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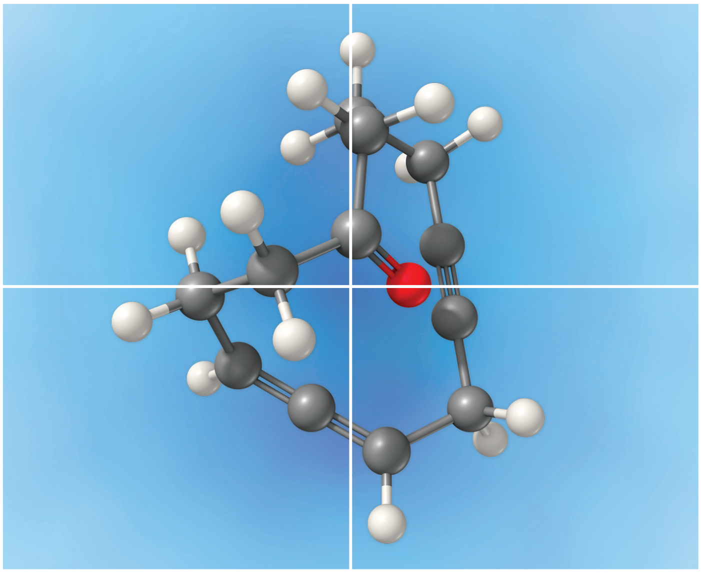

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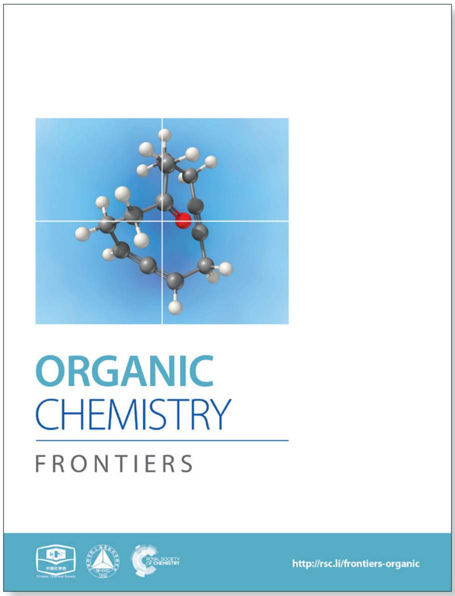

Journal Name

Tutorial Account

Nickel-Catalyzed Reductive Coupling of Alkyl Halides with Other Electrophiles: Concept and Mechanistic Considerations

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Jun Gu,[a] Xuan Wang,[a] Weichao Xue[b] and Hegui Gong*[a,b]

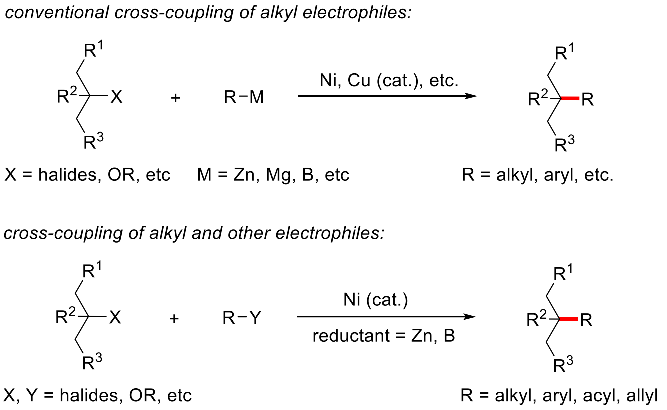
The formation of C–C bonds directly from catalytic reductive cross-coupling of two different electrophiles represents one of the practical synthetic protocols that differs from the conventional nucleophile/electrophile coupling methods. Particularly the reductive coupling of alkyl electrophiles with other electrophiles is still a challenge. This account summarizes the advances of the formation of $C(sp^3)$–$C(sp^3)$ bonds between two alkyl electrophiles, with emphasis on the control of chemoselectivity that is exceedingly challenging to achieve due to similar structures and reactivities of two unactivated alkyl halides. The coupling of alkyl halides with aryl or acyl electrophiles was also discussed based on the chemistry developed by our group, followed by a brief overview for the reactions of tertiary alkyl halides. In the end, a brief outlook of the challenges in this exciting field was illustrated. Whereas the reaction mechanisms generating alkyl-alkyl products are proposed to involve reactions of Ni(I) species with alkyl halides to generate R_{alkyl}–Ni(III)–R_{alkyl} intermediates through a radical/Ni cage–rebound process, evidence seemingly supports that a radical chain mechanism governs the acylation and arylation of alkyl halides. The latter features a cage-escaped alkyl radical.

1. Introduction

The construction of C–C bonds through transition metal-catalyzed reactions of a nucleophile with an electrophile represents the main research directions in the field of cross-coupling chemistry, wherein the catalytic coupling of alkyl electrophiles or alkyl nucleophiles is generally more challenging than the aryl counterparts.[1,2] It was not until early this century, the development of Pd- and Ni-catalyzed cross coupling of a variety of organometallic nucleophiles with alkyl electrophiles achieved rapid advance after enormously innovative studies by Fu and many others (Scheme 1).[3] Alternatively, coupling of alkyl nucleophiles particularly *tertiary* ones with different electrophiles has also evolved as an important protocol to alkyl compounds.[4] Both strategies generally necessitate prepreparation of nucleophile, which may become problematic for those bearing β-functional groups susceptible for elimination.[5]

Unlike the conventional coupling method that requires organometallic nucleophiles, direct coupling of two readily accessible electrophiles under reductive conditions provides an alternative yet more straightforward means to the construction of C–C bonds. Not only preparation of organometallic nucleophilic reagents is avoided, but the reaction mechanisms may be distinctive from a classic scenario pertaining to transmetallation of a nucleophile to a metal center.

Scheme 1. Conventional coupling vs reductive coupling of alkyl electrophiles.



The concept of homocoupling of two electrophiles can be dated back to the Wurtz and Ullmann reactions that were discovered 160 and 100 years ago for the generation of alkyl–alkyl and aryl–aryl compounds, respectively.[6] The Wurtz reactions are characteristic of poor dimerization efficiency and harsh reducing conditions, e.g., Na, which tolerates very limited substrates with very narrow functionalities. Consequently, development of more important cross-coupling between two different alkyl electrophiles, especially those unactivated ones using Wurtz protocol is not appealing by

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[a] School of Materials Science and Engineering, Shanghai University, 99 Shang-Da Road, Shanghai 200444, China

[b] Department of Chemistry, Shanghai University, 99 Shang-Da Road, Shanghai 200444, China, E-mail: hegui_gong@shu.edu.cn

† Footnotes relating to the title and/or authors should appear here.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x further considering the poor chemoselectivity between the alkyl coupling partners; competitive homocoupling may become a severe issue due to a statistically controlled process.

