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Insights into Recent Nickel-Catalyzed Reductive and Redox C−C Coupling of Electrophiles, C(sp^3)−H Bonds and Alkenes

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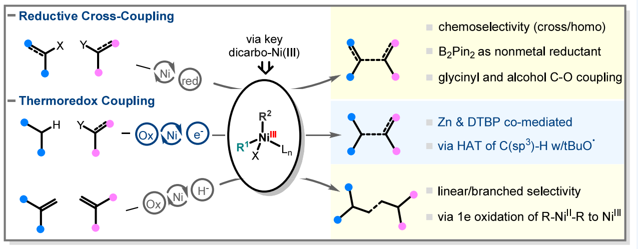

CONSPECTUS: Transition metal-catalyzed reductive cross-coupling of two carbon electrophiles, also known as cross-electrophile coupling (XEC), has transformed the landscape of C−C coupling chemistry. Nickel catalysts, in particular, have demonstrated exceptional performance in facilitating XEC reactions, allowing for diverse elegant transformations by employing various electrophiles to forge C−C bonds. Nevertheless, several crucial challenges remain to be addressed. First, the intrinsic chemoselectivity between two structurally similar electrophiles in Ni-catalyzed C(sp^3)−C(sp^3) and C(sp^2)−C(sp^2) cross-coupling has not been well understood; this necessitates an excess of one of the coupling partners to achieve synthetically useful outcomes. Second, the substitution of economically and environmentally benign nonmetal reductants for Zn/Mn can help scale up XEC reactions and avoid trace metals in pharmaceutical products, but research in this direction has progressed slowly. Finally, it is highly warranted to leverage mechanistic insights from Ni-catalyzed XEC to develop innovative thermoredox coupling protocols, specifically designed to tackle challenges associated with difficult substrates such as C(sp^3)−H bonds and unactivated alkenes.

In this Account, we address the aforementioned issues by reviewing our recent work on the reductive coupling of C−X and C−O electrophiles, the thermoredox strategy for coupling associated with C(sp^3)−H bonds and unactivated alkenes, and the use of diboron esters as nonmetal reductants to achieve reductive coupling. We focus on the mechanistic perspectives of the transformations, particularly how the key C−Ni^{III}−C intermediates are generated, in order to explain the chemoselective and regioselective coupling results. The Account consists of four sections. First, we discuss the Zn/Mn-mediated chemoselective C(sp^2)−C(sp^2) and C(sp^3)−C(sp^3) bond formations based on the coupling of selected alkyl/aryl, allyl/benzyl, and other electrophiles. Second, we describe the use of diboron esters as versatile reductants to achieve C(sp^3)−C(sp^3) and C(sp^3)−C(sp^2) couplings, with an emphasis on the mechanistic consideration for the construction of C(sp^3)−C(sp^2) bonds. Third, we discuss leveraging C(sp^3)−O bonds for effective C(sp^3)−C bond formation via in situ halogenation of alcohols as well as the reductive preparation of α-vinylated and -arylated unusual amino esters. In the final section, we illustrate the thermoredox functionalization of challenging C(sp^3)−H bonds with aryl and alkyl halides to afford C(sp^3)−C bonds by taking advantage of the compatibility of Zn with the oxidant di-*tert*-butylperoxide (DTBP). Furthermore, we discuss a Ni-catalyzed and SiH/DTBP-mediated hydrodimerization of terminal alkenes to selectively forge head-to-head and methyl branched C(sp^3)−C(sp^3) bonds. This process, conducted in the presence or absence of catalytic $CuBr_2$, provides a solution to a long-standing challenge: site-selective hydrocoupling of unactivated alkenes to produce challenging C(sp^3)−C(sp^3) bonds.

KEY REFERENCES

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reductive coupling conditions, showing the advantage of using $C(sp^3)-O$ bond electrophiles.

- Gong Y.; Su, L.; Zhu, Z.; Ye, Y.; Gong, H. Nickel-Catalyzed Thermal Redox Functionalization of $C(sp^3)-H$ Bonds with Carbon Electrophiles. *Angew. Chem., Int. Ed.* **2022**, *61*, e202201662.[3] The high compatibility of Zn and DTBP enabled efficient Ni-catalyzed $C(sp^3)-H$ coupling with alkyl/aryl halides, wherein the transient Ni(I) species reduce DTBP to tBuO radical that undergoes HAT of the $C(sp^3)-H$ bond to afford an alkyl radical intermediate.
- Cheng, L.; Liu, J.; Chen, Y.; Gong, H. Nickel-catalyzed hydrodimerization of unactivated terminal alkenes. *Nat. Syn.* **2023**, *2*, 364−372.[4] Hydrodimerization of unactivated terminal alkenes to selectively afford linear $C(sp^3)-C(sp^3)$ bonds was attained under Ni-catalyzed thermoredox conditions using SiH, DTBP and catalytic $CuBr_2$ as hydride and the oxidants, whereas absence of $CuBr_2$ led to methyl-branched alkyl−alkyl products.

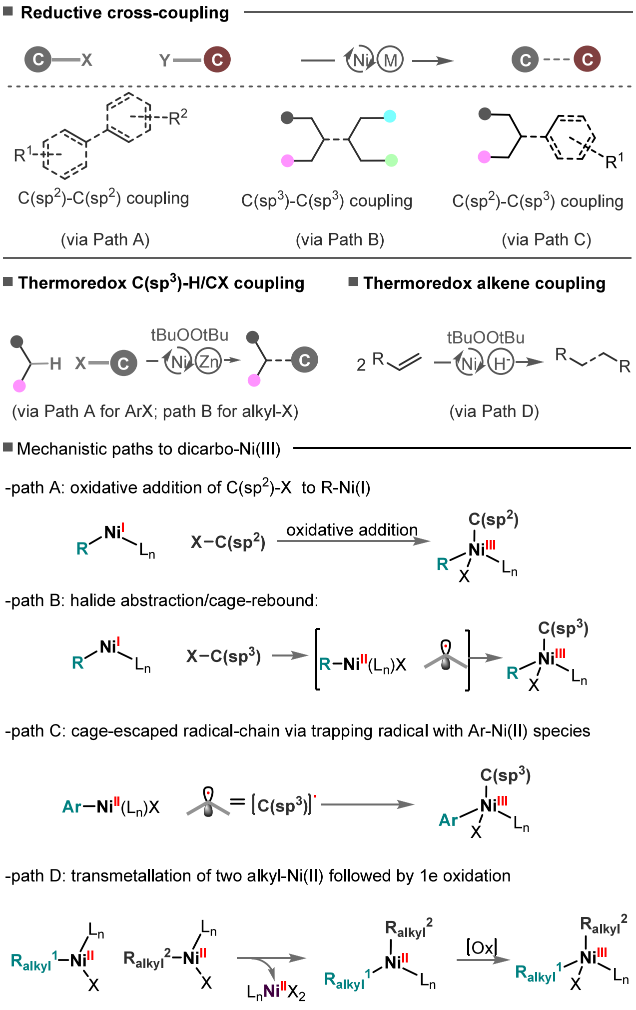


Figure 1. Representative paths to dicarbon−Ni^{III} intermediates involved in the reductive and thermoredox coupling.

1. INTRODUCTION

Nickel-catalyzed cross-electrophile coupling (XEC) has evolved into one of the most effective protocols for C−C bond construction. This methodology is advantageous in that it uses easily accessible electrophiles, works under mild reaction conditions,[5,6] and leverages the high and versatile catalytic activity of Ni which can be attributed to its readily accessible oxidation states Ni^0 to Ni^{III} that enable distinct modes of reactivity through both 1e and 2e redox processes. In contrast, Pd usually invokes only 2e changes between diamagnetic oxidation states Pd^0 and Pd^{II}.[7] Although different mechanistic models have been proposed for the XEC process depending on the electrophiles and other reaction parameters, the formation of key diorgano−Ni^{III} species is commonly accepted, which facilitates reductive elimination to deliver the coupling products.[8,9] In general, there are three ways to form diorgano−Ni^{III} intermediates from organohalides. First, a $C(sp^2)-X$ bond undergoes 2e concerted oxidative addition to a R−Ni^I intermediate as represented by the aryl−aryl and aryl−benzyl coupling, respectively (Figure 1, path A).[10,11] Second, a $C(sp^3)-X$ bond undergoes stepwise oxidative addition to R−Ni^I via halide abstraction to give R−Ni^{II}−X and a $C(sp^3)$ radical, which is followed by a radical cage-rebound to the Ni^{II} center (path B).[12] This scenario is often proposed for the $C(sp^3)-C(sp^3)$ coupling.[13] Third, a radical-chain mechanism is proposed for the $C(sp^3)-C(sp^2)$ coupling, which involves trapping an uncaged a $C(sp^3)$ radical with an in situ and relatively stable $C(sp^2)-Ni^{II}X$ species (path C).[14] Thus, we might be able to explain the chemoselectivity of Ni-catalyzed XEC reactions by gaining insight into how the C−Ni^{III}−C intermediate is formed under the influence of the ancillary ligand, coupling substrates, reductants, additives, and other parameters. The insight could provide guidelines for developing new and challenging XEC reactions.

