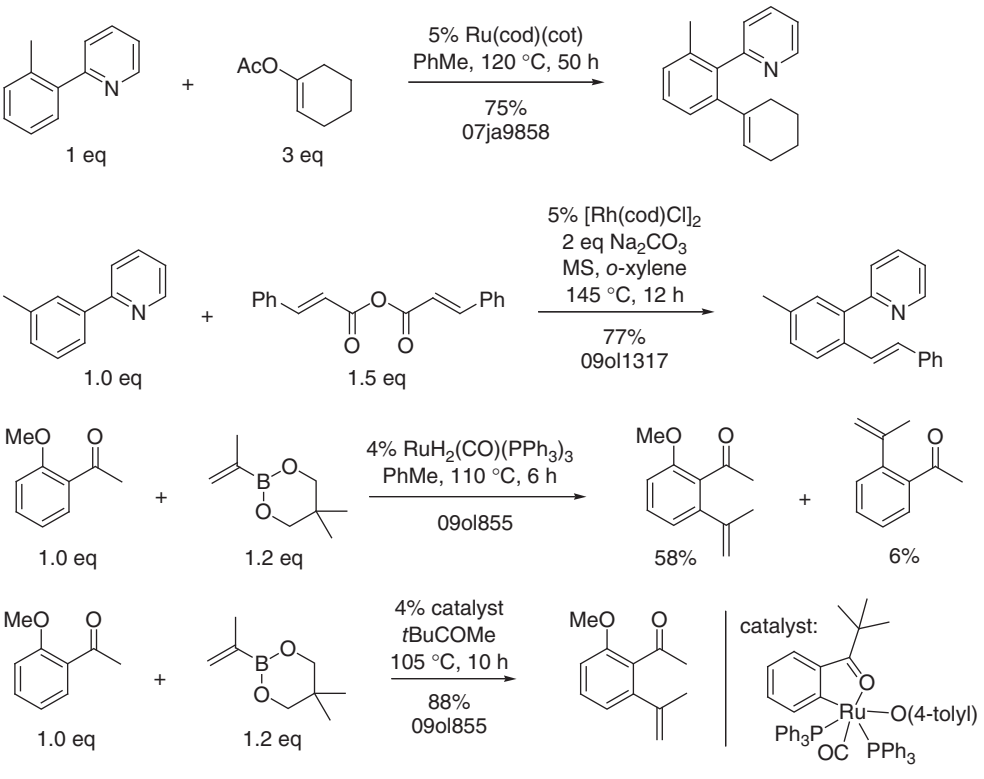
Substituted arenes without chelating groups are usually olefinated with poor regioselectivity. Few examples of meta-selective vinylations have been reported (Scheme 2.7).



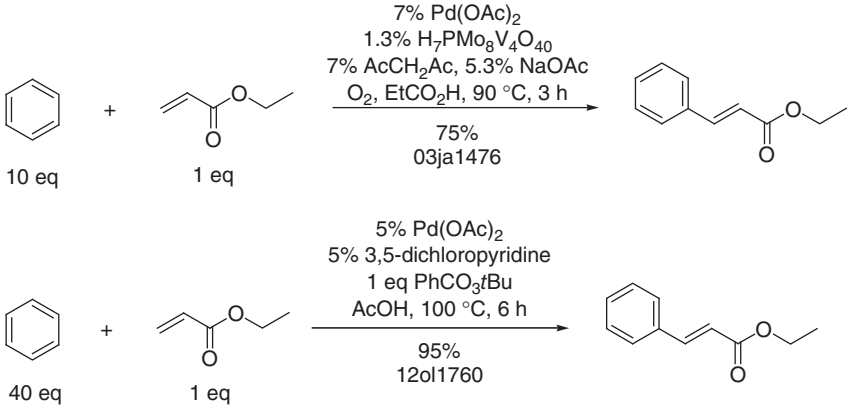
Scheme 2.2 Arene alkenylation and alkynylation with leaving-group-substituted alkenes and alkynes [1–4].



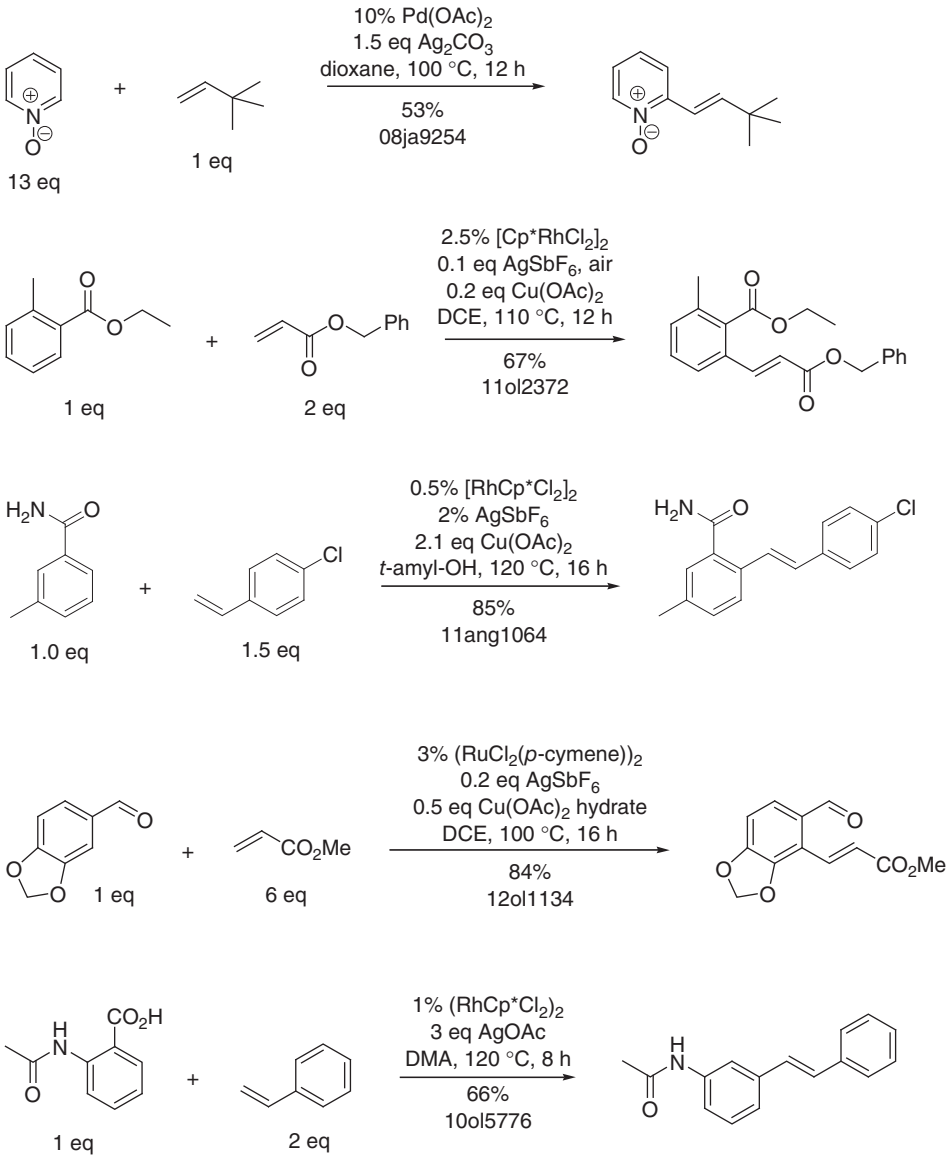
Scheme 2.3 Copper-catalyzed olefination of C–H acidic arenes [9, 10].



Scheme 2.4 Olefination of arenes metallated via chelate formation [13–15].

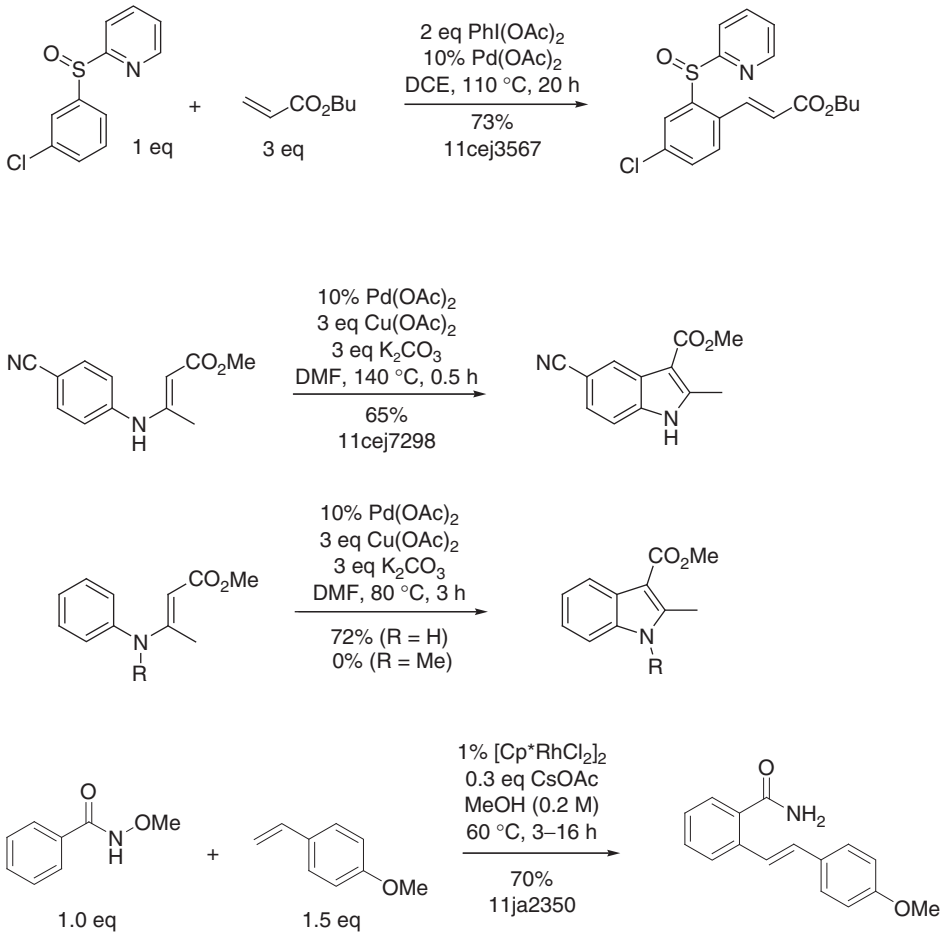


Scheme 2.5 Oxidative vinylation of benzene with acrylates [18, 19]. Further examples: [20–23].



Scheme 2.6 Ortho olefination of substituted arenes [24–31]. Further examples: [32–36].

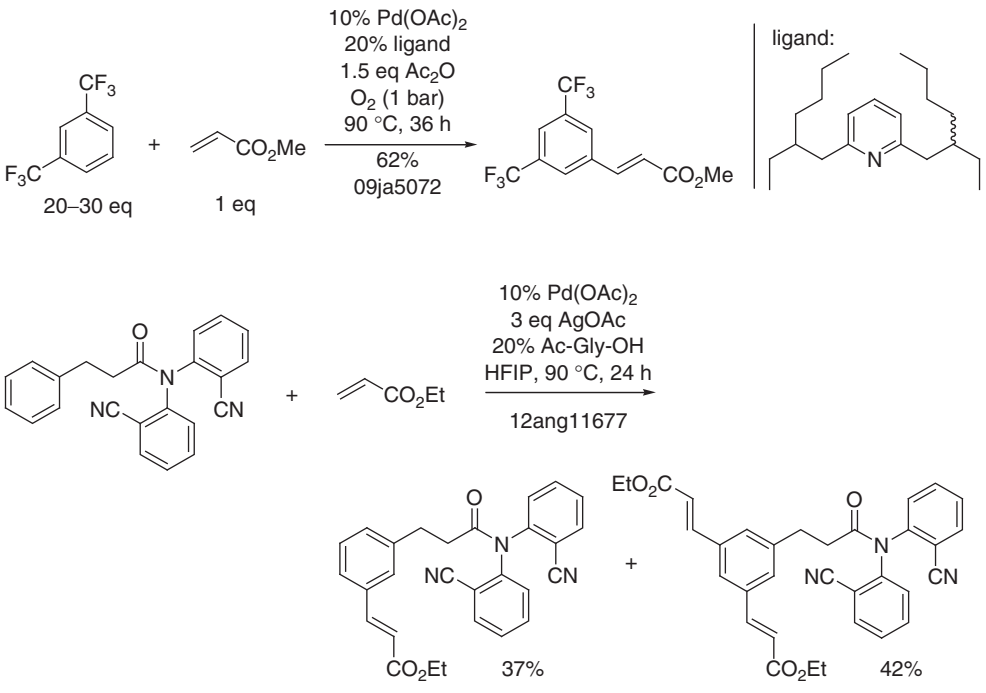
The reaction conditions required for the oxidative olefination of arenes can sometimes bring about the dehydrogenation of alkyl groups. For some starting materials, it has been possible to generate the required olefin and perform its arylation simultaneously (Scheme 2.8). This strategy could be valuable when the intermediate olefin is unstable or otherwise difficult to handle (e.g., owing to its toxicity).



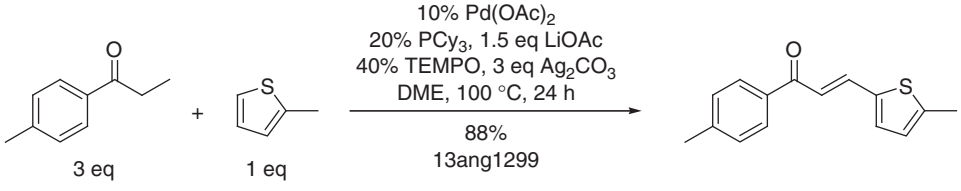
Scheme 2.6 (*continued*)

Typical side reactions of the direct olefination of arenes with olefins include oligomerization of the alkene and intramolecular addition of chelate-forming functional groups to the alkene. In particular, five-membered heterocycles are formed easily, and their formation can be difficult to suppress. Moreover, unsymmetric alkenes devoid of electron-withdrawing or electron-donating groups often yield mixtures of isomers (Scheme 2.9).

Because alkenyl groups do not significantly modify the electronic properties of arenes, one common side reaction of the olefination of arenes is multiple alkenylation. Aryl halides can give mixtures of products of oxidative vinylation and Heck reaction. In the absence of oxidants, some catalysts can cause the formation of alkylarenes instead of alkenylarenes [44]. Complex- or chelate-forming functional groups or impurities capable of deactivating the catalyst (cyanide, imidazoles, pyridines, or sulfur-containing compounds) are a further problem. One more



Scheme 2.7 Meta olefination of arenes [38, 39].

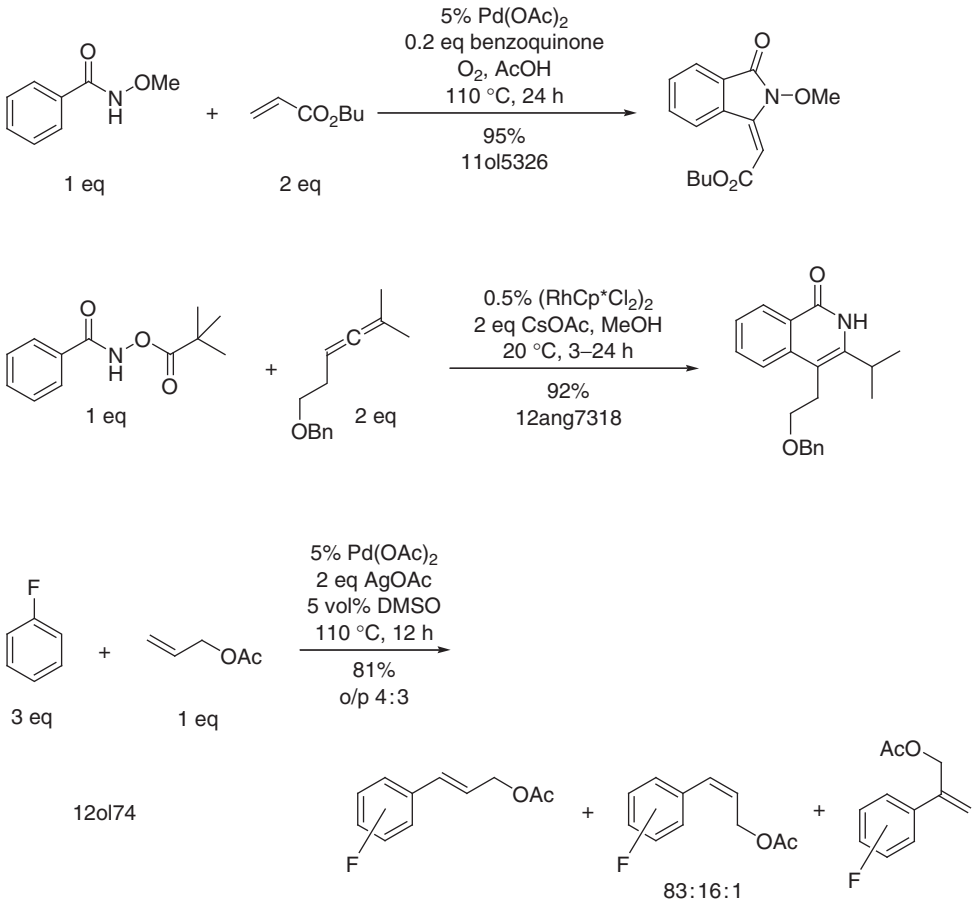


Scheme 2.8 *In situ* generation of an olefin by dehydrogenation [40].

potential side reaction is the oxidative homocoupling of the arene. This happens easily with electron-rich arenes, such as phenols and anilines. High reaction temperatures combined with oxidants and acids or bases can cause the deacylation of electron-rich arenes and other functional group transformations (Scheme 2.10).

Stoichiometric amounts of oxidants render these reactions inherently hazardous. Only oxidation-resistant solvents should be used (haloalkanes, acetonitrile, acetone, or acetic acid), and in large-scale preparations the oxidant should be dosed as the reaction proceeds, to avoid the accumulation of larger quantities of reactants.

Further potential side reactions of the olefination of electron-rich arenes or heteroarenes with electron-deficient alkenes are cycloadditions. Naphthalenes,



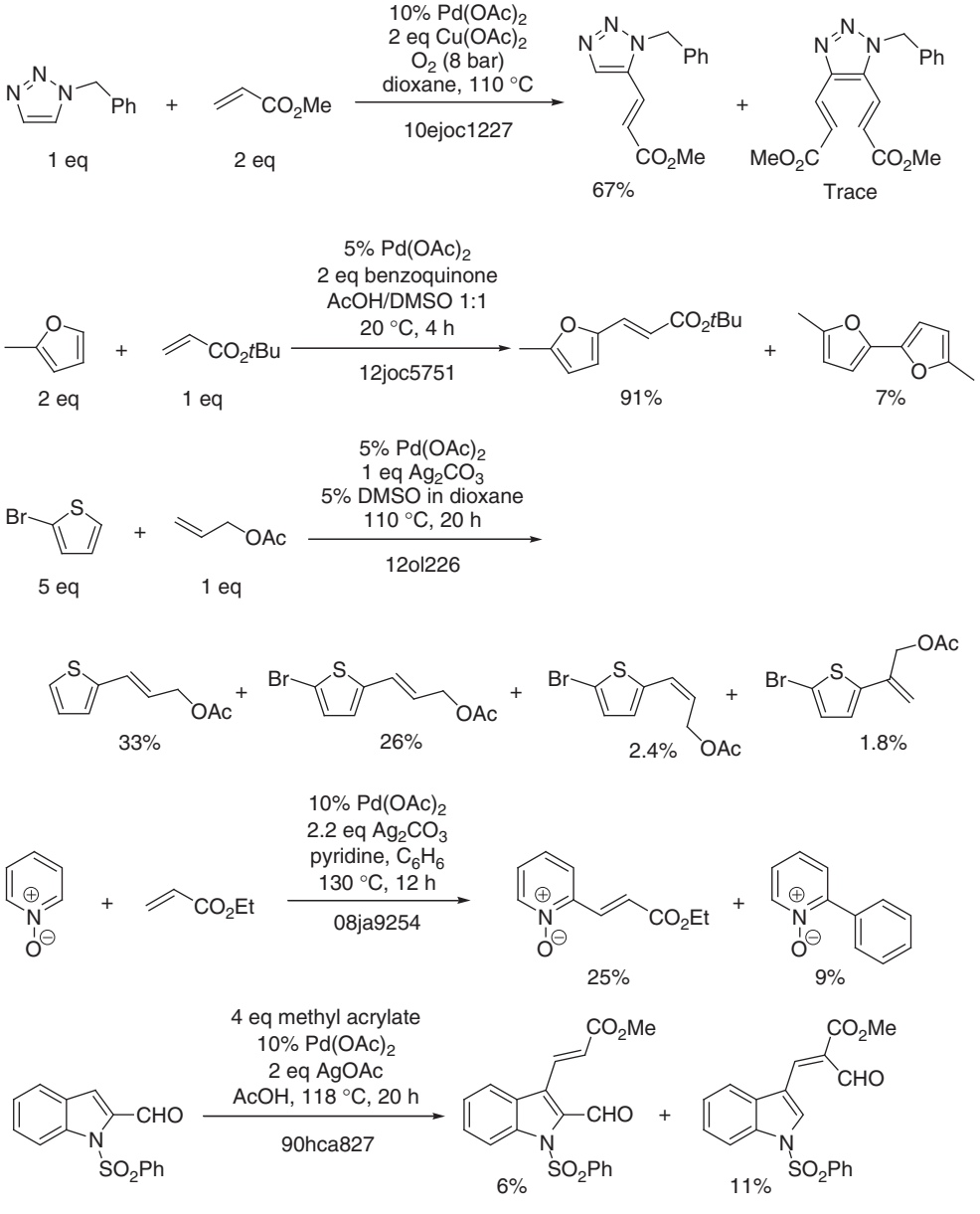
Scheme 2.9 Formation of bicyclic products and regioisomers during the olefination of arenes [41–43].

anthracenes, and furans undergo Diels–Alder reactions with electron-deficient alkenes particularly easily [49] (Scheme 2.11).

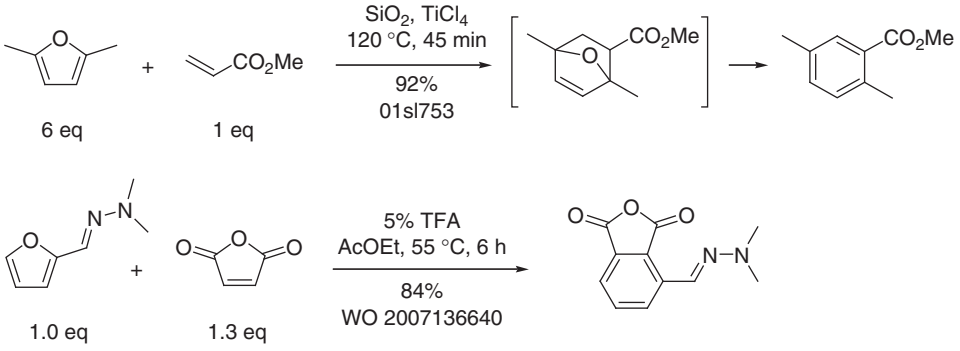
2.4 Olefinations with Alkynes

Alkynes, being synthetic equivalents of vinylhalides, can olefinate arenes directly, for example, in the presence of Pd- or Ru-based catalysts (Scheme 2.12). No oxidants are required, because the reactions are not oxidations but hydroarylations (addition of an arene to an alkyne).

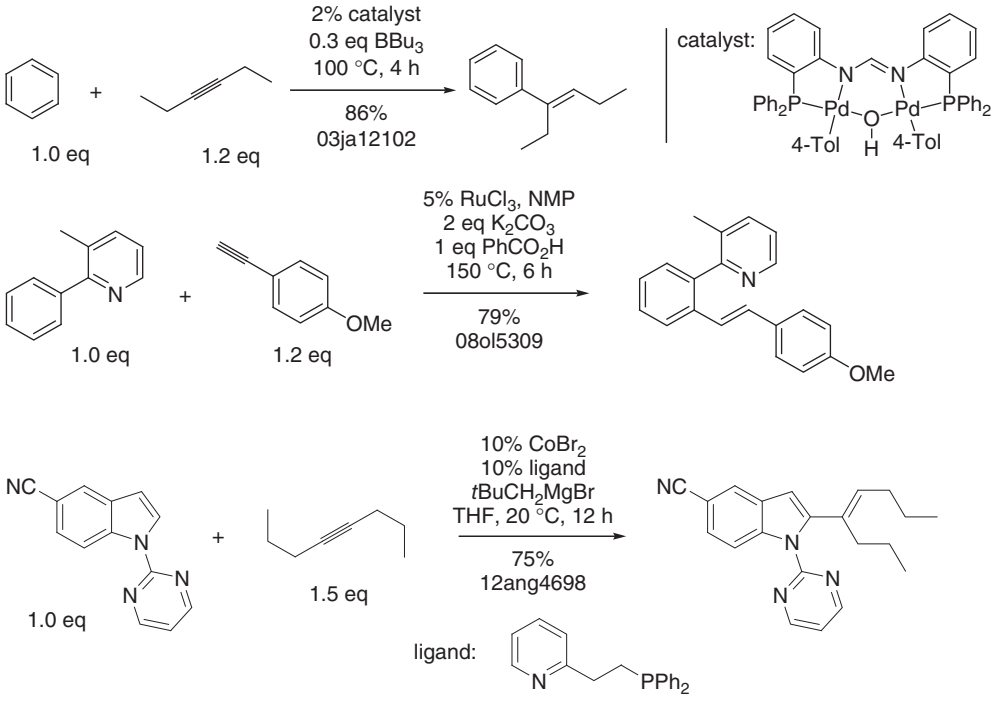
Terminal and internal alkynes often show different reactivity, and some reaction conditions are only suitable for either terminal or internal alkynes, but not for both.



Scheme 2.10 Side reactions during the oxidative olefination of arenes [24, 45–48].



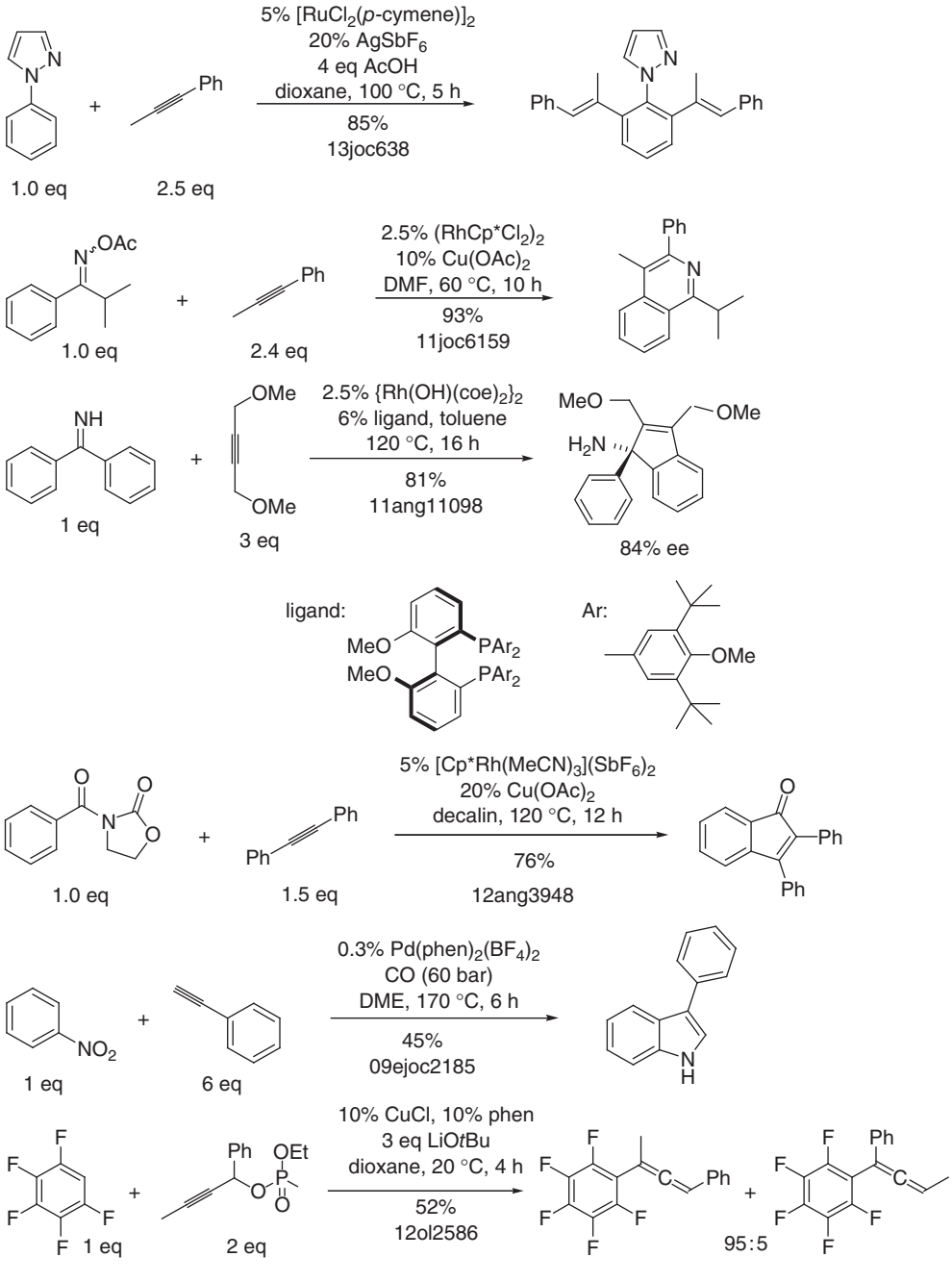
Scheme 2.11 Diels–Alder reactions of furans [50, 51].



Scheme 2.12 Aromatic vinylations with alkynes [52–54].

Thus, in the first example of Scheme 2.12, only internal alkynes can be used, while in the second example only terminal alkynes yield olefinated arenes. Acetylene itself, the most important alkyne, is regrettably hardly ever tested in these new reactions.

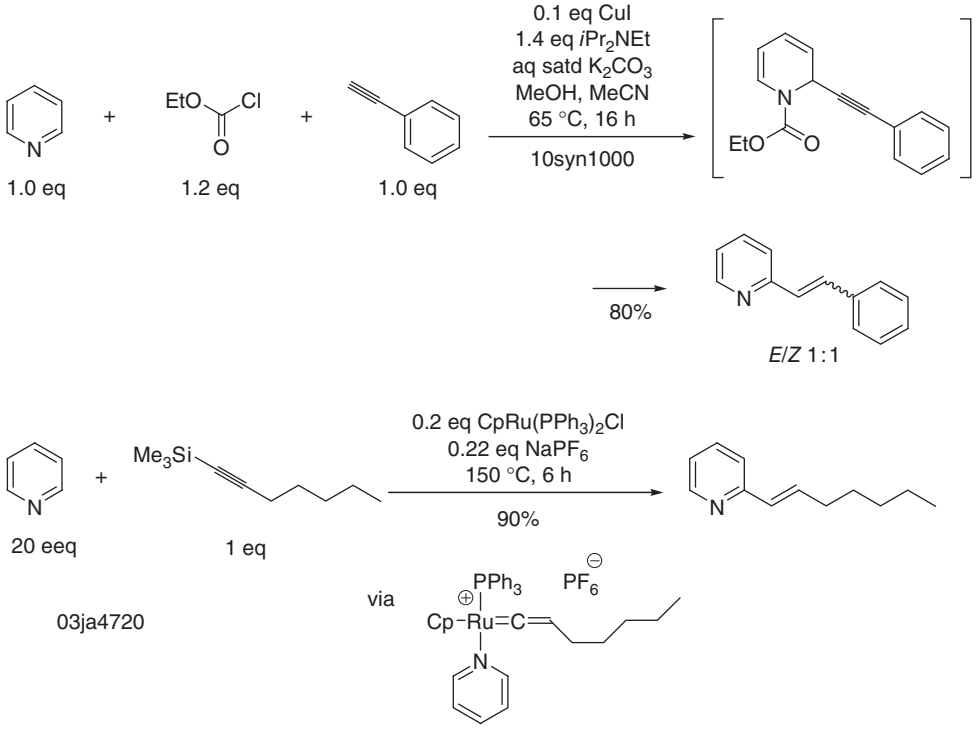
Typical side reactions are similar to those seen with the olefination with alkenes: multiple olefinations, cyclizations, and the formation of mixtures of isomers



Scheme 2.13 Side reactions during the olefination of arenes with alkynes [56–61]. Further examples: [62, 63].

(Scheme 2.13). Moreover, the resulting styrenes may alkylate arenes and cause the formation of geminal diarylalkanes [55]. Some Lewis acids can also catalyze the addition of water, alcohols, amines, or thiols to alkynes.

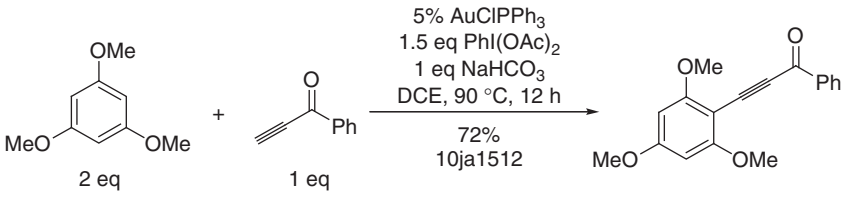
Electron-deficient heteroarenes can be alkynylated by (explosive) copper or silver acetylides. The first intermediates of such reactions are alkynyl dihydroarenes. In the absence of oxidants, the alkynyl group may act as hydrogen acceptor, and cause the rearomatization of the heteroarene. Catalysts and conditions have been identified that allow the one-pot olefination of such electron-deficient arenes with terminal alkynes (Scheme 2.14).



Scheme 2.14 Vinylation of pyridines with alkynes [64, 65]. Further examples: [66].

Methods have also been developed that enable the oxidative alkinylation of arenes (Scheme 2.15). The reaction seems to work best with electron-rich arenes and electron-deficient alkynes. The latter are excellent Michael acceptors, and most nucleophiles will readily add to starting materials and products.

When considering to upscale reactions as those shown above, it should be kept in mind that alkynes tend to oligomerize or explode at high concentrations,



Scheme 2.15 Oxidative alkinylation of arenes [67].

in particular in the presence of transition metals. Moreover, terminal alkynes readily dimerize to 1,3-butadiynes in the presence of air and copper salts (Eglinton reaction).

References

1. Stang, P.J. and Anderson, A.G. (1978) Preparation and chemistry of vinyl triflates. 16. Mechanism of alkylation of aromatic substrates. *J. Am. Chem. Soc.*, **100**, 1520–1525.
2. Roberts, R.M. and Abdel-Baset, M.B. (1976) Friedel–Crafts alkylations with vinyl halides. Vinyl cations and spirobiindans. *J. Org. Chem.*, **41**, 1698–1701.
3. Sun, H., Hua, R., Chen, S., and Yin, Y. (2006) An efficient bismuth(III) chloride-catalyzed synthesis of 1,1-diarylalkenes via Friedel–Crafts reaction of acyl chloride or vinyl chloride with arenes. *Adv. Synth. Catal.*, **348**, 1919–1925.
4. Brand, J.P., Chevalley, C., Scopelliti, R., and Waser, J. (2012) Ethynyl benziodoxolones for the direct alkynylation of heterocycles: structural requirement, improved procedure for pyrroles, and insights into the mechanism. *Chem. Eur. J.*, **18**, 5655–5666.
5. Beletskaya, I.P. and Cheprakov, A.V. (2004) Copper in cross-coupling reactions; the post-Ullmann chemistry. *Coord. Chem. Rev.*, **248**, 2337–2364.
6. Hassan, J., Sévignon, M., Gozzi, C., Schulz, E., and Lemaire, M. (2002) Aryl–aryl bond formation one century after the discovery of the Ullmann reaction. *Chem. Rev.*, **102**, 1359–1469.
7. Sperotto, E., van Klink, G.P.M., van Koten, G., and de Vries, J.G. (2010) The mechanism of the modified Ullmann reaction. *Dalton Trans.*, **39**, 10338–10351.
8. Cohen, T. and Cristea, I. (1976) Kinetics and mechanism of the copper(I)-induced homogeneous Ullmann coupling of *o*-bromonitrobenzene. *J. Am. Chem. Soc.*, **98**, 748–753.
9. Do, H.-Q., Khan, R.M.K., and Daugulis, O. (2008) A general method for copper-catalyzed arylation of arene C–H bonds. *J. Am. Chem. Soc.*, **130**, 15185–15192.
10. Mousseau, J.J., Bull, J.A., and Charette, A.B. (2010) Copper-catalyzed direct alkenylation of *N*-iminopyridinium ylides. *Angew. Chem. Int. Ed.*, **49**, 1115–1118.
11. Daugulis, O., Zaitsev, V.G., Shabashov, D., Pham, Q.-N., and Lazareva, A. (2006) Regioselective functionalization of unreactive carbon–hydrogen bonds. *Synlett*, 3382–3388.
12. Zaitsev, V.G. and Daugulis, O. (2005) Catalytic coupling of haloolefins with anilides. *J. Am. Chem. Soc.*, **127**, 4156–4157.
13. Matsuura, Y., Tamura, M., Kochi, T., Sato, M., Chatani, N., and Kakiuchi, F. (2007) The Ru(cod)(cot)-catalyzed alkenylation of aromatic C–H bonds

with alkenyl acetates. *J. Am. Chem. Soc.*, **129**, 9858–9859.

14. Jin, W., Yu, Z., He, W., Ye, W., and Xiao, W.-J. (2009) Efficient Rh(I)-catalyzed direct arylation and alkenylation of arene C–H bonds via decarbonylation of benzoic and cinnamic anhydrides. *Org. Lett.*, **11**, 1317–1320.
15. Ueno, S., Kochi, T., Chatani, N., and Kakiuchi, F. (2009) Unique effect of coordination of an alkene moiety in products on ruthenium-catalyzed chemoselective C–H alkenylation. *Org. Lett.*, **11**, 855–858.
16. Beletskaya, I.P. and Cheprakov, A.V. (2000) The Heck reaction as a sharpening stone of palladium catalysis. *Chem. Rev.*, **100**, 3009–3066.
17. Le Bras, J. and Muzart, J. (2011) Intermolecular dehydrogenative Heck reactions. *Chem. Rev.*, **111**, 1170–1214.
18. Yokota, T., Tani, M., Sakaguchi, S., and Ishii, Y. (2003) Direct coupling of benzene with olefins catalyzed by $Pd(OAc)_2$ combined with heteropolyoxometalate under dioxygen. *J. Am. Chem. Soc.*, **125**, 1476–1477.
19. Kubota, A., Emmert, M.H., and Sanford, M.S. (2012) Pyridine ligands as promoters in $Pd^{II/0}$-catalyzed C–H olefination reactions. *Org. Lett.*, **14**, 1760–1763.
20. Yamada, T., Sakaguchi, S., and Ishii, Y. (2005) Oxidative coupling of benzenes with α,β-unsaturated aldehydes by the $Pd(OAc)_2$/molybdovanadophosphoric acid/O_2 system. *J. Org. Chem.*, **70**, 5471–5474.
21. Milstein, D., Weissman, H., and Song, X.P. (2002) Method for the production of aryl alkenes. WO Patent 02055455.
22. Vasseur, A., Harakat, D., Muzart, J., and Le Bras, J. (2013) Aerobic dehydrogenative Heck reactions of heterocycles with styrenes: a negative effect of metallic co-oxidants. *Adv. Synth. Catal.*, **355**, 59–67.
23. Shang, X., Xiong, Y., Zhang, Y., Zhang, L., and Liu, Z. (2012) Pd(II)-catalyzed direct olefination of arenes with allylic esters and ethers. *Synlett*, 259–262.
24. Cho, S.H., Hwang, S.J., and Chang, S. (2008) Palladium-catalyzed C–H functionalization of pyridine *N*-oxides: highly selective alkenylation and direct arylation with unactivated arenes. *J. Am. Chem. Soc.*, **130**, 9254–9256.
25. Park, S.H., Kim, J.Y., and Chang, S. (2011) Rhodium-catalyzed selective olefination of arene esters via C–H bond activation. *Org. Lett.*, **13**, 2372–2375.
26. Patureau, F.W., Besset, T., and Glorius, F. (2011) Rhodium-catalyzed oxidative olefination of C–H bonds in acetophenones and benzamides. *Angew. Chem. Int. Ed.*, **50**, 1064–1067.
27. Padala, K. and Jeganmohan, M. (2012) Highly regio- and stereoselective ruthenium(II)-catalyzed direct *ortho*-alkenylation of aromatic and heteroaromatic aldehydes with activated alkenes under open atmosphere. *Org. Lett.*, **14**, 1134–1137.
28. Mochida, S., Hirano, K., Satoh, T., and Miura, M. (2010) Synthesis of stilbene and distyrylbenzene derivatives through rhodium-catalyzed *ortho*-olefination and decarboxylation of benzoic acids. *Org. Lett.*, **12**, 5776–5779.
29. García-Rubia, A., Fernández-Ibañez, M.A., Gomez Arrayás, R., and Carretero, J. (2011) 2-Pyridyl sulfoxide: a versatile and removable directing group for the Pd^{II}-catalyzed direct C–H olefination of arenes. *Chem. Eur. J.*, **17**, 3567–3570.
30. Neumann, J.J., Rakshit, S., Dröge, T., Würtz, S., and Glorius, F. (2011) Exploring the oxidative cyclization of substituted *N*-aryl enamines: Pd-catalyzed formation of indoles from anilines. *Chem. Eur. J.*, **17**, 7298–7303.
31. Rakshit, S., Grohmann, C., Besset, T., and Glorius, F. (2011) Rh(III)-catalyzed directed C–H olefination using an oxidizing directing group: mild, efficient, and versatile. *J. Am. Chem. Soc.*, **133**, 2350–2353.
32. Boele, M.D.K., van Strijdonck, G.P.F., de Vries, A.H.M., Kamer, P.C.J., de Vries, J.G., and van Leeuwen, P.W.N.M. (2002) Selective Pd-catalyzed oxidative coupling of anilides with olefins through C–H bond activation at room temperature. *J. Am. Chem. Soc.*, **124**, 1586–1587.
33. Zhang, X., Fan, S., He, C.-Y., Wan, X., Min, Q.-Q., Yang, J., and Jiang, Z.-X. (2010) $Pd(OAc)_2$ catalyzed olefination of

highly electron-deficient perfluoroarenes. *J. Am. Chem. Soc.*, **132**, 4506–4507.

34. Padala, K. and Jeganmohan, M. (2011) Ruthenium-catalyzed *ortho*-alkenylation of aromatic ketones with alkenes by C–H bond activation. *Org. Lett.*, **13**, 6144–6147.
35. Zheng, L. and Wang, J. (2012) Direct oxidative coupling of arenes with olefins by Rh-catalyzed C–H activation in air: observation of a strong cooperation of the acid. *Chem. Eur. J.*, **18**, 9699–9704.
36. Liu, B., Fan, Y., Gao, Y., Sun, C., Xu, C., and Zhu, J. (2013) Rhodium(III)-catalyzed *N*-nitroso-directed C–H olefination of arenes. High-yield, versatile coupling under mild conditions. *J. Am. Chem. Soc.*, **135**, 468–473.
37. Wang, C., Chen, H., Wang, Z., Chen, J., and Huang, Y. (2012) Rhodium(III)-catalyzed C–H activation of arenes using a versatile and removable triazene directing group. *Angew. Chem. Int. Ed.*, **51**, 7242–7245.
38. Zhang, Y.-H., Shi, B.-F., and Yu, J.-Q. (2009) Pd(II)-catalyzed olefination of electron-deficient arenes using 2,6-dialkylpyridine ligands. *J. Am. Chem. Soc.*, **131**, 5072–5074.
39. Truong, T. and Daugulis, O. (2012) Directed functionalization of C–H bonds: now also *meta* selective. *Angew. Chem. Int. Ed.*, **51**, 11677–11679.
40. Shang, Y., Jie, X., Zhou, J., Hu, P., Huang, S., and Su, W. (2013) Pd-catalyzed C–H olefination of (hetero)arenes by using saturated ketones as an olefin source. *Angew. Chem. Int. Ed.*, **52**, 1299–1303.
41. Wrigglesworth, J.W., Cox, B., Lloyd-Jones, G.C., and Booker-Milburn, K.I. (2011) New heteroannulation reactions of *N*-alkoxybenzamides by Pd(II) catalyzed C–H activation. *Org. Lett.*, **13**, 5326–5329.
42. Wang, H. and Glorius, F. (2012) Mild rhodium(III)-catalyzed C–H activation and intermolecular annulation with allenes. *Angew. Chem. Int. Ed.*, **51**, 7318–7322.
43. Li, Z., Zhang, Y., and Liu, Z.-Q. (2012) Pd-catalyzed olefination of perfluoroarenes with allyl esters. *Org. Lett.*, **14**, 74–77.
44. Ackermann, L., Novák, P., Vicente, R., and Hofmann, N. (2009) Ruthenium-catalyzed regioselective direct alkylation of arenes with unactivated alkyl halides through C–H bond cleavage. *Angew. Chem. Int. Ed.*, **48**, 6045–6048.
45. Jiang, H., Feng, Z., Wang, A., Liu, X., and Chen, Z. (2010) Palladium-catalyzed alkenylation of 1,2,3-trizoles with terminal conjugated alkenes by direct C–H bond functionalization. *Eur. J. Org. Chem.*, **2010**, 1227–1230.
46. Vasseur, A., Harakat, D., Muzart, J., and Le Bras, J. (2012) ESI-MS studies of the dehydrogenative Heck reaction of furans with acrylates using benzoquinone as the reoxidant and DMSO as the solvent. *J. Org. Chem.*, **77**, 5751–5758.
47. Zhang, Y., Li, Z., and Liu, Z.-Q. (2012) Pd-catalyzed olefination of furans and thiophenes with allyl esters. *Org. Lett.*, **14**, 226–229.
48. Pindur, U. and Adam, R. (1990) Thermal 1,6-electrocyclization reactions of acceptor-substituted 2,3-divinyl-1*H*-indoles yielding functionalized carbazoles. *Helv. Chim. Acta*, **73**, 827–838.
49. Rodríguez-Escrich, C., Davis, R.L., Jiang, H., Stiller, J., Johansen, T.K., and Jørgensen, K.A. (2013) Breaking symmetry with symmetry: bifacial selectivity in the asymmetric cycloaddition of anthracene derivatives. *Chem. Eur. J.*, **19**, 2932–2936.
50. de la Hoz, A., Díaz-Ortiz, A., Fraile, J.M., Gómez, M.V., Mayoral, J.A., Moreno, A., Saiz, A., and Vázquez, E. (2001) Synergy between heterogeneous catalysis and microwave irradiation in an efficient one-pot synthesis of benzene derivatives via ring-opening of Diels–Alder cycloadducts of substituted furans. *Synlett*, 753–756.
51. Muller, G.W., Saindane, M., Ge, C., Kothare, M.A., Cameron, L.M., and Rogers, M.E. (2007) Process for the preparation of substituted 2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione. WO Patent 2007136640.
52. Tsukada, N., Mitsuboshi, T., Setoguchi, H., and Inoue, Y. (2003) Stereoselective *cis*-addition of aromatic C–H bonds to

alkynes catalyzed by dinuclear palladium complexes. *J. Am. Chem. Soc.*, **125**, 12102–12103.

53. Cheng, K., Yao, B., Zhao, J., and Zhang, Y. (2008) $RuCl_3$-catalyzed alkenylation of aromatic C–H bonds with terminal alkynes. *Org. Lett.*, **10**, 5309–5312.

54. Ding, Z. and Yoshikai, N. (2012) Mild and efficient C2-alkenylation of indoles with alkynes catalyzed by a cobalt complex. *Angew. Chem. Int. Ed.*, **51**, 4698–4701.

55. Li, H.-J., Guillot, R., and Gandon, V. (2010) A gallium-catalyzed cycloisomerization/Friedel–Crafts tandem. *J. Org. Chem.*, **75**, 8435–8449.

56. Hashimoto, Y., Hirano, K., Satoh, T., Kakiuchi, F., and Miura, M. (2013) Regioselective C–H bond cleavage/alkyne insertion under ruthenium catalysis. *J. Org. Chem.*, **78**, 638–646.

57. Too, P.C., Chua, S.H., Wong, S.H., and Chiba, S. (2011) Synthesis of azaheterocycles from aryl ketone *O*-acetyl oximes and internal alkynes by Cu–Rh bimetallic relay catalysts. *J. Org. Chem.*, **76**, 6159–6168.

58. Tran, D.N. and Cramer, N. (2011) Enantioselective rhodium(I)-catalyzed [3 + 2] annulations of aromatic ketimines induced by directed C–H activations. *Angew. Chem. Int. Ed.*, **50**, 11098–11102.

59. Li, B.-J., Wang, H.-Y., Zhu, Q.-L., and Shi, Z.-J. (2012) Rhodium/copper-catalyzed annulation of benzimides with internal alkynes: indenone synthesis through sequential C–H and C–N cleavage. *Angew. Chem. Int. Ed.*, **51**, 3948–3952.

60. Ragaini, F., Ventriglia, F., Hagar, M., Fantauzzi, S., and Cenini, S. (2009) Synthesis of indoles by intermolecular cyclization of unfunctionalized nitroarenes and alkynes: one-step synthesis of the skeleton of fluvastatin. *Eur. J. Org. Chem.*, **2009**, 2185–2189.

61. Nakatani, A., Hirano, K., Satoh, T., and Miura, M. (2012) A concise access to (polyfluoroaryl)allenes by Cu-catalyzed direct coupling with propargyl phosphates. *Org. Lett.*, **14**, 2586–2589.

62. Chidipudi, S.R., Khan, I., and Lam, H.W. (2012) Functionalization of C_{sp3}–H and C_{sp2}–H bonds: synthesis of spiroindenes by enolate-directed ruthenium-catalyzed oxidative annulation of alkynes with 2-aryl-1,3-dicarbonyl compounds. *Angew. Chem. Int. Ed.*, **51**, 12115–12119.

63. Dong, W., Wang, L., Parthasarathy, K., Pan, F., and Bolm, C. (2013) Rhodium-catalyzed oxidative annulation of sulfoximines and alkynes as an approach to 1,2-benzothiazines. *Angew. Chem. Int. Ed.*, **52**, 11573–11576.

64. Beveridge, R.E. and Arndtsen, B.A. (2010) A direct, copper-catalyzed functionalization of pyridines with alkynes. *Synthesis*, 1000–1008.

65. Murakami, M. and Hori, S. (2003) Ruthenium-mediated regio- and stereoselective alkenylation of pyridine. *J. Am. Chem. Soc.*, **125**, 4720–4721.

66. Agawa, T. and Miller, S.I. (1961) Reaction of silver acetylide with acylpyridinium salts: *N*-benzoyl-2-phenylethynyl-1,2-dihydropyridine. *J. Am. Chem. Soc.*, **83**, 449–453.

67. de Haro, T. and Nevado, C. (2010) Gold-catalyzed ethynylation of arenes. *J. Am. Chem. Soc.*, **132**, 1512–1513.

3
Electrophilic Arylation of Arenes

3.1
General Aspects

Most arene arylations belong to one of the reaction types sketched in Scheme 3.1. In the first step, an arene is metallated by the insertion of a metal into a C–H or C–X bond. The second step can proceed either via the formation of a diarylmetal intermediate which undergoes reductive elimination or by aromatic nucleophilic substitution. In many of the examples presented below, radicals are formed as intermediates.

Only few examples of the arylation of unsubstituted arenes with aryl halides had been reported until recently [1]. The oldest examples are copper-catalyzed, Ullmann-type reactions of aryl halides (mostly iodides) with other arenes or heteroarenes. Usually, though, the Ullmann reaction [2, 3] converts aryl halides into homodimers. Yields of heterodimers are, therefore, often low. Further disadvantages of the Ullmann reaction are the required stoichiometric amounts of copper and the high reaction temperature. Typical side reactions of the Ullmann reaction include halogen exchange, reductive dehalogenation, and nucleophilic aromatic substitutions.

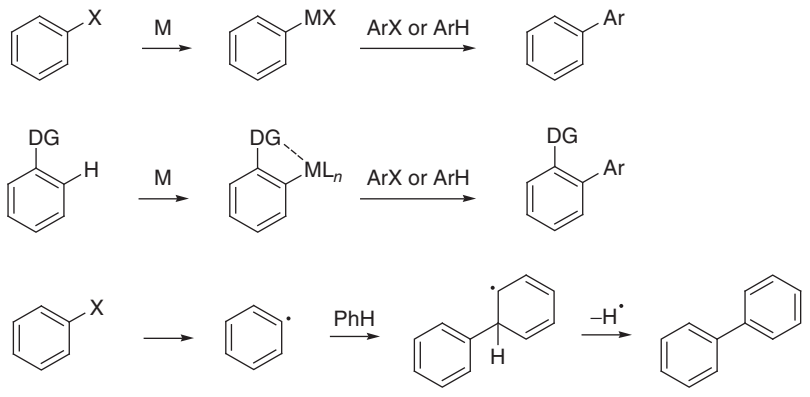
In recent decades, a number of more convenient alternatives to the classic Ullmann conditions have been developed [4]. The improvements include the use of only catalytic amounts of transition metals, lower reaction temperatures, and a better functional group tolerance.

3.2
Arylations with Aryl Halides

3.2.1
Via Cationic Intermediates

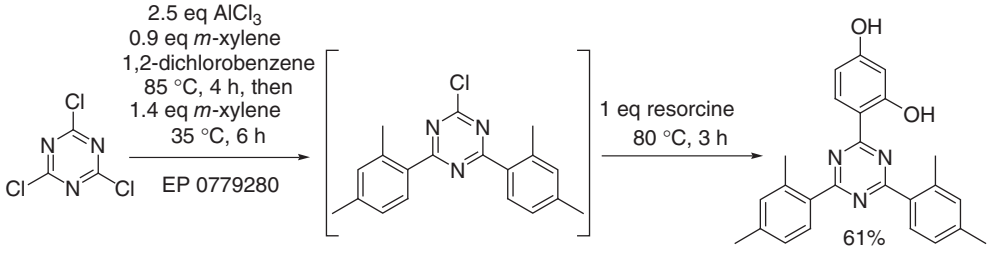
Most aryl halides are not electrophilic enough to arylate electron-rich arenes in the absence of catalysts. Even in the presence of strong Lewis acids, aryl halides usually remain unchanged. Only highly electrophilic heteroarenes, such as 2,4,6-trichlorotriazine (cyanuric chloride), or arenes capable of

Side Reactions in Organic Synthesis II: Aromatic Substitutions, First Edition. Florencio Zaragoza Dörwald.



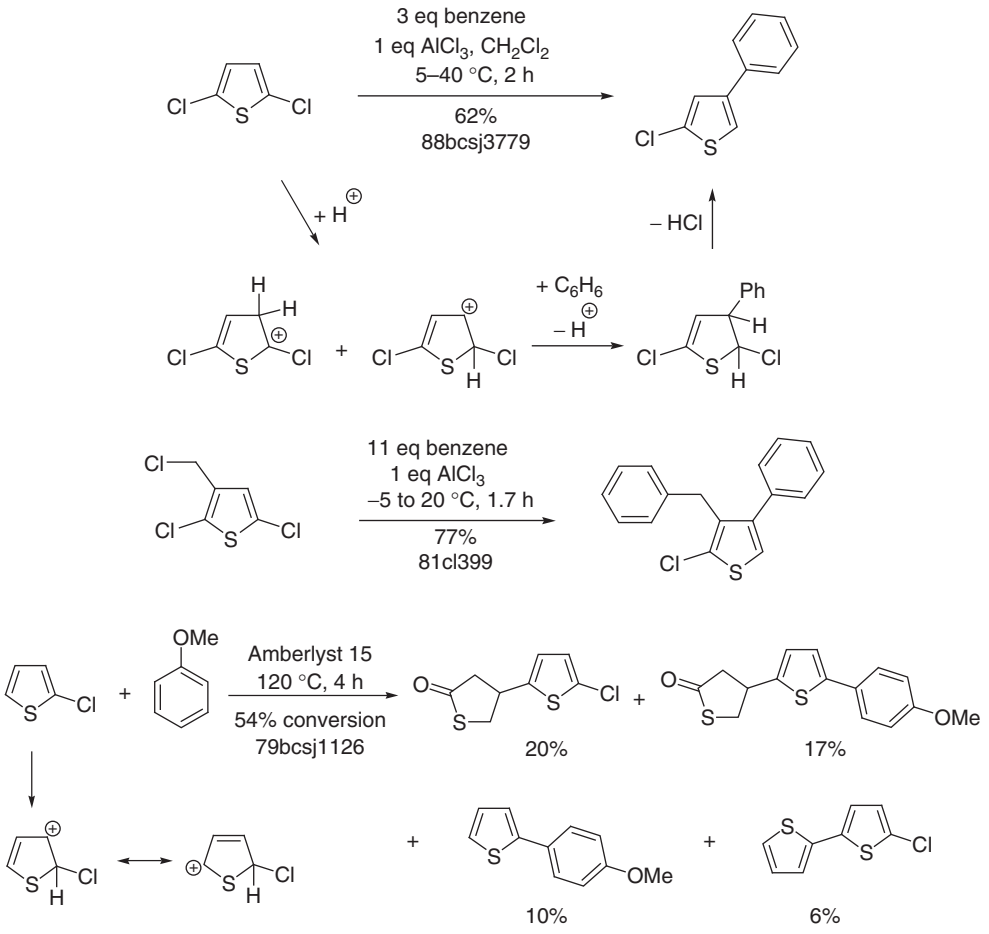
Scheme 3.1 Mechanisms of biaryl formation. M, metal; X, hydrogen or leaving group; DG, directing group.

forming stabilized cations by halogen abstraction or protonation (e.g., 9,10-dichloroanthracene and thiophene) arylate other arenes in the presence of $AlCl_3$ (Scheme 3.2).



Scheme 3.2 Arylation of cyanuric chloride [5]. Further examples: [6].

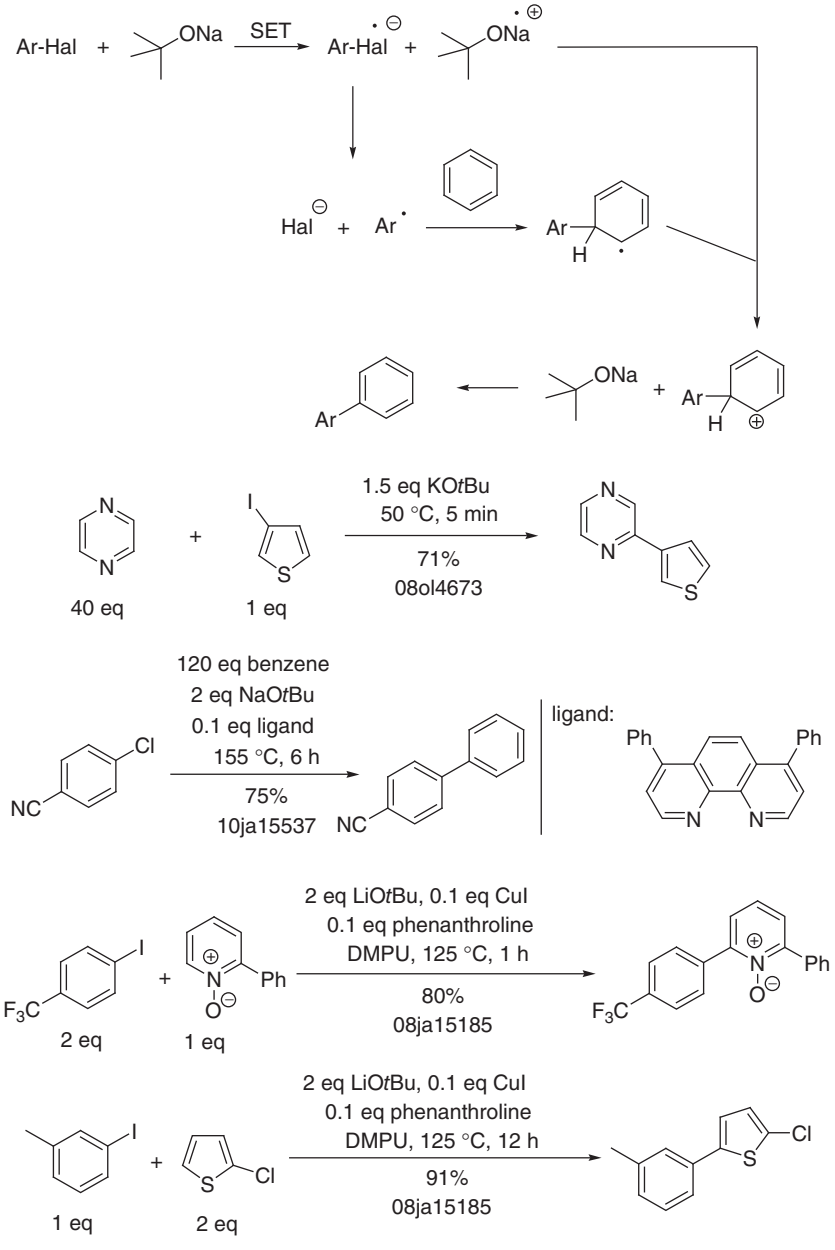
Because the complete abstraction of halides from arenes to generate aryl cations is unfavorable (because no effective charge delocalization is possible in aryl cations), most transition-metal-free arylations with aryl halides will proceed via an addition–elimination mechanism. In acid-catalyzed arylations, the aryl halide can be protonated to yield a more reactive intermediate, which will, however, not necessarily react at the halogen-bearing carbon atom (Scheme 3.3). Nor will it react forcibly with the most stable or representative resonance formula because this will also be the least reactive one. The complexity of such reactions is further increased by reactions of the protonated with the unprotonated aryl halide (Scheme 3.3, last equation).



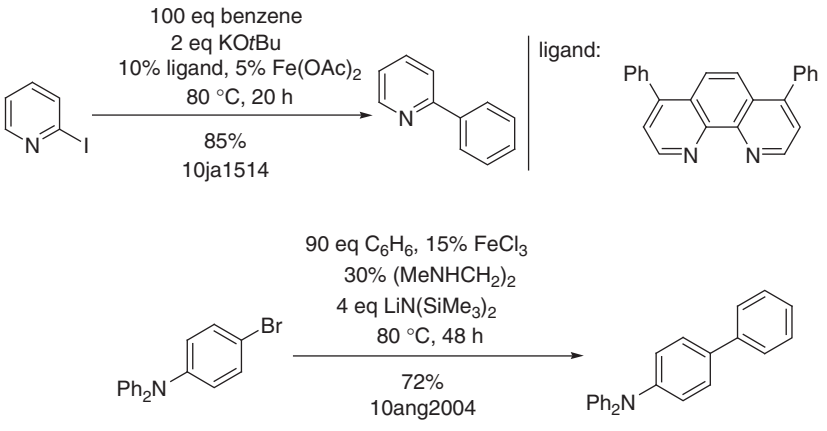
Scheme 3.3 Acid-mediated arylations of 2-chlorothiophenes [7–9].

3.2.2
Via Radicals

Most arylations with aryl halides proceed either via metal–halogen exchange or by the formation of aryl radicals. The latter can be generated in several ways, for instance, by treatment of aryl halides with tertiary alkanolates (Scheme 3.4). The best results are usually obtained with two arenes of unlike electron density, and with a large excess of the ''radical accepting'' arene (to prevent homodimer formation). Examples of uncatalyzed reactions of this type and alcoholate-mediated arylations catalyzed by transition metals have been reported (Scheme 3.4). Radical-based mechanisms have also been proposed for copper-catalyzed, Ullmann-type arylations with aryl halides [10].



Scheme 3.4 Transition-metal-catalyzed arylations with aryl halides mediated by strong bases [11–15]. Further examples: [16].



Scheme 3.4 (*Continued*)

Because radicals are less sensitive than charged intermediates to variations of electron density in the reacting partner, their regioselectivity is usually low. Accordingly, mixtures of regioisomers are often obtained during arylations with aryl radicals (Scheme 3.5).

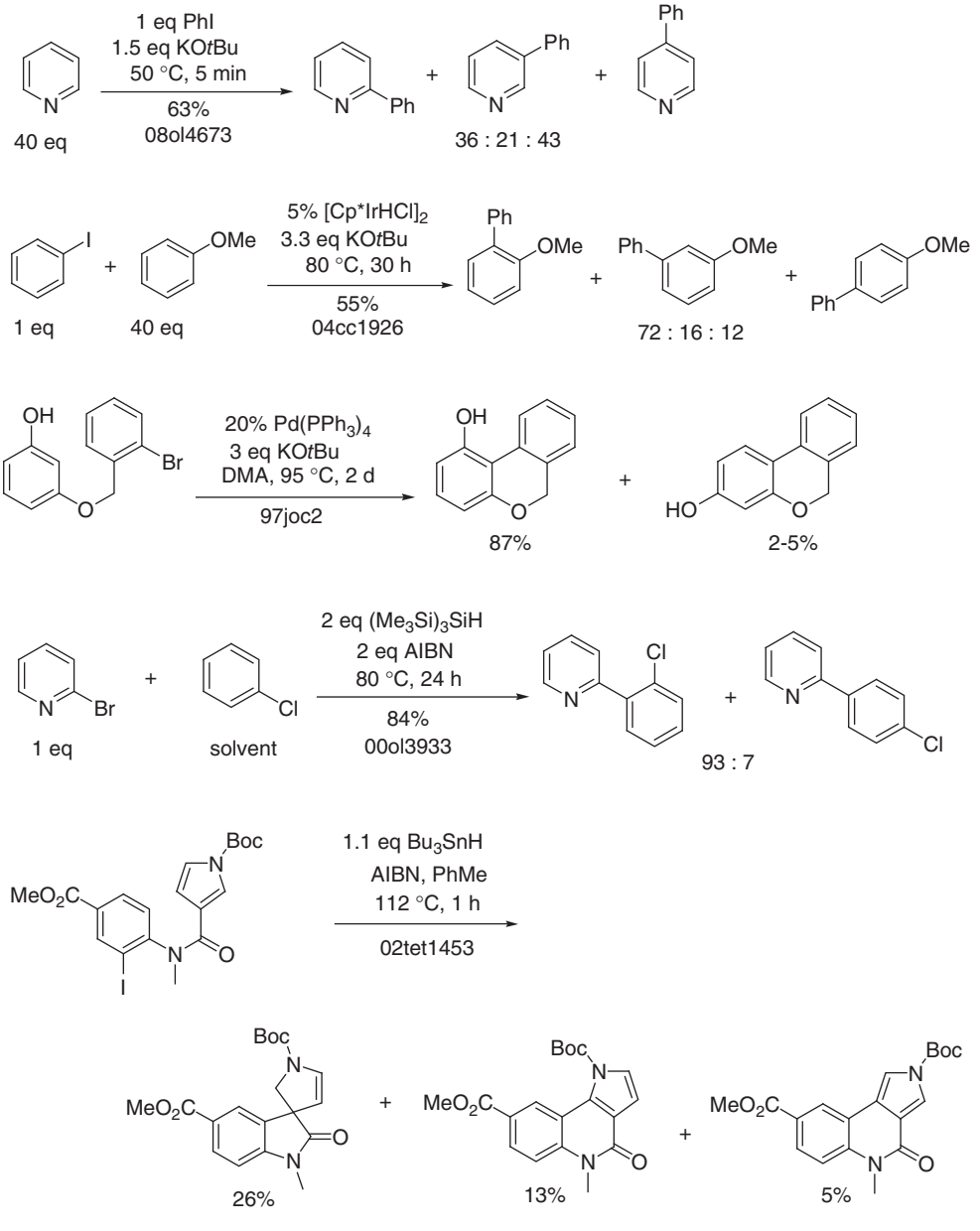
Reactions performed in the presence of a large excess of a strong base can easily yield unexpected products. If weakly acidic compounds are deprotonated, they often become strong reducing reagents, and will be oxidized by even weak oxidants. Air and other potential oxidants (ketones, polyhaloalkanes, or nitro compounds) should be meticulously excluded from the reaction mixture. Moreover, strong bases can lead to aryne formation and thereby to mixtures of regioisomers.

Aryl radicals can also be generated by thermolysis of benzoylperoxides (Scheme 3.6). This reaction is of little scope, because acylperoxides are also acylating reagents and can oxidize many functional groups (amines, thioethers, sulfoxides, olefins, ketones, arenes, etc.). Moreover, the outcome of these reactions varies strongly depending on the substitution pattern at the arene [21, 22]. Many peroxides, including diacylperoxides, are explosive, and can detonate spontaneously.

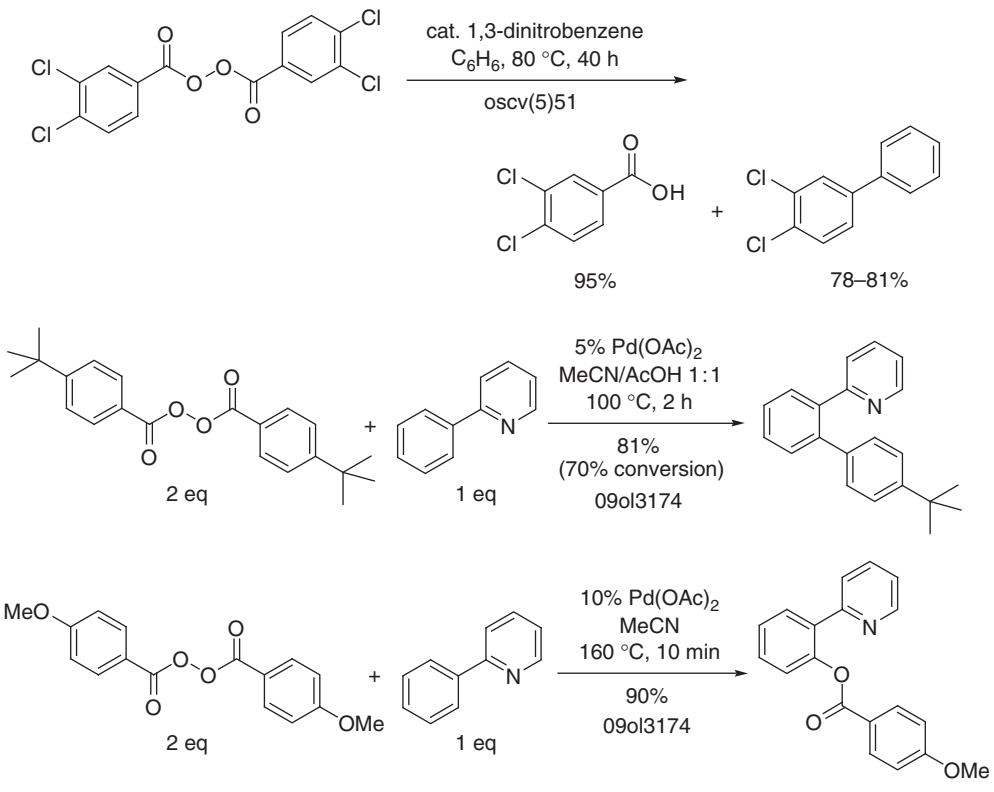
Radicals are short-lived intermediates, and often require high concentrations of a radical acceptor to give satisfactory yields. Processes that compete with the main reaction include radical dimerization (homocoupling), reduction (e.g., H-transfer from the solvent or other hydrogen donors), or reaction with oxygen to form peroxyl radicals. Radicals can also induce the oligomerization of alkenes or alkynes.

3.2.3
Via Transition-Metal Chelates

Arenes substituted with a coordinating functional group can be metallated under mild conditions and without strong bases by chelate formation. Arylruthenium



Scheme 3.5 Formation of regioisomers during arylations with aryl radicals [11, 17–20].



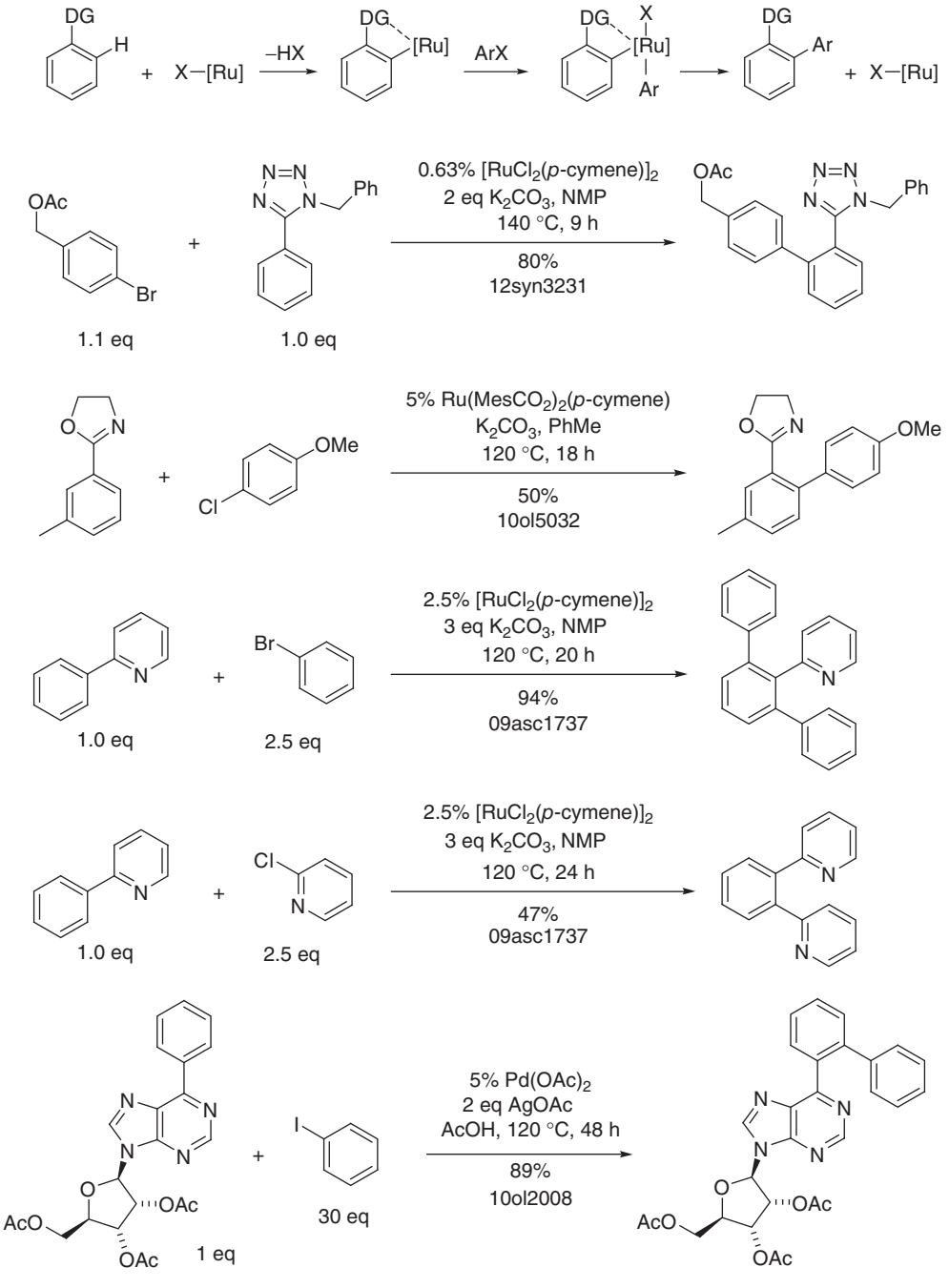
Scheme 3.6 Generation and reactions of aryl radicals from diacylperoxides [23, 24].

and -palladium chelates generated this way can react with aryl halides to yield biaryls after reductive elimination and regeneration of the catalyst (Scheme 3.7).

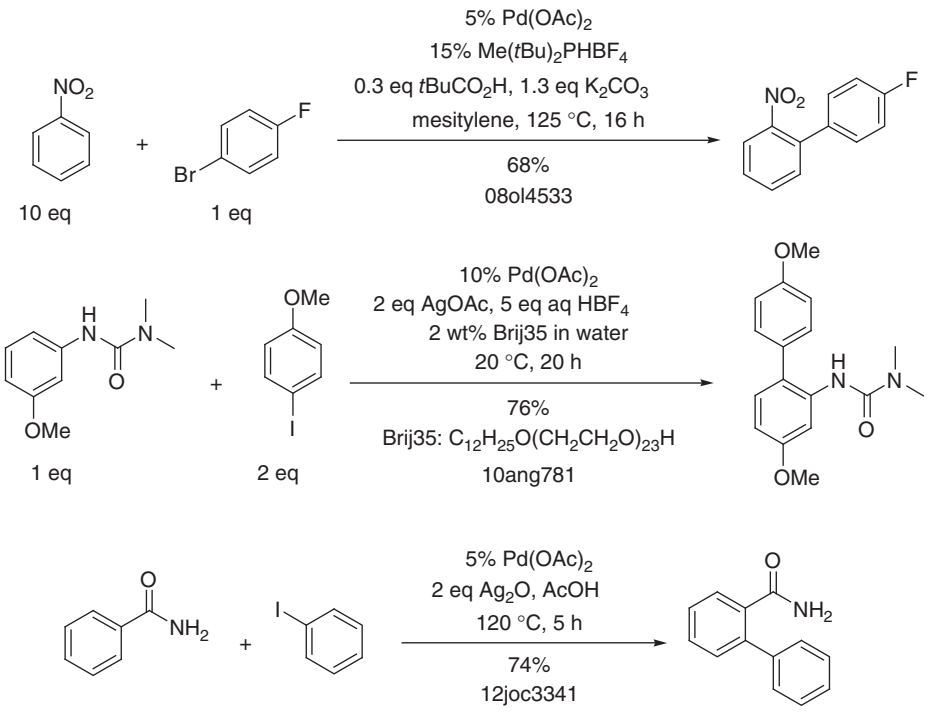
3.2.4
By Transition-Metal Catalysis

A number of arylation reactions with aryl halides have been reported that are assumed to proceed by metallation of an unsubstituted arene without chelate formation. Though not strictly necessary, oxidants are sometimes added to these reactions. The regioselectivity can be low and difficult to predict (Scheme 3.8), but the principles governing the regioselectivity (or lack of it) are slowly being understood [33]. Moreover, products of homocoupling are occasionally obtained as byproducts.

One typical side reaction of transition-metal-catalyzed arylations with aryl halides is the homocoupling of the aryl halide. This reaction can occur under amazingly



Scheme 3.7 Arylations via intermediate transition-metal chelate formation [25–31]. Further examples: [32].



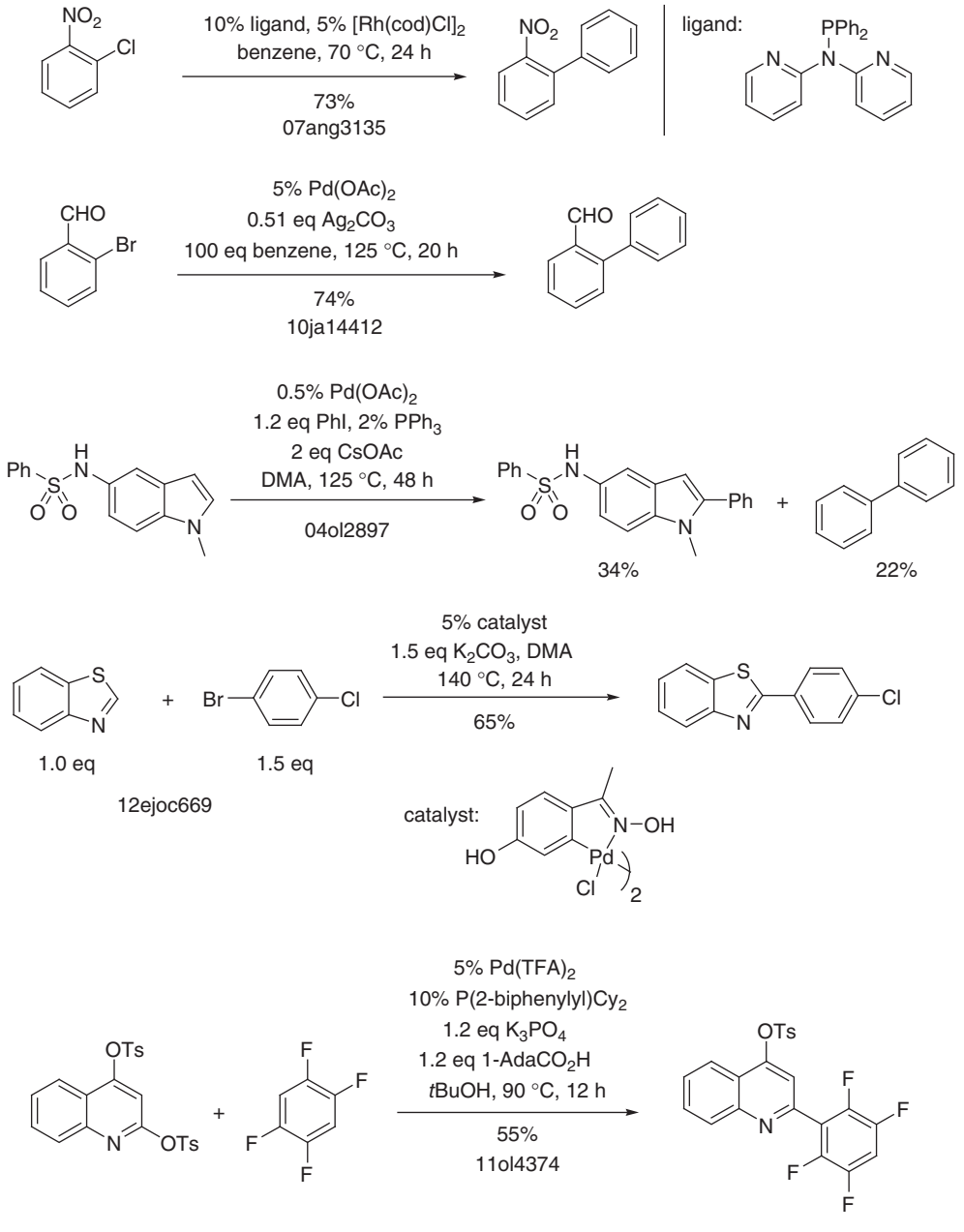
Scheme 3.7 (*Continued*)

mild conditions [46–48] (Scheme 3.9). To prevent homocoupling, in most of the examples given above one of the reactants must be used in a large excess.

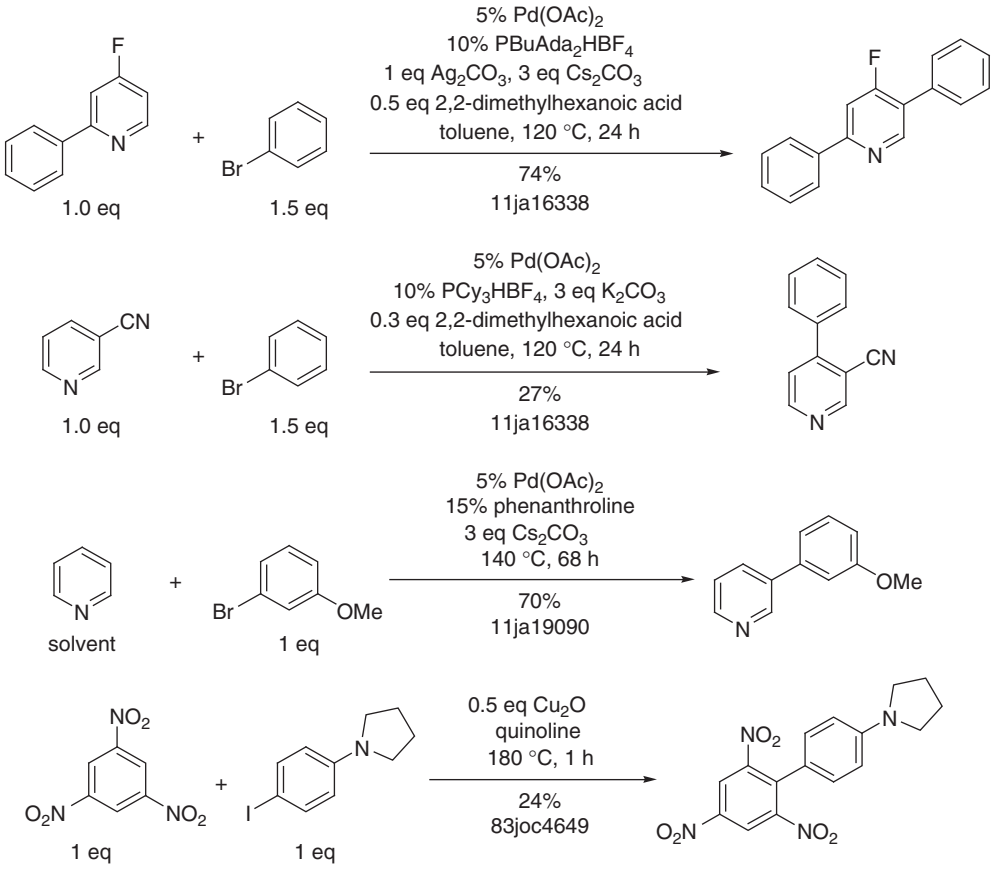
3.3 Arylations with Diazonium Salts

A further simple way to generate aryl radicals is the treatment of arenediazonium salts with aqueous base (Gomberg–Bachmann reaction). Thereby, diazo anhydrides (Ar–N=N–O–N=N–Ar) are formed that undergo thermal homolysis to yield aryl radicals. In the presence of a large excess of another arene, arylation occurs, and unsymmetric biaryls result (Scheme 3.10). Alternatively, aryl radicals may also be generated by the photolysis of arenediazonium salts [51].

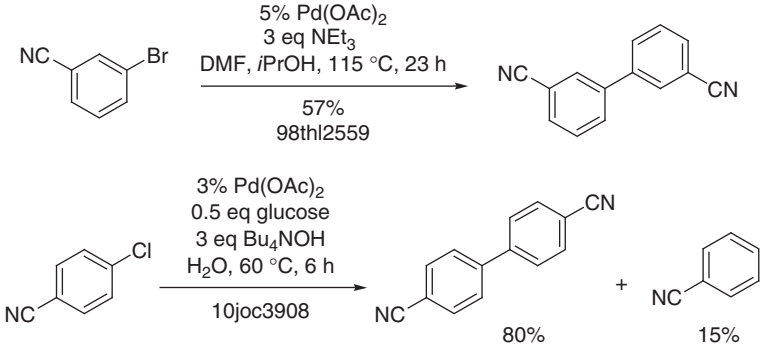
Not all aryl- or heteroarylamines can be converted to diazonium salts. Electron-deficient heteroarenediazonium salts (e.g., those prepared from 2- or 4-aminopyridines or 2-aminopyrimidines) undergo fast aromatic nucleophilic substitution of nitrogen, and are often hydrolyzed to hydroxyarenes. Diazonium salts prepared from 2-(primary alkyl)anilines are base-labile, and readily cyclize to indazoles [60]. The diazotization of electron-rich anilines can occasionally lead to



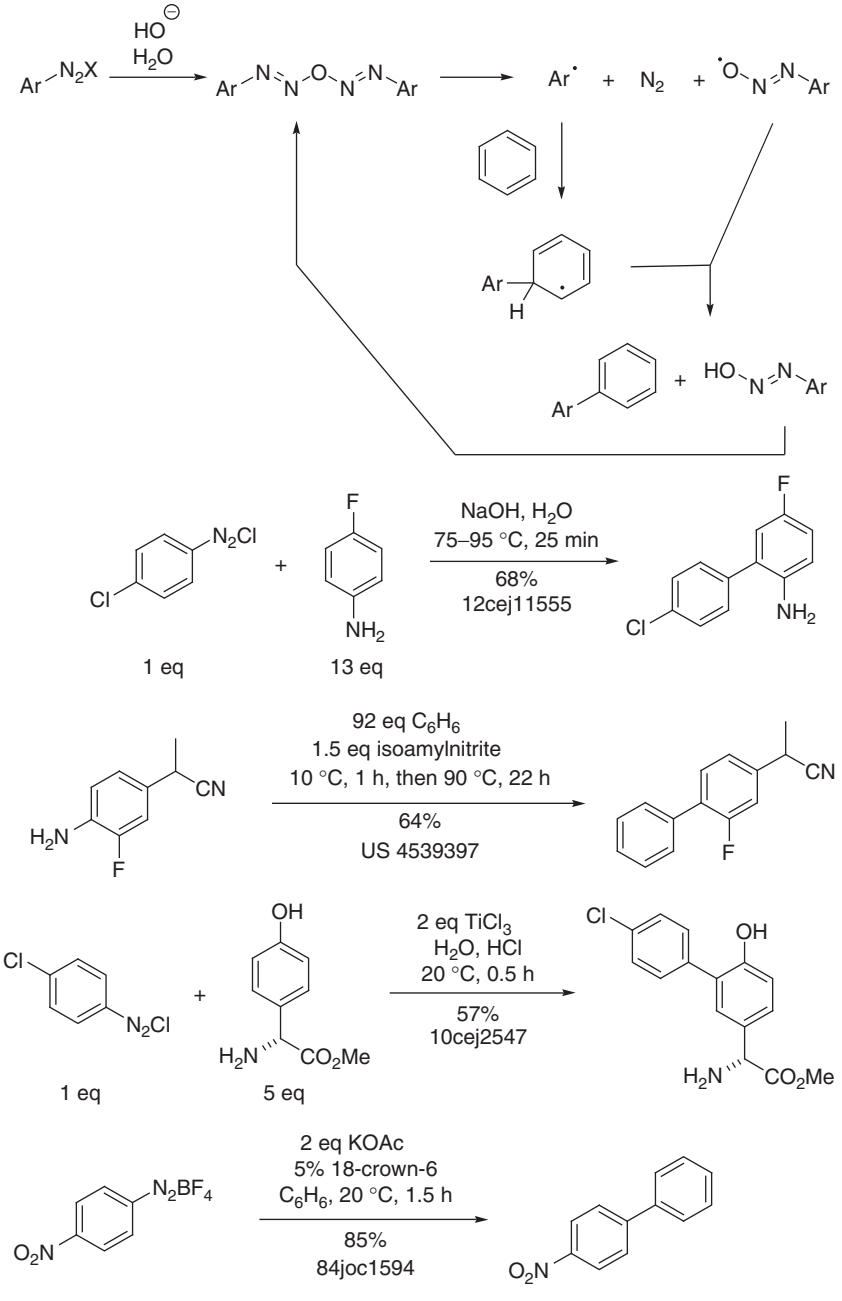
Scheme 3.8 Transition-metal-catalyzed arylation of unsubstituted arenes with aryl halides or tosylates [34–41]. Further examples: [33, 42–45].



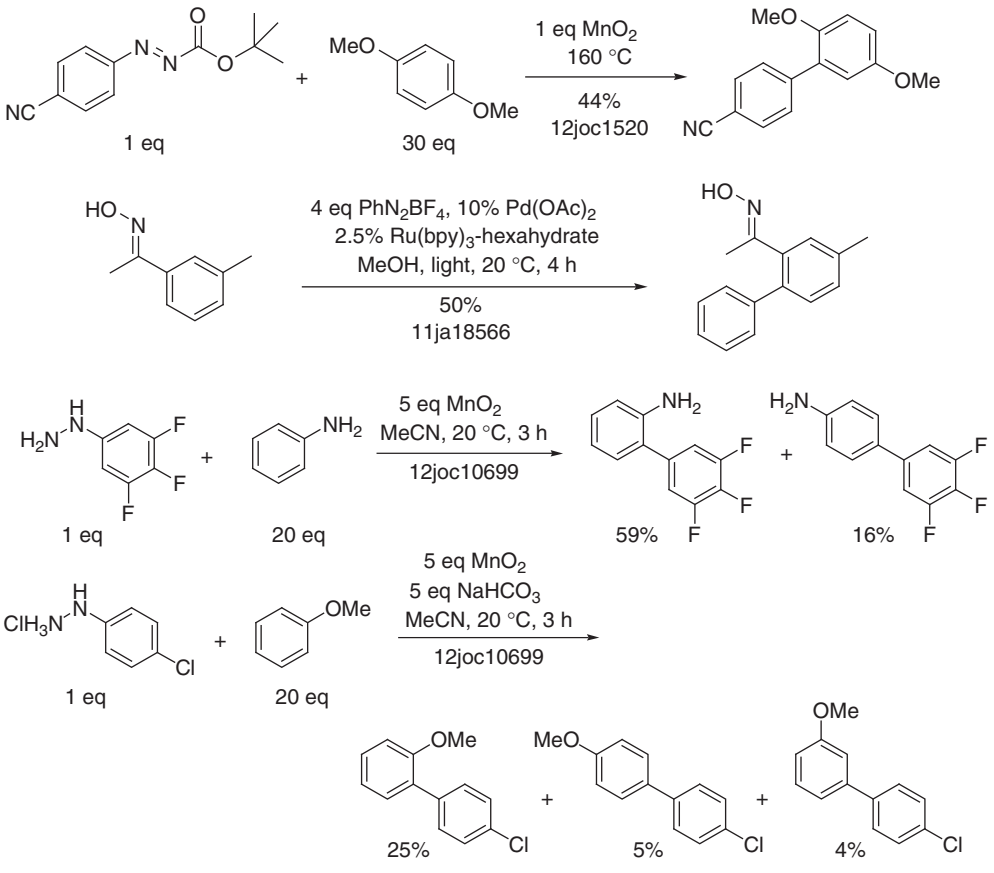
Scheme 3.8 (*Continued*)



Scheme 3.9 Homocoupling of aryl halides [49, 50].



Scheme 3.10 Arylations with aryl radicals generated from diazonium salts [52–58]. Further examples: [59].



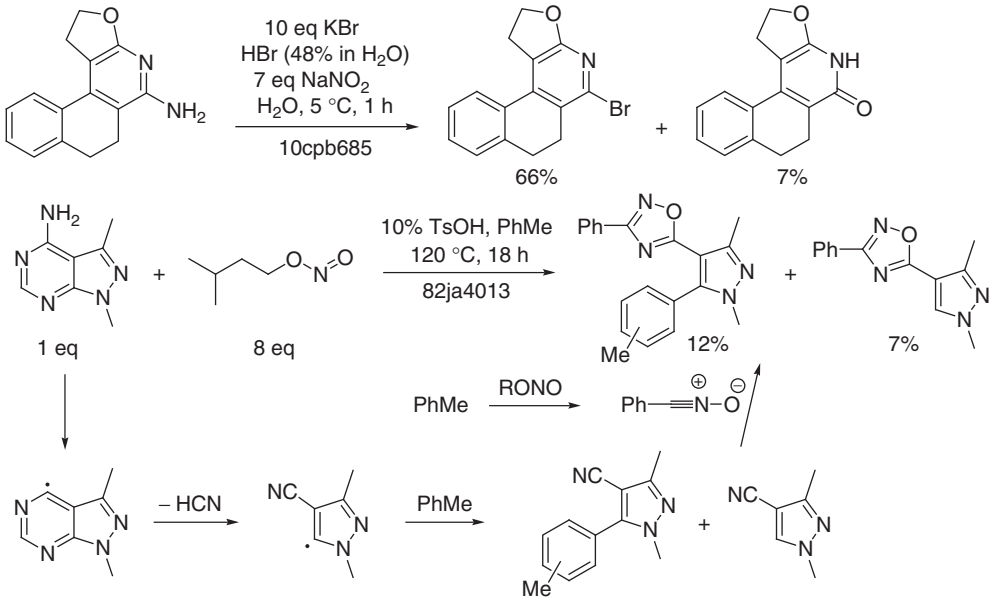
Scheme 3.10 (*Continued*)

aromatic nitrosation or nitration [61]. Some heteroaryl radicals rearrange to more stable radicals faster than adding to arenes (Scheme 3.11).

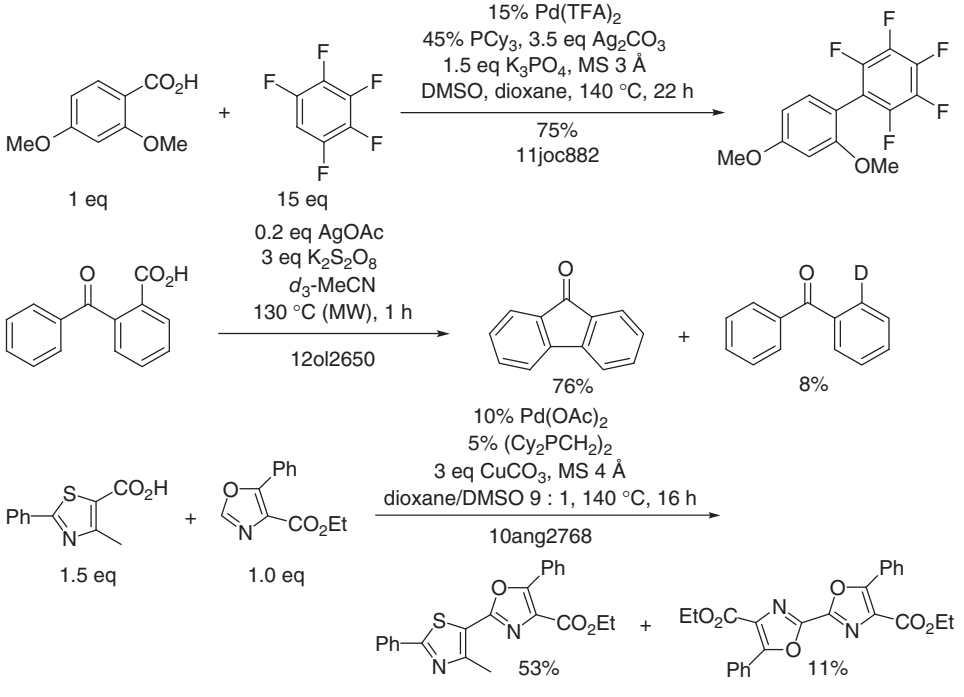
3.4 Arylations with Other Functionalized Arenes

Benzoic and heteroaromatic acids are further precursors for aryl radicals or metallated arenes, and can be used for the arylation of aromatic C–H bonds (Scheme 3.12). Benzoyl radicals, formed by the oxidation of benzoic acid salts, decarboxylate so quickly to aryl radicals that no byproducts resulting from the benzoyl radicals are usually observed.

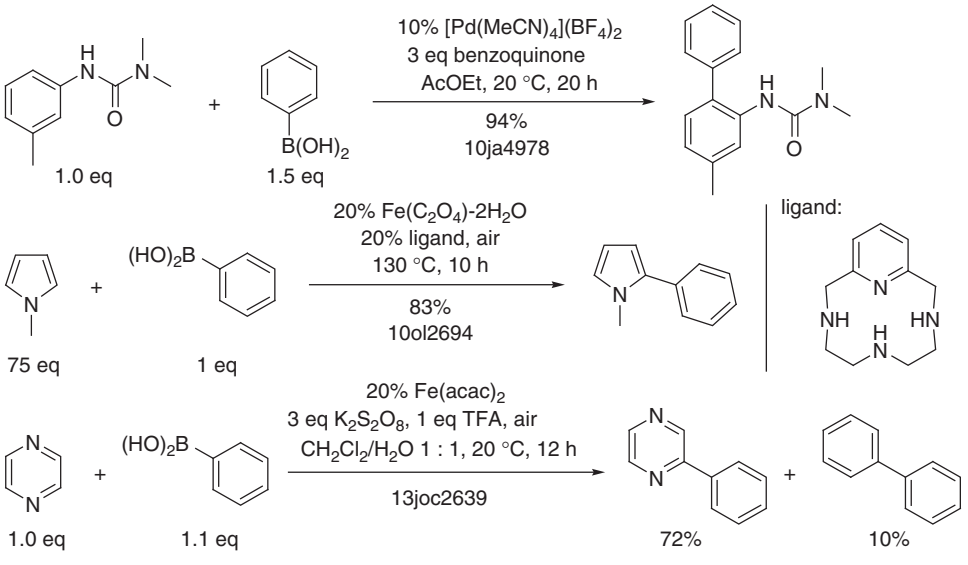
Arylpalladium complexes generated by metallation of aromatic C–H groups through chelate formation readily undergo homocoupling reactions. To achieve



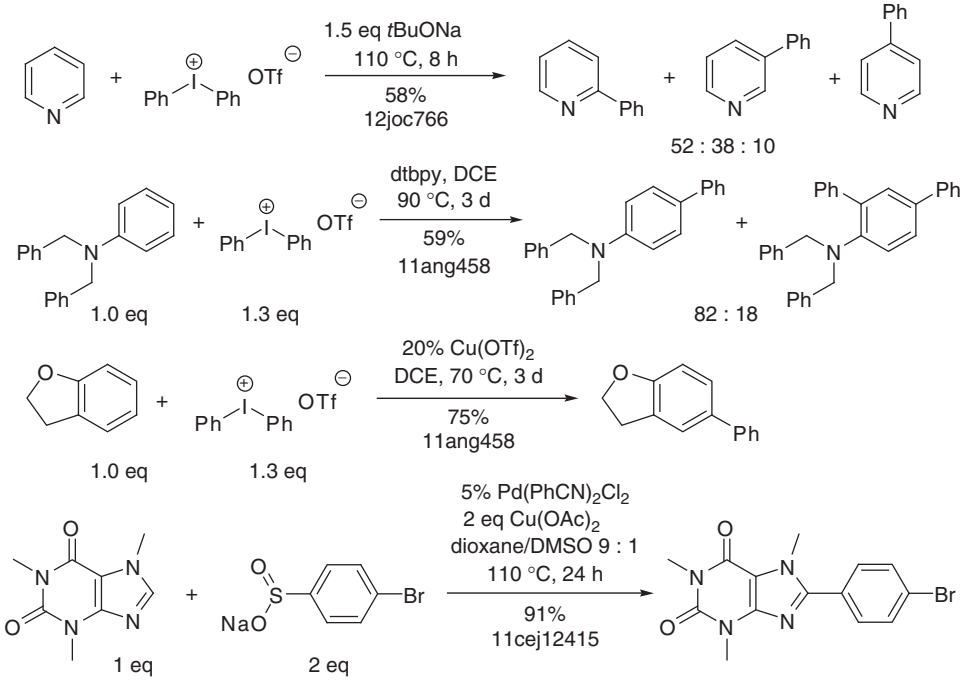
Scheme 3.11 Decomposition pathways of 2-pyridine and 4-pyrimidinediazonium salts [62, 63].



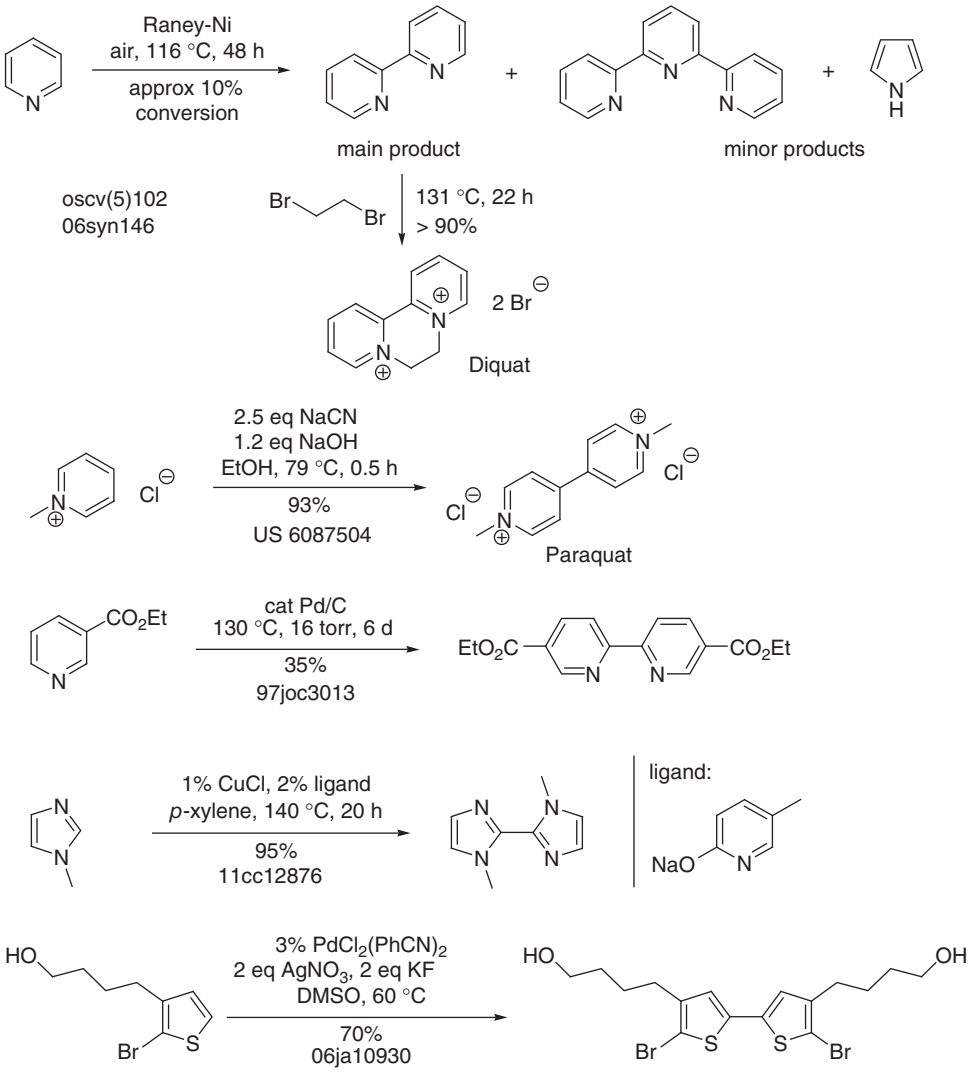
Scheme 3.12 Arylations with arenecarboxylic acids [64–66]. Further examples: [67].



Scheme 3.13 Palladium- and iron-catalyzed arylation of aromatic C–H groups with boronic acids [68–70].