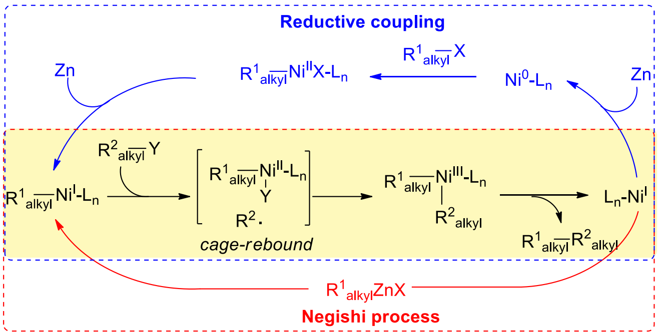
The challenges for the development of efficient cross-coupling between two unactivated alkyl electrophiles prompted us to quest whether a transition-metal-catalyzed reductive cross-coupling protocol is feasible to afford C(sp^3)–C(sp^3) bonds. Further, can the same concept be extended to the coupling alkyl halides with a wide set of other electrophiles? Third, how would the reaction mechanisms operate for these novel types of reductive coupling reactions? In this account, we emphasize our discussion on these three perspectives based upon our group's recent discoveries on Ni-catalyzed reductive coupling chemistry of alkyl halides (Scheme 1). The concurrent or earlier discoveries from other groups through reductive coupling, including electrochemical coupling or in situ formation of organometallics/coupling between two electrophiles have been nicely reviewed,[7] and will not be detailed. Outlook of the challenges in the reductive coupling chemistry will be addressed in the end of this minireview.

1. 1 C(sp^3)–C(sp^3) bond formation

In order to achieve effective cross-coupling between two different yet structurally similar alkyl electrophiles, the catalytic conditions should first be able to override the intrinsically poor chemoselectivities of the coupling partners, which may induce severe competition with homocoupling. Second, the catalyst should competently inhibit possible β-H elimination bypaths that are often found for alkyl substrates and may become problematic.

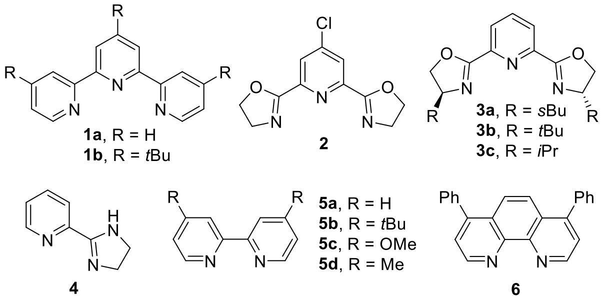
Encouraged by the success in Fu's Ni-catalyzed Negishi coupling of alkylzincs with alkyl halides,[8] we were curious whether two alkyl halides were suited for Ni-catalyzed conditions using Zn as the terminal reductant. In the mechanistic studies for the Ni-catalyzed Negishi coupling, Vicic has indicated that a Terpy–Ni^{I}–R^1_{alkyl} (Terpy = **1a**, Figure 1) complex is able to transfer one electron to an alkyl halide (R^2_{alkyl}–X) which results in alkyl radical.[9] A rapid combination of the resultant Terpy–Ni^{II}–R^1_{alkyl} with R^2_{alkyl} radical yields R^1_{alkyl}–Ni^{III}(Terpy)–R^2_{alkyl} (*a cage-rebound process*). Reductive coupling gives R^1_{alkyl}–R^2_{alkyl} product and terpy–Ni^{I}–X intermediate which is readily converted into terpy–Ni^{I}–R^1_{alkyl} by transmetallation with R^1_{alkyl}-Zn, allowing the catalytic process to continue (Scheme 2, red box).

Scheme 2. Proposed reaction mechanisms for reductive coupling and Negishi reactions involving *cage-rebound* process for the formation of Ni^{III}.



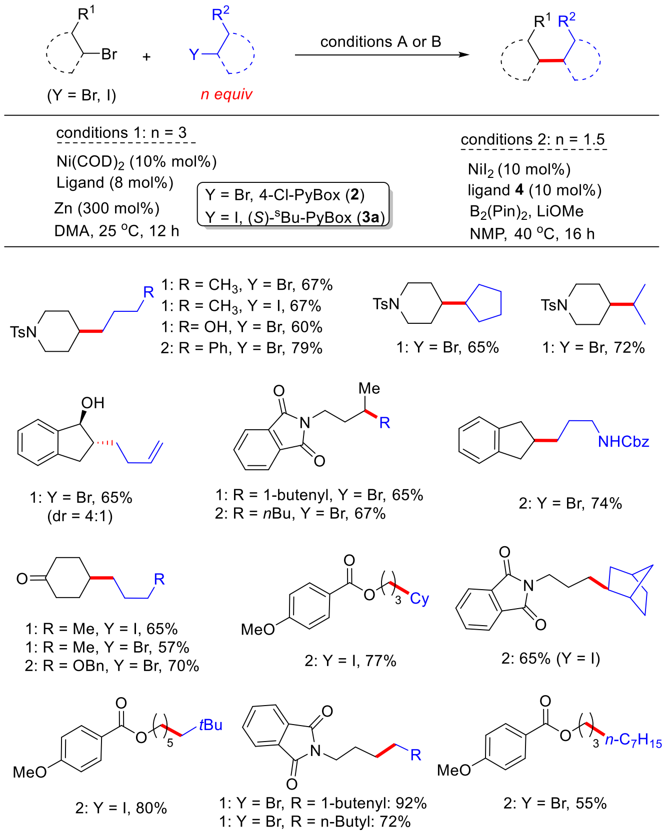
To turn the Negishi reaction process to a reductive coupling mechanism whereby an organozinc reagent are replaced with an alkyl halide and a reductant such as Zn, a rational design would require a suitable reductant that effectively reduces the R^1_{alkyl}–Ni^{II}–L$_n$ intermediate to R^1_{alkyl}–Ni^{I}–L$_n$. The former species is generated by oxidative addition of R^1_{alky}–X (X = halide) to Ni^0–L$_n$, which can be generated by reduction of L$_n$–Ni^{I}–X with Zn (Scheme 2, blue box). The formation of L$_n$–Ni^{I}–X complex follows the scenario in Negishi coupling shown in the yellow box (Scheme 2), which would otherwise undergo a transmetallation process with an organozinc reagent. This reductive coupling proposal features *double oxidative addition* of alkyl halides to low valent Ni complexes. The lifetime of the Ni intermediates, the rates of oxidative addition of alkyl halides to the Ni intermediates and reduction of the Ni complexes should be highly matched. In particular, possible reduction of R^1_{alkyl}–Ni^{I} and R^1_{alkyl} –Ni^{III}–R^2_{alkyl} by Zn should be negligible, allowing their involvement in the oxidative addition of alkyl halides or reductive elimination steps to be viable.

Figure 1. The structures of ligands.

