

Transition Metal (Ni, Cu, Pd)-Catalyzed Alkene Dicarbofunctionalization Reactions

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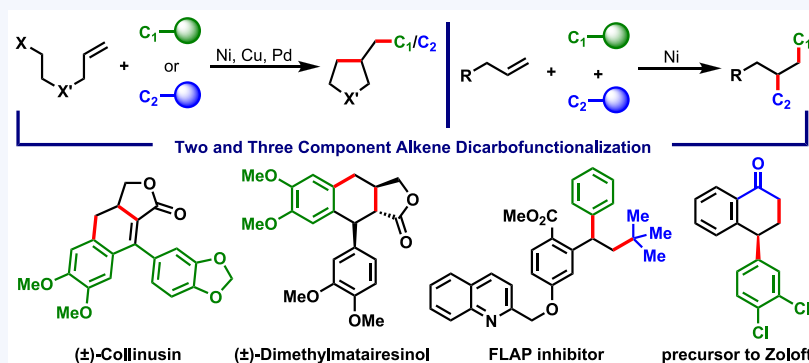


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CONSPECTUS: Recently, alkene dicarbofunctionalization, i.e., the powerful organic synthesis method of alkene difunctionalization with two carbon sources, emerged as a formidable reaction with immense promise to synthesize complex molecules expeditiously from simple chemicals. This reaction is generally achieved with transition metals (TMs) through interception by carbon sources of an alkylmetal $[\beta\text{-H-C}(\text{sp}^3)\text{-[M]}]$ species, a key intermediate prone to undergo rapid $\beta\text{-H}$ elimination. Related prior reports, since Paolo Chiusoli and Catellani's work in 1982 [*Tetrahedron Lett.* **1982**, 23, 4517], have used bicyclic and disubstituted terminal alkenes, wherein $\beta\text{-H}$ elimination is avoided by geometric restriction or complete lack of $\beta\text{-H}$'s. With reasoning that $\beta\text{-H-C}(\text{sp}^3)\text{-[M]}$ intermediates could be rendered amenable to interception with the use of first row late TMs and formation of coordination-assisted transient metallacycles, these two strategies were implemented to address the $\beta\text{-H}$ elimination problem in alkene dicarbofunctionalization reactions.

Because first row late TMs catalyze $\text{C}(\text{sp}^3)\text{-C}(\text{sp}^3)$ coupling, Cu and Ni were anticipated to impart sufficient stability to $\beta\text{-H-C}(\text{sp}^3)\text{-[M]}$ intermediates, generated catalytically upon alkene carbometallation, for their subsequent interception by carbon electrophiles/nucleophiles in three-component reactions. Additionally, such an innate property could enable alkene difunctionalization with carbon coupling partners through entropically driven cyclization/coupling reactions. The cyclometalation concept to stabilize intractable $\beta\text{-H-C}(\text{sp}^3)\text{-[M]}$ intermediates was hypothesized when three-component reactions were performed. The idea of cyclometalation to curtail $\beta\text{-H}$ elimination is founded upon Whitesides's [*J. Am. Chem. Soc.* **1976**, 98, 6521] observation that metallacycles undergo $\beta\text{-H}$ elimination much slower than acyclic alkylmetals.

In this Account, examples of alkene dicarbofunctionalization reactions demonstrate that Cu and Ni catalysts could enable cyclization/coupling of alkenylzinc reagents, alkyl halides, and aryl halides to afford complex carbo- and heterocycles. In addition, forming coordination-assisted transient nickellacycles enabled regioselective performance of three-component dicarbofunctionalization of various alkenyl compounds. In situ reaction of $[\text{M}]\text{-H}$ with alkenes generated after $\beta\text{-H}$ elimination induced an unprecedented metallacycle contraction process, in which six-membered metal-containing rings shrank to five-membered cycles, allowing creation of new carbon–carbon bonds at allylic (1,3) positions. Applications of these regioselective alkene dicarbofunctionalization reactions are discussed.

