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Complementary Strategies for Directed sp³ C-H Functionalization: A Comparison of Transition-Metal Catalyzed Activation, Hydrogen Atom Transfer and Carbene/Nitrene Transfer

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Abstract

sp^3 C-H bond functionalization streamlines chemical synthesis by allowing the use of simple molecules and providing novel synthetic disconnection. Due to recent intense efforts devoted to develop new reactions based on the approach of C-H functionalization, its benefits in molecule derivatization and complex molecule synthesis have been recognized. This article discusses the strength and weakness of three main approaches, transition-metal catalyzed C-H activation, 1, n hydrogen atom transfer and transition-metal catalyzed carbene/nitrene transfer, for directed functionalization of unactivated sp^3 C-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 literature. The aim of this review is to provide guidance for users of C-H functionalization reactions and inspire future research in this area.

Graphical Abstract

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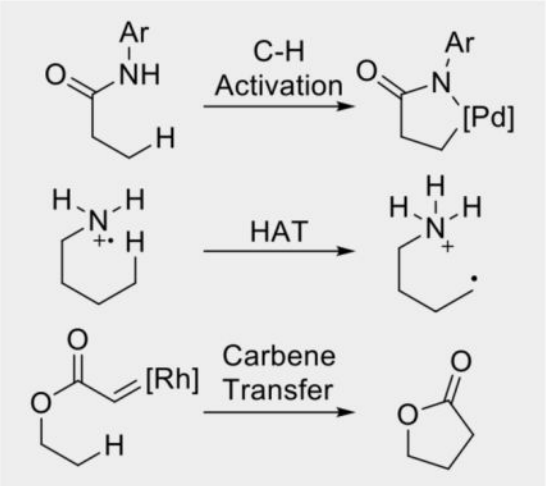
Dedicated to Professor Al Padwa on the occasion of his 80th birthday



Keywords

C-H functionalization; transition metal; hydrogen atom transfer; carbene; nitrene

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 methodology. Maturation of this technology[1] would lead to novel means to disconnect a molecule in retrosynthetic analyses and thus potentially provides more efficient synthetic routes from simple starting materials.

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

In most cases, the key to breaking inert sp^3 C-H bonds and to address selectivity is the employment of a directing group (Fig. 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 directed functionalization of unactivated sp^3 C-H bonds. The focus will be to compare and contrast the three strategies and discuss their complementarity in hopes that this review article will serve as a guide for users of directed C-H functionalization reactions, as well as for synthetic chemists to develop new transformations. In this review, unactivated 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, while there is significant advance in undirected sp^3 C-H functionalization in recent years, it is beyond the scope of this review. Readers who are interested in undirected sp^3 C-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 proximity of a specific C-H bond, lowering the energy barrier of 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 sp^2 C-H bonds are in general stronger than their sp^3 counterparts, it might appear that the activation of sp^3 C-H bonds is less challenging. The literature suggests the opposite trend. In addition to the ubiquity of sp^3 C-H bonds, this observation could be explained by the relative bond strength of the metal-carbon bonds. In general, a metal-sp^3 bond is weaker than a metal-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 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 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 is a brief review on seminal reports on sp^3 C-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.

2.1. Palladium Catalysis[7]

2.1.1 Early Work—A seminal report from Dyker described Pd(II)-catalyzed synthesis of benzocyclobutene **7** from aryl iodide **5** and aryl bromide **6** featuring the activation of methyl C-H bonds (Scheme 2).[8] In the proposed catalytic cycle, Pd(0) oxidatively adds to the C-I bond to form aryl Pd(II) intermediate **A1**. This oxidative addition brings the palladium catalyst close to the methyl group, 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**, 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 future development of C-H activation reactions.

Three other seminal reports on palladium catalyzed sp^3 C-H activation, using nitrogen as directing groups, were contributed by Sanford, Yu and Daugulis. Sanford reported a palladium-catalyzed nitrogen-directed sp^3 C-H oxygenation. This work was inspired by related stoichiometric studies by others[9] and her previous work on the activation of sp^2 C-H bonds (Scheme 3).[10] Nitrogen, in the forms of imines and pyridines, was previously established as a competent directing group for acetoxylation of sp^2 and benzylic sp^3 C-H bonds with $Pd(OAc)_2$ as the pre-catalyst and $PhI(OAc)_2$ as the stoichiometric oxidant. For instance, imine **8** undergoes acetoxylation to form **9**. Based on this established protocol, Sanford developed an oxime-directed acetoxylation of unactivated primary C-H bonds.[11] It is believed that after the coordination of the oxime nitrogen 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 found that pyridine can also be applied as a directing group for acetoxylation of primary C-H bonds, as illustrated by the conversion of pyridine **12** to **13**. Yu[12] reported palladium(II)-catalyzed iodination of unactivated primary sp^3 C-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 discovered that picolinamides can serve as a bidentate ligand for palladium-catalyzed C-H activation.[14] In this report, unactivated sp^3 C-H bonds are arylated with aryl iodides. For instance, picolinamide **16** can be arylated at the methyl C-H bond to yield **18**. It is noteworthy that this work 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 different groups.

2.1.2 Functionalization with Different Directing Groups

(I) Aryl/Vinyl Halides: Various groups were inspired by reports from Dyker to use aryl halides or triflates as a traceless directing group. Baudoin 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*-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** bearing one less carbon between the linker and the methyl C-H bond, the presence of a benzylic quaternary carbon 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 showed that these putative palladium-alkyl intermediates can be intercepted by aryl boronic acids [16] or anilines, [17] resulting in arylation or amination of the methyl C-H bonds (Scheme 5). Thus, the arylated product **25** can be obtained from aryl bromide **23** and boronic acid **24**, while the aminated product **28** arises from aryl bromide **26** and aniline **27** respectively. However, these reactions are only applicable to substrates bearing substitutions at 2, 4 and 6 positions relative to the halogen. The key to the success of these reactions are the sterics provided by these substituents to disfavor Suzuki cross-coupling and Buchwald-Hartwig amination.

As demonstrated by reports from Fagnou, in contrast to Baudoin's cyclobutene synthesis, 5-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** is reported by Fuji and Ohno.[19] In this reaction, the presence of a quaternary carbon 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 and Baudoin for the synthesis of cyclopentanes **34a** and **34b** from aryl chloride **33**.[20]

Baudoin 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 further demonstrated that α-bromo acrylamide **37** is also a competent substrate in this chemistry and showed that monocyclic pyrrolidine derivatives can be obtained from acyclic precusors.[22] The mechanism of these transformations is believed to be the same as in the case of aryl halides.

In all previously discussed examples, the putative aryl palladium(II) intermediates prior to the activation of sp^3 C-H bonds are generated from aryl or vinyl halides. On the contrary, Fagnou showed that sp^2 C-H activation of pivaloylpyrrole **39** can generate the aryl palladium species **D1**, which can undergo sp^3 C-H activation to form 6-membered palladacycle **D2** (Scheme 8).[23] Similar to previous examples, reductive elimination results in the formation of a 5-membered ring. In addition, as demonstrated by Minami and Hiyama, silylethynyl aryl ether **41** undergoes palladium-catalyzed intramolecular hydroalkylation featuring the activation of one of the methyl C-H bonds.[24] In the proposed mechanism, the vinyl palladium intermediate **E2**, prior to C-H activation of the methyl C-H bond, is formed from the addition of PivOH across the alkyne in Pd(0) complex **E1**.[25] The 7-membered palladacycle **E3** generated through C-H activation undergoes reductive elimination to give the observed product **42**.

(II) Oximes: After the seminal work by Sanford, more reactions with oximes as a directing group have appeared. Yu and Che reported palladium-catalyzed oxime-directed C-H amidation (Scheme 9).[26] In this protocol, an amide or a sulfonamide is employed as a nitrogen source and potassium persulfate ($K_2S_2O_8$) as an oxidant. Thus, the methyl C-H bond of **43** can be amidated with trifluoroacetamide **44** to afford **45**. With the use of

diphenyliodonium salt **47**, Chen accomplished C-H arylation of oxime **46** to give **48** (Scheme 9).[27]

(III) Pyridines: For the functionalization of pyridines, in addition to the aforementioned oxygenation by Sanford, formation of C-C bonds is also possible. Daugulis[28] and Yu[29] independently disclosed pyridine-directed arylation and alkylation of primary C-H bonds (Scheme 10). Sanford demonstrated that electrophilic alkenes can be installed at a primary C-H bond adjacent to a pyridine.[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. β-H elimination results in a net incorporation of the electrophilic alkene into the methyl C-H bond. The pyridine nitrogen can then cyclize onto the alkene through aza-Michael addition to yield the bicyclic pyridinium. Further manipulation yields valuable bicyclic amines.

(IVa) Amines (Amides): In most cases for the functionalization of amines, an electron-withdrawing group is installed on the nitrogen to generate a directing group for C-H activation. Daugulis first demonstrated that bidentate picolinamides can serve as a directing group for palladium(II)-catalyzed C-H functionalization of amines (Scheme 3). Since then, the incorporation of different functionalities at unactivated primary C-H bonds with the same picolinamide directing group has been developed by various groups (Scheme 11). The key to success is the appropriate choice of a reaction partner that is used to trap the putative alkyl-palladium intermediates. For instance, by switching an aryl iodide to an alkyl iodide, Chen developed a protocol for the alkylation of the C-H bond in **56**.[31] Both Daugulis[32] and Chen[33] observed that when $PhI(OAc)_2$ is applied as an oxidant, intramolecular C-H amination takes place, resulting in the synthesis of 4- or 5-membered nitrogen heterocycles **60** or **64**. The ring size depends on the distance between the primary C-H bond and the nitrogen. Chen also realized that when an alcohol is used as a co-solvent, there is a switch in chemo-selectivity and intermolecular C-H oxygenation becomes the predominant pathway.[34] Thus, methoxylation of amide **61** takes place to give **62** when methanol is applied as a solvent. In addition, Z.-J. Shi and B.-F. Shi reported the coupling of amides and diboron esters [35] or alkynes[36] at unactivated C-H bonds respectively. These protocols allow for the borylation or alkenylation of the primary C-H bonds of picolinamides **65** and **68**.

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

(IVb) Amines (Sulfonamides): Yu reported that primary C-H bonds can be arylated with aryl boronic acids after installing a sulfonyl group on amines, as exemplified by the arylation of boronate ester **75** of trifluoromethanesulfonamide **74** (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.

(IVc) Amines (Free Amines): Sometimes pre-functionalization of amines is not required before the C-H activation step and a free amine can serve as a directing group. Gaunt reported the synthesis of strained aziridines (**81**) from bulky secondary amines (**80**) featuring the formation of a 4-membered palladacycle through nitrogen directed cleavage of a primary C-H bond (Scheme 14). [40] Oxidation of Pd(II) to Pd(IV) by $PhI(OAc)_2$ drives reductive elimination, as in Sanford and Yu's reaction, 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 5-membered palladacycle. Initially, only sterically hindered secondary amines were competent substrates since it is believed that the sterics of the amines was needed to disfavor the formation of an off-cycle bis(amine)Pd(II) complex. [41] Subsequent work showed with $AdCO_2H$ and benzoquinone as additives, even non-bulky secondary amines can be used as substrates to synthesize β-lactams. [42] The putative 4-membered palladacycle can also be intercepted by aryl boronic acids, resulting in net arylation of the C-H bonds.[43] With amine **84**, arylated product **85** can be accessed. When the methyl is an additional bond away from the nitrogen, C-H activation still occurs at the primary C-H bond. Thus, the methyl group in protected amino-alcohol **86** undergoes acetoxylation with $Pd(OAc)_2$ 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 *insitu* to obviate the need to pre-functionalize the amine before the C-H activation step. 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 palladium-catalyzed activation of unactivated sp^3 C-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 is 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, in Yu's report, even cyclic substrates, such as cyclohexyl amine **96**, can be derivatized.

(IVd) Amines (Hydrazones): Dong reported that hydrazones can be installed on sulfonamides and serve as a directing group for sp^3 C-H activation (Scheme 16). [48] Thus, 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.

(Va) Carbonyl Groups (8-aminoquinoline amides): The functionalization of carbonyl compounds with palladium-catalyzed sp^3 C-H activation is the most explored and well-developed. In most cases, it is the β C-H bonds of the carbonyl compounds that are functionalized. Daugulis first observed that 8-aminoquinoline amides can serve as a directing group for this purpose, where 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 due to the contributions of different research groups. For the formation of C-C bonds, alkylation of **103**, alkynylation of **106**, and alkenylation of **109** and **101** were developed by Daugulis, [49] Tobisu and Chatani, [50] Chen[51] and Rao [52] respectively. The geometry of vinyl iodide **110** is preserved in Chen's system for the alkenylation of amide **109**.

In addition to C-C bonds, reactions for the incorporation of various heteroatoms at the β-position have been developed (Scheme 18). Corey's system for C-H acetoxylation of **114** relies on the use of oxone as an oxidant. [53] Besset applies *N*-thiotrifluoromethylphthalimide **117** as an oxidant to achieve C-H thiotrifluoromethylation of **116**. [54] With sodium salts of arylsulfonates as a sulfur source and Ag_2CO_3 as an external oxidant, Shi developed a protocol for C-H sulfonylation. [55] Kuninobu and Kanai showed that C-H silylation of **121** can be achieved with disilane **122**.[56] As demonstrated by Xu, the use of NFSI as an electrophilic fluorine source results in C-F bond formation at the unactivated C-H bonds.[57] To incoporate other halogens at the β-position, Rao modifies 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, is used to realize C-H chlorination and bromination with NCS or NBS respectively, to afford halogenated **126**.

(Vb) Carbonyl Groups (perfluorinated amides): In addition to 8-aminoquinoline, perfluorinated amides are a versatile directing group for β functionalization of carbonyl compounds. With 2,3,5,6-tetrafluoro-4-trifluoromethylbenzamide as a directing group, Yu developed protocols that allow the incorporation of various functionalities at unactivated sp^3 C-H bonds (Scheme 19). For C-C bond formation, 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] can be achieved. In these reactions, amides with or without α substitution are competent substrates, providing a method to functionalize both natural or unnatural amino-acids.

Using the same directing group, the formation of C-C bonds can be applied to the synthesis of nitrogen-heterocycles with an appropriate choice of reaction partners (Scheme 20). When electrophilic benzyl acrylate **78** is employed, olefination of the C-H bond in amide **134** is followed by aza-Michael addition, affording 5-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 6-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). Using hydroxylamine **139** as an electrophilic nitrogen source, the intermolecular C-H amination of amide **138** yields aminated **140**. [64] When the palladium alkyl intermediate is trapped with Selectfluor **141**, a fluorine atom can be incorporated into the C-H bond of amide **127**.[65] Borylation can be realized with B_2pin_2 to afford amide **143**.[66] The resulting C-B bond can be converted to 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.

(Vc) Carbonyl Groups (O-Methyl Hydroxamic Acids and Carboxylic acids): To provide an alternative method to functionalize carboxylic acid derivatives, Yu pioneered the use of *O*-methyl hydroxamic acids and free carboxylic acids as the directing groups (Scheme 22). The initial report from Yu allows arylation or alkylation of primary C-H bonds β to *O*-methyl hydroxamic acids[67] and carboxylic acids[68] bearing α quaternary centers. An improved protocol established from the same group tolerates the presence of α C-H bonds of *O*-methyl hydroxamic acids[69] and carboxylic acids. [70] Thus, amino acids 1**45** and **147** can be derivatized using *O*-methyl hydroxamic acids and carboxylic acids as a directing group.

(Vd) Carbonyl Groups (Peptides): Yu demonstrated that peptides can be functionalized via palladium-catalyzed C-H activation at the 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 instance, dipeptide **150** and tripeptide **152** can be arylated at the β positions of the amino acids at the N-terminus.

(Ve) Carbonyl Groups (ketones and aldehydes): The carbonyl oxygen of aldehydes and ketones is weakly basic and does not have an appreciably acidic proton to generate an anion. These factors had inhibited the development of C-H activation with aldehydes and ketones until Yu, Li, and Ge's recent contributions (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 amino-carboxylic acids such as **155** and **158**, a transient bidentate imine directing group is formed under the reaction conditions. Yu,[72] Li and Ge[73] demonstrated that the β primary C-H bonds of ketone **154** and aldehyde **157** can be arylated with aryl iodides **50** and **89** with this strategy.

(Vf) Carbonyl Groups (γ Functionalization): The above representative examples show that C-H bonds β to the carbonyl compounds are typically activated. However, the γ C-H bond of an amide can be occasionally functionalized (Scheme 25). Corey observed that carbonyl compound **160**, which contains a sterically bulky substituent NPhth at the α position, experiences C-H activation preferentially at the γ primary C-H bond over a β tertiary 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 the functionalization of a γ primary C-H bond, the β carbon is fully substituted such that β C-H activation is not a possibility. For instance, Yu showed that the γ C-H bonds of amide **162** can be olefinated[74] or arylated.[75]

(VI) Alcohol Derivatives: In order to functionalize alcohols (Scheme 26), Dong employs an oxime as a directing group. The system is analogous to that reported by Sanford, however the sp^3 C-H bonds are located on the side of the oxygen, instead of the nitrogen. Oxygenation of the β primary 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] The mechanism involving a Pd(II)/Pd(IV) is believed to be operative.

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

2.2. Catalysis with Other Noble Transition Metals

Other noble transition metals are also competent catalysts for the activation of unactivated sp^3 C-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 with different reaction conditions.

2.2.1 Ruthenium—When amide **170** is heated with a catalytic amount of $Ru_3(CO)_{12}$ under an atmosphere of carbon monoxide and ethylene, Chatani observed that succinimide **171** is formed (Scheme 28).[79] In the proposed mechanism, 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**. σ bond metathesis results in the activation of the methyl C-H bond to generate **F3**. Carbonylation takes place to give 6-membered metallacycle **F4**. A final reductive elimination yields the observed product **171**.

2.2.2 Iridium

(I) Iridium(I): A three-step protocol for Ir-catalyzed alcohol-directed silylation of primary C-H bonds was reported by Hartwig (Scheme 29).[80] Similar to his previous work on sp^2 C-H bond activation,[81] an Ir(I)-catalyzed reaction is first applied to silylate the alcohol in order 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, affording a 1,3 diol as the final product. Therefore, 1,3 diol **174** can be synthesized from alcohol **172** with hydrosilane **173** as an intermediate. Hartwig 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 to a C-O, C-N or C-C bond with subsequent reactions.

(II) Iridium(III): Chang developed a protocol for 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** with $[Cp^*IrCl_2]_2$ as a pre-catalyst and $AgBF_4$ as a co-catalyst. Zeng and Ke 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 and Shi, arylation of primary C-H bonds can be accomplished with the same directing group and the same Ir pre-catalyst.[86] Oxime 1**82** is arylated with diaryliodonium salt **47** to afford **183**.

2.2.3 Rhodium

Rhodium(III): You[87] and Glorius[88] accomplished pyridine directed C-H functionalization with Rh(III) precatalysts (Scheme 31). You achieves amination of pyridine **12** with nitrobenzenesulfonamide ($NsNH_2$) as the nitrogen source and $PhI(OAc)_2$ as an oxidant.

Arylation of pyridine **185** relies on the use of boroxine **186** in Glorius's protocol. Various groups subsequently reported rhodium(III)-catalyzed sp^3 amination with other nitrogen sources or under different reaction conditions.[89]

2.3. With Earth-Abundant Metal Catalysts

Recent efforts have been devoted 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 catalysis is still very limited. No functional groups other than carbonyl compounds have been employed as competent directing groups. Therefore, at this time, only 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

(I) Nickel(0): Nickel, likely because of its position above palladium in the periodic table, was the initial focus. Nakao and Hiyama first employed low valent $Ni(cod)_2$ as the precatalyst and $AlMe_3$ as the co-catalyst for sp^3 C-H activation (Scheme 32).[90] 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 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**. C(sp^3)-H activation takes place to give 5-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 from reductive elimination of the final intermediate **G5**.

(II) 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 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 Chatani and Ge. Using Ni(II) as a precatalyst in conjunction with carbonate bases, β primary C-H bonds of amide **191** can undergo arylation with aryl iodides [91] or alkylation with alkyl iodides.[92] Shi showed Ni(II)-catalyzed alkenylation of amide **191** with vinyl iodides [93] to afford alkenylated products. As reported by Zhang, alkenylation can also accomplished with phenylacetylenes. [94] Various groups also simultaneously reported C-H thiolation using the same directing group.[95]

Synthesis of nitrogen-heterocycles from amides can also be catalyzed by nickel(II). As demonstrated by Ge, 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 first involving C-H iodination and subsequent S_N2 is proposed by Chatani.[97] In addition, DMF can be used as a carbonylating agent. Amide **195** undergoes

carbonylative cyclization to form succinimide **185** with $NiBr_2$ catalyst and $Cu(acac)_2$ cocatalyst.[98]

2.3.2 Iron—The 8-aminoquinoline directing group also enabled Fe-catalyzed C-H activation. Nakamura and Ilies achieved iron-catalyzed β-arylation of primary C-H bonds of carbonyl compound **197** with ArMgBr and Ar_2Zn (Scheme 35). [99] For instance, Subsequent reports from the same group demonstrate that methylation and vinylation of primary C-H bonds can be realized with $AlMe_3$[100] and vinyl boronates[101] respectively. In all these reactions, 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 8-aminoquinoline-directed C-H activation. As reported by Zhang, using $Co(OAc)_2$ as the precatalyst, 5-membered pyrrolidinone **202** can be accessed from acyclic amide **116** and phenylacetylene **201** (Scheme 36).[102] In this case, concomitant alkynylation and cyclization occurs. Li and Ge showed that amide **203** undergoes β-lactamization in the absence of an alkyne under similar reaction conditions to afford β-lactam **204**. [103] Intermolecular amination can be achieved when a perfluorinated amide is added as a nitrogen source. Sundararaju[104] and Gaunt[105] independently found that $Co(acac)_2$ catalyzes the carbonylative cyclization of amide **116** for access to succinimide **207** in the presence of carbon monoxide.

2.3.4 Copper—Ge 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 oxidize copper(II) to copper(III) to drive reductive elimination to form the C-N bond. Yang and You 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 and Ge, 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 **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 **189**. 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 a X-H bond which is stronger than the breaking C-H bond. Radicals that are capable of abstracting a hydrogen atom from an unactivated sp^3 C-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, resulting in the installation of a functional group at the original C-H bond.

Intramolecular hydrogen atom transfer is often favored, compared to an intermolecular event, due to a lower entropic cost. In this case, the reactive radical species can be viewed as a directing group. In most cases, 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 functionalities that can be incorporated 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. Therefore, 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 sp^3 C-H bonds is nitrogen radicals.[112] The N-H bond of a neutral amine has a comparable bond energy to that of a sp^3 C-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 with an electron-withdrawing group.

3.1.1 Generation and Transformations

(I) 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 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. 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 *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 halogen, along with $Pb(OAc)_4$ or $PhI(OAc)_2$, is used to generate a nitrogen-halogen bond from a N-H bond. [115] The presence of an electron-withdrawing group (nitro, cyano, phosphonyl and carbonyl groups) on nitrogen 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. Reports from Togo and Yokoyama,[116] and Fan[117] demonstrated that sulfonyl groups on nitrogen are also compatible with this chemistry. Muniz reported a catalytic variant of the Suarez modification. In his protocol, 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 therefore formed. A subsequent step would afford a pyrrolidine as the final product. In addition, Yu 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 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 NIS. As exemplified by the aforementioned reactions, only halogenation of C-H bonds has been accomplished with *in-situ* generation of a nitrogen-halogen bond as the nitrogen radical precursor.

(II) Reduction of N-X Bonds: When the nitrogen 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 sp^3 C-H bonds (Scheme 43).[120] 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**. 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 is demonstrated by Yu with photoredox catalysis. [122] The N-Cl bond in sulfonamide **233** is reduced by the excited photocatalyst $[Ir(ppy)_2(dtbpy)]PF_6$. Through 1,5 HAT, an alkyl radical is generated. The 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 nitrogen at a higher oxidation level is employed as the nitrogen radical precursor.

(III) Abstraction of Hydrogen Atoms: The abstraction of a hydrogen atom provides another means to form a nitrogen radical from a N-H bond. Chiba showed that the reaction between the N-H bond in hydrazone **235** with TEMPO can generate a nitrogen radical (Scheme 45).[123] Although the nitrogen radical generated in this case is stabilized by the alpha nitrogen atom, the equilibrium between the nitrogen radical **237** and the alkyl radical **238** provides a small 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 in **239** gives aza-diene **240**, which can cyclize to give dihydropyrazole **236**. Yu 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**.

(IV) Oxidation of N-H Bonds: A less common method to generate a nitrogen radical is through the oxidation of a N-H bond. Nikishin 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** that can realize 1,5 HAT to generate an alkyl radical δ to the nitrogen. Oxidation of the alkyl radical **248** to carbocation **249** promotes cyclization to 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 is reported by Shi.[126] With Ag catalysis 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 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** in this case is 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 subsequent nucleophilic substitution. Except for Chiba's system with amidines, in all the reactions relying on the oxidation of the N-H bond to generate the nitrogen radical, 5-membered-ring products through intramolecular C-H amination are obtained.

Most recent research incorporates photoredox catalysis into the oxidation of N-H bonds. Rovis [129] and Knowles [130] simultaneously and independently disclosed remote alkylation of unactivated sp^3 C-H bonds directed by an amide (Scheme 47). In the Rovis system, 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** using Knowles' protocol. 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. 1,5 HAT and trapping of the alkyl radical **260** with the electrophilic alkene generates a radical α to an electron-withdrawing group (**261**). Reduction of **261** turns over the photocatalyst and final protonation affords the alkylated product **262**. In Rovis' system, mechanistic work suggests 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 nitrogen to acidify the N-H bond and the use of a strong base, K_3PO_4. On the other hand, a concerted proton-coupled-electron-transfer event is believed to operate in Knowles' system. 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 Rovis and Knowles are complementary.

3.2. Oxygen Radicals

Oxygen radicals are more electrophilic and reactive than nitrogen radicals due to the higher electronegativity of oxygen; thus, 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) than sp^3 C-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).

3.2.1 Generation and Transformations

(I) 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 the homolytic cleavage of the oxygen radical precursor. The

first reported C-H functionalization reaction with oxygen radicals is the Barton reaction (Scheme 49).[132] Cleavage of the N-O bond of 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 1,5 fashion. The resulting alkyl radical **281** combines with the nitrosyl radical, which after subsequent tautomerization and acetoxylation of **282** 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 with an oxygen-halogen bond, chlorination of the C-H bond can be accomplished.[133] Similarly, Cekovic achieved the formation of a C-S bond using a O-S precursor.[134] In these examples, the mechanisms are similar and a resulting C-X bond is formed at the C-H bond δ to the directing oxygen radical.

When the oxygen radical is formed through homolytic cleavage of an O-X bond, there is limited success in trapping the alkyl radicals with an external partner (Scheme 51). Cekovic observed that when a large excess of an electrophilic alkene is employed, alkylation of the alkyl radical can out-compete the trapping of the X radical formed during homolysis of the O-X bond. [135] When 80 equiv. of acrylonitrile **288** is used in the photochemical decomposition of nitrile ester **287**, trapping of the alkyl radical δ to the oxygen 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 O-S bond as the oxygen radical precursor can be trapped by ethyl acrylate **54**. In these cases, the alkyl radical α 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.

(II) Reduction of O-X Bonds: A strategy to avoid simultaneous formation of an oxygen radical and another radical from an O-X bond is the use of a stoichiometric reductant. As reported by Cekovic, when alkyl hydroperoxide **294** is treated with a stoichiometric amount of $FeSO_4$, the O-O bond is reduced 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 the copper(II) salt, thiocyanation, azidation and halogenation of the C-H bond can be accomplished.

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 from 1,5 HAT is free to react with a radical partner (Scheme 53). In Chen's system, the Hantzsch ester **298** (HE) 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. 1,5 HAT generates an alkyl radical which is then coupled with electrophilic alkene **297**. Elimination of the sulfonyl radical affords alkylated product **299**.

It can be concluded from Cekovic's and Chen's work 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, providing a strategy to form

various bonds at the C-H bond with the use of different reaction partners. However, some O-X bonds are unstable to handle and access to these are generally non-trivial.

(III) Free Alcohols as Precursors: An O-H bond is another common class of oxygen radical precursors. $Pb(OAc)_4$ is 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 one of the acetates 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 1,5 HAT, the alkyl radical **307** generated is intercepted by the lead(III) acetate to form Pb-alkyl species **308**. Heterolytic cleavage of the Pb-C bond yields carbocation **309**, which is prone to cyclization to afford tetrahydrofuran **304**. Alternatively, Pd-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 a O-H bond is to generate an oxygen-halogen bond *in-situ* followed by its homolytic cleavage. For instance, with the conditions reported by Suarez (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 Chiba's example where TEMPO is 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 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-center radical **319**, which abstract a hydrogen atom from TEMPO-H to afford **313**.

In almost all reactions in which an O-H bond is used to generate an oxygen radical, intramolecular C-O oxygenation occurs to give a 5-membered oxygen heterocycle. The only exception is reported by Ryu and Sonoda, 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]

(IV) Cleavage of Epoxides: Epoxides are also sometimes used to generate oxygen radicals. Rawal [141] and Kim [142] independently disclosed the functionalization of sp^3 C-H bonds with oxygen radicals formed from epoxides (Scheme 58). In both reports, a radical that is α to the epoxide is first generated. Subsequent homolytic cleavage of the C-O bond is driven by the ring strain of the epoxide and gives the oxygen radical. [143] In Rawal's work, Barton-McCombie deoxygenation is applied to epoxide **325** to generate the alkyl radical α to the epoxide (**327**). For Kim, such an intermediate is generated by the addition of the tributyltin radical to the alkene in **330**. The alkyl radicals generated from 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.

(V) Electronic Excitation of Carbonyl Groups: The final class of oxygen radical precursors are 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* of the carbonyl group (Scheme 59). This results in the formation of a diradical species, with both the carbonyl carbon and oxygen possessing radical character. The carbonyl oxygen radical is able to abstract a hydrogen atom through 1,5 HAT. The resulting alkyl radical re-combines with the carbonyl carbon radical, 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 illustrating 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 sp^3 C-H functionalization.

3.3 Vinyl and Aryl Radicals

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

3.3.1 Generation and Transformations

(I) Reduction of Aryl or Vinyl Halides: Generally, a vinyl or aryl radical is generated through the reduction of the corresponding halide with Bu_3SnH under photochemical or thermal conditions. The reactive tributyltin radical cleaves the carbon-halogen 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 first demonstrated that vinyl radicals generated from vinyl halides and tributyltin hydride can be used to functionalize sp^3 C-H bonds (Scheme 60).[145] In this case, an allylic C-H bond in **340** 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 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 a catalytic amount of Bu_3SnH under the reaction conditions and is particularly beneficial for the functionalization of unactivated sp^3 C-H bonds. Since hydrogen atom transfer from unactivated sp^3 C-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 sp^3 C-H functionalization using aryl radicals is reported by Curran (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 a hydrogen atom from a C-H bond β 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 sp^3 C-H functionalization.

(II) Radical Addition to Alkynes: An alternative method to generate a vinyl radical is through the radical addition to an alkyne. For the conversion of alkyne **348** to cyclopentane **349**, Malacria showed that the addition of an α-silyl radical to an alkyne generates vinyl radical **350** (Scheme 63).[148] This vinyl radical can undergo 1,5 HAT to give primary alkyl radical **351**. As in Curran's reaction, radical cyclization onto the alkene takes place to afford the cyclized product **349**. Malacria 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 from 1,5 HAT with 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**.

(III) Reduction of Aryl Triazenes: Reduction of aryl triazenes under acidic conditions is another means to generate aryl radicals. Baran 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, elimination of $HNEt_2$ from **358** yields diazonium **360**, which is reduced by TEMPO to give aryl radical **361**. 1,7 HAT gives tertiary radical **362**. Subsequent oxidation and deprotonation accounts for the formation of alkene Y.

From the above representative examples, it can be observed that the alkyl radicals generated from 1,5 HAT with aryl or vinyl radicals thus far only undergo intramolecular events, such as cyclizing onto tethered alkenes or 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 6 electrons in the outermost electron shell. The lack of an octet configuration renders them highly unstable and able to break unactivated sp^3 C-H bonds despite their bond strength. Modern methods rely on transition-metal catalysis such that such reactive species are generated under relatively mild conditions. Along with the interaction between these species and the transition metal catalysts to form metal carbenoids/nitrenoids, control of selectivity can be achieved (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] Therefore, with dirhodium(II) catalysis as an illustration, the following discussion aims to provide readers with a fundamental understanding of intramolecular C-H insertion with carbene transfer and C-H amination with nitrene transfer. Readers who seek a deeper and more thorough insight in this area are encouraged to access these recent reviews.

4.1. Carbene Transfer

A diazo functionality is the typical precursor of a transition metal carbenoid. Generally, an electron-withdrawing group, often a carbonyl, 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, resulting in the formation of a C-C bond.

The potential of dirhodium catalysts for C-H insertion was first reported by Teyssie (Scheme 66).[155] He 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 with the solvent, cyclopentane **339**. Wenkert 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 found that unactivated sp^3 C-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 carbene.[157] The mechanism of the C-H insertion step is believed to be concerted, yet asynchronous, leaving a partial positive charge at the carbon 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 discovered that Rh(II) dimers show obvious advantages in the chemistry of C-H amination (Scheme 67).[159] Both carbamate **375** and sulfamate **377** are competent substrates although the two substrate classes offer different regioselectivity. The formation of a five-membered ring is favoured 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 is offered by Du Bois, who suggests that the formation of the 5-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

(I) Carbene Transfer: Carbene transfer has been used to facilitate natural product synthesis in the context of 5- and 6-membered rings (Scheme 68). For instance, Taber used Rh(II)-catalyzed C-H insertion as a key reaction to access pentalenolactone E **386**.[160] With a catalytic amount of dirhodium acetate, α-diazo-β-keto ester **382** undergoes intramolecular C-H insertion to form cyclopentanone **383**, affording the tricyclic framework of the natural product. Taber 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 accessed the same core of pentalenolactone E **387** with Rh(II)-catalyzed C-H insertion with a different disconnection strategy.[162] In this case, the sixmembered lactone **389** is obtained from precursor α-diazoketone **388**.

(II) Nitrene Transfer: Nitrogen is one of the most common heteroatoms present in natural products. 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 instance, in the synthesis of (−)-tetrodotoxin **395**, intramolecular nitrene transfer of carbamate **393** affords **394** with Rh(II) catalysis. [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, 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 carbons, 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

(I) 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 sp^3 C-H bonds to transition-metal catalyzed C-H activation. Primary alkyl metal species are more stable than their secondary counterparts, which are in turn 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 Pt species **396** and **398**, suggesting their higher thermodynamic stability than their secondary or tertiary counterparts.

In parallel to the thermodynamics of the corresponding transition metal alkyl species, activation of secondary C-H bonds is more difficult than primary C-H bonds. This trend is illustrated with a report by Hartwig. In his 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, the activation of secondary C-H bonds with transition-metal catalysis can be achieved, as exemplified by many recent reports.

In contrast, transition-metal catalyzed activation of tertiary C-H bonds is rare. Dong recently demonstrated Pd-catalyzed acetoxylation of tertiary C-H bonds is possible at the bridgehead

of [2.2.1] bicycloheptane (Scheme 72)[76, 166]. In addition, it is noteworthy that the activation of tertiary C-H bonds of cyclopropanes[167] and cyclobutanes[168] have been achieved.

(II) 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 sp^3 C-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, therefore suppressing undesired side reactions. Secondary and primary C-H bonds and 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]

(IIIa) 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, yet 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). When α-diazo-β-keto ester **405** is treated with $Rh_2(OAc)_4$ catalyst, cyclopentanones **406** and **407** are formed in a regioisomeric ratio of 2.3:1, indicating 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 sometimes can be enhanced by choice of a different dirhodium(II) catalyst. Scheme 74 shows that when α-diazo-β-keto ester **408** undergoes intramolecular C-H insertion with the $Rh_2(OAc)_4$ catalyst, lactone **409** is formed preferentially to lactone **410**, reflecting the higher reactivity of more electron-rich tertiary C-H bonds than 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, sterics sometimes override electronics and becomes the governing factor. With $Rh_2(OAc)_4$ as the catalyst, the C-H insertion of 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 predicted by the electronics of the C-H bonds since the benzyl group is more capable of stabilising 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 regioselectivity is observed and cyclopentanone **413** is formed exclusively. The sterically less hindered primary C-H bonds show a higher reactivity with the use of bulky dirhodium(II) catalyst in this case.

(IIIb) Transfer of Nitrenes: Similarly, a higher reactivity of more electron-rich C-H bonds for metal-catalyzed nitrene transfer is observed. Du Bois 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 with the choice of catalysts. With significantly more sterically-demanding $Rh_2(TPA)_4$ **415**, a diminished 4.5:1 ratio of **418** to **418** is obtained.

5.2. Position of C-H Bonds Relative to Directing Groups

(I) Transition-Metal Catalyzed C-H Activation: The stability of the ring size of the metallocycles has a significant impact on the site-selectivity of the reactions. Formation of 4-, 5-, and 6-membered ring is possible with 5-membered ring being the most common. The logical extension of the feasibility to form these ring sizes is that C-H bonds β, γ, δ to the directing groups can potentially be activated (Scheme 77).

