Engaging Radicals in Transition-Metal Catalyzed Cross-Coupling with Alkyl Electrophiles: Recent Advances

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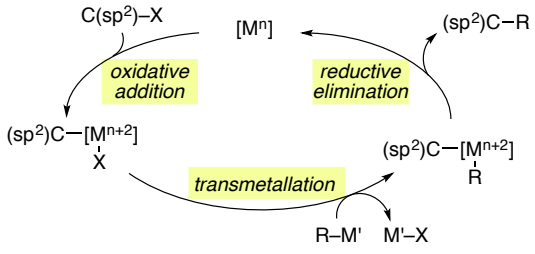
ABSTRACT: Transition-metal catalyzed cross-coupling reactions have created an epoch in modern synthetic organic chemistry, offering a variety of insights in retrosynthetic tactics to synthesize targeted complex molecules in medicine and materials-based applications. Despite numerous types of combinations between nucleophiles, electrophiles, and transition-metal catalysts available for the cross-coupling reactions, construction of covalent bonds including sp^3-hybridized carbon(s) still remains a challenge due to the inherent diverse reactivity of the alkyl species (i.e. alkyl halides, alkyl metals) involved in the catalytic cycle. To realize this goal, the methods to leverage alkyl radicals have recently emerged. This perspective highlights and discusses recent advances on transition-metal catalyzed cross coupling reactions that engage alkyl radicals for C(sp^3)-N and C(sp^3)-Si bond formation with alkyl halides as well as use of carboxylic acid derivatives as surrogates of alkyl halides in decarboxylative C(sp^3)-C(sp^2)/C(sp^3)/B couplings.

KEYWORDS: *catalysis, cross-coupling, single-electron-transfer, radicals, alkyl electrophiles*

Introduction

Development of transition-metal catalyzed cross-coupling reactions has fostered tremendous advancement of modern synthetic chemistry for production of pharmaceuticals, fine chemicals, and functional materials.[1] The power of cross-coupling reactions has been demonstrated in a wide range of successful combinations between organometallic nucleophiles and organic electrophiles with various transition-metal catalysts of choice. Mechanistically, when C(sp^2)-aryl or -alkenyl electrophiles (typically their halides or pseudo halides) are used as the coupling partners, the processes could be initiated by double-electron oxidative addition, that is followed by transmetallation (Scheme 1).[2] The final bond forming processes are accomplished by double-electron reductive elimination, releasing the final products from the catalytic cycle along with regeneration of active lower valent transition metal species ([M]^n). The overall catalytic cycle is therefore maintained by [M]^n/[M]$^{n+2}$.

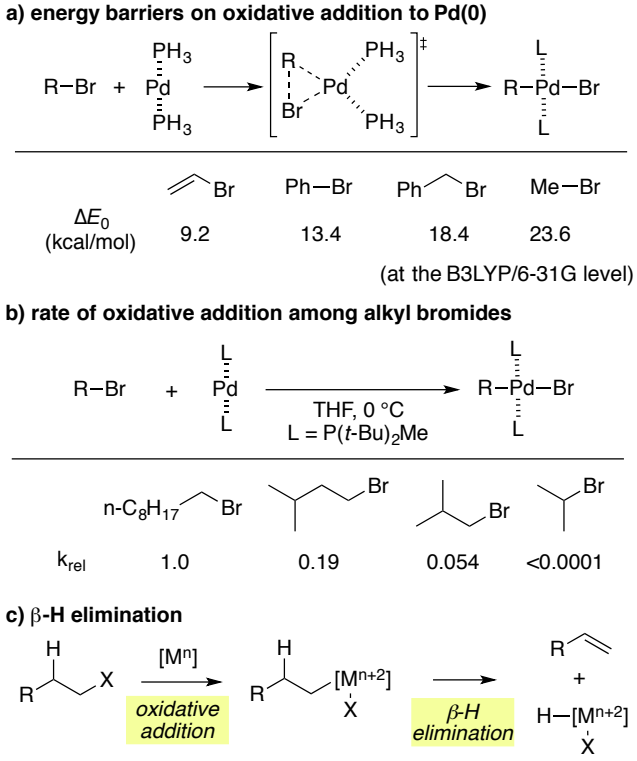


Scheme 1. Overall catalytic cycle of cross-couplings of C(sp^2)-aryl or -alkenyl electrophiles

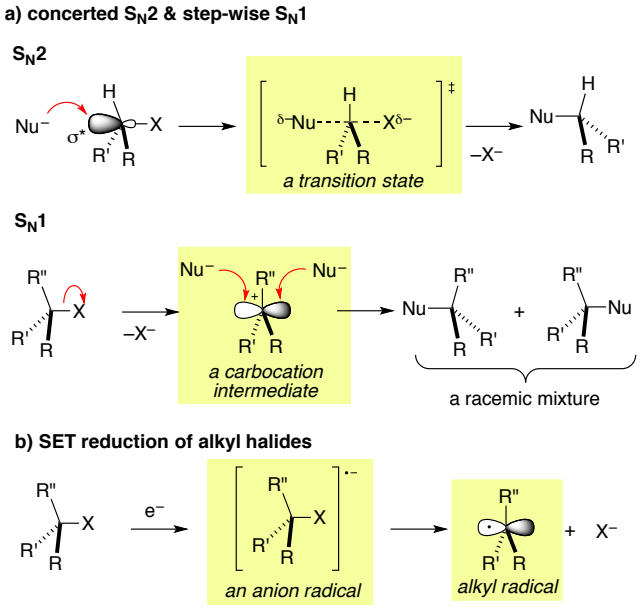
On the other hand, implementation of transition-metal catalyzed cross couplings with alkyl (pseudo)halides still remains a challenge. Commonly, higher energy is required for alkyl halides to undergo double-electron oxidative addition into lower valent transition metals because of more electron-rich nature of the C(sp^3)-X bonds and lack of π*-orbitals to stabilize the transition state for oxidative addition through back-bonding interaction. In fact, the DFT calculation on the activation energy barriers of oxidative addition of various organic halides to the Pd(0) complex indicated that those of alkyl bromides are higher than those of vinyl and phenyl bromides (Scheme 2a).[3a] Moreover, the reaction rate of oxidative addition becomes slower with increase in steric hindrance of alkyl halides (Scheme 2b).[3b] Higher energy barriers required in the oxidative addition of bulkier alkyl halides naturally renders the reaction conditions of the cross coupling reactions harsh (higher temperature, longer reaction time, etc.), that causes several potential issues associated with β-hydride elimination (when they bear β-hydrogen atoms) (Scheme 2c).[3] The resulting metal hydride species potentially causes undesired hydride reduction of the coupling partners.

