Carbene/Nitrene Transfer

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Complementary Strategies for Directed C(sp^3)–H Functionalization: A Comparison of Transition-Metal-Catalyzed Activation, Hydrogen Atom Transfer, and Carbene/Nitrene Transfer

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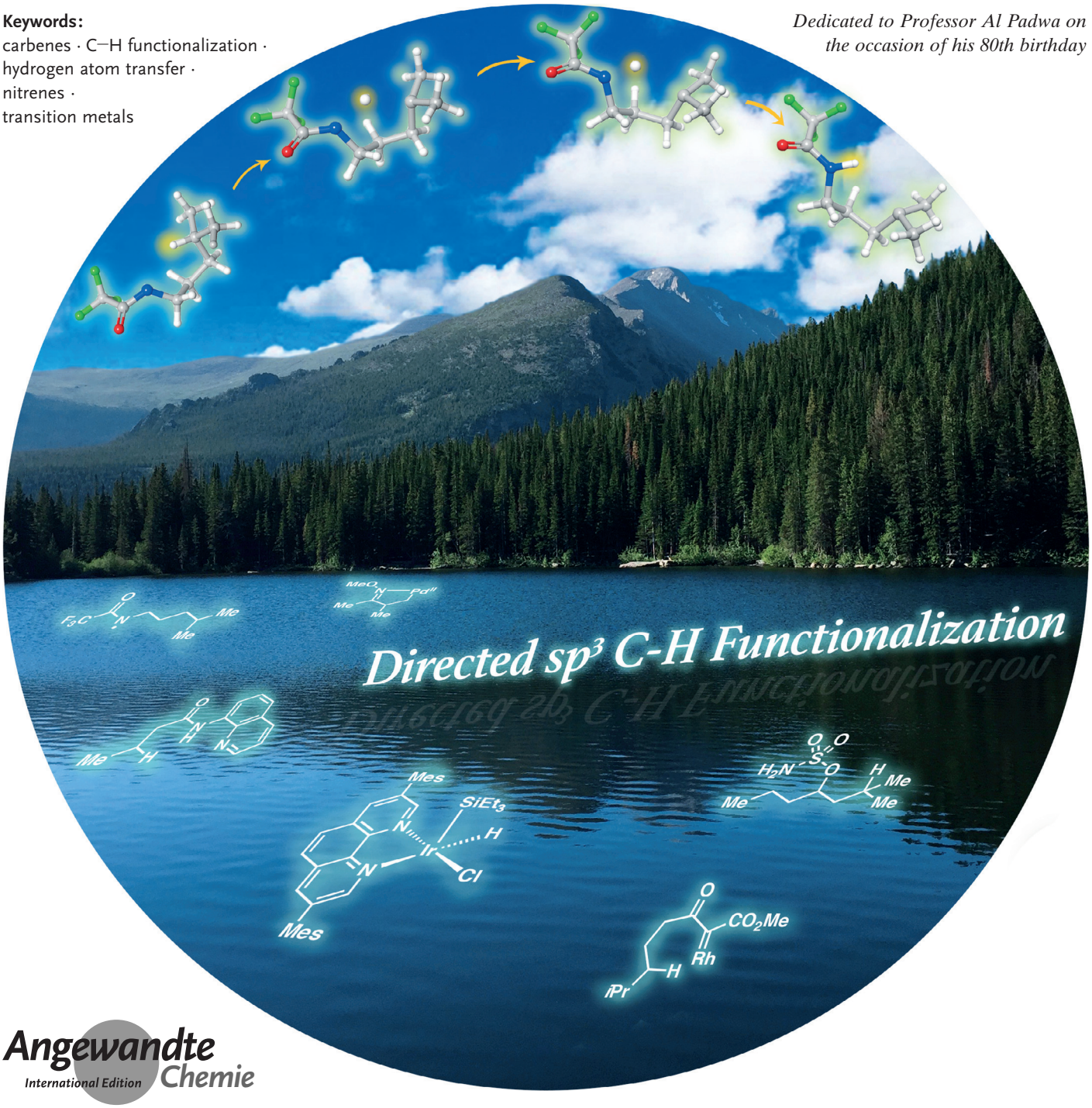
Keywords:
carbenes · C–H functionalization · hydrogen atom transfer · nitrenes · transition metals

Dedicated to Professor Al Padwa on the occasion of his 80th birthday



The functionalization of C(sp³)–H bonds streamlines chemical synthesis by allowing the use of simple molecules and providing novel synthetic disconnections. Intensive recent efforts in the development of new reactions based on C–H functionalization have led to its wider adoption across a range of research areas. This Review discusses the strengths and weaknesses of three main approaches: transition-metal-catalyzed C–H activation, 1,n-hydrogen atom transfer, and transition-metal-catalyzed carbene/nitrene transfer, for the directed functionalization of unactivated C(sp³)–H bonds. For each strategy, the scope, the reactivity of different C–H bonds, the position of the reacting C–H bonds relative to the directing group, and stereochemical outcomes are illustrated with examples in the literature. The aim of this Review is to provide guidance for the use of C–H functionalization reactions and inspire future research in this area.

From the Contents

1. Introduction

Nearly all organic molecules are extensively adorned with C–H bonds, whose lack of reactivity excludes them from being labeled a "functional group". Methods to achieve direct C–H functionalization to derivatize organic molecules constitute a powerful tool.[1] In contrast to conventional organic reactions, C–H functionalization obviates the need for a pre-existing functional handle, and represents an opportunity to modify a site of a molecule that was previously unattainable by traditional methods. Maturation of this technology[1] would lead to novel means to disconnect a molecule in retrosynthetic analyses and, thus, potentially provide more efficient synthetic routes from simple starting materials.

A cursory examination of the strengths of typical C–H bonds underscores one of the main challenges associated with C–H functionalization: their high enthalpic stability. The trend also suggests that aliphatic C(sp³)–H bonds should be easiest to functionalize. While this is true in reactions that proceed through homolytic bond cleavage, it is not true for metal-catalyzed C–H bond activation, as the latter ignores the relative strengths of the M–C bonds generated. It is noteworthy that M–C(sp²) bonds tend to be much stronger than the corresponding metal–alkyl bonds (Figure 1).[2,3] Whereas C(sp²)–H functionalization has received tremendous attention and has witnessed significant advances in recent decades, the functionalization of unactivated C(sp³)–H bonds has been perceived to be more challenging. Furthermore, the ubiquity of C(sp³)–H bonds in organic molecules poses a selectivity problem. Although it seemed impossible to develop a synthetically useful transformation based on the functionalization of such bonds a few decades ago, some successes have emerged in this area in recent years, as exemplified by the number of publications and the applications of C(sp³)–H functionalization reactions in natural product synthesis.

In most cases, the key to breaking inert C(sp³)–H bonds and to address selectivity is the employment of a directing group (Figure 2). The presence of the directing group lowers the energy barrier for cleaving the C–H bonds and directs a specific C–H bond for reaction through a cyclic transition state. This Review aims to summarize the three main strategies—transition-metal-catalyzed C–H activation, 1,*n*-hydrogen atom transfer, and metal-catalyzed carbene/nitrene transfer—for the directed functionalization of unactivated C(sp³)–H bonds. The focus will be on comparing and contrasting the three strategies as well as discussing their complementarity in the hope that this Review will serve as a guide for users of directed C–H functionalization reactions,

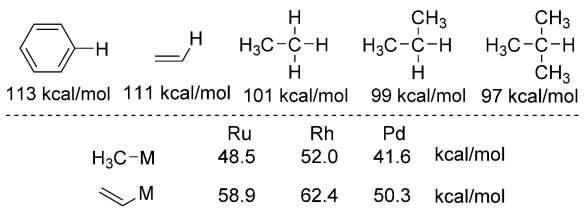


Figure 1. Challenges in C–H functionalization.

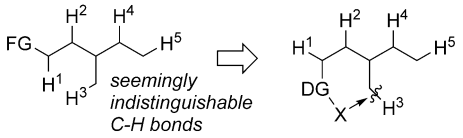


Figure 2. Use of a directing group in C–H functionalization.

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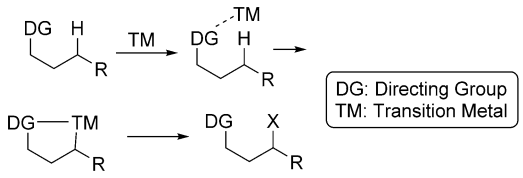
as well as for synthetic chemists to develop new transformations. In this Review, unactivated C(sp^3)C- > H bonds are those primary, secondary, and tertiary C–H bonds not activated by a heteroatom (e.g. oxygen and nitrogen) or a π system (e.g. alkenes or aromatic systems). The functionalization of cyclopropyl and cyclobutyl C–H bonds is also not included in this Review. In addition, although there has been significant advances in undirected C(sp^3)–H functionalization in recent years, it is beyond the scope of this Review. Readers who are interested in undirected C(sp^3)–H functionalization are encouraged to read the relevant reviews.[4]

2. Transition-Metal-Catalyzed C–H Activation

Transition-metal catalysis is currently the predominant focus for the functionalization of C–H bonds. The transition-metal catalyst coordinates to a Lewis basic functional group on the molecule, which brings the catalyst into the proximity of a specific C–H bond, thereby lowering the energy barrier for the cleavage of this C–H bond. The resulting alkyl metal intermediate can be trapped with a reactive partner to form a C–X bond (Scheme 1). Since C(sp^2)–H bonds are, in general, stronger than C(sp^3)–H bonds, it might appear that the activation of C(sp^3)–H bonds would be less challenging. The literature suggests the opposite trend. In addition to the ubiquity of C(sp^3)–H bonds, this observation could be explained by the relative bond strength of the metal–carbon bonds. In general, a metal–C(sp^3) bond is weaker than a metal–C(sp^2) bond. This relative bond strength is illustrated with the iridium complexes in Figure 3. For iridium(III) complexes **1** and **2**, which are ligated with phosphines and cyclopentadienyl groups, the Ir–Ph bond is 30 kcal mol^{-1} stronger than the Ir–Cy bond.[5] The rhodium complexes ligated by Tp also show that the Rh–Ph bond in **3** has a bond energy 16 kcal mol^{-1} higher than the Rh–Me bond in **4** (Figure 3).[6] This difference in bond energies affords a plausible explanation for the fact that it is more difficult to activate a C(sp^3)–H bond than a C(sp^2)–H bond in transition-metal catalysis. The following gives a brief overview of seminal reports on C(sp^3)–H activation catalyzed by transition-metal complexes through the formation of a metal–carbon bond and does not represent an exhaustive list of all research in this area.



Scheme 1. Transition-metal-catalyzed C–H activation.

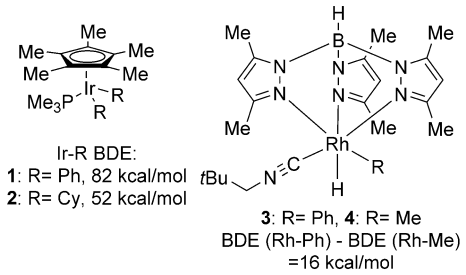
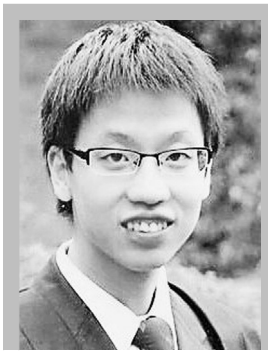


Figure 3. Weaker carbon–metal bonds with sp^3-hybridized carbon atoms.

2.1. Palladium Catalysis[7]

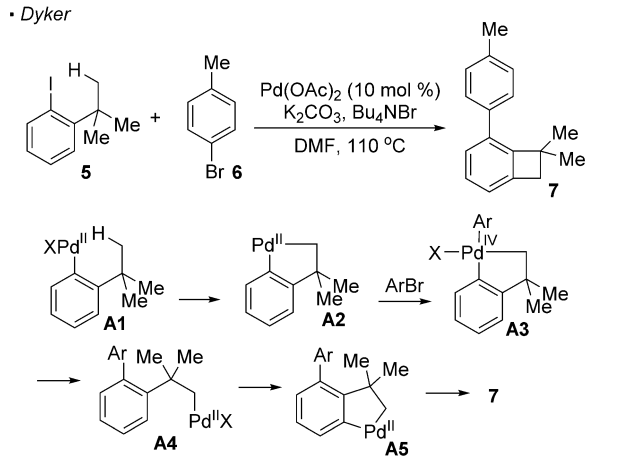
2.1.1. Early Work

A seminal report by Dyker described the Pd^{II}-catalyzed synthesis of benzocyclobutene **7** from aryl iodide **5** and aryl bromide **6** that featured the activation of methyl C–H bonds (Scheme 2).[8] In the proposed catalytic cycle, Pd^0 adds oxidatively to the C–I bond to form aryl-Pd^{II} intermediate **A1**. This oxidative addition brings the palladium catalyst close to the methyl group, thus facilitating the activation of the methyl C–H bond through cyclopalladation to give **A2**. Another oxidative addition into the aryl bromide leads to Pd^{IV} intermediate **A3**, thereby driving reductive elimination to form a C(sp^2)–C(sp^2) bond. Activation of the C(sp^2)–H bond in **A4** at the *ortho* position generates another palladacycle **A5**. The final C(sp^2)–C(sp^3) bond is forged by the reductive elimination of this Pd^{II} species. Overall, the reaction represents the activation of C(sp^3)–H bonds, with an aryl iodide as a traceless directing group. This later inspired various groups to use vinyl halides and triflates as a traceless directing group in the subsequent development of C–H activation reactions.



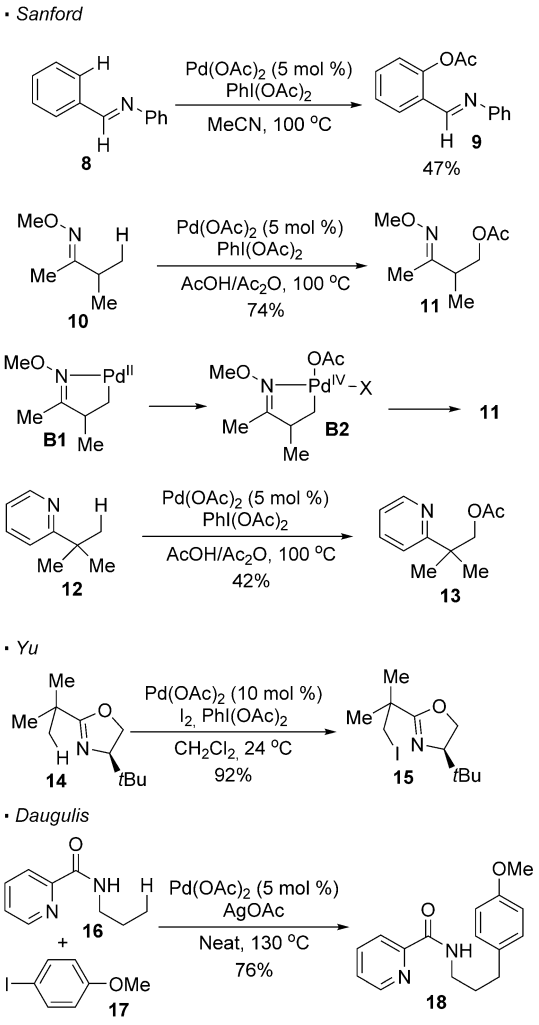
John Chun Kit Chu obtained his BSc in Chemistry at the University of Hong Kong. With the support of a Croucher Scholarship, he pursued his PhD in Chemistry under the supervision of Prof. Tomislav Rovis at Colorado State University. Currently, he is a postdoctoral researcher as a Marie Curie Fellow in the Group of Prof. Matthew Gaunt at the University of Cambridge. His research focuses on the development of novel organic transformations.

Tomislav Rovis was born in Zagreb (Croatia), but was raised in Canada. He received his BSc from the University of Toronto and completed his PhD there with Prof. Mark Lautens. After postdoctoral research (NSERC) at Harvard with Prof. David A. Evans, he began his independent career in 2000 at Colorado State University, was promoted in 2005, and named John K. Stille Chair in 2008. In 2016, he joined Columbia University where he is currently Professor of Chemistry.



Scheme 2. Aryl halides as directing groups.

Three other seminal reports on palladium-catalyzed C(sp^3)–H activation, using nitrogen as a directing group, were contributed by the research groups of Sanford, Yu, and Daugulis. Sanford and co-workers reported a palladium-catalyzed nitrogen-directed C(sp^3)–H oxygenation. This work was inspired by related stoichiometric studies by other research groups[9] and their previous work on the activation of C(sp^2)–H bonds (Scheme 3).[10] Nitrogen, in the form of imines and pyridines, was previously established to be a competent directing group for the acetoxylation of C(sp^2)–H and benzylic C(sp^3)–H bonds with $Pd(OAc)_2$ as the precatalyst and $PhI(OAc)_2$ as the stoichiometric oxidant. For example, imine **8** undergoes acetoxylation to form **9**. Based on this established procedure, Sanford and co-workers developed an oxime-directed acetoxylation of unactivated primary C–H bonds.[11] It is believed that after the coordination of the oxime nitrogen atom to the palladium(II) catalyst, a concerted metalation/deprotonation event between the substrate and the Pd^{II} catalyst leads to the formation of alkyl-Pd^{II} intermediate **B1**. Oxidation of Pd^{II} to Pd^{IV} by $PhI(OAc)_2$ drives reductive elimination to furnish the C–O bond. In addition, Sanford and co-workers found that pyridine can also be applied as a directing group for the acetoxylation of primary C–H bonds, as illustrated by the conversion of pyridine **12** into **13**. Yu and co-workers[12] reported the palladium(II)-catalyzed iodination of unactivated primary C(sp^3)–H bonds of oxazolines, substrates that had previously been shown to undergo cyclopalladation with a stoichiometric amount of palladium[13] (Scheme 4). Iodine is included as an additional oxidant, accounting for the observed iodination of oxazoline **14** to **15**, instead of acetoxylation. In addition, Daugulis and co-workers discovered that picolinamides can serve as a bidentate ligand for palladium-catalyzed C–H activation.[14] In this report, unactivated C(sp^3)–H bonds are arylated with aryl iodides. For example, picolinamide **16** can be arylated at the methyl C–H bond to yield **18**. It is noteworthy that this study represents the first example of an intermolecular C–C bond-forming reaction. Since these initial reports, various transformations based on Pd catalysis have been developed by various research groups.

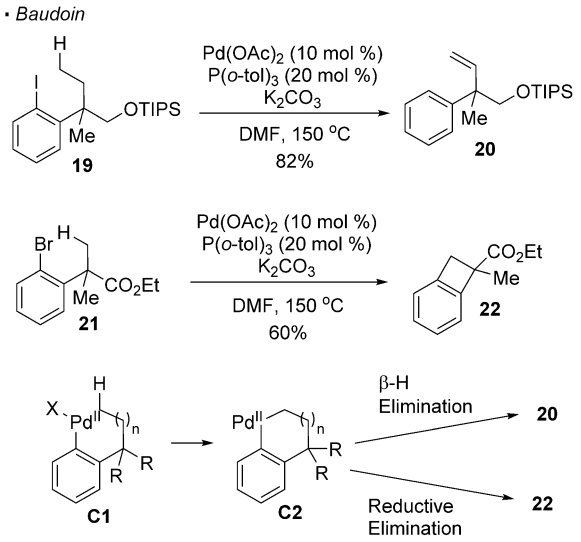


Scheme 3. Nitrogen as a directing group.

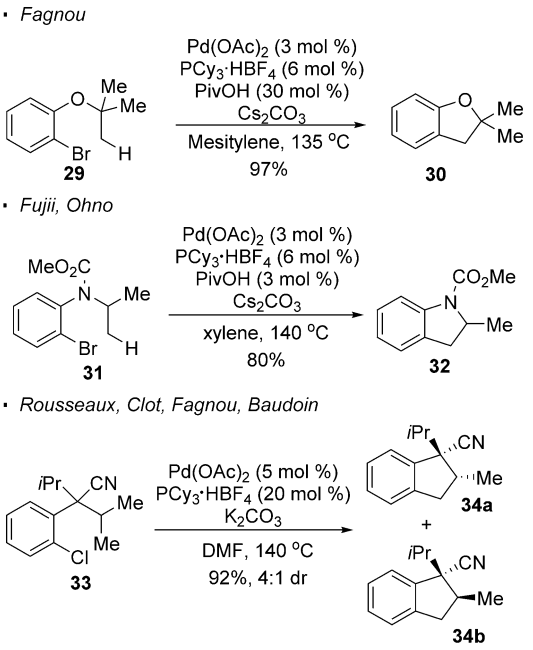
2.1.2. *Functionalization with Different Directing Groups*

2.1.2.1. *Aryl/Vinyl Halides*

Various research groups were inspired by reports from Dyker to use aryl halides or triflates as a traceless directing group. Baudoin et al. discovered that dehydrogenation of the ethyl group in aryl iodide **19** takes place when it is heated under basic conditions with a catalytic system of $Pd(OAc)_2$/$P(o\text{-tol})_3$ (Scheme 4).[15] Compared to Dyker's system, the terminal C–H bond that undergoes activation is one-bond further away from the directing vinyl halide. In the proposed mechanism, after oxidation addition into the C–I bond and C–H activation of the methyl group to form **C2**, β-hydride elimination results in the formation of an alkene and a palladium hydride. The observed product **20** is formed through a final reductive elimination, which furnishes a C–H bond. For aryl bromide **21** with one less carbon atom between the linker and the methyl C–H bond, the presence of a benzylic quaternary carbon atom renders β-H elimination impossible. In this case, benzocyclobutene **22** is the observed product because reductive elimination of intermediate **C2** takes place. In addition, Buchwald and co-workers showed

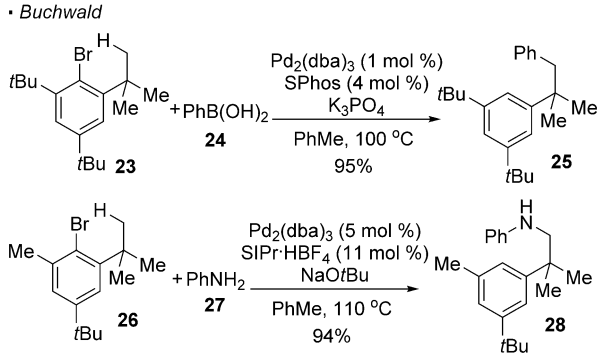


Scheme 4. Dehydrogenation and cyclobutane synthesis with aryl halides.



Scheme 6. Synthesis of five-membered rings with aryl halides. Cy = cyclohexyl, Piv = pivaloyl.

that these putative palladium-alkyl intermediates can be intercepted by aryl boronic acids[16] or anilines,[17] thereby resulting in arylation or amination of the methyl C–H bonds (Scheme 5). Thus, the arylated product **25** can be obtained

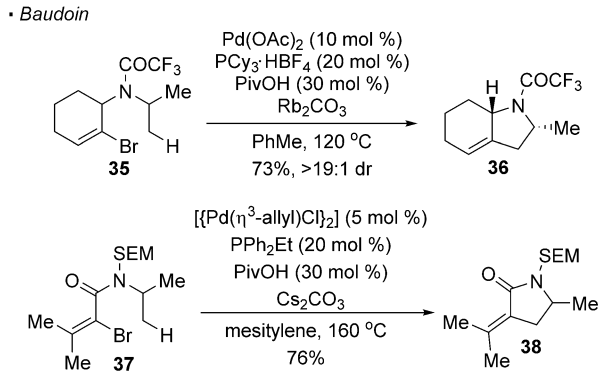


Scheme 5. Trapping of putative palladium-alkyl intermediates. dba = dibenzylideneacetone.

from aryl bromide **23** and boronic acid **24**, while the aminated product **28** arises from aryl bromide **26** and aniline **27**. However, these reactions are only applicable to substrates bearing substitutions at the 2-, 4-, and 6-positions relative to the halogen atom. The key to the success of these reactions are the steric effects provided by these substituents to disfavor Suzuki cross-coupling and Buchwald–Hartwig amination.