In this Account, we first summarize our recent work on the reductive coupling of two different electrophiles, i.e., the Zn/Mn-mediated Ni-catalyzed chemoselective coupling of aryl halides with vinyl halides,[1] thiocarbonates,[15] and alkyl/allyl/benzyl electrophiles,[13,16−18] yielding aryl−vinyl, aryl thioesters, and alkyl−alkyl coupling products, respectively. The chemoselectivity can be explained by considering the Ni catalyst's ability to bias the coupling electrophiles leading to the formation of C−Ni^{III}−C intermediates. In the second section, we discuss the use of diboron esters as nonmetal reductants to achieve the Ni-catalyzed $C(sp^3)-C(sp^3)$ and $C(sp^3)-C(sp^2)$ coupling reactions.[13b,19] Mechanistic studies of the aryl−alkyl coupling suggested that reduction of Ni^{II} to Ni^0 by the diboron agent constitutes the turnover-limiting step, which offers new insight into the difference between diboron- and Zn/Mn-mediated coupling events. In addition, we review two efficient C−O bond coupling reactions, enabling the preparation of unnatural amino esters from bench stable glycinyl α-C−O substrates and the in situ halogenation/arylation of alcohols to afford alkyl−aryl coupling products.[2,20] The final section summarizes the thermoredox coupling of $C(sp^3)-H$ with carbon electrophiles mediated by Zn/DTBP,[3] as well as the site-selective hydrocoupling of unactivated terminal alkenes effected by SiH/DTBP.[4] Mechanistic insights into reductive coupling chemistry led us to develop these new reactions, which highlight the formation of C−Ni^{III}−C intermediates through oxidative addition of organohalides to $C(sp^3)-Ni^I$ (path A) or via transmetalation between two alkyl−Ni^{II} species to afford dialkyl−Ni^{II} followed by 1e oxidation (path D, Figure 1).

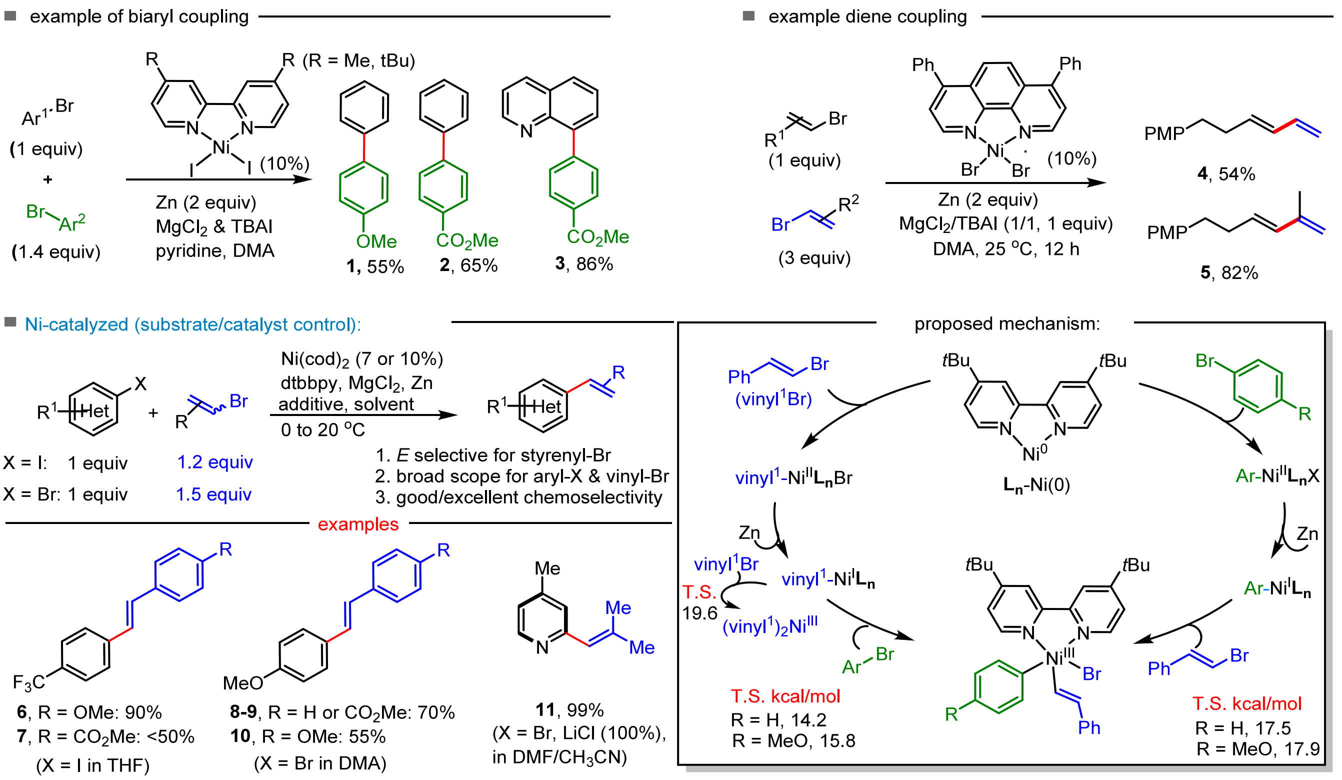


Figure 2. Cross-coupling of aryl and vinyl halides. dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine

2. ZN-MEDIATED C(SP^2)−C(SP^2) AND C(SP^3)−C(SP^3) COUPLING

The effectiveness of a Ni-catalyzed XEC process can be significantly influenced by the competitive homocoupling of individual electrophiles. The ratios of cross-coupled to homocoupled products, known as chemoselectivity, are often dictated by the nature of the substrates and catalysts. Specifically, C(sp^3)−C(sp^2) coupling tends to exhibit high chemoselectivities. This is attributed to the nickel catalyst's ability to effectively bias C(sp^3) and C(sp^2) electrophiles, which possess distinctive stereoelectronic properties. Consequently, equimolar coupling partners can be employed. On the contrary, inhibiting the undesired homocoupling in the Ni-catalyzed Ar^1−Ar^2, vinyl^1−vinyl^2 and alkyl^1−alkyl^2 XEC frameworks remains challenging. In this section, we emphasize our observations that subtle stereoelectronic changes in the electrophiles can significantly alter the chemoselectivities when an appropriate nickel catalyst is selected.

2.1. Selective Preparation of Vinylarenes

Control of chemoselectivity is difficult in a single Pd-, Ni- or Co-catalyzed C(sp^2)−C(sp^2) XEC system.[21] Although a Pd/Ni-dual catalytic protocol has offered a handle to address this challenge,[22] exploration of the Ar−Ar and vinyl−vinyl bond forming conditions using Ni as the sole catalyst is nontrivial as it provides insight into the steric and electronic effects of the substrates on the chemoselectivity. For instance, Ni/bipyridine-catalyzed dimerization of two aryl bromides is moderately efficient when one of the halides is 1.4 equiv in excess (e.g., **1**−**2**, Figure 2).[23] However, a good yield was observed for **3** from the reaction of 8-bromoquinoline (BrQu) with methyl 4-bromobenzoate (BrBzo), likely owing to the favorable *N*-directing and unfavorable steric effects of quinoline that collectively dictate a preferred catalytic path involving Qu−Ni^{III}−Bzo species over those of Qu−Ni^{III}−Qu and Bzo−Ni^{III}−Bzo (path A, Figure 1).[10] Likewise, the coupling of two different vinyl bromides proved to be essentially a statistic-governed selectivity. By comparison, the coupling of 2-bromopropene with a PMP-capped *α*-vinyl bromide was more effective than that with bromoethene, possibly due to the enhanced steric effect that slows down the homodimerization and thus promotes the cross-selectivity (**4** vs **5**, Figure 2).[24]

Vinyl−aryl scaffolds are pervasive in natural products, drug compounds, and conjugated organic materials. We have uncovered a Ni/bipyridine-catalyzed reductive coupling protocol for the preparation of vinyl arenes, wherein good results were attained when the electronic properties of aryl halides and vinyl halides are matched.[1] In the reactions of electron-poor aryl iodides with 1.2 equiv of (*E*)-styryl bromides (vinyl^1-Br), styryl bromides bearing electron-rich and -neutral groups on the phenyl rings (e.g., **6**) were much more effective than those containing electron-withdrawing groups (e.g., **7**). By replacing THF with DMA, electron-rich aryl bromides (e.g., 4-bromoanisole) effectively coupled with 1.5 equiv of styryl bromides containing electron-deficient/-neutral groups on the phenyls (e.g., **8**−**9**), but moderate yields were observed for those bearing electron-rich groups (e.g., **10**). The method can be extended to the preparation of vinyl heteroarenes, as exemplified by **11**. DFT calculations in the gas phase indicated that the energy barrier of oxidative addition of bromobenzene to vinyl^1−(dtbbpy)Ni^I is 3.3 kcal/mol less than that of styryl bromide to Ph−Ni$_I$; both afford the Ph−(dtbbpy)Ni^{III}(Br)−vinyl^1 intermediate. This number decreases to 2.1 kcal/mol when bromobenzene is replaced with 4-bromoanisole. The results hint that aryl and vinyl halides with the appropriate electronic properties could be differentiated by a suitable Ni catalyst, leading to satisfactory chemoselectivities.