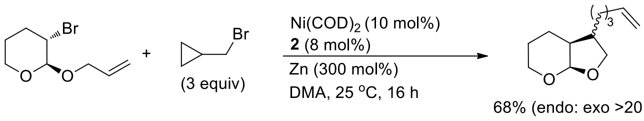


The proof-of-concept studies were established in 2009 based upon the coupling of 4-bromo-1-tosylpiperidine with *n*-butyl bromide. The optimized reaction conditions provided the C(sp^3)–C(sp^3) product in 67% yield, which required the secondary alkyl bromide to be limiting reagents (conditions 1, Figure 2).[10a] To ensure good selectivity, *n*-BuBr needed to be 3 equivalents in excess with 4-Cl-PyBox (**2**) being the ligand. Likewise, coupling of 4-bromo-1-tosylpiperidine with 3 equiv of *n*-PrI also afforded the product in 67% yield encompassing (s)-sBu-Pybox (**3a**) as the ligand. With these optimized conditions, a number of alkyl halides (3 equiv) were compatible with 1 equiv of other alkyl bromides, which tolerated functional groups including free hydroxyl (Figure 2). More interestingly, bromocyclopentane and isopropyl bromide also displayed fairly good selectivity when coupling with 1 equiv of 4-bromo-1-tosylpiperidine, although the secondary bromides were structurally similar. Both cyclic and open-chain secondary alkyl bromide (limiting reagents) demonstrated good reactivities with 3 equiv of primary alkyl bromides and iodides. The most notable selectivity was observed in the coupling of phthalimylpropyl bromide (1 equiv) with 1-butenylbromide (3 equiv) which generated the product in 92% yield, suggesting a high chemoselectivity can be tuned by variation of substituents on the alkyl halides.

Figure 2. Selected examples for the synthesis of alkyl–alkyl products using Ni/Zn and Ni/(Bpin)$_2$ reductive conditions.



Although the details of the reaction mechanism is still under investigation, the radical nature for both alkyl coupling partners was evidenced in the ring-closure and ring-opening of the radical clocks shown in equation 1.[10a]

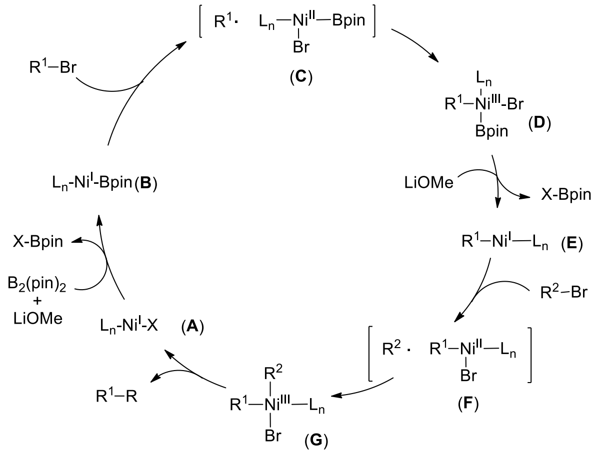


(1)

The requirement for three equivalents of a second alkyl halide in excess in the Ni/Zn reductive coupling conditions indicates the catalyst moderately differentiates the alkyl coupling partners, wherein competitive homocoupling is severe.[10b,c] Improvement of the chemoselectivity by Ni/ligand screening is not successful. However, when the reductant was changed to (Bpin)$_2$, the coupling of secondary alkyl bromides (1 equiv) with primary bromides disclosed much improved coupling efficiency, in which only 1.5 equiv of primary bromides were employed (Conditions 2, Figure 2).[11] Unfunctionalized alkyl bromides, e.g, cyclohexylbromide were not effective. However 1.5 equiv of cyclohexyliodide could be used to couple with 1 equiv of primary alkyl bromide. The excellent chemoselectivity is attributed to the formation of Ni-Bpin complex which effectively differentiates the upcoming alkyl coupling partners either by steric or by electronic reasons, or both. Indeed, the coupling of 1-iodo-2,2-dimethylpropane (more hindered 1°-alkyl iodide) and an ester-tethered bromopentane (less hindered) afforded the product in 80% yield (Figure 2).

A catalytic cycle proposed in Scheme 3 involves borylation of Ni^{I}–X complex (**A**) to generate a Bpin–Ni^{I} species **B**, which undergoes one electron transfer to (or halide abstraction from) R^1–X leading to R^1 radical and a Ni^{II} intermediate **C**. Rapid combination (*cage-rebound*) of the two species affords Bpin–Ni^{III}(R^1)–Br (complex **D**) (Scheme 3). Subsequent elimination of Bpin–X (X = Br or OMe, etc.) gives a R^1–Ni^{I} species **E**, which was oxidatively added by R^2–Br, involving a second rapid combination (*cage-rebound*) of R^2 radical and a Ni^{II} complex **F** to produce a R^1–Ni^{III}–R^2 intermediate **G**. Reductive elimination of **G** gives the product and regenerates Ni^{I}–X complex **A**.[11]

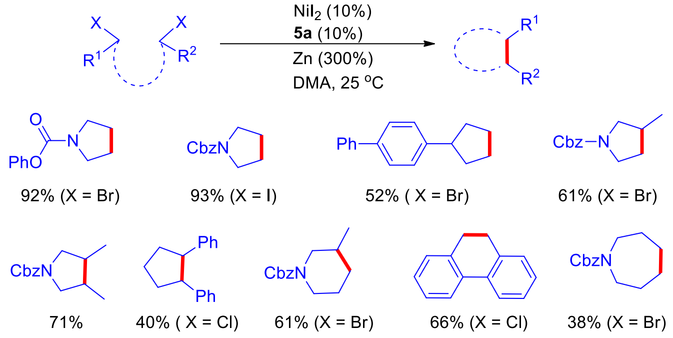
Scheme 3. A proposed double oxidative mechanism involving cage-rebound process for the Ni/B$_2$(pin)$_2$ conditions.



It should be noted that Fu and Liu have disclosed interesting Ni-catalyzed borylation of alkyl halides utilizing very similar reaction conditions to those in Figure 2 except for solvents and bases. In contrast to Fu's catalytic proposal, elimination of R^1–Bpin from complex **D** may become energetically disfavoured under our reaction conditions.[12]

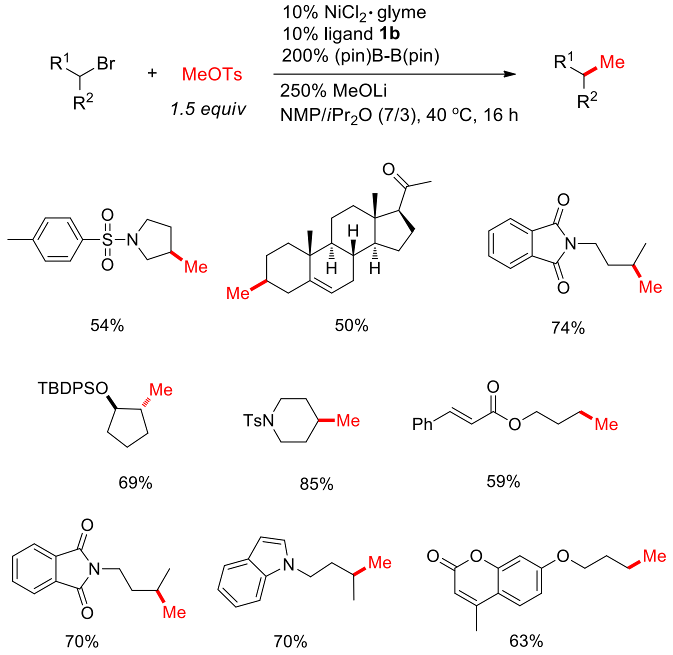
The Ni/Zn reductive coupling strategy was applicable to the cyclization of alkyl dihalides (Figure 3).[13] The competitive oligomerization and cyclization process required pre-organization of dihalides. Under NiI$_2$/ligand catalytic conditions, five and six-membered rings could be facilely constructed. The more challenging seven-membered ring could also be obtained in nearly 40% yield.