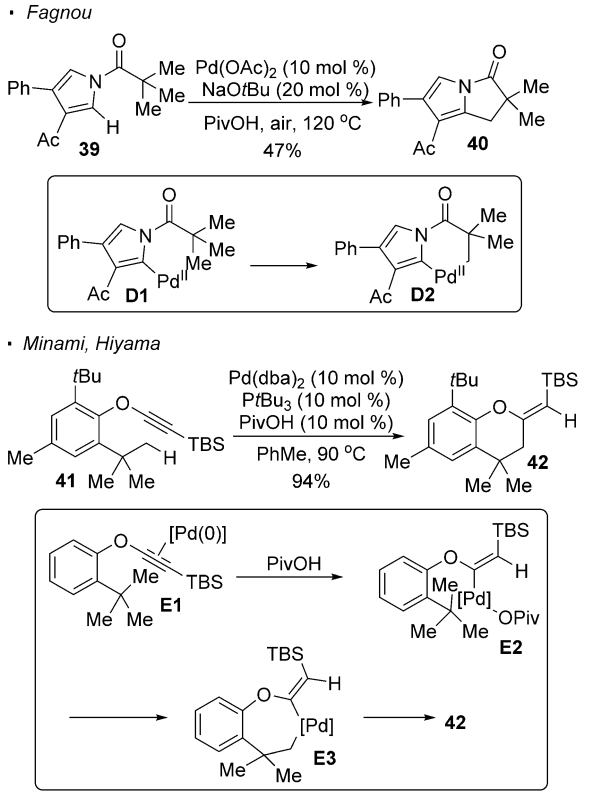
Fagnou and co-workers demonstrated that, in contrast to the cyclobutene synthesis by Baudoin et al., five-membered rings can be formed when the methyl group is placed one bond further away from the aryl halides (Scheme 6).[18] This reaction allows access to benzofuran **30** from aryl bromide **29**. Extension of this strategy to the synthesis of indoline **32** from **31** has been reported by Fuji, Ohno, and co-workers.[19] In this reaction, the presence of a quaternary carbon atom to disfavor β-H elimination is not required to achieve the desired reactivity. Less-reactive aryl chlorides are also competent substrates, as shown in the subsequent report from Rousseaux, Clot, Fagnou, Baudoin et al. for the synthesis of cyclopentanes **34a** and **34b** from aryl chloride **33**.[20]

Baudoin and co-workers successfully extended the scope of these reactions to embrace the use of vinyl halides as a traceless directing group. Thus, the methyl C–H bond in vinyl bromide **35** can be activated for the synthesis of bicyclic pyrrolidine **36** (Scheme 7).[21] In a subsequent report, Baudoin and co-workers further demonstrated that α-bromoacrylamide **37** is also a competent substrate in this reaction and showed that monocyclic pyrrolidine derivatives can be obtained from acyclic precursors.[22] The mechanism of these transformations is believed to be the same as in the case of aryl halides.



Scheme 7. Vinyl halides as a traceless directing group. SEM = 2-(trimethylsilylethoxymethyl).

In all the examples discussed previously, the putative aryl-palladium(II) intermediates prior to the activation of C(sp^3)–H bonds are generated from aryl or vinyl halides. In contrast, Liégault and Fagnou showed that C(sp^2)–H activation of pivaloylpyrrole **39** can generate the aryl-palladium species **D1**, which can undergo C(sp^3)–H activation to form six-membered palladacycle **D2** (Scheme 8).[23] Similar to previous

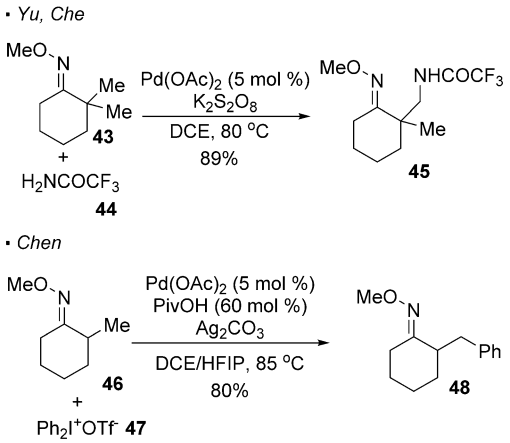


Scheme 8. Generation of aryl-/vinyl-palladium through other means. TBS = *tert*-butyldimethylsilyl.

examples, reductive elimination results in the formation of a five-membered ring. In addition, as demonstrated by Minami, Hiyama et al., silylethynyl aryl ether **41** undergoes palladium-catalyzed intramolecular hydroalkylation with activation of one of the methyl C–H bonds.[24] In the proposed mechanism, the vinyl-palladium intermediate **E2** is formed, prior to C–H activation of the methyl C–H bond, from the addition of PivOH across the alkyne in Pd^0 complex **E1**.[25] The seven-membered palladacycle **E3** generated through C–H activation undergoes reductive elimination to give the observed product **42**.

2.1.2.2. Oximes

After the seminal work by Sanford and co-workers, more reactions with oximes as a directing group have appeared. Thu, Yu, and Che reported a palladium-catalyzed oxime-directed C–H amidation (Scheme 9).[26] In this approach, an amide or a sulfonamide is employed as a nitrogen source and potassium persulfate ($K_2S_2O_8$) as an oxidant. Thus, the methyl

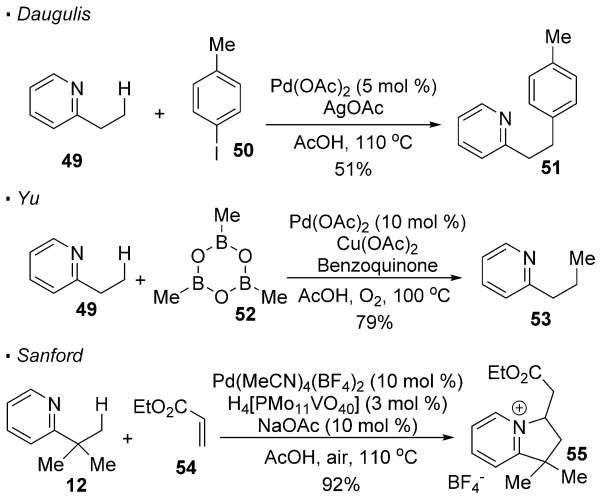


Scheme 9. Oxime-directed C–H activation. DCE = 1,2-dichloroethane, HFIP = hexafluoroisopropanol, Tf = trifluoromethanesulfonyl.

C–H bond of **43** can be amidated with trifluoroacetamide (**44**) to afford **45**. Chen and co-workers used diphenyliodonium salt **47** to accomplish the C–H arylation of oxime **46** to give **48** (Scheme 9).[27]

2.1.2.3. Pyridines

Pyridines can be functionalized not only by the aforementioned oxygenation described by Sanford and co-workers, but also through the formation of C–C bonds. The groups of Daugulis[28] and Yu[29] independently disclosed the pyridine-directed arylation and alkylation of primary C–H bonds (Scheme 10). Sanford and co-workers demonstrated that electrophilic alkenes can be installed at a primary C–H bond adjacent to a pyridine ring.[30] For example, olefination of pyridine **12** with ethyl acrylate (**54**) gives pyridinium **55**. In the proposed mechanism, after C–H activation, the alkyl-palladium species adds across the electrophilic alkene. A β-H elimination results in a net incorporation of the electrophilic alkene into the methyl C–H bond. The pyridine nitrogen



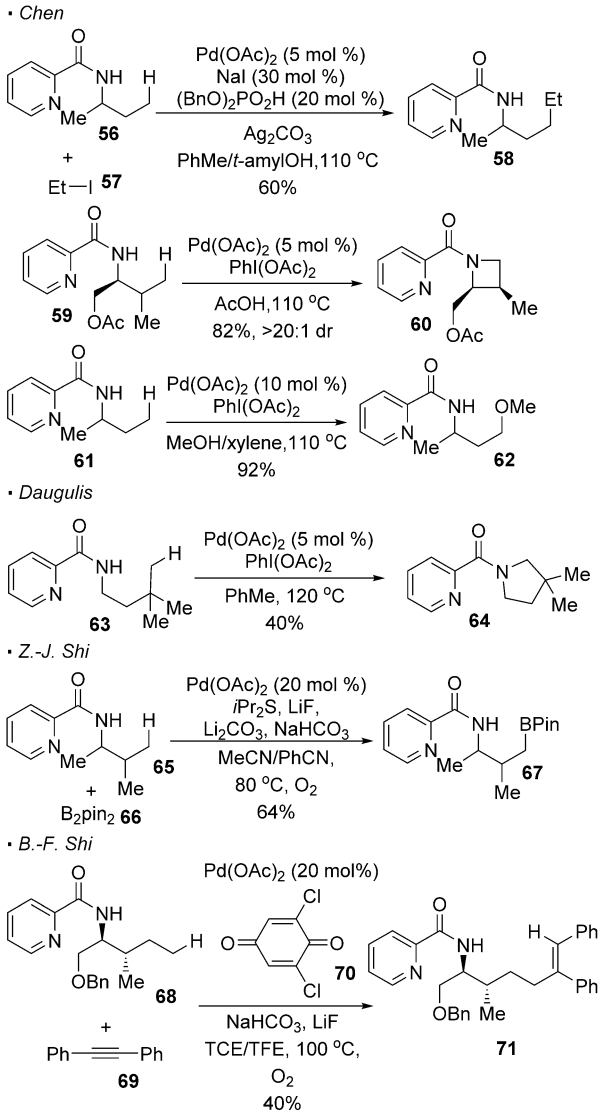
Scheme 10. Derivatization of pyridines through C–H activation.

atom can then cyclize onto the alkene through aza-Michael addition to yield the bicyclic pyridinium compound. Further manipulation yields valuable bicyclic amines.

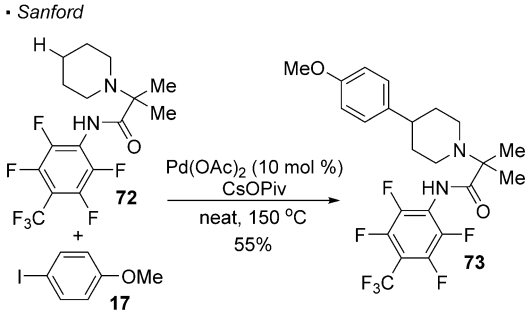
2.1.2.4. Amines (Amides)

In most cases, amines are functionalized by installing an electron-withdrawing group on the nitrogen atom to generate a directing group for C–H activation. Daugulis and co-workers first demonstrated that bidentate picolinamides can serve as a directing group for the palladium(II)-catalyzed C–H functionalization of amines (Scheme 3).[14] Since then, the incorporation of different functionalities at unactivated primary C–H bonds with the same picolinamide directing group has been developed by various research groups (Scheme 11). The key to success is the appropriate choice of reaction partner that is used to trap the putative alkyl-palladium intermediates. For example, by switching from an aryl iodide to an alkyl iodide, Chen and co-workers developed a procedure for the alkylation of the C–H bond in **56**.[31] The research groups of both Daugulis[32] and Chen[33] observed that when $PhI(OAc)_2$ is applied as an oxidant, intramolecular C–H amination takes place, thereby resulting in the synthesis of the four- or five-membered nitrogen heterocycles **60** or **64**. The ring size depends on the distance between the primary C–H bond and the nitrogen atom. Chen and co-workers also found that there is a switch in the chemoselectivity when an alcohol is used as a cosolvent, and intermolecular C–H oxygenation becomes the predominant pathway.[34] Thus, the methoxylation of amide **61** takes place to give **62** when methanol is applied as a solvent. In addition, the groups of Z.-J. Shi and B.-F. Shi reported the coupling of amides with diboron esters[35] and alkynes,[36] respectively, to unactivated C–H bonds. These procedures allow for the borylation or alkenylation of the primary C–H bonds of picolinamides **65** and **68**.

Sanford and co-workers exploited palladium-catalyzed transannular C–H functionalization to develop a procedure for the derivatization of medicinally relevant alicyclic amines (Scheme 12).[37] The 4-position of piperidine **72** can be arylated after the nitrogen atom has been alkylated and linked to a perfluorinated amide, a directing group first introduced by Yu and co-workers (see Scheme 19), to afford its derivative **73**.



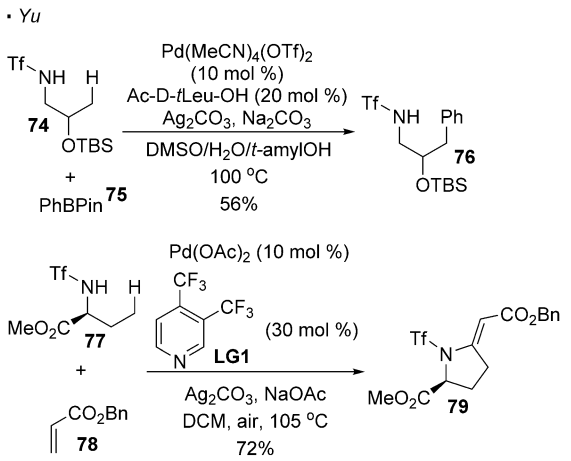
Scheme 11. Use of picolinamides for amine functionalization. B_2pin_2 = bis(pinacolato)diboron, Bn = benzyl, TCE = 1,1,2,2-tetrachloroethane, TFE = 2,2,2-trifluoroethanol.



Scheme 12. Transannular C–H activation of alicyclic amines.

2.1.2.5. Amines (Sulfonamides)

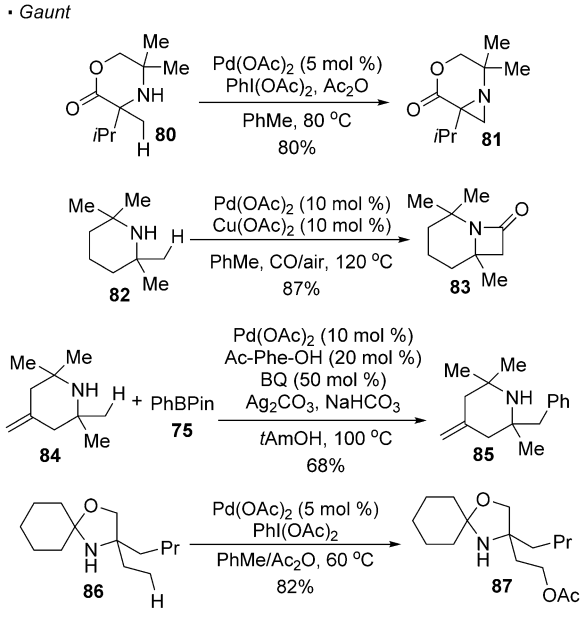
Yu and co-workers reported that primary C–H bonds can be arylated with aryl boronic acids after installing a sulfonyl group on to amines, as exemplified by the arylation of trifluoromethanesulfonamide **74** with the boronate ester **75** (Scheme 13).[38] Olefination of the C–H bond with an acrylate or styrene is another possibility.[39] After the installation of the alkene at the C–H bond of amide **77**, an intramolecular Heck reaction takes place to account for the formation of the cyclized product **79**. It should be noted that in both cases, an exogenous ligand is the key to achieve the desired reactivity.



Scheme 13. Sulfonamides as directing groups for the functionalization of amines.

2.1.2.6. *Amines (Free Amines)*

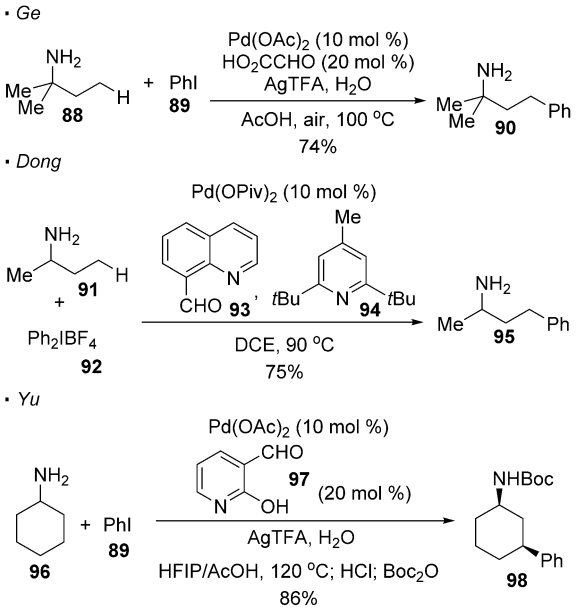
Sometimes the prefunctionalization of amines is not required before the C–H activation step and a free amine can serve as a directing group. Gaunt and co-workers reported the synthesis of strained aziridines **81** from bulky secondary amines **80**. The synthesis featured the formation of a four-membered palladacycle through nitrogen-directed cleavage of a primary C–H bond (Scheme 14).[40] The oxidation of Pd^{II} to Pd^{IV} by $PhI(OAc)_2$ drives the reductive elimination—as in the reactions of Sanford and Yu—to form a C–N bond and afford aziridines. In the presence of CO, β-lactams **83** are the observed product. However, the formation of the β-lactams is mechanistically different from that of the aziridines. Carbonylation of the amine precedes the C–H activation step and generates a five-membered palladacycle.



Scheme 14. C–H functionalization of free amines. BQ = benzoquinone.

Initially, only sterically hindered secondary amines were competent substrates, since it was believed that the steric effects of the amines were needed to disfavor the formation of a catalytically inactive bis(amine)Pd^{II} complex.[41] Subsequent studies showed that even non-bulky secondary amines can be used as substrates to synthesize β-lactams if $AdCO_2H$ and benzoquinone are used as additives.[42] The putative four-membered palladacycle can also be intercepted by aryl boronic acids, thereby resulting in net arylation of the C–H bonds.[43] Arylated product **85** can be accessed from amine **84**. When the methyl group is an additional bond away from the nitrogen atom, the C–H activation still occurs at the primary C–H bond. Thus, the methyl group in protected amino alcohol **86** undergoes acetoxylation with the $Pd(OAc)_2$ catalyst and $PhI(OAc)_2$ to afford **87**.[44]

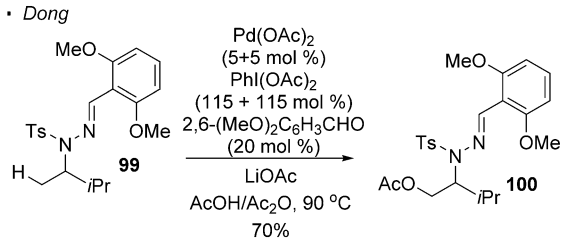
Free primary amines have never been shown to direct C–H activation. Nevertheless, a directing group can be generated in situ to obviate the need to prefunctionalize the amine before the C–H activation step. The groups of Ge,[45] Dong,[46] and Yu[47] independently showed that a stoichiometric or catalytic amount of an aldehyde can be used as an additive for the palladium-catalyzed activation of unactivated $C(sp^3)$–H bonds of primary amines (Scheme 15). The condensation between the aldehyde and the primary amine generates a bidentate imine as a transient directing group. This strategy can be successfully applied to the arylation of primary aliphatic amines or anilines such as **88** and **91** with aryl iodonium salts or aryl iodides. It should be noted that the approach of Yu and co-workers enabled even cyclic substrates, such as cyclohexylamine (**96**), to be derivatized.



Scheme 15. In situ generated imines as directing groups. Boc = *tert*-butyloxycarbonyl, TFA = trifluoroacetate.

2.1.2.7. Amines (Hydrazones)

Dong and co-workers reported that hydrazones can be installed on sulfonamides and serve as a directing group for C(sp^3)–H activation (Scheme 16).[48] Thus, the palladium-catalyzed acetoxylation of hydrazone **99** can be accomplished with $PhI(OAc)_2$ as the oxidant. After the C–H activation, the N–N bonds can be cleaved by Zn to afford sulfonamides.

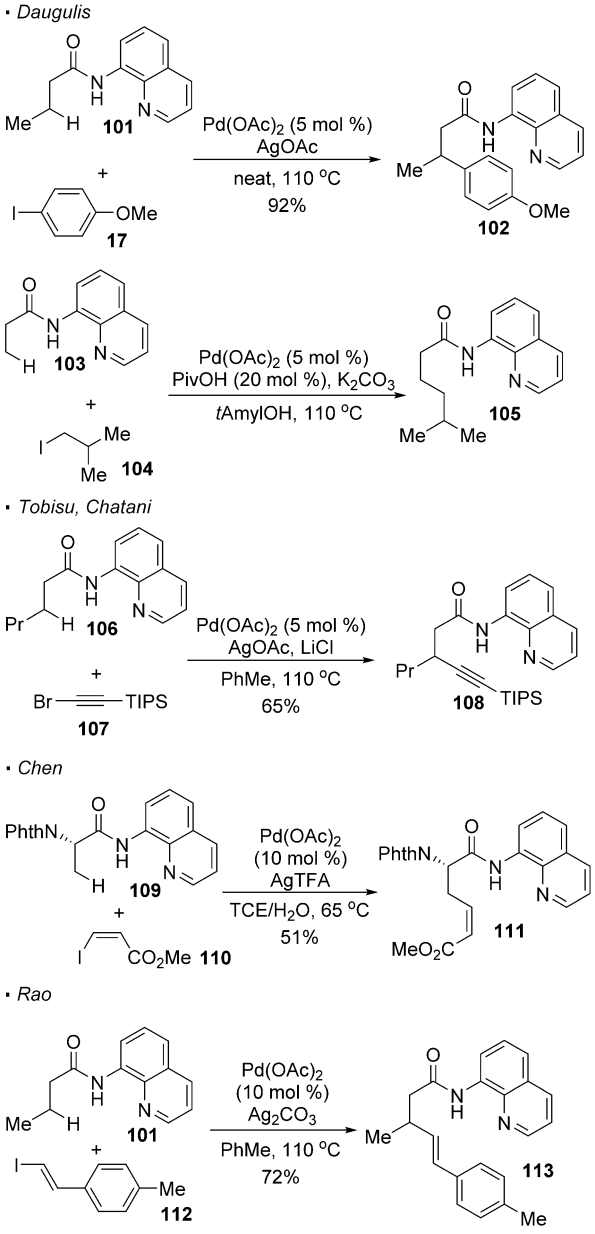


Scheme 16. Hydrazone-directed C–H activation. Ts = tosyl.

2.1.2.8. Carbonyl Groups (8-Aminoquinoline Amides)

The functionalization of carbonyl compounds through palladium-catalyzed C(sp^3)–H activation is the most explored and well-developed reaction. In most cases, it is the β-C–H bonds of the carbonyl compounds that are functionalized. Daugulis and co-workers first observed that 8-aminoquinoline amides can serve as a directing group for this purpose, whereby a β-methylene C–H bond of amide **101** is arylated to afford **102** (Scheme 17).[14] The incorporation of various functional groups at these C–H bonds has been rendered possible as a result of the contributions of different research groups. For the formation of C–C bonds, the alkylation of **103**, the alkynylation of **106**, and the alkenylation of **109** and **101** were developed by the groups of Daugulis,[49] Tobisu and Chatani,[50] Chen,[51] and Rao,[52] respectively. The geometry of vinyl iodide **110** is preserved in Chen's system during the alkenylation of amide **109**.

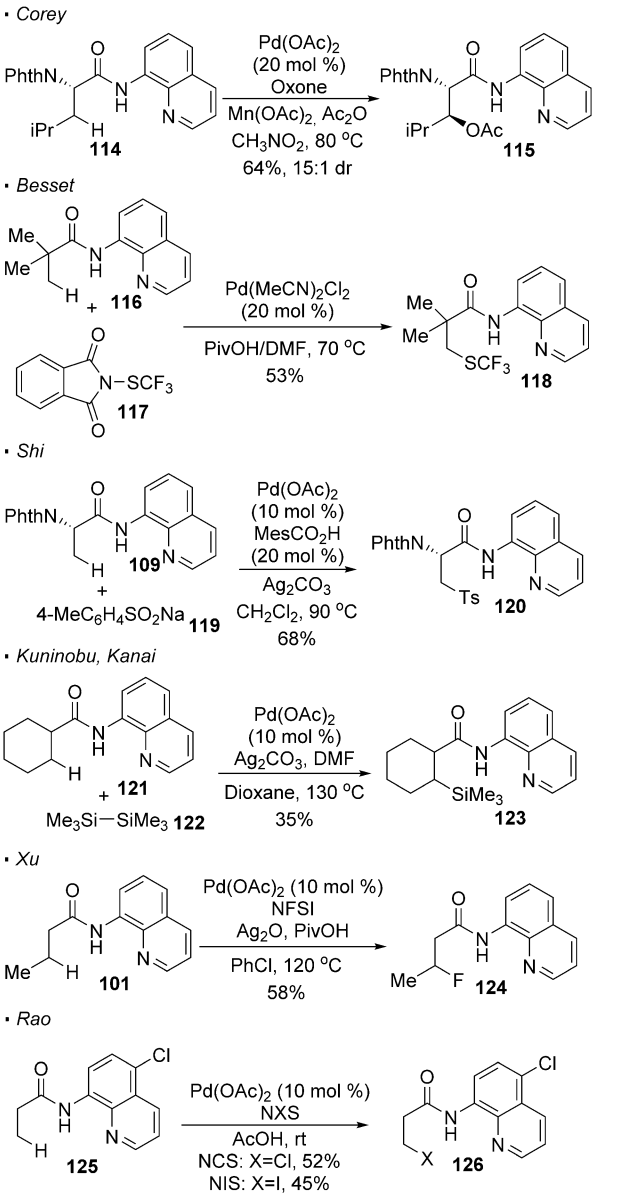
In addition to C–C bonds, reactions have been developed for the incorporation of various heteroatoms at the β-position (Scheme 18). The system developed by Corey and co-workers for the C–H acetoxylation of **114** relies on the use of oxone as an oxidant.[53] Besset and co-workers applied *N*-thiotrifluoromethylphthalimide (**117**) as an oxidant to achieve the C–H thiotrifluoromethylation of **116**.[54] With sodium salts of aryl sulfonates as a sulfur source and Ag_2CO_3 as an external oxidant, Shi and co-workers developed a procedure for C–H sulfonylation.[55] Kanyiva, Kuninobu, and Kanai showed that the C–H silylation of **121** can be achieved with disilane **122**.[56] As demonstrated by Xu and co-workers, the use of NFSI as an electrophilic fluorine source results in C–F bond formation at the unactivated C–H bonds.[57] To incorporate other halogens at the β-position, Rao and co-workers modified the directing group because 8-aminoquinoline is prone to electrophilic aromatic substitution.[58] Thus, 5-chloro-8-aminoquinoline **125**, which is less reactive towards electrophilic aromatic substitution, was used to realize C–H chlorination and bromination with NCS or NBS, respectively, to afford halogenated **126**.