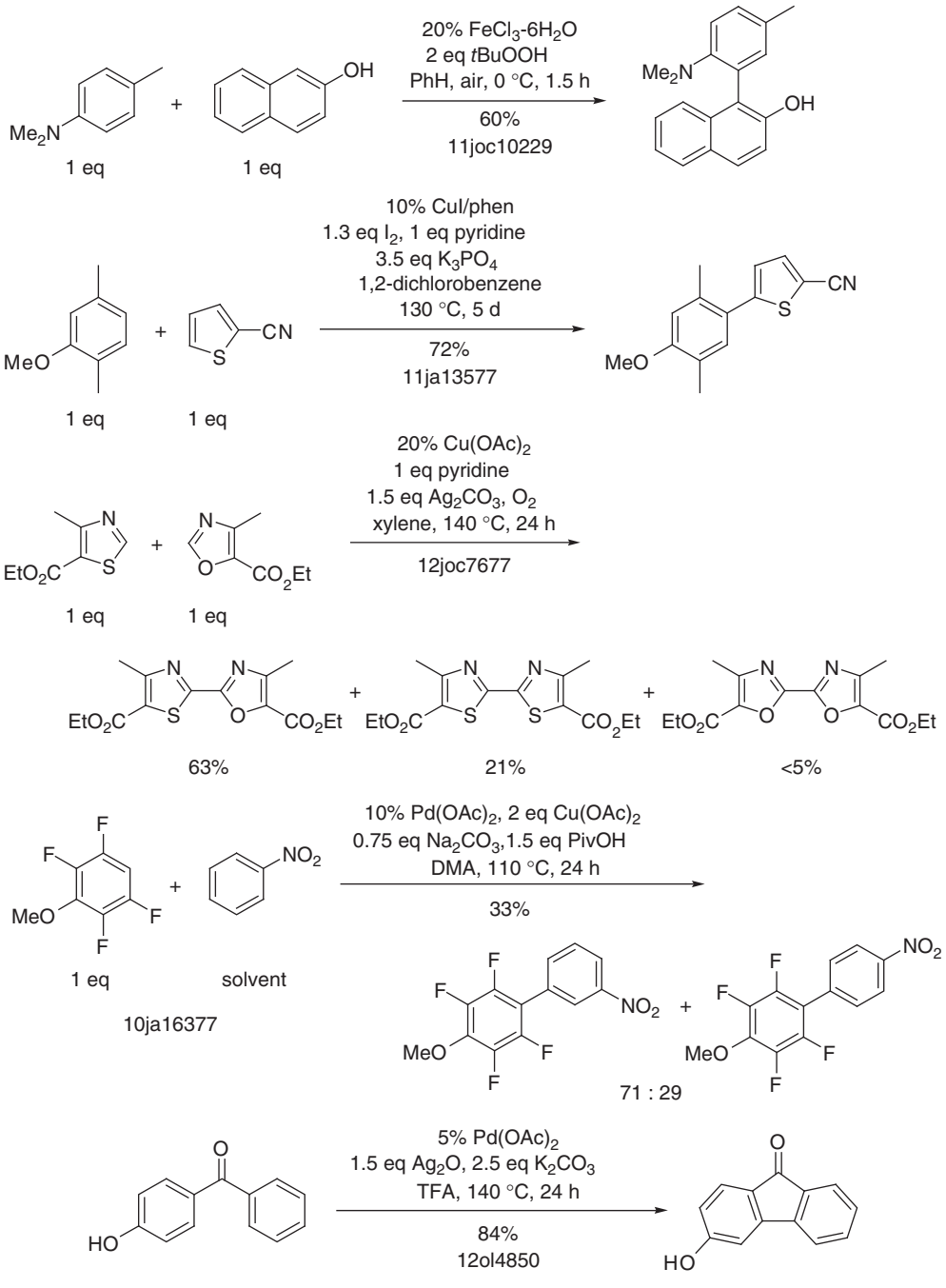


Scheme 3.14 Arylation of arenes with arene iodonium salts and sulfinates [71–73].

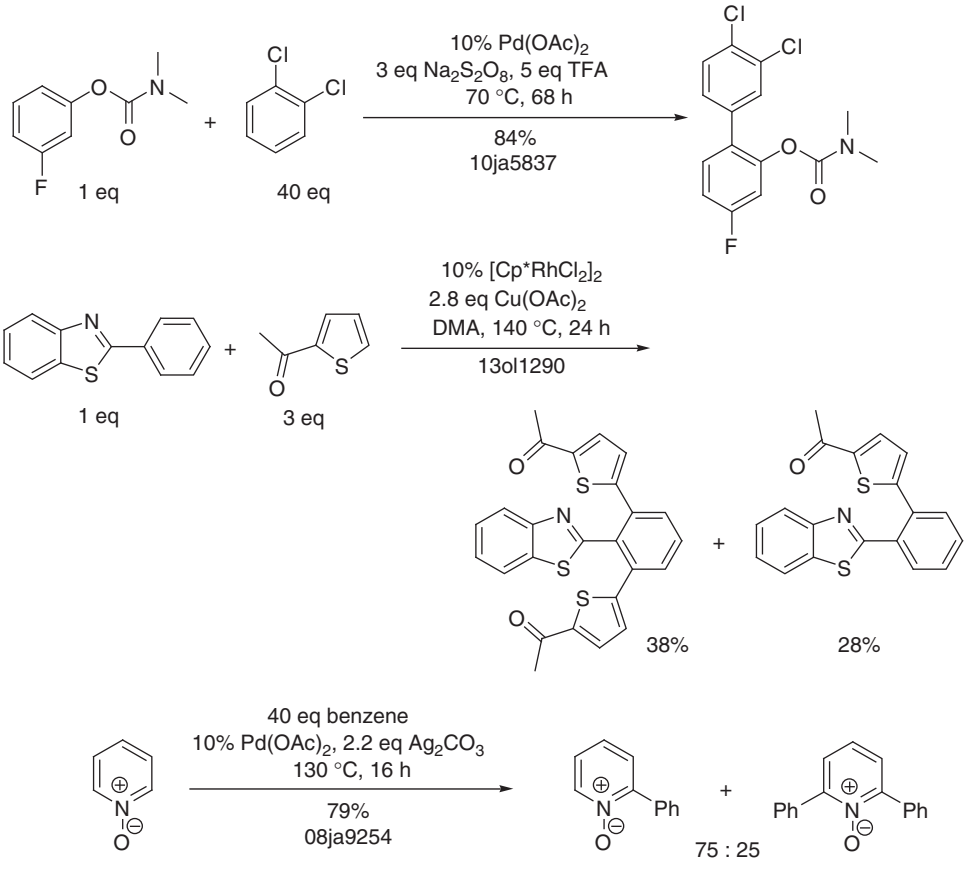


Scheme 3.15 Oxidative homodimerization of arenes [75–81].

heterocouplings, the challenge is to find oxidants that will not react with the nucleophilic coupling partner or with the metallated arene but just convert Pd(0) to Pd(II). One such oxidant is benzoquinone, a suitable reagent for oxidative Suzuki couplings. Although benzoquinone can undergo Heck reaction with aryl-palladium complexes, coupling with the boronic acid is faster. Similar arylations with arylboronic acids have been achieved with iron catalysis and air as oxidant (Scheme 3.13).



Scheme 3.16 Oxidative heterodimerization of arenes [82, 84–90]. Further examples: [91–96].

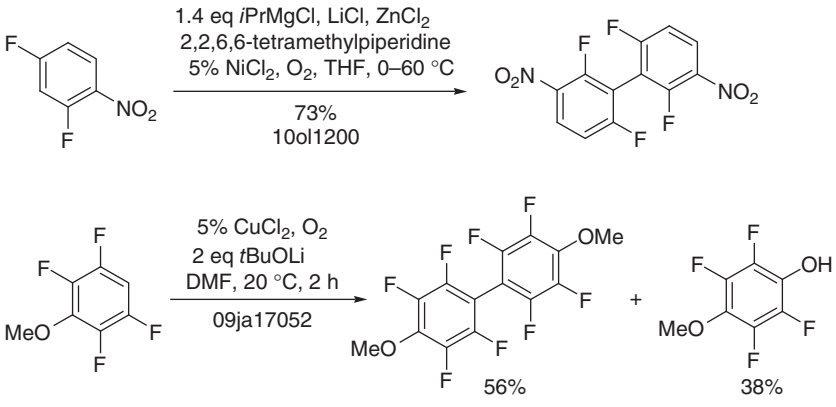


Scheme 3.16 (*Continued*)

A number of other aromatic electrophiles have been used for the preparation of biaryls from unsubstituted arenes. These include aryl iodonium salts, sulfonyl chlorides, and sulfinates (Scheme 3.14). Few examples of such reactions have been reported, and little is known about their scope and functional group tolerance.

3.5 Arylations with Unsubstituted Arenes

Oxidative dimerizations of arenes offer an attractive approach to large, symmetric molecules. Important syntheses of this type include couplings of phenols to symmetric 2,2′- or 4,4′-dihydroxybiphenyls (e.g., for the synthesis of binaphthol [74]) and the oxidative dimerization of pyridine to 2,2′-bipyridine, the key intermediate for the herbicide diquat (Scheme 3.15).



Scheme 3.17 Oxidative dimerization of metallated arenes [97, 98].

The oxidative coupling of two different arenes is a more difficult reaction, prone to yielding regioisomeric mixtures of homo and heterodimers [82]. Careful selection of the reacting partners and reaction conditions, though, can sometimes lead to high-yielding biaryl syntheses (Scheme 3.16). Common side reactions include oxidative transformations of functional groups, oxidation to quinones, as well as hydroxylation, amidation, sulfenylation, and halogenation of the arenes. In the presence of oxygen and copper salts, *N*,*N*-dimethylformamide (DMF) can be oxidized to cyanide [83], which can lead to the cyanation of arenes or the poisoning of transition-metal catalysts.

Acidic arenes can be metallated and dimerized by oxidants to yield symmetric biaryls (Scheme 3.17). Potential side reactions include reaction of the metallated arene with the oxidant and aromatic nucleophilic substitutions.

Mixtures of oxidants, and flammable organic solvents, and strong bases can decompose violently, and are usually too dangerous for large-scale preparations. Reactions such as those shown in Scheme 3.17 should better be conducted in less flammable solvents and with solid or liquid oxidants that allow a more precise and controlled dosing.

References

1. Kuhl, N., Hopkinson, M.N., Wencel-Delord, J., and Glorius, F. (2012) Beyond directing groups: transition-metal-catalyzed C–H activation of simple arenes. *Angew. Chem. Int. Ed.*, **51**, 10236–10254.
2. Hassan, J., Sévignon, M., Gozzi, C., Schulz, E., and Lemaire, M. (2002) Aryl–aryl bond formation one century after the discovery of the Ullmann reaction. *Chem. Rev.*, **102**, 1359–1469.
3. Fanta, P.E. (1964) The Ullmann synthesis of biaryls, 1945–1963. *Chem. Rev.*, **64**, 613–632.
4. Lyons, T.W. and Sanford, M.S. (2010) Palladium-catalyzed ligand-directed C–H functionalization reactions. *Chem. Rev.*, **110**, 1147–1169.

5. Orban, I., Holer, M., and Kaufmann, A. (1997) Verfahren zur Herstellung von 2-(2,4-Dihydroxyphenyl)-4,6-bis-(2,4-dimethylphenyl)-s-triazin. EP Patent 0779280.
6. Gupta, R.B., Jakiela, D.J., Venimadhavan, S., and Cappadona, R. (2000) Process for preparing triazines using a combination of Lewis acids and reaction promoters. WO Patent 0029392.
7. Sone, T., Inoue, M., and Sato, K. (1988) A new and simple route to 3-arylthiophenes. *Bull. Chem. Soc. Jpn.*, **61**, 3779–3781.
8. Sone, T., Kawasaki, H., Nagasawa, S., Takahashi, N., Tate, K., and Sato, K. (1981) Unusual Friedel–Crafts reaction of 2,5-dichloro-3-(chloromethyl)thiophene with benzene and some alkylbenzenes. *Chem. Lett.*, 399–402.
9. Sone, T., Shiromaru, O., Igarashi, S., Kato, E., and Sawara, M. (1979) Acid-catalyzed oligomerization of thiophene nuclei. III. Reactions of 2-chlorothiophene with cation exchange resin and 100% orthophosphoric acid. Formation of the dimer type products containing a tetrahydro-2-thiophenone moiety. *Bull. Chem. Soc. Jpn.*, **52**, 1126–1130.
10. Jones, G.O., Liu, P., Houk, K.N., and Buchwald, S.L. (2010) Computational explorations of mechanisms and ligand-directed selectivities of copper-catalyzed Ullmann-type reactions. *J. Am. Chem. Soc.*, **132**, 6205–6213.
11. Yanagisawa, S., Ueda, K., Taniguchi, T., and Itami, K. (2008) Potassium *t*-butoxide alone can promote the biaryl coupling of electron-deficient nitrogen heterocycles and haloarenes. *Org. Lett.*, **10**, 4673–4676.
12. Shirakawa, E., Itoh, K., Higashino, T., and Hayashi, T. (2010) *tert*-Butoxide-mediated arylation of benzene with aryl halides in the presence of a catalytic 1,10-phenanthroline derivative. *J. Am. Chem. Soc.*, **132**, 15537–15539.
13. Do, H.-Q., Khan, R.M.K., and Daugulis, O. (2008) A general method for copper-catalyzed arylation of arene C–H bonds. *J. Am. Chem. Soc.*, **130**, 15185–15192.
14. Vallée, F., Mousseau, J.J., and Charette, A.B. (2010) Iron-catalyzed direct arylation through an aryl radical transfer pathway. *J. Am. Chem. Soc.*, **132**, 1514–1516.
15. Liu, W., Cao, H., and Lei, A. (2010) Iron-catalyzed direct arylation of unactivated arenes with aryl halides. *Angew. Chem. Int. Ed.*, **49**, 2004–2008.
16. Fagnou, K., Leclerc, J.-P., Campeau, L.-C., and Stuart, D.R. (2008) Use of *N*-oxide compounds in coupling reactions. US Patent 2008132698.
17. Fujita, K., Nonogawaa, M., and Yamaguchi, R. (2004) Direct arylation of aromatic C–H bonds catalyzed by Cp*Ir complexes. *Chem. Commun.*, 1926–1927.
18. Hennings, D.D., Iwasa, S., and Rawal, V.H. (1997) Anion-accelerated palladium-catalyzed intramolecular coupling of phenols with aryl halides. *J. Org. Chem.*, **62**, 2–3.
19. Martínez-Barrasa, V., García de Viedma, A., Burgos, C., and Alvarez-Builla, J. (2000) Synthesis of biaryls via intermolecular radical addition of heteroaryl and aryl bromides onto arenes. *Org. Lett.*, **2**, 3933–3935.
20. Escolano, C. and Jones, K. (2002) Aryl radical cyclisation onto pyrroles. *Tetrahedron*, **58**, 1453–1464.
21. Linhardt, R.J., Murr, B.L., Montgomery, E., Osby, J., and Sherbine, J. (1982) Mechanism for diacyl peroxide decomposition. *J. Org. Chem.*, **47**, 2242–2251.
22. Srinivas, S. and Taylor, K.G. (1990) Amine-induced reactions of diacyl peroxides. *J. Org. Chem.*, **55**, 1779–1786.
23. Hey, D.H. and Perkins, M.J. (1973) Arylbenzenes: 3,4-dichlorobiphenyl. *Org. Synth.*, Coll. Vol. **5**, 51–54.
24. Yu, W.-Y., Sit, W.N., Zhou, Z., and Chan, A.S.-C. (2009) Palladium-catalyzed decarboxylative arylation of C–H bonds by aryl acylperoxides. *Org. Lett.*, **11**, 3174–3177.
25. Seki, M. (2012) An efficient C–H arylation of a 5-phenyl-1*H*-tetrazole derivative: a practical synthesis of an angiotensin II receptor blocker. *Synthesis*, **44**, 3231–3237.
26. Ackermann, L., Vicente, R., Potukuchi, H.K., and Pirovano, V. (2010) Mechanistic insight into direct arylations with

ruthenium(II) carboxylate catalysts. *Org. Lett.*, **12**, 5032–5035.

27. Pozgan, F. and Dixneuf, P.H. (2009) Ruthenium(II) acetate catalyst for direct functionalisation of sp^2-C–H bonds with aryl chlorides and access to tris-heterocyclic molecules. *Adv. Synth. Catal.*, **351**, 1737–1743.
28. Guo, H.-M., Jiang, L.-L., Niu, H.-Y., Rao, W.-H., Liang, L., Mao, R.-Z., Li, D.-Y., and Qu, G.-R. (2011) Pd(II)-catalyzed *ortho* arylation of 6-arylpurines with aryl iodides via purine-directed C–H activation: a new strategy for modification of 6-arylpurine derivatives. *Org. Lett.*, **13**, 2008–2011.
29. Caron, L., Campeau, L.-C., and Fagnou, K. (2008) Palladium-catalyzed direct arylation of nitro-substituted aromatics with aryl halides. *Org. Lett.*, **10**, 4533–4536.
30. Nishikata, T., Abela, A.R., and Lipshutz, B.H. (2010) Room temperature C–H activation and cross-coupling of aryl ureas in water. *Angew. Chem. Int. Ed.*, **49**, 781–784.
31. Li, D.-D., Yuan, T.-T., and Wang, G.-W. (2012) Palladium-catalyzed *ortho*-arylation of benzamides via direct sp^2 C–H bond activation. *J. Org. Chem.*, **77**, 3341–3347.
32. Kametani, Y., Satoh, T., Miura, M., and Nomura, M. (2000) Regioselective arylation of benzanilides with aryl triflates or bromides under palladium catalysis. *Tetrahedron Lett.*, **41**, 2655–2658.
33. Lapointe, D., Markiewicz, T., Whipp, C.J., Toderian, A., and Fagnou, K. (2011) Predictable and site-selective functionalization of poly(hetero)arene compounds by palladium catalysis. *J. Org. Chem.*, **76**, 749–759.
34. Proch, S. and Kempe, R. (2007) An efficient bimetallic rhodium catalyst for the direct arylation of unactivated arenes. *Angew. Chem. Int. Ed.*, **46**, 3135–3138.
35. Mousseau, J.J., Vallée, F., Lorion, M.M., and Charette, A.B. (2010) Umpolung direct arylation reactions: facile process requiring only catalytic palladium and substoichiometric amount of silver salts. *J. Am. Chem. Soc.*, **132**, 14412–14414.
36. Lane, B.S. and Sames, D. (2004) Direct C–H bond arylation: selective palladium-catalyzed C2-arylation of *N*-substituted indoles. *Org. Lett.*, **6**, 2897–2900.
37. Zhang, G., Zhao, X., Yan, Y., and Ding, C. (2012) Direct arylation under catalysis of an oxime-derived palladacycle: search for a phosphane-free method. *Eur. J. Org. Chem.*, **2012**, 669–672.
38. Fan, S., Yang, J., and Zhang, X. (2011) Pd-catalyzed direct cross-coupling of electron-deficient polyfluoroarenes with heteroaromatic tosylates. *Org. Lett.*, **13**, 4374–4377.
39. Guo, P., Joo, J.M., Rakshit, S., and Sames, D. (2011) C–H arylation of pyridines: high regioselectivity as a consequence of the electronic character of C–H bonds and heteroarene ring. *J. Am. Chem. Soc.*, **133**, 16338–16341.
40. Ye, M., Gao, G.-L., Edmunds, A.J.F., Worthington, P.A., Morris, J.A., and Yu, J.-Q. (2011) Ligand-promoted C3-selective arylation of pyridines with Pd catalysts: gram-scale synthesis of (±)-preclamol. *J. Am. Chem. Soc.*, **133**, 19090–19093.
41. Effenberger, F., Agster, W., Fischer, P., Jogun, K.H., Stezowski, J.J., Daltrozzo, E., and Kollmannsberger-von Nell, G. (1983) Synthesis, structure, and spectral behavior of donor–acceptor substituted biphenyls. *J. Org. Chem.*, **48**, 4649–4658.
42. Lafrance, M. and Fagnou, K. (2006) Palladium-catalyzed benzene arylation: incorporation of catalytic pivalic acid as a proton shuttle and a key element in catalyst design. *J. Am. Chem. Soc.*, **128**, 16496–16497.
43. Lafrance, M., Shore, D., and Fagnou, K. (2006) Mild and general conditions for the cross-coupling of aryl halides with pentafluorobenzene and other perfluoroaromatics. *Org. Lett.*, **8**, 5097–5100.
44. Fall, Y., Reynaud, C., Doucet, H., and Santelli, M. (2009) Ligand-free-palladium-catalyzed direct 4-arylation of isoxazoles using aryl bromides. *Eur. J. Org. Chem.*, **2009**, 4041–4050.
45. Liégault, B., Petrov, I., Gorelsky, S.I., and Fagnou, K. (2010) Modulating reactivity and diverting selectivity in palladium-catalyzed heteroaromatic direct arylation through the use of a chloride activating/blocking group. *J. Org. Chem.*, **75**, 1047–1060.

46. Dhital, R.N., Kamonsatikul, C., Somsook, E., Bobuatong, K., Ehara, M., Karanjit, S., and Sakurai, H. (2012) Low-temperature carbon–chlorine bond activation by bimetallic gold/palladium alloy nanoclusters: an application to Ullmann coupling. *J. Am. Chem. Soc.*, **134**, 20250–20253.
47. Li, J.-H., Xie, Y.-X., and Yin, D.-L. (2003) New role of CO_2 as a selective agent in palladium-catalyzed reductive Ullmann coupling with zinc in water. *J. Org. Chem.*, **68**, 9867–9869.
48. Kashiwabara, T. and Tanaka, M. (2005) Pd-catalyzed desulfonylative homocoupling of arenesulfonyl chlorides in the presence of hexamethyldisilane forming biaryls. *Tetrahedron Lett.*, **46**, 7125–7128.
49. Penalva, V., Hassan, J., Lavenot, L., Gozzi, C., and Lemaire, M. (1998) Direct homocoupling of aryl halides catalyzed by palladium. *Tetrahedron Lett.*, **39**, 2559–2560.
50. Monopoli, A., Calò, V., Ciminale, F., Cotugno, P., Angelici, C., Cioffi, N., and Nacci, A. (2010) Glucose as a clean and renewable reductant in the Pd-nanoparticle-catalyzed reductive homocoupling of bromo- and chloroarenes in water. *J. Org. Chem.*, **75**, 3908–3911.
51. Hari, D.P., Schroll, P., and König, B. (2012) Metal-free, visible-light-mediated direct C–H arylation of heteroarenes with aryl diazonium salts. *J. Am. Chem. Soc.*, **134**, 2958–2961.
52. Pratsch, G., Wallaschkowski, T., and Heinrich, M.R. (2012) The Gomberg–Bachmann reaction for the arylation of anilines with aryl diazotates. *Chem. Eur. J.*, **18**, 11555–11559.
53. Ramachandran, V. (1985) (Alkoxydiazo)halobenzeneacetonitriles. US Patent 4539397.
54. Wetzel, A., Pratsch, G., Kolb, R., and Heinrich, M.R. (2010) Radical arylation of phenols, phenyl ethers, and furans. *Chem. Eur. J.*, **16**, 2547–2556.
55. Beadle, J.R., Korzeniowski, S.H., Rosenberg, D.E., Garcia-Slanga, B.J., and Gokel, G.W. (1984) Phase-transfer-catalyzed Gomberg–Bachmann synthesis of unsymmetrical biarenes: a survey of catalysts and substrates. *J. Org. Chem.*, **49**, 1594–1603.
56. Jasch, H., Höfling, S.B., and Heinrich, M.R. (2012) Nucleophilic substitutions and radical reactions of phenylazocarboxylates. *J. Org. Chem.*, **77**, 1520–1532.
57. Kalyani, D., McMurtrey, K.B., Neufeldt, S.R., and Sanford, M.S. (2011) Room-temperature C–H arylation: merger of Pd-catalyzed C–H functionalization and visible-light photocatalysis. *J. Am. Chem. Soc.*, **133**, 18566–18569.
58. Jasch, H., Scheumann, J., and Heinrich, M.R. (2012) Regioselective radical arylation of anilines with arylhydrazines. *J. Org. Chem.*, **77**, 10699–10706.
59. Wetzel, A., Ehrhardt, V., and Heinrich, M.R. (2008) Synthesis of amino- and hydroxybiphenyls by radical chain reaction of arenediazonium salts. *Angew. Chem. Int. Ed.*, **47**, 9130–9133.
60. Crestey, F., Collot, V., Stiebing, S., and Rault, S. (2006) A new and efficient synthesis of 2-azatryptophans. *Tetrahedron*, **62**, 7772–7775.
61. Ferrarini, P.L., Mori, C., Badawneh, M., Manera, C., Martinelli, A., Miceli, M., Romagnoli, F., and Saccomanni, G. (1997) Unusual nitration of substituted 7-amino-1,8-naphthyridine in the synthesis of compounds with antiplatelet activity. *J. Heterocycl. Chem.*, **34**, 1501–1510.
62. Okuda, K., Deguchi, H., Kashino, S., Hirota, T., and Sasaki, K. (2010) Polycyclic *N*-heterocyclic compounds. Part 64: Synthesis of 5-amino-1,2,6,7-tetrahydrobenzo[*f*]furo[2,3-*c*] isoquinolines and related compounds. Evaluation of their bronchodilator activity and effects on lipoprotein lipase mRNA expression. *Chem. Pharm. Bull.*, **58**, 685–689.
63. Press, J.B., Eudy, N.H., Lovell, F.M., Morton, G.O., and Siegel, M.M. (1982) A remarkable fragmentation reaction of a pyrimidyl radical. *J. Am. Chem. Soc.*, **104**, 4013–4014.
64. Zhao, H., Wei, Y., Xu, J., Kan, J., Su, W., and Hong, M. (2011) Pd/PR_3-catalyzed cross-coupling of aromatic carboxylic acids with electron-deficient polyfluoroarenes via combination of

decarboxylation with sp^2 C–H cleavage. *J. Org. Chem.*, **76**, 882–893.

65. Seo, S., Slater, M., and Greaney, M.F. (2012) Decarboxylative C–H arylation of benzoic acids under radical conditions. *Org. Lett.*, **14**, 2650–2653.
66. Zhang, F. and Greaney, M.F. (2010) Decarboxylative C–H cross-coupling of azoles. *Angew. Chem. Int. Ed.*, **49**, 2768–2771.
67. Xie, K., Yang, Z., Zhou, X., Li, X., Wang, S., Tan, Z., An, X., and Guo, C.-C. (2010) Pd-catalyzed decarboxylative arylation of thiazole, benzoxazole, and polyfluorobenzene with substituted benzoic acids. *Org. Lett.*, **12**, 1564–1567.
68. Nishikata, T., Abela, A.R., Huang, S., and Lipshutz, B.H. (2010) Cationic palladium(II) catalysis: C–H activation/Suzuki–Miyaura couplings at room temperature. *J. Am. Chem. Soc.*, **132**, 4978–4979.
69. Wen, J., Qin, S., Ma, L.-F., Dong, L., Zhang, J., Liu, S.-S., Duan, Y.-S., Chen, S.-Y., Hu, C.-W., and Yu, X.-Q. (2010) Iron-mediated direct Suzuki–Miyaura reaction: a new method for the *ortho*-arylation of pyrrole and pyridine. *Org. Lett.*, **12**, 2694–2697.
70. Singh, P.P., Aithagani, S.K., Yadav, M., Singh, V.P., and Vishwakarma, R.A. (2013) Iron-catalyzed cross-coupling of electron-deficient heterocycles and quinone with organoboron species via innate C–H functionalization: application in total synthesis of pyrazine alkaloid botryllazine A. *J. Org. Chem.*, **78**, 2639–2648.
71. Wen, J., Zhang, R.-Y., Chen, S.-Y., Zhang, J., and Yu, X.-Q. (2012) Direct arylation of arene and *N*-heteroarenes with diaryliodonium salts without the use of transition metal catalyst. *J. Org. Chem.*, **77**, 766–771.
72. Ciana, C.-L., Phipps, R.J., Brandt, J.R., Meyer, F.-M., and Gaunt, M.J. (2011) A highly *para*-selective copper(II)-catalyzed direct arylation of aniline and phenol derivatives. *Angew. Chem. Int. Ed.*, **50**, 458–462.
73. Liu, B., Guo, Q., Cheng, Y., Lan, J., and You, J. (2011) Palladium-catalyzed desulfitative C–H arylation of heteroarenes with sodium sulfinates. *Chem. Eur. J.*, **17**, 13415–13419.
74. Matsushita, M., Kamata, K., Yamaguchi, K., and Mizuno, N. (2005) Heterogeneously catalyzed aerobic oxidative biaryl coupling of 2-naphthols and substituted phenols in water. *J. Am. Chem. Soc.*, **127**, 6632–6640.
75. Sasse, W.H.F. (1973) 2,2′-Dipyridine. *Org. Synth.*, Coll. Vol. **5**, 102–107.
76. Coe, B.J., Curati, N.R.M., and Fitzgerald, E.C. (2006) Unusually facile syntheses of diquat (6,7-dihydrodipyrido[1,2-*a*:2′,1′-*c*]pyrazinediium) and related cations. *Synthesis*, 146–150.
77. Xiao, Y., Chu, L., Sanakis, Y., and Liu, P. (2009) Revisiting the IspH catalytic system in the deoxyxylulose phosphate pathway: achieving high activity. *J. Am. Chem. Soc.*, **131**, 9931–9933.
78. Tsou, C.-P., Lin, S.-C., Huang, T.-K., and Chen, C.-Y. (2000) Process for the preparation of 1,1′-dialkyl-4,4′-bipyridinium salt compounds. US Patent 6087504.
79. Newkome, G.R., Gross, J., and Patri, A.K. (1997) Synthesis of unsymmetrical 5,5′-disubstituted 2,2′-bipyridines. *J. Org. Chem.*, **62**, 3013–3014.
80. Zhu, M., Fujita, K.-I., and Yamaguchi, R. (2011) Efficient synthesis of biazoles by aerobic oxidative homocoupling of azoles catalyzed by a copper(I)/2-pyridonate catalytic system. *Chem. Commun.*, **47**, 12876–12878.
81. Takahashi, M., Masui, K., Sekiguchi, H., Kobayashi, N., Mori, A., Funahashi, M., and Tamaoki, N. (2006) Palladium-catalyzed C–H homocoupling of bromothiophene derivatives and synthetic application to well-defined oligothiophenes. *J. Am. Chem. Soc.*, **128**, 10930–10933.
82. Do, H.-Q. and Daugulis, O. (2011) A general method for copper-catalyzed arene cross-dimerization. *J. Am. Chem. Soc.*, **133**, 13577–13586.
83. Kim, J., Choi, J., Shin, K., and Chang, S. (2012) Copper-mediated sequential cyanation of aryl C–B and arene C–H bonds using ammonium iodide and DMF. *J. Am. Chem. Soc.*, **134**, 2528–2531.
84. Chandrasekharam, M., Chiranjeevi, B., Gupta, K.S.V., and Sridhar, B. (2011)

Iron-catalyzed regioselective direct oxidative aryl–aryl cross-coupling. *J. Org. Chem.*, **76**, 10229–10235.

85. Qin, X., Feng, B., Dong, J., Li, X., Xue, Y., Lan, J., and You, J. (2012) Copper(II)-catalyzed dehydrogenative cross-coupling between two azoles. *J. Org. Chem.*, **77**, 7677–7683.

86. Wei, Y. and Su, W. (2010) $Pd(OAc)_2$-catalyzed oxidative C–H/C–H cross-coupling of electron-deficient polyfluoroarenes with simple arenes. *J. Am. Chem. Soc.*, **132**, 16377–16379.

87. Li, H., Zhu, R.-Y., Shi, W.-J., He, K.-H., and Shi, Z.-J. (2012) Synthesis of fluorenone derivatives through Pd-catalyzed dehydrogenative cyclization. *Org. Lett.*, **14**, 4850–4853.

88. Zhao, X., Yeung, C.S., and Dong, V.M. (2010) Palladium-catalyzed *ortho*-arylation of *O*-phenylcarbamates with simple arenes and sodium persulfate. *J. Am. Chem. Soc.*, **132**, 5837–5844.

89. Reddy, V.P., Qiu, R., Iwasaki, T., and Kambe, N. (2013) Rhodium-catalyzed intermolecular oxidative cross-coupling of (hetero)arenes with chalcogenophenes. *Org. Lett.*, **15**, 1290–1293.

90. Cho, S.H., Hwang, S.J., and Chang, S. (2008) Palladium-catalyzed C–H functionalization of pyridine *N*-oxides: highly selective alkenylation and direct arylation with unactivated arenes. *J. Am. Chem. Soc.*, **130**, 9254–9256.

91. Han, W., Mayer, P., and Ofial, A.R. (2011) Palladium-catalyzed dehydrogenative cross-couplings of benzazoles with azoles. *Angew. Chem. Int. Ed.*, **50**, 2178–2182.

92. Wencel-Delord, J., Nimphius, C., Wang, H., and Glorius, F. (2012) Rhodium(III) and hexabromobenzene—a catalyst system for the cross-dehydrogenative coupling of simple arenes and heterocycles with arenes bearing directing groups. *Angew. Chem. Int. Ed.*, **51**, 13001–13005.

93. Fan, S., Chen, Z., and Zhang, X. (2012) Copper-catalyzed dehydrogenative cross-coupling of benzothiazoles with thiazoles and polyfluoroarene. *Org. Lett.*, **14**, 4950–4953.

94. Chen, F., Feng, Z., He, C.-Y., Wang, H.-Y., Guo, Y.-L., and Zhang, X. (2012) Pd-catalyzed dehydrogenative cross-coupling of polyfluoroarenes with heteroatom-substituted enones. *Org. Lett.*, **14**, 1176–1179.

95. He, C.-Y., Fan, S., and Zhang, X. (2010) Pd-catalyzed oxidative cross-coupling of perfluoroarenes with aromatic heterocycles. *J. Am. Chem. Soc.*, **132**, 12850–12852.

96. Mukhopadhyay, S., Rothenberg, G., Gitis, D., and Sasson, Y. (2000) Tandem one-pot palladium-catalyzed reductive and oxidative coupling of benzene and chlorobenzene. *J. Org. Chem.*, **65**, 3107–3110.

97. Truong, T., Alvarado, J., Tran, L.D., and Daugulis, O. (2010) Nickel, manganese, cobalt, and iron-catalyzed deprotonative arene dimerization. *Org. Lett.*, **12**, 1200–1203.

98. Do, H.-Q. and Daugulis, O. (2009) An aromatic Glaser–Hay reaction. *J. Am. Chem. Soc.*, **131**, 17052–17053.

4
Electrophilic Acylation of Arenes

4.1
General Aspects

The acylation of arenes and heteroarenes with electrophilic acylating reagents, in particular the Lewis acid-mediated version, is called after their developers, the Friedel–Crafts acylation (Scheme 4.1). This reaction gives quick access to a large variety of aromatic ketones, and is one of the most important C–C bond-forming reactions. In most instances, stoichiometric amounts of $AlCl_3$ are required, because the products deactivate one equivalent of Lewis acid. Stoichiometric amounts of other Lewis acids ($TiCl_4$, $SnCl_4$, or $FeCl_3$), trifluoroacetic anhydride [1], or catalysis by Brønsted acids (HF, HCl, H_3PO_4, MsOH, or TfOH), Lewis acids ($ZnCl_2$, Fe_2O_3 [2], or $BHal_3$), or insoluble acids [3, 4] can also mediate Friedel–Crafts acylations if the arene is nucleophilic enough. As alternative to one equivalent of $AlCl_3$, a mixture of $AlCl_3$ and Al may be used, because the HCl formed will oxidize Al to $AlCl_3$. Under microwave irradiation, Zn powder [5] and Al powder [6] can also be used as catalysts. Friedel–Crafts acylations can also be conducted in neat HF or TfOH without any further catalysts. For large-scale industrial processes, where waste disposal and recycling are important issues, catalytic processes or recoverable acids (e.g., HF or trifluoroacetic acid) are particularly valuable.

Intramolecular Friedel–Crafts acylations usually proceed more readily than intermolecular reactions. Electron-donating groups direct acylations into their ortho and para positions.

Electron-rich arenes, such as alkoxyarenes or alkylarenes, or electron-rich heteroarenes (pyrroles, indoles, and thiophenes) undergo Friedel–Crafts acylation most easily, and may not require stoichiometric but just catalytic amounts of acid. In fact, electron-rich arenes will often decompose or oligomerize in the presence of large amounts of strong acids, so that weaker acids *must* be used (see Scheme 4.33).

In most Friedel–Crafts acylations, acyl halides are used as the acylating reagent, but with electron-rich arenes even weak acylating agents may be sufficiently reactive, for instance, anhydrides, carboxylic esters [7] or acids, nitriles, or amides [8] (Scheme 4.2). Less electron-rich arenes, however, require

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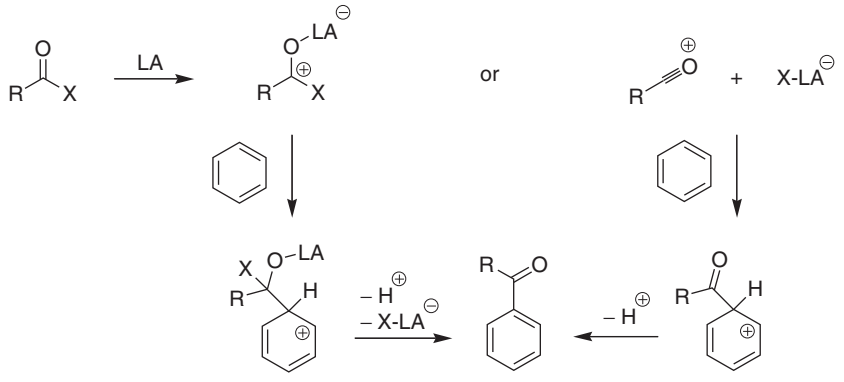
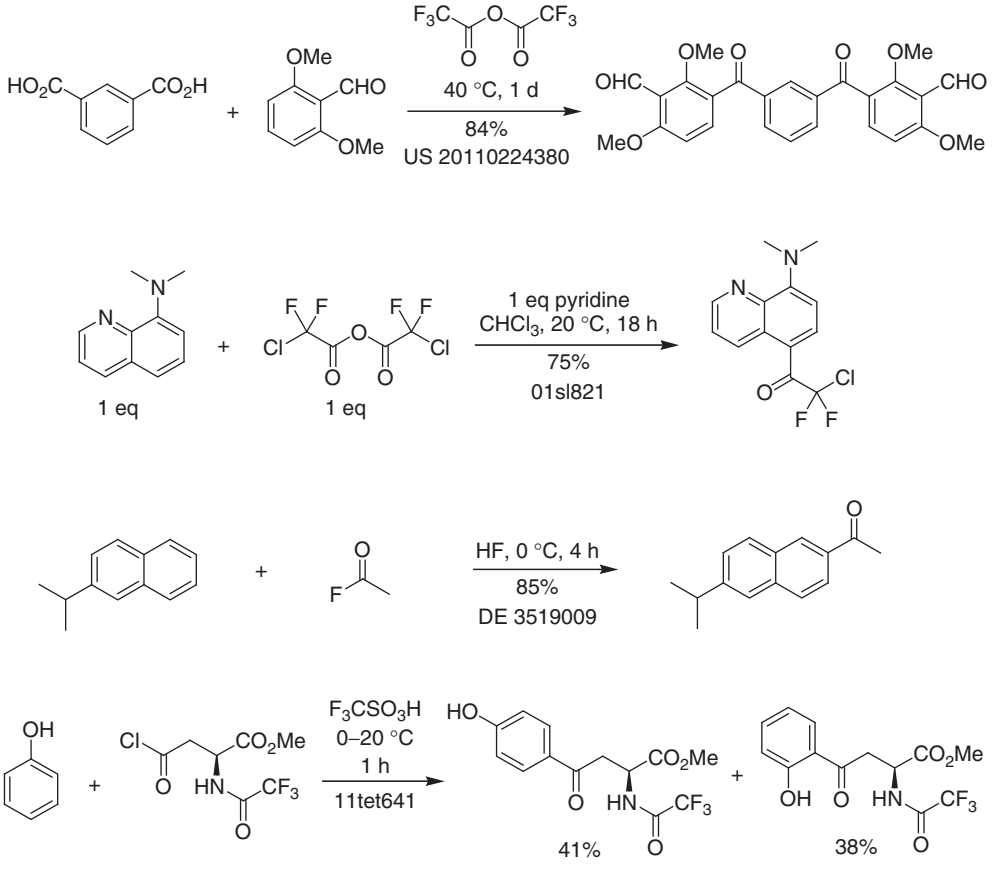


Scheme 4.1 Mechanism of the Friedel–Crafts acylation. X = leaving group, LA = Lewis acid, R = alkyl, aryl.

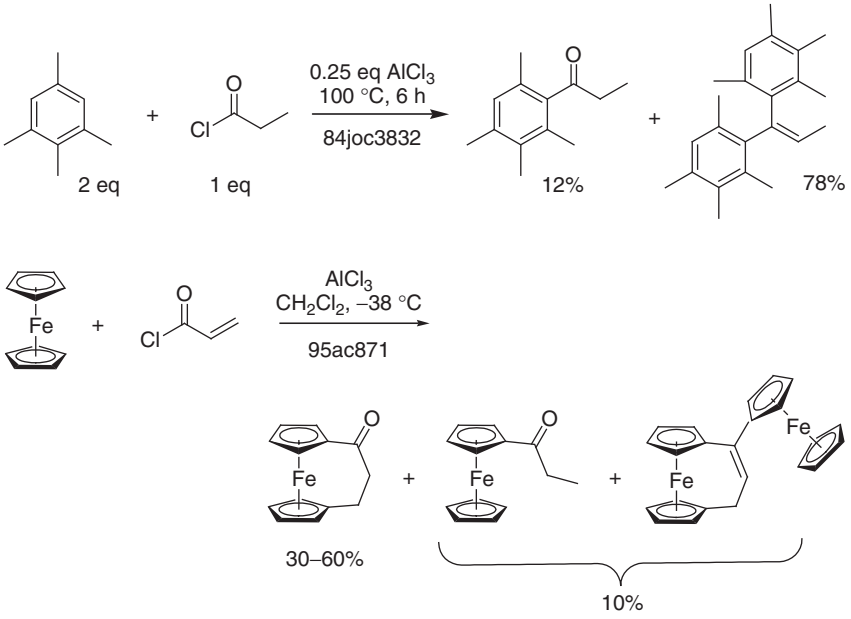


Scheme 4.2 Examples of Friedel–Crafts acylations [9–12].

strong acylating agents, such as acyl halides, ketenes, or mixed carboxylic sulfonic anhydrides.

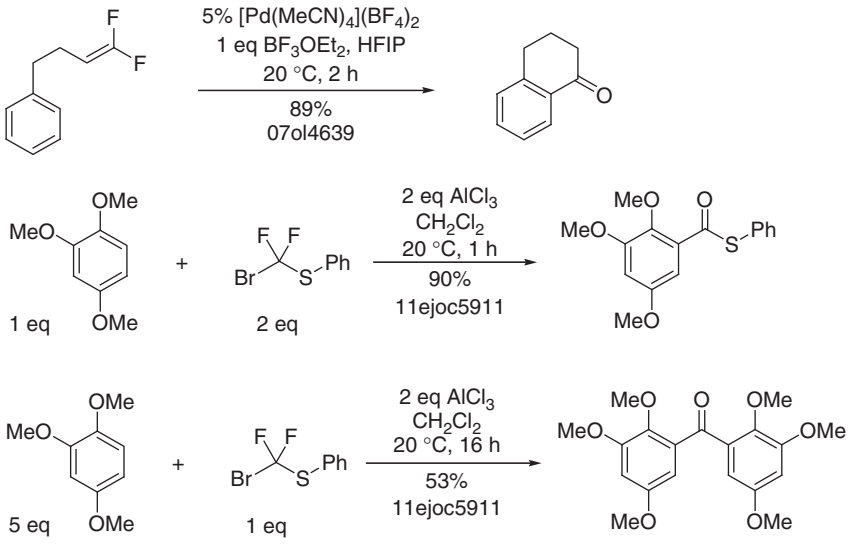
If a high reaction temperature is required, the choice of the solvent may become difficult. Most suitable (i.e., non-nucleophilic) solvents (e.g., CCl_4, $CHCl_3$, CH_2Cl_2, 1,2-dichloroethane, or ethers) are not stable under forcing Friedel–Crafts conditions. If the arene itself cannot be used as solvent, nitrobenzene, nitromethane, or sulfolane [13] may be an option. Friedel–Crafts acylations in ionic liquids have also been reported [14, 15], but not all ionic liquids are sufficiently stable for this purpose. Imidazolium salts are particularly reactive toward acylating reagents [16].

Because ketones may act as electrophiles under Friedel–Crafts conditions, an excess of arene can lead to hydroxyalkylations and olefin formation (Friedel–Crafts alkylation; Schemes 1.37 and 4.3).



Scheme 4.3 Vinylation as side reaction of Friedel–Crafts acylations [17, 18].

Arylketones can also be prepared from unsubstituted arenes by alkylation with 1,1,1-trihaloalkanes or synthetic equivalents thereof, followed by hydrolysis (Scheme 4.4). Potential side reactions include the halogenation of the arene and the reaction of the product as an electrophile or a halogenating reagent.



Scheme 4.4 Friedel–Crafts acylations with vinyl and alkyl halides [19, 20].

4.2
Problematic Arenes

4.2.1
Dealkylation/Isomerization of Arenes

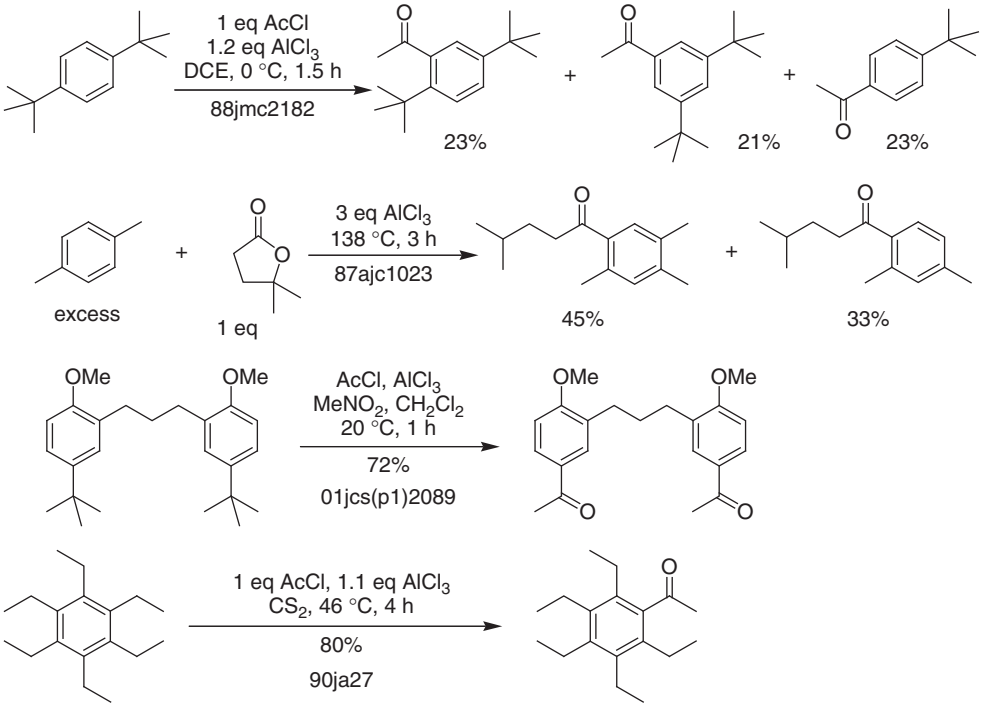
A number of arenes do not undergo Friedel–Crafts acylation in the expected way. Electron-rich alkylarenes may isomerize or be dealkylated upon treatment with acids. In fact, secondary or tertiary alkyl groups may serve as the leaving group for aromatic electrophilic substitutions (ipso substitution), in the same way as protons, metals, or trialkylsilyl groups.

Electron-rich alkylbenzenes with benzylic C–H groups are potential hydride donors, and can reduce carbocations while themselves undergoing oligomerization by Friedel–Crafts alkylation (Scheme 4.5).

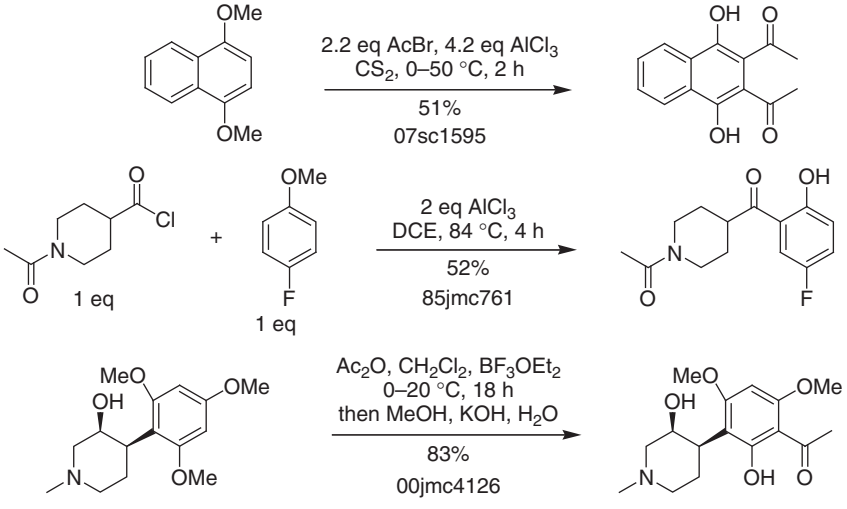
Alkoxybenzenes can be dealkylated during Friedel–Crafts acylations to yield 2-acylphenols (Scheme 4.6). In polyalkoxyarenes, mostly the 2-alkoxy group is dealkylated, which points to chelate formation as the main driver of this reaction. Depending on the acid used, the alkyl cations formed during such dealkylations may also alkylate arenes.

4.2.2
Styrenes

Olefins and alkynes can also be acylated by acyl halides. Electron-rich alkenes (enol ethers and enamines) react with strongly electrophilic acyl halides (e.g., trihaloacetyl

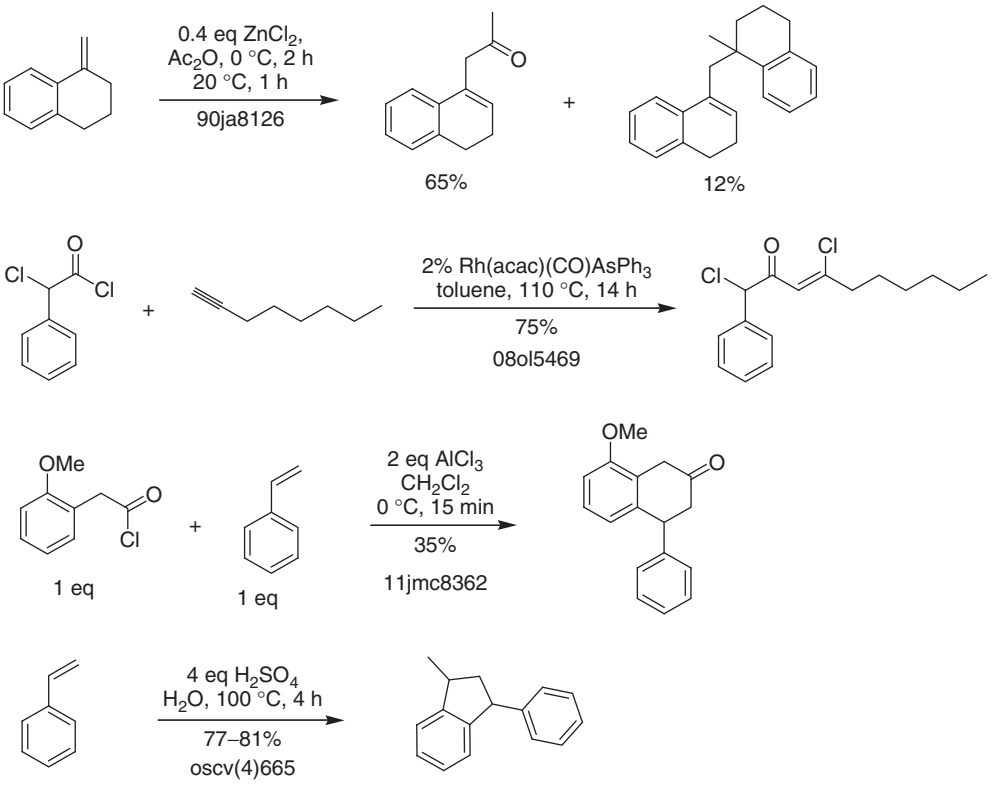


Scheme 4.5 Examples of alkyl group migration, reduction, and ipso substitution during Friedel–Crafts acylations [21–24].



Scheme 4.6 Ether cleavage during Friedel–Crafts acylations [25–27].

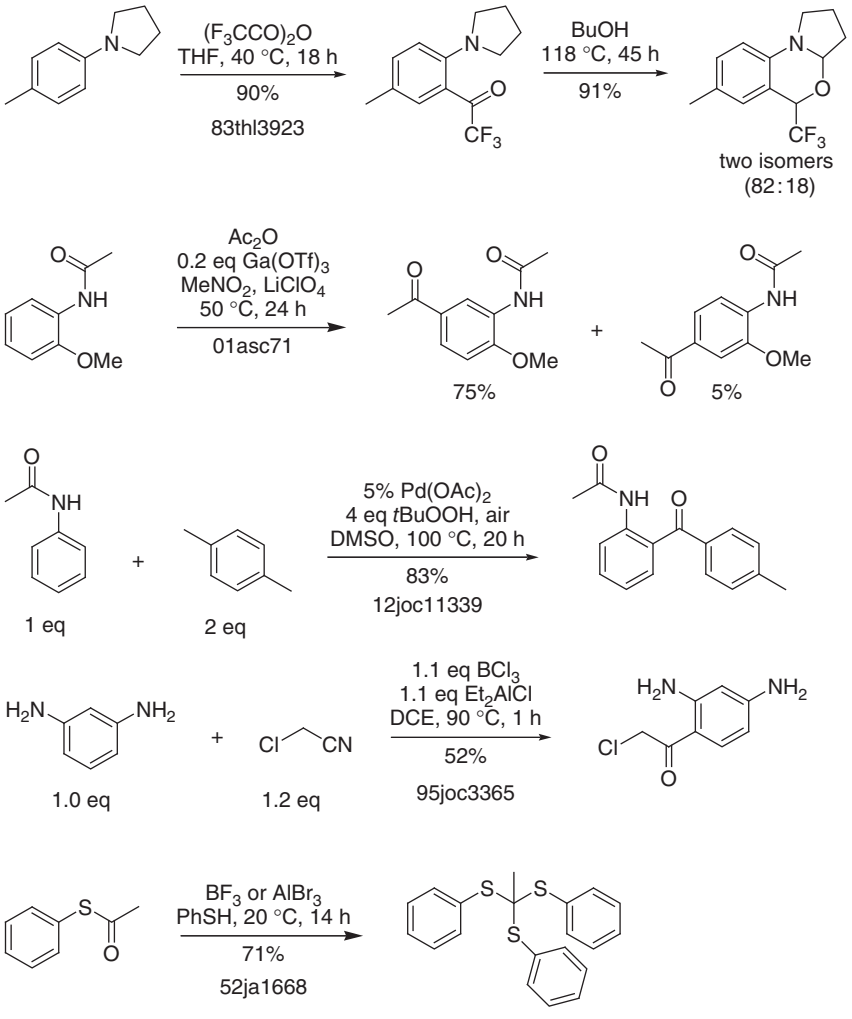
chlorides and phosgene) without any additional catalyst [28]. Less nucleophilic olefins, though, will often require catalysis. In styrenes and alkynylbenzenes, acylation of the alkene/alkyne can compete with the acylation of the arene. Depending on the starting materials and the precise conditions, enones or 2-haloethylketones can result. Oligomerization of the alkene or alkyne is a common side reaction (Scheme 4.7).



Scheme 4.7 Acylation of alkenes and alkynes [29–32]. Further examples: [33, 34].

4.2.3
Anilines, Phenols, and Thiophenols

Anilines and phenols will first be acylated at the heteroatom during Friedel–Crafts acylations, but the resulting anilides and arylesters still undergo C-acylation with the expected ortho/para selectivity. To avoid N-acylation of anilines, mixtures of nitriles and boron trihalides can be used as acylating reagents instead of acyl halides or anhydrides. Anilides can be selectively ortho-acylated via Pd catalysis [35] (Scheme 4.8).



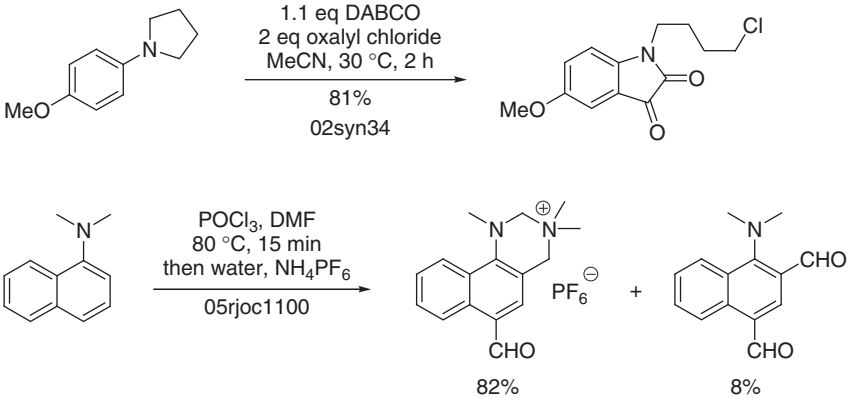
Scheme 4.8 Reaction of aniline and thiophenol derivatives with electrophiles [36–40]. Further examples: [41].

Treatment of anilides and arylesters with acids can bring about the migration of the acyl group from the heteroatom to carbon (Fries rearrangement). Esters of thiophenols do not undergo Fries rearrangement, but yield orthoesters instead [42].

Arenes with basic functional groups (amines, pyridines, imidazoles, ketones, amides, ureas, etc.) will consume one additional equivalent of acid during Friedel–Crafts acylations, and may form insoluble salts. Because Friedel–Crafts acylations are usually conducted in nonpolar solvents, salts may precipitate and

prevent efficient stirring and mixing of the starting materials. One way to solve this problem is to use small amounts of DMF (*N*,*N*-dimethylformamide) [43] or sulfolane as solvent, or to skip the solvent and melt the starting materials together with an excess of $AlCl_3$ [44].

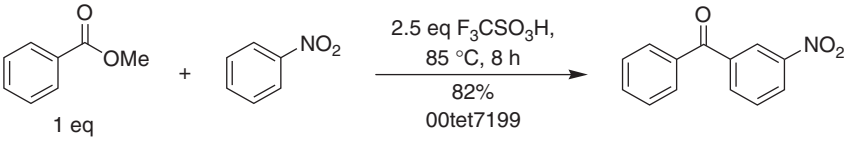
Tertiary amines, including *N*,*N*-dialkylanilines, are sometimes dealkylated by acylating reagents under surprisingly mild conditions [45, 46] (Scheme 4.9). Particularly easy are demethylations, debenzylations, and detritylations.



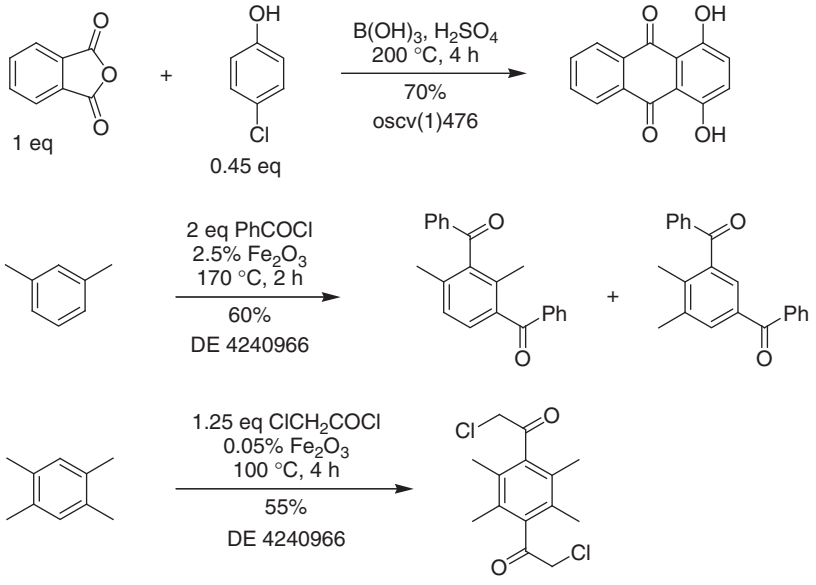
Scheme 4.9 Dealkylation of tertiary amines by acylating reagents [47, 48].

4.2.4
Electron-Deficient Arenes

Electron-deficient arenes cannot be readily acylated. A few examples have been reported of intermolecular Friedel–Crafts acylations of sulfonylarenes, benzonitriles, other benzoic acid derivatives, or electron-deficient heteroarenes (pyridines, pyrimidines, triazoles, or pyrazoles). In most examples, these were activated by electron-donating substituents. Nitroarenes and arylketones, though, undergo Friedel–Crafts acylations under forcing conditions (Schemes 4.10 and 4.11).



Scheme 4.10 Benzoylation of nitrobenzene [49].



Scheme 4.11 Friedel–Crafts acylation of acylbenzenes [50, 51].

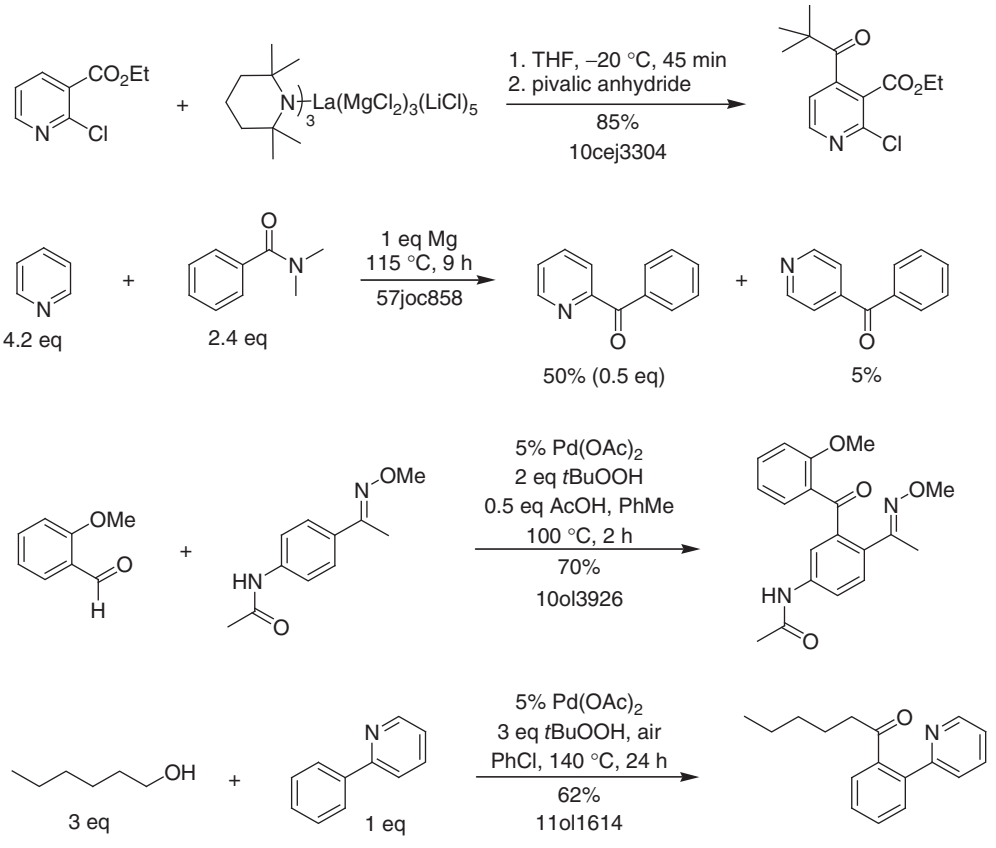
The Friedel–Crafts acylations usually stop after the first acylation, because acyl groups strongly deactivate arenes toward electrophilic attack. At higher temperature, however, it is sometimes possible to perform two acylations of the same arene, even ortho or para to the first introduced acyl group (Scheme 4.11).

If electrophilic acylation is too difficult, electron-poor arenes and heteroarenes can sometimes be acylated via metallation [52–57] or by acyl radicals [58, 59] (Scheme 4.12). Oxidative acylations, such as the last two examples in Scheme 4.12, can be difficult to optimize because of the many potential side reactions, such as aromatic hydroxylation [60].

4.2.5 Azoles

Often, pyrroles, imidazoles, and indoles undergo Friedel–Crafts acylation under surprisingly mild reaction conditions (Scheme 4.13). The regioselectivity, though, can be difficult to predict. The high yield in the last example in Scheme 4.13 is remarkable because ketene formation and ketene dimerization can, in principle, compete with the acylation of the imidazole.

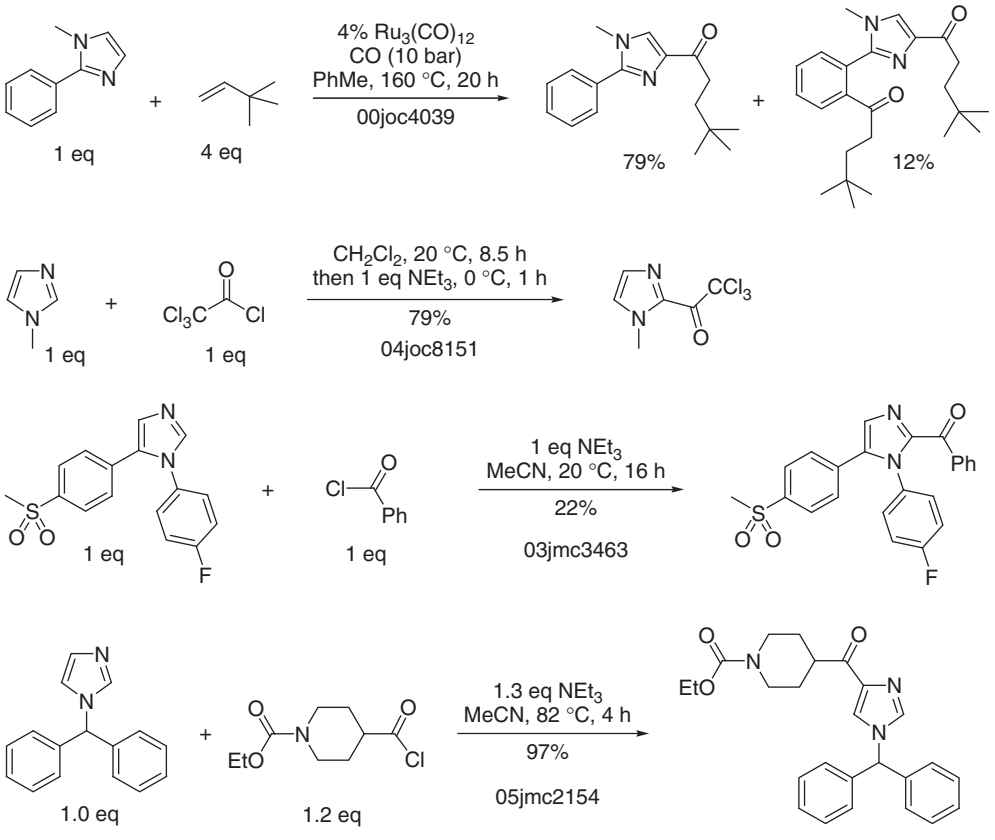
During the C-acylation of azoles, a number of additional reactions can lead to unexpected results. Some azoles and azines dimerize upon treatment with strong electrophiles (Scheme 4.14), presumably via intermediate carbene formation, which can cause problems in Friedel–Crafts acylations and other



Scheme 4.12 Acylation of electron-deficient arenes via metallation [52, 59, 61, 62]. Further examples: [63, 64].

electrophilic substitution reactions (alkylations, halogenations, nitrations, etc.). Despite its high thermal stability, imidazole is remarkably unstable under conditions of Schotten–Baumann acylations, and is usually cleaved to 1,2-bis(acylamino)ethylenes (Bamberger cleavage [70]). Dimerization or oligomerization of heterocycles can sometimes be avoided by strong acids, which reduce the nucleophilicity of heteroarenes and prevent the formation of carbenes.

The regioselectivity of the Friedel–Crafts acylation of indoles depends on the precise substitution pattern and reaction conditions, and can be difficult to predict. Even the type of acylating reagent and the solvent can influence the regioselectivity of the acylation [72]. Unlike pyrrole, unsubstituted indole is usually acylated at position 3 [73]. Occasionally, though, the acylation of benzylic positions and dimerization are also observed (Scheme 4.15).

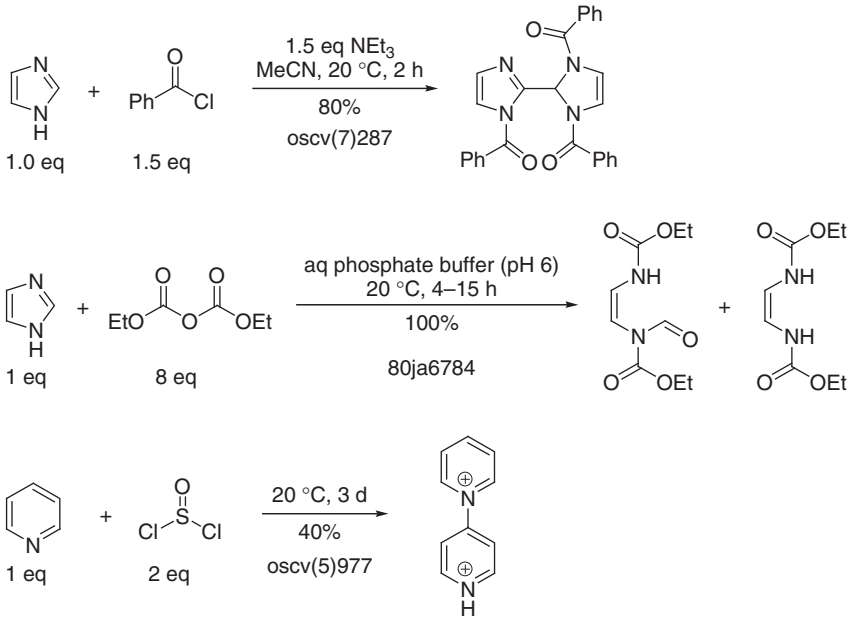


Scheme 4.13 Friedel–Crafts acylation of imidazoles [65–68]. Further examples: [69].

4.3
Problematic Electrophiles

4.3.1
Problematic Acyl Halides

Some acyl halides can decompose upon treatment with acids and cause the formation of unexpected products. If decarbonylation of the corresponding acyl cation yields a stable carbocation, decarbonylation and alkylation by this carbocation may become significant (Scheme 4.16). Other readily decarbonylating acyl halides include oxalyl chloride, other α-oxoacyl halides, and α-amino or α-oxycarboxylic acid-derived acylating reagents [77–80]. Only electron-rich arenes (anisoles, thiophenes, etc.) will yield the expected ketones in Friedel–Crafts acylations with such unstable acyl halides. The decarbonylation of acyl halides can



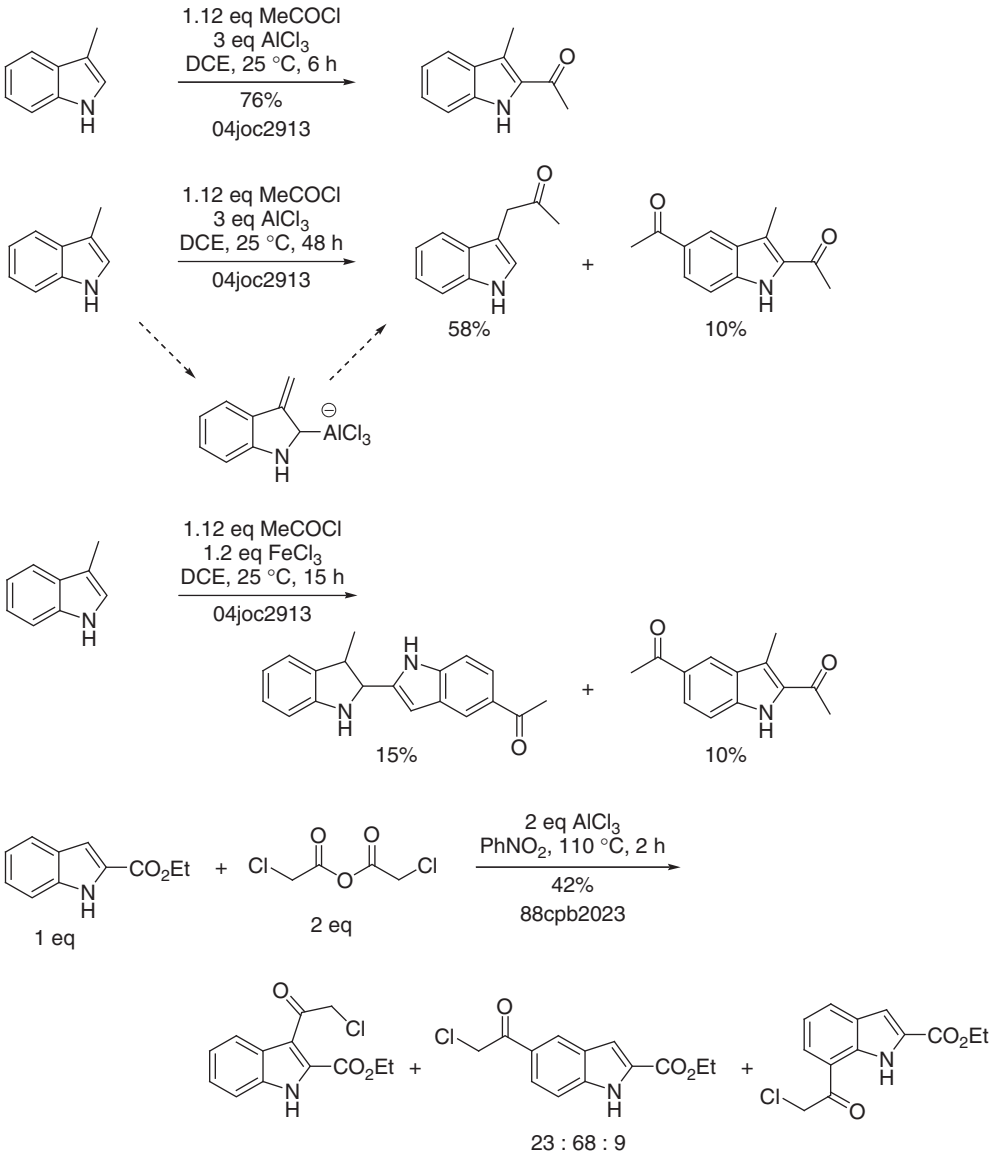
Scheme 4.14 Dimerization and cleavage of heteroarenes upon treatment with electrophiles [16, 70, 71].

be catalyzed by traces of Pd [81–83] or Rh [84, 85], and clean reactors and stirring bars (or chelate forming ligands) should be used to prevent this side reaction.

Acid-mediated rearrangements or the cleavage of strained carbo- or heterocycles are other potential side reactions of Friedel–Crafts acylations. Arylthioethers, cyclopropanes [88, 89], and many other compounds are acid-labile, and can rearrange under the strongly acidic reaction conditions (Scheme 4.17).

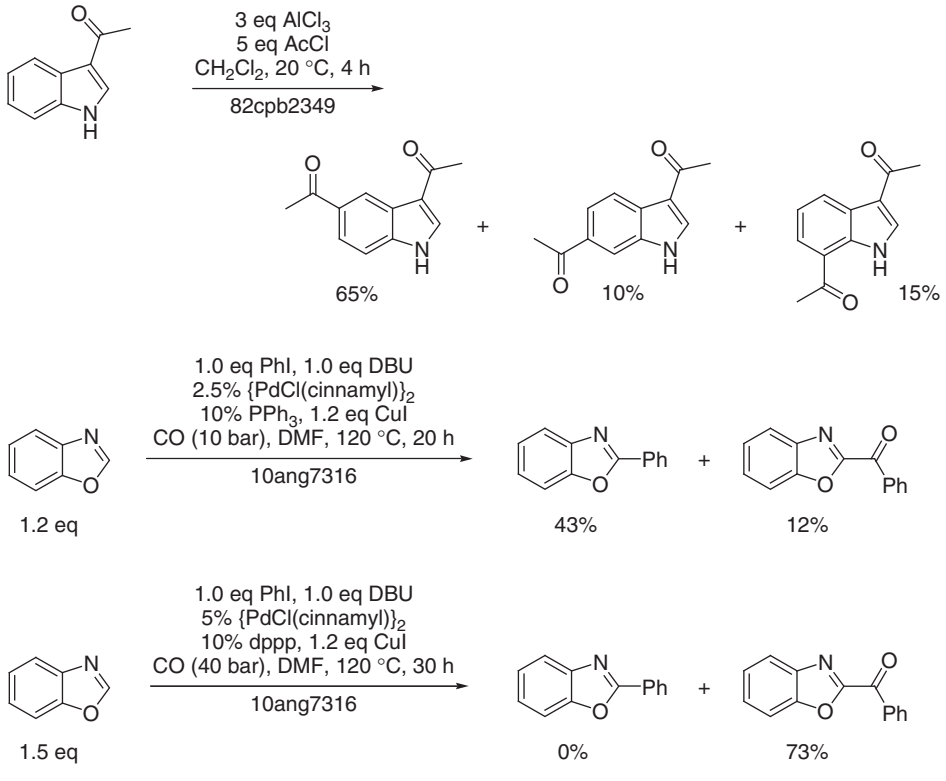
Acrylic acid derivatives can react both as acylating and alkylating reagents. Acryloyl chlorides usually acylate first. Cyclization of arylvinylketones to indanones is sometimes observed, especially with α-substituted acrylates (Scheme 1.28). A further side reaction is the addition of chloride or other nucleophiles to the highly electrophilic vinyl group of the product (Scheme 4.18).

Strong electrophiles, such as trichloroacetyl chloride, phosgene, or trifluoroacetic anhydride, can act as oxidants. When these reagents are used with triethylamine as base, acylated enamines are regularly formed as byproducts [95, 96] (Scheme 4.19). Tertiary amines can also be N-acylated and dealkylated by acyl or sulfonyl halides. These are some of the reasons why acylations under anhydrous conditions with tertiary amines as base often yield complex product mixtures. Inorganic aqueous bases (Schotten–Baumann conditions)



Scheme 4.15 Acylation of indoles and benzoxazoles [72, 74–76].

are far superior for the preparation of amides or sulfonamides to anhydrous conditions. Alternatively, the tertiary alkylamine may be replaced by pyridine or (the cheaper) 3-picoline. 2-Alkylpyridines are not suitable bases for acylation reactions because these bases are readily acylated at the (acidic) 2-alkyl group [97].



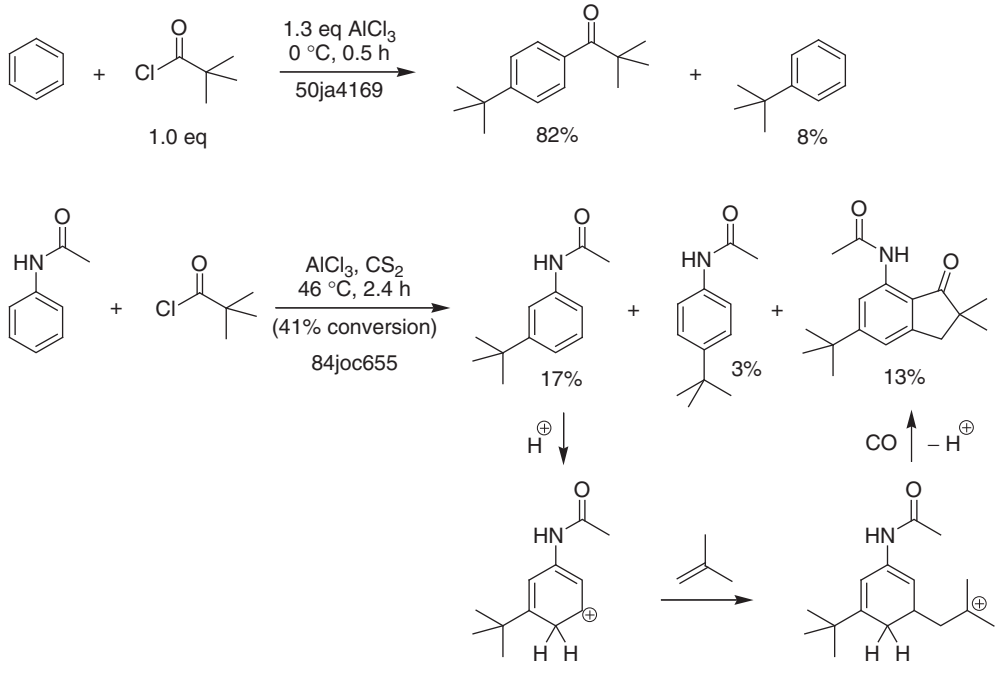
Scheme 4.15 (*Continued*)

4.3.2
Carboxylic Esters and Lactones

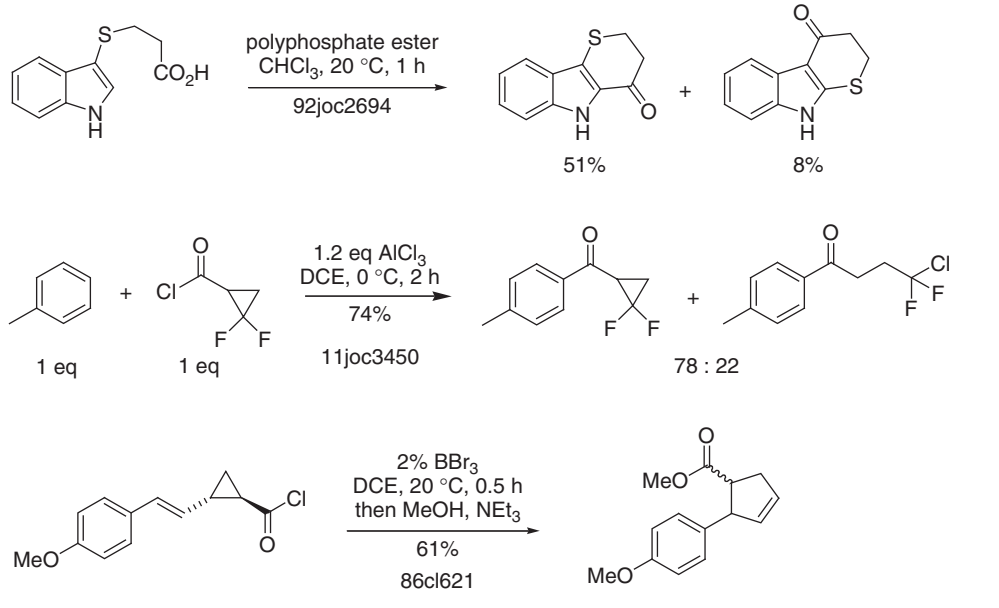
Lactones and noncyclic carboxylic acid esters are dielectrophiles that can react with nucleophiles as either alkylating or acylating reagents. Simple alkyl esters usually alkylate arenes, but under optimized conditions Friedel–Crafts acylations can be achieved (Scheme 4.20).

Butyrolactones and valerolactones react with arenes in the presence of $AlCl_3$ first as alkylating reagents to yield ω-arylalkanoic acids. If the reaction is allowed to proceed, acylation may ensue, to yield cyclic or acyclic ketones. If polyphosphoric acid is used as catalyst, though, acylation of arenes is the first reaction (Scheme 4.21).

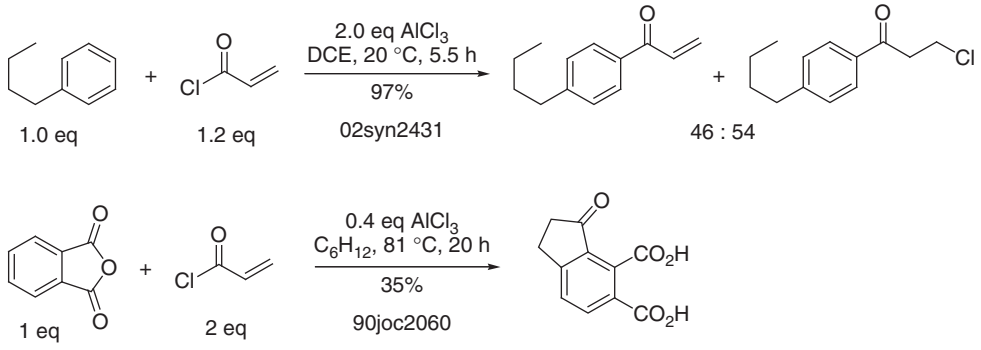
If the reaction conditions are too harsh, ring fission of lactones can occur before reaction with the arene. The resulting carbocations may rearrange to more stable cations by hydride migration or yield olefins, and cause the formation of unexpected isomers (Scheme 4.22).



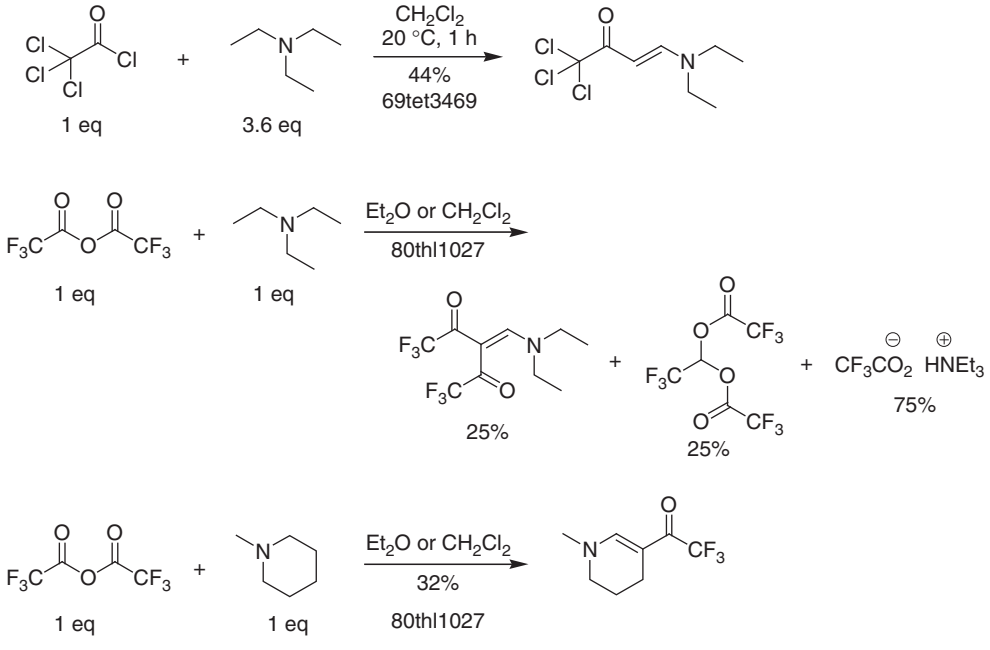
Scheme 4.16 Friedel–Crafts acylations with pivaloyl chloride [86, 87].



Scheme 4.17 Acid-mediated transformations of acyl halides [90–92].



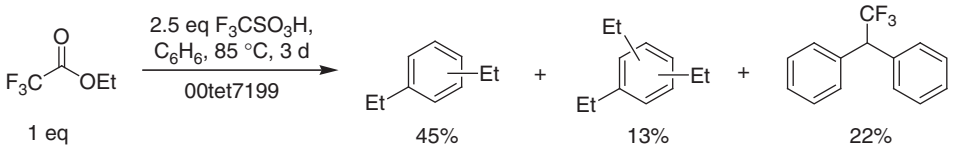
Scheme 4.18 Friedel–Crafts acylation with acryloyl chloride [93, 94].

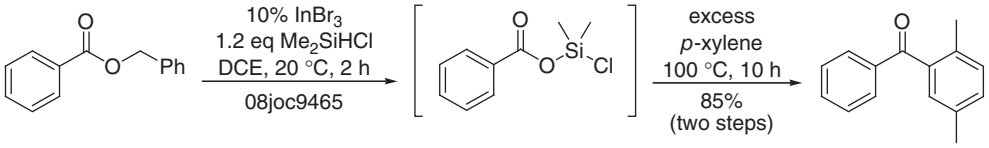


Scheme 4.19 Oxidation of trialkylamines by acylating reagents [98, 99].

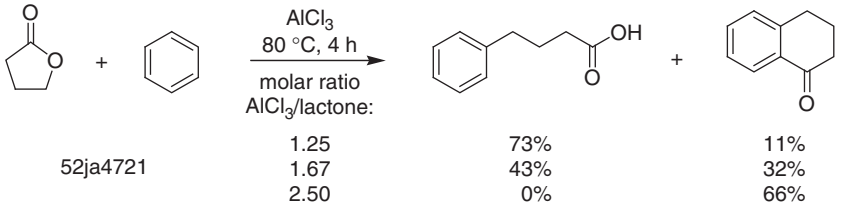
Hard organometallic reagents, such as Grignard or organolithium compounds, however, react with lactones first by adding to the carbonyl group, to yield ω-hydroxyalkylketones (Scheme 4.23). Soft organometallics, for example, cuprates, however, are often alkylated by lactones [104].

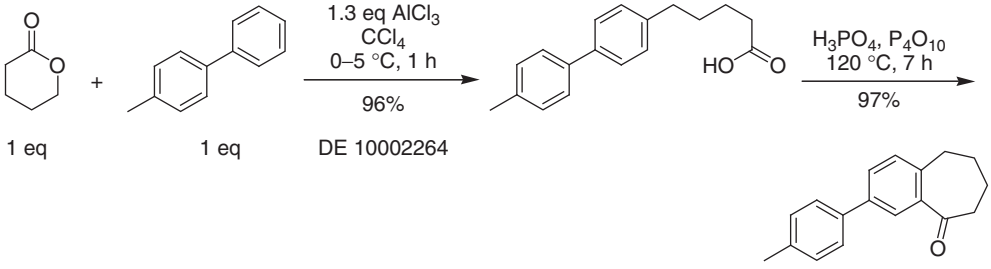
In propiolactones, the reactivity toward nucleophiles is reversed: in the presence of strong Lewis acids, propiolactones acylate arenes. The same is true for hard organometallics [108, 109], whereas soft organometallics are preferentially alkylated [108, 110] (Scheme 4.24).

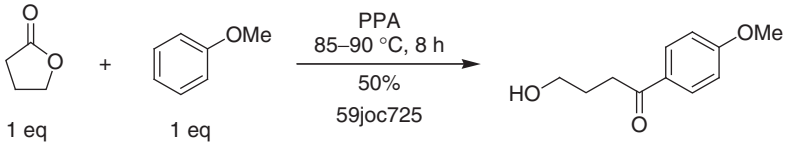




Scheme 4.20 Friedel–Crafts acylations and alkylations with esters [7, 49].



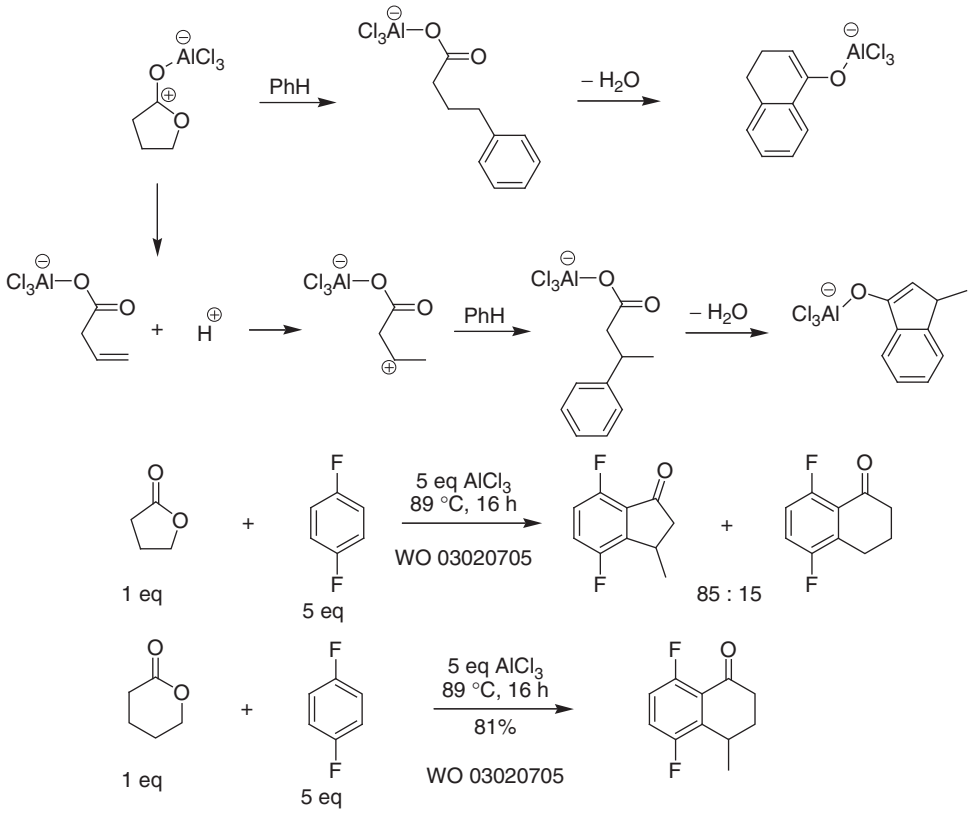




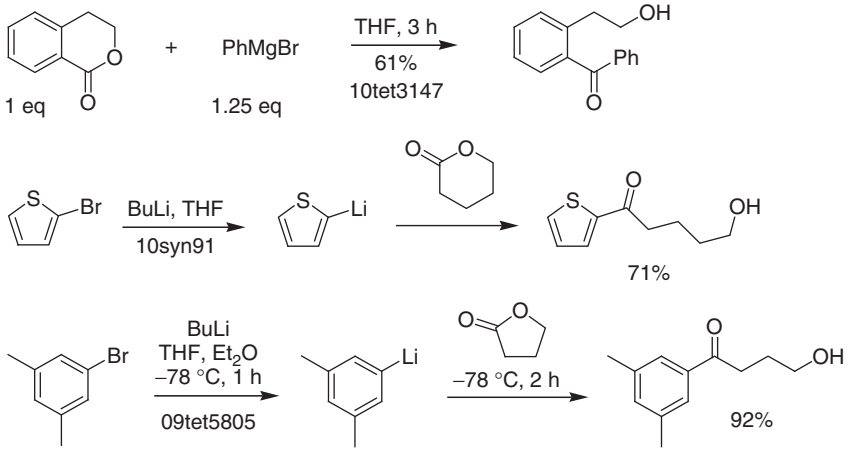
Scheme 4.21 Friedel–Crafts acylations and alkylations with butyrolactones and valerolactones [100–102].

4.3.3
Carbonic Acid Derivatives

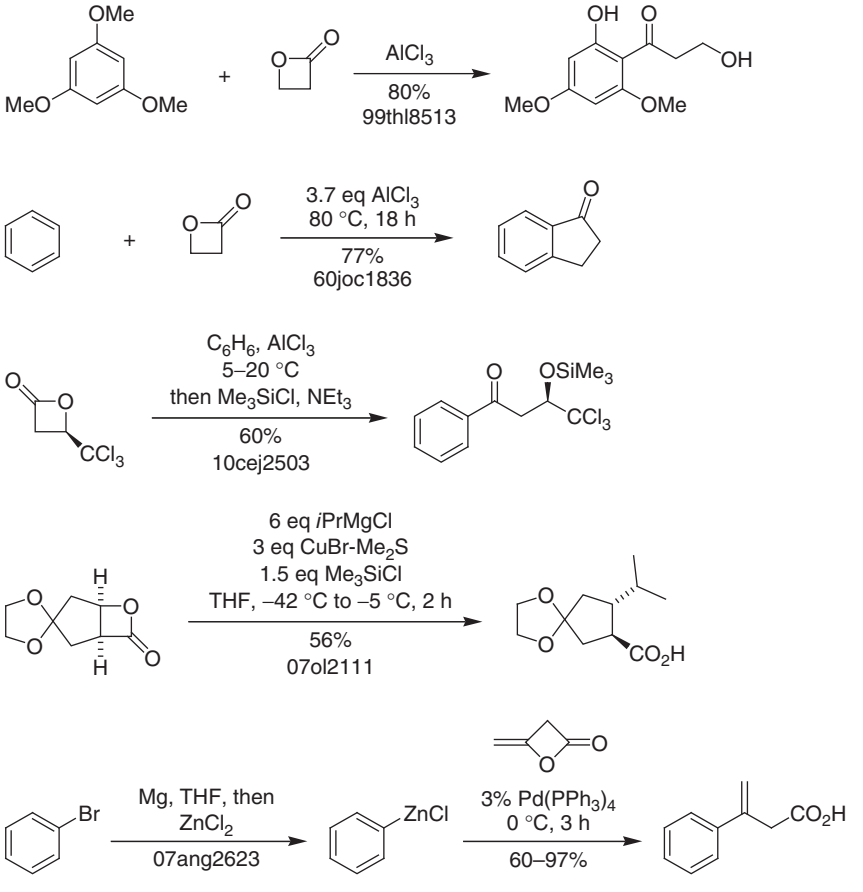
Carbon dioxide can react with arenes in the presence of either strong bases or strong acids. One important example of this reaction is the preparation of



Scheme 4.22 Friedel–Crafts acylations with lactones [103].



Scheme 4.23 Reaction of lactones with organomagnesium and organolithium compounds [105–107].

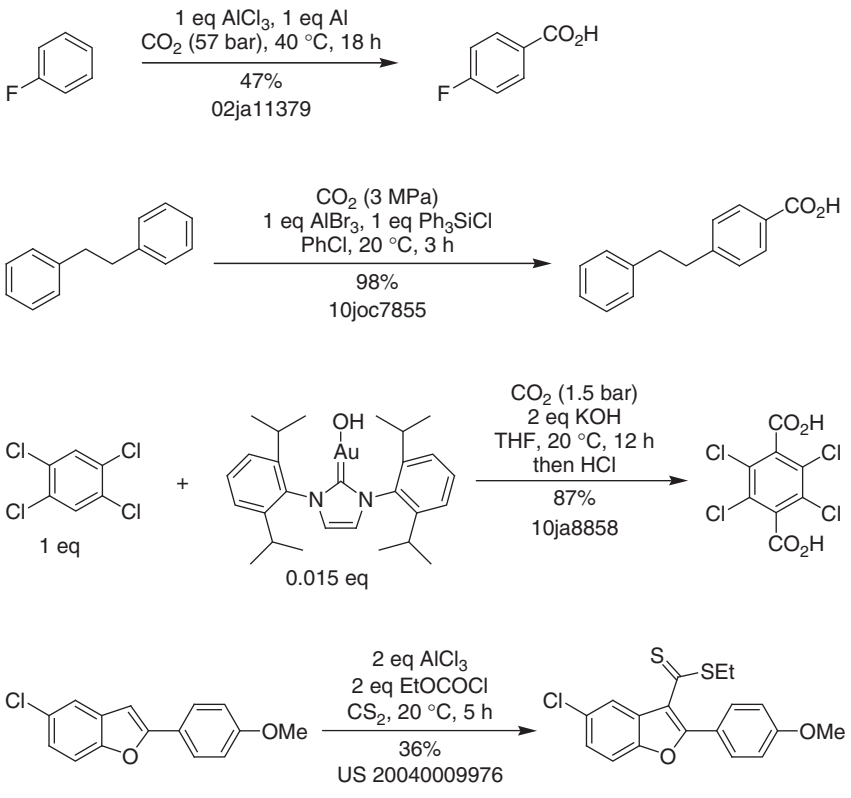


Scheme 4.24 Reaction of propiolactones with various nucleophiles [111–115].

salicylic acid by the carboxylation of sodium phenolate (100 bar, up to 190 °C; Kolbe–Schmitt synthesis). Unfortunately, this valuable reaction is of limited scope, and only gives high yields with some phenolates [116], but not with alkoxyarenes, anilines, or thiophenols. Even dilithiated carbazoles do not readily react with CO_2 [117].

A number of alternative (but more expensive) reaction conditions have been developed that enable the direct carboxylation with CO_2 of less strongly activated arenes (Scheme 4.25). The first example in Scheme 4.25 proceeds via an arylaluminum intermediate.

Carbon disulfide is also quite unreactive in the presence of $AlCl_3$ and arenes, and is often used as solvent for Friedel–Crafts reactions. Electron-rich arenes, though, can be dithiocarboxylated with CS_2 (Scheme 4.25). For instance, toluene is converted to dithio-4-toluic acid in the presence of $AlBr_3$ (24% yield after 24 h at 20 °C [118]).

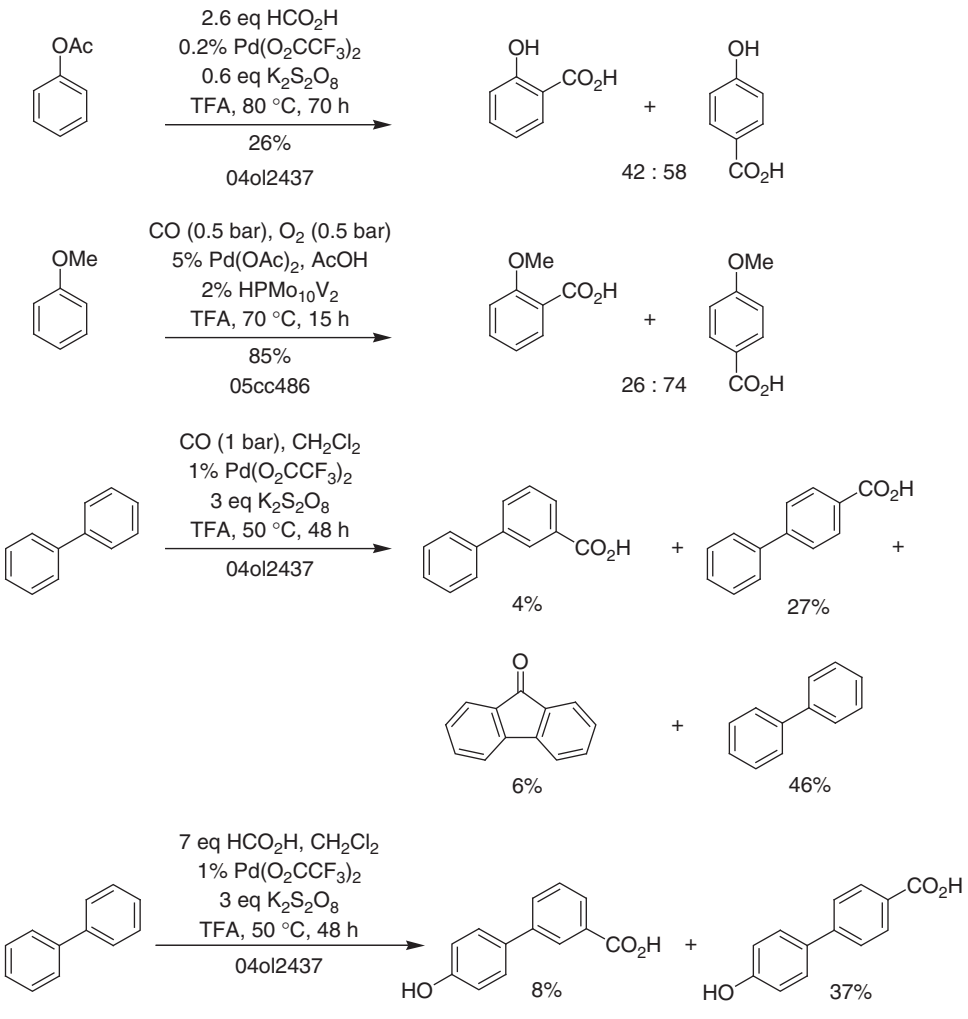


Scheme 4.25 Carboxylation of arenes with CO_2 [118–120] and CS_2 [121].

An alternative to the reaction with unreactive CO_2 are Pd-, Rh-, or Ru-catalyzed carbonylations with CO or formic acid (Scheme 4.26). Aryl bromides are the most common starting materials for Pd-catalyzed carbonylations, but unsubstituted arenes can also be used [53, 55, 122] (Scheme 4.26). Further alternatives include acetylation followed by haloform reaction, or lithiation followed by treatment with CO_2. As shown by the last reaction in Scheme 4.26, Pd catalysis in the presence of carboxylic acids and oxidants can also lead to aromatic hydroxylation. In the presence of alcohols, alkoxylations may also occur [123].

Phosgene or triphosgene can be used to prepare benzoyl chlorides [126], but benzophenones are common byproducts. A synthetic equivalent of phosgene is oxalyl chloride, which decarbonylates in the presence of $AlCl_3$, and can be used to prepare benzoyl chlorides in high yield (Scheme 4.27).

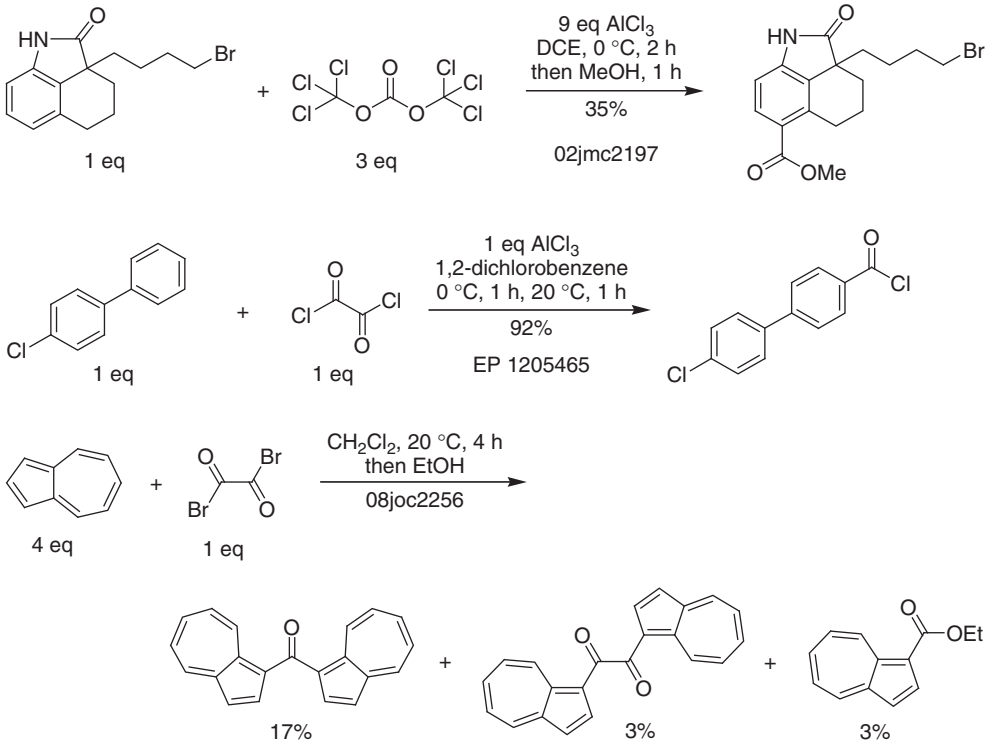
Cyanogene halides (Hal–CN) may react either as electrophilic cyanidation reagents or as halogenating agents. Halogenation is particularly preferred with



Scheme 4.26 Pd-catalyzed carboxylation of arenes [124, 125].

cyanogen bromide and in the absence of strong Lewis acids (Scheme 4.28; for cyanations, see, e.g., [131]).

