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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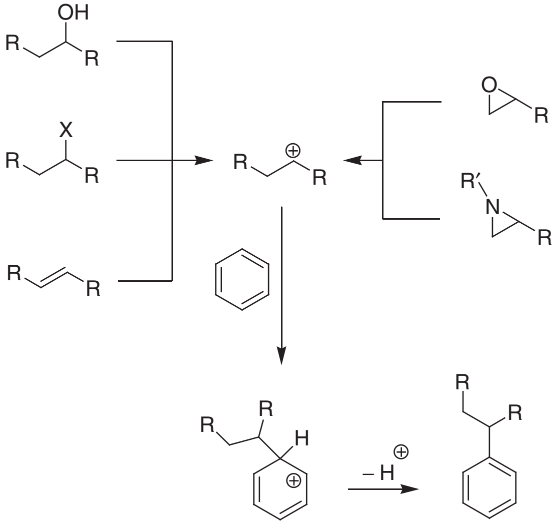


Scheme 1.1 Mechanism of the Friedel–Crafts alkylation.

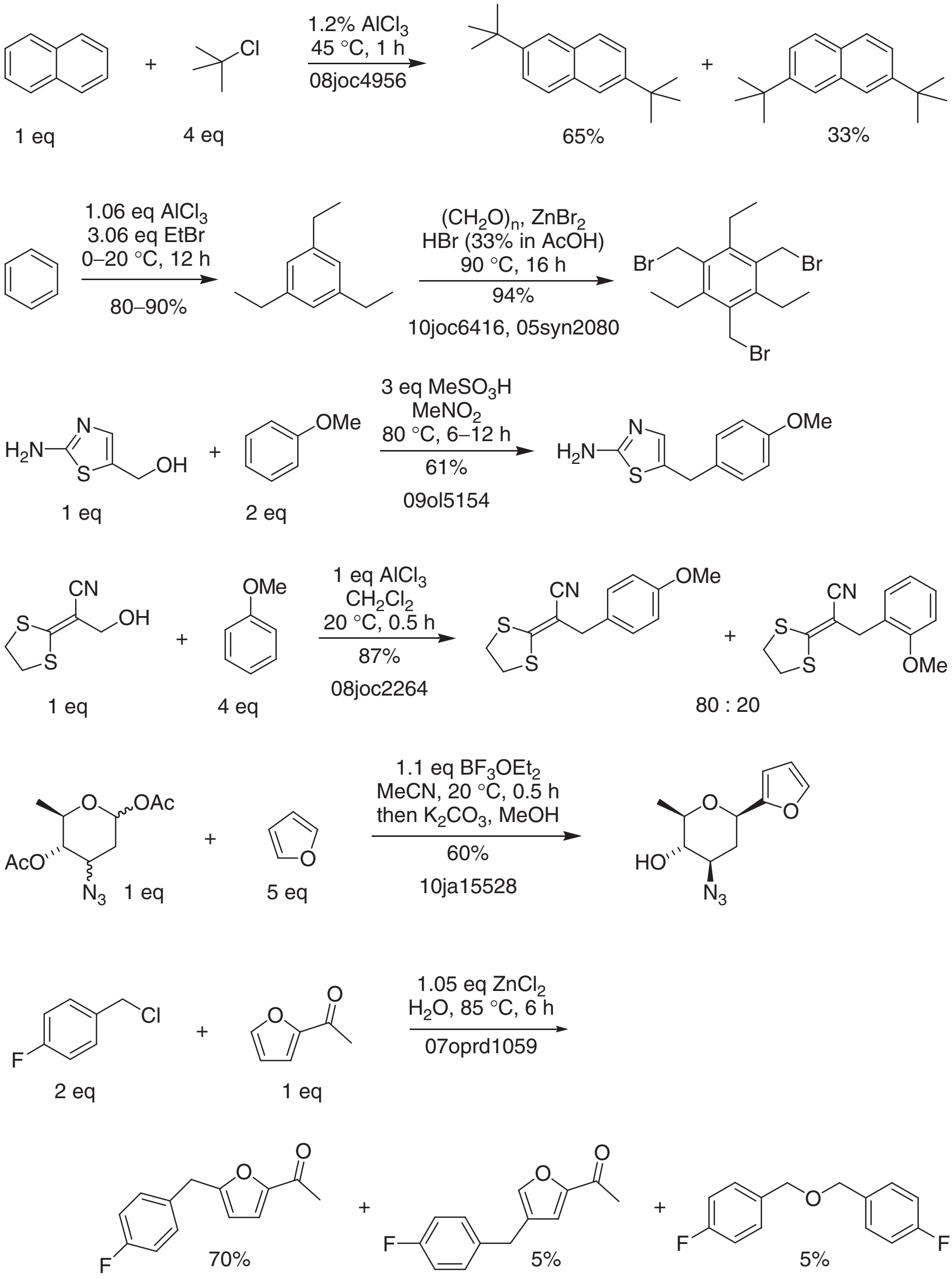
cyclic configurationally stable cations, arylations can occur with retention of configuration [18].

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].

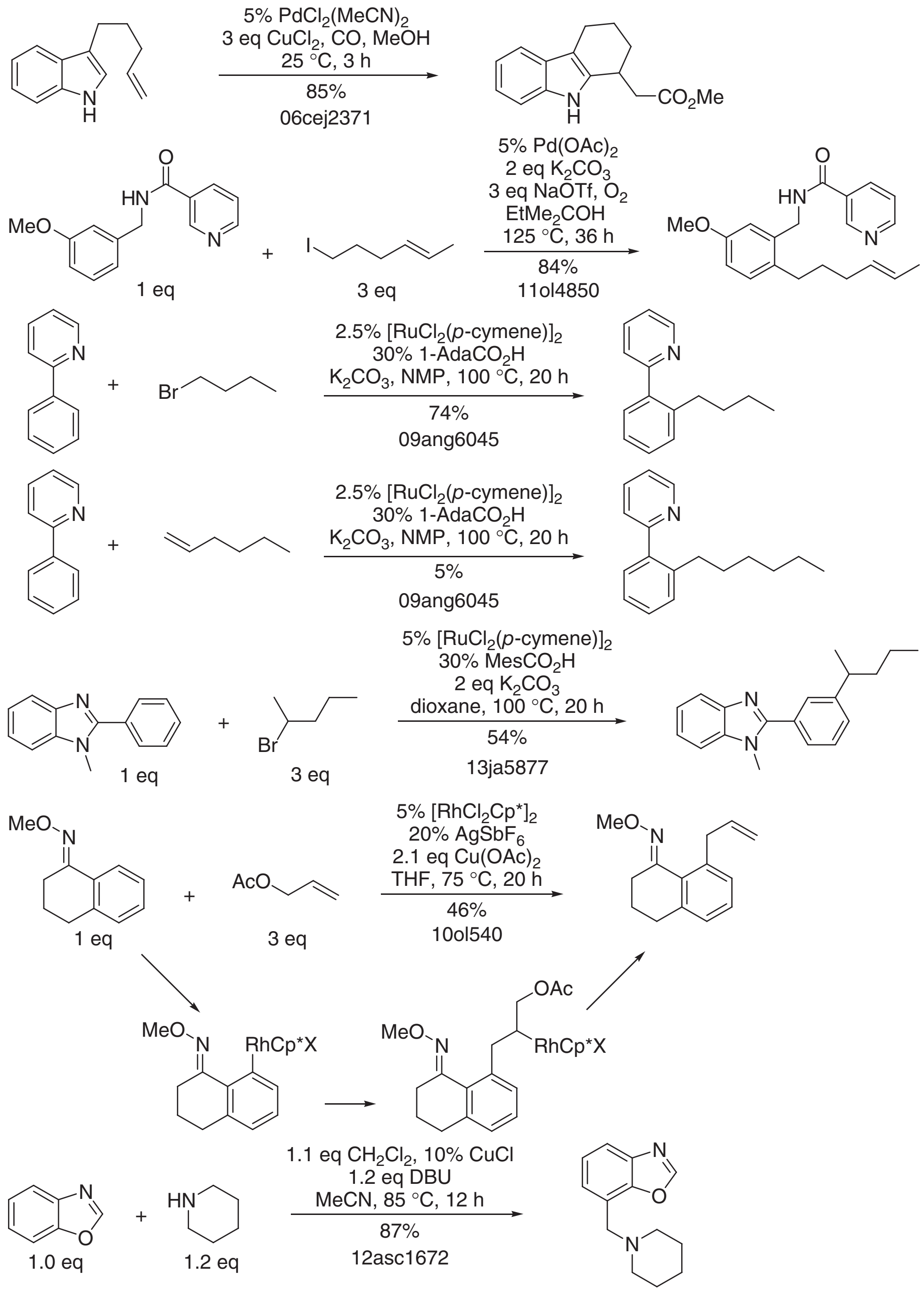
1.1.1
Catalysis by Transition-Metal Complexes

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).

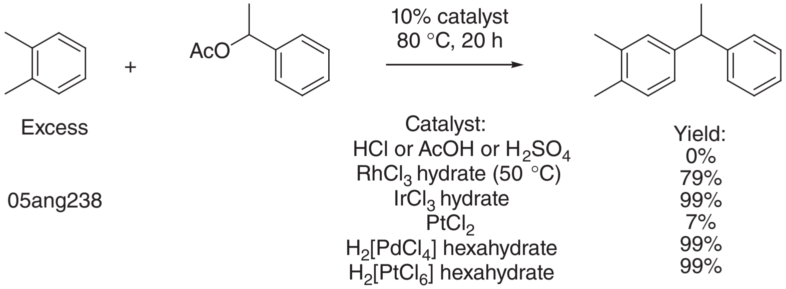
Reactions where carbocation formation is the slowest (rate-determining) step can be catalyzed by any compound capable of stabilizing the intermediate carbocation (and thereby promote its formation). This form of catalysis should be most pronounced in nonpolar solvents, in which free carbocations are 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

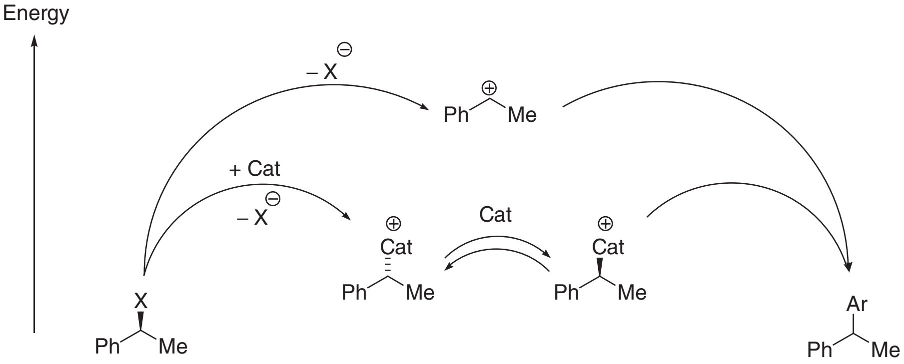


Scheme 1.2 Examples of Friedel–Crafts alkylations [11–17].