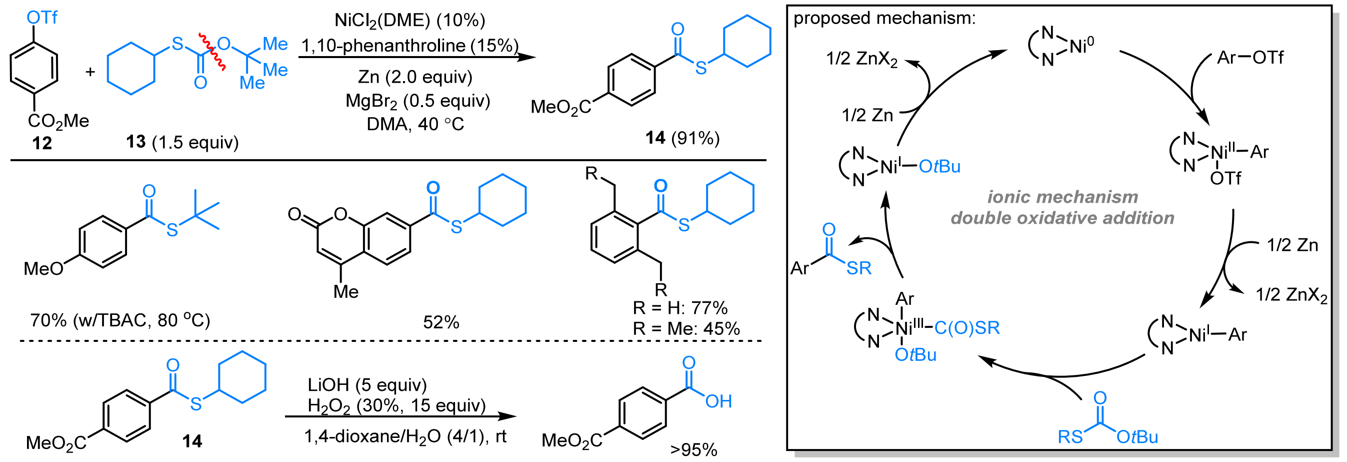


Figure 3. Coupling of aryltriflates with OtBu alkylthiocarbonates.

In addition, we observed that homodimerization of methyl 4-iodobenzoate is slower than that of (*E*)-styryl bromide. The formation of vinyl^1−L_nNi^{III}(Br)−vinyl^1 is 19.6 kcal uphill in the oxidative step, which is higher than those (14.2 or 17.5 kcal) to form Ph−(dtbbpy)Ni^{III}−vinyl^1 (Figure 2), indicating that homodimerization of the individual halide can be disfavored.

2.2. Selective Preparation of Aryl Thioesters

The Ni-catalyzed XEC strategy proved useful for the preparation of aryl acid derivatives, as illustrated by Tsuji and Martin in the reductive carboxylation of aryl electrophiles with CO_2 to generate aryl acids.[25] However, direct formation of aryl esters from the coupling of aryl halides/pseudohalides with acyl electrophiles has not been explored. Recently, we showed that aryl triflate **12** coupled with O-tBu S-alkyl thiocarbonate **13** is an effective thiocarbonyl precursor via selective C−O bond cleavage to afford arylthioester **14** under Ni-catalyzed reductive conditions.[15] The method exhibits remarkable substrate compatibility—both electron-deficient and -rich aryl triflates that are readily derived from phenols feed well into the process. Heteroaromatics, including indoles and hymecromone, were tolerated. More importantly, 2,6-dimethyl and 2,6-diethyl phenyltriflates provided the thioesters in 77% and 45% yields, respectively, indicating the potency of the method for the preparation of sterically congested aryl acids. The thioesters derived from primary and tertiary alkyl thiols were as effective as the secondary counterparts. Oxidative saponification of **14** to the carboxylic acid was highly efficient and selective upon treatment with hydroxide and H_2O_2. Exposure of an equimolar mixture of **12** and **13** to L_nNi^0 indicated that **12** is more prone to undergo oxidative addition. A mechanism similar to aryl−vinyl coupling was proposed (Figures 2 and 3). First, oxidative addition of aryltriflate to Ni^0 gives Ar−Ni^{II} followed by SET reduction to give Ar−Ni^I. Second, oxidative addition of the thiocarbonate to the Ar−Ni^I intermediate results in Ar−Ni^{III}−C(=S)R prior to its ejection of the product. The reason why the Ni catalyst preferentially inserts into the C−O over the C−S bond of the thiocarbonate is not clear at this time.

2.3. Zn-Mediated $C(sp^3)$−$C(sp^3)$ Bond Construction

Inspired by the Ni-catalyzed alkyl−alkyl Negishi cross-coupling established by Knochel and Fu,[26] we reported a Ni/PyBox-catalyzed reductive cross-coupling of two unactivated alkyl halides to afford $C(sp^3)$−$C(sp^3)$ bonds in moderate chemoselectivity in early 2011 (see Figure 4).[13a] The method accommodates structurally similar alkyl partners but requires one of them to be 3 equiv in excess. Alkyl radical intermediates are believed to be involved in the formation of alkyl−Ni^I to which oxidative addition of a second alkyl halide (C^2−X) affords the alkyl−Ni^{III}−C^2 intermediate via a radical-cage process (Figure 1, path B). The preference of the alkyl halides toward the nickel intermediates is profoundly difficult to identify; in the instance of secondary and primary alkyl bromide coupling, the secondary $C(sp^3)$−Br is more prone to homolysis but may possess disfavored kinetics in the coupling process due to elevated steric bulkiness.

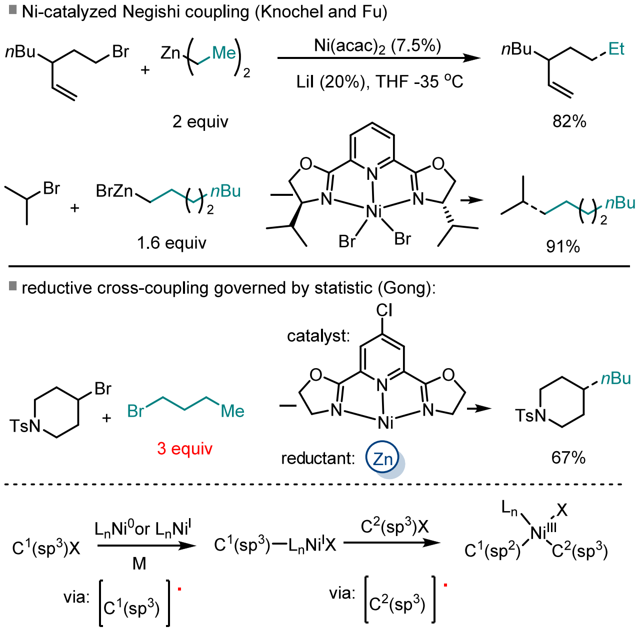


Figure 4. Ni-catalyzed Negishi and reductive $C(sp^3)$−$C(sp^3)$ coupling.

The Ni/Zn reductive coupling strategy has proven to be effective in the intramolecular cyclization of suitable alkyl dihalides, yielding five- to seven-membered rings in moderate to good yields.[16] Additionally, the reaction extends to the coupling of allyl carbonates with unactivated primary,

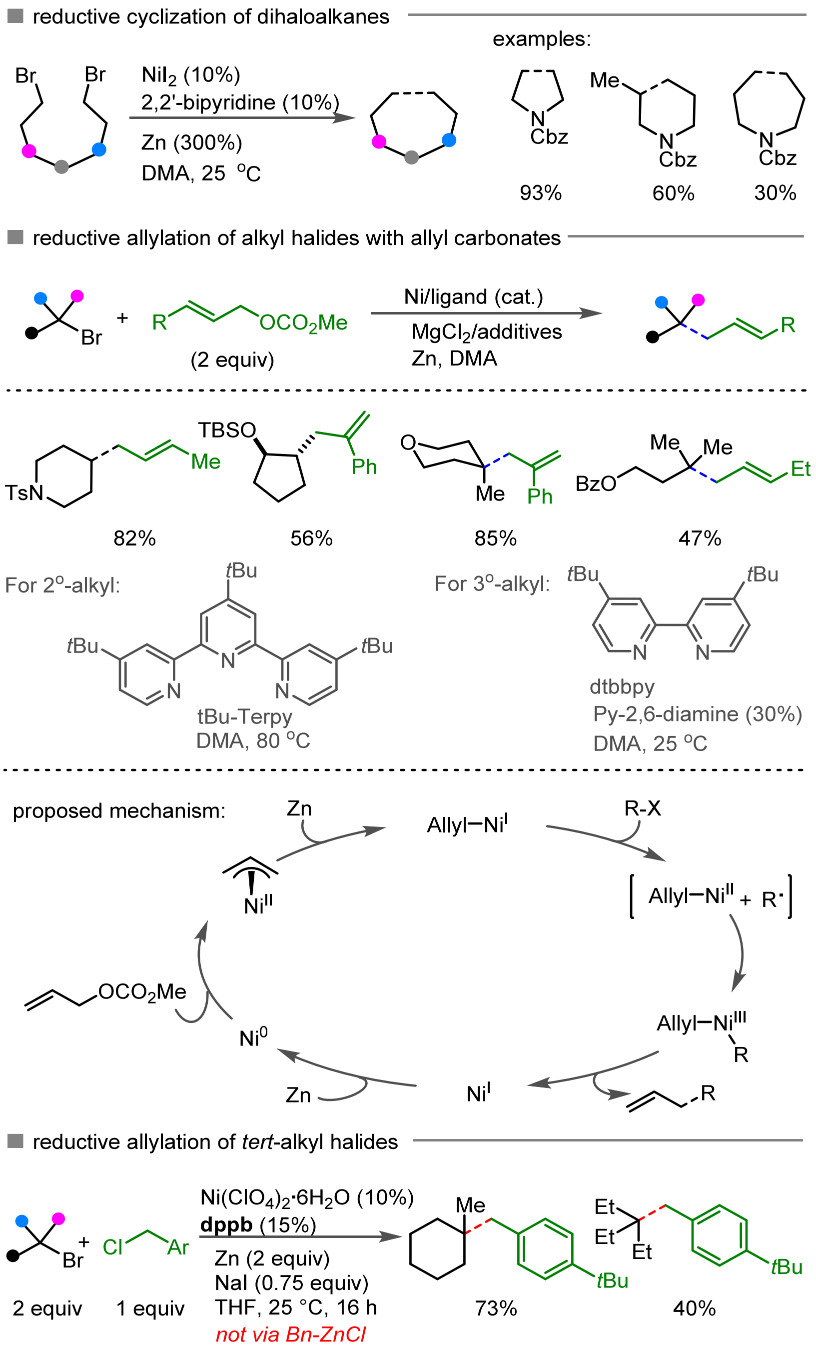


Figure 5. Representative examples of the reductive $C(sp^3)-C(sp^3)$ bond construction.

