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C–H Functionalization

Catalytic Functionalization of C(sp^2)–H and C(sp^3)–H Bonds by Using Bidentate Directing Groups

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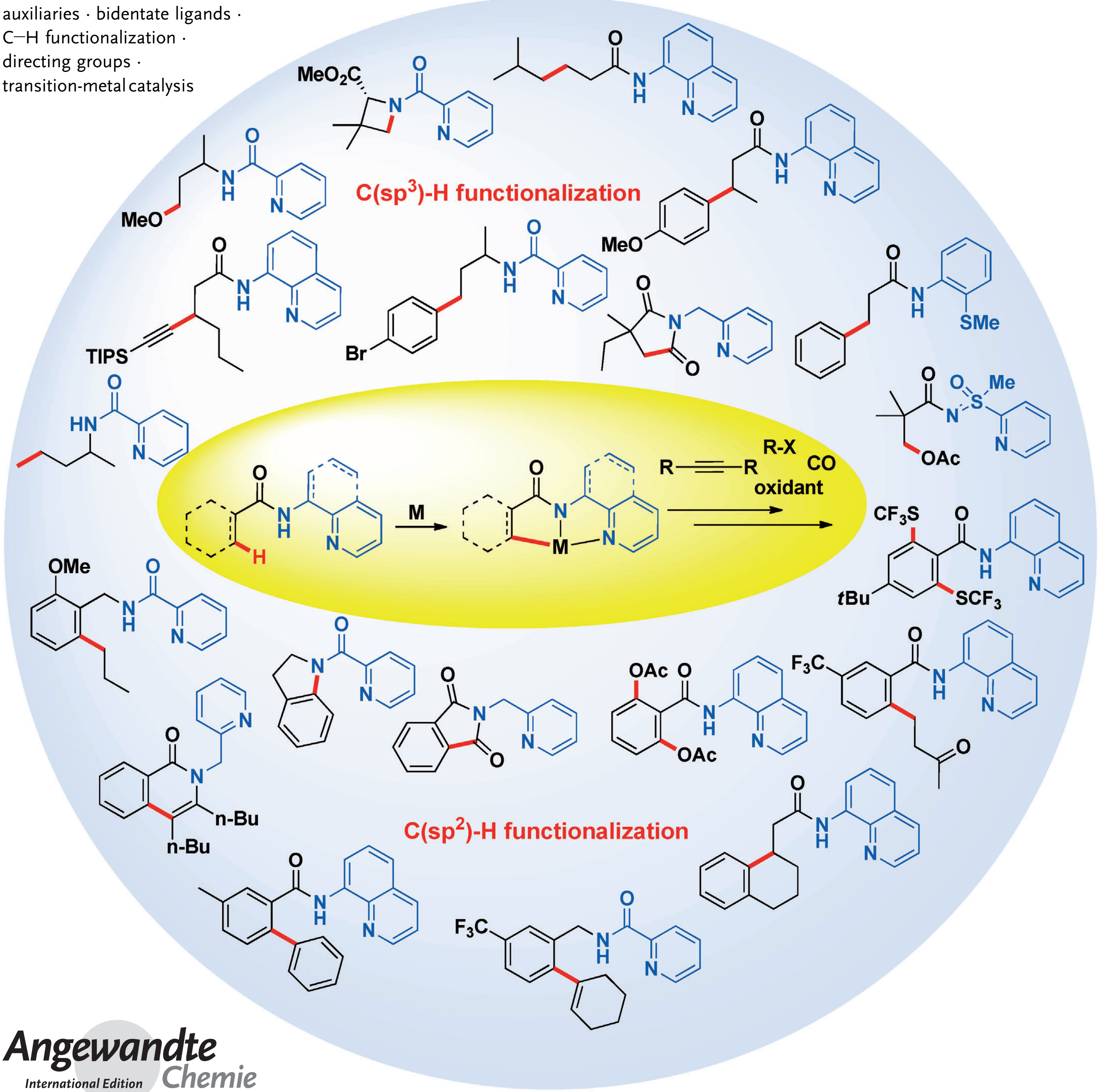
auxiliaries · bidentate ligands · C–H functionalization · directing groups · transition-metal catalysis



C–H bonds are ubiquitous in organic compounds. It would, therefore, appear that direct functionalization of substrates by activation of C–H bonds would eliminate the multiple steps and limitations associated with the preparation of functionalized starting materials. Regioselectivity is an important issue because organic molecules can contain a wide variety of C–H bonds. The use of a directing group can largely overcome the issue of regiocontrol by allowing the catalyst to come into proximity with the targeted C–H bonds. A wide variety of functional groups have been evaluated for use as directing groups in the transformation of C–H bonds. In 2005, Daugulis reported the arylation of unactivated $C(sp^3)$*–H bonds by using 8-aminoquinoline and picolinamide as bidentate directing groups, with* $Pd(OAc)_2$ *as the catalyst. Encouraged by these promising results, a number of transformations of C–H bonds have since been developed by using systems based on bidentate directing groups. In this Review, recent advances in this area are discussed.*

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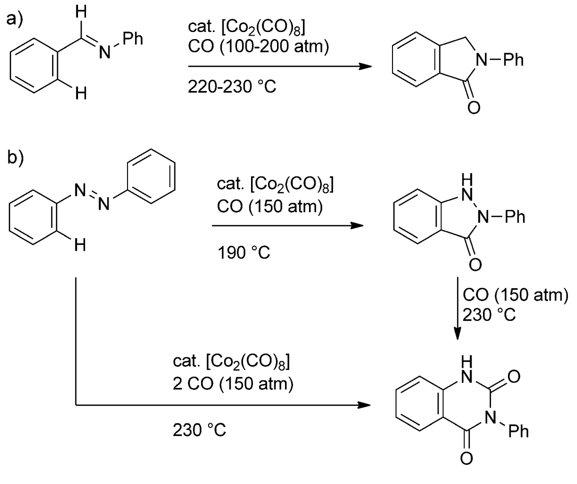
1. Introduction

The production of the wide spectrum of substances required by modern society in an environmentally benign fashion poses a great and pressing challenge for chemists. Among the many strategies available, transition-metal-catalyzed reactions have proved to be one of the most important and promising routes to the economical and straightforward formation of complex organic frameworks.[1] Currently used methods rely on the use of reactive functional groups, such as halides or unsaturated bonds, which can interact with the metal to form a new C–M bond that is involved in further reactions such as cross-coupling reactions. In these cases, however, several steps are necessary to synthesize the substrates from readily available starting materials, and the production of a substantial amount of by-product waste accompanies these reactions. Over the past several decades, transition-metal-catalyzed activation reactions of carbon–hydrogen bonds have opened an entirely new dimension in synthetic organic chemistry. The direct catalytic cleavage and transformation of C–H bonds,[2,3] which are ubiquitous in organic molecules, removes the need for preparing a functionalized intermediate. This allows the desired product to be obtained in fewer steps and offers a virtually unlimited library of simple starting materials and new perspectives in retrosynthesis. Thus, the development of new methods and synthetic strategies in which C–H bonds can be activated and used as a simple functional group represents one of the most stimulating and promising areas of research today in the field of synthetic organic chemistry.

Given the large number and diversity of C–H bonds generally present in a molecule, a remaining ongoing challenge in those strategies involves the ability to control the regioselectivity of the reactions. The most common strategies for achieving the highly regioselective functionalization of a single C–H bond involves the use of functional groups or atoms that are able to coordinate to a metal center and deliver the catalyst to a proximal C–H bond, generally via the formation of a thermodynamically stable five- or six-membered metallacyclic intermediate. These methods are commonly referred to as directed C–H bond functionalization.[2,4] The majority of reactions studied to date involve the cleavage of aromatic $C(sp^2)$–H bonds at the *ortho* position to the directing group.[5] The ease of activating this type of bond can be attributed to the stabilizing interaction of the arene π system with the transition metal and by the formation of a strong aryl–metal bond. From a historical viewpoint, some of the oldest examples of transition-metal-catalyzed, regioselective functionalization of a C–H bond by a directed activation of a C–H bond were reported in the mid-1950s (Scheme 1).[6] Murahashi showed that the reaction of an aldimine in the presence of $[Co_2(CO)_8]$ and high-pressure



Scheme 1. Cobalt-catalyzed *ortho*-carbonylation of C–H bonds.

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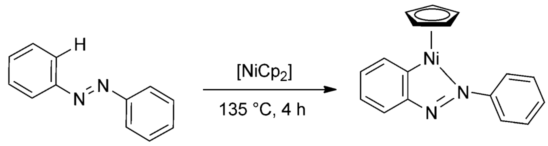
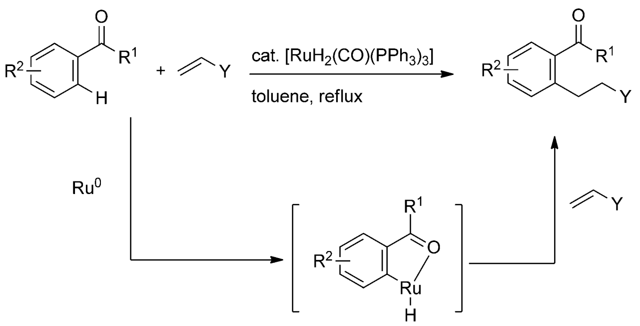
carbon monoxide at high temperatures led to the insertion of CO into the *ortho*-C(sp^2)–H bond of an aromatic aldimine, thereby affording an isoindolinone derivative as the product (Scheme 1 a).[6a]

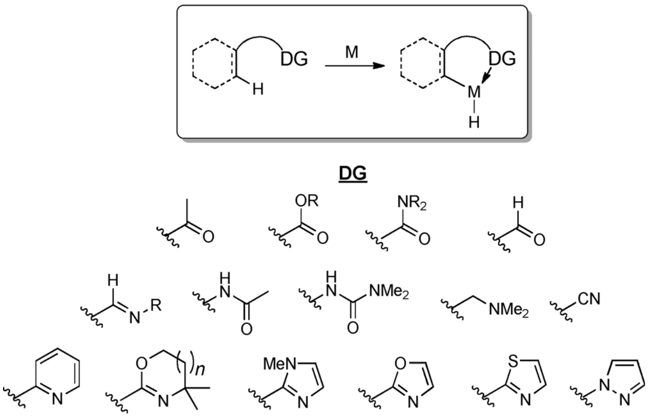
He subsequently found that azobenzene reacted similarly (Scheme 1 b), leading to the insertion of one or two molecules of carbon monoxide, depending on the reaction conditions used.[6b] At that time, the mechanisms of these transformations were not well understood and it was only in 1963 that Kleiman and Dubeck published the first characterization of a cyclometalated complex, thus highlighting the ability of some functional groups to promote the insertion of a transition metal into an *ortho*-C(sp^2)–H bond.[7] They found that a stoichiometric amount of [NiCp$_2$] (Cp = C_5H_5) reacts with azobenzene to form a five-membered *ortho*-nickelacycle (Scheme 2). Substantial progress was made in the field in the following 30 years, but mainly dealt with the stoichiometric use of the metal.



