Aryl Alkylation

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Beyond Friedel and Crafts: Directed Alkylation of C–H Bonds in Arenes

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Alkylation of arenes is one of the most fundamental transformations in chemical synthesis and leads to privileged scaffolds in many areas of science. Classical methods for the introduction of alkyl groups to arenes are mostly based on the Friedel–Crafts reaction, radical additions, metalation, or prefunctionalization of the arene: these methods, however, suffer from limitations in scope, efficiency, and selectivity. Moreover, they are based on the innate reactivity of the starting arene, favoring the alkylation at a certain position and rendering the introduction of alkyl chains at other positions much more challenging. This can be addressed by the use of a directing group that facilitates, in the presence of a metal catalyst, the regioselective alkylation of a C–H bond. These directed alkylations of C–H bonds in arenes will be comprehensively summarized in this Review.

1. Introduction

The alkylation of arenes is one of the most fundamental transformations in chemical synthesis. Alkylated arenes are indeed ubiquitous molecules, with a broad range of applications in fine chemicals, drugs, agrochemicals, as well as in polymer and material sciences, just to mention a few.

Nowadays, the regioselective alkylation of arenes still mostly relies on the use of the Friedel–Crafts reaction,^[1] a reaction which suffers, however, from severe limitations (harsh reaction conditions, low chemo- and/or regioselectivities, as well as poor reactivity of certain classes of substrates). The main alternatives that have been developed are mostly based on the stoichiometric metalation of the arene followed by reaction with an electrophile^[2]—a strategy which suffers from major limitations in terms of functional group compatibility—or on its stepwise prefunctionalization followed by a metal-catalyzed cross-coupling. Therefore, the development of new, robust, and reliable chemical transformations allowing the selective alkylation of arenes is still an especially active area of research which has been extensively investigated over the last decade. Such processes—mostly based on C–H functionalization—have already had a strong impact in various areas of chemical sciences.

During the past decades, the direct (metal-catalyzed in most cases) functionalization of C–H bonds has emerged as an especially powerful alternative for the formation of carbon–carbon and carbon–heteroatom bonds. Recent advances in this field have enabled the development of a series of remarkably efficient processes for the direct introduction of alkyl groups onto aromatic scaffolds that now appear to be robust and reliable alternatives to the classical alkylation reactions.^[3] Compared to the introduction of aryl groups or other functionalities, the alkylation of C–H bonds is typically much more challenging due to possible β -hydride elimination pathways. For these reactions to be of any synthetic usefulness, they also need to be highly regioselective. In addition to the use of the innate reactivity of heteroarenes, which will be covered in a second review,^[4] the most common strategy to control the regioselectivity of direct alkylation reactions relies on the use of a directing group that will allow the selective

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activation of a single C–H bond in the starting arene.^[5,6] A large variety of directing groups have been successfully introduced for the *ortho*-alkylation, and more rarely the *meta*- and *para*-alkylation, of a wide range of arenes, which has led to the development of a series of efficient and highly regioselective processes.

A series of diverse alkylating agents have been introduced for the directed alkylation of C–H bonds in arenes: they include alkenes, alkyl halides, organometallic reagents, alkanes, epoxides, peroxides, or alcohols, with the first two being the most commonly used.

These reactions will be overviewed in this Review, with an emphasis on the most general ones and on their selectivity. They have been classified primarily according to the nature of the directing group, on the C–H bond (*ortho*, *meta*, or *para*)

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functionalized in the process, and finally on the nature of the reagent used for the alkylation. This structure should allow the reader to have a clear and precise idea of all the reactions that have been reported for the alkylation of a certain class of (hetero)arenes, as well as of the nature of the alkylating agents that have been used to do so. Although this Review will mostly focus on metal-catalyzed reactions, some metal-free processes, which also proved to be efficient for the alkylation of a broad range of arenes, will also be included. However, and as an important note, the use of Lewis or Brønsted acid catalysis, which can be considered as Friedel–Crafts alkylations and would therefore be outside the scope of this Review, will not be covered.^[7] For the sake of conciseness and clarity, only the most representative and significant examples of reactions for the introduction of specific alkyl groups, such as benzyl, allyl, succinimides, or hydroxyalkyl chains, will be discussed and intramolecular variants will not be covered. The introduction of fluorinated alkyl chains, for which there has been many developments lately, is also outside the scope of this Review. As a note, and for simplicity, all the C–H bonds whose alkylation will be discussed are C(sp²)–H bonds: they will be denoted “C–H” rather than “C(sp²)–H” throughout this Review.

2. Carbonyl Derivatives as Directing Groups

Carbonyl and carboxy derivatives are among the most common directing groups reported to date for the alkylation of C–H bonds in arenes. They indeed combine good coordination properties—which is required for the selective activation of a C–H bond—and excellent synthetic usefulness as a result of the number of transformations that can be performed from these functional groups. Moreover, the regioselectivity of the C–H bond alkylation is often complementary to that of the typical Friedel–Crafts reaction, which favors alkylation at the *meta* position. Among all the reagents reported to date for the alkylation of arenes containing such directing groups, alkenes are probably the most common ones: their use will be overviewed in the next sections.

2.1. Alkylation with Alkenes

As a result of their availability, alkenes are convenient reagents for the directed alkylation of arenes, which in addition proceeds with perfect atom economy.^[8] For such reactions to be of any synthetic usefulness, potential issues associated with selectivity must be addressed. In addition to the C–H bond of the starting arene that is cleaved in the process, the regioselectivity (i.e. formation of the branched or linear product) and potential double alkylation (yielding for example to *ortho,ortho'*-dialkylated arenes) need to be fully controlled.

2.1.1. Alkylation of Arylketones with Alkenes

A major breakthrough in this area was reported by the Murai group, who disclosed in 1993 a remarkably efficient ruthenium-catalyzed^[9] *ortho*-alkylation of arylketones^[10] with a range of alkenes.^[11] The key to the successful development of this process lies in the use of a low-valent ruthenium complex, RuH₂(CO)(PPh₃)₃, which facilitates the coordination of the aromatic ketone. Upon reaction with catalytic amounts of this complex, a range of (hetero)aromatic ketones were shown to be readily alkylated with a set of mono- or disubstituted alkenes to afford the corresponding linear products in high yields (Scheme 1). Notable features of this process include its total selectivity, with the double alkylation being observed only in the presence of an excess of the alkene and prolonged reaction times, and the use of an equimolar ratio of the starting arylketone and the alkene, which is sufficient for the reaction to proceed efficiently. Certain substrates, such as nonstrained cyclic alkenes or ketones such as 1-indanone, which is unable to form a proper chelate, were found to be reluctant reaction partners, and isomerization of the alkene prior to the alkylation can be a serious side reaction with isomerizable alkenes.^[11b]

The mechanism typically invoked to rationalize the whole transformation involves the generation of a coordinately unsaturated ruthenium(0) complex from the RuH₂(CO)(PPh₃)₃ precatalyst followed by oxidative addition into the C–H bond *ortho* to the ketone to yield a transient ruthenium-(II) hydride. Subsequent coordination of the alkene and migratory insertion followed by reductive elimination pro-

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Scheme 1. Ruthenium-catalyzed *ortho*-alkylation of arylketones with alkenes according to Murai and co-workers.

vides the alkylated product together with the regenerated catalyst. This ruthenium(0) catalyst would be generated by reduction of the starting alkene, and all steps except the final reductive elimination, which is believed to be the rate-limiting step, would be in equilibrium. Various experimental and theoretical results support this mechanism. Indeed, deuterium scrambling experiments starting from acetophenone deuterated on the aromatic ring revealed that the deuterium atoms in the *ortho* position can undergo D/H exchange with the proton of the alkene during the course of the reaction, thus supporting the formation of a transient ruthenium hydride.^[12] Various DFT studies are also in favor of this mechanism: they point to a rate-limiting reductive elimination and also demonstrate that an alternative pathway involving insertion of the alkene into the Ru–C bond rather than into the Ru–H bond, proposed as an alternative in the original report, is less favorable.^[13] Further studies by Kakiuchi and Murai revealed that the whole alkylation can actually proceed at room temperature, with the thermal activation only being required for the formation of the active catalyst.^[12] This eventually led to the discovery of an activated ruthenium catalyst, Ru(*o*-C₆H₄PPh₂)H(CO)(PPh₃)₂—readily generated by treatment of the original catalyst with trimethylvinylsilane at 90 °C for

1–5 h—which is able to perform the C–H alkylation at room temperature.

This process was later extended by Grigg and Savic to the directed alkylation of acylpyridines [Scheme 2, Eq. (1)] and indoles [Scheme 2, Eq. (2)]: although the reaction was found to be efficient in both cases, double alkylation was observed in

Scheme 2. Ruthenium-catalyzed *ortho*-alkylation of acylpyridines and indoles with alkenes.

some cases and 2-acylpyridine itself was found to be a poor substrate, certainly because of the formation of a chelate that inhibits the activation of the C–H bond.^[14] The reaction was also shown to be efficient with ferrocenylketones,^[15a] 3-arylbzofurans,^[15b,c] thioxanthenes,^[16] as well as for the directed alkylation of ring C of aromatic diterpenoids^[17] and also found efficient applications in polymer science.^[18] Ethylene can be replaced by a combination of tetraethylammonium bromide and potassium hydroxide for the introduction of an ethyl group.^[19]

Other ruthenium complexes were found to be effective for the directed alkylation of arylketones, with some of them being remarkably efficient in terms of turnover number (TON) or reaction temperature. Chaudret and co-workers indeed reported in 1998 that RuH₂(H₂)₂(PCy₃)₂ (Cy = cyclohexyl) enables the alkylation of acetophenone and benzophenone with ethylene at room temperature.^[20] Busch and Leitner later showed that this catalyst could be efficiently generated in situ by hydrogenation of commercially available Ru(cod)(2-methylallyl)₂ (cod = 1,5-cyclooctadiene) in the presence of tricyclohexylphosphine. A range of acetophenone derivatives could be readily alkylated with ethylene at room temperature by using this convenient procedure [Scheme 3, Eq. (1)].^[21] An analogue of this catalyst in which the two tricyclohexylphosphine ligands are replaced with a more constrained phosphine, tricyclopentylphosphine, turned out to be even more efficient, since it was shown to catalyze the alkylation of acetophenone to 2-ethylacetophenone within 35 min (90 % conversion), whereas 10 h were needed with the previous catalyst.^[22]

In a further attempt at addressing the low activity and/or air and moisture sensitivity of most low-valent ruthenium(0) or ruthenium(II) complexes, Darses, Genet, and co-workers

Scheme 3. Other ruthenium-based catalysts for the *ortho*-alkylation of arylketones with alkenes.

reported in 2006 an efficient alternative for the in situ generation of a versatile low-valent ruthenium catalyst through the reduction of $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ with sodium formate in the presence of triphenylphosphine [Scheme 3, Eq. (2)].^[23] This procedure compares well with the one originally reported by Murai and co-workers. Its versatility lies in the fact that the electronic and steric properties of the catalyst can be easily modulated by simply changing the nature of the phosphine used, as shown by its extension to the use of styrenes [Scheme 3, Eq. (3)],^[24] substrates that give mixtures of linear and branched products using the procedure developed by Murai and co-workers.^[11b] Other catalyst precursors include ruthenium trichloride,^[25] and the reaction was also shown to be efficiently performed under protic conditions^[26] or with metallic ruthenium supported on cerium oxide.^[27] Maleimides can also be used as alkylating agents.^[28]

Since many ruthenium complexes are able to oxidize benzylic alcohols by hydride transfer or to isomerize allylic alcohols, the ketone directing group required for the Murai alkylation can be formally replaced by an alcohol. Indeed, an oxidation/alkylation sequence was shown to efficiently convert benzylic alcohols into the corresponding *ortho*-alkylated arylketones when using acetone, the hydride acceptor, as a cosolvent [Scheme 4, Eq. (1)].^[29] A tandem isomerization/alkylation from benzylic and allylic alcohols was also shown to be operative to give the same products [Scheme 4, Eq. (2)], thus extending the synthetic potential of the Murai reaction.^[30] However, significant amounts of dialkylation were observed with many substrates in both cases.

The efficiency of the ruthenium-catalyzed *ortho*-alkylation of ketones prompted the search for alternative catalysts based on other metals, notably with the aim of addressing some of the limitations met with ruthenium complexes, the main one being the scope of the reaction with respect to the alkenes tolerated as alkylating agents (competing isomerization of the alkenes, low reactivity of electron-rich or -poor alkenes, etc.). In a seminal contribution, the Brookhart group showed that a rhodium(I) bisolefin complex,^[31] $\text{Cp}^*\text{Rh}(\text{C}_2\text{H}_5\text{SiMe}_3)_2$, was an efficient catalyst for the *ortho*-alkylation of arylketones. This catalyst actually has similar

Scheme 4. Use of benzylic or benzylic and allylic alcohols in tandem ruthenium-catalyzed oxidation or isomerization/*ortho*-alkylation sequences.

features to the one developed by Murai and co-workers, the major interest of this rhodium catalyst being the formation of linear products only when using 1-pentene, although with incomplete conversions.^[32] Various iridium complexes were in addition shown to be efficient catalysts,^[33] notably for branched-selective (with styrene) and enantioselective alkylations, but the scope of these processes were either only briefly evaluated or limited to specific alkenes, such as norbornene.