secondary, and tertiary halides, as previously outlined in our reviews.[17] The preferential formation of the allyl−Ni^I complex to which oxidative addition of unactivated alkyl halides via a radical cage-rebound process is proposed to furnish allyl−Ni^{III}−alkyl is proposed to account for the chemoselectivity.

Recently, we achieved success in coupling tertiary alkyl halides with primary benzylic halides, resulting in the delivery of benzylated all-carbon quaternary centers in good yields (Figure 5).[18] Control studies indicated the noninvolvement of benzylic zinc reagent in the coupling process. A reaction mechanism akin to alkyl allylation was proposed, involving the formation of a benzyl−Ni^I species, followed by halide abstraction and a radical cage-rebound process, yielding the key tertiary alkyl−Ni^{III}−Bn intermediate (Figure 5).

3. B_2PIN_2-MEDIATED $C(SP^3)$−C BOND FORMATION

Metal reductants, particularly Zn and Mn, have been the dominant force in the XEC field,[6] outperforming organoreductants like TDAE in terms of pricing, accessibility and stability.[27] Interestingly, B_2Pin_2 as a reductant in the XEC chemistry has garnered much less attention despite its initial disclosure in the Ni-catalyzed alkyl−alkyl coupling in 2013.[13b] B_2Pin_2 stands out for its economic viability, solubility in most solvents, and environmental friendliness. The ease of removing boron residue with methanol makes it an excellent alternative to Zn/Mn, especially for large-scale reactions. Therefore, the advancement of diboron ester as a nonmetal reductant is seen as opening a new avenue for Ni-catalyzed cross-electrophile coupling chemistry.

3.1. C(sp^3)−C(sp^3) Coupling

We have documented the efficacy of B_2Pin_2 as a nonmetallic reductant in mediating the Ni-catalyzed reductive coupling of two different alkyl halides.[13b] The method significantly enhanced the chemoselectivity in the coupling of a primary and a secondary alkyl halide when compared to Ni/Zn-mediated conditions. Notably, the amount of primary alkyl bromide could be reduced from 3 to 1.5 equiv, resulting in an increase in cross-coupling yield from 67% to 75% (Figures 4 vs 6). Fortunately, we managed to circumvent the issue of competitive alkyl borylation, which leads to the formation of C−B bonds, as disclosed by Fu.[28] This was achieved through careful selections of the ligand/base/solvents, as exemplified in the methylation and trifluoromethylation of alkyl halides. In these instances, the use of Mn and Zn failed to catalyze the desired transformation.

We initially proposed that the chemoselectivity in the coupling of secondary and primary alkyl halides was directed by a putative L_nNi^I−BPin intermediate. Recently, we performed more detailed mechanistic investigation focusing on the reaction of (dtbbpy)$NiBr_2$ with B_2Pin_2 and observed that Ni^{II} was essentially reduced to Ni^0 at a slow rate.[19] Although the exact details of how the nickel catalyst selectively reacts with the coupling partners remain unclear, this observed process, in conjunction with the steric and electronic effects of the secondary and primary alkyl halides, is likely to collectively play crucial roles in determining the chemoselectivity.

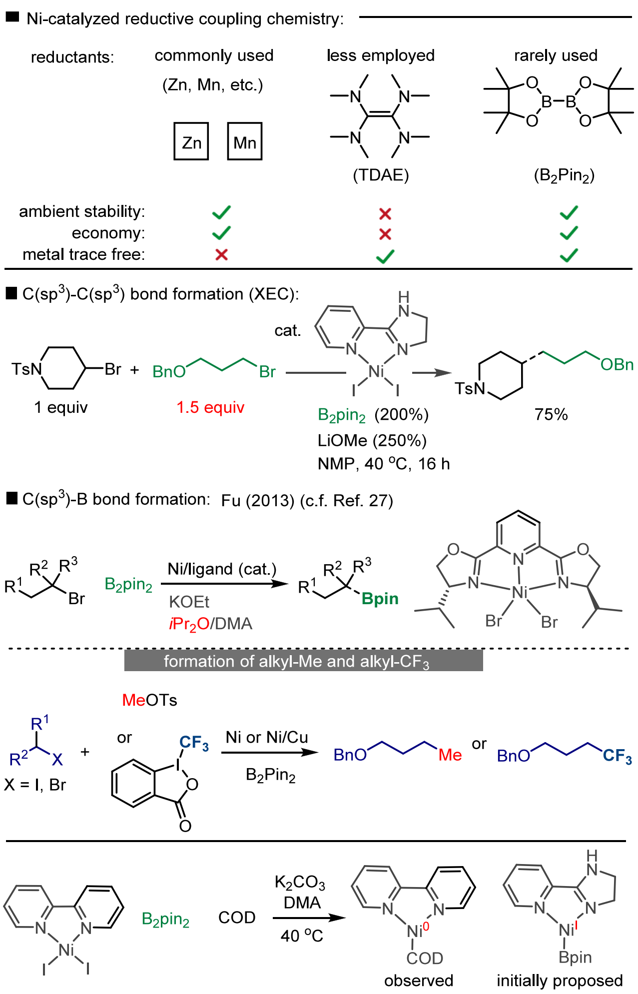


Figure 6. Diboron ester-mediated C(sp^3)−C(sp^3) cross-coupling reactions.

3.2. C(sp^3)−C(sp^2) Bond Construction

An extension of Ni/B_2Pin_2-mediated XEC protocol has recently been accomplished for the coupling of aryl halides with alkyl electrophiles to forge C(sp^2)−C(sp^3) bonds.[19] The alkyl electrophiles encompass halides, Katritzky salts, and tosylates, with the method proving to be particularly suitable for heteroaryl halides. Notably, substitution patterns in bromopyridines did not significantly influence coupling results, and the notorious dimerization of 2-bromopyridine, yielding the bipyridine, was not problematic.

Our mechanistic studies support the idea that the formation of L_nNi^0 is likely a rate-determining step. Subsequent observations revealed the presence of a significant amount of $Ar^1L_nNi^{II}X$ (Figure 7) in the reaction of Ar^1I with nHexBr after 3 h. This aligns with the finding that the preformed $Ar^1L_nNi^{II}$ complex remains stable in the reaction mixture. Moreover, the reaction of nHexBr with an equimolar mixture of Ar^2I and

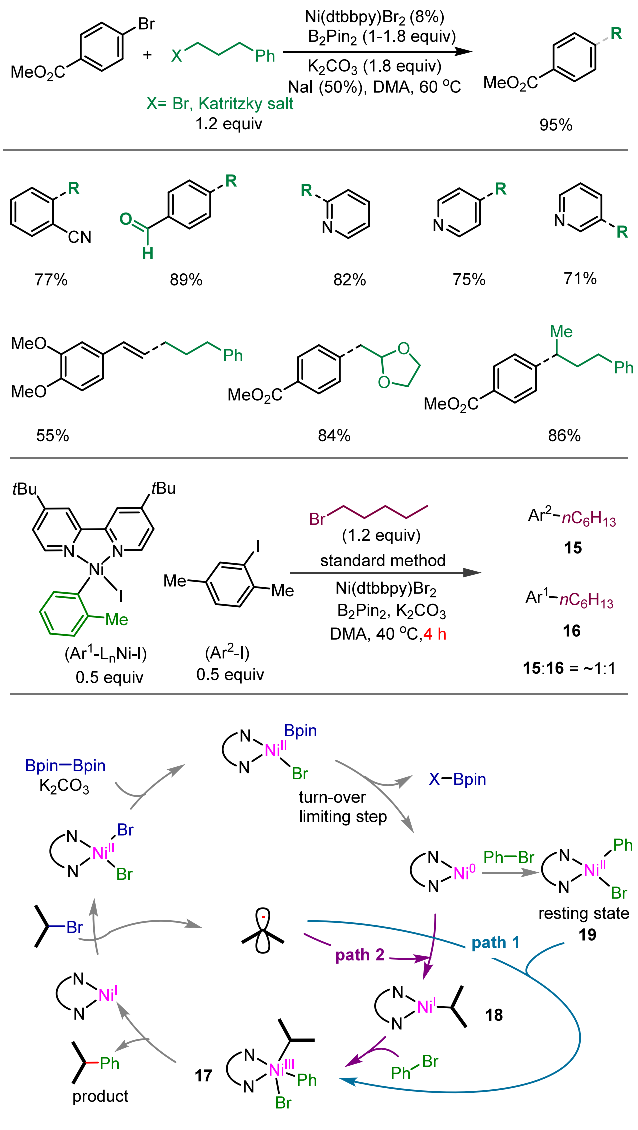


Figure 7. B_2Pin_2-mediated C(sp^3)−C(sp^2) coupling of alkyl and aryl halides.