Scheme 2. Pioneering example of a metallacycle resulting from the *ortho*-metalation of a C–H bond.



Scheme 3. Ruthenium-catalyzed *ortho*-alkylation of aromatic ketones with olefins.



Scheme 4. Some important chemical functions that act as a monodentate directing group.

The development of catalytic reactions by using this strategy has been more sporadic and only a few examples were published during the same period.[8] In 1993, Murai et al. reported on the highly efficient and selective ruthenium-catalyzed *ortho*-alkylation of aromatic ketones with olefins (Scheme 3).[9] This result represented a real breakthrough, in that it showed, for the first time, that the directed C–H bond functionalization strategy could be used as an efficient and valuable tool in organic synthesis.

A large number of studies based on this approach appeared in the literature following the publication of these findings, and this transformation was rapidly expanded to other directing groups (Scheme 4), reactions (arylations, vinylations, oxidations, etc), and transition-metal catalysts.[2]

A large variety of catalytic reactions involving C(sp^2)–H bonds of arenes, heteroarenes, and alkenes have been developed to date.[2,3] Directed C–H bond functionalization can now be considered to be a reliable strategy for the transformation of a C–H bond into a new C–X bond (X = C, O, N, F, Cl, Br, I, Si). Benzylic or C(sp^3)–H bonds in the α position to a heteroatom also undergo functionalization relatively easily, likely because of their weakness and the influence of a proximal aromatic system or a lone pair of electrons with the metal.[3k,q] In comparison, the directed functionalization of unactivated C(sp^3)–H bonds remains underdeveloped and continues to be highly challenging because of the absence of stabilizing orbital interactions with the metal center, as is the case with unsaturated

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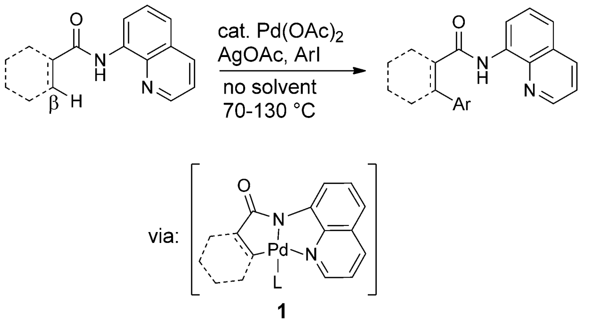
Guy Rouquet received his PhD in organic chemistry from Bordeaux University (France) under the guidance of Prof. Yannick Landais, in collaboration with Prof. Philippe Renaud (Bern University, Switzerland). He then joined the research group of Prof. Naoto Chatani at Osaka University (Japan) as a postdoctoral researcher, where he was involved in research on new C–H bond-activation reactions. He is currently a postdoctoral researcher in the group of Prof. Steven V. Ley at Cambridge University (UK).

hydrocarbons. From a general point of view, despite the great advances in the field of catalytic directed C–H bond functionalization, a large number of transformations remain to be discovered and some inherent limitations also remain. To extend the concept of directed C–H bond functionalization beyond its limits, the development of new types of directing groups is a promising strategy for achieving catalytic transformations that cannot be completed with conventional systems currently available. It is well known that bidentate directing groups promote the activation of C–H bonds via the formation of a stoichiometric amount of a stable metallacycle. This is exemplified by the studies of van Koten and coworkers.[10] In 2005, the use of bidentate directing groups for the catalyzed directed C–H functionalization of C(sp^3)–H and C(sp^2)–H bonds was highlighted by Daugulis and coworkers.[11a] They showed that an 8-aminoquinoline directing group can be employed to promote the palladium-catalyzed arylation of β-C–H bonds of various aliphatic and aromatic amides (Scheme 5).



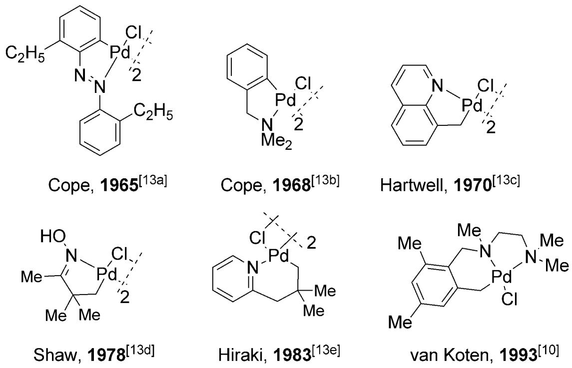
Scheme 5. Palladium-catalyzed arylation of C–H bonds by C–H bond activation promoted by a bidentate directing group.

It was further demonstrated that the directing group coordinates to the metal center in a bidentate fashion during the formation of the intermediate metallacycle (**1**, Scheme 5). The bidentate coordination confers new properties to the intermediate metalated complex, thus allowing a transformation which is known to be problematic with conventional systems (see Section 2.1. for a more detailed discussion). Following this result, numerous reports have appeared in the literature, thus confirming that bidentate directing groups are promising tools for achieving transformations that have not been achieved with conventional monodentate systems (Scheme 4). Bidentate directing groups can today be considered an interesting alternative to monodentate systems for the development of new catalytic strategies for the functionalization of C–H bonds.

This Review higlights recent progress concerning directed C(sp^3)–H and C(sp^2)–H bond functionalization through the aid of a bidentate directing group. The focus of this Review is transition-metal-catalyzed reactions; however, a few noncatalytic transformations are described, because we think they may be of help in the development of catalytic processes.

2. Palladium Catalysis

Most directed C–H activation reactions involving a bidentate directing group involve the use of a Pd^{II} catalyst and their mechanisms are generally rationalized by a Pd^{II}/Pd^{IV} catalyst system.[12a–d] However, the exact nature of those mechanisms is still a subject of debate.[12d–f] The ability of palladium(II) to activate C–H bonds through chelation-assisted processes has been known since the 1960s. Nitrogen directing groups were found to promote the insertion of palladium into an *ortho*-C–H bond (Scheme 6), which led to the formation of stable and isolable cyclopalladated complexes of palladium(II) when palladium(II) reagents were used as the palladium source.[13a,b]

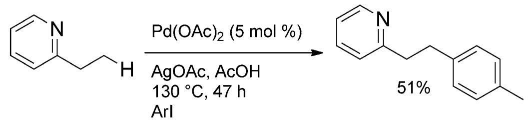


Scheme 6. Some pioneering examples of Pd^{II} palladacycles resulting from a directed C–H activation.

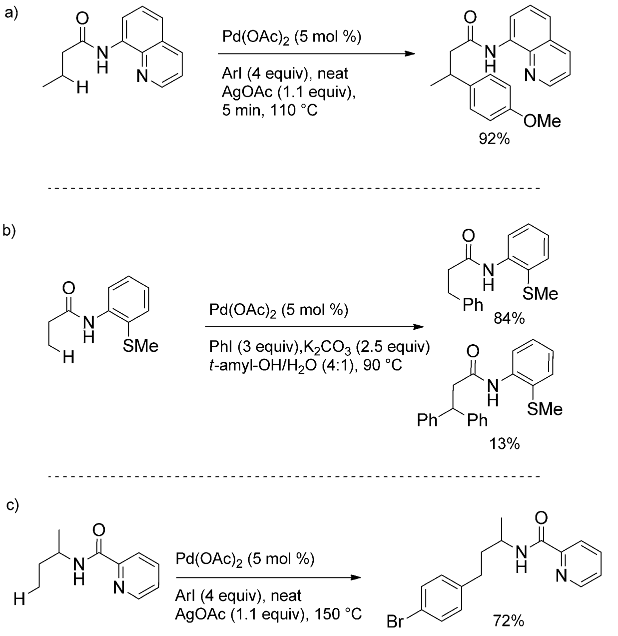
This noteworthy reactivity was then extended to activated and unactivated C(sp^3)–H bonds.[13c–e] A large variety of monodentate directing groups were then developed and applied in the palladium-catalyzed formation of C–C and C–X bonds.[2e,g] In contrast, the exploitation of bidendate directing groups in palladium-catalyzed transformations has emerged only very recently, even though examples of C–H activation via the formation of a cyclopalladated complexes involving a bidentate coordination can be found earlier in the literature (Scheme 6).[10]

2.1. Arylation and Alkenylation of C–H Bonds

Palladium-catalyzed C–H arylations have been studied intensively.[2,3] However, the palladium-catalyzed arylation of C(sp^3)–H bonds remains a challenging transformation and most examples deal with the functionalization of "*tert*-butyl groups" because the metal cannot be lost by β-hydride elimination in this configuration. In 2005, Shabashov and Daugulis reported that the primary C(sp^3)–H bond of 2-ethylpyridine underwent a clean Pd^{II}-catalyzed arylation (Scheme 7).[14] However, the scope of this reaction was very limited. They reasoned that it would be possible to improve the generality of the method if the pyridine moiety was used as part of a removable auxiliary and, thus, suggested the use of the easily detachable 8-aminoquinoline (Scheme 8a) or



Scheme 7. Palladium-catalyzed arylation of 2-ethylpyridine.

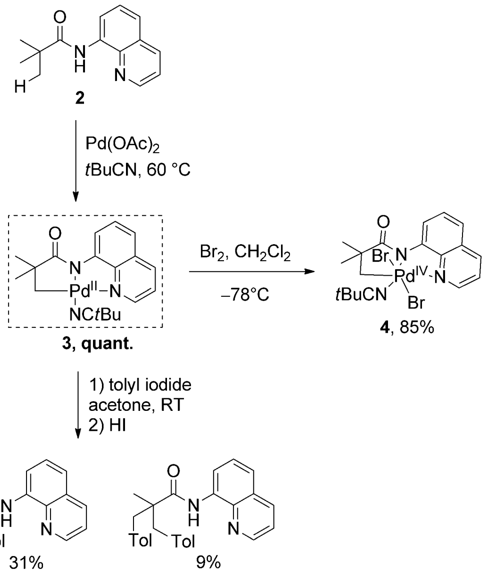


Scheme 8. Pd-catalyzed arylation of unactivated C(sp^3)−H bonds of 8-aminoquinoline amides and picolinamide derivatives.

picolinic acid (Scheme 8c) as directing groups. It was also anticipated that the double coordination of the metal by those auxiliaries would facilitate the reaction by stabilizing Pd^{IV} species,[12a–d] which were suspected to be involved in the mechanism.