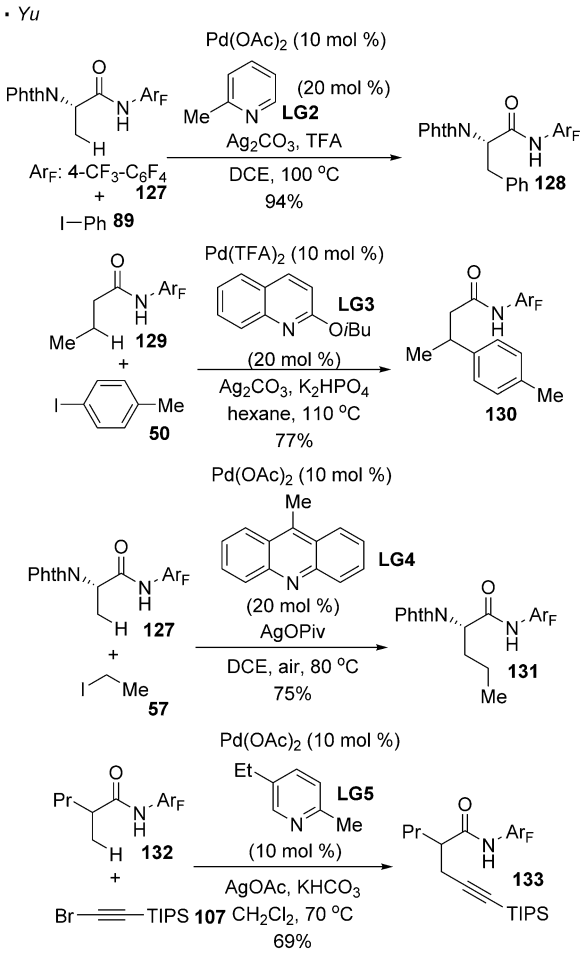
Scheme 17. Formation of C–C bonds with 8-aminoquinolines. PhthN = phthalimidoyl.

2.1.2.9. Carbonyl Groups (Perfluorinated Amides)

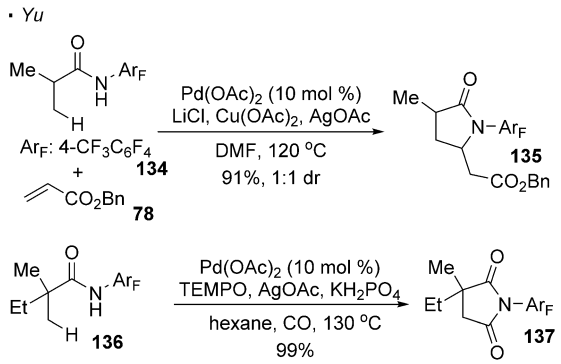
In addition to 8-aminoquinoline, perfluorinated amides are a versatile directing group for the β-functionalization of carbonyl compounds. With 2,3,5,6-tetrafluoro-4-trifluoromethylbenzamide as a directing group, Yu developed procedures that allow the incorporation of various functionalities at unactivated C(sp^3)–H bonds (Scheme 19). The arylation of amides **127** and **129** with aryl iodides,[59] alkylation of amide **127** with ethyl iodide **57**,[60] and alkynylation of amide 1**32** with alkynyl bromide **107**[61] led to C–C bond formation. In these



Scheme 18. Formation of C–X bonds with 8-aminoquinolines. Mes = mesityl, NCS = *N*-chlorosuccinimide, NFSI = *N*-fluorobenzenesulfonimide, NIS = *N*-iodosuccinimide.



Scheme 19. Formation of C–C bonds with perfluorinated amides. TIPS = triisopropylsilyl.

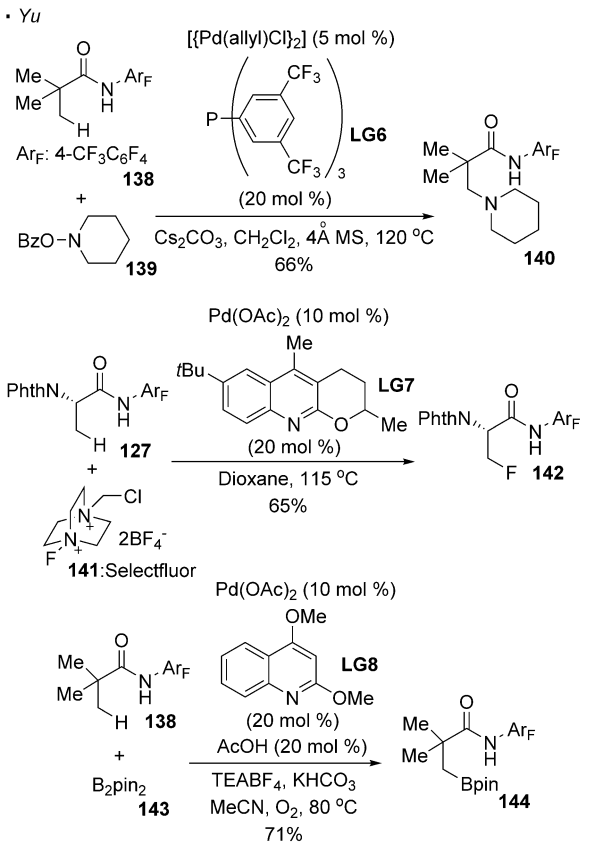


Scheme 20. Synthesis of nitrogen heterocycles from perfluorinated amides. TEMPO = 2,2,6,6-tetramethylpiperidine *N*-oxyl.

reactions, amides with or without α substitution are competent substrates, thus providing a method to functionalize both natural or unnatural amino acids.

Using the same directing group and an appropriate choice of reaction partners, the formation of C–C bonds can be applied to the synthesis of nitrogen heterocycles (Scheme 20). When electrophilic benzyl acrylate (**78**) is employed, olefination of the C–H bond in amide **134** is followed by aza-Michael addition to afford five-membered pyrrolidinone **135** as the final product.[62] In the presence of carbon monoxide, the putative palladium-alkyl intermediate formed from **136** can be carbonylated.[63] The resulting six-membered palladacycle then undergoes reductive elimination to afford succinimide **137**.

Unsurprisingly, the formation of bonds other than C–C bonds can be achieved (Scheme 21). By using hydroxylamine **139** as an electrophilic nitrogen source, the intermolecular C–H amination of amide **138** yields aminated **140**.[64] A fluorine atom can be incorporated into the C–H bond of amide **127** when the palladium-alkyl intermediate is trapped with Selectfluor (**141**).[65] Borylation can be realized with



Scheme 21. Formation of C–X bonds with perfluorinated amides. TEA = tetraethylammonium, MS = molecular sieves.

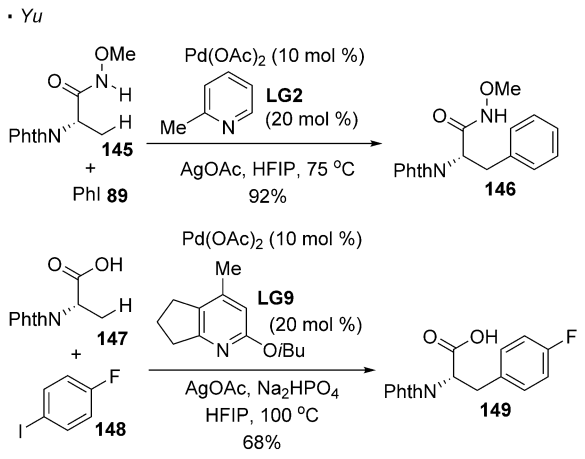
B_2pin_2 to afford amide **143**.[66] The resulting C–B bond can be converted into an array of functionalities. In all these examples with perfluorinated amines as the directing group, the exogenous ligands are essential to achieve the desired reactivity.

2.1.2.10. *Carbonyl Groups (O-Methylhydroxamic Acids and Carboxylic Acids)*

To provide an alternative method to functionalize carboxylic acid derivatives, Yu and co-workers pioneered the use of *O*-methylhydroxamic acids and free carboxylic acids as the directing groups (Scheme 22). The initial procedure developed by Yu and co-workers allows the arylation or alkylation of primary C–H bonds in the β-position to *O*-methylhydroxamic acids[67] and carboxylic acids[68] bearing α quaternary centers. An improved procedure established by the same group tolerates the presence of α-C–H bonds in the *O*-methylhydroxamic acids[69] and carboxylic acids.[70] Thus, amino acids 1**45** and **147** can be derivatized using *O*-methylhydroxamic acids and carboxylic acids as a directing group.

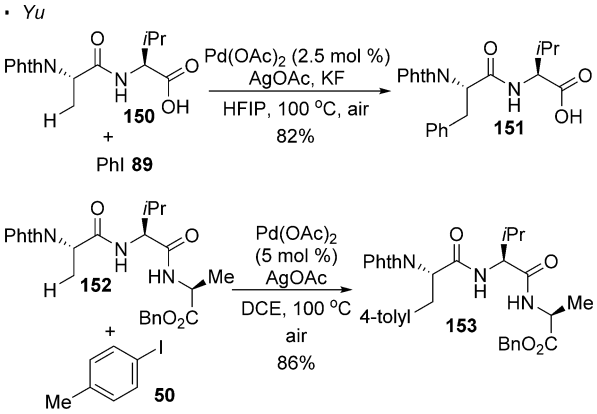
2.1.2.11. *Carbonyl Groups (Peptides)*

Yu and co-workers demonstrated that peptides can be functionalized by palladium-catalyzed C–H activation at the



Scheme 22. C–H functionalization with *O*-methylhydroxamic acids and carboxylic acids.

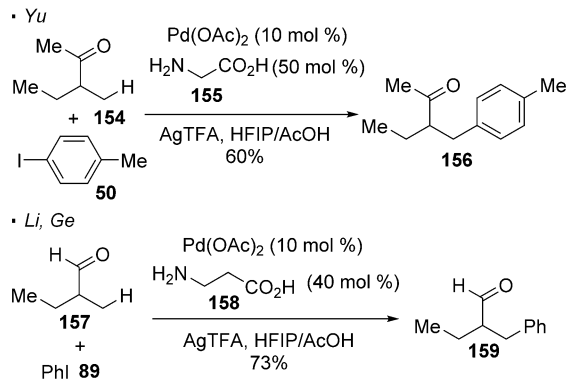
N terminus.[71] Such a strategy does not require the manipulation of directing groups, since the native amino acid moiety can serve as a directing group (Scheme 23). For example, dipeptide **150** and tripeptide **152** can be arylated at the β-positions of the amino acids at the N terminus.



Scheme 23. C–H functionalization of peptides.

2.1.2.12. *Carbonyl Groups (Ketones and Aldehydes)*

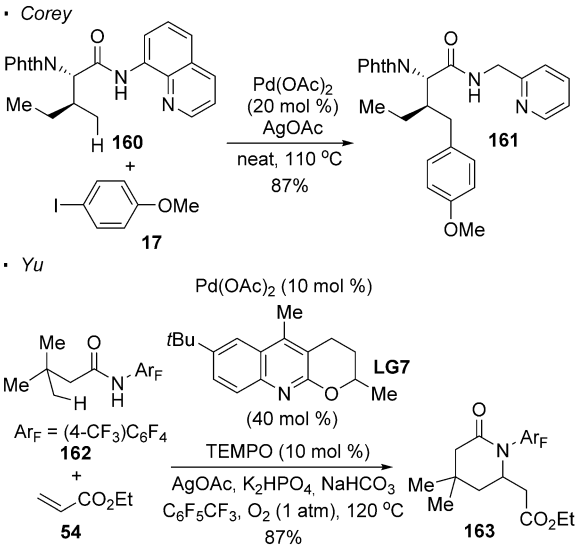
The carbonyl oxygen atom of aldehydes and ketones is weakly basic and these compounds do not have an appreciably acidic proton to generate an anion that can serve as a directing group. These factors had inhibited the development of C–H activation with aldehydes and ketones until the recent contributions from Yu and co-workers as well as Li, Ge, and co-workers (Scheme 24). They addressed the low basicity of these carbonyl groups by converting them into a more basic functionality in situ. By adding a sub-stoichiometric amount of aminocarboxylic acids such as **155** and **158**, a transient bidentate imine directing group is formed under the reaction conditions. Yu and co-workers[72] as well as Li, Ge, and co-workers[73] demonstrated that the primary β-C–H bonds of ketone **154** and aldehyde **157** can be arylated with aryl iodides **50** and **89** with this strategy.



Scheme 24. In situ generation of directing groups from carbonyl groups.

2.1.2.13. Carbonyl Groups (γ-Functionalization)

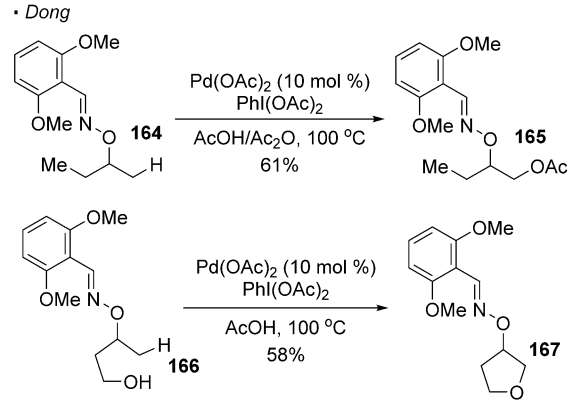
The above representative examples show that C–H bonds in the β-position of the carbonyl groups are typically activated. However, the γ-C–H bond of an amide can occasionally be functionalized (Scheme 25). Corey and co-workers observed that carbonyl compound **160**, which contains a sterically bulky substituent NPhth at the α-position, experiences C–H activation preferentially at the primary γ-C–H bond over a tertiary β-C–H bond.[53] It is proposed that the α substituent in this substrate leads to a conformational bias that favors the activation of the γ-C–H bond. In this case, activation of the β-C–H bonds is also disfavored because of the more challenging formation of a palladium-alkyl species from a tertiary C–H bond than a primary C–H bond. Alternatively, to achieve functionalization of a primary γ-C–H bond, the β-carbon atom is fully substituted such that β-C–H activation is not a possibility. For example, Yu and co-workers showed that the γ-C–H bonds of amide **162** can be olefinated[74] or arylated.[75]



Scheme 25. γ-Functionalization of carbonyl compounds.

2.1.2.14. Alcohol Derivatives

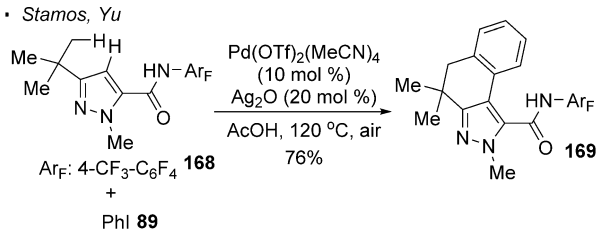
Dong and co-workers employed an oxime as a directing group to functionalize alcohols (Scheme 26). The system is analogous to that reported by Sanford and co-workers; however, the C(sp^3)–H bonds are located on the side of the oxygen atom, instead of the nitrogen atom. Oxygenation of the primary β-C–H bonds can be accomplished with oxime **164** to afford **165**.[76] An intramolecular variant of the reaction with oxime **166** provides cyclic ether **167** as the product.[77] A mechanism involving Pd^{II}/Pd^{IV} is believed to be operative.



Scheme 26. C–H activation of alcohol derivatives.

2.1.2.15. Pyrazoles

As demonstrated by Stamos, Yu, and co-workers, pyrazoles are also a competent directing group for C(sp^3)–H activation (Scheme 27).[78] For the reaction of pyrazole **168**, one of the methyl groups is arylated with phenyl iodide. The subsequent activation of two C(sp^2)–H bonds results in the formation of tricyclic product **169**.



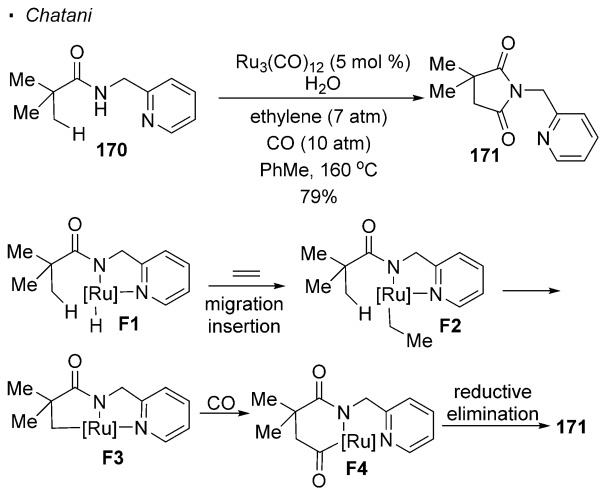
Scheme 27. Pyrazole-directed C–H activation.

2.2. Catalysis with Other Noble Transition Metals

Other noble transition metals are also competent catalysts for the activation of unactivated C(sp^3)–H bonds, although they are less studied. Except in one case (Hartwig's Ir^I-catalyzed silylation and borylation, see below), all the reactions can be accomplished by palladium catalysis under different reaction conditions.

2.2.1. Ruthenium

When amide **170** was heated with a catalytic amount of $Ru_3(CO)_{12}$ under an atmosphere of carbon monoxide and ethylene, Chatani and co-workers observed that succinimide **171** is formed (Scheme 28).[79] In the proposed mechanism,



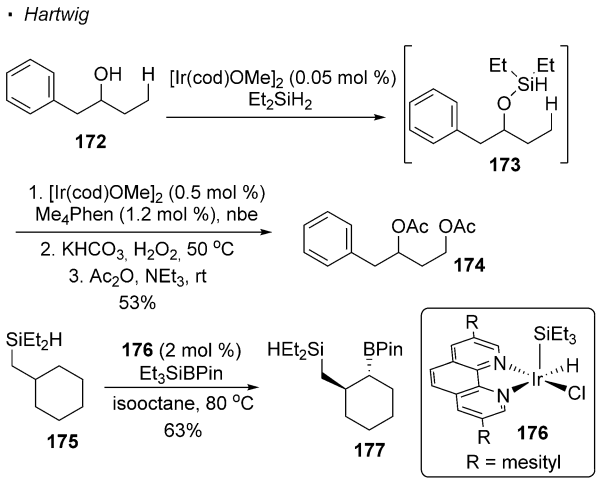
Scheme 28. Ru-catalyzed C–H activation.

the Ru catalyst forms Ru hydride from the amidyl N–H bond, a molecule of ethylene inserts into the Ru hydride bond to form Ru-ethyl intermediate **F2**, a σ-bond metathesis results in activation of the methyl C–H bond to generate **F3**, and carbonylation takes place to give six-membered metallacycle **F4**. A final reductive elimination yields the observed product **171**.

2.2.2. Iridium

2.2.2.1. Iridium(I)

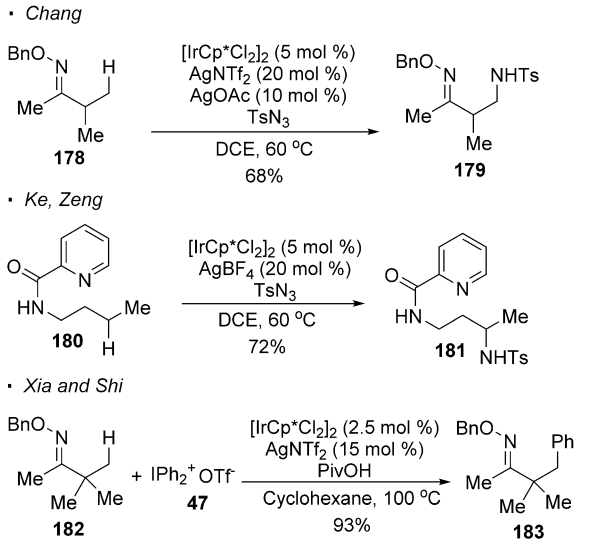
A three-step procedure for the Ir-catalyzed alcohol-directed silylation of primary C–H bonds was reported by Simmons and Hartwig (Scheme 29).[80] Similar to their previous study on $C(sp^2)$–H bond activation,[81] an Ir^I-catalyzed reaction is first applied to silylate the alcohol to install a hydrosilane as the directing group. Without the isolation of the hydrosilane intermediate, silylation of the C–H bonds is accomplished with a second Ir-catalyzed reaction. A C–O bond is formed by a Tamao–Fleming oxidation, thereby affording a 1,3-diol as the final product. Thus, 1,3-diol **174** can be synthesized from alcohol **172**, with hydrosilane **173** as an intermediate. The Hartwig group later showed that Ir^{III} catalyst **176** can be applied to silylate[82] or borylate[83] secondary C–H bonds, as exemplified by the borylation of the cyclohexyl C–H bond of hydrosilane **175** to afford boronate **177**. The resulting C–B bond can be converted into a C–O, C–N, or C–C bond with subsequent reactions.



Scheme 29. Ir^I-catalyzed borylation. cod = 1,5-cyclooctadiene, Phen = 1,10-phenanthroline.

2.2.2.2. Iridium(III)

Chang and co-workers developed a procedure for the Ir^{III}-catalyzed oxime-directed amination of primary C–H bonds with tosyl azide as a nitrogen source (Scheme 30).[84] Aminated oxime **179** can be obtained from oxime **178** by using $[Cp^*IrCl_2]_2$ as a precatalyst and $AgBF_4$ as a co-catalyst. Zeng,



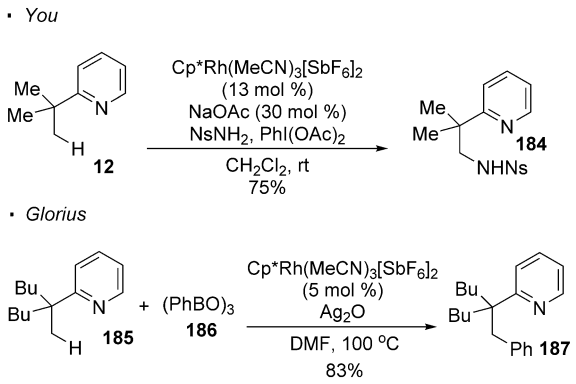
Scheme 30. Ir^{III}-catalyzed C–H amination and arylation. Cp* = C_5Me_5.

Ke, and co-workers later showed that amide **180** is also a competent substrate for the same transformation with secondary C–H bonds under similar reaction conditions.[85] As reported by Xia, Shi, and co-workers, the arylation of primary C–H bonds can be accomplished with the same directing group and the same Ir precatalyst.[86] Oxime 1**82** is arylated with diaryliodonium salt **47** to afford **183**.

2.2.3. Rhodium

2.2.3.1. Rhodium(III)

The research groups of You[87] and Glorius[88] accomplished the pyridine-directed C–H functionalization with Rh^{III} precatalysts (Scheme 31). You and co-workers achieved



Scheme 31. Rh^{III}-catalyzed C–H amination of pyridines. Ns = nosyl.

the amination of pyridine **12** by using nitrobenzenesulfonamide ($NsNH_2$) as the nitrogen source and $PhI(OAc)_2$ as an oxidant. The arylation of pyridine **185** relies on the use of boroxine **186** in the procedure developed by Glorius and co-workers. Various groups subsequently reported rhodium(III)-catalyzed sp^3 aminations by using other nitrogen sources or different reaction conditions.[89]

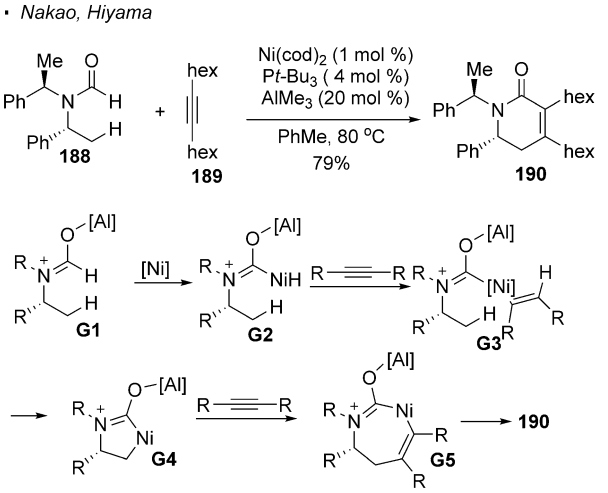
2.3. Catalysis with Earth-Abundant Metals

Recently, efforts have been made to replace noble metals with less-expensive first-row earth-abundant metals. However, from the following representative examples, it can be concluded that the scope of transformations that can be achieved with first-row transition-metal catalysts is still very limited. No functional groups other than carbonyl compounds have been employed as competent directing groups. Therefore, at this time, only the β-functionalization of carbonyl groups can be accomplished. In addition, with the exception of Ni^0 catalysis, only reactivity previously demonstrated with palladium catalysis has been reported.