Nevertheless, these problems, especially with sterically hindered alkyl halides, could not be complemented by classical nucleophilic substitution reactions (Scheme 3a): the concerted S_N2 reactions are very sensitive to the steric nature of both nucleophiles and electrophiles and the stepwise S_N1 reactions involving a carbocation intermediate generally require tertiary alkyl electrophiles under acidic reaction conditions and affords a racemic mixture of the substitution products. On the other hand, the leveraging of alkyl radicals could offer a solution to forge covalent bonds including sp^3-hybridized carbon(s). In such processes, generation of the alkyl radicals is initiated by

single-electron-reduction of alkyl halides, that further fosters the coupling reactions (Scheme 3b).

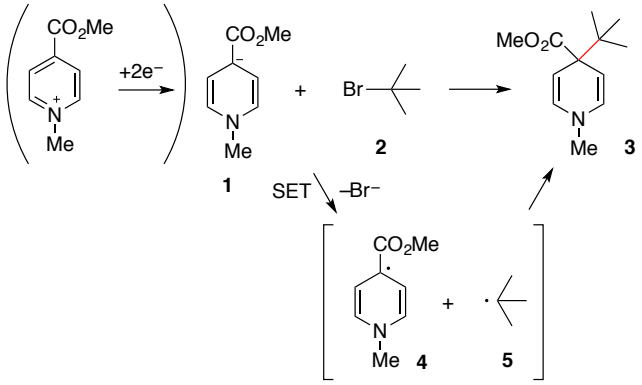


Scheme 2. Oxidative addition of organic halides



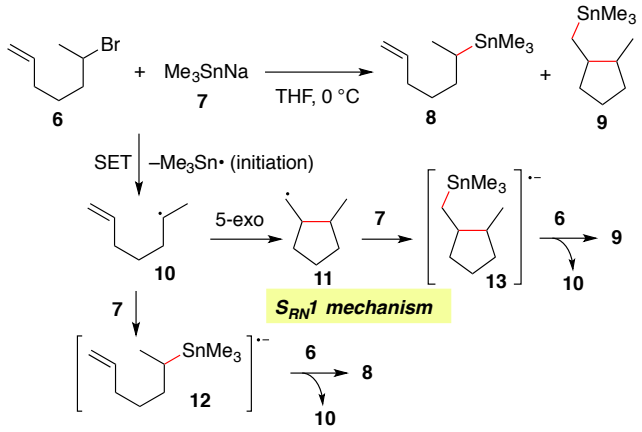
Scheme 3. Substitution reactions with alkyl (pseudo)halides

Earlier examples showed a great potential to utilize alkyl halides as precursors of alkyl radicals to realize the desired alkyl coupling reactions. Lund observed that the reaction of enolate **1**, generated under electrochemical reduction of the corresponding pyridinium salt, with *t*-butyl bromide (**2**) afforded *tert*-butylated product **3**.[4] This unprecedented C-C bond formation between two quaternary carbons is mediated by single-electron-transfer (SET) from enolate **1** to *t*-butyl bromide **2** to form α-carbonyl radical **4** and *t*-butyl radical **5**, which are subsequently coupled to afford product **3** (Scheme 4).



Scheme 4. C(sp³)-C(sp³) coupling of electrogenerated anions with *t*-butyl bromide

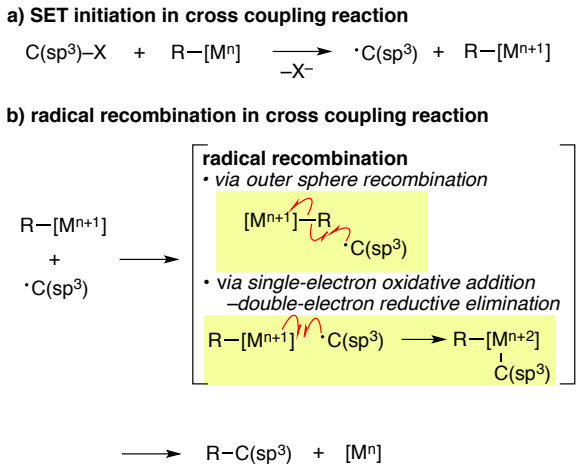
Ashby revealed that the reaction of alkenyl bromide **6** with sodium trimethyltin (**7**) afforded a mixture of acylic substituted product **8** and stannylmethyl cyclopentane **9** (Scheme 5).[5] The detailed mechanistic studies uncovered that the process is initiated by SET to generate secondary alkyl radical **10**, which undergoes kinetically fast 5-exo cyclization to give cyclopentanylmethyl radical **11**. These alkyl radicals **10** and **11** maintain radical chain under $S_{RN}1$ mechanism;[6] namely, recombination of alkyl radicals **10** and **11** with sodium trimethyltin (**7**) generate the corresponding anion radicals **12** and **13**, that induce SET to alkyl bromide **6** to afford products **8** and **9**, respectively, along with generation of alkyl radical **10**.



Scheme 5. Substitution reaction of alkyl bromides with Me_3SnNa

However, these types of radical-mediated coupling reactions of alkyl halides often suffer from difficult control of the process due to highly reactive radical intermediates and therefore, the successful examples have been quite limited. In turn, use

of transition-metal catalysis has recently fostered development of such radical-mediated cross couplings with alkyl electrophiles under milder reaction conditions with precise control from readily available and bench-stable starting materials. Lower valent organometal species (R-[M^n]) generally play a role as the SET reductants to alkyl halides, forming alkyl radicals along with higher valent organometal species (R-[M^{n+1}]) (Scheme 6a). Subsequent radical recombination either via outer sphere recombination or via sequence of single-electron oxidative addition and double-electron reductive elimination could close the catalytic processes to afford the coupling products with regeneration of the lower valent metal species ([M]^n), that can maintain the further catalytic turnover (Scheme 6b). Thus, the catalytic cycle with alkyl radicals potentially involves three kinds of the oxidation states, [M]^n/[M]$^{n+1}$/[M]$^{n+2}$, enabling unprecedented cross coupling processes that are hardly achieved by the conventional double-electron pathways (Scheme 1). In this decade, tremendous advancements have been accomplished for use of alkyl electrophiles in transition-metal catalyzed cross-couplings.[7] This perspective highlights and discusses several advances in C(sp^3)-N and C(sp^3)-Si bond formation with alkyl (pseudo)halides that engage alkyl radicals in transition metal-catalyzed cross couplings. In the last part, the method that leverages carboxylic acids as surrogates of alkyl halides will be highlighted. It should be noted that Ni-catalyzed C-C cross-coupling with alkyl halides that largely involve alkyl radicals is out of the scope in this perspective as the details have recently been reviewed elsewhere.[8,9]