A recent review by the Ilies/Nakamura group clearly highlights the remarkable potential of iron complexes for C–H activation.^[34] Indeed, a simple iron complex, $\text{Fe}(\text{PMe}_3)_4$, efficiently catalyzes the selective alkylation of arylketones with a broad range of alkenes, as reported by Kakiuchi. These include aryl-, alkyl-, silyl-, as well as oxygen- and nitrogen-substituted alkenes, which all give excellent selectivities for the linear products (Scheme 5).^[35] The reaction can be performed in hexane or without solvent at temperatures ranging from 50 to 70 °C. The main limitation actually lies in the fact that apart from cyclohexyl phenyl ketone, enolizable ketones such as acetophenone are not alkylated under the reaction conditions. The mechanism would be similar to that of the ruthenium-catalyzed alkylation of arylketones.

The activation of other C–H bonds is clearly more challenging, since most carbonyl-derived directing groups inherently favor the activation of the *ortho*-C–H bond. In

Scheme 5. Iron-catalyzed *ortho*-alkylation of arylketones with alkenes.

a continuation of their studies on the use of cooperative Lewis acid/metal catalysis, the Sakaki and Nakao group disclosed in 2016 an especially interesting catalyst combination for the *para*-selective directed alkylation of aromatic ketones.^[36] The use of a bulky aluminum phenoxide that coordinates to the ketone activates the *para* C–H bond, which is then selectively alkylated with an alkene in the presence of catalytic amounts of Ni(cod)₂ and an N-heterocyclic carbene (NHC) as the ligand (Scheme 6). The regioselectivity is excellent in all cases (from 96:4 to 99:1 in favor of the *para* isomer) and a wide range of both arylketones and alkenes can be used. The resting state of the catalyst is a bis(alkene)nickel(0) complex. DFT calculations indicated that ligand exchange with the arylketone coordinated to the aluminum Lewis acid ultimately results in the formation of a σ complex. Cleavage of the coordinated C(sp²)–H bond and formation of one C(sp³)–H and two Ni–C bonds then proceed in a concerted manner to

furnish an alkyl(aryl)nickel complex, in which an agnostic interaction between a hydrogen atom and the nickel center was observed. Geometric isomerization next affords a T-shaped intermediate and a final reductive elimination yields the alkylated arene-nickel complex.

2.1.2. Alkylation of Arylaldehydes with Alkenes

The success met by the Murai group in the ruthenium-catalyzed directed alkylation of arylketones with alkenes prompted them to extend their process to other directing groups. In 2001, they reported the extension of their procedure to the use of benzaldehyde derivatives.^[37] This turned out to be rather challenging because of severe side reactions, such as decarbonylation or hydroacylation. It was quickly found that the presence of sterically hindered substituents at the *ortho* position of the benzaldehyde and the presence of an electron-donating substituent were critical to prevent the attack of the ruthenium catalyst on the carbonyl group, but this strongly limits the scope of the directed alkylation. Representative examples are shown in Scheme 7. The low yields obtained in the cases of 3-formylthiophene and 3-formyl-1-methylindole can be attributed to the formation of substantial amounts (30–40%) of deformylated alkylated products.

Scheme 6. Aluminum/nickel co-catalyzed *para*-alkylation of arylketones with alkenes.

Scheme 7. Ruthenium-catalyzed *ortho*-alkylation of arylaldehydes with alkenes.

2.1.3. Alkylation of Arylimines with Alkenes

A logical extension clearly was the use of aromatic imines in such alkylation reactions. As a consequence of the excellent coordination properties of imines with different metals, a broad range of procedures have been developed over the years for the directed *ortho*-alkylation of aromatic imines. As an important note, the imine is directly hydrolyzed to the corresponding aldehyde in most cases.

In a continuation of their studies, the Murai group was actually among the first ones to consider an alkylation with alkenes.^[38] Among all the ruthenium catalysts evaluated, Ru₃(CO)₁₂ was the best one to limit the dehydrogenative coupling to the corresponding alkenylated products. Upon reaction with an excess of the alkene in the presence of this catalyst, a series of *N-tert*-butylimines were shown to be readily alkylated in fair to good yields and with minimum amounts of by-products resulting from dehydrogenative cross-coupling (Scheme 8). In some cases, a double alkylation

Representative examples

Scheme 8. Ruthenium-catalyzed *ortho*-alkylation of arylimines with alkenes.

at the *ortho* and *ortho'* positions was observed. A remarkably selective catalyst-specific alkylation *ortho* to the imine or the ketone was developed for aromatic substrates possessing both an imine and a ketone.^[38b] This alkylation was later extended to aromatic hydrazones^[39] and to furfural derivatives by using a temporary bidentate aminoimine directing group.^[40]

Rhodium catalysis has also been shown to be quite efficient for the directed *ortho*-alkylation of imines. Pioneering studies by the Jun group demonstrated that the readily available Wilkinson complex efficiently mediated the alkylation of *N*-benzylketenimines with a broad range of alkenes, providing an efficient entry to *ortho*-alkylated aromatic ketones after hydrolysis [Scheme 9, Eq. (1)].^[41] This procedure nicely complements the ruthenium-catalyzed alkylation of arylimines, since a much broader range of alkenes can be used, namely various olefins with or without allylic protons. Remarkably, internal alkenes also reacted after complete isomerization to the corresponding terminal alkenes, and even *gem*-disubstituted alkenes reacted, although with moderate efficiency. In sharp contrast to the procedure developed by Murai and co-workers, electron-withdrawing substituents on the aromatic ring gave a much better reactivity than electron-donating ones. Other advantages are that catalytic amounts of benzylamine could be used when directly starting from the arylketone,^[42] performing the reaction under microwave irradiation without solvent enabled a faster reaction,^[43] and the rhodium-catalyzed *ortho*-alkylation of imines could be efficiently implemented for the functionalization of azines^[44] and polybutadiene,^[45] while a self-assembled supported catalytic system enabled an easy recovery of the catalyst.^[46]

The alkylation of aldimines turned out to be less efficient and required an additional ligand, 2-amino-3-picoline, to furnish, after hydrolysis, ketones resulting from a domino hydroacylation/*ortho*-alkylation.^[41] Double alkylation was favored with other catalytic systems, unless one position was blocked.^[47] The mechanism proposed for this reaction closely follows the one previously described for the ruthenium-catalyzed alkylation of arylketones.

Representative examples

Scheme 9. Rhodium-catalyzed *ortho*-alkylation of arylimines with alkenes. Bn = benzyl, EWG = electron-withdrawing group, OPiv = pivalate, TFE = 2,2,2-trifluoroethanol.

Jun and co-workers later extended their procedure to conjugated alkenes: acrylates, acrylamides, acrylonitriles, and vinylsulfones were all shown to be excellent substrates [Scheme 9, Eq. (2)] and they were also shown to be more reactive than non-activated alkenes.^[48] A carboxylate-enhanced,^[49] broadly applicable rhodium-based catalytic system was reported by Li and co-workers for the *ortho*-alkylation of ketoximes with activated alkenes such as acrolein or conjugated ketones [Scheme 9, Eq. (3)].^[50a] Carrying out the reaction with catalytic amounts of [Cp*RhCl₂]₂ and AgSbF₆ in the presence of potassium pivalate led to the alkylation proceeding at 40 °C, and the greater stability of the ketoximes facilitated the isolation of the alkylated products without hydrolysis. Mechanistic studies provided strong support for a reversible C–H bond activation and suggested the proto-demetalation to be the rate-limiting step, while the metalation proceeds by a carboxylate-assisted electrophilic-type activation. As a note, the Ackermann group later on reported an efficient rhodium(III)-catalyzed oxime-directed alkylation/nucleophilic addition domino process in the presence of additional ethyl glyoxylate.^[50b]

Besides ruthenium and rhodium complexes as well as an isolated example of an iridium-catalyzed alkylation of an iminoferrocene,^[51] various cobalt^[52] catalysts were recently introduced by the Yoshikai group for the *ortho*-alkylation of aromatic imines. Upon reaction with catalytic amounts of cobalt(II) bromide, 1,10-phenanthroline, and a Grignard reagent, various imines are smoothly alkylated with a range

of alkenes to the corresponding linear (L) products, except in the case of styrene derivatives that furnish the branched (B) isomers^[53] predominantly [Scheme 10, Eq. (1)].^[54] The room-temperature conditions are in stark contrast to those used with ruthenium and rhodium catalysts, which typically require high temperatures. Isomerizable alkenes perform well under the reaction conditions and with some substrates, such as 2-acetonaphthone-derived imines, the regioselectivity is complementary to that obtained with ruthenium complexes.

Scheme 10. Cobalt-catalyzed *ortho*-alkylation of arylimines with alkenes. PMP = *p*-methoxyphenyl.

With styrene derivatives, alternative catalytic systems based on the use of PCy_3 ^[55] or $\text{P(4-F-C}_6\text{H}_4)_3$ ^[56] provide excellent selectivity in favor of the branched products [Scheme 10, Eq. (2)], whereas using a combination of $[2,4\text{-(MeO)}_2\text{-C}_6\text{H}_3]_2\text{PPh}$ and either 2-methoxypyridine or DBU as a Lewis base completely switches the selectivity in favor of the linear isomers [Scheme 10, Eq. (3)].^[57] products that can also be obtained with an NHC ligand.^[55] This was further extended to the branched-selective *ortho*-alkylation of aromatic aldimines^[58] and to the enantioselective alkylation of 3-iminoindoles with styrenes,^[59] a reaction that can also be performed in combination with an isomerization starting from nonconjugated alkenes^[60] or, in a non-enantioselective manner, with simple iron catalysts.^[61]

Interestingly, N–H imines were also found to be efficient substrates for directed alkylations with alkenes^[62] and the Yoshikai group reported in 2016 that the Grignard reagents required in all these procedures could be efficiently replaced by simple magnesium metal.^[63]

Although the use of alkenes for the alkylation of arylcarbonyl derivatives has been extensively studied, limitations still remain in terms of scope. Some of these

limitations can be addressed by using other alkylating reagents, with alkyl halides being especially attractive candidates: their use will be summarized in the following section.

2.2. Alkylation of Arylimines with Alkyl Halides

Arylketones have not been used as substrates for the directed alkylation with alkyl halides. However, various efficient processes, mostly based on ruthenium and cobalt catalysis, have been reported recently for the selective directed alkylation of aromatic imines with such reagents.^[64] Regioselective *ortho*-alkylation of arylketenimines can indeed be selectively achieved with carboxylate-assisted ruthenium catalysis, as demonstrated by the Ackermann group: upon reaction with catalytic amounts of $[\text{RuCl}_2(\textit{p}\text{-cymene})]_2$ and 1-adamantanecarboxylic acid in the presence of potassium carbonate in xylene followed by reduction of the alkylated products, a set of imines were smoothly alkylated with a broad range of primary alkyl bromides, as illustrated with the representative examples in Scheme 11 [Eq. (1)].^[65] Starting from *meta*-substituted imines, the alkylation was found to be mostly controlled by steric interactions, except in the case of an electronegative heteroatom, such as fluorine, that favored the alkylation at the most hindered position. Mechanistic studies revealed this reaction to proceed through an initial cyclometalation followed by activation of the alkyl bromide and reductive elimination.

An even broader process was reported by the Yoshikai group, who disclosed in 2013 an NHC/cobalt catalytic system

Scheme 11. Ruthenium- and cobalt-catalyzed *ortho*-alkylation of arylimines with alkyl halides. 1-AdCO₂H = 1-adamantanecarboxylic acid.

that was able to promote the alkylation of a range of aromatic imines with primary and secondary alkyl bromides and chlorides at room temperature [Scheme 11, Eq. (2)]. The main limitation is the requirement of an excess of a Grignard reagent, which clearly limits the functional groups tolerated.^[66] The stereochemical outcome of the reactions involving secondary alkyl halides suggests a single-electron transfer from a cobalt species to the starting alkyl halide to generate an alkyl radical, although a full mechanistic proposal was not reported. This process was further extended to the use of pivalophenone N–H imines, which were shown to be excellent benzonitrile surrogates for directed C–H alkylation, with the corresponding benzonitriles being generated in a subsequent step either by irradiation in the presence of a peroxide or by reaction with a catalytic amount of copper(II) acetate under aerobic conditions.^[67]

Further studies by the Ackermann group on the ruthenium-catalyzed alkylation of imines culminated in the development of a highly regioselective *meta*-alkylation with secondary and tertiary alkyl bromides (Scheme 12).^[68] The

Scheme 12. Ruthenium-catalyzed *meta*-alkylation of arylimines with alkyl halides. Boc = *tert*-butoxycarbonyl, Ile = isoleucin, TMP = 3,4,5-trimethoxyphenyl.

use of a catalytic system really close to the one used with primary alkyl bromides led to a clean *meta*-selective alkylation of TMP-imines occurring. The reaction was shown to proceed through a radical-based mechanism and the selectivity is most certainly due to an *ortho*-ruthenation activating the *meta* position towards radical addition, as will be discussed later with aryloxazolines (see Section 3.2.3, Scheme 21). The carboxylate was noted to have a strong effect, with 1-adamantylcarboxylic acid or Piv-Ile-OH providing the best results. A broad range of TMP-imines could be successfully alkylated with a series of alkyl bromides, and further derivatization of the alkylated products to an impressive diversity of *meta*-substituted arenes highlighted the synthetic potential of this procedure.