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





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

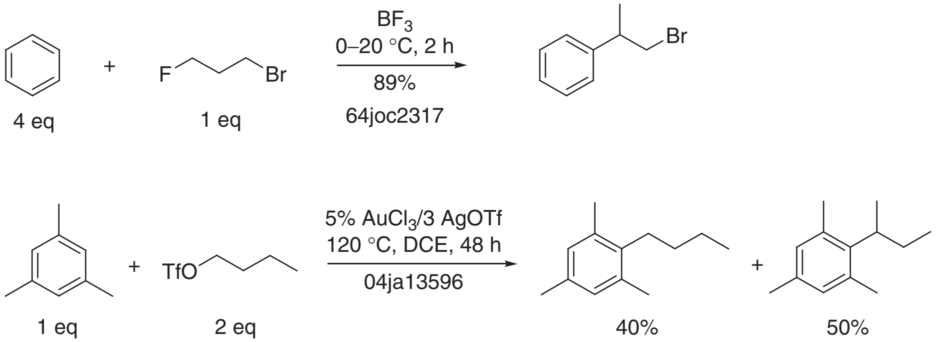
transient formation of benzylic metal complexes (Scheme 1.4). Because racemization is also observed in these instances, the intermediate complexes are likely to undergo fast transmetallation. Ru-based catalysts have been developed that enable the preparation of enantiomerically enriched alkylbenzenes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

1.1.2
Typical Side Reactions

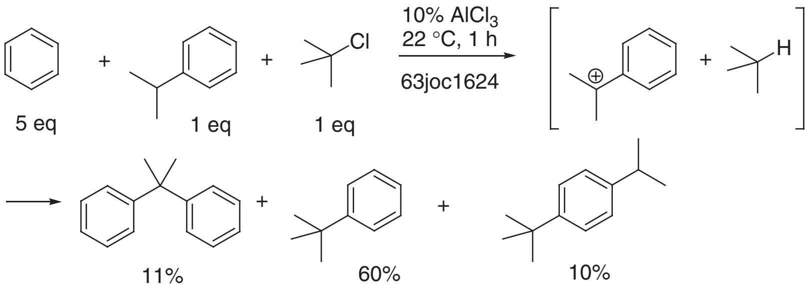
The rearrangement of intermediate carbocations is a common side reaction in Friedel–Crafts chemistry (Scheme 1.5). Rearrangements can sometimes be avoided with the aid of transition-metal-based catalysts, because the intermediate complexes are less reactive than uncomplexed carbocations.

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).

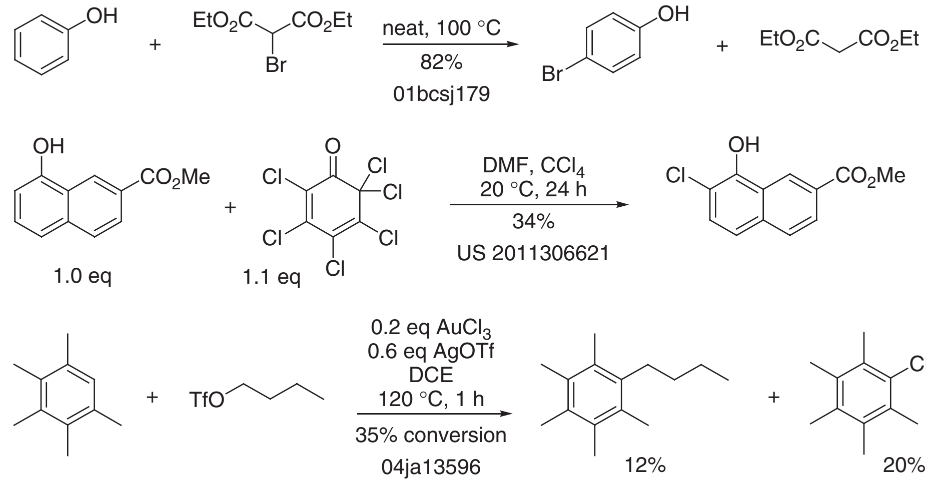
When using noble metal halides as catalysts, or α-haloketones, α-haloesters (Section 1.3.5), or perhaloalkanes as electrophiles, arenes may undergo halogenation instead of alkylation (Scheme 1.7). Alkyl halides with the halogen



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].

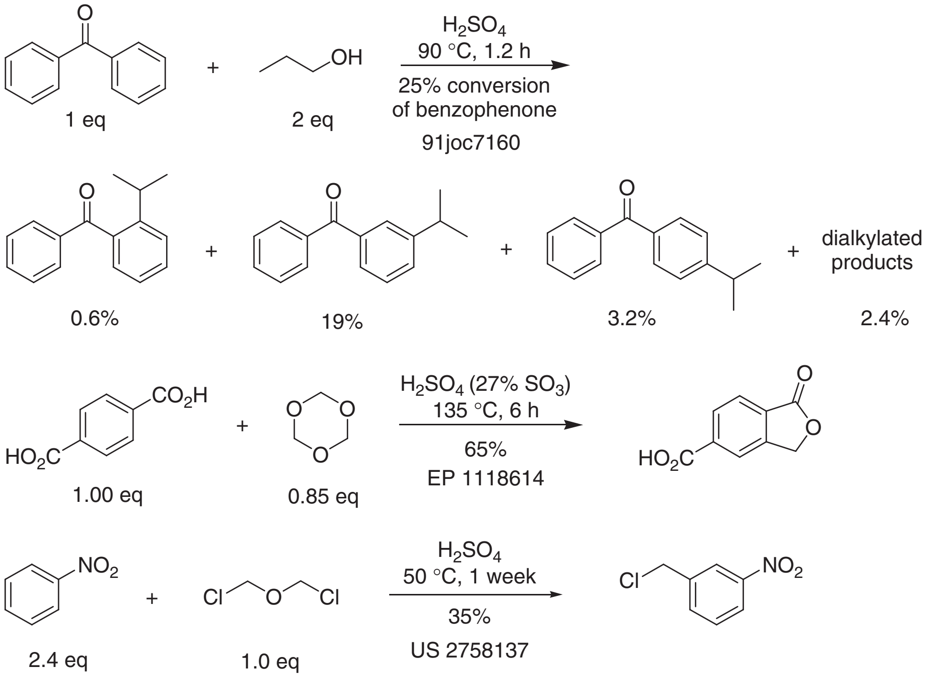
bound to good leaving groups (positions where a carbanion would be stabilized) are electrophilic halogenating reagents.

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

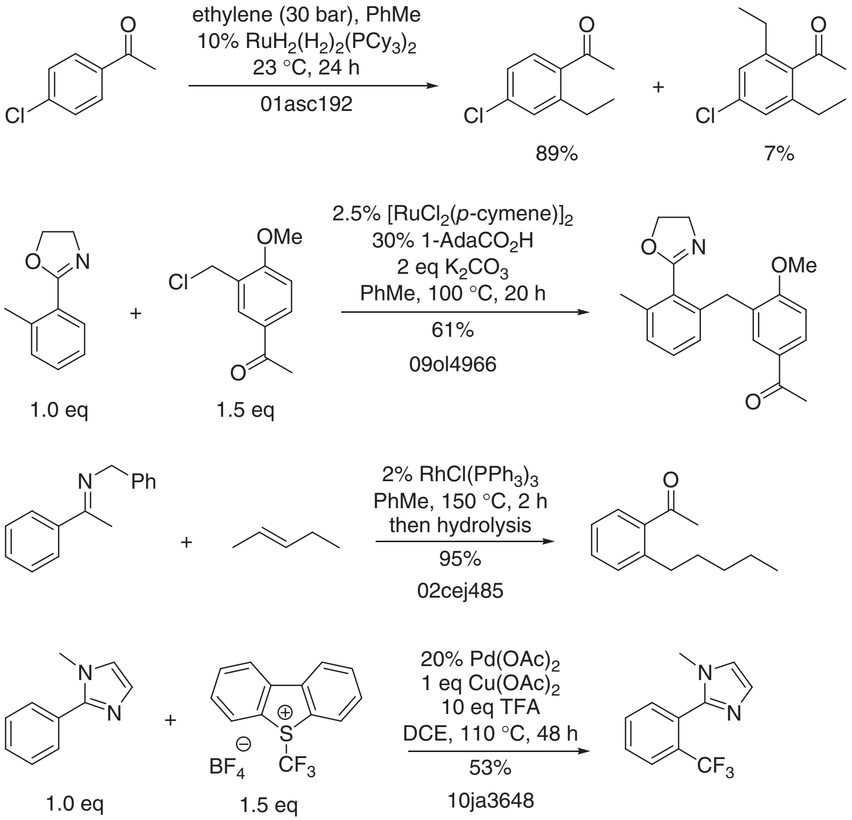
1.2.1
Electron-Deficient Arenes

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).



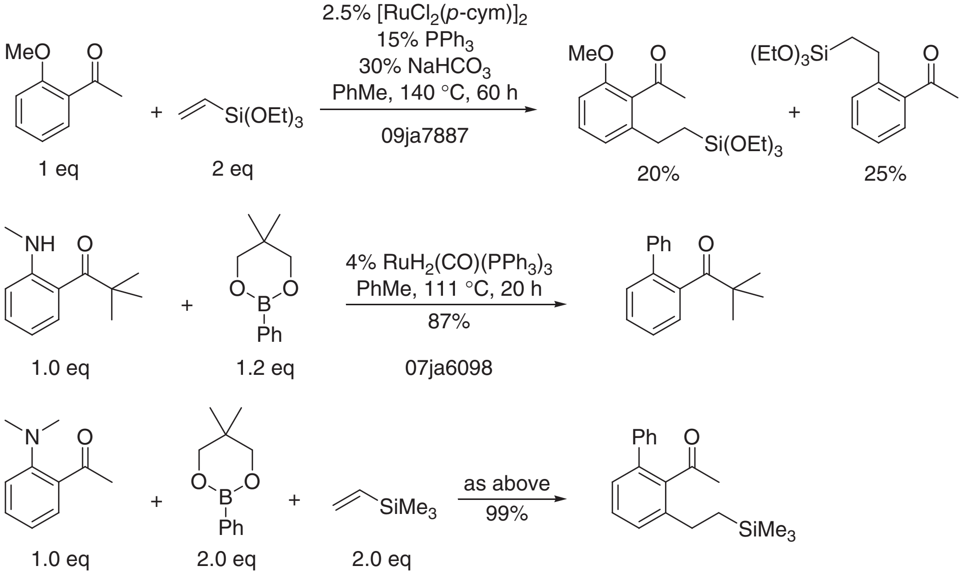
Scheme 1.8 Friedel–Crafts alkylation of electron-deficient arenes [36–38].

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].

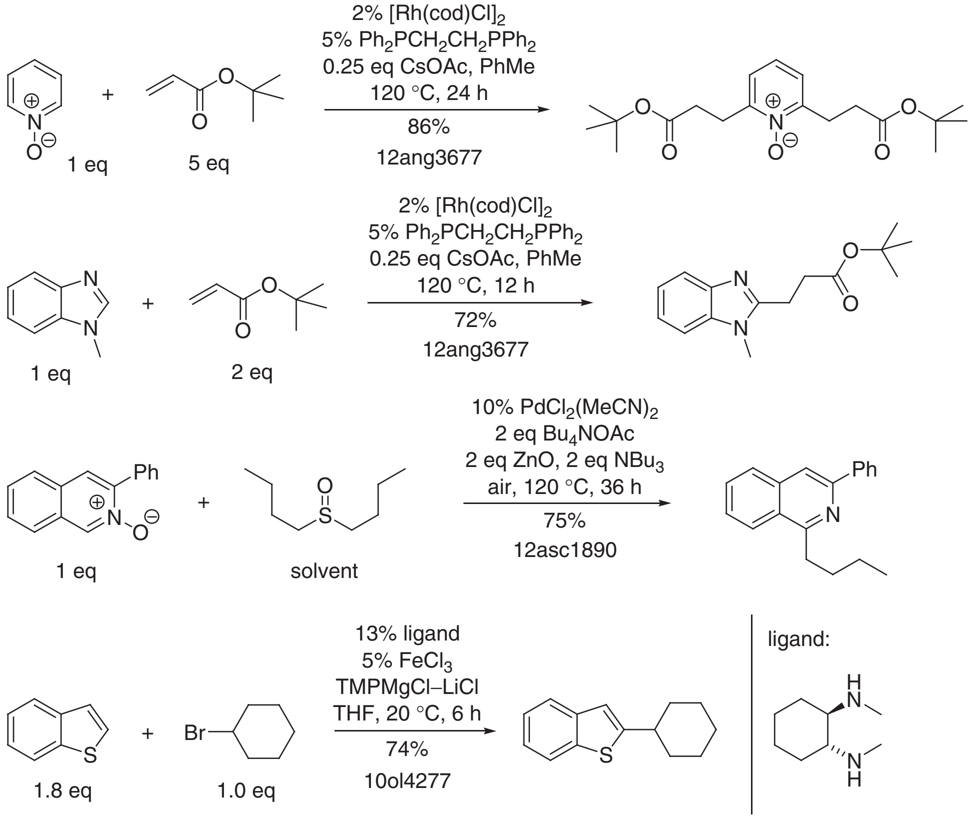
Some heteroarenes, such as pyridine *N*-oxides, thiazoles, or imidazoles, are strongly C–H acidic, and can be metallated catalytically even without chelate formation. In the examples in Scheme 1.11, the intermediates are, in fact, metal carbene complexes.