A few examples of Friedel–Crafts reactions with carbonic acid derivatives, such as carbamoyl chlorides (R_2NCOCl), aryl chloroformates (ArOCOCl), or isocyanates, have been reported (Scheme 4.29). These reactions work best with electron-rich arenes, which even react with carbamates or ureas [136]. Aliphatic chloroformates (ROCOCl) cannot be used as C-acylating reagents under acidic conditions because these reagents mainly *alkylate* arenes [137]. At high temperatures and in the presence of $AlCl_3$, aryl chloroformates can be converted to aryl chlorides (Scheme 8.65).

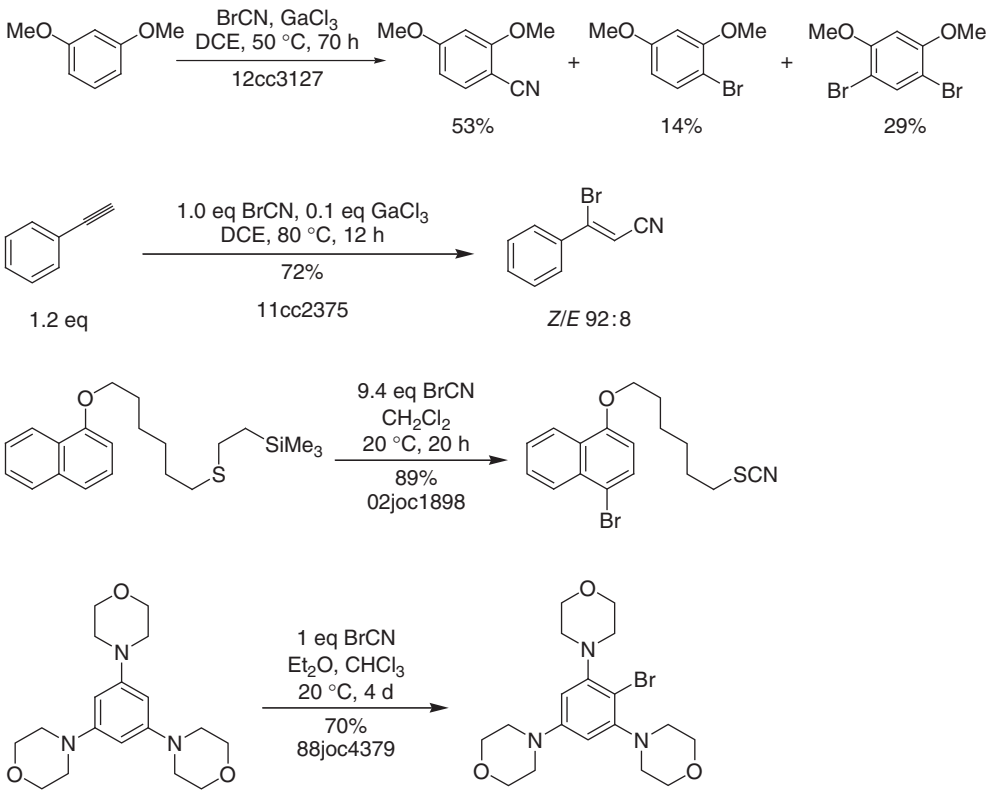


Scheme 4.27 Reaction of triphosgene and oxalyl chloride with arenes [127–129]. Further examples: [130].

4.3.4
Formic Acid Derivatives

Formyl halides decompose to CO and hydrogen halide, and are too shortlived for synthetic applications [141]. Only formyl fluoride (bp 29 °C) is sufficiently stable to be used in Friedel–Crafts acylations, and has in fact been used to prepare benzaldehydes [142]. Benzaldehydes can also be prepared by treating arenes with HCl/CO in the presence of $AlCl_3$ (Gattermann–Koch reaction, e.g., [143]).

Mixed anhydrides usually acylate with the less electrophilic acyl group, and the mixed acetic–formic acid anhydride will therefore acetylate and not formylate arenes. No Friedel–Crafts acylations with formic acid esters have been reported, probably because formates readily decarbonylate under acidic (and basic) conditions [144]. Certain catalysts, though, can promote the formylation of benzene or other arenes with formic acid [145]. Electron-rich aryl formates do undergo Fries rearrangement in fair yields [146]. The best yields for electrophilic formylations, however, are achieved with the Vilsmeier reaction ($DMF/POCl_3$). Further alternatives include the Reimer–Tiemann reaction



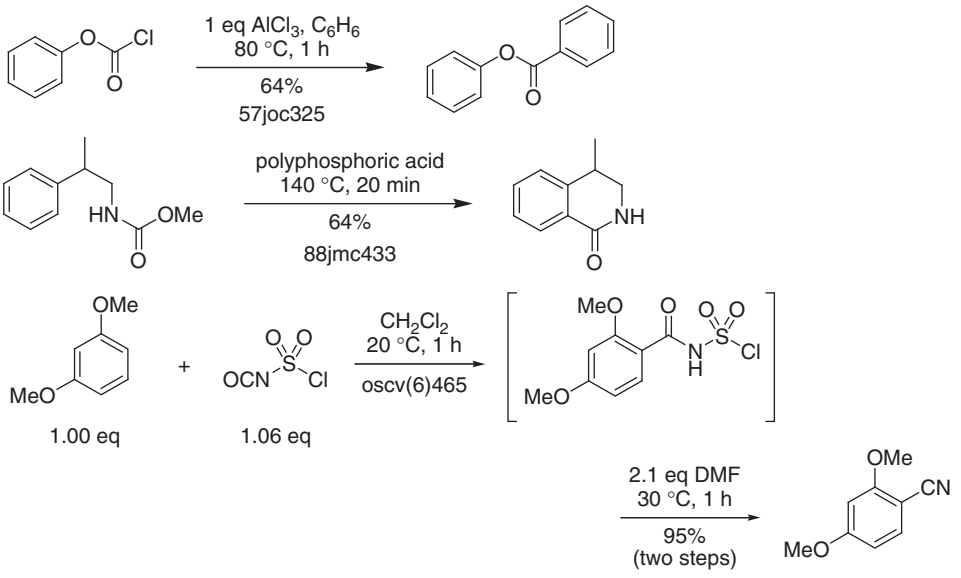
Scheme 4.28 Cyanations and brominations with BrCN [132–135].

(formylation of phenols with chloroform and a base, e.g., [147]) and formylations with urotropine (Duff reaction, e.g., [148]), formaldehyde, HCN, or $MeOCHCl_2$ (Scheme 4.30).

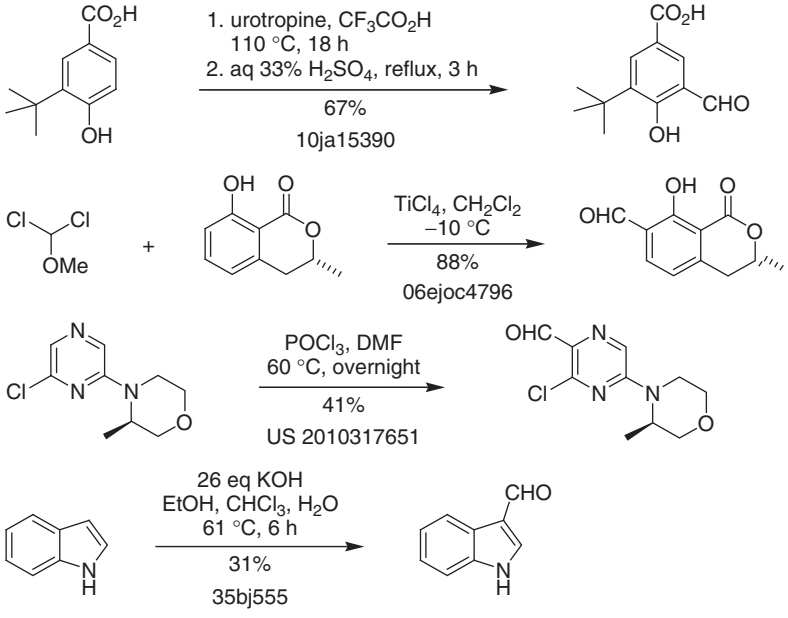
The formylating intermediate of the Reimer–Tiemann reaction is dichlorocarbene [153], and only phenols and pyrroles can usually be formylated. A complementary reaction is the vicarious nucleophilic substitution with the trichloromethyl anion at strongly electron-deficient arenes to yield dichloromethyl arenes, which are synthetic equivalents of benzaldehydes [154].

Because uncomplexed carbenes are highly reactive and therefore only sparsely selective, yields of the Reimer–Tiemann reaction are generally low. Typical byproducts result from the attack of the carbene at substituted positions, from cyclopropane formation, and from reactions of dichlorocarbene or the trichloromethyl anion with functional groups (Scheme 4.31). Under optimized conditions, the yield of some of these byproducts may be sufficient for preparative purposes [155].

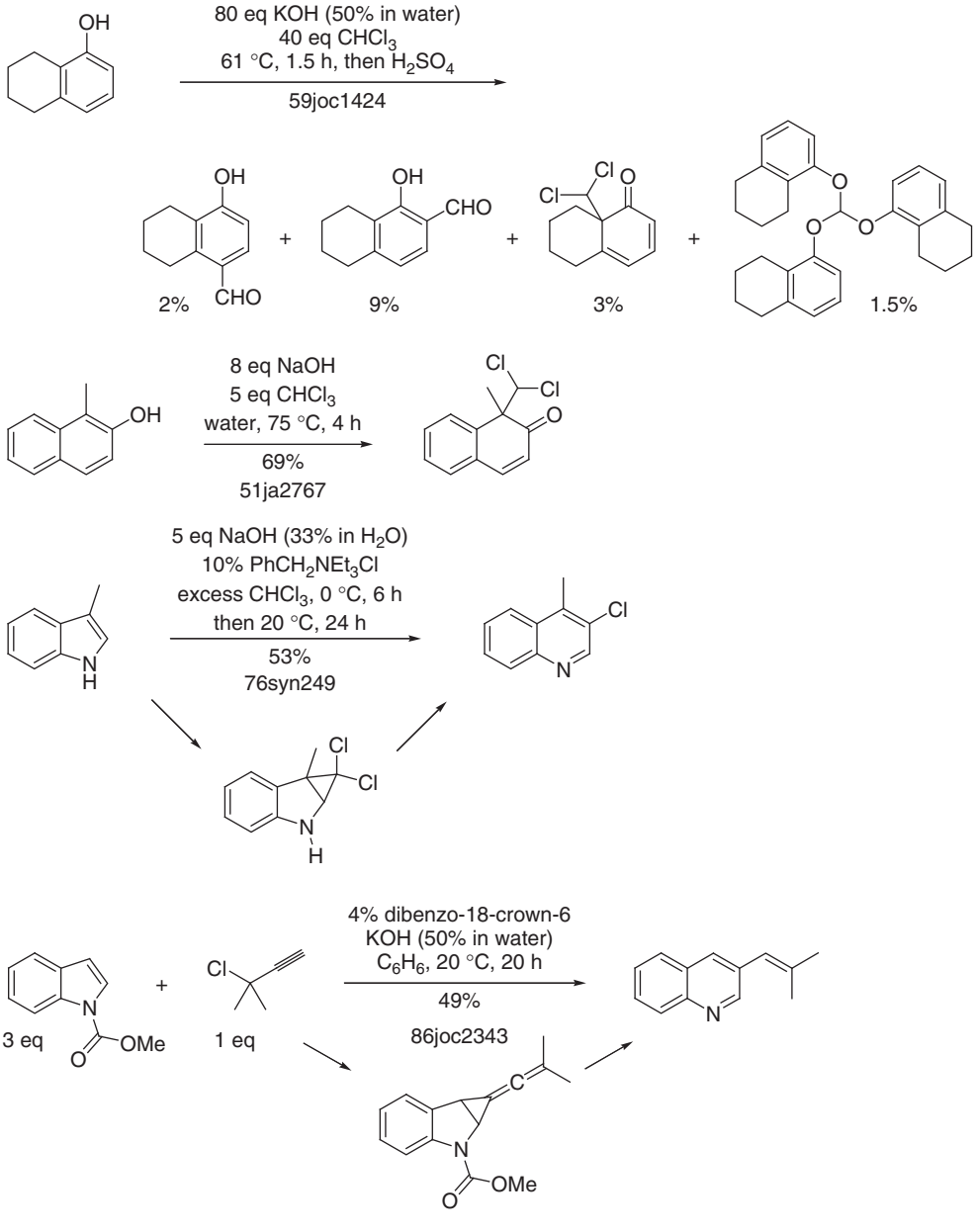
Electrophilic formylations proceed well only with electron-rich arenes. Electron-deficient arenes and heteroarenes are better formylated via metallation or by



Scheme 4.29 Friedel–Crafts carboxylation with carbonic acid derivatives [138–140].

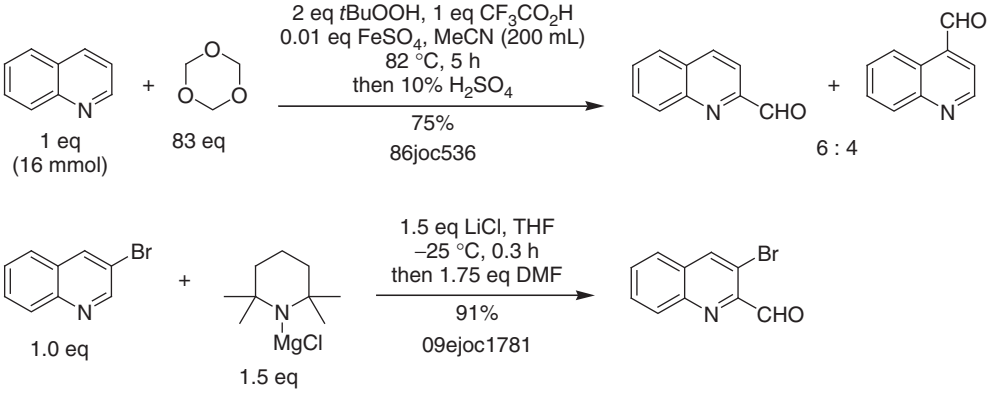


Scheme 4.30 Examples of electrophilic aromatic formylations [149–152].



Scheme 4.31 Side reactions of the Reimer–Tiemann reaction [156–159]. Further examples: [160].

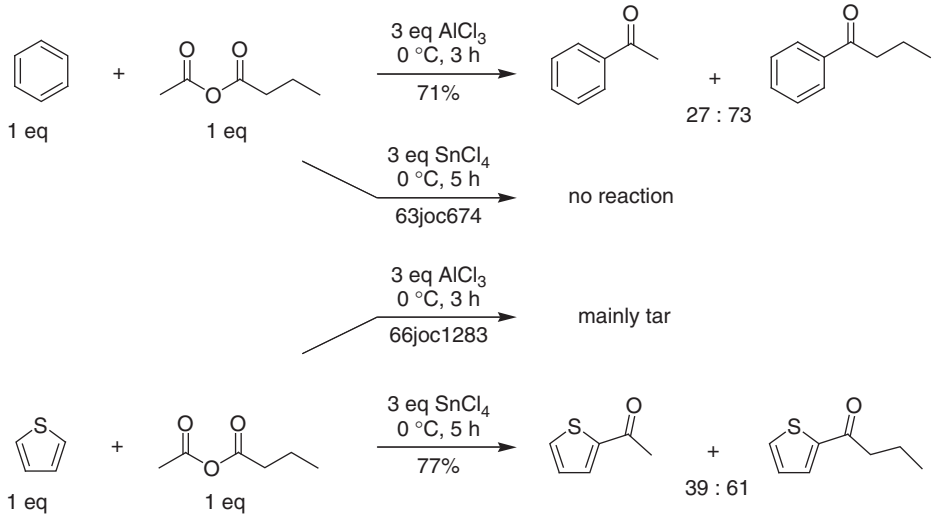
radical formylations. The regioselectivity of the latter, though, is often poor (Scheme 4.32).



Scheme 4.32 Formylation of electron-deficient arenes [56, 161].

4.3.5
Mixed Carboxylic Anhydrides and Other Polyelectrophiles

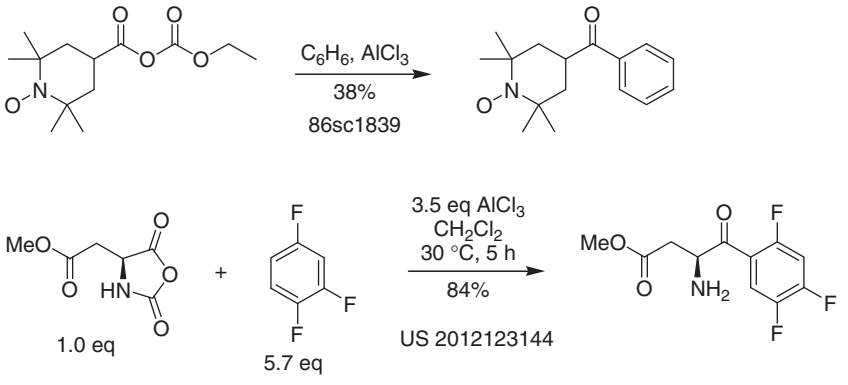
Electrophiles with more than one electrophilic functional group of similar reactivity are inherently problematic. One important class of polyelectrophiles is mixed carboxylic anhydrides. Counterintuitively, these react with arenes under acidic conditions mainly with the *less* electrophilic carbonyl group (Scheme 4.33).



Scheme 4.33 Selectivity of mixed anhydrides in Friedel–Crafts acylations [162, 163].

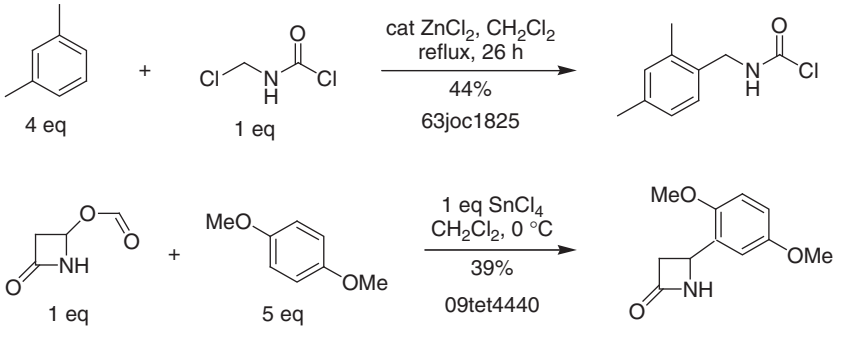
For instance, acylations of arenes with the mixed acetic–formic anhydride do not yield benzaldehydes but acetophenones. The reason for this could be that the less electrophilic acyl group forms an acyl cation more readily. To achieve higher chemoselectivity, one of the two acyl groups must be sterically shielded or strongly deactivated electronically.

In contrast to mixed carboxylic anhydrides, mixed carboxylic carbonic anhydrides react in the expected way with the more electrophilic acyl group (Scheme 4.34).



Scheme 4.34 Friedel–Crafts acylation with mixed carboxylic carbonic anhydrides [164, 165].

The acid-mediated conversion of acetals and related compounds into carbocations often proceeds faster than the formation of acyl cations. Therefore, compounds containing both a reactive acyl group and the synthetic equivalent of an acetal substructure can react faster as alkylating reagent than as acylating reagent (Scheme 4.35). Under basic reaction conditions, though, the acyl group is often more reactive [166].



Scheme 4.35 Friedel–Crafts alkylation with aldehyde derivatives [167, 168].

References

1. Smyth, T.P. and Corby, B.W. (1997) Industrially viable alternative to the Friedel–Crafts acylation reaction: tamoxifen case study. *Org. Process Res. Dev.*, **1**, 264–267.
2. Sharghi, H., Jokar, M., Doroodmand, M.M., and Khalifeh, R. (2010) Catalytic Friedel–Crafts acylation and benzoylation of aromatic compounds using activated hematite as a novel heterogeneous catalyst. *Adv. Synth. Catal.*, **352**, 3031–3044.
3. Sartori, G. and Maggi, R. (2011) Use of solid catalysts in Friedel–Crafts acylation reactions. *Chem. Rev.*, **111**, PR181–PR214.
4. Fürstner, A., Voigtländer, D., Schrader, W., Giebel, D., and Reetz, M.T. (2001) A "hard/soft" mismatch enables catalytic Friedel–Crafts acylations. *Org. Lett.*, **3**, 417–420.
5. Paul, S., Nanda, P., Gupta, R., and Loupy, A. (2003) Zinc mediated Friedel–Crafts acylation in solvent-free conditions under microwave irradiation. *Synthesis*, **2003**, 2877–2881.
6. Gopalakrishnan, M., Sureshkumar, P., Kanagarajan, V., and Thanusu, J. (2005) Aluminum metal powder (atomized) catalyzed Friedel–Crafts acylation in solvent-free conditions: a facile and rapid synthesis of aryl ketones under microwave irradiation. *Catal. Commun.*, **6**, 753–756.
7. Nishimoto, Y., Babu, S.A., Yasuda, M., and Baba, A. (2008) Esters as acylating reagent in a Friedel–Crafts reaction: indium tribromide catalyzed acylation of arenes using dimethylchlorosilane. *J. Org. Chem.*, **73**, 9465–9468.
8. Raja, E.K., DeSchepper, D.J., Lill, S.O.N., and Klumpp, D.A. (2012) Friedel–Crafts acylation with amides. *J. Org. Chem.*, **77**, 5788–5793.
9. Seo, A., Imai, H., Iwase, N., Takata, T., Koyama, Y., and Yonekawa, M. (2011) Crosslinker, crosslinked polymer material, and production method of the crosslinked polymer material. US Patent 2011/0224380.
10. Médebielle, M., Keirouz, R., Okada, E., and Ashidab, T. (2001) Tetrakis(dimethylamino)ethylene (TDAE) mediated addition of heterocyclic difluoromethyl anions to heteroaryl aldehydes. A facile synthetic method for new *gem*-difluorinated alcohols derived from 4-bromo-1-naphthylamine and 8-quinolylamine. *Synlett*, 821–823.
11. Steinbach, R. and Ruppert, I. (1986) Verfahren zur selektiven Acylierung aromatischer Verbindungen. DE Patent 3519009.
12. Murashigea, R., Hayashia, Y., Ohmoria, S., Toriia, A., Aizua, Y., Mutoa, Y., Muraic, Y., Odaa, Y., and Hashimoto, M. (2011) Comparisons of *O*-acylation and Friedel–Crafts acylation of phenols and acyl chlorides and Fries rearrangement of phenyl esters in trifluoromethanesulfonic acid: effective synthesis of optically active homotyrosines. *Tetrahedron*, **67**, 641–649.
13. Tilstam, U. (2012) Sulfolane: a versatile dipolar aprotic solvent. *Org. Process Res. Dev.*, **16**, 1273–1278.
14. Boon, J.A., Levisky, J.A., Pflug, J.L., and Wilkes, J.S. (1986) Friedel–Crafts reactions in ambient-temperature molten salts. *J. Org. Chem.*, **51**, 480–483.
15. Hardacre, C., Nancarrow, P., Rooney, D.W., and Thompson, J.M. (2008) Friedel–Crafts benzoylation of anisole in ionic liquids: catalysis, separation, and recycle studies. *Org. Process Res. Dev.*, **12**, 1156–1163.
16. Bastiaansen, L.A.M. and van Lier, P.M. (1990) Imidazole-2-carboxaldehyde. *Org. Synth.*, Coll. Vol. **7**, 287–290.
17. El-Khawaga, A.M. and Roberts, R.M. (1984) Friedel–Crafts reactions of tetramethylphenyl ketones with tetramethylbenzenes. *J. Org. Chem.*, **49**, 3832–3834.
18. Trnka, T.M. and Kerber, R.C. (1995) An unexpected by-product in the Friedel–Crafts acrylation of ferrocene. *Acta Crystallogr.*, **C51**, 871–873.
19. Yokota, M., Fujita, D., and Ichikawa, J. (2007) Activation of 1,1-difluoro-1-alkenes with a transition-metal

complex: palladium(II)-catalyzed Friedel–Crafts-type cyclization of 4,4-(difluorohomoallyl)arenes. *Org. Lett.*, **9**, 4639–4642.

20. Kuhakarn, C., Surapanich, N., Kamtonwong, S., Pohmakotr, M., and Reutrakul, V. (2011) Friedel–Crafts-type alkylation with bromodifluoro (phenylsulfanyl)methane through α-fluorocarbocations: syntheses of thioesters, benzophenones and xanthones. *Eur. J. Org. Chem.*, **2011**, 5911–5918.

21. Kagechika, H., Kawachi, E., Hashimoto, Y., Himi, T., and Shudo, K. (1988) Retinobenzoic acids. 1. Structure–activity relationships of aromatic amides with retinoidal activity. *J. Med. Chem.*, **31**, 2182–2192.

22. Rae, I.D. and Woolcock, M.L. (1987) Hydride transfers during Friedel–Crafts reactions of 5,5-dimethyl-4,5-dihydrofuran-2(3*H*)-one. *Aust. J. Chem.*, **40**, 1023–1029.

23. Yamato, T., Fujita, K., and Tsuzuki, H. (2001) Medium-sized cyclophanes. Part 58. Synthesis and conformational studies of [2.*n*]metacyclophan-1-enes and [*n*.1]metacyclophanes. *J. Chem. Soc., Perkin Trans. 1*, 2089–2097.

24. Downton, P.A., Mailvaganam, B., Frampton, C.S., Sayer, B.G., and McGlinchey, M.J. (1990) Unequivocal proof of slowed chromium tricarbonyl rotation in a sterically crowded arene complex: an X-ray crystallographic and variable-temperature high-field NMR study of $(C_6Et_5COCH_3)Cr(CO)_3$. *J. Am. Chem. Soc.*, **112**, 21–32.

25. Li, W.-M., Lai, H.-Q., Ge, Z.-H., Ding, C.-R., and Zhou, Y. (2007) Solvent affected facile synthesis of hydroxynaphthyl ketones: Lewis acids promoted Friedel–Crafts and demethylation reaction. *Synth. Commun.*, **37**, 1595–1601.

26. Strupczewski, J.T., Allen, R.C., Gardner, B.A., Schmid, B.L., Stache, U., Glamkowski, E.J., Jones, M.C., Ellis, D.B., Huger, F.P., and Dunn, R.W. (1985) Synthesis and neuroleptic activity of 3-(1-substituted-4-piperidinyl)-1,2-benzisoxazoles. *J. Med. Chem.*, **28**, 761–769.

27. Kim, K.S., Sack, J.S., Tokarski, J.S., Qian, L., Chao, S.T., Leith, L., Kelly, Y.F., Misra, R.N., Hunt, J.T., Kimball, S.D., Humphreys, W.G., Wautlet, B.S., Mulheron, J.G., and Webster, K.R. (2000) Thio- and oxoflavopiridols, cyclin-dependent kinase 1-selective inhibitors: synthesis and biological effects. *J. Med. Chem.*, **43**, 4126–4134.

28. Moriguchi, T., Endo, T., and Takata, T. (1995) Addition–elimination reaction in the trifluoroacetylation of electron-rich olefins. *J. Org. Chem.*, **60**, 3523–3528.

29. Song, Z. and Beak, P. (1990) Investigation of the mechanisms of ene reactions of carbonyl enophiles by intermolecular and intramolecular hydrogen–deuterium isotope effects: partitioning of reaction intermediates. *J. Am. Chem. Soc.*, **112**, 8126–8134.

30. Kashiwabara, T., Fuse, K., Hua, R., and Tanaka, M. (2008) Rhodium-complex-catalyzed addition reactions of chloroacetyl chlorides to alkynes. *Org. Lett.*, **10**, 5469–5472.

31. Bedini, A., Lucarini, S., Spadoni, G., Tarzia, G., Scaglione, F., Dugnani, S., Pannacci, M., Lucini, V., Carmi, C., Pala, D., Rivara, S., and Mor, M. (2011) Toward the definition of stereochemical requirements for MT2-selective antagonists and partial agonists by studying 4-phenyl-2-propionamidotetralin derivatives. *J. Med. Chem.*, **54**, 8362–8372.

32. Rosen, M.J. (1963) 1-Methyl-3-phenylindane. *Org. Synth.*, Coll. Vol. **4**, 665–667.

33. Zhou, H., Zeng, C., Ren, L., Liao, W., and Huang, X. (2006) $GaCl_3$-catalyzed chloroacylation of alkynes: a simple, convenient and efficient method to β-chlorovinyl ketones. *Synlett*, 3504–3506.

34. Iwai, T., Fujihara, T., Terao, J., and Tsuji, Y. (2012) Iridium-catalyzed addition of aroyl chlorides and aliphatic acid chlorides to terminal alkynes. *J. Am. Chem. Soc.*, **134**, 1268–1274.

35. Fang, P., Li, M., and Ge, H. (2010) Room temperature palladium-catalyzed decarboxylative *ortho*-acylation of acetanilides with α-oxocarboxylic acids. *J. Am. Chem. Soc.*, **132**, 11898–11899.

36. Verboom, W., van Dijk, B.G., and Reinhoudt, D.N. (1983) Novel applications of the '*t*-amino effect' in heterocyclic chemistry; synthesis of 5*H*-pyrrolo- and 1*H*,6*H*-pyrido[1,2-*a*][3,1]benzoxazines. *Tetrahedron Lett.*, **24**, 3923–3926.
37. Kobayashi, S., Komoto, I., and Matsuo, J. (2001) Catalytic Friedel–Crafts acylation of aniline derivatives. *Adv. Synth. Catal.*, **343**, 71–74.
38. Yin, Z. and Sun, P. (2012) Palladium-catalyzed direct *ortho*-acylation through an oxidative coupling of acetanilides with toluene derivatives. *J. Org. Chem.*, **77**, 11339–11344.
39. Merlic, C.A., Motamed, S., and Quinn, B. (1995) Structure determination and synthesis of fluoro nissl green: an RNA-binding fluorochrome. *J. Org. Chem.*, **60**, 3365–3369.
40. Tarbell, D.S. and Herz, A.H. (1953) An attempted Fries reaction with thiolesters. The formation of trithioorthoesters. *J. Am. Chem. Soc.*, **75**, 1668–1672.
41. Staskun, B. (1964) Nuclear acylation of arylamines. *J. Org. Chem.*, **29**, 2856–2860.
42. Aslam, M., Davenport, K.G., and Stansbury, W.F. (1991) Anhydrous hydrogen fluoride catalyzed Friedel–Crafts reactions of thioaromatic compounds. *J. Org. Chem.*, **56**, 5955–5958.
43. Yous, S., Poupaert, J.H., Lesieur, I., Depreux, P., and Lesieur, D. (1994) $AlCl_3$–DMF reagent in the Friedel–Crafts reaction. Application to the acylation reaction of 2(3*H*)-benzothiazolones. *J. Org. Chem.*, **59**, 1574–1576.
44. Yin, L., Hu, Q., and Hartmann, R.W. (2013) Tetrahydropyrroloquinolinone type dual inhibitors of aromatase/aldosterone synthase as a novel strategy for breast cancer patients with elevated cardiovascular risks. *J. Med. Chem.*, **56**, 460–470.
45. Lemoucheux, L., Rouden, J., Ibazizene, M., Sobrio, F., and Lasne, M.–.C. (2003) Debenzylation of tertiary amines using phosgene or triphosgene: an efficient and rapid procedure for the preparation of carbamoyl chlorides and unsymmetrical ureas. Application in carbon-11 chemistry. *J. Org. Chem.*, **68**, 7289–7297.
46. Dillard, R.D., Carr, F.P., McCullough, D., Haisch, K.D., Rinkema, L.E., and Fleisch, J.H. (1987) Leukotriene receptor antagonists. 2. The [[(tetrazol-5-ylaryl)oxy]methyl]acetophenone derivatives. *J. Med. Chem.*, **30**, 911–918.
47. Cheng, Y., Zhan, Y.-H., and Meth-Cohn, O. (2002) A simple route to *N*-ω-chloroalkylisatins from cyclic *t*-anilines, oxalyl chloride and DABCO. *Synthesis*, 34–38.
48. Semenova, O.N., Kudryavtseva, Y.A., Ermolenko, I.G., and Patsenker, L.D. (2005) Behavior of dimethylaminonaphthalenes in the Vilsmeier–Haak reaction. *Russ. J. Org. Chem.*, **41**, 1100–1101.
49. Hwang, J.P., Prakash, G.K.S., and Olah, G.A. (2000) Trifluoromethanesulfonic acid catalyzed novel Friedel–Crafts acylation of aromatics with methyl benzoate. *Tetrahedron*, **56**, 7199–7203.
50. Bigelow, L.A. and Reynolds, H.H. (1941) Quinizarin. *Org. Synth.*, Coll. Vol. **1**, 476–478.
51. Siegel, W. and Schroeder, J. (1994) Verfahren zur Herstellung mehrfach acylierter Aromaten. DE Patent 4240966.
52. Xiao, F., Shuai, Q., Zhao, F., Baslé, O., Deng, G., and Li, C.-J. (2011) Palladium-catalyzed oxidative sp^2 C–H bond acylation with alcohols. *Org. Lett.*, **13**, 1614–1617.
53. Asaumi, T., Chatani, N., Matsuo, T., Kakiuchi, F., and Murai, S. (2003) Ruthenium-catalyzed C–H/CO/olefin coupling reaction of *N*-arylpyrazoles. Extraordinary reactivity of *N*-arylpyrazoles toward carbonylation at C–H bonds. *J. Org. Chem.*, **68**, 7538–7540.
54. Snégaroff, K., Nguyen, T.T., Marquise, N., Halauko, Y.S., Harford, P.J., Roisnel, T., Matulis, V.E., Ivashkevich, O.A., Chevallier, F., Wheatley, A.E.H., Gros, P.C., and

Mongin, F. (2011) Deprotonative metalation of chloro- and bromopyridines using amido-based bimetallic species and regioselectivity-computed CH acidity relationships. *Chem. Eur. J.*, **17**, 13284–13297.

55. Kochi, T., Urano, S., Seki, H., Mizushima, E., Sato, M., and Kakiuchi, F. (2009) Ruthenium-catalyzed amino- and alkoxycarbonylations with carbamoyl chlorides and alkyl chloroformates via aromatic C–H bond cleavage. *J. Am. Chem. Soc.*, **131**, 2792–2793.

56. Rohbogner, C.J., Wunderlich, S.H., Clososki, G.C., and Knochel, P. (2009) New mixed Li/Mg and Li/Mg/Zn amides for the chemoselective metallation of arenes and heteroarenes. *Eur. J. Org. Chem.*, **2009**, 1781–1795.

57. Kaminski, T., Gros, P., and Fort, Y. (2003) Side-chain retention during lithiation of 4-picoline and 3,4-lutidine: easy access to molecular diversity in pyridine series. *Eur. J. Org. Chem.*, **2003**, 3855–3860.

58. Fontana, F., Minisci, F., Barbosa, M.C.N., and Vismara, E. (1991) Homolytic acylation of protonated pyridines and pyrazines with α-keto acids: the problem of monoacylation. *J. Org. Chem.*, **56**, 2866–2869.

59. Chan, C.-W., Zhou, Z., Chan, A.S.C., and Yu, W.-Y. (2010) Pd-catalyzed *ortho*–C–H acylation/cross coupling of aryl ketone *O*-methyl oximes with aldehydes using *tert*-butyl hydroperoxide as oxidant. *Org. Lett.*, **12**, 3926–3929.

60. Zheng, X., Song, B., and Xu, B. (2010) Palladium-catalyzed regioselective C–H bond *ortho*-acetoxylation of arylpyrimidines. *Eur. J. Org. Chem.*, **2010**, 4376–4380.

61. Wunderlich, S.H. and Knochel, P. (2010) Atom-economical preparation of aryl– and heteroaryl–lanthanum reagents by directed *ortho*-metalation by using TMP_3[La]. *Chem. Eur. J.*, **16**, 3304–3307.

62. Bachman, G.B. and Schisla, R.M. (1957) The direct *C*-acylation of pyridine. *J. Org. Chem.*, **22**, 858.

63. Frank, R.L. and Smith, P.V. (1955) 4-Ethylpyridine. *Org. Synth.*, Coll. Vol. **3**, 410–412.

64. Zhou, W., Li, H., and Wang, L. (2012) Direct carbo-acylation reactions of 2-arylpyridines with α-diketones via Pd-catalyzed C–H activation and selective C(sp2)–C(sp2) cleavage. *Org. Lett.*, **14**, 4594–4597.

65. Chatani, N., Fukuyama, T., Tatamidani, H., Kakiuchi, F., and Murai, S. (2000) Acylation of five-membered *N*-heteroaromatic compounds by ruthenium carbonyl-catalyzed direct carbonylation at a C–H bond. *J. Org. Chem.*, **65**, 4039–4047.

66. Jaramillo, D., Liu, Q., Aldrich-Wright, J., and Tor, Y. (2004) Synthesis of *N*-methylpyrrole and *N*-methylimidazole amino acids suitable for solid-phase synthesis. *J. Org. Chem.*, **69**, 8151–8153.

67. Almansa, C., Alfón, J., de Arriba, A.F., Cavalcanti, F.L., Escamilla, I., Gómez, L.A., Miralles, A., Soliva, R., Bartrolí, J., Carceller, E., Merlos, M., and García-Rafanell, J. (2003) Synthesis and structure–activity relationship of a new series of COX-2 selective inhibitors: 1,5-diarylimidazoles. *J. Med. Chem.*, **46**, 3463–3475.

68. Janssens, F., Leenaerts, J., Diels, G., De Boeck, B., Megens, A., Langlois, X., van Rossem, K., Beetens, J., and Borgers, M. (2005) Norpiperidine imidazoazepines as a new class of potent, selective, and nonsedative H_1 antihistamines. *J. Med. Chem.*, **48**, 2154–2166.

69. Heckel, A. and Dervan, P.B. (2003) U-pin polyamide motif for recognition of the DNA minor groove. *Chem. Eur. J.*, **9**, 3353–3366.

70. Grace, M.E., Hosemore, M.J., Semmel, M.L., and Pratt, R.F. (1980) Kinetics and mechanism of the Bamberger cleavage of imidazole and of histidine derivatives by diethyl pyrocarbonate in aqueous solution. *J. Am. Chem. Soc.*, **102**, 6784–6789.

71. Evans, R.F. and Brown, H.C. (1973) 4-Pyridinesulfonic acid. *Org. Synth.*, Coll. Vol. **5**, 977–981.

72. Murakami, Y., Tani, M., Tanaka, K., and Yokoyama, Y. (1988) Synthetic studies on indoles and related compounds. XV. An unusual acylation of ethyl indole-2-carboxylate in the Friedel–Crafts acylation. *Chem. Pharm. Bull.*, **36**, 2023–2035.
73. Ottoni, O., Neder, A.de.V.F., Dias, A.K.B., Cruz, R.P.A., and Aquino, L.B. (2001) Acylation of indole under Friedel–Crafts conditions – an improved method to obtain 3-acylindoles regioselectively. *Org. Lett.*, **3**, 1005–1007.
74. Pal, M., Dakarapu, R., and Padakanti, S. (2004) A direct access to 3-(2-oxoalkyl)indoles via aluminum chloride induced C–C bond formation. *J. Org. Chem.*, **69**, 2913–2916.
75. Hino, T., Torisawa, Y., and Nakagawa, M. (1982) The acetylation of 3-acylindoles. *Chem. Pharm. Bull.*, **30**, 2349–2356.
76. Wu, X.-F., Anbarasan, P., Neumann, H., and Beller, M. (2010) Palladium-catalyzed carbonylative C–H activation of heteroarenes. *Angew. Chem. Int. Ed.*, **49**, 7316–7319.
77. Yonezawa, N., Hino, T., Matsuda, K., Matsuki, T., Narushima, D., Kobayashi, M., and Ikeda, T. (2000) Specific and chemoselective multi-α-arylation reaction of benzoylformic acid with or without decarbonylation in P_2O_5–MsOH and related acidic media. *J. Org. Chem.*, **65**, 941–944.
78. Seong, M.R., Lee, H.J., and Kim, J.N. (1998) Decarbonylative diarylation reaction of *N*-tosylated α-amino acids. *Tetrahedron Lett.*, **39**, 6219–6222.
79. Yonezawa, N., Hino, T., Tokita, Y., Matsuda, K., and Ikeda, T. (1997) Structural requirements for decarbonylative α,α-diarylation reaction of 2-methoxyalkanoic acids in phosphorus pentoxide-methanesulfonic acid mixture yielding 1,1-diarylalkane homologs. *Tetrahedron*, **53**, 14287–14296.
80. Palmer, M.H. and McVie, G.J. (1966) The elimination of carbon monoxide from acid chlorides. A new method for chloromethyl ether formation. *Tetrahedron Lett.*, **7**, 6405–6408.
81. Burhardt, M.N., Taaning, R., Nielsen, N.C., and Skrydstrup, T. (2012) Isotope-labeling of the fibril binding compound FSB via a Pd-catalyzed double alkoxycarbonylation. *J. Org. Chem.*, **77**, 5357–5363.
82. Verbicky, J.W., Dellacoletta, B.A., and Williams, L. (1982) Palladium catalyzed decarbonylation of aromatic acyl chlorides. *Tetrahedron Lett.*, **23**, 371–372.
83. Tsuji, J., Ohno, K., and Kajimoto, T. (1965) Organic syntheses by means of noble metal compounds XX. Decarbonylation of acyl chloride and aldehyde catalyzed by palladium and its relationship with the Rosenmund reduction. *Tetrahedron Lett.*, **6**, 4565–4568.
84. Ohno, K. and Tsuji, J. (1968) Organic syntheses by means of noble metal compounds. XXXV. Novel decarbonylation reactions of aldehydes and acyl halides using rhodium complexes. *J. Am. Chem. Soc.*, **90**, 99–107.
85. Blum, J., Oppenheimer, E., and Bergmann, E.D. (1967) Decarbonylation of aromatic carbonyl compounds catalyzed by rhodium complexes. *J. Am. Chem. Soc.*, **89**, 2338–2341.
86. Pearson, D.E. (1950) Pivalophenones from Friedel–Crafts and Grignard reactions. *J. Am. Chem. Soc.*, **72**, 4169–4170.
87. Maslak, P., Fanwick, P.E., and Guthrie, R.D. (1984) Aluminum chloride catalyzed reaction of acetanilide with pivalyl chloride. *J. Org. Chem.*, **49**, 655–659.
88. Iwama, T., Matsumoto, H., and Kataoka, T. (1997) Acid-promoted isomerisation of 1-acceptor-1-sulfenyl-substituted 2-vinylcyclopropanes with C^1–C^2 bond fission and novel 1,5-sulfenyl rearrangement. *J. Chem. Soc., Perkin Trans. 1*, 835–843.
89. Hogeveen, H., Roobeek, C.F., and Volger, H.C. (1972) Inversion of configuration in a fused cyclopropane ring opening by hydrochloric acid. *Tetrahedron Lett.*, **13**, 221–226.
90. Hamel, P., Girard, Y., and Atkinson, J.G. (1992) Acid-catalyzed isomerization of 3-indolyl sulfides to

2-indolyl sulfides: first synthesis of 3-unsubstituted 2-(arylthio)indoles. Evidence for a complex intermolecular process. *J. Org. Chem.*, **57**, 2694–2699.

91. Dolbier, W.R., Cornett, E., Martinez, H., and Xu, W. (2011) Friedel–Crafts reactions of 2,2-difluorocyclopropanecarbonyl chloride: unexpected ring-opening chemistry. *J. Org. Chem.*, **76**, 3450–3456.

92. Sakito, Y. and Suzukamo, G. (1986) Lewis acid catalyzed rearrangement of vinylcyclopropanecarbonyl chloride to cyclopentenecarbonyl chloride. *Chem. Lett.*, 621–624.

93. Ward, R.S., Davies, J., Hodges, G., and Roberts, D.W. (2002) Synthesis of quaternary alkylammonium sulfobetaines. *Synthesis*, 2431–2439.

94. Gaviña, F., Costero, A.M., and González, A.M. (1990) Reactive annulenones: a comparative study. *J. Org. Chem.*, **55**, 2060–2063.

95. Itaya, T. and Kanai, T. (1997) New reactions of phosgene with tertiary amines. *Heterocycles*, **46**, 101–104.

96. Talley, J.J. (1981) Oxidation of tertiary amines by hexachloroacetone. *Tetrahedron Lett.*, **22**, 823–826.

97. Kawasi, M., Teshima, M., Saito, S., and Tani, S. (1998) Trifluoroacetylation of methylpyridines and other methylazines: a convenient access to trifluoroacetonylazines. *Heterocycles*, **48**, 2103–2109.

98. Fraser, R.R. and Swingle, R.B. (1969) The oxidation of triethylamine by trichloroacetyl chloride. *Tetrahedron*, **25**, 3469–3475.

99. Schreiber, S.L. (1980) Hydrogen transfer from tertiary amines to trifluoroacetic anhydride. *Tetrahedron Lett.*, **21**, 1027–1030.

100. Truce, W.E. and Olson, C.E. (1952) The aluminum chloride-catalyzed condensation of γ-butyrolactone with benzene. *J. Am. Chem. Soc.*, **74**, 4721.

101. Meudt, A., Scherer, S., Nörenberg, A., and Vogt, W. (2001) Verfahren zur Herstellung von 3-*p*-Tolyl-8,9-dihydro-7*H*-benzocyclohepten-6-carbonsäure. DE Patent 10002264.

102. House, H.O. and McCaully, R.J. (1959) Polyphosphoric acid-catalyzed reaction of anisole with γ-butyrolactone. *J. Org. Chem.*, **24**, 725–726.

103. Sahlberg, C., Antonov, D., Wallenberg, H., and Noreen, R. (2003) Urea and thiourea derivatives as non-nucleoside reverse transcriptase inhibitors. WO Patent 03020705.

104. Davissont, V.J. and Poulter, C.D. (1993) Farnesyl-diphosphate synthase. Interplay between substrate topology, stereochemistry, and regiochemistry in electrophilic alkylations. *J. Am. Chem. Soc.*, **115**, 1245–1260.

105. Pirrung, M.C., Roy, B.G., and Gadamsetty, S. (2010) Structure–reactivity relationships in (2-hydroxyethyl)benzophenone photoremovable protecting groups. *Tetrahedron*, **66**, 3147–3151.

106. Miao, L., DiMaggio, S.C., and Trudell, M.L. (2010) Hydroxyarylketones via ring-opening of lactones with aryllithium reagents: an expedient synthesis of (±)-anabasamine. *Synthesis*, 91–97.

107. Andrews, D.M., Arnould, J.-C., Boutron, P., Délouvrie, B., Delvare, C., Foote, K.M., Hamon, A., Harris, C.S., Lambert-van der Brempt, C., Lamorlette, M., and Matusiak, Z.M. (2009) Fischer synthesis of isomeric thienopyrrole LHRH antagonists. *Tetrahedron*, **65**, 5805–5816.

108. Nelson, S.G., Wan, Z., and Stan, M.A. (2002) S_N2 ring opening of β-lactones: an alternative to catalytic asymmetric conjugate additions. *J. Org. Chem.*, **67**, 4680–4683.

109. Shen, K.-H., Kuo, C.-W., and Yao, C.-F. (2007) An efficient Grignard-type procedure for the preparation of *gem*-diallylated compounds. *Tetrahedron Lett.*, **48**, 6348–6351.

110. Smith, N.D., Wohlrab, A.M., and Goodman, M. (2005) Enantiocontrolled synthesis of α-methyl amino acids via Bn_2N-α-methylserine-β-lactone. *Org. Lett.*, **7**, 255–258.

111. Kraus, G.A. and Wang, X. (1999) A direct synthesis of aflatoxin M_2. *Tetrahedron Lett.*, **40**, 8513–8514.

112. Rinehart, K.L. and Gustafson, D.H. (1960) α-Indanone from β-propiolactone. *J. Org. Chem.*, **25**, 1836.

113. Tiseni, P.S. and Peters, R. (2010) Catalytic asymmetric formation of δ-lactones from unsaturated acyl halides. *Chem. Eur. J.*, **16**, 2503–2517.

114. Zhang, W., Matla, A.S., and Romo, D. (2007) Alkyl C–O ring cleavage of bicyclic β-lactones with Normant reagents: synthesis of a Merck IND intermediate. *Org. Lett.*, **9**, 2111–2114.

115. Sun, X., Zhou, L., Wang, C.-J., and Zhang, X. (2007) Rh-catalyzed highly enantioselective synthesis of 3-arylbutanoic acids. *Angew. Chem. Int. Ed.*, **46**, 2623–2626.

116. Baine, O., Adamson, G.F., Barton, J.W., Fitch, J.L., Swayampati, D.R., and Jeskey, H. (1954) A study of the Kolbe–Schmitt reaction. II. The carbonation of phenols. *J. Org. Chem.*, **19**, 510–514.

117. Katritzky, A.R., Rewcastle, G.W., and Vazquez de Miguel, L.M. (1988) Improved syntheses of substituted carbazoles and benzocarbazoles via lithiation of the (dialkylamino)methyl (aminal) derivatives. *J. Org. Chem.*, **53**, 794–799.

118. Nemoto, K., Yoshida, H., Egusa, N., Morohashi, N., and Hattori, T. (2010) Direct carboxylation of arenes and halobenzenes with CO_2 by the combined use of $AlBr_3$ and R_3SiCl. *J. Org. Chem.*, **75**, 7855–7862.

119. Olah, G.A., Török, B., Joschek, J.P., Bucsi, I., Esteves, P.M., Rasul, G., and Prakash, G.K.S. (2002) Efficient chemoselective carboxylation of aromatics to arylcarboxylic acids with a superelectrophilically activated carbon dioxide–Al_2Cl_6/Al system. *J. Am. Chem. Soc.*, **124**, 11379–11391.

120. Boogaerts, I.I.F. and Nolan, S.P. (2010) Carboxylation of C–H bonds using *N*-heterocyclic carbene gold(I) complexes. *J. Am. Chem. Soc.*, **132**, 8858–8859.

121. Takeuchi, K., Jirousek, M.R., Paal, M., Ruhter, G., and Schotten, T. (2004) Hypoglycemic imidazoline compounds. US Patent 2004009976.

122. Zhang, H., Shi, R., Gan, P., Liu, C., Ding, A., Wang, Q., and Lei, A. (2012) Palladium-catalyzed oxidative double C–H functionalization/carbonylation for the synthesis of xanthones. *Angew. Chem. Int. Ed.*, **51**, 5204–5207.

123. Wang, G.-W. and Yuan, T.-T. (2010) Palladium-catalyzed alkoxylation of *N*-methoxybenzamides via direct sp^2 C–H bond activation. *J. Org. Chem.*, **75**, 476–479.

124. Shibahara, F., Kinoshita, S., and Nozaki, K. (2004) Palladium(II)-catalyzed sequential hydroxylation–carboxylation of biphenyl using formic acid as a carbonyl source. *Org. Lett.*, **6**, 2437–2439.

125. Ohashi, S., Sakaguchi, S., and Ishii, Y. (2005) Carboxylation of anisole derivatives with CO and O_2 catalyzed by $Pd(OAc)_2$ and molybdovanadophosphates. *Chem. Commun.*, 486–488.

126. Neubert, M.E. and Fishel, D.L. (1990) Preparation of 4-alkyl and 4-halobenzoyl chlorides: 4-pentylbenzoyl chloride. *Org. Synth.*, Coll. Vol. **7**, 420–424.

127. Kikuchi, C., Ando, T., Watanabe, T., Nagaso, H., Okuno, M., Hiranuma, T., and Koyama, M. (2002) 2a-[4-(Tetrahydropyridoindol-2-yl)butyl]tetrahydrobenzindole derivatives: new selective antagonists of the 5-hydroxytryptamine$_7$ receptor. *J. Med. Chem.*, **45**, 2197–2206.

128. Rodefeld, L., Klausener, A., and Ullrich, F.-W. (2002) Verfahren zur Herstellung von gegebenfalls substituierten Biphenylcarbonsäurechloriden. EP Patent 1205465.

129. Ito, S., Okujima, T., Kikuchi, S., Shoji, T., Morita, N., Asao, T., Ikoma, T., Tero-Kubota, S., Kawakami, J., and Tajiri, A. (2008) Synthesis and intramolecular pericyclization of 1-azulenyl thioketones. *J. Org. Chem.*, **73**, 2256–2263.

130. Sokol, P.E. (1973) Mesitoic acid. *Org. Synth.*, Coll. Vol. **5**, 706–708.

131. Gore, P.H., Kamounah, F.S., and Miri, A.Y. (1979) Friedel–Crafts cyanation of some reactive aromatic hydrocarbons. *Tetrahedron*, **35**, 2927–2929.

132. Okamoto, K., Watanabe, M., Murai, M., Hatano, R., and Ohe, K. (2012) Practical synthesis of aromatic nitriles via

gallium-catalysed electrophilic cyanation of aromatic C–H bonds. *Chem. Commun.*, **48**, 3127–3129.

133. Murai, M., Hatano, R., Kitabata, S., and Ohe, K. (2011) Gallium(III)-catalysed bromocyanation of alkynes: regio- and stereoselective synthesis of β-bromo-α,β-unsaturated nitriles. *Chem. Commun.*, **47**, 2375–2377.

134. Chambert, S., Thomasson, F., and Décout, J.-L. (2002) 2-Trimethylsilylethyl sulfides in the von Braun cyanogen bromide reaction: selective preparation of thiocyanates and application to nucleoside chemistry. *J. Org. Chem.*, **67**, 1898–1904.

135. Effenberger, F., Mack, K.-E., Niess, R., Reisinger, F., Steinbach, A., Stohrer, W.-D., Stezowski, J.J., Rommel, I., and Maier, A. (1988) Aminobenzenes. 19. Dimeric σ-complexes: intermediates in the oxidative dimerization of aromatics. *J. Org. Chem.*, **53**, 4379–4386.

136. Raja, E.K., Lill, S.O.N., and Klumpp, D.A. (2012) Friedel–Crafts-type reactions with ureas and thioureas. *Chem. Commun.*, **48**, 8141–8143.

137. Hoi, B. and Janicaud, J. (1945) Friedel–Crafts reaction with ethyl chloroformate. *Bull. Soc. Chim. Fr.*, **12**, 640–642.

138. Coppock, W.H. (1957) New synthesis of aryl esters of aromatic acids. *J. Org. Chem.*, **22**, 325–326.

139. Grunewald, G.L., Sall, D.J., and Monn, J.A. (1988) Conformational and steric aspects of the inhibition of phenylethanolamine *N*-methyltransferase by benzylamines. *J. Med. Chem.*, **31**, 433–444.

140. Lohaus, G. (1988) 2,4-Dimethoxybenzonitrile. *Org. Synth.*, Coll. Vol. **6**, 465–468.

141. Dowideit, P., Mertens, R., and von Sonntag, C. (1996) Non-hydrolytic decay of formyl chloride into CO and HCl in aqueous solution. *J. Am. Chem. Soc.*, **118**, 11288–11292.

142. Olah, G.A. and Kuhn, S.J. (1960) Formylation with formyl fluoride: a new aldehyde synthesis and formylation method. *J. Am. Chem. Soc.*, **82**, 2380–2382.

143. Coleman, G.H. and Craig, D. (1943) *p*-Tolualdehyde. *Org. Synth.*, Coll. Vol. **2**, 583–586.

144. Bagno, A., Bukala, J., and Olah, G.A. (1990) Superacid-catalyzed carbonylation of methane, methyl halides, methyl alcohol, and dimethyl ether to methyl acetate and acetic acid. *J. Org. Chem.*, **55**, 4284–4289.

145. Goettmann, F., Fischer, A., Antonietti, M., and Thomas, A. (2006) Metal-free catalysis of sustainable Friedel–Crafts reactions: direct activation of benzene by carbon nitrides to avoid the use of metal chlorides and halogenated compounds. *Chem. Commun.*, 4530–4532.

146. Ziegler, G., Haug, E., Frey, W., and Kantlehner, W. (2001) Orthoamides. Part LVII. Can aromatic aldehydes be prepared from aryl formates via the Fries rearrangement? *Z. Naturforsch., B: Chem. Sci.*, **56**, 1178–1187.

147. Russell, A. and Lockhart, L.B. (1955) 2-Hydroxy-1-naphthaldehyde. *Org. Synth.*, Coll. Vol. **3**, 463–464.

148. Allen, C.F.H. and Leubner, G.W. (1963) Syringic aldehyde. *Org. Synth.*, Coll. Vol. **4**, 866–869.

149. Song, F., Wang, C., Falkowski, J.M., Ma, L., and Lin, W. (2010) Isoreticular chiral metal-organic frameworks for asymmetric alkene epoxidation: tuning catalytic activity by controlling framework catenation and varying open channel sizes. *J. Am. Chem. Soc.*, **132**, 15390–15398.

150. Saito, F., Kuramochi, K., Nakazaki, A., Mizushina, Y., Sugawara, F., and Kobayashi, S. (2006) Synthesis and absolute configuration of (+)-pseudodeflectusin: structural revision of aspergione B. *Eur. J. Org. Chem.*, **2006**, 4796–4799.

151. Sasaki, S., Kusumoto, T., Nomura, I., and Maezaki, H. (2010) Pyrazinooxazepine derivatives. US Patent 2010317651.

152. Boyd, W.J. and Robson, W. (1935) The synthesis of indole-3-aldehyde and its homologues. *Biochem. J.*, **29**, 555–561.

153. Wynberg, H. and Meijer, E.W. (1982) The Reimer–Tiemann reaction. *Org. React.*, **28**, 1–36.

154. Beier, P., Pastyríková, T., and Iakobson, G. (2011) Preparation of SF_5 aromatics by vicarious nucleophilic substitution reactions of nitro(pentafluorosulfanyl)benzenes with carbanions. *J. Org. Chem.*, **76**, 4781–4786.

155. Fuson, R.C. and Miller, T.G. (1952) The von Auwers rearrangement in the naphthalene series. *J. Org. Chem.*, **17**, 316–320.

156. Wynberg, H. and Johnson, W.S. (1959) Synthetic applications of the abnormal Reimer–Tiemann reaction. *J. Org. Chem.*, **24**, 1424–1428.

157. Dodson, R.M. and Webb, W.P. (1951) Polycyclic compounds. I. The Reimer–Tiemann reaction with 1-alkyl-2-naphthols. *J. Am. Chem. Soc.*, **73**, 2767–2769.

158. Kwon, S., Nishimura, Y., Ikeda, M., and Tamura, Y. (1976) An improved procedure for ring expansion of indoles into 3-haloquinolines by use of phase transfer catalysts. *Synthesis*, **1976**, 249.

159. Wenkert, E., Angell, E.C., Ferreira, V.F., Michelotti, E.L., Piettre, S.R., Sheu, J.-H., and Swindell, C.S. (1986) Synthesis of prenylated indoles. *J. Org. Chem.*, **51**, 2343–2351.

160. De Angelis, F., Inesi, A., Feroci, M., and Nicoletti, R. (1995) Reaction of electrogenerated dichlorocarbene with methylindoles. *J. Org. Chem.*, **60**, 445–447.

161. Giordano, C., Minisci, F., Vismara, E., and Levi, S. (1986) A general, selective, and convenient procedure of homolytic formylation of heteroaromatic bases. *J. Org. Chem.*, **51**, 536–537.

162. Edwards, W.R. and Sibille, E.C. (1963) Mixed carboxylic anhydrides in the Friedel–Crafts reaction. *J. Org. Chem.*, **28**, 674–679.

163. Edwards, W.R. and Eckert, R.J. (1966) Friedel–Crafts acylation of thiophene with mixed acetic anhydrides. *J. Org. Chem.*, **31**, 1283–1285.

164. Hidega, K., Csekóa, J., and Hankovszkya, H.O. (1986) Synthesis of nitroxide paramagnetic ketones from nitroxide acid chlorides and anhydrides by Friedel–Crafts acylation. *Synth. Commun.*, **16**, 1839–1847.

165. Soukup, M. (2012) Manufacturing process for sitagliptin from L-aspartic acid. US Patent 2012/123144.

166. Loeffler, H.-P., Thym, S., Koenig, K.-H., and Zeeh, B. (1980) Neue Bis-(*N*-halogenmethyl)carbamidsäureester und Verfahren zu ihrer Herstellung. DE Patent 2826012.

167. Hoover, F.W., Stevenson, H.B., and Rothrock, H.S. (1963) Chemistry of isocyanic acid. I. Reactions of isocyanic acid with carbonyl compounds. *J. Org. Chem.*, **28**, 1825–1830.

168. Zambron, B., Masnyk, M., Furman, B., and Chmielewski, M. (2009) An entry to 4-aryl-azetidinones via alkylation of nucleophilic arenes using four-membered acyliminium cations. *Tetrahedron*, **65**, 4440–4446.

5
Electrophilic Halogenation of Arenes

5.1
General Aspects

Halogenation is an important tool for the functionalization of arenes. Most halogenations proceed by electrophilic aromatic substitution of hydrogen or other electropositive groups, for example, silanes, boranes, main group and transition metals, and secondary or tertiary alkyl groups. The halogens are ortho/para directing but only slightly deactivating, and polyhalogenation is a common side reaction. Regioselectivity is often an issue, too.

One alternative mechanism, which often dominates when arenes are easily oxidized (i.e., have low oxidation half-wave potentials), is single-electron transfer between the arene and the halogenating reagent. The intermediate radical cation can then either abstract a halide from the halogenating reagent, to yield a pair of radicals, or abstract a halogen radical to yield a protonated aryl halide. Halogen radicals can also be formed by thermal or photochemical homolytic cleavage of the halogenating reagent, and add to the arene. A further potential mechanism is the classical radical chain halogenation (last equation, Scheme 5.1).

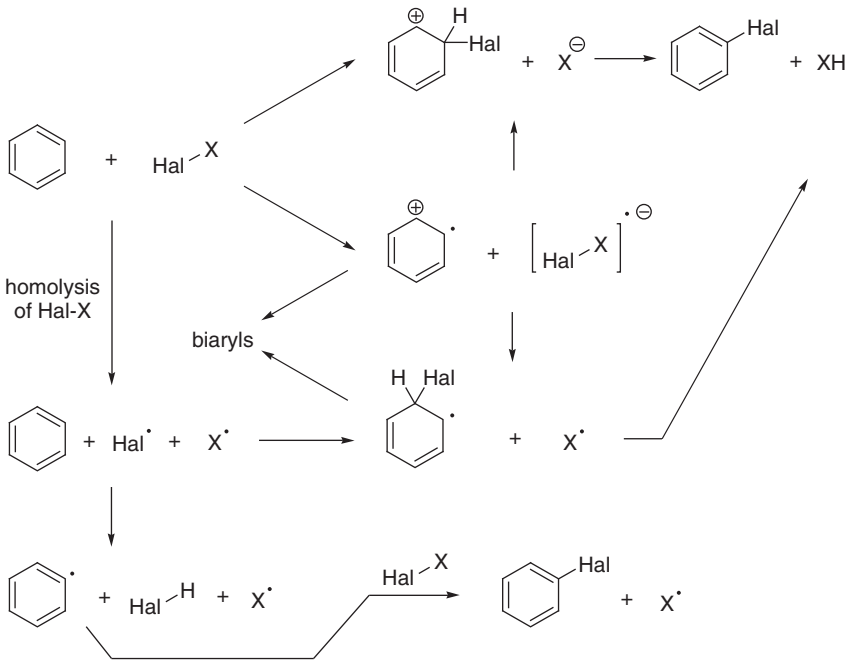
Large-scale halogenations are usually performed with elemental halogens or, less wastefully, with halides and an oxidant (O_2, H_2O_2, or electrochemical oxidation). Gas-phase halogenations at high temperatures or gas-phase photohalogenations are conducted on a very large scale. Reagents such as PCl_5, SO_2Cl_2, $SOCl_2$, $CuCl_2$, and $ArSO_2Cl$ can also be used for oxidative chlorinations. For small-scale preparations, a more precise dosing of halogenating agent can best be achieved with solid halogenating reagents, such as *N*-halo amides or imides.

When interhalogens are used as the halogenating reagent, it is usually the heavier halogen that forms the bond to carbon, but not always (Scheme 5.2). The selectivity depends on whether the halogenation proceeds via ions or radicals [1].

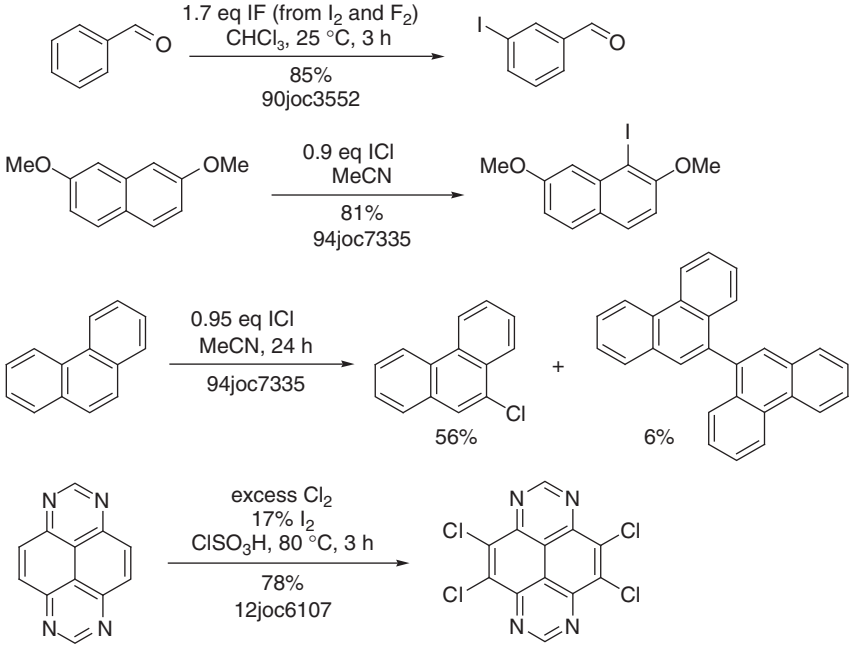
5.2
Typical Side Reactions

The outcome of halogenations with non-halogens can be difficult to predict, because more than one product can be formed. Non-radical halogenations with

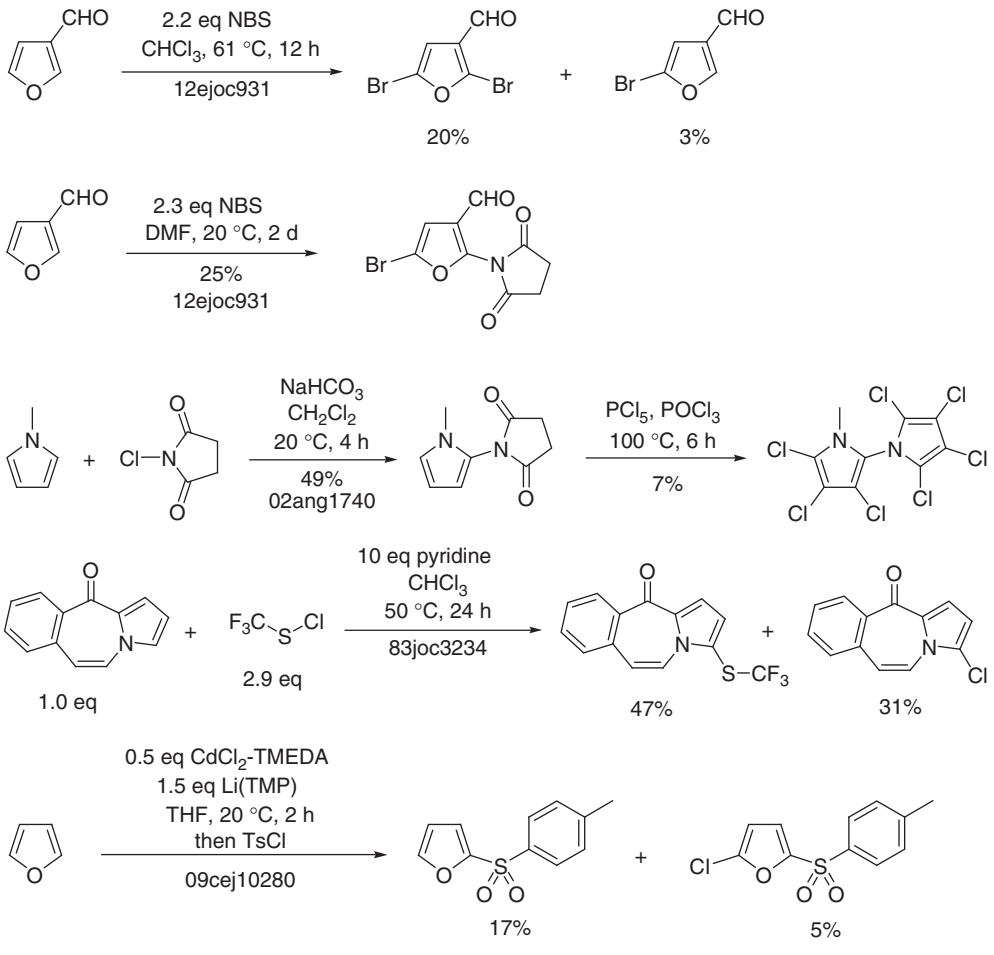
Side Reactions in Organic Synthesis II: Aromatic Substitutions, First Edition. Florencio Zaragoza Dörwald.



Scheme 5.1 Mechanisms of aromatic halogenations.



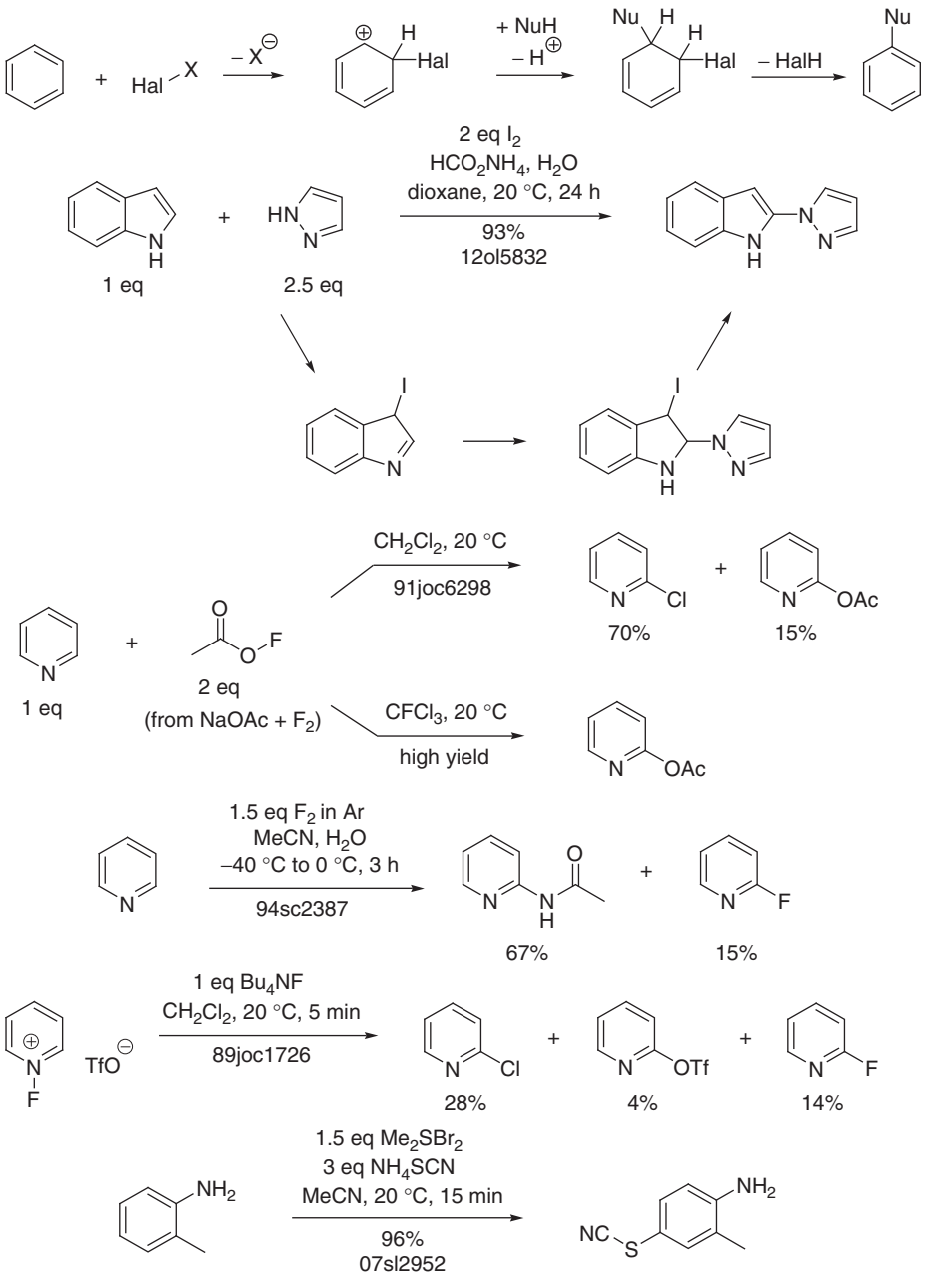
Scheme 5.2 Halogenation with mixed halogens [1–3].



Scheme 5.3 Halogenations with non-halogens [5–8].

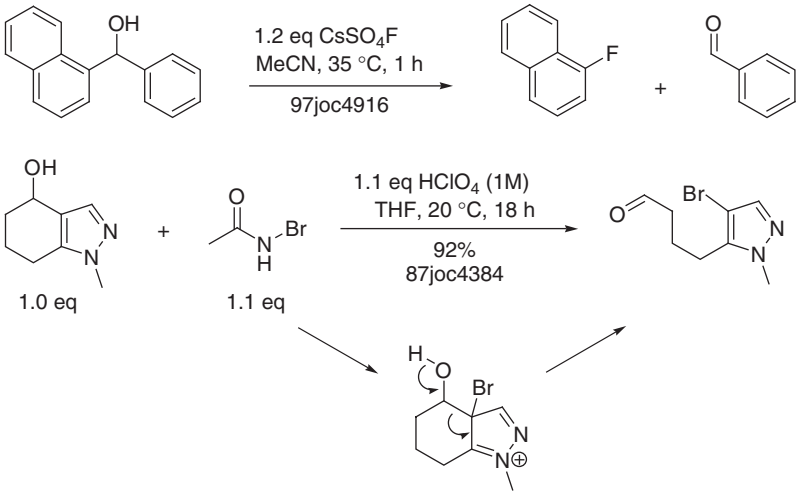
N-halosuccinimides, for instance, often yield *N*-arylsuccinimides instead of aryl halides. Similarly, sulfonyl halides do not only halogenate but often also act as sulfonylating reagents (Scheme 5.3). *N*-Halosuccinimides are unsuitable for the halogenation of unreactive substrates because *N*-halosuccinimides readily isomerize into unreactive 3-halosuccinimides [4]. A better alternative is trichloroisocyanuric acid.

Aromatic halogenations in the presence of nucleophiles can lead to arylation of the latter. This often happens during fluorinations, but can also occur with brominations or iodinations (Scheme 5.4). Alternatively, a nucleophile present in the reaction mixture may be oxidized by the halogenating reagent, and be converted into a competing electrophile. Such side reactions can be avoided only by excluding other nucleophiles from the reaction mixture. During fluorinations, though, even dichloromethane may act as chloride donor.



Scheme 5.4 Competition of other nucleophiles with halides during halogenations [9–13]. Further examples: [14].

Instead of hydrogen, other substituents may be replaced during aromatic electrophilic halogenations. Particularly sensitive are tertiary and secondary alkyl groups, as well as alkyl groups that readily form a stable carbocation, such as 1-hydroxyalkyl or benzyl groups (Scheme 5.5).



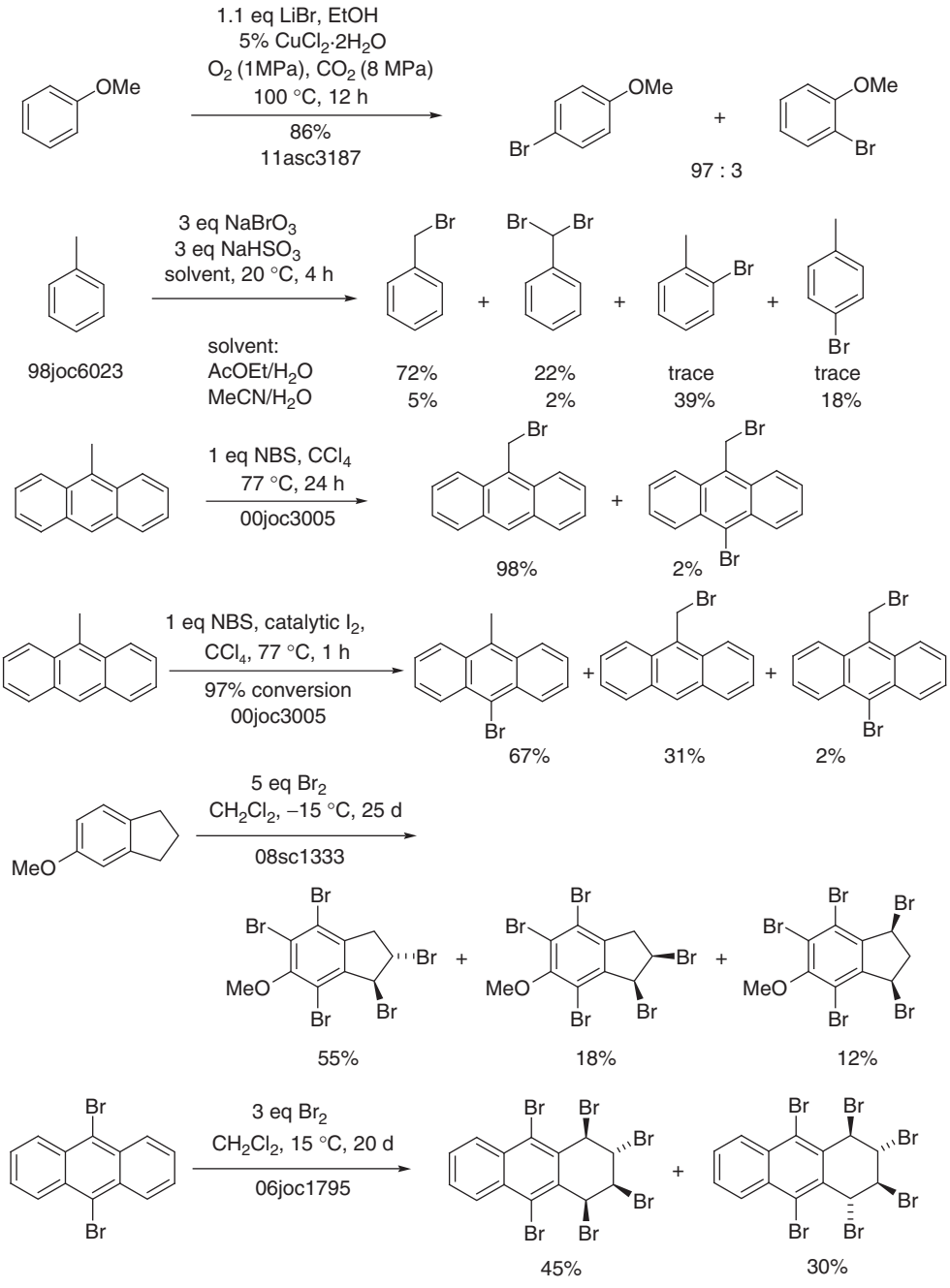
Scheme 5.5 Electrophilic substitution of hydroxyalkyl groups [15, 16].

Aromatic iodinations can be accomplished by treatment of arenes with potassium iodide and oxone [17]. An excess of oxone may, however, convert aryl iodides into iodonium salts, which are strong oxidants, and can bring about the Hofmann rearrangement of amides [18], aromatic hydroxylations, biaryl formation [19], or other oxidations.

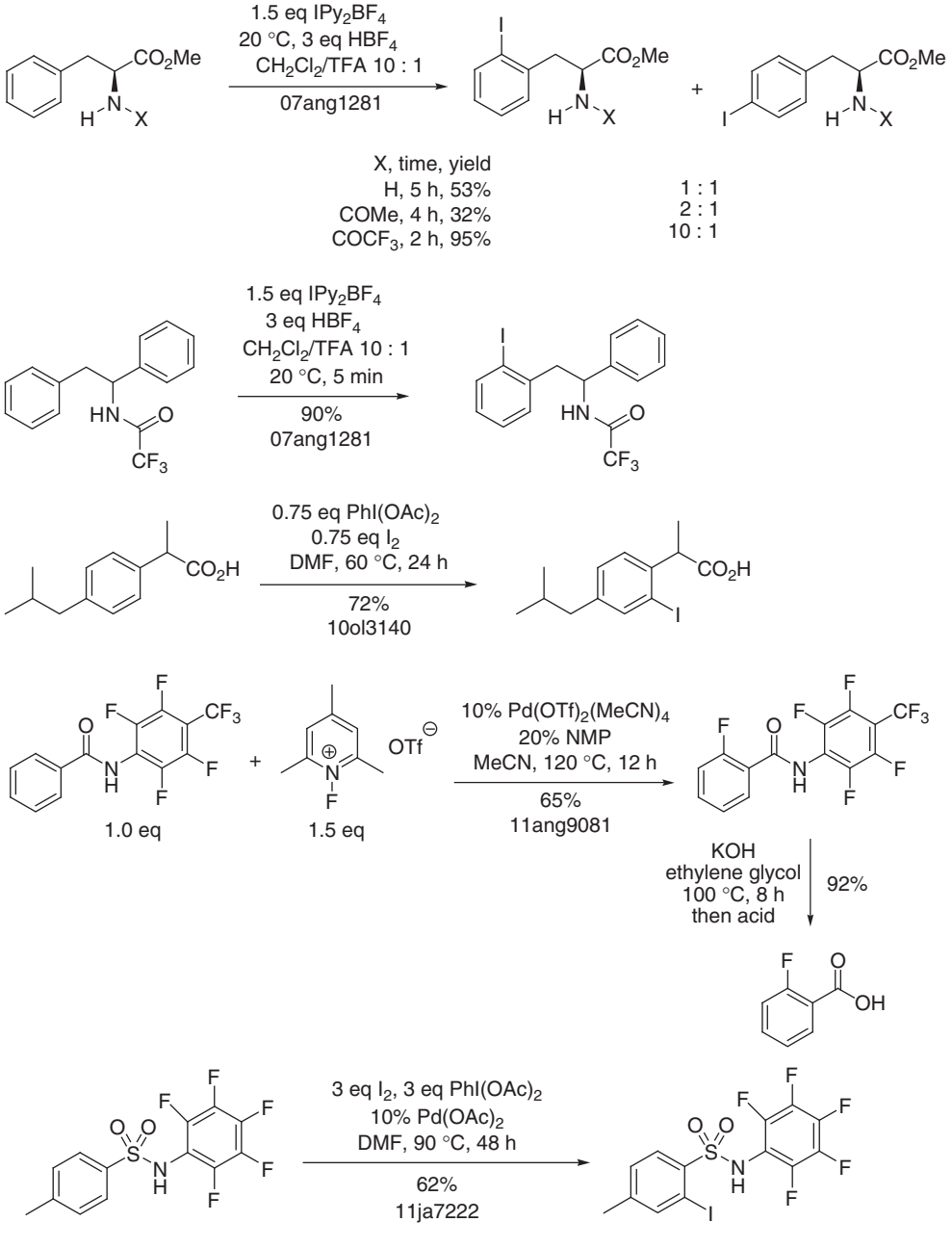
5.3 Regioselectivity

Electrophilic aromatic halogenations show similar regioselectivities as other electrophilic aromatic substitutions, but mixtures of regioisomers are often obtained (Scheme 5.6). Halogenations via radicals are even less regioselective than ionic halogenations, and can also cause aliphatic halogenation. Small amounts of iodine or the hydrogen halide formed during the reaction can modify the regioselectivity of halogenations, and it will therefore usually be easier to optimize the regioselectivity of aromatic halogenations if the reaction mixture is buffered (e.g., by using an acid or a base as solvent), to keep the proton concentration approximately constant throughout the reaction.

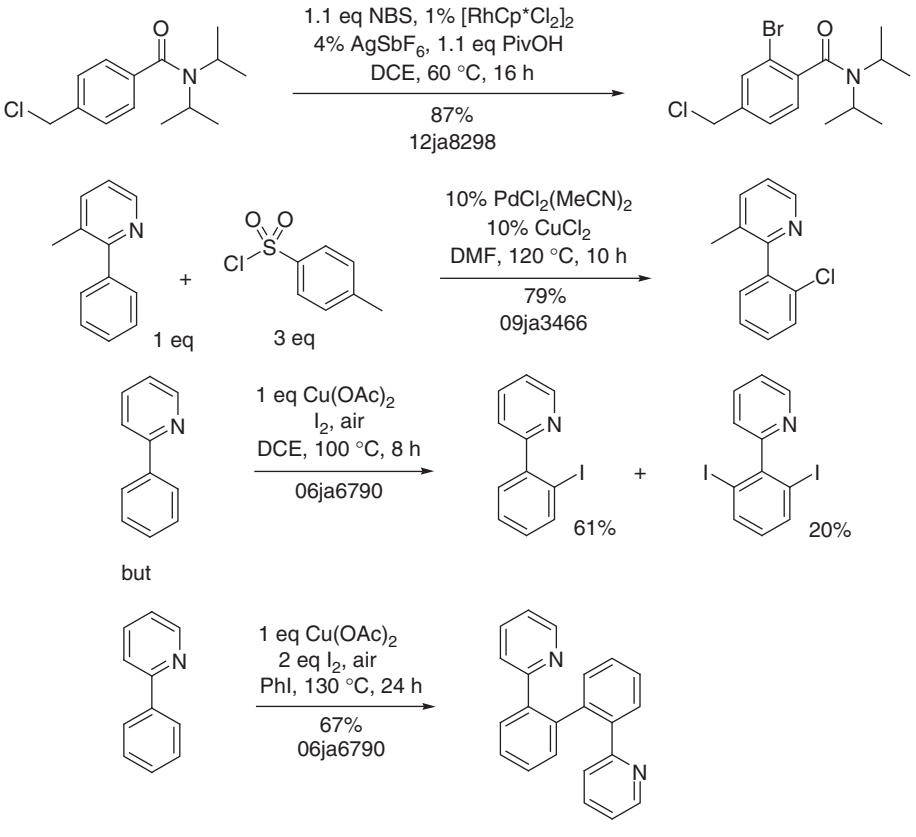
High regioselectivities can sometimes be attained by intermediate chelate formation, or by intramolecular transfer of Hal^+ (Scheme 5.7). In most reported examples, the halogenation is directed into the ortho position of phenyl groups.



Scheme 5.6 Regioselectivity of brominations [20–24].



Scheme 5.7 Directed regioselective halogenations [25–31]. Further examples: [32].

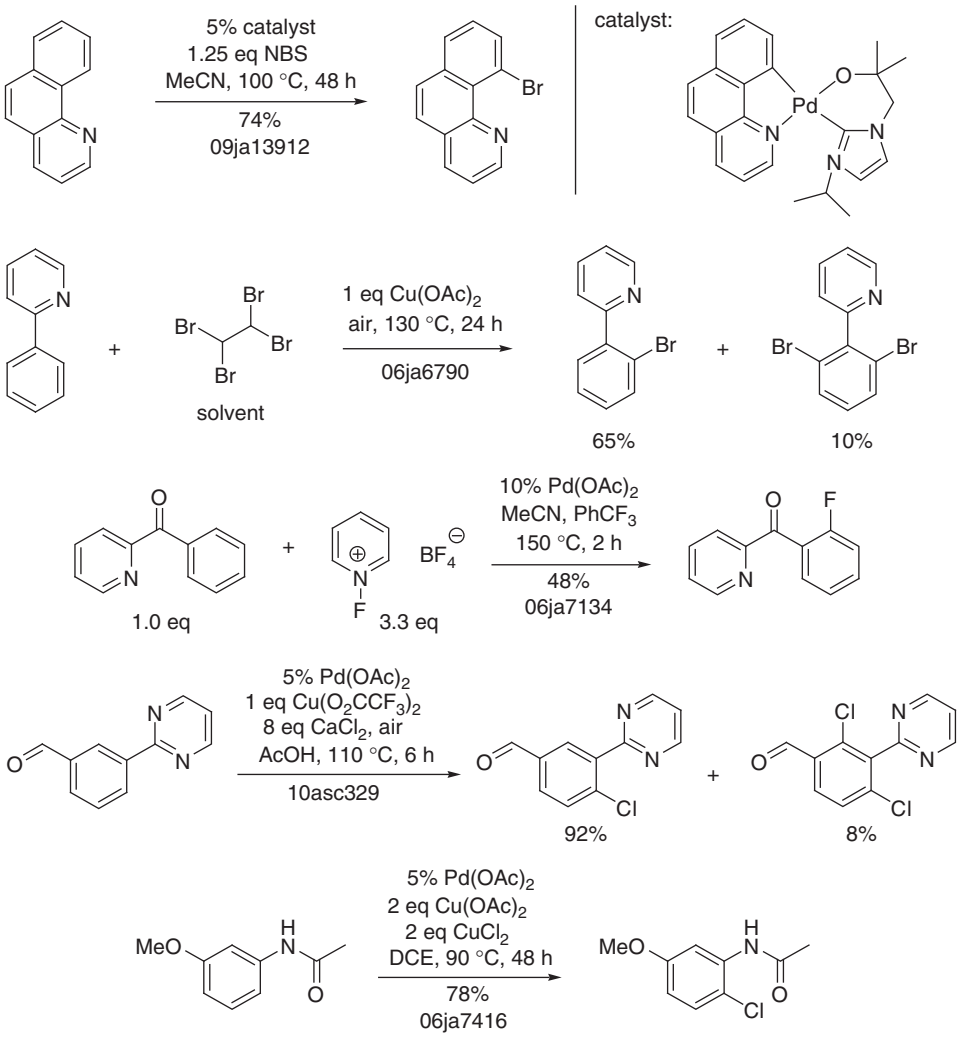


Scheme 5.7 (*Continued*)

5.4 Catalysis

Aromatic halogenations can be catalyzed by enhancing the electrophilicity of the halogenating reagent (usually with acids), or by enhancing the nucleophilicity of the arene (often by bases or by metallation). Examples of transition-metal catalysis have been reported in which aromatic metallation occurs before halogenation (Scheme 5.8). An alternative mechanism is single-electron transfer from the arene to a metal cation, followed by addition of the halide to the arene, oxidation, and deprotonation.

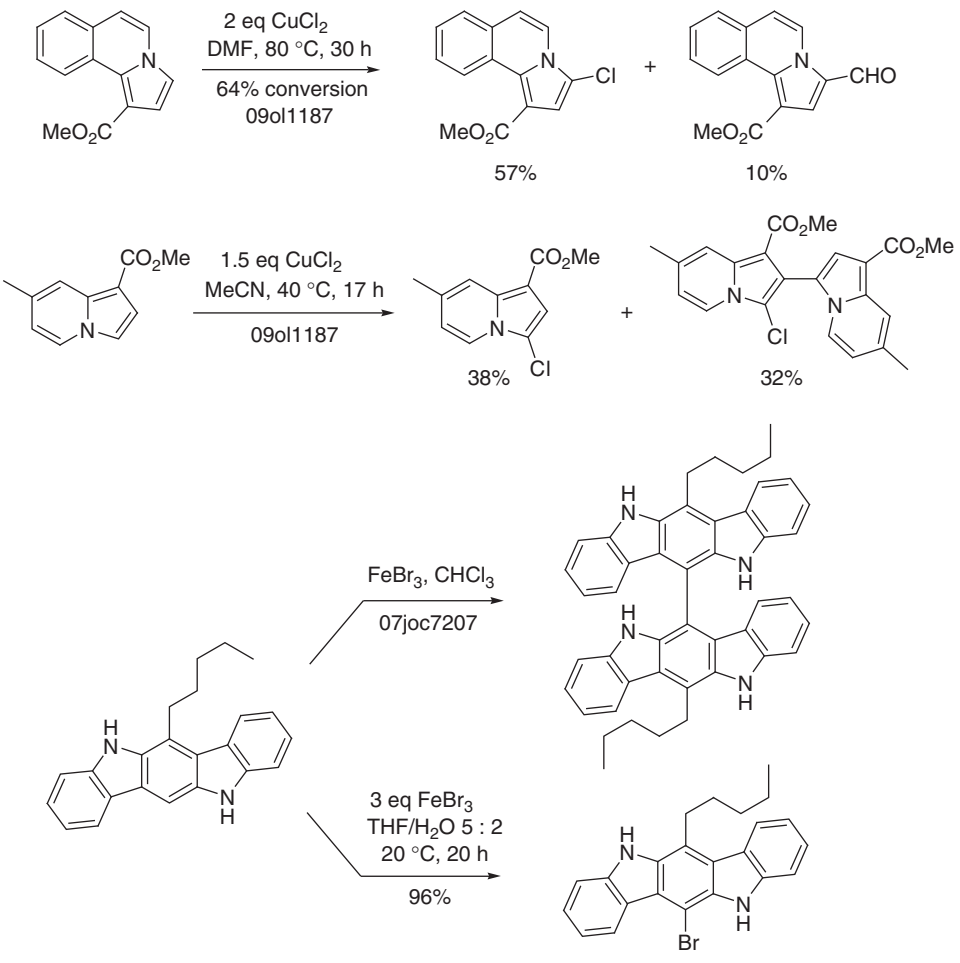
Halogenations in the presence of transition metals can yield numerous unexpected products. Common side reactions include oxidative dimerization of the arene [14], hydroxylation, and various functional group transformations. If reactive solvents are used, such as dimethyl sulfoxide (DMSO) or *N*,*N*-dimethylformamide (DMF), strong Lewis acids can cause still further unwanted transformations (Scheme 5.9).



Scheme 5.8 Catalyzed aromatic electrophilic halogenations [31, 33–36]. Further examples and mechanistic studies: [37–40].

5.5 Fluorinations

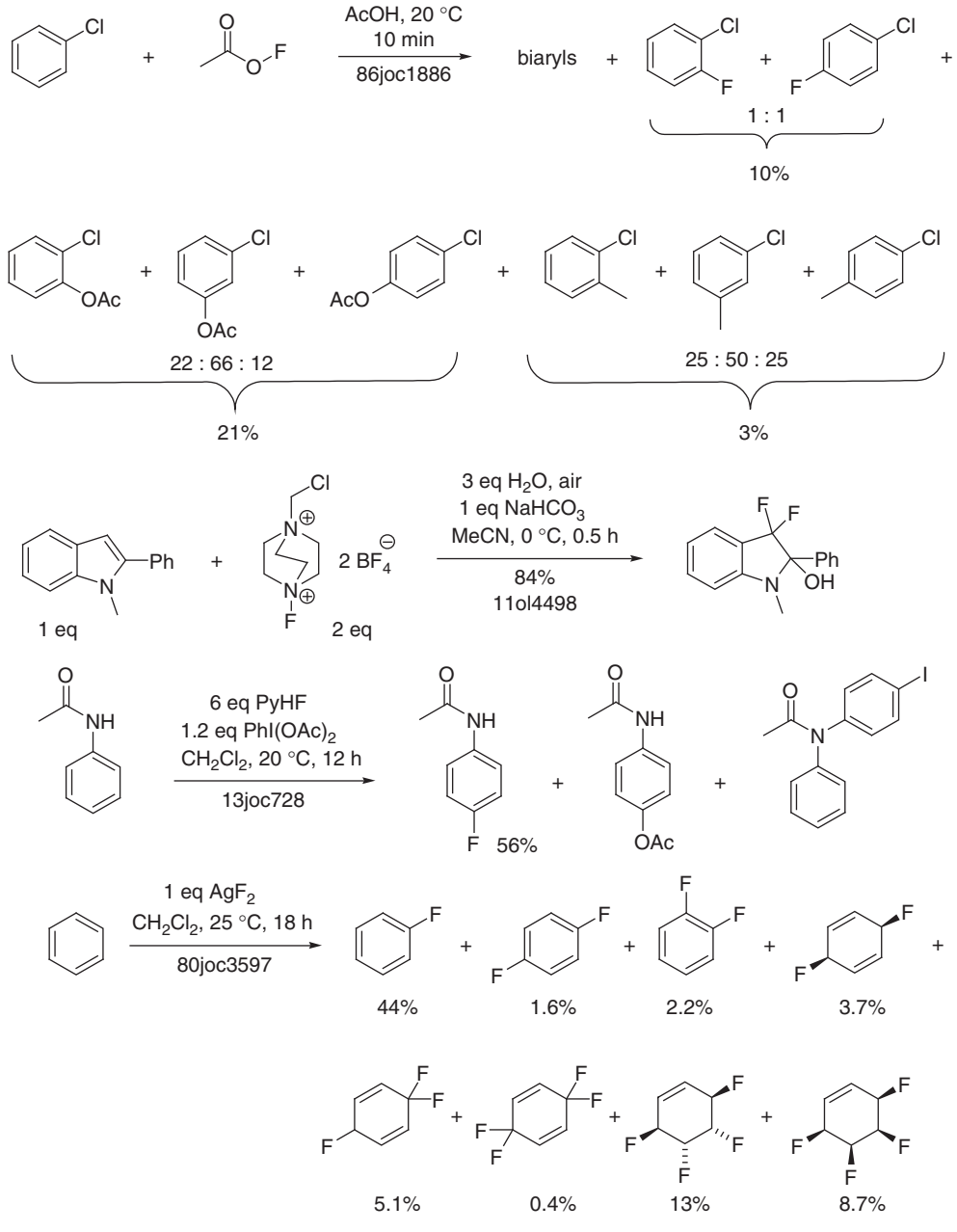
The high reactivity of elemental fluorine, the exothermicity of C–F bond formation, the basicity of fluoride, and other properties of fluorine complicate fluorinations. Direct electrophilic fluorination with F_2/N_2 mixtures is possible, but rarely used because of its low selectivity. Other fluorinating reagents have been developed that are easier to handle and enable more selective fluorinations.



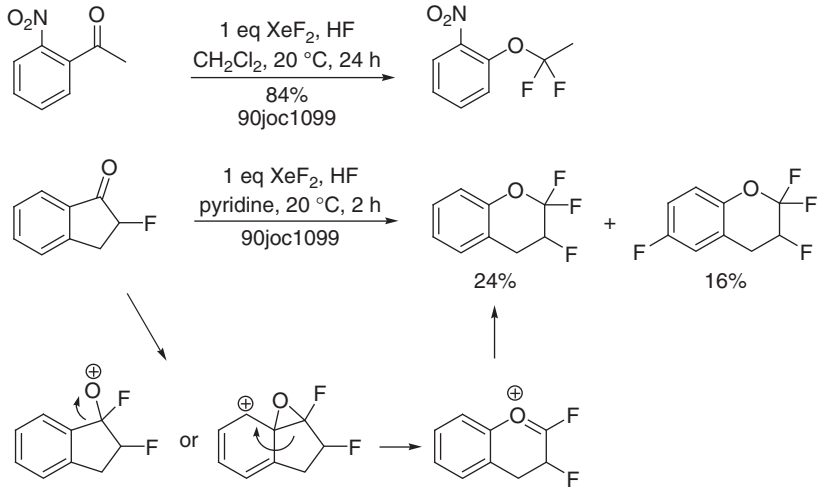
Scheme 5.9 Formylation and arene dimerization as side reactions of halogenations in the presence of transition metals [41, 42].

Typical side reactions of electrophilic aromatic fluorinations include multiple fluorination, dearomatization [43], substitution of other halogens or hydroxyl groups by fluorine, and reactions of the substrate with other nucleophiles or with the solvent (e.g., hydroxylation or acetoxylation; see Scheme 5.4). Treatment of arenes with synthetic equivalents of F^+ in the presence of other nucleophiles can yield little fluoroarene and a lot of arylated nucleophile (see, e.g., [44] and Scheme 5.10). Electrophilic fluorinations usually require the absence of oxidizable solvents and nucleophiles. Most potential intermediates X–F will not fluorinate, because fluoride is usually the better leaving group.

The reaction of strong fluorinating reagents with acetophenones can bring about deacylation and the formation of fluorinated arylethers (Scheme 5.11). Sulfur fluorides will usually convert acetophenones into 1,1-difluoroethylbenzenes.

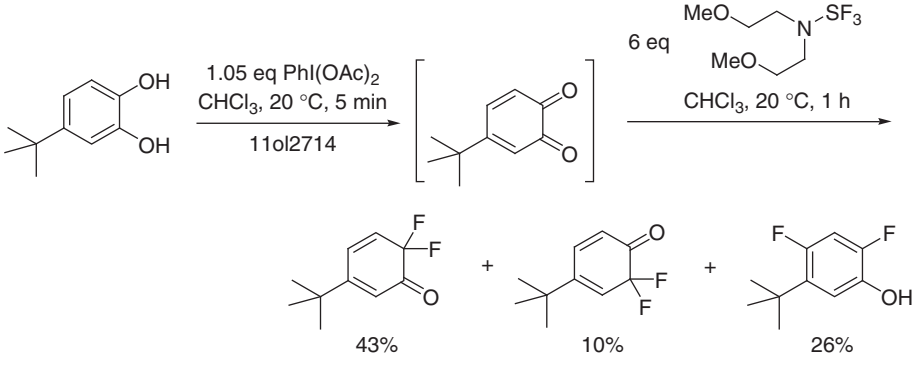


Scheme 5.10 Electrophilic fluorinations [43, 45–47]. Further examples: [48].



Scheme 5.11 Reaction of acetophenones with XeF_2 [49].

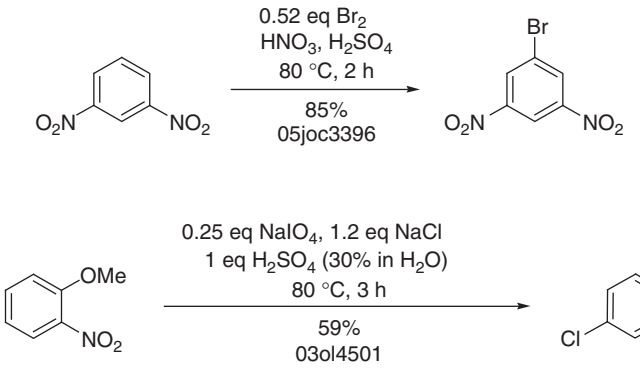
Sulfur fluorides (SF_4 or R_2NSF_3) are the reagents of choice to convert carbonyl groups into geminal difluorides. These reagents are not well suited for electrophilic aromatic fluorinations, but may do so anyway in the case of catechols (Scheme 5.12). Polyhydroxybenzenes, such as catechol, resorcinol (1,3-dihydroxybenzene), or phloroglucinol (1,3,5-trihydroxybenzene), can behave as ketones and thus undergo oxygen–fluorine exchange upon treatment with sulfur fluorides.



Scheme 5.12 Fluorination of catechols [50].

5.6 Electron-Deficient Arenes

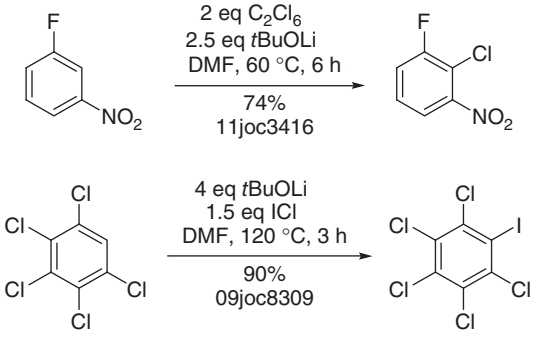
Electron-deficient benzenes can often be halogenated cleanly, as long as they do not contain sensitive functional groups (Scheme 5.13). Strong mineral acids (H_2SO_4



Scheme 5.13 Halogenation of electron-deficient arenes [51, 52]. Further examples: [53].

or HNO_3) are best suited as solvents, and the reactivity of the halogenating reagent may be further enhanced by aluminum halides or other Lewis acids.

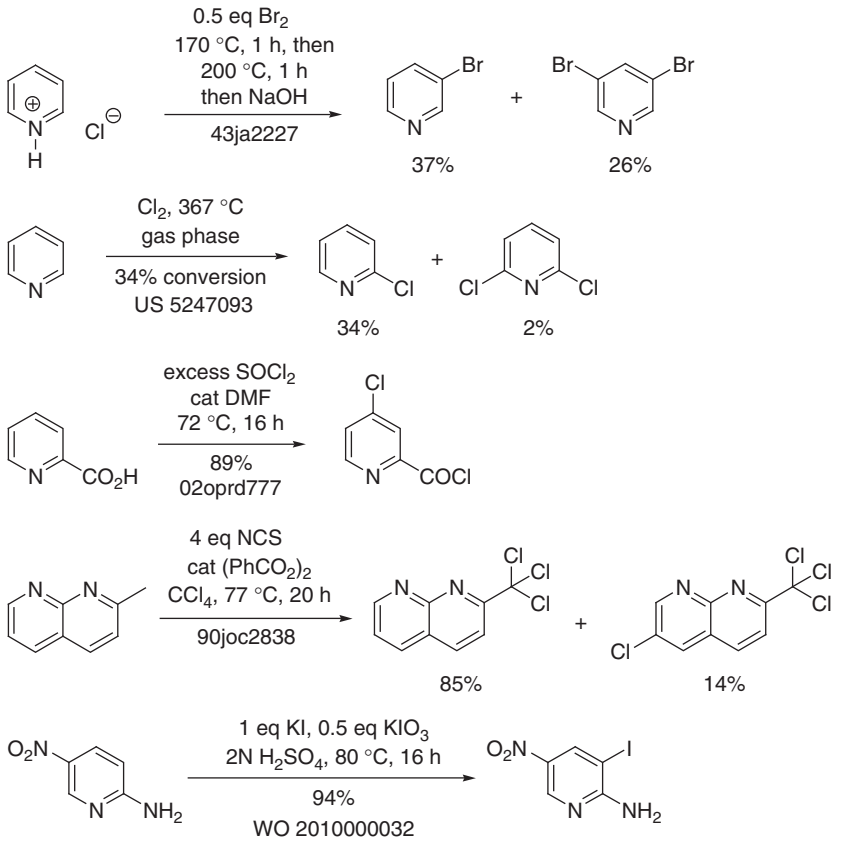
Polyhaloarenes or other acidic arenes can be halogenated via *in situ* metallation by strong bases (Scheme 5.14). A requirement for the base is that it should be unreactive toward the halogenating reagent, and only few bases fulfill this requirement. Tertiary alcoholates seem to be well suited, but one must be cautious, nevertheless, because mixtures of strong bases and electrophiles can decompose violently. On a larger scale, such reactions should be conducted in a dose-controlled manner, that is, by adding either the base or the halogenating reagent slowly, as the reaction proceeds.