2.3.1. Nickel

2.3.1.1. Nickel(0)

Nickel, likely because of its position above palladium in the Periodic Table, was the initial focus. Nakao, Hiyama et al. first employed low-valent $Ni(cod)_2$ as the precatalyst and $AlMe_3$ as the co-catalyst for $C(sp^3)$–H activation (Scheme 32).[90] The nickel(0)-catalyzed dehydrogenative [4+2] cycloaddition of formamide **188** and alkyne **189** can be accomplished to access piperidone **190**. In the proposed mechanism, $AlMe_3$ acts as a Lewis acid to activate the formamide. This allows the Ni catalyst to oxidatively add to

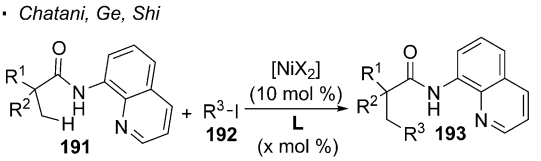


Scheme 32. Nickel(0)-catalyzed [4+2] cycloaddition. hex = hexyl.

the carbonyl C–H bond to form nickel hydride **G2**. Insertion of the alkyne into the metal–hydride bond results in the formation of vinyl-nickel intermediate **G3**. A $C(sp^3)$–H activation then takes place to give five-membered nickelacycle **G4**. An alkyne can insert into one of the Ni–C bonds to expand the ring size of the nickelacycle. The observed piperidine product **190** is formed by reductive elimination of the final intermediate **G5**.

2.3.1.2. Nickel(II)

Compared to its low-valent counterpart, nickel(II) is a more appealing catalyst because of its lower cost and ease of handling. In all these examples with nickel(II) catalysis, 8-aminoquinoline, first introduced by Daugulis and co-workers for palladium catalysis, is used as a directing group (Scheme 33).[14] Various functionalities can be incorporated into the molecule at these unactivated C–H bonds. This is exemplified by initial reports from the groups of Chatani and Ge. By using Ni^{II} as a precatalyst in conjunction with

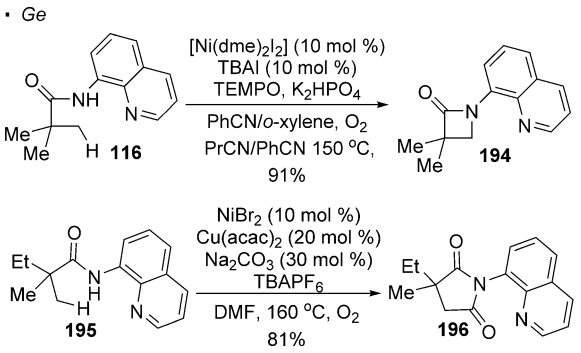


R^1, R^2 R^3	X	L x	Conditions	Yield
Ph, Ph 4-OMe-C_6H_4	OTf	$MesCO_2H$ 20	Na_2CO_3 DMF, 140 °C	72%
Pr, Et C_5H_{11}	acac	dppbz 10	Cs_2CO_3 PhMe, 150 °C	86%
-$(CH_2)_5$- (*E*)-Styrenyl	acac	BINOL 40	Li_2CO_3, KTFA DMSO, 140 °C	78%

Scheme 33. Nickel(II)-catalyzed C–H functionalization.

carbonate bases, primary β-C–H bonds of amide **191** can undergo arylation with aryl iodides[91] or alkylation with alkyl iodides.[92] Shi and co-workers showed the Ni^{II}-catalyzed alkenylation of amide **191** with vinyl iodides[93] to afford alkenylated products. As reported by Zhang and co-workers, alkenylation can also be accomplished with phenylacetylenes.[94] Various groups also simultaneously reported C–H thiolation using the same directing group.[95]

The synthesis of nitrogen heterocycles from amides can also be catalyzed by nickel(II). As demonstrated by Ge and co-workers, in the absence of an exogenous partner to trap the nickel-alkyl intermediate, reductive elimination can occur to give β-lactam **194** (Scheme 34).[96] An alternative mechanism



Scheme 34. Synthesis of nitrogen heterocycles through Ni^{II} catalysis. acac = acetylacetonate, Pr = propyl, TBA = tetrabutylammonium.

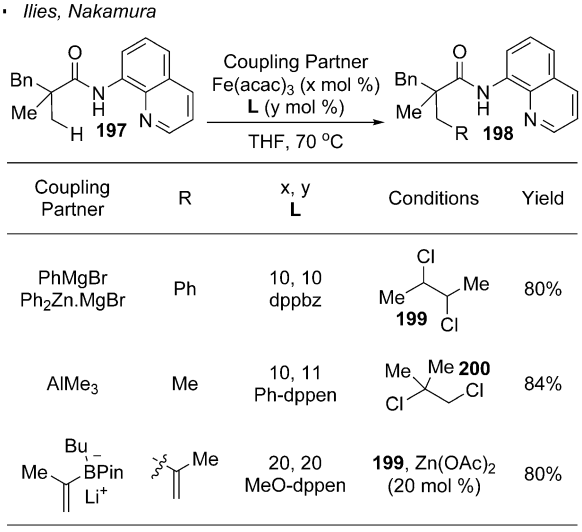
first involving C–H iodination and a subsequent S_N2 reaction is proposed by Aihara and Chatani.[97] In addition, DMF can be used as a carbonylating agent. Amide **195** undergoes carbonylative cyclization to form succinimide **196**, with $NiBr_2$ used as the catalyst and $Cu(acac)_2$ as co-catalyst.[98]

2.3.2. *Iron*

The 8-aminoquinoline directing group also enables Fe-catalyzed C–H activation. Nakamura, Ilies, and co-workers achieved the iron-catalyzed β-arylation of the primary C–H bonds of carbonyl compound **197** by using ArMgBr and Ar_2Zn (Scheme 35).[99] Subsequent reports from the same group demonstrate that the methylation and vinylation of primary C–H bonds can be realized with $AlMe_3$[100] and vinyl boronates,[101] respectively. In all these reactions, the chlorinated hydrocarbons **199** or **200** are added as an oxidant.

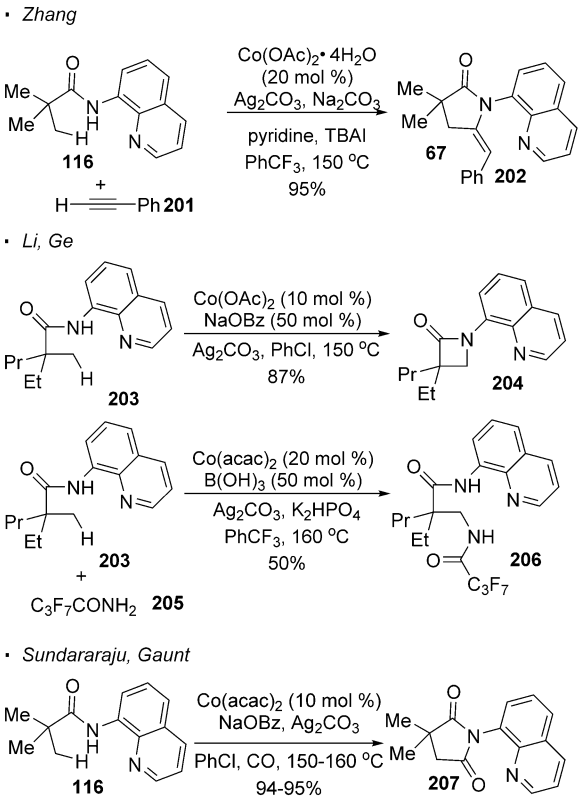
2.3.3. *Cobalt*

Cobalt has also been shown to be a competent catalyst for C–H activation directed by 8-aminoquinoline. As reported by Zhang et al., the use of $Co(OAc)_2$ as the precatalyst allows five-membered pyrrolidinone **202** to be accessed from acyclic amide **116** and phenylacetylene **201** (Scheme 36).[102] In this case, concomitant alkynylation and cyclization occurs. Li, Ge, and co-workers showed that amide **203** undergoes β-lactamization in the absence of an alkyne under similar reaction



Coupling Partner	R	x, y L	Conditions	Yield
PhMgBr $Ph_2Zn.MgBr$	Ph	10, 10 dppbz	**199**	80%
$AlMe_3$	Me	10, 11 Ph-dppen	**200**	84%
		20, 20 MeO-dppen	**199**, $Zn(OAc)_2$ (20 mol %)	80%

Scheme 35. Fe-catalyzed formation of C–C bonds.

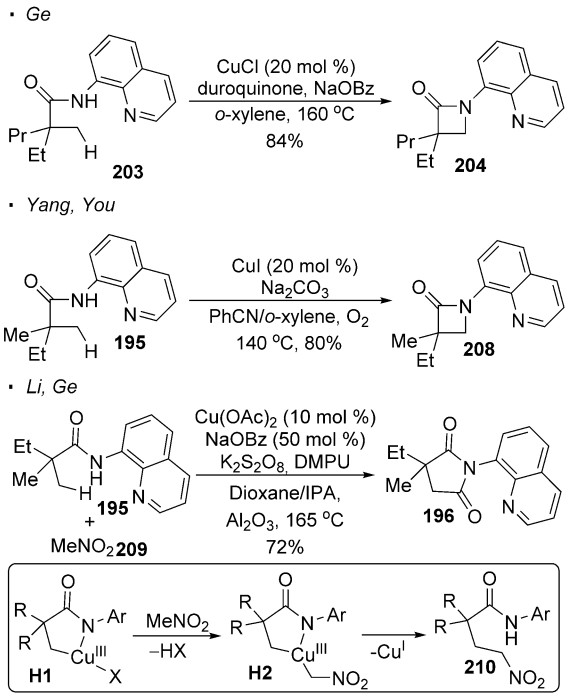


Scheme 36. Co-catalyzed C–H functionalization. Bz = benzoyl.

conditions to afford β-lactam **204**.[103] Intermolecular amination can be achieved when a perfluorinated amide is added as a nitrogen source. The Sundararaju[104] and Gaunt[105] research groups independently found that $Co(acac)_2$ catalyzes the carbonylative cyclization of amide **116** in the presence of carbon monoxide for access to succinimide **207**.

2.3.4. Copper

Ge and co-workers developed the synthesis of β-lactam **204** from amide **203** with copper(I) chloride as the catalyst (Scheme 37).[106] In this reaction, duroquinone is believed to

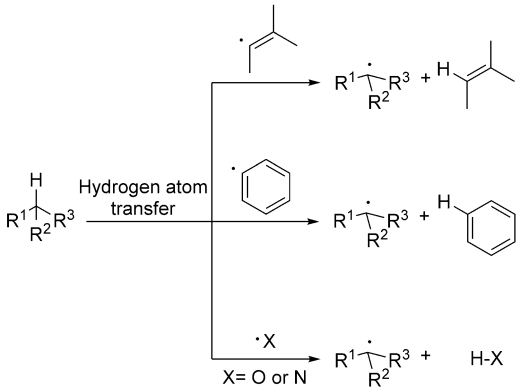


Scheme 37. Cu-catalyzed C–H functionalization. DMPU = *N*,*N*′-dimethylpropyleneurea, IPA = isopropyl alcohol.

oxidize copper(II) to copper(III) to drive the reductive elimination to form the C–N bond. Yang, You, and co-workers later showed that O_2 can serve as an alternative oxidant with copper(I) iodide as the catalyst.[107] The copper-(II) acetate catalyzed carbonylative cyclization of amide **195** to afford succinimide **196**, reported by Li, Ge, and co-workers, relies on nitromethane **209** as a formal source of carbon monoxide.[108] In the proposed mechanism, a nitronate ligand binds to the copper(III)-alkyl species **H1** through ligand exchange to form intermediate **H2**. Reductive elimination forms a C–C bond to generate intermediate **210**, which is further transformed to the observed cyclized product **196**. Intermolecular C–H amination has also been established, but a stoichiometric amount of a copper salt is required.[109]

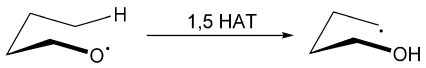
3. Hydrogen Atom Transfer to Reactive Radical Species

A conceptually distinct approach to C(sp^3)–H activation relies on established radical reactivity.[110] In this case, a hydrogen atom is transferred from the carbon center to a highly reactive radical species. The driving force of this hydrogen atom transfer is the formation of an X–H bond which is stronger than the breaking C–H bond. Radicals that are capable of abstracting a hydrogen atom from an unactivated C(sp^3)–H bond are typically oxygen radicals, nitrogen radicals, and aryl/vinyl radicals (Scheme 38). The resulting alkyl radical from the C–H bond can be trapped with a radical partner, thereby resulting in the installation of a functional group at the original C–H bond.



Scheme 38. Hydrogen atom transfer.

Intramolecular hydrogen atom transfer is often favored over an intermolecular event because of its lower entropic cost. In this case, the reactive radical species can be viewed as a directing group. In most cases, a 1,5-hydrogen atom transfer (1,5-HAT) is the predominant pathway, in which the cleaved C–H bond is located five bonds away from the reactive radical (Scheme 39).[111] The functionality that can be incor-



Scheme 39. 1,5-Hydrogen atom transfer.

porated into the C–H bonds is contingent on the identity of the reactive radical (oxygen/nitrogen/vinyl/aryl), as well as the method to generate the radical. These aspects will be the primary focus of the following discussion.

3.1. Nitrogen Radicals

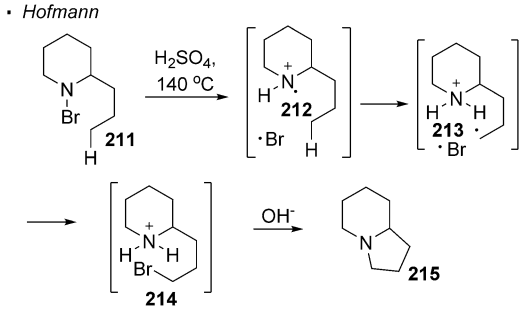
The first class of radicals that are capable of abstracting a hydrogen atom from inert C(sp^3)–H bonds is nitrogen radicals.[112] The N–H bond of a neutral amine has a comparable bond energy to that of a C(sp^3)–H bond, so there is a lack of appreciable driving force for hydrogen atom transfer to occur.[113] To realize 1,5-HAT, the nitrogen radical is rendered more electrophilic through either protonation or substitution with an electron-withdrawing group.

3.1.1. Generation and Transformations

3.1.1.1. Homolysis of N–X Bonds

The most common method to generate a nitrogen radical is through the homolytic cleavage of a nitrogen–heteroatom

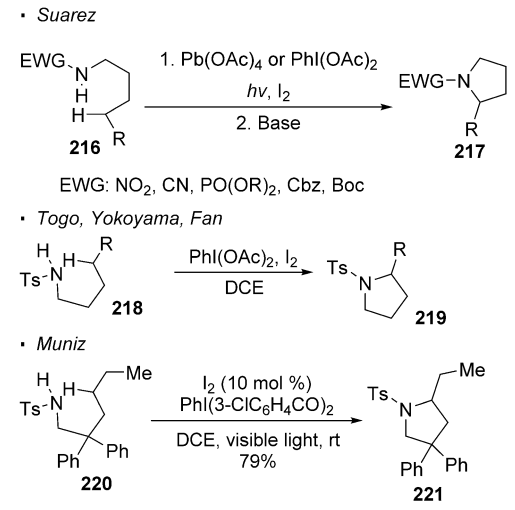
bond (Scheme 40). In the Hofmann–Löffler–Freytag (HLF) reaction, a nitrogen–halogen bond is subjected to thermal or photochemical conditions in the presence of a strong acid.[114] For example, the nitrogen–bromine bond in amine **211** breaks



Scheme 40. Generation of nitrogen radicals by homolysis of N–X bonds.

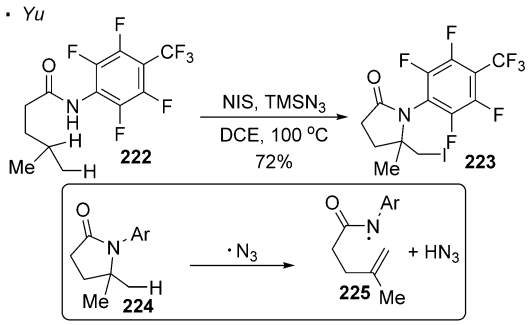
homolytically to give the nitrogen radical **212** and a bromine radical. The protonated nitrogen radical abstracts a hydrogen atom from the δ-C–H bond to give alkyl radical **213**. The combination of the alkyl radical and the halogen radical results in the formation of a carbon–halogen bond. A subsequent basic workup leads to a S_N2 reaction and affords pyrrolidine **215** as the final product. In all these cases, the nitrogen radical is generated concurrently with a halogen radical. Therefore, the alkyl radical formed from 1,5-HAT is inevitably intercepted by the halogen radical. This invariably leads to the formation of a carbon–halogen bond.

More recent research has been devoted to the investigation of the in situ generation of a nitrogen–halogen bond from a N–H bond (Scheme 41). This obviates the handling of unstable nitrogen–halogen bonds. With the Suarez modification, elemental halogens, along with $Pb(OAc)_4$ or $PhI(OAc)_2$, are used to generate a nitrogen–halogen bond from a N–H bond.[115] The presence of an electron-withdrawing group



Scheme 41. In situ generation of N–X bonds. EWG = electron-withdrawing group.

(nitro, cyano, phosphonyl, and carbonyl groups) on the nitrogen atom makes the nitrogen radical reactive enough to realize HAT. Thus, amine derivative **216** bearing various electron-withdrawing groups is a competent substrate for the HLF reaction. Togo, Hoshina, and Yokoyama[116] as well as Fan et al.[117] demonstrated that sulfonyl groups on the nitrogen atom are also compatible with this reaction. Martínez and Muniz reported a catalytic variant of the Suarez modification. In this procedure, iodine is employed as a catalyst for the reaction of sulfonamide **220** to afford HLF product **221**.[118] For all these transformations described above, the formation of the nitrogen radical is also accompanied by a halogen radical and, as in the traditional HLF reaction, a carbon–halogen bond is formed. A subsequent step would afford a pyrrolidine as the final product. In addition, Yu and co-workers showed that when amide **222** is subjected to NIS and $TMSN_3$, the δ-C–H bond is aminated and the ε-C–H bond is iodinated to give γ-lactam **223** (Scheme 42).[119] It is proposed that an azide radical can

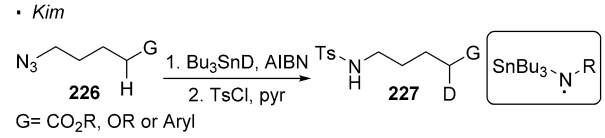


Scheme 42. γ- and ε-functionalization with nitrogen radicals. TMS = trimethylsilyl.

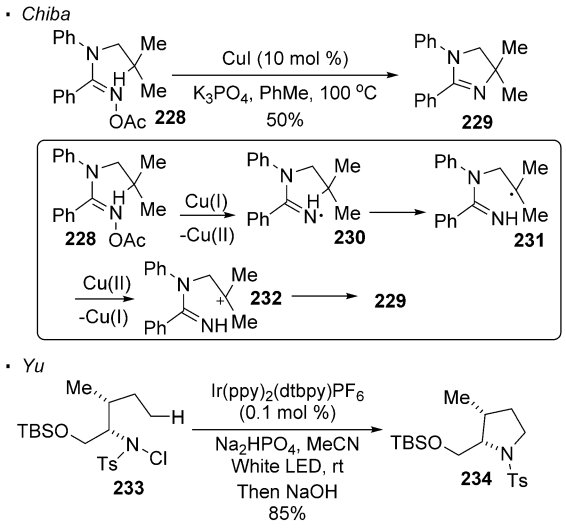
abstract a hydrogen atom from the original HLF product **224** to give a nitrogen radical and an alkene. Cyclization of the nitrogen radical onto the alkene generates an alkyl radical which captures an iodine atom from the NIS. As exemplified by the aforementioned reactions, only the halogenation of C–H bonds has been accomplished with in situ generation of a nitrogen–halogen bond as the nitrogen radical precursor.

3.1.1.2. ***Reduction of N–X Bonds***

When the nitrogen atom is at a higher oxidation level, reduction provides a means to generate a nitrogen radical. Decomposition of organic azides with various reducing agents is not discussed here since the resulting neutral nitrogen radicals are not reactive enough to break unactivated $C(sp^3)$–H bonds (Scheme 43).[120] Chen and Chiba reported a copper-catalyzed intramolecular amination of the tertiary C–H bond of amidoxime **228** (Scheme 44).[121] In the proposed catalytic cycle, the copper(I) catalyst reduces the N–O bond to amidinyl radical **230**. A 1,5-HAT generates alkyl radical **231**, which is oxidized by copper(II) to carbocation **232**. Cyclization then occurs to give dihydroimidazole **229**. An analogous route to generate a nitrogen radical has been demonstrated by Qin and Yu with photoredox catalysis.[122]



Scheme 43. Generation of nitrogen radicals by reduction of organic azides. AIBN = 2,2'-azobisisobutyronitrile, pyr = pyridine.

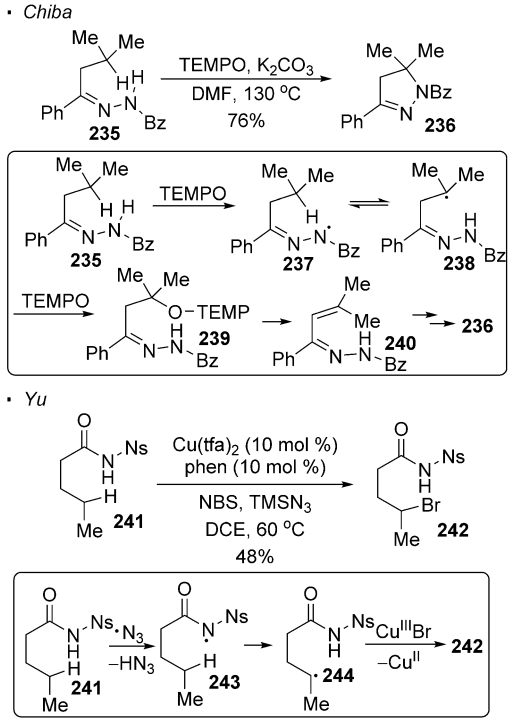


Scheme 44. Catalytic reduction of N–X bonds. dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridyl, ppy = 2-phenylpyridinato.

The N–Cl bond in sulfonamide **233** is reduced by the excited photocatalyst $[Ir(ppy)_2(dtbpy)]PF_6$. The 1,5-HAT leads to generation of an alkyl radical. Oxidation of the alkyl radical to a carbocation turns over the photocatalyst and allows cyclization to afford the HLF product **234**. Overall, only intramolecular amination to give the HLF products has been achieved when a nitrogen atom at a higher oxidation level was employed as the nitrogen radical precursor.

3.1.1.3. ***Abstraction of Hydrogen Atoms***

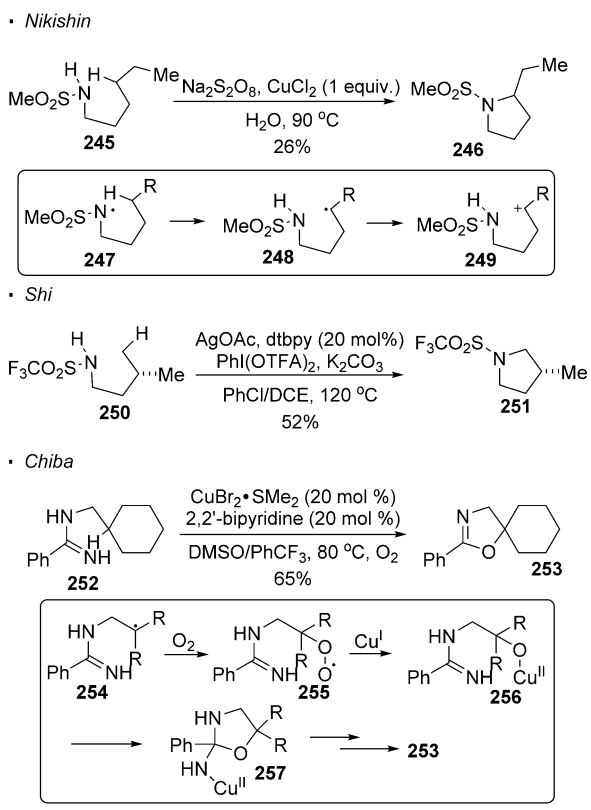
The abstraction of a hydrogen atom provides another means to form a nitrogen radical from a N–H bond. Chiba and co-workers showed that the reaction between the N–H bond in hydrazone **235** and TEMPO can generate a nitrogen radical (Scheme 45).[123] Although the nitrogen radical generated in this case is stabilized by the α-nitrogen atom, the equilibrium between the nitrogen radical **237** and the alkyl radical **238** provides a low concentration of the alkyl radical. The trapping of the alkyl radical by TEMPO results in the formation of a C–O bond. Subsequent elimination of TEMPO-H from **239** gives aza-diene **240**, which can cyclize to give dihydropyrazole **236**. Yu and co-workers also demonstrated that sulfonamide **241** undergoes C–H bromination with NBS and $TMSN_3$ in the presence of a copper(II) catalyst (Scheme 45).[124] In the proposed mechanism, an azide radical generated in situ abstracts a hydrogen atom from the N–H bond to form nitrogen radical **243**. The alkyl radical **244** formed by 1,5-HAT can react with in situ generated copper(III) bromide to afford the observed brominated **242**.



Scheme 45. Generation of nitrogen radicals by abstraction of hydrogen.