Figure 3. Cyclization of alkyl dihalides.



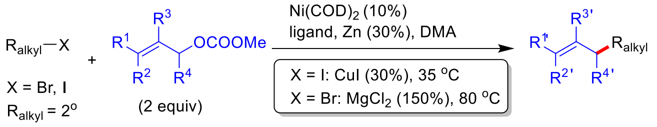
Although the reductive coupling methods are effective for a variety of two different alkyl halides, methyl halides, particularly the easily accessible methyl iodide was not satisfactory, possibly due to rapid dimerization or formation of MeZnX. With the Ni/(Bpin)$_2$ conditions, this problem could be solved, using MeOTs as methylation source (Figure 4).[14] The use of NiCl$_2$ as precatalyst was pivotal, indicating possible in situ conversion of MeOTs into MeCl, which avoids the side reactions at high concentrations by pre-addition of MeI.

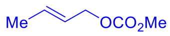
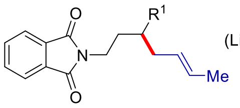
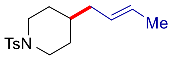
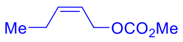
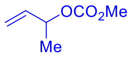
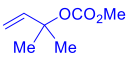
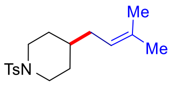
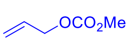
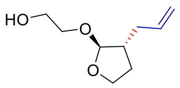
Figure 4. Methylation of alkyl halides with MeOTs.



The challenging selectivity issues residing in the coupling of two different alkyl halides could be significantly abbreviated when allylic type electrophiles were used as the coupling partners. The allylation of primary and secondary alkyl halides under Ni(COD)$_2$/Zn conditions generated the allylated alkanes in good to excellent yields, although for alkyl bromides, ligand **1b** and MgCl$_2$ were necessary while ligand **3c** and CuI were inevitable for alkyl iodides (Table 1).[15] The reaction conditions tolerated functional groups including free alcohol and phthalimide. When unsymmetrical allylic carbonates were subjected to allylic alkylation conditions, addition of alkyl to the less hindered allylic carbons took place. The use of *cis* or *trans*-alkenes always resulted in *trans*-products (Table 1, entries 3–6). Alkyl iodides and bromides in many cases displayed distinctive coupling reactivities, e.g., for 3-methyl allylic carbonate, alkyl bromides appeared to be more efficient (Table 1, entries 3–6), whereas opposite results were disclosed for 1,1'-dimethyl allylic carbonate (Table 1, entries 9–10).

Table 1. Allylation of alkyl halides

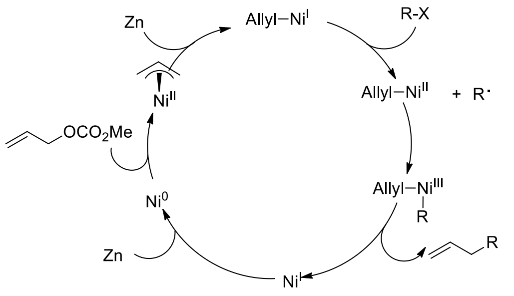


entry	allylic substrates	prodcut	yield
1 2			R^1 = H, X= Br: 62 (Ligand = ^{i}Pr-PyBox **3c**) R^1 = Me, X = Br: 62
3 4			X = I: 65% X = Br: 82%
5 6		as above	X = I: 40% X = Br: 89%
7 8		as above	X = I: 88% X = Br: 90%
9 10			X = I: 80% X = Br: 70%
11			X = Br: 82%

In the course of our studies, we noticed that for individual allylic alkylation, such as primary alkyl bromide in Table 1, entry 1, further tuning the reaction parameters (ligand **3c**, CuI and MgCl$_2$ both 20 mol%) enabled optimal reaction yields. Weix later revealed that under NiCl$_2$(dme)/**1b**/Mn conditions, the coupling of 1.5 equiv of 3-aryl allylic acetate with a variety of alkyl halides was also effective, wherein the catalyst loading can be reduced to 5 mol%.[16]

Although the insight into the reaction mechanism requires more experimental studies, the formation of allylic Ni complex may be involved as one of the key intermediates, which is faster than oxidative addition of alkyl halides to low valent Ni. One electron reduction with Zn giving allyl–Ni(I) intermediate, which undertakes similar oxidative addition process (*cage-rebound*) with alkyl halides to that disclosed in Negishi coupling (Scheme 2) generating allyl-Ni^{III}-alkyl intermediate. Subsequent reductive elimination gives the allylated products and L$_n$–Ni^I that can be reduced by Zn to regenerate Ni^0 and allow the catalytic process to continue (Scheme 4).[15]

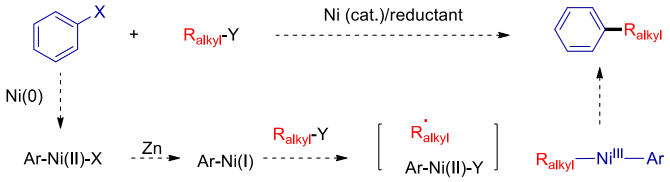
Scheme 4. Proposed double oxidative addition catalytic cycle for allylation of alkyl halides



2. C(sp^3)-C(sp^2) bond formation

The success in the reductive cross-coupling of two C(sp^3)–X electrophiles suggests that subtle chemoselectivity difference between the two intrinsically similar coupling partners can be adjusted with the suitable choices of catalytic conditions. In principle, the reactivity gap is enhanced between an alkyl and a C(sp^2)-X electrophile, and hence should result in better chemoselectivity. For instance, if a similar mechanism for alkyl/alkyl coupling reactions operates for the coupling of alkyl/aryl halides (Scheme 5), one would anticipate that oxidative addition of an aryl halide to Ni^0 to form Ar-Ni^{II} should be more favoured than to give R$_{alkyl}$-Ni^{II}. Subsequent key steps may involve reduction of the Ar-Ni^{II} intermediate to Ar-Ni^I that is more prone to the oxidative addition by alkyl halides than aryl ones to generate R$_{alkyl}$-Ni^{III}-Ar through *a cage rebound* process.