Besides alkyl halides, benzyl phosphates can also be used under cobalt-Pyphos catalysis for the *ortho*-benzylation of aromatic imines,^[69] and arylketoximes can be alkylated with epoxides under palladium catalysis.^[70]

2.3. Alkylation with Alkylmetal Reagents

In addition to alkenes and alkyl halides, alkylmetal reagents are attractive alkylating agents, notably because of their easy transmetalation with metal complexes. They were indeed shown to be especially convenient reagents for challenging direct alkylation reactions, but their use for the directed alkylation of carbonyl derivatives remains elusive—the main difficulty in this case is the potential competitive addition of some alkylmetal reagents to the directing group.

2.3.1. Methylation of Arylketones and Arylaldehydes with Trimethylaluminum and Potassium Alkyltrifluoroborates

The Ilies/Nakamura group reported in 2016 an especially interesting direct *ortho*-methylation of arylketones, a simple methyl group being especially difficult to introduce by C–H activation despite the broad interest of this transformation because of the “magic methyl” effect in medicinal chemistry and agrochemistry. Upon reaction with iron(III) acetylacetonate and a new tridentate phosphine ligand, 4-[bis[2-(diphenylphosphanyl)phenyl]phosphanyl]-*N,N*-dimethylaniline, which fills the coordination sphere of iron(III) once coordinated to the methyl group and to the metalated ketone, a range of arylketones were shown to be efficiently methylated with trimethylaluminum in the presence of 2,3-dichlorobutane as the oxidant [Scheme 13, Eq. (1)].^[71] Competing dimethylation was observed in some cases—a reaction that can be facilitated by increasing the catalytic loading and the amount of trimethylaluminum—and attempts at a directed ethylation with triethylaluminum resulted in competing reduction, addition, and dimerization.

Scheme 13. Iron- and iridium-catalyzed *ortho*-alkylation of arylketones and arylaldehydes with trimethylaluminum and potassium alkyltrifluoroborates. Fe(acac)₃ = iron(III) acetylacetonate, DCE = 1,2-dichloroethane.

A more general procedure enabling the introduction of a range of alkyl groups was reported in 2018 by the Sorensen group. Upon reaction with potassium alkyltrifluoroborates and an iridium(III)-based catalyst used in combination with catalytic amounts of aniline to enable the generation of a transient imine facilitating the *ortho*-metalation, a range of aromatic aldehydes were shown to be efficiently arylated, the main limitation being the double arylation at the *ortho* and *ortho'* positions with sterically and/or electronically unbiased substrates [Scheme 13, Eq. (2)].^[72]

2.3.2. Alkylation of Aryloximes with Alkylmetal Reagents

Aromatic oximes could also be efficiently alkylated at the *ortho* position with potassium alkyltrifluoroborates in the presence of catalytic amounts of a rhodium complex, [RhCp*Cl₂]₂, and silver hexafluoroantimonate together with silver fluoride, as demonstrated by the Li group (Scheme 14).^[73] The rhodium catalyst enables the competitive β -H elimination to be suppressed by the coordinative saturation enforced by the Cp* ligand and the cyclometalated group in the transient Cp*Rh(aryl)(alkyl) species, while silver fluoride acts as the terminal oxidant required to close the catalytic cycle. Various aryloximes were readily alkylated and the regioselectivity was found to be excellent. An electrochemical palladium-catalyzed procedure has also been reported.^[74]

Scheme 14. Rhodium-catalyzed *ortho*-alkylation of aromatic oximes with potassium alkyltrifluoroborates. DCE = 1,2-dichloroethane.

As shown with all the examples in this section, carbonyl derivatives act as highly efficient directing groups for the directed alkylation of C–H bonds in arenes with regioselectivities that could not be obtained using a Friedel–Crafts reaction. A broad range of carbonyl derivatives, including ketones, aldehydes, ketenimines, aldimines, or oximes, efficiently coordinate to various metal catalysts to provide the alkylated products in good yields and high levels of selectivity, mostly by using alkenes, alkyl halides, or alkylmetal reagents as alkylating agents. All the procedures reported to date are actually complementary and the choice of one over another should be based on the position to be alkylated as well as on the nature of both the directing group and the alkyl group to be introduced. Although most processes favor the alkylation

of the *ortho*-C–H bond, some procedures, however, allow for high levels of selectivity for the *meta*- and *para*- alkylation, even if more studies are still needed in this direction. The versatility of carbonyl derivatives, which can be readily transformed into a range of functional groups, also increases the synthetic usefulness and the attractiveness of these directed alkylation reactions.

In addition to carbonyl derivatives, many other directing groups have been introduced for the selective alkylation of C–H bonds in arenes. The use of carboxylic acids and their derivatives will be overviewed in the following section.

3. Carboxy-Derived Directing Groups

Carboxy derivatives are indeed quite attractive as directing groups in C–H activation processes and they can also be readily transformed into a range of functional groups. Although amides—to which an additional coordinating group can be easily attached to facilitate the selective activation of a C–H bond—are clearly the most utilized, carboxylic acids and other derivatives have also proven their efficiency over the years for directed alkylation with the same classes of reagents overviewed in Section 2. The use of alkenes will be discussed first.

3.1. Alkylation with Alkenes

As with carbonyl derivatives, alkenes are attractive reagents for the carboxy-directed alkylation of C–H bonds, provided that the regioselectivity of the addition of the metalated arene to the double bond can be fully controlled.

3.1.1. Alkylation of Aromatic Carboxylic Acids with Alkenes

Whereas most classes of carboxylic acid derivatives have proven to act as efficient directing groups in C–H alkylation reactions, the carboxylic acid moiety itself has been scarcely studied, despite its clear synthetic relevance; this can be attributed to its intrinsically weak coordinating properties. The first general process for the *ortho*-alkylation of benzoic acids with conjugated alkenes was in fact only reported in 2018 by the Gooßen group, who demonstrated that in the presence of catalytic amounts of [RuCl₂(*p*-cymene)]₂ and using Li₃PO₄ as the base, a broad range of benzoic acids could be readily alkylated with activated alkenes—including acrylic acid with cesium fluoride as the base—in water and in good to excellent yields (Scheme 15).^[75a] The electronic properties of the starting benzoic acids were shown to have little influence on the outcome of the reaction, and *meta*-substituted benzoic acids were predominantly alkylated at the least hindered position. The alkylation could be successfully extended to heteroarenes and an *in situ* decarboxylation—catalyzed in a one-pot process by copper(I) oxide and phenanthroline—could be favored at higher temperatures. Shortly after, a rhodium/copper co-catalyzed carboxy-directed *ortho*-alkylation with conjugated ketones *in situ* generated by dehydrogenation of the corresponding ketones,^[75b] as well as a ruthenium-

Scheme 15. Ruthenium-catalyzed *ortho*-alkylation of aromatic acids with alkenes.

nium-catalyzed oxidation/alkylation with allylic alcohols, were reported.^[75c]

In the case of maleimides, the directed alkylation can be followed by an *in situ* decarboxylation, with the carboxylic acid in the starting benzoic acid, therefore, acting as a traceless directing group.^[76]

3.1.2. Alkylation of Benzoates with Alkenes

In a continuation of their studies, the Murai group extended their ruthenium-catalyzed *ortho*-alkylation of aromatic ketones and imines with alkenes to the use of aromatic esters.^[77] These substrates turned out to be less reactive and required the presence of an additional electron-withdrawing group on the starting benzoate and an excess of the alkene for the reaction to proceed, as highlighted with the representative examples shown in Scheme 16. As regards the scope with respect to the alkene, only the most reactive ones (vinylsilanes and ethylene) have been reported.

Scheme 16. Ruthenium-catalyzed *ortho*-alkylation of aromatic esters with alkenes.

3.1.3. Alkylation of Aromatic Amides with Alkenes

The ruthenium-catalyzed alkylation of aromatic amides still seems to be restricted to certain substrates. Although the Murai procedure was indeed shown to be efficient for the

tetraalkylation of perylene bisimides^[78] and provided mixtures of alkylated and alkenylated products when cyclic imidates were used as substrates,^[79] its use with simple amides has remained elusive. The Ackermann group, however, reported in 2015 that conjugated ketones were excellent reaction partners for the carboxylate-assisted, ruthenium-catalyzed C–H *ortho*-alkylation of monodentate amides with excellent levels of regioselectivity in degassed water [Scheme 17, Eq. (1)].^[80] The regioselectivity starting from *meta*-substituted benzamides was found to be mostly governed by steric factors, except with heteroatom substituents, such as a fluorine atom or a dioxolane, which were found to have a considerable *ortho*-orienting effect. This reaction can also be performed from the corresponding allylic alcohols in the presence of an additional oxidant under ruthenium or rhodium catalysis^[81] and maleimides can be used as alkylating agents.^[82]

Iridium catalysis was also shown to provide remarkably efficient systems for the branched-selective *ortho*-alkylation of benzamides with a range of alkenes—the formation of branched products is much more challenging to achieve. Indeed, the Bower group showed that monosubstituted alkenes can be efficiently used for the branched-selective *ortho*-alkylation of a series of aromatic amides using a cationic iridium(I) catalyst modified with an electron-deficient biphosphine ligand with a wide bite angle [Scheme 17, Eq. (2)].^[33a] Subsequent DFT studies revealed an unusual mechanism: instead of the commonly accepted Chalk–Harrod-type mechanism invoked by Bower and co-workers and involving oxidative addition into the C–H bond after coordination of the substrate to the iridium catalyst, migratory insertion of the alkene into the Ir–H bond, and reductive elimination to form a C–C bond, the migratory insertion proceeds into the Ir–C bond and the reductive elimination then forms a C–H bond.^[83] As for the branched selectivity, whereas a migratory insertion placing the substituent β to the metal—to yield branched-selective products—is usually unfavorable due to electronic factors and steric repulsions around the forming C–C bond, the use of a phosphine with a wide bite angle overcomes these interactions because of a severe steric interaction between the substituent on the alkene and the phosphine. Moreover, the use of a hydroxo-iridium/chiral diene catalyst led to an enantioselective alkylation of *N*-sulfonylbenzamides with vinyl ethers being recently reported.^[84]

In addition to ruthenium and iridium complexes, cobalt catalysts have proven their efficiency for the directed *ortho*-alkylation of benzamides. Immediately after the first publication of the Yoshikai group on the cobalt-catalyzed directed regiodivergent alkylation of arenes,^[55] Nakamura and co-workers reported in 2011 an efficient alkylation of benzamides with a broad range of alkenes [Scheme 17, Eq. (3)].^[85] Terminal mono- and disubstituted alkenes as well as internal alkenes (undergoing an isomerization prior to the alkylation) were shown to be convenient substrates for the *ortho*-alkylation of primary benzamides in the presence of an inexpensive cobalt catalyst in combination with DMPU as the ligand and with additional cyclohexylmagnesium chloride at room temperature. Notable features of this procedure include

Representative examples

Representative examples

Proposed mechanism

Representative examples

Scheme 17. Ruthenium-, iridium-, and cobalt-catalyzed *ortho*-alkylation of aromatic amides with alkenes. BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate anion, $\text{d}^{\text{F}}\text{ppb}$ = 1,2-bis[di(2-fluorophenyl)phosphino]benzene, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)pyrimidinone, Mes = mesityl.

the broad scope of alkenes that can be used and its rather broad functional-group tolerance. However, when the start-

ing benzamide has two equally reactive positions, double alkylation tends to predominate. By using a Cp^* -carbonyl-cobalt(III) catalyst in the presence of AgSbF_6 , conjugated ketones can be used as alkylating agents, with acrolein providing benzazepinones from an alkylation/cyclocondensation sequence.^[86]

The main advantage associated with the use of amides as directing groups for the directed alkylation of C–H bonds lies in the possibility of embedding an additional coordinating moiety in the substrate, with the bidentate chelation facilitating the overall process.^[87] From this standpoint, and inspired by the pioneering studies of the Daugulis group on the use of 8-aminoquinoline amides as directing groups,^[88] Chatani and co-workers reported in 2013 an efficient directed alkylation of such substrates with conjugated ketones catalyzed by $\text{RuCl}_2(\text{PPh}_3)_3$.^[89a] Among all the bidentate chelating amides evaluated, 8-aminoquinoline amide turned out to be the most efficient and facilitated the *ortho*-alkylation of a range of amides with a broad set of conjugated ketones, including β -substituted ones (even if the reactions did not go to completion with such substrates; Scheme 18). The selectivity

Representative examples

Scheme 18. Ruthenium-catalyzed *ortho*-alkylation of bidentate chelating amides with alkenes.

was, however, found to strongly depend on the substrate: *ortho*-substituted amides were smoothly alkylated, while *meta*- and *para*-substituted ones gave substantial amounts of products resulting from a double alkylation at the *ortho* and *ortho'* positions. Importantly, the bidentate amide could be efficiently transformed to the corresponding carboxylic acid or aldehyde upon alkaline hydrolysis or reaction with the Schwartz reagent. The versatility of this directing group, therefore, compensates to some extent the loss of molecular weight inherent with its cleavage. This alkylation was later extended to the use of conjugated esters,^[90] styrenes,^[91] dihydrofurans, and unsaturated γ -lactones^[92] as well as maleimides^[93a] and *N*-vinylphthalimide^[93b] in the presence of a rhodium catalyst. An alternative and quite versatile catalytic system based on an iron catalyst was also recently reported by the Ilies/Nakamura group.^[89b]

3.2. Alkylation with Alkyl Halides

Besides alkenes, alkyl halides have also been used for the development of efficient processes for the directed alkylation of C–H bonds in aromatic carboxylic acids and their derivatives.