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 5-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 6-membered palladacycle is formed preferentially to a 5-membered ring. In addition, for the functionalization of carbonyl groups, β C-H bonds are usually activated.[14] However, a γ methyl group can be activated over the less reactive β tertiary C-H bond (Scheme 25).[53]

(II) Hydrogen Atom Transfer: 1,5 HAT is almost always the predominant pathway due to a favourable 6-membered transition state. 1,4 HAT has never been reported to be synthetically useful for the functionalization of unactivated sp^3 C-H bonds. Products from 1,6 HAT are sometimes observed in small amounts in conjunction with the 1,5 HAT products. For instance, Mihailovic observed that for the formation of cyclic ethers with oxygen radicals, the ratio of 1,5 HAT to 1,6 HAT is around 12:1 (Scheme 78).[174] Long-range HAT is accompanied by a high entropy cost and is uncommon. A successful example is reported by Baran for the desaturation of aliphatic compounds (Scheme 64).[150] Another example is reported by Nishio (Scheme 79) for the synthesis of amide **423** from ketone **422**.[175] Upon irradiation with UV light, diradical **424** is formed. The oxygen radical abstracts a hydrogen atom from the methyl C-H bond through 1,8 HAT, 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 and the geometry constraint imposed by the sp^2 hybridized atoms which significantly reduces the entropy cost for 1,8 HAT. Breslow 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, 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 sp^3 C-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 observed that the vinyl radical generated by nitrate radical addition 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 [5.3.0]-bicyclodecane **437** or [4.4.0]-bicyclodecane **439**. The ratio of the two products reflects a 3:1 ratio of 1,5 HAT and 1,6 HAT. Moreover, Baran reported a HLF reaction with carbamates for the synthesis of 1,3-diols featuring 1,6 HAT (Scheme 82).[179] Possibly due to the presence of three sp^2 hybridized atoms, the relative energy of 1,5 HAT and 1,6 HAT changes. As reflected by the 1.1 to 1 product ratio of **441** and **442**, 1,5 and 1,6 HAT are almost equally favorable. By disfavouring 1,5 HAT with 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 instance, in Penenory's reaction of aryl iodide **447**, 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, resulting in arylation of the ε C-H bond. Summarizing from these representative examples, synthetically useful transformations based on 1,6 HAT are possible if geometric or electronic bias is in place to disfavor 1,5 HAT.

Although the predominance of 1,5 HAT and 1,6 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 instance, in Chiba's synthesis of oxazolines (Scheme 46), the amine is first converted to an amidine such that the iminyl NH responsible for 1,5 HAT is located at the β-position relative to the original nitrogen.[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.

(IIIa) 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 electronics/sterics 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** undergoes 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.[172] The preference to form a 5-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, increasing the selectivity for cyclobutanone **453**. On the other hand, with bulky $Rh_2(TPA)_4$ catalyst **415**, the reaction at the more sterically hindered tertiary C-H bond is completely shut down, resulting in exclusive formation of cyclopentanone **490**.

(IIIb) Transfer of Nitrenes: As discussed earlier, for intramolecular rhodium-catalyzed nitrene transfer, formation of 5-membered and 6-membered rings is the most common (Scheme 67). For carbamates, 5-membered oxazolidinones are the predominant product.

Sulfamates and phosphoramidates show complementary selectivity and favour the formation of 6-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

(I) Transition-Metal Catalyzed C-H Activation: The prospect of controlling absolute stereochemistry in transition-metal catalyzed C-H activation has been demonstrated by various groups. Initial reports focused on the use of aryl halides or triflates as a traceless directing group for the enantioselective formation of 5-membered rings.

Kündig first demonstrated that chiral NHC ligand **LG10** on palladium can induce asymmetry for the synthesis of tricyclic **456** from vinyl bromide **455** through the activation of a secondary C-H bond (Scheme 85).[181] Cramer later showed that the same transformation can be achieved with chiral phosphine ligand **LG11**.[182] Thus, tricyclic **459** can be obtained with vinyl triflate **457**. For the activation of primary C-H bonds, Kagan showed that the use of chiral phosphine Me-DUPHOS **L12** allows for the desymmetrization of vinyl bromide **460** to access indoline **461** (Scheme 86). [183] For the synthesis of enantiomerically-enriched dihydroindene **463** from vinyl bromide **462**, Clot and Baudoin utilized axially chiral phosphine **L13** (Scheme 87).[184]

Yu demonstrated enantioselective palladium-catalyzed carbonyl-directed sp^3 C-H activation. With a modified amino acid as a chiral ligand on palladium, differentiation of the two pro-stereogenic methyl groups can be accomplished, albeit with moderate stereoselectivity in most cases (Scheme 88).[185] For instance, in the γ-arylation of amide **464**, the ee obtained was 29% with chiral ligand **L14**. This initial report confirms that the chiral ligands on transition metals can exert stereochemical control in carbonyl-directed C-H activation. In subsequent work, Yu showed that in the event of arylation of β secondary C-H bonds of carbonyl compounds, a high level of stereochemical control can be obtained by using chiral bidentate acetyl-protected aminoethyl quinoline ligand **L15** on palladium.[186] Thus, amide **129** can be arylated to access enantiomerically-enriched product **467**. In addition, desymmetrization of amide **134** can be achieved with **L16** such that the new stereogenic center is established at the α position of the carbonyl group. [187] Enantiomerically-enriched **468** can undergo C-H arylation, alkynylation, alkylation, oxygenation, amination or bromination at the methyl group with another C-H activation reaction, allowing access to products with various functionalities.

A recent report from Gaunt indicates that desymmetrization of sterically hindered secondary amines can be achieved to form enantiomerically-enriched aziridines with chiral phosphoric acid TRIP as a chiral ligand on the palladium catalyst (Scheme 89).[188] For instance, C-H activation of a methyl C-H bond of secondary amine **469** can be accomplished to access aziridine **470**.

Despite these advances, the stereochemical outcome for the activation of a C-H bond of a tertiary stereogenic center has not been studied due to the challenging formation of tertiary alkyl metal species. However, some alkyl transition metal intermediates are

configurationally stable and give enantiomerically enriched products, suggesting the possibility of preserving the stereochemistry of a tertiary stereogenic center in transition-metal catalyzed C-H activation.[189]

The effect of a pre-existing stereogenic center on the stereochemical outcome of metal-catalyzed sp^3 C-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 instance, 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 6-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.

(II) 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 chemistry of intermolecular addition of alkyl radicals was disclosed by Porter, Giese and Lindner (Scheme 91).[190] They found that a *tert*-butyl radical can add to chiral electrophilic alkene **475** with excellent diastereoselectivity. Hydrolysis of the two amides could provide an enantiomerically-enriched compound.

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 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 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).[191] In addition, *tert*-butyl radical adds to vinylogous ester **480** with excellent enantio- and diastereoselectivity with a sub-stoichiometric amount of chiral aluminium(III) complex **482**.[192] The use of a chiral Lewis acid for functionalization of unactivated sp^3 C-H bonds has not been explored although Meggers recently applied this concept to functionalize sp^3 C-H bonds activated by oxygen (Scheme 93).[193] In this case, an oxygen radical is generated from an N-O bond and is used to abstract a hydrogen atom of the C-H bond, as in Chen's system.[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 sp^3 C-H bonds.

It should be noted that the newly formed stereogenic centers thus far in the chemistry of alkyl radicals are at the radical trap but not at the carbon atom of the alkyl radical. Transformations that successfully differentiate two prochiral hydrogens or groups in the substrate with 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 instance, when Rovis examined the use of enantiomerically-enriched substrate **488** for nitrogen-directed C-C bond formation at unactivated sp^3 C-H bonds, the alkylated product **489** is obtained as a racemic mixture (Scheme 94).[129]

In addition, a highly diastereoselective reaction with chiral substrates would be non-trivial. 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 that typically involve metalacyclic intermediates, the alkyl radical intermediate, existing in acylic forms, 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.

(III) Transfer of Carbenes/Nitrenes: Asymmetric metal-catalyzed carbene transfer is well-established. Doyle developed novel chiral dirhodium catalysts for the enantioselective synthesis of 5-membered lactones through C-H insertion. With Rh_2(4*S*-MPPIM)$_4$ **491**, γ-lactone **492** can be obtained from acyclic diazo-ester **490** with high enantioselectivity (Scheme 95).[194] Doyle 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**.[195] The application of asymmetric C-H insertion is demonstrated by Doyle in the synthesis of natural product (+)-isolauricerisinol **498** (Scheme 96).[194] Diazo-ester **496** undergoes enantioselective dirhodium-catalyzed intramolecular C-H insertion to yield γ lactone **497**, which is further elaborated to afford the natural product. In addition, Taber used chiral dirhodium(II) catalyst **500** to favour the formation of the desired diastereomer **501** through C-H insertion of **499** for the synthesis of (−)-astrogorgiadiol **502**.[196]

For enantioselective nitrene transfer, only molecules with activated sp^3 C-H bonds (i.e. allylic or benzylic) are competent substrates. This is exemplified by reports from Che,[197] Davis[198] and Du Bois. [199] Highly enantioselective asymmetric intramolecular nitrene transfer to unactivated sp^3 C-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 observed that cyclopentane **504** is obtained with excellent diastereoselectivity (Scheme 97). [200] A simple cyclic 5-membered transition state **J1** that places both the phenyl and methyl groups at pseudo-equatorial positions is proposed to account for the observed diastereomer.

An example of a highly diastereoselective intramolecular nitrene transfer is reported by Du Bois (Scheme 98). The intramolecular C-H amination of sulfamate **505** with Rh_2oct_4 proceeds with excellent diastereoselectivity. [201] Again, cyclic transition state **K1** with all substituents at the pseudo-equatorial positions is invoked. The opposite diastereomer can be obtained when sulfamide **507** is employed as the substrate.[202] In this case, the methyl group is placed at the pseudo-axial position to minimize A(1,3) strain with the NBoc group in transition state **K2**.

With a tertiary stereogenic center, retention of stereochemistry is observed for both dirhodium(II)-catalyzed intramolecular carbene or nitrene transfer (Scheme 99). In Taber's synthesis of (+)-sulcatine G, 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.[203] Similarly, Du Bois observed that the intramolecular C-H amination of chiral sulfamate ester **512** under dirhodium(II) catalysis proceeds without any sign of racemization in product **513**.[204] In both dirhodium(II)-catalyzed C-H insertion and amination, the stereochemical outcome can be explained by the aforementioned concerted, yet asynchronous, mechanism.

5.4. Scope of Functional Groups that can be Incorporated

The relative breadth of the scope of the three strategies is reflected by the content contribution of this review. [205] As discussed in the following, transition-metal catalyzed C-H activation allows a wide variety of functionalities to be incorporated into sp^3 C-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). On the other hand, for carbene and nitrene transfer, only C-C and C-N bond formation is possible, arguably the two most common and most important types of bonds.

(I) 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 forms at the unactivated sp^3 C-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.

(II) 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 as follows:

For the use of nitrogen radicals, except for one example in which C-H oxygenation is achieved,[128] only halogenation or intramolecular amination of unactivated sp^3 C-H bonds could be realized with nitrogen radicals before recent reports from 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 leading to cyclization by the nitrogen. The keys to success of Rovis and Knowles' photocatalytic systems 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 that 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, allowing for the formation of a carbon-carbon bond.

With oxygen radicals, formation of various bonds at a C-H bond is possible only when the alcohol is pre-activated through the formation of O-O or O-S bonds. This pre-activation step is not trivial and O-O or O-S bonds are difficult to handle, limiting the practicality and feasibility of the use of oxygen radicals. On the other hand, Chen demonstrates that with photoredox catalysis, alkylation of C-H bonds can 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 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 method to generate the vinyl or aryl radicals is 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 out-compete the reduction of the alkyl radical by Bu_3SnH. This criterion might have limited any favorable processes to only intramolecular events. Recently, there appears to be novel protocols to generate aryl or vinyl radicals with photoredox catalysis.[206] These methods obviate the use of Bu_3SnH and might offer a solution to address the limited scope for sp^3 C-H functionalization with aryl radicals.

(III) Transfer of Carbenes/Nitrenes: Metal-catalyzed carbene/nitriene transfer allows intramolecular C-H insertion or amination, resulting in the formation of 5- or 6-membered carbocycles and heterocycles. These products are sometimes hydrolyzable to give acyclic molecules, allowing access to not only cyclic molecules with these C-H functionalization reactions. However, the functionalities that can be incorporated into the substrates are very limited. Only C-C and C-N bond formation can be achieved. 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 sp^3 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 would be devoted to address the limitations associated with each strategy, adding more tools to the C-H functionalization toolbox.

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 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, with more to come. The challenges to activate unactivated tertiary C-H bonds have promising initial results in stoichiometric studies. The development of new directing groups might allow for the activation of the wealth of C-H bonds at positions that are currently not possible.

The research on hydrogen atom transfer has 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 sp^3 C-H bonds. In particular, this merged strategy has allowed the first C-C bond formation reaction with nitrogen radicals and the use of 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 sp^3 C-H bonds, obviating/simplifying the pre-functionalization 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 functionalization of C-H bonds that cannot be targeted with current methodology.

Current research on the transfer of carbenes/nitrenes in the functionalization of unactivated sp^3 C-H bond mainly focuses on intermolecular reactions, [207] the obvious frontier of this chemistry. 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 would 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 sp^3 C-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 collaboratively provide powerfule tools in the synthetic arsenal.

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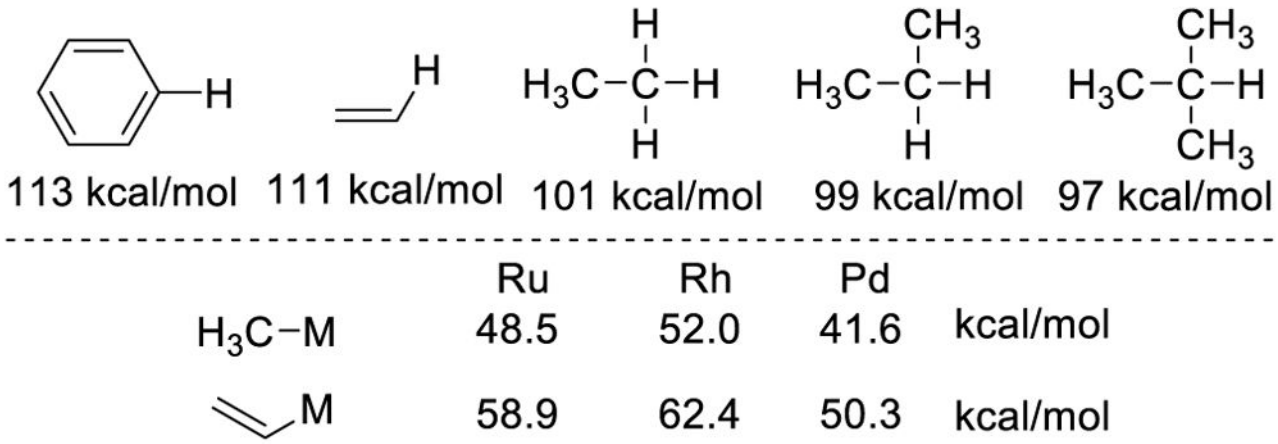


Figure 1.
Challenges in C-H Functionalization

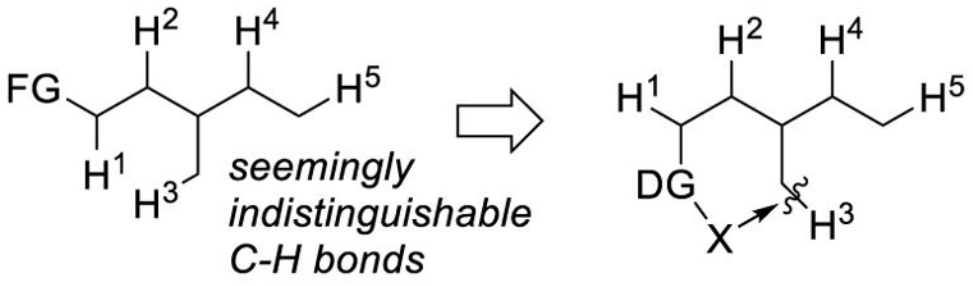


Figure 2.
Use of a Directing Group in C-H Functionalization

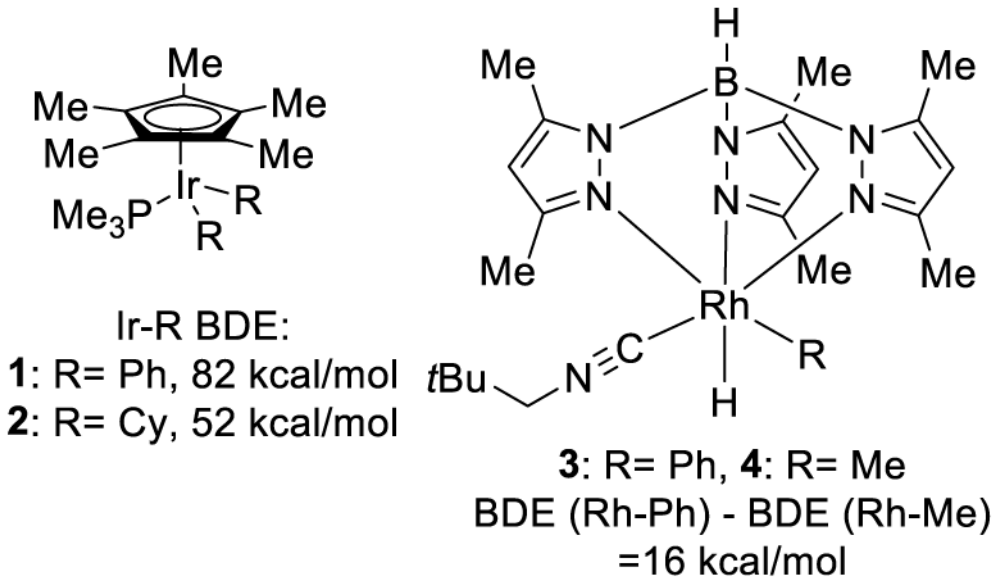
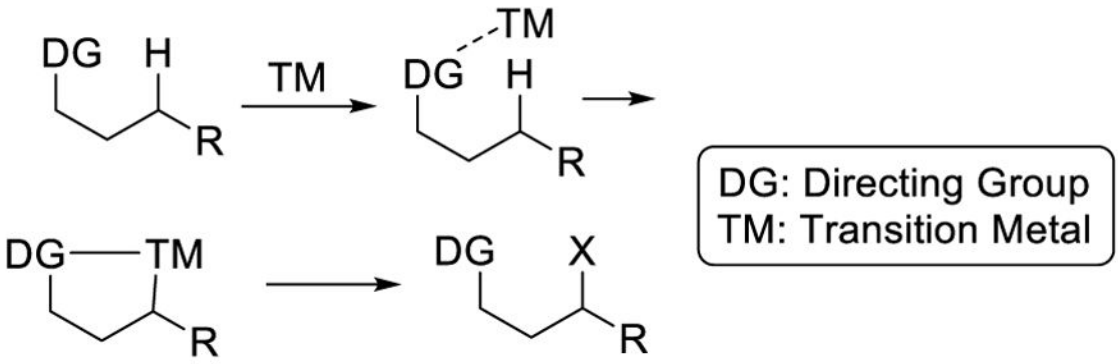
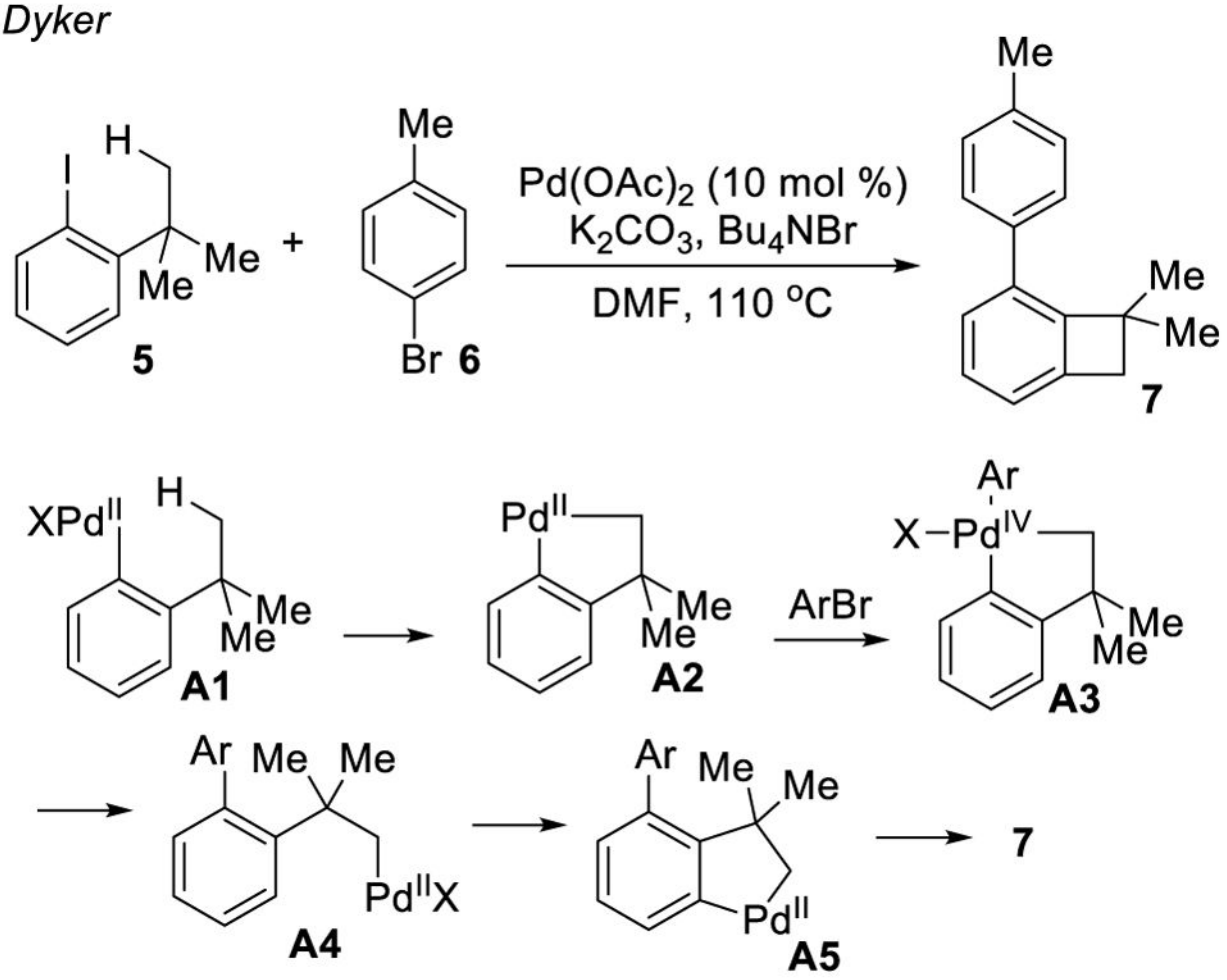


Figure 3.
Weaker Carbon-Metal Bonds with sp^3 Carbons

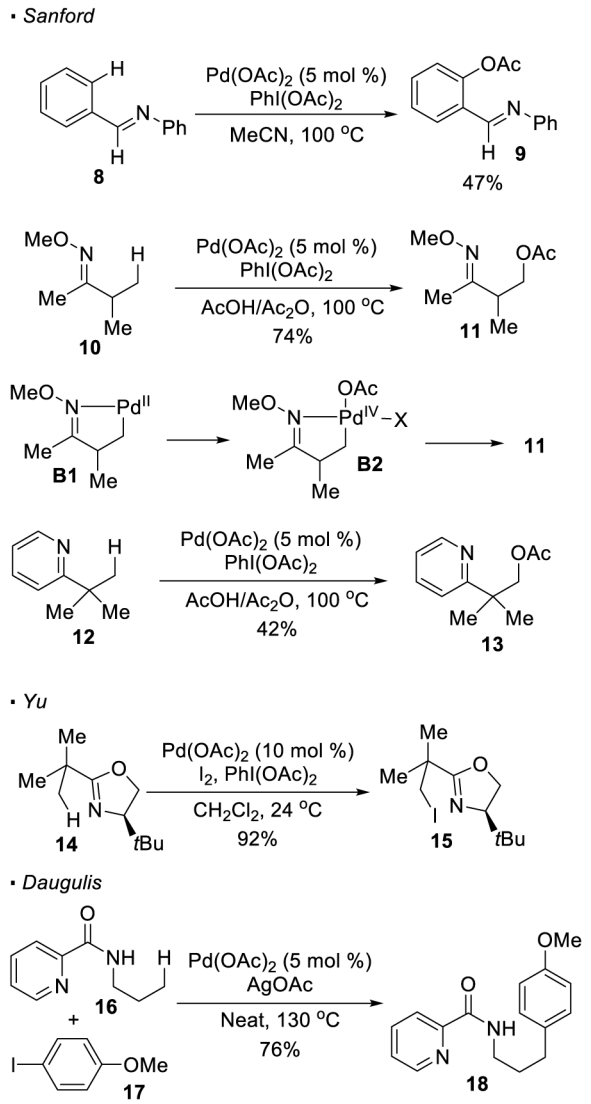


Scheme 1.
Transition-Metal Catalyzed C-H Activation

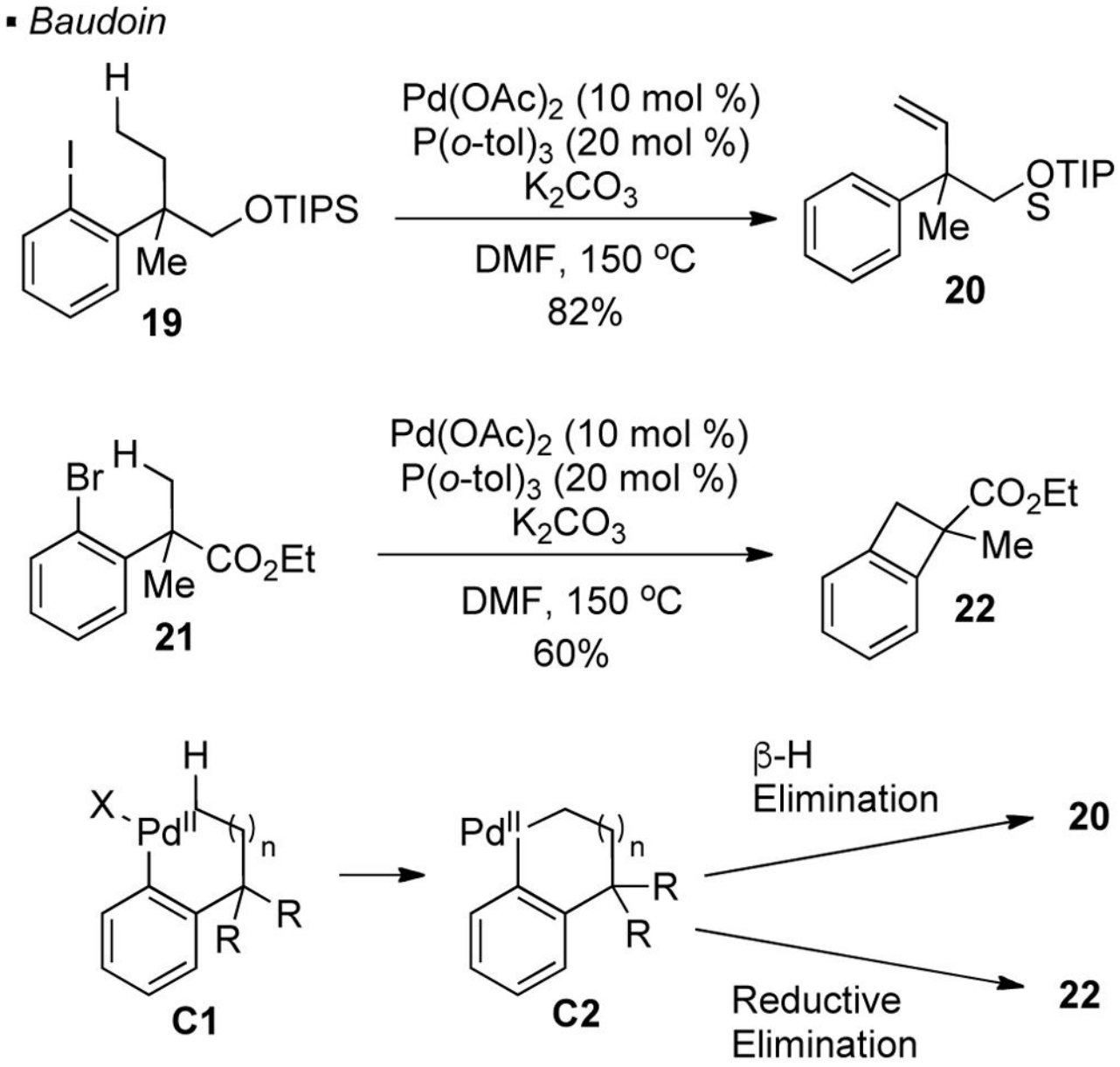
▪ *Dyker*



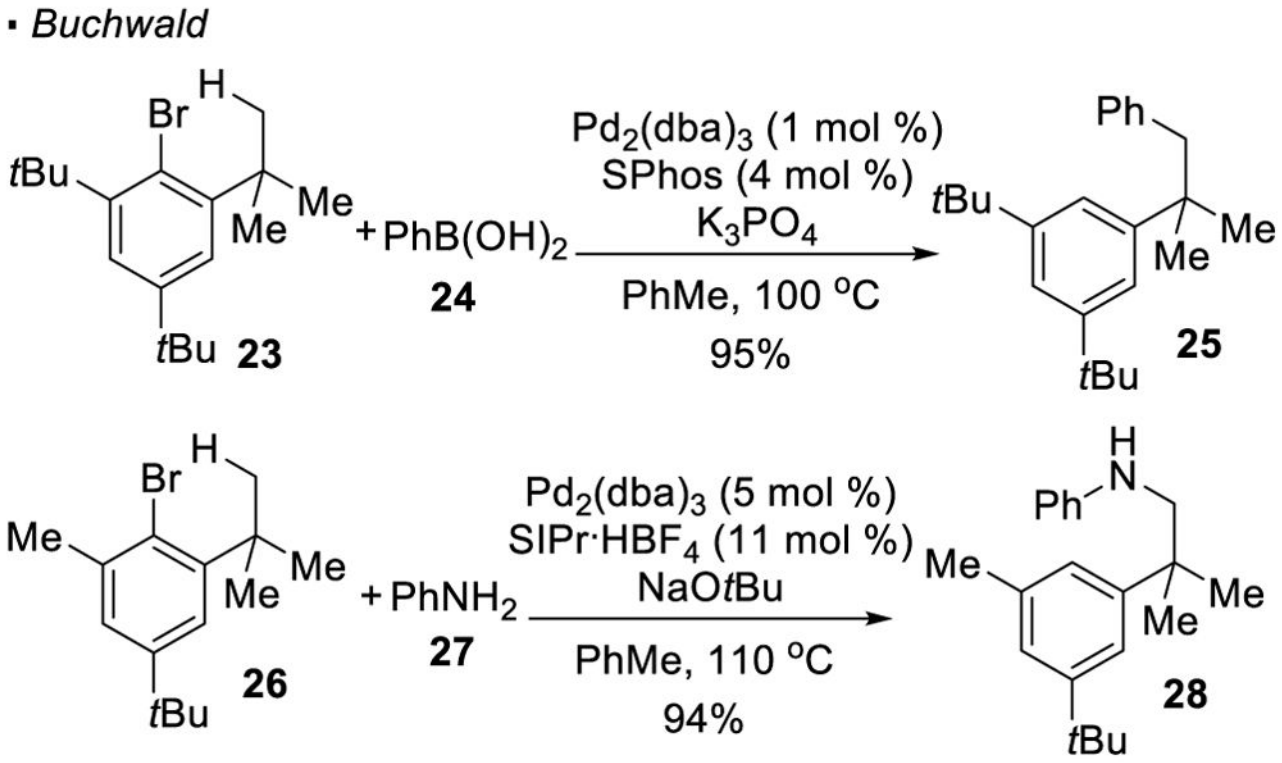
Scheme 2.
Aryl Halides as Directing Groups