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.

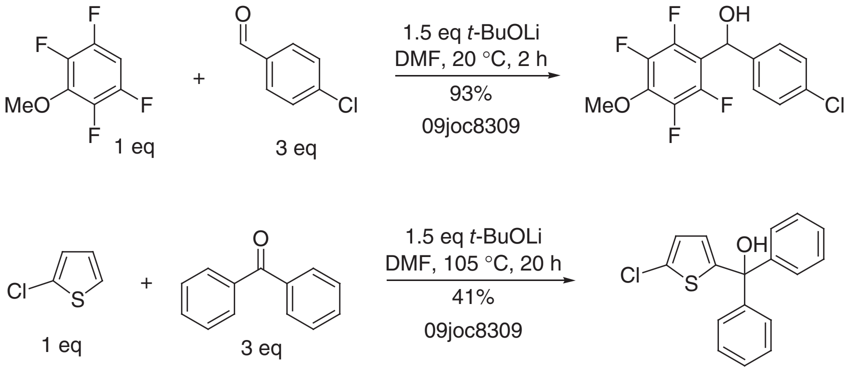
Electron-deficient arenes and heteroarenes, such as pyridinium salts, can react with carbon-centered, electron-rich radicals. These can be generated from alkanes, alkyl halides, carboxylic acids, and some diacylperoxides [58] (Scheme 1.13), or by oxidation of boranes [59]. The regioselectivity of such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

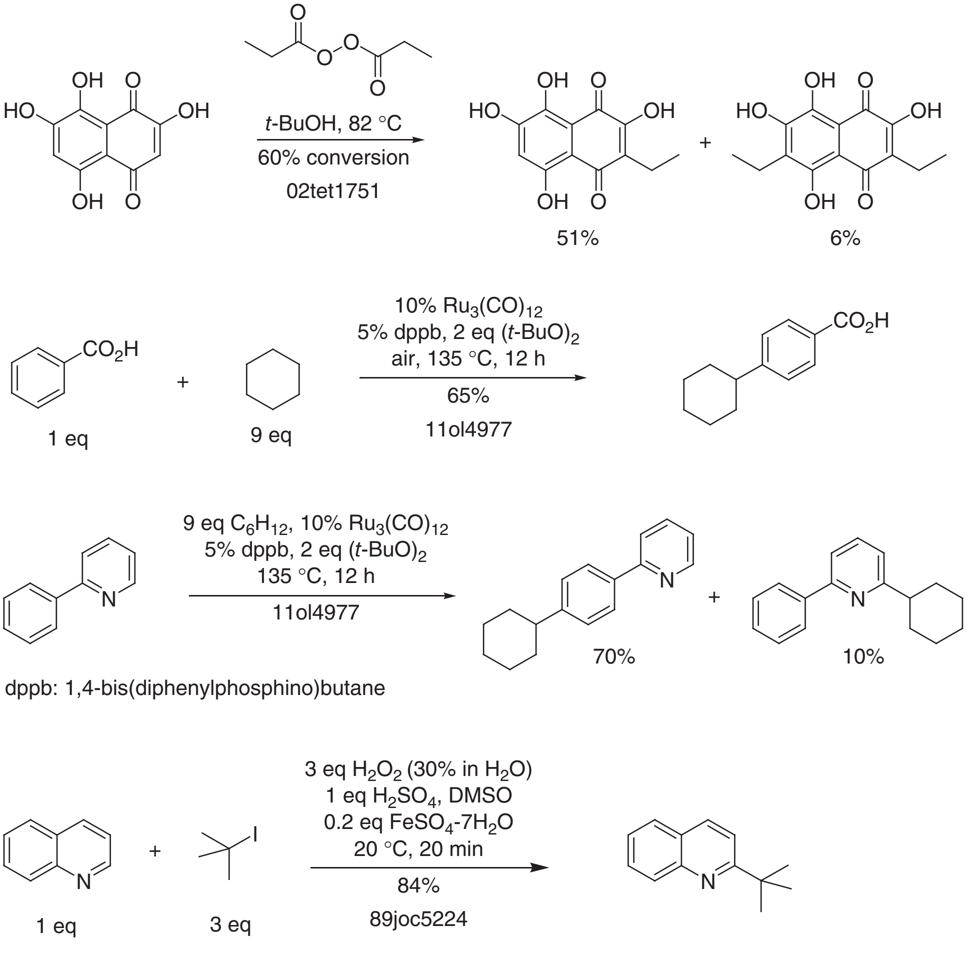


Scheme 1.12 Metallation and alkylation of C–H acidic arenes [57].

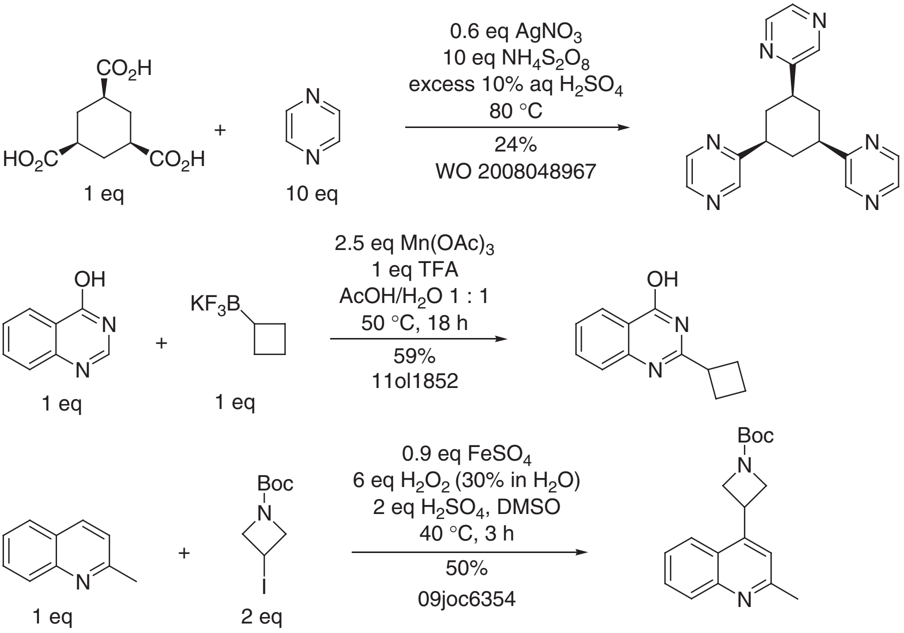
are tautomers of enones and may themselves act as electrophiles (see below). Moreover, phenols readily dimerize to biaryls in the presence of oxidants.

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].

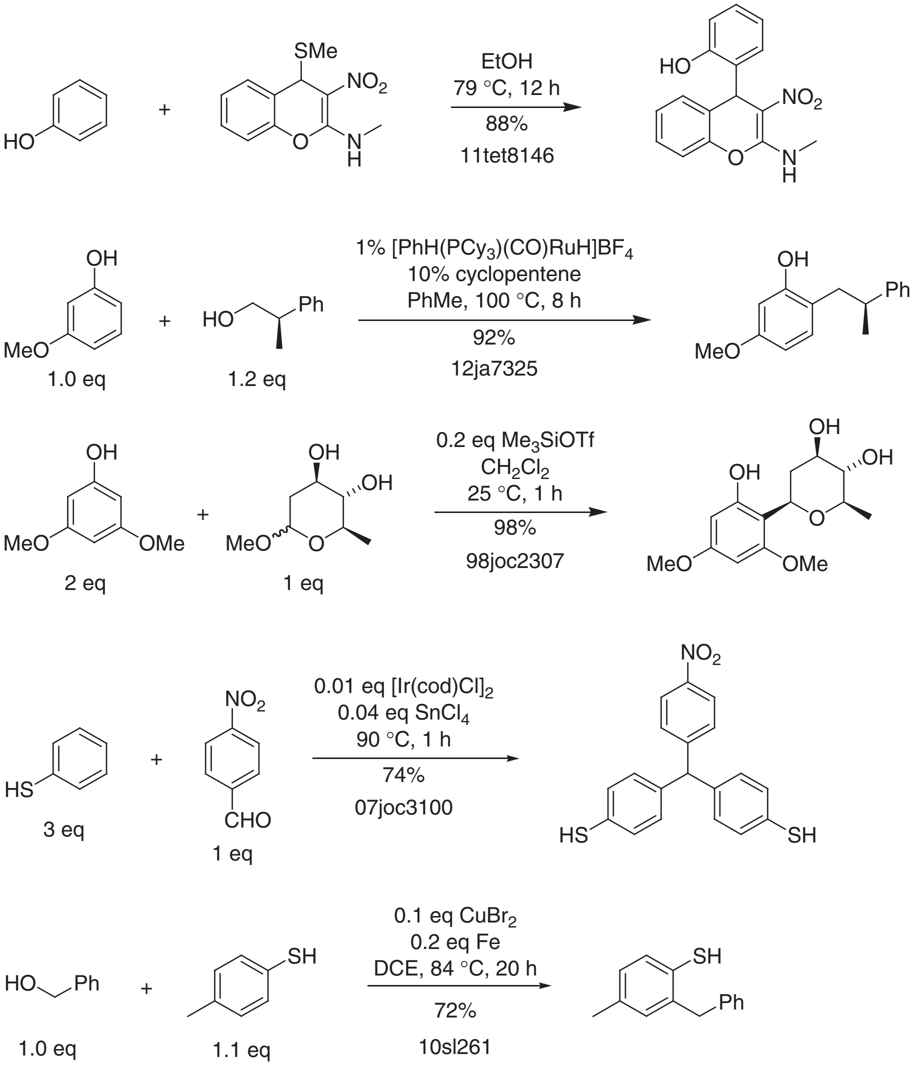


Scheme 1.13 (*Continued*)

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.

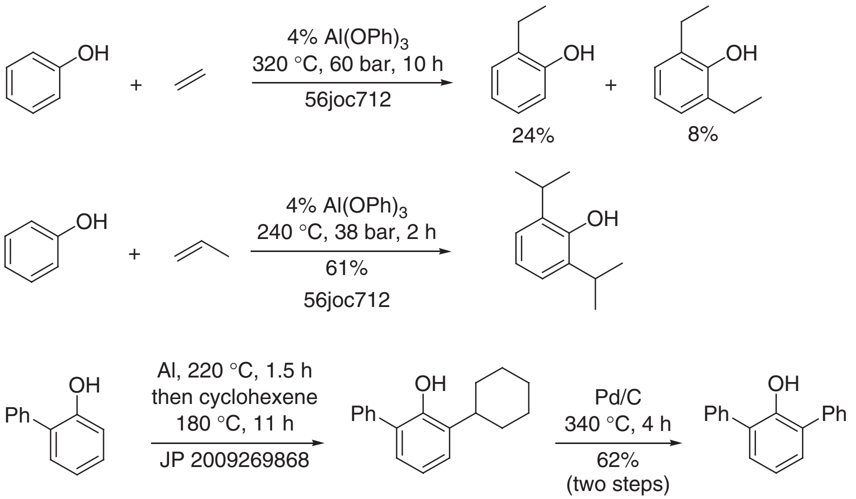


Scheme 1.14 C-Alkylation of phenols and thiophenols under acidic conditions [67–71].