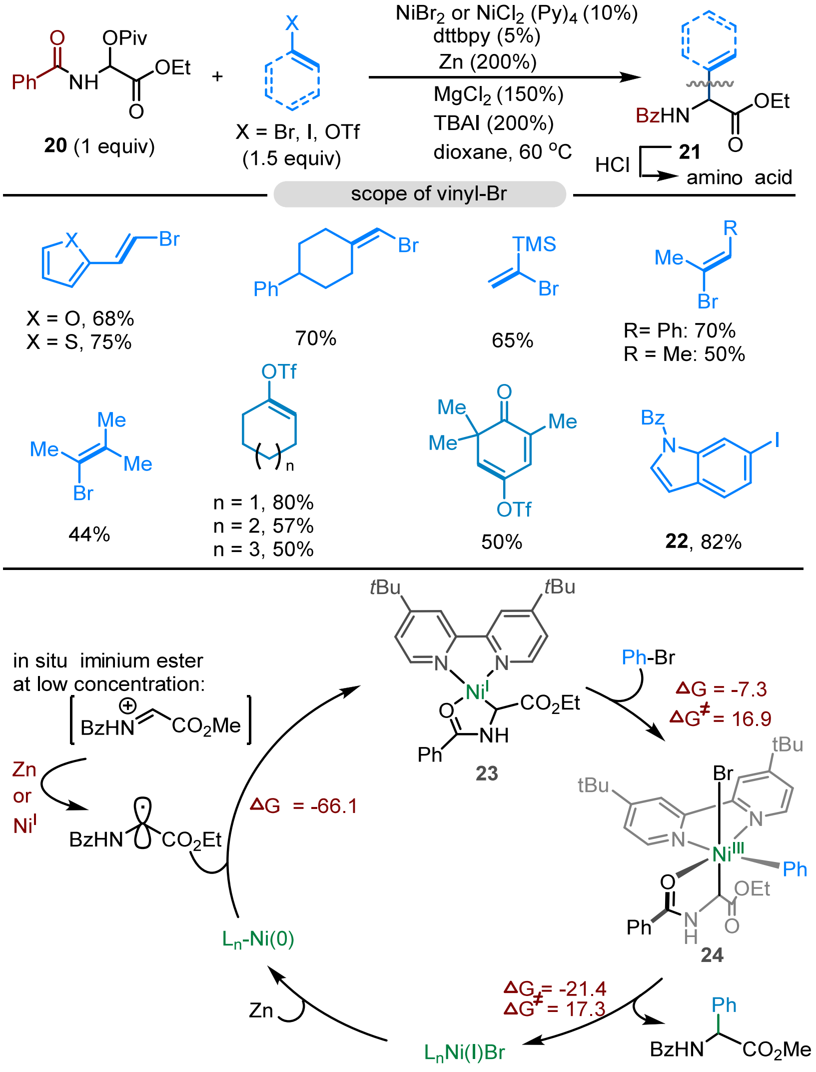


Figure 8. Reductive formation of unusual amino esters from α-PivO-glycine.

preformed $Ar^1L_nNi^{II}$ slightly favored the formation of Ar^2–nHex (**15**). These results suggest that a mechanism involving an $ArNi^{II}$ intermediate is not the predominant path, given that the higher concentration of the preformed Ar^1Ni^{II} complex should favor **16** (Figure 7) over in situ-formed Ar^2Ni^{II}. Therefore, it is proposed that two modes of radical-chain paths for the formation of $Ar{-}L_nNi^{III}(X){-}alkyl$ (**17**) may concurrently operate. These paths involve either the addition of an alkyl radical to L_nNi^0 followed by the oxidative addition of an aryl halide to the resultant alkyl–L_nNi^I (**18**, path 1, Figure 7) or the trapping of the alkyl radical with $Ar{-}L_nNi^{II}X$ (**19**, resting state) generated from oxidative addition of ArX to L_nNi^0 (path 2).

4. REDUCTIVE ARYLATION OF C(SP^3)–O SUBSTRATES

Alcohols are abundant feedstocks that have gained increasing interests in transition metal catalyzed coupling chemistry.[29] However, the direct conversion of alkyl alcohols to $C(sp^3)$–C products in the XEC regime is still in the early stages of development and is currently constrained to activated ones, such as benzyl alcohol.[30] Therefore, methods based on the installation of activating groups to facilitate $C(sp^3)$–O bond reductive coupling have become increasingly important and have achieved significant success in recent years. Noteworthy examples include the coupling of redox-neutral oxalates and the formal coupling of alcohols through in situ activation of C–O bonds.[31−34] These strategies offer advantages due to the easy accessibility of substrates. Importantly, they allow the circumvention of the laborious conversion of alcohols to more commonly used alkyl halides, which in some cases are not bench-stable. In the following examples, we illustrate how $C(sp^3)$–O bond substrates are utilized to access unusual α-amino esters and alkyl–aryl products through the incorporation of preinstalled and in situ activating groups.

4.1. Preparation of Unusual α-Amino Esters

Usual α-amino acids have found broad applications across the fields of drug discovery, ligand development, biomaterials, and protein engineering, thus attracting tremendous attention in organic synthesis.[35,36] While conventional methods generally emphasize the addition of organometallic reagents or alkyl radicals to iminium salts, or the hydrogenation of alkylidene precursors, they suffer from issues such as limited substrate scope, difficulty in removing *N*-protecting groups, and operational arduousness. Moreover, methods for α-vinyl amino acids remain elusive, as they are challenging to attain via hydrogenation protocols.

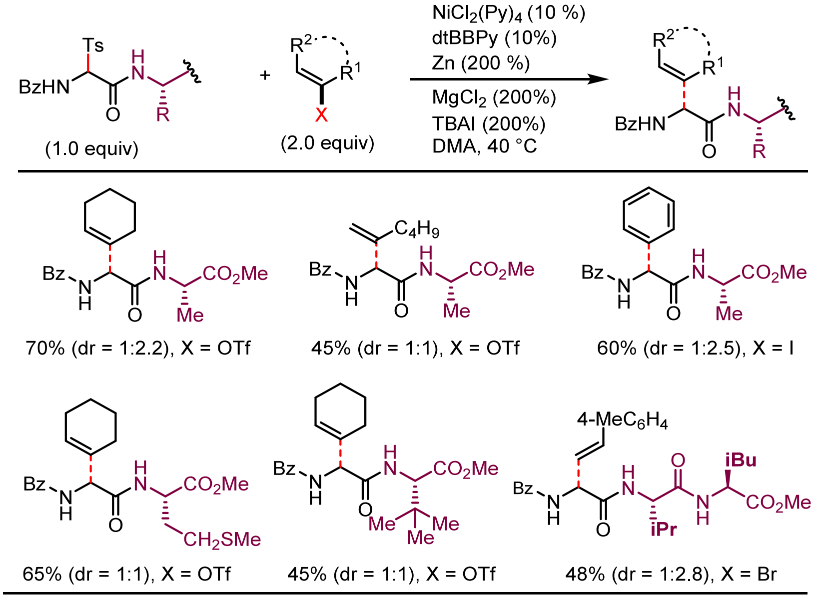


Figure 9. Reductive functionalization of α-Ts-substituted peptides.

We have advanced a reductive coupling strategy through the coupling of readily accessible and bench-stable *N*-benzoyl α-PivO-glycine ester **20** with C(sp^2)-electrophiles, aiming to address the issues encountered in the known methods. The use of aryl/vinyl halides and triflates effectively yielded aryl/vinyl amino esters in good to high yields. The method accommodates a wide range of noncyclic vinyl bromides bearing conjugated aryl and vinyl groups, as well as alkyl substituents. Di- and trisubstituted alkenyl bromides resulted in the corresponding tri- and tetra-substituted alkenyl-decorated amino esters in synthetically useful yields. Cyclic and open-chain vinyl triflates, easily converted from ketones, were successfully integrated into the method, providing a facile protocol for accessing macrocycle- and branched vinyl-decorated amino esters that are otherwise challenging to attain using known methods. The Bz-protected product **21** can be readily hydrolyzed under acidic conditions to give amino acid salts. Finally, the same method is applicable to (hetero)aryl halides, e.g., **22**. In comparison, the bench-unstable α-Br or -Cl-glycine analogue of **20** was too reactive/unstable under the present method and did not yield detectable results.