3.2.1. Alkylation of Benzoic Acids with Alkyl Halides

Although the use of benzoic acids might seem counter-intuitive because of a possible competitive alkylation of the acid moiety, a report by the Yu group nevertheless demonstrated the feasibility of this approach. They used, however, only 1,2-dichloroethane and dibromomethane, which resulted in a C–H alkylation/O-alkylation that provided benzolactones,^[94] or epoxides, which afforded 3,4-dihydroisocoumarins.^[95] As an alternative to allylic halides, the Gooßen group showed that allylic acetates could be used for a carboxylate-directed *ortho*-allylation of benzoic acids under ruthenium catalysis, with this procedure being compatible with both electron-rich and electron-poor substrates as well as linear and branched allyl acetates.^[96]

Mono- and bidentate amides actually represent the main directing groups utilized in such reactions: an overview of the most efficient processes developed to date for the directed alkylation of aromatic amides with alkyl halides will be presented in the following section.

3.2.2. Alkylation of Aromatic Amides with Alkyl Halides

Despite the fact that they are much more readily available, the use of simple monodentate amides has been far less investigated than their bidentate analogues. Apart from a really specific palladium-catalyzed *meta*-arylation of perylene bisimides,^[97] examples are indeed limited to the palladium(II)-catalyzed alkylation of *N*-arylamides with simple alkyl iodides developed by the Yu group, who identified 9-methylacridine or quinoline derivatives to be efficient ligands in the presence, in most cases, of additional pentafluorobenzoic acid to suppress the competing N-alkylation [Scheme 19, Eq. (1)],^[98] and to the cobalt-catalyzed alkylation of secondary benzamides with alkyl chlorides reported in 2011 by the Nakamura group [Scheme 19, Eq. (2)].^[99] Although primary alkyl halides perform well in both cases, the reaction is more problematic with more substituted alkylating agents and the use of unsubstituted or *para*-substituted carboxamides is either problematic or has not been reported.

Manganese dichloride was also shown to be an efficient precatalyst but limited to the alkylation of pyridine derivatives^[100a] and allyl carbonates can also be used for the rhodium(III)-catalyzed directed *ortho*-allylation of aromatic amides under mild conditions.^[100b]

In sharp contrast, the use of bidentate aromatic amides has been investigated much more and various metals have been shown over the years to efficiently catalyze their *ortho*-alkylation. The main catalytic systems reported with 8-aminoquinoline-derived benzamides are shown in Scheme 20 [Eq. (1)] and include palladium,^[88b,101] nickel,^[102]

Scheme 19. Palladium- and cobalt-catalyzed *ortho*-alkylation of monodentate aromatic amides with alkyl halides.

and iron-based^[103] catalyst systems. In 2015, the Chen group reinvestigated the palladium-catalyzed alkylation reported by Shabashov and Daugulis,^[88b] which resulted in the development of an especially efficient catalytic system based on a combination of palladium(II) acetate and a phosphate [Scheme 20, Eq. (1), insert 1]. This system enables a clean monoalkylation with both primary and secondary alkyl iodides, with the alkylation, which could be used for sequential *ortho*-alkylations, moreover, being stereoretentive.^[101a] This palladium-catalyzed directed alkylation was also extended to thiophene derivatives^[101b] and a 5-methoxy-8-aminoquinoline-derived carboxamide could be efficiently cleaved with cerium ammonium nitrate.^[101a]

In addition to these palladium-catalyzed reactions, the Chatani^[102a,b] and Ackermann^[102c] groups reported efficient nickel-based catalytic systems for the *ortho*-alkylation of 8-aminoquinoline-derived aromatic amides: although the conditions reported by Chatani and co-workers were shown to be efficient with primary alkyl bromides [Scheme 20, Eq. (1), insert 2],^[102a,b] the versatile conditions of Ackermann and co-workers enabled the use of a broad range of secondary alkyl bromides, but harsher reaction conditions were required, since both a strong base and high temperatures are required [Scheme 20, Eq. (1), insert 3].^[102c] Iron-based systems have been mostly studied by the Cook^[103a,b] and Ilies/Nakamura^[103c] groups. The main advantage of the procedures developed by the Cook group lies in the vast set of alkyl bromides that can be used—including secondary ones with additional BHT to suppress the over-alkylation—and the remarkably short

Scheme 20. *Ortho*-alkylation of bidentate aromatic amides with alkyl halides. BHT = butylated hydroxytoluene, DME = dimethoxyethane, dppe = bis(diphenylphosphino)ethane, dppe = bis(diphenylphosphino)ethylene, OTF[−] = triflate, TMEDA = *N,N,N',N'*-tetramethylethylenediamine.

reaction times [Scheme 20, Eq. (1), insert 4].^[103a,b] The catalytic system developed by Ilies/Nakamura and co-workers can be employed with primary and secondary tosylates—interesting surrogates of the corresponding halides in such reactions [Scheme 20, Eq. (1), insert 5].^[103c] Phenyl allyl ethers can also be used as allylating agents when treated with 8-aminoquinoline-derived aromatic amides in the presence of an iron catalyst,^[103d] and phenyltrimethylammonium iodide was shown to be an especially efficient methylation agent in combination with nickel catalysis.^[104] Epoxides can also be used in place of alkyl halides in such reactions.^[70] As a note, a combination of chromium(III) chloride and an NHC has been recently reported as an alternative catalytic system.^[105]

Following these studies, the Ackermann group reported in 2016 that triazole assisted the *ortho*-alkylation of bidentate aromatic amides especially efficiently. A large variety of bidentate amides derived from triazolymethyl (TAM) could be efficiently and regioselectively alkylated upon reaction with a range of primary and secondary alkyl bromides in the presence of an excess of phenylmagnesium bromide and catalytic amounts of iron(III) acetylacetonate and 1,2-bis(diphenylphosphino)ethane [Scheme 20, Eq. (2)].^[106] An advantage of this directing group is that it can be cleaved under mild conditions to the corresponding carboxylic acid upon reaction with NOBF₄. A simpler catalytic system based on catalytic manganese(II) chloride was reported later for the alkylation of such bidentate amides with primary alkyl bromides.^[107]

Moreover, *N*-(2-methylbenzoyl)amino ester derivatives can also act as efficient bidentate directing groups in palladium catalysis, but the substrate scope is rather narrow.^[108]

3.2.3. Alkylation of Aromatic Imidates with Alkyl Halides

In addition to carboxylic acids and amides, cyclic imidates have also proven their efficiency as directing groups in C–H alkylation reactions. After reporting a regioselective ruthenium-catalyzed benzylation^[109] and a cobalt-catalyzed alkylation^[110] of *o*-methyl-benzimidates, the Ackermann group reported a remarkably selective *meta*-alkylation of aryloxazolines (Scheme 21).^[111] Upon reaction with activated α -bromoesters in the presence of a ruthenium(II) carboxylate catalyst and triphenylphosphine, a clean *meta*-alkylation occurs in moderate to good yields. Extensive mechanistic studies led to the regioselectivity observed being attributed to a reversible carboxylate-assisted C–H ruthenation followed by a single-electron transfer from the cyclometalated ruthenium(II) complex to the alkyl bromide to generate, after bromide transfer, the cyclometalated ruthenium(III) intermediate. Radical addition to the aromatic moiety then proceeds at the position *para* to the ruthenium—calculated radical Fukui indices favor this position and highlight the

Scheme 21. Ruthenium-catalyzed *meta*-alkylation of aryloxazolines with activated alkyl bromides.

synergistic ruthenium/phosphine effect—followed by subsequent aromatization and proto-demetalation. The *ortho*-alkylation of 2-aryloxazolines with alkyl iodides using stoichiometric palladium has also been reported.^[112]

3.3. Alkylation with Alkylmetal Reagents

Compared to alkenes and alkyl halides, alkylmetal reagents have been less utilized for directed *ortho*-alkylations, despite their strong potential for the introduction of methyl groups, as highlighted in the benzoic acid series.

3.3.1. Alkylation of Benzoic Acids with Alkylmetal Reagents

The directed *ortho*-methylation of benzoic acids has indeed been shown to be efficiently performed with methylboronic acid or with trimethylaluminum. The Yu group actually reported in 2007 that methylboronic acid could efficiently perform the methylation of benzoic acid derivatives using palladium(II) acetate in the presence of benzoquinone and silver carbonate, although the scope of this transformation was, however, not fully studied since only two examples were reported.^[113] Later, they reported an efficient extension of this reaction to the more challenging introduction of butyl chains—for which potential β -hydride elimination is problematic—through the combination of palladium(II) acetate and a monoprotected amino acid ligand, *N*-acetylvaline, which was found to significantly improve the reaction [Scheme 22, Eq. (1)].^[114] The use of this procedure for the site-selective methylation of a medically relevant molecule possessing three carboxy moieties, BMS-98947-055-01, as well as its remarkable use for the total synthesis of (+)-hongoquercin A, clearly demonstrates the potential of this reaction.^[115] Later, the Ilies/Nakamura group, in a continuation of their studies on C–H activation reactions, demonstrated that trimethylaluminum, which has already been described above for the methylation of arylketones (Scheme 13), was especially effective for the iron-catalyzed *ortho*-methylation of a broad range of benzoic acids [Scheme 22, Eq. (2)].^[72] Substrates with a single substituent at the *para* position, however, gave significant amounts of dimethylation and, interestingly, esters and amides were also shown to be efficient directing groups.

3.3.2. Alkylation of Aromatic Amides with Alkylmetal Reagents

As previously mentioned, amides are among the most widely used directing groups, and their efficiency in directed *ortho*-alkylations with a range of alkylmetal reagents was unambiguously demonstrated. Simple monodentate amides could be successfully used: although only a single example of palladium-catalyzed alkylation of a peculiar *N*-arylbenzamide with potassium butyltetrafluoroborate was reported,^[116] the cobalt-catalyzed *ortho*-alkylation of secondary benzamides with Grignard reagents reported in 2011 by Nakamura and co-workers proceeds smoothly at room temperature using air as the sole oxidant [Scheme 23, Eq. (1)].^[117] The nature of the substituent on the nitrogen atom has a dramatic impact on the

Representative examples

Representative examples

Scheme 22. Palladium- and iron-catalyzed *ortho*-alkylation of benzoic acids with alkylmetal reagents.

Representative examples

Scheme 23. Cobalt- and manganese-catalyzed *ortho*-alkylation of monodentate aromatic amides with Grignard reagents.

selectivity of the alkylation, with *N*-methylbenzamides mostly favoring dialkylation while *N*-phenyl- or *N*-isopropyl derivatives preferentially give the monoalkylated products. The use of secondary Grignard reagents did not provide the corresponding alkylated products, which is the main limitation of most procedures relying on alkylmetal reagents.

More recently, an especially simple procedure for the *ortho*-methylation of secondary benzamides with methylmagnesium bromide based on the use of $\text{MnCl}_2 \cdot 2\text{LiCl}$ without any extraneous ligand in combination with 1-bromo-2-chloroethane as the oxidant was reported [Scheme 23, Eq. (2)].^[118] The attractive features of this procedure include the simplicity of the catalytic system, its high catalytic turnover, and its rather broad scope and good selectivity, even if double methylation can be problematic with a number of substrates.

Bidentate amides have also been shown to efficiently direct the *ortho*-alkylation of arenes. 8-Aminoquinoline-derived aromatic amides can indeed be methylated with trimethylaluminum at their *ortho* positions in the presence of catalytic amounts of iron(III) acetylacetonate, bis(diphenylphosphino)ethylene (dppen), and 2,3-dichlorobutane [Scheme 24, Eq. (1)].^[119] 2,3-Dichlorobutane would reoxidize

the putative iron(I) intermediate back to an iron(III) species, while the dppen ligand would stabilize this iron(I) catalytic end product through metal-to-ligand charge transfer. The scope of this methylation was found to be rather broad, except, and this is the main limitation of the majority of the procedures overviewed up to this point, with substrates possessing two identical C–H bonds *ortho* to the directing group, for which double methylation is, here again, favored. Moreover, the reaction could be successfully extended to ethylation with triethylaluminum, and air-stable bis(trimethylaluminum)·DABCO (DABCO = 1,4-diazabicyclo[2.2.2]octane) could be used in place of the more hazardous trimethylaluminum. A cobalt-catalyzed version of this reaction was later reported.^[120]

A broader variety of alkyl groups can be introduced when switching to alkylzinc halides generated in situ from the corresponding Grignard reagents and $\text{ZnCl}_2 \cdot \text{TMEDA}$ in the presence of the same catalytic system and the mild dichloroalkane oxidant 1,2-dichloroisobutane [Scheme 24, Eq. (2)].^[121] Primary, including methyl, and cyclic secondary alkyl groups could be readily introduced, but an acyclic secondary Grignard reagent underwent isomerization to furnish a mixture of linear and branched alkylation products. Dicumyl peroxide was also shown to be an efficient reagent for the methylation of 8-aminoquinoline-derived aromatic amides under nickel catalysis,^[122] and the directing group in 8-aminoquinoline-derived aromatic amides can also be functionalized itself under radical conditions.^[123]

Readily cleavable triazole-derived bidentate amides introduced by the Ackermann group were also shown to be efficient directing groups. Their manganese-^[107] and iron-catalyzed^[124] methylation and ethylation with the corresponding Grignard reagents were especially efficient, with the double alkylation at the *ortho* and *ortho'* positions once again representing the main limitation of these procedures [Scheme 24, Eq. (3)].