Scheme 5.14 Halogenation of C–H acidic arenes by *in situ* metallation [54, 55].

5.6.1 Pyridines

Pyridine is as electron-deficient as nitrobenzene, and is therefore difficult to halogenate. Treatment of pyridine with bromine leads to polymers, and only pyridinium salts can be brominated (under forcing conditions) in fair yield (Scheme 5.15).



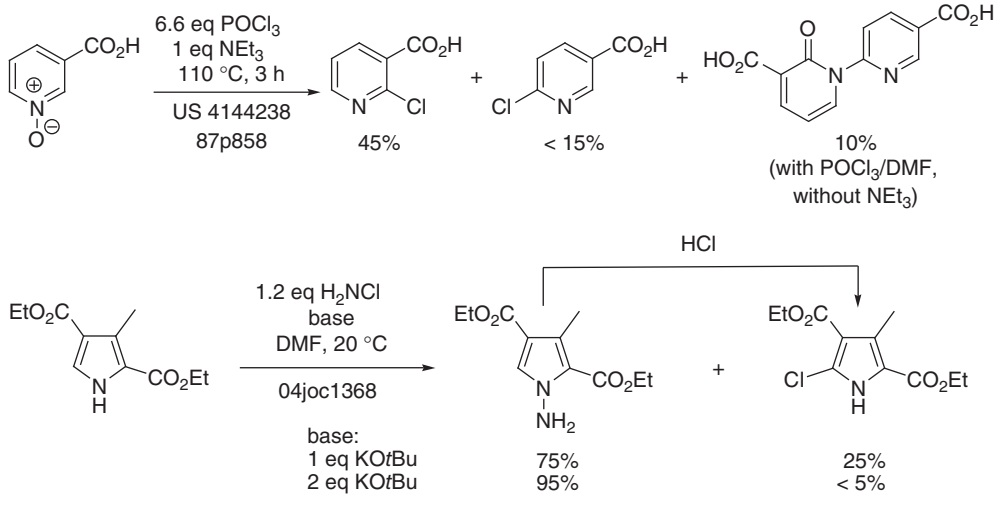
Scheme 5.15 Halogenation of pyridines [56–60]. Further examples: [61].

Lewis acid ''catalysis'' requires an excess of Lewis acid because the pyridine will neutralize one equivalent of the acid. The chlorination of pyridine is best accomplished thermally or photochemically in the gas phase [56].

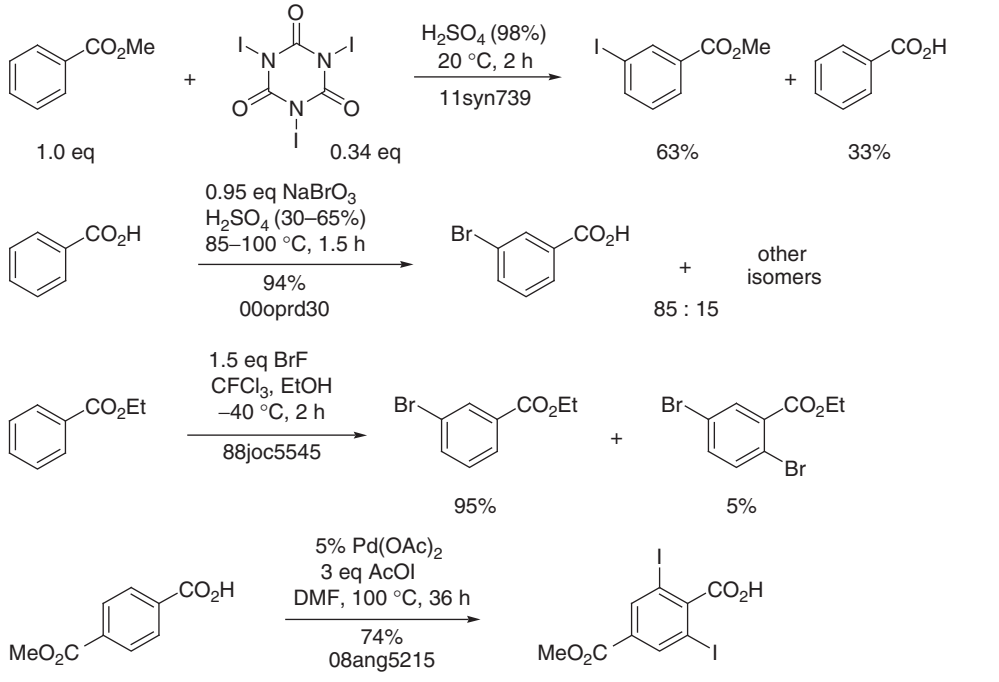
The reactivity of pyridines can be enhanced by conversion to the *N*-oxides. By treatment with $POCl_3$ or phosgene, pyridine *N*-oxides are converted to 2-chloropyridines in high yield. Similarly, *N*-aminopyrroles are converted to 2-chloropyrroles by treatment with HCl (Scheme 5.16).

5.6.2 Benzoic Acid Derivatives

Benzoic acid derivatives are often halogenated with poor or unpredictable regioselectivity. After an initial halogenation of position 3 (meta), the second halogenation usually occurs at position 6 (ortho) (Scheme 5.17). Large amounts of Lewis acids may be required to achieve high yields [65]. Carbonyl groups are usually meta-directing, but can also be ortho-directing by chelate formation or intramolecular



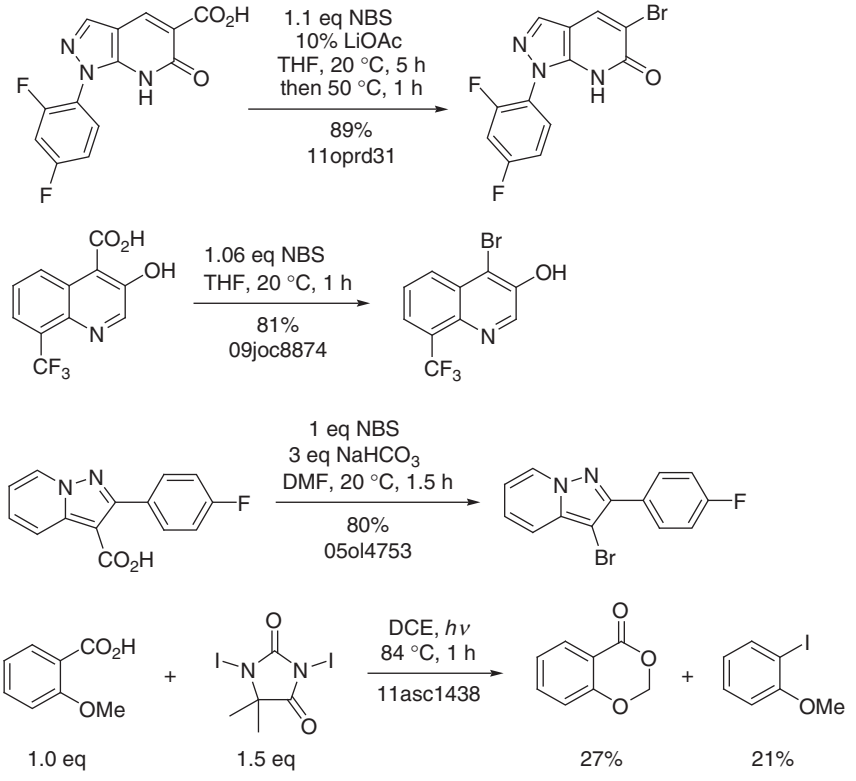
Scheme 5.16 Chlorination of pyridine *N*-oxides and pyrroles [62–64].



Scheme 5.17 Halogenation of benzoic acids and benzoates [66–69].

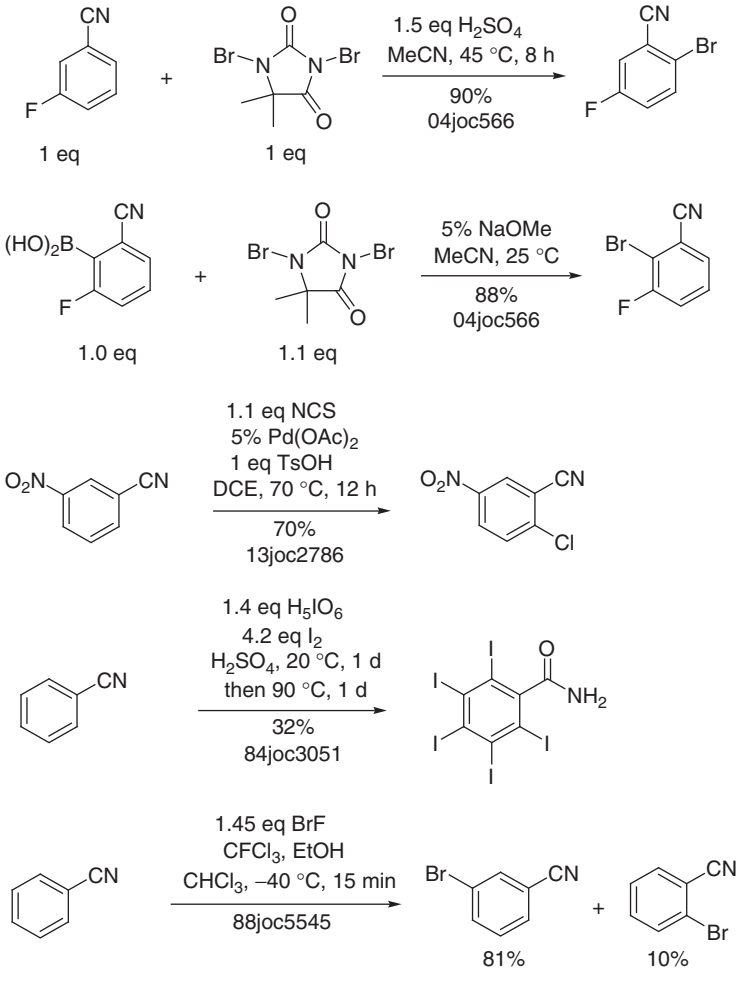
Hal^+ transfer. In the presence of strong acids, benzoyl cations may be formed that are strongly deactivated and difficult to halogenate. Moreover, esters, amides, or nitriles may undergo hydrolysis or alcoholysis upon treatment with strong acids.

One further problem of the halogenation of benzoic acids is their propensity to decarboxylate, in particular in the presence of transition metals [70–73]. Decarboxylative halogenation (Hunsdiecker reaction) usually occurs upon treating silver salts of benzoic acids with halogens, but may also take place without salt formation and in the absence of silver (Scheme 5.18). Hydroxybenzoic acids, naphthalenecarboxylic acids, cinnamic acids, and many heteroarenecarboxylic acids decarboxylate particularly easily.



Scheme 5.18 Decarboxylative halogenations [74–77].

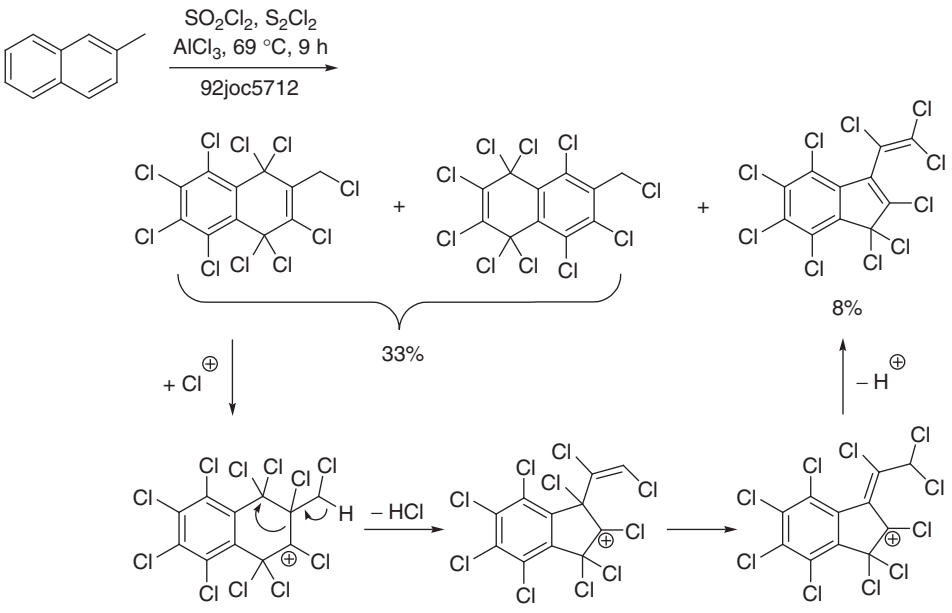
Benzonitriles can also be difficult to halogenate, and mixtures of meta- and ortho-halogenated products often result [65] (Scheme 5.19). Moreover, cyanogroups are readily hydrated or hydrolyzed in the presence of strong acids or bases. The resulting amides will be N-halogenated by most halogenating reagents, and undergo Hofmann rearrangement when treated with bases.



Scheme 5.19 Halogenation of benzonitriles [68, 78–80]. Further examples: [81].

5.7
Electron-Rich Arenes

The halogenation of electron-rich arenes and heteroarenes proceeds readily, and can be difficult to control. Multiple halogenations, arene hydroxylation, formation of quinones or quinone imines (from arylethers, phenols, or anilines), loss of aromaticity, and even C–C bond cleavage can occur if an excess of halogenating reagent, a strong oxidant, or too stringent reaction conditions are used. In fluorinations with F_2, this is often observed but also chlorinations can cause rearrangements and C–C bond cleavage (Scheme 5.20).



Scheme 5.20 Exhaustive chlorination of methylnaphthalene [82].

5.7.1
Phenols and Arylethers

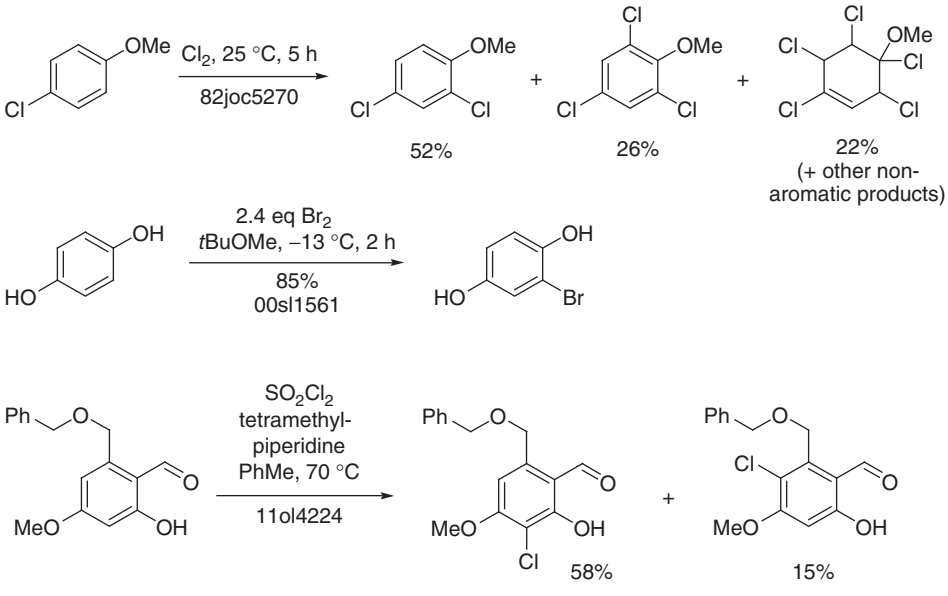
The uncontrolled chlorination of phenol yields polychlorinated cyclohexenones, cyclohexadienones, and benzoquinones. At high temperatures, even chlorinated dibenzodioxines may be formed. Clean monohalogenation of phenols and alkoxybenzenes requires low reaction temperatures and a slight excess of halogenating agent only. Scavengers such as amines or thioethers may be used to diminish the reactivity of the halogenating reagent and improve the selectivity. Under carefully controlled conditions, even hydroquinones can be monohalogenated without significant quinone formation (Scheme 5.21).

Alkylphenols can be readily dealkylated during halogenations if the reaction mixture is not buffered (Scheme 5.22). Similar dealkylations are also frequently observed with other electron-rich alkylarenes (see, e.g., Scheme 5.5). In the absence of bases, halogenations with halogens will generate hydrogen halides, which can catalyze numerous unwanted transformations.

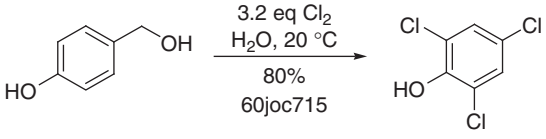
During halogenations of 2-aryl or 2-heteroarylphenols, cyclization to benzofurans may occur (Scheme 5.23).

5.7.2
Anilines

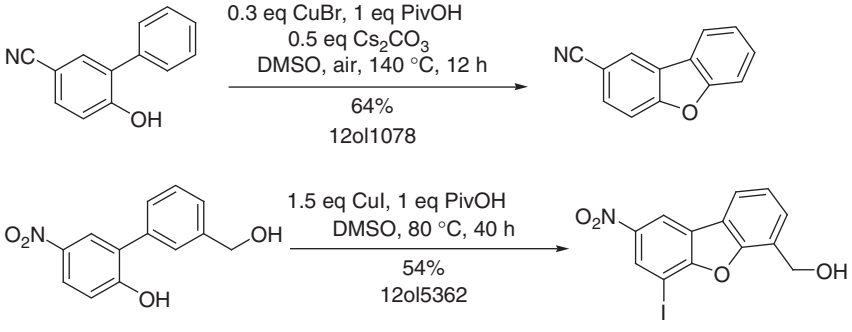
Under basic conditions, anilines are readily halogenated, but may also be oxidized (e.g., to quinones) and polymerized. Better yields are often obtained under acidic



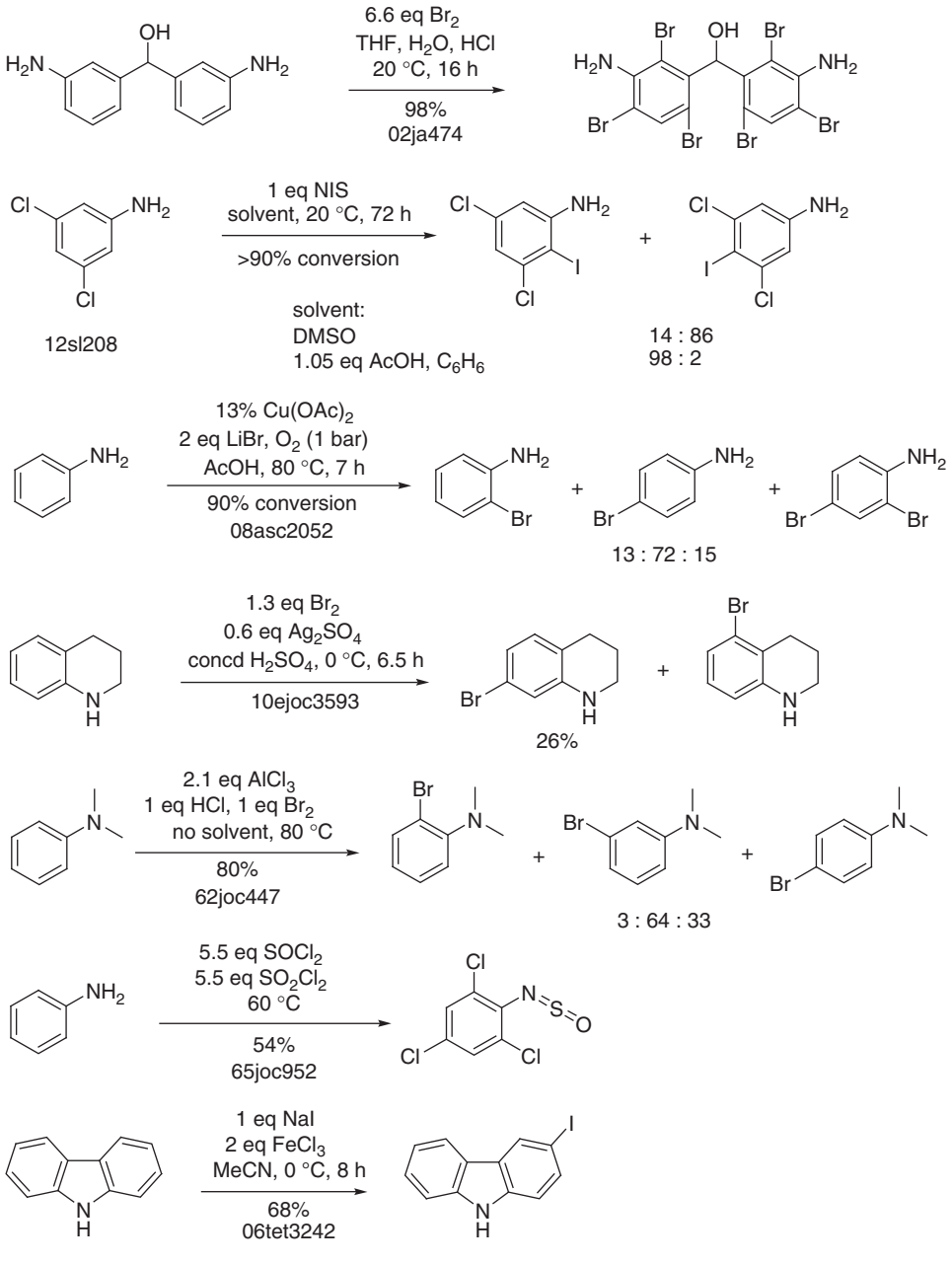
Scheme 5.21 Halogenation of phenols and arylethers [83–85].



Scheme 5.22 Dealkylation of phenols during halogenation [86].



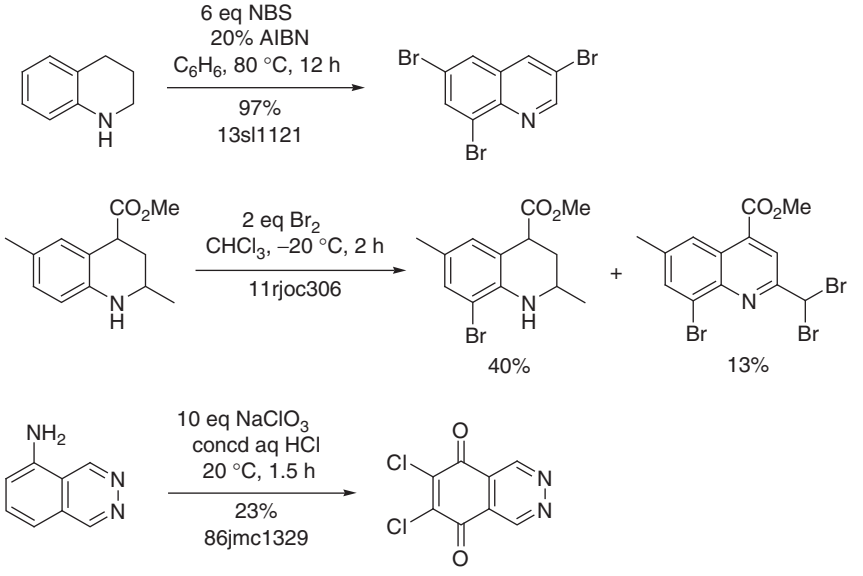
Scheme 5.23 Formation of benzofurans from 2-arylphenols [87, 88].



Scheme 5.24 Halogenation of anilines [91–97].

reaction conditions. Weak acids (e.g., AcOH) lead mostly to ortho/para halogenations, while strong acids (e.g., H_2SO_4 as solvent) can sometimes promote meta halogenations, but only rarely are pure products obtained [89, 90] (Scheme 5.24).

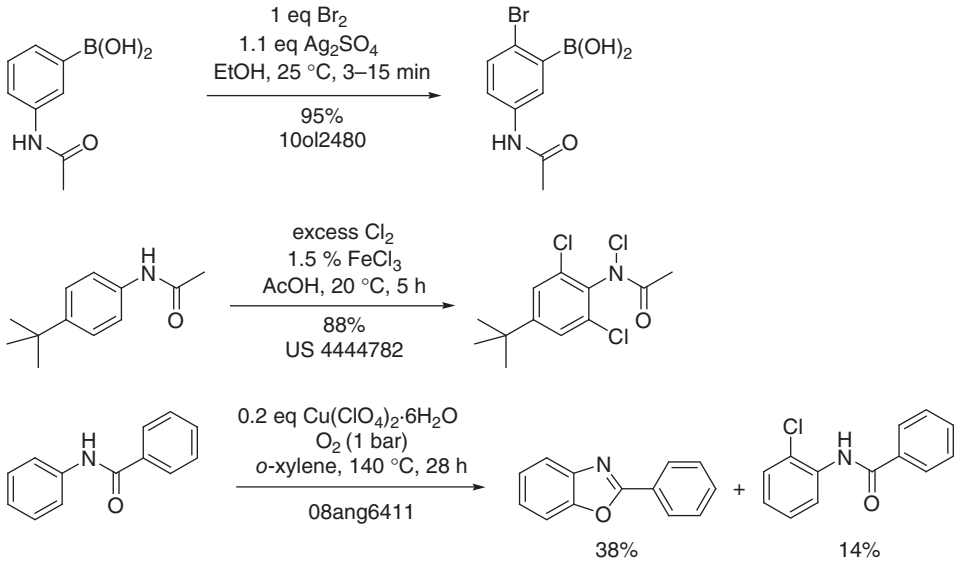
Some typical side reactions of the halogenation of anilines include the halogenation or dehydrogenation of alkyl groups and the oxidation to quinones (Scheme 5.25). One older technical process for the production of benzoquinone is, in fact, the oxidation of aniline [98]. The oxidation of anilines with H_2O_2 in acetic acid can lead to the formation of nitroso and nitrobenzenes [99].



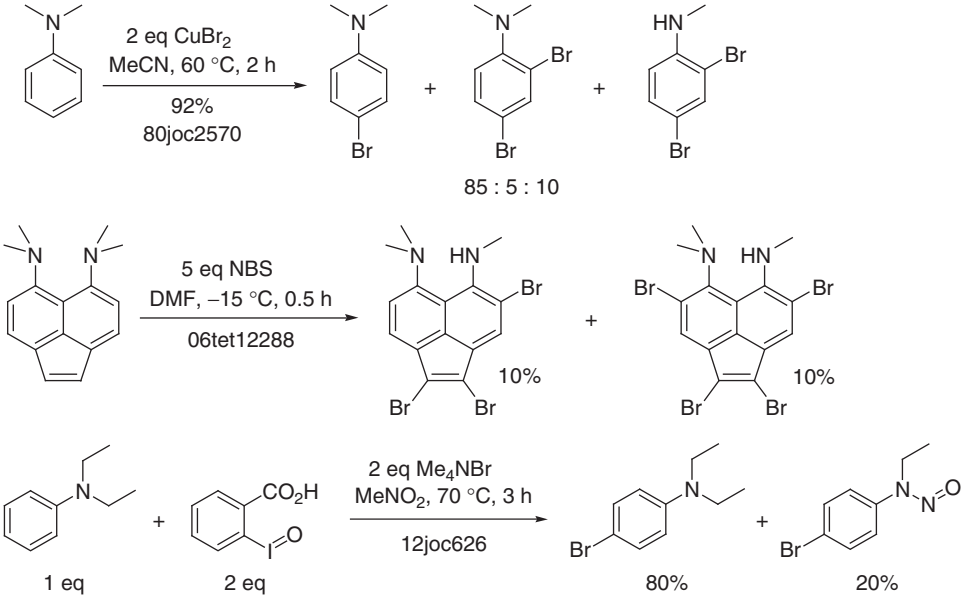
Scheme 5.25 Dehydrogenation and oxidation of anilines [100–102].

N-Acylated anilines are ortho/para halogenated under most reaction conditions. As with unacylated anilines, N-halogenation can readily occur [103], but the products are halogenating reagents themselves and are readily reduced. One further competing process during the halogenation of anilides is the cyclization to benzoxazoles (Scheme 5.26). This cyclization can become dominant for thioamides (cyclization to benzothiazoles) or *N*-aryl amidines (cyclization to benzimidazoles), because thiazoles and imidazoles are quite stable aromatic heteroarenes (more aromatic than oxazoles) that are readily formed.

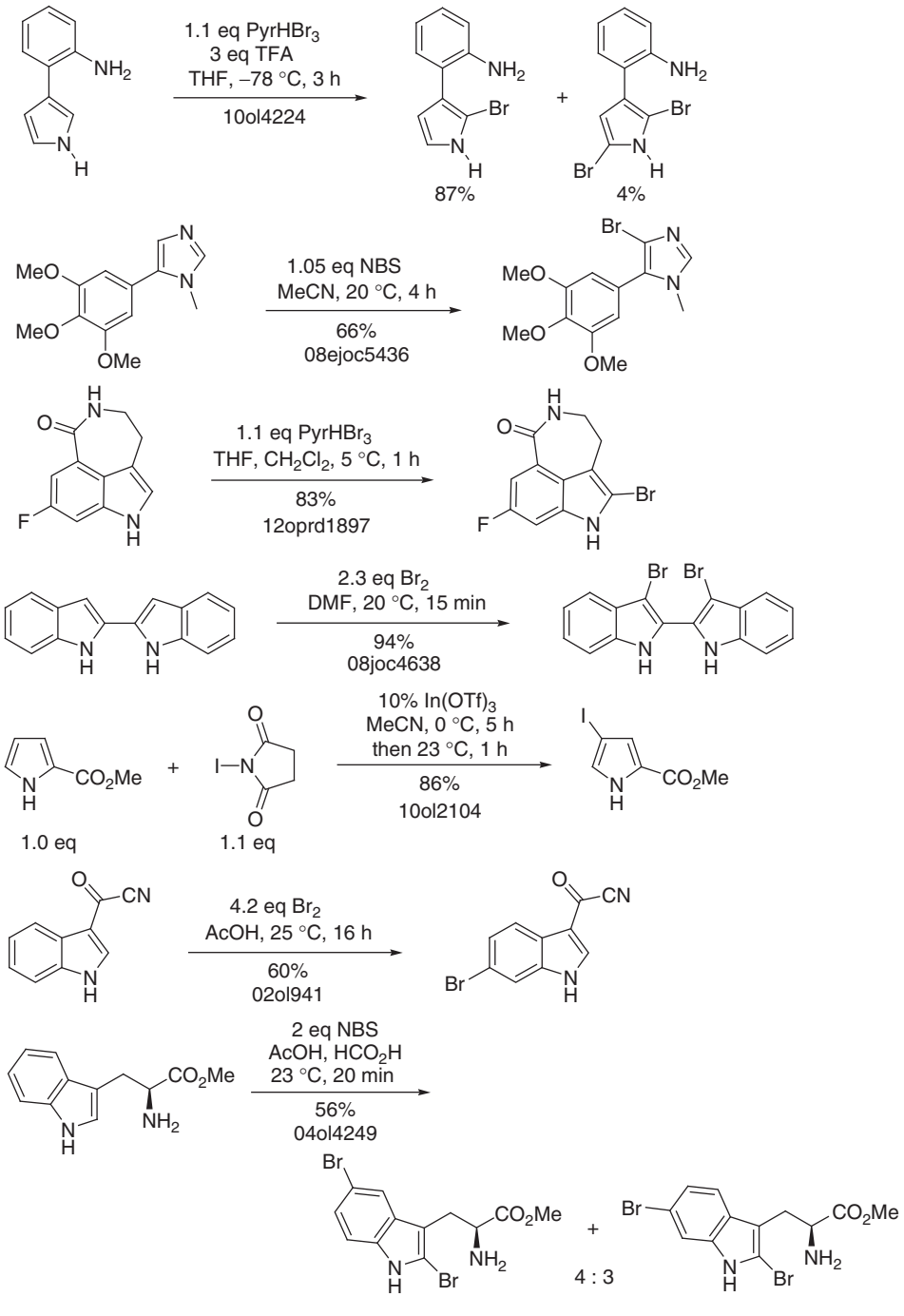
Tertiary amines can be dealkylated by treatment with halogens or cyanogen halides. N-Dealkylation is therefore a potential side reaction during the halogenation of *N*-alkylanilines (Scheme 5.27).



Scheme 5.26 Halogenation of *N*-acylanilines [104–106].



Scheme 5.27 N-Dealkylation of anilines during bromination [107–109].

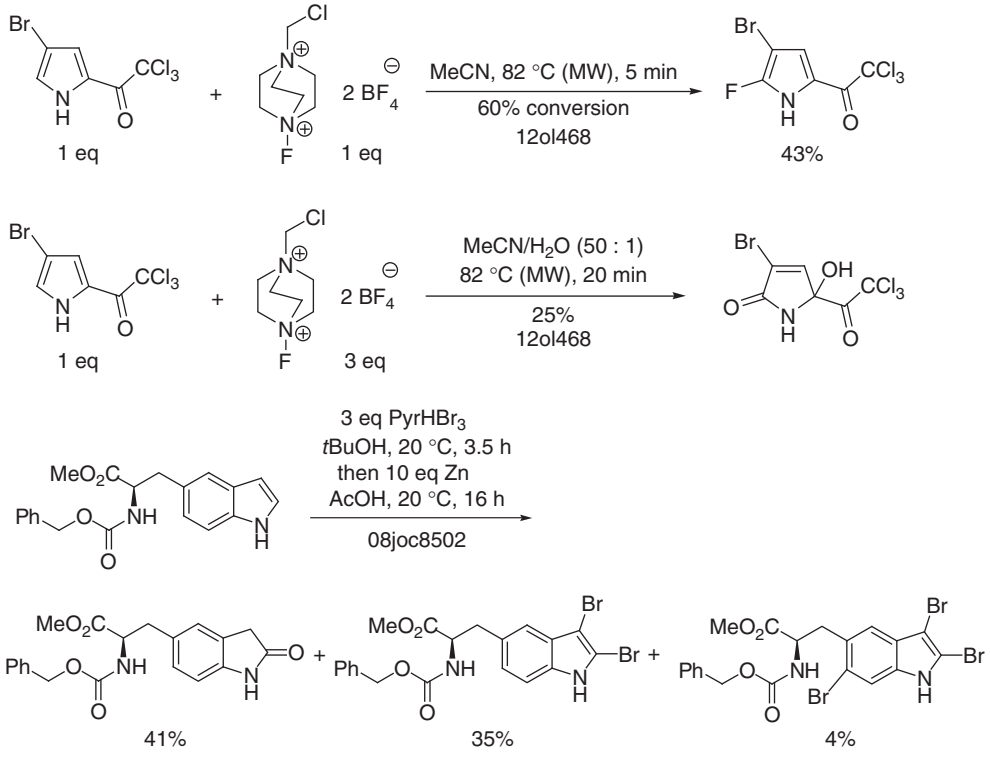


Scheme 5.28 Examples of the halogenation of azoles [110–116]. Further examples: [117].

5.7.3
Azoles

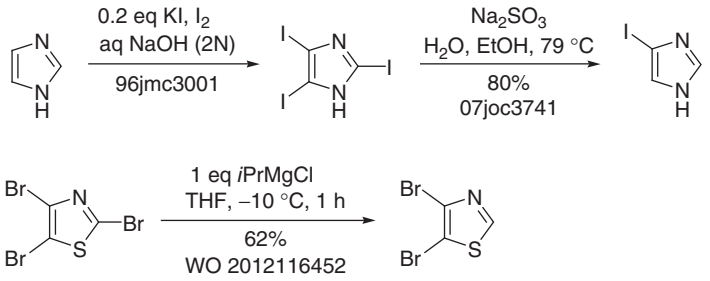
Most azoles can be halogenated cleanly, but some optimization of the reaction conditions may be required. Pyrroles and indoles are highly nucleophilic, and will often be halogenated faster than most other electron-rich arenes (Scheme 5.28).

As in the case of electron-rich arenes, the halogenation of electron-rich azoles can be beset with byproducts caused by intermediate radical formation or other oxidations. Hydroxylation or the formation of lactams is occasionally observed during the halogenation of pyrroles and indoles (Scheme 5.29).

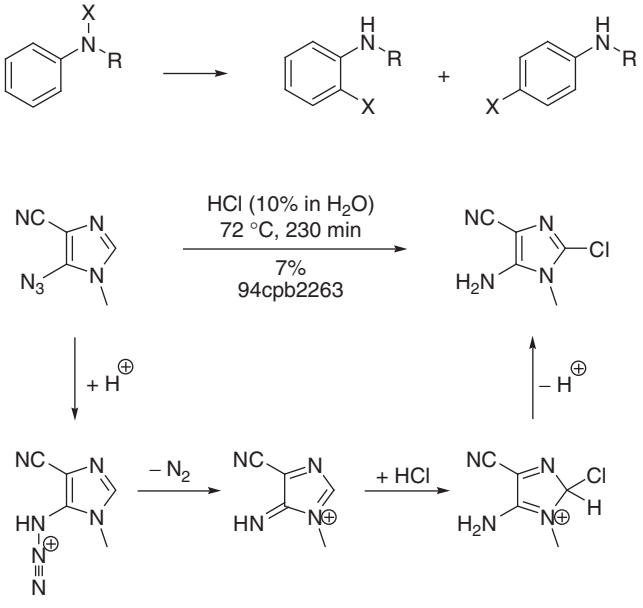


Scheme 5.29 Lactam formation during the halogenation of azoles [118, 119].

The regioselective halogenation of azoles can sometimes be difficult. A possible alternative is the exhaustive halogenation of an azole, followed by selective reductive dehalogenation (Scheme 5.30). The regioselectivity of such dehalogenations, however, is highly substrate-dependent and again difficult to predict.



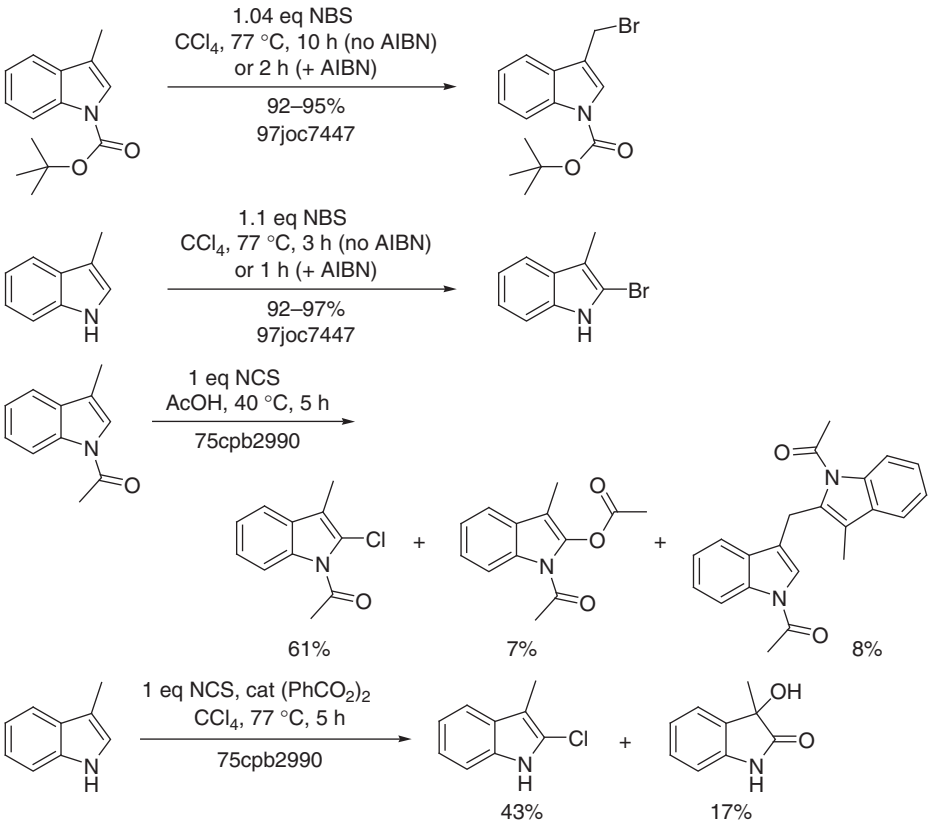
Scheme 5.30 Examples of the dehalogenation of polyhaloimidazoles and -thiazoles [120–122].



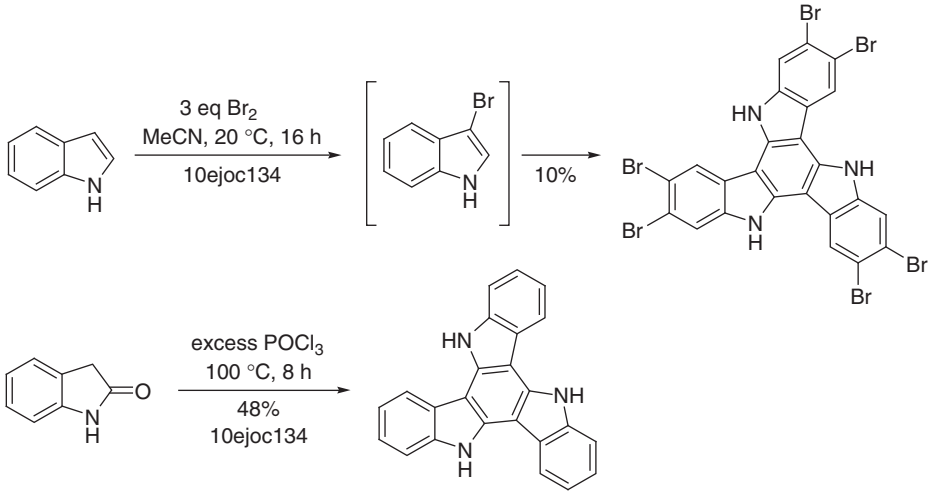
Scheme 5.31 Halogenation of an azidoimidazole [124].

Arenes substituted with heteroatoms bearing a leaving group (aryl azides, *N*-arylhydroxylamines, *N*-halo-*N*-arylamides, *N*-arylhydrazines, etc.) can rearrange to yield disubstituted arenes [123]. Such rearrangements sometimes also occur with azoles and other heteroarenes (Scheme 5.31).

Side-chain halogenation is a further side reaction observed during the halogenation of azoles, which may even occur in the absence of radical starters (Scheme 5.32). Indoles halogenated in positions 2 or 3 are unstable, and sometimes trimerize to benzenes during their formation (Scheme 5.33).



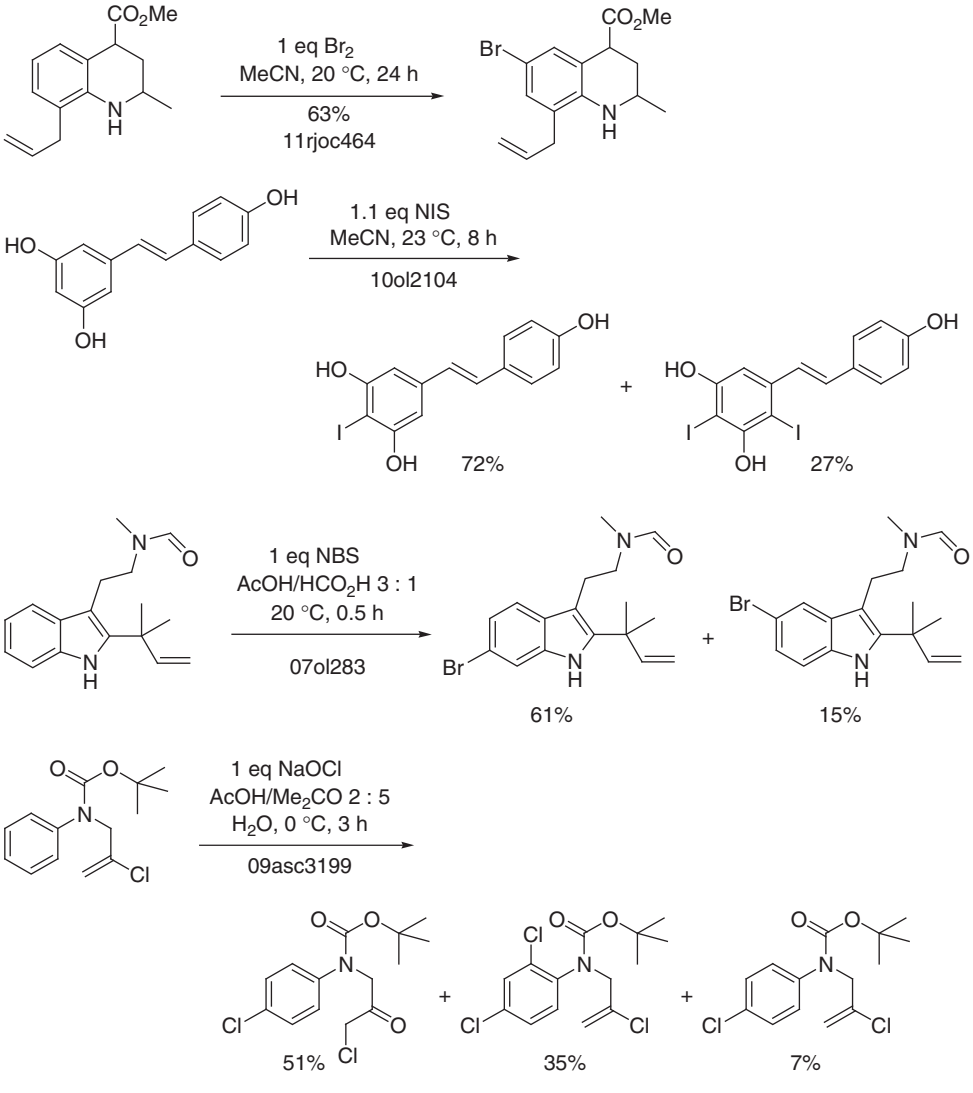
Scheme 5.32 Side reactions during the halogenation of alkylindoles [125, 126].



Scheme 5.33 Trimerization of 2- and 3-haloindoles [127].

5.8
Sensitive Functional Groups

Halogens and most halogenating reagents are strong oxidants. Halogenations are therefore often accompanied by dehydrogenations and radical oligomerizations. Many functional groups react with halogenating reagents, and selective halogenations can require careful control of the reaction conditions. Avoiding an excess of halogenating reagent, adjusting the pH, or adding a scavenging reagent



Scheme 5.34 Aromatic halogenation of olefin-containing arenes [114, 128–130].

to consume the excess halogenating reagent (amines or thioethers) sometimes suffices to achieve highly selective aromatic halogenations.

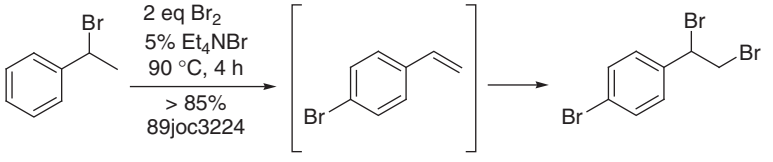
5.8.1 Alkenes

The addition of halogens to alkenes is a fast reaction, and only highly reactive arenes will be halogenated faster than alkenes. A few instances of such reactions have been reported, but yields are mostly low. One exception is iodination: normal alkenes do not react with iodine, so aromatic iodination is possible in the presence of olefins (Scheme 5.34).

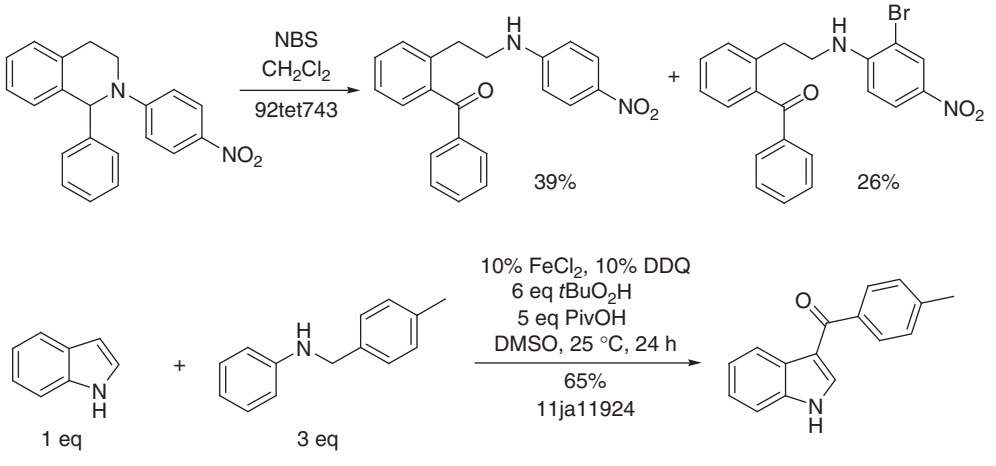
Compounds that undergo β-elimination during halogenations may be transformed into 1,2-dihalides or halohydrins, depending on the halogenating reagent used (Scheme 5.35; see also Scheme 5.6).

5.8.2 Amines

When tertiary amines are treated with halogens, iminium ions are usually formed, which undergo hydrolysis to yield aldehydes or ketones and dealkylated amines



Scheme 5.35 Bromination of a benzyl bromide [131].



Scheme 5.36 Oxidative cleavage of amines [134, 135].

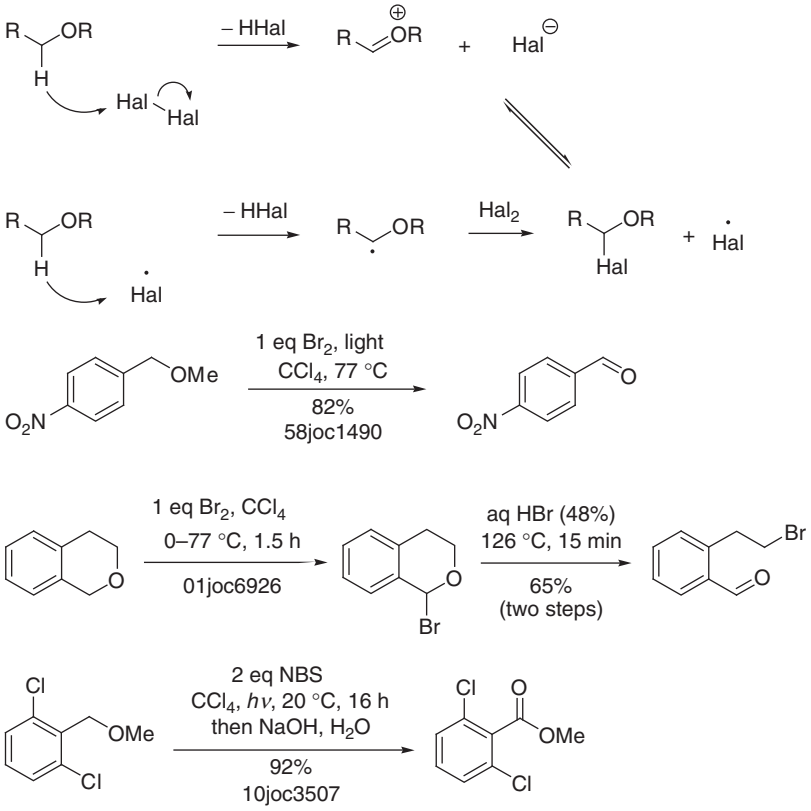
[132, 133]. When amines are dealkylated under oxidative conditions, the removed alkyl groups can be converted into reactive alkylating or acylating reagents. These newly formed reactive intermediates may cause alkylation or acylation of electron-rich arenes (Scheme 5.36).

5.8.3
Ethers

Electron-rich benzylic ethers are sensitive to oxidants, and can be converted to aldehydes or ketones during halogenation reactions. These reactions proceed either via radicals or by hydride abstraction (Scheme 5.37).

5.8.4
Thiols and Thioethers

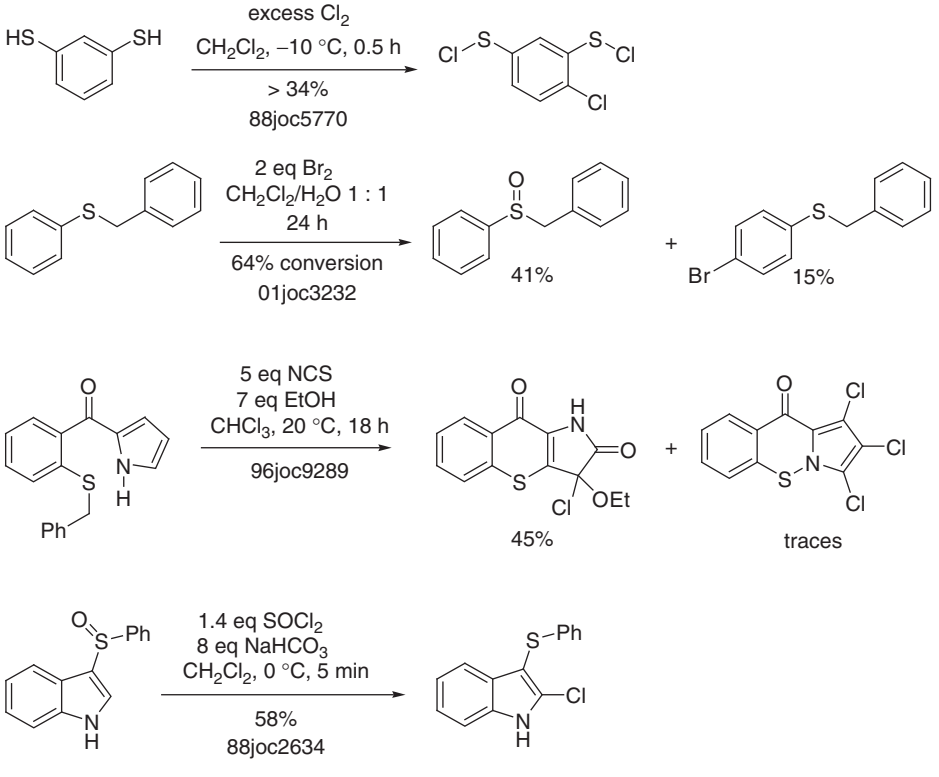
Most thiols are strong reducing reagents and will be oxidized to symmetric disulfides by halogens. A large excess of halogen can lead to the halogenation of



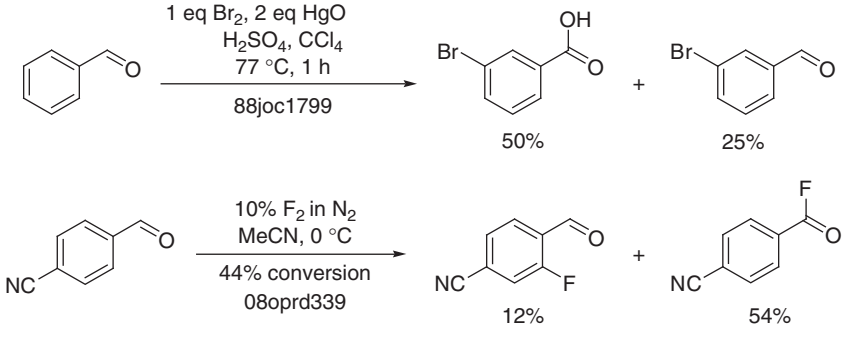
Scheme 5.37 Oxidation of ethers upon treatment with halogenating reagents [136–138]. Further examples: [139].

thiols at sulfur. Both sulfenyl halides and disulfides can react with electron-rich arenes to yield aryl thioethers, in particular when activated by halogenating agents or Lewis acids.

Thioethers will usually be converted to sulfoxides and then to sulfones when treated with a halogenating reagent in the presence of water. This can sometimes be avoided by using acetic acid as solvent, or by avoiding protic solvents altogether.



Scheme 5.38 Halogenation of thiols, thioethers, and sulfoxides [140–143].

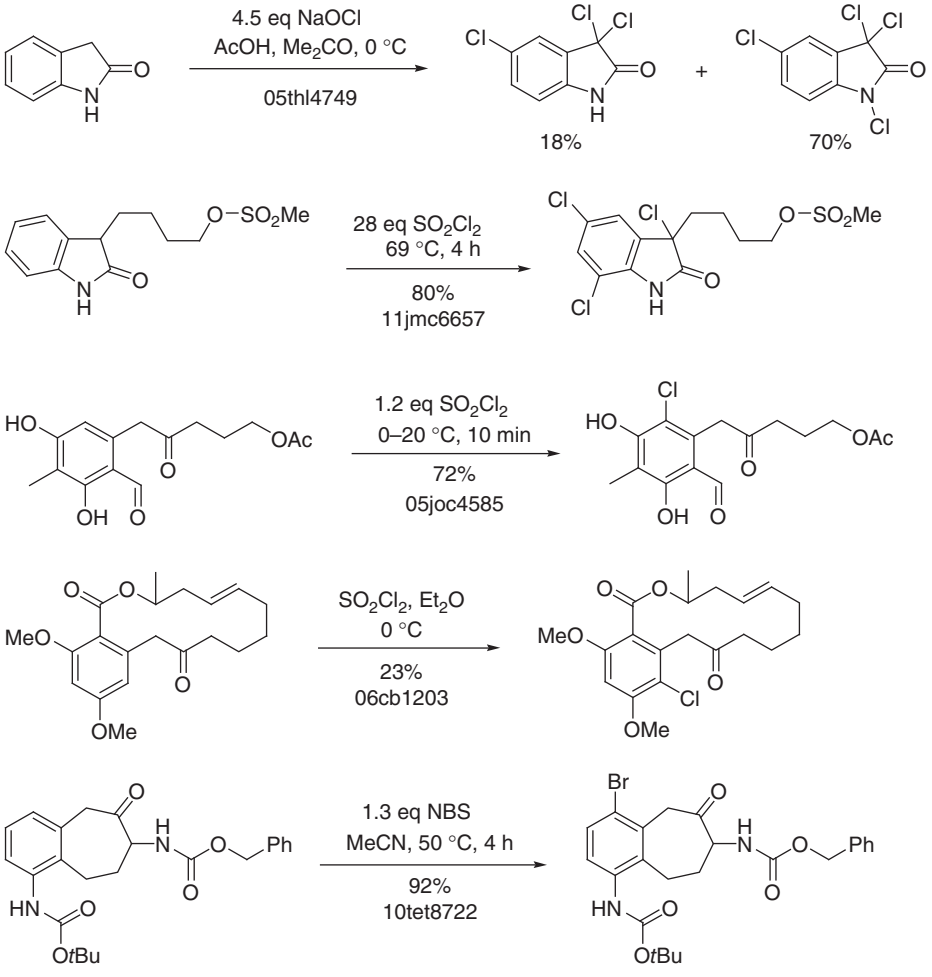


Scheme 5.39 Halogenation of benzaldehydes [144, 145].

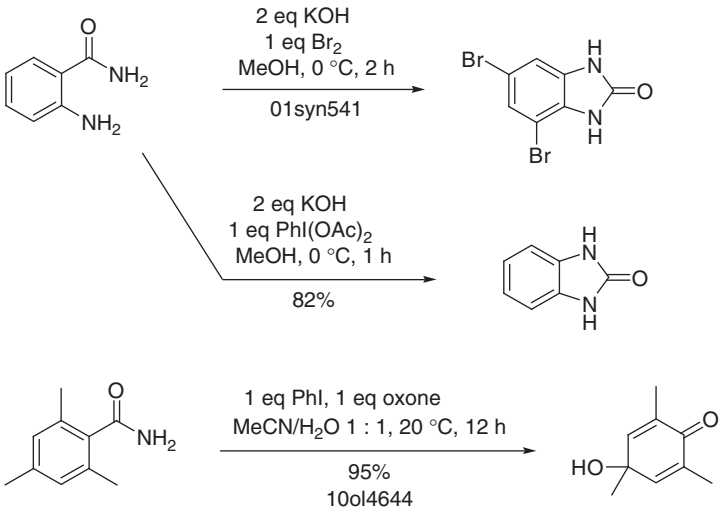
Thioethers and sulfoxides will be attacked by most halogenating reagents to yield electrophilic intermediates that are capable of reacting with various functional groups in unpredictable ways (Scheme 5.38).

5.8.5
Aldehydes, Ketones, and Other C–H Acidic Compounds

Aldehyde-derived acetals, aminals, oximes, hydrazones, and hydrates are potent hydride donors, and can be oxidized by halogenating reagents. Accordingly, the oxidation of aldehydes can sometimes be prevented by excluding water, alcohols, and amines from the reaction mixture. The oxidation of aldehydes is, nevertheless, a common side reaction of halogenations (Scheme 5.39).



Scheme 5.40 Halogenation of C–H acidic ketones and amides [146–150].



Scheme 5.41 Halogenation and oxidation of benzamides [18, 151].

Alkylketones and other C–H acidic compounds are readily halogenated at carbon. In the case of strongly C–H acidic compounds, these reactions are reversible. Electron-rich arenes, such as phenols or acylated anilines, will usually be halogenated faster than ketones (Scheme 5.40).

5.8.6 Amides

Amides are readily N-halogenated. In the case of ammonia-derived amides, the resulting products undergo dehydrohalogenation upon treatment with bases and rearrange to isocyanates (Hofmann rearrangement). With some oxidants, Hofmann rearrangement may even occur in the absence of bases. If an excess of oxidant is used in the presence of water, the intermediate amine may be oxidized further, for instance, to quinones (Scheme 5.41).

References

1. Turner, D.E., O'Malley, R.F., Sardella, D.J., Barinelli, L.S., and Kaul, P. (1994) The reaction of iodine monochloride with polycyclic aromatic compounds: polar and electron transfer pathways. *J. Org. Chem.*, **59**, 7335–7340.
2. Rozen, S. and Zamir, D. (1990) A novel aromatic iodination method using F_2. *J. Org. Chem.*, **55**, 3552–3555.
3. Geib, S., Martens, S.C., Zschieschang, U., Lombeck, F., Wadepohl, H., Klauk, H., and Gade, L.H. (2012) 1,3,6,8-Tetraazapyrenes: synthesis, solid-state structures, and properties as redox-active materials. *J. Org. Chem.*, **77**, 6107–6116.
4. Yamazaki, T., Matoba, K., Imoto, S., and Terashima, M. (1976) Studies on *O*-alkylated imides. II. Some reactions

of *O*-ethyl succinimide and *O*-ethyl 4,4-dimethylglutarimide. *Chem. Pharm. Bull.*, **24**, 3011–3018.

5. Singh, A.P., Lee, K.M., Kim, K., Jun, T., and Churchill, D.G. (2012) Metal-free intermolecular $C_{fur}-N_{succ}$ bond coupling of highly substituted 3-furancarbaldehydes and their use in *meso*-substituted BODIPY synthesis. *Eur. J. Org. Chem.*, **2012**, 931–939.
6. Wu, J., Vetter, W., Gribble, G.W., Schneekloth, J.S., Blank, D.H., and Görls, H. (2002) Structure and synthesis of the natural heptachloro-1′-methyl-1,2′-bipyrrole (Q1). *Angew. Chem. Int. Ed.*, **41**, 1740–1743.
7. Bélanger, P.C., Atkinson, J.G., Rooney, C.S., Britcher, S.F., and Remy, D.C. (1983) Synthesis of 2-, 3-, and 9-substituted 11-oxo-11*H*-pyrrolo [2,1-*b*][3]benzazepines. *J. Org. Chem.*, **48**, 3234–3241.
8. Snégaroff, K., L'Helgoual'ch, J.-M., Bentabed-Ababsa, G., Nguyen, T.T., Chevallier, F., Yonehara, M., Uchiyama, M., Derdour, A., and Mongin, F. (2009) Deprotonative metalation of functionalized aromatics using mixed lithium–cadmium, lithium–indium, and lithium–zinc species. *Chem. Eur. J.*, **15**, 10280–10290.
9. Wu, W.-B. and Huang, J.-M. (2012) Highly regioselective C–N bond formation through C–H azolation of indoles promoted by iodine in aqueous media. *Org. Lett.*, **14**, 5832–5835.
10. Hebel, D. and Rozen, S. (1991) Utilizing acetyl hypofluorite for chlorination, bromination, and etherification of the pyridine system. *J. Org. Chem.*, **56**, 6298–6301.
11. Kiselyov, A.S. and Strekowski, L. (1994) Carboxamidation of pyridines by the system of elemental fluorine-carbonitrile-water: a useful alternative to the Chichibabin amination. *Synth. Commun.*, **24**, 2387–2392.
12. Umemoto, T. and Tomizawa, G. (1989) Preparation of 2-fluoropyridines via base-induced decomposition of *N*-fluoropyridinium salts. *J. Org. Chem.*, **54**, 1726–1731.
13. Bhalerao, D.S. and Akamanchi, K.G. (2007) Efficient and novel method for thiocyanation of aromatic and heteroaromatic compounds using bromodimethylsulfonium bromide and ammonium thiocyanate. *Synlett*, 2952–2956.
14. Li, Y.-X., Ji, K.-G., Wang, H.-X., Ali, S., and Liang, Y.-M. (2011) Iodine-induced regioselective C–C and C–N bonds formation of *N*-protected indoles. *J. Org. Chem.*, **76**, 744–747.
15. Stavber, S., Košir, I., and Zupan, M. (1997) Reactions of alcohols with cesium fluoroxysulfate. *J. Org. Chem.*, **62**, 4916–4920.
16. LeTourneau, M.E. and Peet, N.P. (1987) Functionalized pyrazoles from indazol-4-ols. *J. Org. Chem.*, **52**, 4384–4387.
17. Narender, N., Srinivasu, P., Kulkarni, S.J., and Raghavan, K.V. (2002) Regioselective oxyiodination of aromatic compounds using potassium iodide and oxone®. *Synth. Commun.*, **32**, 2319–2324.
18. Zagulyaeva, A.A., Banek, C.T., Yusubov, M.S., and Zhdankin, V.V. (2010) Hofmann rearrangement of carboxamides mediated by hypervalent iodine species generated in situ from iodobenzene and oxone: reaction scope and limitations. *Org. Lett.*, **12**, 4644–4647.
19. Pradal, A., Toullec, P.Y., and Michelet, V. (2011) Gold-catalyzed oxidative acyloxylation of arenes. *Org. Lett.*, **13**, 6086–6089.
20. Liu, A.-H., He, L.-N., Hua, F., Yang, Z.-Z., Huang, C.-B., Yu, B., and Lia, B. (2011) *In situ* acidic carbon dioxide/ethanol system for selective oxybromination of aromatic ethers catalyzed by copper chloride. *Adv. Synth. Catal.*, **353**, 3187–3195.
21. Kikuchi, D., Sakaguchi, S., and Ishii, Y. (1998) An alternative method for the selective bromination of alkylbenzenes using $NaBrO_3/NaHSO_3$ reagent. *J. Org. Chem.*, **63**, 6023–6026.
22. Duan, S., Turk, J., Speigle, J., Corbin, J., Masnovi, J., and Baker, R.J. (2000) Halogenations of anthracenes and dibenz[*a*,*c*]anthracene with

N-bromosuccinimide and *N*-chlorosuccinimide. *J. Org. Chem.*, **65**, 3005–3009.

23. Tutar, A., Berkil, K., Hark, R.R., and Balci, M. (2008) Bromination of 5-methoxyindane: synthesis of new benzoindenone derivatives and ready access to 7*H*-benzo[*c*]fluoren-7-one skeleton. *Synth. Commun.*, **38**, 1333–1345.
24. Cakmak, O., Erenler, R., Tutar, A., and Celik, N. (2006) Synthesis of new anthracene derivatives. *J. Org. Chem.*, **71**, 1795–1801.
25. Barluenga, J., Alvarez-Gutiérrez, J.M., Ballesteros, A., and González, J.M. (2007) Direct *ortho* iodination of β- and γ-aryl alkylamine derivatives. *Angew. Chem. Int. Ed.*, **46**, 1281–1283.
26. Mei, T.-S., Wang, D.-H., and Yu, J.-Q. (2010) Expedient drug synthesis and diversification via *ortho*-C–H iodination using recyclable PdI_2 as the precatalyst. *Org. Lett.*, **12**, 3140–3143.
27. Chan, K.S.L., Wasa, M., Wang, X., and Yu, J.-Q. (2011) Palladium(II)-catalyzed selective monofluorination of benzoic acids using a practical auxiliary: a weak-coordination approach. *Angew. Chem. Int. Ed.*, **50**, 9081–9084.
28. Dai, H.-X., Stepan, A.F., Plummer, M.S., Zhang, Y.-H., and Yu, J.-Q. (2011) Divergent C–H functionalizations directed by sulfonamide pharmacophores: late-stage diversification as a tool for drug discovery. *J. Am. Chem. Soc.*, **133**, 7222–7228.
29. Schröder, N., Wencel-Delord, J., and Glorius, F. (2012) High-yielding, versatile, and practical [Rh(III)Cp*]-catalyzed *ortho* bromination and iodination of arenes. *J. Am. Chem. Soc.*, **134**, 8298–8301.
30. Zhao, X., Dimitrijević, E., and Dong, V.M. (2009) Palladium-catalyzed C – H bond functionalization with arylsulfonyl chlorides. *J. Am. Chem. Soc.*, **131**, 3466–3467.
31. Chen, X., Hao, X.-S., Goodhue, C.E., and Yu, J.-Q. (2006) Cu(II)-catalyzed functionalizations of aryl C–H bonds using O_2 as an oxidant. *J. Am. Chem. Soc.*, **128**, 6790–6791.
32. Kalyani, D., Dick, A.R., Anani, W.Q., and Sanford, M.S. (2006) Scope and selectivity in palladium-catalyzed directed C–H bond halogenation reactions. *Tetrahedron*, **62**, 11483–11498.
33. Arnold, P.L., Sanford, M.S., and Pearson, S.M. (2009) Chelating *N*-heterocyclic carbene alkoxide as a supporting ligand for $Pd^{II/IV}$ C–H bond functionalization catalysis. *J. Am. Chem. Soc.*, **131**, 13912–13913.
34. Hull, K.L., Anani, W.Q., and Sanford, M.S. (2006) Palladium-catalyzed fluorination of carbon–hydrogen bonds. *J. Am. Chem. Soc.*, **128**, 7134–7135.
35. Song, B., Zheng, X., Mo, J., and Xua, B. (2010) Palladium-catalyzed monoselective halogenation of C–H bonds: efficient access to halogenated arylpyrimidines using calcium halides. *Adv. Synth. Catal.*, **352**, 329–335.
36. Wan, X., Ma, Z., Li, B., Zhang, K., Cao, S., Zhang, S., and Shi, Z. (2006) Highly selective C–H functionalization/halogenation of acetanilide. *J. Am. Chem. Soc.*, **128**, 7416–7417.
37. Powers, D.C., Benitez, D., Tkatchouk, E., Goddard, W.A., and Ritter, T. (2010) Bimetallic reductive elimination from dinuclear Pd(III) complexes. *J. Am. Chem. Soc.*, **132**, 14092–14103.
38. Powers, D.C., Xiao, D.Y., Geibel, M.A.L., and Ritter, T. (2010) On the mechanism of palladium-catalyzed aromatic C–H oxidation. *J. Am. Chem. Soc.*, **132**, 14530–14536.
39. Stowers, K.J. and Sanford, M.S. (2009) Mechanistic comparison between Pd-catalyzed ligand-directed C–H chlorination and C–H acetoxylation. *Org. Lett.*, **11**, 4584–4587.
40. Li, J.-J., Mei, T.-S., and Yu, J.-Q. (2008) Synthesis of indolines and tetrahydroisoquinolines from arylethylamines by Pd^{II}-catalyzed C–H activation reactions. *Angew. Chem. Int. Ed.*, **47**, 6452–6455.
41. Xia, J.-B. and You, S.-L. (2009) Synthesis of 3-haloindolizines by copper(II) halide mediated direct functionalization of indolizines. *Org. Lett.*, **11**, 1187–1190.

42. Gu, R., Hameurlaine, A., and Dehaen, W. (2007) Facile one-pot synthesis of 6-monosubstituted and 6,12-disubstituted 5,11-dihydroindolo[3,2-*b*]carbazoles and preparation of various functionalized derivatives. *J. Org. Chem.*, **72**, 7207–7213.
43. Zweig, A., Fischer, R.G., and Lancaster, J.E. (1980) New method for selective monofluorination of aromatics using silver difluoride. *J. Org. Chem.*, **45**, 3597–3603.
44. Syvret, R.G., Butt, K.M., Nguyen, T.P., Bulleck, V.L., and Rieth, R.D. (2002) Novel process for generating useful electrophiles from common anions using Selectfluor® fluorination agent. *J. Org. Chem.*, **67**, 4487–4493.
45. Visser, G.W.M., Bakker, C.N.M., Halteren, B.W.V., Herscheid, J.D.M., Brinkman, G.A., and Hoekstra, A. (1986) Fluorination and fluorodemercuration of aromatic compounds with acetyl hypofluorite. *J. Org. Chem.*, **51**, 1886–1889.
46. Lin, R., Ding, S., Shi, Z., and Jiao, N. (2011) An efficient difluorohydroxylation of indoles using selectfluor as a fluorinating reagent. *Org. Lett.*, **13**, 4498–4501.
47. Tian, T., Zhong, W.-H., Meng, S., Meng, X.-B., and Li, Z.-J. (2013) Hypervalent iodine mediated *para*-selective fluorination of anilides. *J. Org. Chem.*, **78**, 728–732.
48. Itoh, N., Sakamoto, T., Miyazawa, E., and Kikugawa, Y. (2002) Introduction of a hydroxy group at the para position and *N*-iodophenylation of *N*-arylamides using phenyliodine(III) bis(trifluoroacetate). *J. Org. Chem.*, **67**, 7424–7428.
49. Zajc, B. and Zupan, M. (1990) Fluorination with xenon difluoride. 37. Room-temperature rearrangement of aryl-substituted ketones to difluoro-substituted ethers. *J. Org. Chem.*, **55**, 1099–1102.
50. Nemoto, H., Nishiyama, T., and Akai, S. (2011) Nucleophilic deoxyfluorination of catechols. *Org. Lett.*, **13**, 2714–2717.
51. Jian, H. and Tour, J.M. (2005) Preparative fluorous mixture synthesis of diazonium-functionalized oligo(phenylene vinylene)s. *J. Org. Chem.*, **70**, 3396–3424.
52. Dewkar, G.K., Narina, S.V., and Sudalai, A. (2003) $NaIO_4$-mediated selective oxidative halogenation of alkenes and aromatics using alkali metal halides. *Org. Lett.*, **5**, 4501–4504.
53. Rajesh, K., Somasundaram, M., Saiganesh, R., and Balasubramanian, K.K. (2007) Bromination of deactivated aromatics: a simple and efficient method. *J. Org. Chem.*, **72**, 5867–5869.
54. Guilarte, V., Castroviejo, M.P., García-García, P., Fernández-Rodríguez, M.A., and Sanz, R. (2011) Approaches to the synthesis of 2,3-dihaloanilines. Useful precursors of 4-functionalized-1*H*-indoles. *J. Org. Chem.*, **76**, 3416–3437.
55. Popov, I., Do, H.-Q., and Daugulis, O. (2009) In situ generation and trapping of aryllithium and arylpotassium species by halogen, sulfur, and carbon electrophiles. *J. Org. Chem.*, **74**, 8309–8313.
56. Toomey, J.E. (1993) Chlorination process. US Patent 5247093.
57. McElvain, S.M. and Goese, M.A. (1943) The halogenation of pyridine. *J. Am. Chem. Soc.*, **65**, 2227–2233.
58. Bankston, D., Dumas, J., Natero, R., Riedl, B., Monahan, M.-K., and Sibley, R. (2002) A scaleable synthesis of BAY 43-9006: a potent Raf kinase inhibitor for the treatment of cancer. *Org. Process Res. Dev.*, **6**, 777–781.
59. Newkome, G.R., Theriot, K.J., Majestic, V.K., Spruell, P.A., and Baker, G.R. (1990) Functionalization of 2-methyl- and 2,7-dimethy1-1,8-naphthyridine. *J. Org. Chem.*, **55**, 2838–2842.
60. Deadman, J.J., Jones, E.D., Le, G.T., Rhodes, D.I., Thien-Thong, N., and van de Graff, N.A. (2010) Compounds having antiviral properties. WO Patent 2010000032.
61. Giblin, G.M.P., Billinton, A., Briggs, M., Brown, A.J., Chessell, I.P., Clayton, N.M., Eatherton, A.J., Goldsmith, P., Haslam, C., Johnson, M.R., Mitchell, W.L., Naylor, A., Perboni, A., Slingsby,

B.P., and Wilson, A.W. (2009) Discovery of 1-[4-(3-chlorophenylamino)-1-methyl-1*H*-pyrrolo[3,2-*c*]pyridin-7-yl]-1-morpholin-4-ylmethanone (GSK554418A), a brain penetrant 5-azaindole CB_2 agonist for the treatment of chronic pain. *J. Med. Chem.*, **52**, 5785–5788.

62. Said, A. (1979) Process for the production of pure white 2-chloronicotinic acid. US Patent 4144238.
63. Kretzschmar, E. and Dietz, G. (1987) Untersuchung eines Nebenproduktes bei der Herstellung von 2-Chlornicotinsäure. *Pharmazie*, **42**, 858.
64. Hynes, J., Doubleday, W.W., Dyckman, A.J., Godfrey, J.D., Grosso, J.A., Kiau, S., and Leftheris, K. (2004) *N*-Amination of pyrrole and indole heterocycles with monochloramine (NH_2Cl). *J. Org. Chem.*, **69**, 1368–1371.
65. Pearson, D.E., Stamper, W.E., and Suthers, B.R. (1963) The swamping catalyst effect. V. The halogenation of aromatic acid derivatives. *J. Org. Chem.*, **28**, 3147–3149.
66. da Ribeiro, R.S., Esteves, P.M., and de Mattos, M.C.S. (2011) Superelectrophilic iodination of deactivated arenes with triiodoisocyanuric acid. *Synthesis*, 739–744.
67. Groweiss, A. (2000) Use of sodium bromate for aromatic bromination: research and development. *Org. Process Res. Dev.*, **4**, 30–33.
68. Rozen, S., Brand, M., and Lidor, R. (1988) Aromatic bromination using BrF with no Friedel–Crafts catalyst. *J. Org. Chem.*, **53**, 5545–5547.
69. Mei, T.-S., Giri, R., Maugel, N., and Yu, J.-Q. (2008) Pd^{II}-catalyzed monoselective *ortho* halogenation of C–H bonds assisted by counter cations: a complementary method to directed *ortho* lithiation. *Angew. Chem. Int. Ed.*, **47**, 5215–5219.
70. Cahiez, G., Moyeux, A., Gager, O., and Poizat, M. (2013) Copper-catalyzed decarboxylation of aromatic carboxylic acids: en route to milder reaction conditions. *Adv. Synth. Catal.*, **355**, 790–796.
71. Dickstein, J.S., Curto, J.M., Gutierrez, O., Mulrooney, C.A., and Kozlowski, M.C. (2013) Mild aromatic palladium-catalyzed protodecarboxylation: kinetic assessment of the decarboxylative palladation and the protodepalladation steps. *J. Org. Chem.*, **78**, 4744–4761.
72. Arroniz, C., Ironmonger, A., Rassias, G., and Larrosa, I. (2013) Direct *ortho*-arylation of *ortho*-substituted benzoic acids: overriding Pd-catalyzed protodecarboxylation. *Org. Lett.*, **15**, 910–913.
73. Goossen, L.J., Rodríguez, N., Melzer, B., Linder, C., Deng, G., and Levy, L.M. (2007) Biaryl synthesis via Pd-catalyzed decarboxylative coupling of aromatic carboxylates with aryl halides. *J. Am. Chem. Soc.*, **129**, 4824–4833.
74. Milburn, R.R., Thiel, O.R., Achmatowicz, M., Wang, X., Zigterman, J., Bernard, C., Colyer, J.T., DiVirgilio, E., Crockett, R., Correll, T.L., Nagapudi, K., Ranganathan, K., Hedley, S.J., Allgeier, A., and Larsen, R.D. (2011) Development of a practical synthesis of a pyrazolopyridinone-based p38 MAP kinase inhibitor. *Org. Process Res. Dev.*, **15**, 31–43.
75. Janz, K. and Kaila, N. (2009) Bromodecarboxylation of quinoline salicylic acids: increasing the diversity of accessible substituted quinolines. *J. Org. Chem.*, **74**, 8874–8877.
76. Stevens, K.L., Jung, D.K., Alberti, M.J., Badiang, J.G., Peckham, G.E., Veal, J.M., Cheung, M., Harris, P.A., Chamberlain, S.D., and Peel, M.R. (2005) Pyrazolo[1,5-*a*]pyridines as p38 kinase inhibitors. *Org. Lett.*, **7**, 4753–4756.
77. Kulbitski, K., Nisnevich, G., and Gandelman, M. (2011) Metal-free efficient, general and facile iododecarboxylation method with biodegradable co-products. *Adv. Synth. Catal.*, **353**, 1438–1442.
78. Szumigala, R.H., Devine, P.N., Gauthier, D.R., and Volante, R.P. (2004) Facile synthesis of 2-bromo-3-fluorobenzonitrile: an application and study of the halodeboronation of aryl boronic acids. *J. Org. Chem.*, **69**, 566–569.

79. Du, B., Jiang, X., and Sun, P. (2013) Palladium-catalyzed highly selective *ortho*-halogenation (I, Br, Cl) of arylnitriles via sp^2 C–H bond activation using cyano as directing group. *J. Org. Chem.*, **78**, 2786–2791.
80. Mattern, D.L. (1984) Direct aromatic periodination. *J. Org. Chem.*, **49**, 3051–3053.
81. Mattern, D.L. and Chen, X. (1991) Direct polyiodination of benzenesulfonic acid. *J. Org. Chem.*, **56**, 5903–5907.
82. García, R., Riera, J., Carilla, J., Juliá, L., Molins, E., and Miravitlles, C. (1992) Extensive chlorination of methylnaphthalenes, Friedel–Crafts alkylation of pentachlorobenzene by heptachloro(chloromethyl)naphthalenes, and related results. *J. Org. Chem.*, **57**, 5712–5719.
83. Watson, W.D. (1982) Formation of nonaromatic products in the chlorination of simple substituted aromatic ethers. *J. Org. Chem.*, **47**, 5270–5276.
84. Barrero, A.F., Alvarez-Manzaneda, E.J., Chahboun, R., and González Díaz, C. (2000) New routes toward drimanes and *nor*-drimanes from (–)-sclareol. *Synlett*, 1561–1564.
85. Yu, M. and Snider, B.B. (2011) Syntheses of chloroisosulochrin and isosulochrin and biomimetic elaboration to maldoxin, maldoxone, dihydromaldoxin, and dechlorodihydromaldoxin. *Org. Lett.*, **13**, 4224–4227.
86. Sarkanen, K.V. and Dence, C.W. (1960) Reactions of *p*-hydroxybenzyl alcohol derivatives and their methyl ethers with molecular chlorine. *J. Org. Chem.*, **25**, 715–720.
87. Zhao, J., Wang, Y., He, Y., Liu, L., and Zhu, Q. (2012) Cu-catalyzed oxidative C(sp^2)–H cycloetherification of *o*-arylphenols for the preparation of dibenzofurans. *Org. Lett.*, **14**, 1078–1081.
88. Zhao, J., Zhang, Q., Liu, L., He, Y., Li, J., Li, J., and Zhu, Q. (2012) CuI-mediated sequential iodination/cycloetherification of *o*-arylphenols: synthesis of 2- or 4-iododibenzofurans and mechanistic studies. *Org. Lett.*, **14**, 5362–5365.
89. Berrier, C., Jacquesy, J.C., and Renoux, A. (1990) Bromination of anilines in superacids. *Bull. Soc. Chim. Fr.*, 93–97.
90. Bieler, N., Ellinger, S., Furrer, M., Ladnak, V., Müller, C., Schmid, L., and Zur Täschler, C. (2012) Process for the selective *meta*-chlorination of alkylanilines. WO Patent 2012022460.
91. Tomioka, H., Watanabe, T., Hattori, M., Nomura, N., and Hirai, K. (2002) Generation, reactions, and kinetics of sterically congested triplet diphenylcarbenes. Effects of bromine groups. *J. Am. Chem. Soc.*, **124**, 474–482.
92. Shen, H. and Vollhardt, K.P.C. (2012) Remarkable switch in the regiochemistry of the iodination of anilines by *N*-iodosuccinimide: synthesis of 1,2-dichloro-3,4-diiodobenzene. *Synlett*, 208–214.
93. Menini, L., da Cruz Santos, J.C., and Gusevskayaa, E.V. (2008) Copper-catalyzed oxybromination and oxychlorination of primary aromatic amines using LiBr or LiCl and molecular oxygen. *Adv. Synth. Catal.*, **350**, 2052–2058.
94. Kolmakov, K., Belov, V.N., Wurm, C.A., Harke, B., Leutenegger, M., Eggeling, C., and Hell, S.W. (2010) A versatile route to red-emitting carbopyronine dyes for optical microscopy and nanoscopy. *Eur. J. Org. Chem.*, **2010**, 3593–3610.
95. Suthers, B.R., Riggins, P.H., and Pearson, D.E. (1962) The swamping catalyst effect. IV. The halogenation of anilines. *J. Org. Chem.*, **27**, 447–451.
96. Ottmann, G. and Hooks, H. (1965) Chlorination of aromatic *N*-sulfinylamines. *J. Org. Chem.*, **30**, 952–954.
97. Mohanakrishnan, A.K., Prakash, C., and Ramesh, N. (2006) A simple iodination protocol via in situ generated ICl using NaI/$FeCl_3$. *Tetrahedron*, **62**, 3242–3247.
98. Vliet, E.B. (1941) Quinone. *Org. Synth.*, Coll. Vol. **1**, 482–484, reference 2 cited therein.
99. Holmes, R.R. and Bayer, R.P. (1960) A simple method for the direct oxidation of aromatic amines to nitroso

compounds. *J. Am. Chem. Soc.*, **82**, 3454–3456.

100. Akrawi, O.A., Mohammed, H.H., and Langer, P. (2013) Synthesis and Suzuki–Miyaura reactions of 3,6,8-tribromoquinoline: a structural revision. *Synlett*, 1121–1124.

101. Zhuravleva, Y.A., Zimichev, A.V., Zemtsova, M.N., and Klimochkin, Y.N. (2011) Bromination of methyl 2-methyl-6-*R*-1,2,3,4-tetrahydroquinoline-4-carboxylates. *Russ. J. Org. Chem.*, **47**, 306–307.

102. Shaikh, I.A., Johnson, F., and Grollman, A.P. (1986) Streptonigrin. 1. Structure–activity relationships among simple bicyclic analogues. Rate dependence of DNA degradation on quinone reduction potential. *J. Med. Chem.*, **29**, 1329–1340.

103. Gassman, P.G. and Campbell, G.A. (1971) The mechanism of the chlorination of anilines and related aromatic amines. The involvement of nitrenium ions. *J. Am. Chem. Soc.*, **93**, 2567–2569.

104. Al-Zoubi, R.M. and Hall, D.G. (2010) Mild silver(I)-mediated regioselective iodination and bromination of arylboronic acids. *Org. Lett.*, **12**, 2480–2483.

105. DeMarinis, R.M. and Hieble, P. (1984) 2-(4-*Tert*-butyl-2,6-dichlorophenylimino)imidazolidine and use as an antihypertension agent. US Patent 4444782.

106. Ueda, S. and Nagasawa, H. (2008) Synthesis of 2-arylbenzoxazoles by copper-catalyzed intramolecular oxidative C–O coupling of benzanilides. *Angew. Chem. Int. Ed.*, **47**, 6411–6413.

107. Doyle, M.P., Van Lente, M.A., Mowat, R., and Fobare, W.F. (1980) Alkyl nitrite–metal halide deamination reactions. 7. Synthetic coupling of electrophilic bromination with substitutive deamination for selective synthesis of multiply brominated aromatic compounds from arylamines. *J. Org. Chem.*, **45**, 2570–2575.

108. Mekh, M.A., Ozeryanskii, V.A., and Pozharskii, A.F. (2006) 5,6-Bis(dimethylamino)acenaphthylene as an activated alkene and "proton sponge" in halogenation reactions. *Tetrahedron*, **62**, 12288–12296.

109. Potturi, H.K., Gurung, R.K., and Hou, Y. (2012) Nitromethane with IBX/TBAF as a nitrosating agent: synthesis of nitrosamines from secondary or tertiary amines under mild conditions. *J. Org. Chem.*, **77**, 626–631.

110. Gu, Z. and Zakarian, A. (2010) Total synthesis of rhazinilam: axial-to-point chirality transfer in an enantiospecific Pd-catalyzed transannular cyclization. *Org. Lett.*, **12**, 4224–4227.

111. Bellina, F., Cauteruccio, S., Di Fiore, A., and Rossi, R. (2008) Regioselective synthesis of 4,5-diaryl-1-methyl-1*H*-imidazoles including highly cytotoxic derivatives by Pd-catalyzed direct C-5 arylation of 1-methyl-1*H*-imidazole with aryl bromides. *Eur. J. Org. Chem.*, **2008**, 5436–5445.

112. Gillmore, A.T., Badland, M., Crook, C.L., Castro, N.M., Critcher, D.J., Fussell, S.J., Jones, K.J., Jones, M.C., Kougoulos, E., Mathew, J.S., McMillan, L., Pearce, J.E., Rawlinson, F.L., Sherlock, A.E., and Walton, R. (2012) Multkilogram scale-up of a reductive alkylation route to a novel PARP inhibitor. *Org. Process Res. Dev.*, **16**, 1897–1904.

113. Qi, T., Qiu, W., Liu, Y., Zhang, H., Gao, X., Liu, Y., Lu, K., Du, C., Yu, G., and Zhu, D. (2008) Synthesis, structures, and properties of disubstituted heteroacenes on one side containing both pyrrole and thiophene rings. *J. Org. Chem.*, **73**, 4638–4643.

114. Zhou, C.-Y., Li, J., Peddibhotla, S., and Romo, D. (2010) Mild arming and derivatization of natural products via an $In(OTf)_3$-catalyzed arene iodination. *Org. Lett.*, **12**, 2104–2107.

115. Miyake, F.Y., Yakushijin, K., and Horne, D.A. (2002) Synthesis of marine sponge bisindole alkaloids dihydrohamacanthins. *Org. Lett.*, **4**, 941–943.

116. Miyake, F.Y., Yakushijin, K., and Horne, D.A. (2004) A concise synthesis of spirotryprostatin A. *Org. Lett.*, **6**, 4249–4251.

117. Miyake, F.Y., Yakushijin, K., and Horne, D.A. (2004) Preparation

and synthetic applications of 2-halotryptamines: synthesis of elacomine and isoelacomine. *Org. Lett.*, **6**, 711–713.

118. Troegel, B. and Lindel, T. (2012) Microwave-assisted fluorination of 2-acylpyrroles: synthesis of fluorohymenidin. *Org. Lett.*, **14**, 468–471.

119. Han, X., Civiello, R.L., Fang, H., Wu, D., Gao, Q., Chaturvedula, P.V., Macor, J.E., and Dubowchik, G.M. (2008) Catalytic asymmetric syntheses of tyrosine surrogates. *J. Org. Chem.*, **73**, 8502–8510.

120. Zhang, X., Yao, X.-T., Dalton, J.T., Shams, G., Lei, L., Patil, P.N., Feller, D.R., Hsu, F.-L., George, C., and Miller, D.D. (1996) Medetomidine analogs as α_2-adrenergic ligands. 2. Design, synthesis, and biological activity of conformationally restricted naphthalene derivatives of medetomidine. *J. Med. Chem.*, **39**, 3001–3013.

121. Lovely, C.J., Du, H., Sivappa, R., Bhandari, M.R., He, Y., and Dias, H.V.R. (2007) Preparation and Diels–Alder chemistry of 4-vinylimidazoles. *J. Org. Chem.*, **72**, 3741–3749.

122. Wu, F., Lu, E., and Barden, C. (2012) Antimicrobial/adjuvant compounds and methods. WO Patent 2012116452.

123. Smith, P.A.S. and Brown, B.B. (1951) The reaction of aryl azides with hydrogen halides. *J. Am. Chem. Soc.*, **73**, 2438–2441.

124. Saito, T., Asahi, Y., Nakajima, S., and Fujii, T. (1994) Purines. LXIV. Synthesis of 9-methyl-2-azaadenine 1-oxide, its *O*-methyl derivative, and 1-substituted 5-azidoimidazole-4-carboxamides. *Chem. Pharm. Bull.*, **42**, 2263–2268.

125. Liu, R., Zhang, P., Gan, T., and Cook, J.M. (1997) Regiospecific bromination of 3-methylindoles with NBS and its application to the concise synthesis of optically active unusual tryptophans present in marine cyclic peptides. *J. Org. Chem.*, **62**, 7447–7456.

126. Hino, T., Nakamura, T., and Nakagawa, M. (1975) Halogenation of 1-substituted skatoles. Preparation of 3-bromomethylindoles. *Chem. Pharm. Bull.*, **23**, 2990–2997.

127. Franceschin, M., Ginnari-Satriani, L., Alvino, A., Ortaggi, G., and Bianco, A. (2010) Study of a convenient method for the preparation of hydrosoluble fluorescent triazatruxene derivatives. *Eur. J. Org. Chem.*, **2010**, 134–141.

128. Zhuravleva, Y.A., Zimichev, A.V., Zemtsova, M.N., and Klimochkin, Y.N. (2011) Unusual bromination of methyl 8-allyl-2-methyl-1,2,3,4-tetrahydroquinoline-4-carboxylate. *Russ. J. Org. Chem.*, **47**, 464–465.

129. Lindel, T., Bräuchle, L., Golz, G., and Böhrer, P. (2007) Total synthesis of flustramine C via dimethylallyl rearrangement. *Org. Lett.*, **9**, 283–286.

130. Pace, V., Martínez, F., Fernández, M., Sinisterra, J.V., and Alcántara, A.R. (2009) Highly efficient synthesis of new α-arylamino-α′-chloropropan-2-ones via oxidative hydrolysis of vinyl chlorides promoted by calcium hypochlorite. *Adv. Synth. Catal.*, **351**, 3199–3206.

131. Dakka, J. and Sasson, Y. (1989) Bromination of α-substituted alkylbenzenes: synthesis of (*p*-bromophenyl)acetylene. *J. Org. Chem.*, **54**, 3224–3226.

132. Chen, C.-K., Hortmann, A.G., and Marzabadi, M.R. (1988) ClO_2 oxidation of amines: synthetic utility and a biomimetic synthesis of elaeocarpidine. *J. Am. Chem. Soc.*, **110**, 4829–4831.

133. Deno, N.C. and Fruit, R.E. (1968) The oxidative cleavage of amines by aqueous bromine at 25 °C. *J. Am. Chem. Soc.*, **90**, 3502–3506.

134. Hedley, K.A. and Stanforth, S.P. (1992) Ring-opening reactions of *N*-aryl-1,2,3,4-tetrahydroisoquinoline derivatives. *Tetrahedron*, **48**, 743–750.

135. Wu, W. and Su, W. (2011) Mild and selective Ru-catalyzed formylation and Fe-catalyzed acylation of free (N–H) indoles using anilines as the carbonyl source. *J. Am. Chem. Soc.*, **133**, 11924–11927.

136. Markees, D.G. (1958) Reaction of benzyl methyl ethers with bromine and *N*-bromosuccinimide. *J. Org. Chem.*, **23**, 1490–1492.

137. Page, P.C.B., Rassias, G.A., Barros, D., Ardakani, A., Buckley, B., Bethell, D., Smith, T.A.D., and Slawin, A.M.Z. (2001) Functionalized iminium salt

systems for catalytic asymmetric epoxidation. *J. Org. Chem.*, **66**, 6926–6931.

138. Mayhoub, A.S., Talukdar, A., and Cushman, M. (2010) An oxidation of benzyl methyl ethers with NBS that selectively affords either aromatic aldehydes or aromatic methyl esters. *J. Org. Chem.*, **75**, 3507–3510.

139. Adimurthy, S. and Patoliya, P.U. (2007) *N*-Bromosuccinimide: a facile reagent for the oxidation of benzylic alcohols to aldehydes. *Synth. Commun.*, **37**, 1571–1577.

140. Miura, Y. and Ohana, T. (1988) Thioaminyl diradicals: an electron spin resonance spectroscopic study. *J. Org. Chem.*, **53**, 5770–5772.

141. Bravo, A., Dordi, B., Fontana, F., and Minisci, F. (2001) Oxidation of organic sulfides by Br_2 and H_2O_2. Electrophilic and free-radical processes. *J. Org. Chem.*, **66**, 3232–3234.

142. Xia, M., Chen, S., and Bates, D.K. (1996) Reactions of benzyl aryl sulfides with excess active halogen reagents. *J. Org. Chem.*, **61**, 9289–9292.

143. Garcia, J., Ortiz, C., and Greenhouse, R. (1988) The regiospecific Pummerer-like introduction of chlorine atoms into pyrrol-3-yl and indol-3-yl sulfoxides. *J. Org. Chem.*, **53**, 2634–2637.

144. Khan, S.A., Munawar, M.A., and Siddiq, M. (1988) Monobromination of deactivated active rings using bromine, mercuric oxide, and strong acid. *J. Org. Chem.*, **53**, 1799–1800.

145. Chambers, R.D., Sandford, G., Trmcic, J., and Okazoe, T. (2008) Elemental fluorine. Part 21. Direct fluorination of benzaldehyde derivatives. *Org. Process Res. Dev.*, **12**, 339–344.

146. Meketa, M.L., Mahajan, Y.R., and Weinreb, S.M. (2005) An efficacious method for the halogenation of β-dicarbonyl compounds under mildly acidic conditions. *Tetrahedron Lett.*, **46**, 4749–4751.

147. Volk, B., Gacsályi, I., Pallagi, K., Poszávácz, L., Gyönös, I., Szabó, E., Bakó, T., Spedding, M., Simig, G., and Szénási, G. (2011) Optimization of (arylpiperazinylbutyl)oxindoles exhibiting selective 5-HT_7 receptor antagonist activity. *J. Med. Chem.*, **54**, 6657–6669.

148. Wei, W.-G. and Yao, Z.-J. (2005) Synthesis studies toward chloroazaphilone and vinylogous γ-pyridones: two common natural product core structures. *J. Org. Chem.*, **70**, 4585–4590.

149. Proisy, N., Sharp, S.Y., Boxall, K., Connelly, S., Roe, S.M., Prodromou, C., Slawin, A.M.Z., Pearl, L.H., Workman, P., and Moody, C.J. (2006) Inhibition of Hsp90 with synthetic macrolactones: synthesis and structural and biological evaluation of ring and conformational analogs of radicicol. *Chem. Biol.*, **13**, 1203–1215.

150. Roux, L., Charrier, C., Defoin, A., Bisseret, P., and Tarnus, C. (2010) Iodine(III)-mediated ring expansion: an efficient and green pathway in the synthesis of a key precursor for the design of aminopeptidase (APN or CD13) inhibitors. *Tetrahedron*, **66**, 8722–8728.

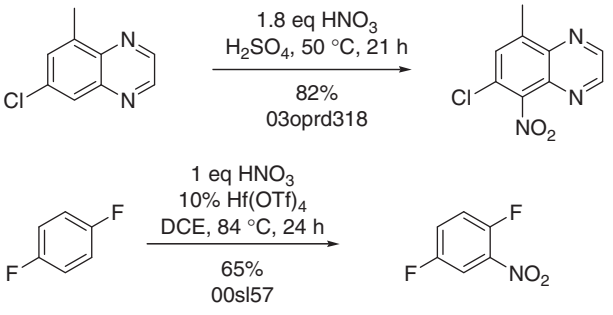
151. Prakash, O., Batra, H., Kaur, H., Sharma, P.K., Sharma, V., Singh, S.P., and Moriarty, R.M. (2001) Hypervalent iodine oxidative rearrangement of anthranilamides, salicylamides and some β-substituted amides: a new and convenient synthesis of 2-benzimidazolones, 2-benzoxazolones and related compounds. *Synthesis*, 541–543.

6
Electrophilic Formation of Aromatic C–N Bonds

6.1
Nitration of Arenes

6.1.1
Mechanisms

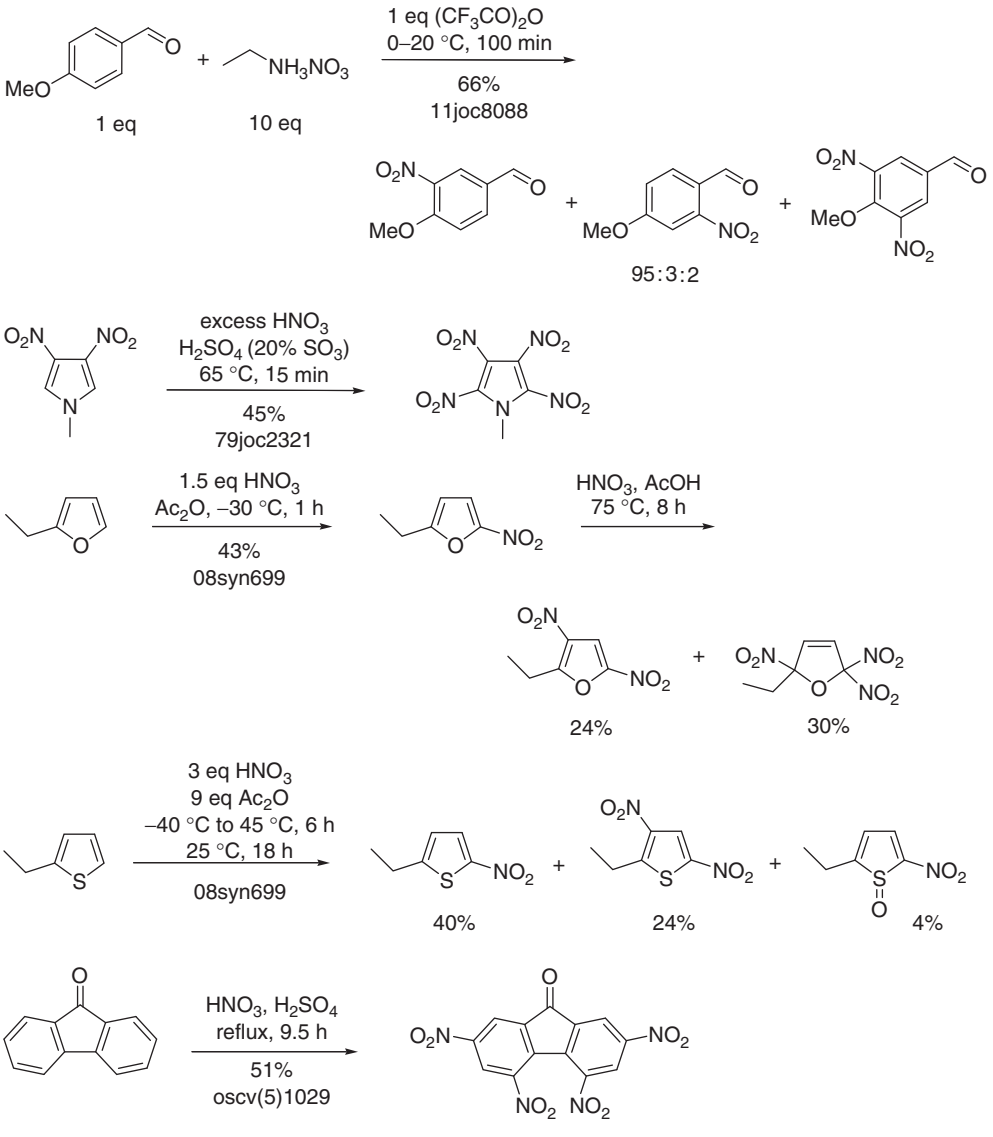
The electrophilic nitration of arenes, a key step for the preparation of most older explosives, is usually performed with NO_2^+ generated from mixtures of nitric and sulfuric acid. Alternatives to sulfuric acid as dehydrating reagent include Ac_2O, trifluoroacetic anhydride, or acidic heterogeneous catalysts [1]. Isolated nitronium salts, for example NO_2BF_4, and O_3/NO_2 [2], are also useful nitrating reagents. Nitrations in ionic liquids [3] and eutectic melts [4] have also been reported. Nitrosations with NO^+ often yield nitroarenes as byproducts [5] (Scheme 6.1).



Scheme 6.1 Examples of aromatic mononitrations [6, 7].

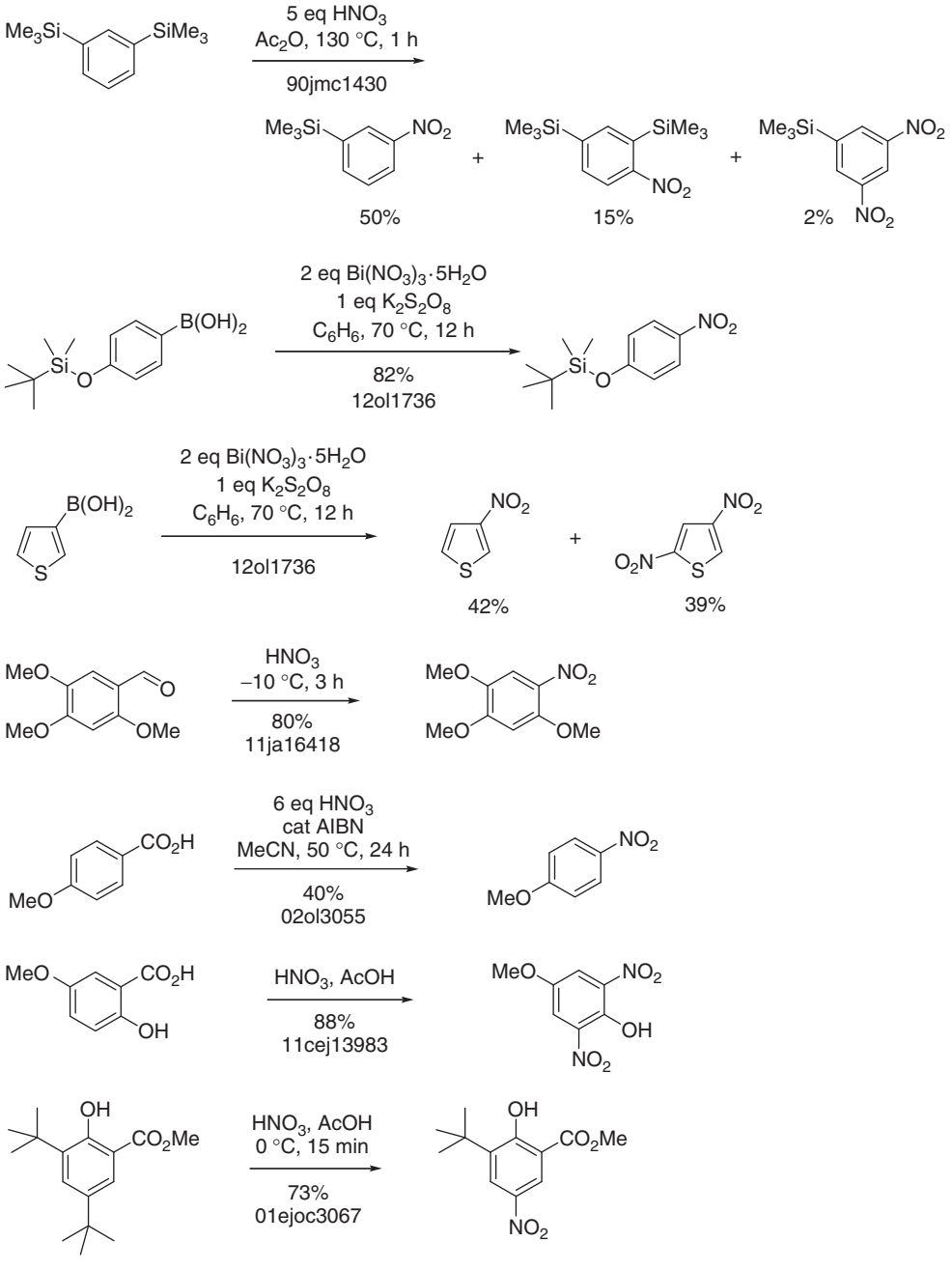
Nitrations proceed by the same mechanism as other electrophilic aromatic substitution reactions. Because of the strong electron-withdrawing effect of the nitro group, multiple nitrations would not usually be expected, but often such products are obtained as byproducts in small quantities (Scheme 6.2). Exhaustive polynitrations require harsh reaction conditions, and will often fail as a result of oxidative degradation of the products. Penta- or hexanitrobenzene, for instance, cannot be prepared by direct nitration but only by nitration of anilines, followed by oxidation or substitution of the activating amino group [8].