3.1.1.4. ***Oxidation of N–H Bonds***

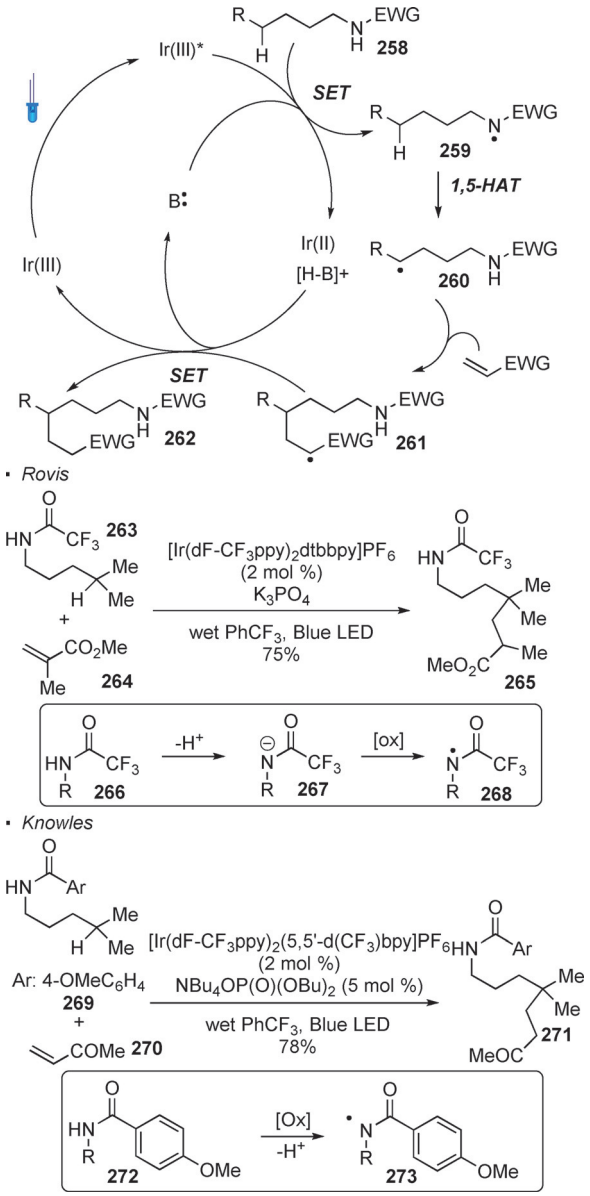
A less common method to generate a nitrogen radical is through the oxidation of a N–H bond. Nikishin et al. reported that, in the presence of a stoichiometric amount of strongly oxidizing $Na_2S_2O_8$, the HLF product can be obtained from sulfonamide **245** (Scheme 46).[125] It is believed that the oxidizing agent oxidizes the N–H bond to give nitrogen radical **247**, which can realize 1,5-HAT to generate an alkyl radical at the δ-position to the nitrogen atom. Oxidation of the alkyl radical **248** to carbocation **249** promotes cyclization to generate pyrrolidine **246** as the final product. Although both the conversion and yield are moderate, this reaction suggests the feasibility of using a N–H bond as a nitrogen radical precursor. Another HLF reaction that possibly involves the oxidation of a N–H bond to generate a nitrogen radical has been reported by Shi and co-workers.[126] In the presence of a Ag catalyst and a hypervalent iodine reagent as the terminal oxidant, sulfonamide **250** undergoes a HLF reaction to form cyclized product **253**. Although the authors propose a concerted metalation/deprotonation mechanism with silver to account for the cleavage of the C–H bond, a nitrogen radical intermediate is proposed in their subsequent report under essentially the same reaction conditions.[127] In addition, Chiba and co-workers reported the generation of nitrogen radicals from the N–H bond of amidine **252** with copper(II) catalysts and oxygen.[128] Instead of being oxidized, the alkyl radical intermediate **254** is in this case trapped by O_2 to form superoxo radical **255**. A Fenton-type fragmentation is proposed to give copper(II) alkoxide intermediate **256**. Dihydrooxazole **257** is formed after a sub-



Scheme 46. Generation of nitrogen radicals by oxidation of N–H bonds.

sequent nucleophilic substitution. Except for Chiba's system with amidines, all the reactions relying on the oxidation of the N–H bond to generate the nitrogen radical lead to the formation of five-membered-ring products through intramolecular C–H amination.

More recent studies incorporate photoredox catalysis into the oxidation of N–H bonds. The groups of Rovis[129] and Knowles[130] simultaneously and independently disclosed the remote alkylation of unactivated C(sp^3)–H bonds directed by an amide (Scheme 47). In the system developed by Chu and Rovis, trifluoroacetamide **263** undergoes alkylation at the tertiary C–H bond with methyl methacrylate (**264**) to form amide **265**. Similarly, alkylated product **271** can be obtained from amide **269** with methyl vinyl ketone (**270**) by using the procedure developed by Knowles and co-workers. In the proposed catalytic cycle of these two reactions, the excited photocatalyst oxidizes amide **258** to yield nitrogen radical **259** in the presence of a base. A 1,5-HAT and trapping of the alkyl radical **260** with the electrophilic alkene generates a radical in the α-position to an electron-withdrawing group (**261**). Reduction of **261** turns over the photocatalyst and a final protonation affords the alkylated product **262**. In the system developed by Chu and Rovis, mechanistic studies suggest a stepwise deprotonation/oxidation event for the generation of the nitrogen radical. Thus, the intermediacy of amidyl anion **267** is proposed. This accounts for the necessity of the strong electron-withdrawing trifluoroacetyl group on the nitrogen atom to acidify the N–H bond and the use of a strong base (K_3PO_4). On the other hand, a concerted



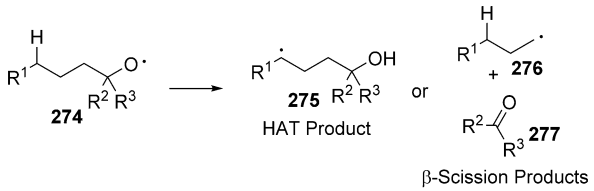
Scheme 47. Formation of C–C bonds with nitrogen radicals. SET = single-electron transfer. [Ir(dF-CF_3ppy)$_2$dtbbpy] = [4,4′-bis(*tert*-butyl)-2,2′-bipyridine]bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl]phenyl]-iridium(III).

proton-coupled-electron-transfer event is believed to operate in the system developed by Knowles and co-workers. Therefore, amides bearing less acidic N–H bonds are competent substrates in the presence of a more oxidizing photocatalyst. This set of conditions allows a broader substrate scope at the expense of selectivity. Thus, the two systems developed by the groups of Rovis and Knowles are complementary.

3.2. Oxygen Radicals

Oxygen radicals are more electrophilic and reactive than nitrogen radicals because of the higher electronegativity of the oxygen atom; thus, a neutral oxygen radical is able to abstract hydrogen atoms from inert C–H bonds without

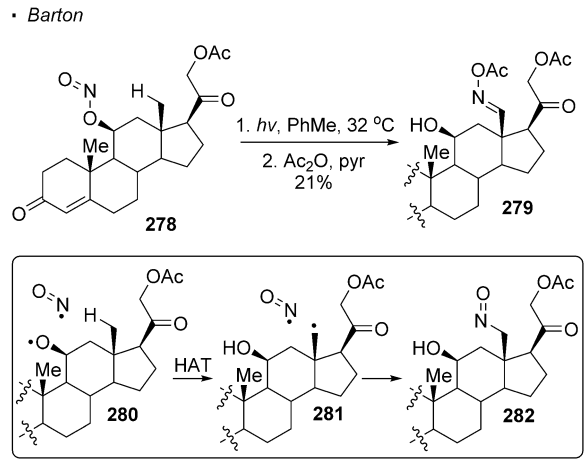
protonation.[131] This process has a favorable thermodynamic force, as indicated by the stronger bond energy of O–H bonds (105 kcal mol^{-1}) compared to C(sp^3)–H bonds. However, because of the strength of the C=O bond, β-scission occasionally out-competes intramolecular hydrogen atom transfer. In β-scission, alkyl radical **276** and ketone **277** are formed from the cleavage of the Cα–Cβ bond (Scheme 48).



Scheme 48. Reactivity of oxygen radicals.

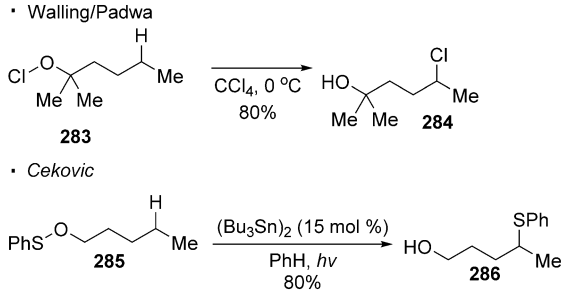
3.2.1. *Generation and Transformations*
3.2.1.1. *Homolysis of O–X Bonds*

One of the most common oxygen radical precursors is an oxygen–heteroatom bond. In most cases, the identity of the heteroatom determines the coupling partner at the C–H bond. Similar to the HLF reaction with nitrogen radicals, the oxygen radical is formed from homolytic cleavage of the oxygen radical precursor. The first reported C–H functionalization reaction with oxygen radicals was the Barton reaction (Scheme 49).[132] Cleavage of the N–O bond of



Scheme 49. The Barton reaction.

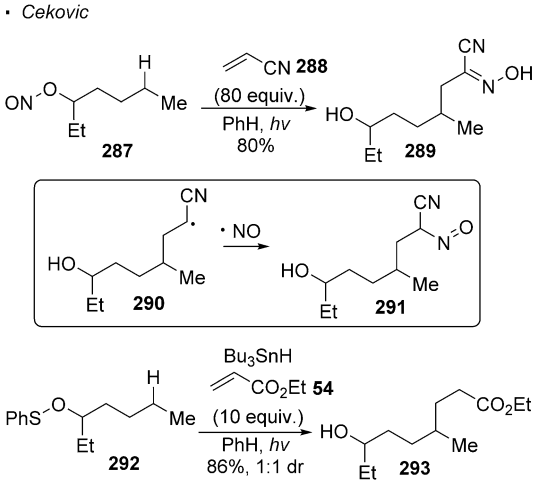
nitrite ester **278** under photochemical conditions generates oxygen radical **280** and a nitrosyl radical. The oxygen radical abstracts a hydrogen atom from the δ-C–H bond in a 1,5-fashion. The resulting alkyl radical **281** combines with the nitrosyl radical to form **282**, which after subsequent tautomerization and acetoxylation affords oxime **279** as the final product. Other examples with an oxygen–heteroatom bond as an oxygen radical precursor are illustrated in Scheme 50. Walling and Padwa demonstrated that chlorination of a C–H bond can be accomplished with an oxygen–halogen bond as



Scheme 50. Use of O–X bonds for the formation of C–X bonds.

precursor.[133] Similarly, Čeković and co-workers achieved the formation of a C–S bond using a O–S precursor.[134] The mechanisms are similar in these examples, and a resulting C–X bond is formed at the C–H bond in the δ-position to the directing oxygen radical.

When the oxygen radical is formed through homolytic cleavage of an O–X bond, there has been limited success in trapping the alkyl radicals with an external partner (Scheme 51). Petrović and Čeković observed that alkylation

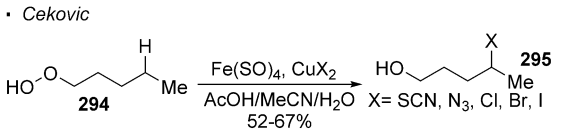


Scheme 51. Use of excess alkenes for C–H alkylation.

of the alkyl radical can out-compete the trapping of the X radical formed during homolysis of the O–X bond when a large excess of an electrophilic alkene is employed.[135] When 80 equiv of acrylonitrile (**288**) is used in the photochemical decomposition of nitrite ester **287**, trapping of the alkyl radical in the δ-position to the oxygen atom by acrylonitrile can be accomplished. The resulting radical **290** combines with the nitrosyl radical to afford intermediate **291**, which tautomerizes to form oxime **289**. Similarly, the alkyl radical generated using the O–S bond as the oxygen radical precursor can be trapped by ethyl acrylate (**54**). In these cases, the alkyl radical in the α-position to the carboxylate abstracts a hydrogen atom from Bu_3SnH. The tributyltin radical formed is believed to scavenge any sulfur radical or abstract a sulfur atom from an O–S bond.

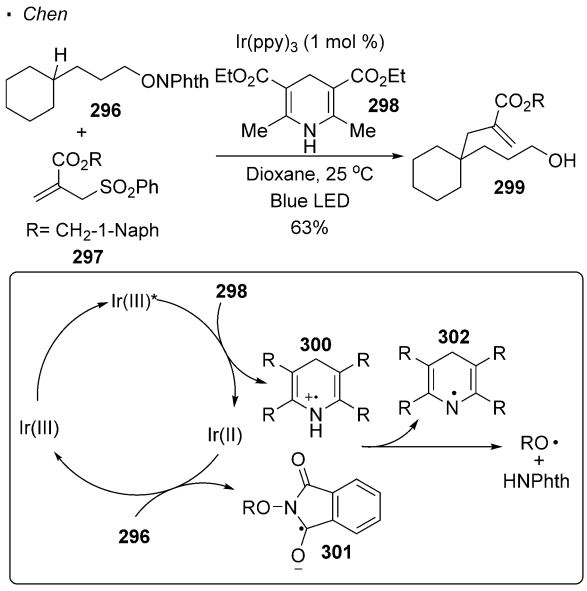
3.2.1.2. Reduction of O–X Bonds

A strategy to avoid the simultaneous formation of an oxygen radical and another radical from an O–X bond is the use of a stoichiometric reductant. As reported by Čeković, treatment of alkyl hydroperoxide **294** with a stoichiometric amount of $FeSO_4$ leads to reduction of the O–O bond to give the oxygen radical without the concomitant formation of a hydroxyl radical (Scheme 52).[136] The alkyl radical formed is, thus, free to react with a copper(II) salt. With the appropriate choice of copper(II) salt, thiocyanation, azidation, and halogenation of the C–H bond can be accomplished.



Scheme 52. Generation of oxygen radicals by the reduction of O–X bonds.

The most recent research incorporates photoredox catalysis such that an oxygen–heteroatom bond is cleaved by reduction to generate the oxygen radical. This strategy wisely avoids the formation of another radical, such that the alkyl radical generated by 1,5-HAT is free to react with a radical partner (Scheme 53). In the system described by Chen and co-workers, the Hantzsch ester **298** is oxidized by the excited photocatalyst $Ir(ppy)_3$ to generate radical cation **300**.[137] The photocatalyst then reduces the phthalimide in **296** to form radical anion **301**, which can undergo proton transfer with **300** and decompose to an oxygen radical. A 1,5-HAT generates an alkyl radical, which is then coupled with electrophilic alkene **297**. Elimination of the sulfonyl radical affords alkylated product **299**.

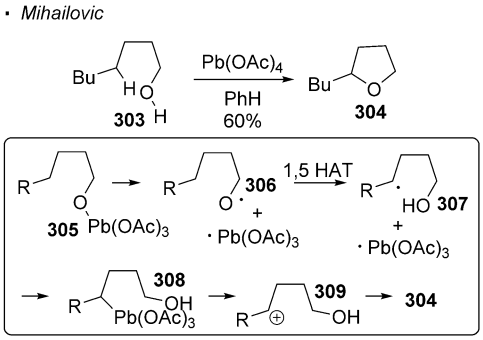


Scheme 53. Generation of oxygen radicals by photoredox catalysis.

It can be concluded from the studies carried out by the groups of Čeković and Chen that when the oxygen radical is generated through single-electron reduction of an O–X bond, trapping of the alkyl radical formed from 1,5-HAT with an external partner is a possibility, thereby providing a strategy to form various bonds at the C–H bond through the use of different reaction partners. However, some O–X bonds are unstable to handle and access to these are generally non-trivial.

3.2.1.3. Free Alcohols as Precursors

Oxygen–hydrogen bonds are another common class of precursors for oxygen radicals. $Pb(OAc)_4$ has been shown to be a competent oxidant for the generation of an oxygen radical in this regard, allowing the formation of ether **304** from alcohol **303** (Scheme 54).[138] Ligand exchange between

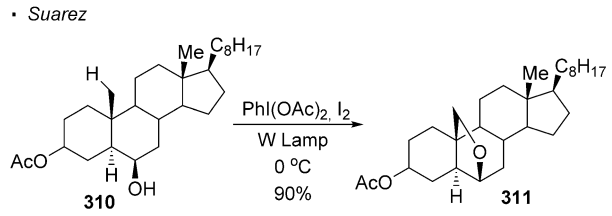


Scheme 54. Generation of oxygen radicals by the oxidation of O–H bonds.

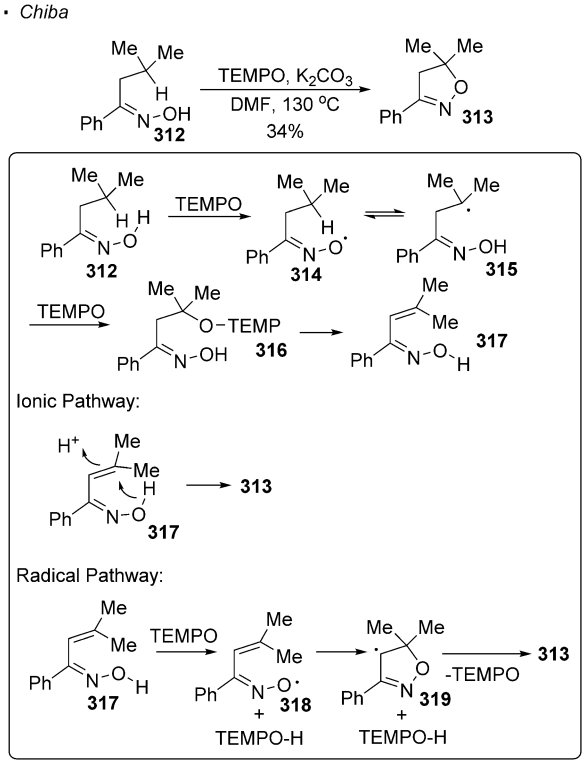
one of the acetate groups and the alcohol provides lead(IV) alkoxide species **305**. It is proposed that homolytic cleavage of the lead–oxygen bond gives oxygen radical **306** and lead(III) acetate. After a 1,5-HAT, the alkyl radical **307** generated is intercepted by the lead(III) acetate to form lead–alkyl species **308**. Heterolytic cleavage of the Pb–C bond yields carbocation **309**, which is prone to cyclization to afford tetrahydrofuran **304**. Alternatively, lead–alkyl intermediate **308** can undergo an intramolecular ligand transfer reaction to give **304** without the involvement of carbocation **309**.

An alternative method to generate an oxygen radical from an O–H bond is to generate an oxygen–halogen bond in situ followed by its homolytic cleavage. For example, under the conditions reported by Suarez and co-workers (I_2 and $PhI(OAc)_2$), tetrahydrofuran **310** can be formed from steroid **311** (Scheme 55).[139] The mechanism is analogous to the HLF reaction discussed previously.

The transfer of the hydrogen atom from the O–H bond is another means to generate an oxygen radical. In the example described by Chiba and co-workers, where TEMPO was used to generate an oxygen radical through hydrogen atom transfer from the O–H bond of an oxime, intramolecular oxygenation of the C–H bond is observed (Scheme 56).[123] In this system, TEMPO abstracts a hydrogen atom from oxime **312** to give oxygen radical **314**. The alkyl radical **315** formed by 1,5-HAT



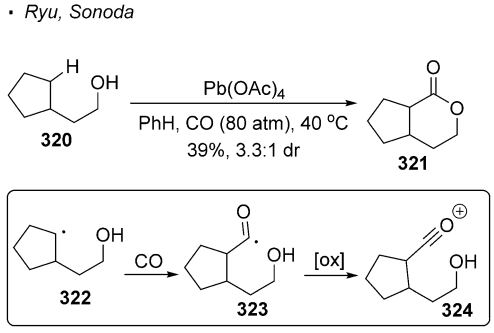
Scheme 55. In situ generation of O–I bonds.



Scheme 56. Formation of isoxazolines.

is trapped by TEMPO to generate intermediate **316**. Elimination of TEMPO-H gives intermediate **317**, which cyclizes to afford dihydroisoxazole **313** through either an ionic or radical mechanism. In the radical pathway, TEMPO abstracts a hydrogen atom from oxime **317**. The resulting oxygen radical **318** effects cyclization to give carbon-centered radical **319**, which abstracts a hydrogen atom from TEMPO-H to afford **313**.

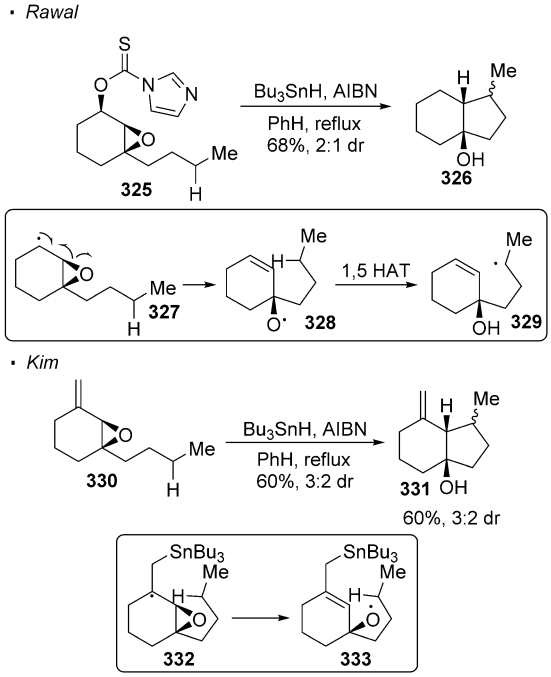
In almost all the reactions in which an O–H bond is used to generate an oxygen radical, intramolecular C–O oxygenation occurs to give a five-membered oxygen heterocycle. The only exception has been reported by Ryu, Sonoda, and coworkers, where a high pressure of CO is applied under the reaction conditions such that alkyl radical **322** undergoes carbonylation before it is oxidized. The oxidation yields acylium ion **324** and affords γ-lactone **321** after cyclization (Scheme 57).[140]



Scheme 57. Formation of γ-lactones through carbonylation.

3.2.1.4. ***Cleavage of Epoxides***

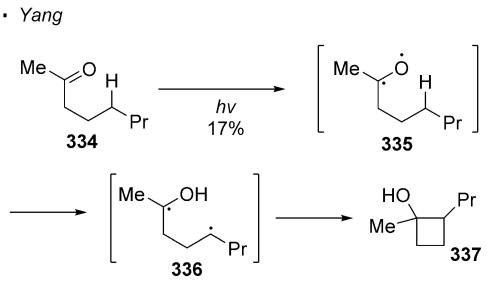
Epoxides are also sometimes used to generate oxygen radicals. The groups of Rawal[141] and Kim[142] independently disclosed the functionalization of $C(sp^3)$–H bonds with oxygen radicals formed from epoxides (Scheme 58). In both reports, a radical is first generated in the α-position to the epoxide. Subsequent homolytic cleavage of the C–O bond is driven by the ring strain of the epoxide and gives the oxygen radical.[143] In the study by Rawal et al., Barton–McCombie deoxygenation was applied to epoxide **325** to generate the alkyl radical in the α-position to the epoxide (**327**). Kim et al. generated such an intermediate by the addition of the tributyltin radical to the alkene in **330**. The alkyl radicals generated from the 1,5-HAT in these two cases are trapped by the tethered alkenes that are formed during the reaction to afford cyclized products **326** and **331**, respectively.



Scheme 58. Epoxides as oxygen radical precursors.

3.2.1.5. Electronic Excitation of Carbonyl Groups

The final class of oxygen-radical precursors is carbonyl groups. When a carbonyl group is illuminated with a UV light, an electron is excited from the n orbital of the oxygen atom to the π* orbital of the carbonyl group (Scheme 59). This results



Scheme 59. Norrish–Yang cyclization.

in the formation of a diradical species, with both the carbonyl carbon and oxygen atoms possessing radical character. The carbonyl oxygen radical is able to abstract a hydrogen atom through 1,5-HAT. The resulting alkyl radical recombines with the carbonyl carbon radical, thereby leading to the formation of cyclobutanol. This is typically known as Norrish type II reactivity or Norrish–Yang cyclization.[144] The formation of cyclobutanol **337** from ketone **334** is an example that illustrates this reactivity. To date, no successful attempts to trap the alkyl radical with a species other than the carbonyl carbon radical have been reported. Therefore, a cyclobutanol is always the product obtained when a carbonyl group is used to form an oxygen radical for intramolecular C(sp^3)–H functionalization.