3.3.3. Alkylation of Aromatic Imidates with Tetraalkyltin Reagents

The alkylation of aromatic imidates with alkylmetal reagents has been far less investigated. Indeed, a single report by the Yu group describes their palladium-catalyzed methylation and ethylation with the corresponding tetraalkyltin derivatives in the presence of stoichiometric amounts of copper(II) acetate and benzoquinone.^[125] Although interesting from a mechanistic point of view, the use of alkyltin derivatives instead of, for example, the corresponding Grignard or tetrafluoroborate reagents is, however, less appealing.

3.4. Alkylation of Aromatic Bidentate Amides by Cross-Dehydrogenative Coupling with Alkanes and Ethers

When looking at all the reagents utilized for the directed alkylation of C–H bonds in arenes, alkanes are clearly the ideal ones, at least from an atom-economical point of view. Their use is, however, especially challenging because of the

Scheme 24. Iron- and manganese-catalyzed *ortho*-alkylation of bidentate aromatic amides with alkylmetal reagents.

number of C(sp³)–H bonds that can be activated in the starting alkane. Activated (mostly toluene derivatives) or cyclic alkanes are, therefore, used—usually in excess—to ensure a selective activation. In terms of the carboxy derivatives used in such formal dehydrogenative cross-coupling reactions, it is not surprising that bidentate aromatic amides occupy the central place because of their excellent coordination ability.

In this context, the Chatani group developed a remarkably efficient nickel(II)-catalyzed oxidative coupling between 5-chloro-8-aminoquinoline-derived amides and toluene derivatives in the presence of heptafluoroisopropyl iodide [Scheme 25, Eq. (1)].^[126] Upon reaction with catalytic amounts of nickel(II) triflate and triphenylphosphine using either toluene as the solvent or 10 equivalents of toluene derivatives in *tert*-butylbenzene, a clean *ortho*-benzylation occurs in excellent yields. In terms of the selectivity, *meta*-substituted amides reacted at the least hindered position in most cases and double benzylation was observed in the absence of substituents on the starting amide. A chlorine substituent on the directing group is needed to prevent its fluoroalkylation. Although three possible mechanisms could be invoked to rationalize this nickel-catalyzed reaction, DFT studies were in favor of an iodine atom transfer, which is in agreement with Chatani's deuterium-labeling and radical inhibition experiments.^[127]

Representative examples

Representative examples

Scheme 25. Nickel- and cobalt-catalyzed *ortho*-alkylation of aromatic bidentate amides with alkanes. DTBP = di-*tert*-butyl peroxide.

A radical mechanism would also be operative in the cobalt-catalyzed *ortho*-alkylation of (pyridine-2-yl)isopropyl-derived bidentate amides with alkanes recently reported by Li and co-workers [Scheme 25, Eq. (2)].^[128] Cycloalkanes, toluene derivatives, as well as ethers and thioethers could be successfully utilized, with linear alkanes not surprisingly yielding mixtures of regioisomers. Despite its efficiency, this alkylation is, however, limited to substrates possessing a single *ortho*-C–H bond; other substitution patterns yield mixtures of mono- and dialkylated products, the stoichiometry of which is impossible to modify since alkanes are used as solvents and thus favor the dialkylation.

As evidenced by all the representative examples overviewed so far, a great deal of effort has been devoted to the development of efficient procedures for the alkylation of C–H bonds in arenes directed by carbonyl and carboxy derivatives. Although the *ortho*-C–H bonds are usually alkylated in a selective manner, some reactions allow clean and highly selective alkylations of *meta*- or *para*-C–H bonds. Depending on the nature of the directing group, post-functionalization can be carried out to afford a range of functional groups, and attention should be paid to this crucial step when using a directed alkylation reaction. Numerous research groups have focused their attention on the use of other directing groups such as anilines, whose directed alkylation will be overviewed in the following section.

4. Anilines and Derivatives as Directing Groups

Alkylated anilines are major molecules and building blocks in many areas of sciences, and the alkylation of anilines and their derivatives is a fundamental transformation. Their directed alkylation has been shown to be remarkably efficient, and the *ortho*, *meta*, and *para* positions can all be activated through the proper choice of directing group and catalyst system. As with other directing groups, alkenes, alkyl halides, and alkylmetal reagents have been the most commonly used alkylating agents.

4.1. Alkylation with Alkenes

4.1.1. Alkylation of Anilines with Alkenes

Anilines themselves do not appear to be the most attractive substrates for directed C–H alkylation because of the potential requirement for a putative four-membered ring chelate upon activation of an *ortho*-C–H bond with the metal catalyst. An early report from Uchimaru, however, demonstrated the feasibility of the ruthenium-catalyzed *ortho*-alkylation of *N*-methylaniline with styrene to afford the branched isolated product in 83 % yield.^[129] Besides this isolated example, the Luo and Hou group recently reported an especially efficient and selective *ortho*-alkylation of *N,N*-dimethylanilines with a range of terminal alkenes using a cationic half-sandwich yttrium catalyst (Scheme 26).^[130] Branched products were obtained and the *ortho*-selectivity nicely complements the formation of *para*-alkylated products in Friedel–Crafts-type alkylations with activated alkenes.

Scheme 26. Yttrium-catalyzed *ortho*-alkylation of *N,N*-dimethylanilines with alkenes.

Based on kinetic isotopic effects and DFT calculations, the mechanism shown in Scheme 26 was proposed, which involves a cationic yttrium catalyst formed in situ from the precatalyst, $[\text{Ph}_3\text{C}][\text{B}(\text{C}_6\text{F}_5)_4]$, and the starting aniline. Coordination of the alkene to this catalyst places its substituent away from the bulky $\text{C}_5\text{Me}_4\text{TMS}$ ligand and a further 1,2-migratory insertion of the alkene gives a six-membered metallacycle complex through a four-center transition state. Coordination of the starting aniline to this intermediate then breaks the metallacycle, and a concerted C–H activation and proto-demetalation finally gives the alkylated aniline and regenerates the active catalyst.

4.1.2. Alkylation of Anilides with Alkenes

Anilides are better substrates for cyclometalations and their directed C–H alkylation has been far more studied. Although there are only isolated examples of the ruthenium-catalyzed Murai reaction with anilides^[80] or related *N*-benzoylindoles,^[131] other metals have proven their efficiency for the alkylation of anilides. In addition to the use of rhodium or iridium catalysis for the alkylation of *N*-acylindolines^[132] or

N-acylindoles^[133] with alkenes, general systems enabling the use of anilides as substrates have been reported through the use of iridium- or nickel-based catalysts that allow their regioselective alkylation at all the *ortho*, *meta*, and *para* positions.

Indeed, the Bower group extended their branched-selective *ortho*-alkylation of aromatic amides^[33a] (Scheme 17) to the analogous reaction with anilides.^[134a] A brief optimization resulted in effective iridium(I) catalysts—the nature of the counterion is important with respect to the nature of the starting alkene—that provided high branched and *ortho* selectivities [Scheme 27, Eq. (1)]. An enantioselective version based on the use of a Kelliphite-type chiral ligand for iridium was subsequently reported.^[134b] In a similar

Scheme 27. Iridium- and aluminum/nickel-catalyzed *ortho*-, *meta*-, and *para*-alkylation of anilides with alkenes.

vein, Nakao and co-workers extended their cooperative nickel/aluminum-catalyzed *para*-alkylation of ketones^[36] (Scheme 6) to anilides.^[135] *N*-Methylanilides were shown to be alkylated with terminal alkenes at their *meta* or *para* positions, with linear products being formed in both cases. The nature of both the substrate and ligand was found to be crucial to reach high levels of selectivity, as well as a bulky aluminum phenoxide that coordinates to the substrate and a nickel(0) precatalyst. Indeed, *N*-methyl-*N*-cyclohexylcarbonylanilines and a less bulky *N*-heterocyclic carbene favors alkylation at the less electron-rich *meta* position [Scheme 27, Eq. (2)], while a bulky carbene orients the alkylation to the less hindered *para* position of *N*-(isopropyl/2-isopentyl)-*N*-*tert*-butylcarbonylanilines [Scheme 27, Eq. (3)]. Although these alkylations are highly regioselective, other isomers are still formed.

β -Substituted acrylates can also be used for the *ortho*-alkylation of acetanilides, even in an enantioselective manner by using chiral iridium catalysts.^[136] Finally, an oxidative alkylation of *N*-(2-pyrimidinyl)anilines with allylic alcohols to yield the corresponding ketones in the presence of a rhodium catalyst and copper(II) acetate as the oxidant was also developed. However, only three examples with *ortho*-substituted starting materials were reported.^[81b]

4.2. Alkylation with Alkyl Halides

4.2.1. Alkylation of Anilines with Alkyl Halides

Since anilines are poor substrates in Friedel–Crafts reactions, because of coordination of the nitrogen atom to the Lewis acid, the development of alternative methods to perform their alkylation is necessary. To date, a single general process has been reported based on the photocatalyzed radical alkylation of *N,N*-dialkylanilines with activated alkyl halides: although this reaction is clearly not a directed C–H alkylation, it still deserves to be described here for the sake of comparison with other methods and because of its complementarity.^[137] Irradiation of catalytic amounts of Ru(bpy)₃Cl₂ and sodium acetate in acetonitrile at room temperature with blue LEDs led to a smooth *ortho*-alkylation occurring (Scheme 28). The reaction is efficient, but the substrate

Scheme 28. Ruthenium-catalyzed photoinduced *ortho*-alkylation of anilines with activated alkyl bromides.

scope is rather restricted, since electron-rich *para*-substituted anilines and α -bromo- α,α -dialkylacetophenones are required. In terms of the selectivity, *ortho*-alkylation is favored over *meta*-alkylation due to its higher electron density. As mentioned above, the aniline moiety is not a directing group in this case.

4.2.2. Alkylation of Anilides with Alkyl Halides

Similar to anilines, little effort has been devoted to the alkylation of anilides with alkyl halides. Whereas Friedel–Crafts alkylations favor the *para* position, directed alkylation should facilitate *ortho*-alkylation and thus be complementary. Indeed, an early report from Tremont and Rahman at Monsanto demonstrated that in situ generated *ortho*-palladated acetanilides—formed upon reaction of the starting acetanilide with excess palladium(II) acetate—smoothly reacted with methyl and ethyl iodide to provide the corresponding alkylated acetanilides (Scheme 29).^[138] Interestingly, increasing the amount of palladium(II) acetate and omitting acetonitrile provided the dialkylated acetanilides in excellent yields. So far, attempts at developing a catalytic version of this reaction have been, however, rather disappointing in terms of efficiency^[138] or selectivity.^[139]

Other approaches devoted to the development of efficient and broadly applicable processes for the directed alkylation of aniline derivatives with alkyl halides have been mostly based on the introduction of a directing group on the nitrogen atom: this will be overviewed in the next subsections.

Scheme 29. Palladium-mediated *ortho*-alkylation of acetanilides with alkyl iodides.

4.2.3. Alkylation of *N*-(2-Pyrimidinyl)anilines with Alkyl Halides

For any directing group to be of any synthetic usefulness, it must, in addition to efficiently directing the alkylation, be cleaved under reasonable conditions. The pyrimidinyl group meets these requirements, and efficient processes for the directed alkylation of *N*-(2-pyrimidinyl)anilines with alkyl halides have been reported recently. It should, in addition, be mentioned that alkylated *N*-(2-pyrimidinyl)anilines are key structural motifs in medicinal chemistry and agrochemistry.