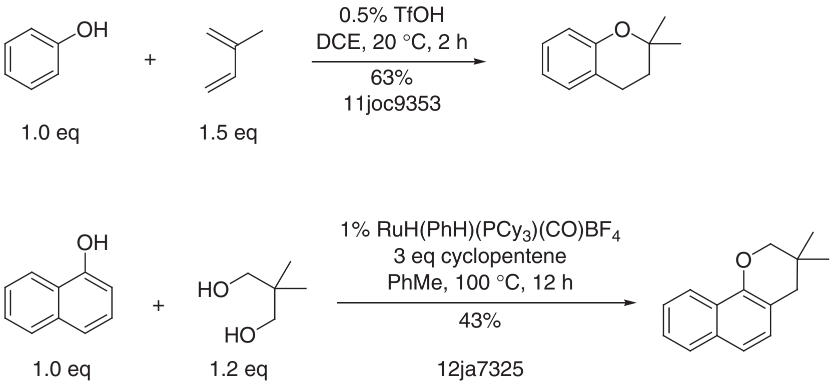
1.2.3
Anilines

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].

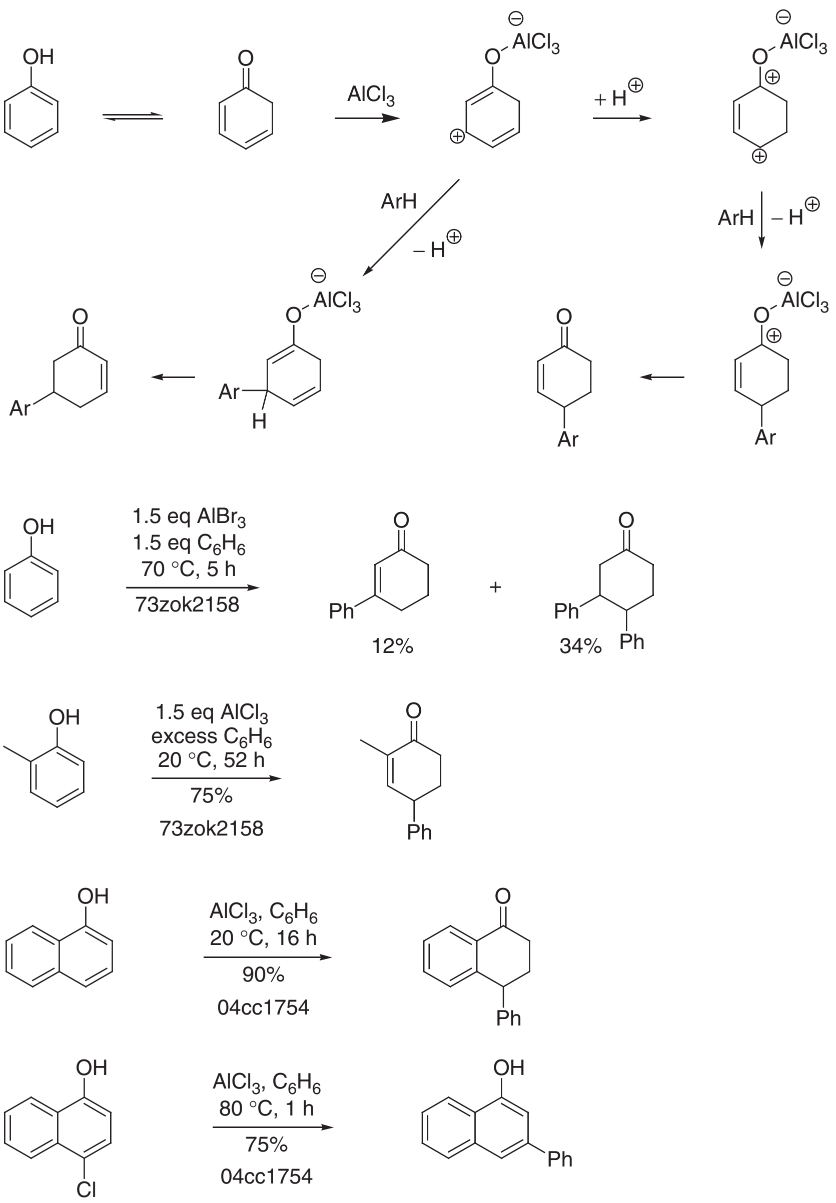


Scheme 1.16 Formation of chromanes from phenols [68, 80].

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.

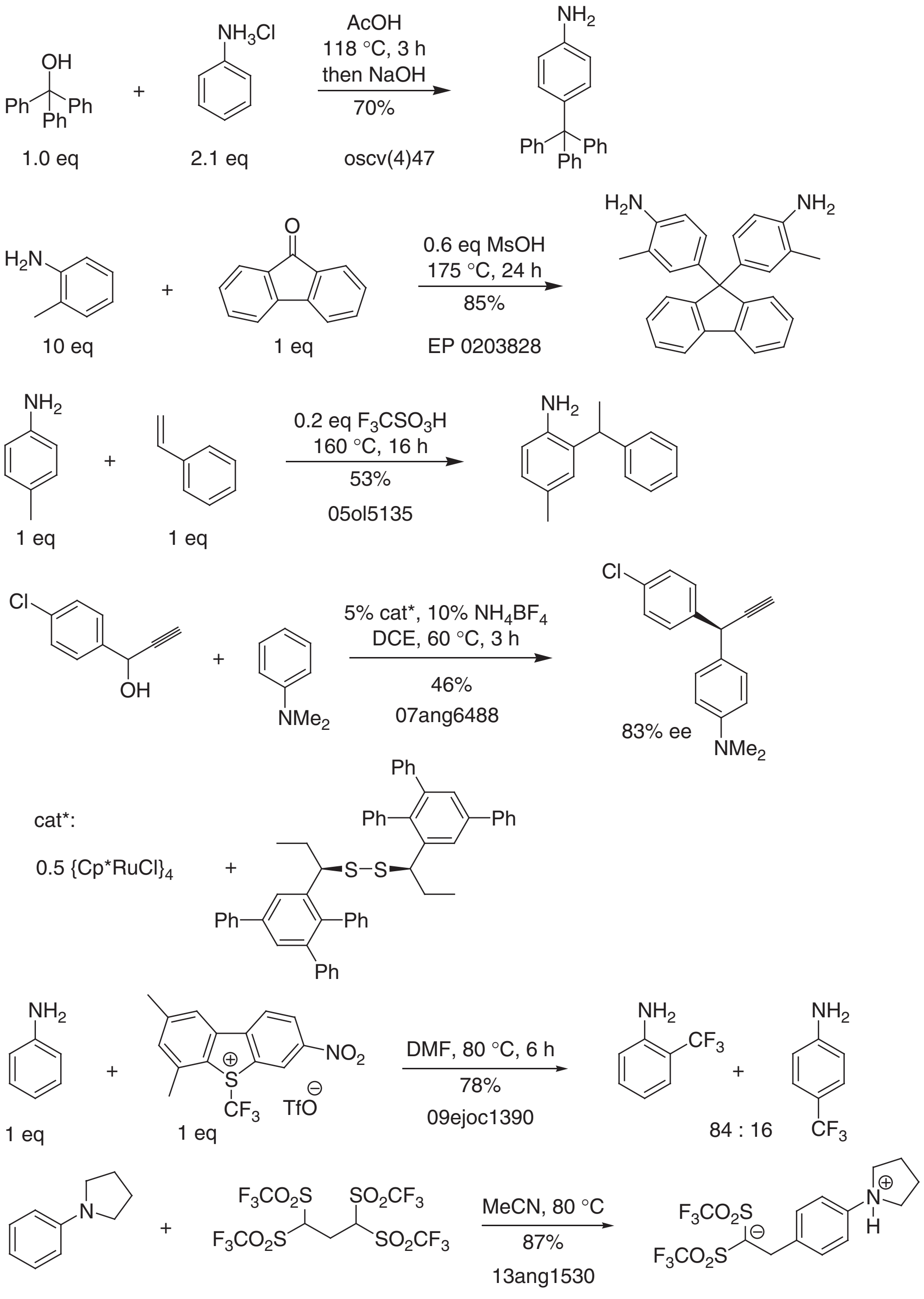
The precise outcome of the reaction of anilines with alkylating reagents can be difficult to predict. Stoichiometric amounts of strong acids usually favor C-alkylations. At high temperatures or in the presence of acids, *N*-alkylanilines may be dealkylated and act as alkylating agents themselves [91–93].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

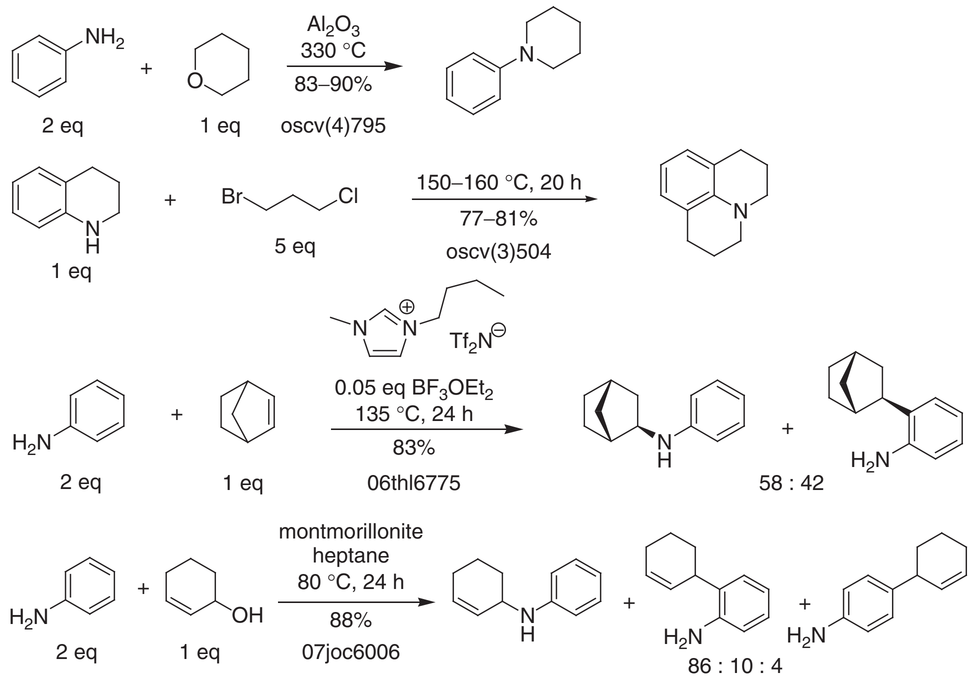


Scheme 1.17 Acid-mediated arylation of phenols [84, 85].