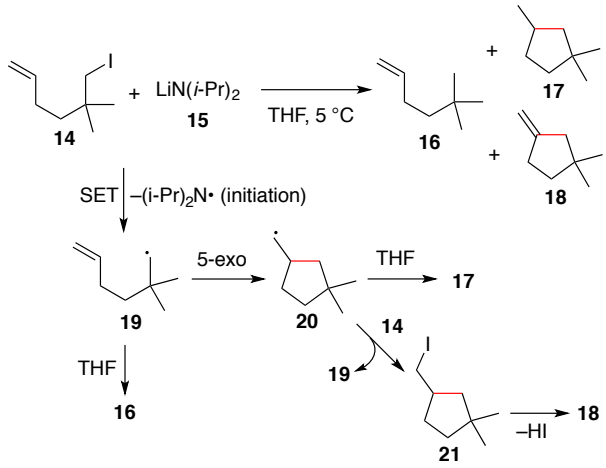


Scheme 6. Cross-coupling with SET process

C(sp^3)-N coupling

Importance of nitrogen-containing organic compounds is represented by their ubiquity in pharmaceuticals and functional materials.[10] Therefore, development of conceptually new C-N bond forming reactions is of paramount importance in the community of synthetic chemistry. In order to forge C(sp^3)-nitrogen bonds, nucleophilic substitution reactions of alkyl halides[11] and reductive amination of aldehydes or ketones[12] are commonly available methods despite certain disadvantage on the substrate scope (sensitive to the sterically bulky substrates).[13] Electrophilic amination of alkyl nucleophiles with rationally designed N-electrophiles has recently been developed, while suffering from the limitation on substituent compatibility.[14,15]

Ashby observed the SET process in the reactions of electron-rich alkali metal amides with alkyl halides (Scheme 7).[16] For example, the reaction of hexenyliodide **14** with LDA (**15**) afforded a mixture of acylic alkene **16**, cyclopentane **17**, and methylenecyclopentane **18** via transient alkyl radical intermediates **19** and **20**. Although the radical chain process could be partially attained through iodine radical abstraction from **14** by **20** to form iodomethylcyclopantane **21**, that is converted into **18**. However, formation of the C(sp^3)-N bond with these radical intermediates does not occur in this case, while they majorly abstract a hydrogen from the solvent (THF).[17]

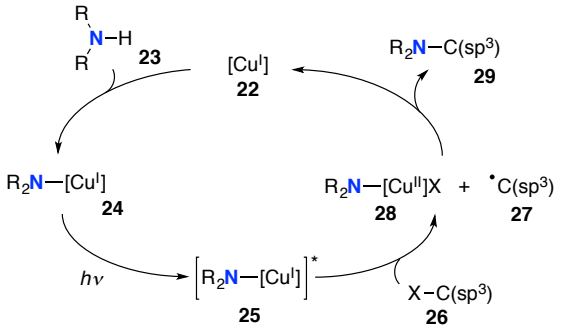


Scheme 7. A reaction of hexenyliodide with LDA

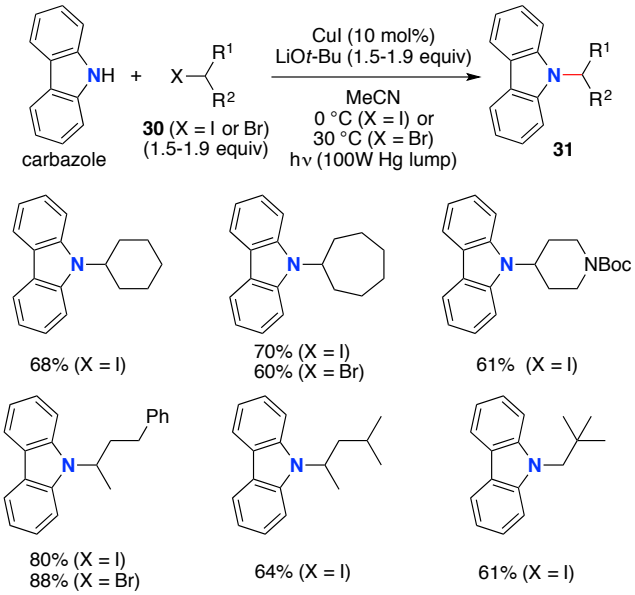
On the other hand, Fu and Peters recently revealed that photo-excited copper(I)-amide complexes undergo SET reduction of alkyl halides to generate alkyl radicals, which can further recombine with nitrogen ligands on the copper to construct C(sp^3)-N bonds (Scheme 8).[18] It should be noted that these reactions tolerate use of hindered primary and secondary alkyl halides with various nitrogen nucleophiles and proceed under surprisingly mild reaction conditions (–40 °C to ambient temperature). The proposed mechanistic scenario is depicted in Scheme 8. Photo-excitation of the Cu(I)-amides **24**, formed via ligand exchange between Cu(I) complexes **22** and amines/amides **23**, is the key to initiate the catalytic processes. The resulting excited state complexes **25** undergo single-electron-reduction of alkyl halides **26**, affording the corresponding alkyl radicals **27** and Cu(II)-amides **28**. Recombination of the alkyl radicals **27** with the nitrogen ligands of **28** forms C(sp^3)-N coupling products **29** with generation of Cu(I) complexes **22**, that maintain the catalytic turnover by forming the complexes **24** with unreacted nitrogen-nucleophiles **23**.