Scheme 3.
Nitrogen as Directing Group

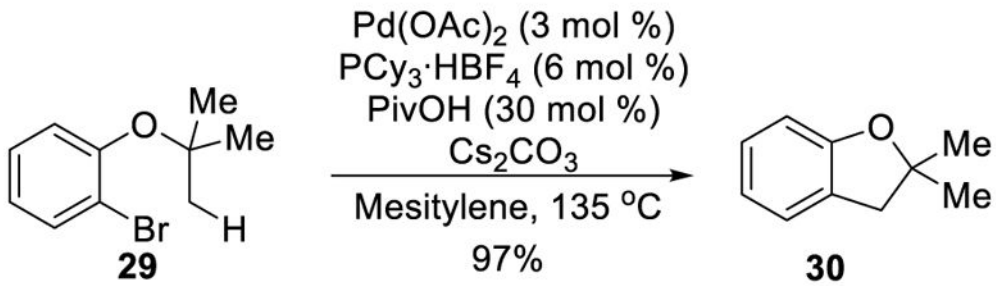


Scheme 4.
Dehydrogenation and Cyclobutane Synthesis with Aryl Halides

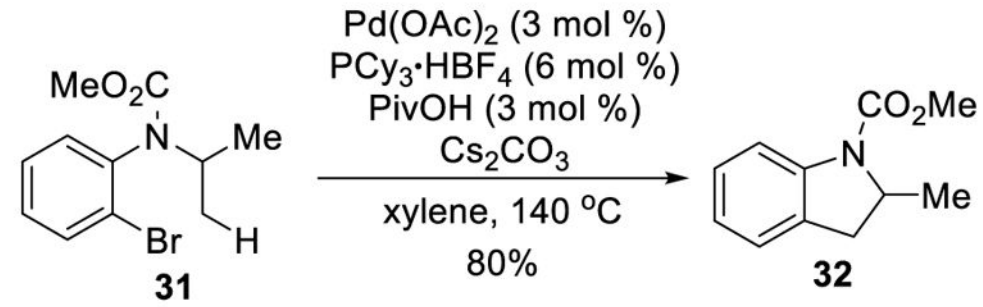


Scheme 5.
Trapping of Putative Palladium-Alkyl Intermediates

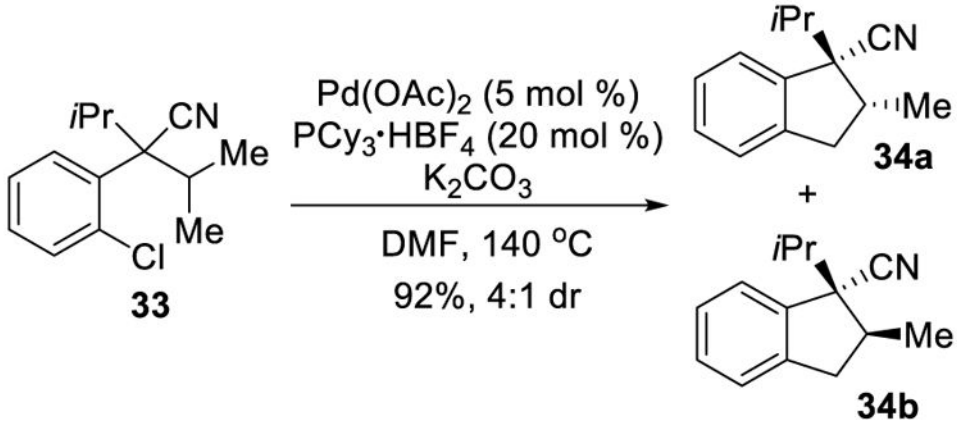
- *Fagnou*



- *Fujii, Ohno*

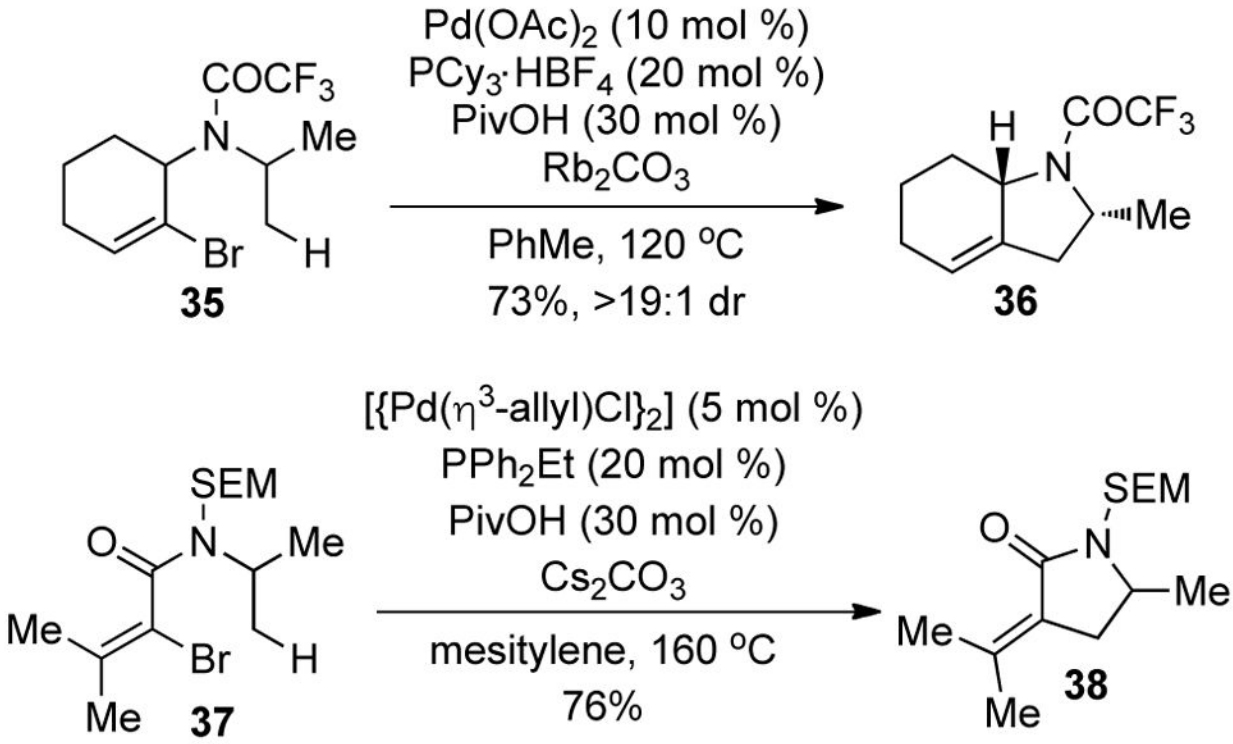


- *Rousseaux, Clot, Fagnou, Baudoin*

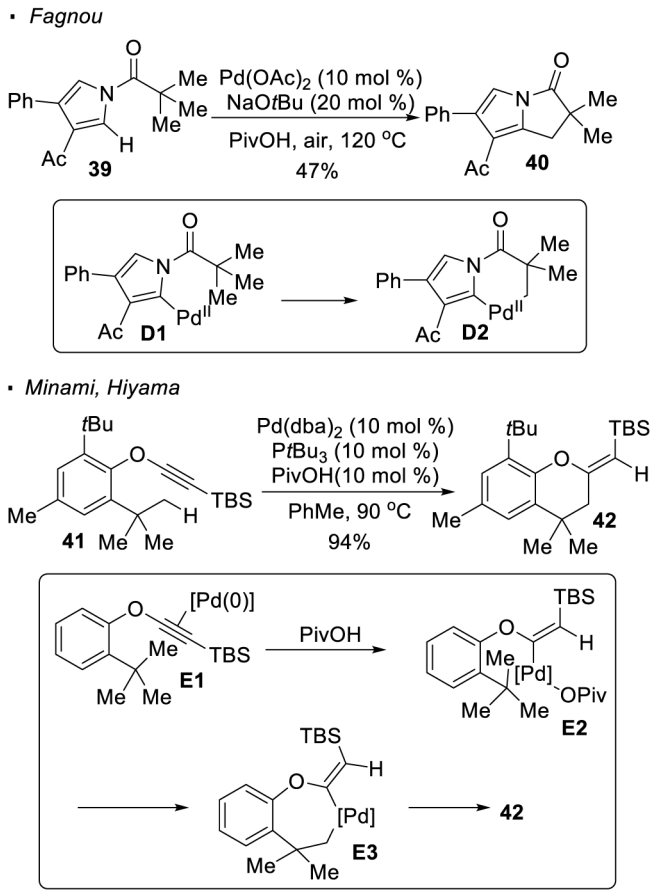


Scheme 6.
Synthesis of 5-Membered Rings with Aryl Halides

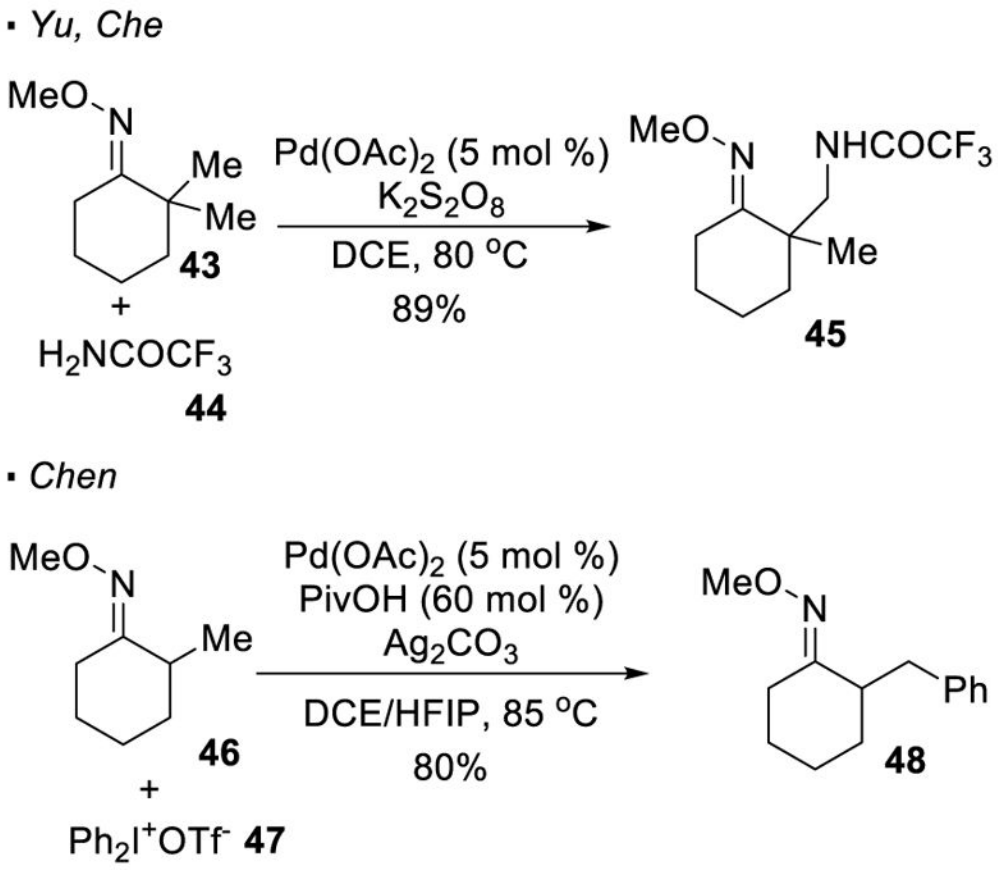
▪ *Baudoin*



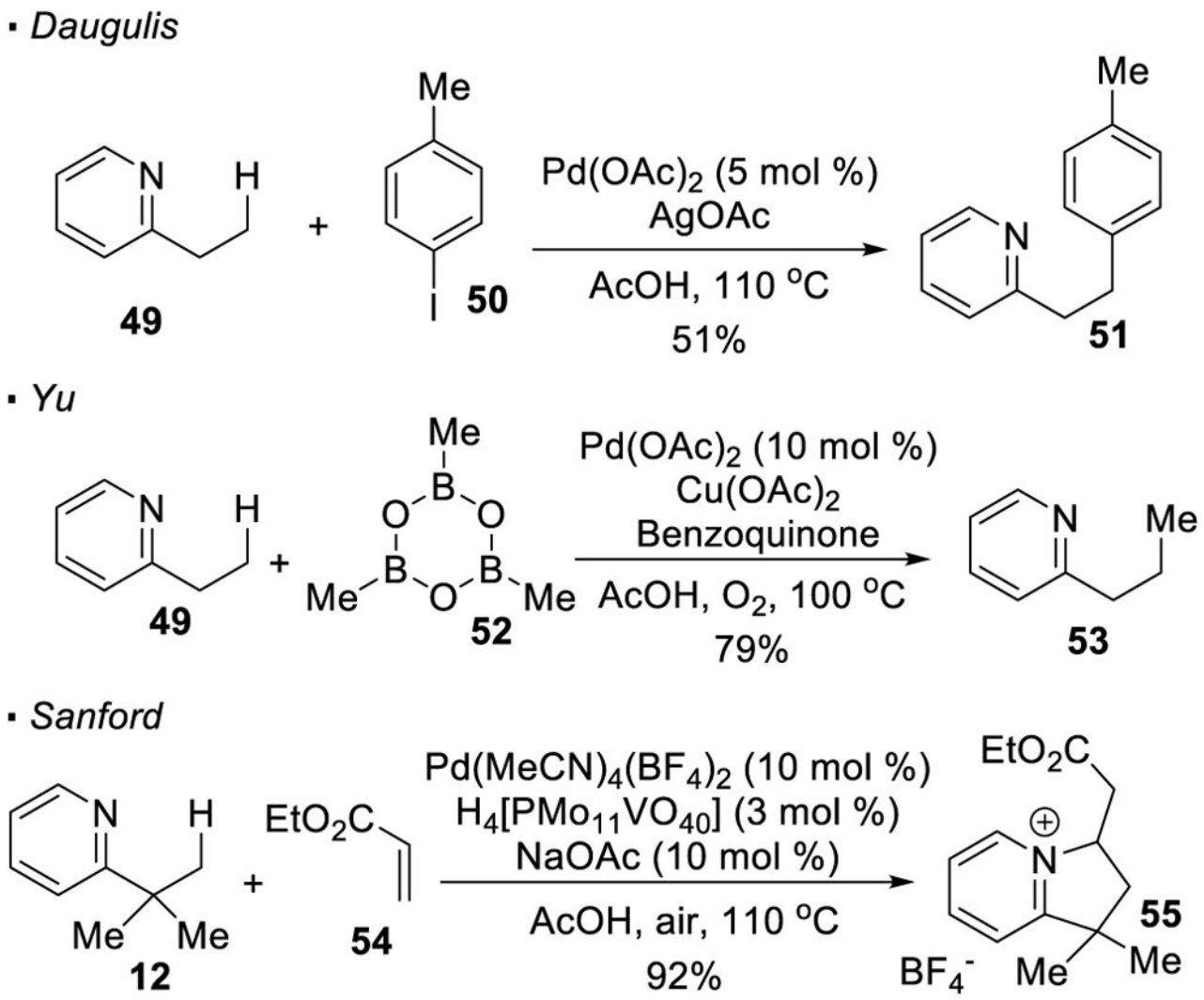
Scheme 7.
Vinyl Halides as Traceless Directing Group



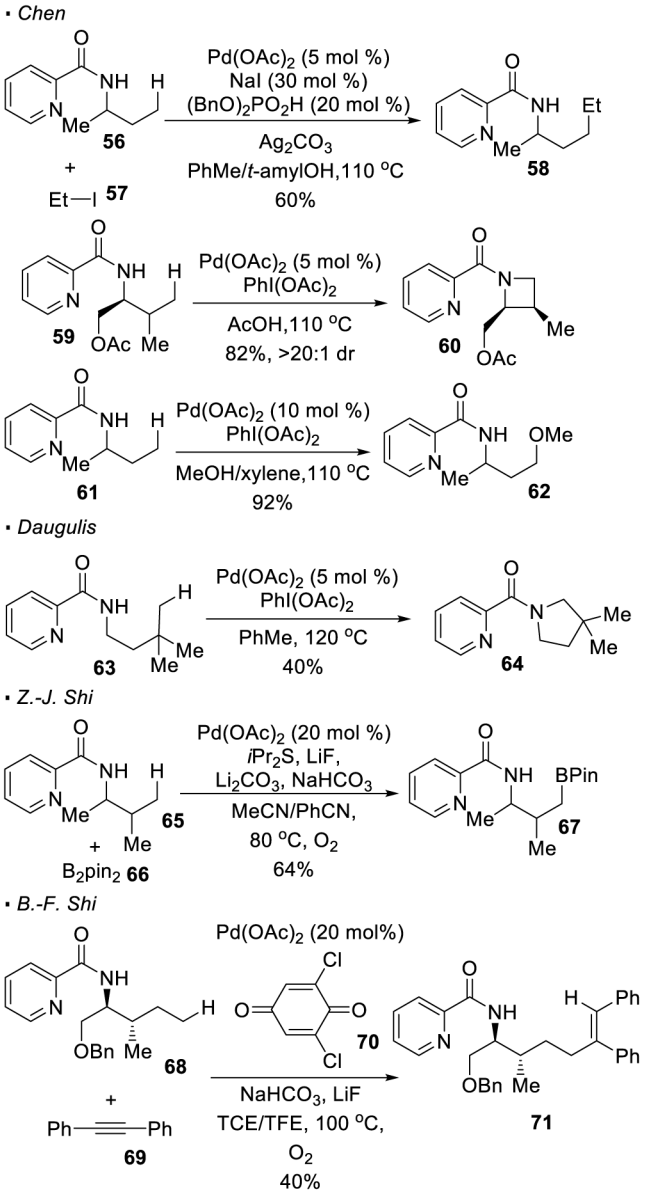
Scheme 8.
Generation of Aryl/Vinyl Palladium through Other Means



Scheme 9.
Oxime-Directed C-H Activation

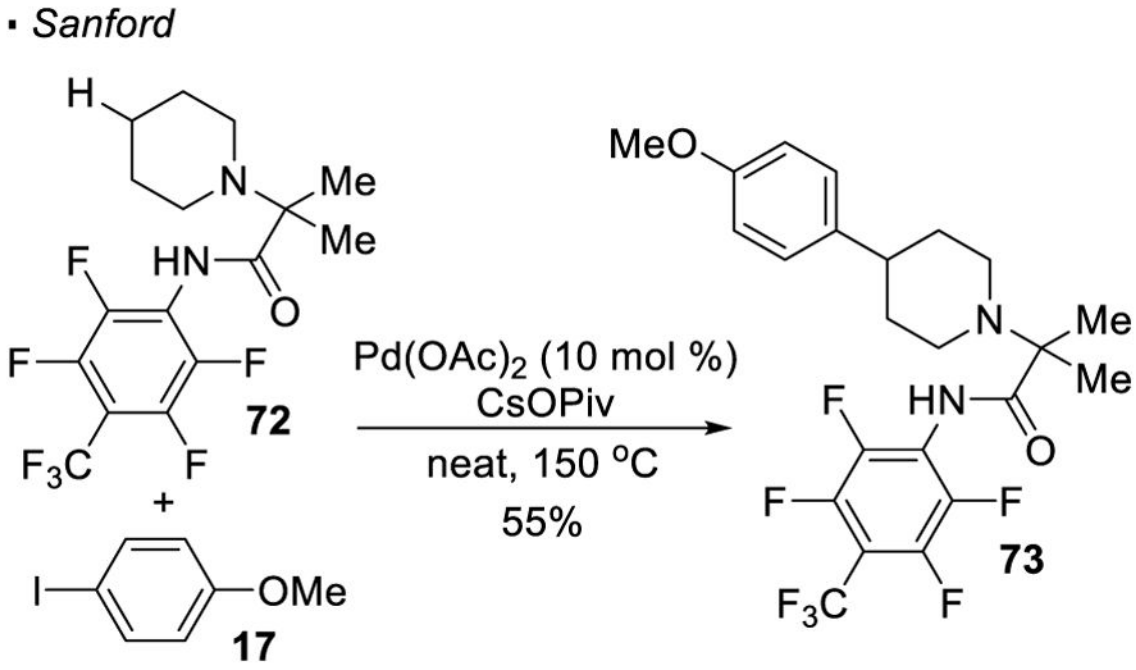


Scheme 10.
Derivatization of Pyridines through C-H Activation



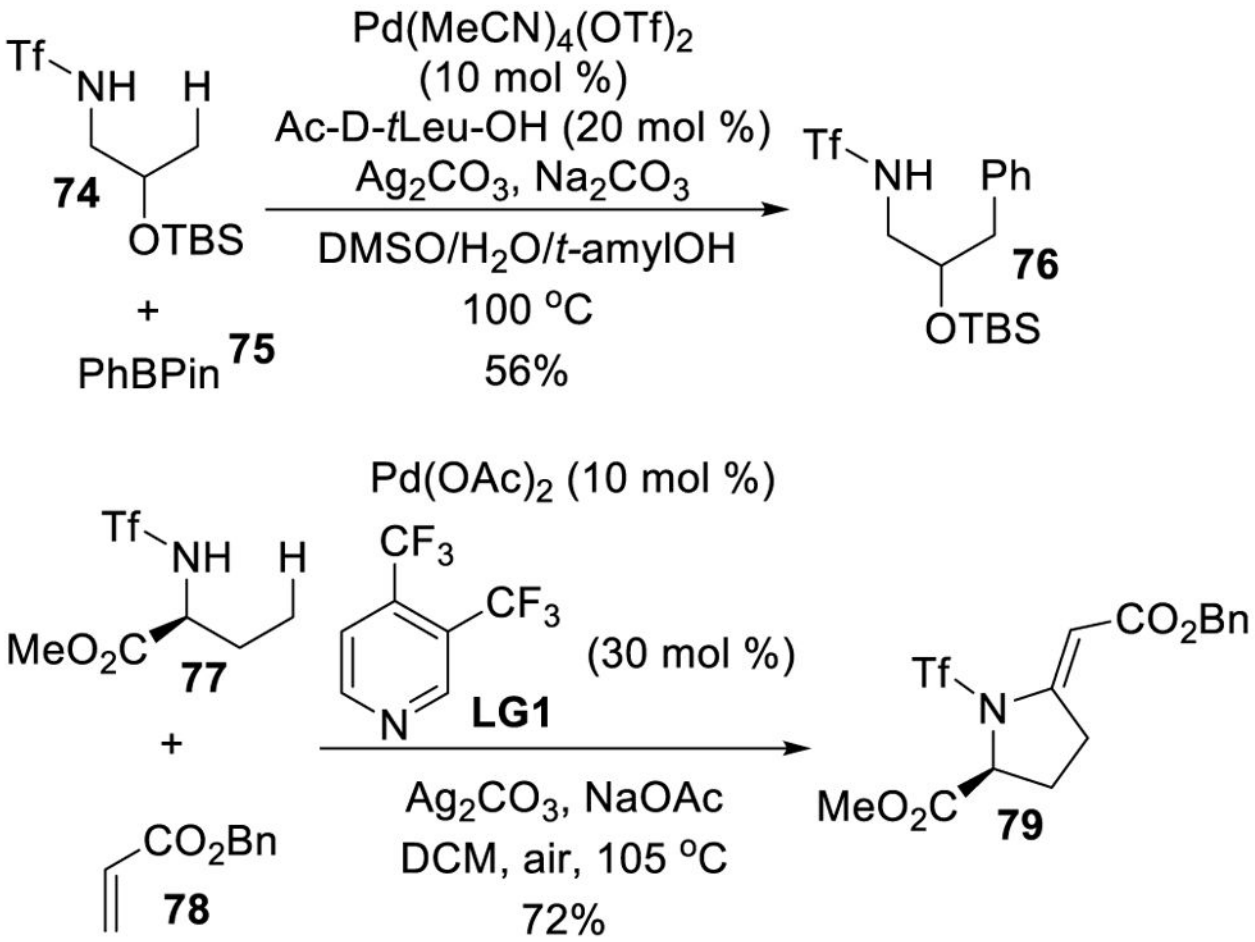
Scheme 11.

Use of Picolinamides for Amine Functionalization



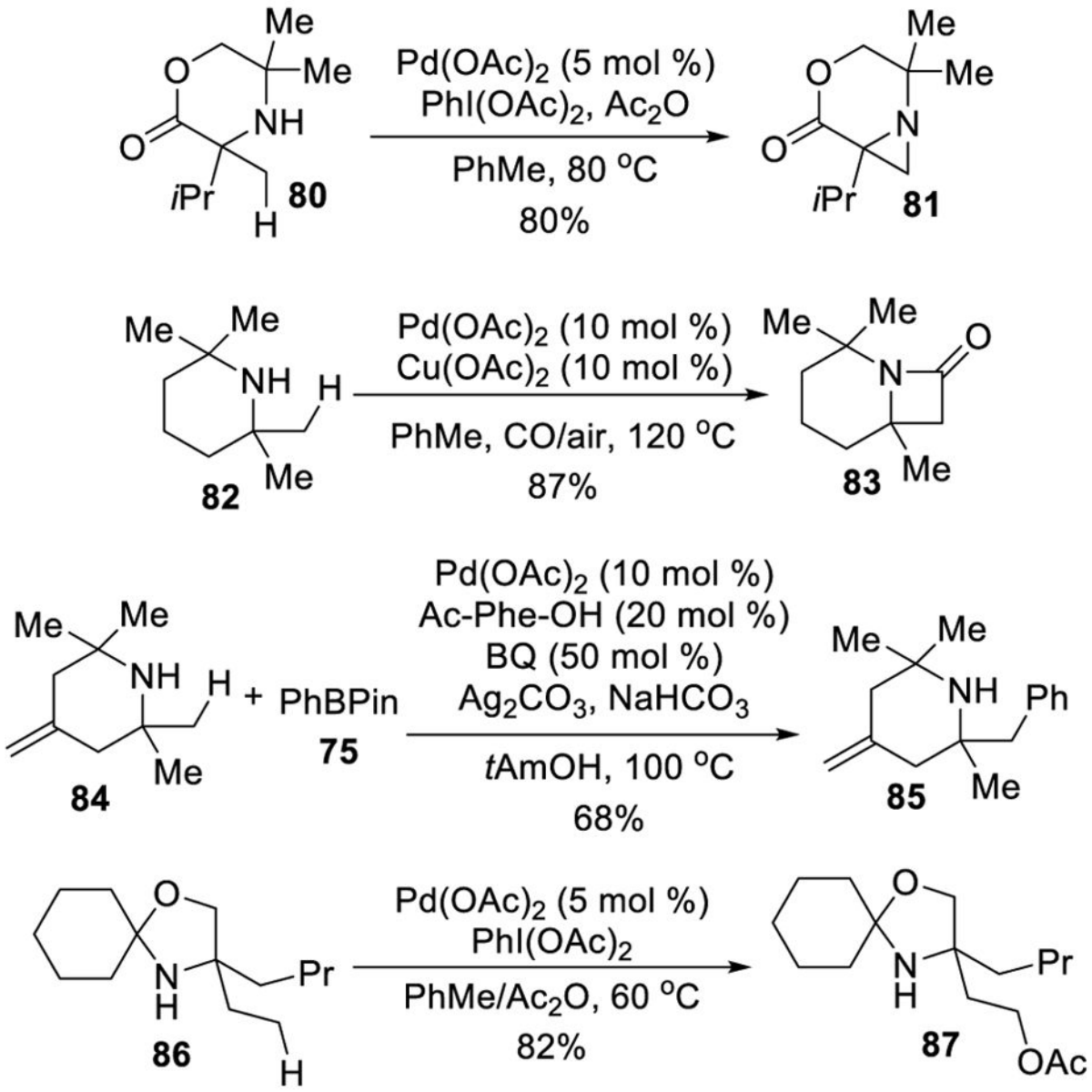
Scheme 12.
Transannular C-H Activation of Alicyclic Amines

▪ *Yu*

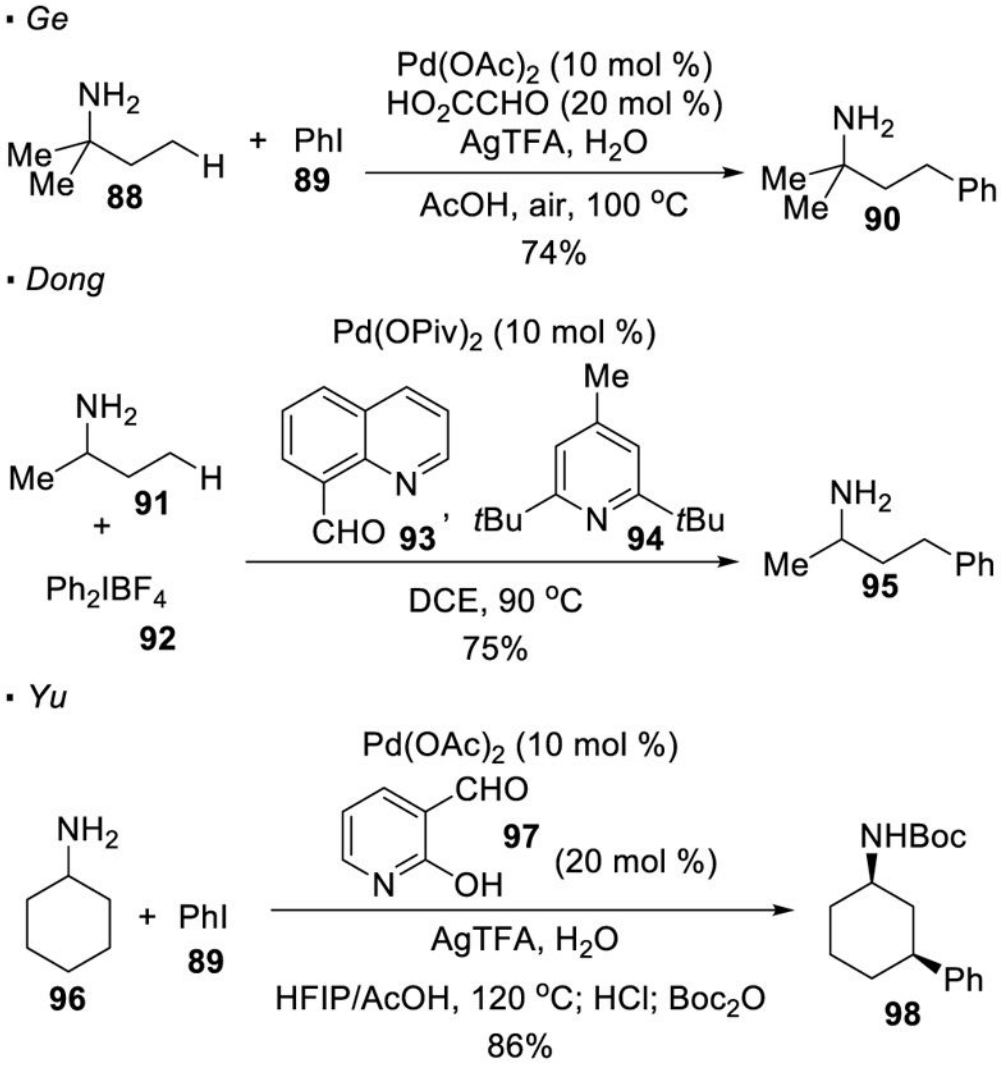


Scheme 13.
Sulfonamides as Directing Group for Functionalization of Amines

▪ *Gaunt*

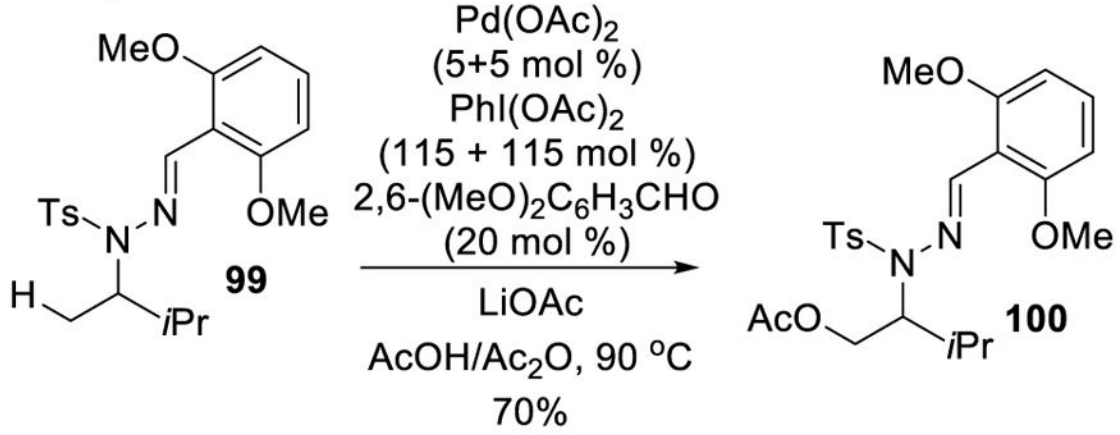


Scheme 14.
C-H Functionalization of Free Amines

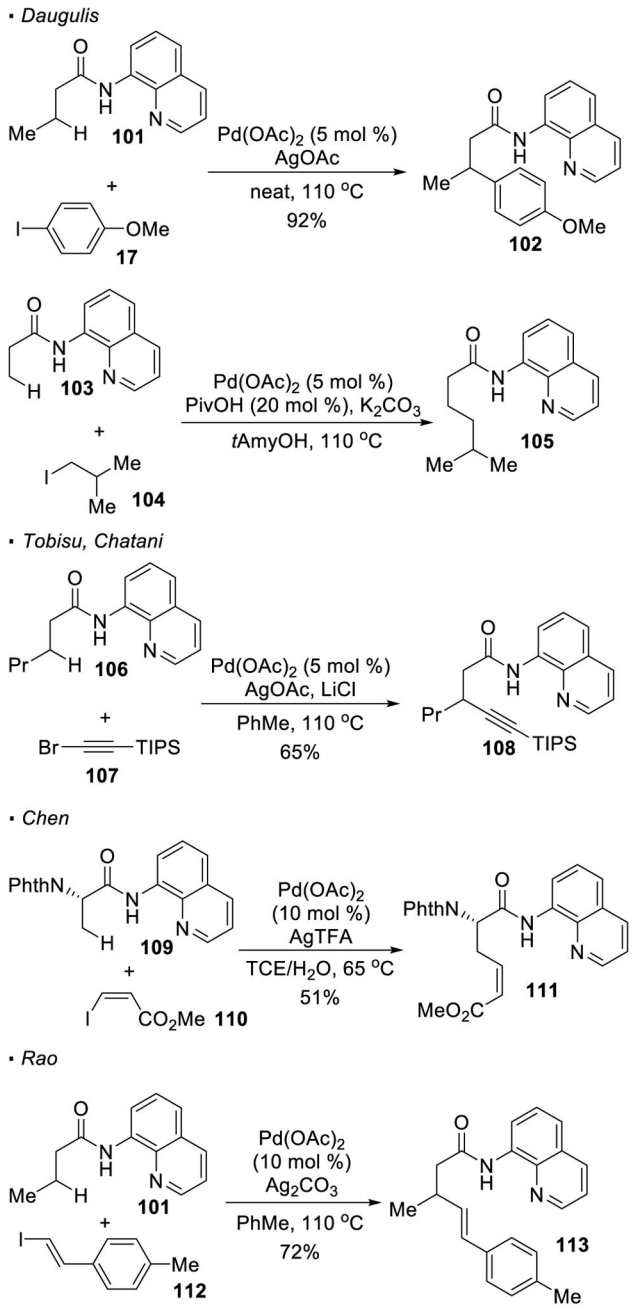


Scheme 15.
In-situ Generated Imines as Directing Groups

▪ *Dong*

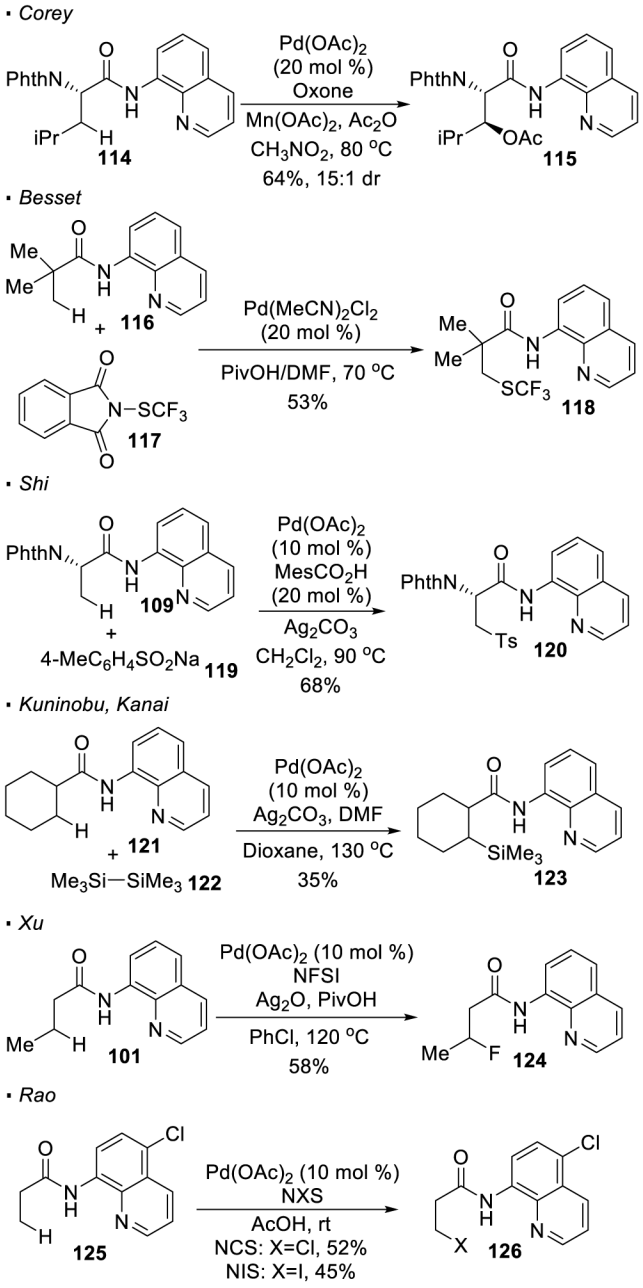


Scheme 16.
Hydrazone-Directed C-H Activation



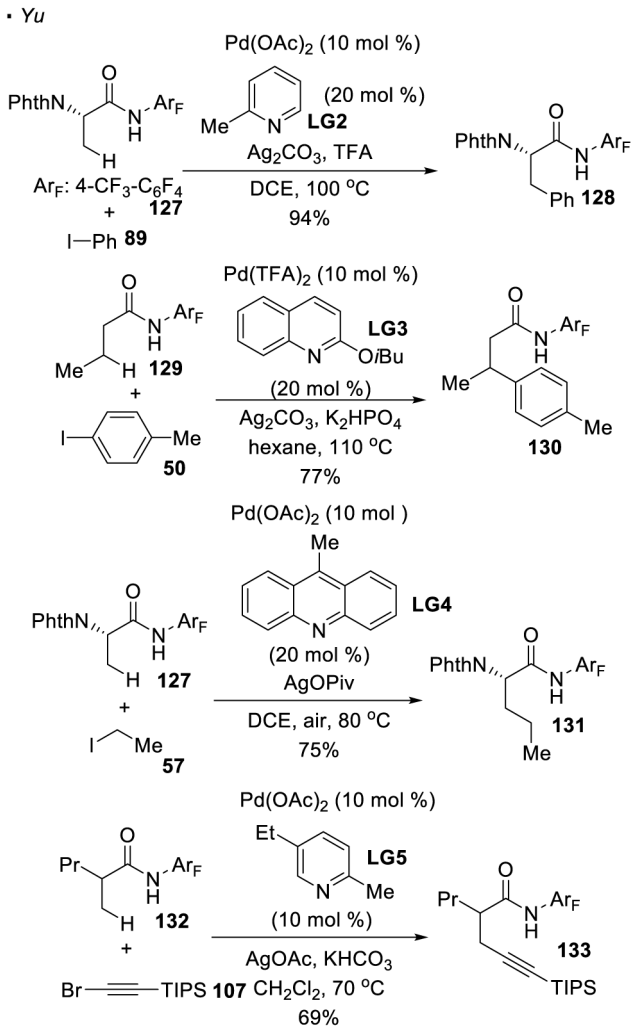
Scheme 17.

Formation of C-C Bonds with 8-aminoquinolines



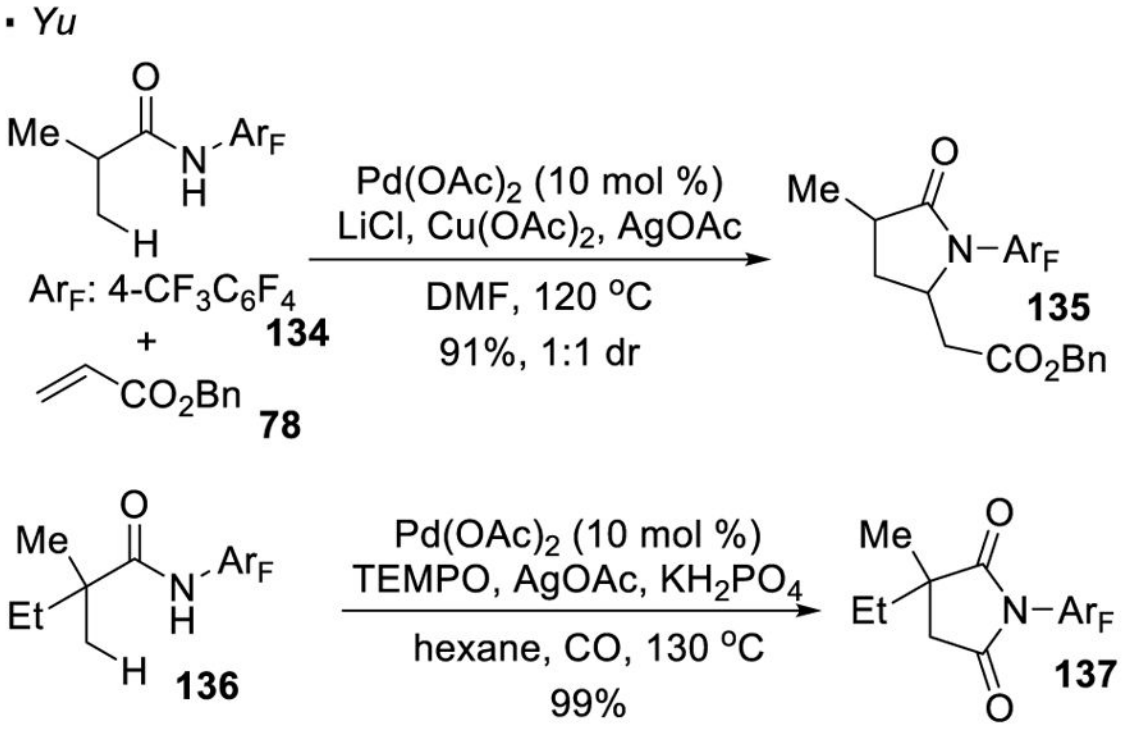
Scheme 18.

Formation of C-X Bonds with 8-aminoquinolines

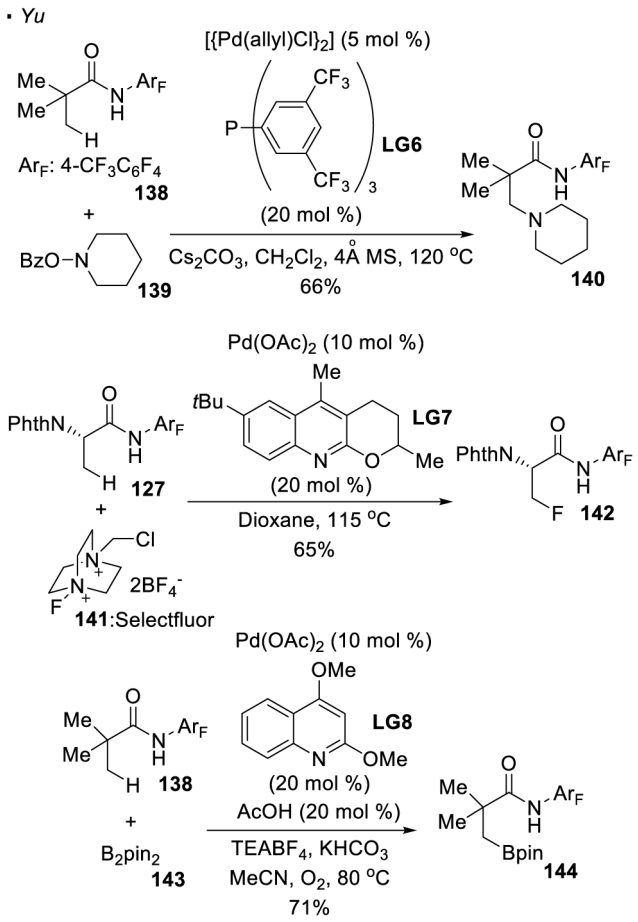


Scheme 19.