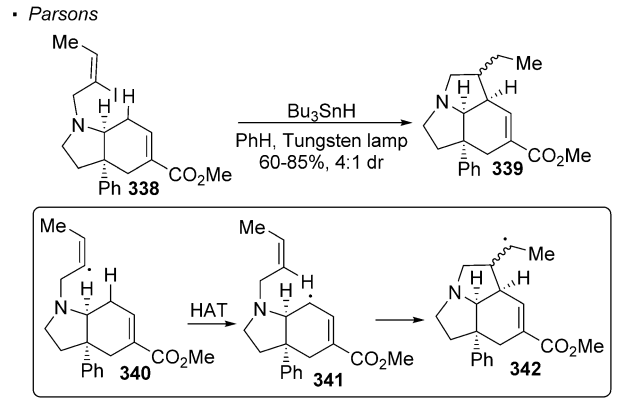
3.3. Vinyl and Aryl Radicals

Vinyl and aryl radicals are the final class of radicals that can cleave unactivated C(sp^3)–H bonds through hydrogen atom transfer. The higher bond strength of a C(sp^2)–H bond (113 kcal mol^{-1}) compared to a C(sp^3)–H bond (95–105 kcal mol^{-1}) provides a thermodynamic driving force for the process.

3.3.1. Generation and Transformations

3.3.1.1. Reduction of Aryl or Vinyl Halides

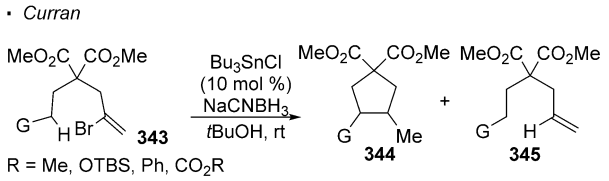
Generally, a vinyl or aryl radical is generated by reduction of the corresponding halide with Bu_3SnH under photochemical or thermal conditions. The reactive tributyltin radical cleaves the carbon–halogen bond through abstraction of the halogen atom. Sometimes AIBN is added to facilitate the formation of the tributyltin radical. The vinyl or aryl halide transfers the halogen to the resulting tributyltin radical to form a vinyl or halogen radical. Parsons and co-workers first demonstrated that vinyl radicals generated from vinyl halides and tributyltin hydride can be used to functionalize C(sp^3)–H bonds (Scheme 60).[145] In this case, an allylic C–H bond in **340**



Scheme 60. Initial report on 1,5-HAT with vinyl halides.

is cleaved in a 1,5-fashion to give intermediate **341**. The allylic radical cyclizes onto the pendent alkene to afford the alkyl radical **342**, which is reduced by Bu_3SnH to give the final product **339**.

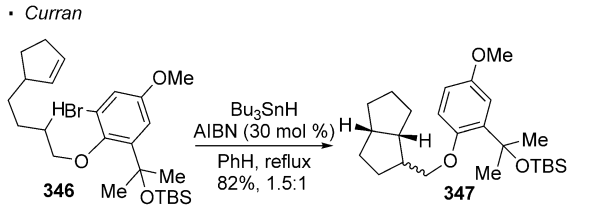
Later, Curran and Shen improved this system by using a catalytic amount of Bu_3SnCl and a stoichiometric amount of $NaBH_3(CN)$ in *t*BuOH (Scheme 61).[146] This system provides



Scheme 61. Catalytic system for 1,5-HAT with C(sp^3)–H bonds.

a catalytic amount of Bu_3SnH under the reaction conditions and is particularly beneficial for the functionalization of unactivated C(sp^3)–H bonds. Since hydrogen atom transfer from unactivated C(sp^3)–H bonds to a vinyl radical is relatively slow, the reduction of the vinyl radical by Bu_3SnH becomes a competitive process. Therefore, a low concentration of Bu_3SnH is sometimes required to avoid the net reduction of the vinyl halide.

An alcohol-directed C(sp^3)–H functionalization using aryl radicals has been reported by Curran and Xu (Scheme 62).[147] In this case, an aryl bromide is installed onto the alcohol through the formation of an aryl ether. In the presence of Bu_3SnH and AIBN under thermal conditions, aryl bromide **346** decomposes to give an aryl radical that can abstract

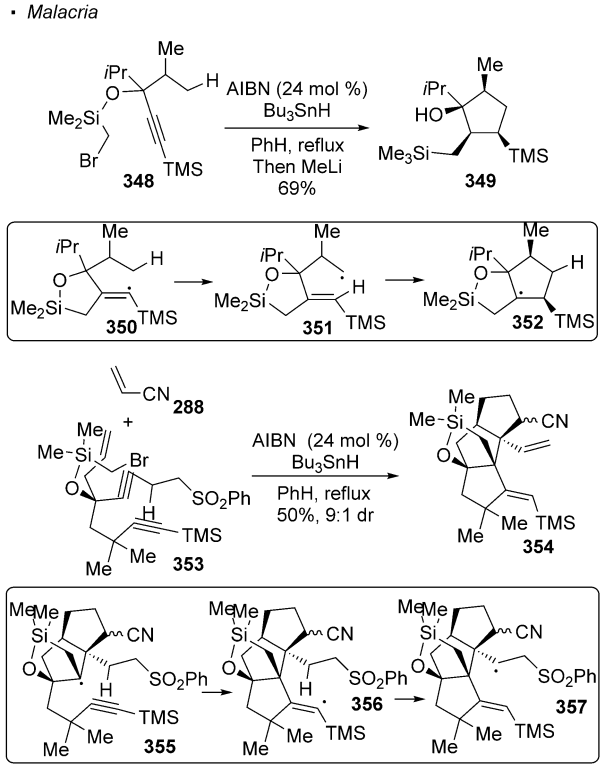


Scheme 62. Derivatization of alcohols with vinyl radicals for 1,5-HAT.

a hydrogen atom from a C–H bond in the β-position to the oxygen atom. The resulting alkyl radical is trapped by a tethered alkene. Hydrogen atom transfer from Bu_3SnH to the final alkyl radical intermediate affords cyclized product **347**. This transformation serves as a strategy to derivatize an alcohol with C(sp^3)–H functionalization.

3.3.1.2. Radical Addition to Alkynes

An alternative method to generate a vinyl radical is through radical addition to an alkyne. For the conversion of alkyne **348** into cyclopentane **349**, Malacria and co-workers showed that the addition of an α-silyl radical to an alkyne generates vinyl radical **350** (Scheme 63).[148] This vinyl radical

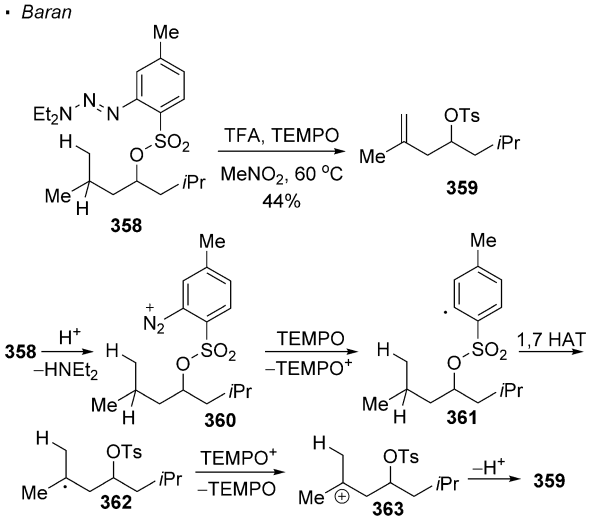


Scheme 63. Generation of vinyl radicals through radical addition to alkynes.

can undergo 1,5-HAT to give primary alkyl radical **351**. As in the reaction carried out by Curran, radical cyclization onto the alkene takes place to afford the cyclized product **349**. Malacria and co-workers also demonstrated that tetracyclic framework **354** can be accessed from acyclic precursor **353** and acrylonitrile **288**.[149] The alkyl radical in intermediate **355** adds to the alkyne to give vinyl radical **356**. The alkyl radical generated by 1,5-HAT in this resulting vinyl radical is located at the position β to the sulfonyl group. Elimination then takes place to give the alkene in the observed tetracyclic product **354**.

3.3.1.3. Reduction of Aryl Triazenes

The reduction of aryl triazenes under acidic conditions is another means to generate aryl radicals. Baran and co-workers demonstrated that alkene **359** can be obtained from aryl triazene **358** in the presence of TFA and TEMPO (Scheme 64).[150] In the proposed mechanism, the elimination of $HNEt_2$ from **358** yields diazonium **360**, which is reduced by TEMPO to give aryl radical **361**. A 1,7-HAT gives tertiary radical **362**. Subsequent oxidation and deprotonation accounts for the formation of alkene **359**.

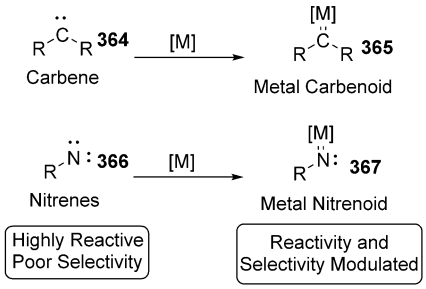


Scheme 64. Generation of aryl radicals from aryl triazenes.

From the above representative examples, it can be observed that the alkyl radicals generated by 1,5-HAT with aryl or vinyl radicals thus far only undergo intramolecular events, such as cyclizing onto tethered alkenes, elimination of an α-leaving group, or oxidation to form carbocations.

4. Metal-Catalyzed Carbene/Nitrene Transfer

Carbenes and nitrenes are carbon and nitrogen atoms with only six electrons in the outermost electron shell. The lack of an octet configuration renders them highly unstable and able to break unactivated C(sp^3)–H bonds, despite their bond strength. Modern methods rely on transition-metal catalysis to generate such reactive species under relatively mild conditions. The interaction between these species and the transition-metal catalysts (with formation of metal carbenoids/nitrenoids) allows the selectivity to be controlled (Scheme 65).[151] The following discussion only includes intramolecular carbene/nitrene transfer because the functional groups serving as the precursors of these reactive species (usually diazo compounds or sulfonamides/carbamates, respectively) can be considered as a directing group. Various reviews on this topic have appeared.[152,153] By using dirhodium(II) catalysis as an illustration, the following discussion aims to provide readers with a fundamental under-



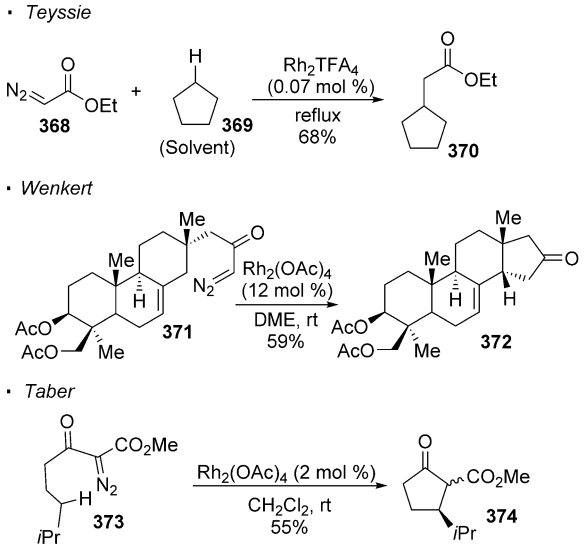
Scheme 65. Metal carbenoids and nitrenoids.

standing of intramolecular C–H insertion with carbene transfer and of C–H amination with nitrene transfer.

4.1. Carbene Transfer

A diazo functionality is a typical precursor of a transition-metal carbenoid. Generally, an electron-withdrawing group, often a carbonyl group, is needed to facilitate the installation of the diazo group, and increase the stability and ease of handling of the resulting diazo-containing molecules.[154] A dirhodium(II) salt can be used to catalyze the decomposition of the diazo group. The resulting rhodium carbenoid intermediate can insert into an alkyl C–H bond, thereby resulting in the formation of a C–C bond.

The potential of dirhodium catalysts for C–H insertion was first reported by Teyssie and co-workers (Scheme 66).[155] They showed that ethyl diazoacetate (**368**) is decomposed in the presence of a catalytic amount of dirhodium(II) trifluoroacetate. The resulting rhodium carbenoid undergoes C–H insertion into the solvent, cyclopentane (**369**). Wenkert et al. first applied this reactivity in the context of an intramolecular reaction.[156] In this case, C–C bond formation occurs at the allylic C–H bond of α-diazo ketone **371**, with dirhodium acetate as a catalyst, to give cyclopentanone **372**. Taber and

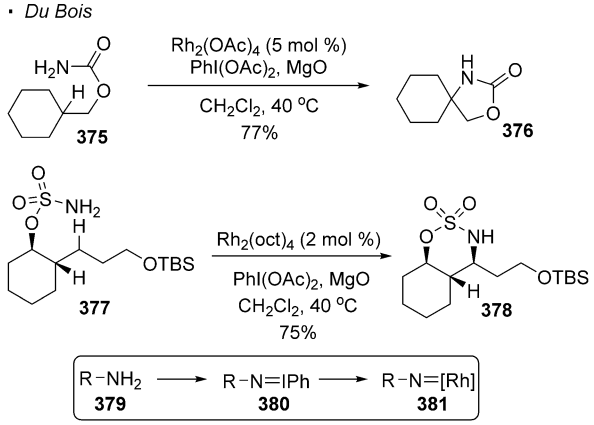


Scheme 66. Rh^{II}-catalyzed intramolecular C–H insertion.

Petty found that unactivated $C(sp^3)$–H bonds also undergo the reaction, as exemplified by the formation of cyclopentanone **374** from α-diazo-β-keto ester **373** through the transfer of a carbene.[157] The mechanism of the C–H insertion step is believed to be concerted, but asynchronous, leaving a partial positive charge at the carbon atom of the C–H bond.

4.2. Nitrene Transfer

Sulfonamides and carbamates are the common precursors to metal nitrenoids. Although intermolecular nitrene transfer was first accomplished with porphyrin-ligated manganese catalysts,[158] Du Bois and co-workers discovered that Rh^{II} dimers show clear advantages for C–H amination (Scheme 67).[159] Both carbamate **375** and sulfamate **377** are



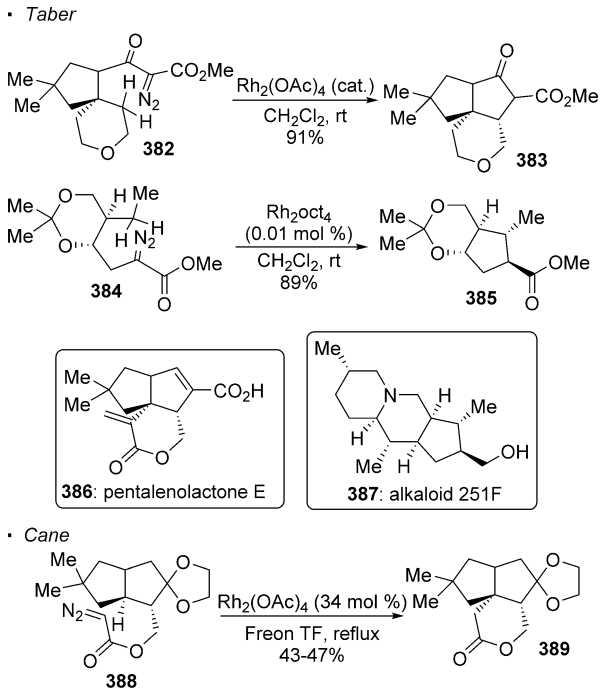
Scheme 67. Rh^{II}-catalyzed intramolecular C–H amination.

competent substrates, although the two substrate classes offer different regioselectivity. The formation of a five-membered ring is favored in the former case, while a six-membered ring is the predominant product in the latter case. In these reactions, the carbamate or the sulfamate reacts with PhI-$(OAc)_2$ in the presence of the base MgO to form iminobenzene **380**, which reacts with the rhodium(II) catalyst to form rhodium nitrenoid **381**. A plausible explanation in the case of sulfamates was offered by Du Bois and co-workers, who suggest that the formation of the five-membered ring product is disfavored due to strain that compresses the N–S–O bond angle. It is proposed that the insertion of the rhodium nitrenoid into the C–H bonds also takes place through a concerted asynchronous mechanism.

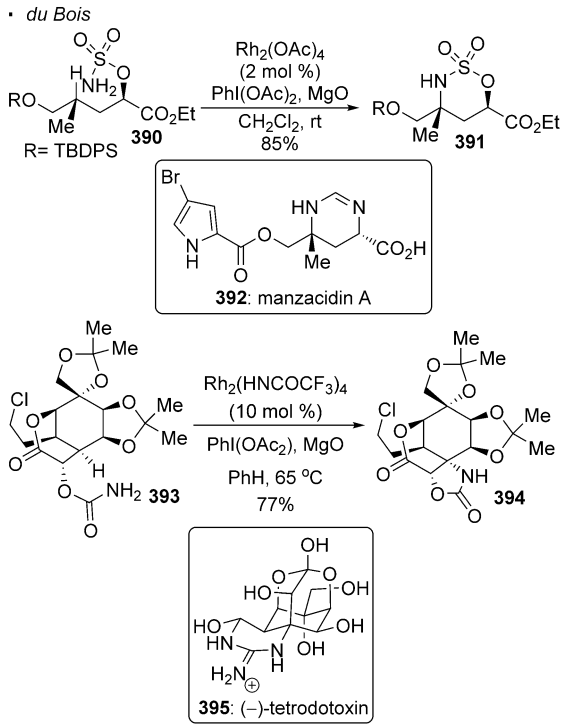
4.3. Synthetic Applications

4.3.1. Carbene Transfer

Carbene transfer has been used to facilitate natural product synthesis through the generation of five- and six-membered rings (Scheme 68). For example, Taber and Schuchardt used Rh^{II}-catalyzed C–H insertion as a key reaction to access pentalenolactone E (**386**).[160] In the pres-



Scheme 68. Application of intramolecular C–H insertion.



Scheme 69. Application of intramolecular C–H amination. TBDPS = *tert*-butyldiphenylsilyl.

ence of a catalytic amount of dirhodium acetate, α-diazo-β-keto ester **382** undergoes intramolecular C–H insertion to form cyclopentanone **383**, thus affording the tricyclic framework of the natural product. Taber and You also illustrated the power of carbene transfer in the synthesis of alkaloid 251F (**387**).[161] Cyclopentane **385**, which can be further elaborated to the natural product, is generated from an intramolecular C–H insertion reaction of α-diazo ester **384** with a catalytic amount of dirhodium(II) octanoate. It should be noted that Cane and Thomas accessed the same core of pentalenolactone E (**38**) by a Rh^{II}-catalyzed C–H insertion with a different disconnection strategy.[162] In this case, the six-membered lactone **389** is obtained from precursor α-diazoketone **388**.

4.3.2. ***Nitrene Transfer***

Nitrogen is one of the most common heteroatoms present in natural products. Wehna and Du Bois demonstrated the power of nitrenoid transfer for installing amine functionalities in total synthesis (Scheme 69). In the synthesis of manzacidin A (**392**), an intramolecular Rh^{II}-catalyzed nitrene transfer of sulfamate **390** installs the required amine functionality at a nearby tertiary C–H bond.[163] The resulting cyclic sulfamate in **391** can be cleaved to accomplish the synthesis of the natural product. Not only can this C–H amination strategy be applied to simple precursors, molecules of high complexity are also competent substrates. For example, in the synthesis of (−)-tetrodotoxin (**395**), the intramolecular nitrene transfer in carbamate **393** through Rh^{II} catalysis affords **394**.[164] It is noteworthy that other functional groups, including acetals, a primary alkyl chloride, and a lactone, are tolerated, and the C–H bond that undergoes amination is very sterically encumbered.

As exemplified by the above examples, the transition-metal-catalyzed transfer of carbenes and nitrenes represents a powerful tool in synthesis. An outstanding feature of this strategy is that very sterically shielded C–H bonds can be functionalized. Tertiary C–H bonds, including those in very hindered positions, can be targeted for reactions to afford quaternary carbon atoms, which are traditionally considered challenging to access. The tolerance of a wide array of functional groups further enhances the utility of this strategy. Carbene or nitrene transfer continues to be a useful method for the construction of difficult targets.

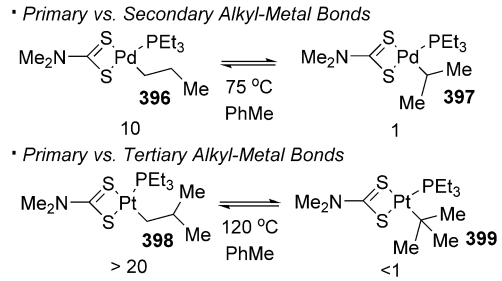
5. Comparison and Complementarity

5.1. Reactivity of Different C–H Bonds

5.1.1. Transition-Metal-Catalyzed C–H Activation

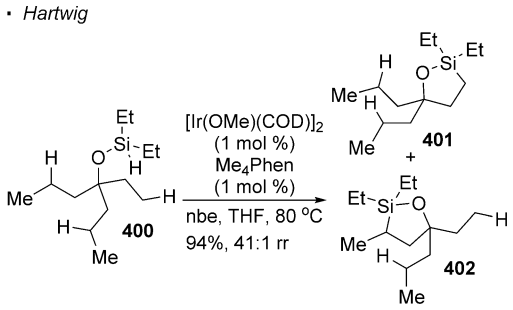
The thermodynamic stability of the corresponding alkyl metal species is an indicator of the reactivity of different kinds of $C(sp^3)$–H bonds to transition-metal-catalyzed C–H activation. Primary alkyl metal species are more stable than their secondary counterparts, which in turn are more stable than the tertiary counterparts.[165] This trend is illustrated in Scheme 70. The equilibrium positions lie far left on the side of the primary alkyl–metal species **396** and **398**, which suggests their higher thermodynamic stability than their secondary or tertiary counterparts.

In parallel to the thermodynamics of the corresponding transition metal alkyl species, the activation of secondary C–H bonds is more difficult than primary C–H bonds. This



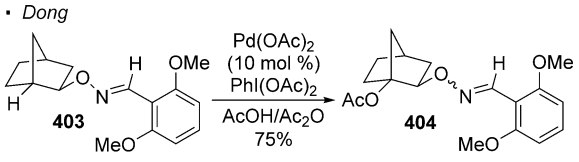
Scheme 70. Relative stability of Pd-alkyl species.

trend is illustrated with a report by Hartwig and co-workers. In their Ir-catalyzed silylation of C–H bonds of **400**, primary C–H bonds are approximately 40 times more reactive than secondary C–H bonds, as reflected by the product distribution of **401** and **402** (Scheme 71).[82] However, secondary C–H bonds can be activated with transition-metal catalysis, as exemplified by many recent reports.



Scheme 71. Relative reactivity of primary and secondary C–H bonds.

In contrast, transition-metal-catalyzed activation of tertiary C–H bonds is rare. Dong and co-workers recently demonstrated that the Pd-catalyzed acetoxylation of tertiary C–H bonds is possible at the bridgehead of bicyclo-[2.2.1]heptane (Scheme 72)[76,166]. In addition, it is noteworthy that the activation of the tertiary C–H bonds of cyclopropanes[167] and cyclobutanes[168] has been achieved.



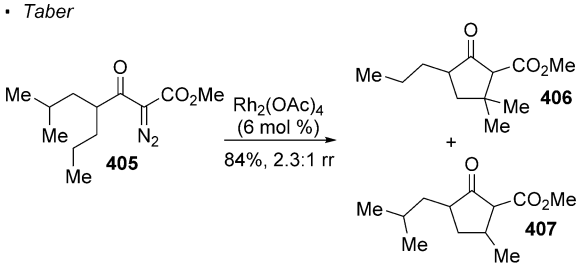
Scheme 72. Pd-catalyzed C–H activation of tertiary C–H bonds.

5.1.2. Hydrogen Atom Transfer

Hydrogen atom transfer represents a complementary approach to transition-metal catalysis. Tertiary C–H bonds are the most reactive among all types of unactivated C(sp^3)–H bonds, partly because of their relatively low bond energy. In addition, alkyl radicals are nucleophilic radicals and react well with electron-deficient radical partners.[169] The higher electron density of tertiary alkyl radicals accelerates their trapping with electron-deficient radical partners, thereby suppressing undesired side reactions. Secondary and primary C–H bonds are less reactive than their tertiary counterparts, but also can give reasonable yields. Unfortunately, the functionalization of primary C–H bonds with hydrogen atom transfer was not demonstrated in the most recent research with photoredox catalysis.[129,130,137]

5.1.3. Transfer of Carbenes

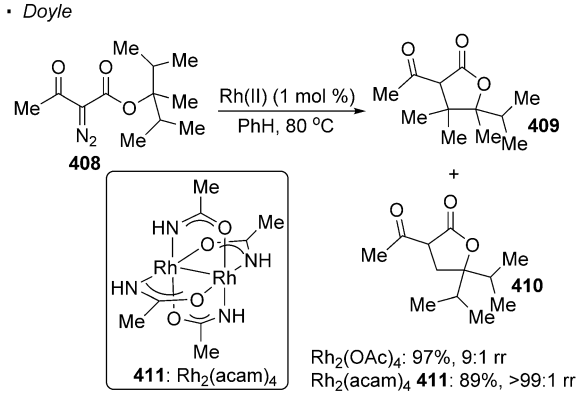
For dirhodium(II)-catalyzed carbene transfer, it is generally observed that more-electron-rich C–H bonds are more reactive. This difference in reactivity is attributed to a concerted, but asynchronous, mechanism in which the transition state has a developing positive charge at the carbon atom of the C–H bond. Therefore, tertiary C–H bonds are more reactive than the secondary or primary counterparts. Taber observed this selectivity with dirhodium(II) catalysis (Scheme 73). Treatment of α-diazo-β-keto ester **405** with the



Scheme 73. Comparison of the reactivity of secondary and tertiary C–H bonds.