Carbazoles are promising nitrogen-nucleophiles for the coupling reactions with primary or secondary alkyl halides (iodides or bromides). For example, carbazole and alkyl iodides **30** could be coupled to provide N-alkylated carbazoles **31** in good yields even at 0 °C in the presence of CuI as a catalyst (10 mol%) and Li*O*t-Bu (1.9 equiv) in CH_3CN under photo irradiation (100-watt Hg lamp) (Scheme 9).[18a] The method allows for using not only secondary alkyl iodides (both cyclic and acyclic) but also sterically hindered primary (neopentyl) iodide. The cross-coupling with alkyl bromides needs slightly

higher temperature (at 30 °C). A cuprate, Li[Cu(carbazolide)$_2$], is supposed to be involved in the catalytic cycle, that was confirmed by a series of control experiments using a well-defined Li[Cu(carbazolide)$_2$] complex.[19]



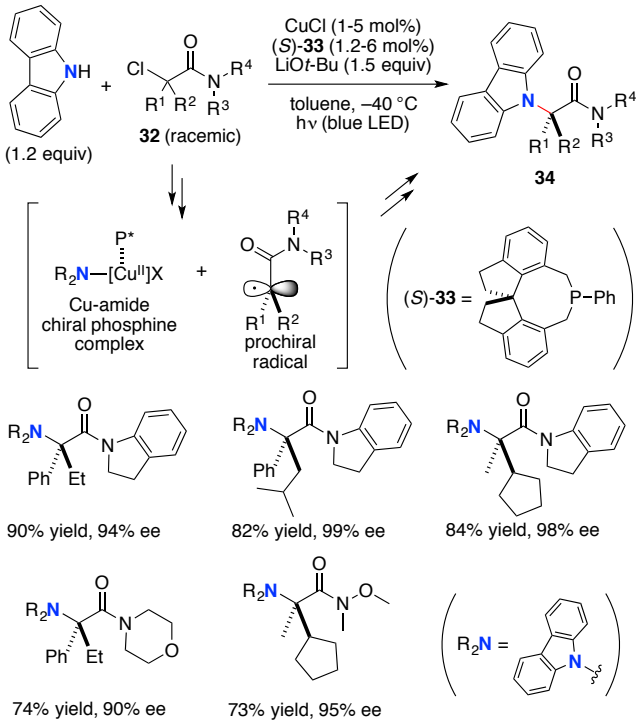
Scheme 8. General catalytic cycle for photo-induced Cu-catalyzed cross coupling of primary and secondary alkyl halides with N-nucleophiles



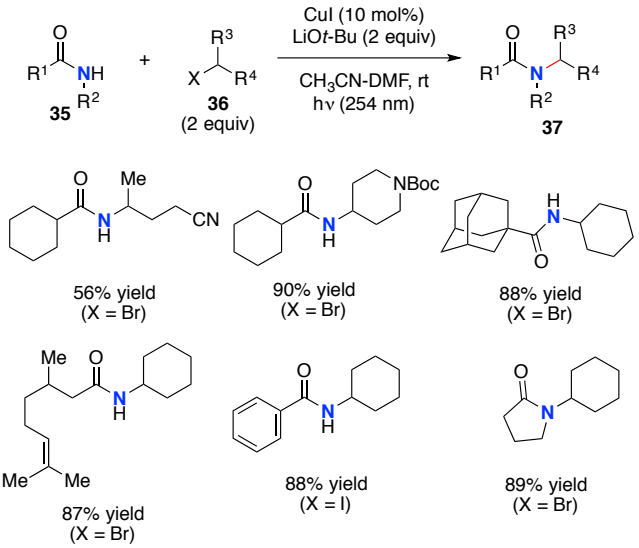
Scheme 9. C(sp^3)-N coupling of carbazole with alkyl halides

Notably, this photo-induced Cu-catalyzed C(sp^3)-carbazole cross-coupling was extended to an asymmetric variant with racemic α-chloro amides **32** as alkyl electrophiles, which takes advantage of the prochiral nature of the resulting radical intermediates for the reactions with the transient Cu-amide complexes with chiral phosphine **33** to afford enantio-rich amide products **34**.[18b] Significantly, the processes could be facilitated by lower catalytic loading of CuCl (1.5–1 mol%) and chiral phosphine ligand **33** (1.2-6 mol%) under visible light (from blue LED) even at –40 °C, for construction of chiral fully substituted carbons at the α-position of amides **34** (Scheme 10).

Under irradiation of light of shorter wave length (254 nm), primary amides **35** could be used for Cu-catalyzed coupling reaction with alkyl halides **36** (Scheme 11).[18c, 20] While the method also allowed for use of γ-lactam and 2-oxazolidinone, other secondary amides were poorly performed for the coupling reactions.



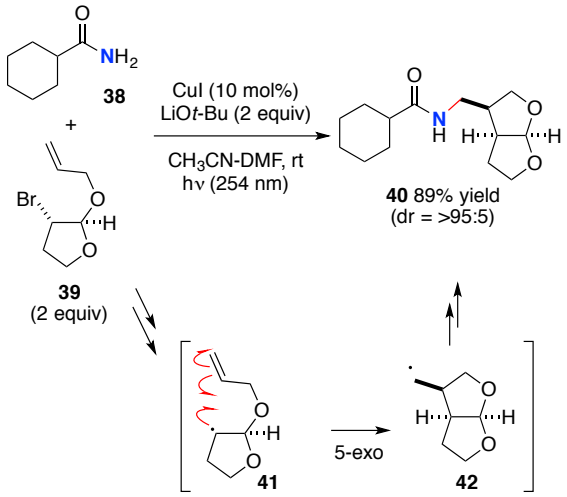
Scheme 10. C(sp^3)-N coupling of carbazole with α-chloroamides



Scheme 11. C(sp^3)-N coupling of amides with alkyl halides

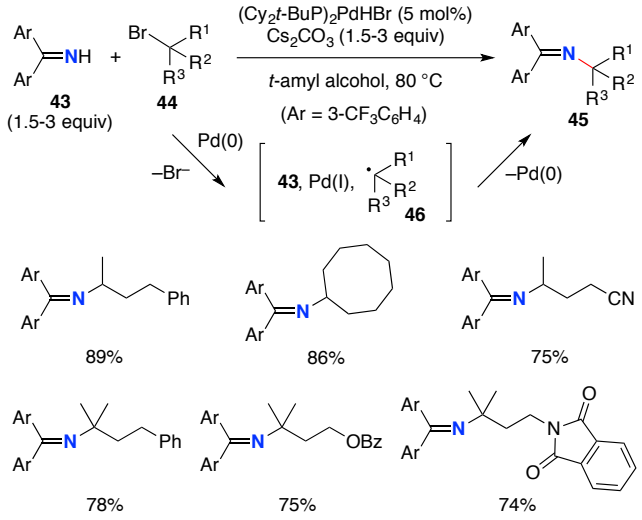
The presence of the alkyl radical intermediates during the C(sp^3)-N cross-coupling reactions was supported by a radical-clock experiment with alkyl bromide **39** having an alkene tether, that affords bicyclo[3.3.0] structure **40** via 5-exo cyclization of putative secondary radical species **41** followed by

the C-N coupling with the resulting cyclized primary radical **42** (Scheme 12).