Formation of C-C Bonds with Perfluorinated Amides



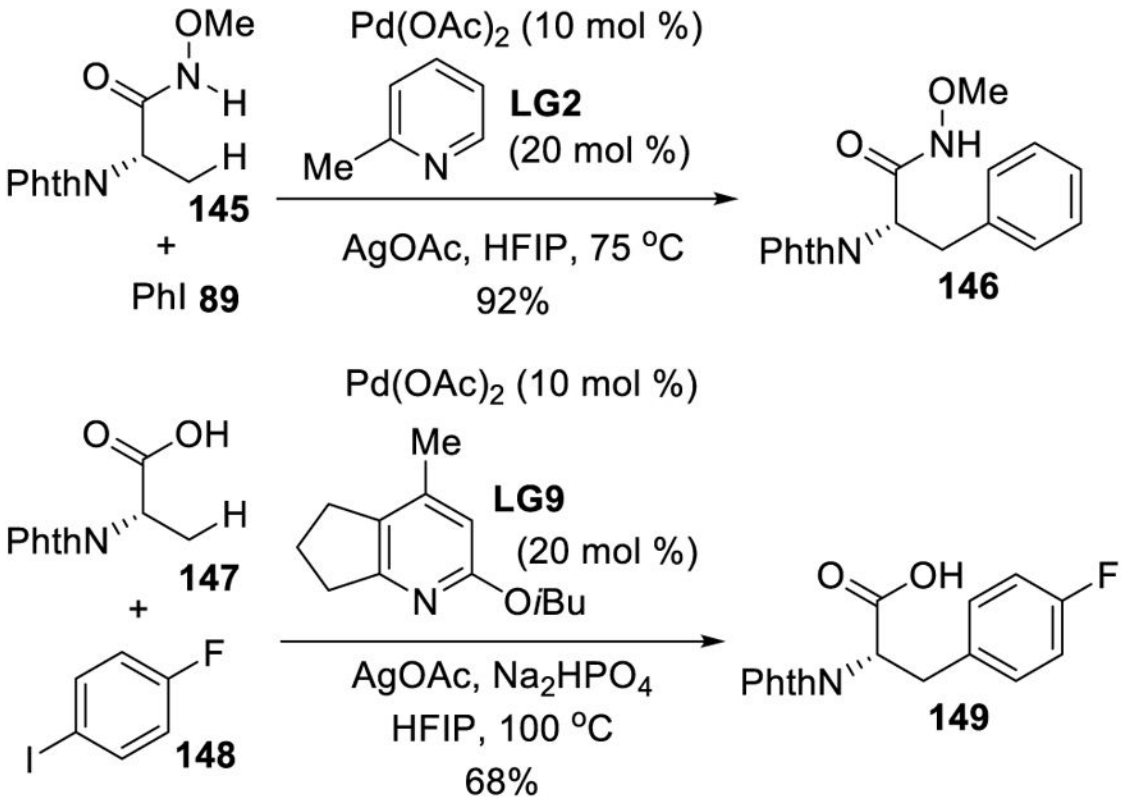
Scheme 20.
Synthesis of Nitrogen-Heterocycles from Perfluorinated Amides



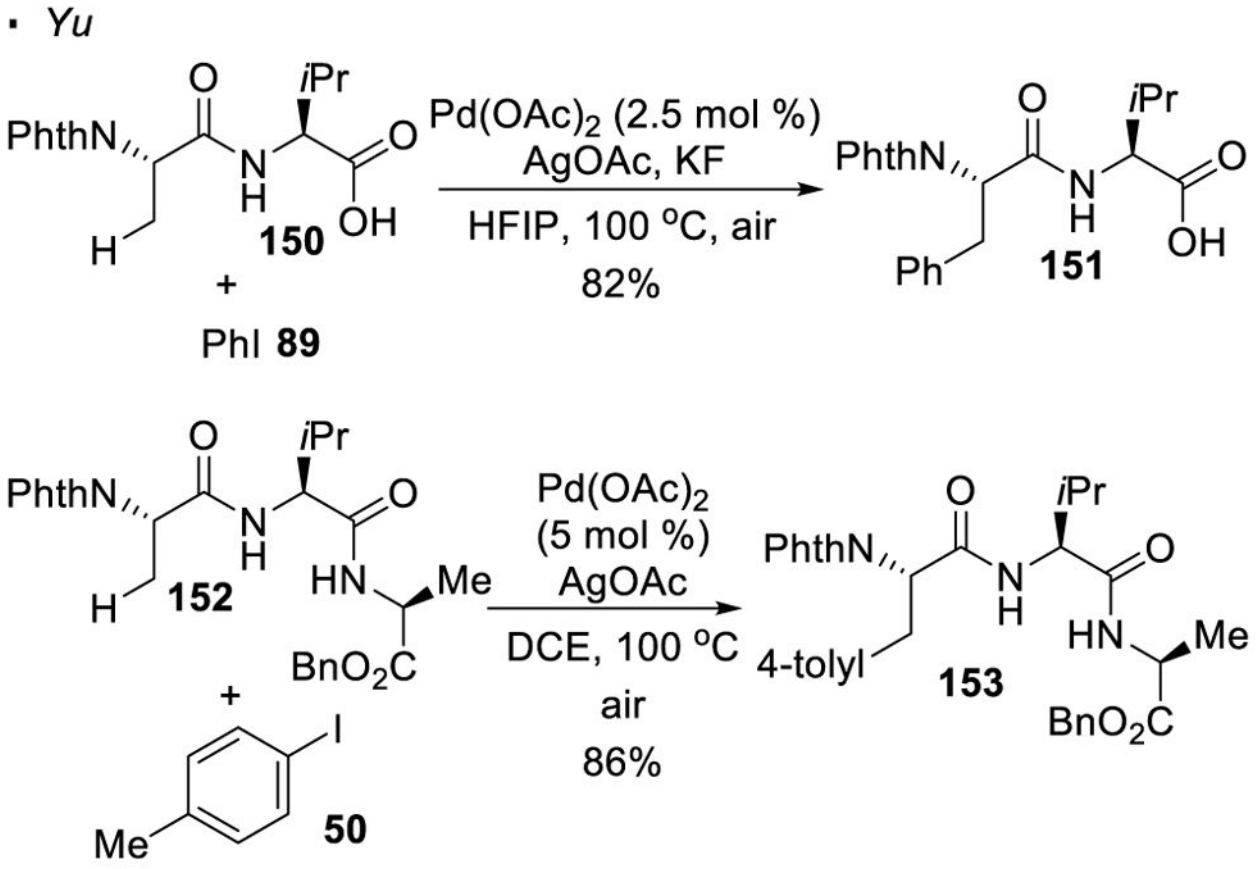
Scheme 21.

Formation of C-X Bonds with Perfluorinated Amides

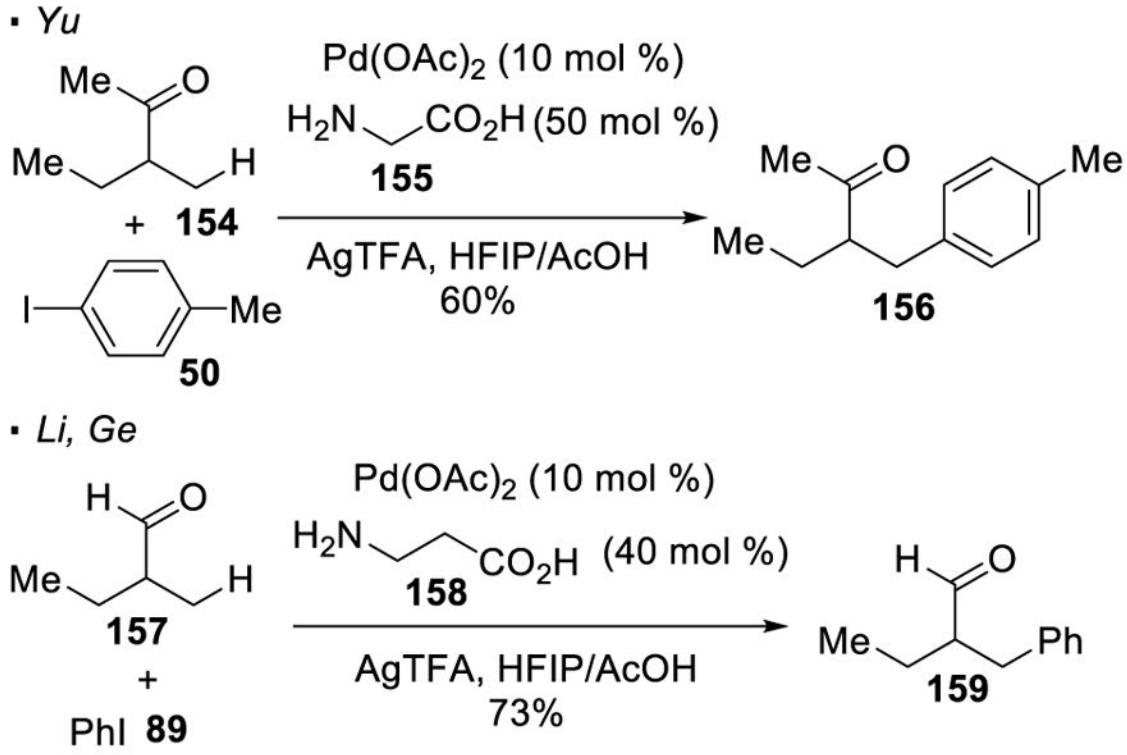
▪ *Yu*



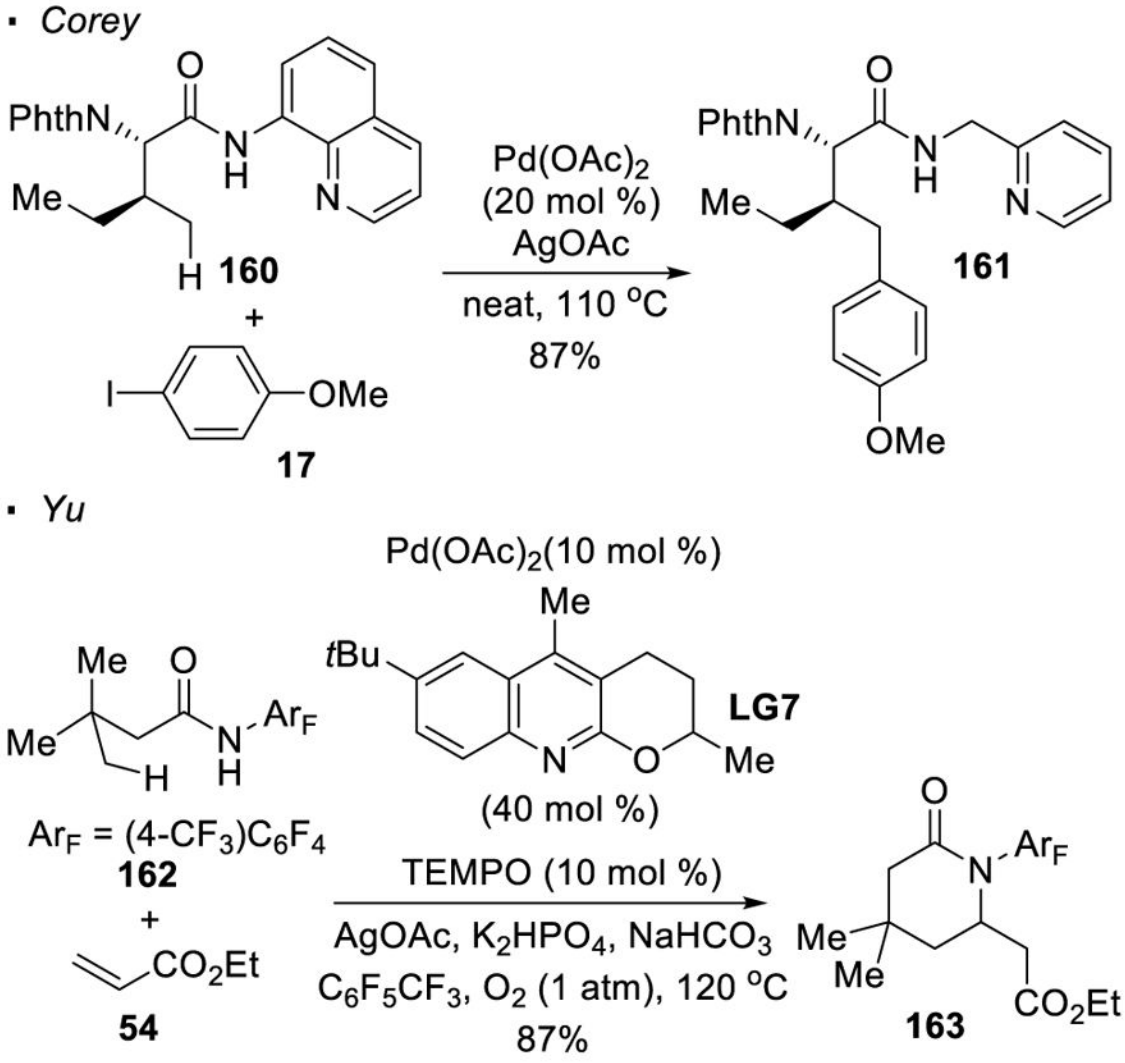
Scheme 22.
C-H Functionalization with *O*-Methyl Hydroxamic acids and Carboxylic Acids



Scheme 23.
C-H Functionalization of Peptides



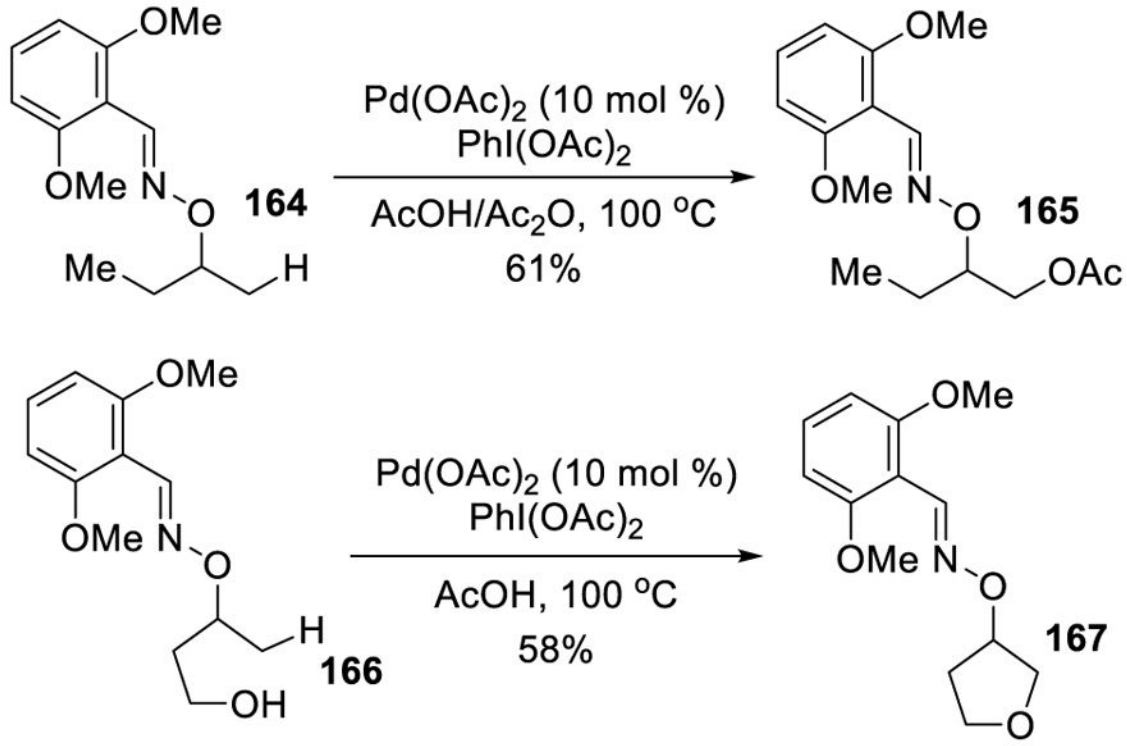
Scheme 24.
In-situ Generation of Directing Group from Carbonyl Groups



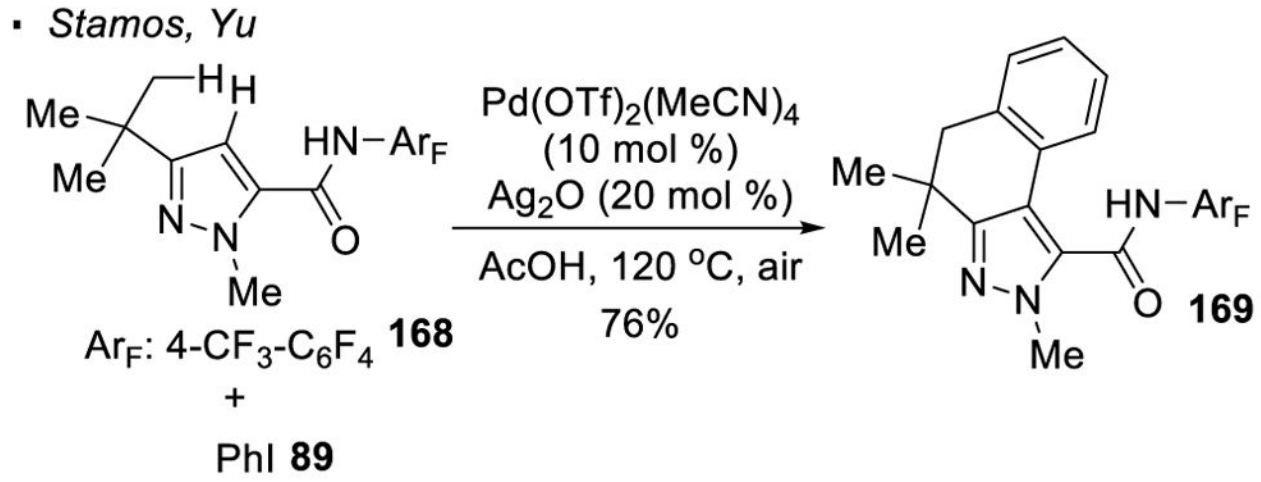
Scheme 25.

γ Functionalization of Carbonyl Compounds

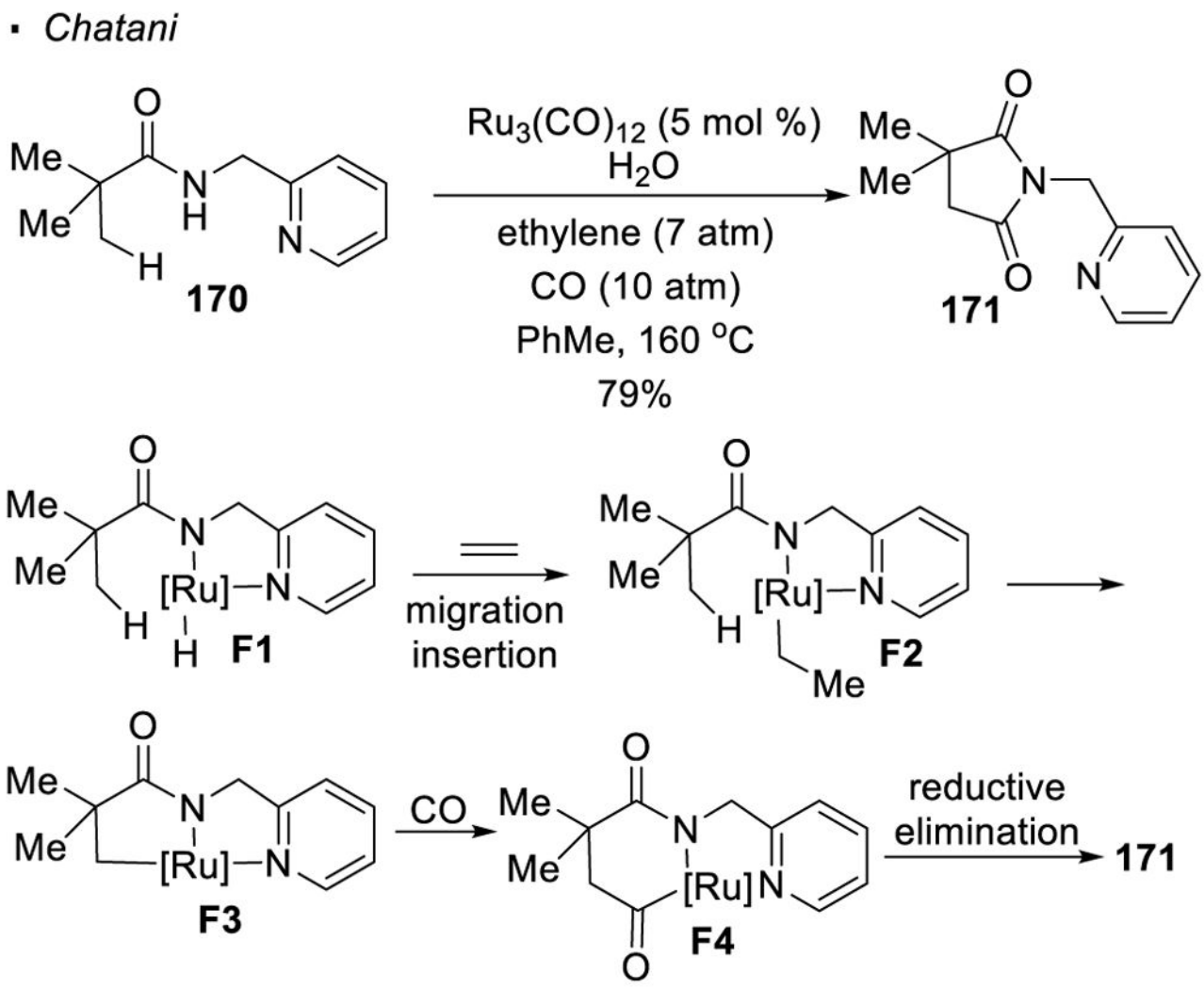
▪ *Dong*



Scheme 26.
C-H Activation of Alcohol Derivatives

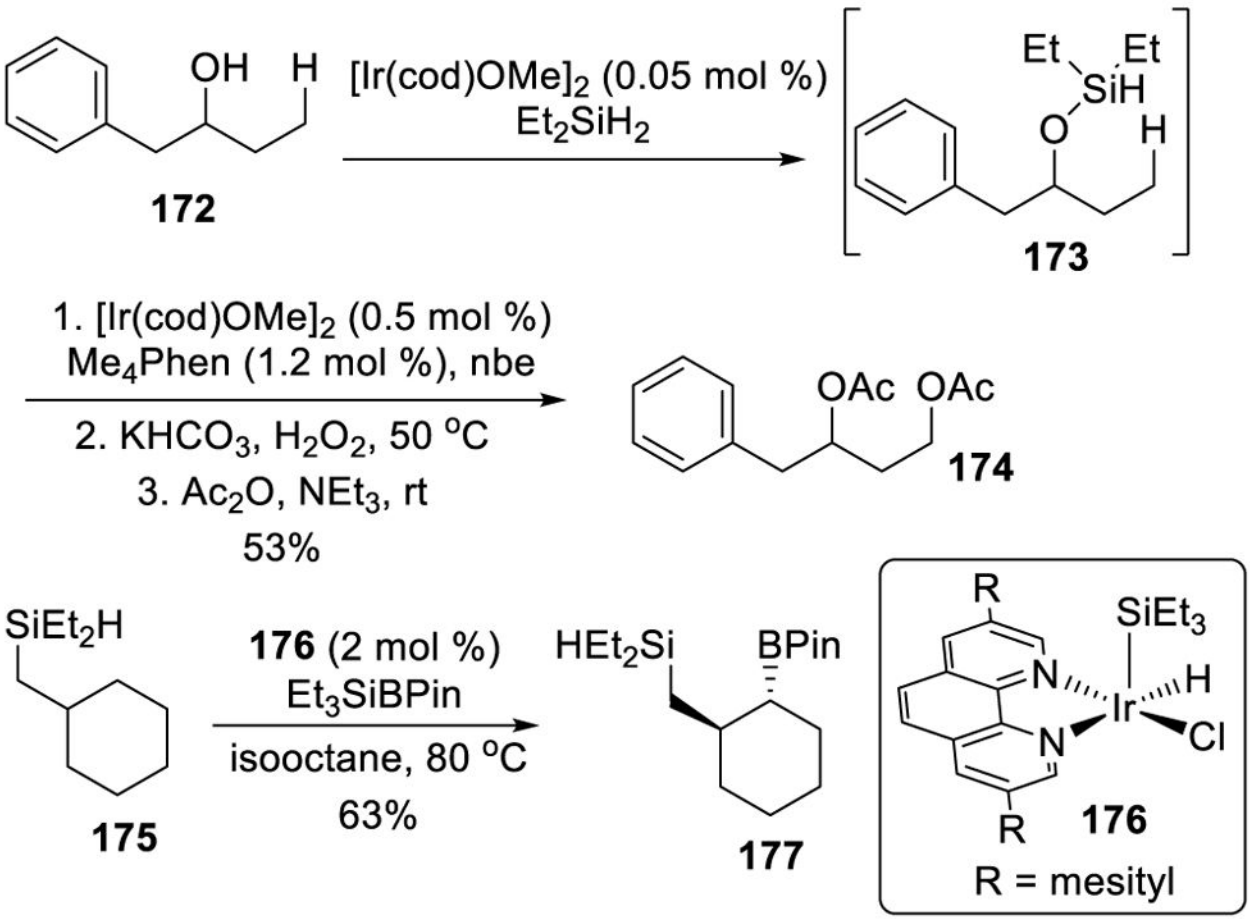


Scheme 27.
Pyrazole-Directed C-H Activation



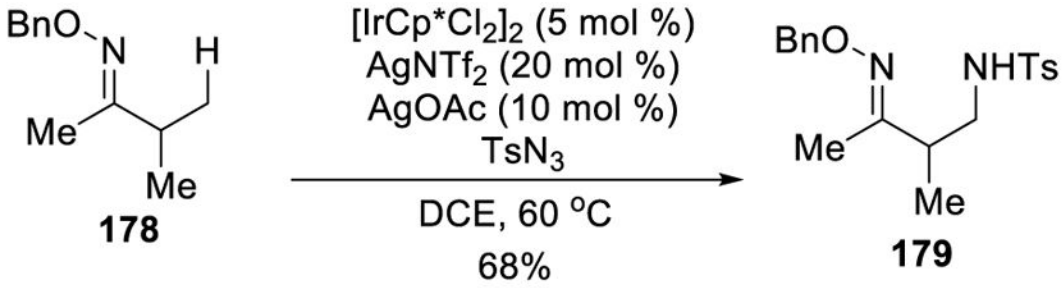
Scheme 28.
Ru-Catalyzed C-H Activation

▪ *Hartwig*

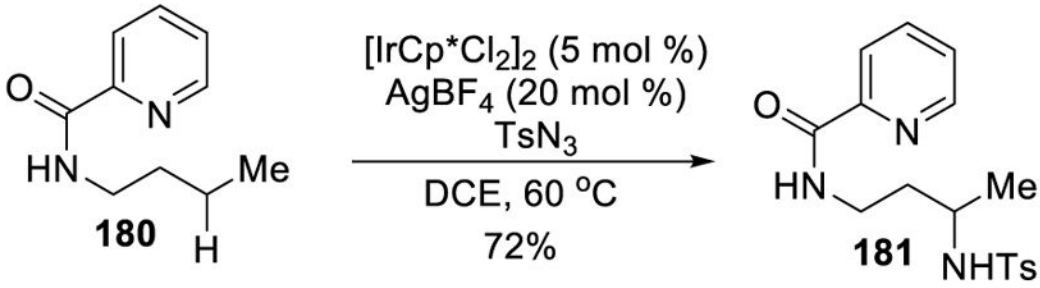


Scheme 29.
Ir(I)-Catalyzed Borylation

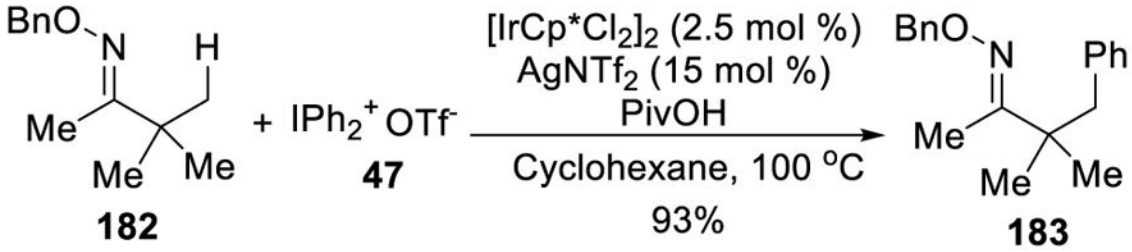
- *Chang*



- *Ke, Zeng*

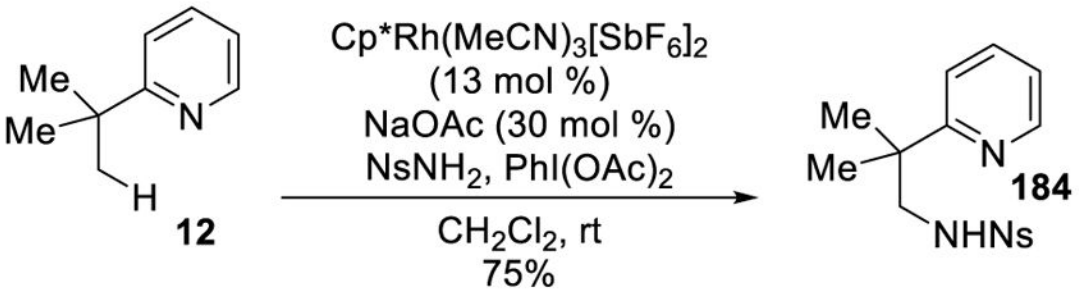


- *Xia and Shi*

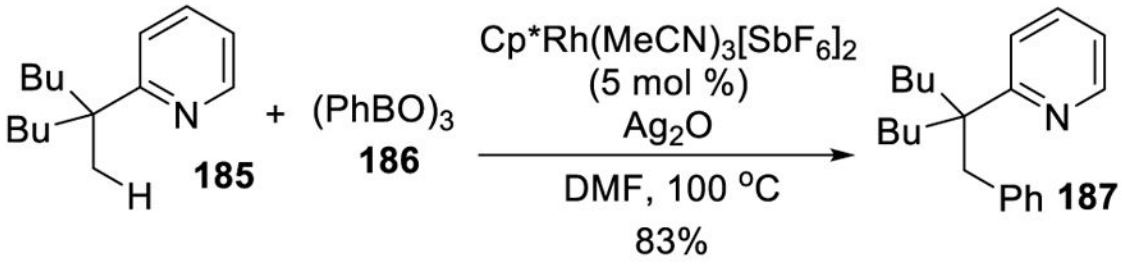


Scheme 30.
Ir(III)-catalyzed C-H Amination and Arylation

- *You*

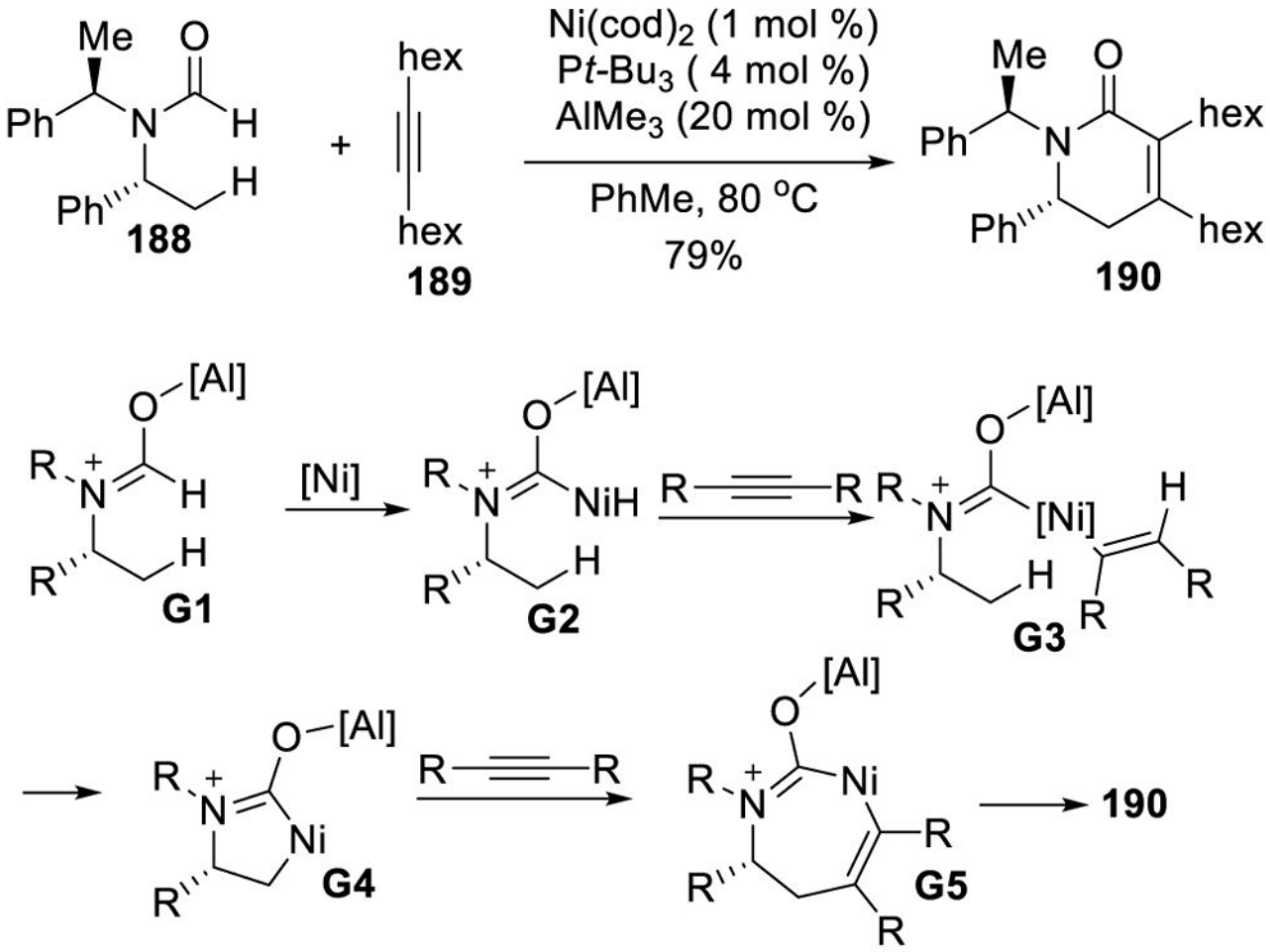


- *Glorius*



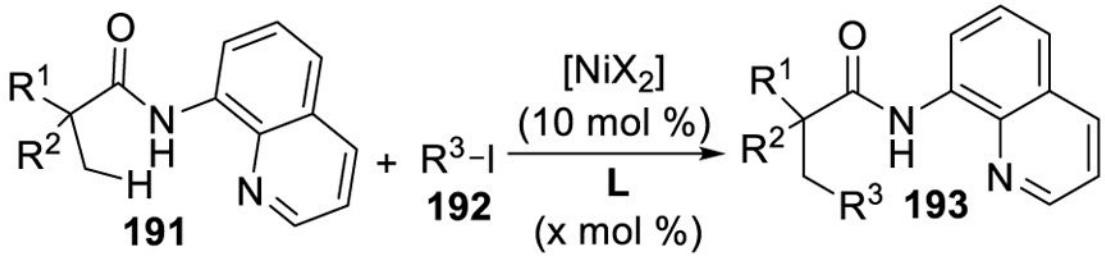
Scheme 31.
Rh(III)-Catalyzed C-H Amination of Pyridines

▪ *Nakao, Hiyama*



Scheme 32.
Nickel(0)-Catalyzed [4+2] Cycloaddition

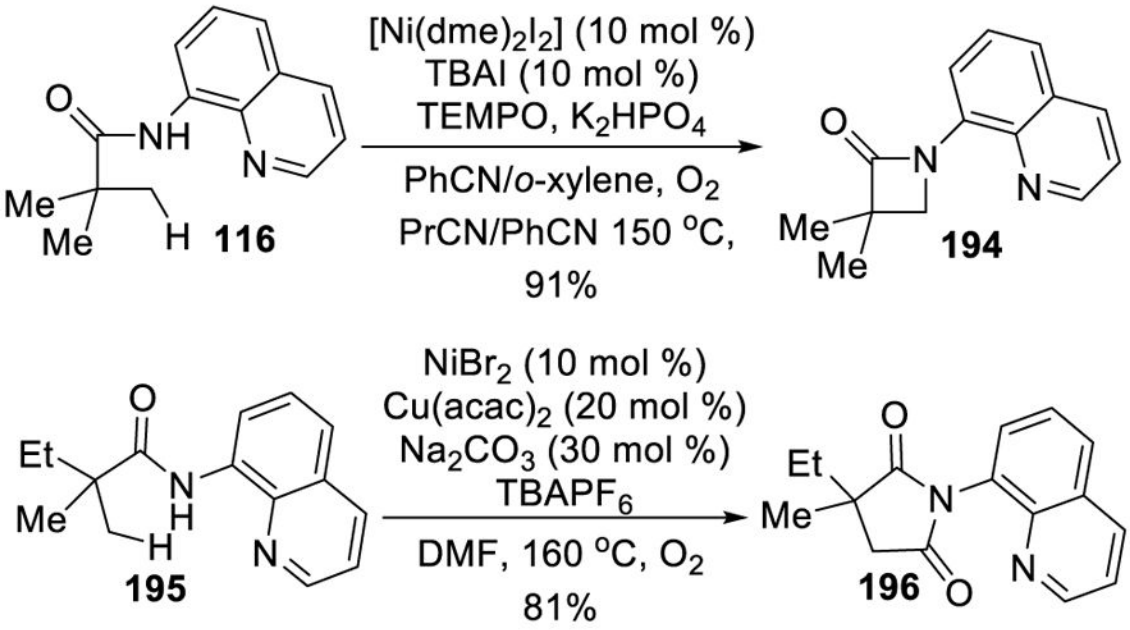
- *Chatani, Ge, Shi*



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%

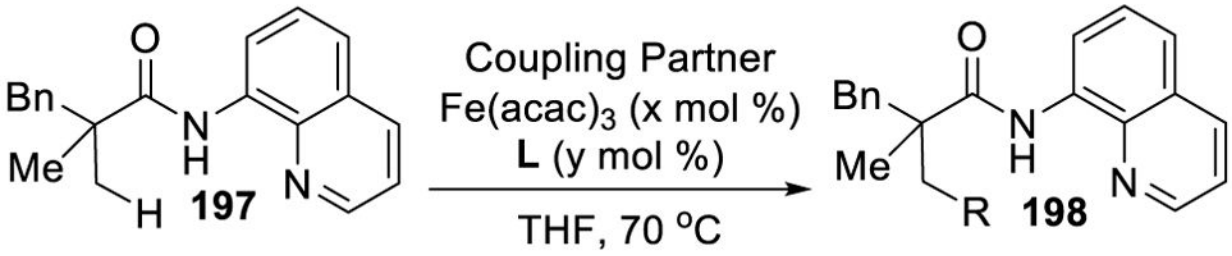
Scheme 33.
Nickel(II)-catalyzed C-H Functionalization