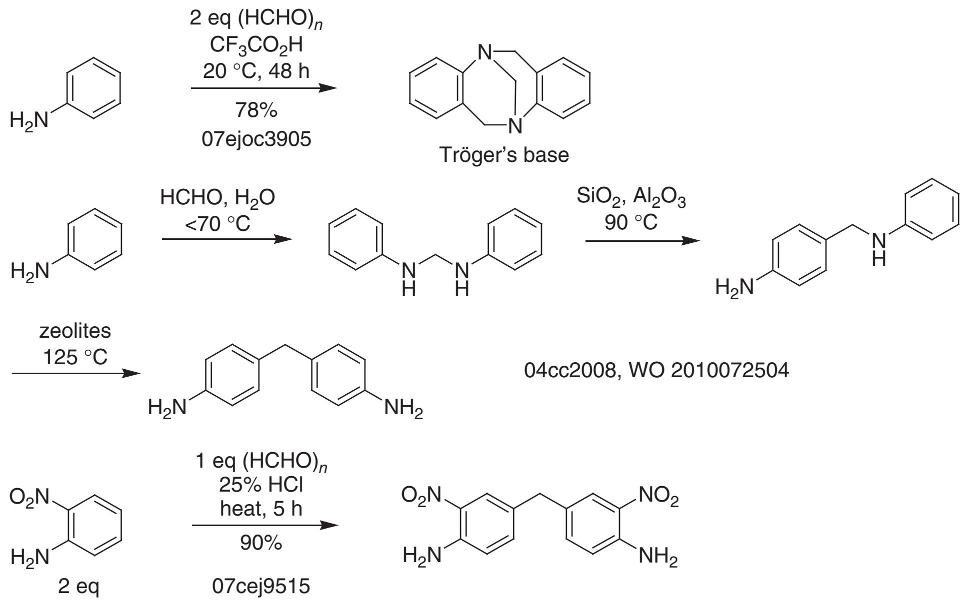
treated with formaldehyde at a low temperature, only aminals, benzylamines, or Tröger's base are formed. At higher temperatures, though, diarylmethanes are the main products (Scheme 1.20). Hydride transfer from aldehydes or anilines to intermediate iminium salts causes the formation of *N*-alkylanilines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



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



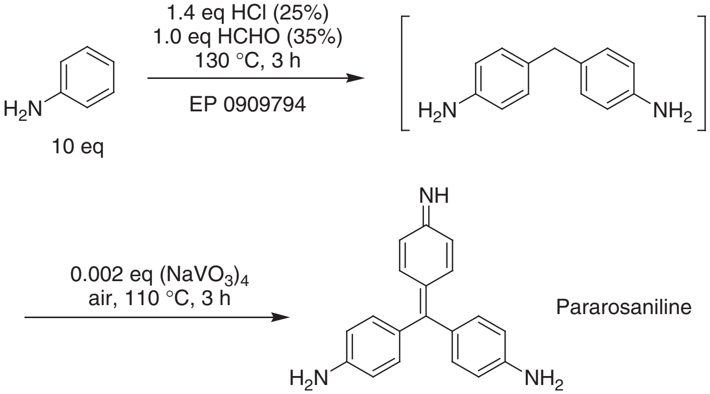
Scheme 1.19 Examples of C- and N-alkylations of anilines [94–97]. Further examples: [98, 99].



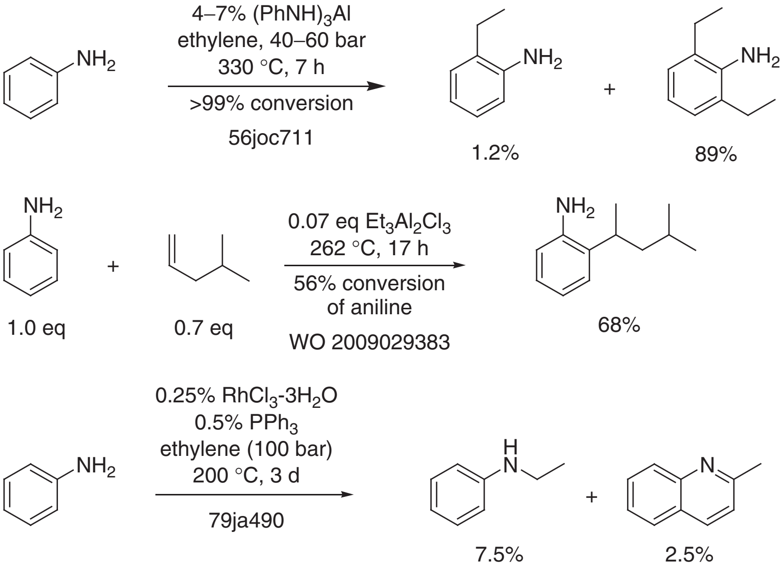
Scheme 1.20 Formation of diarylmethanes from anilines and formaldehyde [100–103].

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].



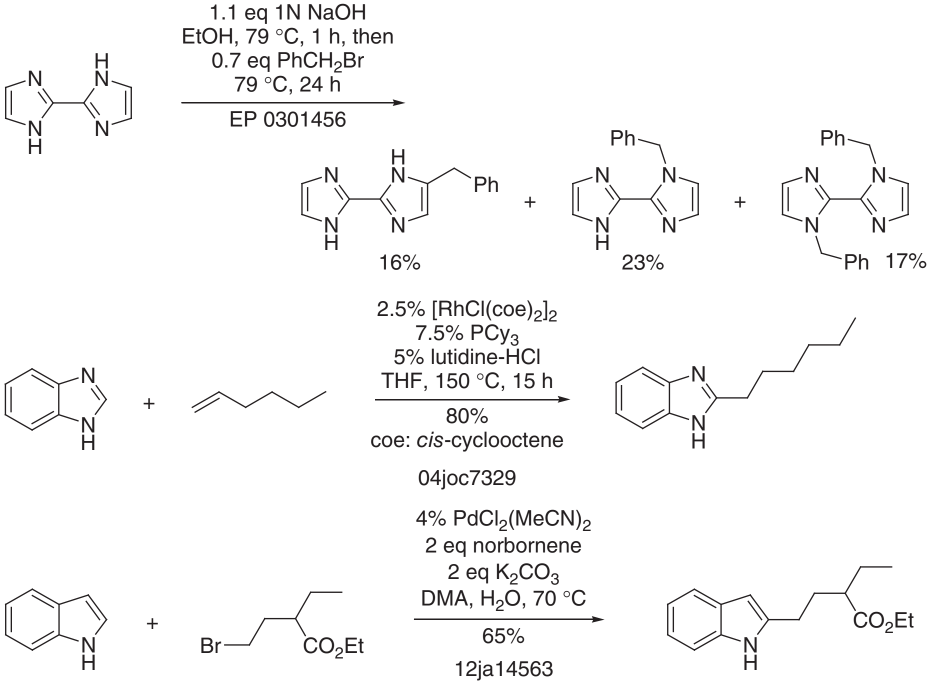
Scheme 1.21 Formation of triarylmethane dyes from diarylmethanes [104].



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.

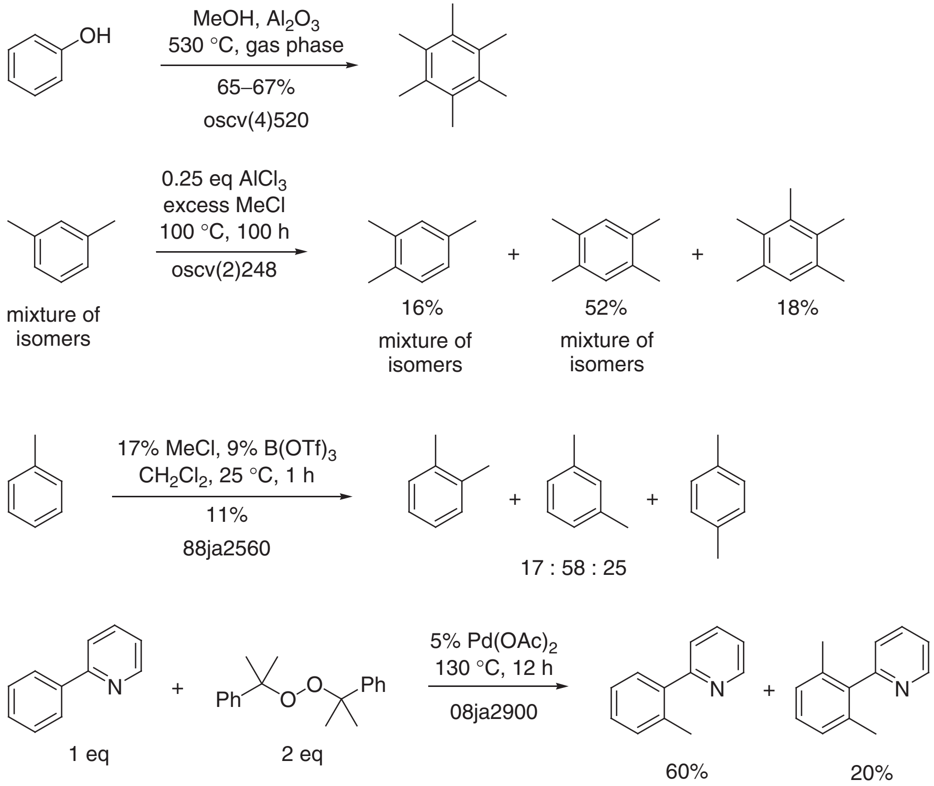


Scheme 1.23 Alkylation of azoles [109–111].

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



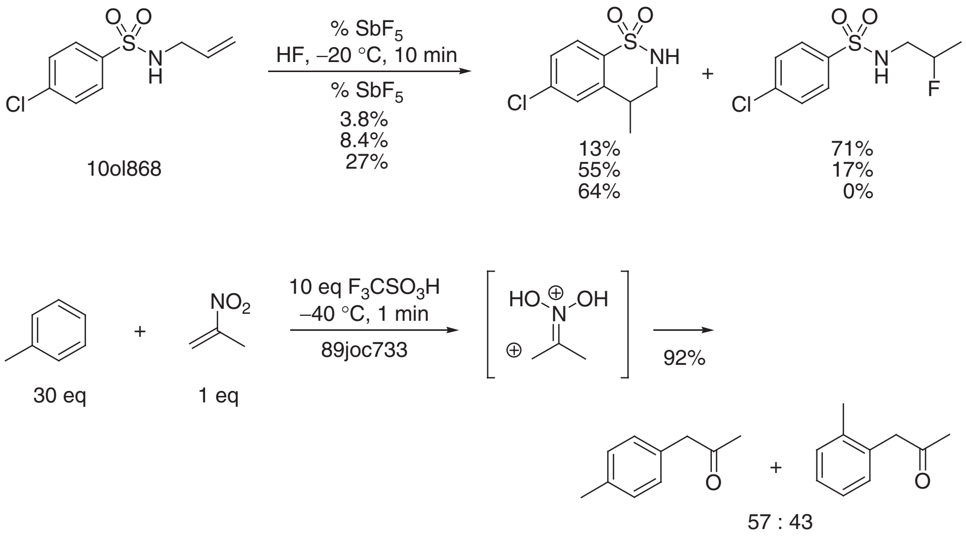
Scheme 1.24 Methylation of arenes with methanol, methyl chloride, and methyl radicals [112–115].

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).