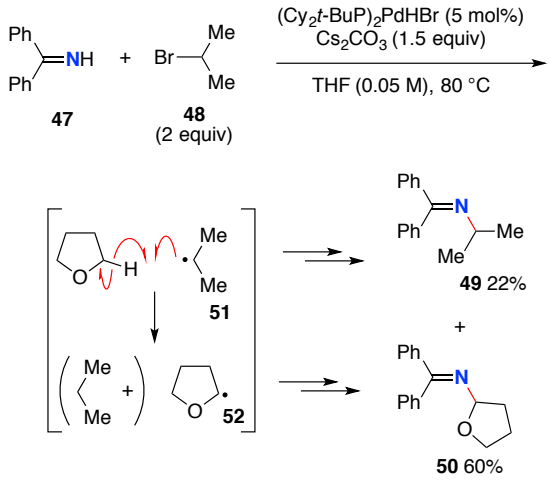
Scheme 12. A radical probe experiment

Hartwig reported use of benzophenone imines **43** as ammonia surrogate N-nucleophiles in Pd-catalyzed cross couplings with secondary or tertiary alkyl bromides **44** for synthesis of protected primary amines **45** (Scheme 13).[21] The processes could be initiated by SET reduction of alkyl bromides **44** by the Pd(0) complex, forming alkyl radicals **46** and Pd(I) species,[22] whereas the detailed mechanism on the C-N bond formation with regeneration of Pd(0) complex is still unclear.



Scheme 13. C(sp^3)-N coupling of *N*-H imine with alkyl bromides

The catalytic cycle involving the alkyl radical intermediates is proposed based on the stereochemical outcome from the reaction of an optically active alkyl bromide (resulting in racemization in the product) and radical clock experiments as well as incorporation of THF in the amination product when the reaction was run in THF. As shown in Scheme 14, the coupling reaction of benzophenone imine (**47**) and 2-bromopropane (**48**) in THF afforded not only *N*-isopropyl imine **49** but also *N*-tetrahydrofuranyl imine **50**; the latter was formed through the coupling reaction with tetrahydrofuranyl radical **52** formed via H-radical abstraction of THF by the initially formed isopropyl radical **51**.

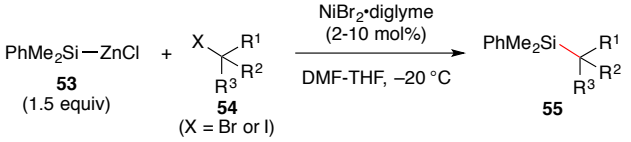


Scheme 14. C(sp^3)-N coupling of *N*-H imine in THF

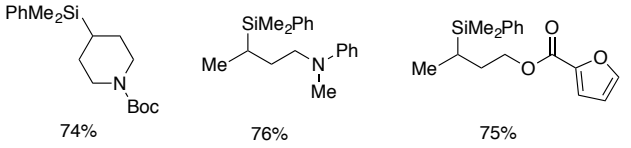
C(sp^3)-Si coupling

Organosilicon compounds are of privileged use not only in synthetic chemistry but also in materials-based applications and medicinal chemistry.[23] Therefore, various types of methods to forge C-Si bonds have been developed. For the formation of C(sp^3)-Si bonds, catalytic hydrosilylation of alkenes with hydrosilanes[24] and electrophilic silylation (coupling of silyl halides with C(sp^3)-nucleophiles)[25] are commonly available despite certain limitation on the substrates used in these processes. On the other hand, nucleophilic silylation (coupling of silyl nucleophiles with C(sp^3)-electrophiles) is an attractive alternative method of choice, whereas the reported examples have been restricted to the use of activated C(sp^3)-electrophiles such as allylic, propargylic, and benzylic ones.[26] Use of alkyl radicals with transition-metal catalysts could dramatically expand scope of the C(sp^3)-Si couplings.

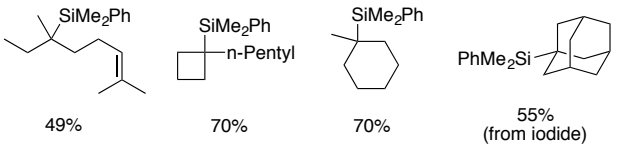
Fu developed Ni-catalyzed cross-couplings of silylzinc chloride ($PhMe_2Si$-ZnCl) **53** with unactivated secondary or tertiary alkyl halides **54**.[27] The processes could be facilitated using a commercially available $NiBr_2$•diglyme catalyst even at –20 °C to deliver organosilicon compounds **55** with wide substituent compatibility (Scheme 15). Competitive experiment between tertiary, secondary and primary alkyl bromides with silylzinc chloride **53** indicated that the reactions of more substituted alkyl bromides are faster in rate (Scheme 16a for tertiary bromide **56** vs secondary bromide **57**). These outcomes suggested that the stability of the radical (Scheme 16b) is crucial rather than steric factor in this C(sp^3)-Si coupling process.



• with secondary alkyl bromides (2 mol% of $NiBr_2$•diglyme)

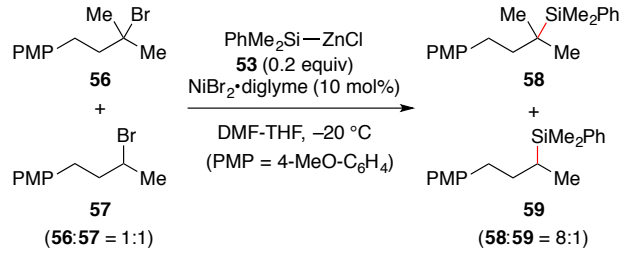


• with tertiary alkyl bromides/iodides (10 mol% of $NiBr_2$•diglyme)