Interestingly, all the positions of *N*-(2-pyrimidinyl)anilines can be selectively alkylated by finely tuning the catalytic system and the nature of the pyrimidine and the alkyl halide. Indeed, *ortho*-alkylation with primary and secondary alkyl bromides is favored in the presence of (DME)NiCl₂, a diamine ligand, and lithium *tert*-butoxide [Scheme 30, Eq. (1)],^[140] while the combination of [RuCl₂(*p*-cymene)]₂ and *N*-pivaloylvaline or *N*-adamantylcarbonylisoleucine orients the alkylation to the *meta* position with tertiary alkyl bromides [Scheme 30, Eq. (2)].^[141] Removing this ligand, switching to α -bromoesters, performing the reaction in *tert*-butyl methyl ether (TBME), and using 5-chloropyrimidine or quinazoline as the directing groups enables a highly *para*-selective alkylation [Scheme 30, Eq. (3)].^[142] The selectivity and substrate scope were found to be good in all cases. In terms of the regioselectivity, a reversible *ortho*-C–H nickelation to yield

Scheme 30. Nickel- and ruthenium-catalyzed *ortho*-, *meta*-, and *para*-alkylation of *N*-(2-pyrimidinyl)anilines with alkyl bromides. SET = single-electron transfer.

a six-membered nickelacycle followed by single-electron transfer, radical rebound, and reductive elimination was proposed to account for the nickel-catalyzed *ortho*-alkylation—although the oxidation states of the transient nickel species have not been unambiguously determined. The rationalization for the *meta*-alkylation closely follows the one described above for the *meta*-selective alkylation of aryloxazolines (Scheme 21).^[111] The selectivity for the *para*-alkylation was proposed to originate from a selective deprotonation of the N–H bond that yielded a four-membered ruthenacycle favoring the *para*-alkylation, with a carbonate as the base. In contrast, the use of carboxylates in *meta*-alkylations favor C–H ruthenation, which leads to radical addition at the *meta* position. All the key intermediates are shown in Scheme 30. Importantly, the pyrimidine directing group could be efficiently cleaved, although under rather harsh acidic conditions.^[140,141] The nickel-catalyzed *ortho*-alkylation could also be extended to purine bases^[143a] and can also be efficiently catalyzed by bimetallic nickel complexes.^[143b] Furthermore, a rhodium-catalyzed alkylation of *N*-(2-pyridyl)aniline with conjugated ketones resulted in the installation of homoallyl groups through an alkylation/transfer hydrogenation/dehydration sequence.^[144]

4.3. Alkylation of Anilides with Alkylmetal Reagents

Alkylmetal reagents are also especially convenient for the introduction of simple alkyl chains, such as a methyl group. In this context, the Sanford group reported an efficient and mild palladium-catalyzed *ortho*-alkylation of anilides with potassium alkyltrifluoroborates in the presence of manganese trifluoride that acts as a source of F^+ to generate high-valent palladium intermediates (Scheme 31).^[145] The alkylation was shown to be both efficient and selective for the introduction of methyl and primary alkyl chains.

Scheme 31. Palladium-catalyzed *ortho*-alkylation of anilides with potassium alkyltrifluoroborates.

To conclude this section, we mention that an isolated example of methylation of a *N*-(4-triazolylcarbonyl)aniline with methylmagnesium bromide under iron catalysis^[124] has been reported as well as a palladium-catalyzed decarboxylative alkylation of *N*-(2-pyrimidinyl)indolines with carboxylic acids,^[146a] an alkylation that can also be performed with paraformaldehyde^[146b] or diazoesters^[146c] under ruthenium and rhodium/iridium catalysis, respectively.

As highlighted in this section, a set of efficient procedures has been reported for the directed alkylation of anilines and their derivatives at all possible positions. For the reactions to be selective, all the reaction parameters, including in some cases the nature of the substrates themselves, must be finely tuned, and most aniline derivatives can be alkylated with high efficiency. Moreover, the introduction of a chelating group on the nitrogen atom facilitates coordination to various metals, which notably promotes challenging *meta*- and *para*-alkylations. Care should be taken, however, to consider the conditions required for the removal of such directing groups.

The next section will be devoted to even more challenging substrates: phenols and their derivatives.

5. Phenols and Derivatives as Directing Groups

As with anilines, the Friedel–Crafts alkylation of phenols is often problematic because of severe polyalkylation and the impossibility to obtain *meta*-alkylated phenols. The use of directed C–H alkylations offers efficient alternatives that address, at least partially, some of these limitations: they will be overviewed in this section.^[147] Directed alkylations of phenols often involve putative four-membered metallacycles and the role of the hydroxy group as a directing group might, therefore, be questioned. Since these intermediates are invoked in most C–H alkylations with such substrates, they will thus be considered as directed C–H alkylations. Metal-catalyzed nondirected alkylations will be briefly described for the sake of comparison, but not Friedel–Crafts-type alkylations.

5.1. Alkylation with Alkenes

Besides an isolated report on the iridium-catalyzed alkylation of phenol with norbornene,^[148] the first general procedures for the metal-catalyzed *ortho*-alkylation of phenols with alkenes were actually reported only fairly recently. Kuninobu and Takai reported in 2009 an efficient rhenium-catalyzed procedure to yield branched products, whereby the regioselectivity with respect to the starting phenol was shown to depend on the nature of the alkene: whereas terminal alkenes provided *ortho*-alkylated phenols [Scheme 32, Eq. (1)], *para*-alkylation was mainly observed with *gem*-disubstituted alkenes [Scheme 32, Eq. (2)].^[149] The mechanism of this transformation was, however, not reported and the exact influence of the hydroxy group is, therefore, unclear. A strong influence of the nature of the starting alkene was

Scheme 32. Rhenium-, yttrium-, and scandium-catalyzed *ortho*- and *para*-alkylation of phenols and anisoles with alkenes.

also noted during the study of the *ortho*-alkylation of anisoles catalyzed by cationic half-sandwich yttrium and scandium complexes: styrene derivatives provided linear products with the yttrium catalyst [Scheme 32, Eq. (3)], while other substituents gave branched alkylated anisoles with the scandium catalyst [Scheme 32, Eq. (4)].^[150] The mechanism proposed for this transformation is similar to that of the yttrium-catalyzed alkylation of anilines developed by the same group and described in Section 4.1.1 (Scheme 26).^[130] The switch in selectivity was attributed to a coordination of the alkene to the intermediate cyclometalated phenol placing an alkyl substituent away from the bulky Cp^* ligand, while placing an aryl substituent close to the metal would be preferred for electronic reasons. This last process could be nicely extended to the polyalkylation of dimethoxyarenes with unconjugated dienes to give new polymers.^[151]

A solution to favor the directed alkylation of phenol derivatives, which implies the formation of highly strained metallacycles starting from phenols and aryl ethers, would be to add another coordinating group to form a larger chelate. Although this has been an efficient strategy in the aniline series, where anilides were shown to be better substrates than anilines, it has surprisingly been rarely used for the alkylation of phenols with alkenes or has been studied with specific substrates only.^[152]

5.2. Alkylation with Alkyl Halides

This strategy enabled the development of a highly *meta*-selective alkylation of *O*-(2-pyridyl)phenols. Based on the *meta*-alkylation of aryloxazolines^[111] and *N*-(2-pyrimidinyl)-anilines^[141] by Ackermann, the Li group extended the strategy to the *meta*-alkylation of phenols with an embedded pyridine directing group (Scheme 33).^[153] A broad range of *O*-(2-pyridyl)phenols could be regioselectively alkylated at their *meta* positions with secondary and tertiary alkyl bromides upon reaction with catalytic amounts of $[\text{RuCl}_2(p\text{-cymene})]_2$ and 1-adamantanecarboxylic acid in the presence of potassium carbonate. Double alkylation does not seem to be an issue and the presence of an *ortho* substituent in the starting material led to the alkylation proceeding, for mechanistic

Scheme 33. Ruthenium-catalyzed *meta*-alkylation of *O*-(2-pyridyl)phenols with alkyl bromides.

reasons, close to this substituent. Electron-poor and *meta*-substituted starting materials were, however, found to be reluctant reaction partners. This process could be elegantly applied to the synthesis of etoxazole, a pesticide, and the directing group—which can be substituted by a pyrimidine—could be removed, but under harsh conditions (TfOH, toluene, 100 °C then Na, MeOH, reflux). The mechanism closely follows the one proposed by the Ackermann group [Schemes 21 and 30, Eq. (2)] and will, therefore, not be described here.

5.3. Alkylation with Alkylmetal Reagents

Only nonbasic alkylmetal reagents can be used for the alkylation of free phenols because of their acidity. Potassium aminomethyltrifluoroborates meet this requirement, and the Wang group showed that they were efficient reagents for the copper-catalyzed *ortho*-aminomethylation of phenols (Scheme 34).^[154] Upon reaction with catalytic amounts of copper(II) acetate and sodium acetate, a range of phenols could be readily aminoalkylated in an open flask regardless of the electronic and steric properties of the starting phenols; however, *meta*-substituted ones gave mixtures of regioisomers. The mechanism proposed involves the formation of a copper(II) phenoxide that coordinates to the nitrogen atom of the aminomethyltrifluoroborates. Further oxidation by copper(II) species generates a boron radical whose homolytic cleavage yields a carbon-centered radical that then adds to the phenol with concomitant reduction of copper(II). Rearomatization and decooordination of the alkylated phenol followed by oxidation of copper(I) to copper(II) finally close the cycle.

Scheme 34. Copper-catalyzed *ortho*-aminomethylation of phenols with potassium aminomethyltrifluoroborates.

5.4. Alkylation with Alcohols

Alkenes, alkyl halides, and alkyltrifluoroborates are efficient reagents for the regioselective alkylation of phenols. Despite the efficiency of processes based on these reagents, the search for alternative alkylating agents has been the focus of various research groups, with the aim of developing broader and/or complementary procedures that would utilize readily available reagents and possibly generate benign by-products. With this goal in mind, the Yi group reported in 2012 an innovative ruthenium-catalyzed dehydrative *ortho*-alkylation of phenols with aliphatic alcohols (Scheme 35).^[155]

Scheme 35. Ruthenium-catalyzed *ortho*-alkylation of phenols with alcohols.

A well-defined cationic ruthenium hydride complex, $[(C_6H_6)(PCy_3)(CO)RuH]BF_4$, was shown to efficiently catalyze this alkylation with a range of primary and secondary alcohols, with the *ortho*-alkylated products being isolated in excellent yields and selectivities. This procedure could be applied with both structurally complex alcohols and phenols. Although the mechanism is still rather unclear, it is proposed to involve an *ortho*-ruthenation of the starting phenol followed by coordination of the alcohol to the strained ruthenacycle. The formation of the alkylated phenol would subsequently involve either oxidative addition at the C–OH bond followed by reductive elimination or σ -bond metathesis.

Except for remote directing groups, which will be overviewed in Section 9, the synthetically most relevant and the most general ones—carbonyl, carboxy, aniline, and phenol derivatives—can be selectively alkylated at most positions. Although removal of the directing group, whenever required, can be problematic in some cases, tremendous advances for the directed alkylation of arenes have been reported. Other directing groups, although seemingly more exotic, have also proven their efficiency in such reactions. This is notably the case with the azo moiety, which will be overviewed in the next section.

6. Azoarenes as Directing Groups

Diazoarenes, in addition to their use in many areas, are also excellent precursors of anilines through reduction. The development of efficient processes for their directed alkylation, therefore, makes sense and several procedures based on the use of various alkylating agents have recently been reported.

Li and Wang disclosed in 2015 an *ortho*-alkylation of symmetrical diazoarenes with allyl acetates, which surprisingly act as alkylation rather than allylation agents [Scheme 36, Eq. (1)].^[156] Upon reaction with an in situ generated cationic rhodium complex, alkylation occurs selectively at the *ortho* position of one of the aromatic rings. The regioselectivity was found to be excellent in all cases and a double monoalkylation of the two aromatic rings could be promoted by using an excess of the allyl acetate.

Alkyl halides can also be used as alkylating agents, as recently reported by the Li/Yang group, who extended Ackermann's ruthenium-catalyzed, carboxylate-assisted *meta*-alkylation^[111,141] to azoarenes.^[157] Whereas secondary and tertiary alkyl bromides furnished, as expected based on Ackermann's mechanistic proposal, *meta*-alkylated azoarenes [Scheme 36, Eq. (2)], the use of primary alkyl bromides surprisingly gave *ortho*-alkylation [Scheme 36, Eq. (3)], although no rationalization for this impressive switch in selectivity was given by the authors. In both cases, increasing the amount of the alkyl halide enables a double monoalkylation of the two aromatic rings. Interestingly, the authors demonstrated that the alkylated azoarenes could be smoothly

reduced to the corresponding anilines by reaction with metallic iron and acetic acid.

Finally, a complementary procedure, from a selectivity point of view, was reported in 2015 for the selective introduction of primary and secondary alkyl chains at the *ortho* position of azoarenes by using the corresponding carboxylic acids [Scheme 36, Eq. (4)].^[146] The reaction with catalytic palladium(II) acetate and iodozobenzene diacetate as the oxidant led to a decarboxylative alkylation to provide the *ortho*-alkylated azoarenes together with minor amounts of *ortho,ortho'*-dialkylated products. As regards the mechanism, although the starting directed palladation proposed by the authors seems reasonable, the rest of the catalytic cycle needs further mechanistic studies.

The next section of this Review will focus on one of the most studied classes of substrates in directed C–H alkylations: arenes possessing a nitrogen-containing heteroarene as an *ortho*-directing group.

7. N-Heteroarenes as Directing Groups

Nitrogen-containing heteroarenes are excellent directing groups and their use in C–H alkylations has been extensively studied. Despite their remarkable efficiency in such processes, the main limitation of these directing groups is that their cleavage or post-functionalization is very difficult in most cases. The most striking example is certainly the 2-pyridyl group, one of the most efficient directing groups for directed alkylations of C–H bonds in arenes, which provides access to *ortho*-alkylated 2-pyridylarenes, not to “*ortho*-alkylated arenes” as it is frequently claimed.