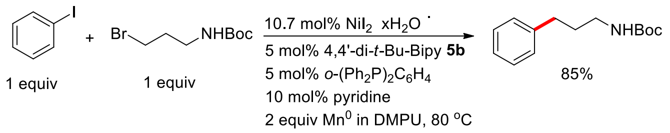
Scheme 5. Proposed double oxidative addition mechanism for arylation of alkyl halides



2.1 Arylation of Alkyl Halides

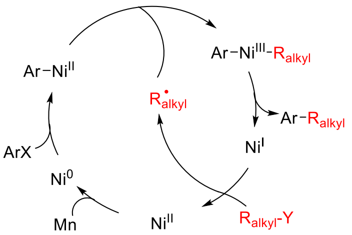
Weix in 2010 disclosed aryl iodides could effectively couple with primary halides to offer the alkyl-aryl products in good yields with excellent chemoselectivity wherein equimolar coupling partners were used. The drawbacks of the reaction conditions comprise use of expensive phosphine ligands and less effective coupling yields for secondary alkyl halides, although improved conditions using **5b** were achieved without enhancing the coupling efficiency.[17]

Scheme 6. Weix's catalytic conditions for arylation of alkyl halides



In Weix's mechanistic studies on the arylation of alkyl halides, a *cage-rebound* mechanism (Scheme 5) is not operative. Instead, addition of R$_{alkyl}$ radical to Ar–Ni^{II}–X that forms Ar–Ni^{III}–R$_{alkyl}$(X) is key (radical chain). Upon reductive elimination, R$_{alkyl}$–Ar is generated associated with Ni^I–X that can abstract halide from R$_{alkyl}$–Y to form Ni^{II}–X(Y) and an alkyl radical. While R$_{alkyl}$ radical diffuses to the solution to combine with Ar–Ni^{II}–X, NiX$_2$ can be reduced to Ni^0 by Mn (Scheme 7). Oxidative addition of ArX to Ni^0 that forms ArNi^{II} and continue the catalytic process. The alkyl radical is initially formed by halide abstraction of Ar-Ni^{II}-X with R$_{alkyl}$-Y which also result in an Ar–Ni^{III}–(X)Y intermeidate.[17]

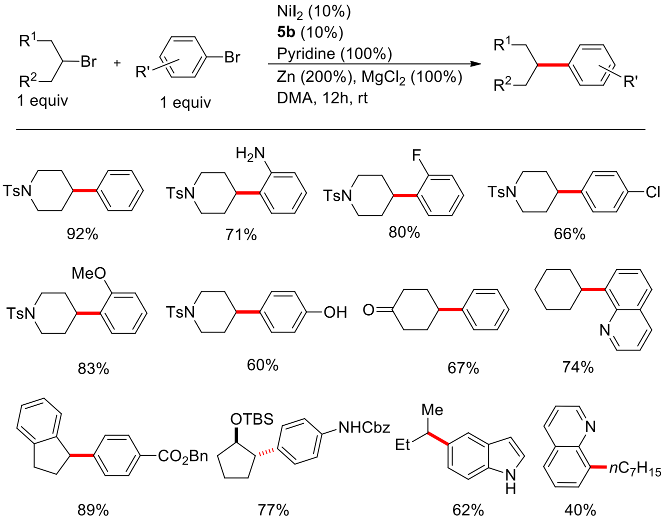
Scheme 7. Weix's radical chain mechanism for arylation of alkyl halides



We recently conducted the DFT calculations (gas phase) based on the coupling of cyclohexyl and phenyl bromides. The results suggested that the rate limiting step for both Weix's radical chain (Scheme 7) and the double oxidative addition (Scheme 5) mechanisms was the addition of cyclohexyl radical to PhNi^{II}, with the energy barrier of 10.42 kcal/mol. As a consequence, the DFT studies cannot exclude the feasibility of the double oxidative addition process.[18a] A close calculation based on the Ni-catalyzed coupling of photoredox-generated benzyl radical with aryl halides revealed that addition of the more stable benzyl radical to either Ni^0 and ArNi^{II} is likely to give Bn–Ni^I and ArNi^{III}Bn, respectively, with energy barriers lower than 5 kcal/mol for both. Subsequent oxidative addition of ArBr to the BnNi^I would lead to the ArNi^{III}Bn species. Therein the reductive elimination becomes rate-determining with an energy barrier of ~10 kcal/mol.[18b] Given the small energy difference between the possible mechanisms, subtle changes of the reaction parameters (e.g., concentrations) may favor one of the reaction pathways.

At the same time, we focused our effort on the coupling of secondary alkyl halides with aryl halides. By addition of 1 equiv of pyridine as additive, the use of ligand **5b** alone offered the coupling products in high yields at room temperature. The reaction conditions however are not as effective as for primary halides that reported in Weix and Peng's conidtions.[19] A variety of functional groups including free amine, alcohol were tolerated. The electron-rich indole and deficient quinoline moieties were also compatible (Figure 5).

Figure 5. Selected examples for arylation of *secondary* alkyl halides

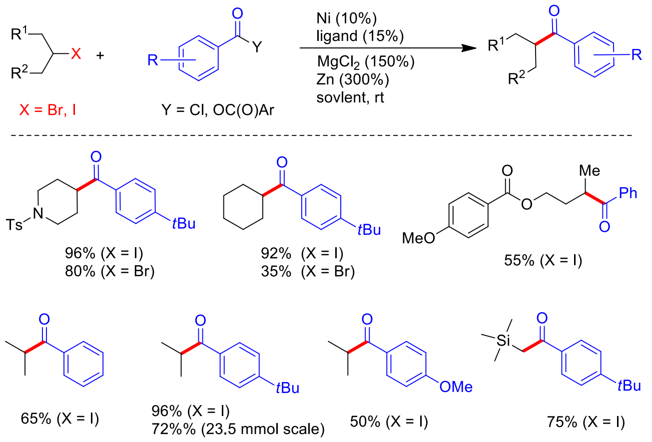


Recently, Molander indicated that heteroaromatic halides could be competently incorporated using slightly modified Ni-catalyzed reductive conditions.[20] The same group also demonstrated the viability for the coupling of 3-bromo-2,1-borazaronaphthalenes (a vinyl halide) with primary and secondary alkyl iodides, generating boron-containing alkylated heterocycles. Lastly, the coupling of heteroaromatic halides with alkyl tosylate was successfully developed which avoided the use of alkyl halides. Similar to our discovery for the coupling of MeOTs, the exchange of halides with tosylate that forms alkyl halide in situ is believed to be the key.[21]

2.2 Acylation of Alkyl Halides

By virtue of the reductive coupling strategy, unsymmetrical ketones could be achieved by exposure of alkyl halides to acid derivatives under $NiCl_2$/Zn conditions.[22] Although an early study indicated that coupling of pyridyl carboxylate with essentially primary alkyl iodides enabled the formation of ketones,[22e] the more accessible acid chlorides have not been disclosed. With 4,4’-Dimethyl-2,2’-bipyridyl (**5d**) or phenanthrene 1,10-phenanthroline (**6**) types of ligands, aroyl chlorides and anhydrides were both suited for acylation of alkyl iodides, whereas alkyl bromides only matches the reactivity of acid anhydrides (Figure 6). $MgCl_2$ was indispensable for promoting the reaction yields. For alkanoyl chlorides, the reaction conditions further required tuning the solvents and ligands as evident in Weix’s studies on their coupling with alkyl iodides.[23] Notably, the alkyl-aryl ketone synthesis can be scaled up. For instance 1-(4-(*tert*-butyl)phenyl)-2-methylpropan-1-one could be prepared in 72% yield (3.6 grams).[22d]

Figure 6. Selected examples for acylation of alkyl halides with acid chlorides and anhydrides.