Side Reactions in Organic Synthesis II: Aromatic Substitutions, First Edition. Florencio Zaragoza Dörwald.

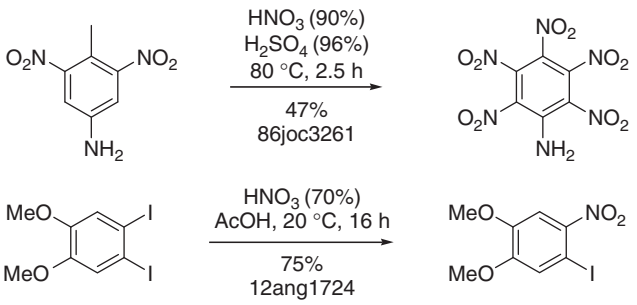


Scheme 6.2 Examples of multiple aromatic nitrations [9–12].

Electrophilic nitrating reagents do not only attack unsubstituted aromatic positions, but can also substitute other groups than hydrogen [13] (Scheme 6.3). These include SiR_3, BR_2, SO_3H, SR, CO_2H, halides [14, 15], alkyl groups [16], formyl groups [17, 18], and other acyl groups. This lack of selectivity is one reason why aromatic nitrations are only rarely applied to structurally complex intermediates.



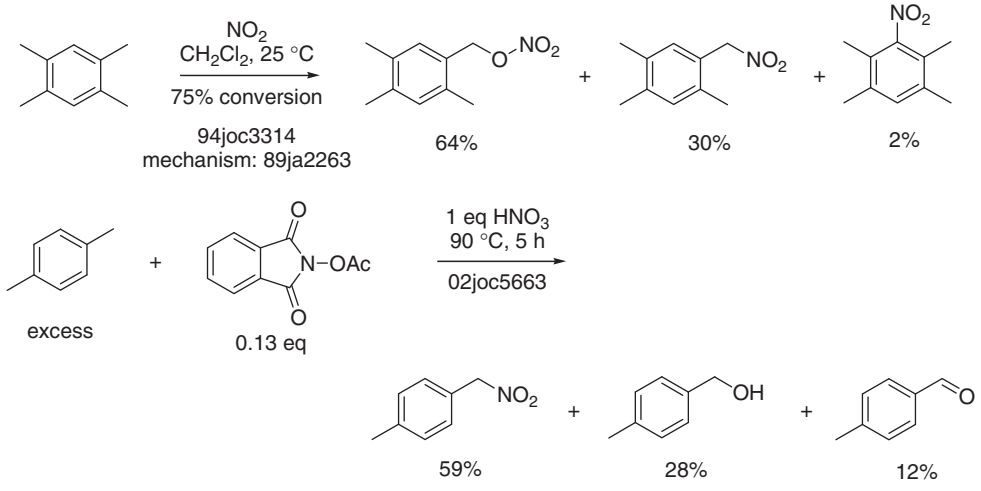
Scheme 6.3 Ipso substitution of various functional groups by nitro groups [8, 19–25].



Scheme 6.3 (*Continued*)

Many functional groups can be oxidized under the conditions of electrophilic nitration. NO_2^+ is a strong oxidant, capable of converting electron-rich arenes into aryl radical cations.

Arenes can also be nitrated with NO_2 [26]. This reaction also proceeds via aryl radical cations (Scheme 6.4), which can lead to a number of byproducts, such as side-chain nitrated products, biaryls, and diarylmethanes or -ethanes. Benzylic nitration is also occasionally observed during nitrations with acetyl nitrate [27].

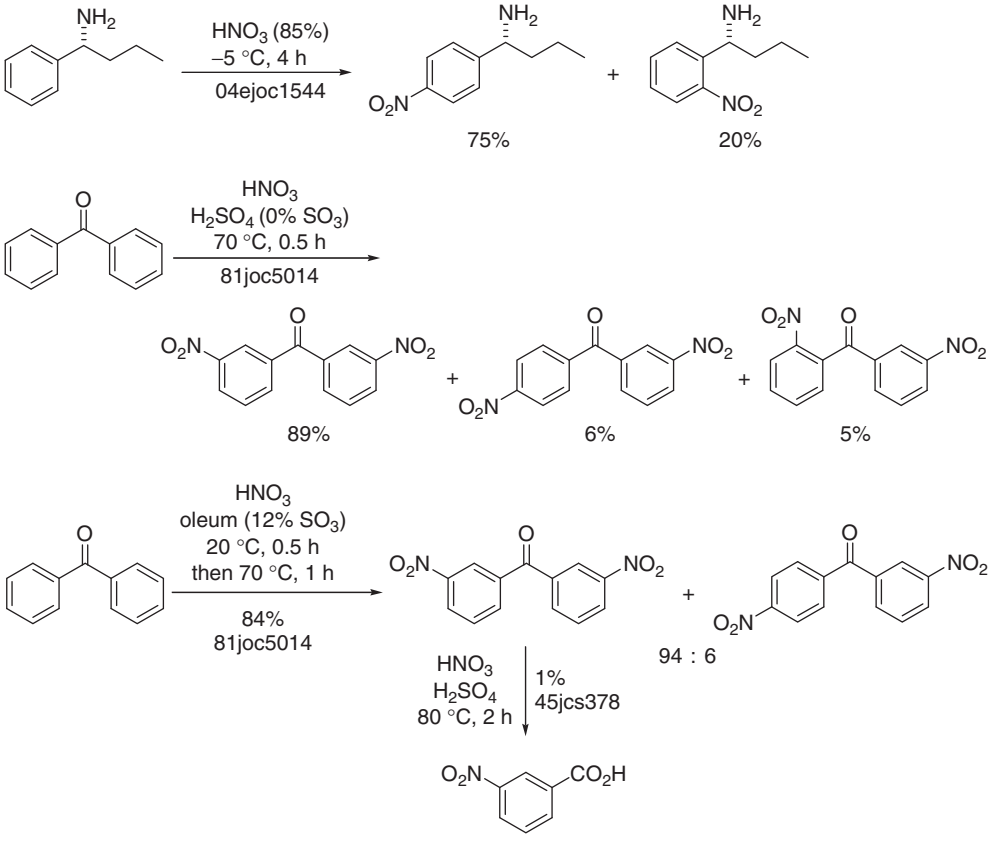


Scheme 6.4 Benzylic nitrations [26, 28, 29].

6.1.2
Regioselectivity

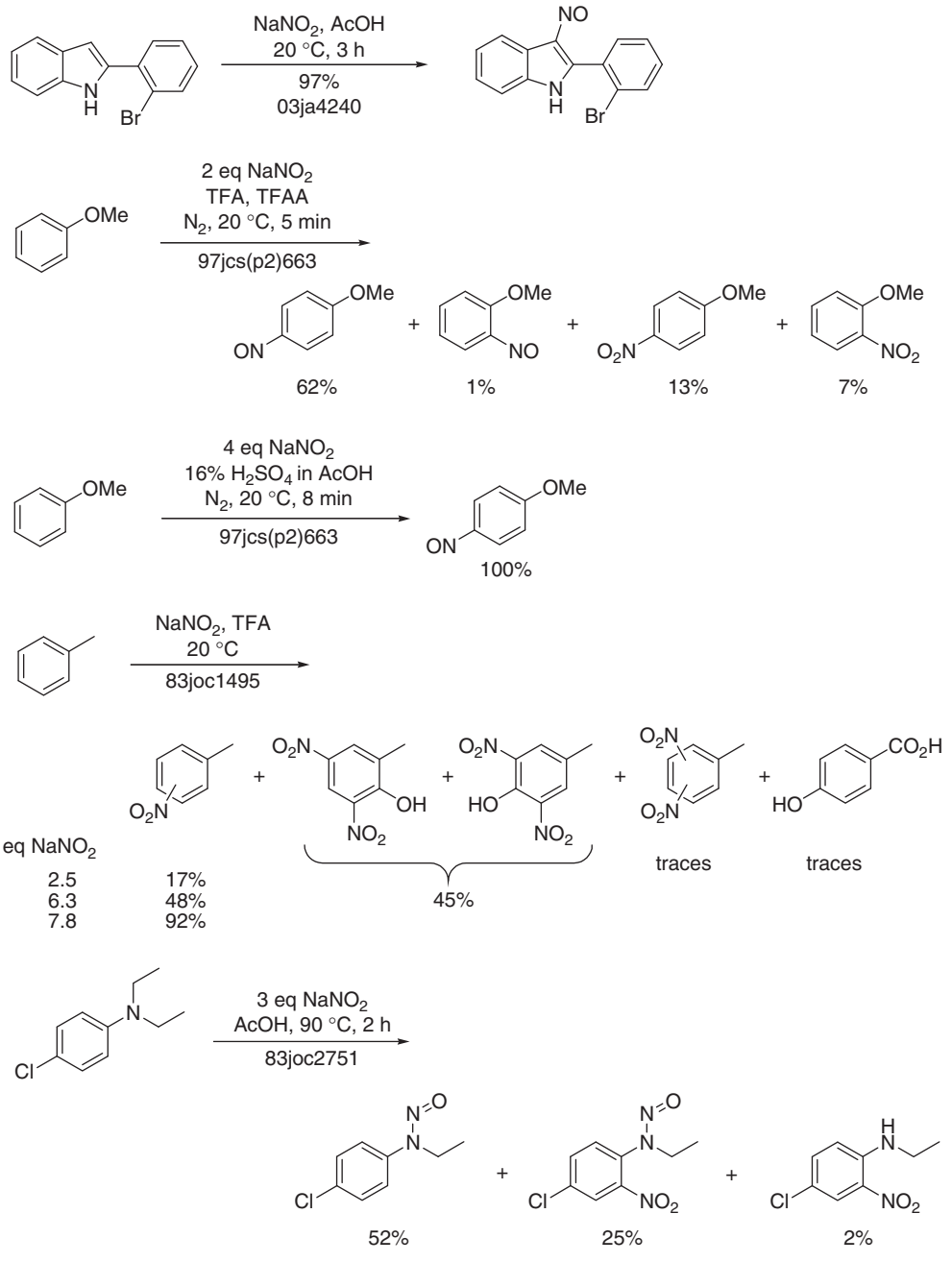
Nitrations often show lower regioselectivity than Friedel–Crafts acylations, and the removal of isomers by recrystallization is not always easy. Sometimes, the

regioselectivity of electrophilic aromatic nitrations is enhanced by using H_2SO_4 with a high concentration of SO_3 as solvent (Scheme 6.5).



Scheme 6.5 Regioselectivity of aromatic nitrations [30–32].

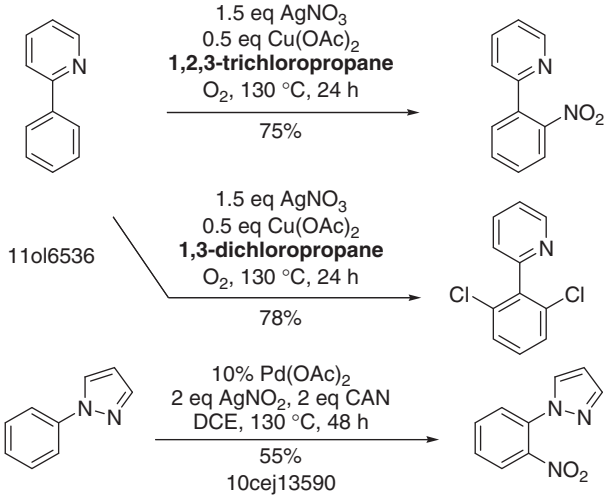
Because nitrosations often proceed with higher regioselectivity than nitrations, and nitrosoarenes can be oxidized in high yield to nitroarenes, for example with peracids or hydrogen peroxide, the sequence nitrosation/oxidation may be a useful alternative to direct nitration [33] (Scheme 6.6). Nitrosations often lead to nitroarenes as byproducts or main products (e.g., [5]), and careful optimization may be required to attain high yields of nitrosoarenes. Nitrous acid can also dealkylate tertiary amines [34].



Scheme 6.6 Reaction of arenes with nitrous acid [35–38].

6.1.3 Catalysis

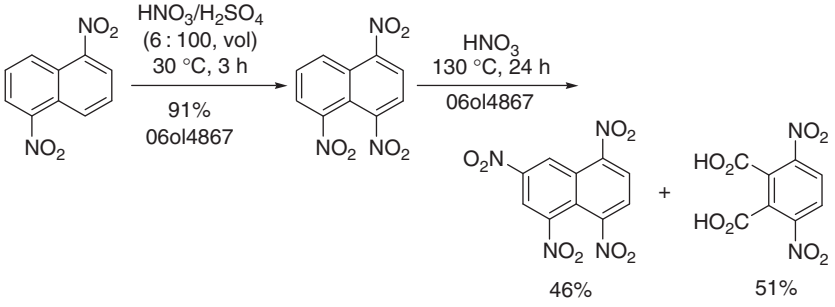
Electrophilic aromatic nitrations can be catalyzed by acids that enhance the concentration of NO_2^+. Some instances of transition-metal catalysis have been reported that probably proceed by intermediate aromatic metallation (Scheme 6.7).



Scheme 6.7 Catalyzed aromatic nitrations [39, 40].

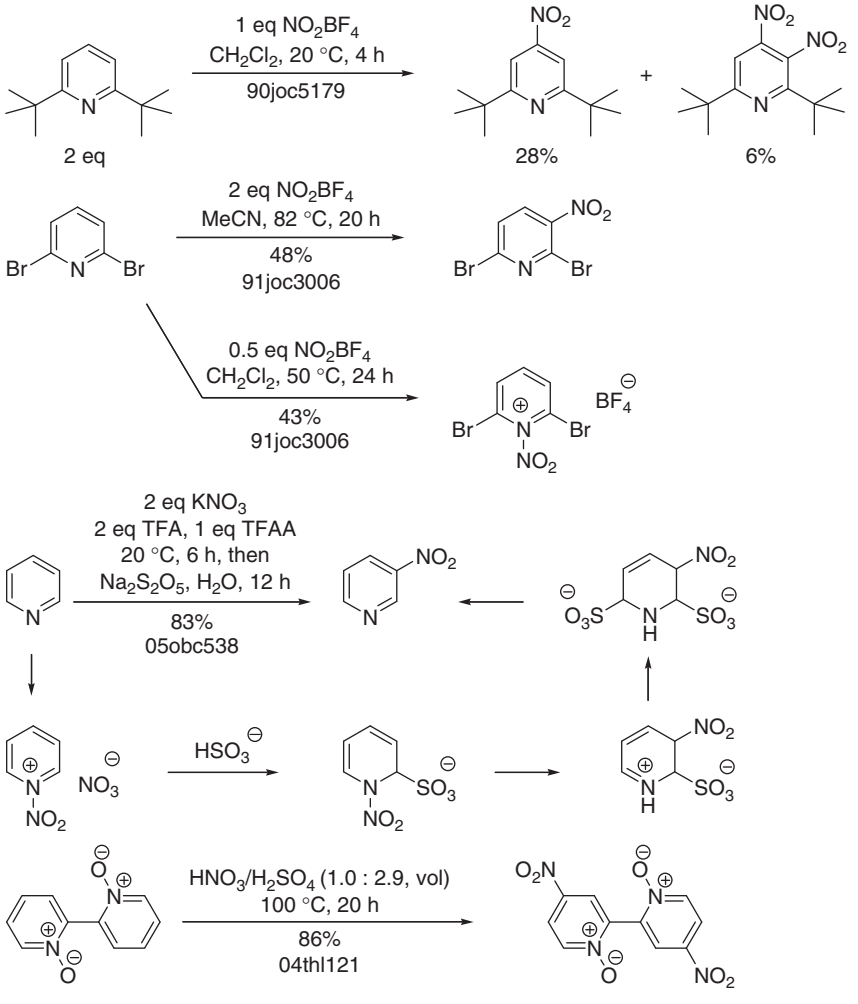
6.1.4 Electron-Deficient Arenes

Even electron-deficient arenes can usually be nitrated. Careful control of the reaction temperature is critical, because electrophilic nitrations are highly exothermic and thermal runaways and explosions are common. At high temperatures, a complete oxidative degradation of the arene may occur (Scheme 6.8).



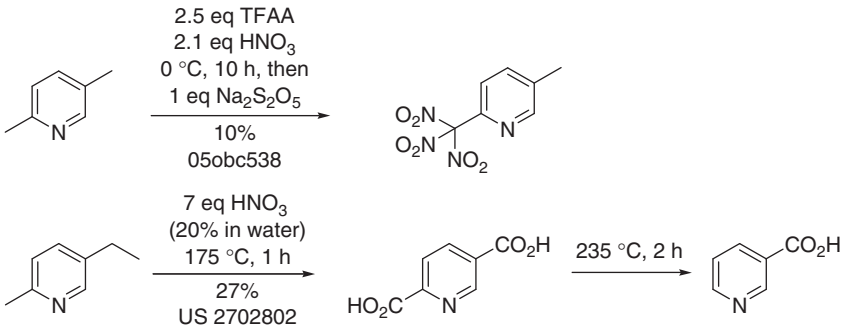
Scheme 6.8 Oxidation of nitronaphthalenes to phthalic acids [41].

Pyridines are electron-deficient heteroarenes and are difficult to nitrate directly. Their *N*-oxides, however, are more electron rich (but also C–H acidic), and undergo nitration regioselectively at position 4 (Scheme 6.9).



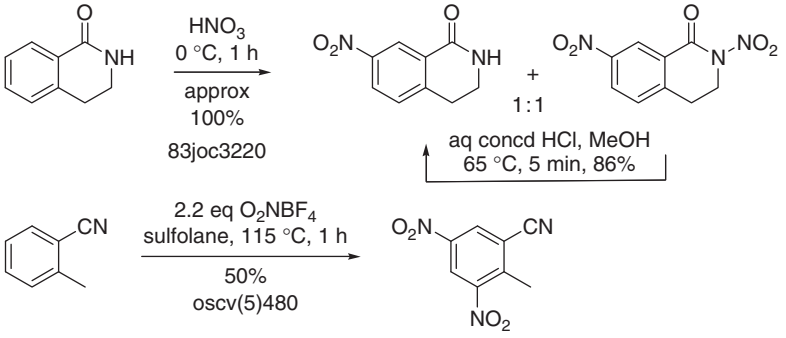
Scheme 6.9 Nitration of pyridines and pyridine *N*-oxides [42–45].

Because pyridines do not readily react with electrophiles, reactions of functional groups attached to pyridines are common side reactions. Pyridines with primary or secondary alkyl groups at positions 2 or 4 are C–H acidic, and can be halogenated, acylated, or nitrated at the alkyl group. The resulting polyhalo- or polynitroalkyl groups are good leaving groups, and can be displaced by nucleophiles (e.g., [46]). Under forcing conditions, alkylpyridines will be oxidized to pyridinecarboxylic acids. Some heteroarenecarboxylic acids undergo partial or complete decarboxylation if heated too strongly [47] (Scheme 6.10).



Scheme 6.10 Reaction of alkylpyridines with nitric acid [44, 48].

Amides with an NH group can be nitrated at nitrogen [49], but this reaction is only rarely observed. Anilides are usually cleanly nitrated at carbon (Scheme 6.11). *N*-Nitramides are strong oxidants, and are readily reduced during work-up by even weak reducing agents.

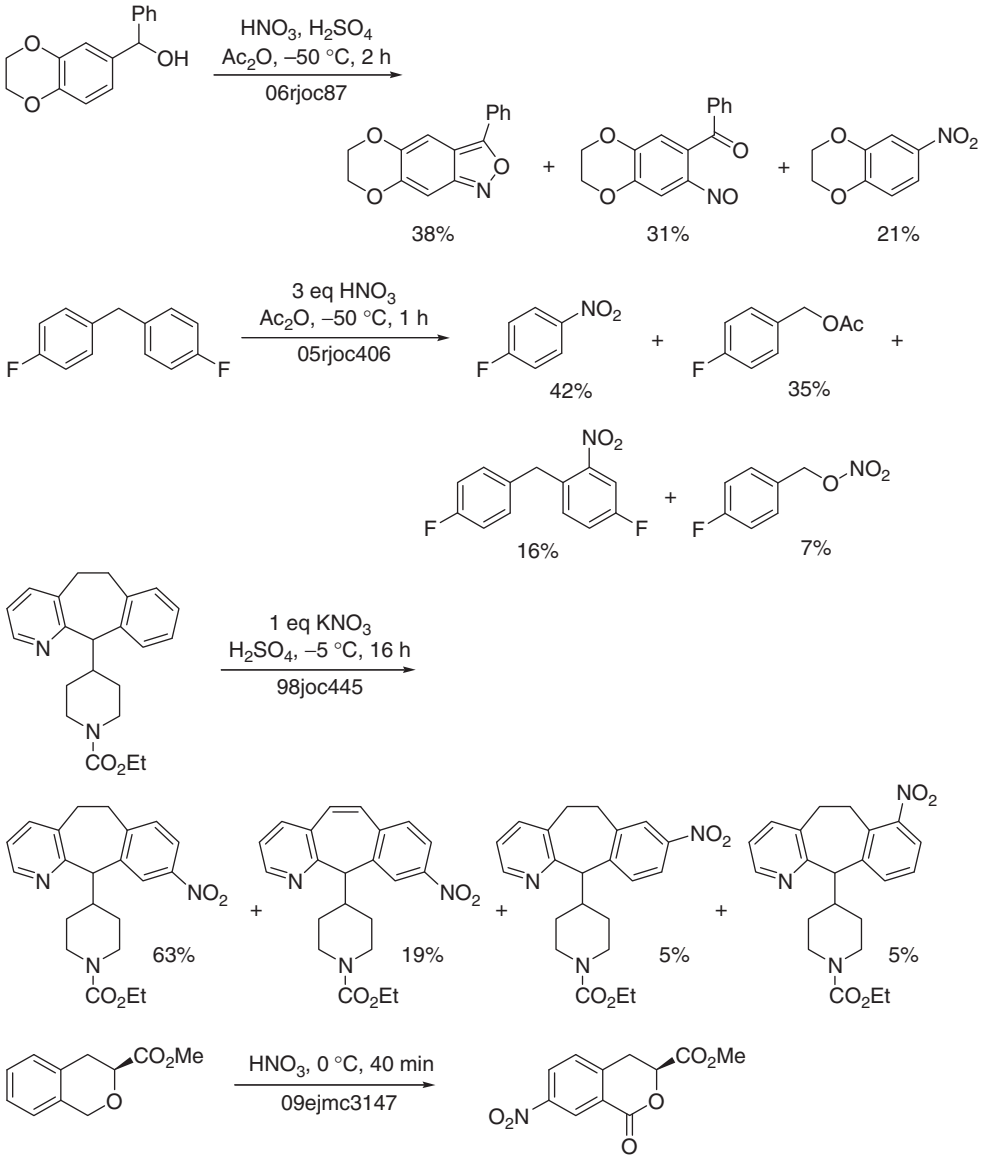


Scheme 6.11 Nitration of benzamides and benzonitriles [50, 51].

6.1.5
Electron-Rich Arenes

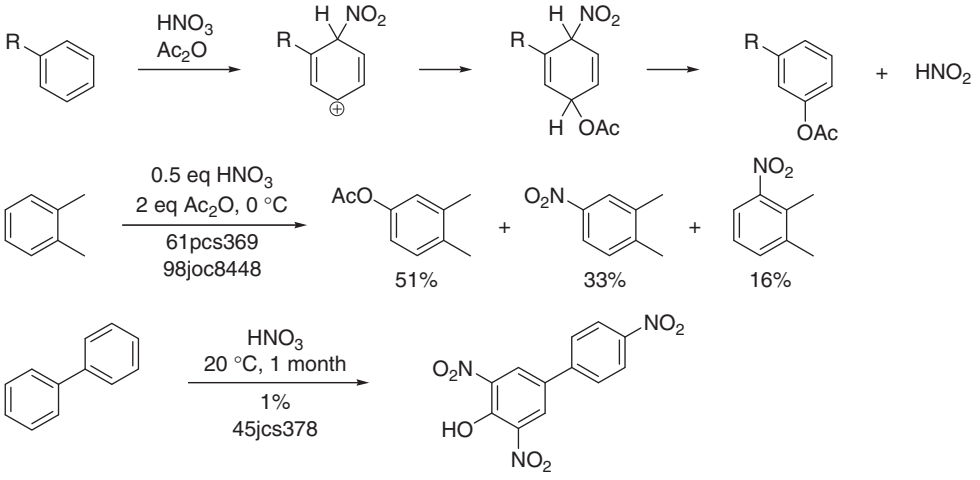
Electrophilic nitrations of reactive arenes are usually conducted at low temperature with a slight excess of nitrating reagent only, to avoid the many potential side reactions. These include dearomatization, polynitration, and oxidative degradation of the arene or its substituents.

Alkyl groups can be dehydrogenated or oxidized to alkyl nitrites, ketones, or carboxylic acids during electrophilic aromatic nitrations. In fact, heating with nitric acid is one of the cheapest and most environmentally friendly methods for the conversion of alkylarenes or -heteroarenes into carboxylic acids. Particularly sensitive are alkyl groups that form stable carbocations (secondary alkyl, allyl, and benzyl) (Scheme 6.12).



Scheme 6.12 Dealkylation and oxidation of alkylarenes by nitric acid [52–55].

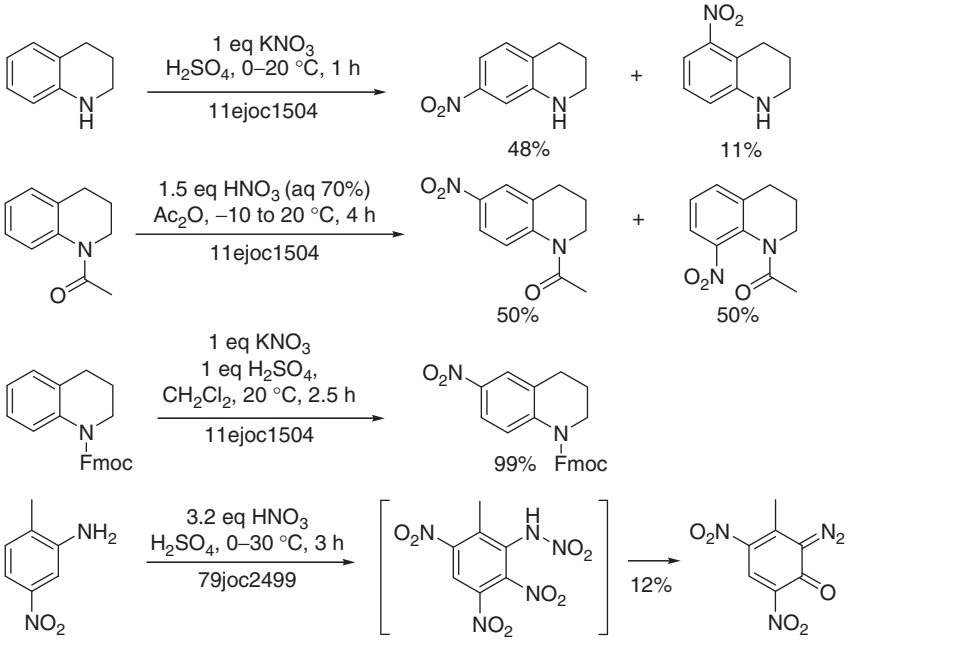
Alkylbenzenes can yield acetoxybenzenes or phenols upon nitration in HNO_3/Ac_2O [56]. Mechanistic studies [57] suggest that these products arise from the 1,4-addition of acetyl nitrate to the arene, followed by elimination of HNO_2 (Scheme 6.13). The formation of phenols may be prevented by using NO_2BF_4 or HNO_3/H_2SO_4 as nitrating reagent. Mixtures of HNO_3 and H_2O_2 can cause extensive hydroxylation of electron-rich arenes [58].



Scheme 6.13 Formation of acetoxybenzenes and phenols during electrophilic nitrations [32, 59, 60].

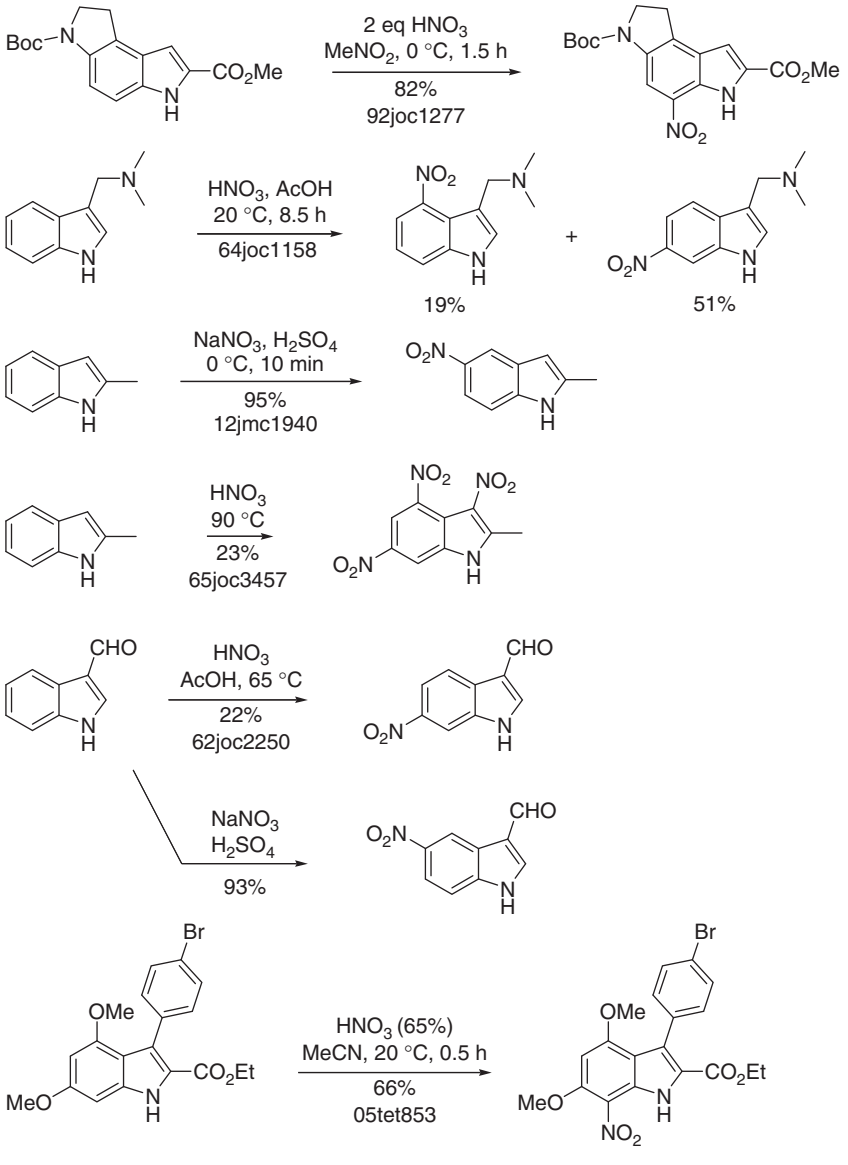
6.1.5.1 **Anilines**

Anilines are nitrated mostly in the meta position in the presence of strong acids, but yield ortho/para nitroanilines if the aniline is not completely protonated (Scheme 6.14). Anilines can also be nitrated at nitrogen (to yield potentially



Scheme 6.14 Nitration of anilines [61, 62].

explosive nitramines), but this requires an unprotonated amino group. The strong acids used for most nitrations usually prevent N-nitration of anilines, and only anilines of low basicity (e.g., polynitroanilines) will undergo N-nitration. In the presence of reducing reagents (e.g., NO_2), aromatic nitramines may be reduced and dehydrated to diazonium salts (last equation, Scheme 6.14).

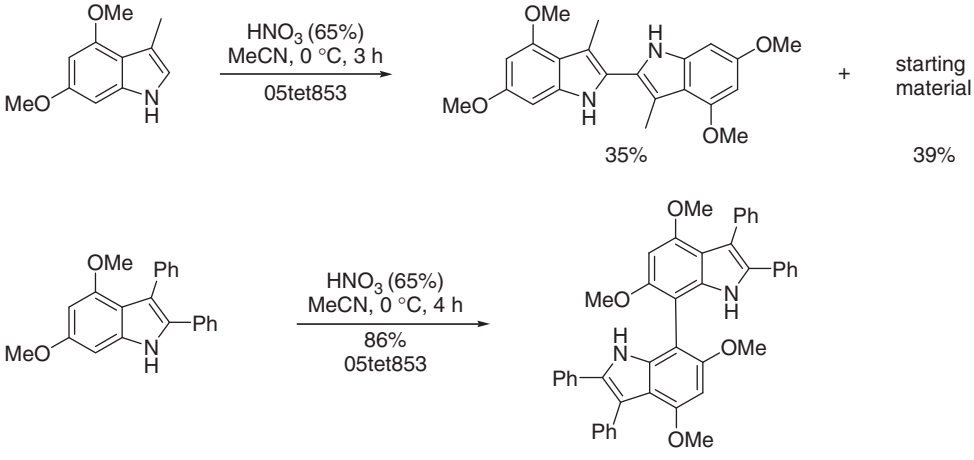


Scheme 6.15 Nitration of indoles [63–68]. Further examples: [47, 69].

6.1.5.2 **Indoles**

The outcome of indole nitration can be difficult to predict. Depending on the precise substitution pattern and reaction conditions, all positions of indole can be nitrated (Scheme 6.15).

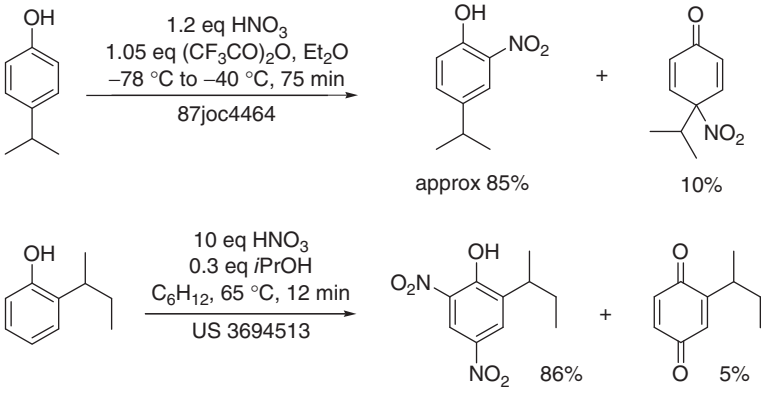
Because indoles readily undergo oxidation by single-electron transfer, oxidative dimerization is a typical side reaction of the treatment of indoles with electrophiles (Scheme 6.16).



Scheme 6.16 Nitric acid-mediated oxidative dimerization of indoles [68].

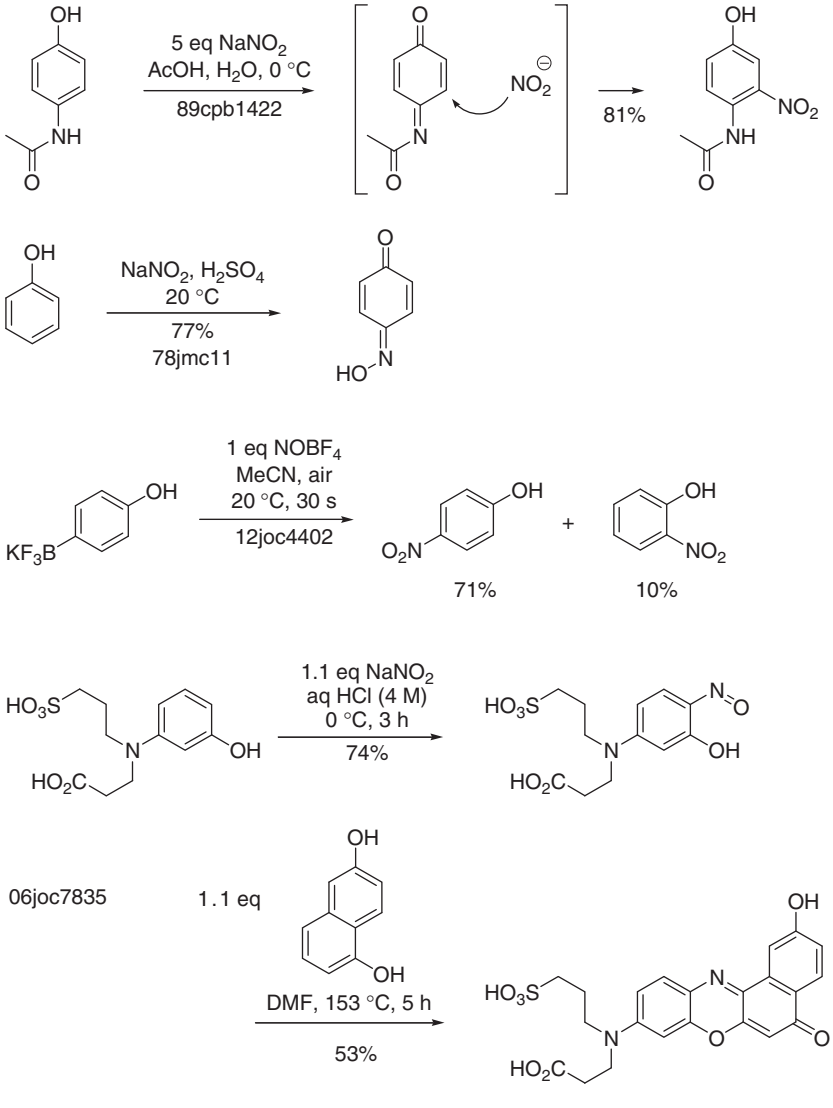
6.1.5.3 **Phenols**

The nitration of phenols with nitric acid is usually ortho/para selective. Important side reactions include multiple nitrations and the oxidation to quinones (Scheme 6.17).



Scheme 6.17 Nitration of phenols [70, 71].

Treatment of phenols with nitrous acid can yield the expected benzoquinone oximes (tautomers of nitrosophenols) but also a number of other products. If a phenol readily forms a quinone upon oxidation (dihydroxybenzenes and aminophenols), meta-nitrated phenols may be formed by conjugate addition of nitrite to the quinone. Nitrosophenols may also be oxidized further to nitrophenols by an excess of nitrous acid (Scheme 6.18). Moreover, nitrosophenols are

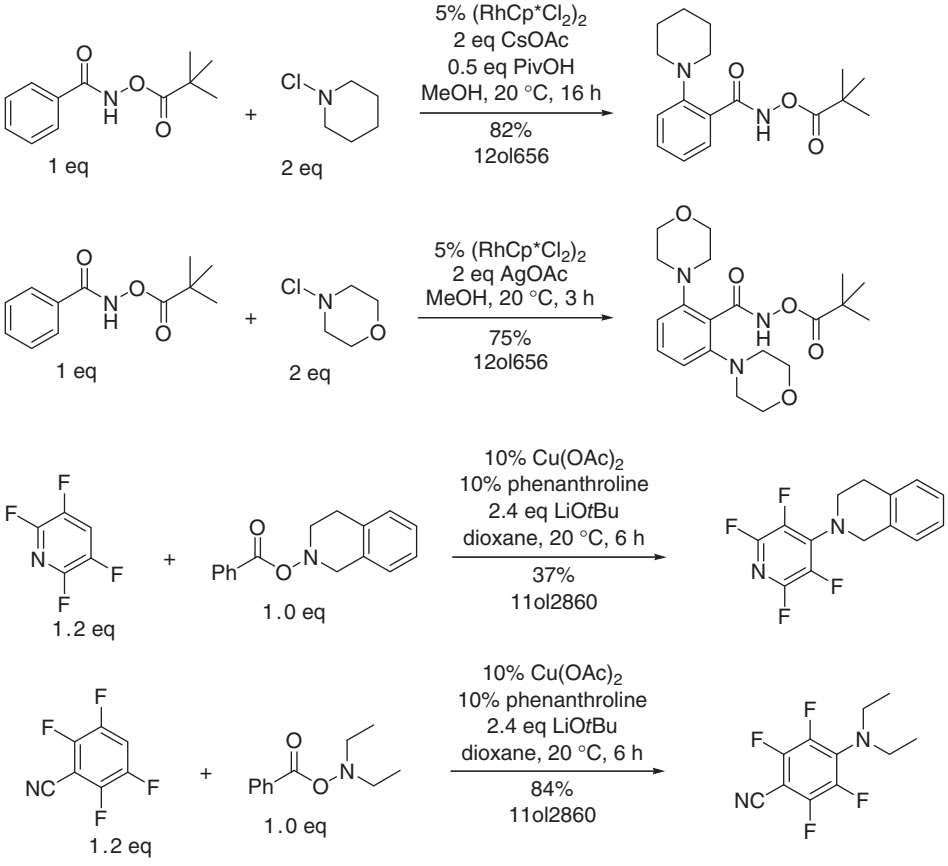


Scheme 6.18 Reaction of phenols with nitrous acid or $NOBF_4$ [72–75].

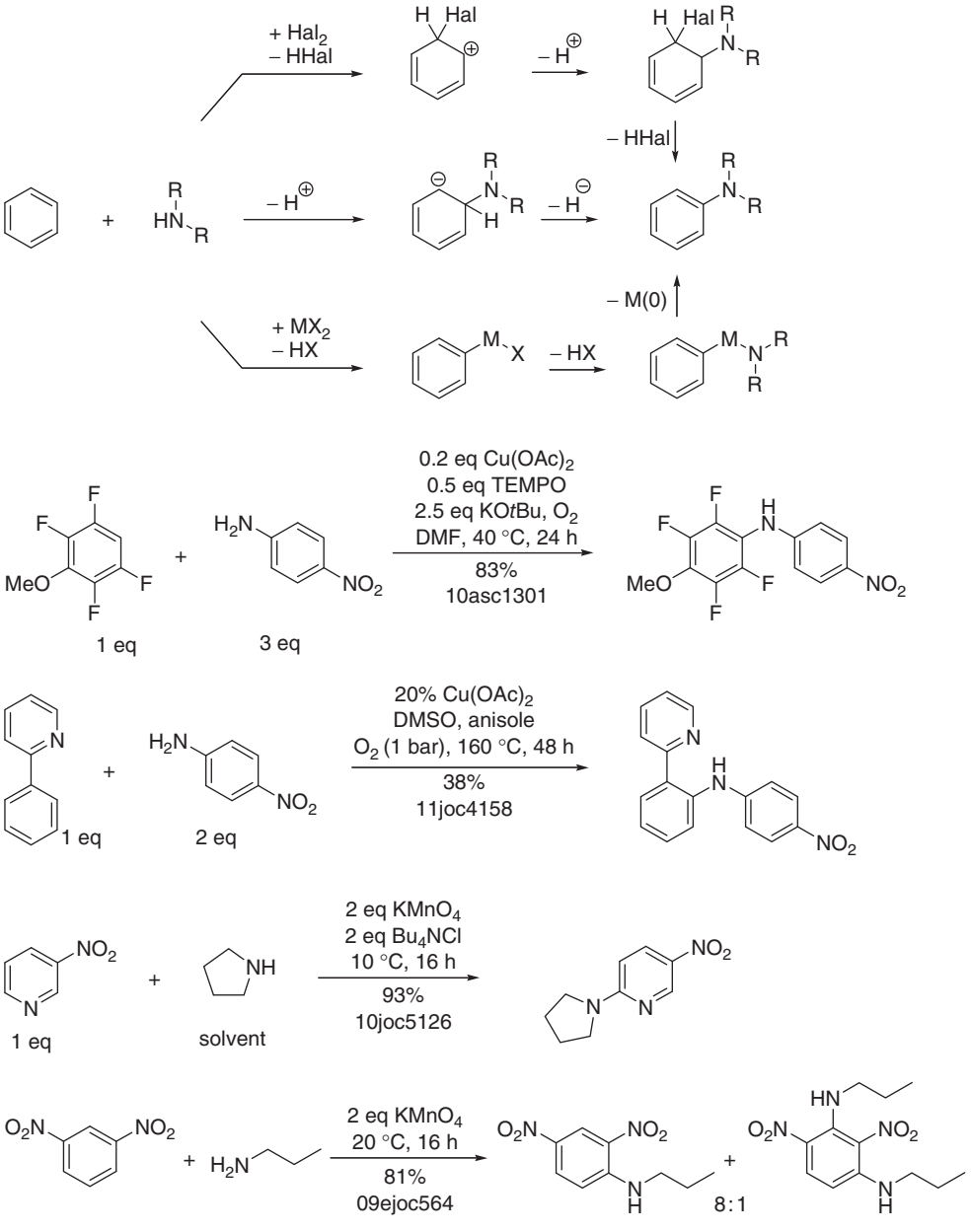
electrophilic aminating reagents, and can aminate other electron-rich arenes. Such reactions can sometimes be prevented by keeping the reaction times short and the temperature low.

6.2
Electrophilic Aromatic Aminations

Electrophilic aminations are inherently problematic because the reactivity of arenes increases upon amination. The yield of monoaminated product can sometimes be increased by using a large excess of arene, but this is not always practical. In recent years, though, a number of useful procedures for electrophilic aromatic amination have been developed (Scheme 6.19).



Scheme 6.19 Intermolecular electrophilic aromatic aminations [76, 77]. Further examples: [78, 79].



Scheme 6.20 Oxidative aromatic aminations with amines [80–83]. Hal, halogen; X, leaving group; R, alkyl, aryl. Further examples: [84, 85].

The amination of unsubstituted aromatic positions can also be achieved by treating electron-rich arenes with halogens and amines (Schemes 6.20 and 6.21), or strongly electron-deficient arenes with amines in the presence of an oxidant. The transition-metal-catalyzed variations of these reactions probably proceed by arene metallation (Scheme 6.20).

6.2.1 Typical Side Reactions

N-Halogenated amines may act as either electrophilic aminating or halogenating reagents. Similarly, substituted hydroxylamines can mediate both aminations and hydroxylations. Moreover, *N*-halo or hydroxylamines are oxidants, and can lead to dehydrogenations, oxidative dimerizations, or the formation of radicals (Scheme 6.21).

Anilines readily undergo oxidation, and tend to oligomerize in the presence of oxidants. Diarylamines can be cyclized to carbazoles, and other aniline derivatives may cyclize to indoles, benzimidazoles, or other heterocycles when treated with oxidants (Scheme 6.22). This could be one further reason for the low yield of most electrophilic aromatic aminations.

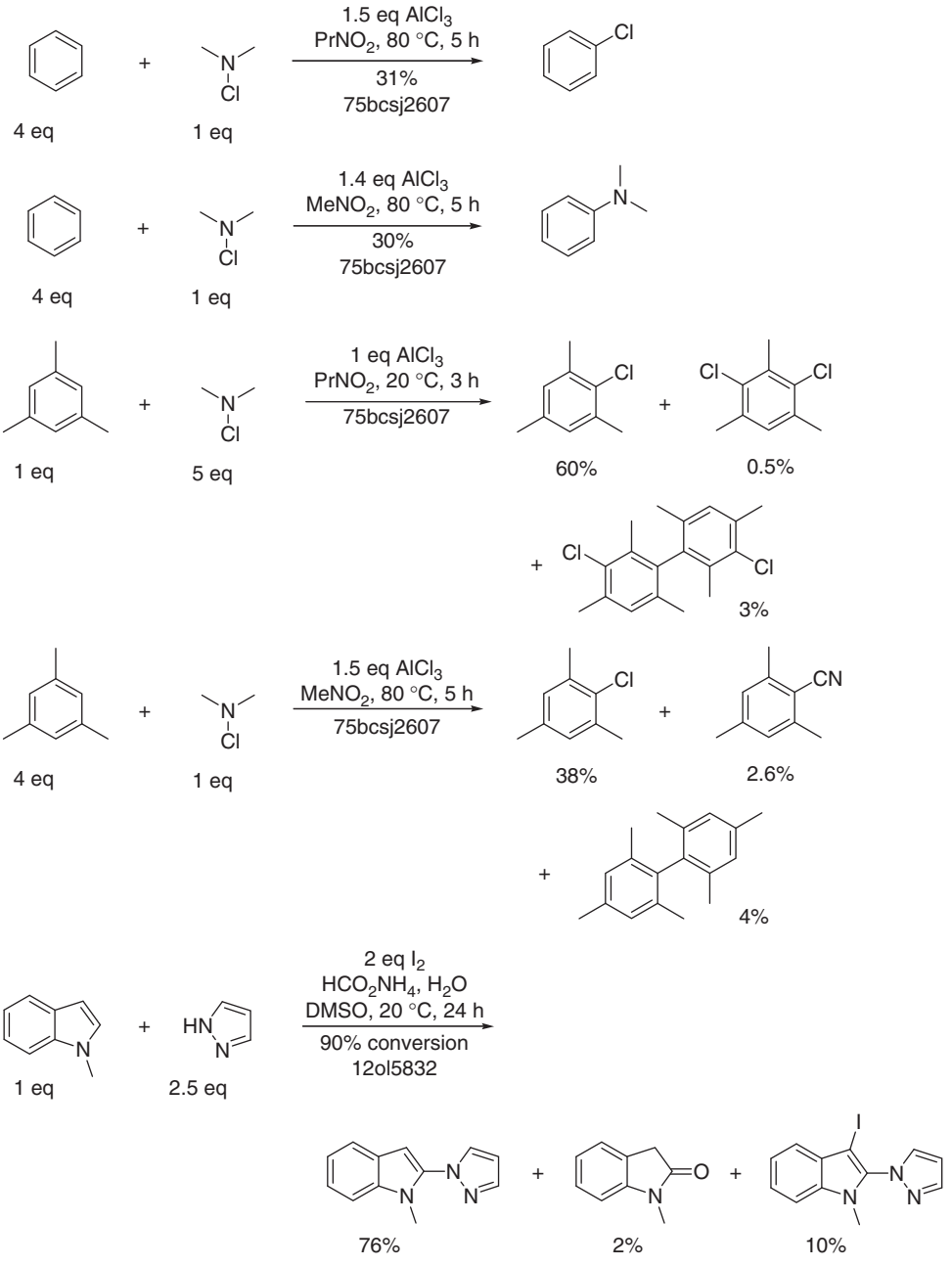
6.3 Electrophilic Aromatic Amidations

Because anilides are not as readily oxidized as anilines, the electrophilic formation of RCON–Ar bonds is often cleaner than electrophilic aromatic amination. Numerous examples of successful aromatic amidations have been reported (Scheme 6.23). As in the case of aminations, these can be realized either with amides bearing a leaving group at nitrogen or with amides and an external oxidant. When using transition-metal catalysts, the reaction can proceed either via C-metallated arenes or via N-metallated amides.

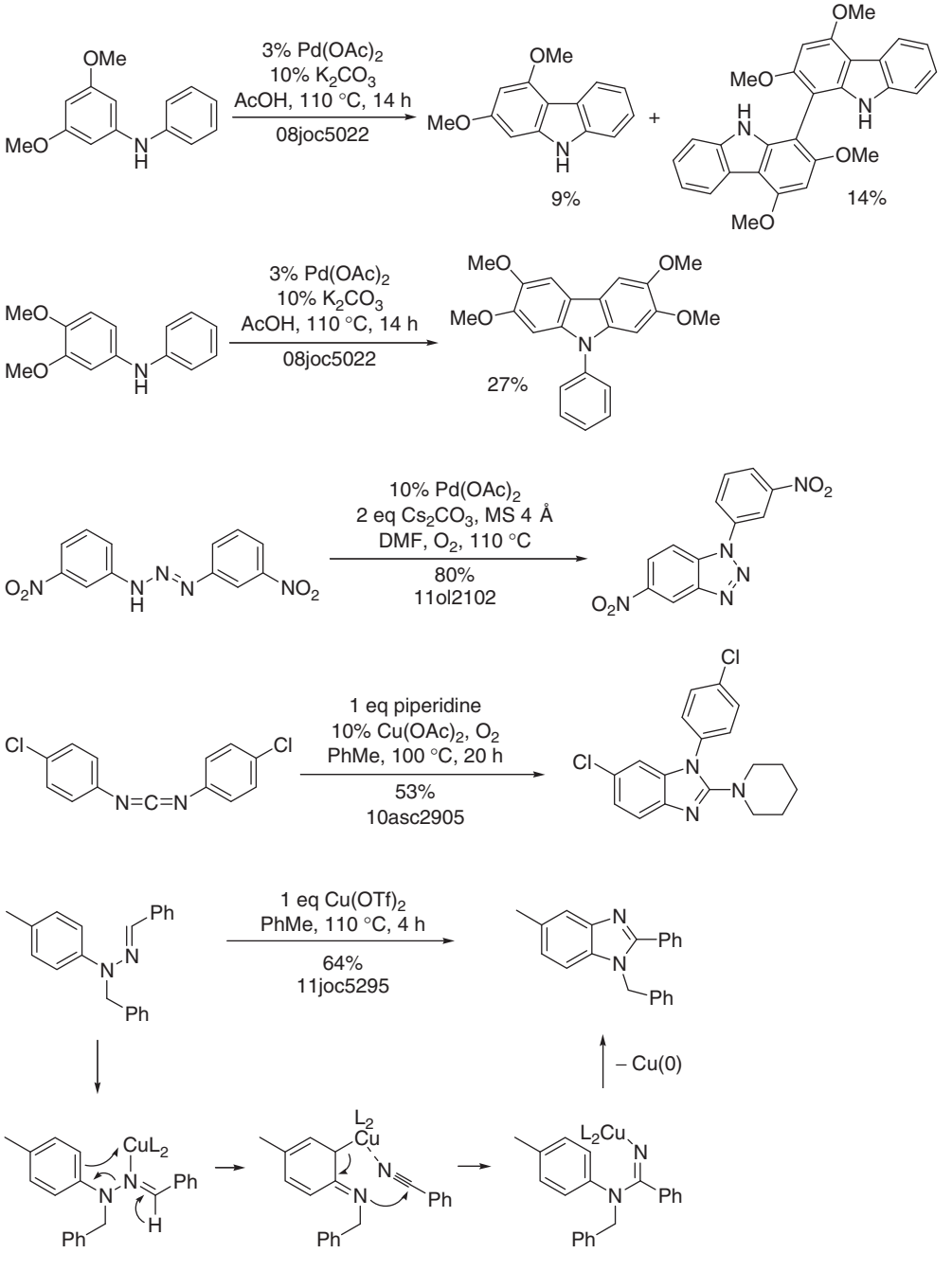
Intramolecular aromatic amidations usually proceed even more smoothly than intermolecular reactions. Closely related to amidations are arylations by nitrenes and benzimidazole preparations by cyclization of *N*-arylamidoximes and intramolecular aminations with nitro compounds (Scheme 6.24).

6.3.1 Typical Side Reactions

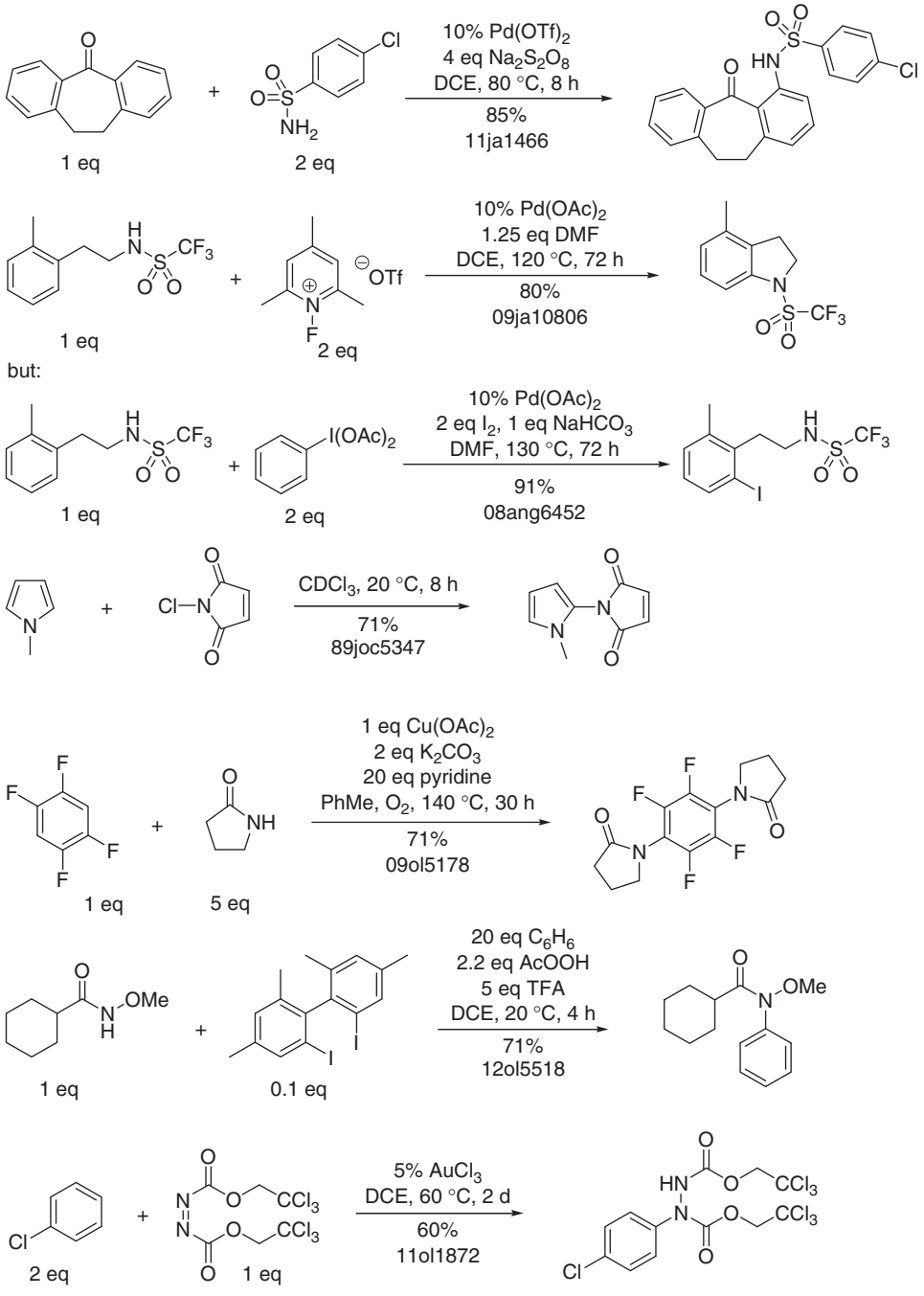
Electrophilic amidations are similar to halogenations, and similar side reactions can be expected. Because amides are poor nucleophiles, other nucleophiles and even halides may compete with amides during arylations. Moreover, the products are often easily halogenated or hydroxylated under the required reaction conditions (Scheme 6.25).



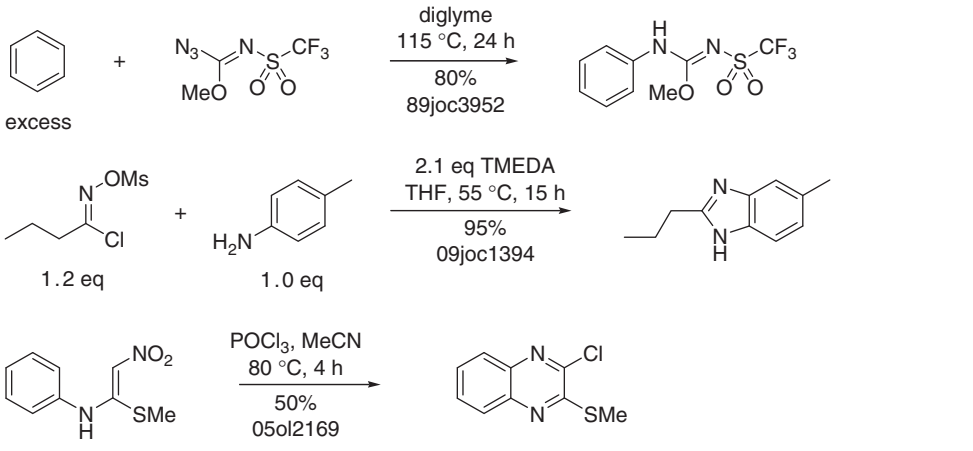
Scheme 6.21 Side reactions during electrophilic aromatic aminations [86, 87]. Further examples: [88].



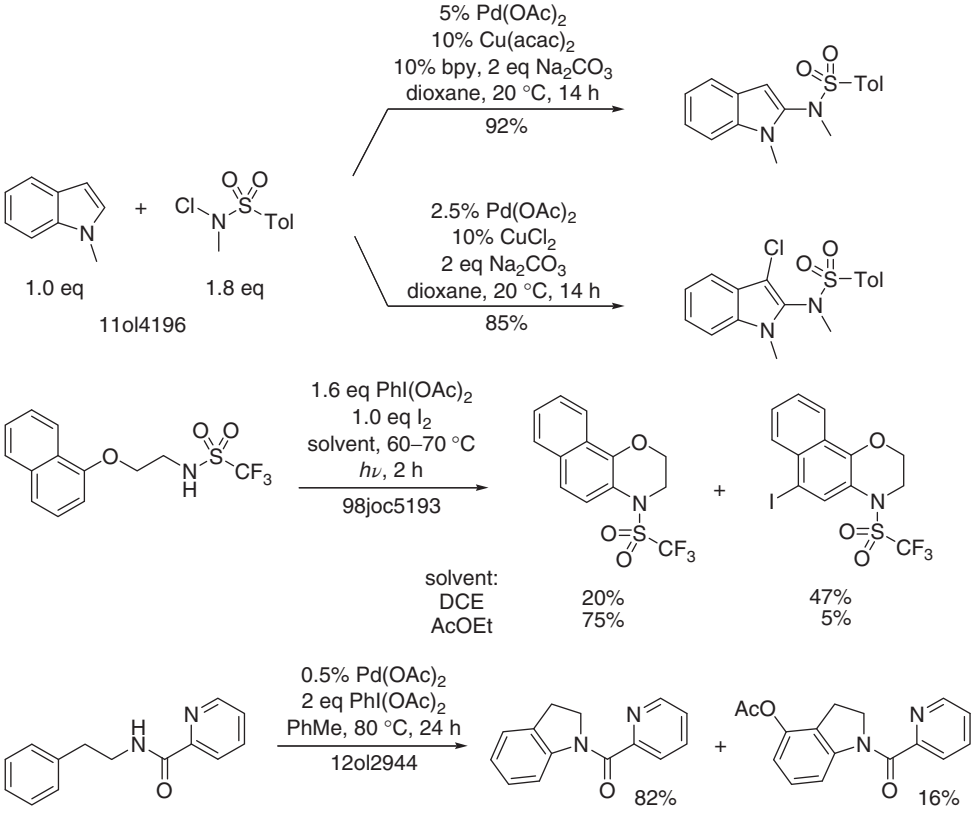
Scheme 6.22 Oxidative transformations of aniline derivatives [89–92].



Scheme 6.23 Examples of electrophilic aromatic amidations and carbamoylations [93–98]. Further examples: [99].

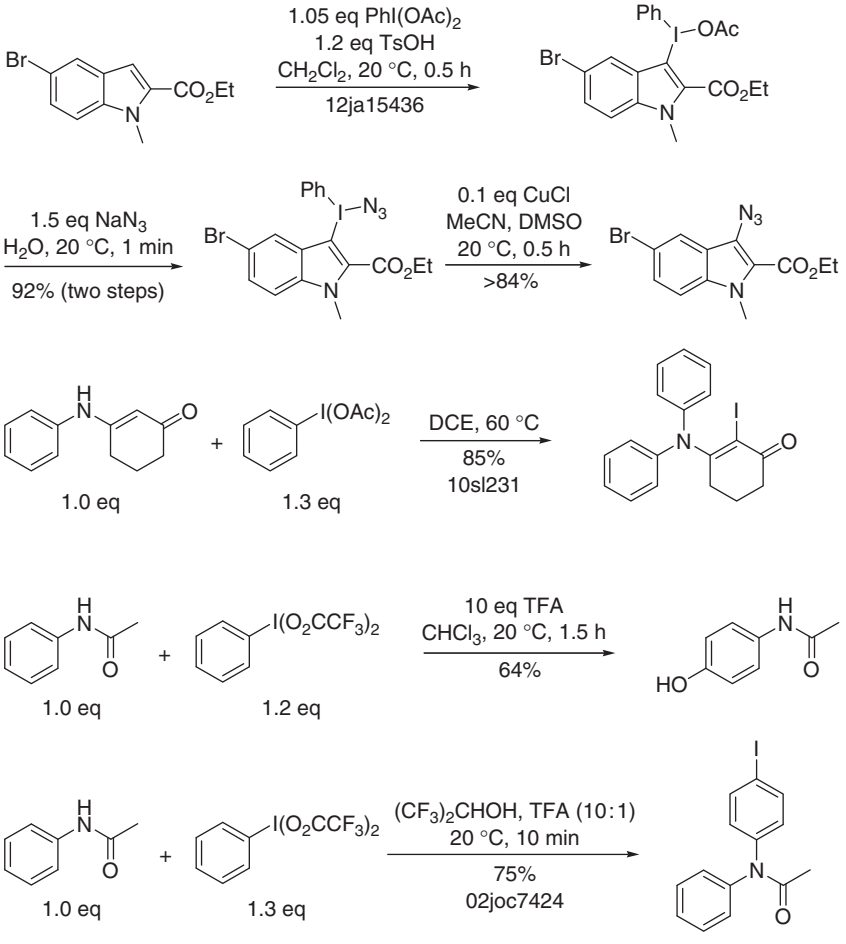


Scheme 6.24 Electrophilic aromatic aminations with azides, oximes, and nitroalkenes [100–102].



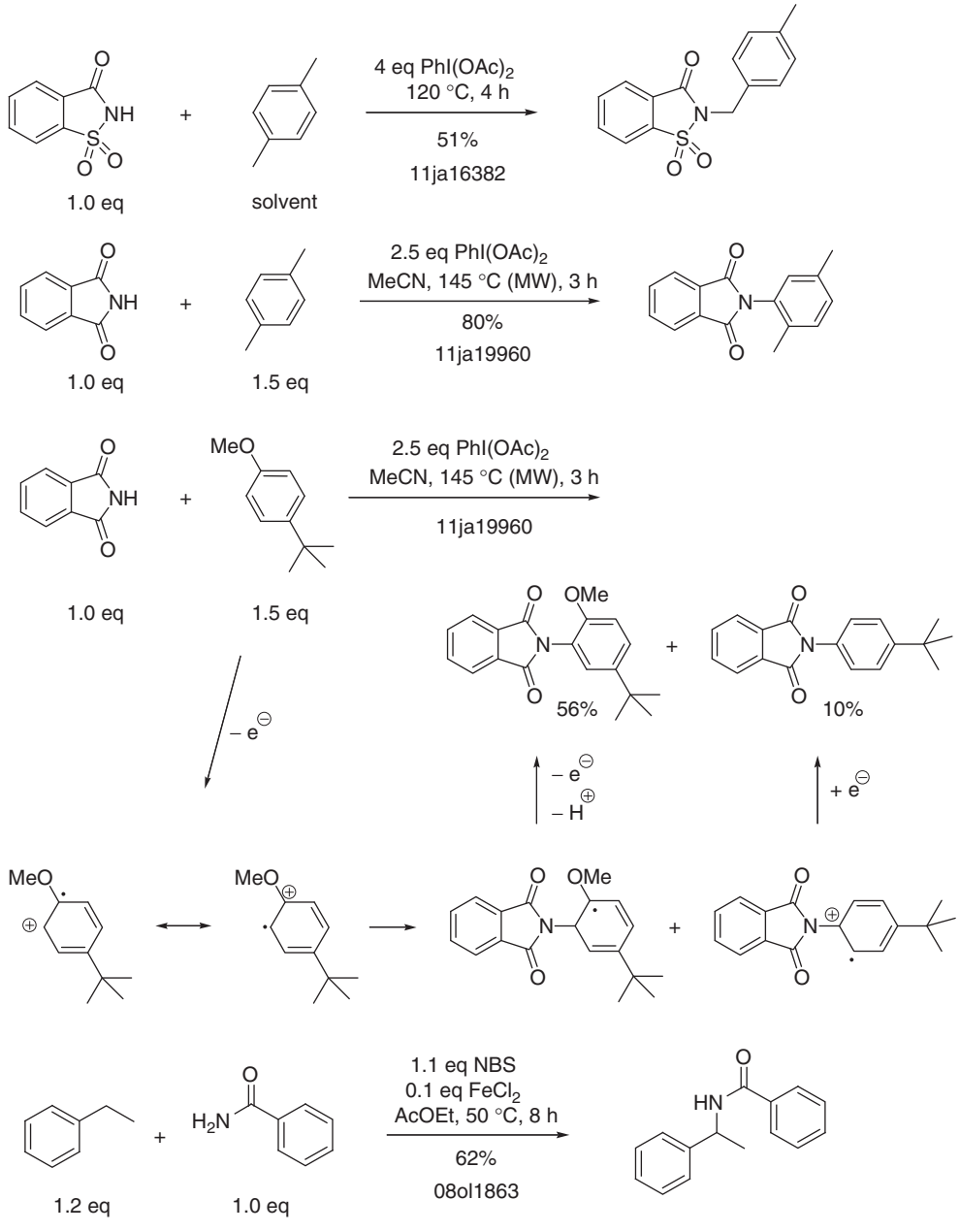
Scheme 6.25 Halogenations and acetoxylation as side reactions of aromatic amidations [103–105].

As external oxidant for amidations, hypervalent iodine compounds are often used, for instance $PhI(OAc)_2$. These may first react with the arene, followed by aromatic nucleophilic displacement of iodobenzene (Scheme 6.26). Such reactions will yield the desired product only when aromatic nucleophilic substitution at the phenyl group is significantly slower than at the oxidized starting arene. Moreover, hypervalent iodine compounds occasionally react as iodinating reagents.



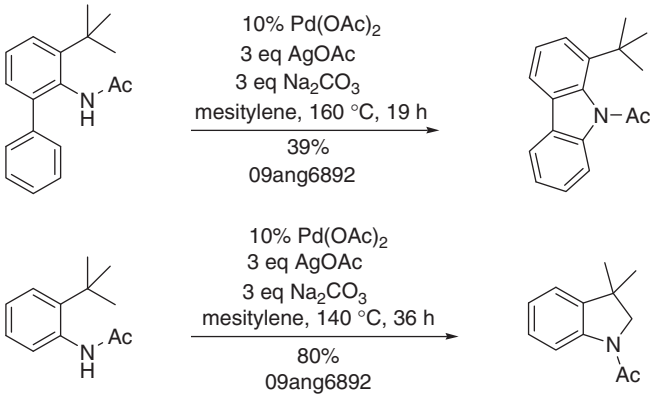
Scheme 6.26 C–N Bond formation with hypervalent iodine reagents [106–108].

As in the case of halogenations and nitrations, benzylic amidation and substitution of other groups than hydrogen are to be expected during aromatic electrophilic amidations (Scheme 6.27).



Scheme 6.27 Benzylic amidation and substitution of methoxy groups as side reactions of aromatic amidations [109–111].

In the case of intramolecular amidations proceeding via N-metallated amides, the amidation of aliphatic non-benzylic positions is sometimes observed (Scheme 6.28).



Scheme 6.28 Intramolecular aliphatic amidation [112]. Further examples: [113, 114].

References

1. Choudary, B.M., Kantam, M.L., Sateesh, M., Rao, K.K., and Raghavan, K.V. (2002) Process for the production of nitroaromatic compounds from aromatic hydrocarbons using modified clay catalysts. US Patent 6376726.
2. Nose, M., Suzuki, H., and Suzuki, H. (2001) Nonacid nitration of benzenedicarboxylic and naphthalenecarboxylic acid esters. *J. Org. Chem.*, **66**, 4356–4360.
3. Laali, K.K. and Gettwert, V.J. (2001) Electrophilic nitration of aromatics in ionic liquid solvents. *J. Org. Chem.*, **66**, 35–40.
4. Mascal, M., Yin, L., Edwards, R., and Jarosh, M. (2008) Aromatic nitration in liquid $Ag_{0.51}K_{0.42}Na_{0.07}NO_3$. *J. Org. Chem.*, **73**, 6148–6151.
5. Koley, D., Colón, O.C., and Savinov, S.N. (2009) Chemoselective nitration of phenols with *tert*-butyl nitrite in solution and on solid support. *Org. Lett.*, **11**, 4172–4175.
6. Marterer, W., Prikoszovich, W., Wiss, J., and Prashad, M. (2003) The nitration of 8-methylquinoxalines in mixed acid. *Org. Process Res. Dev.*, **7**, 318–323.
7. Barrett, A.G.M., Braddock, D.C., Ducray, R., McKinnell, R.M., and Waller, F.J. (2000) Lanthanide triflate and triflide catalyzed atom economic nitration of fluoroarenes. *Synlett*, 57–58.
8. Atkins, R.L., Hollins, R.A., and Wilson, W.S. (1986) Synthesis of polynitro compounds. Hexasubstituted benzenes. *J. Org. Chem.*, **51**, 3261–3266.
9. Aridoss, G. and Laali, K.K. (2011) Ethylammonium nitrate (EAN)/Tf_2O and EAN/TFAA: ionic liquid based systems for aromatic nitration. *J. Org. Chem.*, **76**, 8088–8094.
10. Doddi, G., Mencarelli, P., Razzini, A., and Stegel, F. (1979) Nitration of 1-R-pyrroles: formation of polynitro-1-R-pyrroles and orienting effects in the reactions of 3-nitro-1-R-pyrroles. *J. Org. Chem.*, **44**, 2321–2323.
11. Katritzky, A.R., Vakulenko, A.V., Sivapackiam, J., Draghici, B., and Damavarapub, R. (2008) Synthesis of dinitro-substituted furans, thiophenes, and azoles. *Synthesis*, 699–706.

12. Newman, M.S. and Boden, H. (1973) 2,4,5,7-tetranitrofluorenone. *Org. Synth.*, Coll. Vol. **5**, 1029–1030.
13. Moodie, R.B. and Schofield, K. (1976) Ipso attack in aromatic nitration. *Acc. Chem. Res.*, **9**, 287–292.
14. Takahashi, K., Ohta, M., Shoji, Y., Kasai, M., Kunishiro, K., Miike, T., Kanda, M., and Shirahase, H. (2010) Novel Acyl-CoA: cholesterol acyltransferase inhibitor: indoline-based sulfamide derivatives with low lipophilicity and protein binding ratio. *Chem. Pharm. Bull.*, **58**, 1057–1065.
15. Duggan, S.A., Fallon, G., Langford, S.J., Lau, V.-L., Satchell, J.F., and Paddon-Row, M.N. (2001) Crown-linked porphyrin systems. *J. Org. Chem.*, **66**, 4419–4426.
16. Yamato, T., Kamimura, H., and Furukawa, T. (1997) Medium-sized cyclophanes. 43. First evidence for *anti–syn*-ring inversion under the nitration of 5,13-di-*tert*-butyl-8,16-dimethoxy[2.2]metacyclophane. *J. Org. Chem.*, **62**, 7560–7564.
17. Balogh, M., Pennetreau, P., Hermecz, I., and Gerstmans, A. (1990) Clay-supported iron(III) nitrate: a multifunctional reagent. Oxidation and nitration of nitrogen bridgehead compounds. *J. Org. Chem.*, **55**, 6198–6202.
18. Carpenter, M.S., Easter, W.M., and Wood, T.F. (1951) Nitro musks. I. Isomers, homologs, and analogs of musk ambrette. *J. Org. Chem.*, **16**, 586–617.
19. Yamakawa, T., Kagechika, H., Kawachi, E., Hashimoto, Y., and Shudo, K. (1990) Retinobenzoic acids. 5. Retinoidal activities of compounds having a trimethylsilyl or trimethylgermyl group(s) in human promyelocytic leukemia cells HL-60. *J. Med. Chem.*, **33**, 1430–1437.
20. Manna, S., Maity, S., Rana, S., Agasti, S., and Maiti, D. (2012) *ipso*-Nitration of arylboronic acids with bismuth nitrate and perdisulfate. *Org. Lett.*, **14**, 1736–1739.
21. Donohoe, T.J., Jonesa, C.R., and Barbosa, L.C.A. (2011) Total synthesis of (±)-streptonigrin: *de novo* construction of a pentasubstituted pyridine using ring-closing metathesis. *J. Am. Chem. Soc.*, **133**, 16418–16421.
22. Das, J.P., Sinha, P., and Roy, S. (2002) A nitro-Hunsdiecker reaction: from unsaturated carboxylic acids to nitrostyrenes and nitroarenes. *Org. Lett.*, **4**, 3055–3058.
23. Dantas de Araujo, A., Christensen, C., Buchardt, J., Kent, S.B.H., and Alewood, P.F. (2011) Synthesis of tripeptide mimetics based on dihydroquinolinone and benzoxazinone scaffolds. *Chem. Eur. J.*, **17**, 13983–13986.
24. Scheurer, A., Mosset, P., Bauer, W., and Saalfrank, R.W. (2001) A practical route to regiospecifically substituted (*R*)- and (*S*)-oxazolylphenols. *Eur. J. Org. Chem.*, **16**, 3067–3074.
25. Stupi, B.P., Li, H., Wang, J., Wu, W., Morris, S.E., Litosh, V.A., Muniz, J., Hersh, M.N., and Metzker, M.L. (2012) Stereochemistry of benzylic carbon substitution coupled with ring modification of 2-nitrobenzyl groups as key determinants for fast-cleaving reversible terminators. *Angew. Chem. Int. Ed.*, **51**, 1724–1727.
26. Bosch, E. and Kochi, J.K. (1994) Thermal and photochemical nitration of aromatic hydrocarbons with nitrogen dioxide. *J. Org. Chem.*, **59**, 3314–3325.
27. Occhipinti, G., Liguori, L., Tsoukala, A., and Bjørsvik, H.-R. (2010) A switchable oxidation process leading to various versatile pharmaceutical intermediates. *Org. Process Res. Dev.*, **14**, 1379–1384.
28. Nishiwaki, Y., Sakaguchi, S., and Ishii, Y. (2002) An efficient nitration of light alkanes and the alkyl side-chain of aromatic compounds with nitrogen dioxide and nitric acid catalyzed by *N*-hydroxyphthalimide. *J. Org. Chem.*, **67**, 5663–5668.
29. Masnovi, J.M., Sankararaman, S., and Kochi, J.K. (1989) Direct observation of the kinetic acidities of transient aromatic cation radicals. The mechanism of electrophilic side-chain nitration of the methylbenzenes. *J. Am. Chem. Soc.*, **111**, 2216–2263.
30. Dalmolen, J., van der Sluis, M., Nieuwenhuijzen, J.W., Meetsma, A.,

de Lange, B., Kaptein, B., Kellogg, R.M., and Broxterman, Q.B. (2004) Synthesis of enantiopure 1-aryl-1-butylamines and 1-aryl-3-butenylamines by diastereoselective addition of allylzinc bromide to imines derived from (*R*)-phenylglycine amide. *Eur. J. Org. Chem.*, **2004** (7), 1544–1557.

31. Onopchenko, A., Sabourin, E.T., and Selwitz, C.M. (1981) Selective nitration of benzophenone. *J. Org. Chem.*, **46**, 5014–5017.
32. Bennett, G.M. and Grove, J.F. (1945) By-products in aromatic nitration. Part II. Nitration of diphenyl, quinoline, and benzophenone. *J. Chem. Soc.*, 378–380.
33. Bosch, E. and Kochi, J.K. (1994) Direct nitrosation of aromatic hydrocarbons and ethers with the electrophilic nitrosonium cation. *J. Org. Chem.*, **59**, 5573–5586.
34. Potturi, H.K., Gurung, R.K., and Hou, Y. (2012) Nitromethane with IBX/TBAF as a nitrosating agent: synthesis of nitrosamines from secondary or tertiary amines under mild conditions. *J. Org. Chem.*, **77**, 626–631.
35. Liu, Y. and McWhorter, W.W. (2003) Synthesis of 8-desbromohinckdentine A. *J. Am. Chem. Soc.*, **125**, 4240–4252.
36. Atherton, J.H., Moodie, R.B., Noble, D.R., and O'Sullivan, B. (1997) Nitrosation of *m*-xylene, anisole, 4-nitrophenyl phenyl ether and toluene in trifluoroacetic acid or in acetic–sulfuric acid mixtures under nitric oxide. *J. Chem. Soc., Perkin Trans. 2*, 663–664.
37. Milligan, B. (1983) Some aspects of nitration of aromatics by lower oxidation states of nitrogen. *J. Org. Chem.*, **48**, 1495–1500.
38. Leoppky, R.N. and Tomasik, W. (1983) Stereoelectronic effects in tertiary amine nitrosation: nitrosative cleavage vs. aryl ring nitration. *J. Org. Chem.*, **48**, 2751–2757.
39. Zhang, L., Liu, Z., Li, H., Fang, G., Barry, B.-D., Belay, T.A., Bi, X., and Liu, Q. (2011) Copper-mediated chelation-assisted *ortho* nitration of (hetero)arenes. *Org. Lett.*, **13**, 6536–6539.
40. Liu, Y.-K., Lou, S.-J., Xu, D.-Q., and Xu, Z.-Y. (2010) Regiospecific synthesis of nitroarenes by palladium-catalyzed nitrogen-donor-directed aromatic C–H nitration. *Chem. Eur. J.*, **16**, 13590–13593.
41. Havlík, M., Král, V., and Dolenský, B. (2006) Overcoming regioselectivity issues inherent in bisTröger's base preparation. *Org. Lett.*, **8**, 4867–4870.
42. Olah, G.A., Laali, K., Farooq, O., and Olah, J.A. (1990) C-Nitration of 2,6-di- and 2,4,6-tri-*tert*-butylpyridine with nitronium tetrafluoroborate. *J. Org. Chem.*, **55**, 5179–5180.
43. Duffy, J.L. and Laali, K.K. (1991) Aprotic nitration ($NO_2^+BF_4^-$) of 2-halo- and 2,6-dihalopyridines and transfer-nitration chemistry of their *N*-nitropyridinium cations. *J. Org. Chem.*, **56**, 3006–3009.
44. Katritzky, A.R., Scriven, E.F.V., Majumder, S., Akhmedova, R.G., Vakulenko, A.V., Akhmedov, N.G., Muruganb, R., and Abboudc, K.A. (2005) Preparation of nitropyridines by nitration of pyridines with nitric acid. *Org. Biomol. Chem.*, **3**, 538–541.
45. Kavanagh, P. and Leech, D. (2004) Improved synthesis of 4,4′-diamino-2,2′-bipyridine from 4,4′-dinitro-2,2′-bipyridine-*N*,*N*′-dioxide. *Tetrahedron Lett.*, **45**, 121–123.
46. Newkome, G.R., Theriot, K.J., Majestic, V.K., Spruell, P.A., and Baker, G.R. (1990) Functionalization of 2-methyl- and 2,7-dimethy1-1,8-naphthyridine. *J. Org. Chem.*, **55**, 2838–2842.
47. Panke, G., Schwalbe, T., Stirner, W., Taghavi-Moghadam, S., and Wille, G. (2003) A practical approach of continuous processing to high energetic nitration reactions in microreactors. *Synthesis*, 2827–2830.
48. Aries, R.S. (1955) Process of making isocinchomeronic acid and decarboxylation of same to niacin. US Patent 2702802.
49. Frankel, M.B. and Karl, K. (1968) Preparation of nitramines. US Patent 3390183.
50. Girard, Y., Atkinson, J.G., Bélanger, P.C., Fuentes, J.J., Rokach, J., Rooney, C.S., Remy, D.C., and Hunt, C.A.

(1983) Synthesis, chemistry, and photochemical substitutions of 6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-ones. *J. Org. Chem.*, **48**, 3220–3234.

51. Olah, G.A. and Kuhn, S.J. (1973) 3,5-dinitro-*o*-tolunitrile. *Org. Synth.*, Coll. Vol. **5**, 480–485.

52. Gazzaeva, R.A., Fedotov, A.N., Trofimova, E.V., Popova, O.A., Mochalov, S.S., and Zefirov, N.S. (2006) Synthesis of *o*-nitrosoacylbenzenes from *o*-nitrobenzyl alcohols and their derivatives. *Russ. J. Org. Chem.*, **42**, 87–99.

53. Mochalov, S.S., Gazzaeva, R.A., Fedotov, A.N., Archegov, B.P., Trofimova, E.V., Shabarov, Y.S., and Zefirov, N.S. (2005) Transformations of *para*-substituted benzylcyclopropanes, allylbenzenes, and diphenylmethanes under nitration with nitric acid in acetic anhydride. *Russ. J. Org. Chem.*, **41**, 406–416.

54. Njoroge, F.G., Vibulbhan, B., Pinto, P., Chan, T.-M., Osterman, R., Remiszewski, S., Del Rosario, J., Doll, R., Girijavallabhan, V., and Ganguly, A.K. (1998) Highly regioselective nitration reactions provide a versatile method of functionalizing benzocycloheptapyridine tricyclic ring systems: application toward preparation of nanomolar inhibitors of farnesyl protein transferase. *J. Org. Chem.*, **63**, 445–451.

55. Lakshminarayana, N., Prasad, Y.R., Gharat, L., Thomas, A., Ravikumar, P., Narayanan, S., Srinivasan, C.V., and Gopalan, B. (2009) Synthesis and evaluation of some novel isochroman carboxylic acid derivatives as potential anti-diabetic agents. *Eur. J. Med. Chem.*, **44**, 3147–3157.

56. Bennett, G.M. and Youle, P.V. (1938) Hydroxy-by-products in aromatic nitration. *J. Chem. Soc.*, 1816–1818.

57. Feldman, K.S., McDermott, A., and Myhre, P.C. (1979) Ipso nitration. Preparation of 4-methyl-4-nitrocyclohexadienols and detection of intramolecular hydrogen migration (NIH shift) upon solvolytic rearomatization. *J. Am. Chem. Soc.*, **101**, 505–506.

58. Rodríguez González, R., Gambarotti, C., Liguori, L., and Bjørsvik, H.-R. (2006) Efficient and green telescoped process to 2-methoxy-3-methyl[1,4]benzoquinone. *J. Org. Chem.*, **71**, 1703–1706.

59. Fischer, A., Packer, J., Vaughan, J., and Wright, G.J. (1961) Acetoxylation accompanying nitration with nitric acid–acetic anhydride mixtures. *Proc. Chem. Soc.*, 369–370.

60. Smith, K., Musson, A., and DeBoos, G.A. (1998) A novel method for the nitration of simple aromatic compounds. *J. Org. Chem.*, **63**, 8448–8454.

61. Cordeiro, A., Shaw, J., O'Brien, J., Blanco, F., and Rozas, I. (2011) Synthesis of 6-nitro-1,2,3,4-tetrahydroquinoline: an experimental and theoretical study of regioselective nitration. *Eur. J. Org. Chem.*, **2011** (8), 1504–1513.

62. Nielsen, A.T., Henry, R.A., Norris, W.P., Atkins, R.L., Moore, D.W., Lepie, A.H., Coon, C.L., Spanggord, R.J., and Son, D.V.H. (1979) Synthetic routes to aminodinitrotoluenes. *J. Org. Chem.*, **44**, 2499–2504.

63. Boger, D.L. and Sakya, S.M. (1992) CC-1065 partial structures: enhancement of noncovalent affinity for DNA minor groove binding through introduction of stabilizing electrostatic interactions. *J. Org. Chem.*, **57**, 1277–1284.

64. Hester, J.B. (1964) A synthesis of 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline. *J. Org. Chem.*, **29**, 1158–1160.

65. Robinson, M.W., Overmeyer, J.H., Young, A.M., Erhardt, P.W., and Maltese, W.A. (2012) Synthesis and evaluation of indole-based chalcones as inducers of methuosis, a novel type of nonapoptotic cell death. *J. Med. Chem.*, **55**, 1940–1956.

66. Noland, W.E., Smith, L.R., and Rush, K.R. (1965) Nitration of indoles. III. Polynitration of 2-alkylindoles. *J. Org. Chem.*, **30**, 3457–3469.

67. Noland, W.E. and Rieke, R.D. (1962) New synthetic route to 6-nitroisatin via nitration of 3-indolealdehyde. *J. Org. Chem.*, **27**, 2250–2252.

68. Keawin, T., Rajviroongita, S., and Black, D.S. (2005) Reaction of some 4,6-dimethoxyindoles with nitric acid: nitration and oxidative dimerisation. *Tetrahedron*, **61**, 853–861.

69. Noland, W.E., Smith, L.R., and Johnson, D.C. (1963) Nitration of indoles. II. The mononitration of methylindoles. *J. Org. Chem.*, **28**, 2262–2266.

70. Fischer, A. and Sankararaman, S. (1987) Formation of 4-nitrocyclohexa-2,5-dienols by addition of organolithium reagents to 4-alkyl-4-nitrocyclohexa-2,5-dienones. *J. Org. Chem.*, **52**, 4464–4468.

71. Tobey, S.W. and Lourandos, M.Z. (1972) Direct nitration of alkylphenols with nitric acid. US Patent 3694513.

72. Matsuno, T., Matsukawa, T., Sakuma, Y., and Kunieda, T. (1989) A new nitration product, 3-nitro-4-acetamidophenol, obtained from acetaminophen with nitrous acid. *Chem. Pharm. Bull.*, **37**, 1422–1423.

73. Hodnett, E.M., Prakash, G., and Amirmoazzami, J. (1978) Nitrogen analogues of 1,4-benzoquinones. Activities against the ascitic sarcoma 180 of mice. *J. Med. Chem.*, **21**, 11–16.

74. Molander, G.A. and Cavalcanti, L.N. (2012) Nitrosation of aryl and heteroaryltrifluoroborates with nitrosonium tetrafluoroborate. *J. Org. Chem.*, **77**, 4402–4413.

75. Jose, J. and Burgess, K. (2006) Syntheses and properties of water-soluble Nile red derivatives. *J. Org. Chem.*, **71**, 7835–7839.

76. Grohmann, C., Wang, H., and Glorius, F. (2012) Rh[III]-catalyzed direct C–H amination using *N*-chloroamines at room temperature. *Org. Lett.*, **14**, 656–659.

77. Matsuda, N., Hirano, K., Satoh, T., and Miura, M. (2011) Copper-catalyzed direct amination of electron-deficient arenes with hydroxylamines. *Org. Lett.*, **13**, 2860–2863.

78. Ng, K.-H., Zhou, Z., and Yu, W.-Y. (2012) Rhodium(III)-catalyzed intermolecular direct amination of aromatic C–H bonds with *N*-chloroamines. *Org. Lett.*, **14**, 272–275.

79. Berman, A.M. and Johnson, J.S. (2009) Copper-catalyzed electrophilic amination of diorganozinc reagents: 4-phenylmorpholine. *Org. Synth.*, Coll. Vol. **11**, 684–690.

80. Zhao, H., Wang, M., Su, W., and Honga, M. (2010) Copper-catalyzed intermolecular amination of acidic aryl C–H bonds with primary aromatic amines. *Adv. Synth. Catal.*, **352**, 1301–1306.

81. John, A. and Nicholas, K.M. (2011) Copper-catalyzed amidation of 2-phenylpyridine with oxygen as the terminal oxidant. *J. Org. Chem.*, **76**, 4158–4162.

82. Verbeeck, S., Herrebout, W.A., Gulevskaya, A.V., van der Veken, B.J., and Maes, B.U.W. (2010) ONSH: optimization of oxidative alkylamination reactions through study of the reaction mechanism. *J. Org. Chem.*, **75**, 5126–5133.

83. Gulevskaya, A.V., Verbeeck, S., Burov, O.N., Meyers, C., Korbukova, I.N., Herrebout, W., and Maes, B.U.W. (2009) Synthesis of (alkylamino)nitroarenes by oxidative alkylamination of nitroarenes. *Eur. J. Org. Chem.*, **2009**, 564–574.

84. Masters, K.-S., Rauws, T.R.M., Yadav, A.K., Herrebout, W.A., Van der Veken, B., and Maes, B.U.W. (2011) On the importance of an acid additive in the synthesis of pyrido[1,2-*a*]benzimidazoles by direct copper-catalyzed amination. *Chem. Eur. J.*, **17**, 6315–6320.

85. Lipilin, D.L., Churakov, A.M., Ioffe, S.L., Strelenko, Y.A., and Tartakovsky, V.A. (1999) Nucleophilic aromatic substitution of hydrogen in the reaction of *tert*-alkylamines with nitrosobenzenes – synthesis and NMR study of *N*-(*tert*-alkyl)-*ortho*-nitrosoanilines. *Eur. J. Org. Chem.*, **1999**, 29–35.

86. Yoshifuji, M., Tanaka, S., and Inamoto, N. (1975) Friedel–Crafts reaction of 1,3,5-trialkylbenzenes with sulfur monochloride and *N*-chlorodimethylamine. *Bull. Chem. Soc. Jpn.*, **48**, 2607–2608.

87. Wu, W.-B. and Huang, J.-M. (2012) Highly regioselective C–N bond formation through C–H azolation of indoles promoted by iodine in aqueous media. *Org. Lett.*, **14**, 5832–5835.
88. Li, Y.-X., Ji, K.-G., Wang, H.-X., Ali, S., and Liang, Y.-M. (2011) Iodine-induced regioselective C–C and C–N bonds formation of *N*-protected indoles. *J. Org. Chem.*, **76**, 744–747.
89. Liégault, B., Lee, D., Huestis, M.P., Stuart, D.R., and Fagnou, K. (2008) Intramolecular Pd(II)-catalyzed oxidative biaryl synthesis under air: reaction development and scope. *J. Org. Chem.*, **73**, 5022–5028.
90. Kumar, R.K., Ali, M.A., and Punniyamurthy, T. (2011) Pd-Catalyzed C–H activation/C–N bond formation: a new route to 1-aryl-1*H*-benzotriazoles. *Org. Lett.*, **13**, 2102–2105.
91. He, H.-F., Wang, Z.-J., and Baoa, W. (2010) Copper(II) acetate/oxygen-mediated nucleophilic addition and intramolecular C–H activation/C–N or C–C bond formation: one-pot synthesis of benzimidazoles or quinazolines. *Adv. Synth. Catal.*, **352**, 2905–2912.
92. Guru, M.M., Ali, M.A., and Punniyamurthy, T. (2011) Copper-mediated synthesis of substituted 2-aryl-*N*-benzylbenzimidazoles and 2-arylbenzoxazoles via C–H functionalization/C–N/C–O bond formation. *J. Org. Chem.*, **76**, 5295–5308.
93. Xiao, B., Gong, T.-J., Xu, J., Liu, Z.-J., and Liu, L. (2011) Palladium-catalyzed intermolecular directed C–H amidation of aromatic ketones. *J. Am. Chem. Soc.*, **133**, 1466–1474.
94. (a) Mei, T.-S., Wang, X., and Yu, J.-Q. (2009) Pd(II)-Catalyzed amination of C–H bonds using single-electron or two-electron oxidants. *J. Am. Chem. Soc.*, **131**, 10806–10807; (b) Li, J.-J., Mei, T.-S., and Yu, J.-Q. (2008) Synthesis of indolines and tetrahydroisoquinolines from arylethylamines by Pd^{II}-catalyzed C–H activation reactions. *Angew. Chem. Int. Ed.*, **47**, 6452–6455.
95. De Rosa, M., Cabrera Nieto, G., and Ferrer Gago, F. (1989) Effect of *N*-chloro structure and 1-substituent on σ-substitution (addition–elimination) in pyrroles. *J. Org. Chem.*, **54**, 5347–5350.
96. Wang, Q. and Schreiber, S.L. (2009) Copper-mediated amidation of heterocyclic and aromatic C–H bonds. *Org. Lett.*, **11**, 5178–5180.
97. Samanta, R., Bauer, J.O., Strohmann, C., and Antonchick, A.P. (2012) Organocatalytic, oxidative, intermolecular amination and hydrazination of simple arenes at ambient temperature. *Org. Lett.*, **14**, 5518–5521.
98. Gu, L., Neo, B.S., and Zhang, Y. (2011) Gold-catalyzed direct amination of arenes with azodicarboxylates. *Org. Lett.*, **13**, 1872–1874.
99. Lenaršič, R., Kočevar, M., and Polanc, S. (1999) $ZrCl_4$-Mediated regioselective electrophilic amination of activated arenes with new alkyl arylaminocarbonyldiazenecarboxylates: intermolecular and intramolecular reactions. *J. Org. Chem.*, **64**, 2558–2563.
100. Dabbagh, H.A. and Lwowski, W. (1989) Functionalization of phenyl rings by imidoylnitrenes. *J. Org. Chem.*, **54**, 3952–3957.
101. Yamamoto, Y., Mizuno, H., Tsuritani, T., and Mase, T. (2009) Synthesis of α-chloroaldoxime *O*-methanesulfonates and their use in the synthesis of functionalized benzimidazoles. *J. Org. Chem.*, **74**, 1394–1396.
102. Venkatesh, C., Singh, B., Mahata, P.K., Ila, H., and Junjappa, H. (2005) Heteroannulation of nitroketene *N,S*-arylaminoacetals with $POCl_3$: a novel highly regioselective synthesis of unsymmetrical 2,3-substituted quinoxalines. *Org. Lett.*, **7**, 2169–2172.
103. Liu, X.-Y., Gao, P., Shen, Y.-W., and Liang, Y.-M. (2011) Palladium-/copper-catalyzed regioselective amination and chloroamination of indoles. *Org. Lett.*, **13**, 4196–4199.
104. Togo, H., Hoshina, Y., Muraki, T., Nakayama, H., and Yokoyama, M. (1998) Study on radical amidation onto aromatic rings with (diacyloxyiodo)arenes. *J. Org. Chem.*, **63**, 5193–5200.
105. He, G., Lu, C., Zhao, Y., Nack, W.A., and Chen, G. (2012) Improved protocol

for indoline synthesis via palladium-catalyzed intramolecular C(sp^2)–H amination. *Org. Lett.*, **14**, 2944–2947.

106. Lubriks, D., Sokolovs, I., and Suna, E. (2012) Indirect C–H azidation of heterocycles via copper-catalyzed regioselective fragmentation of unsymmetrical λ^3-iodanes. *J. Am. Chem. Soc.*, **134**, 15436–15442.

107. Chen, Y., Ju, T., Wang, J., Yu, W., Du, Y., and Zhao, K. (2010) Concurrent α-iodination and *N*-arylation of cyclic β-enaminones. *Synlett*, 231–234.

108. Itoh, N., Sakamoto, T., Miyazawa, E., and Kikugawa, Y. (2002) Introduction of a hydroxy group at the *para* position and *N*-iodophenylation of *N*-arylamides using phenyliodine(III) bis(trifluoroacetate). *J. Org. Chem.*, **67**, 7424–7428.

109. Kim, H.J., Kim, J., Cho, S.H., and Chang, S. (2011) Intermolecular oxidative C–N bond formation under metal-free conditions: control of chemoselectivity between aryl sp^2 and benzylic sp^3 C–H bond imidation. *J. Am. Chem. Soc.*, **133**, 16382–16385.

110. Kantak, A.A., Potavathri, S., Barham, R.A., Romano, K.M., and DeBoef, B. (2011) Metal-free intermolecular oxidative C–N bond formation via tandem C–H and N–H bond functionalization. *J. Am. Chem. Soc.*, **133**, 19960–19965.

111. Wang, Z., Zhang, Y., Fu, H., Jiang, Y., and Zhao, Y. (2008) Efficient intermolecular iron-catalyzed amidation of C–H bonds in the presence of *N*-bromosuccinimide. *Org. Lett.*, **10**, 1863–1866.

112. Neumann, J.J., Rakshit, S., Dröge, T., and Glorius, F. (2009) Palladium-catalyzed amidation of unactivated C(sp^3)–H bonds: from anilines to indolines. *Angew. Chem. Int. Ed.*, **48**, 6892–6895.

113. Youn, S.W., Bihn, J.H., and Kim, B.S. (2011) Pd-Catalyzed intramolecular oxidative C–H amination: synthesis of carbazoles. *Org. Lett.*, **13**, 3738–3741.

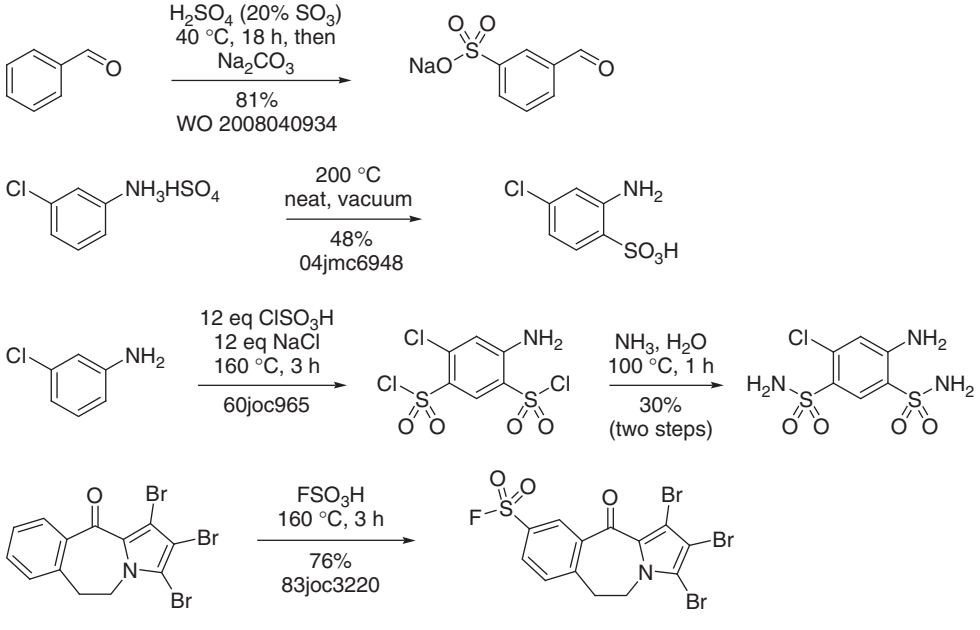
114. Cho, S.H., Yoon, J., and Chang, S. (2011) Intramolecular oxidative C–N bond formation for the synthesis of carbazoles: comparison of reactivity between the copper-catalyzed and metal-free conditions. *J. Am. Chem. Soc.*, **133**, 5996–6005.

7
Electrophilic Formation of Aromatic C–S Bonds

7.1
Sulfonylation

7.1.1
General Aspects

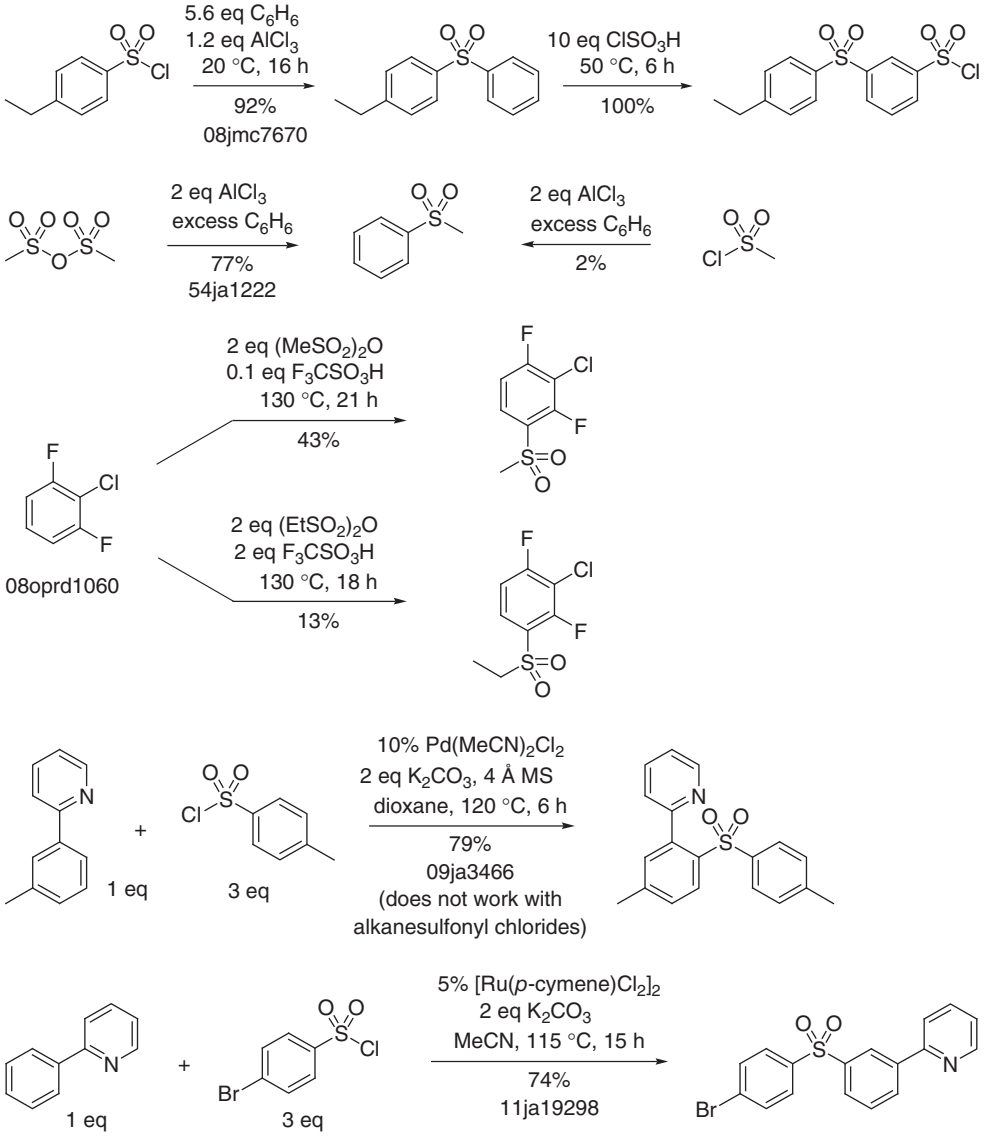
The preparation of arenesulfonic acids, arenesulfonyl chlorides, and sulfones from arenes is a widely used and versatile reaction (Scheme 7.1). The yields are generally high because the products are unreactive and only slowly sulfonylate the excess arene. Sulfones are, though, often obtained as byproducts in small quantities in the synthesis of aromatic sulfonic acids or sulfonyl halides [1].