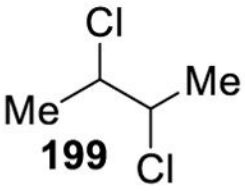
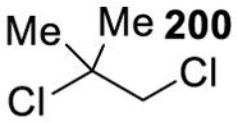
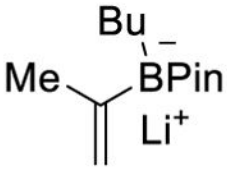
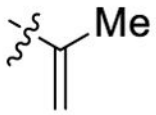
▪ *Ge*



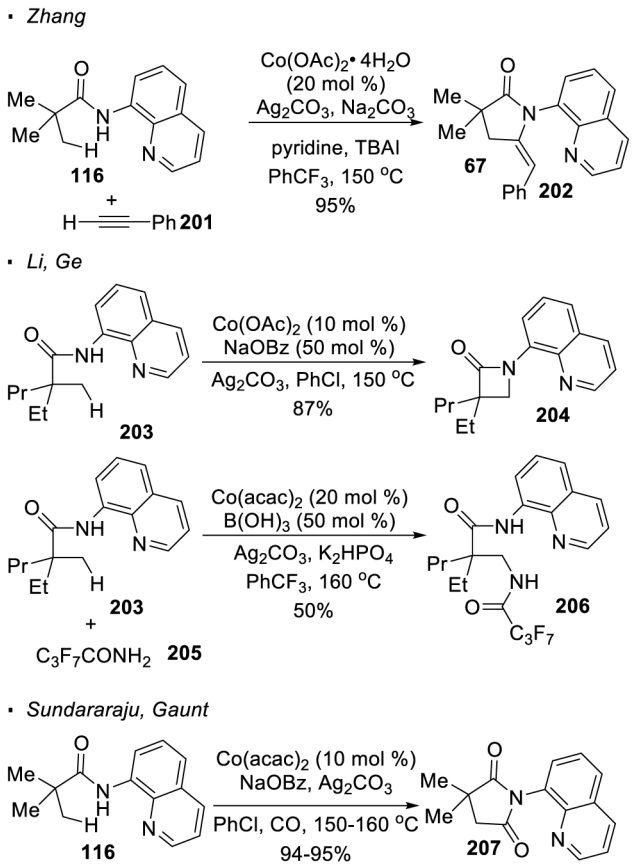
Scheme 34.
Synthesis of Nitrogen Heterocycles with Ni(II) Catalysis

- *Ilies, Nakamura*

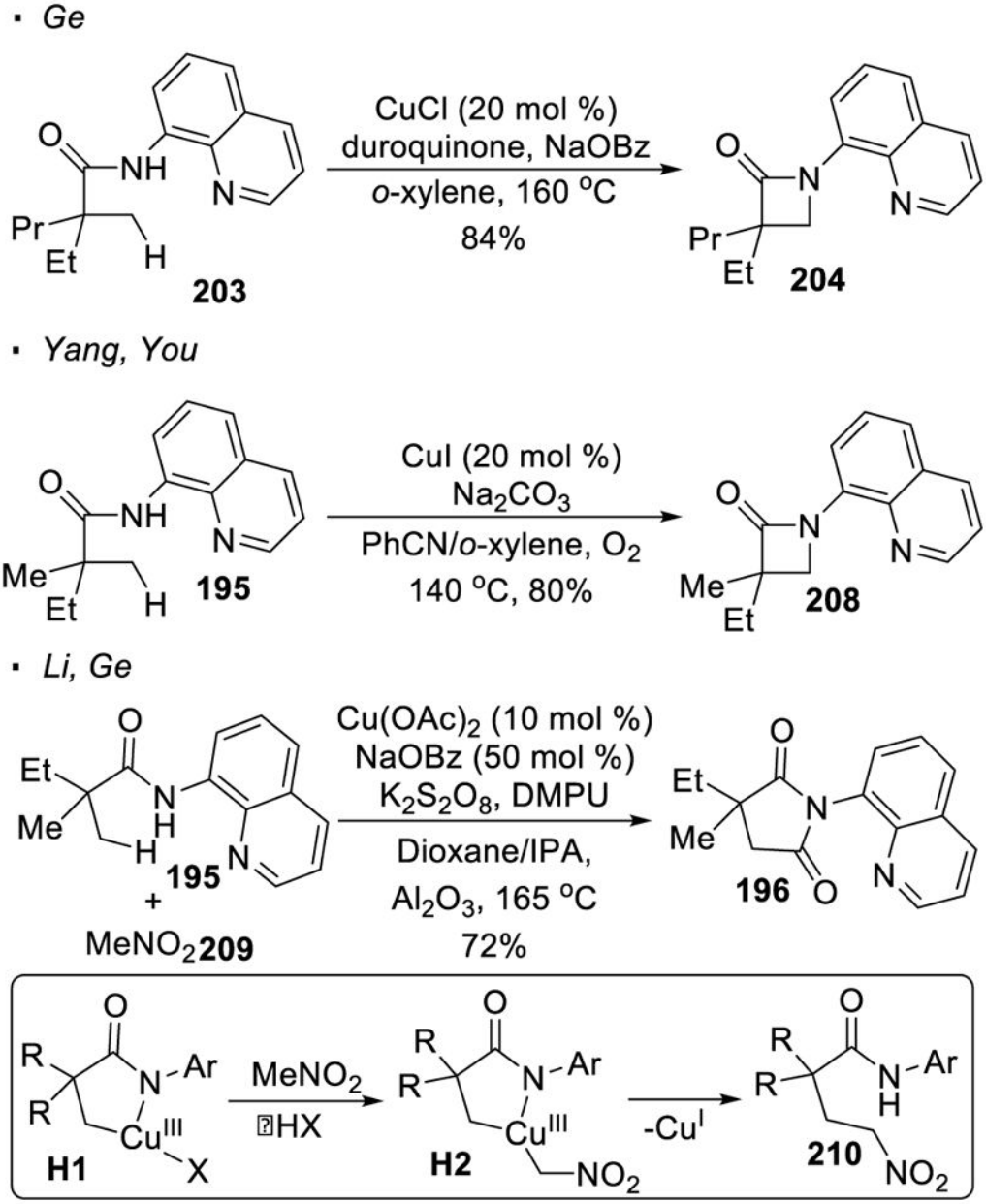


Coupling Partner	R	x, y L	Conditions	Yield
$PhMgBr$ $Ph_2Zn.MgBr$	Ph	10, 10 dppbz	 **199**	80%
$AlMe_3$	Me	10, 11 Ph-dppen	 **200**	84%
		20, 20 MeO-dppen	**199**, $Zn(OAc)_2$ (20 mol %)	80%

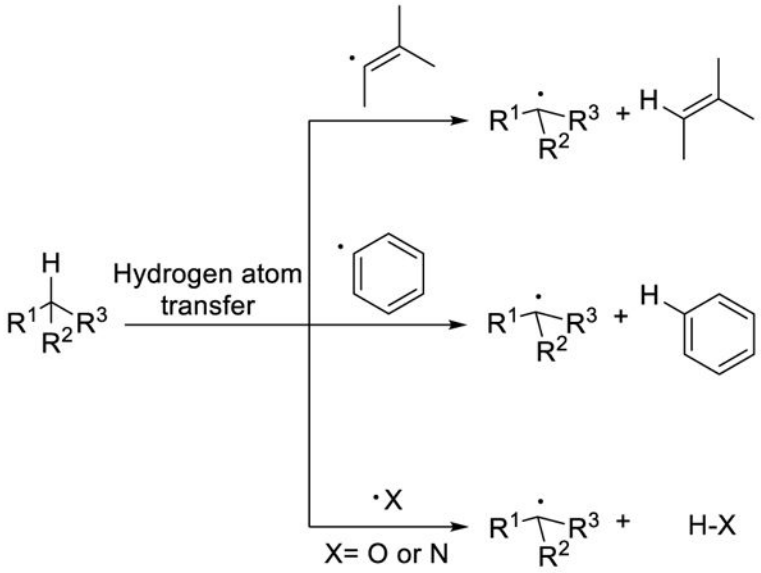
Scheme 35.
Fe-Catalyzed Formation of C-C Bonds



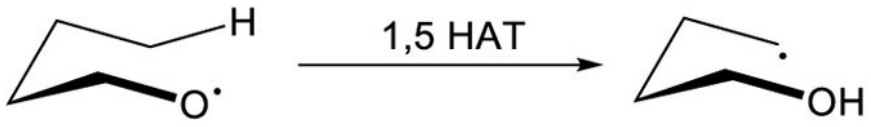
Scheme 36.
Co-Catalyzed C-H Functionalization



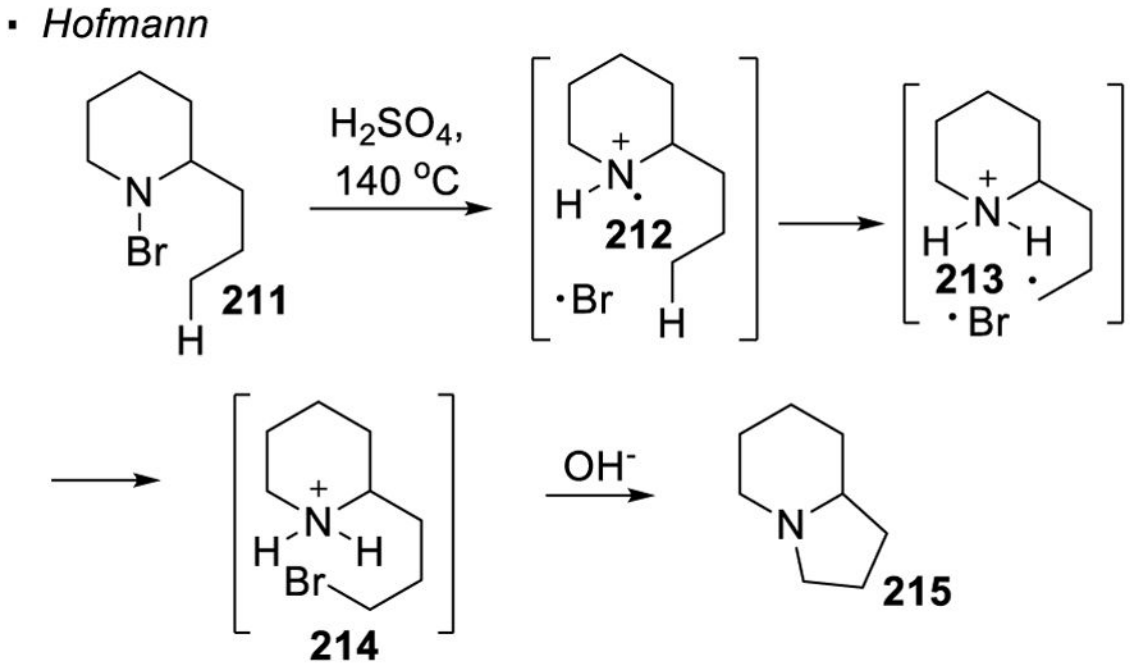
Scheme 37.
Cu-Catalyzed C-H Functionalization



Scheme 38.
Hydrogen Atom Transfer

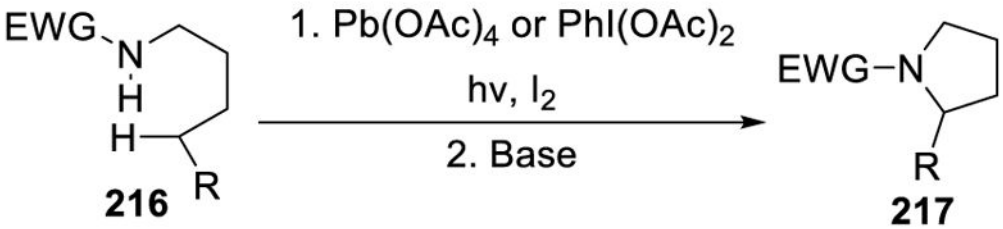


Scheme 39.
1,5 Hydrogen Atom Transfer



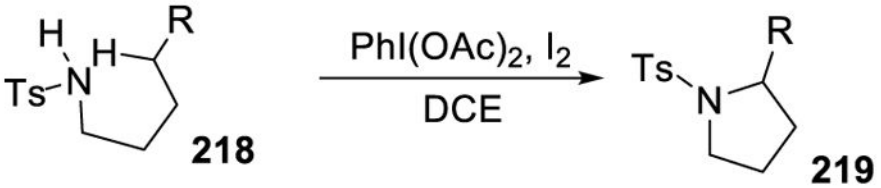
Scheme 40.
Generation of Nitrogen Radicals by Homolysis of N-X Bonds

- *Suarez*

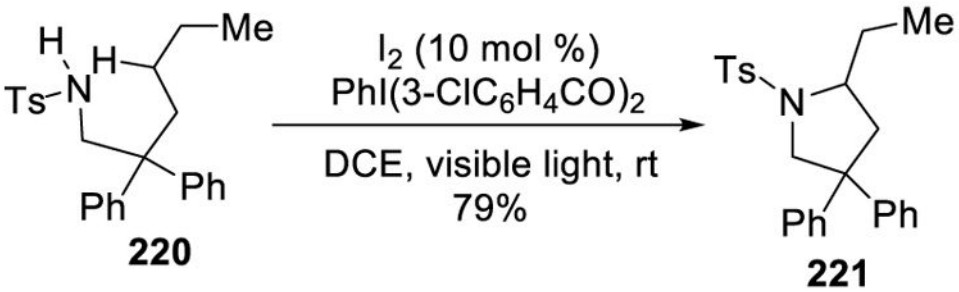


EWG: NO_2, CN, $PO(OR)_2$, Cbz, Boc

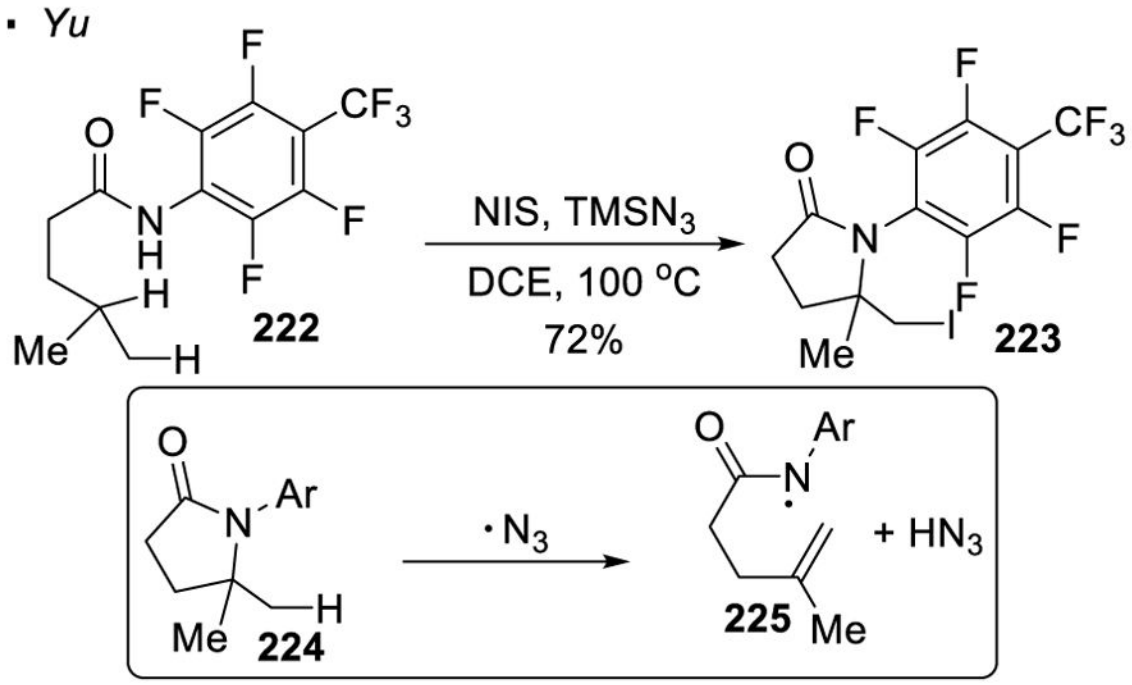
- *Togo, Yokoyama, Fan*



- *Muniz*



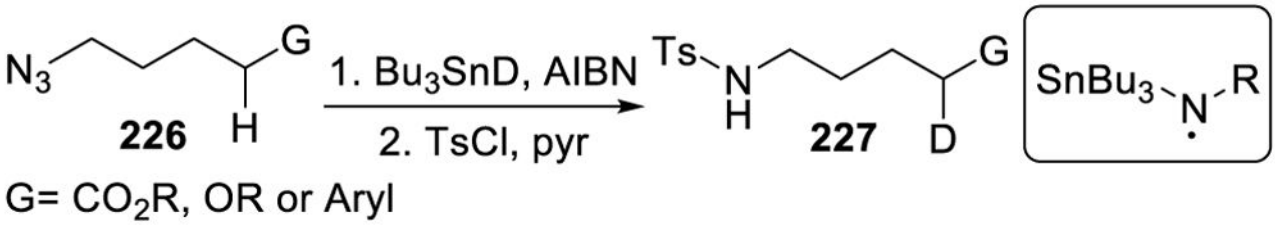
Scheme 41.
In-situ Generation of N-X Bonds



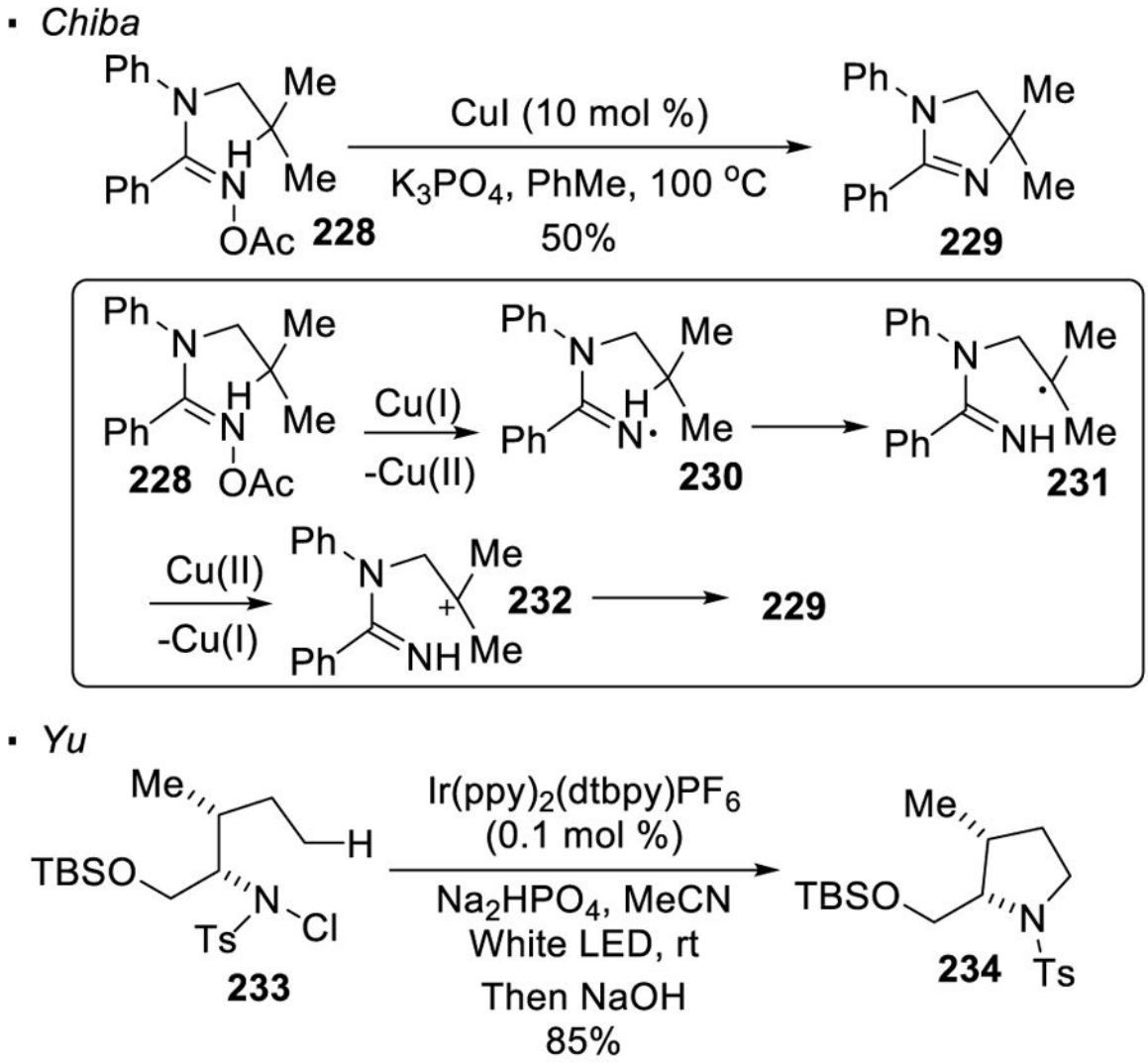
Scheme 42.

γ, ε Functionalization with Nitrogen Radicals

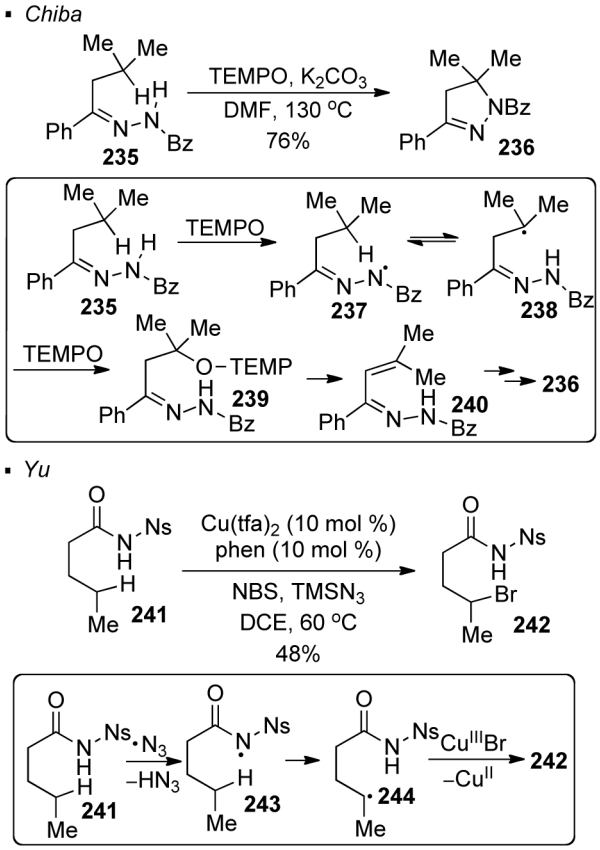
▪ *Kim*



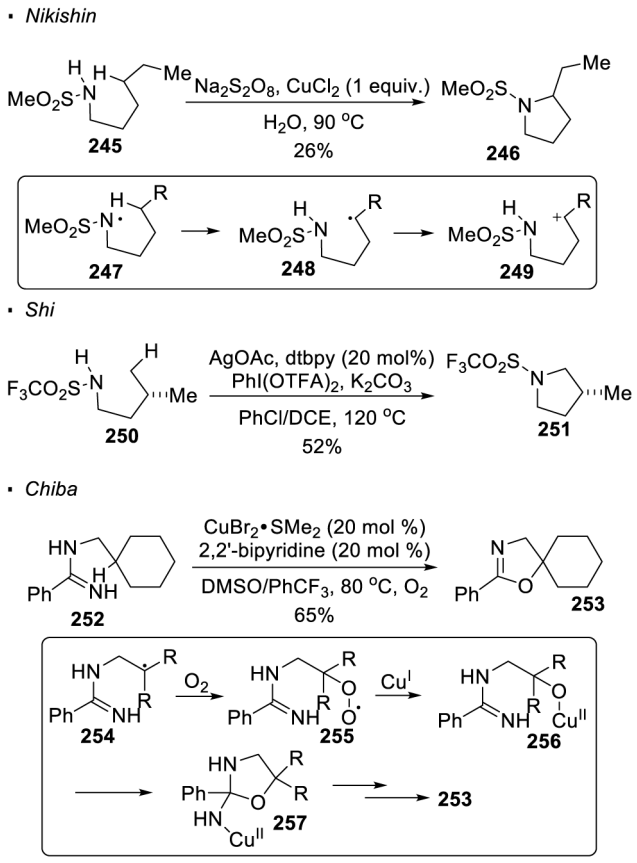
Scheme 43.
Generation of Nitrogen Radicals by Reduction of Organic Azides



Scheme 44.
Catalytic Reduction of N-X Bonds

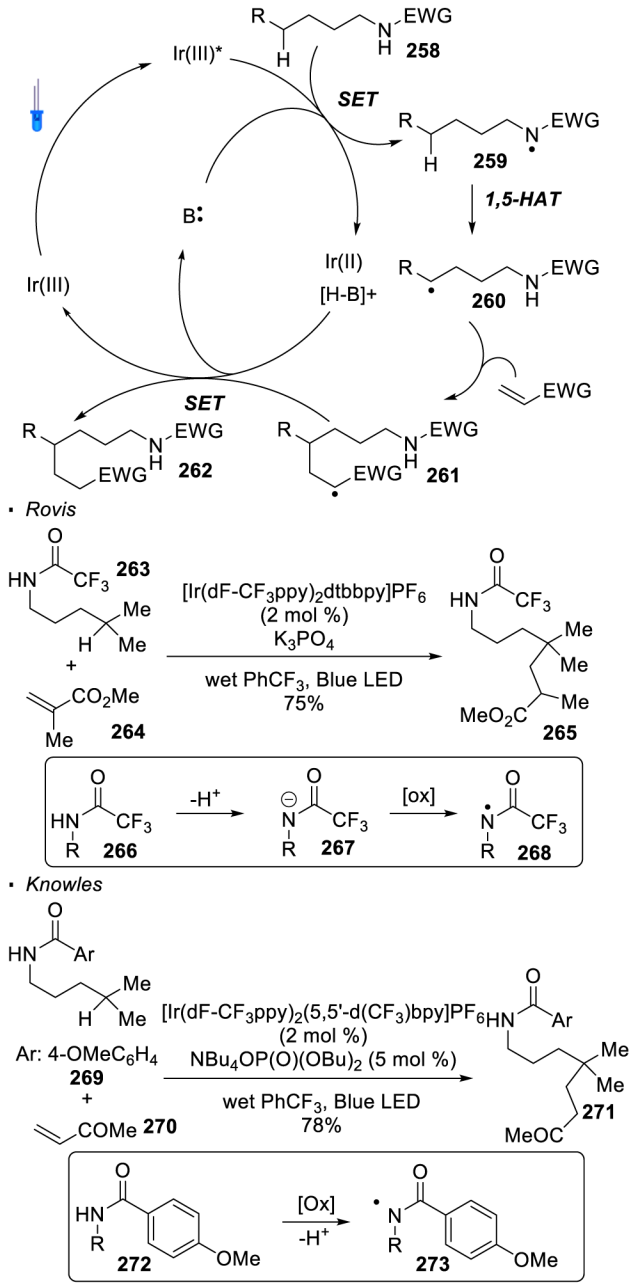


Scheme 45.
Generation of Nitrogen Radicals by Abstraction of Hydrogen

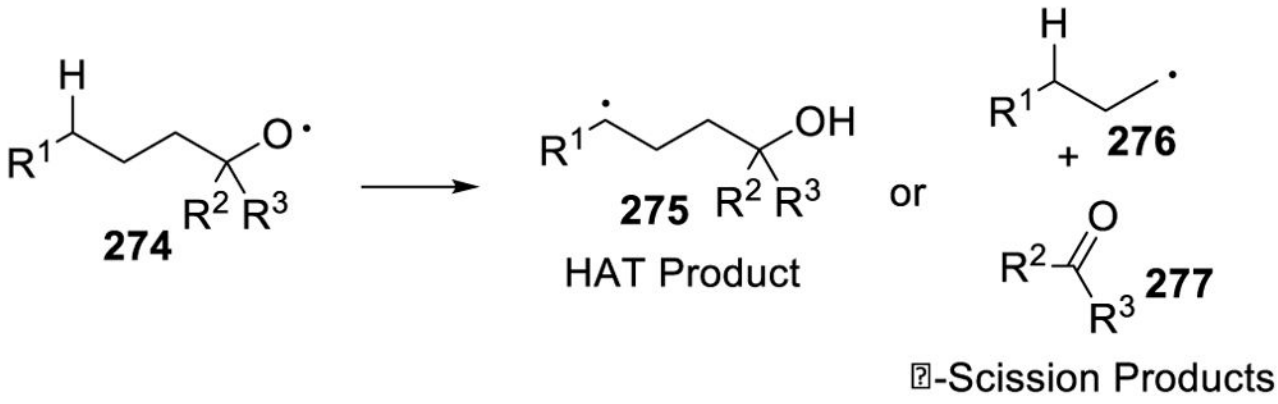


Scheme 46.

Generation of Nitrogen Radicals by Oxidation of N-H Bonds

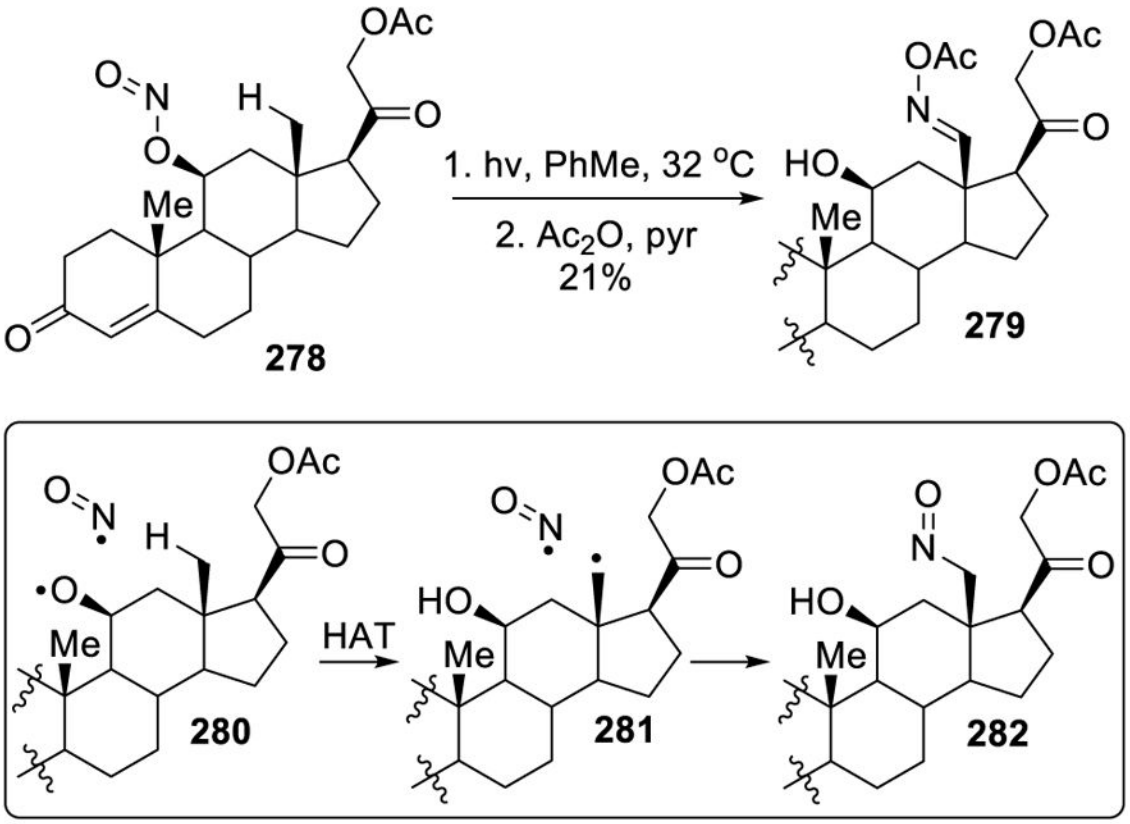


Scheme 47.
Formation of C-C Bonds with Nitrogen Radicals

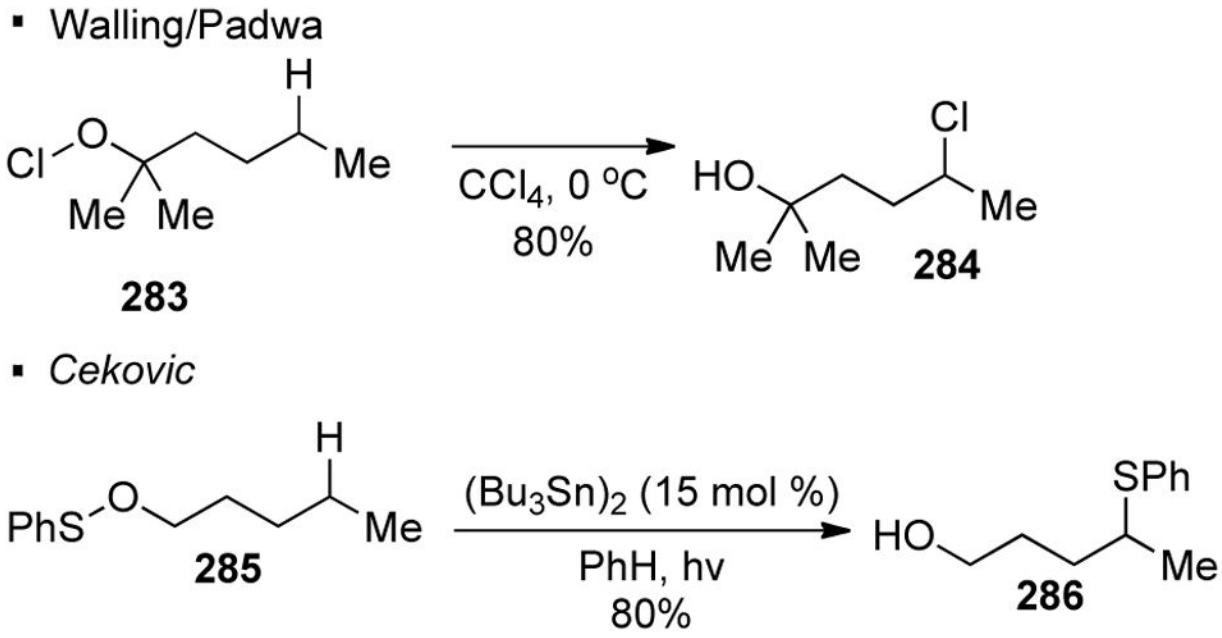


Scheme 48.
Reactivity of Oxygen Radicals

- *Barton*

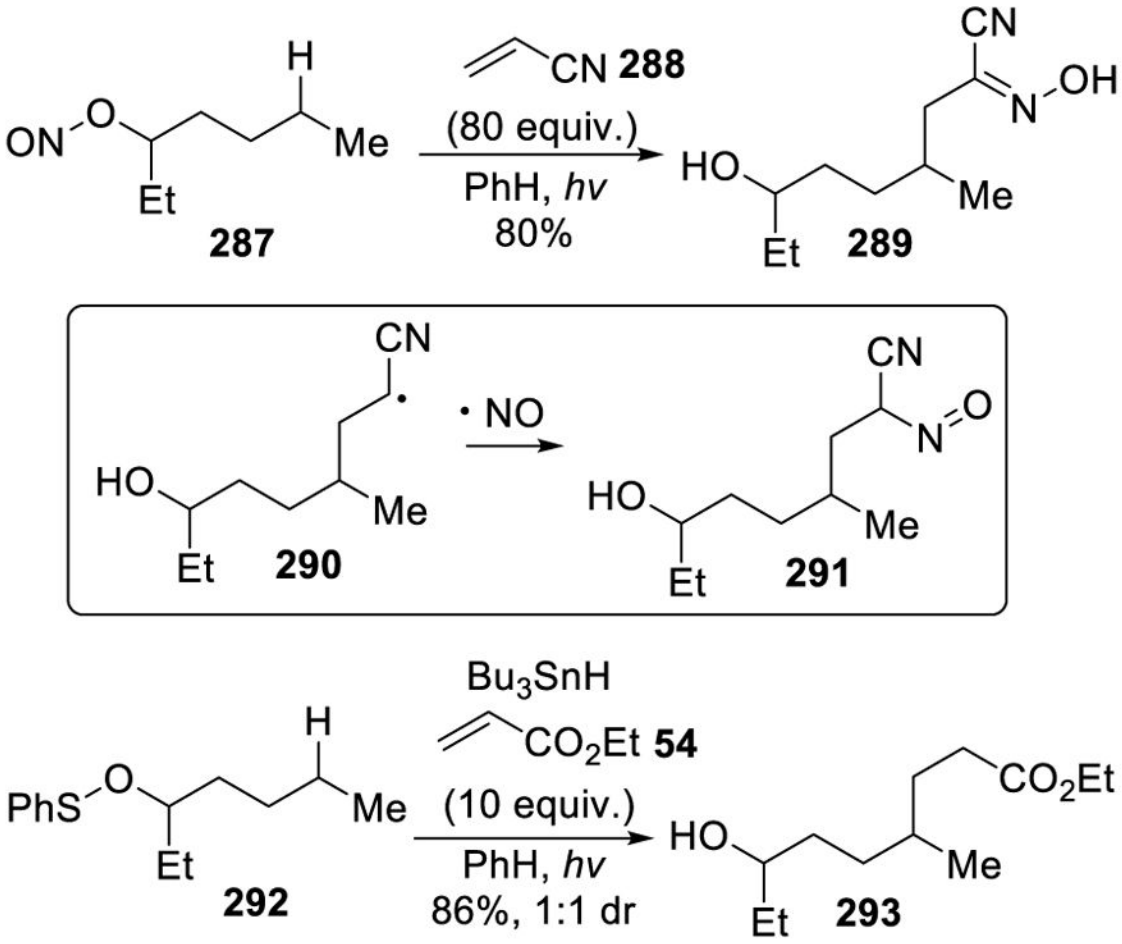


Scheme 49.
The Barton Reaction



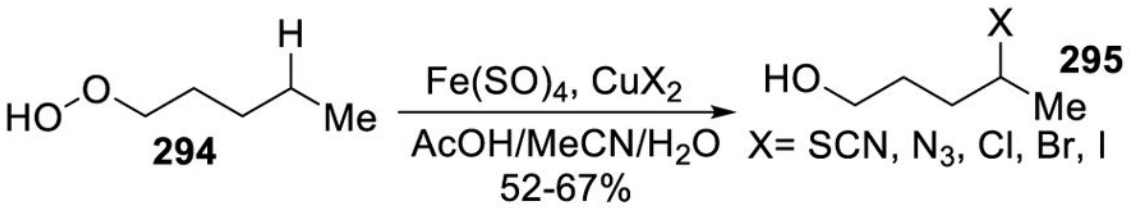
Scheme 50.
Use of O-X Bonds for C-X Bonds Formation