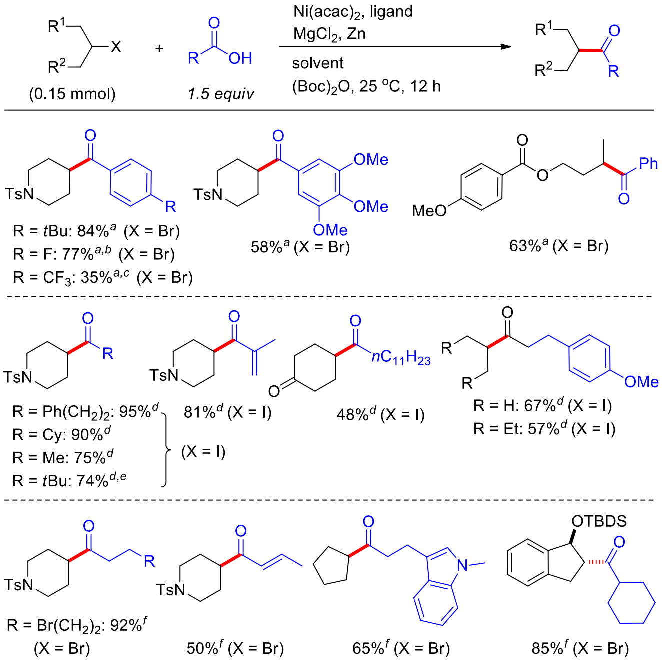


(a) Y = Cl, *Conditions A*: alkyl iodides (1 equiv), ArCOCl (2.0 equiv), $Ni(acac)_2$ (10%), ligand **6** (15%), $MgCl_2$ (150%), Zn (300%), CH_3CN, 25 °C. (b) Y = OC(O)Ar, *Conditions B*: alkyl halides (1 equiv), $(ArCO)_2O$ (2 equiv), $Ni(cod)_2$ (10%), ligand **6** (15%) and CH_3CN for X = I; **5d** and CH_3CN/DMF (3:7) for X = Br, $MgCl_2$ (150%), Zn (300%), 25 °C.

Coupling of alkyl halides with in situ activated aryl acids by formation of anhydrides in the presence of $MgCl_2$ and Boc_2O has also been achieved, allowing direct use of acids to generate ketones.[22c] High coupling yields were observed for the reaction of alkyl bromides with aryl acids wherein more easy-to-handle $Ni(acac)_2$ and ligand **5b** served as the pre-catalyst. A wide range of alkyl halides and acids could effectively provide the ketones even for the acids bearing electron-withdrawing groups (*conditions C*, Figure 7).

For alkyl acids, fine selection of the ligands and solvents was important, allowing efficient construction of alkyl–alkyl ketones (Figure 7, *conditions D and E*).[24] For alkyl iodides, a mixture of solvents CH_3CN/THF (v/v, 4:6) was used, whereas for alkyl bromides, the solvents necessitate DMF/THF (v/v, 2:3) with the concentration of the alkyl bromides (limiting reagents) being doubled.[24] We reasoned that both solvents and ligands were key factors at least for tuning the rates of anhydride formation.

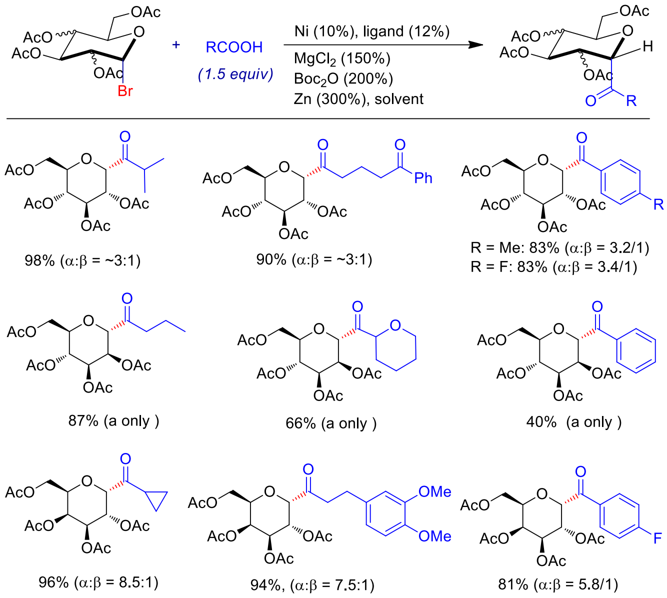
Figure 7. Selected examples for acylation of alkyl halides with in situ activated acids.



(a) *Reaction conditions C*: R–Br (0.15 mmol, 100%), $Ni(acac)_2$ (5%), Zn (300%), $MgCl_2$ (250%) **5b** (7%), CH_3CN/DMF 1/4 (1 mL), 25 °C. (b) CN_3CN/DMF (1/4, 0.5 mL). (c) 10% $Ni(acac)_2$ and 15% **5b** were used. (d) *Reaction Conditions D*: R–I (0.15 mmol, 100%), acid (150%), $Ni(acac)_2$ (10%), **6** (12%), Boc_2O (200 %), Zn (300 %), $MgCl_2$ (150%), CH_3CN/THF (v/v = 4:6, 1 mL), 25 ˚C. (e) 0.5 mL of solvents were used. (f) *Reaction Conditions E*: same as conditions D except alkyl bromides, **5b** and DMF/THF (v/v = 2:3, 0.5 mL) at 20 ˚C.

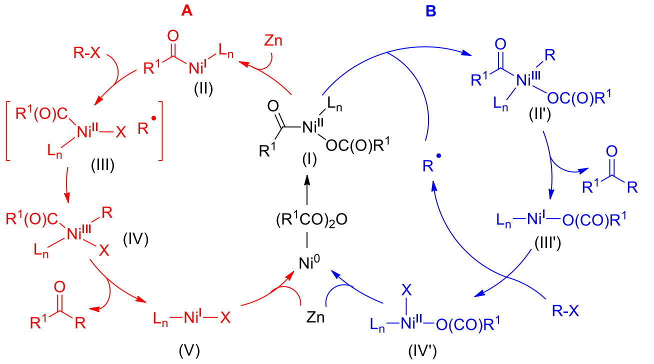
The applicability of the reductive synthesis of ketones to acyl-*C*-glycosides was manifested in the coupling of 1-glycosyl bromide with acids and their derivatives.[24] It should be noted that preparation of either glycosyl or acyl nucleophiles is a challenge. Hence, the previously reported methods to acyl-*C*-glycosides generally requires multi-step protocols by avoiding direct involvement of classic nucleophiles. Under $Ni(acac)_2$/**5b** reductive coupling conditions, a wide set of alkyl acids were suited for acylation of glucosyl, galactosyl and mannosyl bromides in high yields. While moderate and good α-selectivities were observed for glucosides and galactosides, respectively, mannosides were produced in good yields with only α-anomers which suffer from rapid elimination upon column purification. Interestingly, when aryl acids were subjected to the reaction conditions, no products were observed. The addition of BuN_4I, however, turned on the reactivity for aryl acid derivatives.[25] The optimized reaction conditions required $Ni(ClO_4)_2{\cdot}6H_2O$/**5a** to be the precatalyst where acid anhydrides were more effective than in situ activated acids. Likewise, the aroyl C-glycosides displayed similar α-selectivities as well as coupling yields to those for alkanoyl analogs (Figure 8).