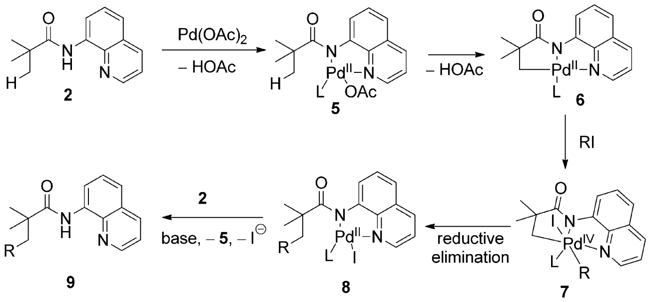
As shown in Scheme 8a, the efficient palladium(II)-catalyzed arylation of challenging methylene β-C(sp^3)−H bonds of amides was effective by employing an 8-aminoquinoline auxiliary. This approach thus offered an interesting method to functionalize various carboxylic acids at the β position by a sequential amidification/C−H activation/saponification sequence (40% aq H_2SO_4, 120°C, 24 h).[11,3f] This result is all the more remarkable when considering the relative difficulty of activating a methylene C(sp^3)−H bond compared with their methyl analogues.[15] The reaction required the combination of a Pd(OAc)$_2$ catalyst in the presence of a base and an excess of an aryl iodide partner at high temperature, with or without a solvent. A second C−H arylation of the resulting tertiary benzylic C−H bond in the final product was not observed, probably because of its bulky nature. The reaction is also effective for the functionalization of the C(sp^2)−H bond in benzoic acid derivatives. The arylation of primary C(sp^3)−H bonds (Scheme 8b) was also achieved if 2-methylthioaniline or 8-aminoquinoline auxiliaries were employed, but the 2-methylthioaniline auxiliary proved to afford a better selectivity for monoarylation. The absence of β-hydride elimination from the metalated intermediates was attributed to the bidentate coordination that would retard the β-hydride elimination step by saturating the coordination sites of the metal. Picolinamide-protected amine derivatives were also suitable substrates, and γ-C−H bond functionalization occurred in good yield (Scheme 8c), thus offering an interesting method for the functionalization of aliphatic amines as well as benzylamines. The γ selectivity likely results from the formation of a kinetically favored five-membered palladacycle intermediate (such as **1**, Scheme 5). The scope of this reaction was recently extended to naphthylamide derivatives by Qi and co-workers through the use of a quinolinamide bidentate system.[16]

To get an insight into the mechanism several complexes which represent potential intermediates in the reaction mechanism were synthesized with a stoichiometric amount of palladium in pyvalonitrile and characterized (Scheme 9). A monomeric palladacycle of palladium(II) **3** stabilized by one molecule of pyvalonitrile was obtained from amide **2**. As expected, bicoordination of the 8-aminoquinoline auxiliary was observed, thus confirming the crucial role of the auxiliary. The reaction of this complex with Br_2 afforded a stable palladium(IV) complex **4**, which suggests the presence of a palladium(IV) intermediate. However, attempts to obtain a palladium(IV) complex by direct reaction of **3** with an aryl iodide was unsucessful and arylation of the C(sp^3)−H bond was observed, thereby suggesting that complex **3** may be a reactive intermediate.



Scheme 9. Synthesis of Pd^{II} and Pd^{IV} complexes.

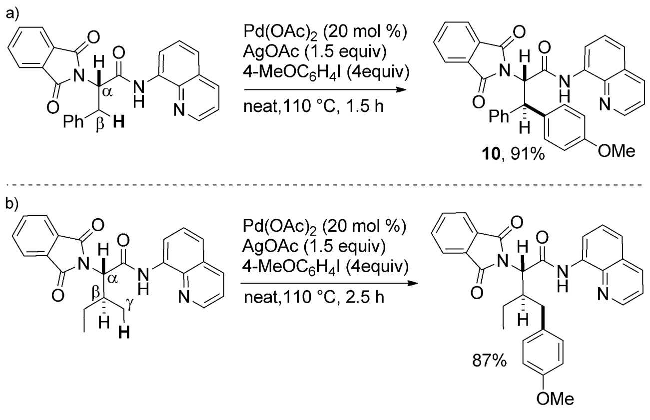
The mechanism shown Scheme 10 with *N*-pivaloyl-8-aminoquinoline (**2**) as the reference substrate was proposed by Shabashov and Daugulis and involves a Pd^{II}/Pd^{IV} process. The initial reaction of Pd(OAc)$_2$ with **2** affords **5**. A rapid cyclometalation of the *tert*-butyl group then gives the palladacycle **6**. Oxidative addition of the aryl iodide to **6** affords the Pd^{IV} species **7**. Reductive elimination followed by a ligand



Scheme 10. Proposed mechanism of the Pd-catalyzed arylation of C–H bond with assistance from bidentate chelation.

exchange then releases **9** and regenerates the palladium amide **5**.

This original report by Shabashov and Daugulis was rapidly followed by other publications. The first, by Corey and co-workers, used this method for the diastereoselective C–H arylation of various non-natural α-protected amino acid derivatives,[17] as illustrated by the arylation of *N*-phthaloylated phenylanaline amide with *p*-iodoanisole (Scheme 11 a).

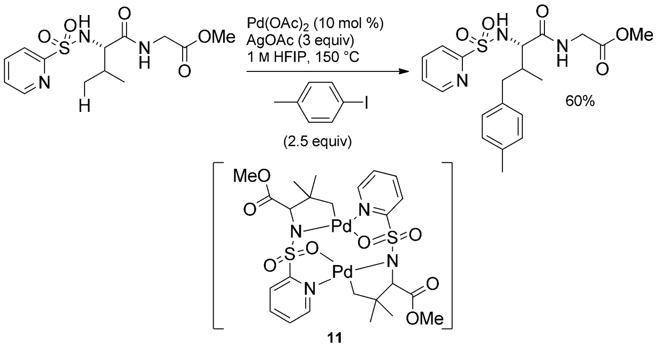


Scheme 11. Palladium-catalyzed β- and γ-C(sp^3)–H arylation of α-protected amino acid derivatives.

The relative difficulty for palladium to activate the bulky tertiary C–H bond in **10** explains the absence of a second arylation of the β-C–H bond. An interesting outcome was observed in the reaction of isoleucine with *p*-iodoanisole under similar reaction conditions (Scheme 11 b). An unexpected arylation of the γ-C–H bond took place, thus indicating that the insertion of palladium into the bulky tertiary β-C–H bond is so attenuated that a competitive *γ*-C–H bond activation can occur.

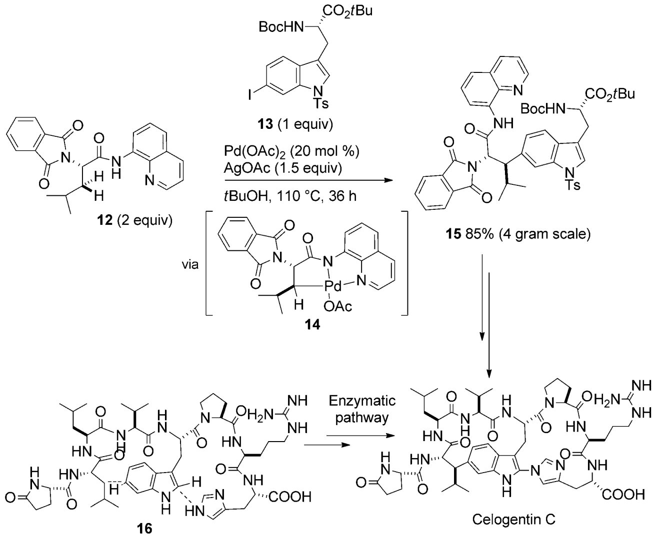
Tran and Daugulis extended the scope of the reaction shown in Scheme 11 to a range of *N*-protected phthaloyl non-natural α-amino acids and aryl partners.[18] They showed that the 2-thiomethylaniline directing group permitted the mono-arylation of the primary β-C(sp^3)–H bond of *N*-phthaloylalanine derivatives under relatively mild conditions (60 °C) and that the directing group could be cleaved under acidic conditions with BF$_3$.Et$_2$O in MeOH at 100 °C to afford the corresponding methyl ester.

An easily removable *N*-(2-*p*yridyl)sulfonyl directing group in the selective functionalization of C(sp^2)–H bonds was reported by Fernandez, Carretero et al.[19a–c] They recently used this group for the efficient γ-arylation of C(sp^3)–H bonds of readily available *N*-(2-*p*yridyl)sulfonamide derivatives of simple amino acid methyl esters.[19d] They notably applied this method to the unprecedented arylation of C(sp^3)–H bonds of dipeptide derivatives (Scheme 12). The one-step cleavage of the 2-pyridylsulfonyl directing group under reductive conditions (Zn powder at 60 °C in THF/aqueous NH$_4$Cl) afforded the free primary amine in good yield. A bimetallic Pd^{II} complex **11** was isolated, thus highlighting the role of the (2-pyridyl)sulfonyl unit.



Scheme 12. Palladium-catalyzed *N*-(2-pyridyl)sulfonyl-directed C(sp^3)–H γ-arylation of amino acid derivatives.

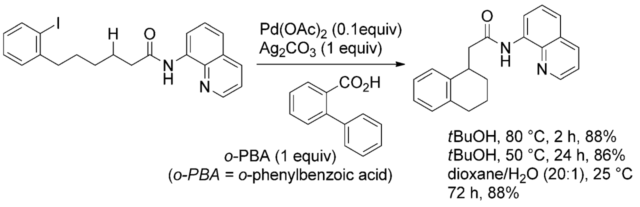
Feng and Chen used the study of Corey and co-workers (Scheme 11) as the starting point for the stereoselective synthesis of the bicyclic peptide celogentin C (Scheme 13).[20] This achievement was the first application of a metal-catalyzed C–H bond activation through formation of a bidentate chelate for the total synthesis of a natural product. Taking inspiration from the proposed natural enzymatic formation of



Scheme 13. Synthesis of celogentin C through a palladium-catalyzed bidentate chelation assisted strategy.

celogentin C from **16**, Feng and Chen suggested that the formation of the C–C bond between the acid portion and the indole moiety should be considered as the key step of the synthesis. The coupling of *N*-phthaloylleucine **12** and the indole derivative **13** afforded the 6-indolylation product **15** in high yield and diastereoselectivity on a gram scale. Feng and Chen proposed that the high diastereoselectivity observed may be due to the coordination by the quinoline moiety, which promotes the formation of the *trans*-palladacycle intermediate **14**. This Pd^{II} intermediate then undergoes cross-coupling with **13** to provide the final arylated product **15**, which has a preferred *erythro* stereochemistry. The product **15** was then used to successfully achieve the synthesis of celogentin C in 23 steps.