▪ *Cekovic*



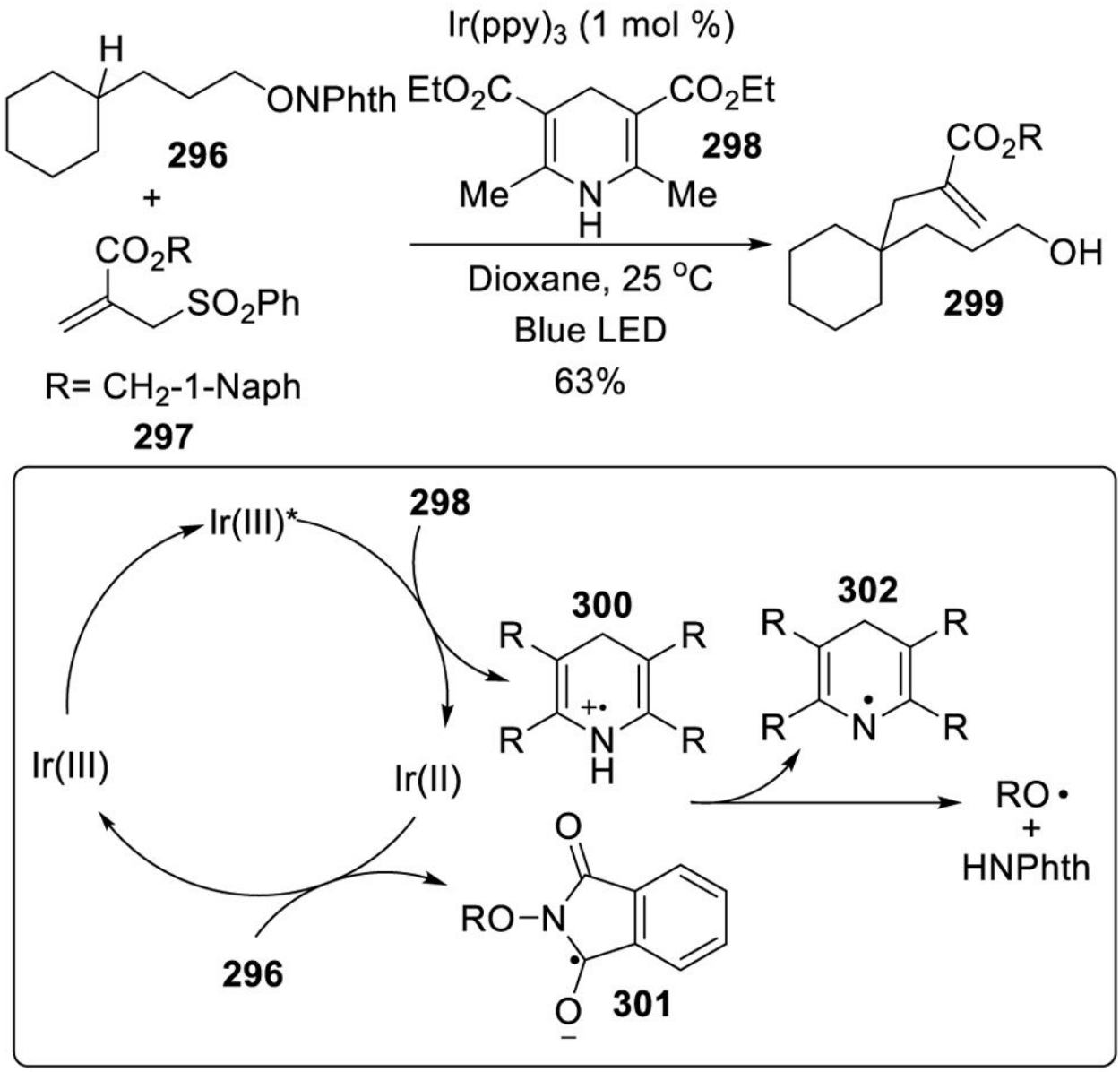
Scheme 51.
Use of Excess Alkenes for C-H Alkylation

▪ *Cekovic*



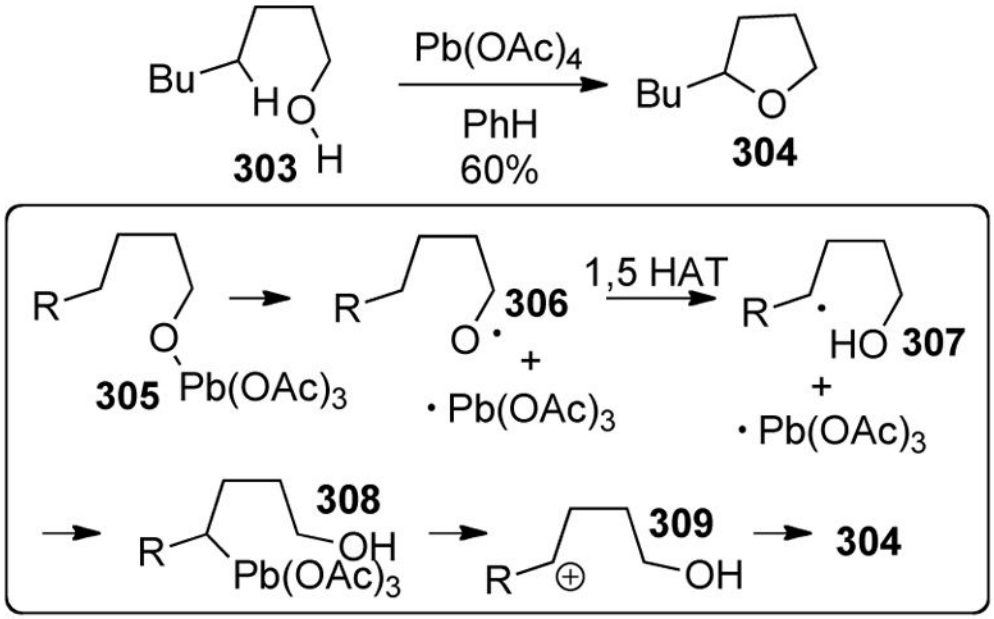
Scheme 52.
Generation of Oxygen Radicals by Reduction of O-X Bonds

- *Chen*



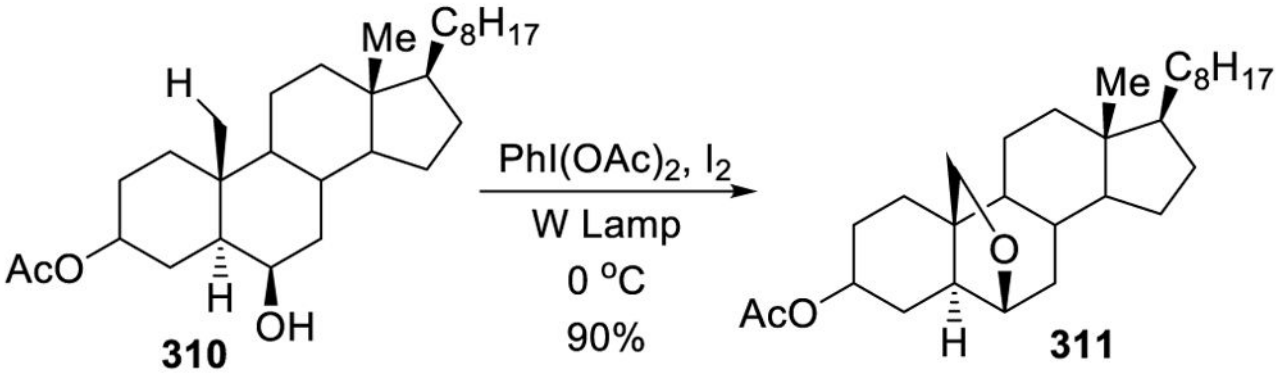
Scheme 53.
Generation of Oxygen Radicals with Photoredox Catalysis

- *Mihailovic*



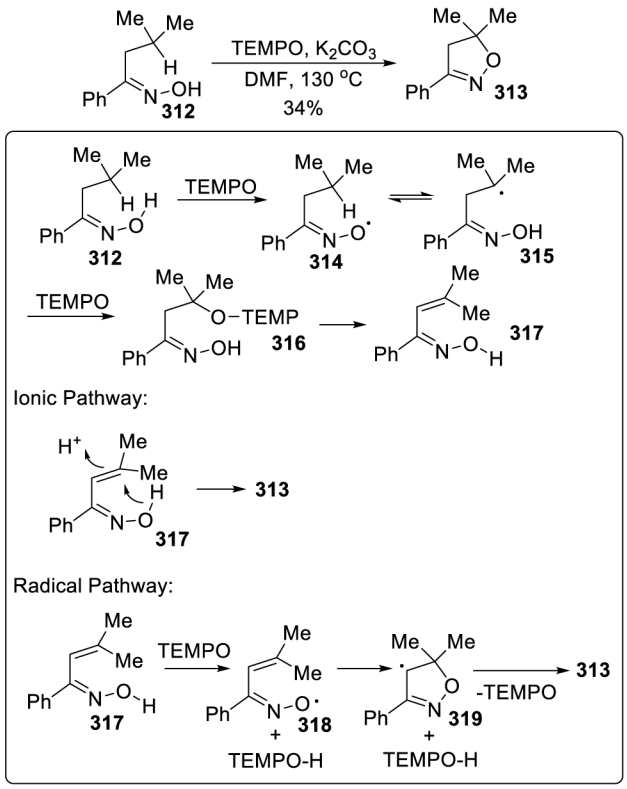
Scheme 54.
Generation of Oxygen Radicals by Oxidation of O-H Bonds

▪ *Suarez*



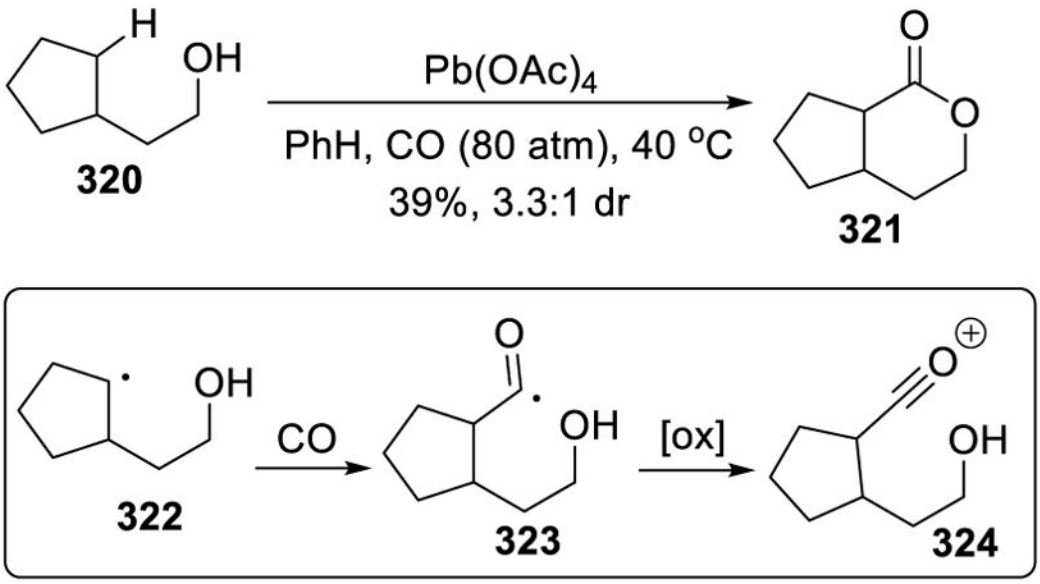
Scheme 55.
In-Situ Generation of O-I Bonds

- *Chiba*

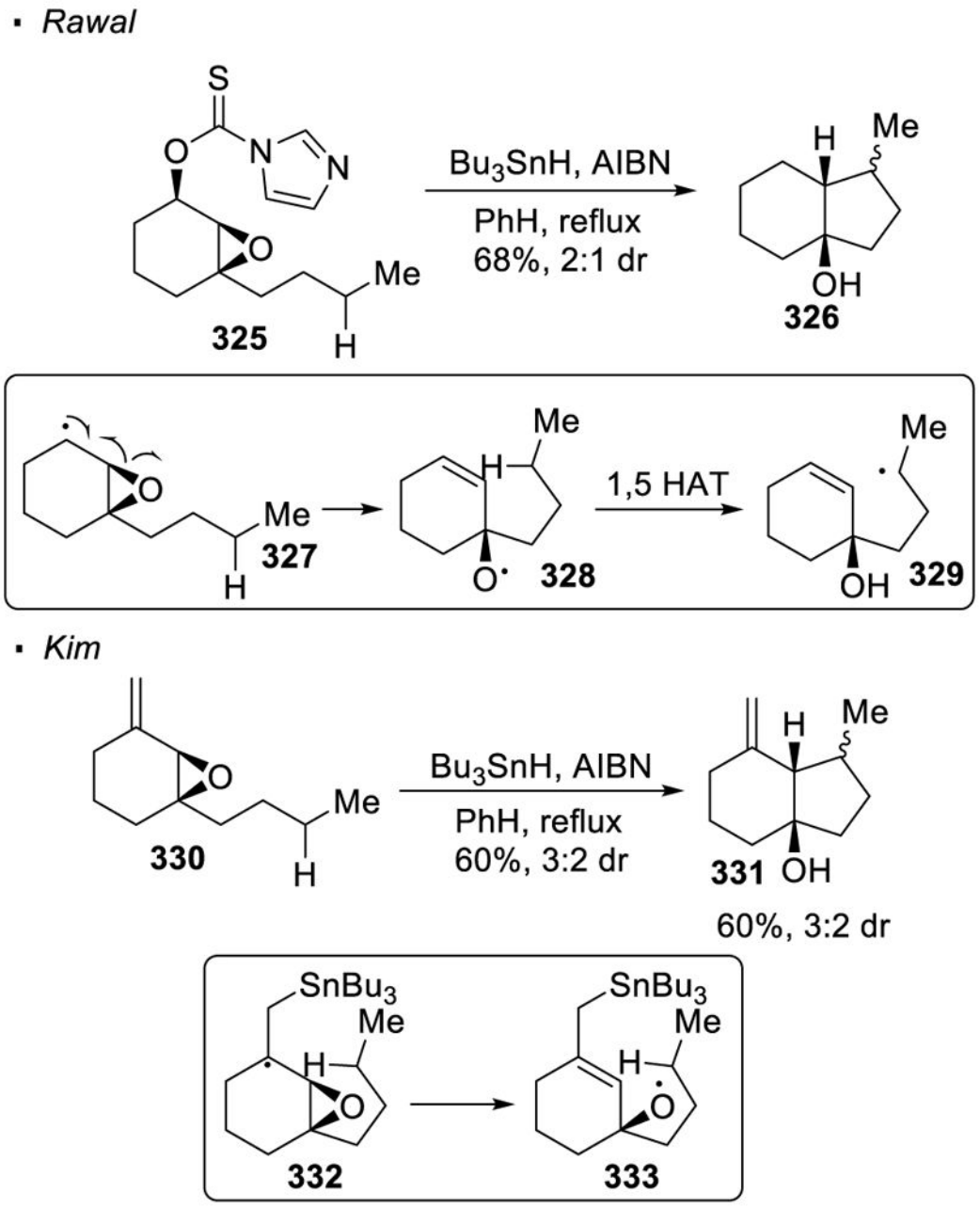


Scheme 56.
Formation of Isoxazolines

▪ *Ryu, Sonoda*

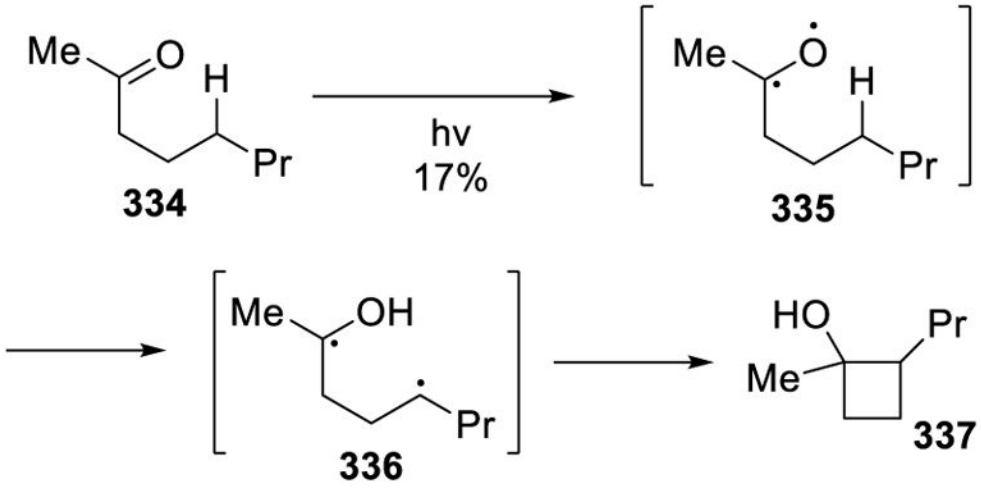


Scheme 57.
Formation of γ-lactones through Carbonylation



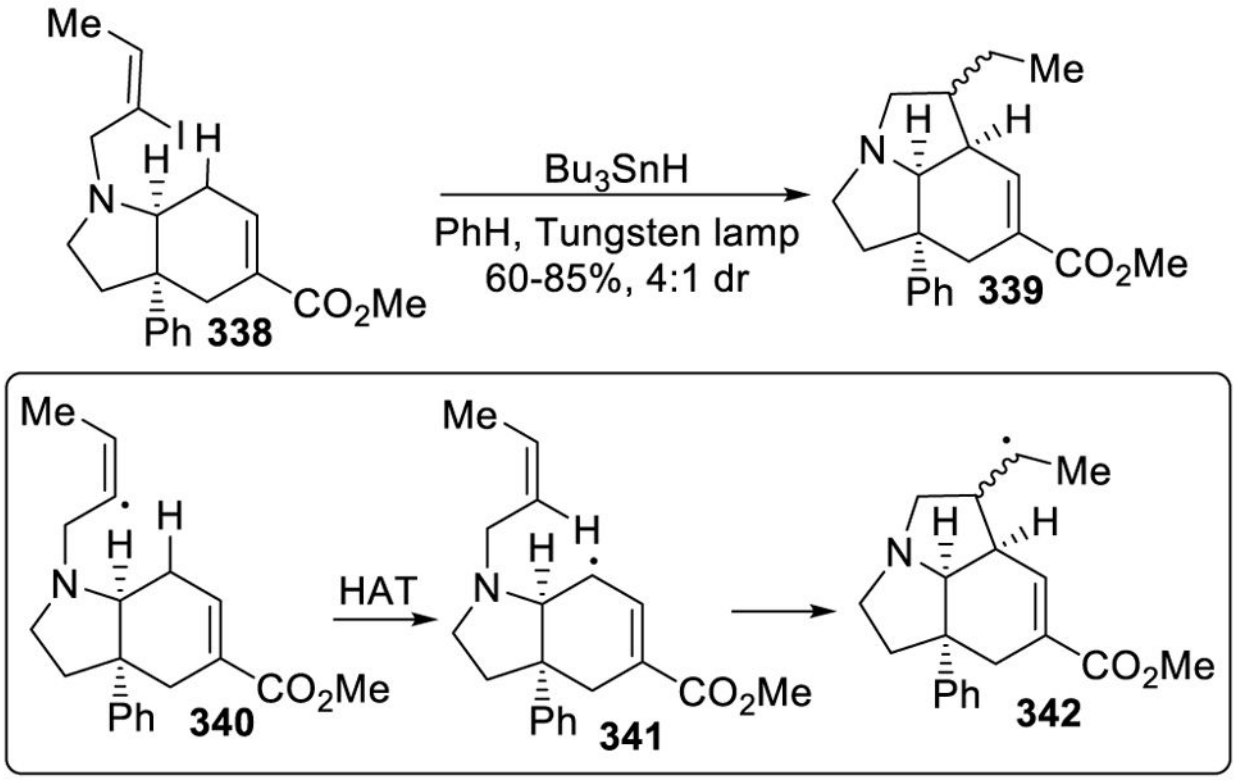
Scheme 58.
Epoxides as Oxygen Radical Precursors

- *Yang*



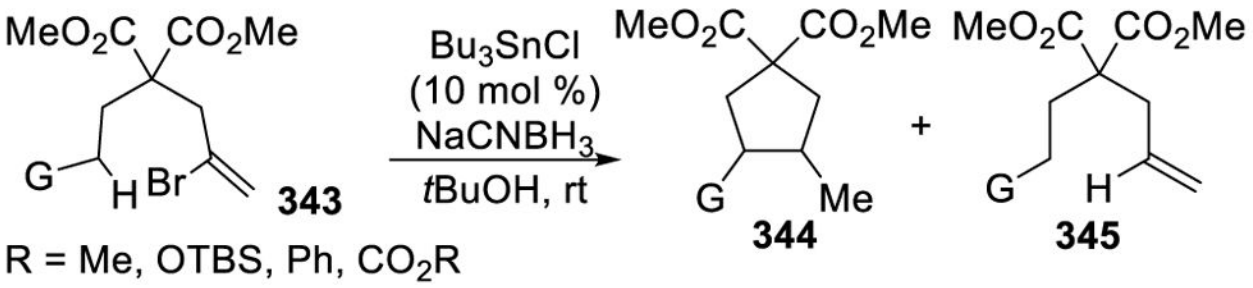
Scheme 59.
Norrish-Yang Cyclization

▪ *Parsons*



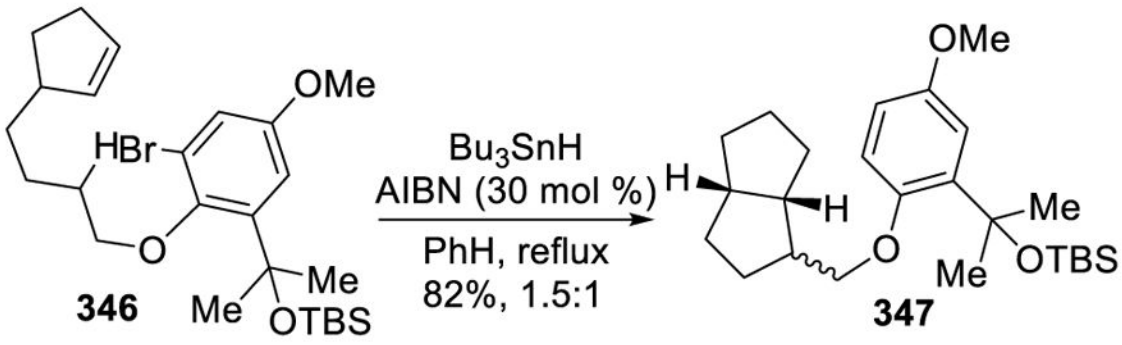
Scheme 60.
Initial report on 1,5 HAT with Vinyl Halides

▪ *Curran*



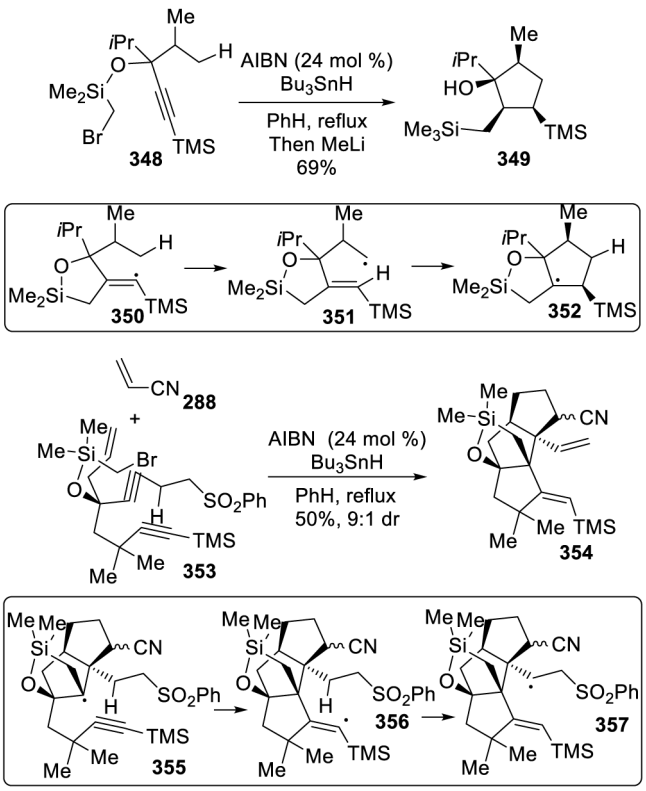
Scheme 61.
Catalytic System for 1,5 HAT with sp^3 C-H Bonds

▪ *Curran*



Scheme 62.
Derivatization of Alcohols with Vinyl Radicals for 1,5 HAT

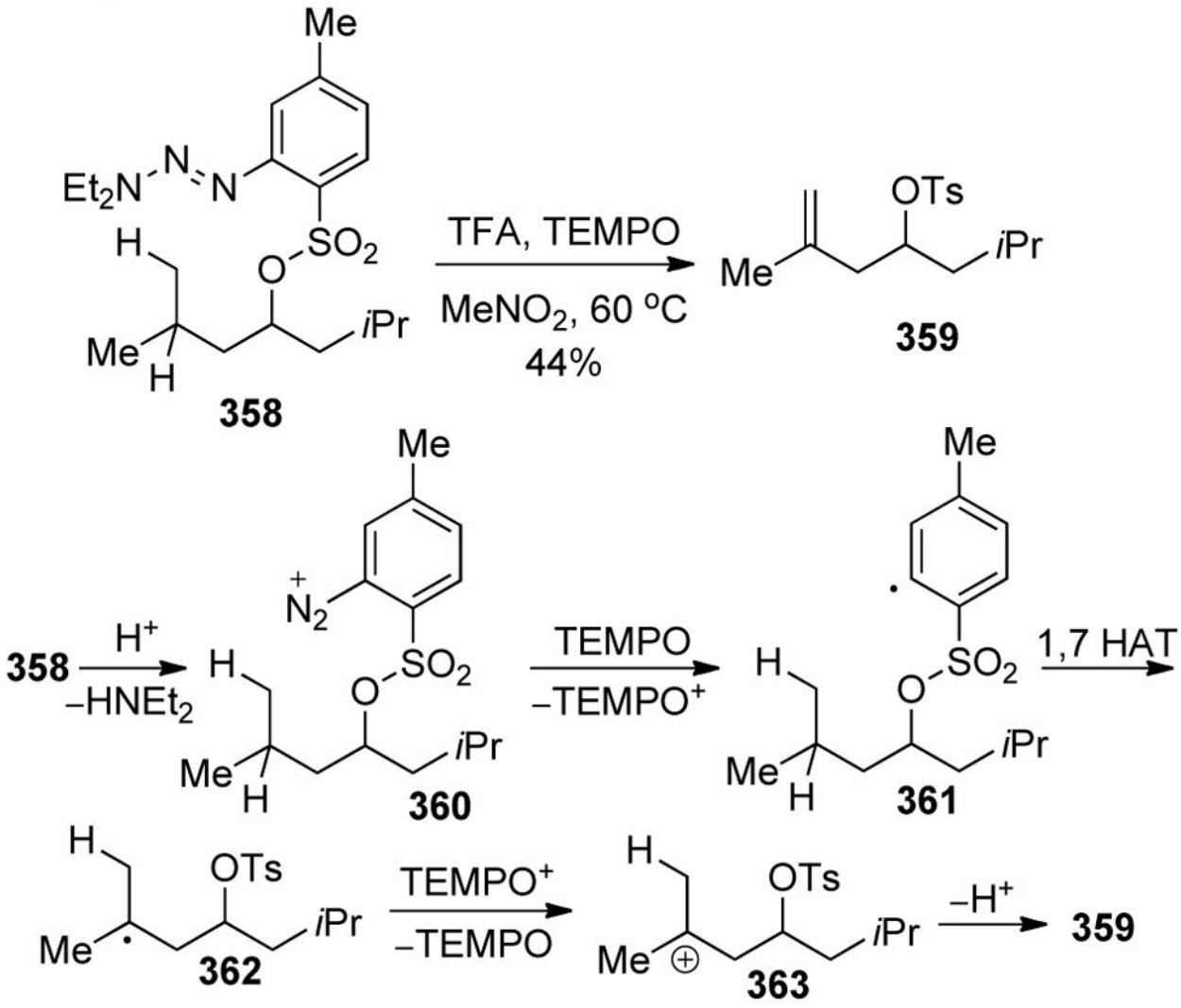
▪ *Malacria*



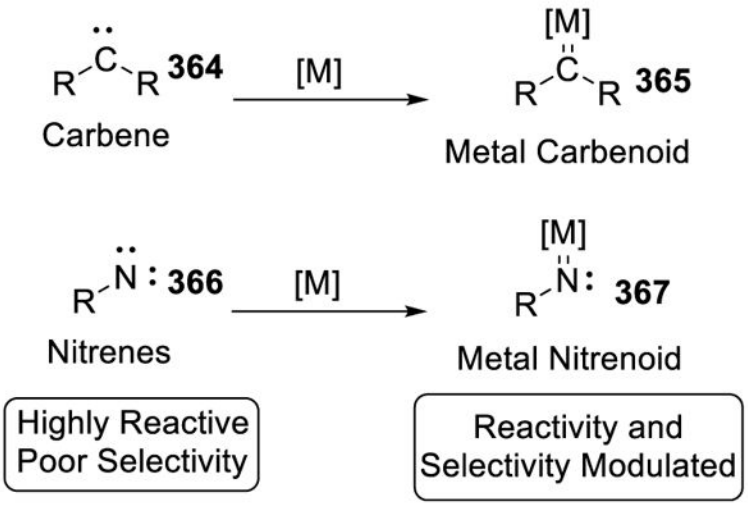
Scheme 63.