$Rh_2(OAc)_4$ catalyst results in the formation of cyclopentanones **406** and **407** in a regioisomeric ratio of 2.3:1, which indicates that the tertiary C–H bonds are approximately 4.6 times more reactive than the secondary C–H bonds.[170]

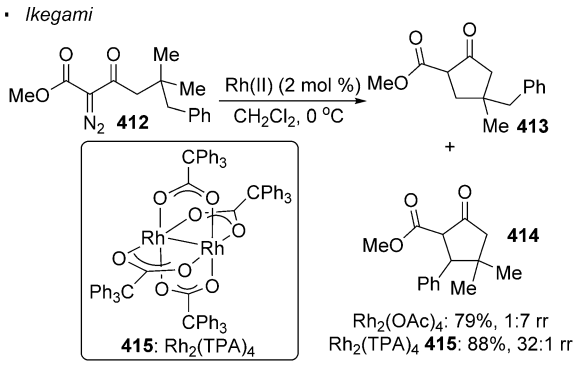
The electronic differentiation of different C–H bonds can sometimes be enhanced by the choice of a different dirhodium(II) catalyst. Scheme 74 shows that when α-diazo-



Scheme 74. Effect of the electronic properties of ligands on the regioselectivity.

β-keto ester **408** undergoes intramolecular C–H insertion with the $Rh_2(OAc)_4$ catalyst, lactone **409** is formed preferentially to lactone **410**, thus reflecting the higher reactivity of the more electron-rich tertiary C–H bonds compared to primary C–H bonds.[171] This ratio of 9:1 is improved to >99:1 with dirhodium(II) tetraacetamide ($Rh_2(acam)_4$, **411**), since dirhodium carboxamides are believed to give rise to a tighter transition state.

However, steric factors sometimes override electronic effects and become the governing factor. With $Rh_2(OAc)_4$ as the catalyst, the C–H insertion in α-diazo-β-keto ester **412** gives cyclopentanones **413** and **414** in a ratio of 1:7 (Scheme 75).[172] This product distribution follows the trend

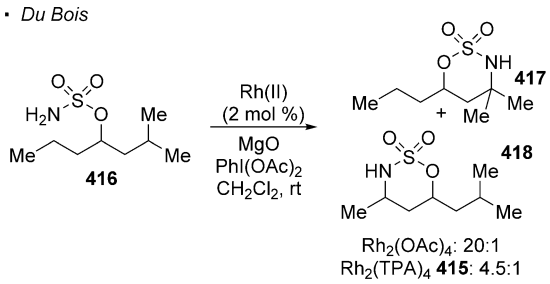


Scheme 75. Effect of the steric properties of ligands on the regioselectivity.

predicted by the electronics of the C–H bonds, since the benzyl group is more capable of stabilizing the developing positive charge in the transition state. On the other hand, when sterically bulky dirhodium(II) tetra(triphenylacetate) ($Rh_2(TPA)_4$, **415**) is employed as the catalyst, a reversal of the regioselectivity is observed and cyclopentanone **413** is formed exclusively. The sterically less hindered primary C–H bonds show a higher reactivity with the bulky dirhodium(II) catalyst in this case.

5.1.4. *Transfer of Nitrenes*

Similarly, a higher reactivity of more electron-rich C–H bonds for metal-catalyzed nitrene transfer is observed. Du Bois and co-workers found that in the intramolecular C–H bond amination of sulfamate ester **416** with $Rh_2(OAc)_4$ as a catalyst, the tertiary C–H bond is 40 times more reactive than the secondary C–H bonds, as reflected by the 20:1 ratio of products **417** and **418** (Scheme 76).[173] The same explanation for the higher reactivity of more-electron-rich C–H bonds in dirhodium(II)-catalyzed C–H amination as in C–H insertion is proposed. The product distribution can be adjusted by the choice of catalysts. A diminished 4.5:1 ratio of **418** to **418** is obtained with significantly more sterically demanding $Rh_2(TPA)_4$ (**415**).

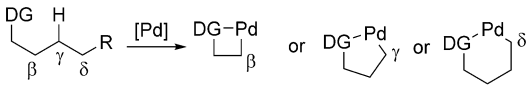


Scheme 76. Regioselectivity of the C–H amination.

5.2. *Position of C–H Bonds Relative to Directing Groups*

5.2.1. *Transition-Metal-Catalyzed C–H Activation*

The stability of the ring size of the metallacycles has a significant impact on the site-selectivity of the reactions. The formation of four-, five-, and six-membered rings is possible, with five-membered rings being the most common. The logical extension of the feasibility to form these ring sizes is that C–H bonds in the β-, γ-, δ-positions to the directing groups can potentially be activated (Scheme 77).

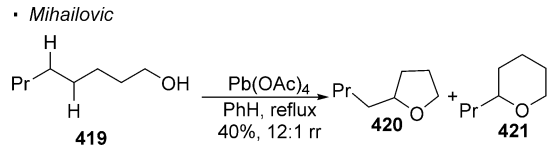


Scheme 77. Transition-metal-catalyzed activation of β-C–H, γ-C–H, and δ-C–H bonds. DG = directing group.

Sometimes the regioselectivity of transition-metal-catalyzed C–H activation is governed by the relative reactivity of different C–H bonds. As discussed earlier, for the reaction of aryl halide **21** with palladium catalysis, the methyl C–H bond is activated through the formation of a five-membered palladacycle (Scheme 4).[15] However, for aryl halide **19**, which bears one additional carbon atom, cyclopalladation takes place at the more reactive methyl C–H bond, instead of the methylene C–H bond. In this case, a six-membered palladacycle is formed preferentially to a five-membered ring. In addition, β-C–H bonds are usually activated for the functionalization of carbonyl groups.[14] However, a γ-methyl group can be activated over the less reactive tertiary β-C–H bond (Scheme 25).[53]

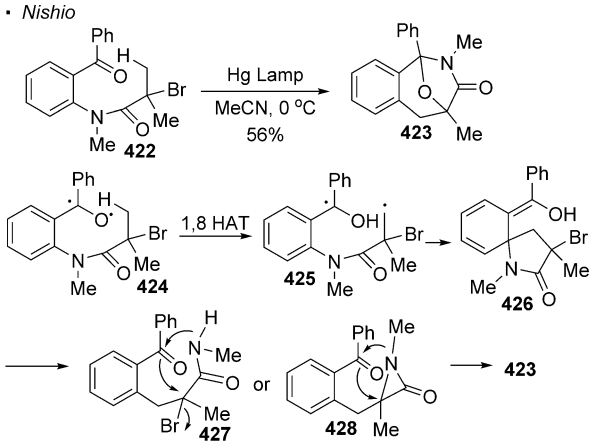
5.2.2. *Hydrogen Atom Transfer*

1,5-HAT is almost always the predominant pathway due to a favorable six-membered transition state. 1,4-HAT has never been reported to be synthetically useful for the functionalization of unactivated $C(sp^3)$–H bonds. Products from 1,6-HAT are sometimes observed in small amounts in conjunction with the 1,5-HAT products. For example, Mihailovic and co-workers observed that the ratio of 1,5-HAT to 1,6-HAT for the formation of cyclic ethers with oxygen radicals is around 12:1 (Scheme 78).[174] Long-range HAT is accompanied by a high entropy cost and is uncommon. A



Scheme 78. Predominance of 1,5-HAT.

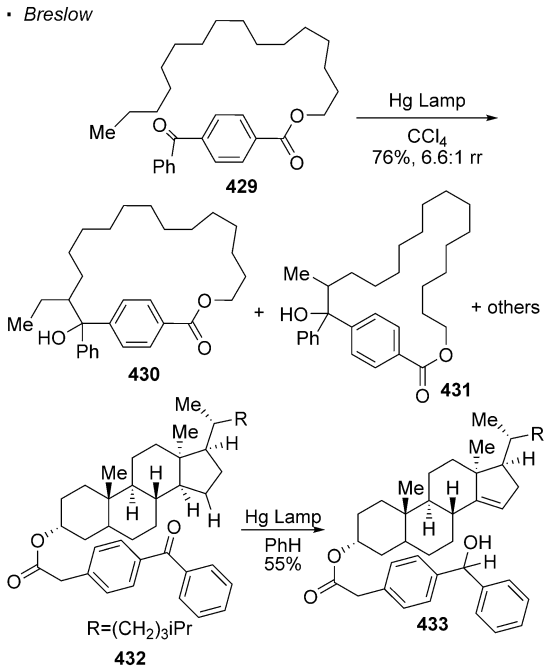
successful example has been reported by Baran and co-workers for the desaturation of aliphatic compounds (Scheme 64).[150] Another example has been reported by Nishio et al. (Scheme 79) for the synthesis of amide **423** from



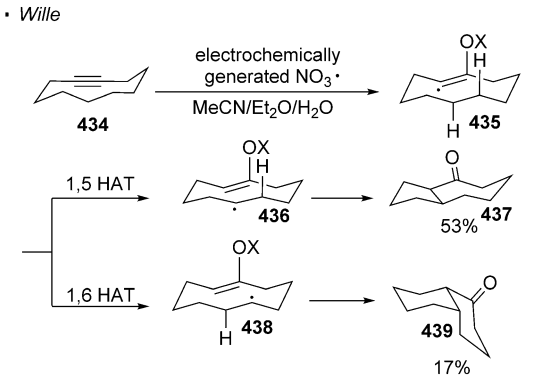
Scheme 79. 1,8-Hydrogen atom transfer.

ketone **422**.[175] Irradiation of **422** with UV light results in the formation of diradical **424**. The oxygen radical abstracts a hydrogen atom from the methyl C–H bond through 1,8-HAT, thereby leading to the formation of alkyl **425**, which cyclizes to give **426**. Amide **423** is formed via either intermediate **427** or **428**. The key to the success is the lack of hydrogen atoms for 1,5-, 1,6-, and 1,7-HAT as well as the geometry constraint imposed by the sp^2-hybridized atoms which significantly reduces the entropy cost for 1,8-HAT. Breslow et al. also investigated long-range HAT for the C–H functionalization of long hydrocarbon chains[176] and complex steroid molecules[177] (Scheme 80). In these reactions, the geometry constraint of the molecules (**429** and **432**) directs the oxygen radical to specific C–H bonds, thereby giving rise to the observed selectivity. Although this work represents a novel concept, it has not been extended to functionalize organic molecules in a general way. Overall, 1,5-HAT is the predominant pathway in the functionalization of unactivated C(sp^3)–H bonds.

The ratio of 1,5-HAT to 1,6-HAT can be adjusted by the geometry of the substrates, although this strategy lacks generality. Wille and Plath observed that the vinyl radical generated by addition of a nitrate radical to cyclooctyne (**434**) could undergo competitive 1,5- and 1,6-HAT (Scheme 81).[178] The resulting alkyl radicals **436** and **438** can add to the alkene to give either bicyclo[5.3.0]decane (**437**) or bicyclo-[4.4.0]decane (**439**). The ratio of the two products reflects

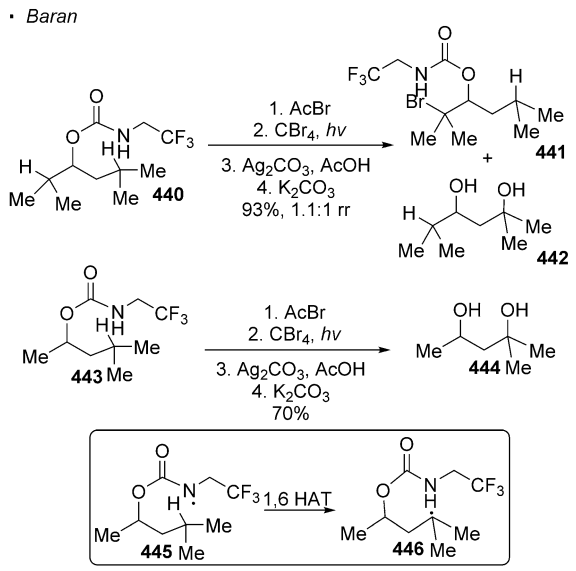


Scheme 80. Long-range HAT.

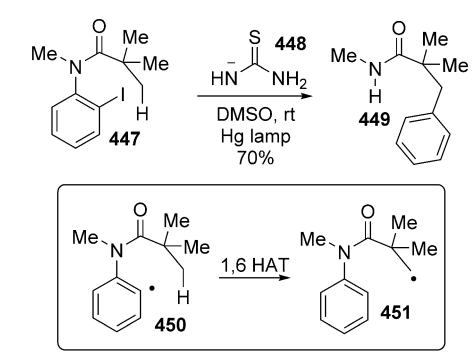


Scheme 81. Effects of geometry on 1,5- and 1,6-HAT.

a 3:1 ratio of 1,5-HAT and 1,6-HAT. Moreover, Baran and co-workers reported a HLF reaction featuring 1,6-HAT with carbamates for the synthesis of 1,3-diols (Scheme 82).[179] Possibly because of the presence of three sp^2-hybridized atoms, the relative energy of the 1,5-HAT and 1,6-HAT changes. As reflected by the 1.1:1 product ratio of **441**/**442**, 1,5- and 1,6-HAT are almost equally favorable. By disfavoring the 1,5-HAT through stronger primary or secondary C–H bonds, 1,6-HAT becomes the dominant pathway and provides access to 1,3-diol **444** from **443**. Synthetically useful transformations featuring 1,6-HAT are also possible when C–H bonds are not present for 1,5-HAT. For example, in the reaction of aryl iodide **447** carried out by Penenory and co-workers, the aryl radical **450** can abstract a hydrogen atom through 1,6-HAT to generate primary radical **451** (Scheme 83).[180] The alkyl radical adds to the aromatic ring, thereby resulting in arylation of the ε-C–H bond. In summary, synthetically useful transformations based on 1,6-HAT are



Scheme 82. 1,6-HAT favored by geometry and bond strengths.



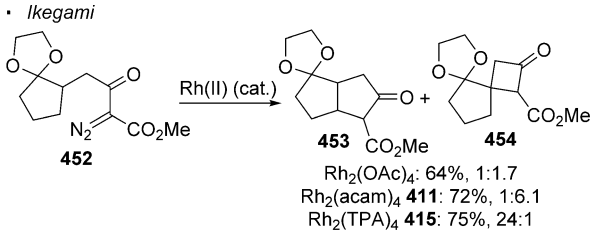
Scheme 83. 1,6-HAT in the absence of C–H bonds for 1,5-HAT.

possible if geometric or electronic bias is in place to disfavor 1,5-HAT.

Although the predominance of 1,5-HAT might appear as a limitation, it should provide a means for rational design to target a particular C–H bond from the directing group. For example, in the synthesis of oxazolines carried out by Chiba and co-workers (Scheme 46), the amine is first converted into an amidine such that the iminyl N–H bond responsible for 1,5-HAT is located at the β-position relative to the original nitrogen atom.[128] Therefore, in contrast to the HLF reaction in which the δ-position is preferentially functionalized, the β-C–H bond relative to the amine is cleaved and oxygenated.

5.2.3. *Transfer of Carbenes*

For intramolecular C–H insertion with dirhodium(II) catalysis, cyclopentanes are preferentially formed over cyclobutanes and cyclohexanes, while the formation of other ring sizes is uncommon. That is, the C–H bond that is four bonds away from the diazo functionality is usually functionalized. However, the selectivity is complicated by other factors including the electronic/steric effects of the competing C–H bonds and the choice of the dirhodium catalyst. This complication can be illustrated by the following example from Ikegami (Scheme 84). α-diazo-β-keto ester **452** under-



Scheme 84. Regioselectivity of C–H insertion.

goes intramolecular C–H insertion with a catalytic amount of $Rh_2(OAc)_4$ to give cyclopentanone **453** and cyclobutanone **454** in a ratio of 1:1.7.[181] The preference to form a five-membered ring is diminished because of the higher reactivity of the more-electron-rich tertiary C–H bond. With $Rh_2(acam)_4$ (**411**) as the catalyst, the electronic effect is reinforced and increases the selectivity for cyclobutanone **454**. On the other hand, with the bulky $Rh_2(TPA)_4$ catalyst (**415**), the reaction at the more sterically hindered tertiary C–H bond is completely shut down, thereby resulting in the exclusive formation of cyclopentanone **453**.

5.2.4. *Transfer of Nitrenes*

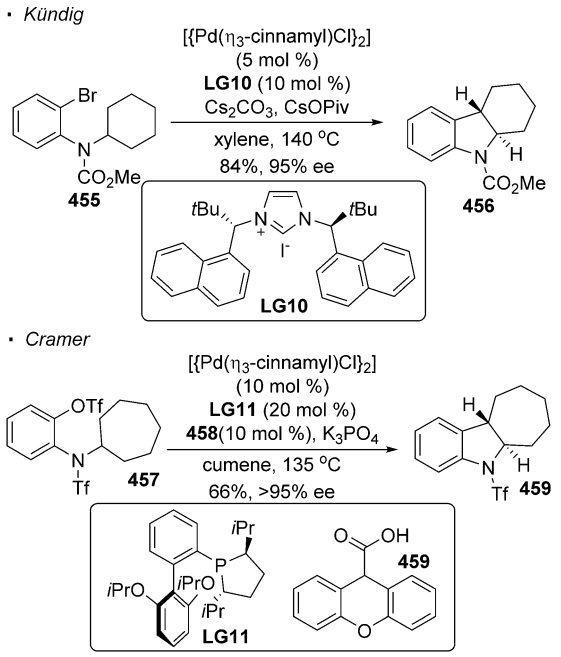
As discussed earlier for intramolecular rhodium-catalyzed nitrene transfer, the formation of five-membered and six-membered rings is the most common outcome (Scheme 67). For carbamates, five-membered oxazolidinones are the predominant product. Sulfamates and phosphoramidates show complementary selectivity and favor the formation of six-membered oxathiazines and oxazaphosphinanes.[159] The formation of other ring sizes, which involves the functionalization of C–H bonds at other positions, remains rare.

5.3. Stereochemical Control

5.3.1. *Transition-Metal-Catalyzed C–H Activation*

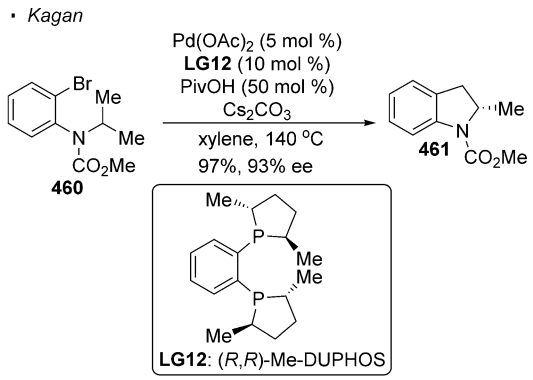
The prospect of controlling the absolute stereochemistry during transition-metal-catalyzed C–H activation has been demonstrated by various research groups. Initial reports focused on the use of aryl halides or triflates as a traceless directing group for the enantioselective formation of five-membered rings.

Kündig and co-workers first demonstrated that chiral NHC ligand **LG10** on palladium can induce asymmetry in the synthesis of tricyclic **456** from vinyl bromide **455** through the activation of a secondary C–H bond (Scheme 85).[182] Cramer and co-workers later showed that the same transformation can be achieved with chiral phosphine ligand **LG11**.[183] Thus, tricyclic **459** can be obtained from vinyl triflate **457**. For the activation of primary C–H bonds, Kagan and co-workers

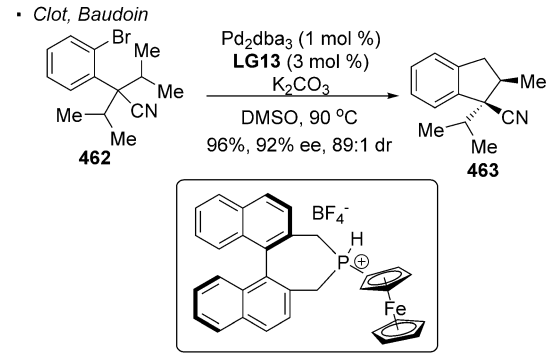


Scheme 85. Asymmetric activation of secondary C–H bonds.

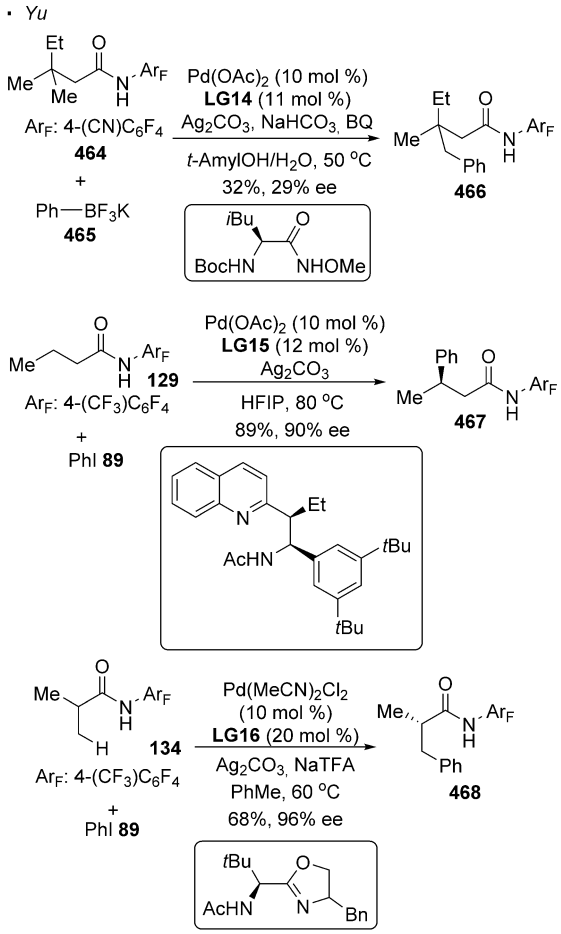
showed that the use of chiral phosphine Me-DUPHOS (**LG12**) allows for the desymmetrization of vinyl bromide **460** to access indoline **461** (Scheme 86).[184] For the synthesis of enantiomerically enriched dihydroindene **463** from vinyl bromide **462**, Clot, Baudoin, and co-workers utilized axially chiral phosphine **LG13** (Scheme 87).[185]



Scheme 86. Asymmetric activation of primary C–H bonds.



Scheme 87. Asymmetric synthesis of cyclopentanes.

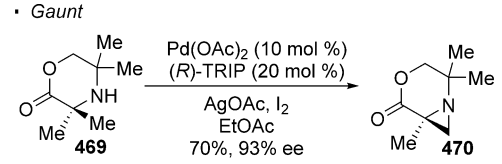


Scheme 88. Asymmetric C–H functionalization of carbonyl compounds.

The Yu research group demonstrated an enantioselective palladium-catalyzed carbonyl-directed C(sp^3)–H activation. The differentiation of the two pro-stereogenic methyl groups can be accomplished, albeit with moderate stereoselectivity in most cases, by using a modified amino acid as a chiral ligand on palladium (Scheme 88).[186] For example, in the γ-arylation of amide **464**, an *ee* value of 29% was obtained with chiral ligand **LG14**. This initial report confirms that the chiral ligands on transition metals can exert stereochemical control during carbonyl-directed C–H activation. In subsequent work, Yu and co-workers showed that a high level of stereochemical control in the arylation of secondary β-C–H bonds of carbonyl compounds can be obtained by using chiral bidentate acetyl-protected aminoethylquinoline ligand **LG15** on palladium.[187] Thus, amide **129** can be arylated to access enantiomerically enriched product **467**. In addition, the desymmetrization of amide **134** can be achieved with **LG16**, such that the new stereogenic center is established at the α-position to the carbonyl group.[188] Enantiomerically enriched

468 can undergo C–H arylation, alkynylation, alkylation, oxygenation, amination, or bromination at the methyl group through another C–H activation reaction, thus allowing access to products with various functionalities.

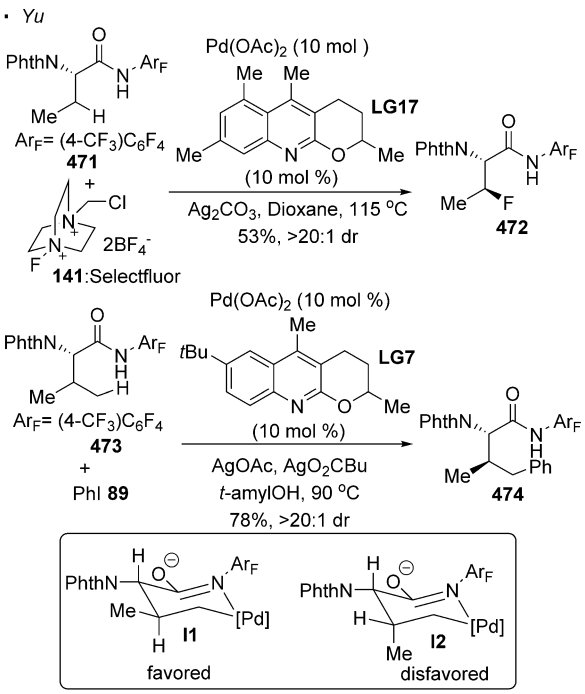
A recent report from Gaunt and co-workers indicates that the desymmetrization of sterically hindered secondary amines can lead to enantiomerically enriched aziridines when the chiral phosphoric acid TRIP is used as a chiral ligand on the palladium catalyst (Scheme 89).[189] In this case, C–H activation of a methyl C–H bond of secondary amine **469** can be accomplished to access aziridine **470**.