The ability of the 8-aminoquinoline auxiliary to enable arylation at the methylene position (Scheme 8) was extended by Chen and co-workers to the more difficult intramolecular transformation.[21] A new method for the construction of a new benzo ring through a Pd^{II}-catalyzed 8-aminoquinoline-directed intramolecular arylation of C(sp^3)–H bonds under mild reaction conditions was thus reported (Scheme 14). A broad range of cyclization reactions was achieved in good yield with a good tolerance of functional groups. The addition of *ortho*-phenylbenzoic acid (*o*-PBA) appeared to be important for the efficiency of the reaction and allowed the catalytic process to proceed under mild conditions, even at near room temperature. Carboxylic acid additives were already known to be benifical when the C–H activation step occurs through a concerted palladation/deprotonation.[22]

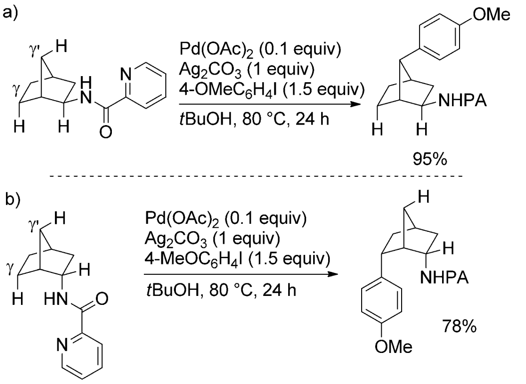


Scheme 14. Construction of a benzo ring through palladium-catalyzed functionalization of unactivated C(sp^3)–H bonds.

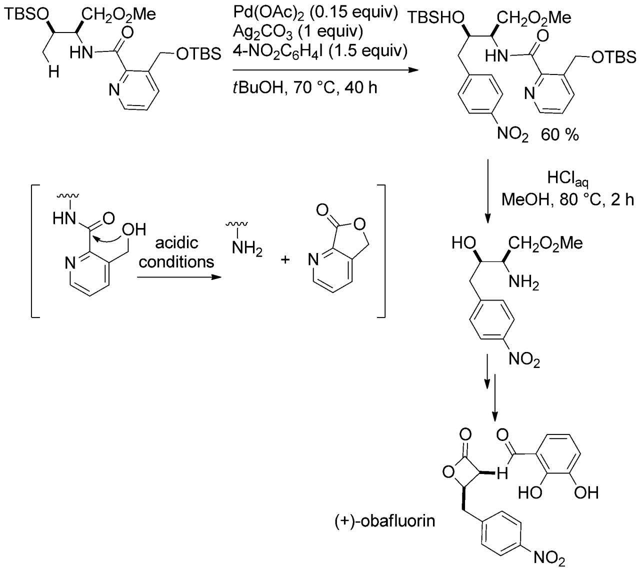
He and Chen reported the picolinamide-directed palladium-catalyzed arylation of the γ-C(sp^3)–H bonds of a variety of aliphatic amines under relatively mild conditions at 80 °C in *t*BuOH or trifluoroethanol as the solvent (Scheme 15).[23] Lower reaction temperatures could be used with prolonged reaction times. It was demonstrated that the regio- and stereoselectivity of the reaction were dependent on the relative conformation of the C–H bond in regard to the directing group (for example, see Scheme 15a and b).

This method was applied to the synthesis of (+)-obafluorin from a readily accessible threonine derivative (Scheme 16). Difficulty in removing the standard picolinamide auxiliary in this synthesis prompted He and Chen to develop a modified picolinamide auxiliary which can be hydrolyzed under milder conditions.

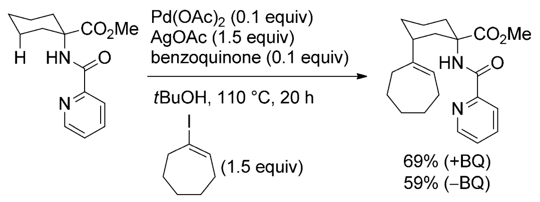
Disubstitued alkenyl iodides were also amenable for use with this method (Scheme 17).



Scheme 15. Selectivity in the palladium-catalyzed C(sp^3)–H γ-arylation of picolinamide derivatives.

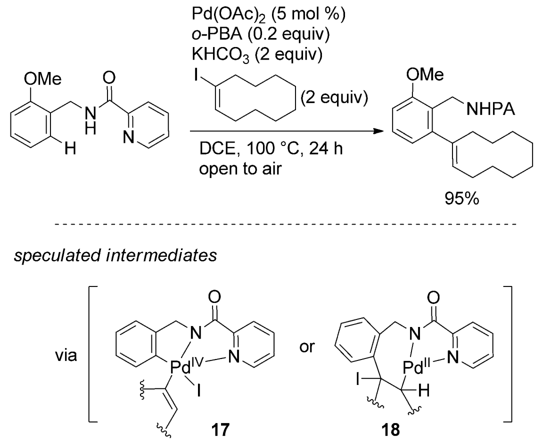


Scheme 16. An easily removable picolinamide auxiliary: application to the formal synthesis of (+)-obafluorin by C(sp^3)–H arylation.



Scheme 17. Palladium-catalyzed C(sp^3)–H γ-vinylation of a picolinamide derivative.

An analogous efficient functionalization of *ortho*-C(sp^2)–H bonds of picolinamide-protected benzylamine substrates with a range of vinyl iodides was then published by Chen and co-workers (Scheme 18).[24] Different reaction mechanisms were suggested to rationalize the results. A Pd^{II}/Pd^{IV} catalysis cycle, similar to the mechanism for the arylation (Scheme 10), by the oxidative addition of a vinyl halide to Pd^{II} to afford a Pd^{IV} intermediate **17** appears reasonable, but a migratory

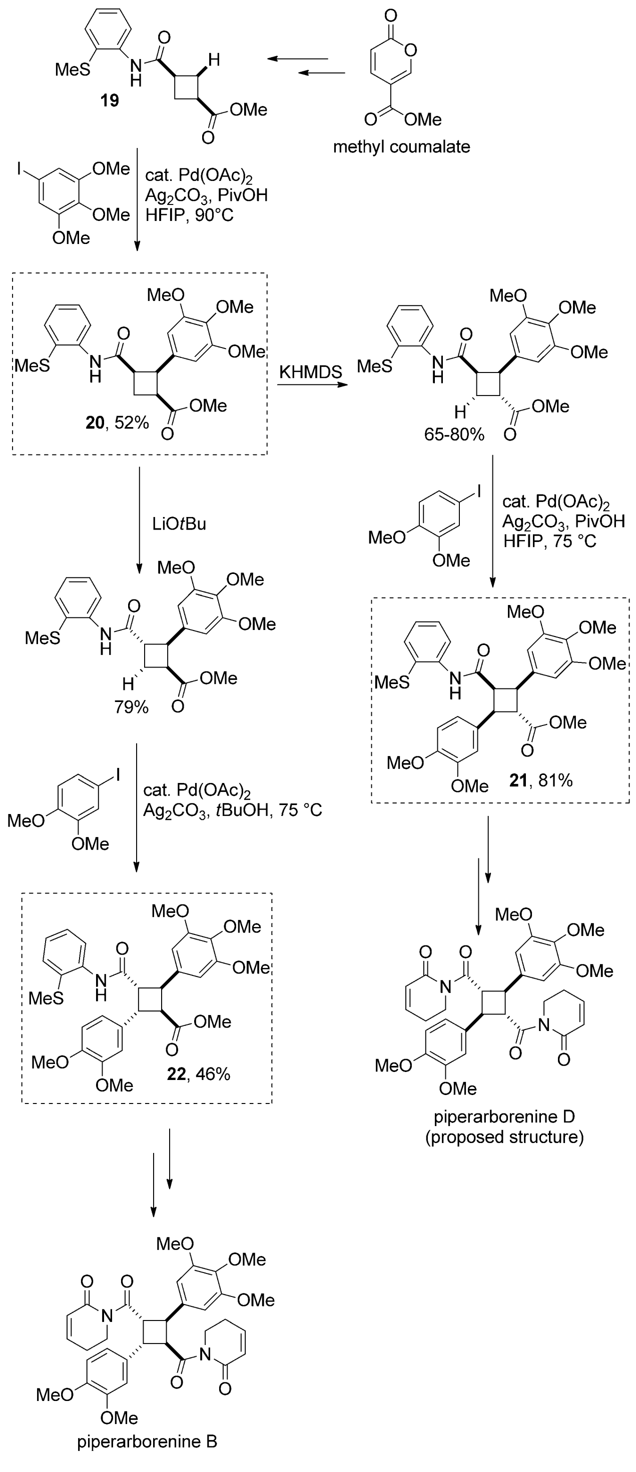


Scheme 18. Palladium-catalyzed alkenylation of *ortho*-C(sp^2)–H bonds of a benzylamine picolinamide.

insertion leading to an intermediate **18** followed by a β-elimination pathway could also be operative.

An elegant new strategy for the construction of unsymmetrical cyclobutanes by using a C–H functionalization was developed by Gutekunst and Baran, and used in the total synthesis of piperarborenine B and piperarborenine D (Scheme 19).[25] This synthesis represents the first example of catalytic transition-metal-mediated C–H activation on a cyclobutane ring and the first example of the use of sequential arylation of C(sp^3)–H bonds in the synthesis of a natural product. The selective arylation of the C–H bond of **19** with 3,4,5 trimethoxyiodobenzene was achieved. From the intermediate **20**, two different pathways were utilized to synthesize both of the desired natural products. The first involved epimerization of the ester moiety followed by a second selective arylation that was successfully achieved under similar reaction conditions, thereby affording the key intermediate **21**. The second route involved epimerization of the amide part, also followed by a selective arylation to give **22**. In both cases, the transformation of the ester and amide group into carboxylic acids followed by a coupling with dihydropyridone yielded the expected final products (piperarborenine B: 7 steps, 7 % overall yield; piperarborenine D: 6 steps, 12 % overall yield).

Baran and co-workers also reported the concise total synthesis of pipercyclobutanamide A based on a directed sequential bidentate palladium-catalyzed arylation/vinylation of the C(sp^3)–H bonds of a cyclobutane ring (Scheme 20).[26]

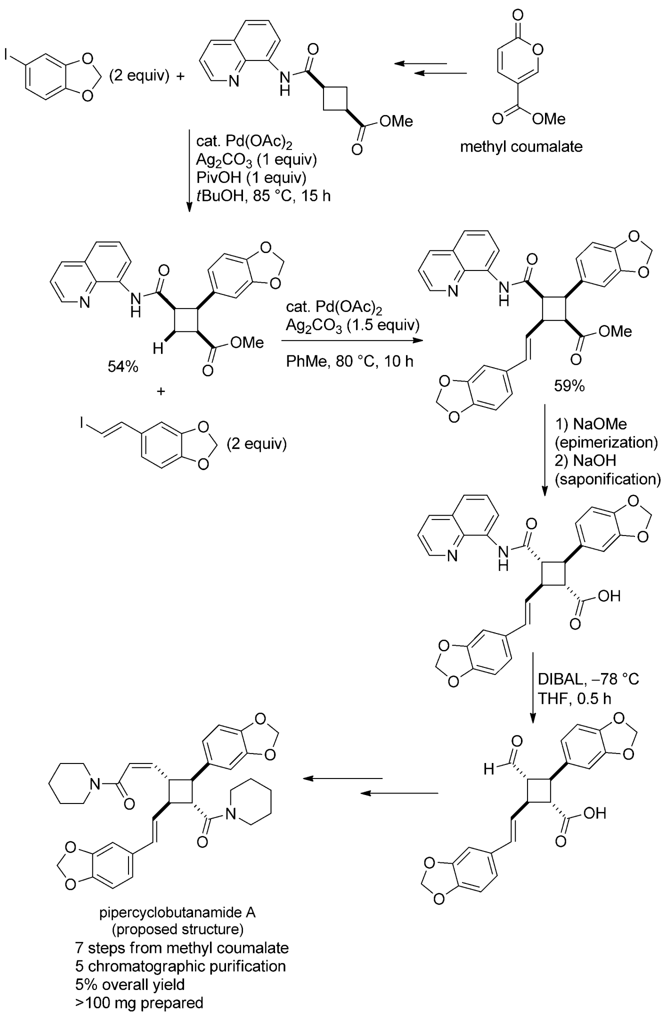


Scheme 19. Total synthesis of piperarborenines by a sequential C(sp^3)–H arylation of a cyclobutane ring.