These directing groups have two main advantages: 1) they provide access to *ortho*-alkylated heteroarenes, useful molecules in various areas, such as medicinal chemistry and agrochemistry and—probably most importantly—2) they are excellent model substrates for directed alkylation reactions and some of the processes developed with such starting materials could then be successfully extended to other directing groups. As a consequence of the great number of directed alkylations reported with these substrates, they will be overviewed in a concise manner, with an emphasis on the most relevant and/or innovative procedures. This section will focus on substrates for which the nitrogen-containing heteroarene directing group is directly linked to the arene to be alkylated. Substrates with a spacer between these two moieties have already been covered in Sections 3.1.3, 3.2.2, 3.3.2, 3.4 (bidentate aromatic amides), 4.2.3 (*N*-(2-pyrimidinyl)anilines), and 5.2 (*O*-(2-pyridyl)phenols) or will be overviewed later (Section 9.5, 2-pyridyl-diisopropylsilyl-substituted arenes).

7.1. Alkylation with Alkenes

2-Phenylpyridine is an ideal substrate for cyclometalation by transition-metal complexes and the Kim group reported, one year after the discovery of the Murai reaction, that such substrates react with terminal alkenes and styrenes in the

Scheme 36. Rhodium-, ruthenium-, and palladium-catalyzed *ortho*- and *meta*-alkylation of azoarenes with allyl acetates, alkyl halides, and aliphatic carboxylic acids.

Scheme 37. Rhodium-, ruthenium-, cobalt-, and iridium-catalyzed *ortho*-alkylation of 2-(N-heteroaryl)arenes with alkenes. coe = cyclooctene, (R)-BINAP = (R)-2,2-bis(diphenylphosphino)-1,1'-binaphthyl, IMes = 1,3-dimesitylimidazol-2-ylidene.

presence of a rhodium(I) catalyst to mainly afford the linear *ortho*-alkylated products (Scheme 37, insert 1),^[158] with a mechanism that is similar to that of the Murai reaction (Scheme 1). Following this discovery, a range of catalysts have been reported for the alkylation of 2-pyridylarenes and related substrates with alkenes: the most representative examples are shown in Scheme 37. As for rhodium-based catalytic systems, they have been subsequently extended to the *ortho*-alkylation of 2-pyridylarenes as well as 1-isoquinoline and 1-pyrazole derivatives with conjugated ketones (Scheme 37, insert 2)^[159]—a reaction that can also be performed from the corresponding allylic alcohols in the presence of an additional oxidant,^[81b] as well as to atropo-selective alkylations^[160] and to the double alkylation of 2,2'-bipyridines.^[161]

Ackermann and co-workers demonstrated that ruthenium(II) complexes can efficiently catalyze the alkylation of similar substrates in the presence of a bulky carboxylate to assist the cleavage of the C–H bond (Scheme 37, insert 3),^[162] Pyridines, imidazoles, and pyrazoles served as efficient directing groups to furnish the linear *ortho*-alkylated products in excellent yields and selectivity without any competing double alkylation. Methylenecyclopropanes can also be used as alkylating agents with ruthenium catalysis^[163] to afford the linear products as well as oxa- and azabicyclic alkenes;^[164] the efficiency of a ruthenium/N-heterocyclic carbene system was also recently demonstrated.^[165] In terms of the scope with respect to the arene to be alkylated, thiophene^[162] and benzofuran^[166] derivatives were shown to be suitable substrates.

The use of cobalt catalysis turned out to be especially efficient for the control of the branched/linear selectivity. The

Yoshikai group reported a regioselectivity-switchable *ortho*-alkylation of 2-arylpyridines with styrenes: whereas the use of an N-heterocyclic carbene provided the linear products (Scheme 37, insert 4), tricyclohexylphosphine furnished the branched isomers almost exclusively (Scheme 37, insert 5).^[55] The proposed mechanism involving chelation-assisted oxidative addition of a cobalt(0) species into the C–H bond, styrene insertion, and reductive elimination was corroborated by DFT studies, which in addition suggested that the ligand-controlled regioselectivity was mainly a result of its bulkiness.^[167] A cationic high-valent Cp*Co^{III} complex was also shown to efficiently catalyze the directed alkylation with conjugated alkenes.^[168]

Iridium catalysis has also proven its synthetic usefulness for the alkylation of arenes directed by N-heteroarenes, notably for the development of enantioselective versions, only with specific substrates, however. Indeed, whereas the iridium-catalyzed *ortho*-alkylation of such substrates with conjugated alkenes provides linear products,^[169] reactions with vinyl ethers were found to be branched-selective.^[170] This logically paved the way for the development of enantioselective versions,^[171] which culminated in a recent report from the Nishimura group on enantioselective hydroxyalkylation with allyl ethers—*isomerized in situ* to the corresponding vinyl ethers prior to the alkylation—with a cationic iridium/BINAP catalyst (Scheme 37, insert 6).^[172] The alkylation^[51] of 2-pyridyl- or 1-isoquinolinylferrocenes induces a planar chirality that could be controlled using chiral diene ligands for iridium.^[173]

As a final note, *ortho*-alkylations with conjugated alkenes have also been reported to proceed under manganese^[174] and rhenium catalysis.^[175]

7.2. Alkylation with Alkyl Halides

Trapping cyclometalated 2-(N-heteroaryl)arenes with alkyl halides is an efficient strategy for the introduction of an alkyl group at the *ortho* position, and a range of metals have been reported to catalyze this reaction (for examples, see Scheme 38). The use of palladium catalysis has surprisingly been reported only recently: the groups of Zhang reported the alkylation of 2-pyridylarenes with primary alkyl iodides (Scheme 38, insert 1)^[176] and Bach demonstrated that electron-poor pyrroles could act as efficient directing groups (Scheme 38, insert 2).^[177] Double *ortho,ortho'*-alkylation was observed with substrates possessing two equally reactive C–H bonds.

The use of cobalt catalysis for the *ortho*-alkylation of 2-pyridylarenes with both primary and secondary alkyl chlorides—attractive alkylating agents—has proven to be remarkably efficient, since it was shown to proceed at room temperature (Scheme 38, insert 3).^[66c,178] It requires, however, a stoichiometric amount of a Grignard reagent, which can be problematic with some substrates.

As for ruthenium complexes, Ackermann's carboxylate-assisted alkylation was found to proceed smoothly at the *ortho* position of a range of substrates when using primary alkyl bromides and iodides (Scheme 38, insert 4),^[65a] while

Scheme 38. Palladium-, cobalt-, and ruthenium-catalyzed *ortho*- and *meta*-alkylation of 2-(N-heteroaryl)arenes with alkyl halides. DMA = dimethylacetamide, IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, NMP = *N*-methyl-2-pyrrolidinone.

the use of secondary (Scheme 38, insert 5)^[179] and tertiary (Scheme 38, insert 6)^[141] alkyl bromides induced a remarkable switch to the *meta* position. This *meta* selectivity was rationalized by an *ortho*-ruthenation activating the *meta* position towards radical addition, as discussed with aryloxazolines in Scheme 21. α -Halo ketones and esters provide the same *meta* selectivity.^[111,180]

A rhodium allylation of 2-pyridyl- and pyrazolylarenes with allyl carbonates has also been described.^[100]

7.3. Alkylation with Alkylmetal Reagents

In addition to alkenes and alkyl halides, various alkylmetal reagents have been used for the selective introduction of alkyl groups at the *ortho* position of 2-(N-heteroaryl)arenes. Pyridines and alkylboron reagents have been mostly used as directing groups and alkylmetal reagents, respectively, with this strategy being especially efficient for the introduction of simple alkyl chains such as a methyl group, which is very difficult to introduce otherwise.

In this context, the group of Yu reported an efficient *ortho*-alkylation of 2-pyridylarenes with trimethylboroxine and alkylboronic acids by simply using a catalytic amount of palladium(II) acetate together with benzoquinone and copper(II) acetate or silver(I) oxide [Scheme 39, Eq. (1)].^[181] Pyrazole could also serve as a directing group, although with less efficiency, and this reaction was later extended to the regioselective alkylation of 2-pyridylthiophenes, -benzothiophenes, -furans, and -pyrroles.^[182] Milder

Scheme 39. Palladium- and rhodium-catalyzed *ortho*-alkylation of 2-(N-heteroaryl)arenes with alkylboron reagents.

reaction conditions through the use of manganese trifluoride have been reported by the Sanford group, but the scope of this procedure was only reported with *ortho*-substituted 2-pyridylarenes, most certainly to avoid dialkylation.^[145] Interestingly, an enantioselective alkylation of 2-benzhydrylpyridines was reported afterwards.^[183]

As an alternative to palladium, rhodium complexes have also been shown to be efficient catalysts for the *ortho*-alkylation of 2-pyridylarenes with potassium alkyltrifluoroborates with excellent levels of regioselectivity [Scheme 39, Eq. (2)].^[73] This reaction was subsequently extended to the use of (benzo)thiazoles as directing groups.^[184]

Grignard reagents could also be used as alkylating agents in the presence of cobalt(II/III) acetylacetonate for the alkylation of three 2-pyridylarenes and benzo[*h*]quinoline.^[117,185]

7.4. Alkylation with Other Reagents

Other reagents have also been reported for the directed alkylation of 2-(N-heteroaryl)arenes. They can be useful in certain cases and include dicumyl- or di-*tert*-butyl peroxide (with palladium catalysis);^[186] carboxylic acids (with palladium catalysis) and cycloalkanes (with ruthenium catalysis),^[147] which however provide mixtures of mono- and dialkylated products in most cases; toluene derivatives, which can be used for the regioselective introduction of benzyl groups at the *ortho*^[187a] or *meta*^[187a,b] positions depending on the ruthenium ligand; and α -carbonylsulfoxonium ylides, which efficiently introduce a methyleneketone *ortho* to various directing groups (pyridine, pyrimidine, quinoline, and pyrazole) in the presence of a rhodium^[188a,b] or a cobalt^[188c] catalyst.

Electrophilic alkylating agents that can be used for the introduction of amino/hydroxymethyl/ethyl groups at the *ortho* position of 2-(N-heteroaryl)arenes include aldehydes,^[189] imines,^[168a] epoxides,^[190] and aziri(d)ines.^[191]

As a logical extension of these studies, coordinating N-heteroarenes have been introduced on the nitrogen atom of

indoles to facilitate their alkylation: a brief overview of these directed alkylations of indoles will be presented in the next section.

8. Directed Alkylation of *N*-(*N*-Heteroaryl)indoles

Whereas Friedel–Crafts alkylation proceeds at the more electrophilic C3-position of indoles, radical alkylation proceeds at the C2-position, but not all types of alkyl radicals can be used for electronic reasons. A solution for the regioselective alkylation of indoles lies in the introduction of a directing group that facilitates the alkylation of a single C–H bond. Although most of the directing groups overviewed up to this point can be utilized, an interesting possibility relies on the introduction of this directing group on the nitrogen atom of the indole to facilitate, in most cases, its C2-alkylation. *N*-(2-Pyridyl)- and *N*-(2-pyrimidyl)indoles have indeed been shown to be excellent substrates, and most reactions overviewed in the previous section can actually be extended to such substrates: only representative examples will be detailed here. However, these directing groups need to be cleavable for their use to be of any synthetic relevance.

8.1. Alkylation with Alkenes

Although the C2-alkylation of *N*-(2-pyri(mi)dy)lindoles with alkenes can be catalyzed by a range of metals including ruthenium,^[162] cobalt,^[168c,192] manganese,^[193] and rhodium,^[194] Ackermann's selectivity-switchable, cobalt-catalyzed alkylation^[192b] is probably the most versatile method reported to date (Scheme 40). Terminal unactivated alkenes could indeed be used for the C2-alkylation of *N*-(2-pyridyl)indoles with catalytic amounts of $\text{Cp}^*\text{Co}(\text{CO})\text{I}_2$ and AgSbF_6 , without or with 1-adamantylcarboxylic acid to provide linear or branched products, respectively. Detailed mechanistic studies revealed a change in the mechanism from a linear-selective ligand-to-ligand hydrogen transfer to a branched-selective carboxylate-assisted internal electrophilic-type substitution in the presence of the carboxylate additive. An especially efficient and appealing enantioselective version based on the use of a chiral carboxylic acid was moreover reported recently.^[192c] As an alternative, *N*-[di(*tert*-butyl)phosphino]indoles can be efficiently alkylated at C7 using a rhodium-catalyzed deconjugative alkylation with conjugated esters and ketones, with the di(*tert*-butyl)phosphino group being readily cleaved under acidic conditions.^[195]

8.2. Alkylation with Alkyl Halides

Although less attractive than alkenes from an atom-economical point of view, alkyl halides are still interesting alkylating agents and avoid the problems associated with control of the linear/branched selectivity met with alkenes. Several procedures have been reported recently for the C2-alkylation of *N*-(2-pyri(mi)dy)lindoles with alkyl halides: whereas Ackermann's cobalt-catalyzed alkylation allows for

Scheme 40. Cobalt-catalyzed linear versus branched C2-alkylation of *N*-(2-pyridyl)indoles with alkenes.

the use of readily available primary alkyl chlorides at room temperature in the presence of a Grignard reagent [Scheme 41, Eq. (1)],^[178] following studies by Punji and co-workers based on a well-defined nickel/tridentate *N*-diethylaminomethylcarbonyl(8-aminoquinoline) catalyst enables the use of primary alkyl iodides, bromides, and chlorides as well as secondary alkyl bromides [Scheme 41, Eq. (2)].^[196]

N-(2-Pyrimidyl)carbazoles can be alkylated at C4 using a ruthenium catalyst and the assistance of a carboxylate through a radical pathway.^[197] In the presence of an additional ancillary directing group at C3, such as an ester, the ruthenium-catalyzed alkylation of *N*-(2-pyrimidyl)indoles with α -bromoesters proceeds at C6,^[198] and when the C2-position is blocked, the reaction proceeds at C7.^[199]

8.3. Methylation with Methylboron Reagents

A simple methyl group cannot be introduced with the previous methods, and the use of methylboron reagents is necessary: methylboronic acid and potassium methyltrifluoroborate have been shown to be efficient reagents for the C2-methylation of *N*-(2-pyri(mi)dy)lindoles with palladium [Scheme 42, Eq. (1)],^[200] ruthenium [Scheme 42, Eq. (2)],^[201] and rhodium^[73] catalysis, with good substrate scopes and functional-group tolerance. The 2-pyridyl group was shown to be cleavable upon reaction with methyl triflate followed by reaction with ammonium formate and $\text{Pd}(\text{OH})_2/\text{C}$.