Figure 8. Selected examples for the synthesis of acyl *C*-glycosides

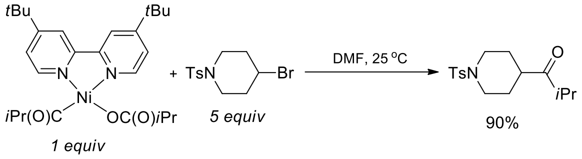


The acylation event may again operate through a *double oxidative addition* or a *radical chain* mechanism. The former involves oxidative addition of anhydrides to Ni^0 generating $R^1C(O)–Ni^{II}–OC(O)R^1$ (**I**) intermediate which may be reduced to $R^1C(O)–Ni^I$ (**II**).[24] Subsequent oxidative addition of alkyl halide to intermediate **II** offers a $RC(O)Ni^{III}–R_{alkyl}$ (**IV**). This process may involve rapid combination of an alkyl radical and a Ni^{II} intermediate (**III**) (cage-rebound, Scheme 8, cycle A). The alternative radical chain process may go through a similar proposal for arylation of alkyl halides (Scheme 7), involving combination of intermediate **I** with an alkyl radical that is diffused to the bulk solution after halide abstraction of alkyl halides by $L_n–Ni^IX$ (Scheme 8, cycle B). Reductive elimination of the resultant $R^1C(O)–Ni^{III}(OC(O)R)–X$ (**II'**) gives the aylcation products and L_n-Ni^IX. Reduction of Ln-Ni^{II} (**IV'**) to Ni(0) allowed continuous generation of intermediate **I**.

Scheme 8. Double oxidative addition (cycle A) vs radical chain mechanism (cycle B) for acylation of alkyl halides

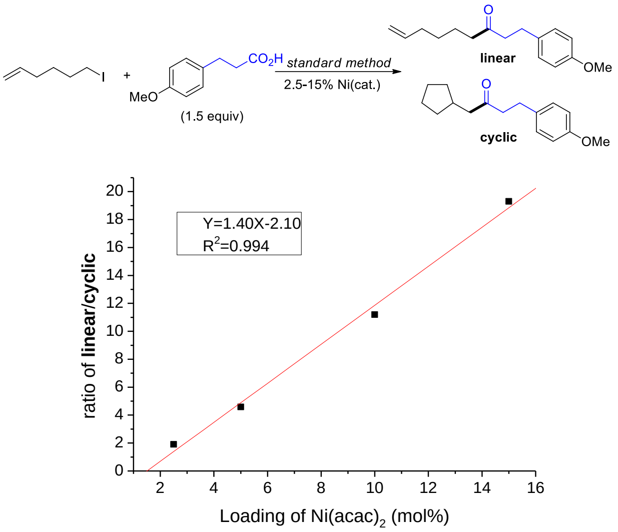


If a radical chain mechanism operates, initial generation of an alkyl radical may arise from halide abstraction of R–X with complex **I** to give a Ni^{III} species. Indeed, the stoichiometric reaction of 4-bromo-1-tosylpiperidine with a *i*PrC(O)–Ni^{II}–OC(O)*i*Pr complex derived from treatment of $(iPrCO)_2O$ with Ni(0) and **5b** gave the desired ketone product in 90% yield (eq 2).[24]



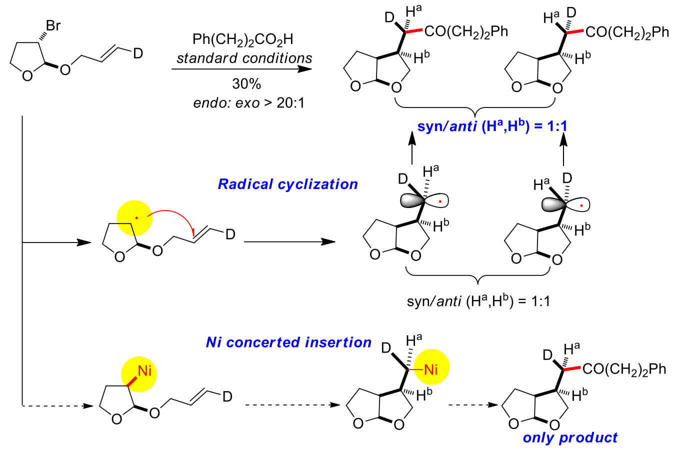
(2)

Figure 9. Dependence of the Ratio of cyclization/linear products on catalyst loading using a radical clock.



Similar to the studies in the Ni-catalyzed reductive arylation of alkyl halides,[17a,] a linear dependence of the ratio of linear/ring closure products (Figure 9) on the concentration of the catalyst loading was detected for the coupling of 6-iodohex-1-ene with 3-phenylpropanoic acid.[24] This result signifies possible diffusion of R_{alkyl} radical from a cage arising from the reaction of complex **III'** with R_{alkyl}–X (Scheme 8, cycle B), which subsequently bonds with the Ni^{II} complex (**I**) to give intermediate (**II'**). A radical-cage-rebound process in cycle A (namely, rapid combination of alkyl radical with **III**) would otherwise be accepted if the ratio of the two products remains constant. However, without direct evidence of isolatable Ni^I and Ni^{III} complexes, the proposed mechanism at this stage is subject to modifications, although a radical chain mechanism appears to be more plausible. In fact, some controversial evidence may reinforce this notion. First, reduction of L_n–$NiBr_2$ by Zn is a very slow process which remains unreacted even after 3h, possibly due to the heterogeneous environment.[24] The addition of $MgCl_2$ promotes the reduction rate which however is unnecessary in many cases.[17,24] Second, the presence of radical inhibitors such as BHT did not erode the yields for ketone synthesis, which is difficult to explain if an alkyl radical diffuses to a bulk solution form a Ni-radical cage.

Scheme 9. Radical cyclization vs Ni-concerted insertion mechanism.



The evidence for the radical nature of the alkyl substrates was confirmed by exposure of the deuterated allyl-pendent alkyl bromide to the reaction conditions, which produced 1:1 mixture syn/anti (H^a, H^b) cyclization/coupling ketone products.[24] This experiment unambiguously rules out a possible alkyl-Ni/alkene insertion mechanism where a single isomer is predicted (Scheme 9).

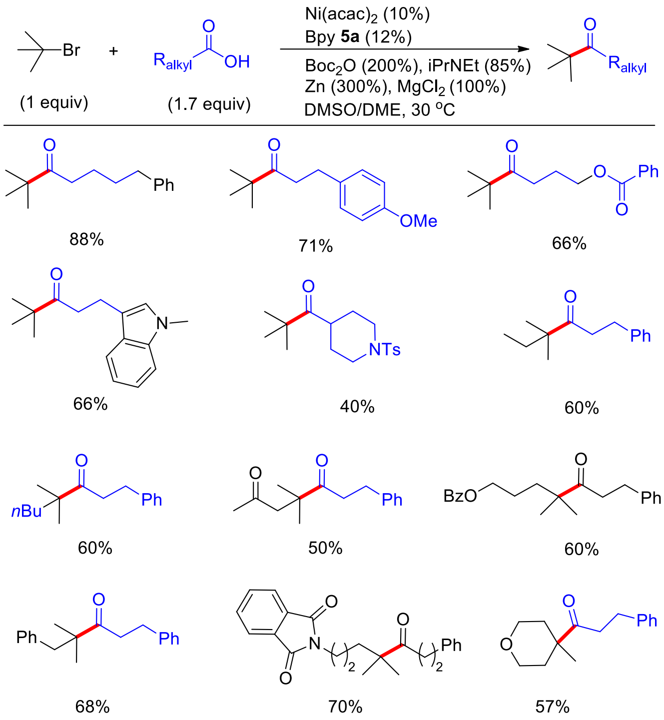
A recent Ni-catalyzed reductive trapping of CO$_2$ with C(sp^3) electrophiles developed by Martin should be noted.[26] The formation of alkyl acids has been achieved from unactivated primary alkyl halides, allylic acetates, benzylic ethers and intramolecular cyclization of alkynyl alkyl bromides. The remarkable regioselectivities that are tuneable using a bidentate and a tetradentate ligand allow effectively construction of branch and linear homoallylic acids.