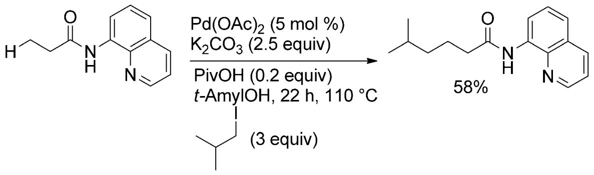
2.2. Alkylation of C–H Bonds

Compared with the arylation or vinylation of C–H bonds, the alkylation of C–H bonds remains underdeveloped.[27] A significant advance was made by Shabashov and Daugulis in parallel with the directed bidentate palladium(II)-catalyzed β-arylation of C(sp^3)–H and C(sp^2)–H bonds.[11b] They successfully expanded his method to C–H alkylation with alkyl iodide or bromide partners (Scheme 21). This reaction represents notable progress, knowing the inherent resistance of alkyl halides toward oxidative addition and the tendency of the resulting alkyl metal complexes toward β-hydride elimination.

A similar alkylation of an *ortho*-C–H bond of picolinamide-protected benzylamines with alkyl halides was then published by Chen and co-workers.[28] Recently, they extended the method to the γ- and δ-C(sp^3)–H alkylation of

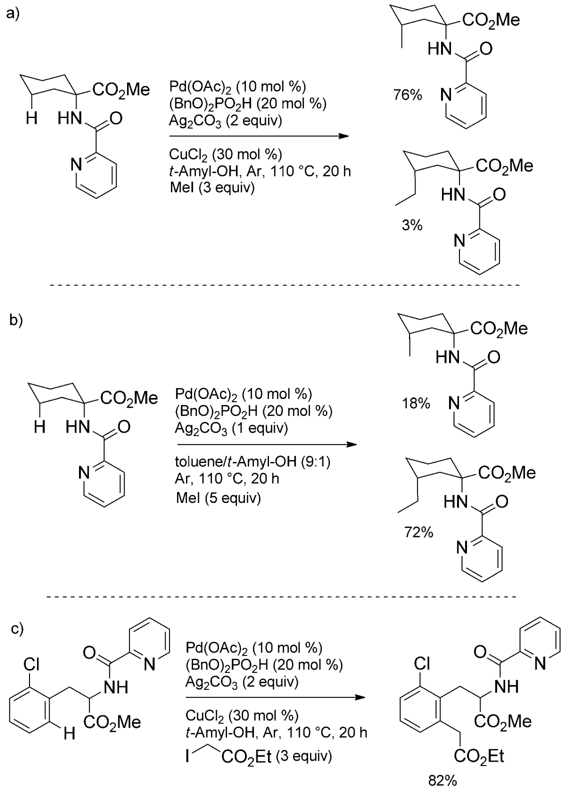


Scheme 20. Total synthesis of the proposed structure of pipercyclobutanamide A by a sequential palladium-catalyzed C(sp^3)—H arylation and alkenylation of a cyclobutane ring.



Scheme 21. Palladium-catalyzed β-alkylation of unactivated C(sp^3)—H bonds of an 8-aminoquinoline amide.

picolinamide-protected aliphatic amines with primary alkyl iodides (Scheme 22).[29] Interestingly, the reaction reached its optimum efficiency when a silver salt was used together with an organic phosphate additive: $(BnO)_2PO_2H$. Various linear primary alkyl iodides were described as efficient alkylating agents and the reaction tolerated a large diversity of amine backbones. Surprisingly a second C(sp^3)—H activation could take place in good yield under specific conditions, thus providing us with an interesting route to sequential functionalization of C—H bonds (Scheme 22 a and b). These reaction conditions also permit the method to be used to activate remote δ-C(sp^2)—H bonds (Scheme 22 c).

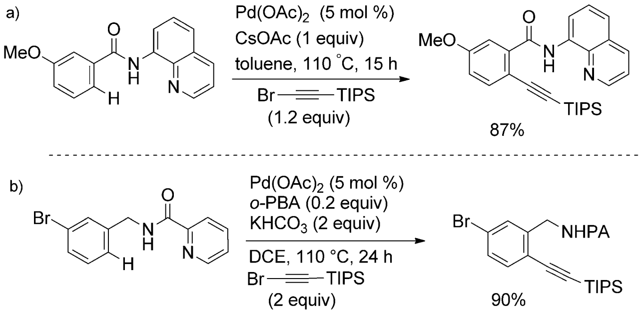


Scheme 22. Palladium-catalyzed picolinamide-directed alkylation and sequential alkylation of unactivated C(sp^3)—H and remote δ-C(sp^2)—H bonds with alkyl iodides.

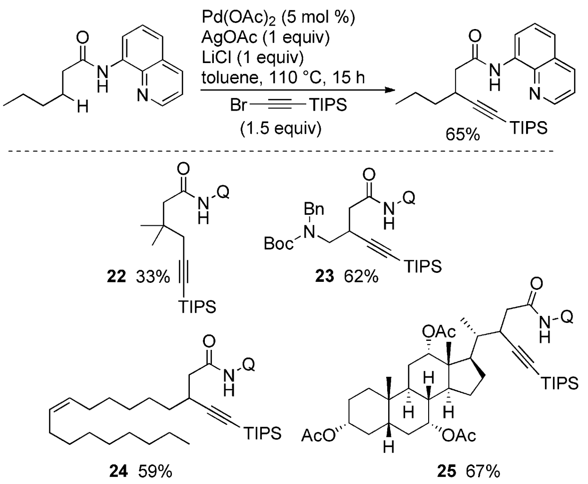
2.3. Alkynylation of C—H Bonds

The direct alkynylation of C—H bonds has recently emerged as a straightforward alternative to the Sonogashira reaction for the construction of C(sp^2)—C(sp) bonds.[30] However, the alkynylation of *ortho*-C—H bonds of benzene derivatives remains relatively unexplored, and methods developed to date offer relatively limited scope in terms of electronically diversity. Tobisu and co-workers have reported a straightforward palladium-catalyzed 8-aminoquinoline-directed *ortho*-alkynylation that is applicable to a range of electronically diverse arenes with a relatively good functional-group tolerance (Scheme 23 a).[31] Subsquent to this study, Chen developed an alternative procedure suitable for picolinamide-protected benzylamine rings (Scheme 23 b).[24]

The first catalytic alkynylation of unactivated C(sp^3)—H bonds has been reported by Tobisu and co-workers (Scheme 24).[32] A variety of aliphatic carboxylic amide derivatives were successfully alkynylated and the current limitation of this method is that only secondary C—H bonds are alkynylated in synthetically useful yields, while primary and tertiary C—H bonds undergo alkynylation with a lower efficiency. When substrates bearing no hydrogen atoms at the



Scheme 23. Palladium-catalyzed direct *ortho*-alkynylation of aromatic carboxylic acid and benzylamine derivatives.

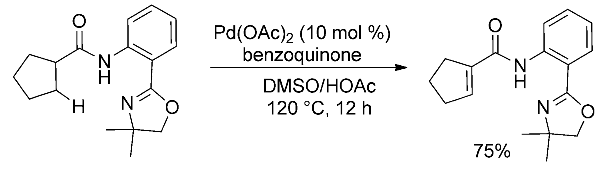


Scheme 24. Palladium-catalyzed direct alkynylation of C(sp^3)−H bonds in aliphatic carboxylic acid derivatives: application to complex molecules.

β position were used, as in **22**, alkynylation occurred regioselectively at the γ position. It was demonstrated that the reaction was applicable to some natural product derived substrates. An aliphatic C−H bond at the β position of oleic acid **24** could be alkynylated in a regioselective manner, even in the presence of normally more reactive allylic C−H bonds. The γ-aminobutyric acid (GABA) derivative **23** underwent alkynylation. Moreover, the steroidal structure **25** was successfully alynylated.

2.4. Dehydrogenation through C−H Bond Activation

A method for a palladium-catalytic dehydrogenation through β-hydride elimination of cyclopentylcarboxamides containing an oxazoline moiety as a bidentate directing group was developed by Yu and co-workers (Scheme 25).[33] However, the catalytic version of the reaction proved to be difficult when open-chain carboxamides were used, but various complexes could be synthesized in a stoichiometric fashion and their structures confirmed by X-ray crystallography, thus proving the presence of a bidentate coordination.



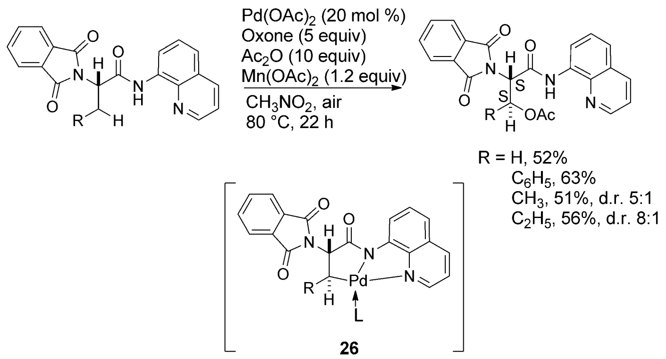
Scheme 25. Dehydrogenation of an unactivated C(sp^3)−H bond.

2.5. Oxidation of C−H Bonds

Palladium-catalyzed directed C−H oxidation reactions with monodentate directing groups are an intensive area of research, and major advances as well as mechanistic considerations have recently been reviewed.[2e,g,3x,12] New transformations involving bidentate directing groups are described in this section.

2.5.1. Formation of Carbon–Oxygen Bonds

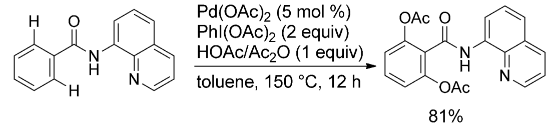
Corey and co-workers reported a palladium-catalyzed procedure for introducing an oxygen atom into the C(sp^3)−H bond of β-hydroxy-α-amino acids (Scheme 26).[17] Under optimized conditions, a diastereoselective acetoxylation took place to afford the expected compounds with a good diastereomeric excess. According to the authors, the formation of the intermediate *trans*-palladacycle **26** could explain the diastereoselective oxidation of the C−Pd bond.