Mechanistically, the α-PivO glycine is suggested to be converted to an iminium ester, which is then reduced to an α-glycinyl carbon (Gly) radical by Zn or L$_n$Ni^I. A radical-chain process is proposed wherein the radical is trapped with Ni^0, giving rise to a benzoyl carbonyl-chelated Ni^I complex (Gly−L$_n$Ni^I, **23**, Figure 8). Subsequently, the oxidative addition of an aryl halide to **23** affords the key Gly−L$_n$Ni^{III}−Ar intermediate, similar to path A in Figure 1. DFT calculations suggest that **23** is significantly thermally stable. The oxidative addition of bromobenzene to **23** requires overcoming an energy barrier of 16.9 kcal/mol, which is slightly lower than the 17.3 kcal/mol barrier for the reductive elimination of the transient Ni^{III} intermediate (**24**, Figure 8). The studies do not exclude an alternative radical-chain process involving the addition of a glycinyl radical to Ar−L$_n$Ni^{II}X (similar to path C, Figure 1), although the formation of Ar−L$_n$Ni^{II}X is much less thermally feasible than that of **23**.

In the meantime, α-Ts-decorated glycinyl ester was found to be equally effective as the PivO analogues, yielding vinylated and arylated amino esters with good results (Figure 9).[37] The method proved to be beneficial for the direct functionalization of dipeptides and tripeptides containing an α-Ts group, which can be readily prepared through the amide condensation of α-Ts-amino acids with *N*-amino esters and peptides. The resultant peptides exhibit low diastereomeric (dr) values.

4.2. Formal Coupling of Unactivated Alcohols via In Situ Halogenation

The direct coupling of unactivated alkyl alcohols under transition-metal catalysis remains an unmet challenge. To effectively incorporate alcohols into the Ni-catalyzed reductive coupling platform, we developed an in situ halogenation process, converting alcohols into alkyl bromides or chlorides within 1−5 min upon exposure to commercial 2-chloro-3-ethylbenzo[*d*]oxazol-3-ium tetrafluoroborate (CEBO) and TBAB/TBAC (Figure 10).[20] The halogenation is highly site-selective, favoring the sterically less hindered hydroxyl group. For symmetric diols, such as propyl- and ethylene diols, monobromination was observed due to the formation of a key intermediate (**25**), where the inductive effect deactivates the second hydroxyl group. For 1,4-butyl diol, the slow addition of CEBO ensured a good yield for monobromination.

The in situ halogenation process integrates well with the Ni-catalyzed coupling conditions, enabling the development of a method for the formal arylation of alcohols. The use of readily available alcohols as electrophiles significantly broadens the scope of alkyl moieties (e.g., those in Figure 10). For instance, in addition to routine secondary alkyl groups, menthol and protected glucose with free hydroxyl groups were facilely functionalized without the prepreparation of alkyl halides. We also noticed that the side product BEO arising from CEBO played a noninnocent role in promoting the coupling yields.

5. THERMOREDOX COUPLING

The success of Ni-catalyzed C(sp^3)−C reductive coupling chemistry, built upon readily accessible alkyl electrophiles, has prompted us to explore whether Ni-catalysis can address the challenging problems associated with the coupling of unactivated C(sp^3)−H bonds and alkenes—frequently the

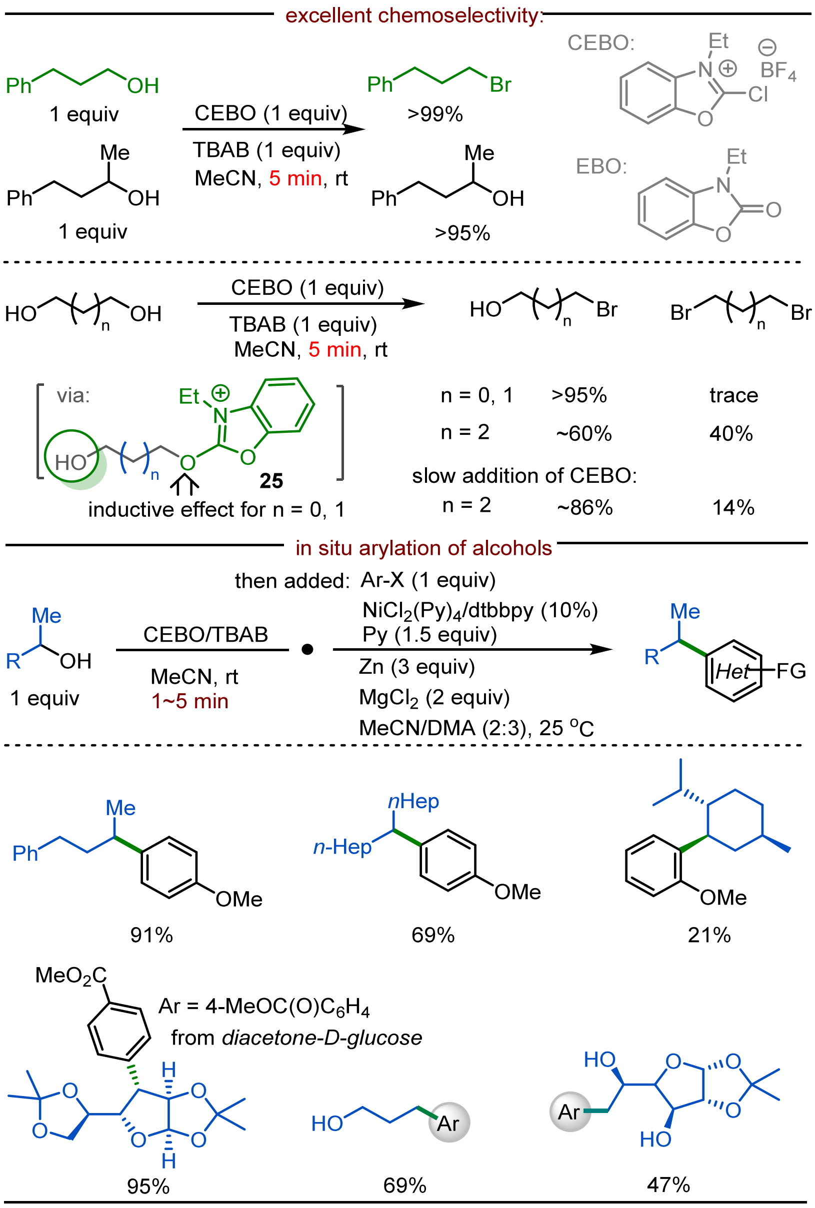


Figure 10. In situ halogenation of alcohols and arylation in one pot.

precursors of alkyl electrophiles. To this end, we developed a thermoredox strategy by simultaneously introducing the external oxidant DTBP to Ni- and Zn-catalyzed reductive reactions, enabling the coupling of strong C(sp^3)−H bonds with carbon electrophiles. Additionally, we introduced DTBP/$CuBr_2$ to NiH-catalyzed conditions, facilitating the direct connection of two unactivated alkenes to forge C(sp^3)−C bonds. These methods have proven effective in the carbon-functionalization of various N-α-, O-α-, and cyclohexyl CH bonds, offering a solution for the site-selective hydrodimerization of unactivated alkenes.[4]

5.1. Functionalization of C(sp^3)−H Bonds with Carbon Electrophiles

The key mechanistic perspectives of nickel-catalyzed C(sp^3)−C cross-electrophile coupling involve the homolysis of a C(sp^3)−X bond, resulting in an alkyl radical. This radical is then trapped with a Ni^n species (n = 0 to 2) to yield a C(sp^3)−Ni^{n+1} intermediate (Figure 1). We postulated that an alkyl radical could be generated from a C(sp^3)−H bond by introducing an appropriate hydrogen-atom-transfer (HAT) oxidant to Ni-catalyzed reductive coupling platforms. Consequently, the thermoredox coupling of C(sp^3)−H bonds with carbon electrophiles can be realized, provided that the oxidant exhibits excellent compatibility with reductive conditions (Figure 11).

A proof-of-concept investigation was successfully conducted, involving the coupling of a wide array of N-α-CH, O-α-CH bonds, and cyclohexane with 1 equiv of aryl bromides in the presence of DTBP and Zn in DMSO.[3] The scope of aryl and alkyl halides is broad (e.g., those in Figure 11). Noteworthy functional groups, such as 2-chloro- and 2-cyanomethyl, survived the reaction conditions. Mechanistic studies suggested that Ni^0 was not involved in the reaction process. Therefore, we proposed a radical-chain cycle highlighting the addition of an alkyl radical to the L_nNiBr_2 salt to give alkyl−$Ni^{III}Br_2$, which is then reduced with Zn to afford the alkyl−Ni^I intermediate (**26**, Figure 12). Oxidative addition of carbon electrophiles