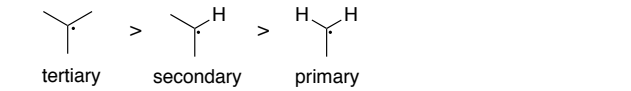


Scheme 15. C(sp^3)-Si coupling of silylzinc reagent with alkyl halides

a) tertiary bromide vs secondary bromide



b) stability trend of alkyl radicals

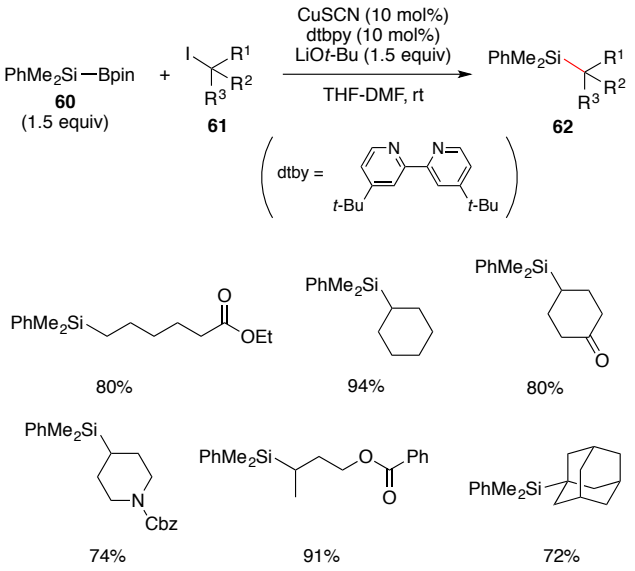


Scheme 16. Kinetic experiment between tertiary and secondary alkyl bromides

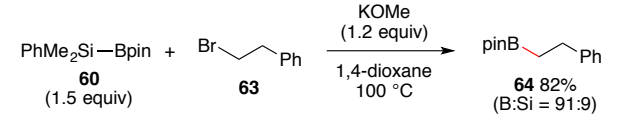
Oestreich reported use of silylborane **60** as a silicon pronucleophile for nucleophilic silylation of unactivated alkyl iodides **61** under specific catalyst combination of CuSCN and 4,4'-di-*t*-butyl-2,2'-bipyridine (dtbpy) at room temperature, providing organosilanes **62** with good functional group compatibility (Scheme 17a).[28] Interestingly, this C(sp^3)-Si coupling with silylborane **60** is in the sharp contrast to the Ito's earlier observation of the C(sp^3)-B coupling in the KOMe-mediated reaction of alkyl bromide **63** with silylborane **60** (Scheme 17b).[29,30]

The DFT calculation led to a proposal of the detailed catalytic cycle, which is comprised of alkyl radical intermediates (Scheme 18). The cationic Cu(I) species **65** is proposed to initiate the catalytic cycle with silyllithium species **66** formed from silylborane **60** and LiO*t*-Bu, providing silyl-Cu(I) species **67**. SET between **67** and alkyl iodides **61** occurs to generate alkyl radicals **68** and silyl-Cu(II) species **69** having large spin population on the Si atom. Outer sphere radical recombination is thus proposed to build C(sp^3)-Si bonds in the products **62** with regeneration of active Cu(I) species **65**, whereas another mechanistic possibility via single-electron oxidative addition followed by C(sp^3)-Si reductive elimination is not ruled out for the formation of **62**.[31]

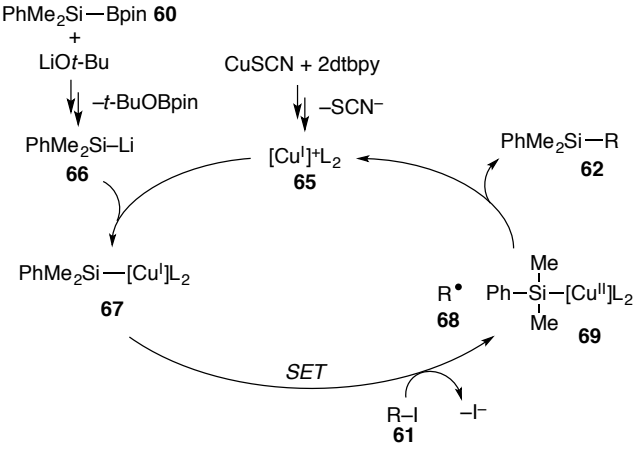
a) Cu-catalyzed C(sp^3)-Si coupling



b) KOMe-Mediated C(sp^3)-B coupling



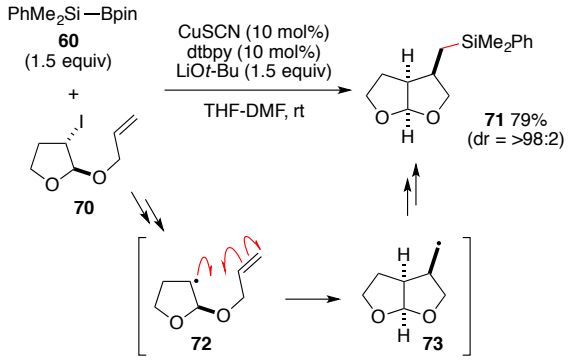
Scheme 17. C(sp^3)-Si coupling of silylborane with alkyl halides



Scheme 18. Catalytic cycle for Cu-catalyzed C(sp^3)-Si coupling of silylborane with alkyl halides

Demonstration of the cascade process with alkyl iodides having an alkene tether supports the presence of alkyl radical species in the C(sp^3)-Si coupling processes. For example, the reaction of iodide **70** delivered bicyclic product **71** through a sequence of 5-*exo* radical cyclization of radical intermediate

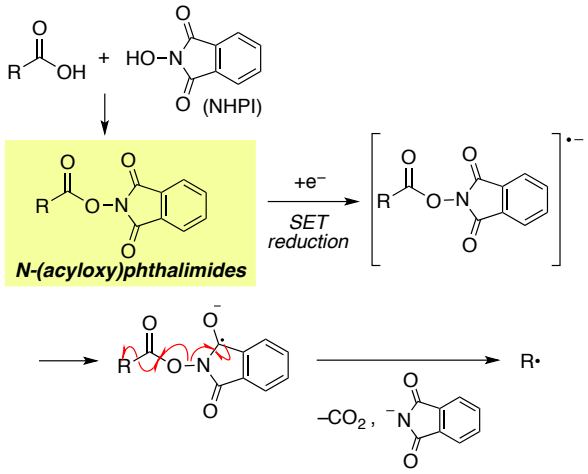
72 and C(sp^3)-Si coupling of as formed cyclized radical **73** (Scheme 19).