Scheme 89. Enantioselective aziridation.

Despite these advances, the stereochemical outcome of the activation of a C–H bond of a tertiary stereogenic center has not been studied because of the challenging formation of tertiary alkyl metal species. However, some alkyl transition metal intermediates are configurationally stable and give enantiomerically enriched products, thus suggesting the possibility of preserving the stereochemistry of a tertiary stereogenic center in transition-metal-catalyzed C–H activation.[190]

The effect of a pre-existing stereogenic center on the stereochemical outcome of metal-catalyzed C(sp^3)–H activation has been studied. A high level of diastereomeric control has been observed in some reactions of palladium-catalyzed C–H activation. In the C–H activation of carbonyl groups, the α-stereogenic centers are found to exert a large effect on the forming stereogenic center (Scheme 90). For example, the palladium-catalyzed β-fluorination of amino acid **471** proceeds with excellent diastereoselectivity to afford **472**.[65] In addition, a high level of stereochemical control is observed in the γ-arylation of amino acids, as exemplified by the functionalization of amide **473** to afford arylated **474**.[75] To account for the observed diastereomer in this reaction, the cyclic six-membered alkyl-palladium intermediate **I1**, which places both the NPhth and the methyl groups at equatorial positions, is proposed. The key to success in achieving high diastereoselectivity in transition-metal-catalyzed C–H activation is a cyclic intermediate that enforces a conformational bias to favor one of the diastereomers.

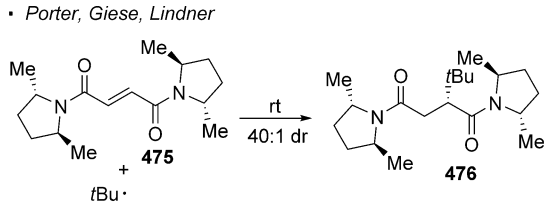


Scheme 90. Diastereoselective C–H activation.

5.3.2. *Hydrogen Atom Transfer*

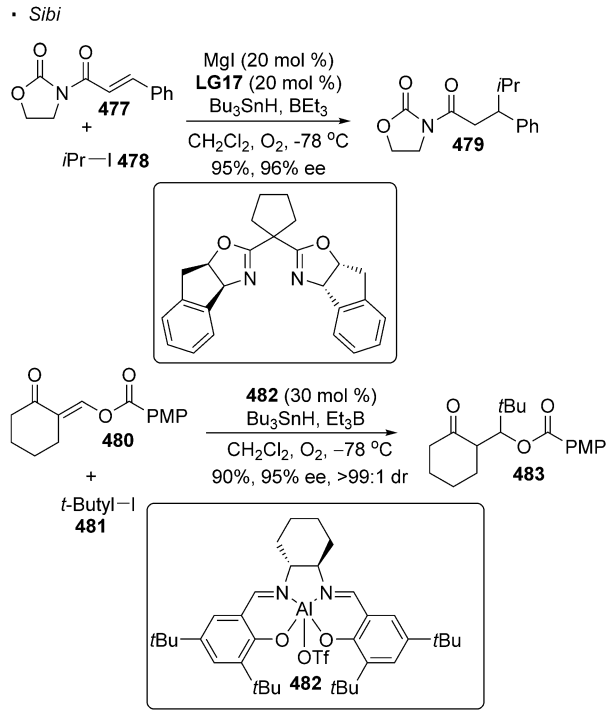
Asymmetric variants of hydrogen atom transfer transformations have not yet been developed. However, previously established asymmetric reactions of alkyl radicals generated by other means suggest the possibility of such a control.

One potential strategy to render a reaction with hydrogen atom transfer asymmetric is to employ a chiral auxiliary. The successful application of a chiral auxiliary in the intermolecular addition of alkyl radicals was disclosed by Porter, Giese, Lindner et al. (Scheme 91).[191] They found that a *tert*-butyl radical can add to chiral electrophilic alkene **475** with excellent diastereoselectivity. Hydrolysis of the two amides provides an enantiomerically enriched compound.



Scheme 91. Use of a chiral auxiliary in reactions of alkyl radicals.

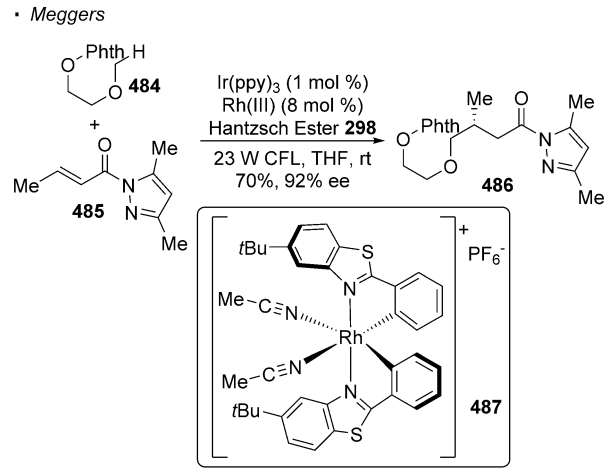
The use of a chiral Lewis acid could potentially serve as an alternative strategy for enantioselective C–H functionalization with hydrogen atom transfer. Since alkyl radicals are nucleophilic, the increase in the electrophilicity of the radical partner leads to a higher rate of radical addition.[169] This opens the possibility of using a chiral Lewis acid to activate a radical partner. Sibi and Ji reported that the addition of isopropyl radical to electrophilic alkene **477** proceeds with an excellent level of stereochemical control in the presence of a chiral bisoxazoline-ligated magnesium catalyst (Scheme 92).[192] In addition, the *tert*-butyl radical adds to vinylogous ester **480** with excellent enantio- and diastereoselectivity in the presence of a sub-stoichiometric amount of chiral aluminum(III) complex **482**.[193] The use of a chiral Lewis acid for the functionalization of unactivated C(sp^3)–H



Scheme 92. Lewis acid catalyzed asymmetric addition of alkyl radicals.

bonds has not been explored, although Meggers and co-workers recently applied this concept to functionalize C(sp^3)–H bonds activated by oxygen (Scheme 93).[194] In this case, an oxygen radical is generated from an N–O bond and is used to abstract a hydrogen atom from the C–H bond, as in the system developed by Chen and co-workers.[137] The addition of the radical to electrophilic alkene **485** is mediated by chiral Rh^{III} catalyst **487**. It is likely that this strategy can be extended to systems involving unactivated C(sp^3)–H bonds.

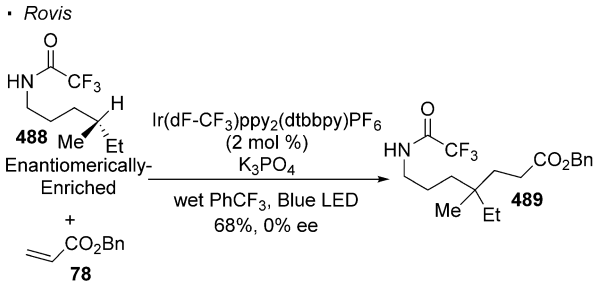
It should be noted that the newly formed stereogenic centers in the reactions of alkyl radicals are thus far at the radical trap but not at the carbon atom of the alkyl radical. Transformations that successfully differentiate two prochiral



Scheme 93. Use of a chiral Lewis acid in HAT.

hydrogen atoms or groups in the substrate with an alkyl radical remain to be developed.

Consistent with other radical reactions, when a hydrogen atom from a stereogenic center is abstracted, the resulting alkyl radical is not configurationally stable. Consequently, the integrity of the stereochemistry is lost. For example, when Chu and Rovis examined the use of enantiomerically enriched substrate **488** for a nitrogen-directed C–C bond formation at unactivated C(sp^3)–H bonds, the alkylated product **489** was obtained as a racemic mixture (Scheme 94).[129]



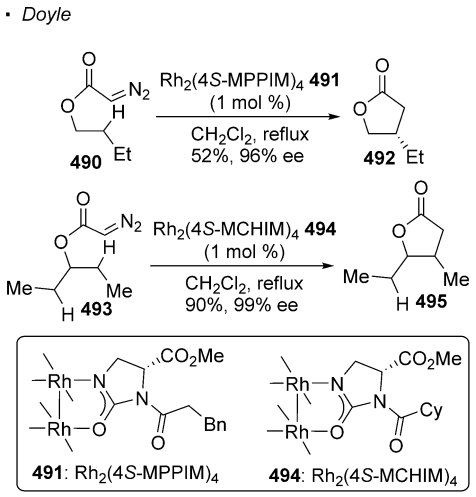
Scheme 94. Loss of stereochemistry in HAT.

A highly diastereoselective reaction with chiral substrates would be nontrivial. The influence of a pre-existing stereogenic center in the substrate is expected to be small on any forming stereogenic center. In contrast to transition-metal catalysis, which typically involves metalacyclic intermediates, the alkyl radical intermediate exists in acylic forms and has no conformational constraints. Therefore, the possibility that a pre-existing stereogenic center in the chiral substrate can control the stereochemical outcome of the reaction is slim.

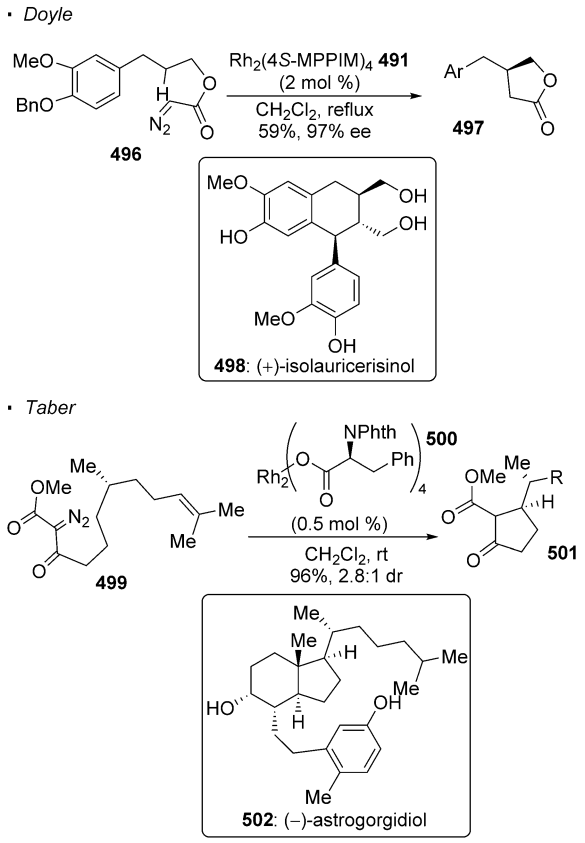
5.3.3. Transfer of Carbenes/Nitrenes

Asymmetric metal-catalyzed carbene transfer is well-established. Doyle and co-workers developed novel chiral dirhodium catalysts for the enantioselective synthesis of five-membered lactones through C–H insertion. The use of Rh_2(4*S*-MPPIM)$_4$ (**491**) allows γ-lactone **492** to be obtained from acyclic diazo ester **490** with high enantioselectivity (Scheme 95).[195] Doyle et al. also showed that two prochiral alkyl groups can be differentiated with Rh_2(4S-MCHIM)$_4$ (**494**). Thus, desymmetrization of diazo ester **493** provides highly enantiomerically enriched γ-lactone **495**.[196] The application of asymmetric C–H insertion has been demonstrated by Doyle and co-workers in the synthesis of natural product (+)-isolauricerisinol (**498**; Scheme 96).[195] Diazo ester **496** undergoes an enantioselective dirhodium-catalyzed intramolecular C–H insertion to yield γ-lactone **497**, which is further elaborated to afford the natural product. In addition, Taber and Malcolm used chiral dirhodium(II) catalyst **500** to favor the formation of the desired diastereomer **501** through C–H insertion of **499** for the synthesis of (−)-astrogorgiadiol (**502**).[197]

Only molecules with activated C(sp^3)–H bonds (i.e. allylic or benzylic) are competent substrates for enantioselective



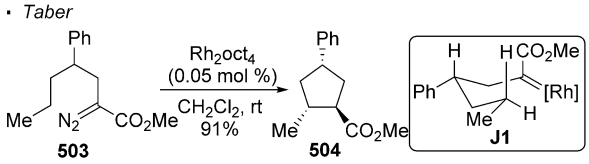
Scheme 95. Asymmetric C–H insertion.



Scheme 96. Applications of asymmetric C–H insertion.

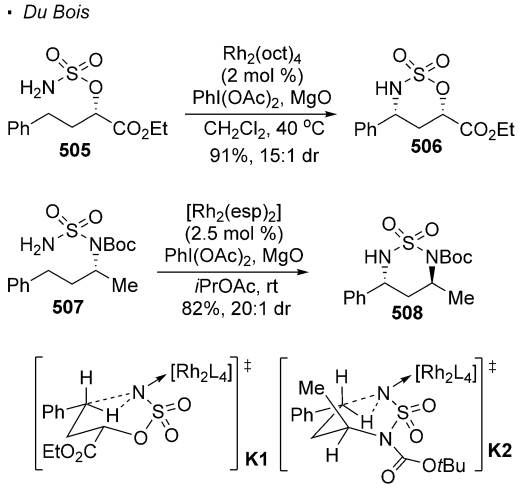
nitrene transfer. This is exemplified by reports from the groups of Che,[198] Davis,[199] and Du Bois.[200] A highly enantioselective asymmetric intramolecular nitrene transfer to unactivated C(sp^3)–H bonds remains to be developed.

Similar to transition-metal catalysis, but in contrast to radical reactions, the cyclic transition state for intramolecular carbene/nitrene transfer provides an opportunity for a pre-existing stereogenic center to communicate effectively with a forming one. Thus, a high level of diastereomeric control is sometimes observed. For example, in the intramolecular C–H insertion of α-diazo ester **503**, Taber et al. observed that cyclopentane **504** is obtained with excellent diastereoselectivity (Scheme 97).[201] A simple cyclic five-membered transition state (**J1**) that places both the phenyl and methyl groups at pseudoequatorial positions is proposed to account for the observed diastereomer.



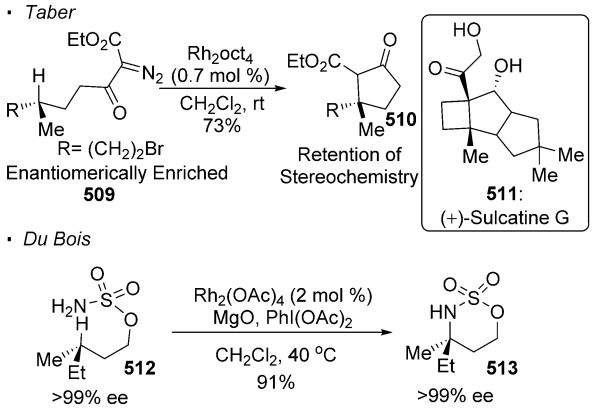
Scheme 97. Diastereoselective C–H insertion.

An example of a highly diastereoselective intramolecular nitrene transfer has been reported by Du Bois and co-workers (Scheme 98). The intramolecular C–H amination of sulfamate **505** with Rh_2oct_4 proceeds with excellent diastereoselectivity.[202] Again, a cyclic transition state (**K1**) with all the substituents in the pseudoequatorial positions is invoked. The opposite diastereomer can be obtained when sulfamide **507** is employed as the substrate.[203] In this case, the methyl group is placed in the pseudoaxial position to minimize $A^{1,3}$ strain with the NBoc group in transition state **K2**.



Scheme 98. Diastereoselective C–H amination. esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropinoate.

With a tertiary stereogenic center, retention of stereochemistry is observed for both dirhodium(II)-catalyzed intramolecular carbene or nitrene transfer (Scheme 99). In the synthesis of (+)-sulcatine G by Taber and Frankowski, a Rh_2oct_4-catalyzed C–H insertion reaction of enantiomerically enriched α-diazo-β-keto ester **509** gives the desired cyclopentanone **510** with complete retention of stereochemistry.[204] Similarly, Du Bois and co-workers observed that the intramolecular C–H amination of chiral sulfamate ester **512**



Scheme 99. Retention of stereochemistry in C–H insertion and amination.

under dirhodium(II) catalysis proceeds without any sign of racemization in product **513**.[205] In both dirhodium(II)-catalyzed C–H insertion and amination, the stereochemical outcome can be explained by the aforementioned concerted, but asynchronous, mechanism.

5.4. Scope of Functional Groups

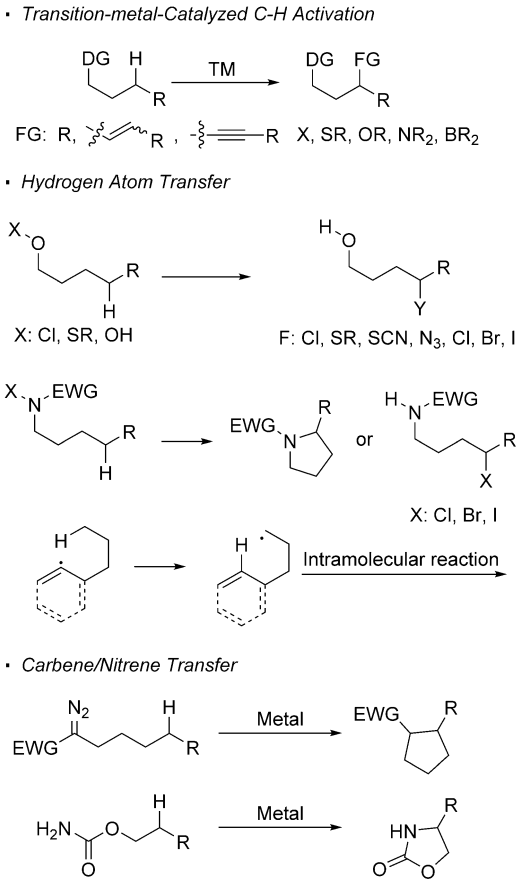
The relative breadth of the scope of the three strategies is reflected by the content of this Review.[206] As discussed in the following, transition-metal-catalyzed C–H activation allows a wide variety of functionalities to be incorporated into C(sp^3)–H bonds (Scheme 100). For hydrogen atom transfer, the scope is limited by the traditional ways to generate the reactive radicals capable of abstracting hydrogen atoms, but the application of photoredox catalysis has shown promising results in extending the scope of this strategy (Scheme 101). For carbene and nitrene transfer, only C–C and C–N bond formation is possible, which are arguably the two most common and most important types of bonds.

5.4.1. Transition-Metal-Catalyzed C–H Activation

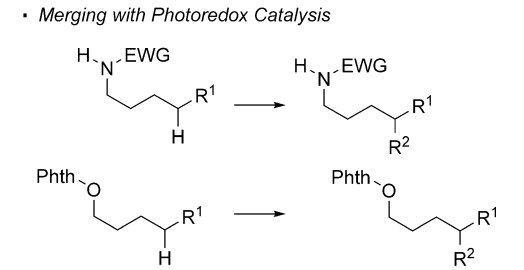
As illustrated in the representative examples in Section 2.1, transition-metal-catalyzed activation provides a means for the formation of various bonds at the unactivated C(sp^3)–H bonds. With the appropriate choice of reaction partners, the formation of C(sp^3)–C(sp^3), C(sp^3)–C(sp^2), C(sp^3)–C(sp), C(sp^3)–O, C(sp^3)–N, C(sp^3)–F, C(sp^3)–S, and C(sp^3)–B bonds is possible. Currently, transition-metal catalysis demonstrates the broadest scope among all the strategies for C–H functionalization.

5.4.2. Hydrogen Atom Transfer

The strategy of hydrogen atom transfer is traditionally limited in the scope of functional groups that can be incorporated at inert C–H bonds. However, the development of photoredox catalysis has significantly advanced the scope.



Scheme 100. Scope of different strategies.



Scheme 101. Broadened scope with photoredox catalysis for HAT.

Except for one example in which C–H oxygenation is achieved,[128] only halogenation or intramolecular amination of unactivated C(sp^3)–H bonds could be realized with nitrogen radicals before recent reports from the groups of Rovis[129] and Knowles[130] (Scheme 47). The incorporation of other functionalities at C–H bonds is challenging, mainly because the trapping of the alkyl radical with a radical couple is often hindered by 1) the presence of other radicals which are formed simultaneously with the nitrogen radicals or 2) the presence of an oxidant that oxidizes the alkyl radical to a carbocation that leads to cyclization with the nitrogen atom. The keys to the success of the photocatalytic systems developed by Rovis and Knowles are 1) the use of an N–H bond as the nitrogen radical precursor that avoids the formation of another radical species that would interfere

with the alkyl radical, and 2) the absence of a stoichiometric amount of a strong oxidant, which would oxidize the alkyl radical to a carbocation. These features of the reactions allow the alkyl radicals to be trapped by an external electrophilic alkene, thus allowing for the formation of a carbon–carbon bond.

With oxygen radicals, the formation of various functional groups at a C–H bond is possible only when the alcohol is preactivated through the formation of O–O or O–S bonds. This preactivation step is not trivial, and O–O or O–S bonds are difficult to handle, thus limiting the practicality and feasibility of the use of oxygen radicals. On the other hand, Chen and co-workers demonstrated that the use of photoredox catalysis allows the alkylation of C–H bonds to be accomplished with an easily prepared and stable N–O bond as a precursor of an oxygen radical (Scheme 53).[137]

Only intramolecular reactions or the oxidation of alkyl radicals generated with aryl or vinyl radicals by intermolecular HAT have been demonstrated. Trapping of the alkyl radicals with external reaction partners has not yet been realized. It is not surprising when the methods to generate the vinyl or aryl radicals are considered. These radicals are typically generated in the presence of Bu_3SnH, which can reduce alkyl radicals. Therefore, the desired reaction between the alkyl radical and an external radical couple must outcompete the reduction of the alkyl radical by Bu_3SnH. Recently, novel procedures appear to have been developed to generate aryl or vinyl radicals with photoredox catalysis.[207] These methods obviate the use of Bu_3SnH and might offer a solution to address the limited scope of the C(sp^3)–H functionalization with aryl radicals.

5.4.3. *Transfer of Carbenes/Nitrenes*

Metal-catalyzed carbene/nitriene transfer allows intramolecular C–H insertion or amination for the formation of five- or six-membered carbocycles and heterocycles. These products can sometimes be hydrolyzed to give acyclic molecules, thereby allowing access also to acyclic molecules. However, the functionalities that can be incorporated into the substrates are very limited. Only C–C and C–N bonds can be formed. This limited scope represents a drawback of metal-catalyzed carbene/nitrene transfer.

6. Summary and Outlook

Each of the three main strategies for the activation of unactivated C(sp^3)–H bonds—transition-metal-catalyzed C–H activation, hydrogen atom transfer, and metal-catalyzed transfer of carbenes/nitrenes—has its own strengths and limitations. It is likely that future efforts will be devoted to address the limitations associated with each strategy, thus broadening the scope of C–H functionalization.

Transition-metal-catalyzed C–H activation is a growing research area. Currently, palladium is the most versatile metal catalyst, while other noble metals sometimes give novel reactivity that deviates from that of palladium. Future efforts will certainly be invested to replace these noble metals with earth-abundant metals, as well as to develop new reactivity with earth-abundant metals. In addition, the latest research has underscored the possibility of asymmetric catalysis, and there is undoubtedly more to come. The activation of unactivated tertiary C–H bonds has shown promising initial results in stoichiometric studies. The development of new directing groups might allow for the activation of the wealth of C–H bonds that are currently not possible.

The research on hydrogen atom transfer had stagnated until the recent development of photoredox catalysis. Initial efforts that incorporated photoredox catalysis into the realm of hydrogen atom transfer have already benefited the functionalization of unactivated C(sp^3)–H bonds. In particular, this merged strategy has allowed the first C–C bond-formation reaction with nitrogen radicals and the use of a simple N–H bond as a radical precursor. Photoredox catalysis will probably dominate research in this direction for the foreseeable future and lead to a wider scope of functionalities that can be incorporated into C(sp^3)–H bonds, thereby obviating/simplifying the prefunctionalization of O–H and N–H for the generation of the radicals. Similar to transition-metal catalysis, more enantioselective reactions remain to be developed and the use of new directing groups should lead to the functionalization of C–H bonds that cannot be targeted with current methodology.

Current research on the transfer of carbenes/nitrenes during the functionalization of unactivated C(sp^3)–H bonds mainly focuses on intermolecular reactions.[208] There have not been many efforts devoted to improving the intramolecular variant, the focus of this Review. However, considering the reliability of intramolecular C–H insertion and amination, this strategy could still find applications in the synthesis of complex natural products or other molecules.

While transition-metal-catalyzed C–H activation, hydrogen atom transfer, and the transfer of carbenes/nitrenes represent three powerful strategies for directed C(sp^3)–H functionalization, they are distinct in terms of the reactivity of different C–H bonds, positions of reacting C–H bonds relative to the directing groups, stereochemical outcome, and the scope of functional groups that can be incorporated. Thus, these strategies are complementary to each other and together provide powerful tools in the synthetic arsenal.

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Conflict of interest

The authors declare no conflict of interest.

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