Scheme 26. Acetoxylation of unactivated C(sp^3)−H bonds in α-amino acid derivatives with an 8-aminoquinoline auxiliary.

An alternative to the above procedure was then reported by Tran and Daugulis in 2012 by using the more straigthforward PhI(OAc)$_2$ as the oxidant in Ac$_2$O as the solvent.[18]

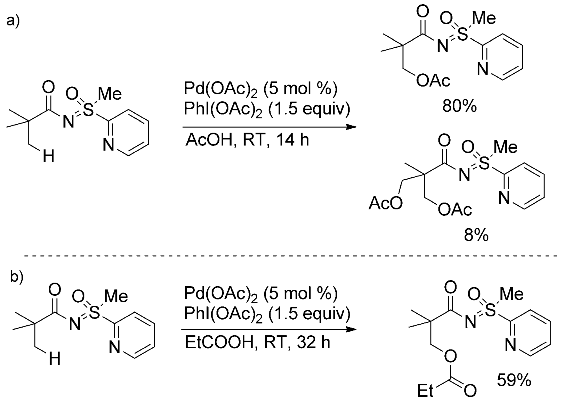
An analogous system was also used by Liang and co-workers (Scheme 27) for the palladium-catalyzed acetoxyla-



Scheme 27. Palladium-catalyzed *ortho*-diacetoxylation of C−H bonds by utilizing an 8-aminoquinoline as a bidentate directing group.

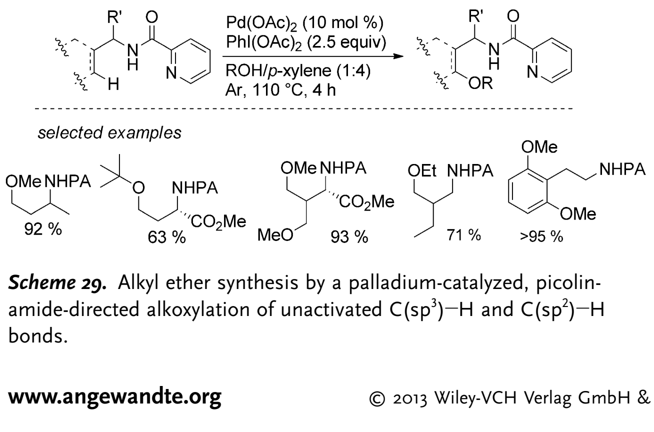
tion of C(sp^2)–H bonds of aryl substrates by utilizing an 8-aminoquinoline or a picolinamide bidentate directing group.[34] When the substrates contained no *ortho* substituent, the reaction furnished difunctionalized acetoxy compounds if two equivalents of oxidant were used under harsh conditions.

Recently, Sahoo and co-workers reported on the development of a new bidentate directing sulfoxinimine group which can promote the monoacetoxylation of C(sp^3)–H bonds at room temperature in the presence of PhI(OAc)$_2$ as the oxidant (Scheme 28 a).[35] By forcing the reaction conditions it was also possible to produce the diacetoxylated compounds exclusively. The directing group can be easily cleaved by simple acid hydrolysis and recycled after recovery. The effect of various carboxylic acid solvents was also examined. Various carboxylate groups, derived from the corresponding carboxylic acid solvents, were successfully incorporated into the oxidation products (Scheme 28 a).



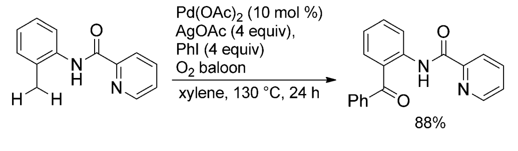
Scheme 28. Pd^{II}-catalyzed primary C(sp^3)–H acetoxylation with a sulfoximine directing group.

Chen and co-workers reported an efficient synthesis of alkyl ethers by the functionalization of C(sp^2)–H and primary C(sp^3)–H bonds of picolinamide-protected amine substrates at the γ or δ positions under oxidative conditions with simple alcohols reagents as the oxygen source to form the ether moiety; this is a rare transformation (Scheme 29).[36] The introduction of primary, secondary, and even tertiary alcohols, including bulky *t*BuOH, occurred efficiently. Formation of the difunctionalized product is generally facilitated and a high regioselective preference for primary over secondary γ-C(sp^3)–H bonds was observed. Various electron-rich and electron-poor aromatic amines also provided the oxidation products in good yields.



Scheme 29. Alkyl ether synthesis by a palladium-catalyzed, picolinamide-directed alkoxylation of unactivated C(sp^3)–H and C(sp^2)–H bonds.

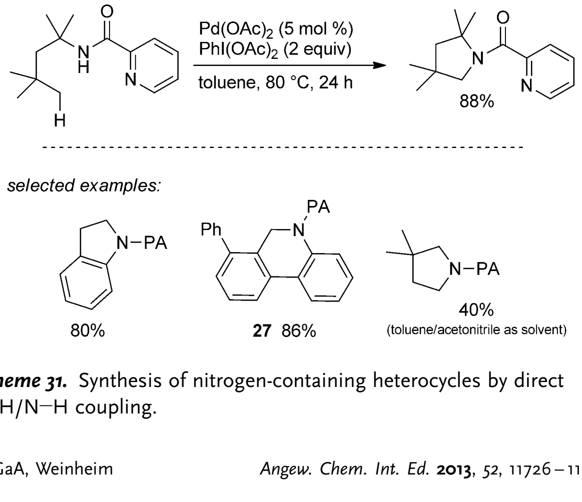
A picolinamide-directed palladium-catalyzed benzylic C–H arylation/oxidation that offers an original method for functionalizing aniline substrates was reported by Zhang and co-workers (Scheme 30).[37] The reaction took place under argon or air, but a dioxygen atmosphere was superior. Screening of the additives indicated that AgOAc gave the best yield. Other palladium catalysts such as PdCl$_2$, [Pd(CH$_3$CN)$_2$Cl$_2$], and [Pd(PPh$_3$)$_2$Cl$_2$] also worked in this transformation but resulted in lower yields. Aryl iodides and aniline derivatives with either electron-withdrawing or electron-donating groups were compatibility with the reaction conditions. Interestingly, this reaction involved a Pd^{II}/Pd^0 process,[38] whereas, until now, all reported palladium-catalyzed reaction mechanisms promoted by a bidentate directing group, usually involved a Pd^{II}/Pd^{IV} mechanism.[12]



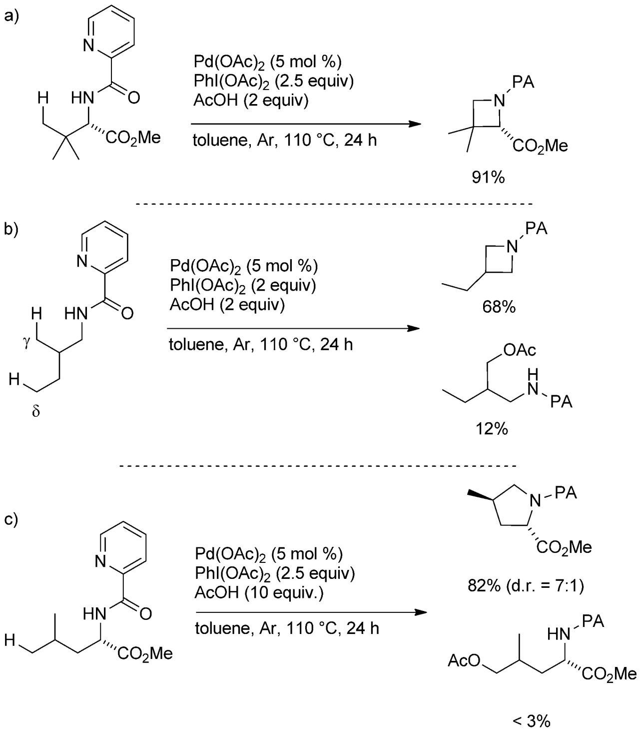
Scheme 30. Palladium-catalyzed arylation/oxidation of a benzylic C–H bond.

2.5.2. *Formation of Carbon–Nitrogen Bonds*

A rare direct palladium-catalyzed intramolecular amination reaction without nitrenes for the construction of nitrogen heterocycles was published by Nadris and Daugulis (Scheme 31).[39] The method made use of a picolinamide bidentate directing group and is applicable to δ-C(sp^2)–H as well as aliphatic and benzylic δ-C(sp^3)–H bonds. Six-membered rings can also be formed with this method, as in **27**, thus demonstrating the potential existence of seven-membered palladacycle intermediates. The cleavage of the picolinamide auxiliary using LiEt$_3$BH under mild conditions was described, which resulted in the formation of a heterocycle bearing a secondary nitrogen function as the final product.



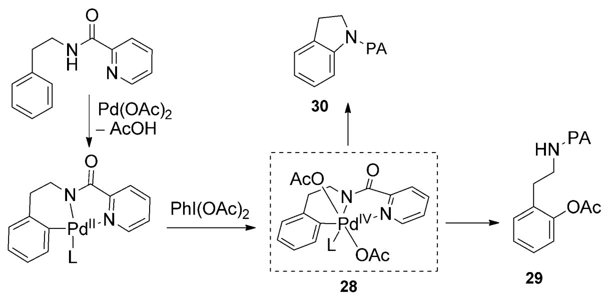
Scheme 31. Synthesis of nitrogen-containing heterocycles by direct C–H/N–H coupling.



Scheme 32. Syntheses of azetidines and pyrrolidine by a palladium-catalyzed intramolecular amination.

An analogous method was published by Chen and co-workers. The palladium-catalyzed intramolecular amination of primary C(sp^3)–H bonds at the γ position of picolinamide-protected amine substrates allows the seemingly unfavorable four-membered azetidine to be obtained (Scheme 32a).[40] Interestingly, the activation of the γ-C(sp^3)–H bond to give a four-membered cycle seems to be preferred over the activation of the δ-C(sp^3)–H bond to give a five-membered ring (Scheme 32b). It was proposed that the formation of a six-membered palladacycle by C(sp^3)–H palladation, which leads to a five-membered ring, is likely to be kinetically less favored. The method was applicable to the cyclization and intramolecular amination of δ-C(sp^3)–H bonds to give the pyrrolidine product if the C–H bond at the γ position is bulky (Scheme 32c). Chen and co-workers also explored the synthesis of indoline compounds from picolinamide-protected β-arylethylamine substrates by the palladium-catalyzed intramolecular amination of *ortho*-C(sp^2)–H bonds.[41]

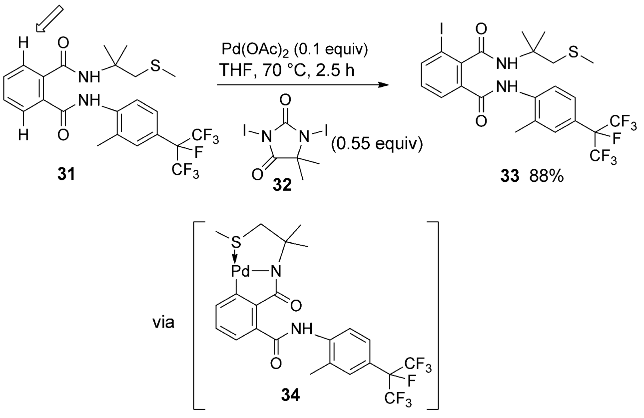
From a general viewpoint, as shown in Scheme 32, a limitation of the reactions presented herein, is the potential formation of acetoxylation products. Formation of a Pd^{IV} intermediate **28**, followed by a subsequent C–O reductive elimination pathway may lead to the formation of the acetoxylated product **29**, which would be in competition with the C–N reductive elimination that leads to the expected cycle **30** (Scheme 33).