3. More challenging *tertiary* alkyl halides in the reductive coupling chemistry

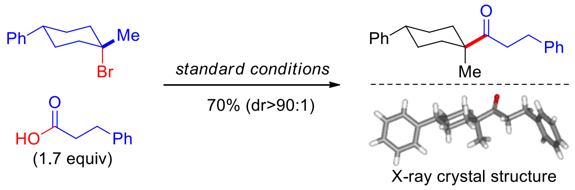
The coupling of *tertiary* alkyl nucleophiles or electrophiles generally displays remarkably distinctive reactivities from their primary and secondary analogues, which generally requires tremendous amount of innovative efforts to obtain high coupling efficiency even though similar coupling protocols are applied.[24] This is possible due to the much enhanced steric bulkiness that promotes β-H elimination and induces reluctance for oxidative addition as well as reductive elimination.

Although the reductive coupling concept has enabled successful coupling of *primary* and *secondary* alkyl halides with other electrophiles, the compatibility of *tertiary* alkyl halides remained unexplored until our development of quaternary ketone synthesis. With 1.7 equiv of alkyl acids in excess, we demonstrated that a wide array of *tertiary* alkyl halides were competent, generating the ketones in good to excellent yields. Suitable choices of solvents proved to be important for the reaction conditions (Figure 10). Noteworthy is no isomerization side reactions that took place in the Ni-catalyzed arylation of *tertiary* Grignard reagents.[27] The mild reaction conditions exhibited excellent functional group tolerance. More interestingly, the coupling of 1,4-*cis*-(4-bromo-4-methylcyclohexyl)benzene with 3-phenylpropanoic acid displayed excellent diastereoselectivity (dr>19:1) by affording the ketone bearing 1-acyl *trans* to 4-phenyl (Scheme 10). This observation differs from the reported Ni-catalyzed Suzuki arylation where 1:1 mixture of diastereomers were obtained.[28]

Figure 10. Selected examples of acylation of tertiary alkyl bromides with alkyl acids.



Scheme 10. Highly diastereoslective synthesis of 1-methyl-4-phenylcyclohexyl)-3-phenylpropan-1-one.



4. Outlook of the future directions of the reductive coupling of alkyl electrophiles

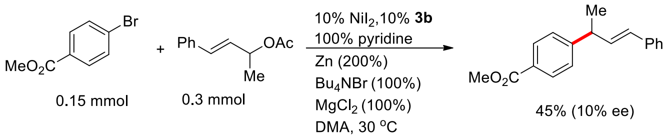
The pronounced progress in the recent reductive coupling of alkyl halides with other electrophiles has reminisced the synthetic communication to reconsider the importance of this powerful approach to the construction of C–C bonds. It also, however, sparks a question where this type of chemistry will head in the next stage.

The compatibility of *tertiary* alkyl halides with many other electrophiles, in particular aryl and alkyl halides is one of the fundamental challenges to be addressed. Changes of the coupling partners may significantly alter the reactivities of *tertiary* alkyl electrophiles, which may in turn spur side reactions such as β-elimination and isomerization of the tertiary alkyl groups.

A next important issue lies in the asymmetric reductive coupling of alkyl halides. The current observations on the reductive C(sp^3)–C(sp^3) and C(sp^3)–C(sp^2) bond formation consistently suggest alkyl radicals are involved for alkyl halides. As a consequence, control of enantioselectivity is complicated since radical chemistry is notoriously difficult in asymmetric synthesis. One of the strategies, however, disclosed by Reisman showed that using benzylic halides, acylation and vinylation could successfully afford high enantioselectivities.[29] On the basis of the radical chain mechanisms in the acylation and arylation of alkyl halides, the results suggest that chiral C(sp^2)–Ni^{II}–L$_n$* intermediates enable facial discrimination of the upcoming addition of more stable radical species.[18b] Unfortunately, no enantiomeric results have been observed for unactivated alkyl halides.

In an early studies in our allyic arylation chemistry, we also observed 10% ee in regioselective synthesis of (*E*)-methyl 4-(4-phenylbut-3-en-2-yl)benzoate using a chiral pybox ligand **3b** (Scheme 11).[30] This result is consistent with the observation that more stable alkyl intermediates are suitable for achieving asymmetric outcomes under the reductive coupling conditions.

Scheme 11. Asymmetric allylation of aryl bromides with allylic acetate.



While the development of asymmetric reductive coupling contributes understanding of the profound steric effects of the reductive coupling chemistry, the details of the reaction mechanisms are far from being well-established. The studies in arylation and acylation of alkyl halides that favor radical chain mechanism as opposed to double oxidative addition process may not be applicable to other conditions by variation of ligands or reaction types such as in alkylation and allylation of alkyl halides. Understanding the reaction insights would on the other hand facilitate the development of new types of reactions pertaining to new electrophiles and incorporating unusual reagents using different metal and reducing reagents, which may significantly expand the future directions of this interesting field. Indeed, trapping alkyl radicals with ArNi^{II} complex as in the radical chain mechanism (Scheme 7) for the arylation of alkyl halides has evoked dual catalytic systems. In addition to the Ni-catalyzed/photo redox methods,[31] alkyl radicals can be generated via Ti-catalyzed epoxide ring opening and cobalt co-catalyzed nucleophilic addition/homolysis from Bn-OMs.[32]

Conclusions

In summary, the recent advance of the Ni-catalyzed reductive coupling coupling of alkyl halides with other electrophiles has resulted in a different view on the synthesis of a variety of important C–C bonds. Under Ni-catalyzed conditions the most challenging chemoselectivity issues between two structurally similar alkyl electrophiles can now be resolved using (Bpin)$_2$ as the terminal reductant, which is much more effective than Ni/Zn conditions.[33] The instrinically high chemoselectivity gaps between alkyl electrophiles and aryl, acyl, allylic eletrophiles and even CO$_2$, on the other hand merit the development of more practical syhtheis of relevant alkyl-based products. In particular, alkyl–aryl products can be produced using equimolar alkyl and aryl halides. In some cases, almost quantitative results are generated.

Although important mechanistic evidence in favor of radical chain cataltyic process has been established for the arylation and acylation of alkyl halides, the current understanidng of this important research field is still in the infant stage. In particular, a cage rebound process cannot be excluded in the formation of C(sp^3)–C(sp^3) bonds that may involve the reaction of a R–Ni^I–L$_n$ species with an alkyl halide. Further efforts to gain the insights into the reaction details should provide more instructive principles for the future develepment of this intersting field. Finally, the reductive coupling protocol may find more practical interests to the synthetic community since alkyl and other electrophiles are generally more readily accessible with no need of pre-preparation of organometallic nucleophiles.

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Notes and references

‡ Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.
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