Generation of Vinyl Radicals through Radical Addition to Alkynes

▪ *Baran*

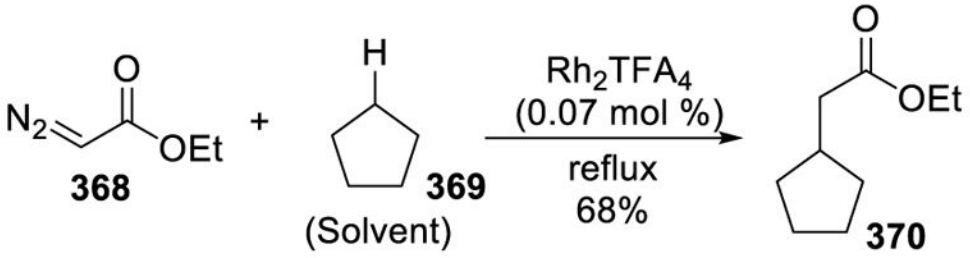


Scheme 64.
Generation of Aryl Radicals from Aryl Triazenes

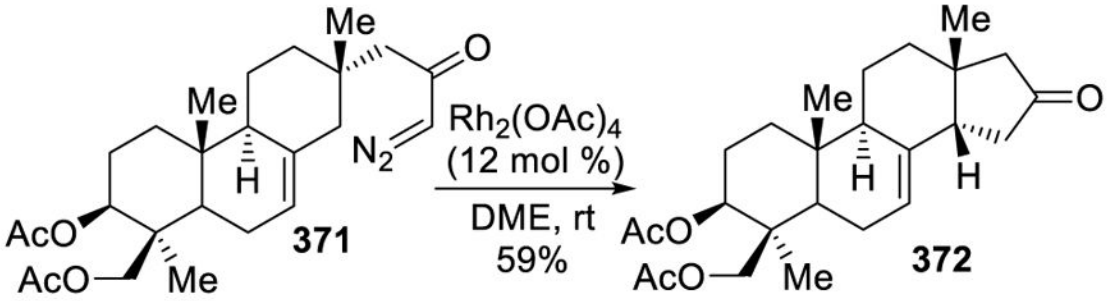


Scheme 65.
Metal Carbenoids and Nitrenoids

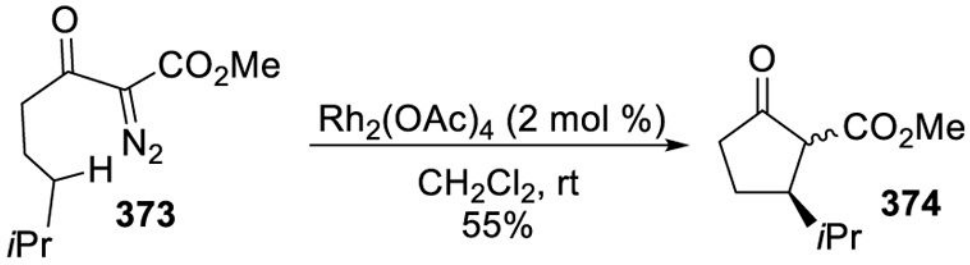
- *Teyssie*



- *Wenkert*

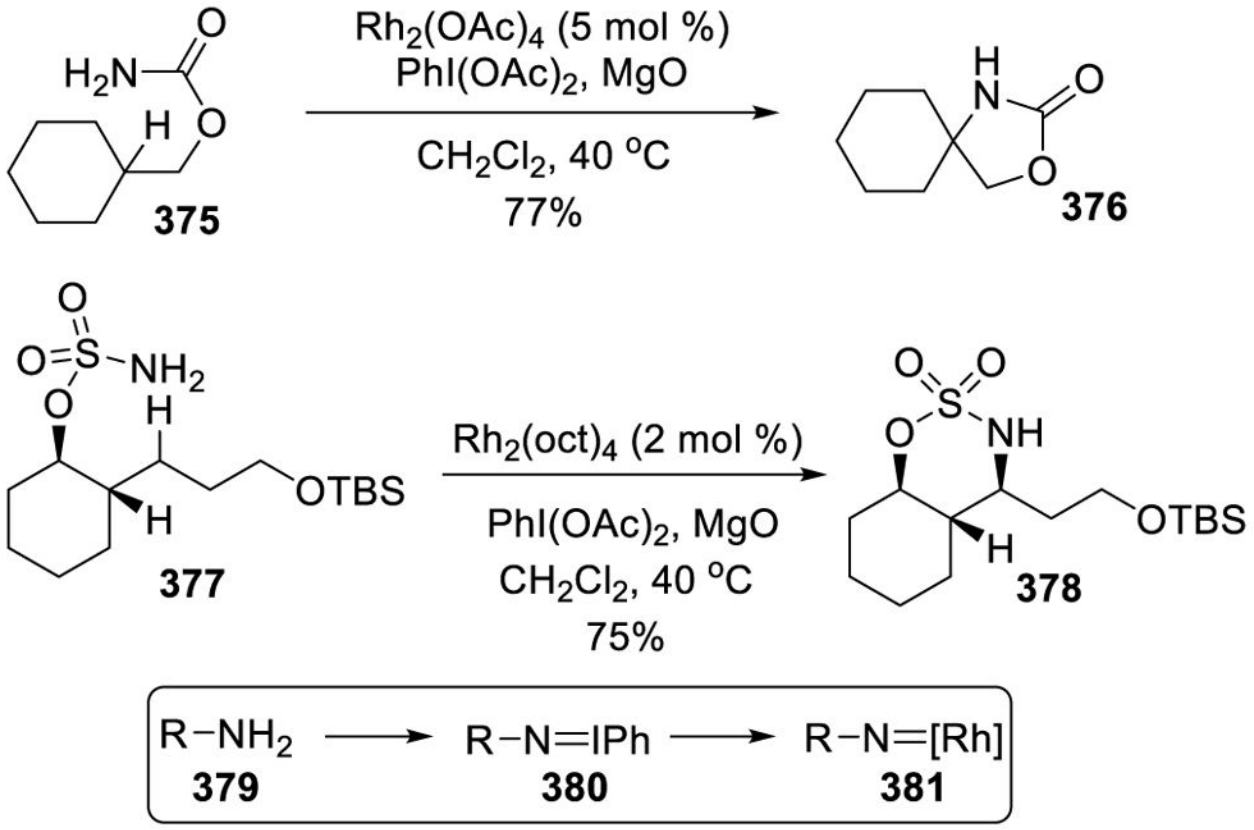


- *Taber*

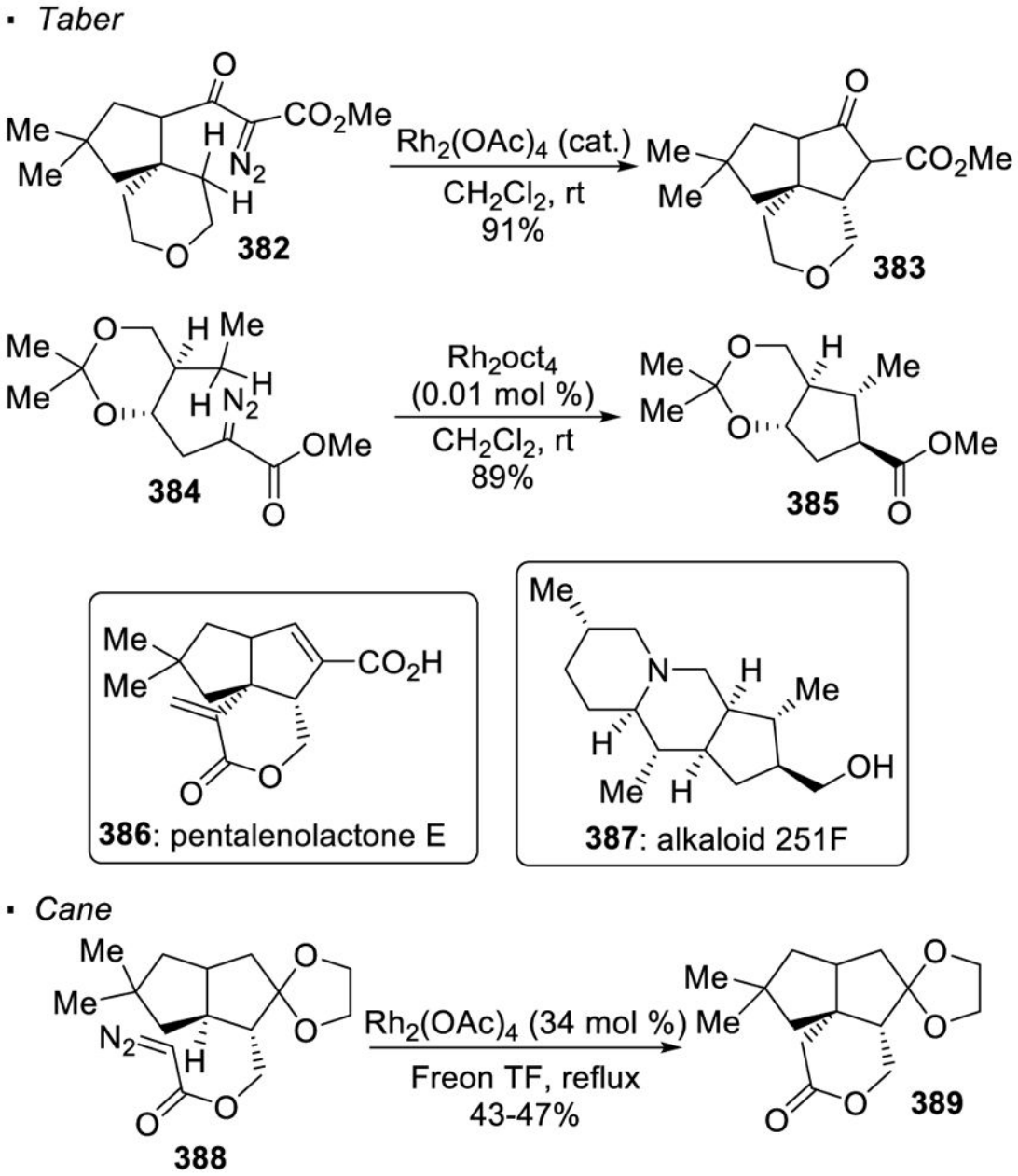


Scheme 66.
Rh(II)-Catalyzed Intramolecular C-H Insertion

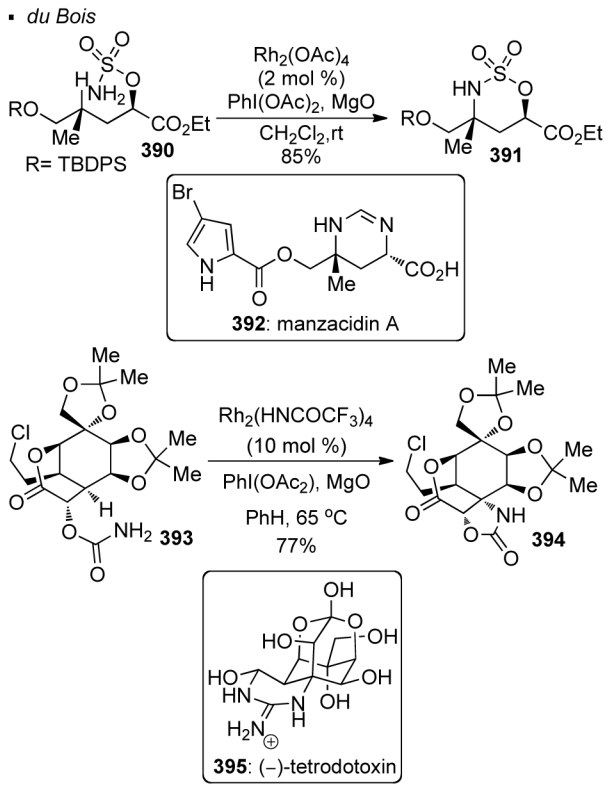
▪ *Du Bois*



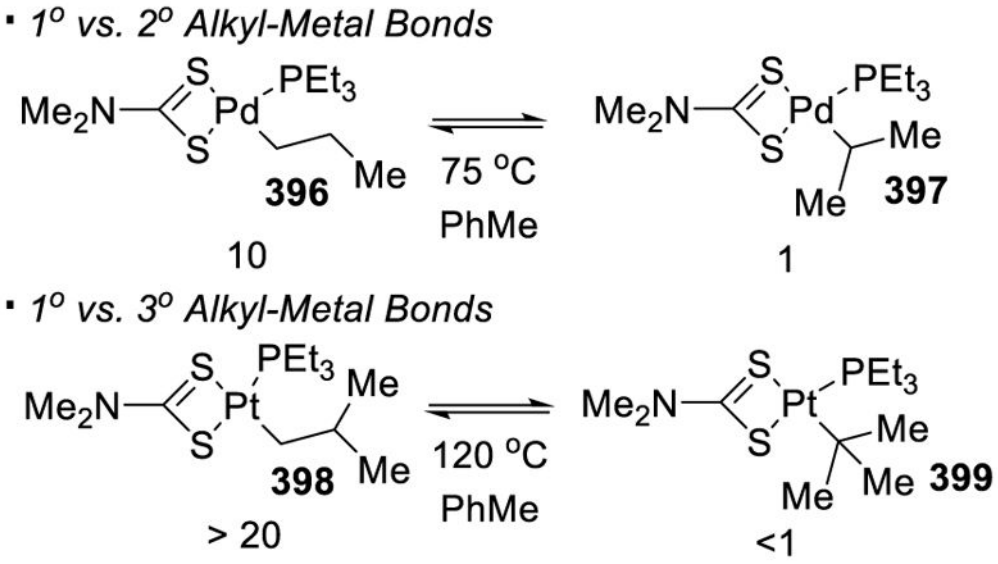
Scheme 67.
Rh(II)-Catalyzed Intramolecular C-H Amination



Scheme 68.
Application of Intramolecular C-H insertion

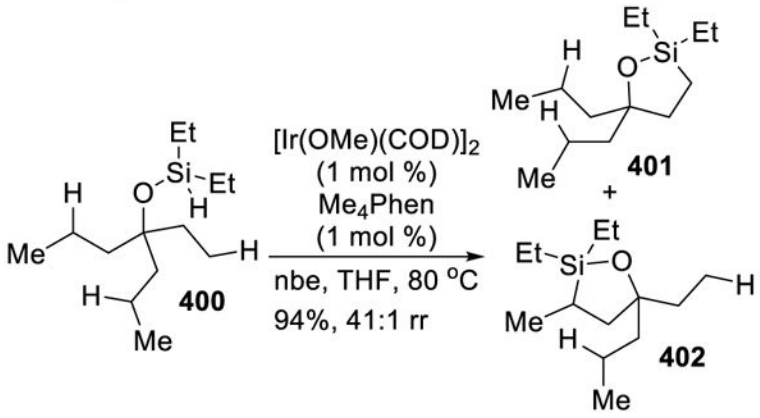


Scheme 69.
Application of Intramolecular C-H Amination



Scheme 70.
Relative Stability of Pd-Alkyl Species

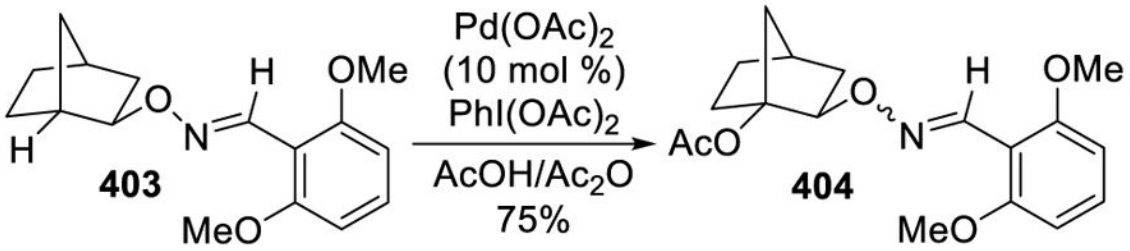
▪ *Hartwig*



Scheme 71.

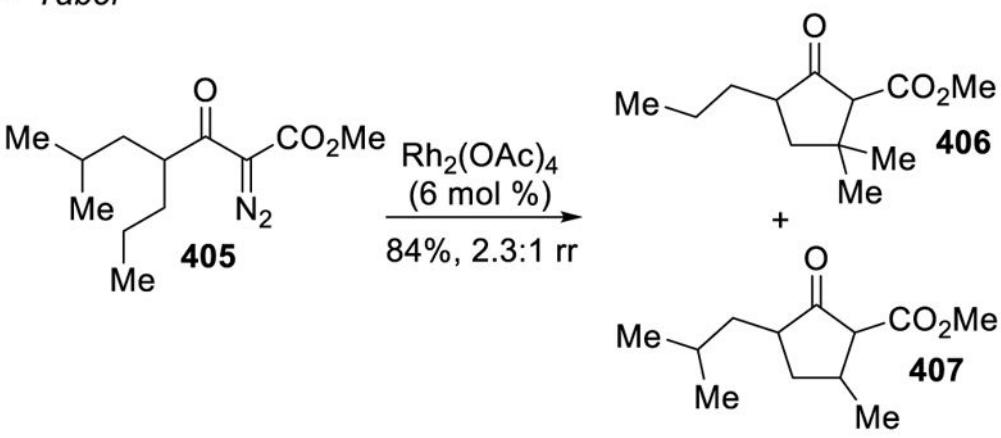
The Relative Reactivity of Primary and Secondary C-H Bonds

▪ *Dong*

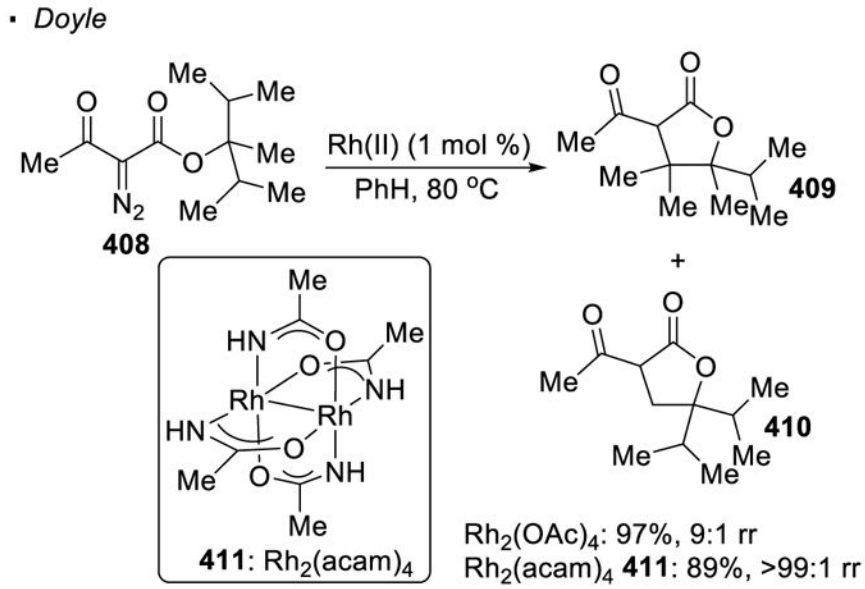


Scheme 72.
Pd-catalyzed C-H Activation of Tertiary C-H Bonds

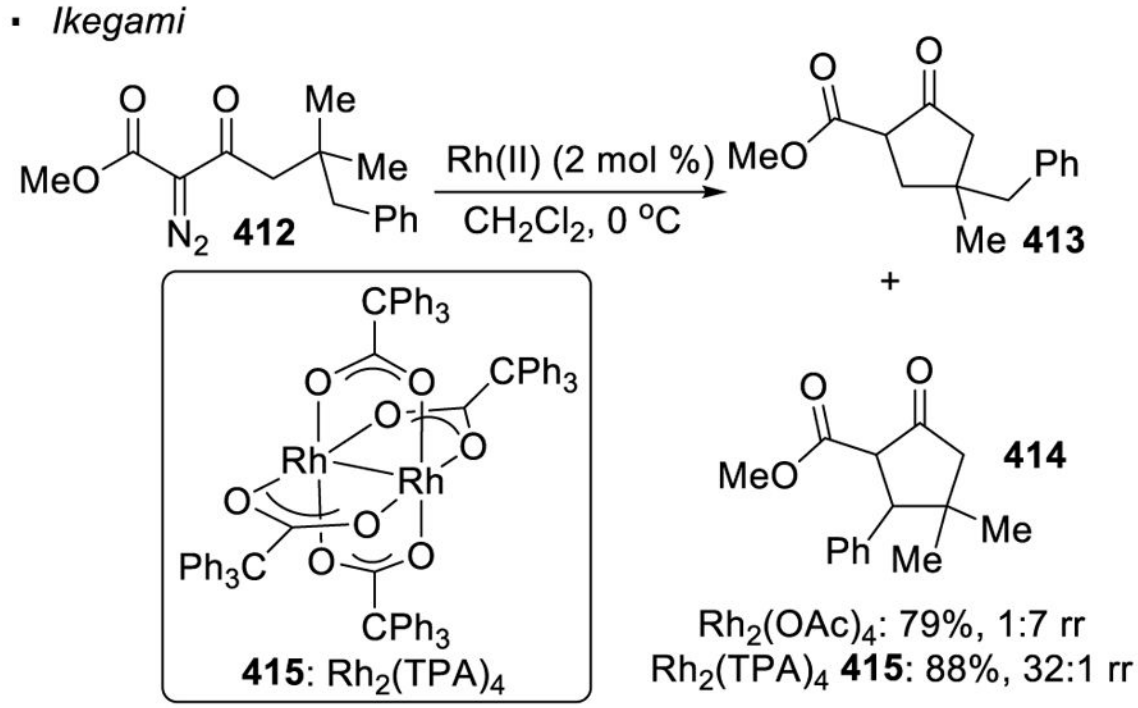
- *Taber*



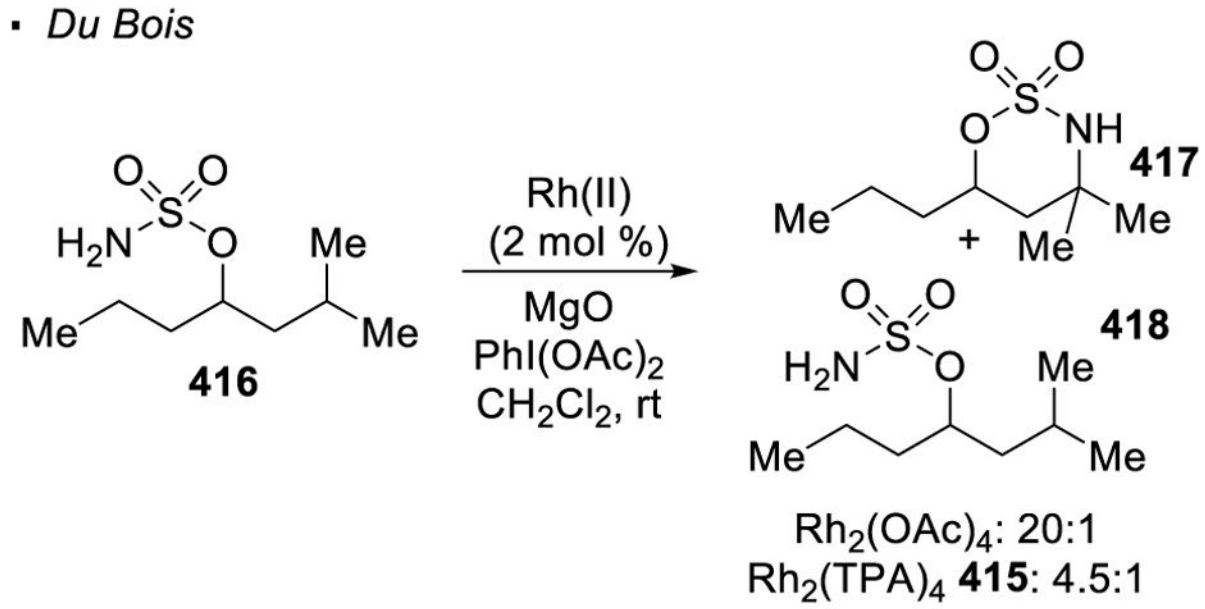
Scheme 73.
Reactivity of 2° vs 3° C-H Bonds



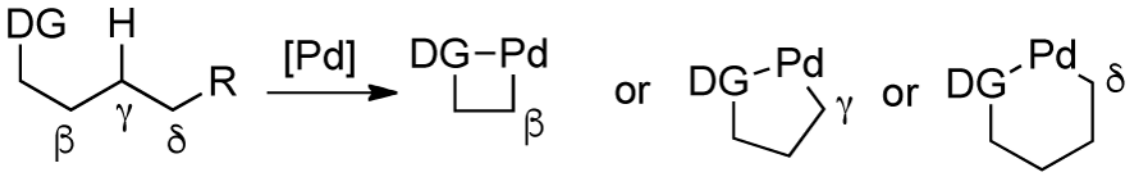
Scheme 74.
Electronic Effects of Ligands on Regioselectivity