Scheme 19. A radical probe experiment

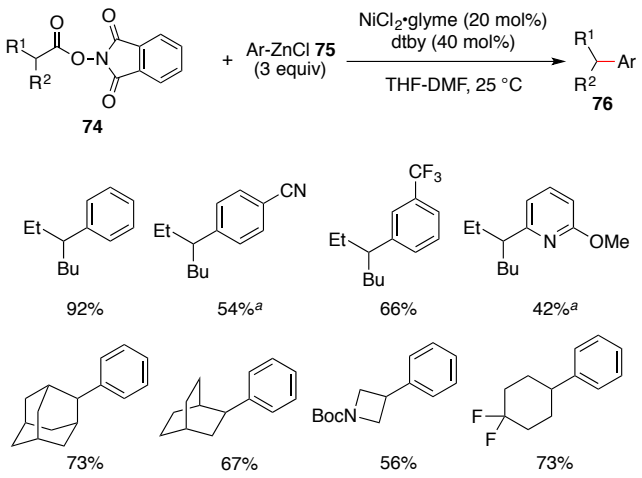
Use of carboxylic acids as an alkyl electrophile

Aliphatic carboxylic acids are ubiquitous in nature and those on various backbones with many other functional groups are commercially available.[32,33] New and practical protocols for radical-mediated catalytic cross-coupling processes have recently emerged using N-(acyloxy)phthalimides as surrogates of alkyl halides. N-(acyloxy)phthalimides, readily prepared from the corresponding carboxylic acids and N-hydroxyphthalimide (NHPI), are defined as redox-active esters, as they could be reduced under SET fashion to fragment into the corresponding C(sp^3)-radicals, carbon dioxide, and phthalimidyl anion (Scheme 20).[34] This redox reactivity of N-(acyloxy)phthalimides (NHPI esters) was discovered by Okada and Oda in the reductive fragmentation of NHPI esters under visible light photoredox catalysis to form alkyl radicals.[34e] This photoredox strategy of NHPI esters was recently utilized by Overman for generation of tertiary radicals and their addition onto electron-deficient alkenes to construct quaternary carbon centers involved in complex natural products.[35] In turn, use of lower valent transition metal catalysts and organometallic nucleophiles enables single-electron-reduction of NHPI esters to generate the corresponding C(sp^3)-radicals, which can facilitate further the cross-coupling processes to form C-C bonds. This section will highlight recent development on C(sp^3)-C(sp^2) and C(sp^3)-C(sp^3) cross coupling reactions using NHPI esters as aliphatic electrophiles.[36]



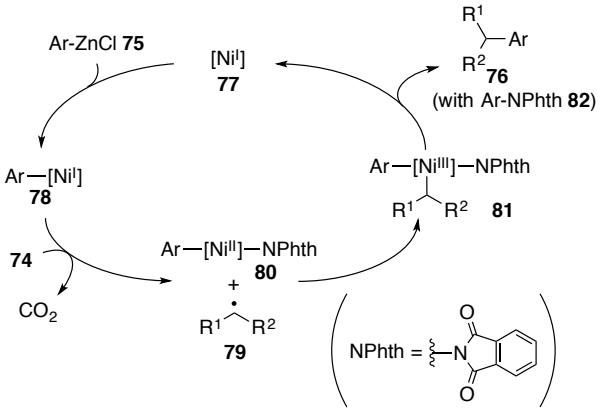
Scheme 20. Reactivity of NHPI esters under SET

Baran reported Ni-catalyzed C(sp^3)-C(sp^2) cross coupling reactions of aliphatic carboxylic acid NHPI esters **74** with arylzinc chlorides **75** (Scheme 21).[37] Using commercially available catalysis systems of $NiCl_2$•glyme and bipyridine ligands, efficient construction of the C(sp^3)-C(sp^2) bonds were accomplished under mild reaction conditions. The catalytic cycle could be initiated by transmetallation between transient Ni(I) species **77** and arylzinc reagents **75** to form aryl-Ni(I) species **78**, that subsequently undergo single-electron-reduction of carboxylic acid NHPI esters to afford the corresponding alkyl radicals **79** with generation of aryl-Ni(II) species **80** (Scheme 22). Recombination between the alkyl radicals **79** and aryl-Ni(II) **80** through single-electron oxidative addition affords aryl-Ni(III)-alkyl complexes **81**, which induce C(sp^2)-C(sp^3) reductive elimination to produce the coupling products **76** with generation of active Ni(I) complexes **77**. The presence of aryl-Ni(III)-alkyl complexes **81** in the catalytic cycle was supported by isolation of N-arylphthalimidea **82** as a side product.



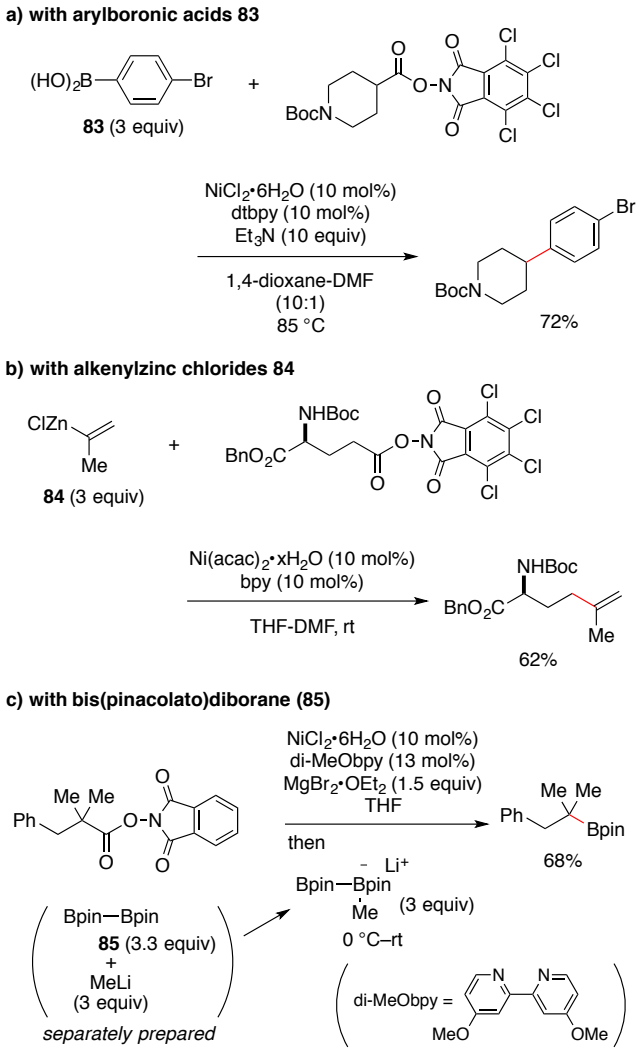
[a] Tetrachloro-NHPI was used.