Scheme 7.1 Examples of the preparation of arene sulfonic acids and sulfonyl halides [2–5].

Side Reactions in Organic Synthesis II: Aromatic Substitutions, First Edition. Florencio Zaragoza Dörwald.

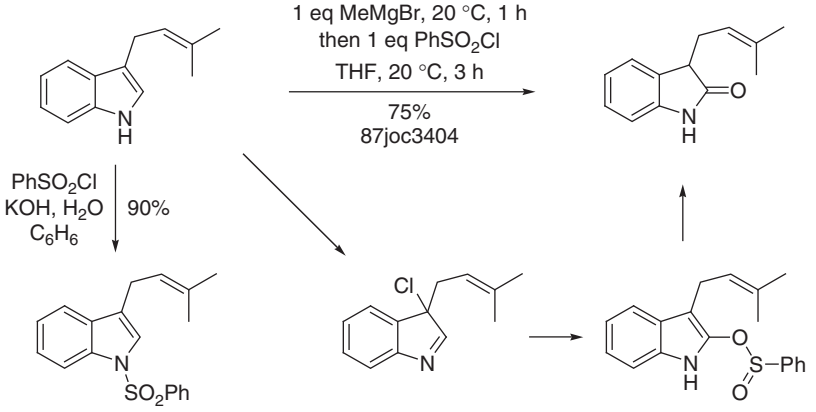
The $AlCl_3$-mediated conversion of arenesulfonyl chlorides into diarylsulfones proceeds smoothly with simple substrates (Scheme 7.2). For alkanesulfonyl halides, though, special catalysts and conditions are required [6]. Sulfonic anhydrides sulfonylate arenes more cleanly than sulfonyl halides [7, 8] because the latter often act as halogenating reagents or oxidants.



Scheme 7.2 Examples of aromatic sulfonylations [7–11]. Further examples: [6, 12, 13].

7.1.2 Typical Side Reactions

One reason for the poor yield of sulfonylations with sulfonyl halides is that the latter often act as halogenating agents instead of sulfonylating agents (Scheme 7.3). In contrast to acyl anions, sulfinates (RSO_2^-) are stable and good leaving groups, and often react as such (e.g., as leaving group in β-eliminations, RSO_2X as synthetic equivalent of X^+). Even the preparation of sulfonamides from sulfonyl chlorides can give low yields when conducted under anhydrous conditions. High yields of sulfonamides are usually obtained only under Schotten–Baumann conditions (in the presence of aqueous base). Hydrolysis of the sulfonyl halide is seldom a problem, because sulfonyl halides, in particular arenesulfonyl chlorides, do not readily react with water or aqueous bases.

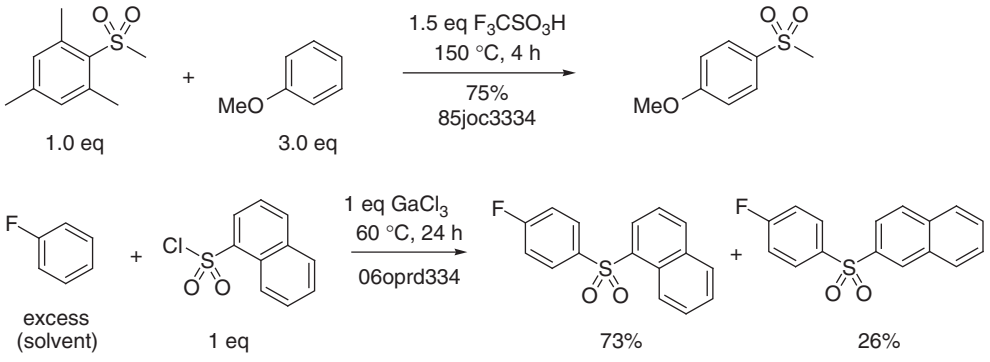


Scheme 7.3 Oxidation of an indole with benzenesulfonyl chloride [14].

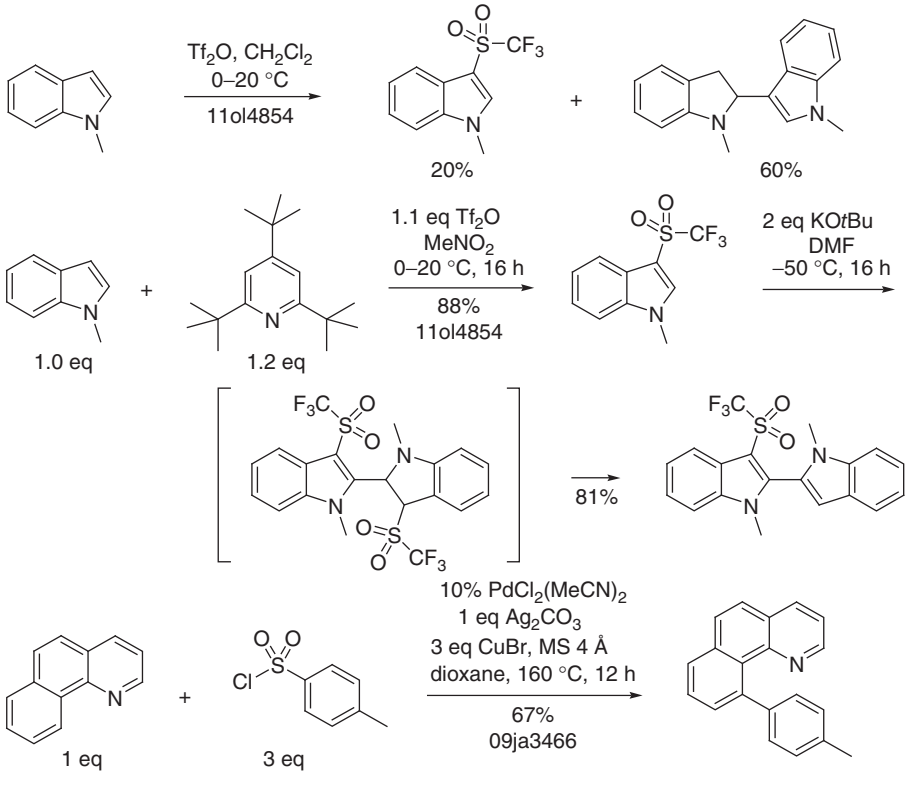
Acid-catalyzed aromatic sulfonylations with sulfonic acid derivatives are reversible, which can lead to the isomerization to more stable isomers, to transsulfonations, or to desulfonations (Scheme 7.4). Such reactions can be suppressed by reducing the reaction temperature and the amount and strength of acid used.

Sulfonic acid derivatives can act as oxidants, and convert electron-rich arenes into radical cations. Biaryls are the typical byproducts formed from intermediate radicals (Scheme 7.5). In the presence of transition metals, arenesulfonyl halides and other derivatives of arenesulfonic acids can also act as arylating reagents [17].

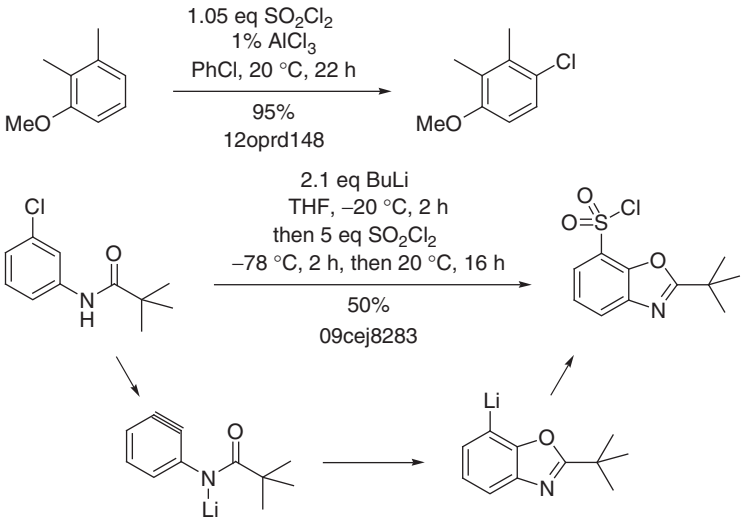
Sulfuryl chloride (SO_2Cl_2) is not a convenient reagent for the preparation of sulfonyl chlorides or sulfones, because this reagent is an even more powerful chlorinating agent than arenesulfonyl chlorides (Scheme 7.6). Only if metallated arenes are to be chlorosulfonylated under anhydrous conditions can sulfuryl chloride be used as electrophile, but the yields tend to be low. The conversion of arenes into arenesulfonyl halides works best with halosulfonic acids ($HalSO_3H$). In



Scheme 7.4 Isomerization of sulfones [15, 16].



Scheme 7.5 Oxidations and arylations with sulfonic acid derivatives [10, 18].



Scheme 7.6 Reaction of arenes with sulfuryl chloride [20, 21].

the presence of iodine, though, even chlorosulfonic acid can act as a chlorinating reagent [19].

7.2 Sulfinylation

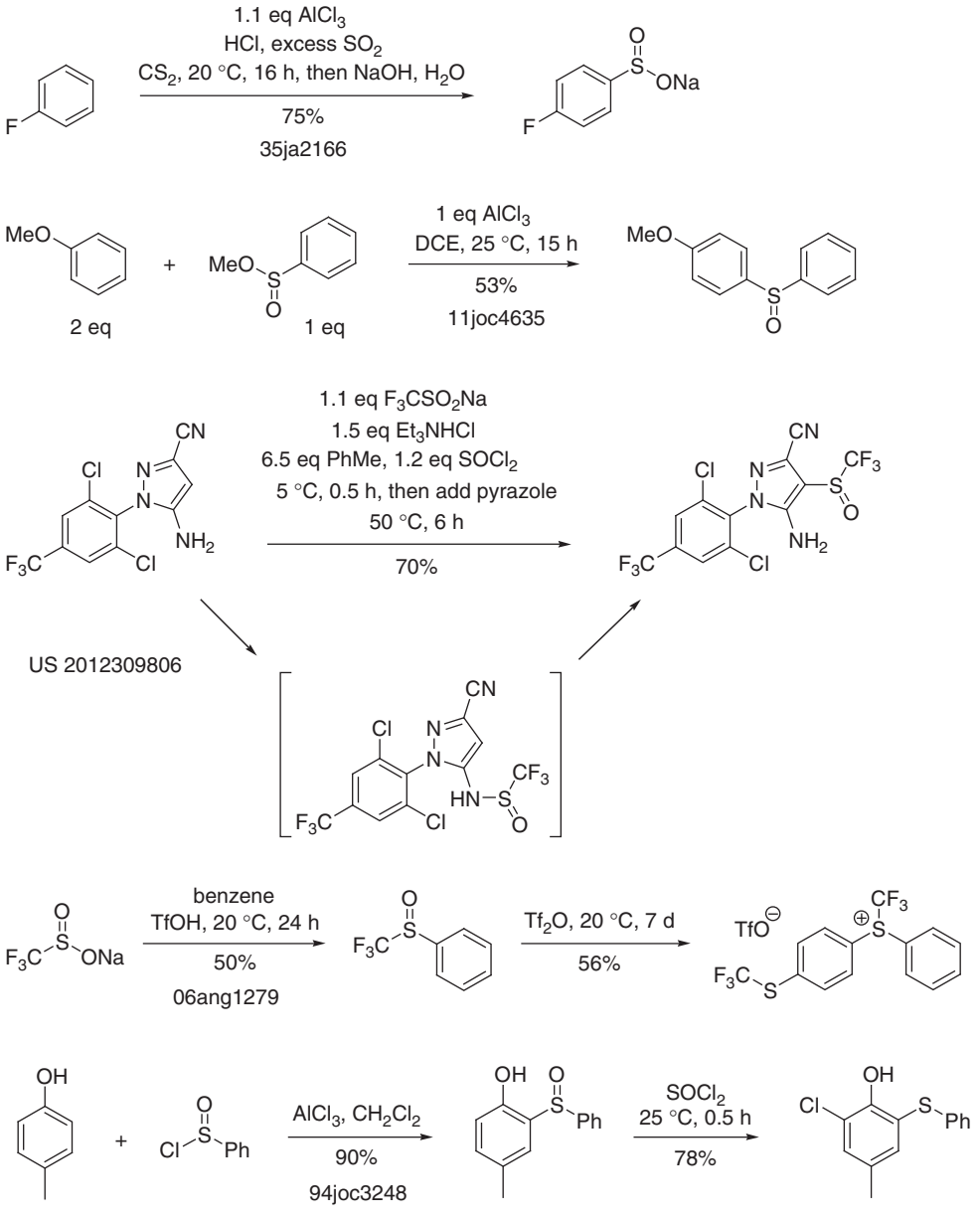
7.2.1 General Aspects

Sulfoxides can be prepared by direct sulfinylation of unsubstituted arenes with sulfinic acid derivatives (Scheme 7.7), but numerous byproducts may result. An alternative to the direct sulfinylation (or sulfonylation) is sulfenylation followed by oxidation [8, 22].

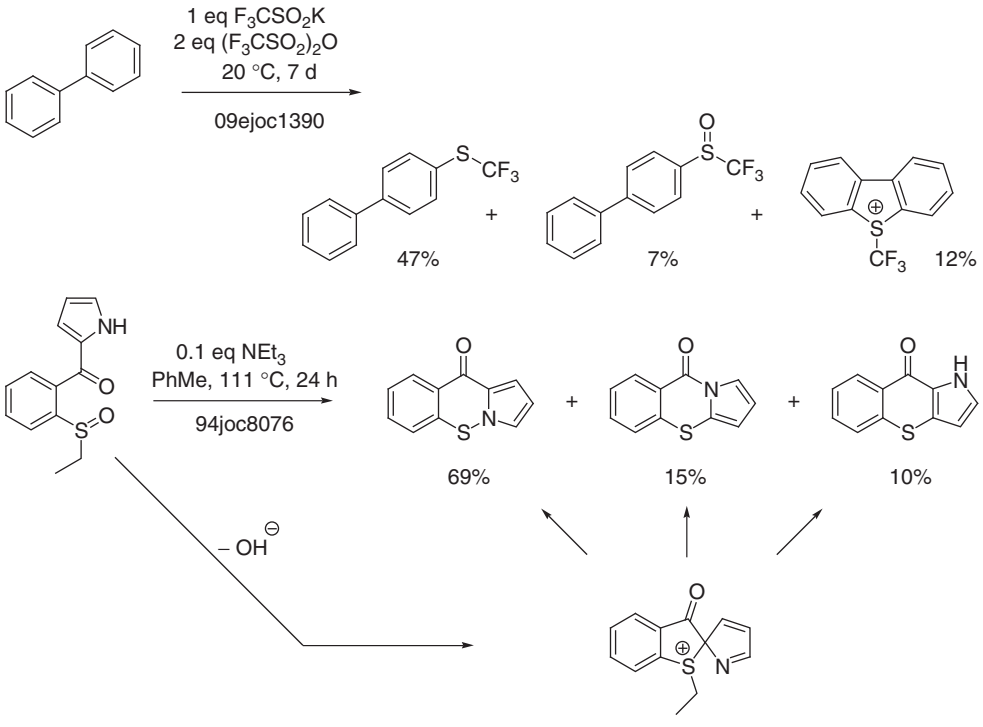
7.2.2 Typical Side Reactions

As shown in Schemes 7.7 and 7.8, sulfinylations are problematic because the resulting sulfinic acids and sulfoxides can react as electrophiles under the reaction conditions required for their preparation. Even poor nucleophiles (e.g., halides) can add to the cationic intermediates generated from sulfoxides and electrophiles. Aliphatic alcohols will usually be oxidized to aldehydes or ketones by sulfoxides in the presence of electrophiles (Swern and Pfitzner–Moffatt oxidations).

Similar to sulfonylations, sulfinylations are reversible. Treatment of aromatic sulfoxides with acids or other catalysts can bring about rearrangement to more

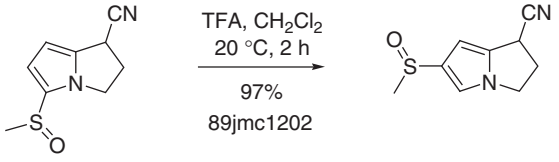


Scheme 7.7 Examples of aromatic sulfinylations [23–27].



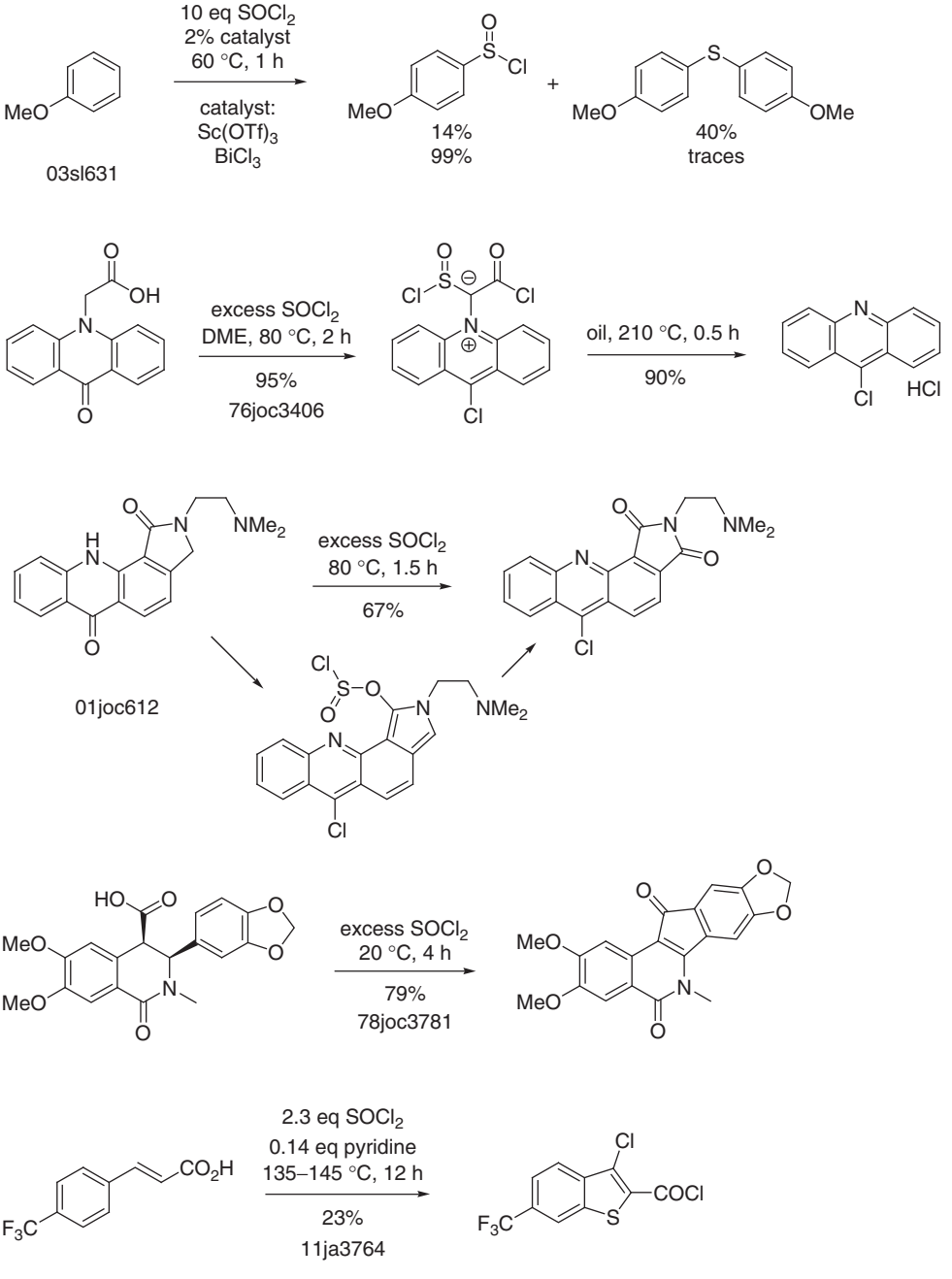
Scheme 7.8 Decomposition reactions of sulfoxides [28, 29].

stable isomers (Scheme 7.9). Moreover, acids such as $AlCl_3$ can cause the disproportionation of sulfoxides into sulfones and thioethers. Strong bases [30], OsO_4 [31], or electrophiles (as in the Pummerer rearrangement) can also induce the disproportionation of sulfoxides or the β-elimination of $ArSO^-$ [32]. Because of this high reactivity of sulfoxides, dimethyl sulfoxide (DMSO) is a hazardous solvent, ill-suited for most large-scale applications.



Scheme 7.9 Acid-mediated rearrangement of a sulfoxide [33]. Further examples: [34].

The preparation of sulfinic acid chlorides or sulfoxides from thionyl chloride has been reported [35], but must be done carefully. In addition to the problems



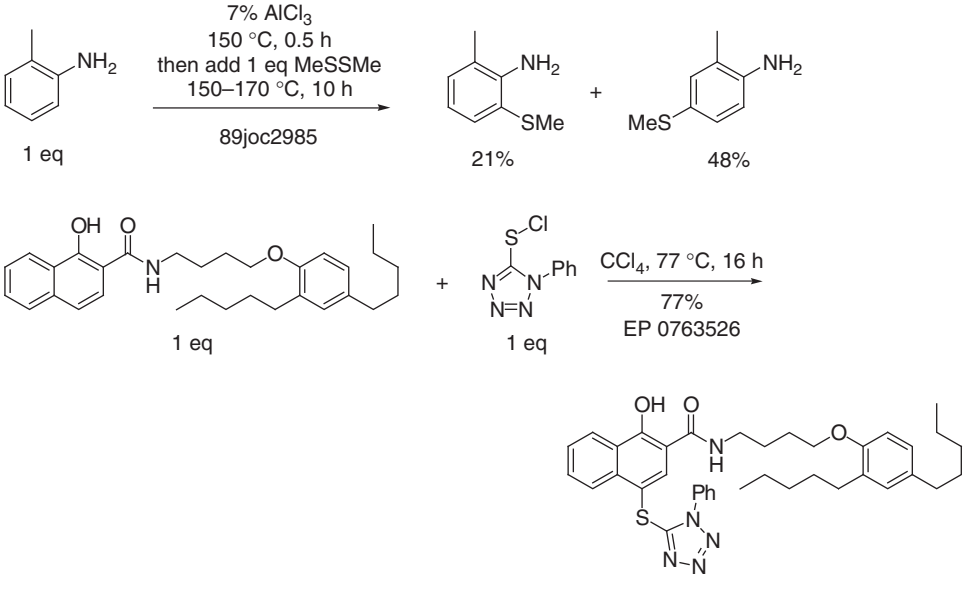
Scheme 7.10 Byproducts formed during reactions with thionyl chloride [36–40]. Further examples: [41].

mentioned above, various functional groups are chlorinated, sulfinylated, dehydrogenated, or otherwise oxidized by thionyl chloride, which can cause the formation of unexpected products (Scheme 7.10). Because of the many potential side reactions of electrophilic sulfinylations, sulfinic acids are usually prepared by reduction of sulfonyl chlorides, and not by electrophilic sulfinylation with $SOCl_2$ or SO_2.

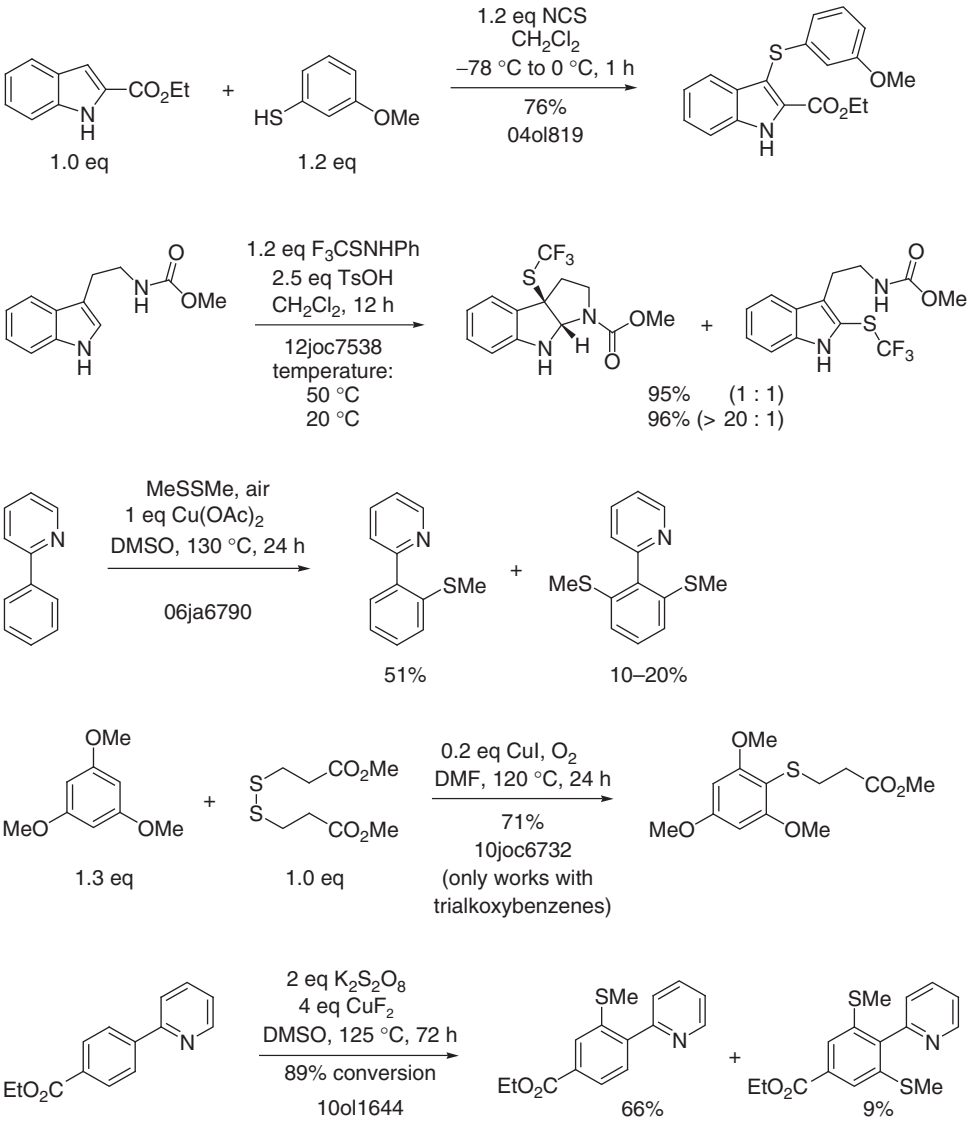
7.3 Sulfenylation

7.3.1 General Aspects

Arylthioethers can be prepared from electron-rich arenes and disulfides [33], thioethers, sulfenyl halides or sulfenyl amides ($RS-NR_2$) [43], or esters (RS–OR) (Scheme 7.11). These reactions can be catalyzed by acids, oxidants [44], and copper or palladium complexes. In the presence of strong acids, arenes react with sulfoxides to sulfonium salts, which can be dealkylated with various nucleophiles to yield thioethers [29, 45].



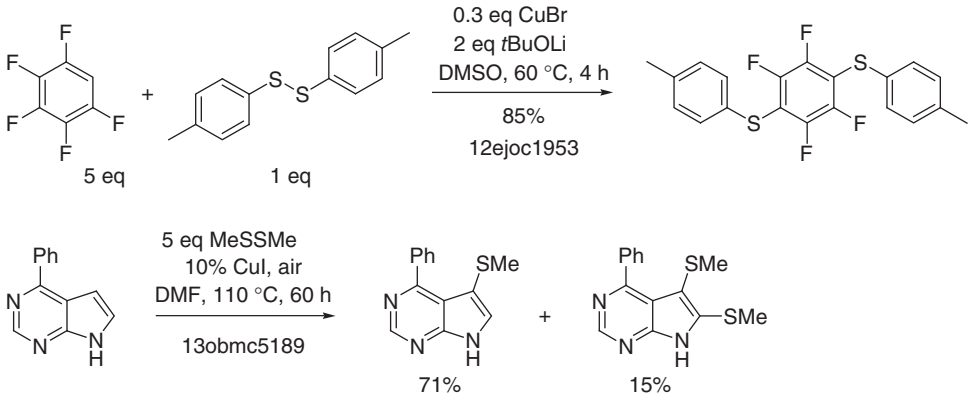
Scheme 7.11 Electrophilic sulfenylation of arenes [42, 46–51]. Further examples: [52].



Scheme 7.11 (*Continued*)

7.3.2 Typical Side Reactions

During sulfenylations with disulfides, thiols are formed as byproducts. These are strongly nucleophilic and can cause unwanted substitution reactions, including the dealkylation of thioethers. Further side reactions include multiple sulfenylation and halogenation of the arene (Scheme 7.12).



Scheme 7.12 Side reactions during electrophilic aromatic sulfenylations [53, 54].

References

1. Tanaka, M. and Souma, Y. (1992) Sulfonation of aromatic compounds in HSO_3F–SbF_5. *J. Org. Chem.*, **57**, 3738–3740.
2. Davidson, A., Moffat, D.F.C., Day, F.A., and Donald, A.D.G. (2008) HDAC inhibitors. WO Patent 2008040934.
3. Valgeirsson, J., Nielsen, E.Ø., Peters, D., Mathiesen, C., Kristensen, A.S., and Madsen, U. (2004) Bioisosteric modifications of 2-arylureidobenzoic acids: selective noncompetitive antagonists for the homomeric kainate receptor subtype GluR5. *J. Med. Chem.*, **47**, 6948–6957.
4. Novello, F.C., Bell, S.C., Abrams, E.L.A., Ziegler, C., and Sprague, J.M. (1960) Diuretics: aminobenzenedisulfonamides. *J. Org. Chem.*, **25**, 965–970.
5. Girard, Y., Atkinson, J.G., Bélanger, P.C., Fuentes, J.J., Rokach, J., Rooney, C.S., Remy, D.C., and Hunt, C.A. (1983) Synthesis, chemistry, and photochemical substitutions of 6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-ones. *J. Org. Chem.*, **48**, 3220–3234.
6. Peyronneau, M., Boisdon, M.-T., Roques, N., Mazières, S., and Le Roux, C. (2004) Total synergistic effect between triflic acid and bismuth(III) or antimony(III) chlorides in catalysis of the methanesulfonylation of arenes. *Eur. J. Org. Chem.*, **2004**, 4636–4640.
7. Field, L. and Settlage, P.H. (1954) Alkanesulfonic acid anhydrides. *J. Am. Chem. Soc.*, **76**, 1222–1225.
8. Parker, J.S., Bower, J.F., Murray, P.M., Patel, B., and Talavera, P. (2008) Kepner–Tregoe decision analysis as a tool to aid route selection. Part 3. Application to a back-up series of compounds in the PDK project. *Org. Process Res. Dev.*, **12**, 1060–1077.
9. Gopalsamy, A., Shi, M., Stauffer, B., Bahat, R., Billiard, J., Ponce-de-Leon, H., Seestaller-Wehr, L., Fukayama, S., Mangine, A., Moran, R., Krishnamurthy, G., and Bodine, P. (2008) Identification of diarylsulfone sulfonamides as secreted frizzled related protein-1 (sFRP-1) antagonist. *J. Med. Chem.*, **51**, 7670–7672.
10. Zhao, X., Dimitrijević, E., and Dong, V.M. (2009) Palladium-catalyzed C–H bond functionalization with arylsulfonyl chlorides. *J. Am. Chem. Soc.*, **131**, 3466–3467.
11. Saidi, O., Marafie, J., Ledger, A.E.W., Liu, P.M., Mahon, M.F., Kociok-Köhn, G., Whittlesey, M.K., and Frost, C.G. (2011) Ruthenium-catalyzed *meta* sulfonation of 2-phenylpyridines. *J. Am. Chem. Soc.*, **133**, 19298–19301.
12. Singh, R.P., Kamble, R.M., Chandra, K.L., Saravanan, P., and Singh, V.K. (2001) An efficient method for aromatic

Friedel–Crafts alkylation, acylation, benzoylation, and sulfonylation reactions. *Tetrahedron*, **57**, 241–247.
13. Shirley, D.A. and Lehto, E.A. (1957) The metalation of 4-*t*-butyldiphenyl sulfone with n-butyllithium. *J. Am. Chem. Soc.*, **79**, 3481–3485.
14. Wenkert, E., Moeller, P.D.R., Piettre, S.R., and McPhail, A.T. (1987) Unusual reactions of magnesium indolates with benzenesulfonyl chloride. *J. Org. Chem.*, **52**, 3404–3409.
15. El-Khawagat, A.M. and Roberts, R.M. (1985) Transsulfonylations between aromatic sulfones and arenes. *J. Org. Chem.*, **50**, 3334–3336.
16. Fleck, T.J., Chen, J.J., Lu, C.V., and Hanson, K.J. (2006) Isomerization-free sulfonylation and its application in the synthesis of PHA-565272A. *Org. Process Res. Dev.*, **10**, 334–338.
17. Yu, X., Li, X., and Wan, B. (2012) Palladium-catalyzed desulfitative arylation of azoles with arylsulfonyl hydrazides. *Org. Biomol. Chem.*, **10**, 7479–7482.
18. Xu, X.-H., Liu, G.-K., Azuma, A., Tokunaga, E., and Shibata, N. (2011) Synthesis of indole and biindolyl triflones: trifluoromethanesulfonylation of indoles with Tf_2O/TTBP (2,4,6-tri-*tert*-butylpyridine) system. *Org. Lett.*, **13**, 4854–4857.
19. Cremlyn, R.J.W. and Cronje, T. (1979) Chlorination of aromatic halides with chlorosulfonic acid. *Phosphorus Sulfur Rel. Elem.*, **6**, 495–504.
20. Allwein, S.P., Roemmele, R.C., Haley, J.J., Mowrey, D.R., Petrillo, D.E., Reif, J.J., Gingrich, D.E., and Bakale, R.P. (2012) Development and scale-up of an optimized route to the ALK inhibitor CEP-28122. *Org. Process Res. Dev.*, **16**, 148–155.
21. Bruyneel, F., Payen, O., Rescigno, A., Tinant, B., and Marchand-Brynaert, J. (2009) Laccase-mediated synthesis of novel substituted phenoxazine chromophores featuring tuneable water solubility. *Chem. Eur. J.*, **15**, 8283–8295.
22. Finikova, O.S., Cheprakov, A.V., and Vinogradov, S.A. (2005) Synthesis and luminescence of soluble *meso*-unsubstituted tetrabenzo- and tetranaphtho[2,3]porphyrins. *J. Org. Chem.*, **70**, 9562–9572.
23. Hann, R.M. (1935) Some derivatives of *p*-fluorophenyl sulfinic acid. *J. Am. Chem. Soc.*, **57**, 2166–2167.
24. Yuste, F., Hernández Linares, A., Mastranzo, V.M., Ortiz, B., Sánchez-Obregón, R., Fraile, A., and García Ruano, J.L. (2011) Methyl sulfinates as electrophiles in Friedel–Crafts reactions. Synthesis of aryl sulfoxides. *J. Org. Chem.*, **76**, 4635–4644.
25. Sukopp, M., Kuhn, O., Gröning, C., Keil, M., and Longlet, J.J. (2012) Process for the sulfinylation of a pyrazole derivative. US Patent 2012309806.
26. Magnier, E., Blazejewski, J.-C., Tordeux, M., and Wakselman, C. (2006) Straightforward one-pot synthesis of trifluoromethyl sulfonium salts. *Angew. Chem. Int. Ed.*, **45**, 1279–1282.
27. Jung, M.E., Kim, C., and von dem Bussche, L. (1994) Vicarious nucleophilic aromatic substitution via trapping of an α-ketosulfonium ion generated by Pummerer-type rearrangement of 2-(phenylsulfinyl)phenols: preparation of biaryls. *J. Org. Chem.*, **59**, 3248–3249.
28. Macé, Y., Raymondeau, B., Pradet, C., Blazejewski, J.-C., and Magnier, E. (2009) Benchmark and solvent-free preparation of sulfonium salt based electrophilic trifluoromethylating reagents. *Eur. J. Org. Chem.*, **2009**, 1390–1397.
29. Bates, D.K. and Tafel, K.A. (1994) Sulfenylation using sulfoxides. Intramolecular cyclization of 2- and 3-acylpyrroles. *J. Org. Chem.*, **59**, 8076–8080.
30. Furukawa, N., Ogawa, S., Matsumura, K., and Fujihara, H. (1991) Extremely facile ligand-exchange and disproportionation reactions of diaryl sulfoxides, selenoxides, and triarylphosphine oxides with organolithium and Grignard reagents. *J. Org. Chem.*, **56**, 6341–6348.
31. Davis, H.R. and Sorensen, D.P. (1959) Disproportionation of organic sulfoxides. US Patent 2870215.
32. Forbes, D.C., Bettigeri, S.V., Al-Azzeh, N.N., Finnigan, B.P., and Kundukulama, J.A. (2009) Sulfenylation chemistry using polymer-supported sulfides. *Tetrahedron Lett.*, **50**, 1855–1857.

33. Muchowski, J.M., Galeazzi, E., Greenhouse, R., Guzmán, A., Peréz, V., Ackerman, N., Ballaron, S.A., Rovito, J.R., Tomolonis, A.J., Young, J.M., and Rooks, W.H. (1989) Synthesis and anti-inflammatory and analgesic activity of 5-aroyl-6-(methylthio)-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic acids and 1-methyl-4-(methylthio)-5-aroylpyrrole-2-acetic acids. *J. Med. Chem.*, **32**, 1202–1207.
34. Carmona, O., Greenhouse, R., Landeros, R., and Muchowski, J.M. (1980) Synthesis and rearrangement of 2-(arylsulfinyl)- and 2-(alkylsulfinyl)pyrroles. *J. Org. Chem.*, **45**, 5336–5339.
35. Reddy, B.M., Sreekanth, P.M., and Lakshmanan, P. (2005) Sulfated zirconia as an efficient catalyst for organic synthesis and transformation reactions. *J. Mol. Catal. A*, **237**, 93–100.
36. Peyronneau, M., Roques, N., Mazières, S., and Le Roux, C. (2003) Catalytic Lewis acid activation of thionyl chloride: application to the synthesis of aryl sulfinyl chlorides catalyzed by bismuth(III) salts. *Synlett*, 631–634.
37. Ning, R.Y., Madan, P.B., Blount, J.F., and Fryer, R.I. (1976) Structure and reactions of an unusual thionyl chloride oxidation product. 9-Chloroacridinium 2-chloro-l-(chlorosulfinyl)-2-oxoethylide. *J. Org. Chem.*, **41**, 3406–3409.
38. Feng, S., Panetta, C.A., and Graves, D.E. (2001) An unusual oxidation of a benzylic methylene group by thionyl chloride: a synthesis of 1,3-dihydro-2-[2-(dimethylamino)ethyl]-1,3-dioxopyrrolo[3,4-*c*]acridine derivatives. *J. Org. Chem.*, **66**, 612–616.
39. Cushman, M. and Cheng, L. (1978) Stereoselective oxidation by thionyl chloride leading to the indeno[1,2-*c*]isoquinoline system. *J. Org. Chem.*, **43**, 3781–3783.
40. Cheng, K., Wang, X., and Yin, H. (2011) Small-molecule inhibitors of the TLR3/dsRNA complex. *J. Am. Chem. Soc.*, **133**, 3764–3767.
41. Higa, T. and Krubsack, A.J. (1975) Oxidations by thionyl chloride. VI. Mechanism of the reaction with cinnamic acids. *J. Org. Chem.*, **40**, 3037–3045.
42. Gillis, H.M., Greene, L., and Thompson, A. (2009) Preparation of sulfenyl pyrroles. *Synlett*, 112–116.
43. Ranken, P.F. and McKinnie, B.G. (1989) Alkylthio aromatic amines. *J. Org. Chem.*, **54**, 2985–2988.
44. Prasad, C.D., Balkrishna, S.J., Kumar, A., Bhakuni, B.S., Shrimali, K., Biswas, S., and Kumar, S. (2013) Transition-metal-free synthesis of unsymmetrical diaryl chalcogenides from arenes and diaryl dichalcogenides. *J. Org. Chem.*, **78**, 1434–1443.
45. Ukai, S. and Hirose, K. (1968) Die Reaktion der Phenolderivate mit Sulfoxiden. IV. (einschließlich der von Sulfiden und Wasserstoffperoxid ausgehenden Reaktion). Die Synthese von 4-thiosubstituierten 1,2-Naphthochinonderivaten. *Chem. Pharm. Bull.*, **16**, 606–612.
46. Delprato, I. and Bertoldi, M. (1997) Process for preparation of 4-mercapto-1-naphthol compounds. EP Patent 0763526.
47. Schlosser, K.M., Krasutsky, A.P., Hamilton, H.W., Reed, J.E., and Sexton, K. (2004) A highly efficient procedure for 3-sulfenylation of indole-2-carboxylates. *Org. Lett.*, **6**, 819–821.
48. Yang, Y., Jiang, X., and Qing, F.-L. (2012) Sequential electrophilic trifluoromethanesulfanylation–cyclization of tryptamine derivatives: synthesis of C(3)-trifluoromethanesulfanylated hexahydropyrrolo[2,3-*b*]indoles. *J. Org. Chem.*, **77**, 7538–7547.
49. Chen, X., Hao, X.-S., Goodhue, C.E., and Yu, J.-Q. (2006) Cu(II)-catalyzed functionalizations of aryl C–H bonds using O_2 as an oxidant. *J. Am. Chem. Soc.*, **128**, 6790–6791.
50. Zhang, S., Qian, P., Zhang, M., Hu, M., and Cheng, J. (2010) Copper-catalyzed thiolation of the di- or trimethoxybenzene arene C–H bond with disulfides. *J. Org. Chem.*, **75**, 6732–6735.
51. Chu, L., Yue, X., and Qing, F.-L. (2010) Cu(II)-mediated methylthiolation of aryl C–H bonds with DMSO. *Org. Lett.*, **12**, 1644–1647.
52. Tran, L.D., Popov, I., and Daugulis, O. (2012) Copper-promoted sulfenylation of

sp^2 C–H bonds. *J. Am. Chem. Soc.*, **134**, 18237–18240.

53. Yu, C., Zhang, C., and Shi, X. (2012) Copper-catalyzed direct thiolation of pentafluorobenzene with diaryl disulfides or aryl thiols by C–H and C–F bond activation. *Eur. J. Org. Chem.*, **2012**, 1953–1959.

54. Klečka, M., Pohl, R., Čejka, J., and Hocek, M. (2013) Direct C–H sulfenylation of purines and deazapurines. *Org. Biomol. Chem.*, **11**, 5189–5193.

8
Aromatic Nucleophilic Substitutions

8.1
General Aspects

Although less important than aromatic electrophilic substitutions, aromatic nucleophilic substitutions are valuable transformations in organic synthesis. Many drugs, agrochemicals, and other structurally complex compounds comprise aromatic nucleophilic substitutions in their industrial syntheses. Numerous reviews have been published [1–4].

8.1.1
Mechanisms

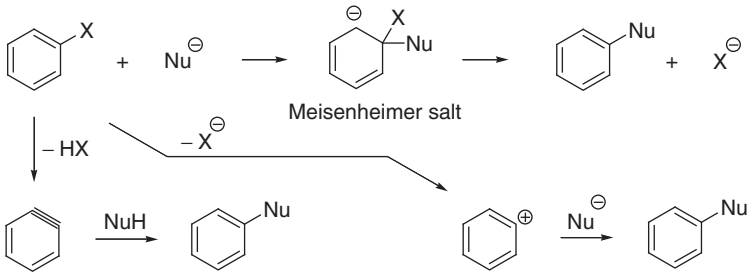
Aromatic nucleophilic substitutions can proceed by an addition–elimination mechanism (S_NAr), by an abstraction–addition mechanism (S_N1), via radicals ($S_{RN}1$), or via intermediate formation of an aryne (Scheme 8.1). The first mechanism is predominant for electron-deficient arenes or heteroarenes capable of delocalizing a negative charge to electronegative atoms. Electron-withdrawing groups in the ortho or para position to the leaving group enhance the rate of S_NAr reactions, whereas electron-donating groups inhibit them. Particularly powerful rate-enhancing groups are diazonium, iminium, nitroso, and nitro groups.

Naphthyl derivatives undergo S_NAr reactions particularly readily (Scheme 8.2) because the dearomatization of naphthalenes requires less energy than that of monocyclic arenes (only one of the two rings of naphthalene is fully aromatic) [5, 6]. 2-Nitronaphthalenes, for instance, behave chemically more as nitroalkenes than as nitroarenes [7].

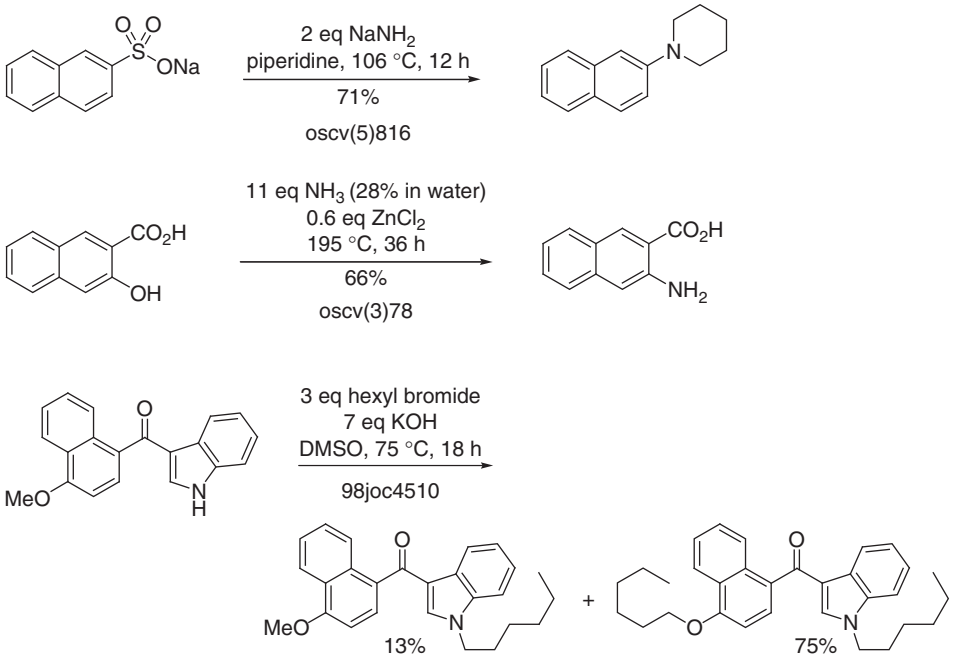
8.1.2
Regioselectivity

Because the addition of a nucleophile to an electron-deficient arene is reversible, smooth substitutions will occur only at arenes with good leaving groups. For S_NAr reactions, good leaving groups include fluoride, nitrite, sulfonates, the remaining halides, and sulfinates. In the presence of oxidants, hydride may also be a suitable

Side Reactions in Organic Synthesis II: Aromatic Substitutions, First Edition. Florencio Zaragoza Dörwald.

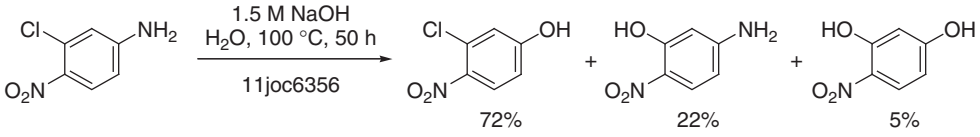


Scheme 8.1 Mechanisms of aromatic nucleophilic substitution.

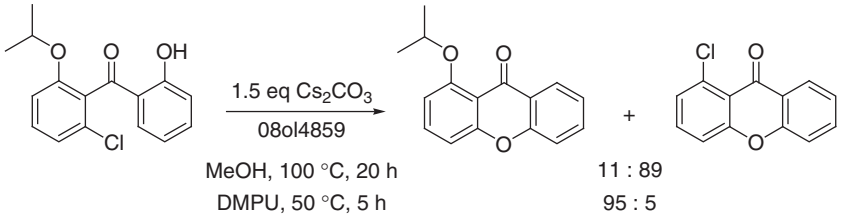


Scheme 8.2 S_NAr reaction at naphthalenes [6, 8, 9].

leaving group. The precise ranking of leaving groups also depends on the solvent (solvation of the nucleophile, the Meisenheimer complex, and the leaving group) and on the nucleophile (hydrogen bonding in the Meisenheimer complex) [10–12]. The amino group, for instance, is a poor leaving group in aprotic solvents, but is easier to displace than chloride by hydroxide in water as solvent (Scheme 8.3). 6-(Alkylsulfonyl)purines react faster with MeOH/DBU (1,8-diazabicyclo[5.4.0] undec-5-ene) than 6-iodopurines, but more slowly with aniline than 6-iodopurines [13]. A further example of solvent effects in aromatic nucleophilic substitutions is given in Scheme 8.4.

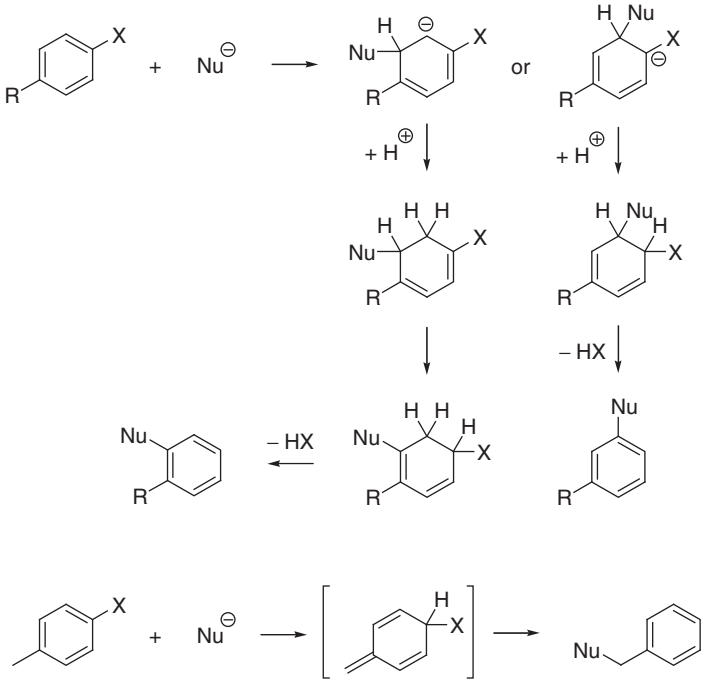


Scheme 8.3 Displacement of amino groups in water [11].

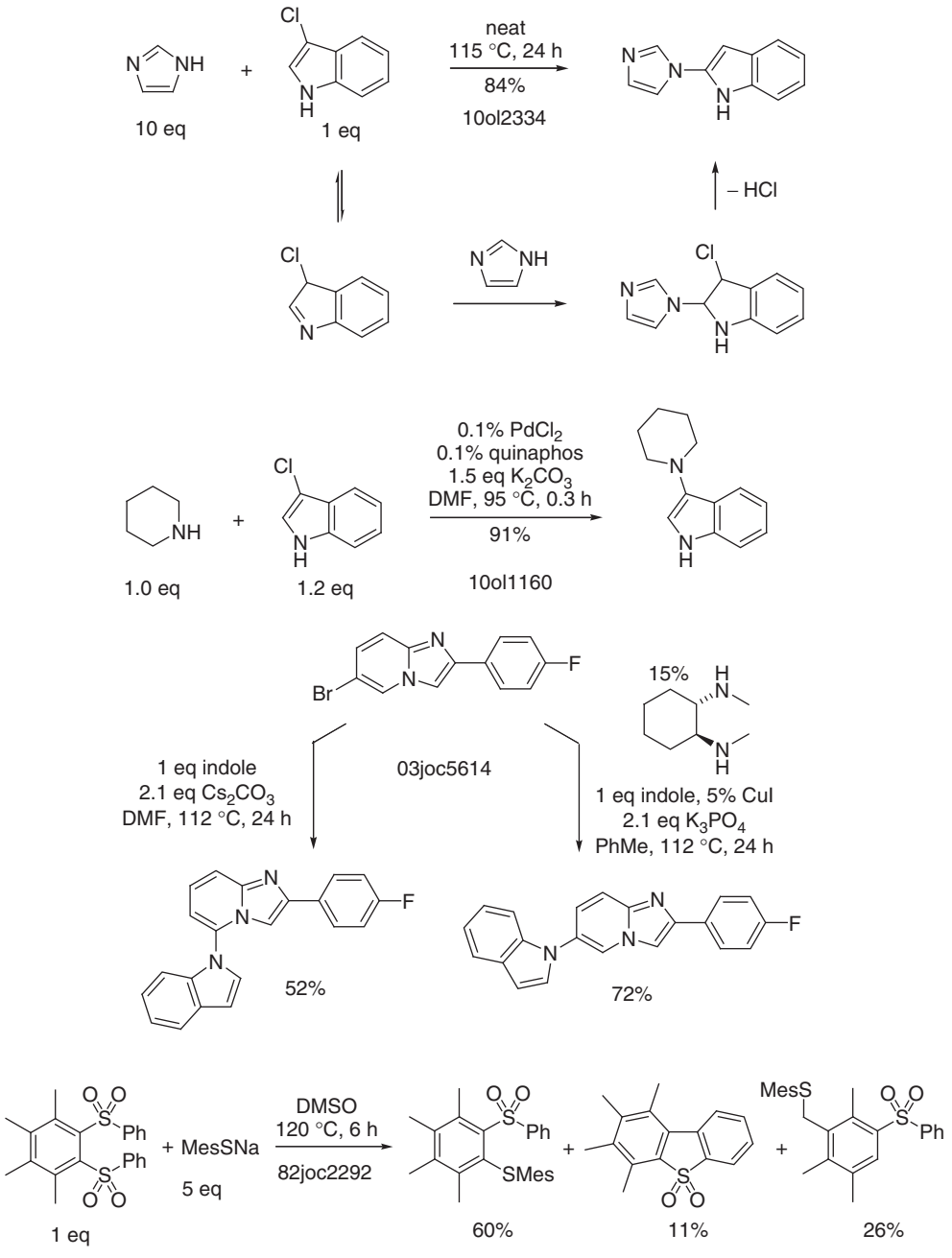


Scheme 8.4 Solvent effects in aromatic nucleophilic substitutions [14].

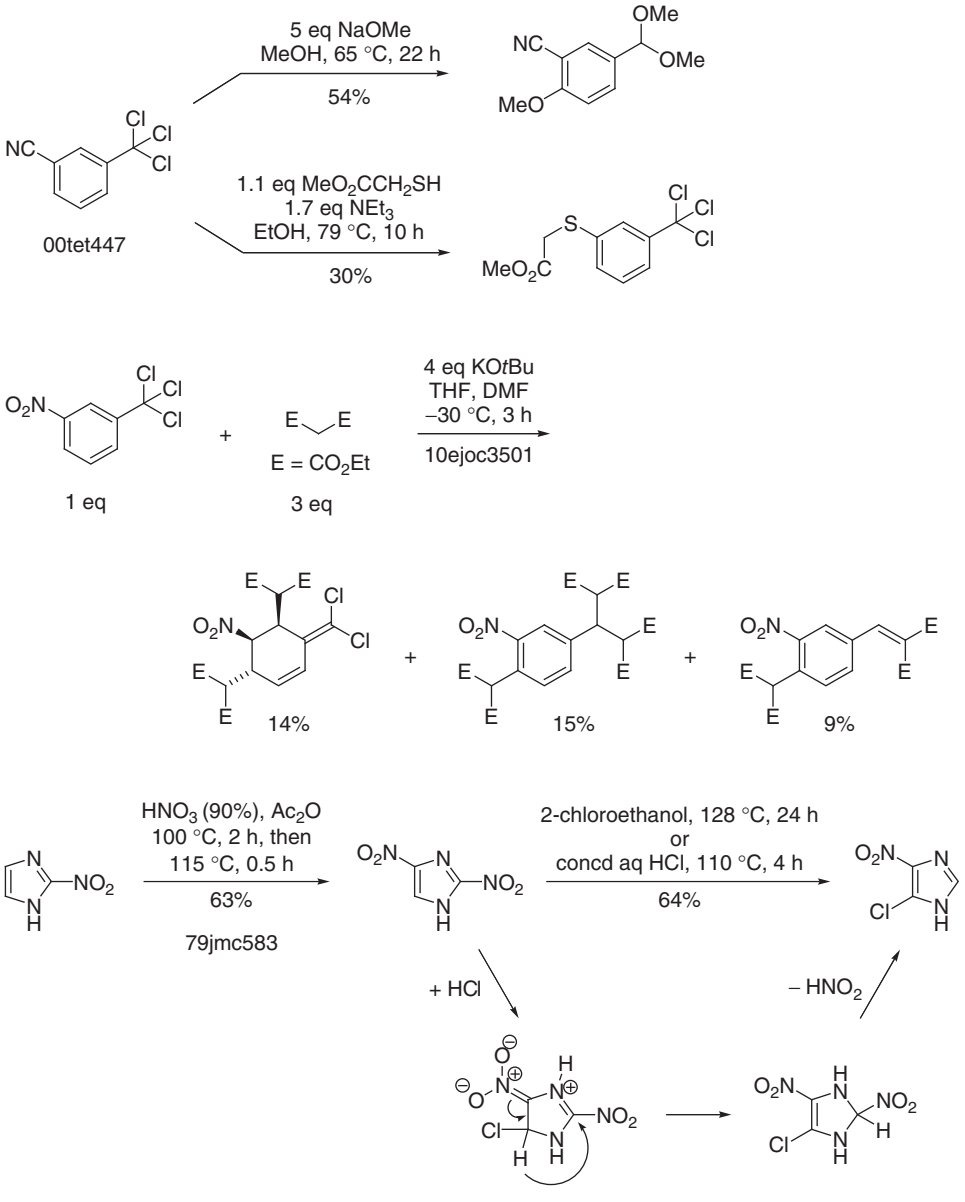
Cine and tele substitutions, that is, the attack of a nucleophile at the adjacent (cine) or more distant (tele) positions of the leaving group, are only rarely observed in aromatic nucleophilic substitutions [15] (Schemes 8.5 and 8.6, see also Scheme 3.3). In most instances, the electrophiles are highly electron-deficient



Scheme 8.5 Mechanisms for cine and tele aromatic nucleophilic substitutions.



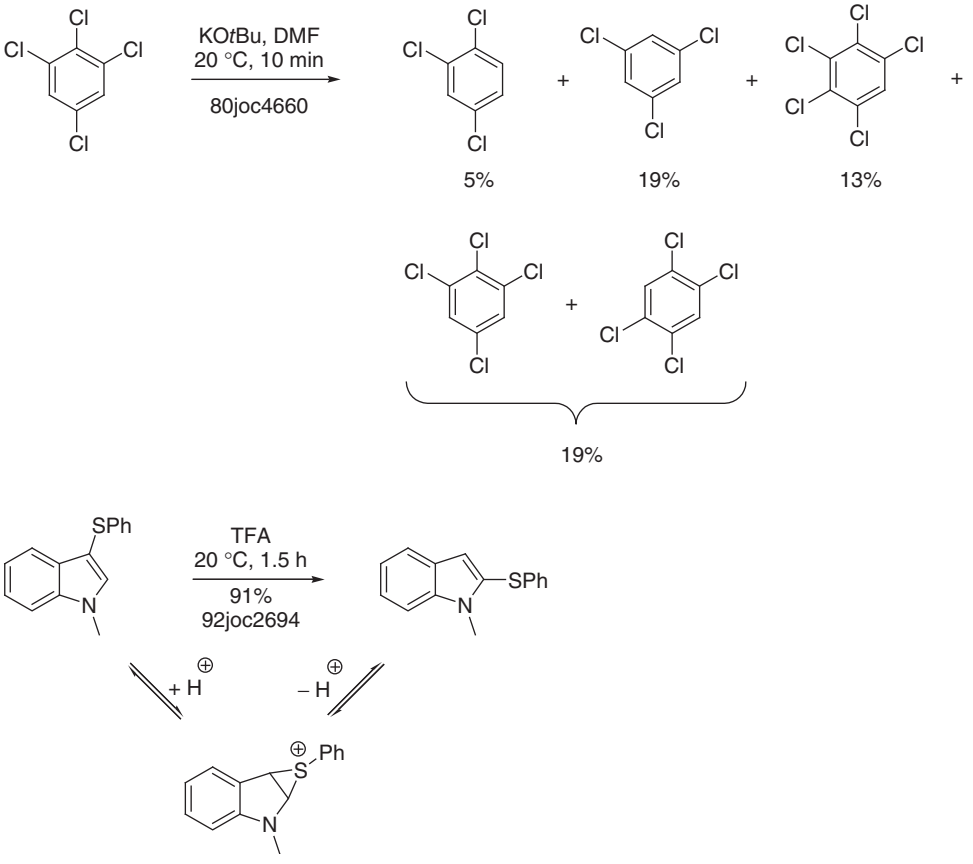
Scheme 8.6 Cine substitution in aromatic nucleophilic substitutions [16–22]. Further examples: [23–26].



Scheme 8.6 (*Continued*)

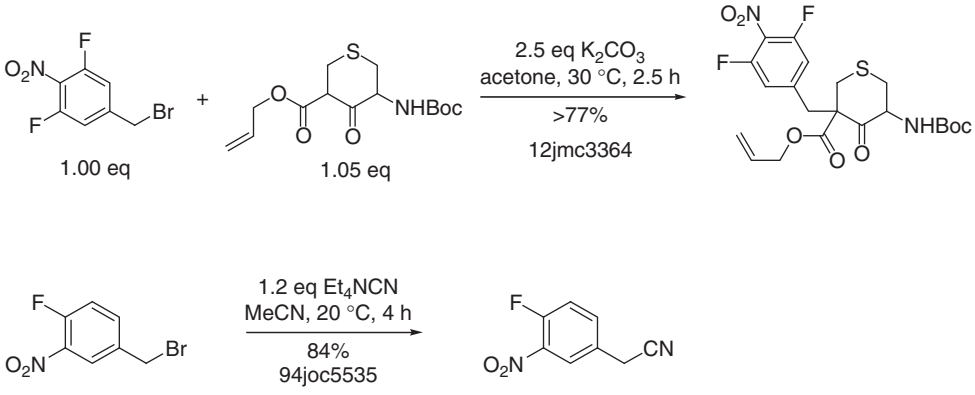
arenes or heteroarenes of low aromaticity, where the non-aromatic intermediates have sufficiently long half-lives for proton transfer reactions and double-bond migrations to occur. Protic solvents often facilitate these startling reactions. One strategy to avoid cine or tele substitutions is to use transition-metal catalysts.

Products of aromatic nucleophilic substitution may also rearrange to more stable isomers. Polyhaloarenes, for instance, readily isomerize in the presence of strong bases (Scheme 8.7). Indolylthioethers can isomerize in the presence of acids, sometimes under remarkably mild reaction conditions (Scheme 8.7).



Scheme 8.7 Isomerization of polyhaloarenes and indolylthioethers [27, 28].

Alkyl halides may compete with the aromatic electrophile during S_NAr reactions. Usually, uncatalyzed S_NAr reactions proceed more slowly than S_N2 reactions of reactive alkyl halides (Scheme 8.8). The precise order of reactivity will, however, depend on the structure of all reagents, the solvent [29], and the precise reaction conditions. Aromatic substitutions can be accelerated by transition-metal catalysis because aryl halides often react faster with transition-metal complexes than alkyl halides.



Scheme 8.8 Aliphatic S_N2 reactions may compete with S_NAr reactions [30, 31].

Benzyl halides can react with nucleophiles either by direct aliphatic S_N2 reaction or by nucleophilic attack at the arene. The latter type of substitution will be favored in electron-deficient arenes, or in arenes of low aromaticity, such as naphthalenes. Nucleophilic attack at the arene will also be favored by steric shielding of the benzylic C–Hal bond. Surprising results, though, are frequent (Scheme 8.9).

Arenes and alkanes can be metallated at unexpected positions by chelate formation. A few examples have been reported of the arylation of alkyl groups using this strategy (Scheme 8.10). Because both the alkane and the aryl halide can be metallated, products of homocoupling can be expected as byproducts in these intriguing reactions.

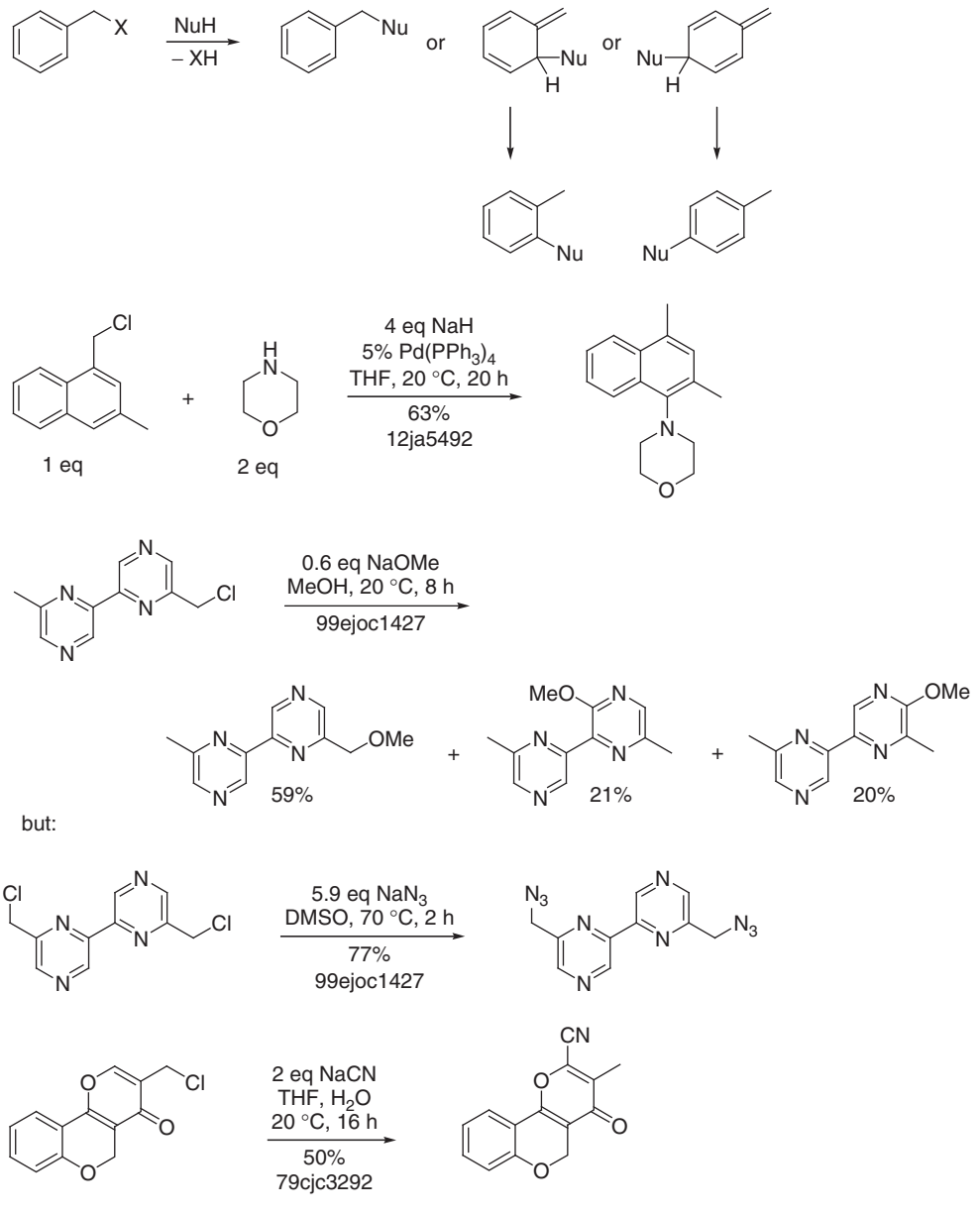
8.1.3
Acid-/Base-Catalysis

Whether aromatic nucleophilic substitutions are catalyzed by acid or base depends on the basicity of both the nucleophile and the electrophile. Protonation will generally increase the electrophilicity of electrophiles but decrease the nucleophilicity of nucleophiles.

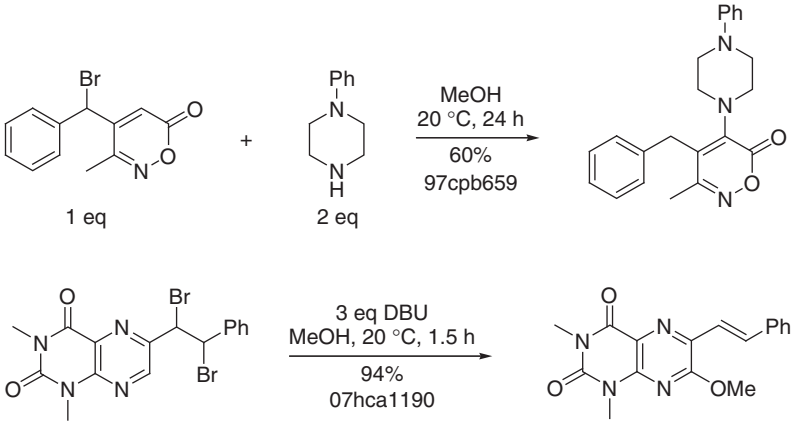
Upon protonation, electron-deficient heteroarenes, such as pyridines, pyrimidines, or pyrazines become more reactive toward nucleophiles. Aromatic nucleophilic substitutions at such heteroarenes can therefore be acid-catalyzed or autocatalytic (if no external acids or bases are added) (Scheme 8.11). This catalytic effect will, however, decrease upon increasing basicity of the nucleophile.

8.1.4
Transition-Metal Catalysis

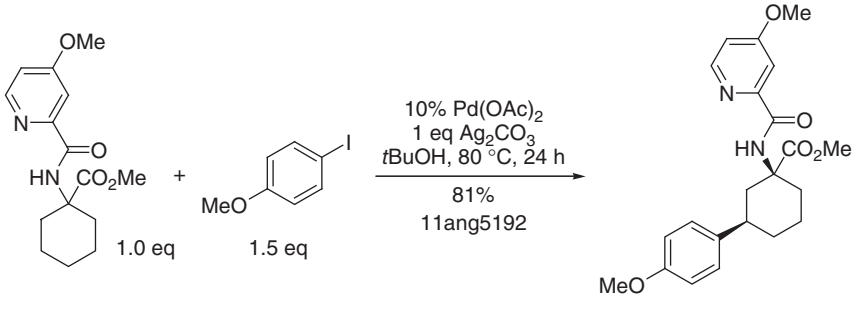
Aromatic nucleophilic substitutions may also be catalyzed by transition metals. Palladium, nickel, and copper complexes can strongly facilitate substitution reactions which would otherwise require high temperatures. For instance, Pd catalysis



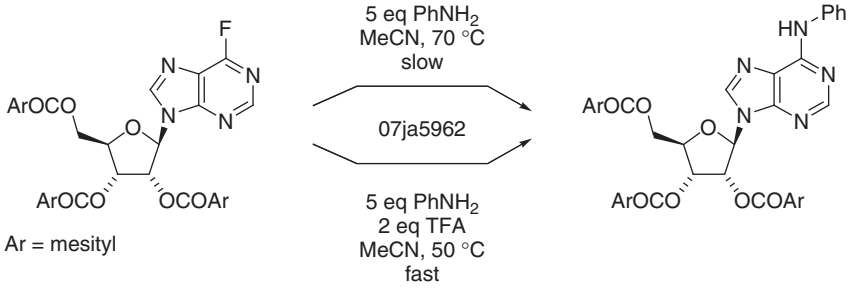
Scheme 8.9 Reaction of benzyl halides with nucleophiles [32–36].



Scheme 8.9 (*Continued*)



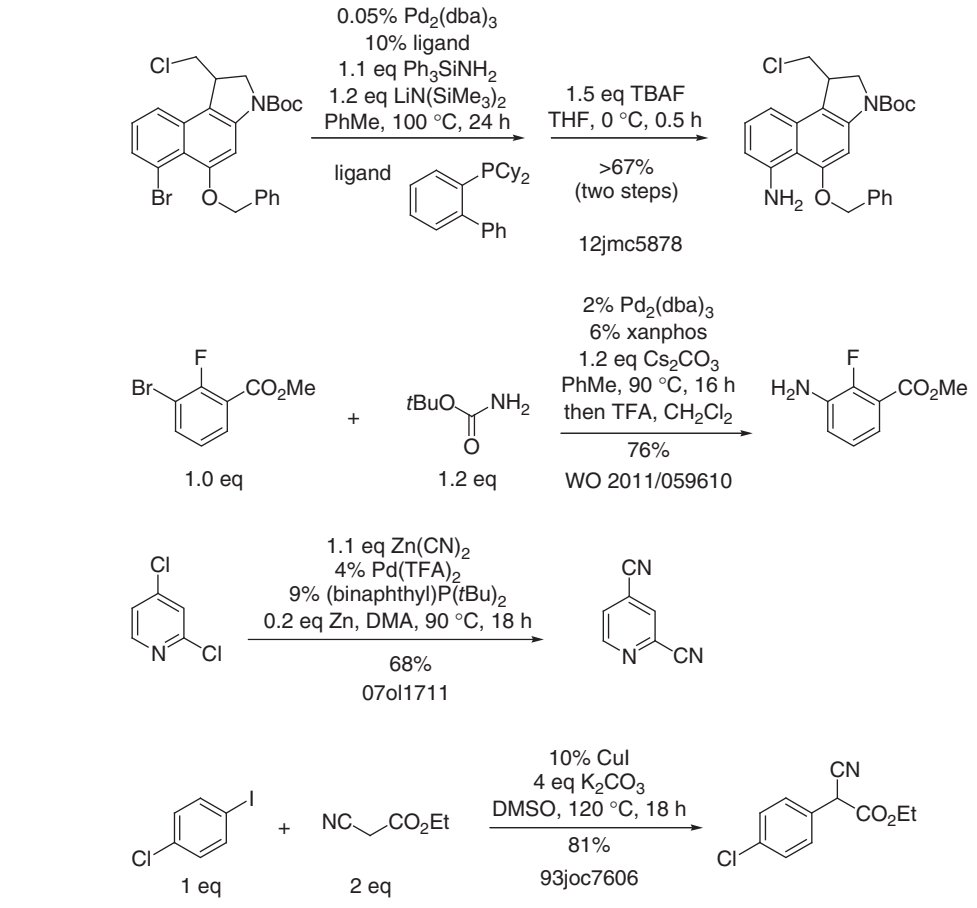
Scheme 8.10 Chelate-mediated arylation of a cyclohexyl group [37].



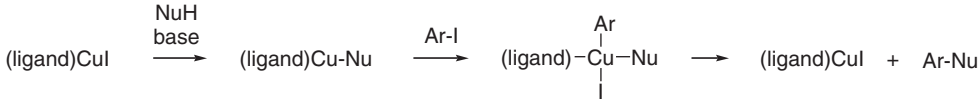
Scheme 8.11 Acid-catalyzed S_NAr reaction of a 6-fluoropurine [13].

can mediate the conversion of aryl bromides into anilines without displacement or elimination at alkyl chlorides (first equation, Scheme 8.12).

The catalysis by copper(I) is assumed to proceed as sketched in Scheme 8.13. Complexation of alcohols or amines with Cu(I) salts enhances their acidity, and leads, in the presence of bases, to the formation of copper alcoholates or amides.



Scheme 8.12 Pd- and Cu-catalyzed aromatic nucleophilic substitutions [38–41].



Scheme 8.13 Mechanism of copper(I)-catalyzed aromatic nucleophilic substitutions [42, 43].

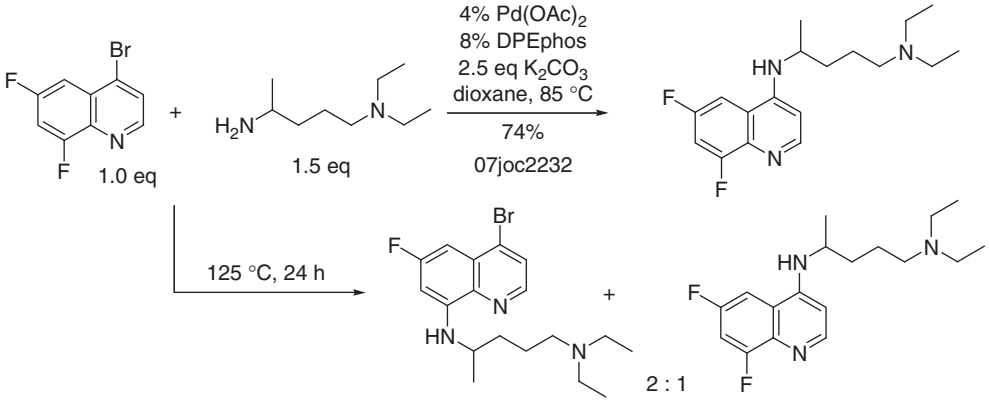
These undergo oxidative addition to aryl iodides or bromides to yield Cu(III) intermediates, which release the product upon regeneration of the catalytically active Cu(I) complex.

Catalysis by Pd complexes is similar to catalysis by copper, the main difference being that oxidative addition of the aryl halide occurs before reaction with the

nucleophile. Moreover, Pd catalysis is better suited for unreactive electrophiles, such as aryl chlorides, sulfonates, or carbamates.

For both metals, strong ligands promote the regeneration of catalytically active complexes, and prevent the formation of stable, catalytically unreactive complexes with the nucleophile. Thus, the use of chelating ligands (1,3-diketones, diphosphines, ethylenediamines, phenanthrolines, bipyridines, amino acids, etc.) has significantly broadened the scope of copper- and palladium-catalyzed aromatic substitutions. Bidentate phosphine ligands even promote Pd-catalyzed aromatic nucleophilic substitutions with thiols, with as little as 0.01% of catalyst [44].

Because transition-metal catalysis proceeds via oxidative addition of an aryl halide to a metal, the reactivity of aryl halides toward nucleophiles is different from that in uncatalyzed S_NAr reactions (Scheme 8.14). Copper catalysis is most effective with aryl iodides and bromides, whereas palladium-based catalysts can be used for aryl chlorides, bromides, iodides, sulfonates, carbamates, and diazonium salts. Aryl fluorides, anilines, nitroarenes, and arylsulfones are usually inert toward copper or palladium complexes.



Scheme 8.14 Selectivity of Pd-catalyzed and uncatalyzed substitutions at a polyhaloquinoline [45].

One potential side reaction of transition-metal-catalyzed S_NAr is biaryl formation (the Ullmann reaction). This reaction is promoted by low concentrations of nucleophile, high temperatures, and the presence of oxidants (e.g., air). Anilines and phenols are particularly prone to undergo oxidative dimerization, and diarylamines and diarylethers can yield carbazoles and dibenzofurans upon oxidative dehydrogenation. Oxidants combined with transition-metal catalysis and high temperatures can also cause a number of other unwanted oxidations, such as dehydrogenations of benzylic amines [46], benzylic alcohols, or other functional groups. If dimethyl sulfoxide (DMSO) is used as solvent for copper-catalyzed S_NAr reactions, further potential byproducts are methylthioethers [47] (Scheme 7.11). In the presence of

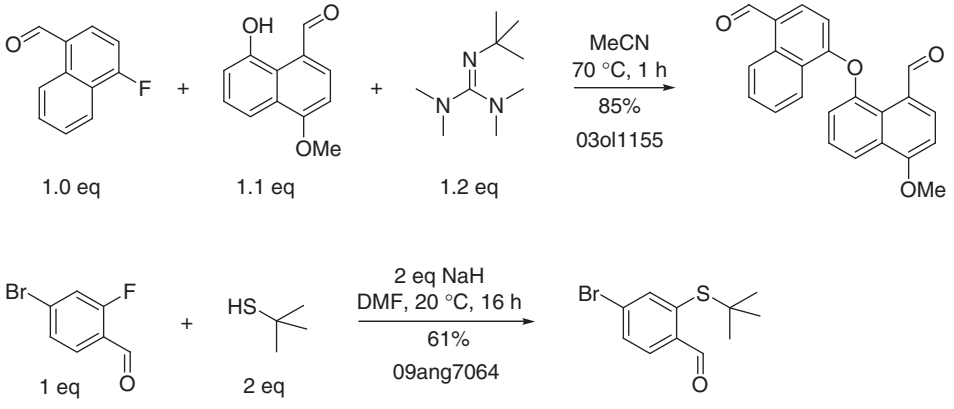
N,N-dimethylformamide (DMF), aryl iodides undergo Pd-catalyzed conversion to *N,N*-dimethylbenzamides [48].

Arylpalladium and arylnickel complexes readily dimerize in the presence of various reducing agents, such as zinc [49], glucose [50], hydroxylamine, isopropanol, hydroquinone, DMF, amines [51], or phosphines [52]. Reducing agents can also promote the formation of unsubstituted arenes (ArH from ArHal).

8.2 Problematic Electrophiles

8.2.1 Incompatible Functional Groups

Because S_NAr reactions often require strong nucleophiles, other functional groups may also react with the nucleophile. Especially sensitive are aldehydes, which may undergo Cannizzaro-type redox reactions, deformylation, or irreversible addition of the nucleophile (to yield, e.g., bisulfite addition products, cyanohydrins, or thioacetals). Nevertheless, numerous successful examples of S_NAr reactions of halogenated benzaldehydes have been reported (Scheme 8.15). Particularly stable (and unreactive) are 4-alkoxy, 4-hydroxy, and 4-aminobenzaldehydes.

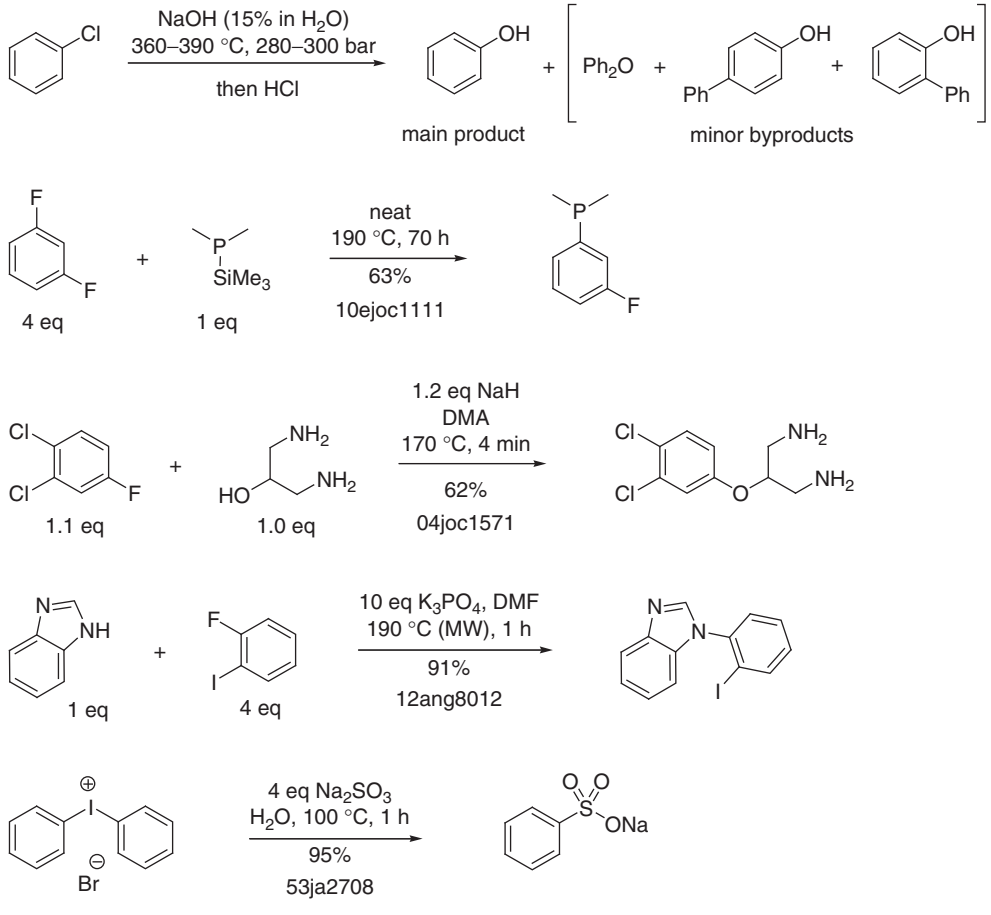


Scheme 8.15 S_NAr reactions of halogenated benzaldehydes [53, 54].

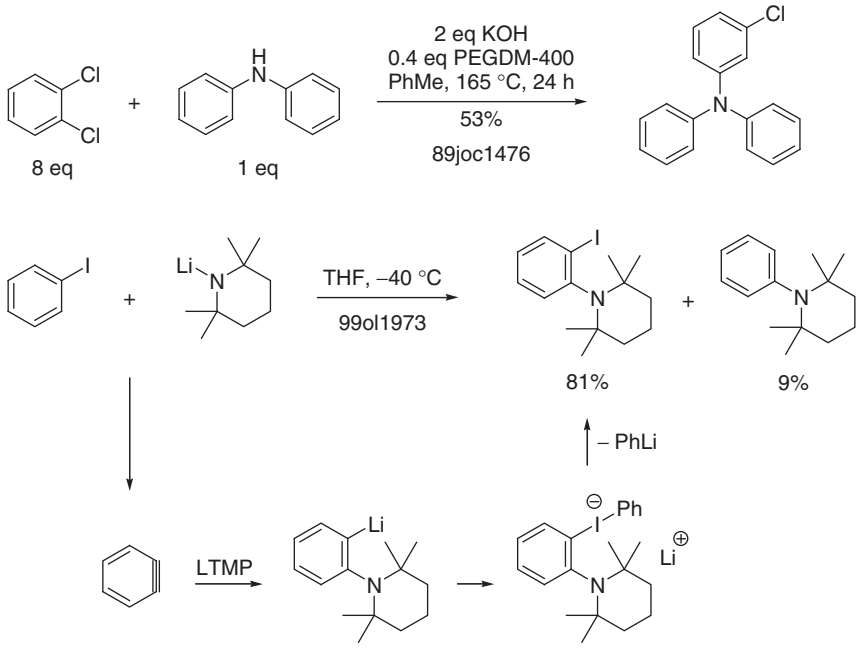
Some nucleophiles, such as thiols, sulfide [55], sulfite, sulfinic acids, alcoholates, and cyanide, may also *reduce* functional groups in the electrophile. Nitro, nitroso, formyl, and diazonium groups are particularly easy to reduce. If the electrophile is very electron deficient and sterically inaccessible, a reduction via single-electron transfer (SET) can also occur.

8.2.2
Non-Activated Arenes

In the absence of transition-metal complexes, non-electron-deficient aryl halides undergo S_NAr under forcing conditions only (Scheme 8.16) or photochemically [56]. If the nucleophile is strongly basic, the reaction may proceed via aryne formation and yield mixtures of regioisomers. Basic nucleophiles and high reaction temperatures can cause numerous side reactions, such as the Cannizzaro reaction of aldehydes and the cleavage of esters, amides, carbonates, carbamates, ketones (Haller–Bauer reaction), sulfones, and sulfoxides [57]. In the presence of oxygen or other oxidants, strong bases can lead to peroxide formation, hydroxylations, or dehydrogenation of many organic compounds. Forcing conditions, in particular in the presence of traces of transition metals, may lead to the displacement of substituents which would usually not be considered as leaving groups.



Scheme 8.16 Uncatalyzed S_NAr reactions at non-electron-deficient arenes [58–64].

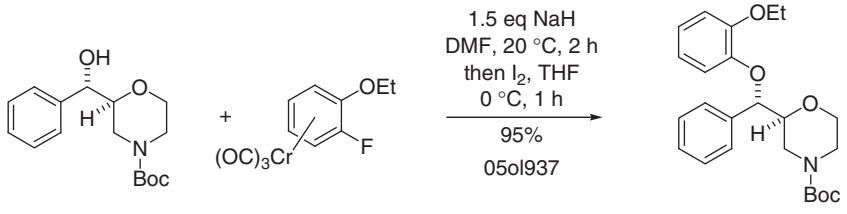


Scheme 8.16 (*Continued*)

One often-used synthesis of phenols consists in treating sulfonic acids with NaOH/KOH melts at 250–300 °C [65, 66]. This reaction generally only yields products of substitution and no regioisomers. In 1926, phenol was produced at Dow in Midland from chlorobenzene and NaOH by pumping the starting materials through a long (about 1 mile) tube at 300 °C (residence time: 10–30 min; Hale–Britton process; first equation in Scheme 8.16) [67].

Fluorine – but also the other halogens – increases the C–H acidity of arenes. Polyhaloarenes may therefore act as electrophilic halogenating reagents (transfer of Hal^+ to nucleophiles), or undergo isomerization (''halogen dance'') in the presence of strong bases (Scheme 8.7).

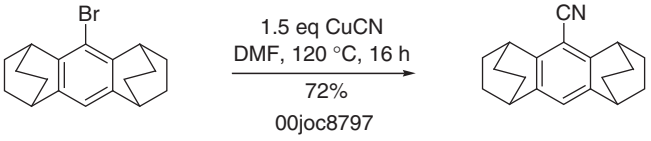
A laboratory trick for the activation of non-electron-deficient aryl halides is complexation with chromium tricarbonyl [68] (Scheme 8.17). Unfortunately, for



Scheme 8.17 S_NAr at arene chromium tricarbonyl complexes [69].

most industrial applications this method will generate too much waste and be too expensive.

Steric demand does not seem to prevent S_NAr reactions from occurring, and many successful examples of substitutions at 2,6-dialkylaryl halides have been reported [70] (Scheme 8.18). The nucleophiles in these examples were, however, rather small (cyanide, halides, azide, nitrite, etc.).



Scheme 8.18 S_NAr reaction at a sterically demanding aryl bromide [71].

8.2.3 Nitroarenes

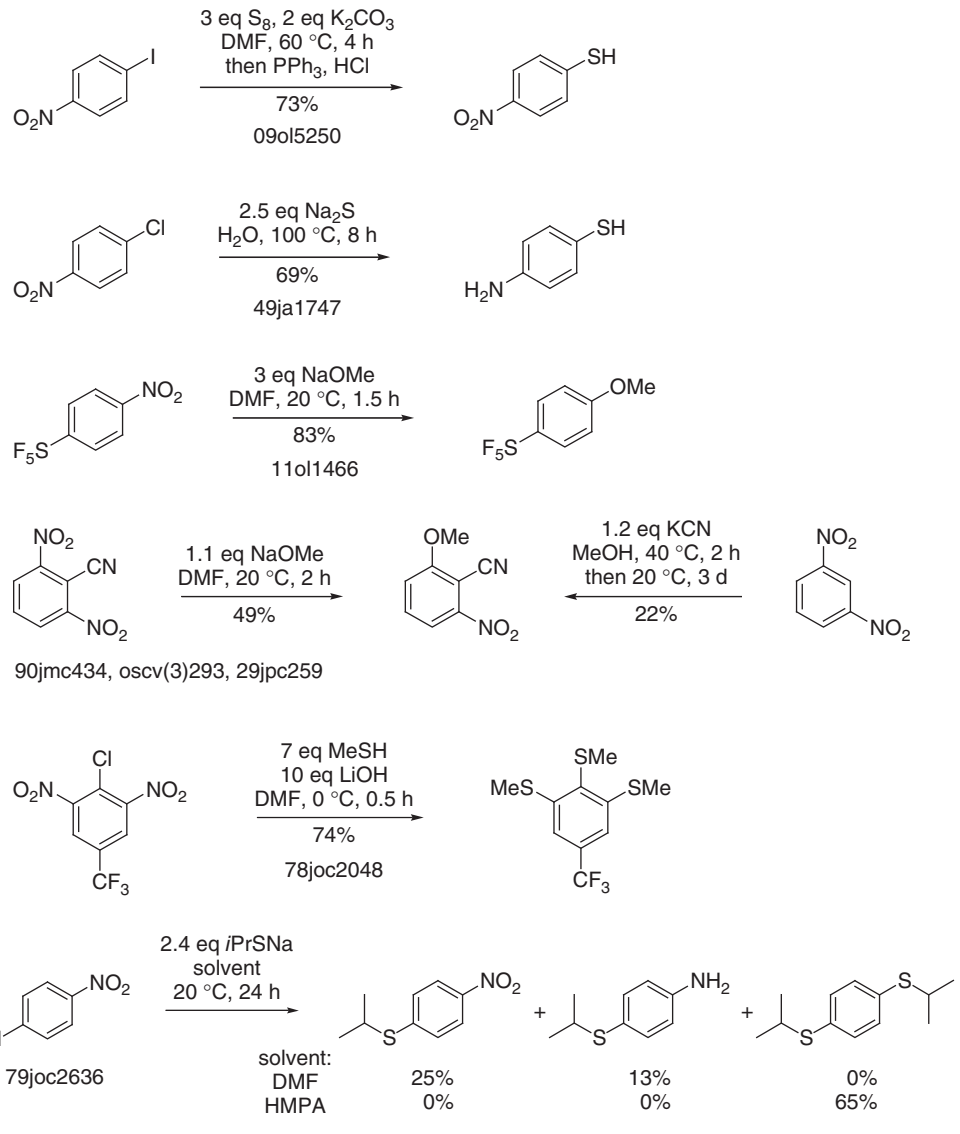
Owing to its strong electron-withdrawing effect, the nitro group is the preferred activating group for S_NAr reactions. 1-Chloro- or 1-fluoro-2,4-dinitrobenzene reacts with many nucleophiles already at room temperature. It should be kept in mind, though, that the nitro group is an excellent leaving group, too, and sometimes it can be difficult to predict which group will be displaced. Moreover, nitroarenes sometimes show little aromatic character, and react more like nitroalkenes. For instance, nitroarenes undergo 1,3-dipolar cycloadditions with azomethine ylides [72]. Nitro groups are also readily reduced by electron-rich nucleophiles, which can lead to a further set of byproducts (Scheme 8.19).

Because of this high reactivity, nitrobenzene is a dangerous solvent, capable of violent decomposition either upon excessive heating or upon treatment with acids or bases. Numerous explosions of nitrobenzene have been reported.

Nitroarenes and some electron-deficient heteroarenes can be alkylated by an addition–elimination mechanism (“vicarious nucleophilic substitution”) (Scheme 8.20). Attack at hydrogen-substituted positions is usually faster than addition to halogen-substituted positions, so that 2- or 4-halonitrobenzenes can undergo, in the presence of an oxidant (the nitroarene, DMSO), displacement of hydrogen faster than displacement of halides [82–85]. The addition of primary or secondary amines to nitroarenes, followed by hydride abstraction, has also been reported [86, 87].

Suitable alkylating reagents for vicarious nucleophilic substitutions are α-halosulfones and related C–H acidic compounds with a leaving group at the acidic C–H group. Unfortunately, this reaction proceeds well only with nitroarenes, and almost no examples have been reported of other electron-deficient arenes undergoing this reaction [92].

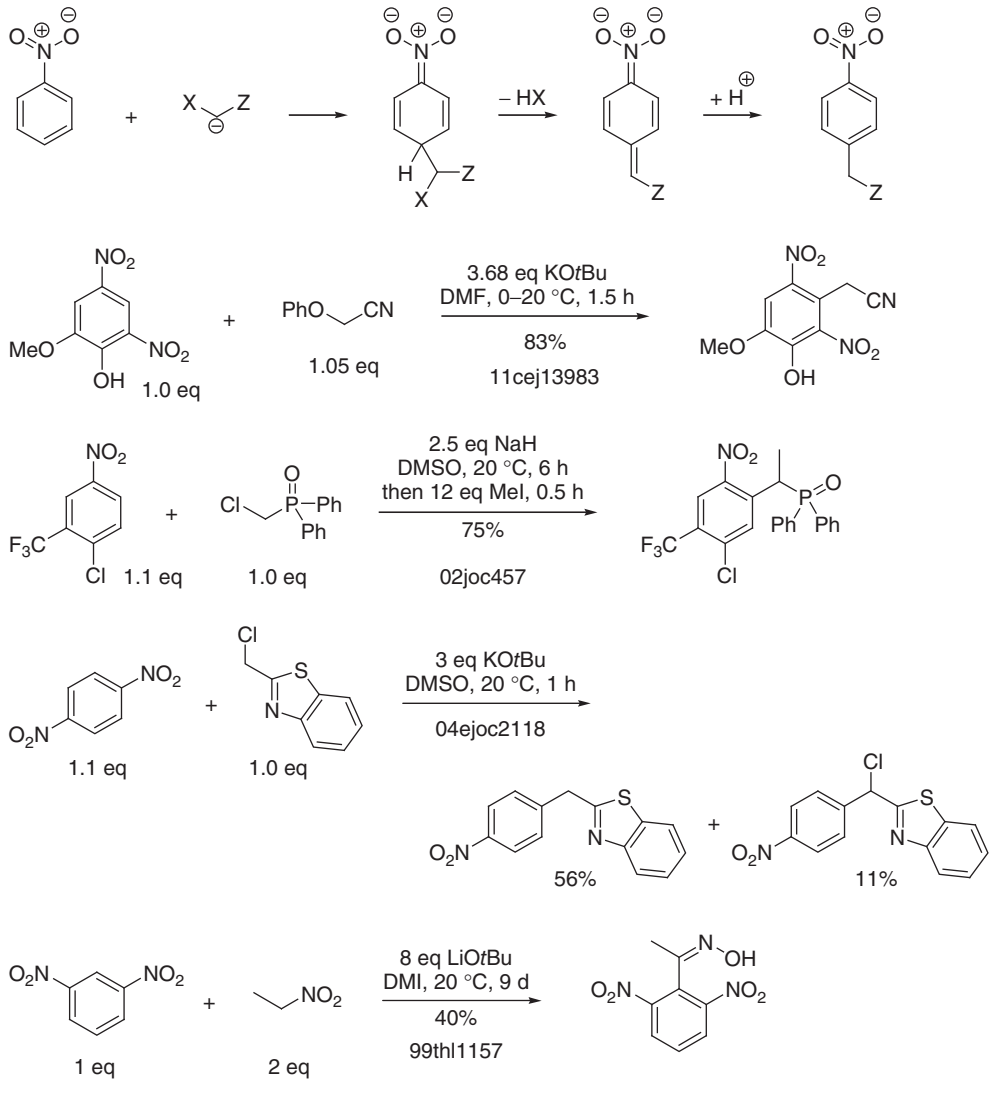
Closely related to the vicarious nucleophilic substitution with carbon nucleophiles are the reactions of nitroarenes with peroxides (Scheme 8.21), hydrazines (e.g.,



Scheme 8.19 S_NAr reactions of nitrobenzenes [73–80]. Further examples: [57, 81].

$H_2N–NMe_3I$ [93]), azides (Section 8.3.6), or hydroxylamines. Because unsubstituted positions at the nitroarene can react as well, the regioselectivity of these reactions is difficult to predict.

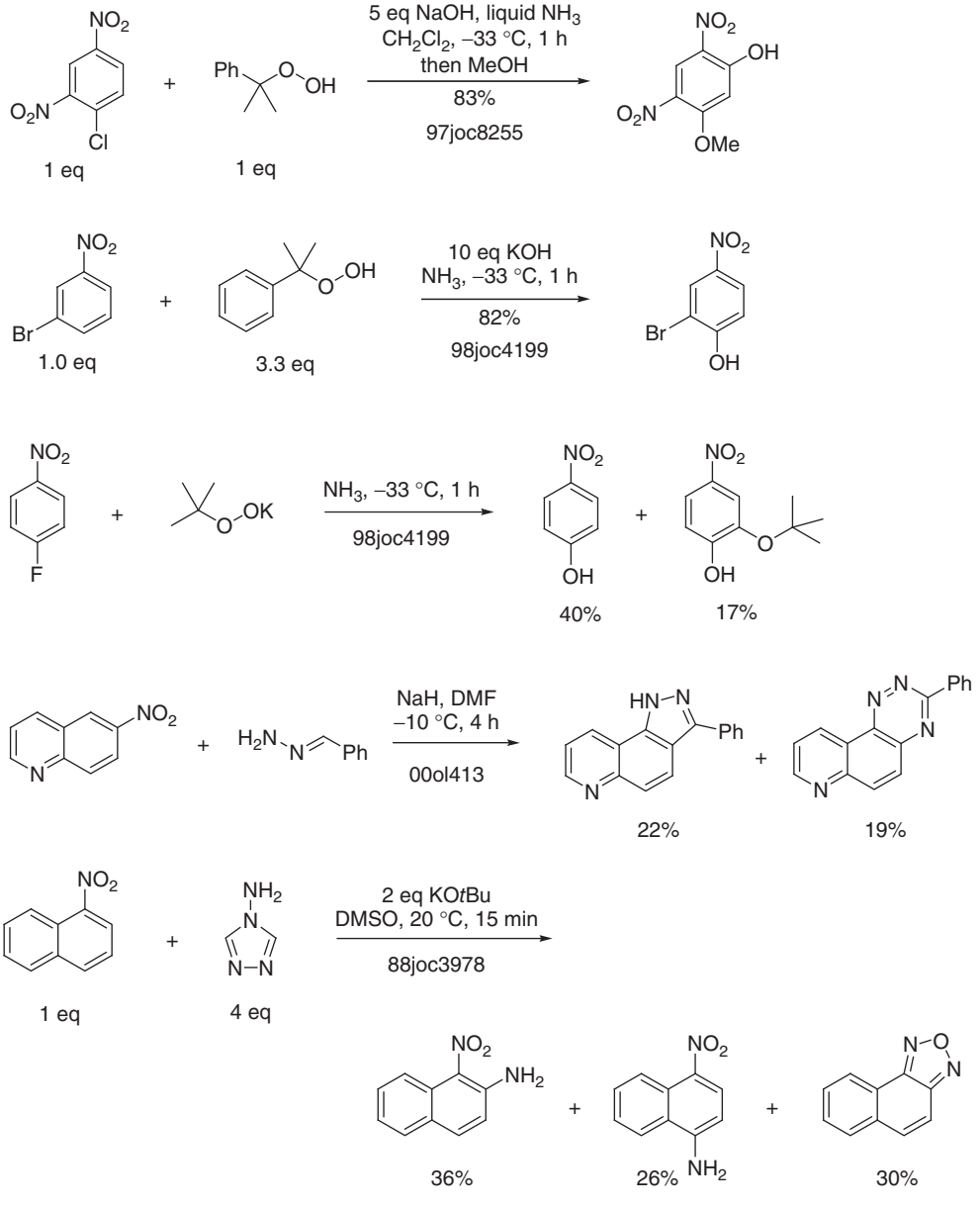
One remarkable but unexpected reaction of nitrobenzenes is the von Richter rearrangement (Scheme 8.22). Upon treatment with cyanide in refluxing aqueous ethanol, 1-nitroarenes are converted into 2-carboxyarenes. This reaction proceeds



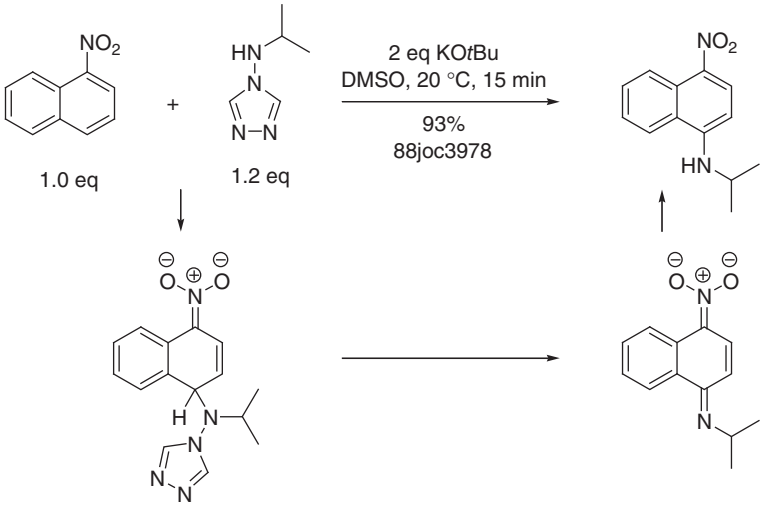
Scheme 8.20 Mechanism and examples of vicarious nucleophilic substitution [88–91]. X, leaving group; Z, electron-withdrawing group.

faster than the aromatic nucleophilic substitution of bromide or chloride because the addition of nucleophiles to unsubstituted positions in arenes is usually faster than the addition to substituted positions [84].

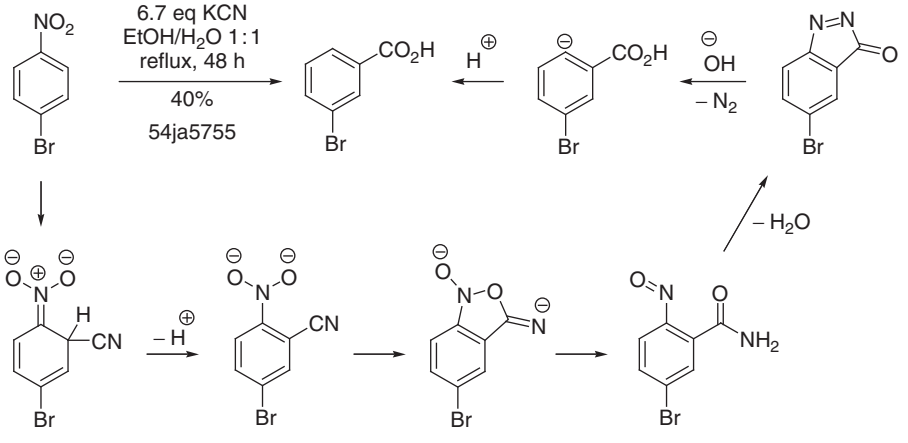
Bromonitrobenzenes can be converted to nitrobenzonitriles by using potassium hexacyanoferrate(II) powder (which does not mediate the von Richter rearrangement [98]) or $Zn(CN)_2$ as cyanide source, and nickel [99], copper, or palladium



Scheme 8.21 Amination and hydroxylation of nitroarenes [94–97]. Further examples: [7].