Scheme 75.
Sterics Effects of Ligands on Regioselectivity

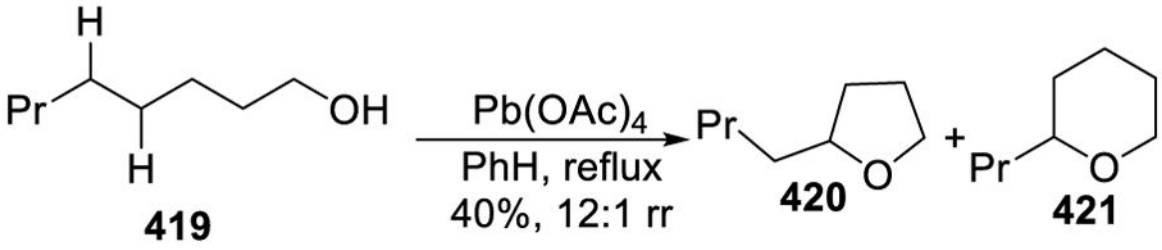


Scheme 76.
Regioselectivity of C-H Amination

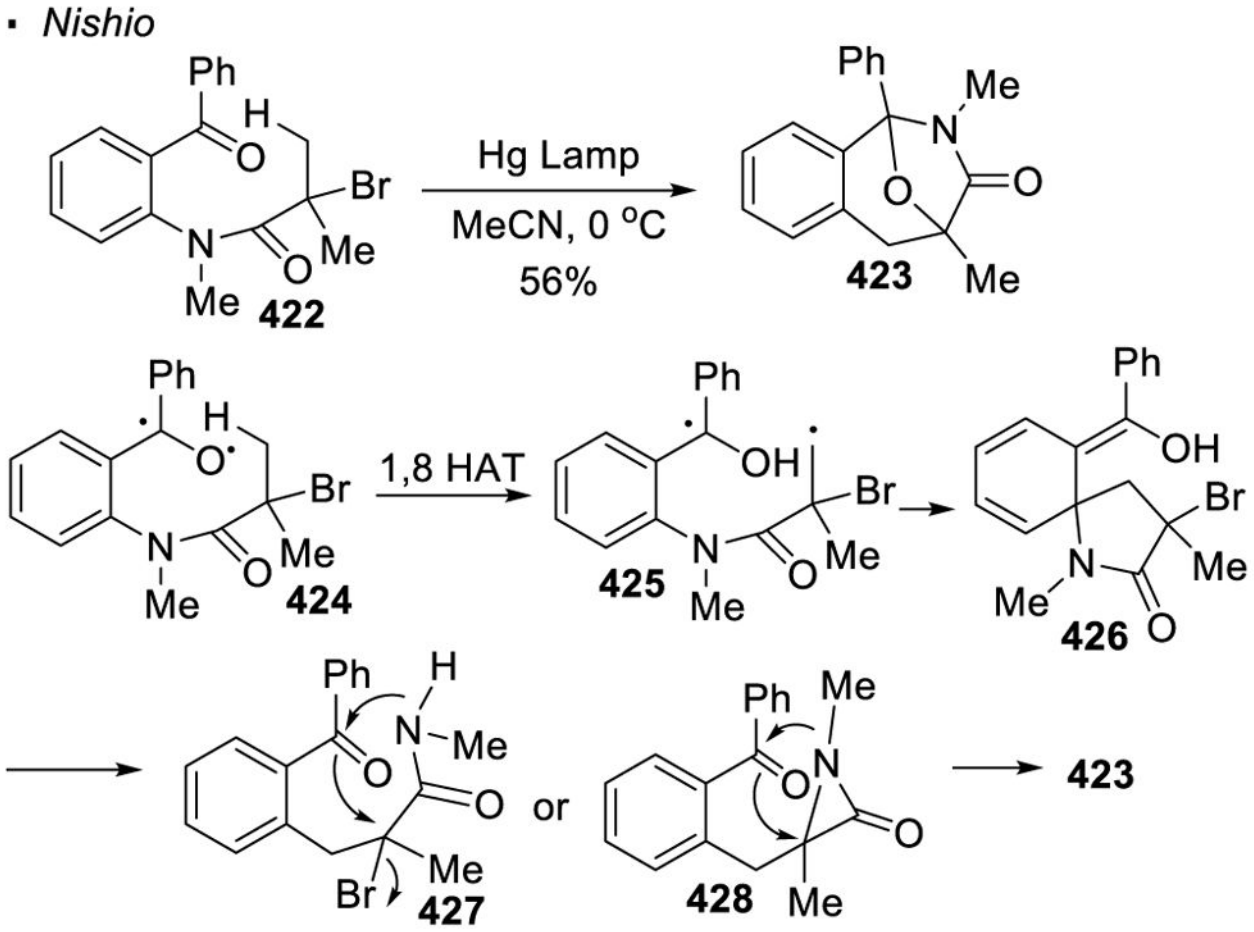


Scheme 77.
Transition-metal Catalyzed Activation of β, γ, δ C-H Bonds

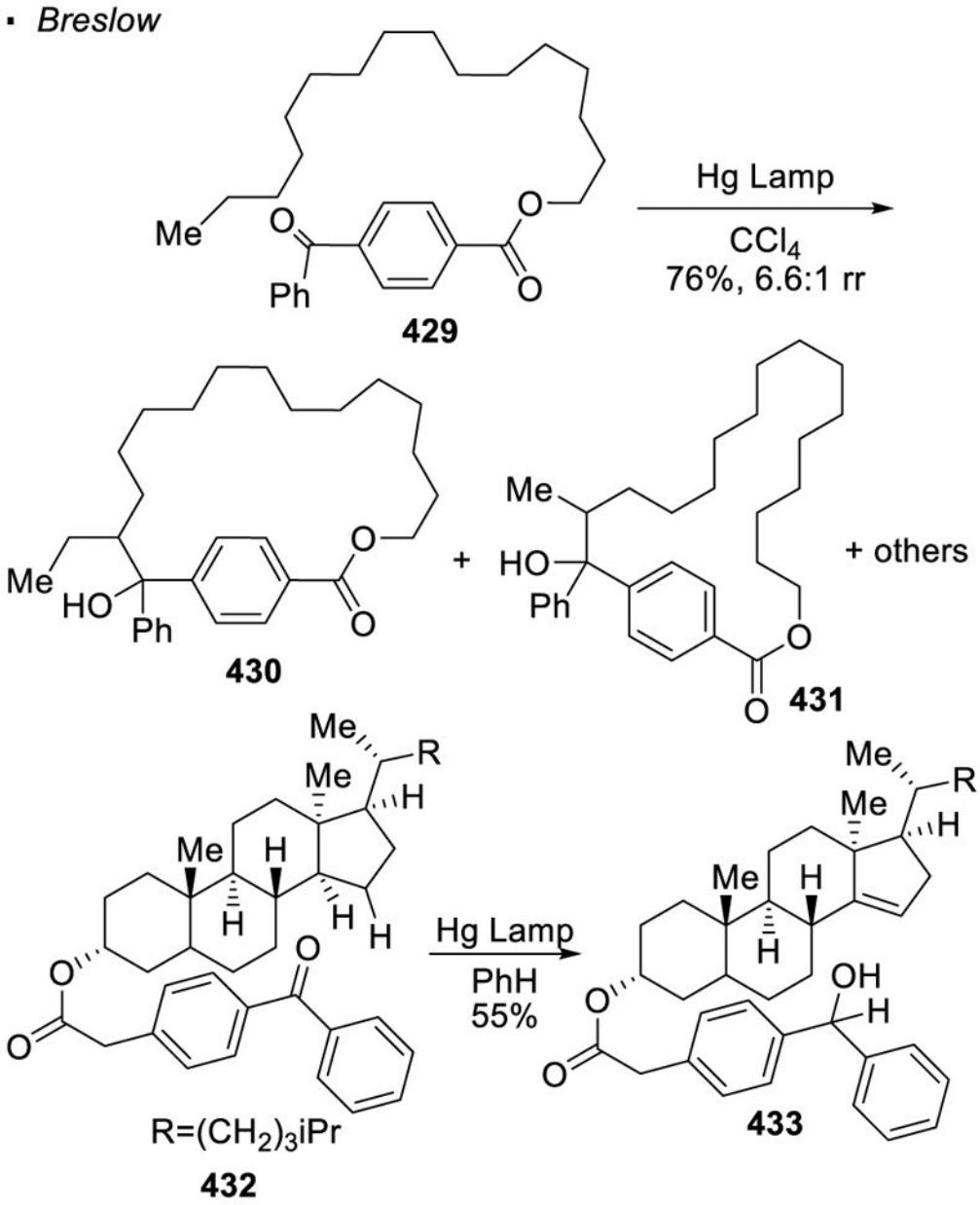
▪ *Mihailovic*



Scheme 78.
Predominance of 1,5 HAT

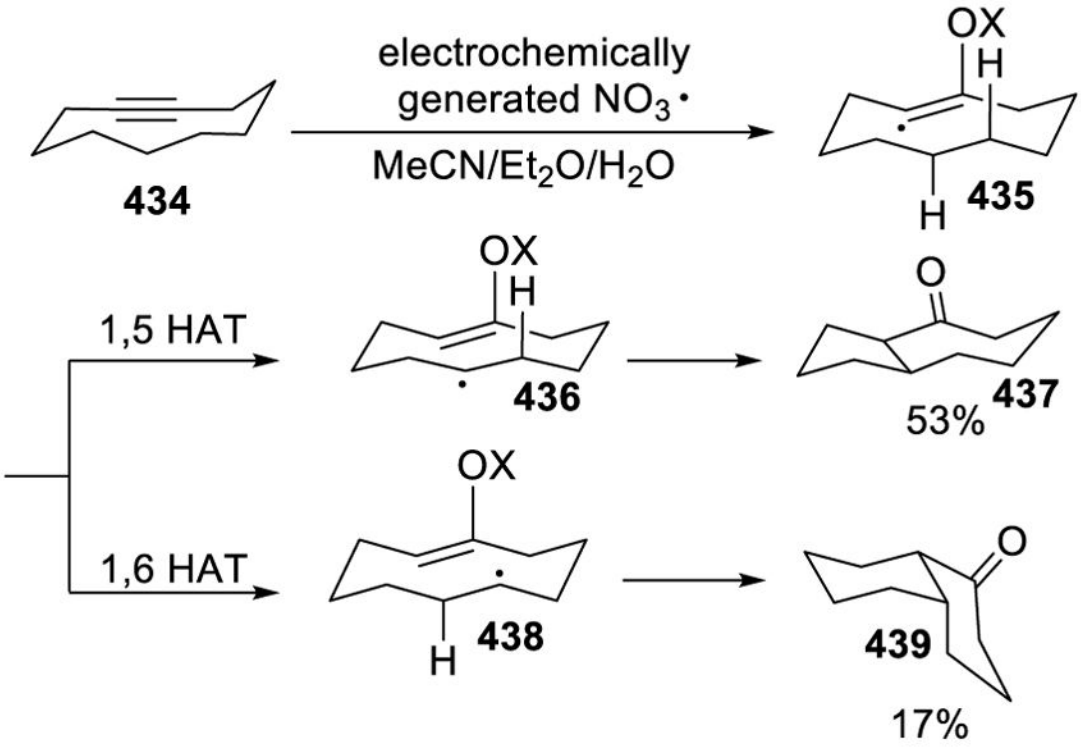


Scheme 79.
1,8 Hydrogen Atom Transfer

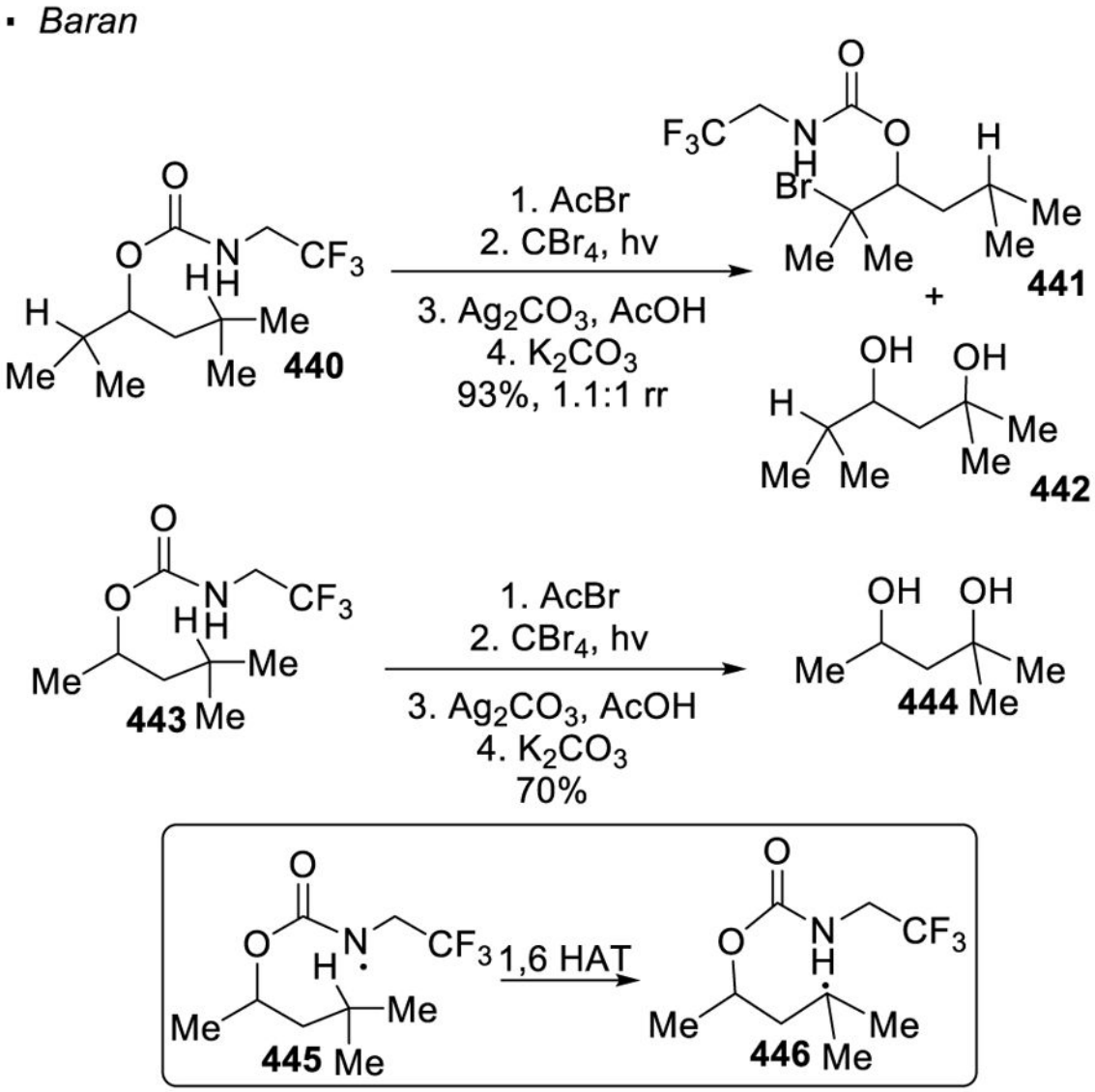


Scheme 80.
Long-Range HAT

▪ *Wille*

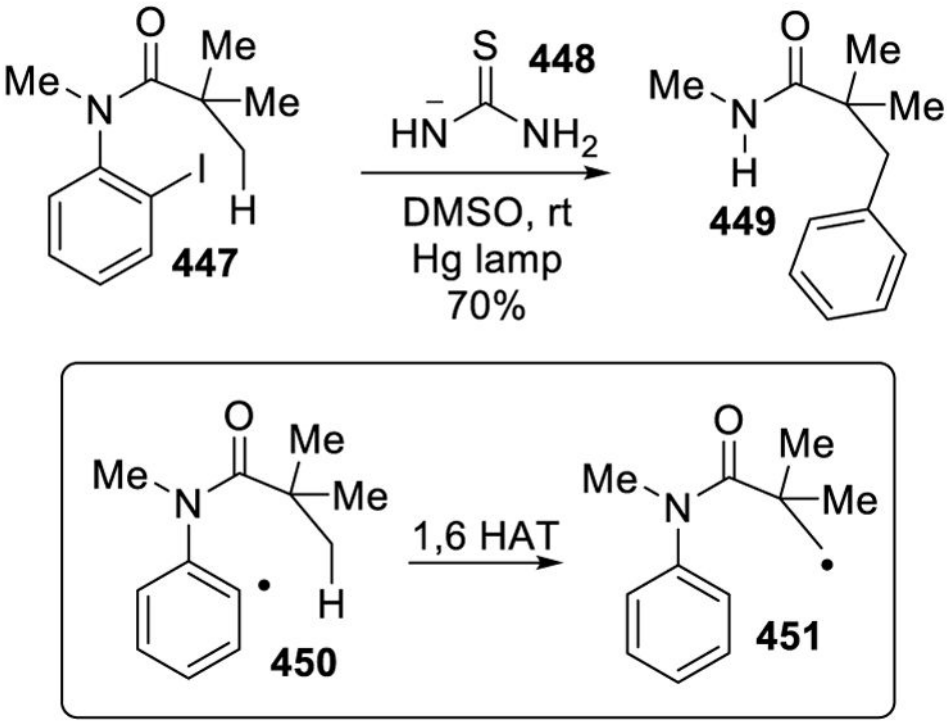


Scheme 81.
Effects of Geometry on 1,5 and 1,6 HAT

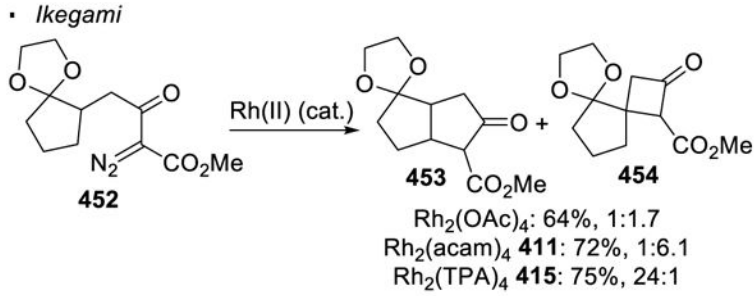


Scheme 82.
1,6 HAT Favored by Geometry and Bond Strengths

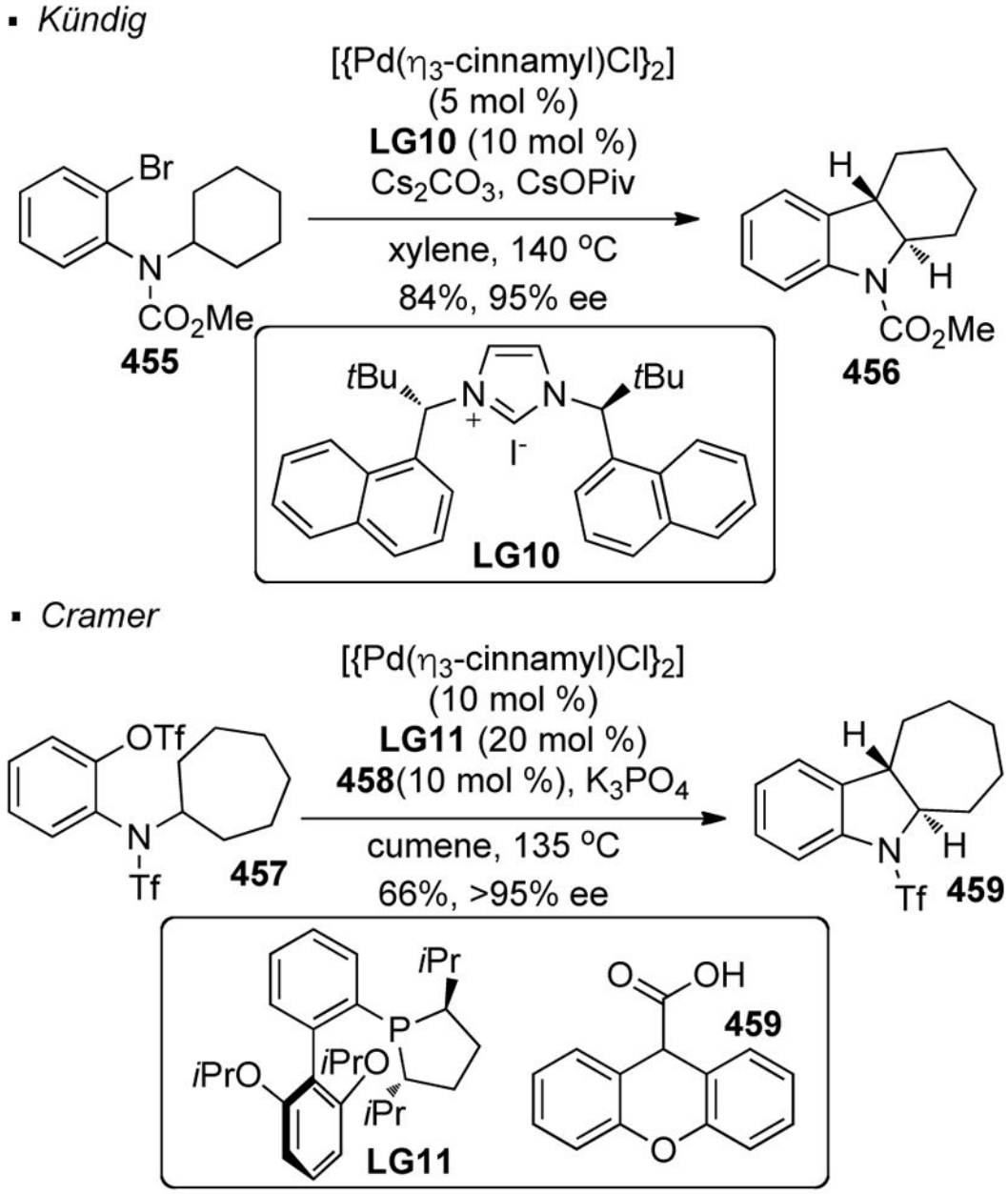
- *Penenory*



Scheme 83.
1,6 HAT with no C-H Bonds for 1,5 HAT

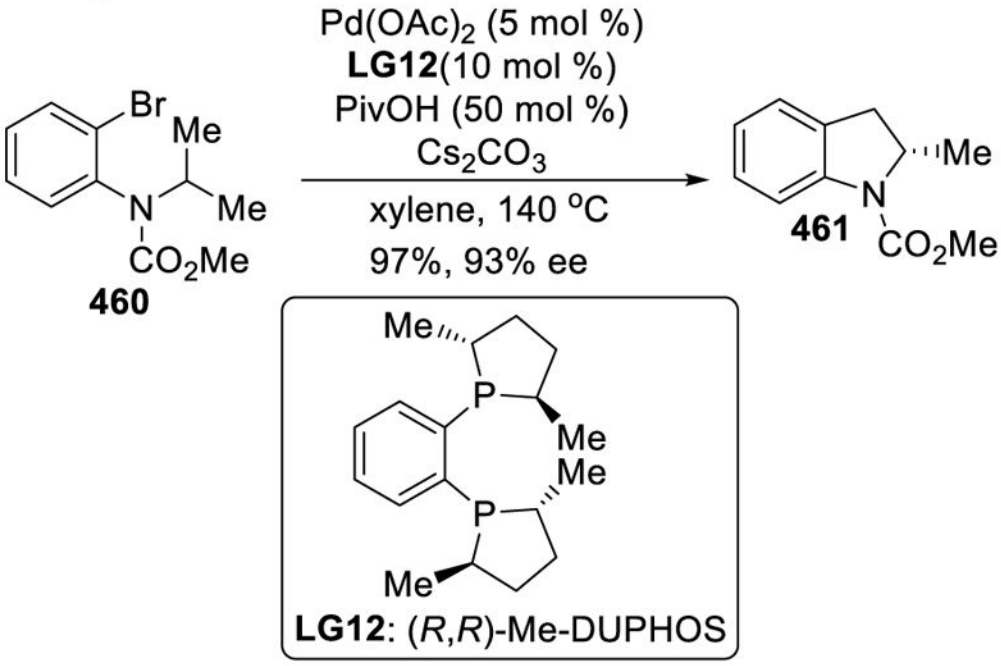


Scheme 84.
Regioselectivity of C-H Insertion

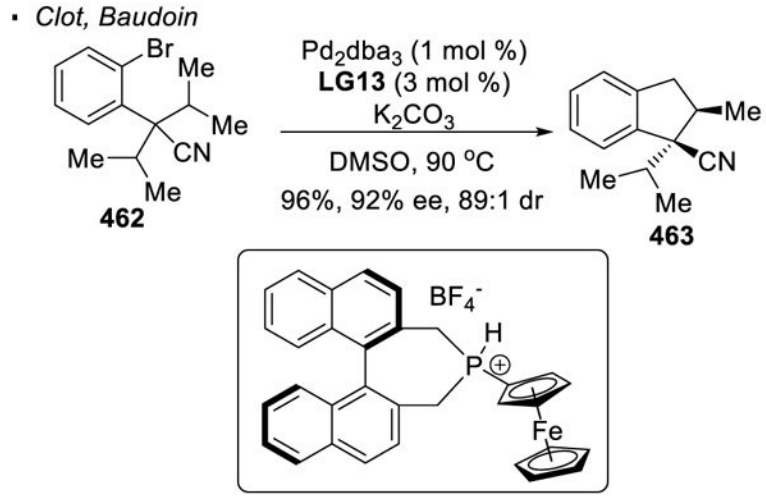


Scheme 85.
Asymmetric Activation of Secondary C-H Bonds

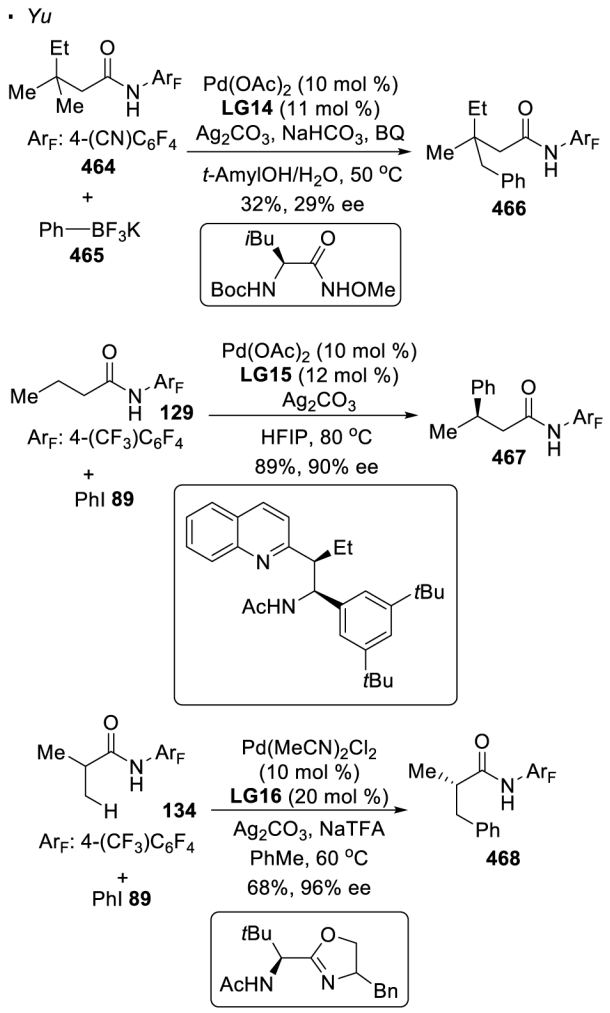
▪ *Kagan*



Scheme 86.
Asymmetric Activation of Primary C-H Bonds



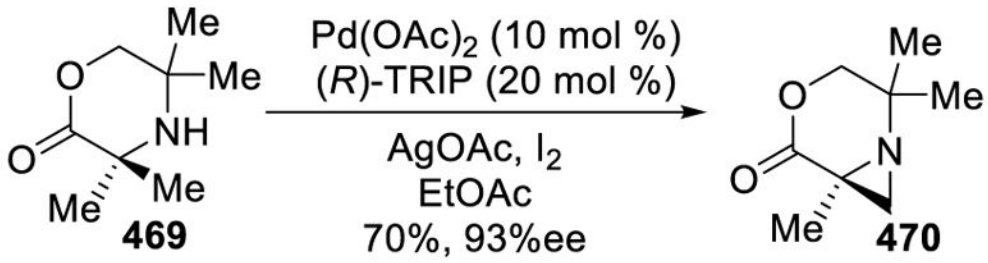
Scheme 87.
Asymmetric Synthesis of Cyclopentanes



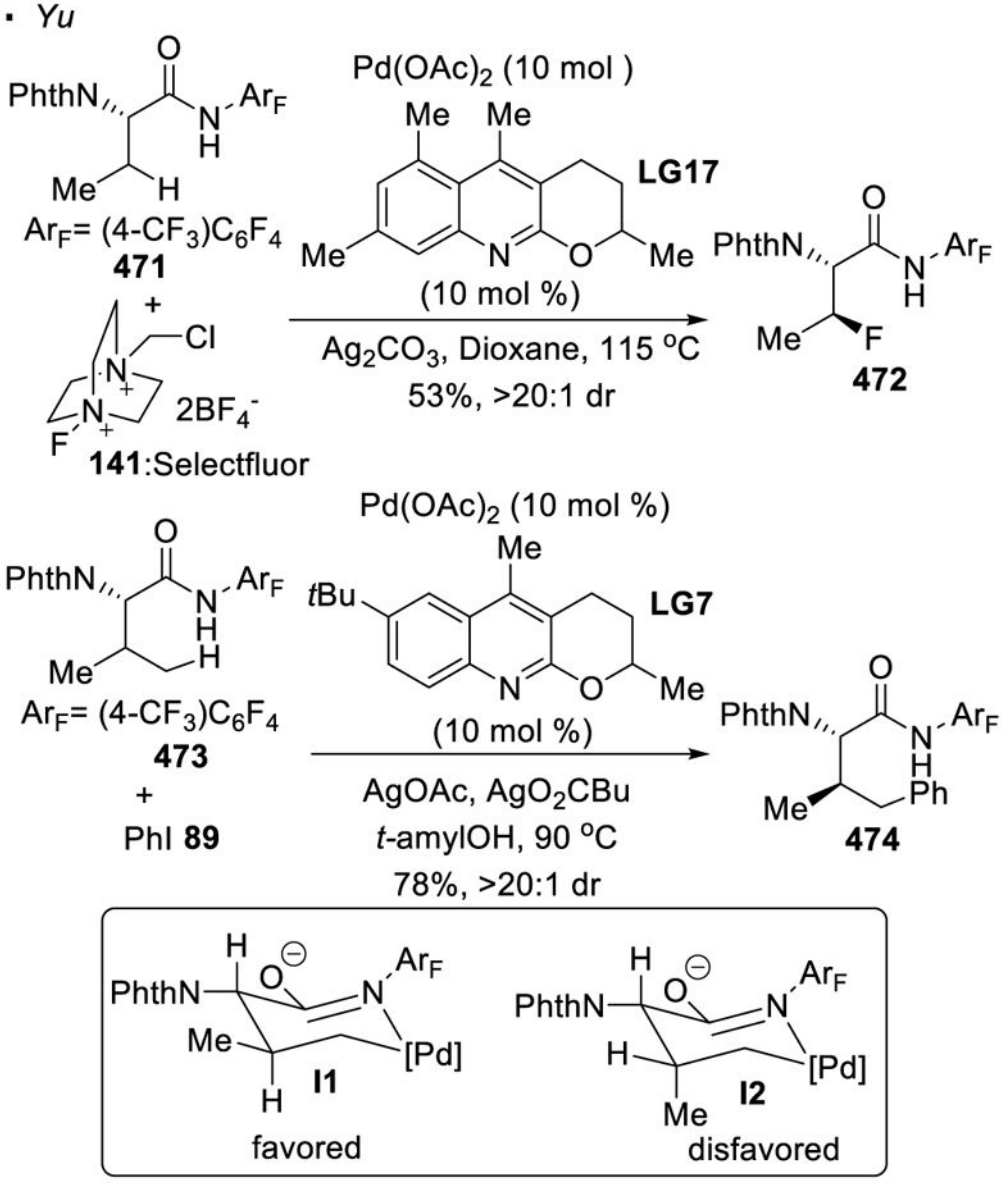
Scheme 88.

Asymmetric C-H Functionalization of Carbonyl Compounds

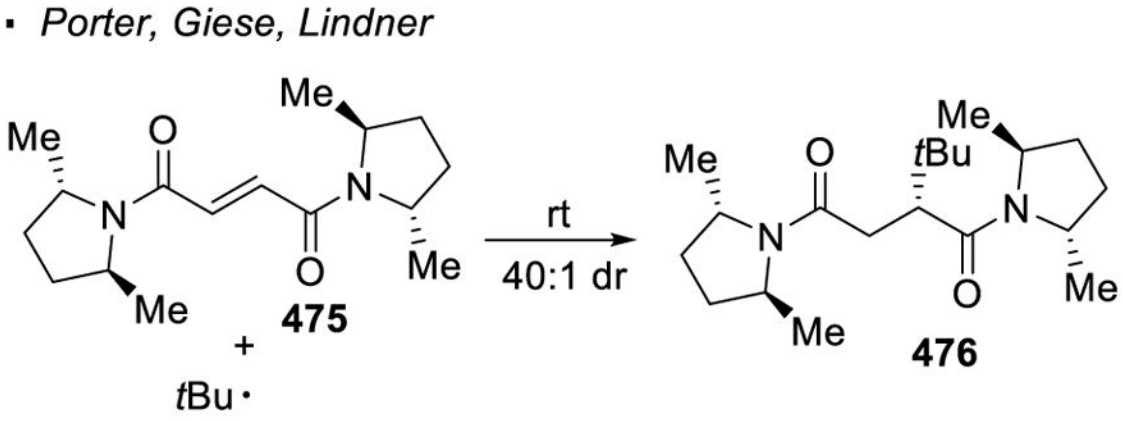
▪ *Gaunt*



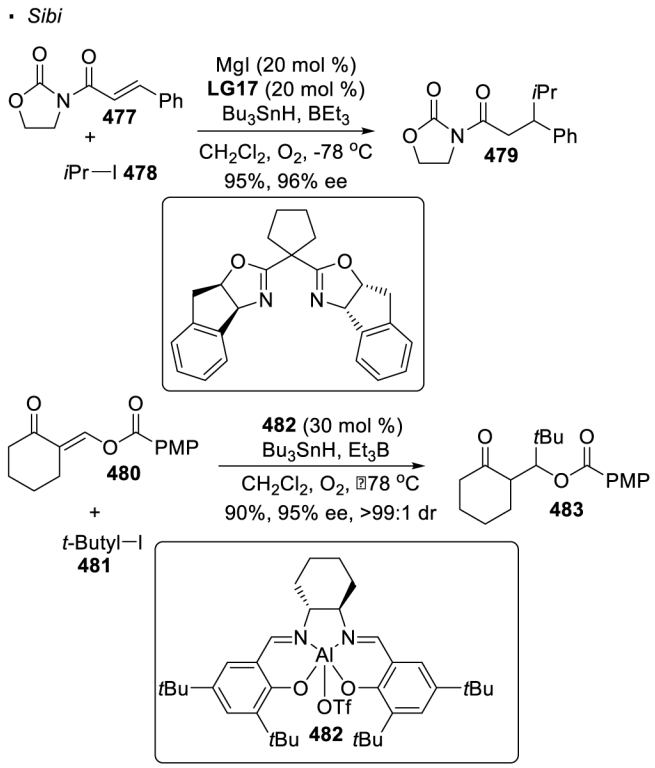
Scheme 89.
Enantioselective Aziridation



Scheme 90.
Diastereoselective C-H Activation

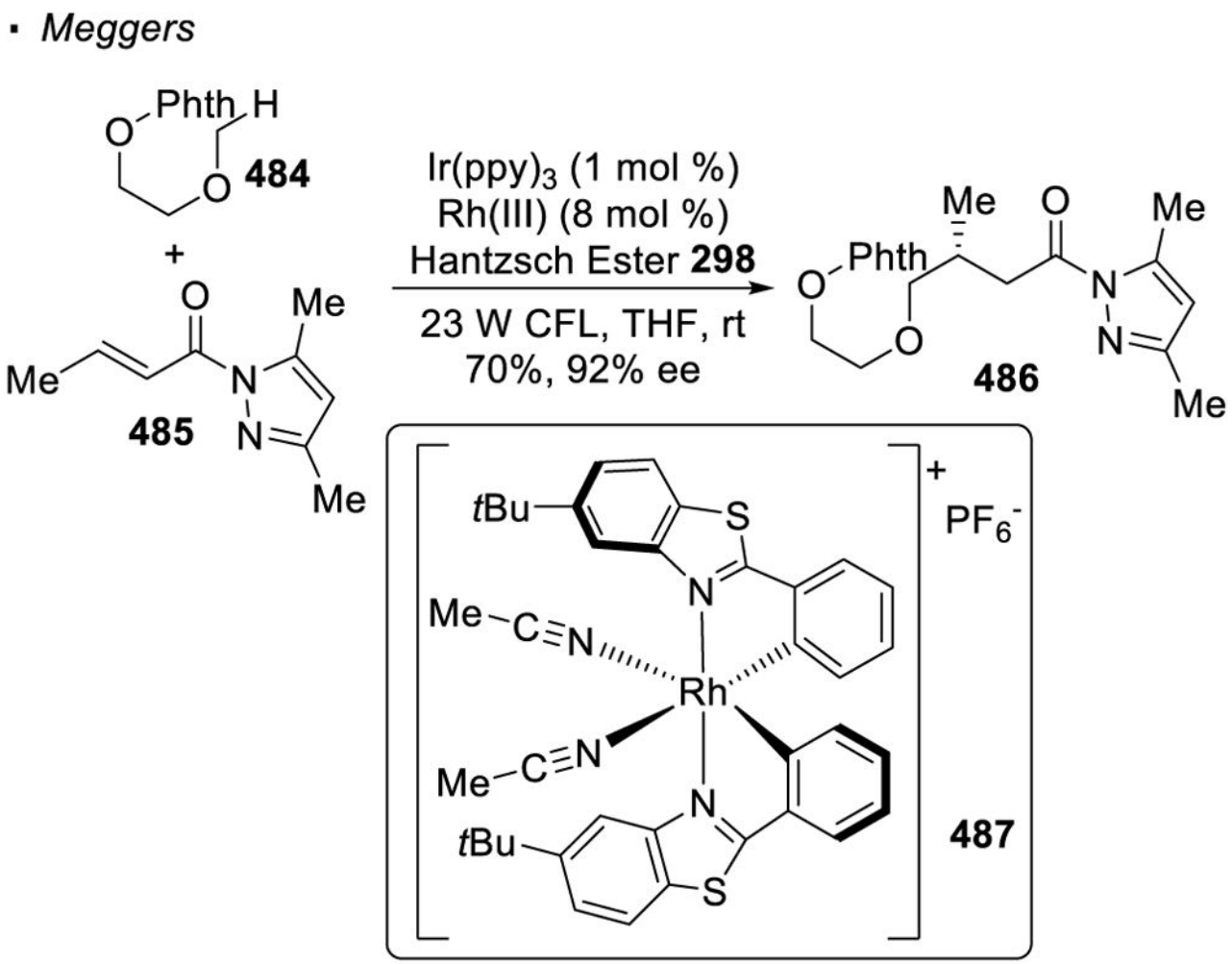


Scheme 91.
Use of Chiral Auxiliary in Chemistry of Alkyl Radicals

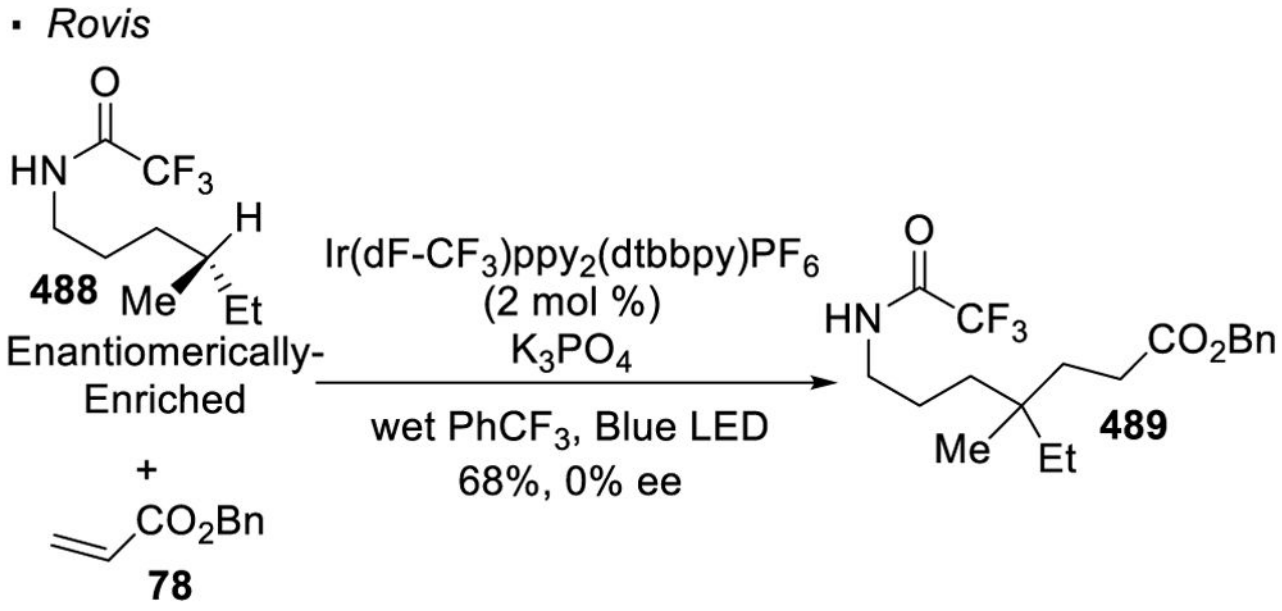


Scheme 92.

Lewis Acid-Catalyzed Asymmetric Addition of Alkyl Radicals

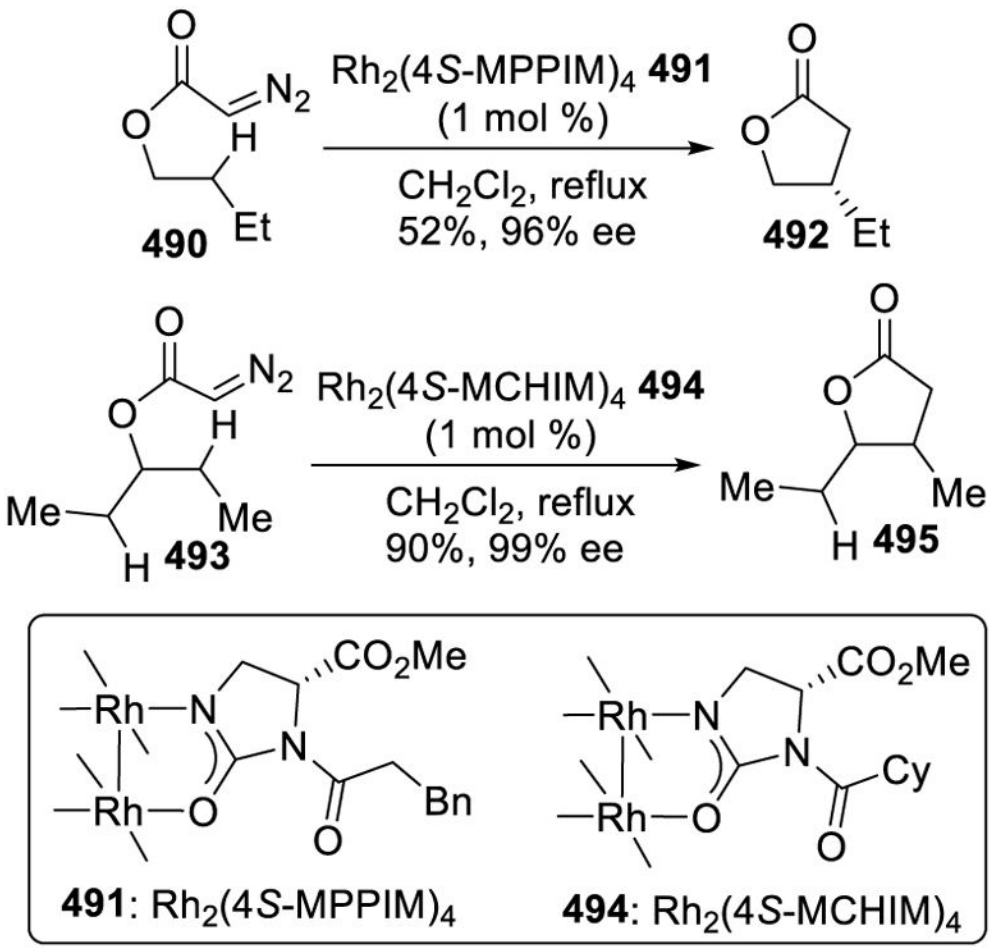


Scheme 93.
Use of Chiral Lewis Acid in HAT

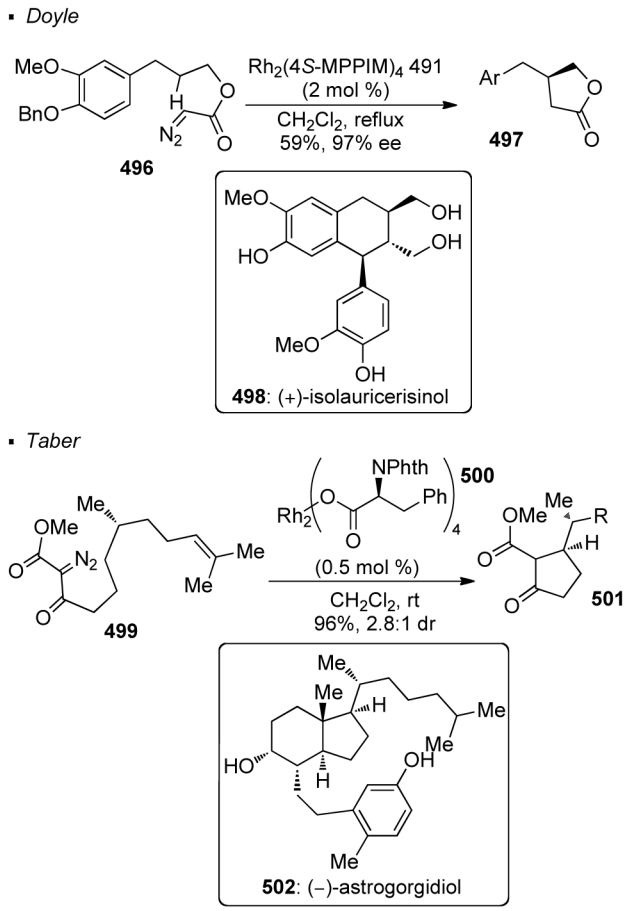


Scheme 94.
Loss of Stereochemistry in HAT

▪ *Doyle*

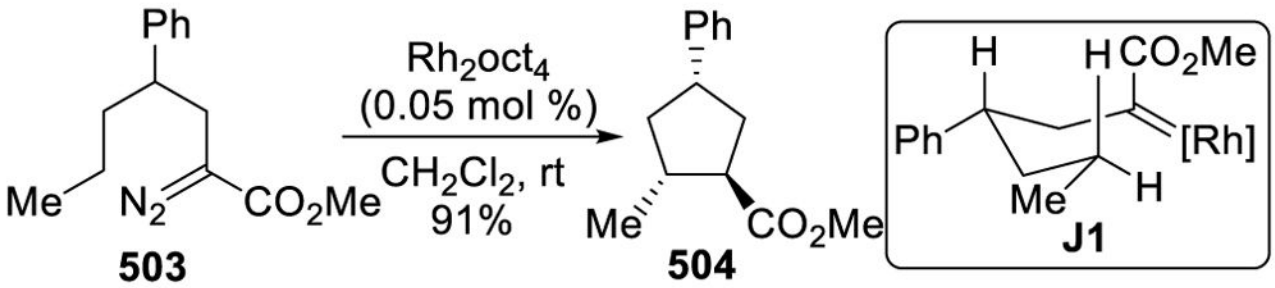


Scheme 95.
Asymmetric C-H Insertion



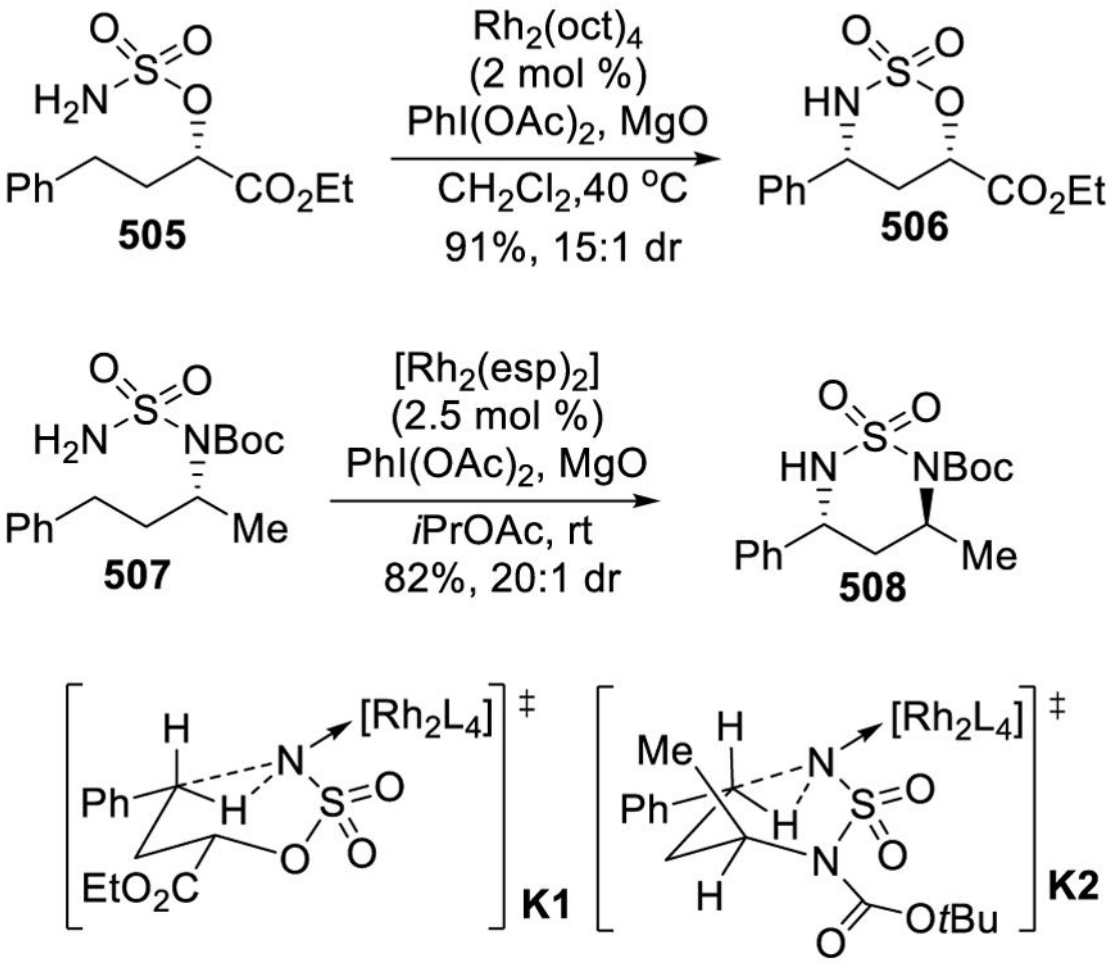
Scheme 96.
Applications of Asymmetric C-H Insertion

▪ *Taber*

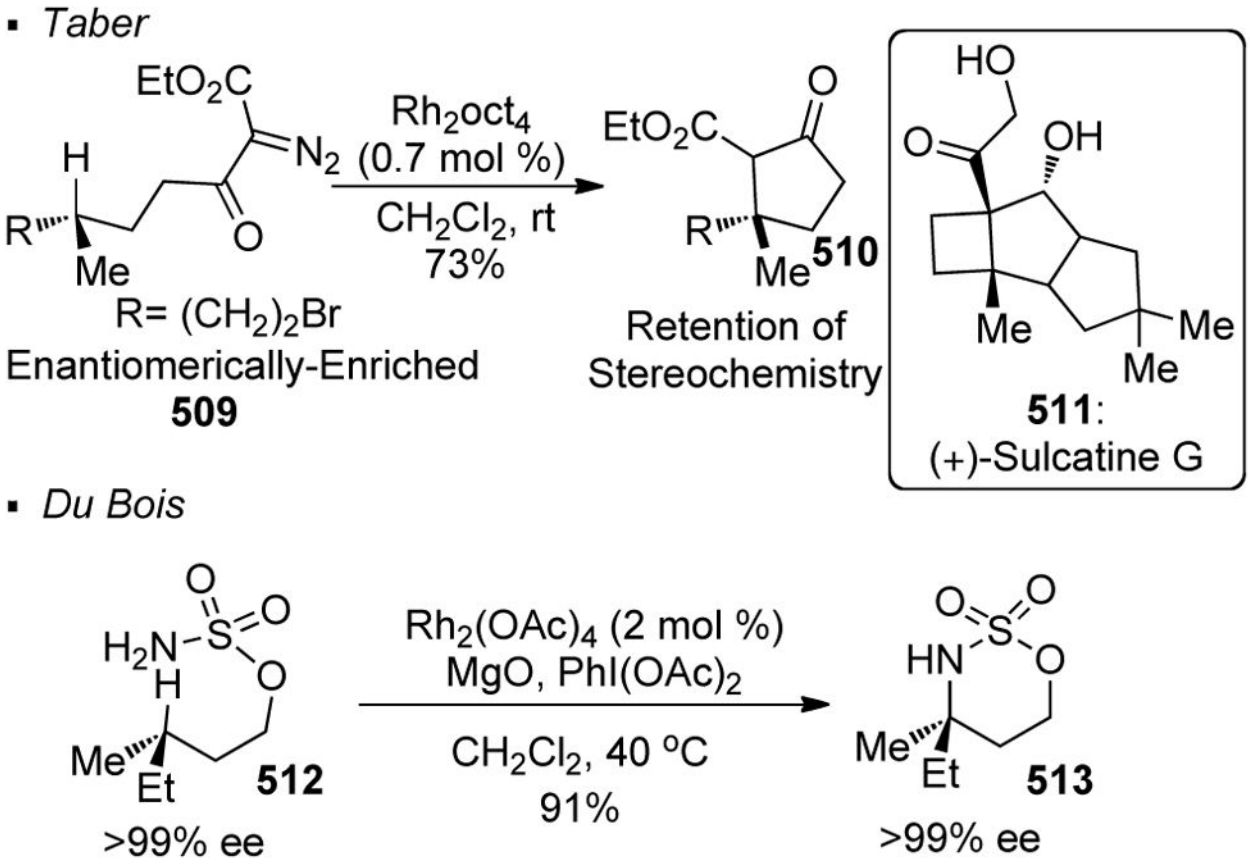


Scheme 97.
Diastereoselective C-H Insertion

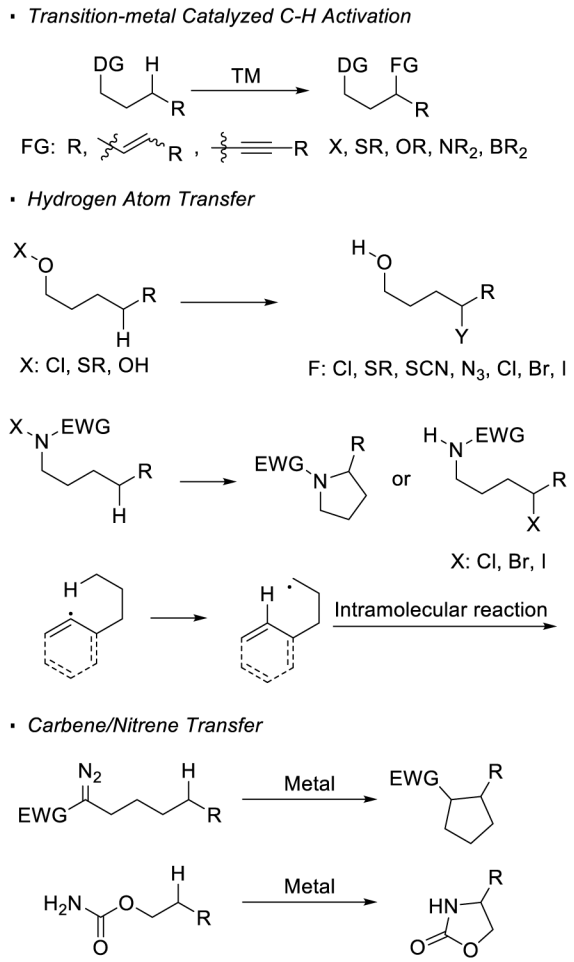
- *Du Bois*



Scheme 98.
Diastereoselective C-H Amination

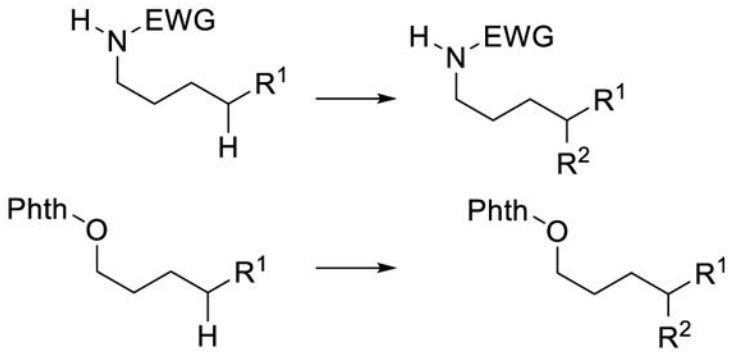


Scheme 99.
Retention of Stereochemistry in C-H Insertion and Amination



Scheme 100.
Scope of Different Strategies

▪ *Merging with Photoredox Catalysis*



Scheme 101.
Broadened Scope with Photoredox Catalysis for HAT