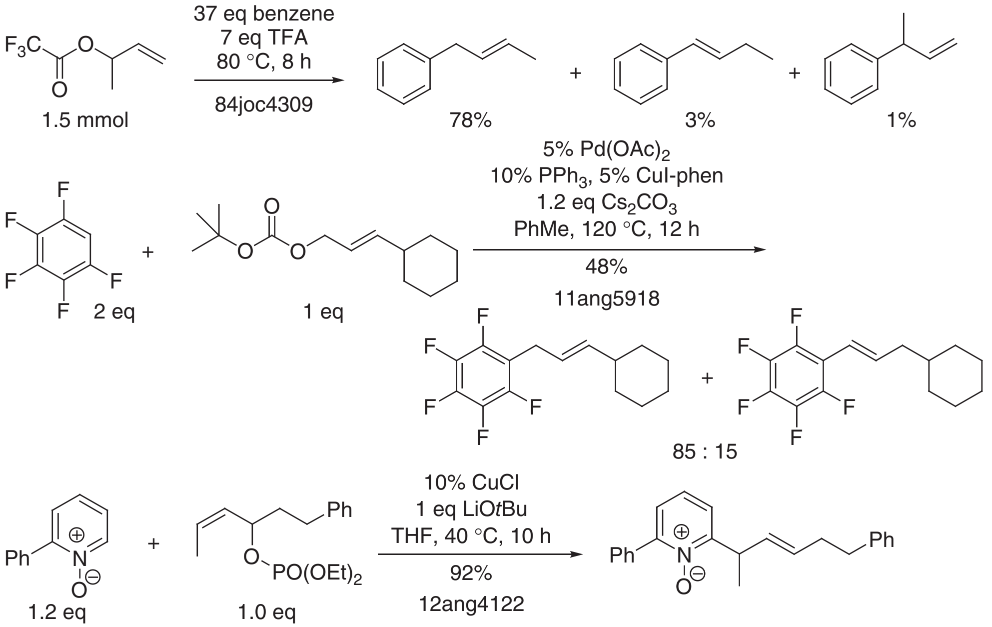
Scheme 1.25 Aromatic alkylations with olefins [120, 121].

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).

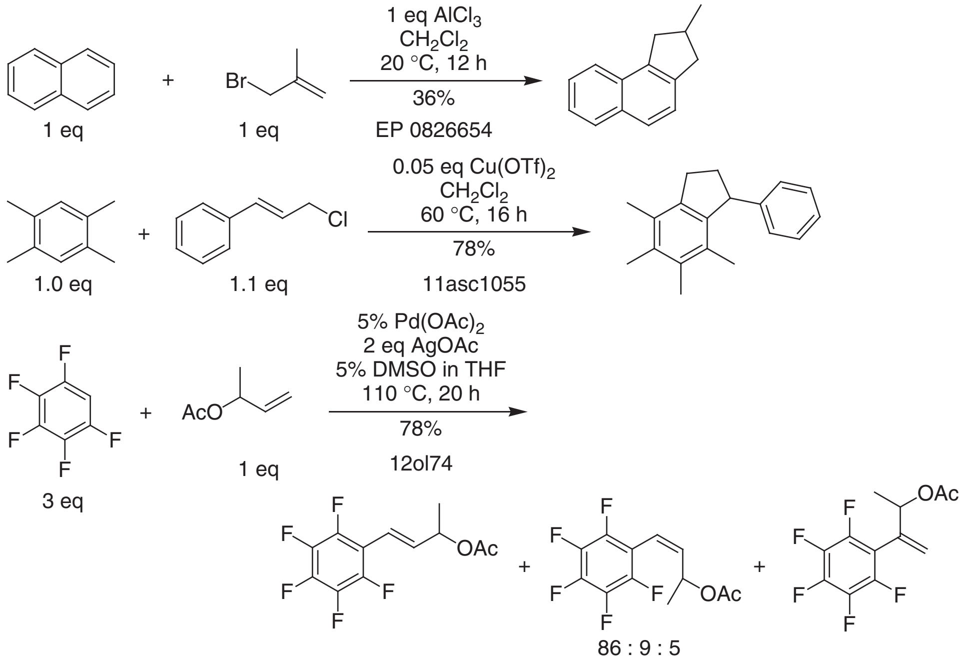
1.3.3
Allylic Electrophiles

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).

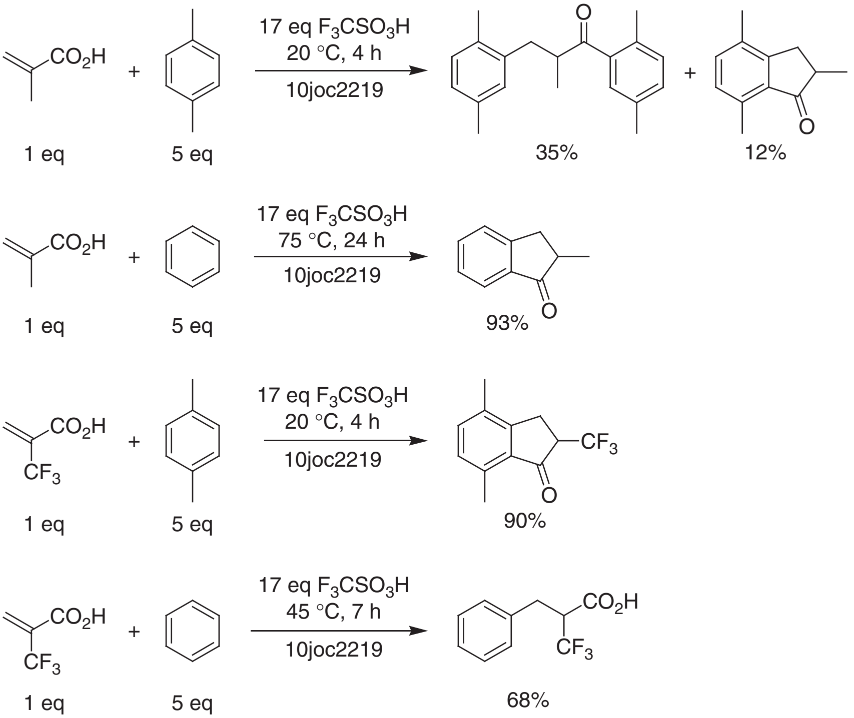


Scheme 1.26 Examples of the alkylation of arenes with allylic electrophiles [122–124]. Further examples: [125, 126].



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).

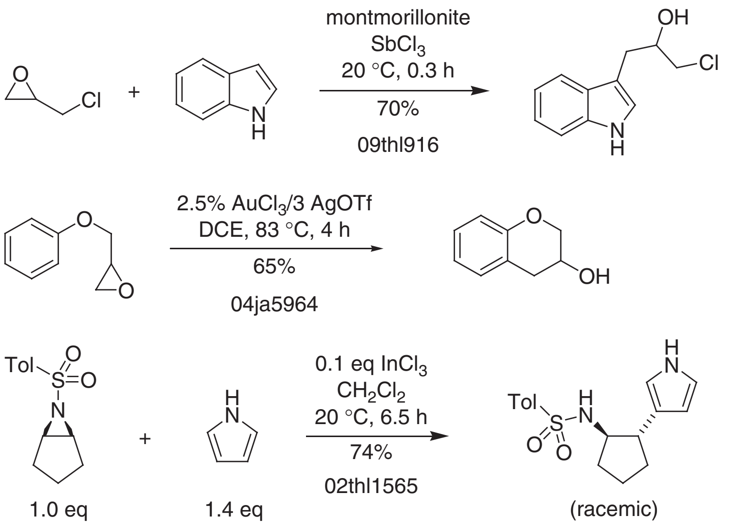


Scheme 1.28 Acid-mediated reactions of acrylic acids with arenes [129].

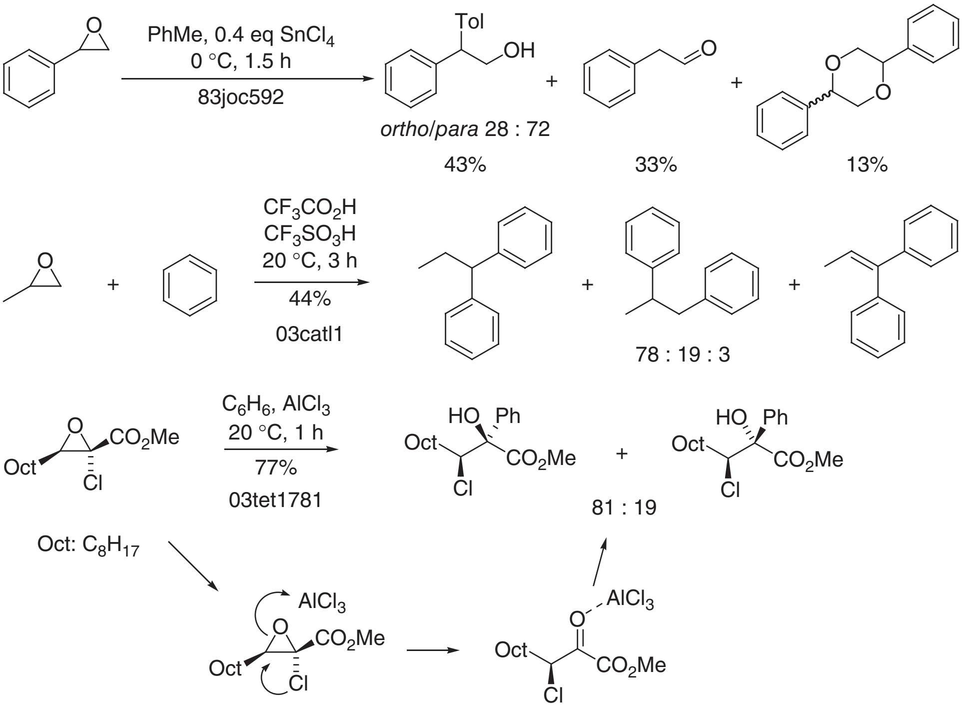
1.3.4
Epoxides

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).



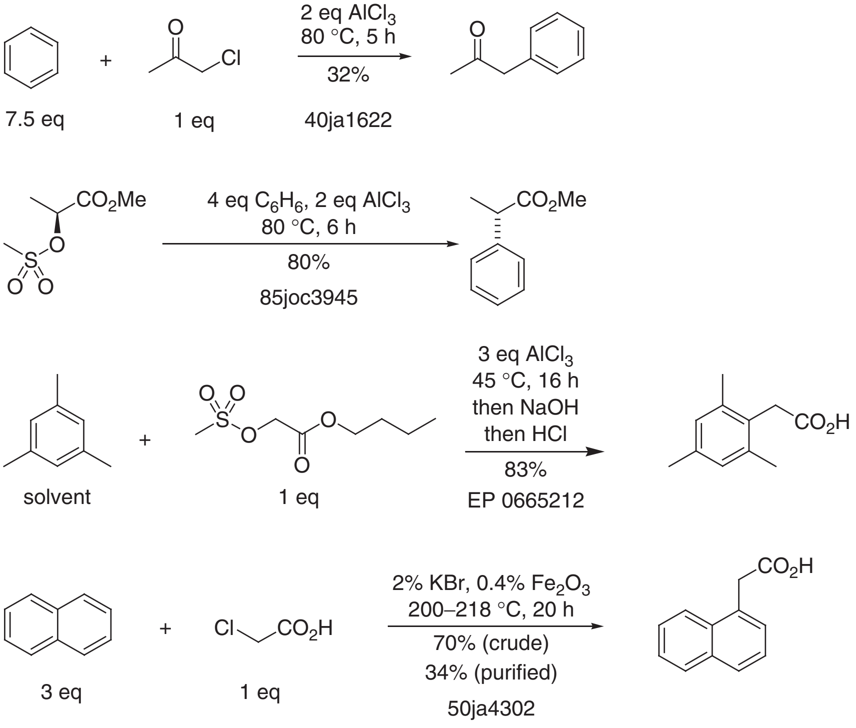
Scheme 1.29 Examples of the alkylation of arenes with epoxides and aziridines [130–132]. Further examples: [133].