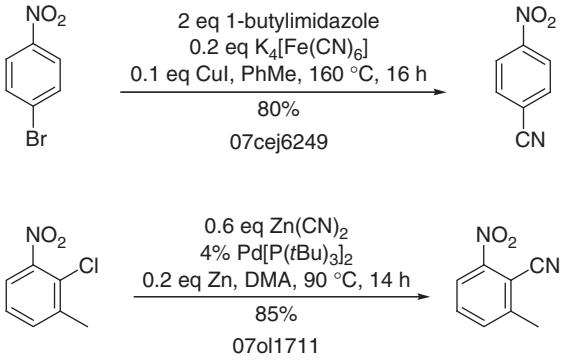


Scheme 8.21 (*Continued*)



Scheme 8.22 Mechanism of the von Richter rearrangement [98].

[100–102] catalysis (Scheme 8.23). In these reactions, it is important to keep the concentration of cyanide as low as possible to prevent the formation of stable, catalytically unreactive transition-metal cyanides. By adding a reducing reagent (Zn or *i*PrOH [103]), catalytically active Pd(0) can be regenerated from unreactive $Pd(CN)_2$, and by working under strictly aprotic basic conditions the formation of HCN can be prevented, which reacts faster with Pd complexes than cyanide [104].



Scheme 8.23 Catalyzed S_NAr reaction of nitrobenzene halides with cyanide [40, 105].

Nitroarenes may also just add cyanide, and then be oxidized to nitrobenzonitriles (Scheme 8.19), or eliminate water to yield 2-nitrosobenzonitriles (Scheme 8.25). The low yield of these reactions is caused by the dual function of the nitroarene as oxidant and as precursor to the product.

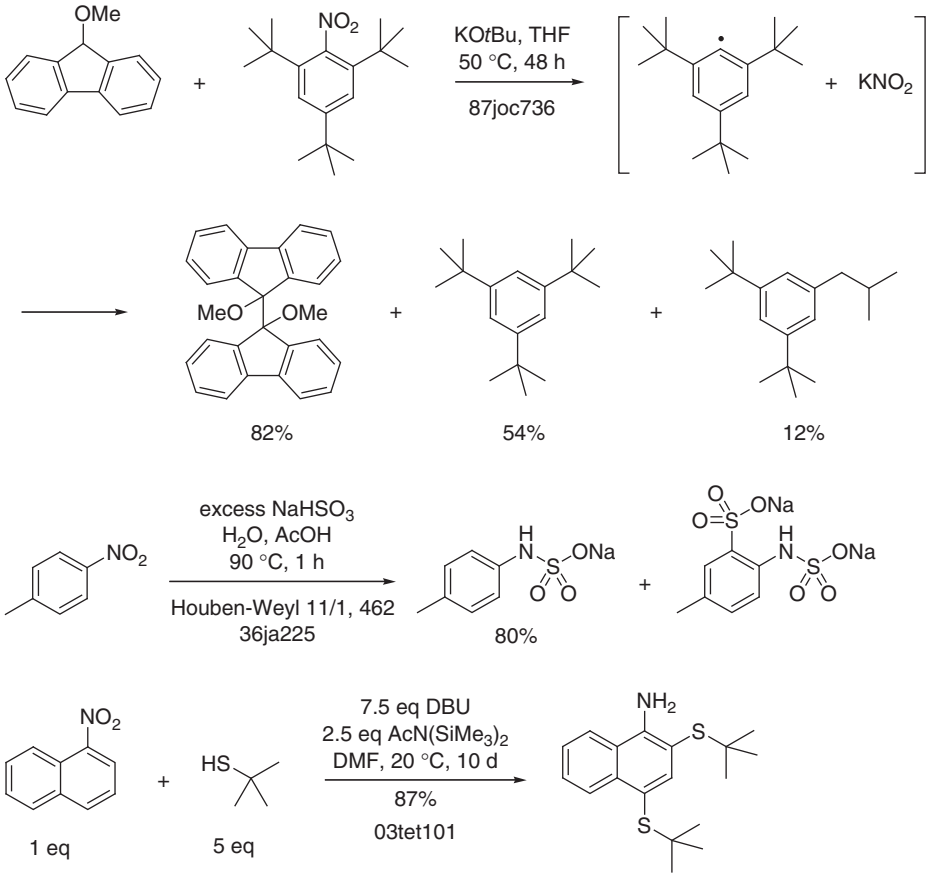
Nitroarenes are readily reduced, either to nitrosoarenes or anilines, or by SET to aryl radicals. Typical nucleophiles that can reduce nitroarenes include sulfide(s), sulfite, and alcoholates (Scheme 8.24). These reductions can sometimes be avoided by lowering the amount of nucleophile or the reaction temperature [79].

Sterically demanding nitroarenes can be precursors for aryl radicals when treated with electron-rich nucleophiles (Scheme 8.24). Because of their steric demand, the resulting radicals will mostly abstract hydrogen from other reaction partners or undergo rearrangement reactions.

Nitroarenes can be reduced by aqueous sulfite. The intermediate nitrosoarenes readily add sulfite, and aminobenzenesulfonic acids or (sulfamino)benzenesulfonic acids are usually obtained (Piria reaction). Intermediate *N*-arylhydroxylamines can rearrange to aminophenols under acidic reaction conditions.

C–H acidic compounds, such as cyanoacetates, malonates, or β-ketoesters, can be condensed with nitrosoarenes. The reaction of cyanoacetates with electron-deficient nitroarenes in the presence of bases leads to the formation of oxalamides of 2-aminobenzonitriles (Scheme 8.25). This reaction proceeds via the formation of 2-nitrosobenzonitriles [110]. With halonitroarenes, this reaction can be prevented by catalyzing the S_NAr process with transition-metal complexes.

The cyanide required for the first reaction in Scheme 8.25 must result from the base-mediated degradation of the cyanoacetamide. In fact, in the presence of bases, cyanoacetic acid derivatives and malononitrile can act as a source of cyanide (Scheme 8.26). Therefore, one potential side reaction of S_NAr reactions

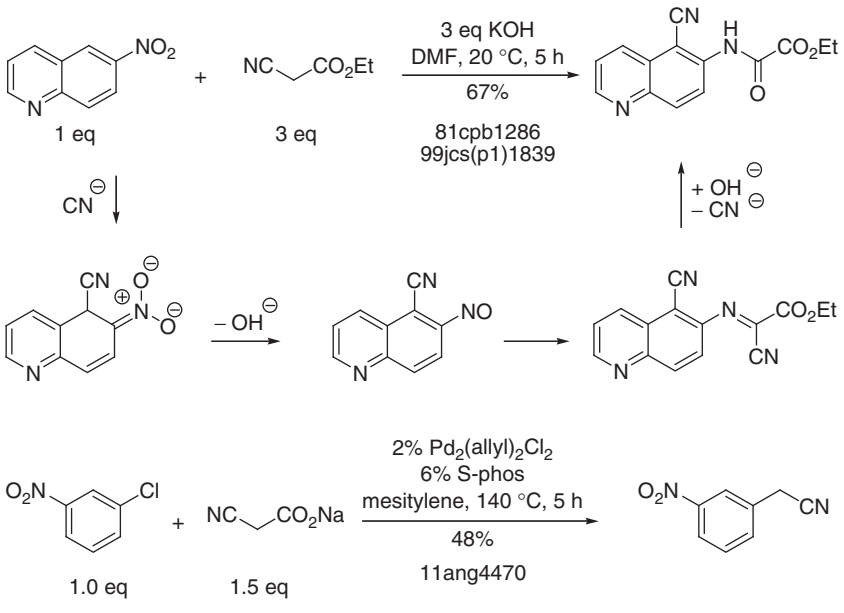


Scheme 8.24 Reduction of nitroarenes by various nucleophiles [106–109].

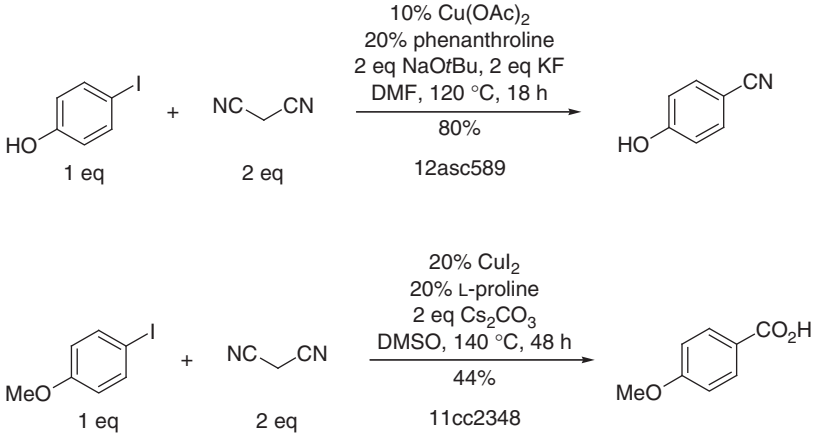
with cyanoacetic derivatives is the formation of benzonitriles or benzoic acids. The latter may also result from oxidative degradation of the arylated cyanoacetic acid derivatives [114].

Nitroarenes are strong oxidants, and can react with alcohols, amines, or other potential hydride donors, in particular in the presence of transition metals. High reaction temperatures, as are sometimes required for S_NAr reactions, and residual catalysts can therefore cause the reduction of nitroarenes and the formation of various byproducts. For instance, the reaction of nitroarenes with primary alcohols can yield quinolines (Scheme 8.27).

Some heteroarenes can undergo ring-opening reactions when treated with nucleophiles. 3-Nitrothiophenes, for instance, are cleaved by secondary amines (Scheme 8.28).



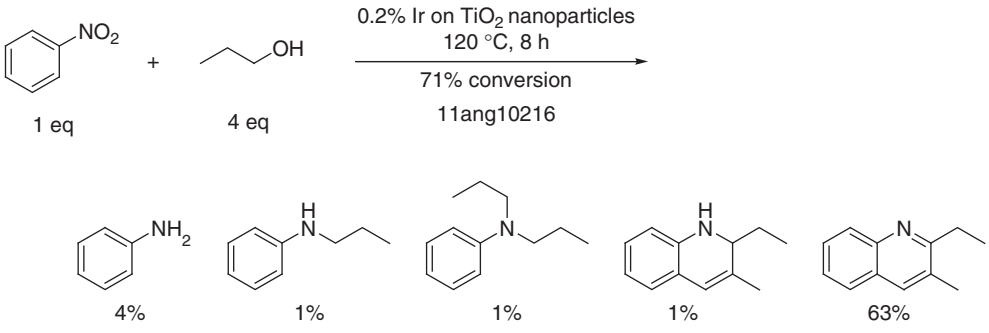
Scheme 8.25 Reaction of cyanoacetic acid derivatives with nitroarenes [110–112]. Further examples: [113].



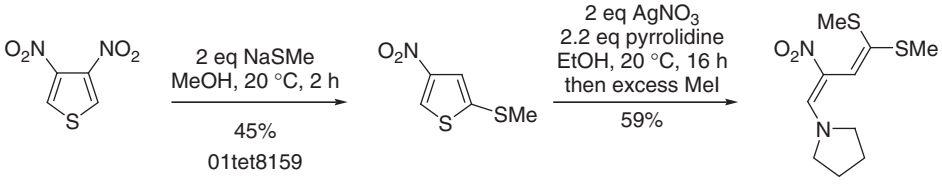
Scheme 8.26 S_NAr reactions of malononitrile [114, 115].

8.2.4
Diazonium Salts

Although elemental nitrogen is an excellent and environmentally friendly leaving group, arenediazonium salts are not always suitable electrophiles for S_NAr reactions. Arenediazonium salts add nucleophiles at nitrogen under basic reaction

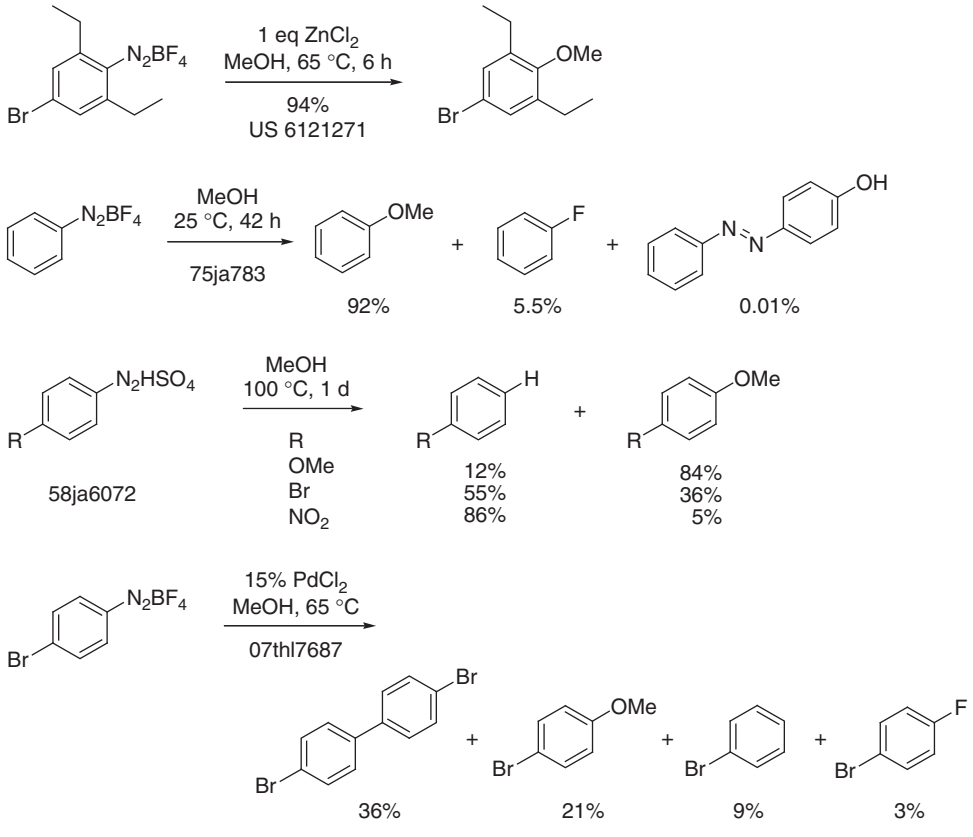


Scheme 8.27 Iridium-catalyzed reaction of propanol with nitrobenzene [116].



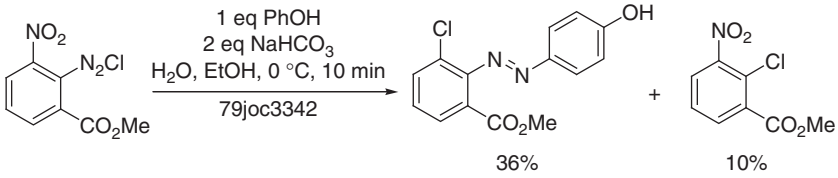
Scheme 8.28 Ring fission of a nitrothiophene [117].

conditions, and are powerful one-electron oxidants. The classical Sandmeyer protocol, which requires substoichiometric but still substantial quantities of copper salts, and related copper-free substitution reactions can convert arenediazonium salts to aryl halides, aryl azides, nitroarenes, phenols, benzoic acids, benzonitriles, benzaldehydes, acetophenones, benzenesulfonyl chlorides, arylthioethers, and arylthiolesters [118]. Vinylations and arylations of arenediazonium salts can be achieved with the Meerwein and Gomberg–Bachmann reactions. There are, however, no high-yielding and generally applicable procedures for the displacement of diazonium groups by amines or alcohols. If arenediazonium salts are treated with alcohols under acidic conditions, mixtures of ethers and reduced arenes result, the ratio depending on the substitution pattern of the arenediazonium salt [119]. Only diazonium salts substituted with alkyl or alkoxy groups or ortho-substituted with groups capable of stabilizing an aryl cation sometimes undergo clean S_NAr reactions in the presence of acids [120] (first example in Scheme 8.29). Under basic reaction conditions, though, amines and alcohols add to the diazonium group to yield triazenes and diazoethers, which decompose thermally via aryl radicals to yield the reduced arenes and other products. Amines and alcohols react with aryl radicals mainly as hydrogen atom donors (H-abstraction from H–C–N/O). Under basic conditions, alcoholates may also reduce diazonium salts by hydride transfer [121].



Scheme 8.29 Reaction of arenediazonium salts with alcohols [119, 122–124].

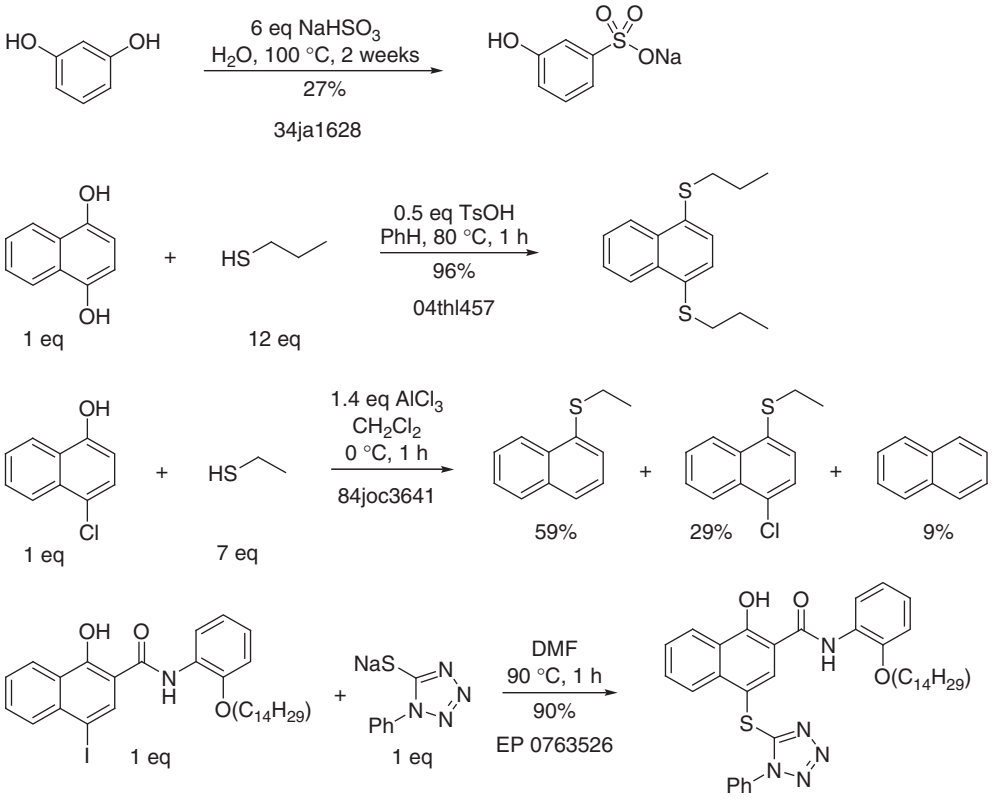
The diazonium group strongly activates arenes for S_NAr reactions. In particular, electron-deficient arenediazonium salts, which require strong acids and higher reaction temperatures to be formed (because the last (dehydration) step is slow), are susceptible to nucleophilic aromatic displacement of ortho halides or nitro groups [125] (Scheme 8.30). Such reactions can be avoided only by excluding potential nucleophiles from the reaction mixture, for example, by using HBF_4 instead of HCl or H_2SO_4 for the diazotization.



Scheme 8.30 S_NAr reactions at arenediazonium salts [126].

8.2.5
Phenols

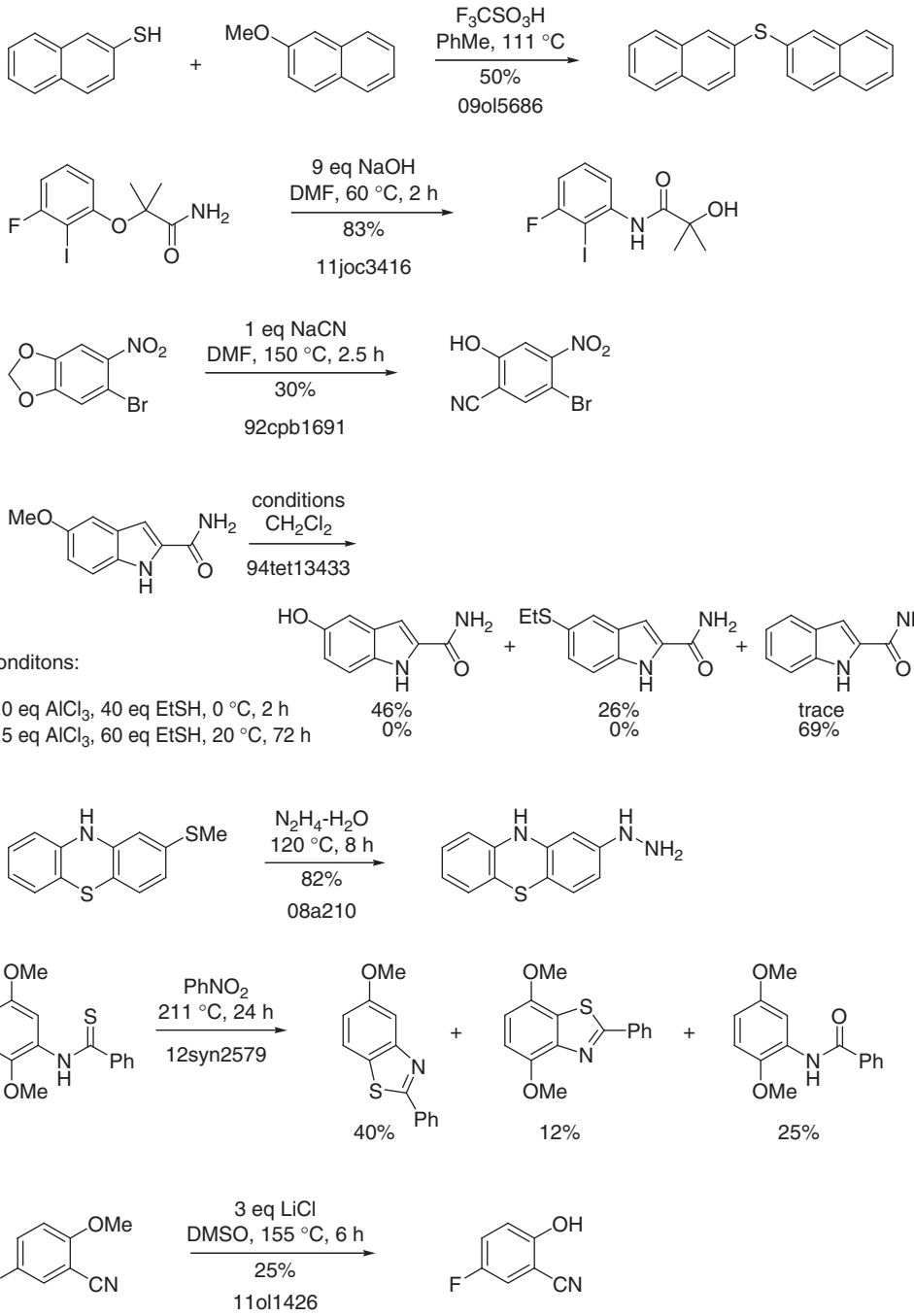
Some phenols, in particular polyhydroxybenzenes and naphthols, occasionally behave as ketones (cyclohexadienones), and undergo facile displacement of the hydroxyl group by ammonia or other nucleophiles. As with ketones (e.g., acetal or enamine formation), such reactions occur preferentially in the presence of acids (Scheme 8.31).



Scheme 8.31 Phenols as electrophiles in S_NAr reactions [127–130].

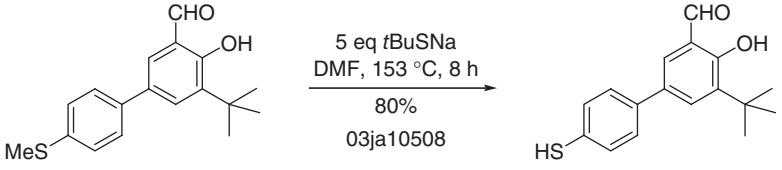
8.2.6
Arylethers and Arylthioethers

Alkoxybenzenes can be suitable electrophiles in S_NAr reactions (Scheme 8.32). Many examples have been reported of the displacement of methoxide from 2-methoxybenzoic acid derivatives by strong nucleophiles [131, 132]. Arylethers may, however, also react as alkylating reagents [133, 134].



Scheme 8.32 Reactions of arylethers with nucleophiles [133, 135–140]. Further examples: [141].

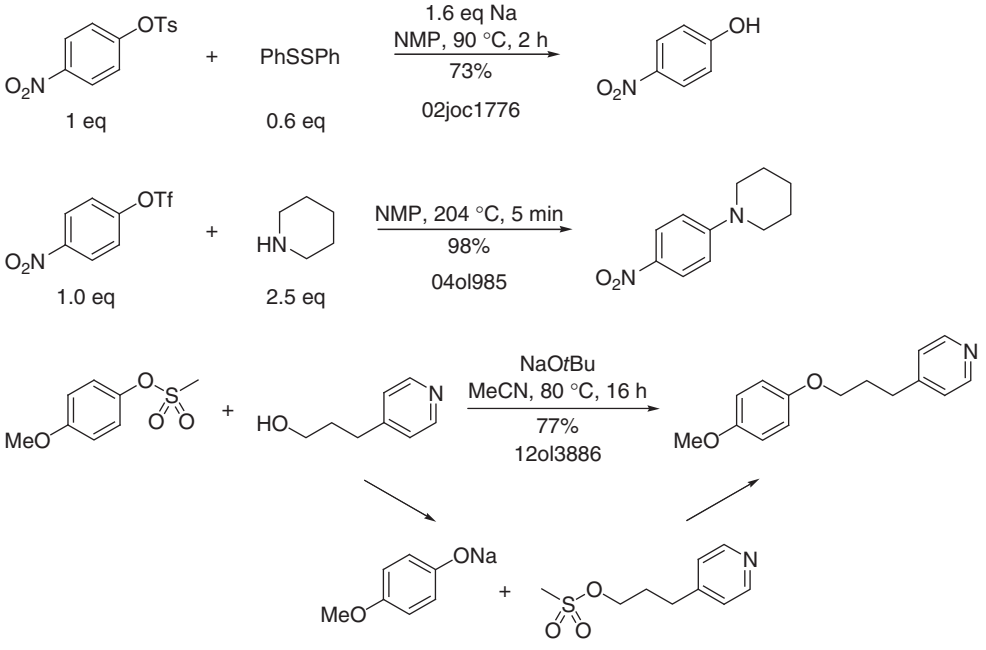
Also arylthioethers can be used to arylate nucleophiles (e.g., Grignard reagents [142]), but may also act as alkylating reagents (Scheme 8.33). For instance, the treatment of aryl halides with thiols can lead to the formation of thiophenols by thiol-mediated dealkylation of the intermediate aryl thioether (Scheme 8.61).



Scheme 8.33 Arylthioethers as alkylating reagents [143]. Further examples: [144].

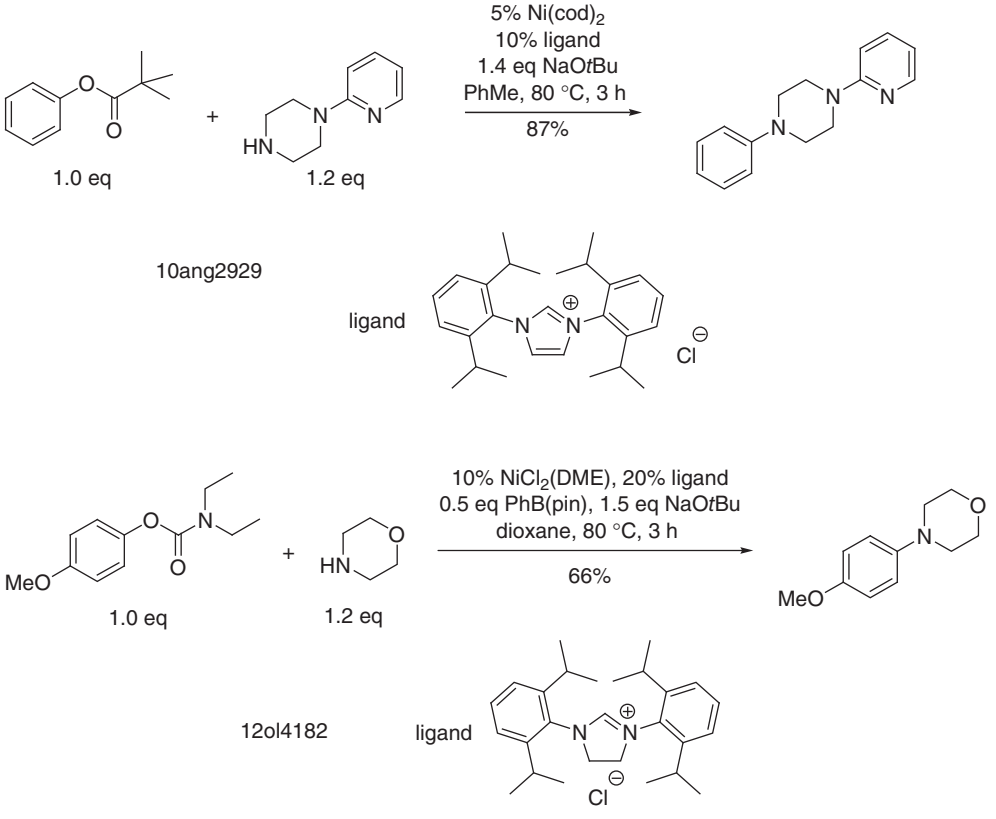
8.2.7
Other Phenol-Derived Electrophiles

Arylsulfonates are suitable electrophiles for S_NAr reactions, but with some nucleophiles cleavage of the S–O bond can occur [145, 146]. Alkanesulfonic acid aryl esters, for instance, are base-labile, and can convert alcoholates to sulfonic esters (Scheme 8.34). S–O Bond cleavage and the formation of phenols can be avoided by using Cu- or Pd-based catalysts.



Scheme 8.34 Arylsulfonates as electrophiles in S_NAr reactions [147–149].

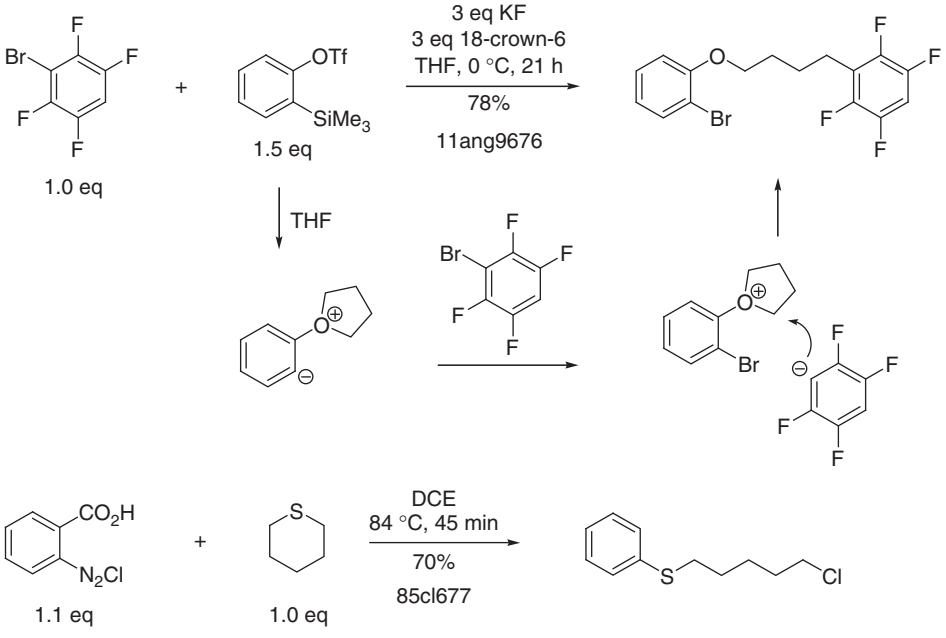
Phenol-derived esters, carbonates, and carbamates are still more readily cleaved by nucleophiles than sulfonates, and are rarely used as electrophiles for S_NAr reactions. Again, with the aid of transition-metal catalysis such reactions can sometimes be accomplished (Scheme 8.35).



Scheme 8.35 Carboxylates and carbamates as leaving group in S_NAr reactions [150, 151]. Further examples: [152].

8.2.8
Arynes

Arynes are a particularly reactive group of electrophilic arylating reagents. These intermediates are generated by β-elimination from aryl halides, diazotized anthranilic acid, or (2-silylaryl)triflates. Owing to the high energy of arynes, even weak nucleophiles will be arylated. The intermediate zwitterions can undergo a wealth of amazing but capricious chemistry (Scheme 8.36).



Scheme 8.36 Reactions of arynes with ethers [153, 154].

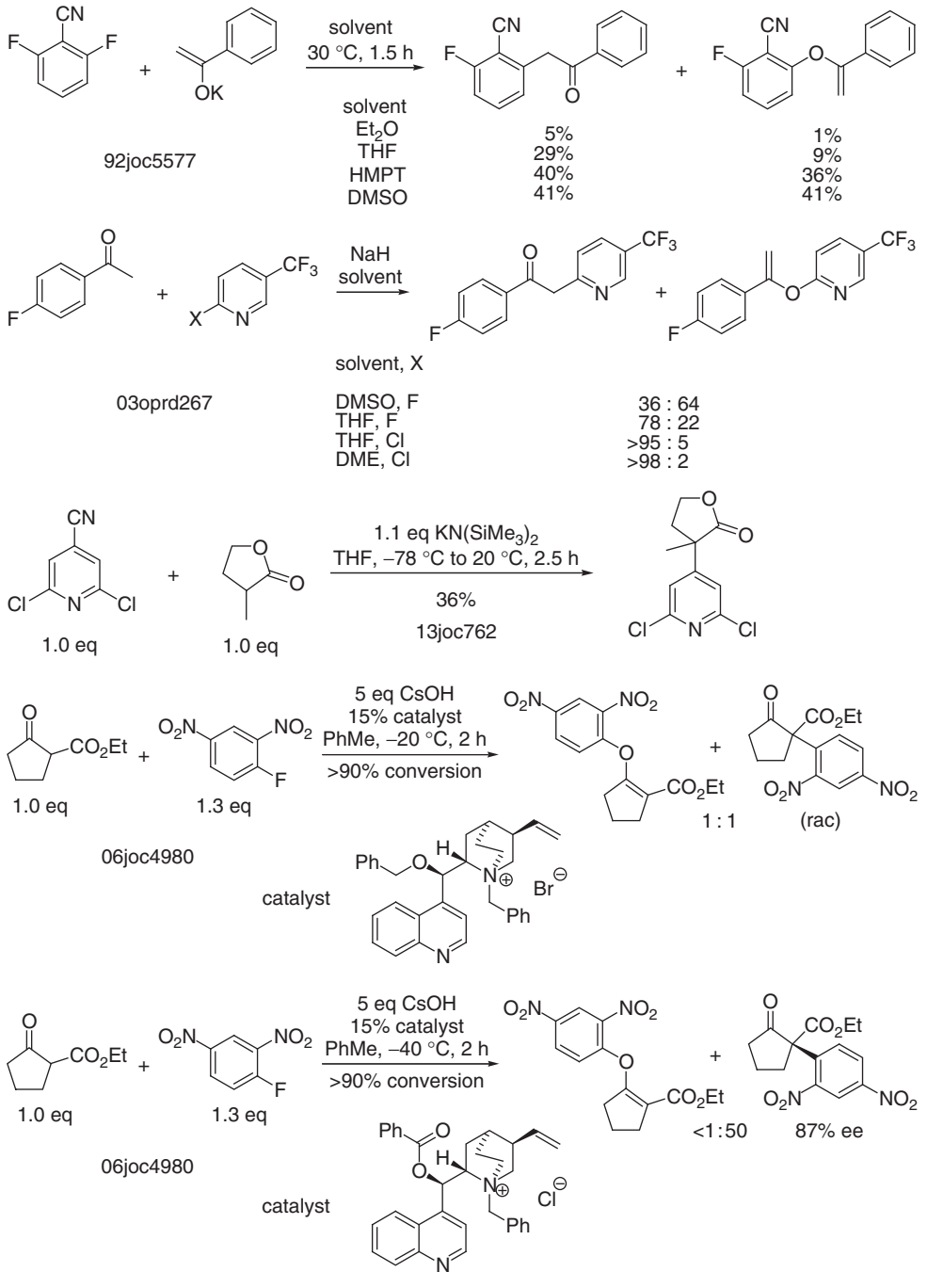
8.3
Problematic Nucleophiles

8.3.1
Enolates

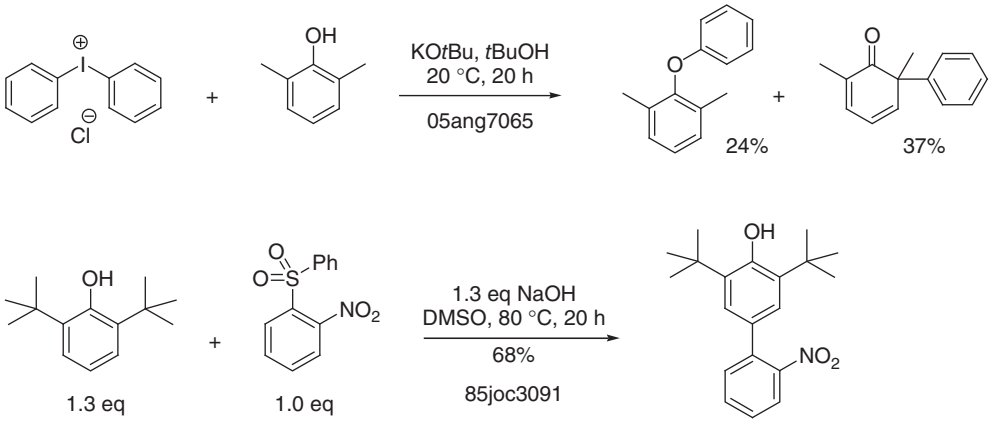
Enolates can, as any other ambident nucleophile, lead to mixtures of isomeric products. In nonpolar solvents, such as ethers, metal enolates do not dissociate completely, and the oxygen-bound metal can prevent O-arylations. Nevertheless, arylations of alkali enolates must usually be optimized by trial and error (Scheme 8.37).

Closely related to ketone enolates are phenolates, which may also undergo either C- or O-arylation upon treatment with an electrophilic arylating reagent (Scheme 8.38). Numerous parameters can influence the selectivity of such transformations, and high-yielding reaction conditions are sometimes difficult to find.

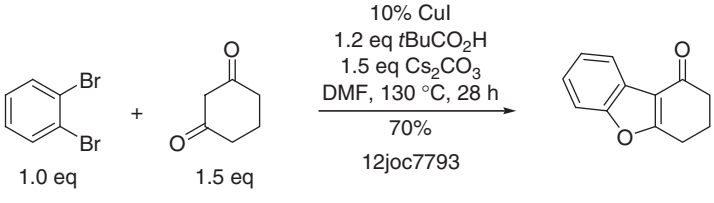
The C-arylation of ketones can also be catalyzed by transition metals, and O-arylation is only rarely seen in these reactions (Scheme 8.39). In the case of Pd-catalyzed C-arylations of ketones, palladium is bound to carbon (and not to oxygen), and reductive elimination leads mainly to C–C bond formation [161].



Scheme 8.37 C- And O-arylation of ketone- and lactone-derived alkali enolates [155–158].



Scheme 8.38 Arylation of phenolates [159, 160].

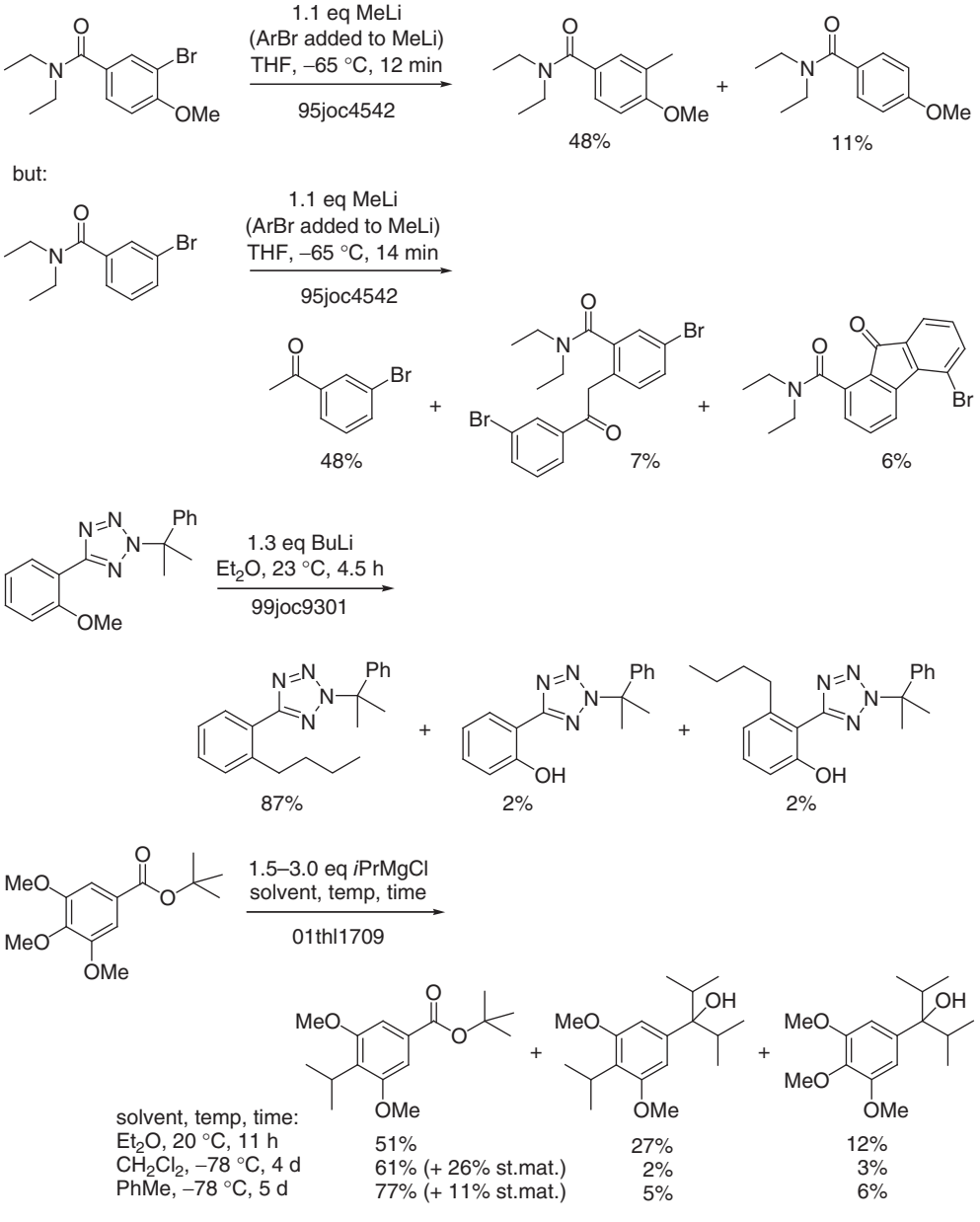


Scheme 8.39 Preparation of benzofurans by C- and O-arylation of 1,3-diketones [162].

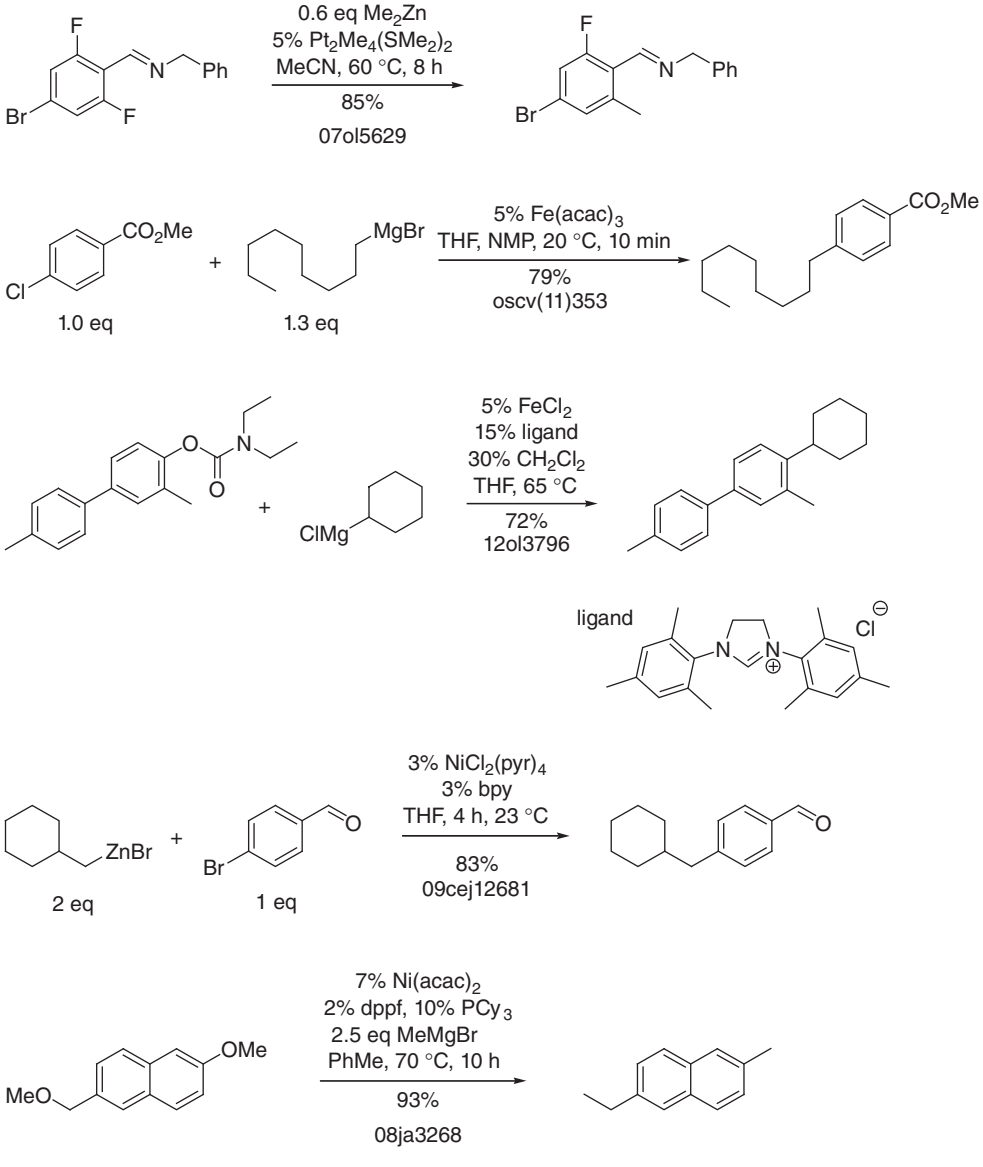
8.3.2
Organomagnesium and Related Organometallic Compounds

Owing to their chemical hardness, instead of reacting as nucleophiles, polar organometallic reagents will usually tend to react as bases, as single electron donors, or lead to halogen–metal exchange. For instance, if aryl halides are treated with BuLi in tetrahydrofuran (THF) at room temperature, butylarenes may result, not by S_NAr but by reaction of ArLi with BuBr [163, 164]. Moreover, many functional groups react with polar organometallics, too. Therefore, these reagents can transform electron-deficient arenes in many different ways, and are only rarely used as nucleophiles for S_NAr reactions (Scheme 8.40).

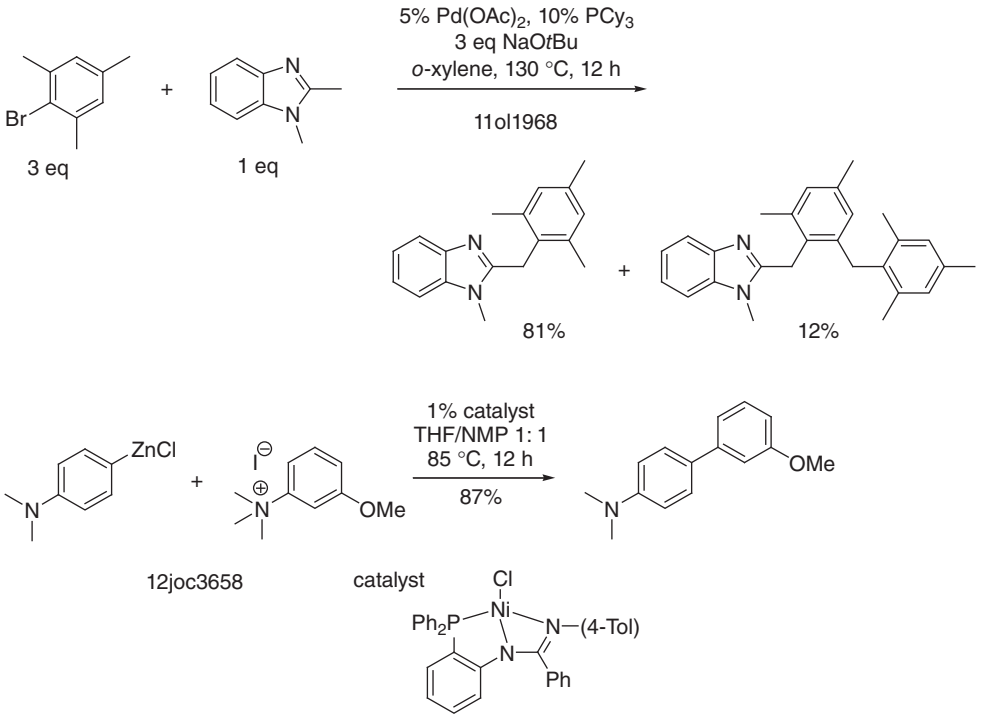
Transition-metal complexes can sometimes catalyze the displacement of leaving groups from arenes by converting polar ''hard'' organometallics into softer organo-transition-metal complexes, or by cleaving the arene–leaving group bond. Numerous examples of transition-metal-catalyzed arylations of polar organometallics have been reported, mostly with complexes of Fe [169], Ni [170, 171], Pt, and Pd [172] (Scheme 8.41).



Scheme 8.40 Uncatalyzed S_NAr reactions of polar organometallic reagents [165–167]. Further examples: [168].



Scheme 8.41 Transition-metal-catalyzed S_NAr reactions with organometallic compounds [169, 173–178].

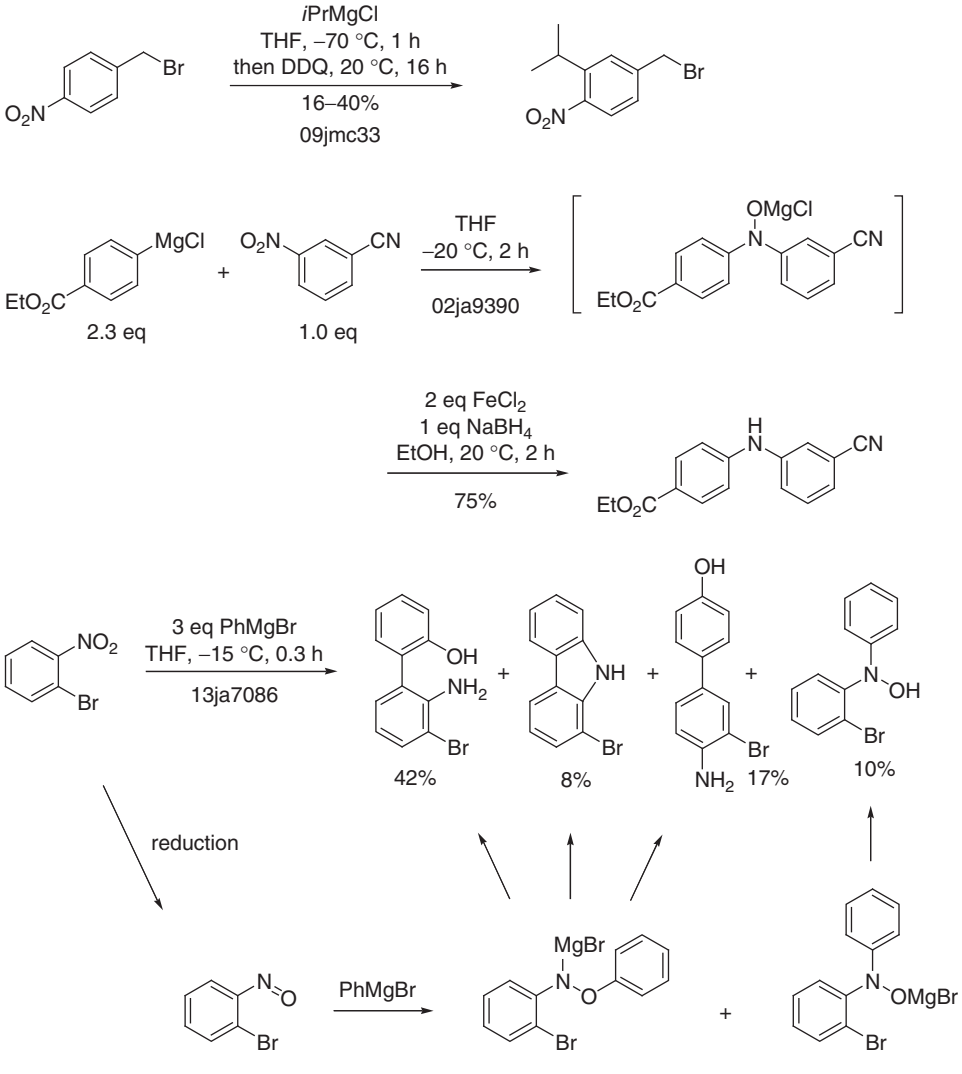


Scheme 8.41 (*Continued*)

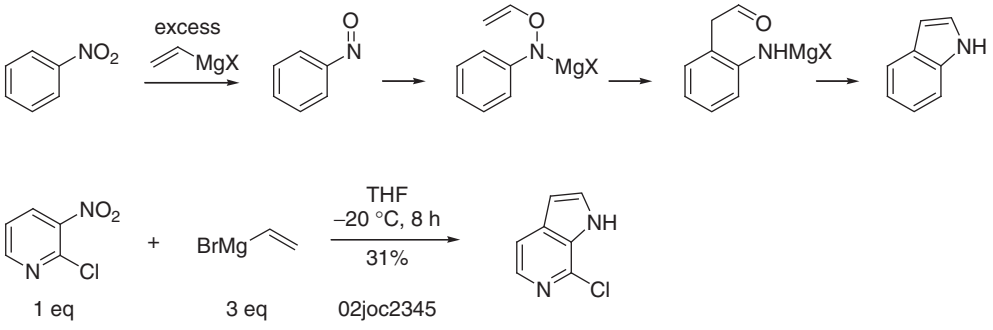
The reaction of polar organometallics with strongly electron-deficient arenes can be complicated by SET and other redox processes. Typical byproducts include the dehalogenated arenes and symmetric biaryls formed by homocoupling of the aryl halide. Grignard reagents can add directly to nitroarenes or reduce them to nitrosoarenes. The latter are electrophilic both at nitrogen and oxygen, and can form C–N or C–O bonds with an excess Grignard reagent (Scheme 8.42).

Closely related to the last example in Scheme 8.42 is the preparation of indoles by treatment of nitroarenes with an excess of a vinylmagnesium halide (Bartoli reaction [182], Scheme 8.43). It is assumed that this reaction also proceeds via an intermediate nitrosoarene. Yields are usually low, also because of the poor regioselectivity of the addition of the Grignard reagent to the nitrosoarene.

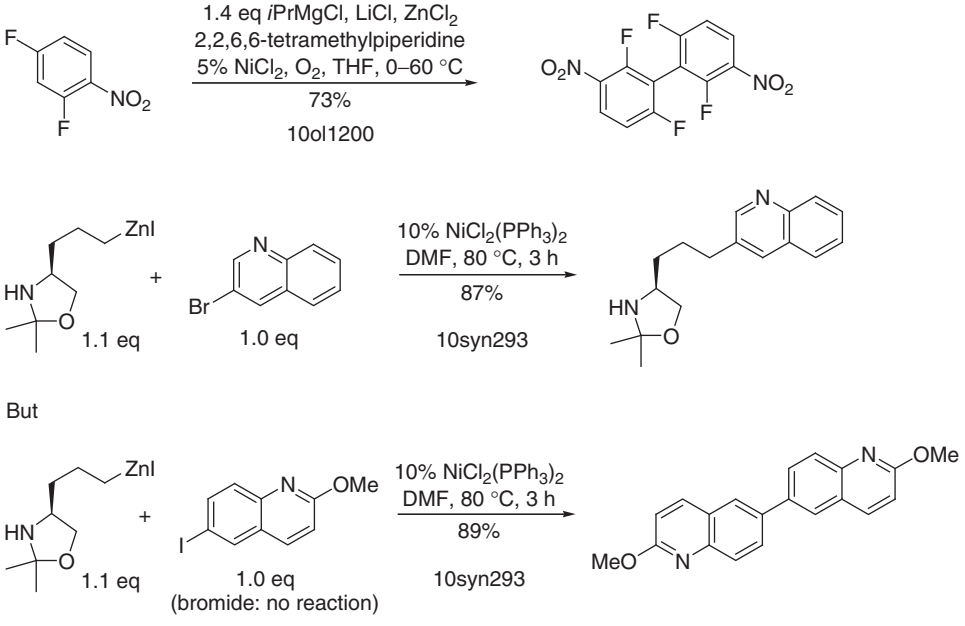
Some arenes are sufficiently acidic to be deprotonated by organomagnesium or related organometallics. In the presence of oxidants (e.g., nitroarenes), biaryls may be formed as byproduct. Biaryls may also be formed upon treatment of electron-deficient aryl halides with polar organometallic reagents in the absence of oxidants (Scheme 8.44).



Scheme 8.42 Reaction of nitroarenes with Grignard reagents [179–181].

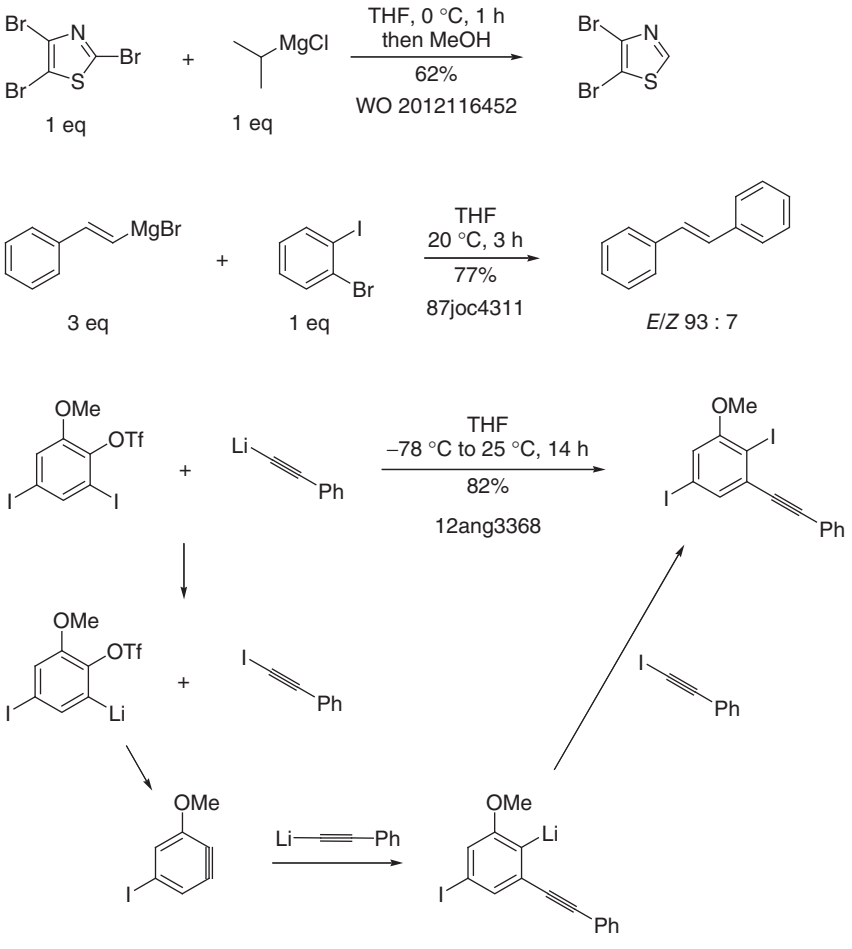


Scheme 8.43 Preparation of indoles from nitroarenes [183].



Scheme 8.44 Biaryl formation by oxidative dimerization of metallated arenes and during Negishi couplings [184, 185]. Further examples [186].

Organolithium and organomagnesium reagents can readily mediate halogen–metal exchange at polyhaloarenes. The resulting metallated arenes may be sufficiently stable to yield dehalogenated arenes upon hydrolysis. Alternatively, β-elimination may occur and cause the formation of arynes. Arynes are strong electrophiles, and can arylate the excess of organometallic reagent (Scheme 8.45).

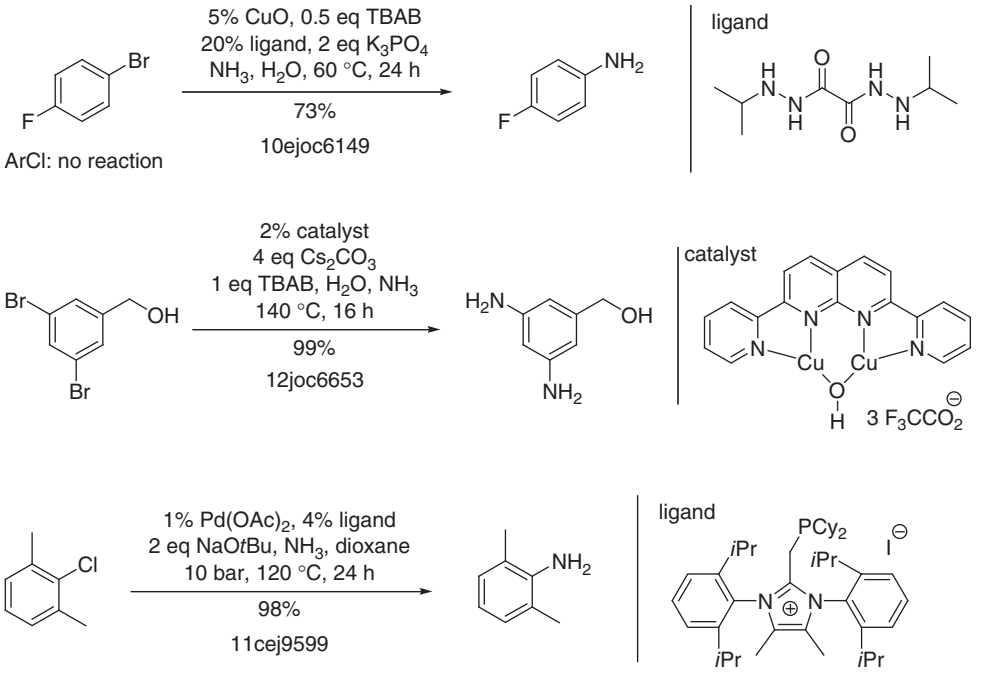


Scheme 8.45 Dehalogenation and aryne formation from aryl halides [187–189].

8.3.3
Ammonia

A number of successful S_NAr reactions with ammonia have been reported (Scheme 8.46). Although di- or triarylamines may also be formed, these potential byproducts can usually be avoided by using a large excess of ammonia. If this strategy fails, amides [190], azide (Section 8.3.6), or $(Me_3Si)_2NH$ can be used as (more expensive) alternative to ammonia.

Compared to aliphatic amines, ammonia is less nucleophilic and a weaker base. Therefore, other nucleophiles present in the reaction mixture (water, alcohols, or the newly formed aniline) may react with electrophiles at similar rates as ammonia.



Scheme 8.46 Monoarylation of ammonia [191–193]. Further examples: [194].

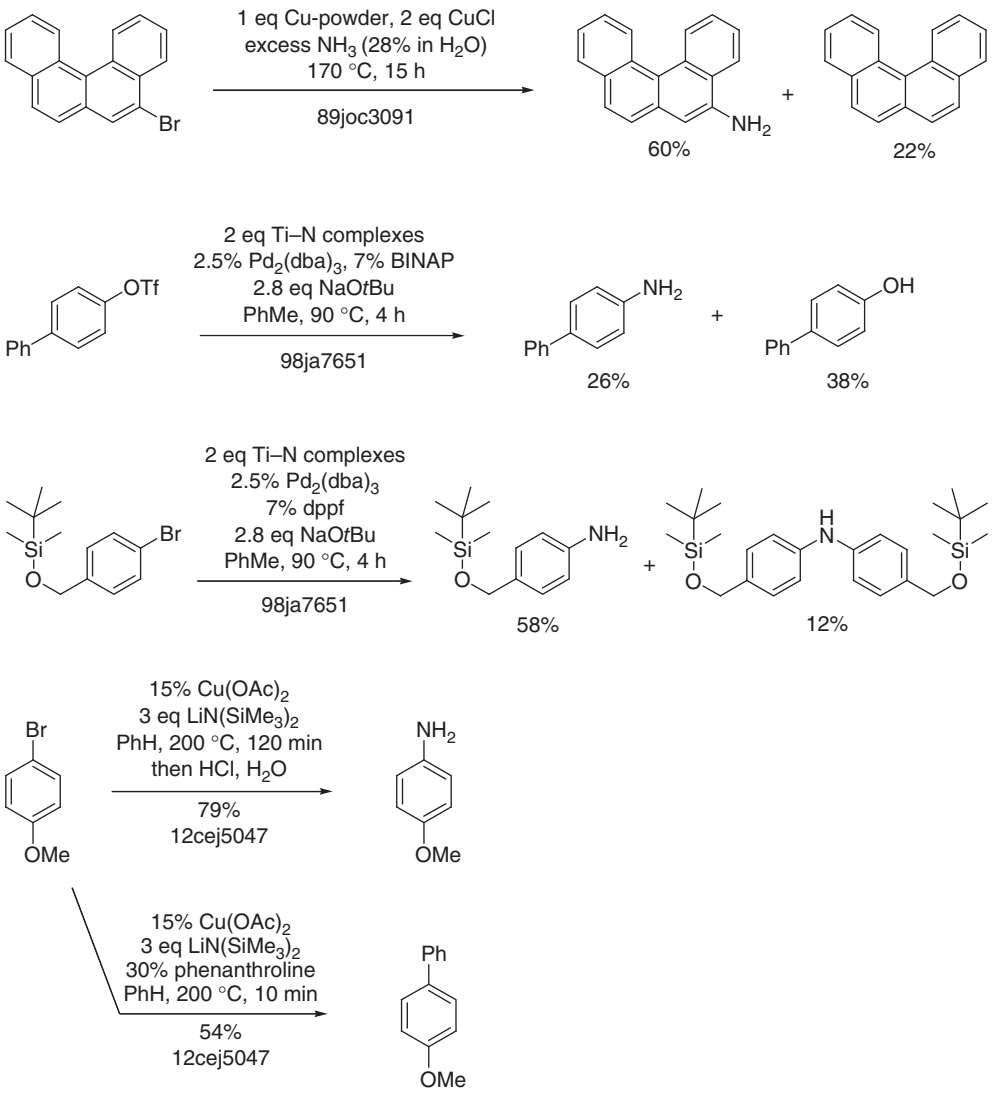
Other side reactions include reduction of the electrophile and biaryl formation (Scheme 8.47).

A further potential synthetic equivalent of ammonia is nitrite. While nitrite reacts with alkyl halides to yield mixtures of nitroalkanes and alkyl nitrites, arylation of nitrite mostly yields nitroarenes (Scheme 8.48), which can be reduced to anilines, for example, by hydrogenation.

8.3.4
Primary and Secondary Amines

Most amines react with electron-deficient arenes in the expected way, and S_NAr is a valuable and often used strategy for the preparation of substituted anilines (Scheme 8.49). Occasionally, though, unexpected side reactions may occur. For catalyzed aromatic nucleophilic substitutions, the identification of suitable catalysts can be an issue, because many amines form stable, unreactive complexes with copper and other transitions metals.

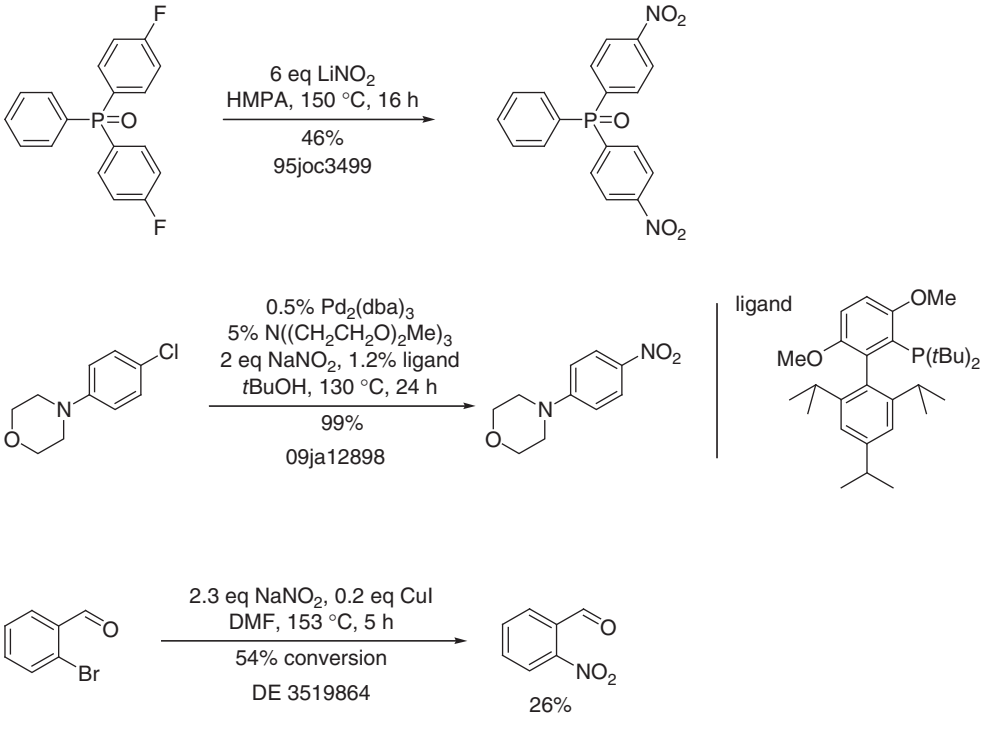
For unreactive aryl halides, transition-metal catalysis and strong bases may be required, and arynes and thus mixtures of regioisomeric products are sometimes



Scheme 8.47 Byproduct formation during S_NAr with ammonia and synthetic equivalents thereof [195–197].

formed. As alternative to low-boiling amines, their formamides can sometimes be used in S_NAr reactions [206, 207].

For the N-arylation of aliphatic or aromatic amines, suitable bases include hydroxide, alcoholates, and carbonates, which indicates that amines react much faster as nucleophiles than oxygen bases. Occasionally, though, phenols can result

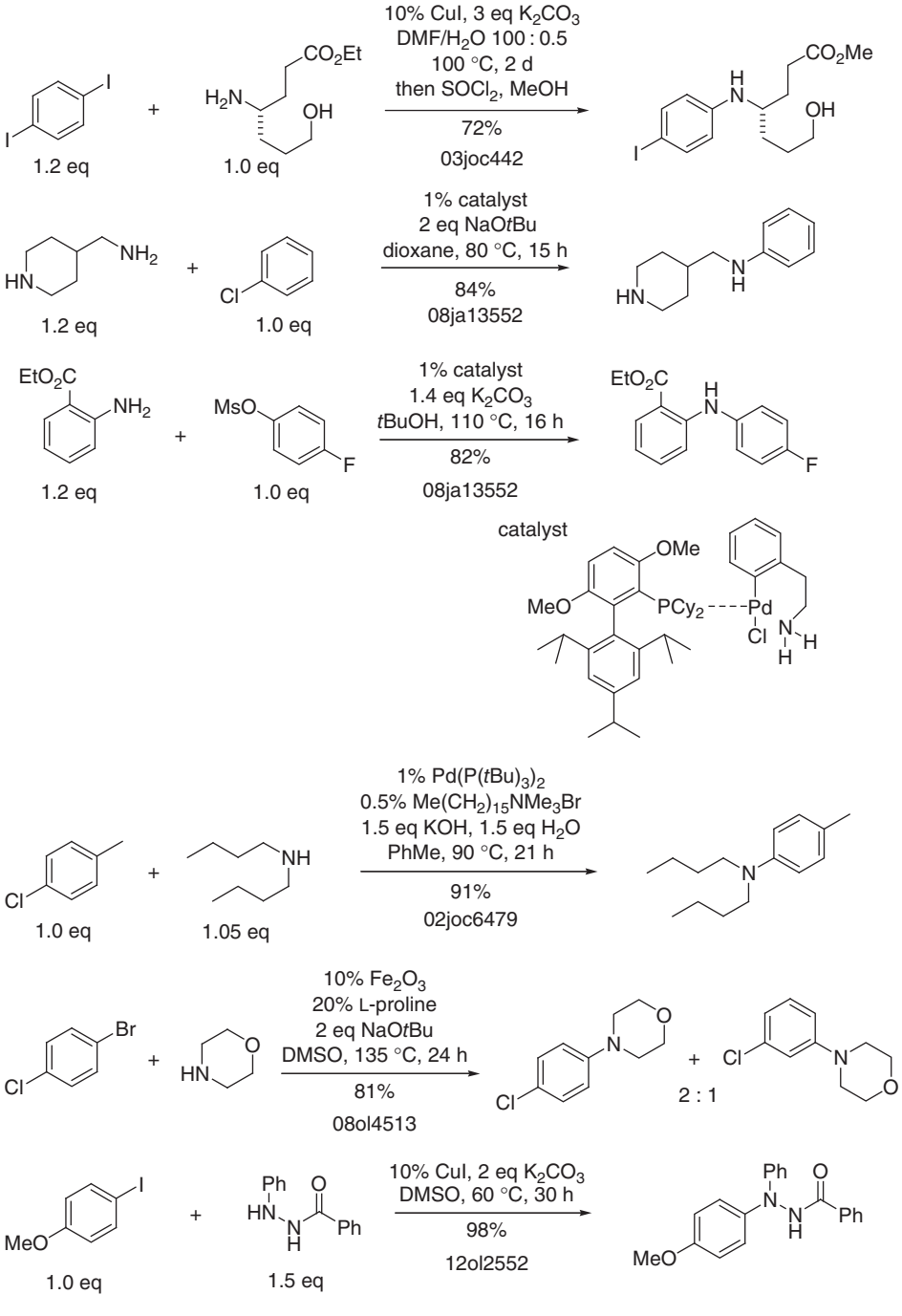


Scheme 8.48 Arylation of nitrite [198–200].

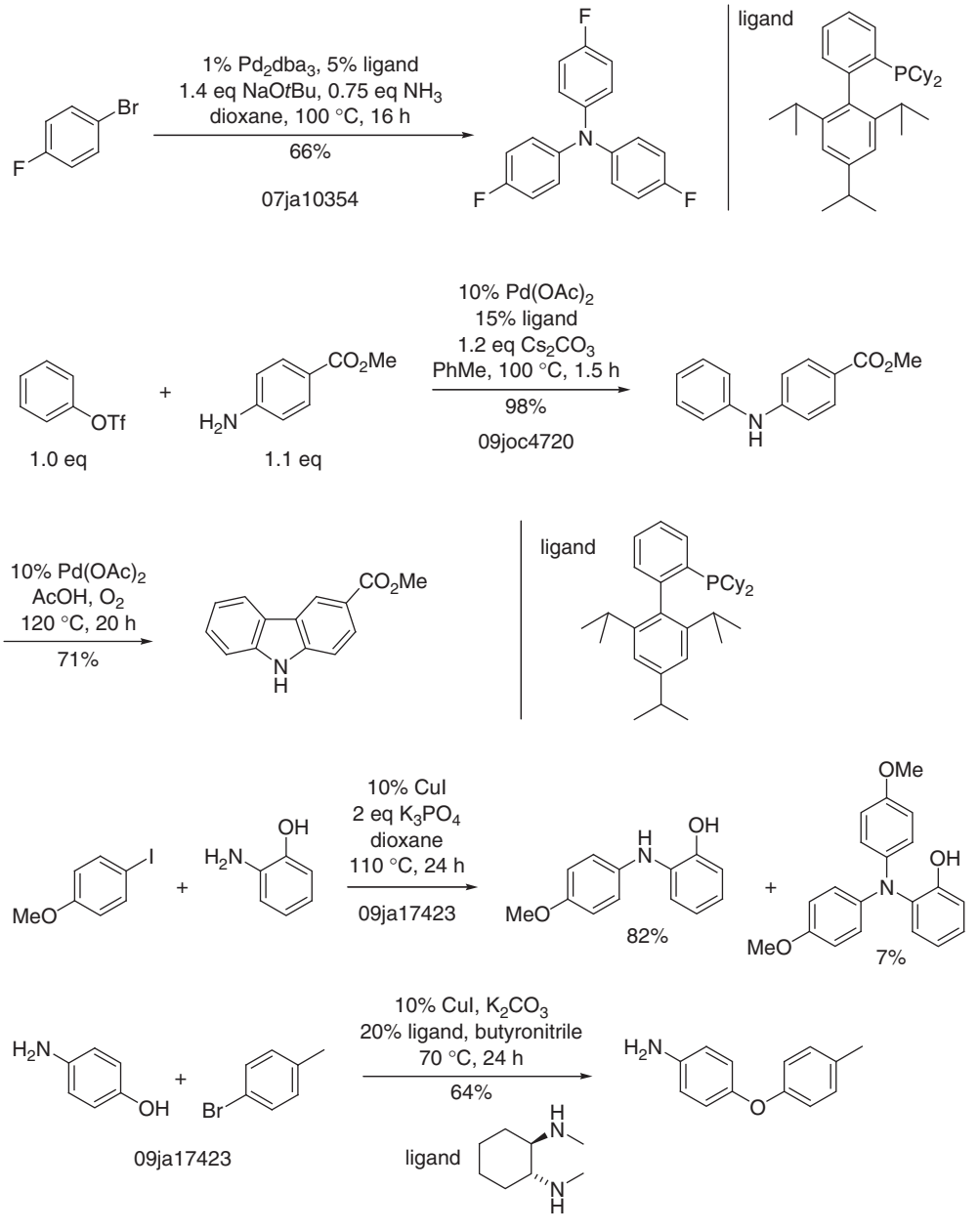
as byproducts [208]. Amines that are easily dehydrogenated (e.g., benzylamines) can cause the reduction of the electrophile. Di- and triarylamines are also readily oxidized (e.g., to carbazoles), and air must be rigorously excluded during the preparation of such compounds, in particular if strong bases are used. Strong bases can always lead to weird byproducts (Scheme 8.50) and should be avoided if possible.

8.3.5
Tertiary Amines

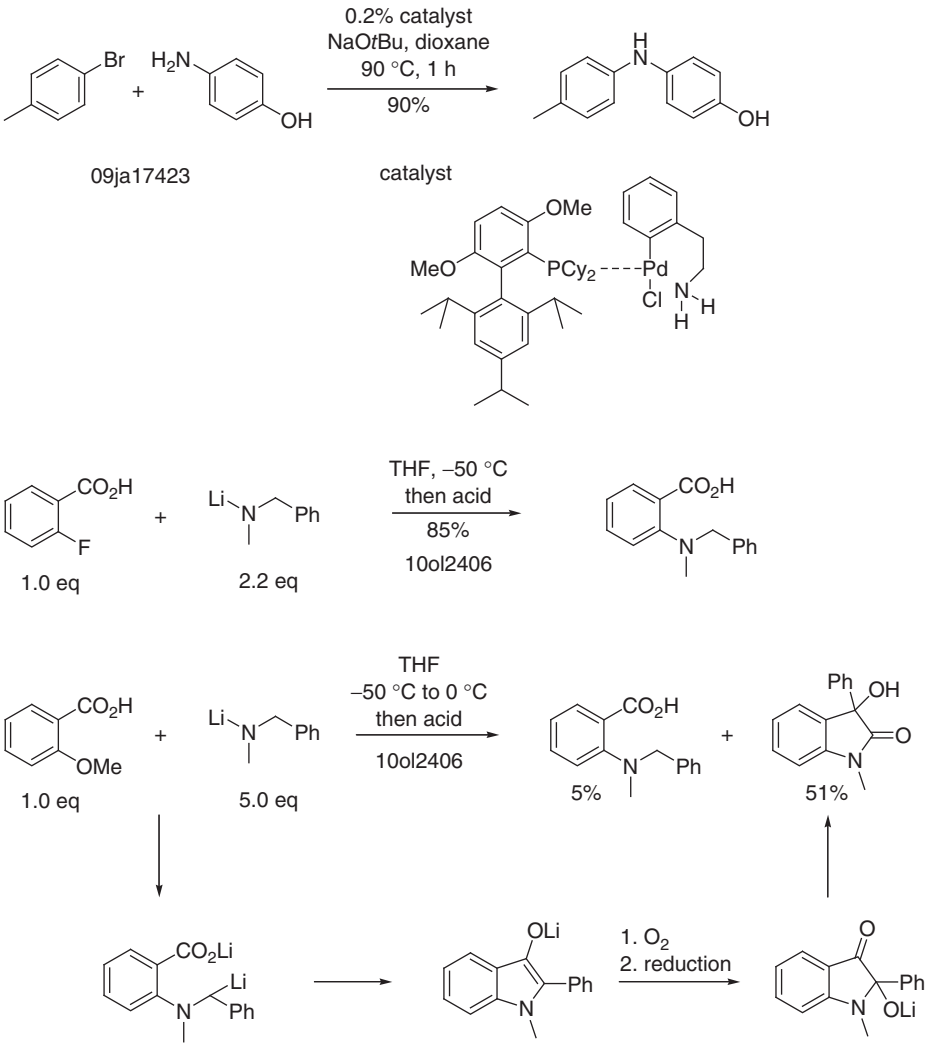
N-Aryl quaternary ammonium salts are difficult to prepare by N-arylation of tertiary amines because the products are quickly dealkylated by the tertiary amine (Scheme 8.51). Because tertiary amines are not always nucleophilic enough for S_NAr reactions, strongly electrophilic arylating reagents, such as arynes, may be required to achieve N-arylation of tertiary amines.



Scheme 8.49 N-Arylation of amines [201–205].



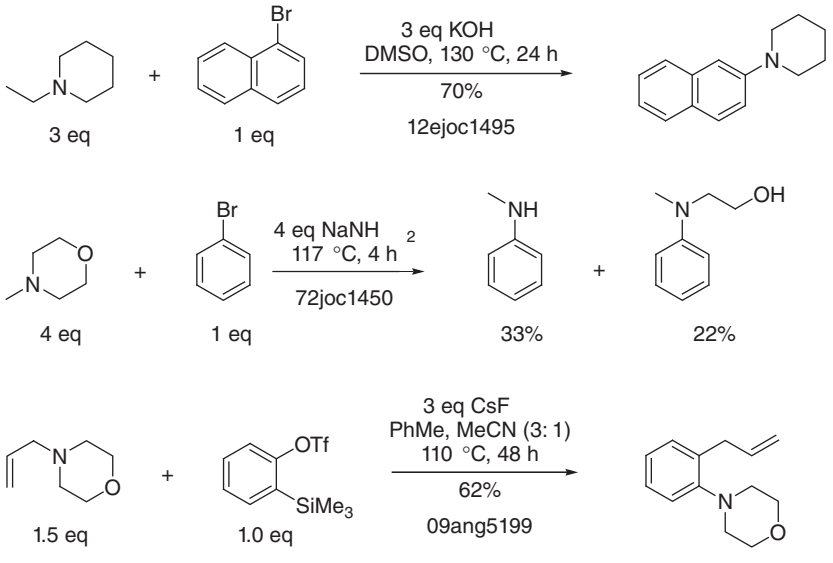
Scheme 8.50 N-Arylation of alkylamines and anilines [132, 209–211].



Scheme 8.50 (*Continued*)

8.3.6
Azides

S_NAr reactions with metal azides often yield anilines instead of aryl azides (Scheme 8.52). The reduction of the initially formed azide can be caused by even weak reducing reagents, for instance, by NaO*t*Bu [215], ethanol [216], HBr, or by an excess of metal azide [217]. Nevertheless, many examples of



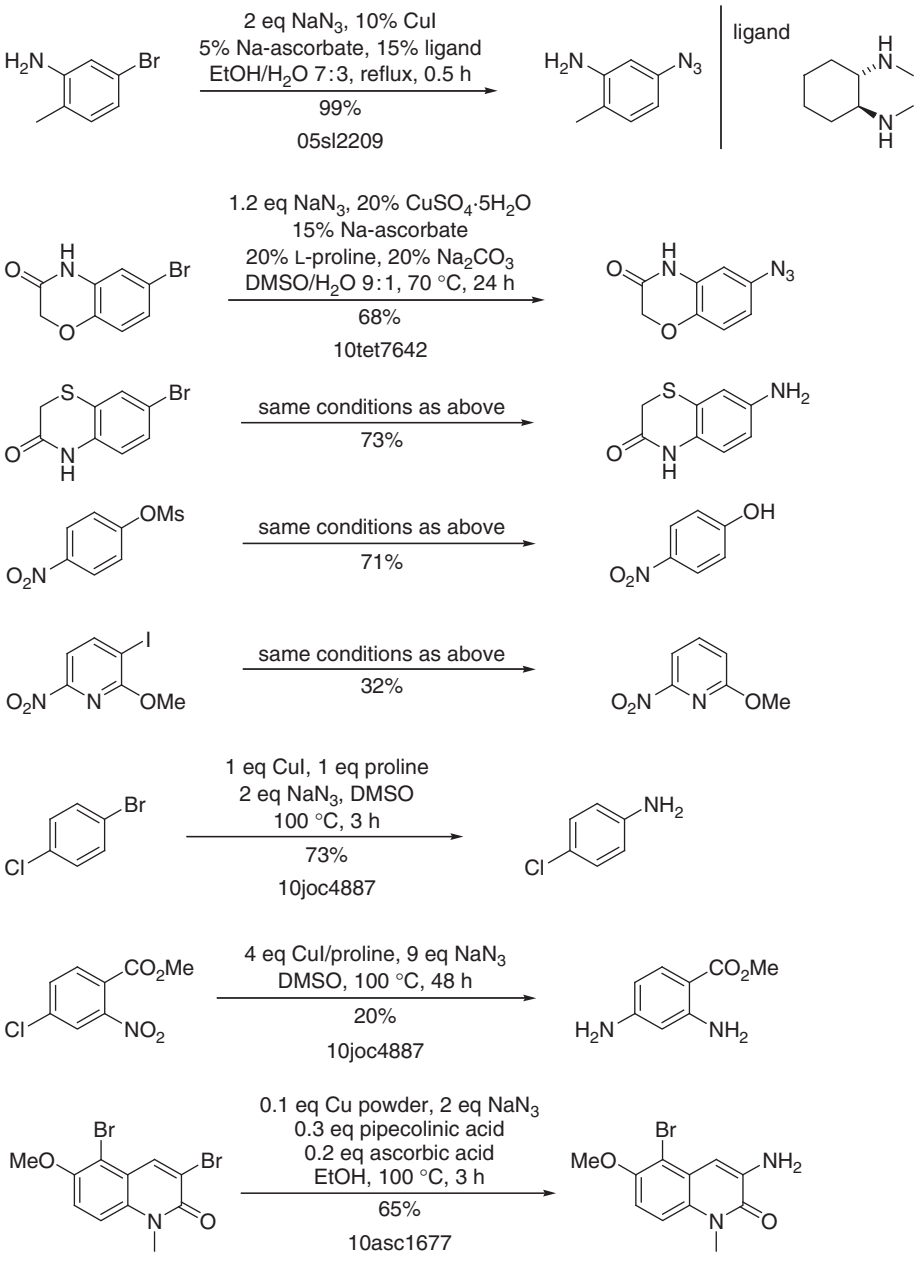
Scheme 8.51 Arylation of tertiary amines by arynes [212–214].

successful preparations of aryl azides from aryl halides have been reported [218]. Best results were obtained with Cu(I)–diamine complexes as catalysts, and in the presence of ascorbate (to regenerate Cu(I) from Cu(II)). In addition to the reduction of intermediate azides to anilines, typical side reactions during S_NAr with azide include the reduction of nitro groups and the reduction to unsubstituted arenes.

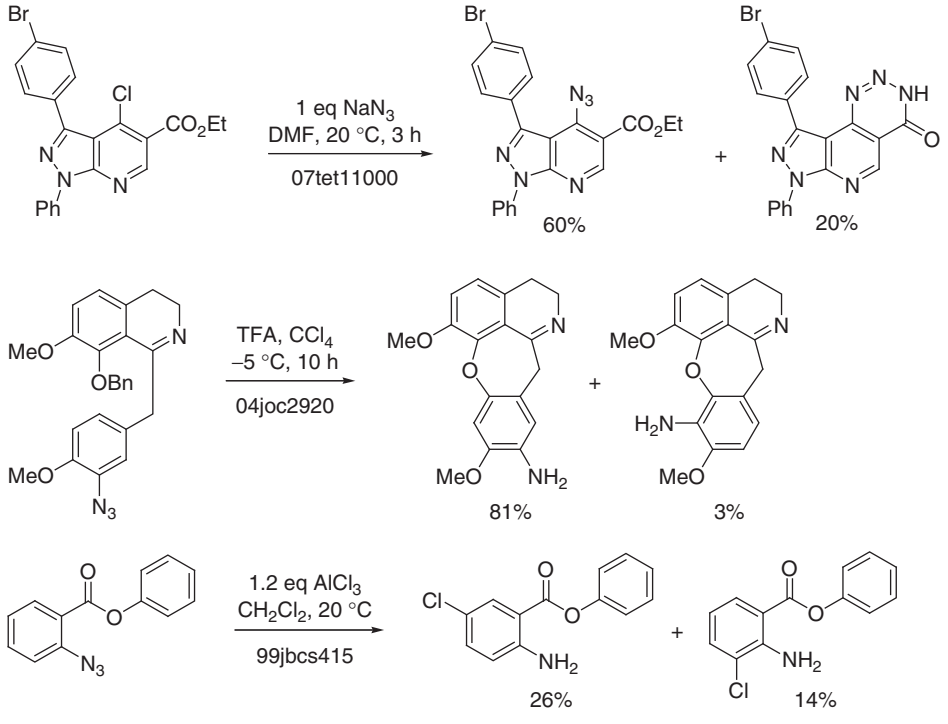
Organic azides undergo 1,3-dipolar cycloadditions and can react as nucleophiles with a number of functional groups. Ketones, for instance, react with azides under acidic conditions to yield amides, and 2-azidobenzoates can cyclize to yield benzotriazinones (Scheme 8.53). Moreover, aryl azides are thermally labile, and react with various acids to yield substituted anilines (as do *N*-arylhydroxylamines). Acidic reaction conditions generally accelerate azide decomposition, whereas most azides are quite stable in the presence of bases [222].

8.3.7 Hydroxide

The main side reactions of aromatic nucleophilic substitutions with hydroxide are the formation of diarylethers and the transformation of functional groups (Scheme 8.54). Byproducts of the preparation of phenol from chlorobenzene include diphenylether and 2- and 4-phenylphenol (Scheme 8.16).



Scheme 8.52 S_NAr reactions with azide [216, 217, 219, 220]. Further examples: [221].



Scheme 8.53 Reactions of aryl azides [223–225].

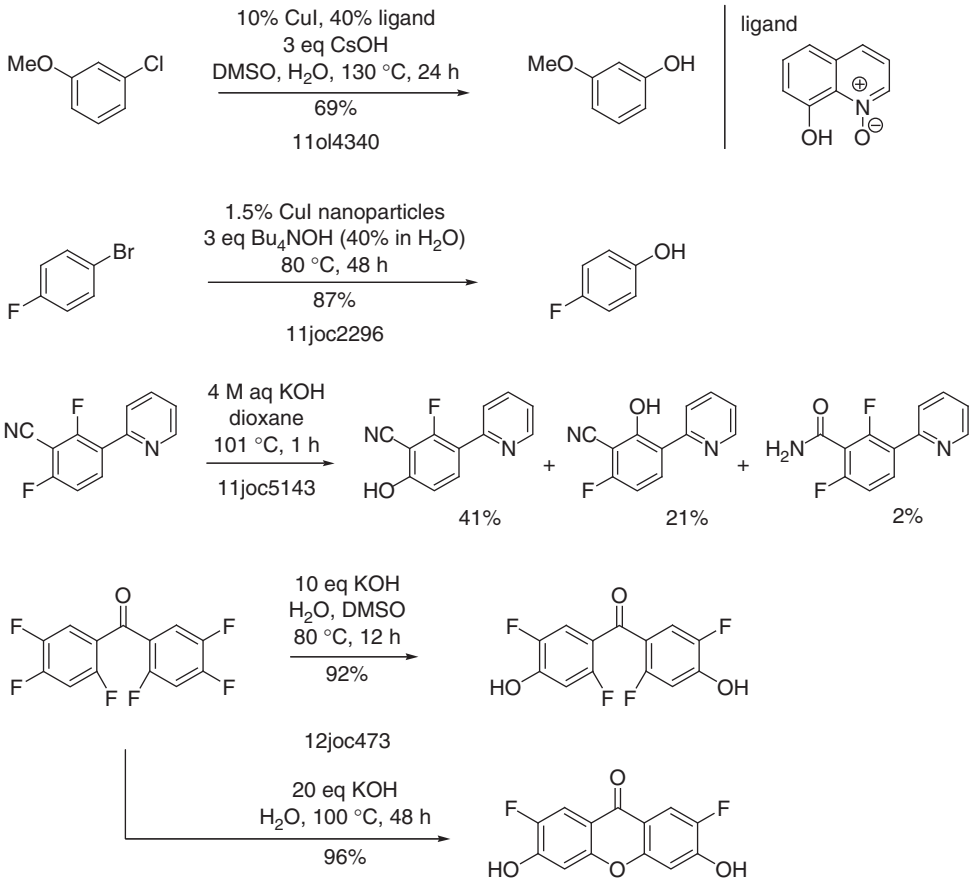
Phenols may also be formed upon treatment of aryl halides with carbonate or carboxylates. These nucleophiles are less basic than hydroxide and usually do not saponify carboxylic esters (Scheme 8.55).

Benzoic acids and arenesulfinic acids can undergo decarboxylative/desulfinylative substitution in the presence of Pd- or other transition-metal complexes [230–234]. This is a potential side reaction of the transition-metal-catalyzed O-arylation of benzoic and arenesulfinic acids.

8.3.8 Alcohols

Because of the hardness of alkoxides, these often react rather as bases than as nucleophiles. Nevertheless, numerous examples of successful aromatic nucleophilic substitution with alcoholates have been reported (Scheme 8.56).

Deprotonated aliphatic alcohols with α-hydrogen are not only strong bases but also potent hydride donors and thus reducing reagents (dry alcoholates may

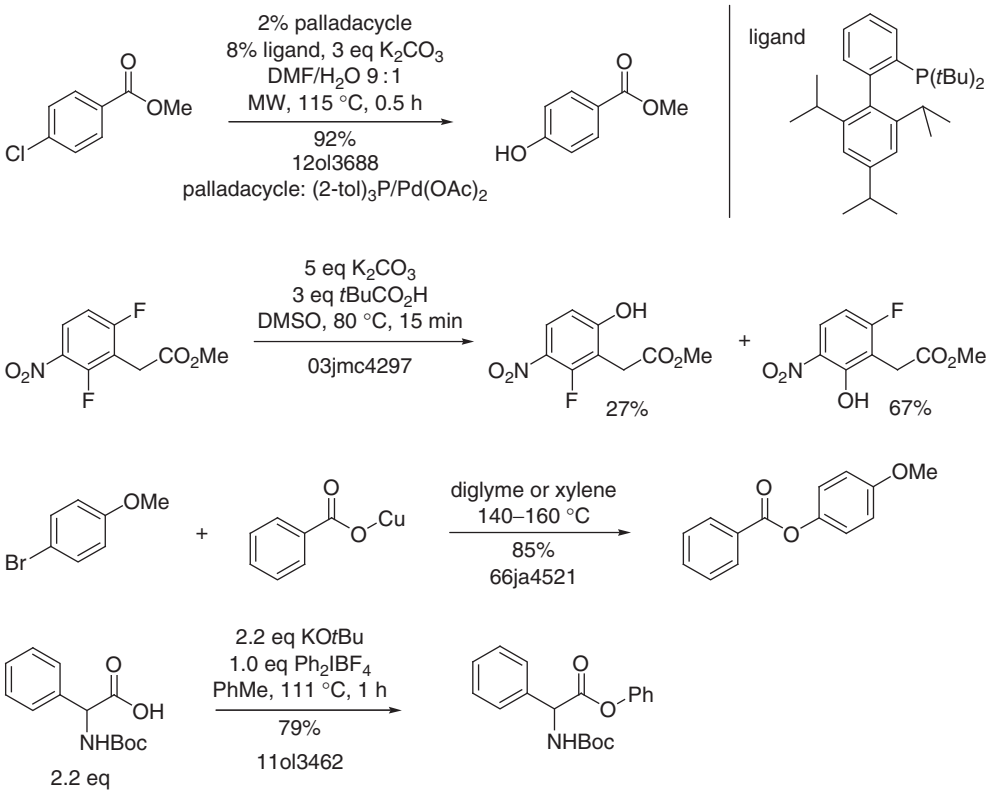


Scheme 8.54 Conversion of aryl halides into phenols [226–229].

ignite in air). Hence, the O-alkylation or O-arylation of alcoholates does not always give high yields of ethers, and β-eliminations, reductions, and the cleavage of carboxylic or carbonic acid derivatives are often seen as side reactions. In the last example in Scheme 8.57, the reduction may also have been caused by iodide.

Aminoalcohols can be selectively arylated either at nitrogen or at oxygen (Scheme 8.58). Treatment of the resulting products with strong bases can cause aryl group migration from oxygen to nitrogen [247].

The O-arylation of aliphatic alcohols can also be catalyzed by palladium complexes. However, even in the presence of these catalysts, numerous byproducts may result (Scheme 8.59).

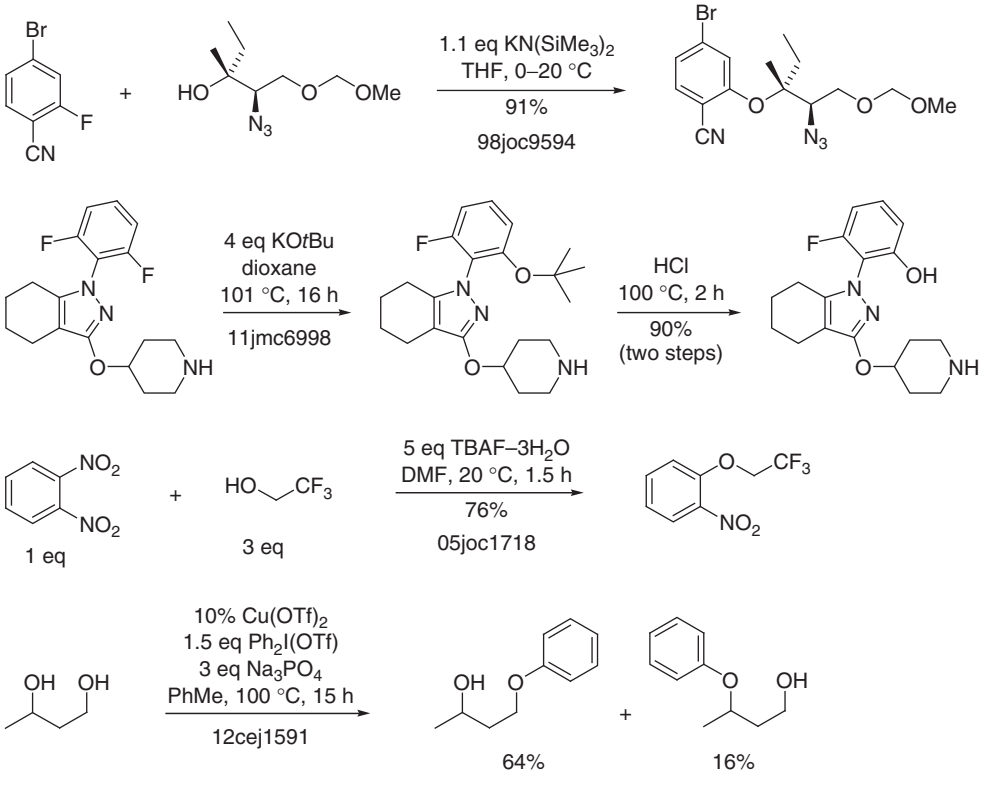


Scheme 8.55 Arylation of carbonates and carboxylates [235–238].

8.3.9 Thiols

Although thiols are strong nucleophiles and in principle suitable for S_NAr reactions, thiols are also strong reducing reagents and capable of reacting with a number of functional groups. Nevertheless, numerous high-yielding examples of aromatic nucleophilic substitutions with thiols have been reported (Scheme 8.60). Despite the strength of many sulfur–metal bonds, these reactions can sometimes be catalyzed by transition-metal complexes.

Common side reactions of the arylation of alkylmercaptanes with aryl halides are the reductive dehalogenation of the aryl halide as well as the formation of thiophenols, diarylthioethers, and dialkylthioethers. The latter result from the cleavage of intermediate arylalkylthioethers by an excess of thiol (Scheme 8.61), and their formation may be prevented by catalysis and lower reaction temperatures.



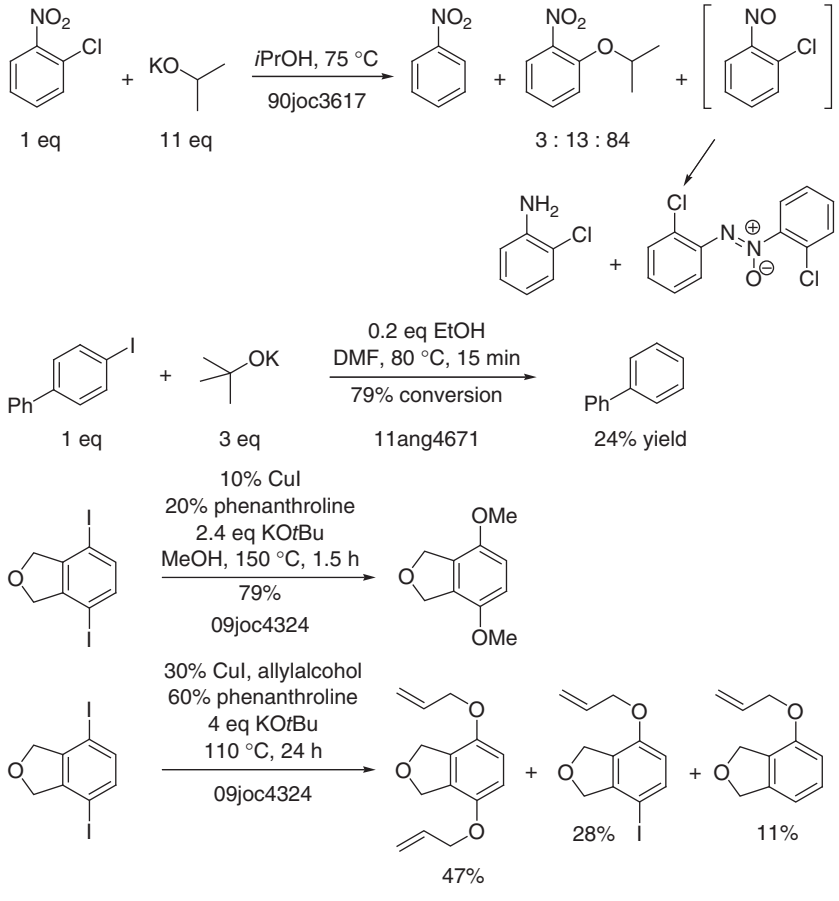
Scheme 8.56 Aromatic nucleophilic substitutions with alcohols [239–242].

Because of the high nucleophilicity of thiols, even weak electrophiles can effectively compete with aryl halides. Alkylesters or carbonates, for instance, readily alkylate thiols, and should not be used as solvents for these reactions [262].

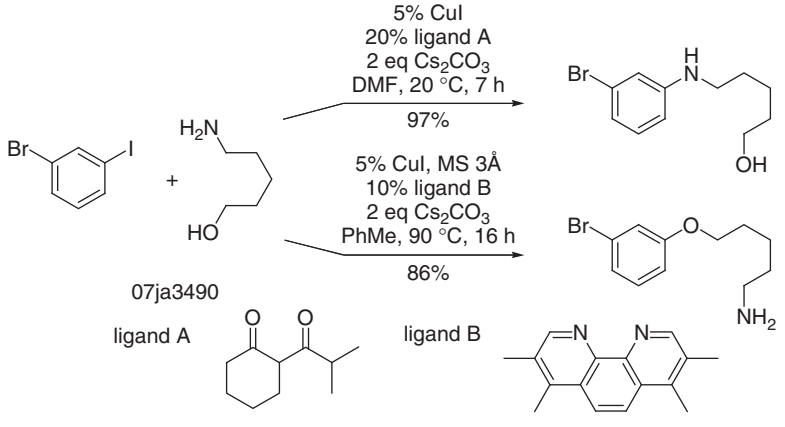
Synthetic equivalents of H_2S are thiocyanate salts (M^+ SCN^-). Aryl halides usually react with thiocyanate at sulfur, but the resulting arylthiocyanates can rearrange to isothiocyanates. In the presence of water, the intermediate thiocyanates may also be hydrolyzed to thiophenols, which can be arylated by the electrophile (Scheme 8.62).