Scheme 33. Synthesis of a nitrogen-containing heterocycle by direct C–H/N–H coupling: competitive formation of acetoxylated compounds.

2.5.3. *Formation of Carbon–Iodine Bonds*

In 2001, researchers at Nihon Nohyaku reported on a new *ortho*-C–H halogenation of carboxylic acid derivatives with electrophilic halogenating reagents as the terminal oxidant.[42] A study of the scope of the reaction revealed that some directing groups having two potential coordinative atoms were able to achieve site-selective *ortho*-halogenation of C–H bonds of some benzamides derivatives. For example, amide subtrates **31** with a 2-(methylthio)ethanamine-directing group can promote an *ortho*-C(sp^2)–H iodination catalyzed by palladium acetate with simple iodination reagents **32** (Scheme 34). The ability of the methylthiobenzamide function to control the regioselectivity (instead of the simple phenylbenzamide function) to provide **33** led to the speculation that a bidentate complex intermediate such as **34** might be involved in the mechanism. Bromination and chlorination reactions were also described with *N*-bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS), respectively. However, the crucial role of the bidentate directing group was not highlighted by the authors, likely because of a lack of an overview at the time the reaction was discovered.



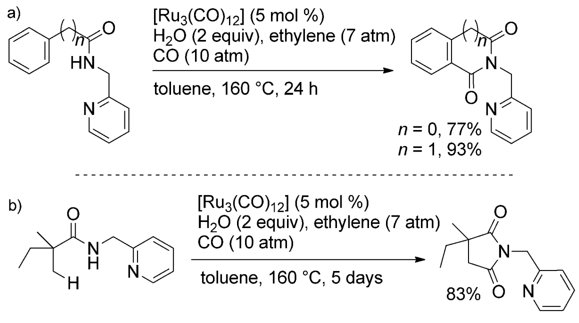
Scheme 34. An *ortho*-directed iodination reaction promoted by a bidentate directing group.

3. *Ruthenium Catalysis*

3.1. *Carbonylation of C–H Bonds*

Since the pioneering investigations of Moore et al. in 1992,[43a] ruthenium has proved to be a versatile catalyst for

C–H carbonylation reactions, notably thanks to the extensive studies of Murai and Chatani.[43b] In 2009, Chatani and co-workers reported on the Ru^0-catalyzed C–H carbonylation of amides bearing a 2-aminomethylpyridine bidentate auxiliary (Scheme 35 a with $n=0$).[44] This study represents the first example of a ruthenium-catalyzed C–H activation in which a bidentate directing group is used. They started their studies with the observation that carbonyl groups have rarely been used as directing groups in the carbonylation of C–H bonds. The hypothesis is that the coordination of a carbonyl group, which has a relatively poor coordination ability, must compete with the higher pressure of CO, thus inhibiting the reactivity of the catalyst. Chatani and co-workers reasoned that a bidentate system would bind tightly to the catalyst even under a higher CO pressure, thereby permitting the catalyst to come into proximity to a C–H bond, which may then be cleaved. They further successfully applied these reaction conditions to the *ortho*-carbonylation of aromatic acetamides (Scheme 35 a with $n=1$),[45] thereby affording a six-membered cycle. Extension of the reaction to the carbonylation of unactivated $C(sp^3)$–H bonds was successful (Scheme 35 b).[46] C–H bonds of methyl groups are preferentially carbonylated over those of methylene groups, thus resulting in the high regioselectivity. This reactivity was attributed mainly to steric factors.



Scheme 35. Carbonylation of *ortho*-C–H bonds and unactivated $C(sp^3)$–H bonds by utilizing a bidentate chelation system.

The dinuclear ruthenium complexes **35**, **36**, and **37** were obtained by the reaction of amide substrates with a stoichiometric amount of $[Ru_3(CO)_{12}]$, and their structures were confirmed by X-ray crystallography (Figure 1).[44–46] The ability of the 2-aminomethylpyridine auxiliary to bind to ruthenium in the expected bidentate fashion was thus confirmed.

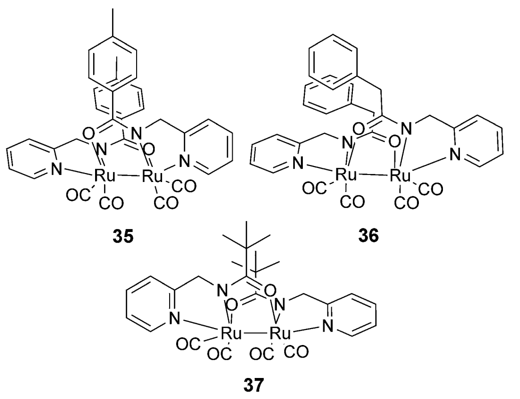
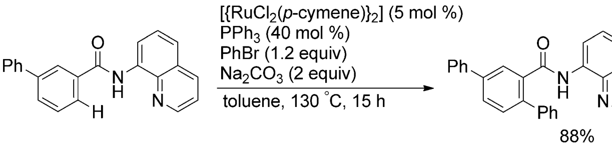


Figure 1. Isolated intermediate of the ruthenium-catalyzed C–H carbonylation reaction.



Scheme 36. Ruthenium-catalyzed C–H arylation of aromatic amides promoted by an 8-aminoquinoline bidentate directing group.

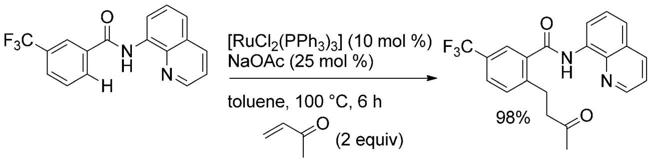
3.2. Arylation of C–H Bonds

Directed ruthenium-catalyzed arylation reactions are well documented today.[3h,l,u,ab] Oi, Inoue et al. published the first example of the chelation-assisted Ru^{II}-catalyzed arylation of C–H bonds.[47] In 2013, the first Ru^{II}-catalyzed *ortho*-arylation of aromatic amides with a bidentate directing group was reported (Scheme 36).[48] The reaction offers high regioselectivity, very good yield, and a wide scope. The reaction of *meta*-substituted substrates resulted in selective phenylation at the less-hindered C–H bonds, irrespective of the electronic nature of the substituent. This finding indicates that the regioselectivity was controlled by the steric nature of the substituent groups. A variety of amides and aryl bromides were applicable to the arylation reaction. Aryl iodides and triflates were also reported to be coupling partners.

3.3. Alkylation of C–H Bonds

Murai et al. published in 1993 the ruthenium-catalyzed *ortho*-C–H bond alkylation of aromatic ketones with olefins with the help of a directing group (Scheme 3).[9] Since that report, the family of ruthenium-catalyzed C–H alkylations has been extended to other useful partners. Notably, Ackermann et al.[49] found that alkyl halides were interesting alkylating agents and their use was recently reviewed.[27] Despite the significant promising progress in the field, various challenges remain. For example, a strong limitation of the chelation-assisted ruthenium-catalyzed alkylation of *ortho*-C–H bonds of aromatic substrates with olefins is that a large range of olefins bearing functional groups remain unusable, thus limiting the method to basic olefin partners.[50]

Recently, Rouquet and Chatani reported that a removable 8-aminoquinoline bidentate directing group allowed the ruthenium-catalyzed alkylation of *ortho*-C–H bonds of aromatic amides by 1,4-addition to various α,β-unsaturated ketones (Scheme 37).[51] Electron-rich and electron-poor amides were efficiently alkylated in this reaction and a large variety of enones could be used. Dialkylation took place if both C–H bonds were indistinguishable (*p*-substituted amides), but the alkylation proceeded preferentially at the



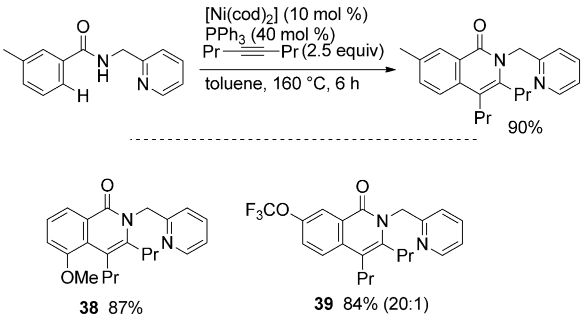
Scheme 37. An 8-aminoquinoline-promoted, ruthenium-catalyzed C−H alkylation of aromatic amides by a 1,4-addition to enones.

less substituted C−H bonds with *m*-substituted amides. However, substitution at the most substituted side occurred exclusively with some *m*-substituents, such as fluorine, that were able to coordinate the catalyst.

4. Nickel Catalysis

4.1. Alkenylation of C−H Bonds

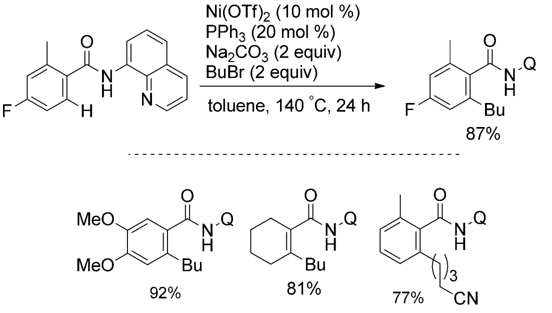
Nickel, an abundant and low-cost transition metal, is of prime interest for the catalyzed transformation of C−H bonds and its exploitation has been reported in many reactions.[52] However, since the first report by Kleimann and Dubeck of the directed insertion of nickel into a C−H bond,[7] no examples of Ni-catalyzed transformations of *ortho*-C−H bonds in the presence of a directing group have been reported. Chatani and co-workers reported the first nickel-catalyzed transformation of *ortho*-C−H bonds through application of a directing group.[53] They found that a bidentate 2-prydinylmethylamine directing group was able to promote efficiently, at high temperature, the Ni^0-catalyzed *ortho*-C−H addition of amides to internal alkyne substrates followed by an insertion into the N−H bond of the amide to afford cyclic isoquinoline derivatives (Scheme 38). The reaction of *m*-substituted amides led to functionalization at the less-hindered C−H bond. However, they noted that some hetero-aromatic groups (such as a *m*-methoxy group in **38**) led to cleavage of the more-hindered C−H bond. Interestingly, this effect can be reversed with an appropriate substitution (**38** versus **39**). In this reaction the regioselectivity is, thus, oriented by steric effects but also by the electronic nature of the substituents if they contain a lone pair of electrons (as is the case for C−H addition to enones).[51] In contrast to the previous reported [{Cp*RhCl$_2$}$_2$]-[54] or [{RuCl$_2$(*p*-cymene)}$_2$]-catalyzed reaction[55] to afford isoquinolinones, this nickel-catalyzed reaction did not require a stoichiometric amount of a metal oxidant.