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

1.3.5
α-Haloketones and Related Electrophiles

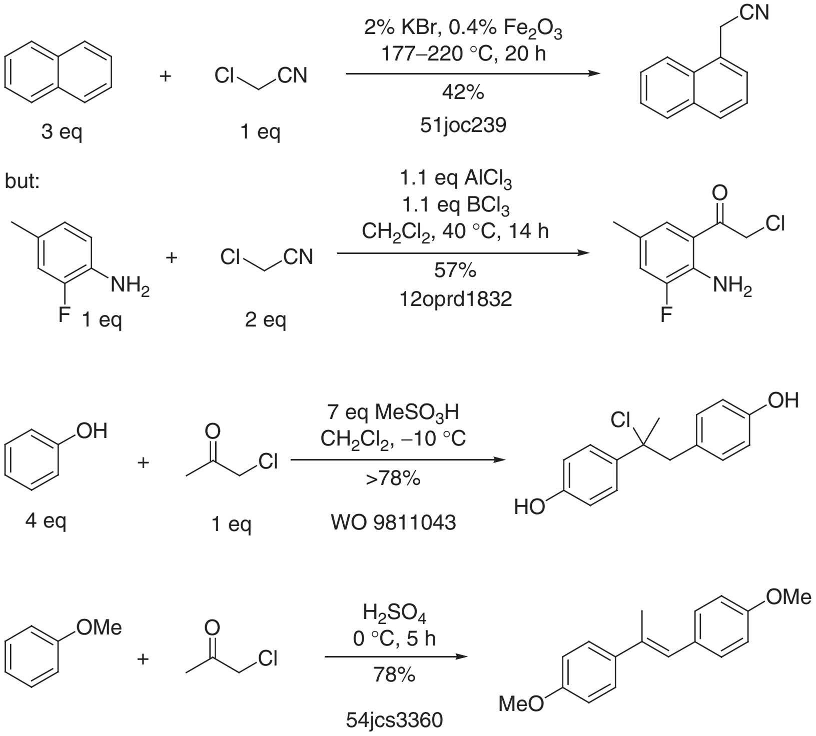
Alkylhalides with the halogen attached to a C−H acidic position (α-haloketones, α-haloesters, α-halonitriles, etc.) display a peculiar reactivity. Removal of the halide to produce a (destabilized) carbocation is difficult, and only a few examples of acid-catalyzed arene alkylations with such electrophiles 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].

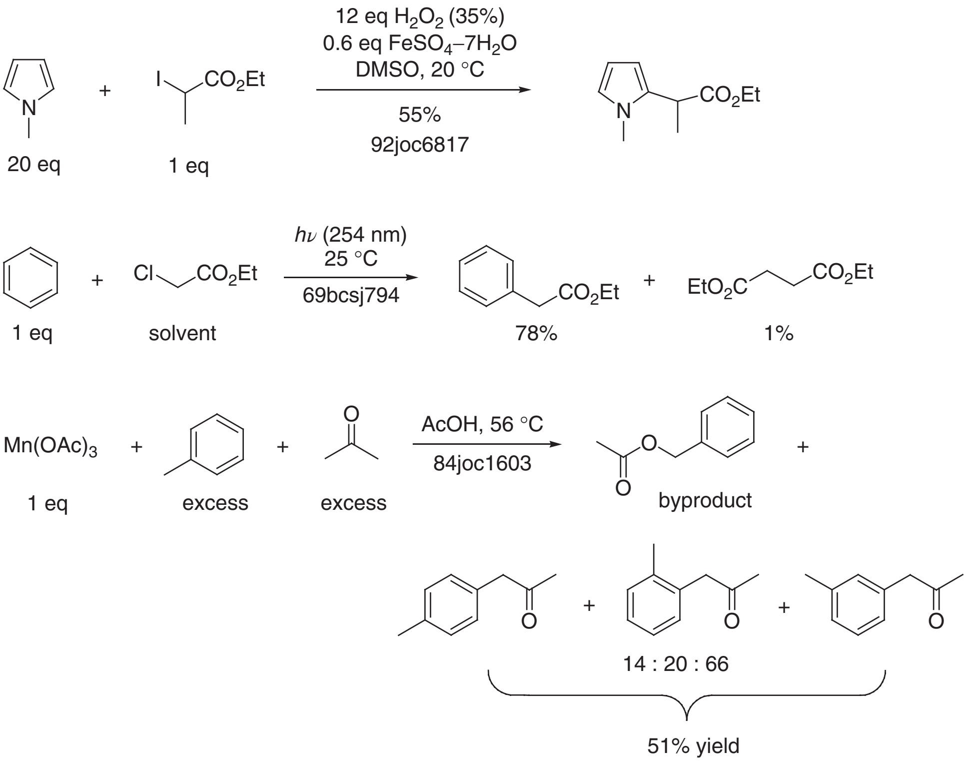
only, the arene cannot usually be used as solvent, because it would not allow the required UV light to reach the haloester (second example in Scheme 1.33).

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



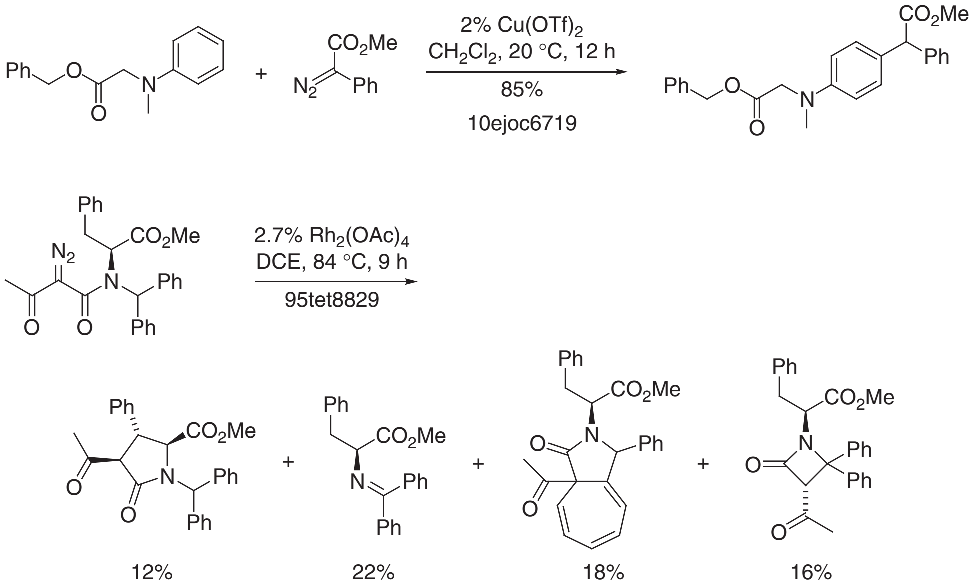
Scheme 1.33 Arylation of α-haloesters and ketones via radicals [149–151].

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



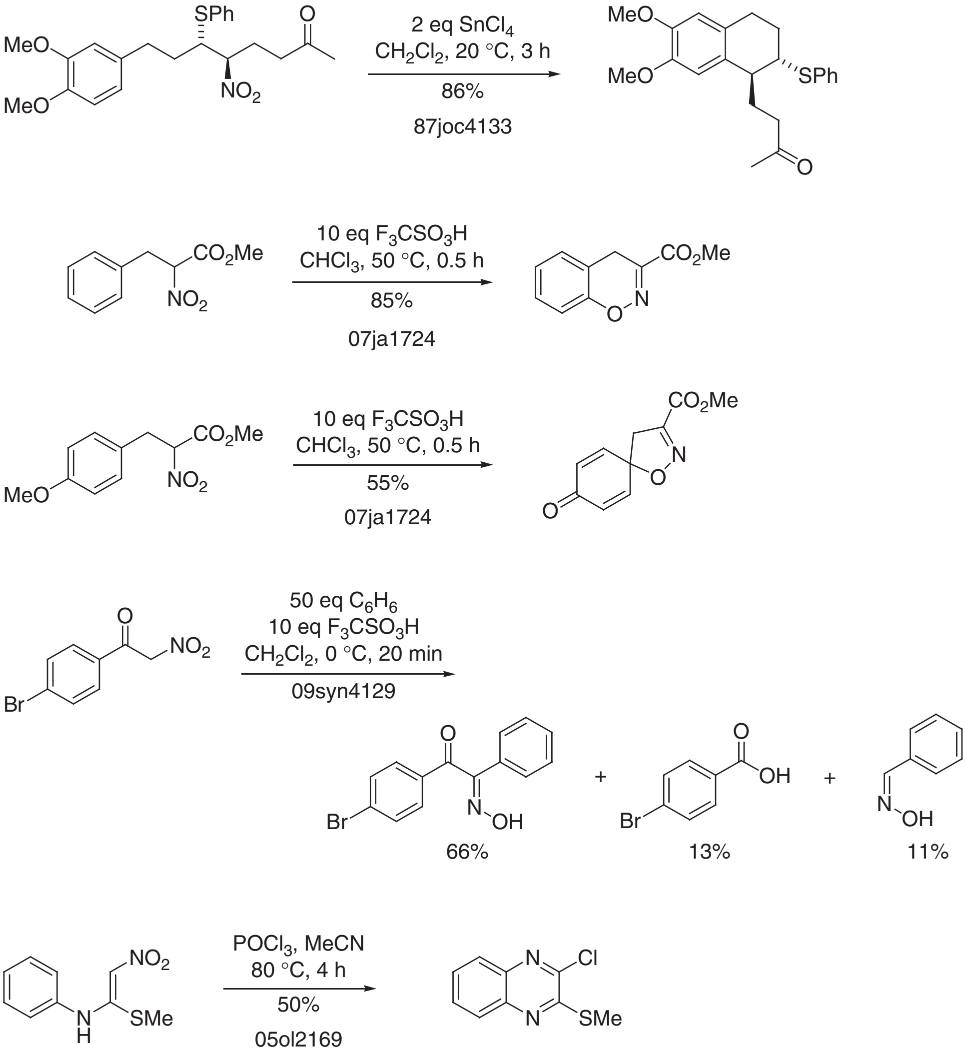
Scheme 1.34 Reaction of α-diazoesters with arenes [152, 153].

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).

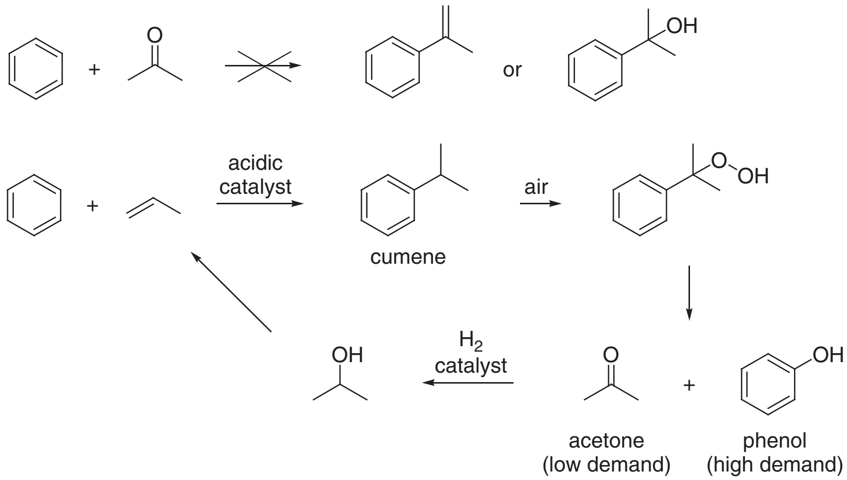
Potential side reactions of the Friedel–Crafts alkylation with ketones is the formation of diarylmethanes, the oligomerization of the products, and aldol condensation of the starting ketone. Moreover, in the presence of oxidants, ketones may be α-arylated via intermediate radical formation [151]. If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



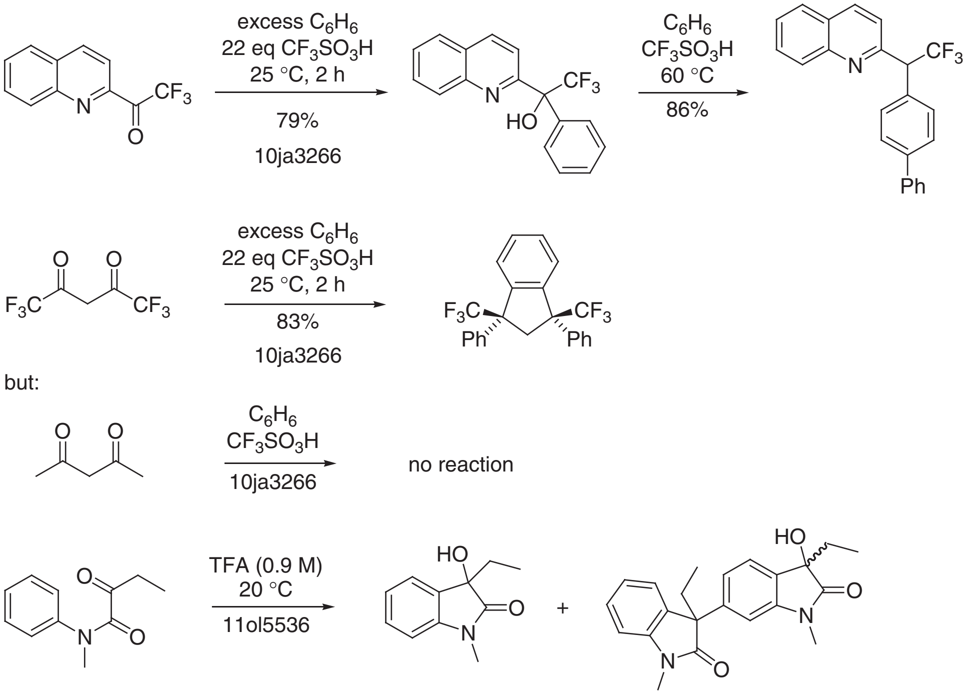
Scheme 1.35 Reactions of nitroalkanes with arenes [154–157]. Further examples: [158].