Representative examples

Representative examples

Scheme 41. Cobalt- and nickel-catalyzed C2-alkylation of *N*-(2-pyridyl)indoles with alkyl halides.

Scheme 42. Palladium- and ruthenium-catalyzed C2-methylation of *N*-(2-pyridyl)indoles with methylboron reagents.

Other reagents for the C2-alkylation of *N*-(2-pyridyl)indoles include toluene derivatives,^[202] α -carbonyl-sulfoxonium ylides,^[188b,c] and diazo derivatives.^[203]

In most cases discussed up to now, the directing group was directly connected to the arene to be alkylated. An interesting strategy lies in the placement of a spacer between these two moieties, which broadens the range of substrates amenable to directed C–H alkylations and/or allows access to C–H bonds that are rather difficult to activate. The use of these “remote” directing groups will be covered in Section 9.

9. Remote Directing Groups

For clarity, the main classification utilized in this section will be based on the nature of the starting arene, not on the alkylating agents, and we will start this overview on benzylic amine derivatives. Mechanisms associated with these reactions are mainly based on those already discussed, and so will not be presented, unless strictly required.

9.1. Directed Alkylation of Benzylic Amine Derivatives

Benzylic amines are key structural motifs of various natural products and bioactive molecules, as well as key building blocks. Their directed alkylation represents an important transformation which is complementary to the directed alkylation of aromatic imines/reduction sequence overviewed in Section 2. Efficient procedures based on the introduction of a coordinating group on the nitrogen atom have been developed to perform such a task. In this context, a broadly applicable palladium-catalyzed *ortho*-alkylation of benzylic picolinamides with alkyl halides was reported by the Chen group in 2011, a reaction for which molecular oxygen was used as the oxidant and sodium triflate was found to have a dramatic impact [Scheme 43, Eq. (1)].^[204] A range of primary alkyl iodides, bromides, and even chlorides could also be successfully utilized, as well as, to a lesser extent,

Representative examples

Representative examples

Scheme 43. Palladium- and iron-catalyzed *ortho*-alkylation of benzylic amine derivatives with alkyl halides and Grignard reagents.

isopropyl iodide. *Ortho*- and *meta*-substituted benzylic picolinamides gave good yields and regioselectivities, while double *ortho,ortho'*-dialkylation was observed in other cases. The picolinamide moiety could be cleaved by alkaline hydrolysis. Related processes for the alkylation of benzylic quinolone-2-carboxamides with α -bromoketones,^[205] the dimethylation of tyrosine-derived homobenzylic picolinamides with iodomethane under palladium catalysis,^[206] and the (di)methylation of other benzylic picolinamides with trimethylaluminum under iron catalysis^[119] were later reported.

In a related approach, the Ackermann group extended the use of its triazole-derived directing amides to the methylation and ethylation of benzylic triazole-4-carboxamides with the corresponding Grignard reagents in the presence of catalytic amounts of iron(III) chloride and bis(diphenylphosphine)-ethylene (dppen) as well as 2,3-dichlorobutane or 1,2-dichloro-2-methylpropane as the oxidant [Scheme 43, Eq. (2)].^[207] The reaction proceeded smoothly to provide products resulting from alkylation of all the *ortho*-C–H bonds, and the directing group could be cleaved by acidic hydrolysis.

An enantioselective *meta*-alkylation of homobenzylamines has also been recently reported, although with moderate efficiency.^[208] The extension of most of these procedures to bidentate amides derived from 1-naphthylamines results in selective alkylation at the *peri* (or C8) position.^[119, 204, 207, 209]

9.2. Directed Alkylation of Benzylic Alcohols

In sharp contrast to their nitrogen analogues, benzylic alcohols or their derivatives have not been used as directing groups in C–H alkylation reactions per se. As the corresponding aromatic ketones are excellent substrates for the ruthenium-catalyzed Murai reaction and, as previously commented, many ruthenium complexes are able to oxidize benzylic alcohols by hydride transfer, an oxidation/C–H alkylation followed by an in situ reduction upon addition of formic acid enables a formal C–H *ortho*-alkylation of benzylic alcohols (Scheme 44).^[29b] However, and depending on the nature of the alkene utilized, some products proved difficult to reduce and were isolated as ketones.

Scheme 44. Ruthenium-catalyzed formal directed *ortho*-alkylation of benzylic alcohols with alkenes.

9.3. Directed Alkylation of Benzylic Carboxylic Acids and Derivatives

In a continuation of their studies on the C–H alkylation of arylcarboxylic acids, the Yu group extended their procedure

Representative examples

Scheme 45. Palladium-catalyzed *ortho*-alkylation of benzylic carboxylic acids with potassium alkyltrifluoroborates.

to benzylic derivatives. They demonstrated that the *ortho*-alkylation of benzylic carboxylic acids with potassium alkyltrifluoroborates could be efficiently catalyzed by a combination of palladium(II) acetate and Boc-Thr(*t*Bu)-OH in the presence of lithium carbonate and silver carbonate with additional benzoquinone in some cases (Scheme 45).^[114] A range of primary alkyl groups as well as a cyclopropane could be efficiently introduced, whereas secondary alkyltrifluoroborates failed to react. Moreover, alkylboronic acids were found to be compatible coupling partners after a simple modification of the inorganic base. As for the benzylic carboxylic acids, *ortho*- and *meta*-substituted substrates gave excellent results, while others were prone to competing dialkylation. The alkylation of aryloxazolines reported by the same group could also be extended to the methylation and ethylation of benzylic derivatives with the corresponding tetraalkyltin reagents, but its scope was studied only with substrates dialkylated at the benzylic position.^[125]

By combining the directed C–H palladation with the Catellani reaction,^[210] the Yu group next developed an efficient *meta*-alkylation with norbornene as a transient mediator.^[211a] An improved procedure was then reported using 2-carbomethoxynorbornene to promote, in combination with palladium(II) acetate and a tailor-made quinoline ligand, the *meta*-alkylation of benzylic carboxamides with a range of primary alkyl iodides (Scheme 46).^[211b] The catalytic cycle proposed for this transformation starts with a palladation of the C–H bond followed by migratory insertion (or carbopalladation) of the norbornene, a second palladation, oxidative addition, reductive elimination, norbornene deinsertion, and protonolysis. As a note, simpler directing groups can be used for such *meta*-alkylations, as recently demonstrated by the palladium-catalyzed *meta*-alkylation of nosyl-protected phenylalanine derivatives with alkyl iodides.^[212]

9.4. Directed Alkylation of Benzylic Sulfonic Acids and Derivatives

Yu and co-workers next extended this reaction to the use of benzylic sulfonamides with similar success and selectivity

Representative examples

Proposed mechanism

Scheme 46. Palladium-catalyzed, norbornene-mediated *meta*-alkylation of benzylic carboxamides with alkyl iodides.

trends [Scheme 47, Eq. (1)].^[213] Whereas the regioselectivity of this reaction is based on the use of the Catellani reaction to selectively alkylate the *meta*-C–H bond after a selective *ortho*-palladation, another strategy for the directed alkylation of this position is based on a specifically designed directing group that acts as a template and brings the coordinated catalyst close to this *meta*-C–H bond. A remarkable example of this elegant strategy was reported in 2017 by the Maiti group by using a 2-(pyrimidin-5-yl)phenol-derived benzyldisulfonyl ester.^[214] Upon reaction with allylic alcohols and catalytic amounts of palladium(II) acetate and *N*-acetylglutamine in the presence of silver acetate, a smooth *meta*-alkylation occurred to yield the corresponding γ -oxo-alkylated products resulting from an in situ isomerization of the allylic alcohol [Scheme 47, Eq. (2)]. The *meta*-alkylated products were formed predominantly, although not exclu-

Scheme 47. Palladium-catalyzed *meta*-alkylation of benzylic sulfonamides with alkyl iodides and benzylic sulfonates/phosphonates with allyl alcohols. HFIP = hexafluoroisopropanol.

sively, and the same conditions could be applied to benzylic phosphonates [Scheme 47, Eq. (3)] as well as to one ester.

9.5. Directed Alkylation of Homobenzylic Carboxamides

The directing group can even be placed further away provided that it acts as an efficient template for the regioselective alkylation of a single C–H bond. The feasibility of this approach was demonstrated by the Yu group, who designed a cleavable U-shaped template containing coordinating nitriles that enabled the activation of a *meta*-C–H bond in homobenzylic carboxamides.^[215] Although this method was extensively used for the *meta*-arylation of these substrates, only a single *meta*-methylation was reported.

In all these cases, the directing group can be further transformed to other functional groups. When considering the options available with all the directing groups overviewed, a fully removable and highly versatile group that could be transformed to a variety of functional groups would be rather attractive. The silicon-based 2-pyri(mi)dyldiisopropylsilyl directing group introduced by the Gevorgyan group meets these requirements, and will be overviewed in the next subsection.

9.6. Directed Alkylation of 2-Pyri(mi)dyldiisopropylsilyl-Substituted Arenes

Inspired by the directed alkylation with alkylboron derivatives reported by Yu and co-workers,^[114] Sarkar and

Scheme 48. Palladium-catalyzed *ortho*-alkylation of 2-pyridyl- and 2-pyrimidyl-diisopropylsilyl-substituted arenes with alkylboronic acids and further functionalization.

Gevorgyan developed an efficient *ortho*-alkylation of 2-pyrimidyl-diisopropylsilyl- and 2-pyridyl-diisopropylsilyl-substituted arenes with alkylboronic acids (Scheme 48).^[216] Besides the efficiency and selectivity of this alkylation, the main attractiveness of the 2-pyrimidyl-diisopropylsilyl directing group lies in the range of post-functionalizations that are possible, as highlighted in Scheme 48.

10. Other Directing Groups

Although this Review does not intend to be fully exhaustive and focuses on the most significant and relevant examples, it ought to be mentioned that other directing groups have been studied in the literature for the directed alkylation of arenes. They might serve as a basis for future developments and include nitriles,^[217] sulfones,^[118,218] sulfoximines,^[219] *N*-oxides,^[220] nitrosoamines,^[73] and azomethine imines.^[73]

11. Summary and Outlook

Future developments will clearly require the introduction of new directing groups. Directed alkylations of C–H bonds in arenes have enabled the remarkably efficient introduction of a broad range of alkyl chains into various aromatic cores with surgical precision. By properly choosing the directing group and the catalytic system, the regioselectivity can be finely

tuned and C–H bonds that were not accessible with standard techniques can now be alkylated. Regiodivergent alkylations have appeared and they should have a strong impact in many areas of science where there is a need for polysubstituted arenes. The recent introduction of cleavable/functionalizable directing groups broadens the variety of alkylated arenes that can be obtained by directed C–H alkylations.

The main problem of most directing groups is related to their cleavage: unless it is desired in the final molecule, the directing group needs to be cleaved and this step cannot be the limiting one. Efforts should, therefore, be devoted to the development of readily cleavable directing groups to improve their attractiveness. An even better solution relies on transient directing groups that are introduced and cleaved *in situ*.^[221] Indeed, one of the main arguments that is commonly put forward for C–H activation is that it does not require the prefunctionalization of the substrate, an argument that does not stand if additional steps are required for the introduction and cleavage of a directing group, even if it enables reactions that would not be possible in its absence. There is no doubt that efficient transient directing groups will appear in the near future. If they could be used in catalytic amounts, we would then be close to an ideal solution. The development of new catalytic systems will also, of course, be at the core of future developments, since a directing group without an efficient catalytic system is rather useless. In this perspective, the use of electrochemical activation might also enable the development of efficient, innovative, and sustainable processes.^[222]

The Murai reaction is now celebrating its 25th anniversary. A look at all the subsequent developments that were overviewed in this Review shows that directed C–H alkylations of arenes have considerably evolved, and there is no doubt that they will keep doing so.

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Conflict of interest

The authors declare no conflict of interest.

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