Scheme 21. Ni-catalyzed C(sp^3)-aryl coupling of NHPI esters with arylzinc chlorides

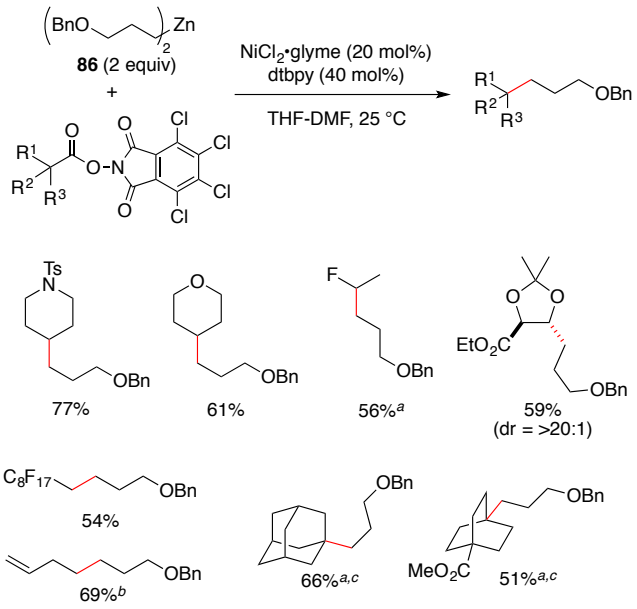


Scheme 22. Catalytic cycle for Ni-catalyzed C(sp^3)-aryl coupling of NHPI esters with arylzinc chlorides

This method was further extended to use of arylboronic acids **83** (Scheme 23a)[38] and alkenylzinc reagents **84** (Scheme 23b)[39] for the C(sp^3)-C(sp^2) cross couplings as well as bis(pinacolato)diborane (**85**) for synthesis of alkyl boronate esters (Scheme 23c).[40] Furthermore, C(sp^3)-C(sp^3) couplings were accomplished using primary or secondary dialkylzinc reagents **86** as nucleophiles (Scheme 24).[41-43] Of worthy to note is that various NHPI esters derived from a range of primary, secondary and tertiary carboxylic acids can be used for these cross-coupling processes. Moreover, instead of the Ni-bipyridine systems, the Fe-diphosphine system could be adopted as the catalyst for coupling reactions with the aliphatic carboxylic acid NHPI esters.[44]



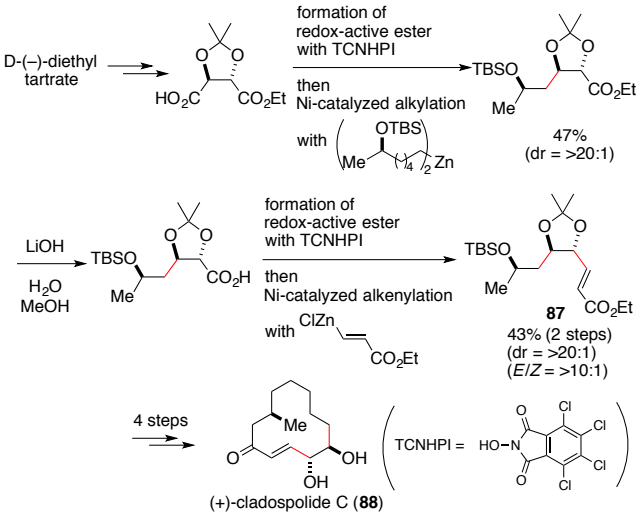
Scheme 23. Ni-catalyzed C(sp^3)-C(sp^2) and C(sp^3)-B coupling of NHPI esters



[a] Normal NHPI esters were used. [b] 2,2'-bipyridine was used. [c] 40 mol% of Ni catalyst and 4,4'-dimethyl-2,2'-bipyridine (di-Mebpy) were used.

Scheme 24. Ni-catalyzed C(sp^3)-C(sp^3) coupling of NHPI esters with dialkylzinc reagents

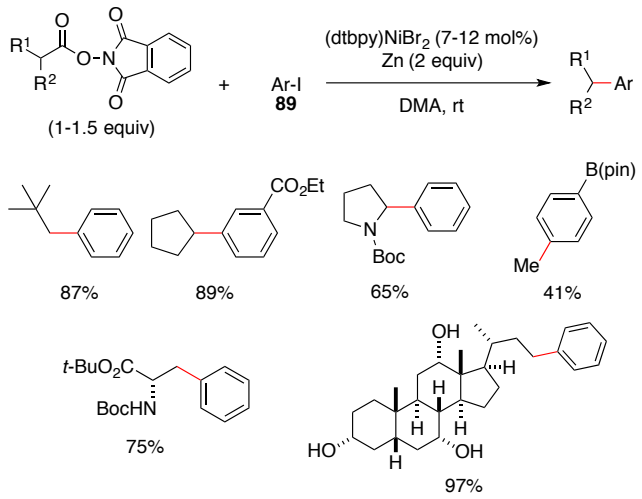
Robustness of the redox-active ester strategy was demonstrated on its extremely broad functional group compatibility as well as wide and practical applicability that can simplify routes for the synthesis of complex molecules. For example, a sequence of Ni-catalyzed C(sp^3)-C(sp^3) and C(sp^3)-alkene couplings of tartrate-derived carboxylic acid assembled **87** having all the functional groups necessary for synthesizing (+)-cladospolide C (**88**) (Scheme 25).[39]



Scheme 25. A concise synthesis of (+)-cladospolide C

On the other hand, Weix disclosed use of aliphatic acid NHPI esters in Ni-catalyzed reductive cross-coupling with aryl iodides **89** (Scheme 26).[45,46] In this case, Zn powder (2 equiv) assists to maintain the catalytic turnover for decarboxylative

coupling of various primary or secondary carboxylic acid NHPI esters.



Scheme 26. Ni-catalyzed reductive coupling of NHPI esters with aryl iodides.

Conclusions and Future Outlook

In this perspective, we have discussed several recent examples of transition-metal-catalyzed cross coupling reactions with aliphatic electrophiles that engage alkyl radicals as a key intermediate. In most cases, these coupling reactions are catalyzed by the first-row transition (base) metals, owing to their superior reactivity to induce the SET process for reductive generation of alkyl radicals from alkyl electrophiles. As the base metals are commonly omnipresent in nature and lower in cost and toxicity, employment of them complementary to the precious transition metals for further development of aliphatic coupling reactions is highly advantageous from the view points of sustainability.[47] More challenges and opportunities still remain for exploration of unconventional aliphatic electrophiles[48] and understanding of the detailed reaction mechanisms that can result in enhancement of the process efficiency such as the catalytic turnovers as well as development of highly stereocontrolled (asymmetric) alkyl couplings. It is our strong belief that the leveraging of alkyl radicals to exploit catalytic alkyl cross coupling continues to flourish and thus enhance our synthetic capability.

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Notes

The authors declare no competing financial interest.

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