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).

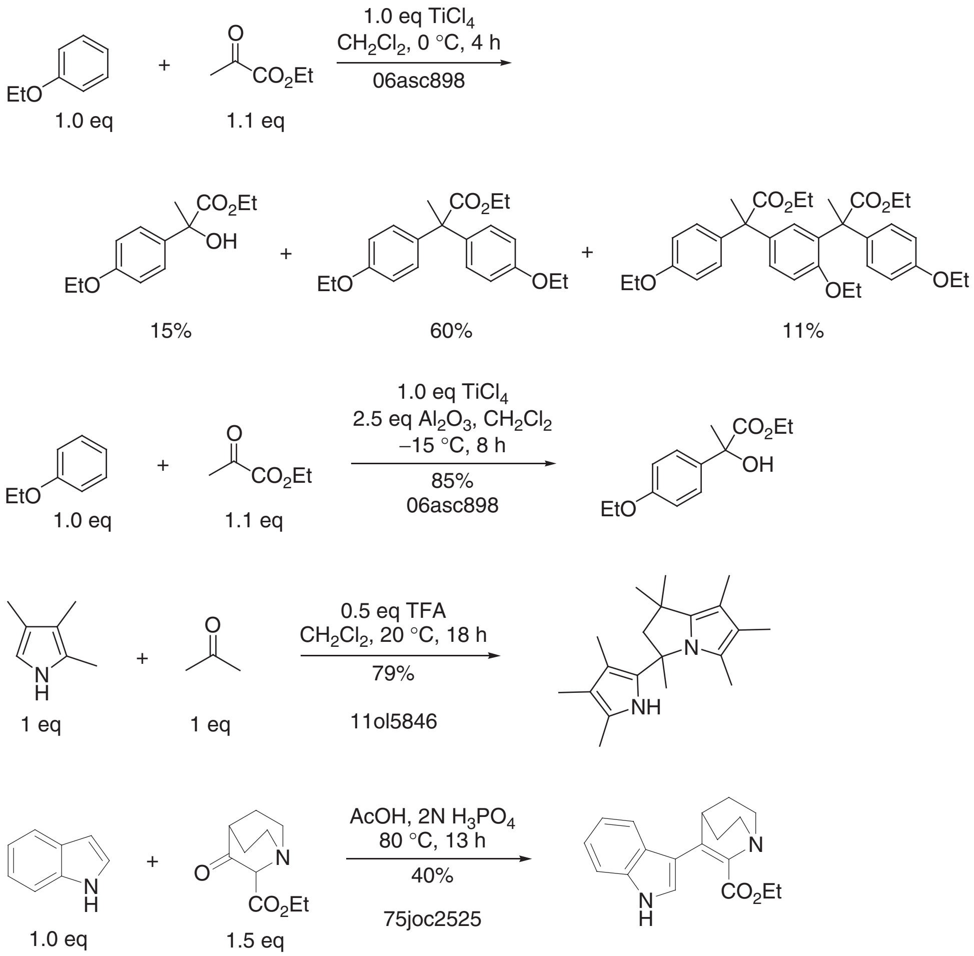
Occasionally, benzylic electrophiles are attacked by nucleophiles not at the benzylic position but at the arene (e.g., first equation in Scheme 1.37). Examples have been reported of the electrophilic arylation of unsubstituted arenes with tetralones and related aryl ketones (Scheme 1.40).



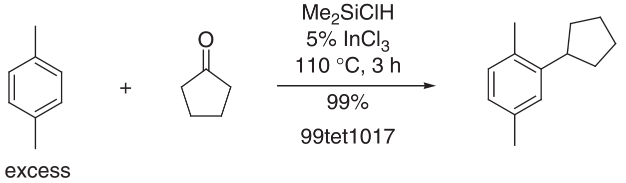
Scheme 1.36 Preparation of phenol and acetone from benzene.



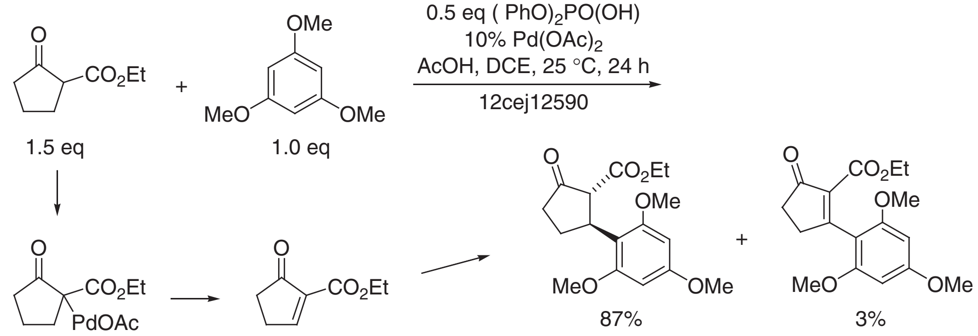
Scheme 1.37 Alkylation of arenes and heteroarenes by ketones [163–167].



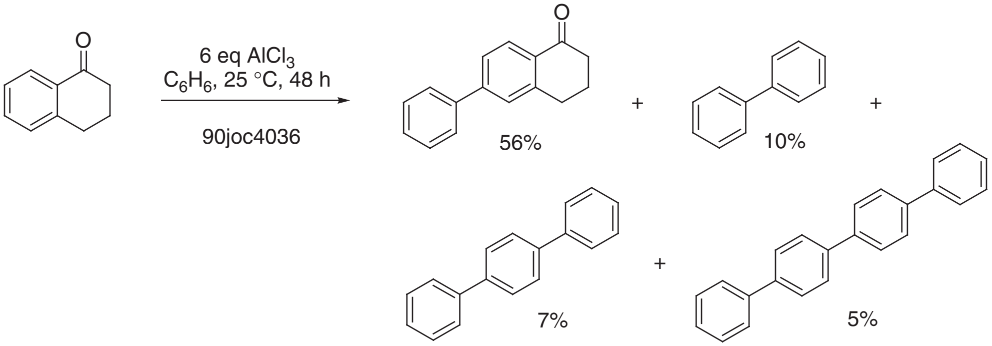
Scheme 1.37 (*Continued*)



Scheme 1.38 Reductive aromatic alkylation with ketones [168].



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



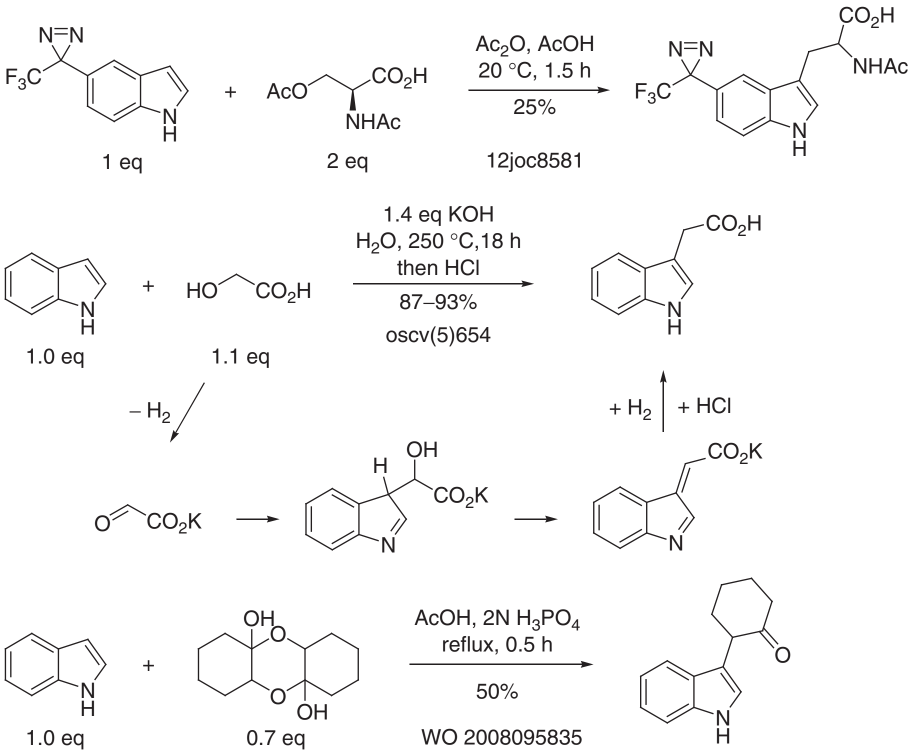
Scheme 1.40 Arylation of benzene with tetralone [83].

1.3.8
Alcohols

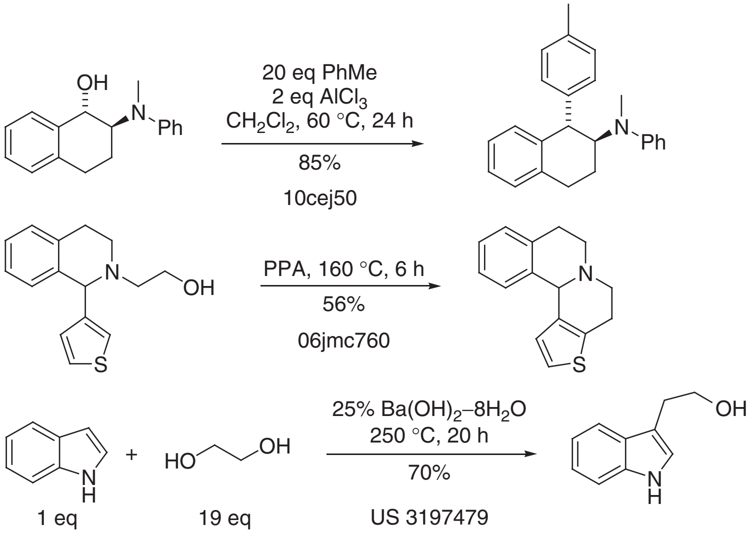
Alcohols are widely used electrophiles for Friedel–Crafts alkylations. Alcohols are often more reactive than alkyl halides, but require more acid to alkylate arenes. Primary, non-benzylic alcohols are rarely used as alkylating reagents, owing to their fast rearrangement to more stable secondary or tertiary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