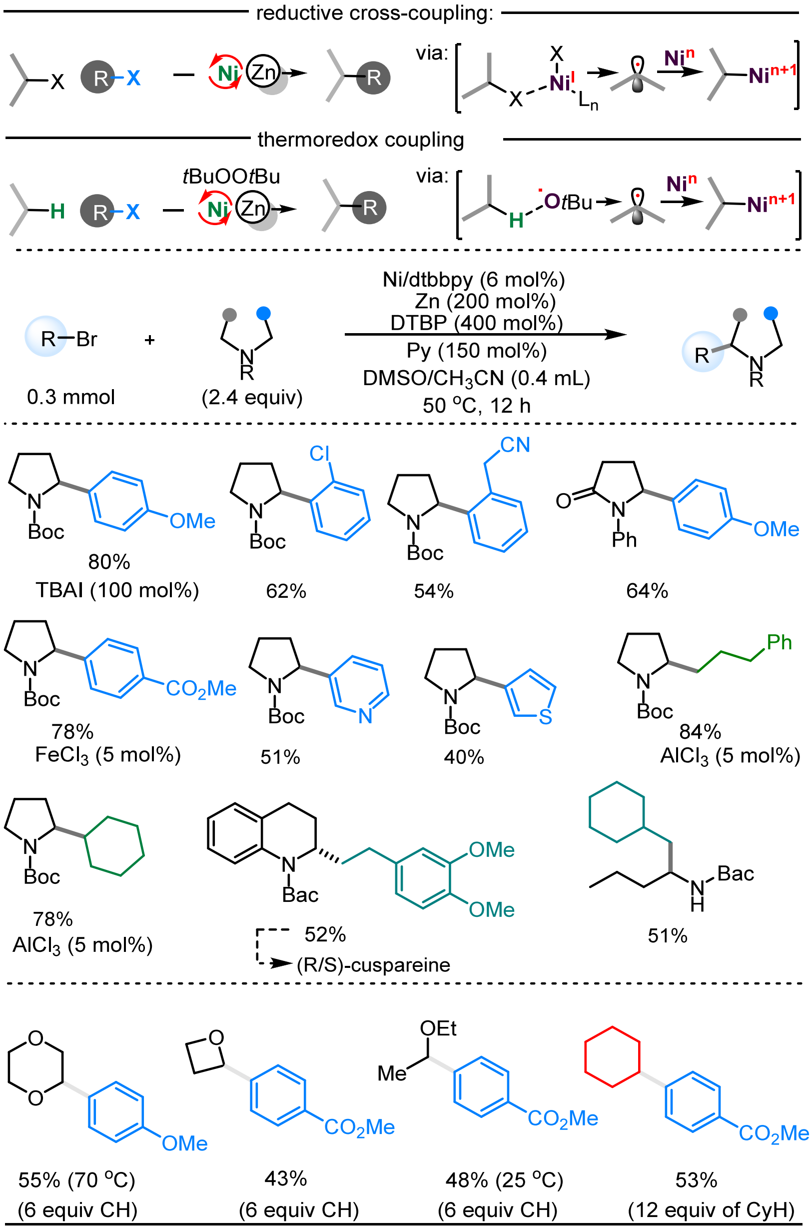


Figure 11. Carbofunctionalization of C(sp^3)−H bonds with organohalides.

with **26** results in the alkyl−Ni^{III}−C species (**27**), which omits the product upon reductive elimination.

The mutual inertness of Zn and DTBP under the reaction conditions is intriguing, as strong oxidants and reductants are generally thought to undergo rapid redox reactions. Instead, we found that DTBP was only decomposed upon exposure to L$_n$NiBr$_2$ and Zn, likely due to single-electron transfer (SET) reduction by the in situ generated L$_n$Ni^I species (**28**), giving tBuO radical and L$_n$Ni^{II}X$_2$ (Figure 12). The (dtbbpy)Ni^I has been shown to have a reduction potential of −1.14 eV (vs SET in CH$_3$CN), rendering the proposed SET process plausible.[38] Thus, the present thermoredox method validates challenging C(sp^3)−H bonds as alkyl radical precursors, integrating with Zn-mediated reductive conditions. It adds a new entry to C(sp^3)−H/electrophile coupling chemistry, which has been extensively investigated based on directing group-mediated 2e-coupling and photoredox coupling strategies.[39,40]

5.2. Site-Selective Hydrodimerization of Unactivated Alkenes

The identification of putative dialkyl−Ni^{III} species in Ni-catalyzed C(sp^3)−H functionalization with alkyl halides inspired us to explore the viability of directly coupling two unactivated alkenes to generate C(sp^3)−C(sp^3) products under NiH/oxidant-mediated conditions.[4] Our initial goal was to generate the key dialkyl−Ni^{III} species by trapping an alkyl radical with an alkyl−Ni^{II} intermediate created through hydrogen-atom-transfer (HAT) of NiH to alkene and NiH/alkene insertion, respectively.[41,42]

Interestingly, using SiH/DTBP as the external oxidant and reductant and (dtbbpy)NiBr$_2$ as the precatalyst, we identified an optimized method for the hydrodimerization of alkene **29**. This method produced a 10:1 ratio of L/B$_1$ (linear vs methyl-branched) products in a total yield of 75% in the presence of catalytic CuBr$_2$ (method A1). In contrast, the absence of CuBr$_2$ delivered a 10:1 ratio of B$_1$/B$_2$ (monomethyl vs

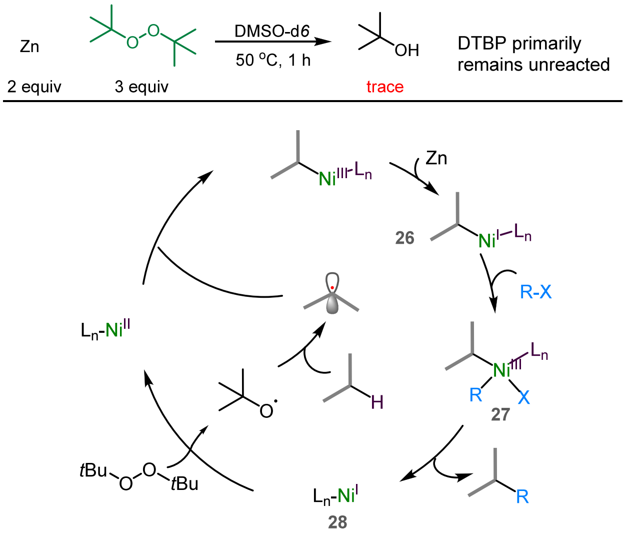


Figure 12. Reaction of Zn and DTBP and the proposed reaction mechanism for $C(sp^3)-H$ coupling with carbon electrophiles (R−Y).

dimethyl-branched) products in a total yield of 72% (method B). The salt additives TBAB and guanidinium chloride proved essential for the transformation, thought to ensure the formation of neutral Ni−halide species and avoid the cationic Ni^{II} species that are prone to alkene isomerization.

Investigation of the reaction mechanism suggests that the linear selectivity may arise from the transmetalation of 2 equiv of linear alkyl−$Ni^{II}X$ (**30**) to give a (dtbbpy)$Ni^{II}-(alkyl)_2$ intermediate (**31**, Figure 13b). This intermediate is oxidized by Cu^{II} through 1e oxidation to give $C(sp^3)-L_nNi^{III}-C(sp^3)$ (**32**) and Cu_I (Figure 13b). Complex (dtbbpy)$NiMe_2$ possesses an irreversible oxidation potential at −0.60 V (vs Fc^+/Fc in THF),[43] whereas the oxidation potential $E^0(Cu^{2+}/Cu^+)$ of $CuBr_2$ is 0.14 V (vs Fc^+/Fc in THF), indicating that the hypothesized single-electron transfer (SET) process is thermally feasible. Following this, reductive elimination of complex **32** gives the hydrodimerized product, wherein the associated L_nNi^I species undergoes a 1e reduction of DTBP to give the tBuO radical and L_nNi^{II}. Trapping the tBuO radical with the Cu^I intermediate regenerates Cu^{II}, and hydride transfer from SiH to L_nNi^{II} gives $L_nNi^{II}H$ that undergoes regioselective migratory insertion into the alkene to afford linear alkyl−Ni^{II}.

The formation of the methyl-branched product was tentatively explained by a possible HAT process (Figure 13c),[44] wherein an alkyl radical is formed upon HAT of NiH or SiH to the alkene, followed by its trapping with an alkyl−$Ni^{II}X$ species to give the branched $C(sp^3)-Ni^{III}-C(sp^3)$ intermediate. Evidence for the involvement of an alkyl radical was supported by the formation of a cyclopropane ring-opening dimer **34** from radical clock **33** (Figure 13c).

The established linear (head-to-head) and methyl-branched hydrodimerization methods proved to be general for a wide array of unactivated terminal alkenes (e.g., Figure 14a). Importantly, terminal alkenes bearing substituents at the allylic carbons or on the 2-alkenyl carbons are effective (e.g., Figure 14b), producing exclusively linear products, even when 1 equiv of $CuBr_2$ was employed at a 0.2 mmol scale. The coupling method is also applicable to the cross-hydrodimerization of a set of terminal alkenes (e.g., Figure 14c), enabling access to various bioactive and naturally occurring products in moderate yields. These include a key intermediate to caeliferin B1 6:0 (**35**) and an intermediate en route to cylindrocyclophane F (**36**), respectively.