Scheme 38. Oxidative cycloaddition of aromatic amides to alkynes through a nickel-catalyzed chelation-assisted *ortho*-C−H bond activation.

4.2. Alkylation of C−H Bonds

The first example of a nickel-catalyzed *ortho*-alkylation of benzamides derivatives with unactivated alkyl halides in which C−H bonds are cleaved was recently published (Scheme 39).[56] The reaction proceeds in a highly selective manner at the less-hindered C−H bond in the reaction of *meta*-substituted aromatic amides. This alkylation reaction was also applicable to various trisubstituted α,β-unsaturated amides. A variety of functionalized alkyl bromides were applicable to the alkylation reaction.

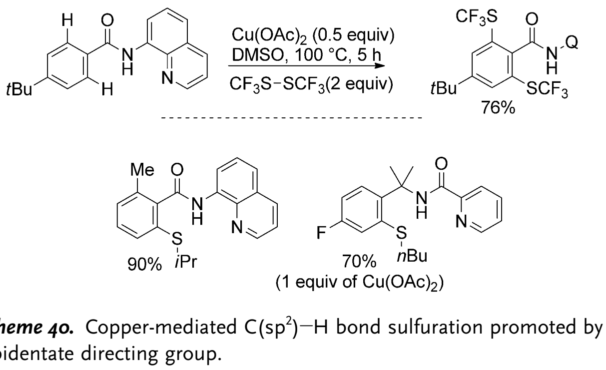


Scheme 39. Nickel-catalyzed C(sp^2)−H alkylation reaction promoted by an 8-aminoquinoline bidentate directing group.

5. Copper Catalysis

5.1. Sulfuration of C−H Bonds

The abundant and cheap metal copper has recently been explored as an alternative catalyst for the functionalization of C−H bonds.[57] Daugulis and co-workers reported a copper-promoted sulfenylation of β-C−H bonds in benzoic acid derivatives and γ-C−H bonds in benzylamine derivatives assisted by a bidentate directing group (Scheme 40).[58] This

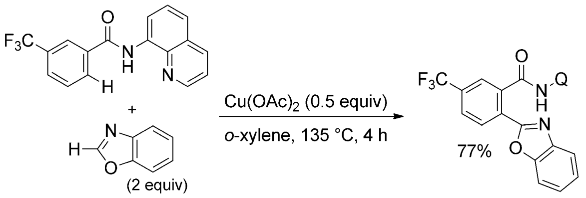


Scheme 40. Copper-mediated C(sp^2)−H bond sulfuration promoted by a bidentate directing group.

method represents the first example of a transition-metal-catalyzed trifluoromethylsulfenylation of C−H bonds. Various amides containing different electron-donating and -withdrawing groups are suitable substrates. The reaction afforded difunctionalized products, even with *m*-substituted amides. The mechanism of the reaction is not well understood and it is not clear whether the reaction is a true catalytic process because of the large amount of copper that is required for the reaction to be efficient.

5.2. Arylation of C−H Bonds

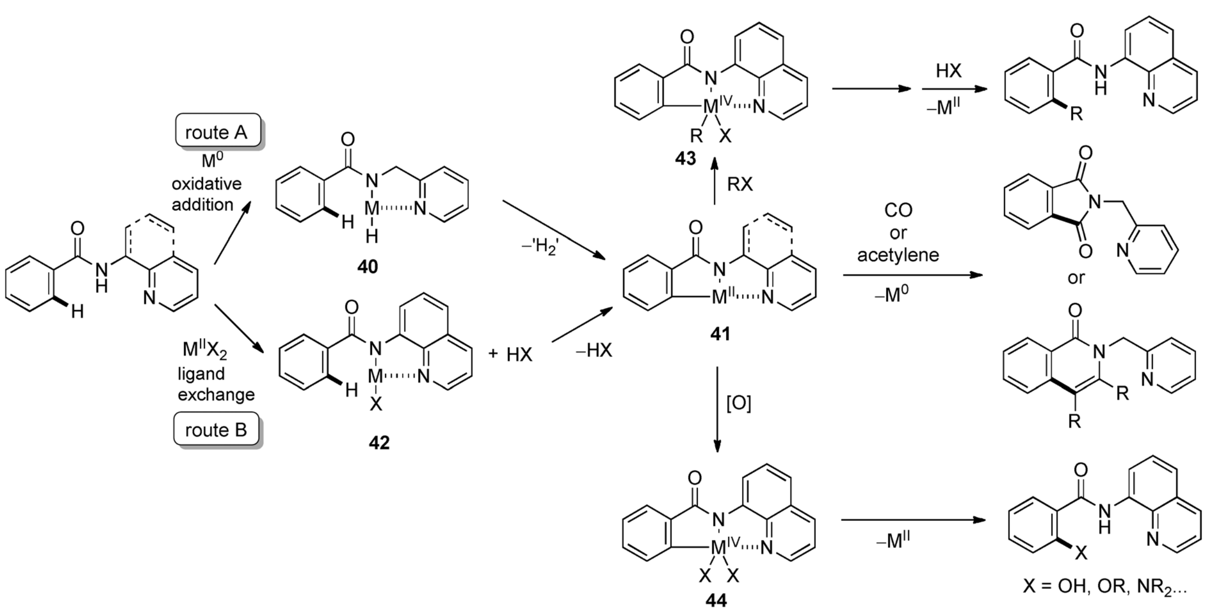
Miura and co-workers recently highlighted the potential of bidentate directing groups for use in direct biaryl coupling through a double C−H activation. They reported that a copper salt can efficiently mediate the C(sp^2)−H/C(sp^2)−H coupling of benzoic acid derivatives and 1,3-azoles when an 8-aminoquinoline bidentate directing group is used in the substrate (Scheme 41).[59] Electronically and sterically diverse substituents at the *o*, *m*, and *p* positions of the amide derivatives are tolerated in this system. If the substrate contains two potentially reactive C−H bonds, then doubly arylated products can be produced, but the reaction of *m*-substituted amides occurred predominantly at the less-congested site. Various azoles partners are also amenable for use in this reaction.



Scheme 41. Copper-mediated oxidative arylation of a C(sp^2)−H bond promoted by a bidentate directing group.

6. Mechanism: General Consideration

Some general mechanistic trends emerge from the collection of reactions presented in this Review, and are summarized in Scheme 42. However, we must keep in mind that some specific reactions, such as those in which the mechanism is relatively unclear, may not be included in this scheme. The reactions involving *N,N*-bidentate directing groups reported thus far proceed through two different mechanisms (routes A and B), depending on the oxidation state of the catalyst. When low-valent transition-metal catalysts, such as Ru^0 or Ni^0, are used as catalysts, route A appears to be the operational mechanism. The coordination of the nitrogen atom to the catalyst followed by oxidative addition of the N−H bond gives the metal hydride complex **40**. A cyclometalated complex **41** is generated with the formal concomitant generation of H$_2$. However, this is not the actual mechanism. In fact, the insertion of an olefin or an alkyne into an H−M bond of **40** followed by σ-bond metathesis gives the cyclometalated complex **41**. An olefin or an alkyne functions as a hydrogen acceptor. The insertion of CO or an alkyne into the cyclometalated complex **41** followed by reductive elimination gives phthalimides or isoquinolones, respectively (Schemes 35 and 38). In the case of Pd^{II}, Ru^{II}, Ni^{II}, or Cu^{II}-catalyzed reactions, the ligand exchange is followed by the coordination of the nitrogen atom to the catalyst to generate complex **42** through route B. The cyclometalated complex **41** is then generated through liberation of HX. The oxidative addition of halide reagents generates metal(IV) intermediate **43**, which then undergoes reductive elimination followed by protonation to afford alkynylation, phenylation, or alkylation



Scheme 42. Mechanism: a general overview.

products. Complex **41** undergoes oxidation to generate the metal(IV) complex **44** followed by reductive elimination to result in the introduction of oxygen, nitrogen, or sulfur functionalities. In route A, 2-pyridinylmethylamine functions as a bidentate directing group. In contrast, an 8-aminoquinoline functions as a more superior auxiliary than 2-pyridinylmethlyamine in route B. This is because 8-aminoquinoline has a more acidic NH bond, which facilitates ligand exchange.

The difference in the mechanism for routes A and B involves how the N–H bonds are activated. This depends on the oxidation state of the catalyst used. However, irrespective of the mechanism, the catalyst is brought into proximity to the N–H bond by coordination of an sp^2 nitrogen atom, and then relayed to the targeted *ortho*-C–H bonds, thus indicating that the presence of a N–H bond plays a key role in the activation of C–H bonds. This explains why the presence of an N–H bond in the substrates as well as the pyridine or quiloline nitrogen atom is crucial for the reaction to proceed. In route A, the catalysis ends with the formation of C–N bonds and regeneration of the M^0 species. In route B, the catalysis ends with protonation after the reductive elimination, which generates a M^{II} species. The reactions involve the incipient formation of covalent Pd–N bonds by oxidative addition or ligand exchange, as in **40** or **42**, and the formation of C–N bonds or the restoration of the N–H bond at the end of the catalytic cycle. All of the bidentate directing groups discussed in this Review are *monoanionic*, bidentate groups, not neutral bidentate groups. This will be the key to make the reaction catalytic, compared with the neutral *N*,*N*-bidentate directing group.[10]

7. Summary and Outlook

The utilization of bidentate directing groups in the directed activation of C–H bonds has significantly grown in popularity since the seminal key discovery by Daugulis and co-workers in 2005. An interesting new collection of methods for the catalytic transformation of C–H bonds into C–C bonds (arylation, vinylation, alkylation, alkynylation, carbonylation), as well as C–X bonds (oxygenation, amination, sulfuration, halogenation) has been developed. Bidentate auxiliaries have also proven to be important for achieving the highly challenging total synthesis of natural products. The ability of this family of directing groups to achieve this compared with the problematic or difficult procedures involving conventionally used monodentate systems have been clearly highlighted throughout the procedures developed to date. New alternatives are, thus, available for planning C–H activation strategies.

Bidendate-chelation-assisted metal-catalyzed C–H functionalization is still in its infancy, and a wide area of research and challenges are now within our reach. Furthermore, structurally new bidentate motifs, as well as the exploitation of new families of metal catalysts must be considered in the future for the discovery of new reactions. The following years promise to be rich in discoveries in this growing area of research.[60]

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