8.3.10 Halides

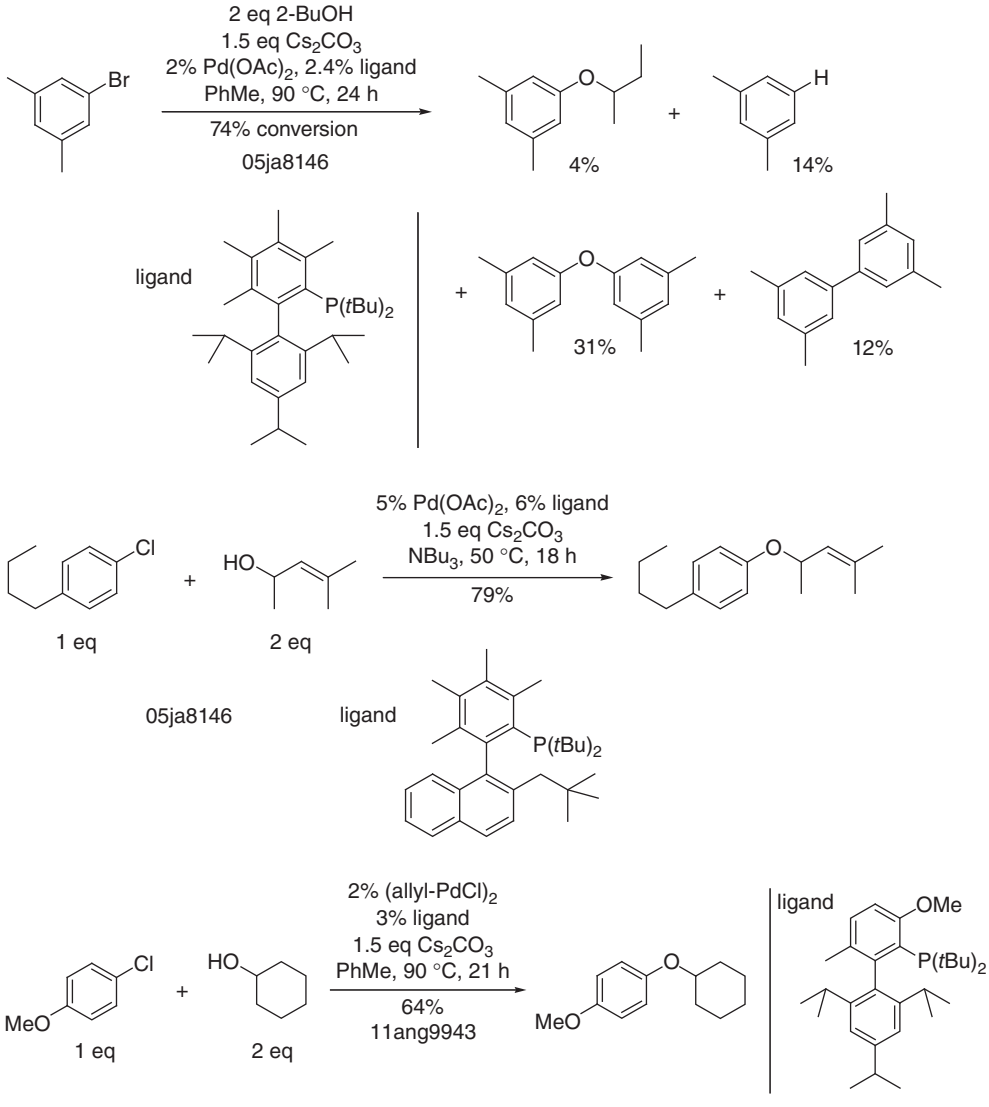
Because of their low nucleophilicity, S_NAr reactions with halides often proceed only slowly (Scheme 8.63). Substitutions by iodide are the easiest, while those with fluoride usually require strictly anhydrous conditions and high temperatures.



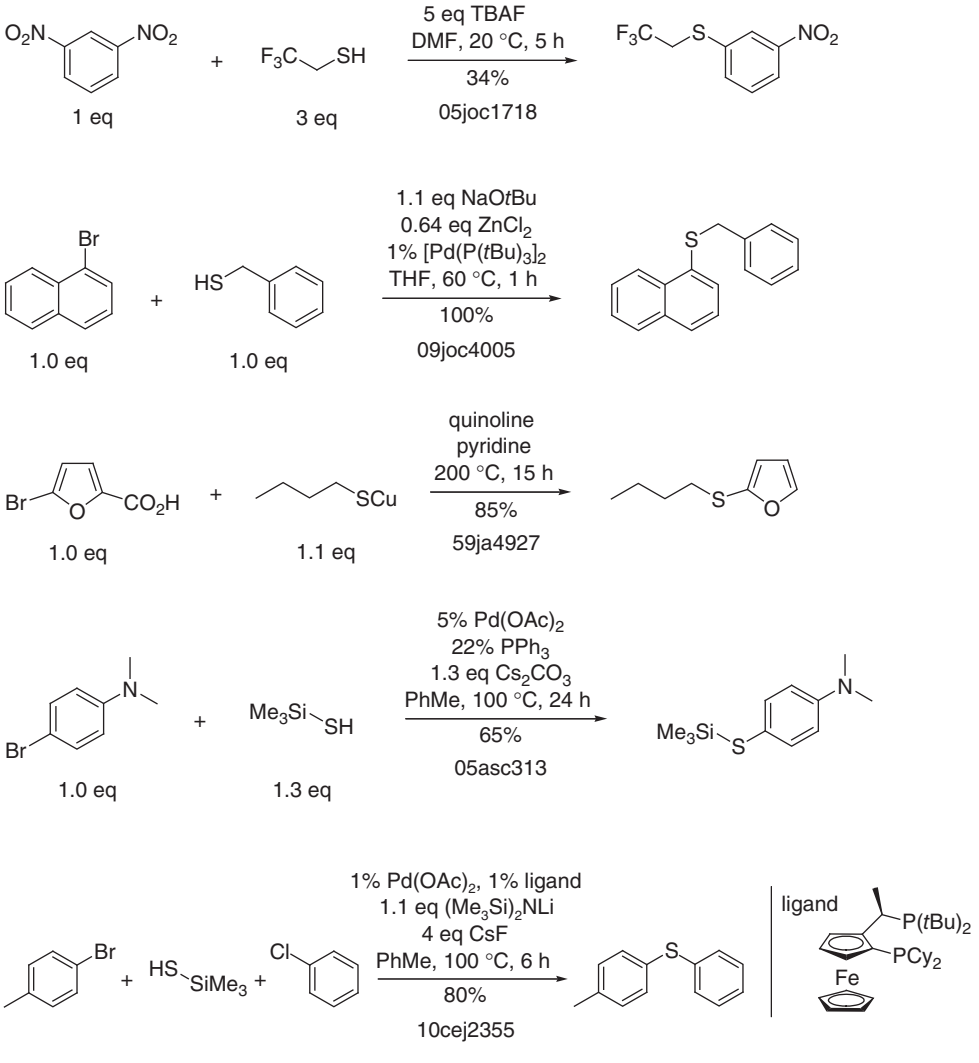
Scheme 8.57 Reaction of alcoholates with aryl halides [243–245]. Further examples: [246].



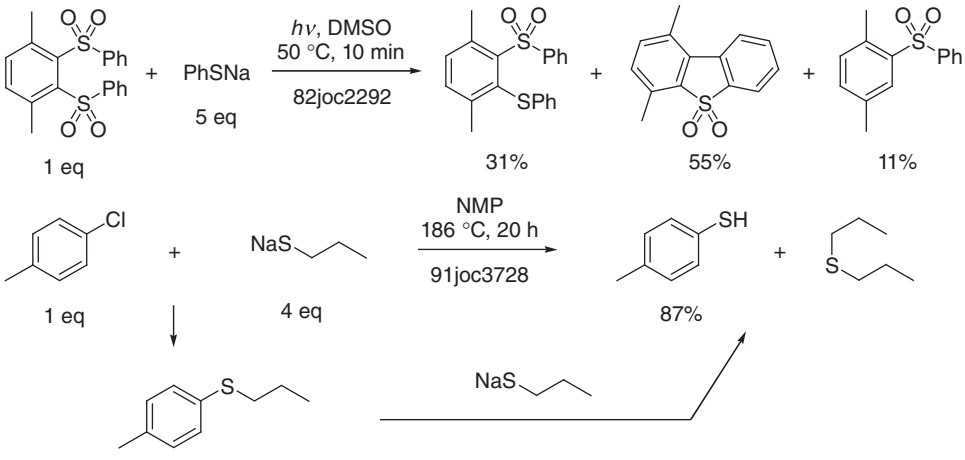
Scheme 8.58 Arylation of aminoalcohols [248].



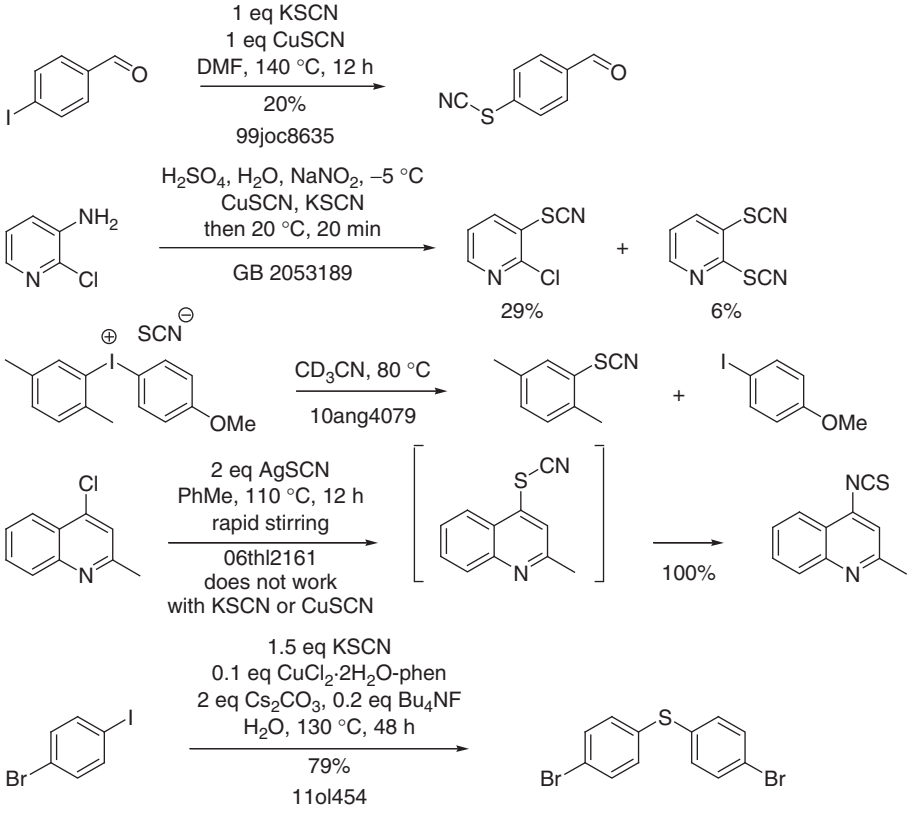
Scheme 8.59 Palladium-catalyzed aromatic nucleophilic substitutions with alcohols [249, 250]. Further examples: [251, 252].



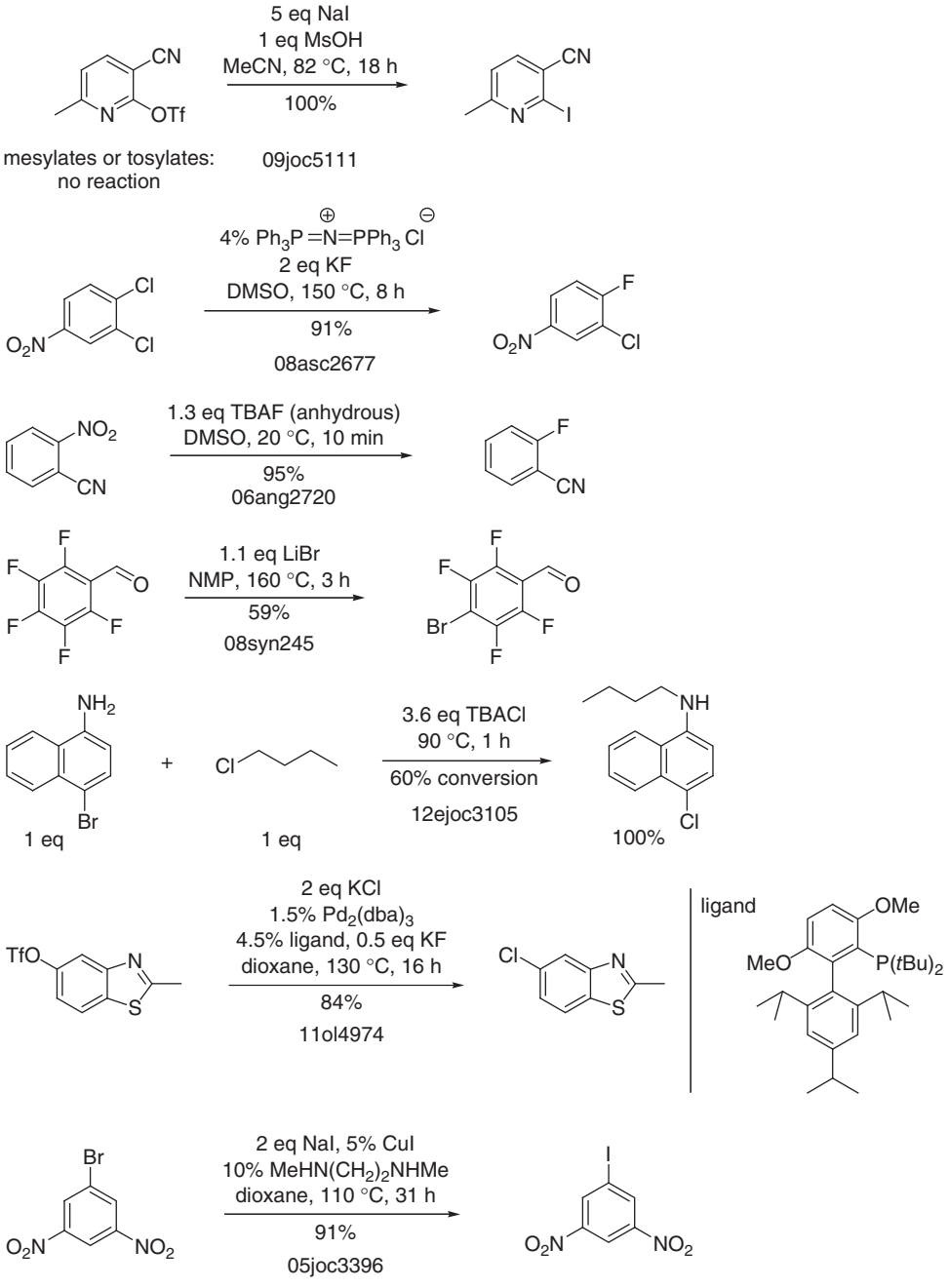
Scheme 8.60 Arylation of thiols [241, 253–256]. Further examples: [44, 257–260].



Scheme 8.61 Reactions of thiolates with arylating reagents [19, 261].



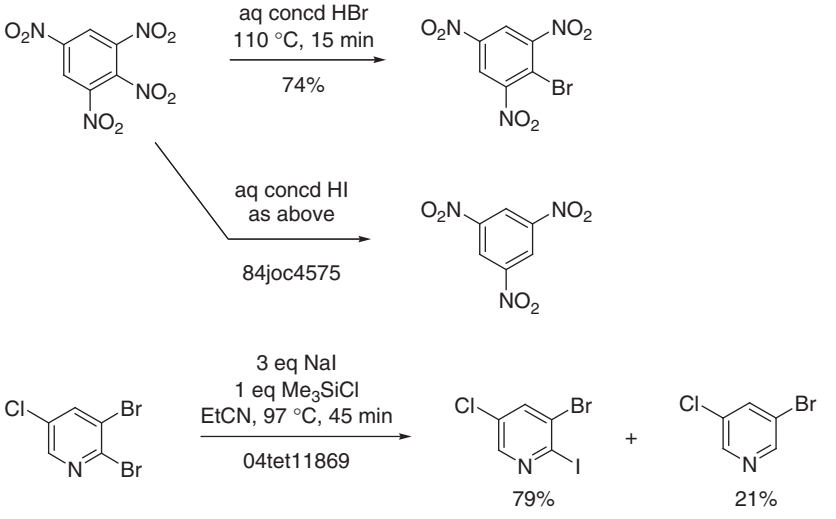
Scheme 8.62 Arylations of metal thiocyanates [263–267].



Scheme 8.63 S_NAr reactions with halides [268–274]. Further examples: [275–278].

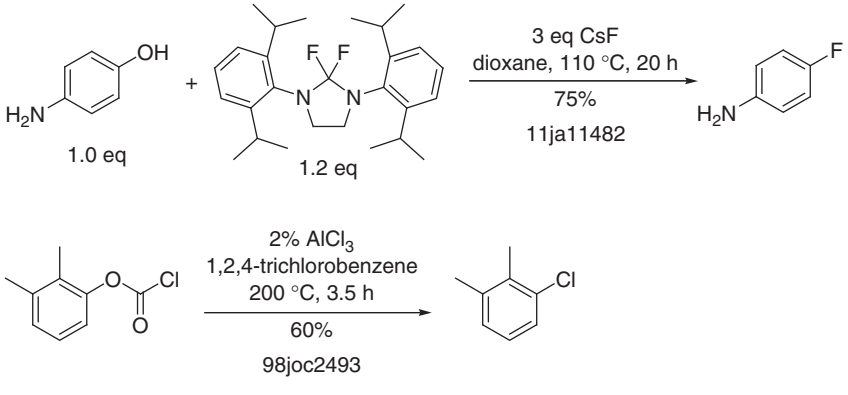
Because fluoride is the most basic halide, it tends to cause most side reactions (cleavage of ethers, oxidation of aldehydes to carboxylic acids, competition by other nucleophiles, or decarboxylations).

Iodide is a good reducing reagent, and can reduce benzylic alcohols [279] and dehalogenate aryl halides. Such reductions proceed particularly readily with electron-deficient arenes, such as polynitrobenzenes or pyridines (Scheme 8.64).



Scheme 8.64 Reductions by iodide [280, 281].

Phenols can be activated *in situ* by 2-haloimidazolium halides, which can then undergo halodeoxygenation (Scheme 8.65). Alternatively, phenols may be converted to triflates or other fluorinated sulfonates, and then transformed into aryl fluorides by palladium-catalyzed S_NAr with fluoride [282].



Scheme 8.65 Conversion of phenols or derivatives thereof into aryl halides [283, 284].

References

1. Buncel, E., Dust, J.M., and Terrier, F. (1995) Rationalizing the regioselectivity in polynitroarene anionic σ-adduct formation. Relevance to nucleophilic aromatic substitution. *Chem. Rev.*, **95**, 2261–2280.
2. Ellis, G.P. and Romney-Alexander, T.M. (1987) Cyanation of aromatic halides. *Chem. Rev.*, **87**, 779–794.
3. Traynham, J.G. (1979) Ipso substitution in free-radical aromatic substitution reactions. *Chem. Rev.*, **79**, 323–330.
4. Bunnett, J.F. and Zahler, R.E. (1951) Aromatic nucleophilic substitution reactions. *Chem. Rev.*, **51**, 273–412.
5. López Ortiz, F., Iglesias, M.J., Fernández, I., Andújar Sánchez, C.M., and Ruiz Gómez, G. (2007) Nucleophilic dearomatizing (DNAr) reactions of aromatic C,H-systems. A mature paradigm in organic synthesis. *Chem. Rev.*, **107**, 1580–1691.
6. Huffman, J.W., Wu, M.-J., and Lu, J. (1998) A very facile S_NAr reaction with elimination of methoxide. *J. Org. Chem.*, **63**, 4510–4514.
7. Muruganantham, R. and Namboothiri, I. (2010) Phosphonylpyrazoles from Bestmann–Ohira reagent and nitroalkenes: synthesis and dynamic NMR studies. *J. Org. Chem.*, **75**, 2197–2205.
8. Bunnett, J.F., Brotherton, T.K., and Williamson, S.M. (1973) *N*-β-Naphthylpiperidine. *Org. Synth.*, Coll. Vol. **5**, 816–818.
9. Allen, C.F.H. and Bell, A. (1955) 3-Amino-2-naphthoic acid. *Org. Synth.*, Coll. Vol. **3**, 78–82.
10. Um, I.-H., Im, L.-R., Kang, J.-S., Bursey, S.S., and Dust, J.M. (2012) Mechanistic assessment of S_NAr displacement of halides from 1-halo-2,4-dinitrobenzenes by selected primary and secondary amines: Brønsted and Mayr analyses. *J. Org. Chem.*, **77**, 9738–9746.
11. Imoto, M., Matsui, Y., Takeda, M., Tamaki, A., Taniguchi, H., Mizuno, K., and Ikeda, H. (2011) A probable hydrogen-bonded Meisenheimer complex: an unusually high S_NAr reactivity of nitroaniline derivatives with hydroxide ion in aqueous media. *J. Org. Chem.*, **76**, 6356–6361.
12. Um, I.-H., Min, S.-W., and Dust, J.M. (2007) Choice of solvent (MeCN vs H_2O) decides rate-limiting step in S_NAr aminolysis of 1-fluoro-2,4-dinitrobenzene with secondary amines: importance of Brønsted-type analysis in acetonitrile. *J. Org. Chem.*, **72**, 8797–8803.
13. Liu, J. and Robins, M.J. (2007) S_NAr displacements with 6-(fluoro, chloro, bromo, iodo, and alkylsulfonyl)purine nucleosides: synthesis, kinetics, and mechanism. *J. Am. Chem. Soc.*, **129**, 5962–5968.
14. Hintermann, L., Masuo, R., and Suzuki, K. (2008) Solvent-controlled leaving-group selectivity in aromatic nucleophilic substitution. *Org. Lett.*, **10**, 4859–4862.
15. Suwiński, J. and Świerczek, K. (2001) *Cine*- and *tele*-substitution reactions. *Tetrahedron*, **57**, 1639–1662.
16. Poirier, M., Goudreau, S., Poulin, J., Savoie, J., and Beaulieu, P.L. (2010) Metal-free coupling of azoles with 2- and 3-haloindoles providing access to novel 2- or 3-(azol-1-yl)indole derivatives. *Org. Lett.*, **12**, 2334–2337.
17. Carpenter, R.D. and Verkman, A.S. (2010) Synthesis of a sensitive and selective potassium-sensing fluoroionophore. *Org. Lett.*, **12**, 1160–1163.
18. Enguehard, C., Allouchi, H., Gueiffier, A., and Buchwald, S.L. (2003) *Ipso*- or *cine*-substitutions of 6-haloimidazo[1,2-*a*]pyridine derivatives with different azoles depending on the reaction conditions. *J. Org. Chem.*, **68**, 5614–5617.
19. Novi, M., Dell'Erba, C., Garbarino, G., and Sancassan, F. (1982) Normal S_NAr, telesubstitution, and electron-transfer pathways in the reactions of methyl-substituted *o*-bis(phenylsulfonyl)benzene derivatives with sodium arenethiolates in dimethyl sulfoxide. *J. Org. Chem.*, **47**, 2292–2298.
20. Giannopoulos, T., Ferguson, J.R., Wakefield, B.J., and Varvounisa, G.

(2000) *Tele* nucleophilic aromatic substitutions in 1-nitro-3- and 1,3-dinitro-5-trichloromethylbenzene, and 3-trichloromethylbenzonitrile. A new synthesis of the 1,4-benzothiazine-3(4*H*)-one ring system from 3-nitrobenzoic acid. *Tetrahedron*, **56**, 447–453.

21. Surowiec, M., Belekos, D., Mąkosza, M., and Varvounis, G. (2010) *Tele* nucleophilic substitutions of hydrogen in *m*-(trichloromethyl)nitrobenzenes with cyano and ester carbanions. *Eur. J. Org. Chem.*, **2010**, 3501–3506.
22. Agrawal, K.C., Bears, K.B., Sehgal, R.K., Brown, J.N., Rist, P.E., and Rupp, W.D. (1979) Potential radiosensitizing agents. Dinitroimidazoles. *J. Med. Chem.*, **22**, 583–586.
23. Li, Y.-X., Ji, K.-G., Wang, H.-X., Ali, S., and Liang, Y.-M. (2011) Iodine-induced regioselective C–C and C–N bonds formation of *N*-protected indoles. *J. Org. Chem.*, **76**, 744–747.
24. Hooper, M.W., Utsunomiya, M., and Hartwig, J.F. (2003) Scope and mechanism of palladium-catalyzed amination of five-membered heterocyclic halides. *J. Org. Chem.*, **68**, 2861–2873.
25. Torr, J.E., Large, J.M., Horton, P.N., Hursthouse, M.B., and McDonald, E. (2006) On the nucleophilic *tele*-substitution of dichloropyrazines by metallated dithianes. *Tetrahedron Lett.*, **47**, 31–34.
26. Mąkosza, M., Varvounis, G., Surowiec, M., and Giannopoulo, T. (2003) *Tele* vs. oxidative substitution of hydrogen in *meta* monochloromethyl, dichloromethyl, and trichloromethyl nitrobenzenes in the reaction with Grignard reagents. *Eur. J. Org. Chem.*, **2003**, 3791–3797.
27. Mach, M.H. and Bunnett, J.F. (1980) Participation of oligochlorobenzenes in the base-catalyzed halogen dance. *J. Org. Chem.*, **45**, 4660–4666.
28. Hamel, P., Girard, Y., and Atkinson, J.G. (1992) Acid-catalyzed isomerization of 3-indolyl sulfides to 2-indolyl sulfides: first synthesis of 3-unsubstituted 2-(arylthio)indoles. Evidence for a complex intermolecular process. *J. Org. Chem.*, **57**, 2694–2699.
29. Miller, J. and Parker, A.J. (1961) Dipolar aprotic solvents in bimolecular aromatic nucleophilic substitution reactions. *J. Am. Chem. Soc.*, **83**, 117–123.
30. Rueeger, H., Lueoend, R., Rogel, O., Rondeau, J.-M., Möbitz, H., Machauer, R., Jacobson, L., Staufenbiel, M., Desrayaud, S., and Neumann, U. (2012) Discovery of cyclic sulfone hydroxyethylamines as potent and selective β-site APP-cleaving enzyme 1 (BACE1) inhibitors: structure-based design and in vivo reduction of amyloid β-peptides. *J. Med. Chem.*, **55**, 3364–3386.
31. Beugelmans, R., Singh, G.P., Bois-Choussy, M., Chastanet, J., and Zhu, J. (1994) S_NAr-based macrocyclization: an application to the synthesis of vancomycin family models. *J. Org. Chem.*, **59**, 5535–5542.
32. Zhang, S., Wang, Y., Feng, X., and Bao, M. (2012) Palladium-catalyzed amination of chloromethylnaphthalene and chloromethylanthracene derivatives with various amines. *J. Am. Chem. Soc.*, **134**, 5492–5495.
33. Bodar-Houillon, F., Elissami, Y., Marsura, A., Ghermani, N.E., Espinosa, E., Bouhmaida, N., and Thalal, A. (1999) Synthesis and experimental electron density of bis(heterocyclic) azines: the case of 6,6′-bis(chloromethyl)-2,2′-bipyrazine. *Eur. J. Org. Chem.*, **1999**, 1427–1440.
34. Philipp, A. and Jirkovsky, I. (1979) Derivatives of fused 3-hydroxymethylpyran-4-ones as a mobile keto–allyl system. *Can. J. Chem.*, **57**, 3292–3295.
35. Bebot, M., Coudert, P., Rubat, C., Vallee-Goyet, D., Gardette, D., Mavel, S., Albuisson, E., and Couquelet, J. (1997) Synthesis and pharmacological evaluation in mice of new non-classical antinociceptive agents, 5-(4-arylpiperazin-1-yl)-4-benzyl-1,2-oxazin-6-ones. *Chem. Pharm. Bull.*, **45**, 659–667.
36. Torigoe, K., Kariya, N., Soranaka, K., and Pfleiderer, W. (2007) Side-chain transformations of 6- and 7-substituted 1,3-dimethyllumazines (= 1,3-dimethylpteridine-2,4(1*H*,3*H*)-diones). *Helv. Chim. Acta*, **90**, 1190–1205.

37. He, G. and Chen, G. (2011) A practical strategy for the structural diversification of aliphatic scaffolds through the palladium-catalyzed picolinamide-directed remote functionalization of unactivated C(sp^3)–H bonds. *Angew. Chem. Int. Ed.*, **50**, 5192–5196.
38. Wolfe, A.L., Duncan, K.K., Parelkar, N.K., Weir, S.J., Vielhauer, G.A., and Boger, D.L. (2012) A novel, unusually efficacious duocarmycin carbamate prodrug that releases no residual byproduct. *J. Med. Chem.*, **55**, 5878–5886.
39. Adams, J., Faitg, T., Kasparec, J., Peng, X., Ralph, J., Rheault, T.R., and Waterson, A.G. (2011) Benzene sulfonamide thiazole and oxazole compounds. WO Patent 2011/059610.
40. Littke, A., Soumeillant, M., Kaltenbach, R.F. III, Cherney, R.J., Tarby, C.M., and Kiau, S. (2007) Mild and general methods for the palladium-catalyzed cyanation of aryl and heteroaryl chlorides. *Org. Lett.*, **9**, 1711–1714.
41. Okuro, K., Furuune, M., Miura, M., and Nomura, M. (1993) Copper-catalyzed reaction of aryl iodides with active methylene compounds. *J. Org. Chem.*, **58**, 7606–7607.
42. Giri, R. and Hartwig, J.F. (2010) Cu(I)-Amido complexes in the Ullmann reaction: reactions of Cu(I)-amido complexes with iodoarenes with and without autocatalysis by CuI. *J. Am. Chem. Soc.*, **132**, 15860–15863.
43. Jones, G.O., Liu, P., Houk, K.N., and Buchwald, S.L. (2010) Computational explorations of mechanisms and ligand-directed selectivities of copper-catalyzed Ullmann-type reactions. *J. Am. Chem. Soc.*, **132**, 6205–6213.
44. Fernández-Rodríguez, M.A., Shen, Q., and Hartwig, J.F. (2006) Highly efficient and functional-group-tolerant catalysts for the palladium-catalyzed coupling of aryl chlorides with thiols. *Chem. Eur. J.*, **12**, 7782–7796.
45. Margolis, B.J., Long, K.A., Laird, D.L.T., Ruble, J.C., and Pulley, S.R. (2007) Assembly of 4-aminoquinolines via palladium catalysis: a mild and convenient alternative to S_NAr methodology. *J. Org. Chem.*, **72**, 2232–2235.
46. Sang, P., Xie, Y., Zou, J., and Zhang, Y. (2012) Copper-catalyzed sequential Ullmann *N*-arylation and aerobic oxidative C–H amination: a convenient route to indolo[1,2-*c*]quinazoline derivatives. *Org. Lett.*, **14**, 3894–3897.
47. Chu, L., Yue, X., and Qing, F.-L. (2010) Cu(II)-mediated methylthiolation of aryl C–H bonds with DMSO. *Org. Lett.*, **12**, 1644–1647.
48. Sawant, D.N., Wagh, Y.S., Tambade, P.J., Bhatte, K.D., and Bhanagea, B.M. (2011) Cyanides-free cyanation of aryl halides using formamide. *Adv. Synth. Catal.*, **353**, 781–787.
49. Li, J.-H., Xie, Y.-X., and Yin, D.-L. (2003) New role of CO_2 as a selective agent in palladium-catalyzed reductive Ullmann coupling with zinc in water. *J. Org. Chem.*, **68**, 9867–9869.
50. Monopoli, A., Caló, V., Ciminale, F., Cotugno, P., Angelici, C., Cioffi, N., and Nacci, A. (2010) Glucose as a clean and renewable reductant in the Pd-nanoparticle-catalyzed reductive homocoupling of bromo- and chloroarenes in water. *J. Org. Chem.*, **75**, 3908–3911.
51. Bergeron-Brlek, M., Giguère, D., Shiao, T.C., Saucier, C., and Roy, R. (2012) Palladium-catalyzed Ullmann-type reductive homocoupling of iodoaryl glycosides. *J. Org. Chem.*, **77**, 2971–2977.
52. Hassan, J., Sévignon, M., Gozzi, C., Schulz, E., and Lemaire, M. (2002) Aryl–aryl bond formation one century after the discovery of the Ullmann reaction. *Chem. Rev.*, **102**, 1359–1469.
53. Wipf, P. and Lynch, S.M. (2003) Synthesis of highly oxygenated dinaphthyl ethers via S_NAr reactions promoted by Barton's base. *Org. Lett.*, **5**, 1155–1158.
54. Bryan, C.S., Braunger, J.A., and Lautens, M. (2009) Efficient synthesis of benzothiophenes on the basis of an unusual palladium-catalyzed vinylic C–S coupling. *Angew. Chem. Int. Ed.*, **48**, 7064–7068.
55. Price, C.C. and Stacy, G.W. (1955) *p*-Aminophenyl disulfide. *Org. Synth.*, Coll. Vol. **3**, 86–87.
56. Bunnett, J.F. and Weiss, R.H. (1988) Radical anion arylation: diethyl

phenylphosphonate. *Org. Synth.*, Coll. Vol. **6**, 451–454.

57. Gandhi, S.S., Gibson, M.S., Kaldas, M.L., and Vines, S.M. (1979) Reactions of some aromatic nitro compounds with alkali metal amides. *J. Org. Chem.*, **44**, 4705–4707.

58. Weissermel, K. and Arpe, H.-J. (1993) *Industrial Organic Chemistry*, VCH Verlagsgesellschaft mbH, Weinheim.

59. Goryunov, L.I., Grobe, J., Le Van, D., Shteingarts, V.D., Mews, R., Lork, E., and Würthwein, E.-U. (2010) Di- and trifluorobenzenes in reactions with Me_2EM (E = P, N; M = $SiMe_3$, $SnMe_3$, Li) reagents: evidence for a concerted mechanism of aromatic nucleophilic substitution. *Eur. J. Org. Chem.*, **2010**, 1111–1123.

60. Sandin, H., Swanstein, M.-L., and Wellner, E. (2004) A fast and parallel route to cyclic isothioureas and guanidines with use of microwave-assisted chemistry. *J. Org. Chem.*, **69**, 1571–1580.

61. Diness, F. and Fairlie, D.P. (2012) Catalyst-free *N*-arylation using unactivated fluorobenzenes. *Angew. Chem. Int. Ed.*, **51**, 8012–8016.

62. Beringer, F.M., Brierley, A., Drexler, M., Gindler, E.M., and Lumpkin, C.C. (1953) Diaryliodonium salts. 11. The phenylation of organic and inorganic bases. *J. Am. Chem. Soc.*, **75**, 2708–2712.

63. Sukata, K. and Akagawa, T. (1989) Poly(ethylene glycol)s and their dimethyl ethers as catalysts for the reaction of aryl halides with diphenylamine in the presence of potassium hydroxide. *J. Org. Chem.*, **54**, 1476–1479.

64. Tripathy, S., LeBlanc, R., and Durst, T. (1999) Formation of 2-substituted iodobenzenes from iodobenzene via benzyne and ate complex intermediates. *Org. Lett.*, **1**, 1973–1975.

65. Hartman, W.W. (1941) *p*-Cresol. *Org. Synth.*, Coll. Vol. **1**, 175–176.

66. Weston, A.W. and Suter, C.M. (1955) 3,5-Dihydroxybenzoic acid. *Org. Synth.*, Coll. Vol. **3**, 288–290.

67. Agnello, L.A. and Williams, W.H. (1960) Synthetic phenol. *Ind. Eng. Chem.*, **52**, 894–900.

68. Loughhead, D.G., Flippin, L.A., and Weikert, R.J. (1999) Synthesis of mexiletine stereoisomers and related compounds via S_NAr nucleophilic substitution of a $Cr(CO)_3$-complexed aromatic fluoride. *J. Org. Chem.*, **64**, 3373–3375.

69. Brenner, E., Baldwin, R.M., and Tamagnan, G. (2005) Asymmetric synthesis of (+)-(*S*,*S*)-reboxetine via a new (*S*)-2-(hydroxymethyl)morpholine preparation. *Org. Lett.*, **7**, 937–939.

70. Kundu, S.K., Tan, W.S., Yan, J.-L., and Yang, J.-S. (2010) Pentiptycene building blocks derived from nucleophilic aromatic substitution of pentiptycene triflates and halides. *J. Org. Chem.*, **75**, 4640–4643.

71. Itakura, H., Mizuno, H., Hirai, K., and Tomioka, H. (2000) Generation, characterization, and kinetics of triplet di[1,2,3,4,5,6,7,8-octahydro-1,4:5,8-di(ethano)anthryl]carbene. *J. Org. Chem.*, **65**, 8797–8806.

72. Lee, S., Chataigner, I., and Piettre, S.R. (2011) Facile dearomatization of nitrobenzene derivatives and other nitroarenes with *N*-benzyl azomethine ylide. *Angew. Chem. Int. Ed.*, **50**, 472–476.

73. Jiang, Y., Qin, Y., Xie, S., Zhang, X., Dong, J., and Ma, D. (2009) A general and efficient approach to aryl thiols: CuI-catalyzed coupling of aryl iodides with sulfur and subsequent reduction. *Org. Lett.*, **11**, 5250–5253.

74. Gilman, H. and Gainer, G.C. (1949) Some 6-quinolyl sulfides and sulfones. *J. Am. Chem. Soc.*, **71**, 1747–1751.

75. Beier, P., Pastyříková, T., Vida, N., and Iakobson, G. (2011) S_NAr reactions of nitro(pentafluorosulfanyl)benzenes to generate SF_5 aryl ethers and sulfides. *Org. Lett.*, **13**, 1466–1469.

76. Harris, N.V., Smith, C., and Bowden, K. (1990) Antifolate and antibacterial activities of 5-substituted 2,4-diaminoquinazolines. *J. Med. Chem.*, **33**, 434–444.

77. Russell, A. and Tebbens, W.G. (1955) 2,6-Dimethoxybenzonitrile. *Org. Synth.*, Coll. Vol. **3**, 293–294.
78. Mauthner, F. (1929) Untersuchungen über die γ-Resorcylsäure. *J. Prakt. Chem.*, **117**, 259–265.
79. Beck, J.R. and Yahner, J.A. (1978) Nitro displacement by methanethiol anion. Synthesis of bis-, tris-, pentakis-, and hexakis(methylthio)benzenes. *J. Org. Chem.*, **43**, 2048–2052.
80. Cogolli, P., Testaferri, L., Tingoli, M., and Tiecco, M. (1979) Alkyl thioether activation of the nitro displacement by alkanethiol anions. A useful process for the synthesis of poly[(alkylthio)benzenes]. *J. Org. Chem.*, **44**, 2636–2642.
81. Montanari, S., Paradisi, C., and Scorrano, G. (1991) Influence of ion pairing, steric effects, and other specific interactions on the reactivity of thioanions with chloronitrobenzenes. Nucleophilic aromatic substitution vs reduction. *J. Org. Chem.*, **56**, 4274–4279.
82. Beier, P., Pastyříková, T., and Iakobson, G. (2011) Preparation of SF_5 aromatics by vicarious nucleophilic substitution reactions of nitro(pentafluorosulfanyl)benzenes with carbanions. *J. Org. Chem.*, **76**, 4781–4786.
83. Mąkosza, M., Chromiński, M., and Sulikowski, D. (2011) Synthesis of nitroaryl derivatives of glycine via oxidative nucleophilic substitution of hydrogen in nitroarenes. *Arkivoc*, 82–91.
84. Mąkosza, M. (2010) Nucleophilic substitution of hydrogen in electron-deficient arenes, a general process of great practical value. *Chem. Soc. Rev.*, **39**, 2855–2868.
85. Mąkosza, M. and Wojciechowski, K. (2004) Nucleophilic substitution of hydrogen in heterocyclic chemistry. *Chem. Rev.*, **104**, 2631–2666.
86. Verbeeck, S., Herrebout, W.A., Gulevskaya, A.V., van der Veken, B.J., and Maes, B.U.W. (2010) ONSH: optimization of oxidative alkylamination reactions through study of the reaction mechanism. *J. Org. Chem.*, **75**, 5126–5133.
87. Gulevskaya, A.V., Verbeeck, S., Burov, O.N., Meyers, C., Korbukova, I.N., Herrebout, W., and Maes, B.U.W. (2009) Synthesis of (alkylamino)nitroarenes by oxidative alkylamination of nitroarenes. *Eur. J. Org. Chem.*, **2009**, 564–574.
88. Dantas de Araujo, A., Christensen, C., Buchardt, J., Kent, S.B.H., and Alewood, P.F. (2011) Synthesis of tripeptide mimetics based on dihydroquinolinone and benzoxazinone scaffolds. *Chem. Eur. J.*, **17**, 13983–13986.
89. Lawrence, N.J., Liddle, J., Bushell, S.M., and Jackson, D.A. (2002) A three-component coupling process based on vicarious nucleophilic substitution (VNS_{AR})-alkylation reactions: an approach to indoprofen and derivatives. *J. Org. Chem.*, **67**, 457–464.
90. Florio, S., Lorusso, P., Luisi, R., Granito, C., Ronzini, L., and Troisi, L. (2004) Vicarious nucleophilic substitution of (chloroalkyl)heterocycles with nitroarenes. *Eur. J. Org. Chem.*, **2004**, 2118–2124.
91. Kawakami, T. and Suzuki, H. (1999) Masked acylation of *m*-dinitrobenzene and derivatives with nitroalkanes under basic conditions: nitromethylation and α-(hydroxyimino)alkylation. *Tetrahedron Lett.*, **40**, 1157–1160.
92. Lemek, T., Groszek, G., and Cmoch, P. (2008) Vicarious nucleophilic substitutions of hydrogen in 1,1,1-trifluoro-*N*-[oxido(phenyl)(trifluoromethyl)-λ^4-sulfanylidene]methanesulfonamide. *Eur. J. Org. Chem.*, **2008**, 4206–4209.
93. Gomez, R., Jolly, S.J., Williams, T., Vacca, J.P., Torrent, M., McGaughey, G., Lai, M.-T., Felock, P., Munshi, V., DiStefano, D., Flynn, J., Miller, M., Yan, Y., Reid, J., Sanchez, R., Liang, Y., Paton, B., Wan, B.-L., and Anthony, N. (2011) Design and synthesis of conformationally constrained inhibitors of non-nucleoside reverse transcriptase. *J. Med. Chem.*, **54**, 7920–7933.

94. Pews, R.G., Lysenko, Z., and Vosejpka, P.C. (1997) A safe cost-efficient synthesis of 4,6-diaminoresorcinol. *J. Org. Chem.*, **62**, 8255–8256.

95. Makosza, M. and Sienkiewicz, K. (1998) Hydroxylation of nitroarenes with alkyl hydroperoxide anions via vicarious nucleophilic substitution of hydrogen. *J. Org. Chem.*, **63**, 4199–4208.

96. Kawakami, T., Uehata, K., and Suzuki, H. (2000) NaH-mediated one-pot cyclocondensation of 6-nitroquinoline with aromatic hydrazones to form [1.2.4]triazino[6,5-*f*]quinolines and/or pyrazolo[3,4-*f*]quinolines. *Org. Lett.*, **2**, 413–415.

97. Katritzky, A.R. and Laurenzo, K.S. (1988) Alkylaminonitrobenzenes by vicarious nucleophilic amination with 4-(alkylamino)-1,2,4-triazoles. *J. Org. Chem.*, **53**, 3978–3982.

98. Bunnett, J.F., Rauhut, M.H., Knutson, D., and Bussell, G.E. (1954) Studies on the conditions, scope and mechanism of the von Richter reaction. *J. Am. Chem. Soc.*, **76**, 5755–5761.

99. Arvela, R.K. and Leadbeater, N.E. (2003) Rapid, easy cyanation of aryl bromides and chlorides using nickel salts in conjunction with microwave promotion. *J. Org. Chem.*, **68**, 9122–9125.

100. Sundermeier, M., Zapf, A., and Beller, M. (2003) A convenient procedure for the palladium-catalyzed cyanation of aryl halides. *Angew. Chem. Int. Ed.*, **42**, 1661–1664.

101. Weissman, S.A., Zewge, D., and Chen, C. (2005) Ligand-free palladium-catalyzed cyanation of aryl halides. *J. Org. Chem.*, **70**, 1508–1510.

102. Sundermeier, M., Zapf, A., Mutyala, S., Baumann, W., Sans, J., Weiss, S., and Beller, M. (2003) Progress in the palladium-catalyzed cyanation of aryl chlorides. *Chem. Eur. J.*, **9**, 1828–1836.

103. Ren, Y., Liu, Z., He, S., Zhao, S., Wang, J., Niu, R., and Yin, W. (2009) Development of an open-air and robust method for large-scale palladium-catalyzed cyanation of aryl halides: the use of *i*-PrOH to prevent catalyst poisoning by oxygen. *Org. Process Res. Dev.*, **13**, 764–768.

104. Ushkov, A.V. and Grushin, V.V. (2011) Rational catalysis design on the basis of mechanistic understanding: highly efficient Pd-catalyzed cyanation of aryl bromides with NaCN in recyclable solvents. *J. Am. Chem. Soc.*, **133**, 10999–11005.

105. Schareina, T., Zapf, A., Mägerlein, W., Müller, N., and Beller, M. (2007) A state-of-the-art cyanation of aryl bromides: a novel and versatile copper catalyst system inspired by nature. *Chem. Eur. J.*, **13**, 6249–6254.

106. Guthrie, R.D., Hartmann, C., Neill, R., and Nutter, D.E. (1987) Carbanions: electron transfer vs. proton capture. 8. Use of sterically protected aromatic nitro compounds as base-resistant, one-electron oxidants. *J. Org. Chem.*, **52**, 736–740.

107. Müller, E. (1957) *Methoden der Organischen Chemie (Houben-Weyl)*, Band **11/1**, Stickstoffverbindungen II, Georg Thieme Verlag, Stuttgart, p. 462.

108. Lauer, W.M., Sprung, M.M., and Langkammerer, C.M. (1936) The Piria reaction. III. Mechanism studies. *J. Am. Chem. Soc.*, **58**, 225–228.

109. Wróbel, Z. (2003) Double thioalkylation/arylation of nitroarenes with the reduction of nitro- to amino group. *Tetrahedron*, **59**, 101–110.

110. Halama, A., Kaválek, J., Macháček, V., and Weidlich, T. (1999) Aromatic nucleophilic substitution of hydrogen: mechanism of reaction of 6-nitroquinoline with cyanide ions, with and without participation of methyl cyanoacetate. *J. Chem. Soc., Perkin Trans. 1*, 1839–1845.

111. Tomioka, Y., Mochiike, A., Himeno, J., and Yamazaki, M. (1981) Studies on aromatic nitro compounds. I. Reaction of 6-nitroquinoline with active methylene compounds in the presence of bases. *Chem. Pharm. Bull.*, **29**, 1286–1291.

112. Shang, R., Ji, D.-S., Chu, L., Fu, Y., and Liu, L. (2011) Synthesis of α-aryl nitriles through palladium-catalyzed decarboxylative coupling of cyanoacetate salts with aryl halides and

triflates. *Angew. Chem. Int. Ed.*, **50**, 4470–4474.

113. Song, B., Rudolphi, F., Himmler, T., and Gooβen, L.J. (2011) Practical synthesis of 2-arylacetic acid esters via palladium-catalyzed dealkoxycarbonylative coupling of malonates with aryl halides. *Adv. Synth. Catal.*, **353**, 1565–1574.

114. Yang, D., Yang, H., and Fu, H. (2011) Copper-catalyzed aerobic oxidative synthesis of aromatic carboxylic acids. *Chem. Commun.*, **47**, 2348–2350.

115. Jiang, Z., Huang, Q., Chen, S., Long, L., and Zhoua, X. (2012) Copper-catalyzed cyanation of aryl iodides with malononitrile: an unusual cyano group transfer process from C(sp^3) to C(sp^2). *Adv. Synth. Catal.*, **354**, 589–592.

116. He, L., Wang, J.-Q., Gong, Y., Liu, Y.-M., Cao, Y., He, H.-Y., and Fan, K.-N. (2011) Titania-supported iridium subnanoclusters as an efficient heterogeneous catalyst for direct synthesis of quinolines from nitroarenes and aliphatic alcohols. *Angew. Chem. Int. Ed.*, **50**, 10216–10220.

117. Dell'Erba, C., Gabellini, A., Novi, M., Petrillo, G., Tavani, C., Cosimelli, B., and Spinelli, D. (2001) Ring opening of 2-substituted 4-nitrothiophenes with pyrrolidine. Access to new functionalized nitro-unsaturated building blocks. *Tetrahedron*, **57**, 8159–8165.

118. Petrillo, G., Novi, M., Garbarino, G., and Filiberti, M. (1989) The reaction between arenediazonium tetrafluoroborates and alkaline thiocarboxylates in DMSO: a convenient access to aryl thiolesters and other aromatic sulfur derivatives. *Tetrahedron*, **45**, 7411–7420.

119. DeTar, D.F. and Kosuge, T. (1958) Mechanisms of diazonium salt reactions. VI. The reaction of diazonium salts with alcohols under acidic conditions; evidence for hydride transfer. *J. Am. Chem. Soc.*, **80**, 6072–6077.

120. Lipilin, D.L., Smirnov, O.Y., Churakov, A.M., Strelenko, Y.A., Tyurin, A.Y., Ioffe, S.L., and Tartakovsky, V.A. (2004) 2-Alkyl-1,2,3,4-benzotetrazinium tetrafluoroborates: their reaction with nucleophiles. *Eur. J. Org. Chem.*, **2004**, 4794–4801.

121. Broxton, T.J. and McLeish, M.J. (1983) Reactions of aryl diazonium salts and alkyl arylazo ethers. 9. Studies of the carbanionic and free radical mechanisms of dediazoniation of substituted 2-chlorobenzenediazonium salts. *J. Org. Chem.*, **48**, 191–195.

122. Dollings, P.J., Dietrich, A.J., and Wrobel, J.E. (2000) Naphtho[2,3-*b*]heteroar-4-yl derivatives. US Patent 6121271.

123. Swain, C.G., Sheats, J.E., and Harbison, K.G. (1975) Evidence for phenyl cation as an intermediate in reactions of benzenediazonium salts in solution. *J. Am. Chem. Soc.*, **97**, 783–790.

124. Robinson, M.K., Kochurina, V.S., and Hanna, J.M. (2007) Palladium-catalyzed homocoupling of arenediazonium salts: an operationally simple synthesis of symmetrical biaryls. *Tetrahedron Lett.*, **48**, 7687–7690.

125. Trimmer, R.W., Stover, L.R., and Skjold, A.C. (1985) Solid-state aromatic S_N2 reactions: displacement of the nitro moiety in arenediazonium salts. *J. Org. Chem.*, **50**, 3612–3614.

126. Oku, A. and Matsui, A. (1979) Diazotization of nitroanthranilic acids. Effect of carboxyl group on the nucleophilic ipso substitution of the nitro group by chloride ion. *J. Org. Chem.*, **44**, 3342–3344.

127. Lauer, W.M. and Langkammerer, C.M. (1934) The action of sodium bisulfite on resorcinol. *J. Am. Chem. Soc.*, **56**, 1628–1629.

128. Charoonniyomporn, P., Thongpanchang, T., Witayakran, S., Thebtaranonth, Y., Phillips, K.E.S., and Katz, T.J. (2004) An efficient one-pot synthesis of bisalkylthioarenes. *Tetrahedron Lett.*, **45**, 457–459.

129. Node, M., Kawabata, T., Ohta, K., Fujimoto, M., Fujita, E., and Fuji, K. (1984) Hard acid and soft nucleophile systems. 8. Reductive dehalogenation of *o*- and *p*-halophenols and their derivatives. *J. Org. Chem.*, **49**, 3641–3643.

130. Delprato, I. and Bertoldi, M. (1997) Process for preparation of 4-mercapto-1-naphthol compounds. EP Patent 0763526.

131. Mino, T., Yamada, H., Komatsu, S., Kasai, M., Sakamoto, M., and Fujita, T. (2011) Atropisomerism at C–N bonds of acyclic amines: synthesis and application to palladium-catalyzed asymmetric allylic alkylations. *Eur. J. Org. Chem.*, **2011**, 4540–4542.

132. Belaud-Rotureau, M., Le, T.T., Phan, T.H.T., Nguyen, T.H., Aissaoui, R., Gohier, F., Derdour, A., Nourry, A., Castanet, A., Nguyen, K.P.P., and Mortier, J. (2010) Synthesis of *N*-aryl and *N*-alkyl anthranilic acids via S_NAr reaction of unprotected 2-fluoro- and 2-methoxybenzoic acids by lithioamides. *Org. Lett.*, **12**, 2406–2409.

133. Mulzer, M. and Coates, G.W. (2011) A catalytic route to ampakines and their derivatives. *Org. Lett.*, **13**, 1426–1428.

134. Wempe, M.F., Jutabha, P., Quade, B., Iwen, T.J., Frick, M.M., Ross, I.R., Rice, P.J., Anzai, N., and Endou, H. (2011) Developing potent human uric acid transporter 1 (hURAT1) inhibitors. *J. Med. Chem.*, **54**, 2701–2713.

135. Wu, D., Pisula, W., Haberecht, M.C., Feng, X., and Müllen, K. (2009) Oxygen- and sulfur-containing positively charged polycyclic aromatic hydrocarbons. *Org. Lett.*, **11**, 5686–5689.

136. Guilarte, V., Castroviejo, M.P., García-García, P., Fernández-Rodríguez, M.A., and Sanz, R. (2011) Approaches to the synthesis of 2,3-dihaloanilines. Useful precursors of 4-functionalized-1*H*-indoles. *J. Org. Chem.*, **76**, 3416–3437.

137. Imakura, Y., Okimoto, K., Konishi, T., Hisazumi, M., Yamazaki, J., and Kobayashi, S. (1992) Regioselective cleavage reaction of the aromatic methylenedioxy ring. V. Cleavage with sodium alkoxides–alcohols, potassium *tert*-butoxide–alcohols, dimsyl anion–methyl alcohol, metallic sodium–alcohols, and sodium cyanide in dipolar aprotic solvents. *Chem. Pharm. Bull.*, **40**, 1691–1696.

138. Caubère, C., Caubère, P., Renard, P., Bizot-Espiart, J.-G., Ianelli, S., Nardelli, M., and Jamart-Grégoire, B. (1994) Functionalisation of the alkoxy group of alkyl aryl ethers. Demethylation, alkylthiolation and reduction of 5-methoxyindoles. *Tetrahedron*, **50**, 13433–13448.

139. Trivedi, A.R., Siddiqui, A.B., and Shah, V.H. (2008) Design, synthesis, characterization and antitubercular activity of some 2-heterocycle-substituted phenothiazines. *Arkivoc*, **2**, 210–217.

140. Barrett, O.V., Downer-Riley, N.K., and Jackson, Y.A. (2012) Thermally induced cyclization of electron-rich *N*-arylthiobenzamides to benzothiazoles. *Synthesis*, **44**, 2579–2586.

141. Pirkle, W.H. and Finn, J.M. (1983) Useful routes to 9-anthryl ethers and sulfides. *J. Org. Chem.*, **48**, 2779–2780.

142. Eberhart, A.J., Imbriglio, J.E., and Procter, D.J. (2011) Nucleophilic *ortho* allylation of aryl and heteroaryl sulfoxides. *Org. Lett.*, **13**, 5882–5885.

143. Gianneschi, N.C., Bertin, P.A., Nguyen, S.T., and Mirkin, C.A. (2003) A supramolecular approach to an allosteric catalyst. *J. Am. Chem. Soc.*, **125**, 10508–10509.

144. Pinehart, A., Dallaire, C., Van Bierbeek, A., and Gingras, M. (1999) Efficient formation of aromatic thiols from thiomethylated precursors. *Tetrahedron Lett.*, **40**, 5479–5482.

145. Sridhar, M., Kumar, B.A., and Narender, R. (1998) Expedient and simple method for regeneration of alcohols, from toluenesulfonates using Mg–MeOH. *Tetrahedron Lett.*, **39**, 2847–2850.

146. Sabitha, G., Abraham, S., Reddy, B.V.S., and Yadav, J.S. (1999) Microwave assisted selective cleavage of sulfonates and sulfonamides in dry media. *Synlett*, 1745–1746.

147. Chakraborti, A.K., Nayak, M.K., and Sharma, L. (2002) Diphenyl disulfide and sodium in NMP as an efficient protocol for in situ generation of thiophenolate anion: selective deprotection of aryl alkyl ethers and alkyl/aryl esters under nonhydrolytic conditions. *J. Org. Chem.*, **67**, 1776–1780.

148. Xu, G. and Wang, Y.-G. (2004) Microwave-assisted amination from aryl triflates without base and catalyst. *Org. Lett.*, **6**, 985–987.

149. Sach, N.W., Richter, D.T., Cripps, S., Tran-Dubé, M., Zhu, H., Huang, B., Cui, J., and Sutton, S.C. (2012) Synthesis of aryl ethers via a sulfonyl transfer reaction. *Org. Lett.*, **14**, 3886–3889.

150. Shimasaki, T., Tobisu, M., and Chatani, N. (2010) Nickel-catalyzed amination of aryl pivalates by the cleavage of aryl C–O bonds. *Angew. Chem. Int. Ed.*, **49**, 2929–2932.

151. Hie, L., Ramgren, S.D., Mesganaw, T., and Garg, N.K. (2012) Nickel-catalyzed amination of aryl sulfamates and carbamates using an air-stable precatalyst. *Org. Lett.*, **14**, 4182–4185.

152. Muto, K., Yamaguchi, J., and Itami, K. (2012) Nickel-catalyzed C–H/C–O coupling of azoles with phenol derivatives. *J. Am. Chem. Soc.*, **134**, 169–172.

153. Yoshida, H., Asatsu, Y., Mimura, Y., Ito, Y., Ohshita, J., and Takaki, K. (2011) Three-component coupling of arynes and organic bromides. *Angew. Chem. Int. Ed.*, **50**, 9676–9679.

154. Nakayama, J., Hoshino, K., and Hoshino, M. (1985) Carbon–sulfur bond cleavage by benzyne generated from 2-carboxybenzenediazonium chloride. *Chem. Lett.*, 677–678.

155. Guedira, N.-E. and Beugelmans, R. (1992) Ambident behavior of ketone enolate anions in S_NAr substitutions on fluorobenzonitrile substrates. *J. Org. Chem.*, **57**, 5577–5585.

156. Renga, J.M., McLaren, K.L., and Ricks, M.J. (2003) Process optimization and synthesis of 3-(4-fluorophenyl)-4,5-dihydro-*N*-[4-(trifluoromethyl)phenyl]-4-[5-(trifluoromethyl)-2-pyridyl]-1*H*-pyrazole-1-carboxamide. *Org. Process Res. Dev.*, **7**, 267–271.

157. Thompson, A.D. and Huestis, M.P. (2013) Cyanide anion as a leaving group in nucleophilic aromatic substitution: synthesis of quaternary centers at azine heterocycles. *J. Org. Chem.*, **78**, 762–769.

158. Kobbelgaard, S., Bella, M., and Jørgensen, K.A. (2006) Improved asymmetric S_NAr reaction of β-dicarbonyl compounds catalyzed by quaternary ammonium salts derived from cinchona alkaloids. *J. Org. Chem.*, **71**, 4980–4987.

159. Ozanne-Beaudenon, A. and Quideau, S. (2005) Regioselective hypervalent-iodine(III)-mediated dearomatizing phenylation of phenols through direct ligand coupling. *Angew. Chem. Int. Ed.*, **44**, 7065–7069.

160. Stahly, G.P. (1985) Synthesis of unsymmetrical biphenyls by reaction of nitroarenes with phenols. *J. Org. Chem.*, **50**, 3091–3094.

161. Cao, C., Wang, L., Cai, Z., Zhang, L., Guo, J., Pang, G., and Shi, Y. (2011) Palladium-catalyzed α-ketone arylation under mild conditions. *Eur. J. Org. Chem.*, **2011**, 1570–1574.

162. Aljaar, N., Malakar, C.C., Conrad, J., Strobel, S., Schleid, T., and Beifuss, U. (2012) Cu-catalyzed reaction of 1,2-dihalobenzenes with 1,3-cyclohexanediones for the synthesis of 3,4-dihydrodibenzo[*b*,*d*]furan-1(2*H*)-ones. *J. Org. Chem.*, **77**, 7793–7803.

163. Merrill, R.E. and Negishi, E. (1974) Tetrahydrofuran-promoted aryl-alkyl coupling involving organolithium reagents. *J. Org. Chem.*, **39**, 3452–3453.

164. Bailey, W.F., Luderer, M.R., and Jordan, K.P. (2006) Effect of solvent on the lithium–bromine exchange of aryl bromides: reactions of *n*-butyllithium and *tert*-butyllithium with 1-bromo-4-*tert*-butylbenzene at 0 °C. *J. Org. Chem.*, **71**, 2825–2828.

165. Patterson, J.W. (1995) The synthesis of mycophenolic acid from 2,4-dihydroxybenzoic acid. *J. Org. Chem.*, **60**, 4542–4548.

166. Norman, D.P.G., Bunnell, A.E., Stabler, S.R., and Flippin, L.A. (1999) Nucleophilic aromatic substitution reactions of novel 5-(2-methoxyphenyl)tetrazole derivatives with organolithium reagents. *J. Org. Chem.*, **64**, 9301–9306.

167. Kojima, T., Ohishi, T., Yamamoto, I., Matsuoka, T., and Kotsukia, H. (2001)

A new practical method for regioselective nucleophilic aromatic alkylation of *ortho*- or *para*-methoxy-substituted aromatic esters with Grignard reagents. *Tetrahedron Lett.*, **42**, 1709–1712.

168. Shindo, M., Koga, K., and Tomioka, K. (1992) A catalytic method for asymmetric nucleophilic aromatic substitution giving binaphthyls. *J. Am. Chem. Soc.*, **114**, 8732–8733.

169. Silberstein, A.L., Ramgren, S.D., and Garg, N.K. (2012) Iron-catalyzed alkylations of aryl sulfamates and carbamates. *Org. Lett.*, **14**, 3796–3799.

170. Kumada, M., Tamao, K., and Sumitani, K. (1988) Phosphine-nickel complex catalyzed cross-coupling of Grignard reagents with aryl and alkenyl halides: 1,2-dibutylbenzene. *Org. Synth.*, Coll. Vol. **6**, 407–411.

171. Kim, C.-B., Jo, H., Ahn, B.-K., Kim, C.K., and Park, K. (2009) Nickel *N*-heterocyclic carbene catalyst for cross-coupling of neopentyl arenesulfonates with methyl and primary alkyl Grignard reagents. *J. Org. Chem.*, **74**, 9566–9569.

172. Cooper, T., Novak, A., Humphreys, L.D., Walker, M.D., and Woodward, S. (2006) User-friendly methylation of aryl and vinyl halides and pseudohalides with DABAL-Me_3. *Adv. Synth. Catal.*, **348**, 686–690.

173. Wang, T., Alfonso, B.J., and Love, J.A. (2007) Platinum(II)-catalyzed cross-coupling of polyfluoroaryl imines. *Org. Lett.*, **9**, 5629–5631.

174. Fürstner, A., Leitner, A., and Seidel, G. (2009) 4-nonylbenzoic acid. *Org. Synth.*, Coll. Vol. **11**, 353–358.

175. Phapale, V.B., Guisán-Ceinos, M., Buñuel, E., and Cárdenas, D.J. (2009) Nickel-catalyzed cross-coupling of alkyl zinc halides for the formation of $C(sp^2)$–$C(sp^3)$ bonds: scope and mechanism. *Chem. Eur. J.*, **15**, 12681–12688.

176. Guan, B.-T., Xiang, S.-K., Wang, B.-Q., Sun, Z.-P., Wang, Y., Zhao, K.-Q., and Shi, Z.-J. (2008) Direct benzylic alkylation via Ni-catalyzed selective benzylic sp^3 C–O activation. *J. Am. Chem. Soc.*, **130**, 3268–3269.

177. Song, G., Su, Y., Gong, X., Han, K., and Li, X. (2011) Pd(0)-Catalyzed diarylation of sp^3 C–H bond in (2-azaaryl)methanes. *Org. Lett.*, **13**, 1968–1971.

178. Zhang, X.-Q. and Wang, Z.-X. (2012) Cross-coupling of aryltrimethylammonium iodides with arylzinc reagents catalyzed by amido pincer nickel complexes. *J. Org. Chem.*, **77**, 3658–3663.

179. Gillespie, R.J., Bamford, S.J., Botting, R., Comer, M., Denny, S., Gaur, S., Griffin, M., Jordan, A.M., Knight, A.R., Lerpiniere, J., Leonardi, S., Lightowler, S., McAteer, S., Merrett, A., Misra, A., Padfield, A., Reece, M., Saadi, M., Selwood, D.L., Stratton, G.C., Surry, D., Todd, R., Tong, X., Ruston, V., Upton, R., and Weiss, S.M. (2009) Antagonists of the human A_{2A} adenosine receptor. 4. Design, synthesis, and preclinical evaluation of 7-aryltriazolo[4,5-*d*]pyrimidines. *J. Med. Chem.*, **52**, 33–47.

180. Sapountzis, I. and Knochel, P. (2002) A new general preparation of polyfunctional diarylamines by the addition of functionalized arylmagnesium compounds to nitroarenes. *J. Am. Chem. Soc.*, **124**, 9390–9391.

181. Gao, H., Ess, D.H., Yousufuddin, M., and Kürti, L. (2013) Transition-metal-free direct arylation: synthesis of halogenated 2-amino-2′-hydroxy-1,1′-biaryls and mechanism by DFT calculations. *J. Am. Chem. Soc.*, **135**, 7086–7089.

182. Dalpozzo, R. and Bartoli, G. (2005) Bartoli indole synthesis. *Curr. Org. Chem.*, **9**, 163–178.

183. Zhang, Z., Yang, Z., Meanwell, N.A., Kadow, J.F., and Wang, T. (2002) A general method for the preparation of 4-and 6-azaindoles. *J. Org. Chem.*, **67**, 2345–2347.

184. Truong, T., Alvarado, J., Tran, L.D., and Daugulis, O. (2010) Nickel, manganese, cobalt, and iron-catalyzed deprotonative arene dimerization. *Org. Lett.*, **12**, 1200–1203.

185. Suhartono, M., Schneider, A.E., Dürner, G., and Göbel, M.W. (2010) Synthetic aromatic amino acids from a Negishi cross-coupling reaction. *Synthesis*, 293–303.

186. Do, H.-Q. and Daugulis, O. (2009) An aromatic Glaser–Hay reaction. *J. Am. Chem. Soc.*, **131**, 17052–17053.

187. Wu, F., Lu, E., and Barden, C. (2012) Antimicrobial/adjuvant compounds and methods. WO Patent 2012116452.

188. Du, C.-J.F. and Hart, H. (1987) Aryne reactions of polyhalobenzenes with alkenyl and alkynyl Grignard reagents. *J. Org. Chem.*, **52**, 4311–4314.

189. Hamura, T., Chuda, Y., Nakatsuji, Y., and Suzuki, K. (2012) Catalytic generation of arynes and trapping by nucleophilic addition and iodination. *Angew. Chem. Int. Ed.*, **51**, 3368–3372.

190. Romero, M., Harrak, Y., Basset, J., Orúe, J.A., and Pujol, M.D. (2009) Direct synthesis of primary arylamines via C–N cross-coupling of aryl bromides and triflates with amides. *Tetrahedron*, **65**, 1951–1956.

191. Meng, F., Zhu, X., Li, Y., Xie, J., Wang, B., Yao, J., and Wan, Y. (2010) Efficient copper-catalyzed direct amination of aryl halides using aqueous ammonia in water. *Eur. J. Org. Chem.*, **2010**, 6149–6152.

192. Liao, B.-S. and Liu, S.-T. (2012) Diamination of phenylene dihalides catalyzed by a dicopper complex. *J. Org. Chem.*, **77**, 6653–6656.

193. Dumrath, A., Lübbe, C., Neumann, H., Jackstell, R., and Beller, M. (2011) Recyclable catalysts for palladium-catalyzed aminations of aryl halides. *Chem. Eur. J.*, **17**, 9599–9604.

194. Huang, M., Lin, X., Zhu, X., Peng, W., Xie, J., and Wan, Y. (2011) A highly versatile catalytic system for *N*-arylation of amines with aryl chlorides in water. *Eur. J. Org. Chem.*, **2011**, 4523–4527.

195. Mirsadeghi, S., Prasad, G.K.B., Whittaker, N., and Thakker, D.R. (1989) Synthesis of the K-region monofluoro- and difluorobenzo[*c*]phenanthrenes. *J. Org. Chem.*, **54**, 3091–3096.

196. Hori, K. and Mori, M. (1998) Synthesis of nonsubstituted anilines from molecular nitrogen via transmetalation of arylpalladium complex with titanium–nitrogen fixation complexes. *J. Am. Chem. Soc.*, **120**, 7651–7652.

197. Pieber, B., Cantillo, D., and Kappe, C.O. (2012) Direct arylation of benzene with aryl bromides using high-temperature/high-pressure process windows: expanding the scope of C–H activation chemistry. *Chem. Eur. J.*, **18**, 5047–5055.

198. Whitaker, C.M., Kott, K.L., and McMahon, R.J. (1995) Synthesis and solid-state structure of substituted arylphosphine oxides. *J. Org. Chem.*, **60**, 3499–3508.

199. Fors, B.P. and Buchwald, S.L. (2009) Pd-catalyzed conversion of aryl chlorides, triflates, and nonaflates to nitroaromatics. *J. Am. Chem. Soc.*, **131**, 12898–12899.

200. Holm, B. (1985) Verfahren zur Herstellung von *o*- und *p*-Nitrobenzaldehyd. DE Patent 3519864.

201. Ma, D., Xia, C., Jiang, J., Zhang, J., and Tang, W. (2003) Aromatic nucleophilic substitution or CuI-catalyzed coupling route to martinellic acid. *J. Org. Chem.*, **68**, 442–451.

202. Fors, B.P., Watson, D.A., Biscoe, M.R., and Buchwald, S.L. (2008) A highly active catalyst for Pd-catalyzed amination reactions: cross-coupling reactions using aryl mesylates and the highly selective monoarylation of primary amines using aryl chlorides. *J. Am. Chem. Soc.*, **130**, 13552–13554.

203. Kuwano, R., Utsunomiya, M., and Hartwig, J.F. (2002) Aqueous hydroxide as a base for palladium-catalyzed amination of aryl chlorides and bromides. *J. Org. Chem.*, **67**, 6479–6486.

204. Guo, D., Huang, H., Xu, J., Jiang, H., and Liu, H. (2008) Efficient iron-catalyzed *N*-arylation of aryl halides with amines. *Org. Lett.*, **10**, 4513–4516.

205. Xiong, X., Jiang, Y., and Ma, D. (2012) Assembly of *N*,*N*-disubstituted hydrazines and 1-aryl-1*H*-indazoles via copper-catalyzed coupling reactions. *Org. Lett.*, **14**, 2552–2555.

206. Petersen, T.P., Larsen, A.F., Ritzén, A., and Ulven, T. (2013) Continuous flow nucleophilic aromatic substitution with dimethylamine generated in situ by decomposition of DMF. *J. Org. Chem.*, **78**, 4190–4195.

207. Chen, W.-X. and Shao, L.-X. (2012) *N*-Heterocyclic carbene-palladium(II)-1-methylimidazole complex catalyzed amination between aryl chlorides and amides. *J. Org. Chem.*, **77**, 9236–9239.

208. Withbroe, G.J., Singer, R.A., and Sieser, J.E. (2008) Streamlined synthesis of the bippyphos family of ligands and cross-coupling applications. *Org. Process Res. Dev.*, **12**, 480–489.

209. Surry, D.S. and Buchwald, S.L. (2007) Selective palladium-catalyzed arylation of ammonia: synthesis of anilines as well as symmetrical and unsymmetrical di- and triarylamines. *J. Am. Chem. Soc.*, **129**, 10354–10355.

210. Watanabe, T., Oishi, S., Fujii, N., and Ohno, H. (2009) Palladium-catalyzed direct synthesis of carbazoles via one-pot *N*-arylation and oxidative biaryl coupling: synthesis and mechanistic study. *J. Org. Chem.*, **74**, 4720–4726.

211. Maiti, D. and Buchwald, S.L. (2009) Orthogonal Cu- and Pd-based catalyst systems for the *O*- and *N*-arylation of aminophenols. *J. Am. Chem. Soc.*, **131**, 17423–17429.

212. Fang, Y., Zheng, Y., and Wang, Z. (2012) Direct base-assisted C–N bond formation between aryl halides and aliphatic tertiary amines under transition-metal-free conditions. *Eur. J. Org. Chem.*, **2012**, 1495–1498.

213. Kametani, T., Kigasawa, K., Hiiragi, M., and Aoyama, T. (1972) Studies on the syntheses of heterocyclic compounds. CDLX. Benzyne reaction. XIII. Benzyne reaction of halogenobenzenes with *N*-alkylmorpholines. *J. Org. Chem.*, **37**, 1450–1453.

214. Cant, A.A., Bertrand, G.H.V., Henderson, J.L., Roberts, L., and Greaney, M.F. (2009) The benzyne aza-Claisen reaction. *Angew. Chem. Int. Ed.*, **48**, 5199–5202.

215. Burnley, J., Carbone, G., and Moses, J.E. (2013) Catalytic reduction of *ortho*- and *para*-azidonitrobenzenes via *tert*-butoxide ion mediated electron transfer. *Synlett*, 652–656.

216. Messaoudi, S., Brion, J.-D., and Alami, M. (2010) An expeditious copper-catalyzed access to 3-aminoquinolinones, 3-aminocoumarins and anilines using sodium azide. *Adv. Synth. Catal.*, **352**, 1677–1687.

217. Markiewicz, J.T., Wiest, O., and Helquist, P. (2010) Synthesis of primary aryl amines through a copper-assisted aromatic substitution reaction with sodium azide. *J. Org. Chem.*, **75**, 4887–4890.

218. D'Anna, F., Marullo, S., and Noto, R. (2008) Ionic liquids/[bmim][N_3] mixtures: promising media for the synthesis of aryl azides by S_NAr. *J. Org. Chem.*, **73**, 6224–6228.

219. Andersen, J., Madsen, U., Björkling, F., and Liang, X. (2005) Rapid synthesis of aryl azides from aryl halides under mild conditions. *Synlett*, 2209–2213.

220. Goriya, Y. and Ramana, C.V. (2010) The [Cu]-catalyzed S_NAr reactions: direct amination of electron deficient aryl halides with sodium azide and the synthesis of arylthioethers under Cu(II)-ascorbate redox system. *Tetrahedron*, **66**, 7642–7650.

221. Zhu, W. and Ma, D. (2004) Synthesis of aryl azides and vinyl azides via proline-promoted CuI-catalyzed coupling reactions. *Chem. Commun.*, 888–889.

222. Boyer, J.H. and Canter, F.C. (1954) Alkyl and aryl azides. *Chem. Rev.*, **54**, 1–57.

223. Kendre, D.B., Toche, R.B., and Jachak, M.N. (2007) Synthesis of novel dipyrazolo[3,4-*b*:3,4-*d*]pyridines and study of their fluorescence behavior. *Tetrahedron*, **63**, 11000–11004.

224. Rodrigues, J.A.R., Abramovitch, R.A., de Sousa, J.D.F., and Leiva, G.C. (2004) Diastereoselective synthesis of cularine alkaloids via enium ions and an easy entry to isoquinolines by aza-Wittig electrocyclic ring closure. *J. Org. Chem.*, **69**, 2920–2928.

225. de Carvalho, M., Sorrilha, A.E.P.M., and Rodrigues, J.A.R. (1999) Reaction of aromatic azides with strong acids: formation of fused nitrogen heterocycles and arylamines. *J. Braz. Chem. Soc.*, **10**, 415–420.

226. Yang, K., Li, Z., Wang, Z., Yao, Z., and Jiang, S. (2011) Highly efficient synthesis of phenols by copper-catalyzed

hydroxylation of aryl iodides, bromides, and chlorides. *Org. Lett.*, **13**, 4340–4343.

227. Xu, H.-J., Liang, Y.-F., Cai, Z.-Y., Qi, H.-X., Yang, C.-Y., and Feng, Y.-S. (2011) CuI-nanoparticles-catalyzed selective synthesis of phenols, anilines, and thiophenols from aryl halides in aqueous solution. *J. Org. Chem.*, **76**, 2296–2300.

228. Kozhevnikov, V.N., Dahms, K., and Bryce, M.R. (2011) Nucleophilic substitution of fluorine atoms in 2,6-difluoro-3-(pyridin-2-yl)benzonitrile leading to soluble blue-emitting cyclometalated Ir(III) complexes. *J. Org. Chem.*, **76**, 5143–5148.

229. Woydziak, Z.R., Fu, L., and Peterson, B.R. (2012) Synthesis of fluorinated benzophenones, xanthones, acridones, and thioxanthones by iterative nucleophilic aromatic substitution. *J. Org. Chem.*, **77**, 473–481.

230. Zhou, C., Liu, Q., Li, Y., Zhang, R., Fu, X., and Duan, C. (2012) Palladium-catalyzed desulfitative arylation by C–O bond cleavage of aryl triflates with sodium arylsulfinates. *J. Org. Chem.*, **77**, 10468–10472.

231. Becht, J.-M. and Le Drian, C. (2011) Formation of carbon–sulfur and carbon–selenium bonds by palladium-catalyzed decarboxylative cross-couplings of hindered 2,6-dialkoxybenzoic acids. *J. Org. Chem.*, **76**, 6327–6330.

232. Bhadra, S., Dzik, W.I., and Goossen, L.J. (2012) Decarboxylative etherification of aromatic carboxylic acids. *J. Am. Chem. Soc.*, **134**, 9938–9941.

233. Duan, Z., Ranjit, S., Zhang, P., and Liu, X. (2009) Synthesis of aryl sulfides by decarboxylative C–S cross-couplings. *Chem. Eur. J.*, **15**, 3666–3669.

234. Makhlynets, O.V., Das, P., Taktak, S., Flook, M., Mas-Ballesté, R., Rybak-Akimova, E.V., and Que, L. (2009) Iron-promoted *ortho*- and/or *ipso*-hydroxylation of benzoic acids with H_2O_2. *Chem. Eur. J.*, **15**, 13171–13180.

235. Yu, C.-W., Chen, G.S., Huang, C.-W., and Chern, J.-W. (2012) Efficient microwave-assisted Pd-catalyzed hydroxylation of aryl chlorides in the presence of carbonate. *Org. Lett.*, **14**, 3688–3691.

236. Parlow, J.J., Stevens, A.M., Stegeman, R.A., Stallings, W.C., Kurumbail, R.G., and South, M.S. (2003) Synthesis and crystal structures of substituted benzenes and benzoquinones as tissue factor VIIa inhibitors. *J. Med. Chem.*, **46**, 4297–4312.

237. Cohen, T. and Lewin, A.H. (1966) The production of organocopper intermediates from radicals in the reactions of aromatic halides and diazonium ions with cuprous benzoate. New synthetic methods for aryl benzoates. *J. Am. Chem. Soc.*, **88**, 4521–4522.

238. Petersen, T.B., Khan, R., and Olofsson, B. (2011) Metal-free synthesis of aryl esters from carboxylic acids and diaryliodonium salts. *Org. Lett.*, **13**, 3462–3465.

239. Woiwode, T.F., Rose, C., and Wandless, T.J. (1998) A simple and efficient method for the preparation of hindered alkyl–aryl ethers. *J. Org. Chem.*, **63**, 9594–9596.

240. Osborne, R., Clarke, N., Glossop, P., Kenyon, A., Liu, H., Patel, S., Summerhill, S., and Jones, L.H. (2011) Efficient conversion of a nonselective norepinephrin reuptake inhibitor into a dual muscarinic antagonist-β_2-agonist for the treatment of chronic obstructive pulmonary disease. *J. Med. Chem.*, **54**, 6998–7002.

241. Tejero, I., Huertas, I., González-Lafont, A., Lluch, J.M., and Marquet, J. (2005) A fast radical chain mechanism in the polyfluoroalkoxylation of aromatics through NO_2 group displacement. Mechanistic and theoretical studies. *J. Org. Chem.*, **70**, 1718–1727.

242. Kuriyama, M., Hamaguchi, N., and Onomura, O. (2012) Copper(II)-catalyzed monoarylation of vicinal diols with diaryliodonium salts. *Chem. Eur. J.*, **18**, 1591–1594.

243. Arca, V., Paradisi, C., and Scorrano, G. (1990) Competition between radical and nonradical reactions of halonitrobenzenes in alkaline alcoholic solutions. *J. Org. Chem.*, **55**, 3617–3621.

244. Shirakawa, E., Zhang, X., and Hayashi, T. (2011) Mizoroki–Heck-type reaction mediated by potassium *tert*-butoxide. *Angew. Chem. Int. Ed.*, **50**, 4671–4674.

245. Yamamoto, Y., Takuma, R., Hotta, T., and Yamashita, K. (2009) Synthesis of 2,5-dihydrofuran-fused quinones from ether-tethered diiododiyne. *J. Org. Chem.*, **74**, 4324–4328.

246. Paradisi, C., Quintily, U., and Scorrano, G. (1983) Anion activation in the synthesis of ethers from oxygen anions and 1-chloro-4-nitrobenzene. *J. Org. Chem.*, **48**, 3022–3026.

247. Sekiguchi, S. and Okada, K. (1975) Aromatic nucleophilic substitution. V. Confirmation of the spiro Janovsky complex in base-catalyzed rearrangement of *N*-acetyl-β-aminoethyl-2,4-dinitrophenyl ether with simultaneous migration of acetyl group. *J. Org. Chem.*, **40**, 2782–2786.

248. Shafir, A., Lichtor, P.A., and Buchwald, S.L. (2007) *N*- versus *O*-arylation of aminoalcohols: orthogonal selectivity in copper-based catalysts. *J. Am. Chem. Soc.*, **129**, 3490–3491.

249. Vorogushin, A.V., Huang, X., and Buchwald, S.L. (2005) Use of tunable ligands allows for intermolecular Pd-catalyzed C–O bond formation. *J. Am. Chem. Soc.*, **127**, 8146–8149.

250. Wu, X., Fors, B.P., and Buchwald, S.L. (2011) A single phosphine ligand allows palladium-catalyzed intermolecular C–O bond formation with secondary and primary alcohols. *Angew. Chem. Int. Ed.*, **50**, 9943–9947.

251. Kataoka, N., Shelby, Q., Stambuli, J.P., and Hartwig, J.F. (2002) Air stable, sterically hindered ferrocenyl dialkylphosphines for palladium-catalyzed C–C, C–N, and C–O bond-forming cross-couplings. *J. Org. Chem.*, **67**, 5553–5566.

252. Torraca, K.E., Huang, X., Parrish, C.A., and Buchwald, S.L. (2001) An efficient intermolecular palladium-catalyzed synthesis of aryl ethers. *J. Am. Chem. Soc.*, **123**, 10770–10771.

253. Eichman, C.C. and Stambuli, J.P. (2009) Zinc-mediated palladium-catalyzed formation of carbon–sulfur bonds. *J. Org. Chem.*, **74**, 4005–4008.

254. Adams, R. and Ferretti, A. (1959) Thioethers from halogen compounds and cuprous mercaptides. II. *J. Am. Chem. Soc.*, **81**, 4927–4931.

255. Kreis, M. and Bräse, S. (2005) A general and efficient method for the synthesis of silyl-protected arenethiols from aryl halides or triflates. *Adv. Synth. Catal.*, **47**, 313–319.

256. Fernández Rodríguez, M.A. and Hartwig, J.F. (2010) One-pot synthesis of unsymmetrical diaryl thioethers by palladium-catalyzed coupling of two aryl bromides and a thiol surrogate. *Chem. Eur. J.*, **16**, 2355–2359.

257. Fernández Rodríguez, M.A. and Hartwig, J.F. (2009) A general, efficient, and functional-group-tolerant catalyst system for the palladium-catalyzed thioetherification of aryl bromides and iodides. *J. Org. Chem.*, **74**, 1663–1672.

258. Sayah, M. and Organ, M.G. (2011) Carbon–sulfur bond formation of challenging substrates at low temperature by using Pd–PEPPSI-IPent. *Chem. Eur. J.*, **17**, 11719–11722.

259. Rout, L., Sen, T.K., and Punniyamurthy, T. (2007) Efficient CuO-nanoparticle-catalyzed C–S cross-coupling of thiols with iodobenzene. *Angew. Chem. Int. Ed.*, **46**, 5583–5586.

260. Baldovino-Pantaleón, O., Hernández-Ortega, S., and Morales-Morales, D. (2006) Alkyl- and arylthiolation of aryl halides catalyzed by fluorinated bis-imino-nickel NNN pincer complexes $[NiCl_2\{C_5H_3N\text{-}2,6\text{-}(CHNAr_f)_2\}]$. *Adv. Synth. Catal.*, **348**, 236–242.

261. Shaw, J.E. (1991) Preparation of thiophenols from unactivated aryl chlorides and sodium alkanethiolates in *N*-methyl-2-pyrrolidone. *J. Org. Chem.*, **56**, 3728–3729.

262. Maiolo, F., Testaferri, L., Tiecco, M., and Tingoli, M. (1981) Fragmentation of aryl alkyl sulfides. A simple, one-pot synthesis of polymercaptobenzenes from polychlorobenzenes. *J. Org. Chem.*, **46**, 3070–3073.

263. Gryko, D.T., Clausen, C., and Lindsey, J.S. (1999) Thiol-derivatized porphyrins

for attachment to electroactive surfaces. *J. Org. Chem.*, **64**, 8635–8647.

264. Edinberry, M.N., Gymer, G.E., and Jevons, S. (1981) Antifungal pyridine-2-thiones. GB Patent 2053189.

265. Wang, B., Graskemper, J.W., Qin, L., and DiMagno, S.G. (2010) Regiospecific reductive elimination from diaryliodonium salts. *Angew. Chem. Int. Ed.*, **49**, 4079–4083.

266. Zhong, B., Al-Awar, R.S., Shih, C., Grimes, J.H., Vieth, M., and Hamdouchi, C. (2006) Novel route to the synthesis of 4-quinolyl isothiocyanates. *Tetrahedron Lett.*, **47**, 2161–2164.

267. Ke, F., Qu, Y., Jiang, Z., Li, Z., Wu, D., and Zhou, X. (2011) An efficient copper-catalyzed carbon–sulfur bond formation protocol in water. *Org. Lett.*, **13**, 454–457.

268. Maloney, K.M., Nwakpuda, E., Kuethe, J.T., and Yin, J. (2009) One-pot iodination of hydroxypyridines. *J. Org. Chem.*, **74**, 5111–5114.

269. Lacour, M.-A., Zablocka, M., Duhayon, C., Majoral, J.-P., and Taillefer, M. (2008) Efficient phosphorus catalysts for the halogen-exchange (halex) reaction. *Adv. Synth. Catal.*, **350**, 2677–2682.

270. Sun, H. and DiMagno, S.G. (2006) Room-temperature nucleophilic aromatic fluorination: experimental and theoretical studies. *Angew. Chem. Int. Ed.*, **45**, 2720–2725.

271. Franzke, A. and Pfaltz, A. (2008) Synthesis of functionalized borate building blocks for the anionic derivatization of neutral compounds. *Synthesis*, 245–252.

272. Monopoli, A., Cotugno, P., Cortese, M., Calvano, C.D., Ciminale, F., and Nacci, A. (2012) Selective *N*-alkylation of arylamines with alkyl chloride in ionic liquids: scope and applications. *Eur. J. Org. Chem.*, **2012**, 3105–3111.

273. Pan, J., Wang, X., Zhang, Y., and Buchwald, S.L. (2011) An improved palladium-catalyzed conversion of aryl and vinyl triflates to bromides and chlorides. *Org. Lett.*, **13**, 4974–4976.

274. Jian, H. and Tour, J.M. (2005) Preparative fluorous mixture synthesis of diazonium-functionalized oligo(phenylene vinylene)s. *J. Org. Chem.*, **70**, 3396–3424.

275. Maggini, M., Passudetti, M., Gonzales-Trueba, G., Prato, M., Quintily, U., and Scorrano, G. (1991) A general procedure for the fluorodenitration of aromatic substrates. *J. Org. Chem.*, **56**, 6406–6411.

276. Maimone, T.J., Milner, P.J., Kinzel, T., Zhang, Y., Takase, M.K., and Buchwald, S.L. (2011) Evidence for in situ catalyst modification during the Pd-catalyzed conversion of aryl triflates to aryl fluorides. *J. Am. Chem. Soc.*, **133**, 18106–18109.

277. Kuduk, S.D., DiPardo, R.M., and Bock, M.G. (2005) Tetrabutylammonium salt induced denitration of nitropyridines: synthesis of fluoro-, hydroxy-, and methoxypyridines. *Org. Lett.*, **7**, 577–579.

278. Janmanchi, K.M. and Dolbier, W.R. (2008) Highly reactive and regenerable fluorinating agent for oxidative fluorination of aromatics. *Org. Process Res. Dev.*, **12**, 349–354.

279. Milne, J.E., Storz, T., Colyer, J.T., Thiel, O.R., Seran, M.D., Larsen, R.D., and Murry, J.A. (2011) Iodide-catalyzed reductions: development of a synthesis of phenylacetic acids. *J. Org. Chem.*, **76**, 9519–9524.

280. Nielsen, A.T., Chafin, A.P., and Christian, S.L. (1984) Nitrocarbons. 4. Reaction of polynitrobenzenes with hydrogen halides. Formation of polynitrohalobenzenes. *J. Org. Chem.*, **49**, 4575–4580.

281. Cottet, F. and Schlosser, M. (2004) Logistic flexibility in the preparation of isomeric halopyridinecarboxylic acids. *Tetrahedron*, **60**, 11869–11874.

282. Wannberg, J., Wallinder, C., Ünlüsoy, M., Sköld, C., and Larhed, M. (2013) One-pot, two-step, microwave-assisted palladium-catalyzed conversion of aryl alcohols to aryl fluorides via aryl nonaflates. *J. Org. Chem.*, **78**, 4184–4189.

283. Tang, P., Wang, W., and Ritter, T. (2011) Deoxyfluorination of phenols. *J. Am. Chem. Soc.*, **133**, 11482–11484.

284. Lui, N., Marhold, A., and Rock, M.H. (1998) Liquid-phase decarboxylation of aromatic haloformates: a new access to chloro- and fluoroaromatics. *J. Org. Chem.*, **63**, 2493–2496.

Epilogue

Economics, Politics, and the Quality of Chemical Research

Prosperity

In the ''first world,'' we enjoy a never-seen degree of prosperity. We spend only a pittance of our salaries on basic needs, and, although an ever-increasing number of people are living off the government, our economies are still eking out some growth. We even spend taxpayers' money on research without any practical use (astronomy, ancient history, paleontology, literary studies, etc.). Opinions may diverge on the pertinence of spending everybody's money on satisfying the curiosity of a few (including mine), but most will agree that prosperity is a good thing, worth contributing to and enhancing further.

What is prosperity and where does it come from? Prosperity means a broad choice of inexpensive, high-quality products for everyone, and is the consequence of high productivity and free trade. Sophisticated tools, free access to information, and free flow of ideas enable each person in a prosperous country to generate high value with little effort, and employees in the private sector of prosperous societies do so. Free trade enables specialization and mass production, and lowers the prices of all products through economies of scale. High productivity and free trade give us spare time to learn new skills and to develop still more sophisticated production processes and cheaper and better products. Therefore, most of us spend less than a few hours per day to produce the food and clothes we need. Fifty years ago, food and clothes represented a much larger fraction of our expenses, owing to lower productivity and more trade barriers.

Increasing productivity naturally brings about deflation. Most people find this natural deflation unbearably painful, in particular the falling salaries. To keep everybody happy, labor unions and central banks actively debase our currencies and thereby cause nominal prices and salaries to rise (inflation), creating the illusion of increasing wealth. Real prices, however, relentlessly fall in prosperous, technologically advancing societies.

Why does productivity rise and poverty decline in developed countries? The main driving force is competition. To earn money, companies must provide their products at a competitive (=low) price. Their earnings are the difference between production costs and sales income (net margin), and each company in a free, capitalistic society will strive to lower their production costs and gain market share by decreasing the price of their products while improving their quality and

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attractiveness for the customers. Forced competition, combined with a sensible patent and copyright law, and the protection of private property rights will naturally bring about technological progress, falling prices, and prosperity for everyone. I say ''forced competition,'' because in free societies government-endorsed price fixing (e.g., minimum wages,[1)] tariffs, other protectionist measures) and monopolies will pop up spontaneously and reduce prosperity unless laws avert this. Even democracies tend to implement protectionist and other prosperity-diminishing schemes, not because politicians are ignorant of the absurdity of these measures but because protectionism is popular and politicians are forced to do what the majority wants [1, 2]. Protectionism and mercantilism[2)] can probably only be curtailed by a better economic education.

Interestingly, growing productivity does not lead to fewer jobs in general, but to fewer low-skill jobs (of low value generation) and more high-skill jobs (of high value generation). Thus, there are usually plenty of jobs in countries with respect for property and contract. Because of our innate drive to avoid physical efforts and unpleasant work, and thus to develop better technologies, we are condemned to live in a world of continuously disappearing low-skill jobs, falling real prices, and increasing demand for high-skill workers. In countries where the disappearance of low-skill jobs is artificially suppressed, no qualified workers are available for high-skill jobs (they have low-skill jobs and no incentive to seek a higher qualification), and the degree of prosperity lags behind that of more liberal countries.

The low quality and high price of governmental ''products'' as well as the low productivity of governmental institutions is a direct consequence of the lack of competition. The government has a local monopoly, and monopolies, as any economic entity, aim to lower their expenses (by reducing the quality of their products) and increase their income (by raising the prices). This would put any private enterprise out of business, but because nobody competes with the

1) Salaries are the price of labor, and should be freely established by supply and demand, as any other price. Of course, salaries cannot be a function of the employee's financial needs, but must correspond to the market value of one's contributions. Price-fixing of salaries will keep them from attaining the optimal level (the level at which employment is maximized), and will usually reduce employment. H. Hazlitt, Economics in One Lesson, Ludwig von Mises Institute, Auburn, Alabama 2008.

2) Mercantilism is the mistaken notion that exports are good for the prosperity of a country and imports are bad, that is, that money is more valuable than goods or services. Mercantilism, the main cause of protectionism (and the US depression of the 1930s, numerous wars, and poverty in the third world), was refuted by Adam Smith, Frédéric Bastiat, and others long ago. By establishing trade barriers to ''protect'' inefficient local producers, the whole country becomes poorer: citizens have to pay higher prices, which leaves them with less money to spend on other things, and producers suffer because of the lower purchasing power of their customers and the smaller market for their goods. Trade barriers prevent efficient mass production and economies of scale, making everything more expensive but nobody richer. Prosperity and strong companies arise when people are allowed to specialize, find their comparative advantage, and purchase the products of *their* choice, no matter where these were produced. It is prosperity-destroying and nobody's duty to protect incompetent producers and their squandering of resources. C. L. Hooper, Mercantilism Lives. April 4, **2011**. Library of Economics and Liberty. *www.econlib.org/library/Columns/y2011/Hoopermercantilism.html*.

government, it can get away with this revenue-enhancing behavior. The only option for unhappy citizens is to leave the country.

A lot of people and companies actually do this, and a scary response of politicians is to enhance international cooperation, and ''harmonize'' laws and taxes (think European Union). Thereby the little competitive pressure on governments to perform, caused by their citizens and companies leaving the country, vanishes, and the cooperating countries turn into dictatorships, with politicians doing as they please. In fact, international ''tax harmonization'' is similar to price fixing between companies, and detrimental for prosperity. We need more international competition, also between governments, not less.

So much for economic essentials, which are, however, often misunderstood. Despite 100 years of failed socialistic experiments and millions in deep poverty because of political meddling and obstruction of free markets and competition, some people still view politicians as benevolent, honest, and wise, and believe that, if such politicians enjoy unrestricted power, society will flourish. They are wrong. The history of mankind is a history of oppression and plunder of the powerless by the powerful.

Slavery and Freedom

When appraising economic systems throughout history, it is not just a matter of their economic performance but also of the degree of justice and freedom for every citizen and of the protection of minorities. The Roman Empire or North America until 1865 may be considered economically sound, but being based on slavery these were inherently unjust and ethically improper. Because a large part of the population did not enjoy freedom, these economies did not attain their full potential of prosperity growth. Just like a free market will provide the optimal price for each good (the price at which the turnover of the good is highest), freedom to choose the profession and business one is best suited for will lead to the most productive society and fastest prosperity growth.

Slavery was abolished throughout the world during the nineteenth century, but a disguised form of slavery was reintroduced in many countries after the Second World War: the welfare state. And just as the abolition of slavery was unthinkable before the nineteenth century, the welfare state has become dogma today.

The modern welfare state is a system of shielding the individual from the consequences of his decisions, of penalizing individual performance-driven affluence, of systematic expropriation of companies and large parts of the population, of a dwindling right to privacy, and of politicians meddling in our choices of when and what to buy, when to work, and how many children to raise. Instead of doing their job (serving the people), many politicians consider their mission to tell us what to do and to control our lives. Governmental employees enjoy a high degree of job security, little performance pressure, generous pensions, and numerous privileges, all financed by the private sector and by loans from future generations of workers and companies [3]. In most countries of the EU, the highest tax bracket

plus ''social contributions'' exceed 50% of income. Of the leftovers, citizens have to pay up to 25% (Scandinavia, 2013) of value-added tax on all their purchases, and for certain items even more. People with high-skill jobs in welfare states work more than 20 years exclusively for feeding public employees and for financing unrealistic promises made by former, never accountable politicians.

Economists have been trying to figure out whether high taxes are harmful to the economic well-being of a country, but they could find no clear correlations between gross domestic product (GDP) growth and taxes or the number of governmental employees [4, 5]. It seems that, as long as taxes do not exceed a certain level, the prosperity of a country mainly depends on the degree of economic freedom [6]. Nevertheless, the numbers required for such comparisons are collected differently in each country, and it is tempting to distort them. Because the public sector is a monopoly and is not forced by competition to be efficient, countries with large public sectors will waste more resources than countries with smaller public sectors.

High taxes combined with no economic freedom, as in socialistic paradises like India, Venezuela, or Cuba, cause, unsurprisingly, rapid economic deterioration and widespread poverty. Once a socialistic majority is firmly established in a country, the return to freedom is difficult. Knowing who will vote for them (the poor), socialistic politicians will always try to impoverish a country, to increase the number of their followers and stay in power. Socialistic policies achieve just that: poverty for everybody.

One aspect economists rarely discuss is the ethical aspect of taxes. The forced dispossession of citizens is theft, and is forbidden by most constitutions. Even the most primitive rules for living together in peace consider theft a crime: for instance, the biblical Ten Commandments. The right to property must have originated early in history, as it allows for an effective collaboration among members of a group. We are a gregarious species, and our tendency to establish a rule of law and property rights within a group is probably genetic. Without property rights, everyone would have to spend valuable time and efforts to protect himself from his neighbors, and no peaceful collaboration among people would be possible. Each of us experiences deep discomfort and a diminished quality of life at the prospect of being robbed or having to pay a price dependent not on what we receive but on what we earn. Outsized cash needs of a thief do not make his stealing less criminal. There are no limits to the money politicians can spend on bribing voters.

The creeping abolishment of property rights by the welfare state (i.e., the legalization of theft) is a return to prehistoric barbarism. It undermines social coherence and continuously diminishes the resources available to enhance prosperity, by transferring them from the efficient private sector to the inefficient public sector. Because the rule of law no longer protects the working citizen in advanced welfare states, he must protect himself by increasing his efforts to minimize or evade taxes. He spends hours not only poring over excessively complex tax forms but also on figuring out what to tell and what not to tell, instead of enjoying his life or doing something productive. Thousands of working hours and creative efforts are wasted.

Enter the industry of tax avoidance and minimization: lawyers, bankers, tax consultants, investment managers, tax-self-help-guide writers, thousands of smart

people doing nothing but to lighten the tax burden of ordinary citizens. Again, this is an economic disaster. Together with the tax collectors (and most politicians), these people produce nothing, and do not add to our prosperity. Well, yes, one could argue that the tax minimization industry enhances prosperity by increasing the wealth and purchasing power of their clients, but the country would be better off by just lowering the tax burden and thereby making tax minimization less worthwhile. A lot of productive resources could be freed up, to develop new drugs, new solar panels, cheaper food, clothes, and so on, and thus increase everybody's prosperity by lowering prices. As Ronald Reagan said (and did) [7], the best way for a government to increase its tax revenue is to cut taxes. By liberating the US economy from the stranglehold of excessive bureaucracy and taxes, he set off two decades of strong prosperity growth and the formation of many innovative, now world-leading companies and millions of new jobs. Similarly, the partial dismantling of global trade barriers during the last 30 years (the ''globalization'') has boosted prosperity in all the participating countries and lifted millions out of poverty. There must be a positive correlation between freedom, ethical correctness, and prosperity. And the less intrusive a government, the more ethically acceptable it is.

The Quality of Chemical Research

When scanning chemical journals, one gets the impression that many chemists are more focused on increasing their number of publications than on solving relevant problems (I am not completely blameless here). Wrong incentives set by the financing institutions are the main reason for this. These boost the quick publication of irrelevant work, and pervert generations of young scientists by teaching them that science is mainly about pretentious publishing and overstating the relevance of one's projects [8]. Although excellent chemical research is being done at most universities, a number of academic research groups do not assess with sufficient objectivity the quality of their projects. So, what are ''good'' research projects?

Most readers probably live in prosperous societies, and believe to be able to afford irrelevant research. Satisfaction at work, though, increases with the perceived relevance of one's efforts, and chemists are no exception here. Moreover, in view of our current more pressing problems (devastation of the oceans, increasing antibiotic resistance of bacteria, irreversible destruction of our atmosphere, lack of universal antiviral agents, etc.) that are seriously threatening the mid-term survival of our species, nobody can afford irrelevant research today.

I would define ''good research'' as ''relevant research,'' and ''relevant'' as something that in a more or less direct way will enhance our productivity and thereby everyone's quality of life and prosperity. So, ''bad research'' would be ''irrelevant research,'' that is, research that would not affect our quality of life and prosperity in any way, and would therefore be a waste of money.

Although many relevant projects may also be commercially relevant, that does not need to be so. In fact, highly relevant research, such as the study of the ozone hole

or other anthropogenic environmental changes, are commercially meaningless but crucial to our future prosperity, and must therefore be energetically pushed and subsidized by governments.

Chemists are in a good position to enhance prosperity by increasing productivity and lowering prices. Industrial chemical research basically deals with questions like ''how can this product be produced cheaper?'' and ''how can the quality of this product be improved without increasing its costs?'' In companies reliant on proprietary materials (pharmaceuticals, agrochemicals, cosmetics, etc.), a further important question is: ''which compound or mixture of compounds will have the properties we are looking for?'' Hence, highly relevant chemical research is the development of improved (= cheaper, cleaner, safer, shorter, simpler, higher yielding, more selective) synthetic methods (not costlier alternatives) and the development of synthetic methods that enable the preparation of new classes of compounds with potentially valuable properties. Mechanistic studies can also be relevant if the resulting knowledge assists the development of improved synthetic methods or new compound classes.

Popular, irrelevant chemical research themes, often disguised and insulated from criticism as ''basic research,'' include

- new, expensive methods and reagents for preparing cheap compounds (i.e., compounds readily accessible by less costly routes);
- syntheses of irrelevant natural or unnatural products (unless the true target is new, valuable synthetic methodology);
- the study of irrelevant reaction mechanisms, kinetics, stereoselectivities, or regioselectivities.

Some critical aspects of organic synthesis that are often ignored by academic chemists, include

- the cost of the required catalyst (price is the most important quality criterion of a synthetic method);
- the recyclability of noble metal catalysts;
- the amount and type of waste generated (ideal: no waste; ok: water, CO_2, N_2, combustible organic compounds; a pain: H_2SO_4, H_3PO_4, salts of Na, K, Mg, Ca, Al, Si; unacceptable: stoichiometric amounts of transition-metal salts);
- the thermal safety and upscalability of reactions.

Concerning the last point above, in recent years the use of microwave heating and closed vials has become widespread (for reactions at temperatures above the boiling point of the solvent). New chemistries developed in closed reactors are particularly difficult to scale up, and therefore less valuable than new chemistries conducted under more realistic conditions.

So, a highly relevant area of chemical research is the modification of important organic transformations so that less expensive catalysts, reagents, and solvents are needed, less critical waste is generated, and the risk of thermal runaway events is reduced. Some specific areas of current high relevance include

- catalysts for the reduction of esters, amides, ureas, carboxylic acids, aldehydes, and ketones with hydrogen under mild conditions (hydrogen is the cheapest, environmentally most friendly reducing agent);
- catalysts for the hydrogenolytic cleavage of aliphatic carbon–heteroatom bonds under mild conditions;
- catalysts for the reductive formation of C–C bonds with hydrogen as reducing reagent;
- catalysts for the selective oxidation of organic compounds with air (e.g., olefins, alcohols, alkyl halides, or ethers to aldehydes, ketones, or carboxylic acids; hydroxylations; etherifications; halogenations; aminations; amidations; dehydrogenations; ethers to acetals or esters, methyl groups to alcohols, aldehydes, or carboxylic acids);
- C–C bond-forming reactions where only hydrogen, water, nitrogen, CO, or CO_2 are formed as byproducts;
- catalysts for the transient conversion of alcohols/enols into strong electrophiles (e.g., for the use of alcohols as alkylating reagents, of phenols as arylating reagents, for the conversion of ketones into vinyl halides or allenes, etc.);
- catalysts for S_N2 reactions (e.g., for the conversion of unreactive alkyl chlorides, alcohols, ethers, esters, thioethers, amines, etc. into other compounds by nucleophilic displacement under mild conditions);
- better software for the prediction of the outcome of reactions (regioselectivity, stereoselectivity, potential byproducts, solvent effects).

Although research can be planned, the results and their significance cannot. The impact of many scientific discoveries that caused strong boosts of prosperity could not have been foreseen. Often, disruptive, high-impact findings originate from unfashionable research subjects or from projects that challenge established views. Such projects are disliked by most peers, and can be difficult to fund. It is therefore important that chemists both in academia and industry are not pushed too hard to deliver quick ''publishable'' or lucrative results, but also get the opportunity to work on visionary, long-term, high risk–high return projects. Also, if financed by public money, these projects should be based on ambitious, worthwhile, and relevant goals.

References

1. Schwartz, P. (2013) Free Trade? Anything But … , Library of Economics and Liberty, March 4, 2013, *www.econlib.org/library/Columns/y2013/Schwartzfreetrade.html* (accessed 11 January 2014).
2. Selick, K. (2008) The Buy-Locally-Owned Fallacy, Library of Economics and Liberty, November 3, 2008, *www.econlib.org/library/Columns/y2008/Selicklocal.html* (accessed 11 January 2014).
3. F. Faust, B. W. Klöckner, *Beamte – Die Privilegierten der Nation. Wie unsere Staatsdiener kassieren, während Deutschland pleite geht.* (*Public Servants – The Privileged of Our Nation. How Our Public Employees Enrich Themselves While Germany Goes Bust*), Wiley-VCH Verlag GmbH, Weinheim 2005.

4. Posner, R. (2011) Too Many Government Workers? The Becker-Posner Blog, *www.becker-posner-blog.com/2011/09/too-many-government-workersposner.html* (accessed 11 January 2014).
5. (a) Myles, G.D. (2000) Taxation and economic growth. *Fiscal Stud.*, **21**, 141–168; (b) Hungerford, T.L. (2013) Corporate Tax Rates and Economic Growth, Economic Policy Institute, Issue Brief 364.
6. The Heritage Foundation (2013) 2013 Index of Economic Freedom, *www.heritage.org/index/book/executive-highlights* (accessed 11 January 2014).
7. Reagan, R. (1990) *An American Life: The Autobiography*, Simon & Schuster, New York.
8. Hampe, M. (2013) Science on the market: what does competition do to research? *Angew. Chem. Int. Ed.*, **52**, 6550–6551.

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