It should be noted that controlling the site selectivity in the dimerization of two alkenes remains a long-standing challenge in organic synthesis. This has often been found problematic in cationic metal-hydride-catalyzed polymerization of terminal

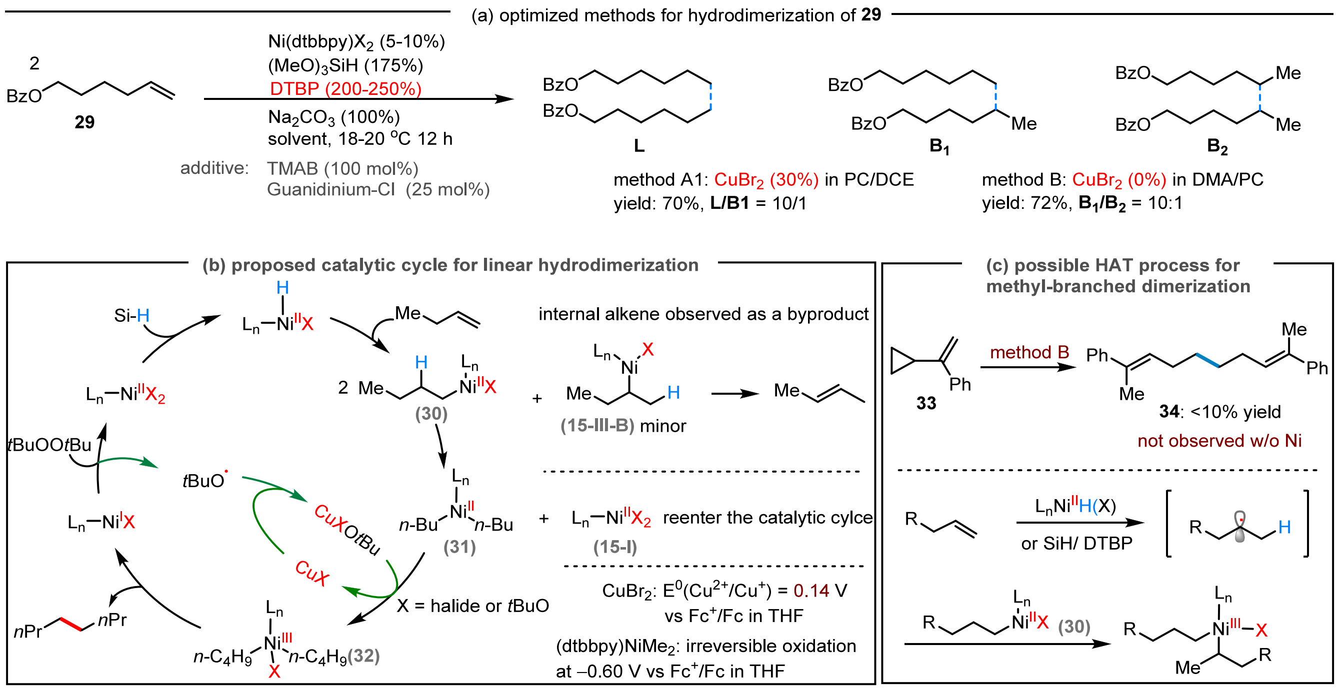
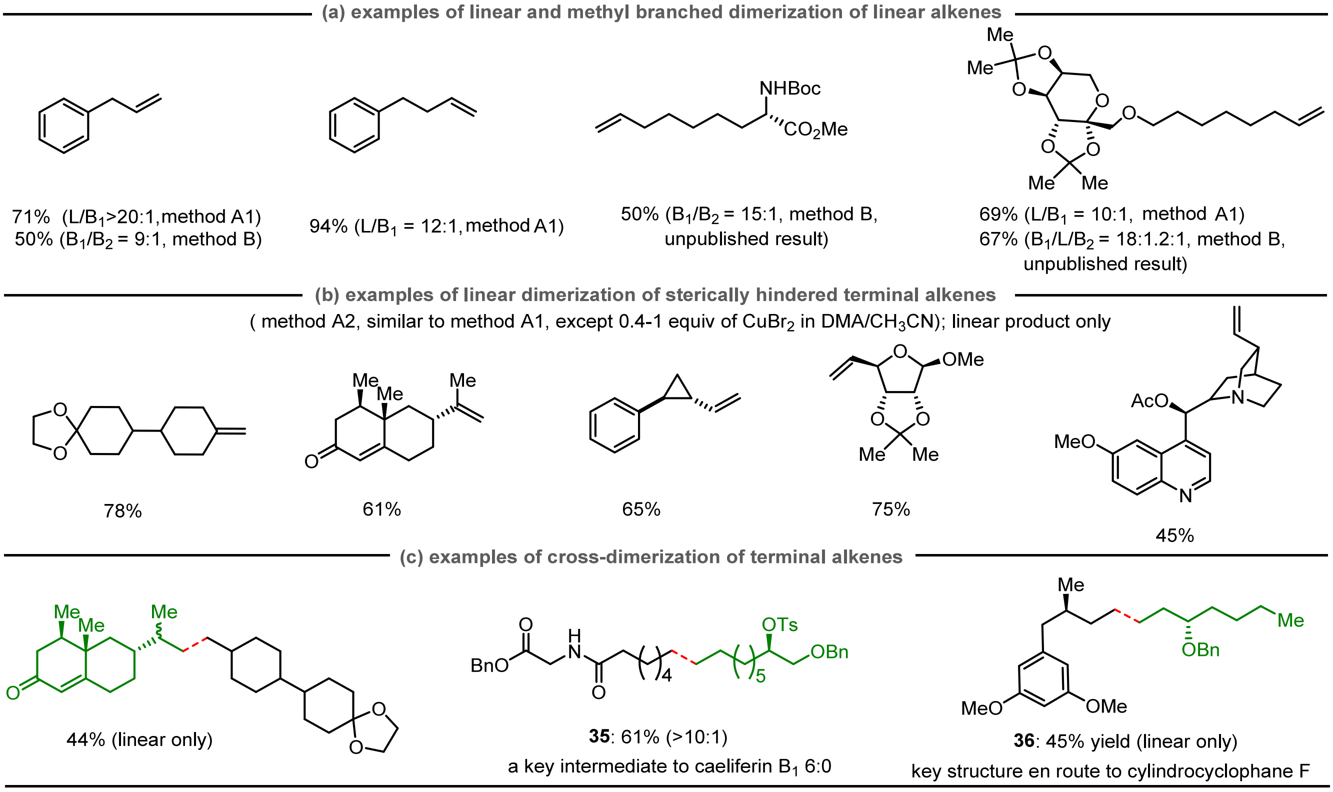


Figure 13. Site-selective hydrodimerization of **29** and proposed mechanisms. PC = propylene carbonate; TMAB = tetramethylammonium bromide; GDC = guanidinium chloride; L= linear; B = branched.



(a) examples of linear and methyl branched dimerization of linear alkenes

(b) examples of linear dimerization of sterically hindered terminal alkenes

(method A2, similar to method A1, except 0.4-1 equiv of CuBr$_2$ in DMA/CH$_3$CN); linear product only

(c) examples of cross-dimerization of terminal alkenes

35: 61% (>10:1)

a key intermediate to caeliferin B$_1$ 6:0

36: 45% yield (linear only)

key structure en route to cylindrocyclophane F

Figure 14. Selected examples of the hydrodimerization of terminal alkenes.

alkenes.[45] Although radical cascade additions and hydrovinylation of alkenes have been widely used for connecting two alkenes, the products are generally obtained in branched forms.[46] Thus, our method for the selective linear and branched hydrodimerization of terminal alkenes provides a solution to this unmet issue.

6. CONCLUSIONS

In this Account, we have reviewed (1) our continuous endeavors in tackling the challenging issues in XEC chemistry and (2) the development of thermoredox coupling of C(sp^3)−H bonds and unactivated alkenes under Ni-catalyzed conditions, with an emphasis on the mechanistic perspectives of the formation of diorgano−Ni^{III} intermediates. First, stereoelectronic bias between the two coupling electrophiles appears to be important for attaining high levels of chemoselectivity, as exemplified by the cross-coupling of aryl and vinyl halides, alkylthio-*tert*-butoxy carbonate with aryl triflates, and secondary and primary alkyl halides. Utilizing B$_2$Pin$_2$ as a reducing agent reveals the slow formation of Ni^0 from Ni^{II} at low concentrations, a key step in the chemoselective C(sp^3)−C(sp^3) cross-coupling. In the B$_2$Pin$_2$-mediated aryl−alkyl coupling, a mechanism concerns the addition of an alkyl radical to Ni^0, followed by the oxidative addition of ArX to the resulting alkyl−Ni^I to give aryl−Ni^{III}−alkyl. The arylation/vinylation of bench-stable *N*-Bz-protected α-PivO-decorated glycine with aryl/vinyl halides offers a convenient entry into unusual amino acids. The proposed dicarbon−Ni^{III} species arises from the oxidative addition of aryl halide to glycinyl−Ni^I that is formed by trapping a *N*-Bz-stabilized radical with Ni^0. We also advanced an in situ halogenation/reductive arylation of unactivated alcohols to afford C(sp^3)−C bonds that facilitate screening of alkyl groups in XEC chemistry. Moreover, our mechanistic understanding of Ni-catalyzed XEC chemistry has led to the development of the thermoredox functionalization of C(sp^3)−H bonds with organohalides. This is achieved through the compatibility of the reductant Zn and the oxidant DTBP. The proposed mechanism involves a C(sp^3)−H HAT to the tBuO radical and oxidative addition of an organohalide to alkyl−Ni^I to furnish the dicarbon−Ni^{III} intermediate. Finally, a combination of SiH/DTBP in the presence and absence of catalytic CuBr$_2$ allows for the site-selective hydrodimerization of unactivated terminal alkenes, generating linear/methyl-branched C(sp^3)−C(sp^3) bonds. The oxidation of a putative dialkyl−Ni^{II} species by Cu^{II} to the dialkyl−Ni^{III} species is thought to be a key mechanistic event for head-to-head selectivity. In closing, this Account will hopefully lead to more efforts to address the chemoselectivity and C(sp^3)−O bond coupling issues in XEC chemistry and to further develop the thermoredox coupling methodology.

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Notes

The authors declare no competing financial interest.

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