KEY REFERENCES

- Basnet, P.; Dhungana, R. K.; Thapa, S.; Shrestha, B.; KC, S.; Sears, J. M.; Giri, R. Ni-Catalyzed Regioselective β,δ -diarylation of Unactivated Olefins in Ketimines via Ligand-Enabled Contraction of Transient Nickellacycles: Rapid Access to Remotely Diarylated Ketones. *J. Am. Chem. Soc.* **2018**, 140, 7782–7786.¹ This work demon-

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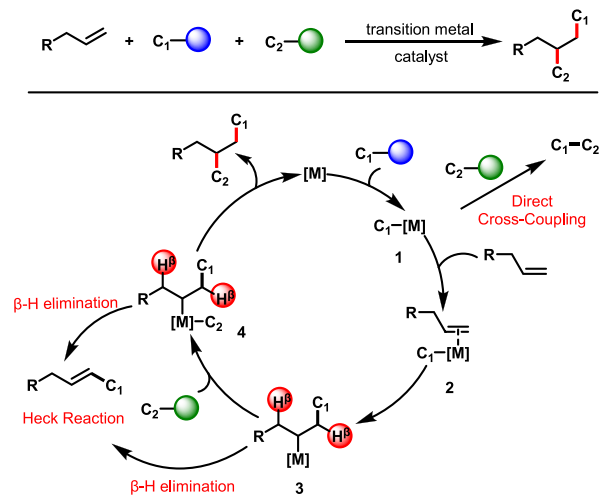


- strates regioselective β,δ -diarylation of unactivated alkenes in ketimines with various aryl halides and arylzinc reagents.
- KC, S.; Dhungana, R.; Shrestha, B.; Thapa, S.; Khanal, N.; Basnet, P.; Lebrun, R.; Giri, R. Ni-Catalyzed Regioselective Alkylarylation of Vinylarenes via $C(sp^3)$ - $C(sp^3)$ / $C(sp^3)$ - $C(sp^2)$ Bond Formation and Mechanistic Studies. *J. Am. Chem. Soc.* **2018**, *140*, 9801–9805.² This work displays regioselective alkylarylation of vinylarenes with primary, secondary, and tertiary alkyl halides, and electronically diverse arylzinc reagents to produce 1,1-diaryllalkanes.
 - Shrestha, B.; Basnet, P.; Dhungana, R. K.; KC, S.; Thapa, S.; Sears, J. M.; Giri, R. Ni-Catalyzed Regioselective 1,2-Dicarbofunctionalization of Olefins by Intercepting Heck Intermediates as Imine-Stabilized Transient Metallacycles. *J. Am. Chem. Soc.* **2017**, *139*, 10653–10656.³ This work describes the use of a readily removable coordinating group to promote Heck carbometallation and stabilize the Heck $C(sp^3)$ -NiX intermediates as metallacycles to suppress β -H elimination and facilitate transmetalation/reductive elimination steps to yield regioselective 1,2-dicarbofunctionalized products.
 - Thapa, S.; Basnet, P.; Giri, R. Copper-Catalyzed Dicarbofunctionalization of Unactivated Olefins by Tandem Cyclization/Cross-Coupling. *J. Am. Chem. Soc.* **2017**, *139*, 5700–5703.⁴ This work illustrates 1,2-difunctionalization of unactivated olefins utilizing alkyl/arylzinc reagents derived from olefin-tethered alkyl/aryl halides that undergo radical cyclization to generate $C(sp^3)$ -Cu complexes in situ, which are then intercepted by aryl and heteroaryl iodides to form the difunctionalized product.

1. INTRODUCTION

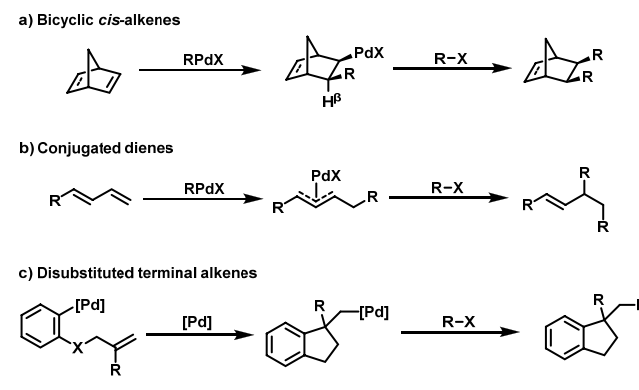
Transition metal (TM)-catalyzed creation of two carbon–carbon bonds across an alkene, termed dicarbofunctionalization

Scheme 1. General alkene dicarbofunctionalization reaction and catalytic cycle



(Scheme 1), is an effective strategy to generate complex molecules from readily available chemicals.^{5,6} This method combines an alkene with two carbon electrophiles/nucleophiles and generates products with stereocenters. Its catalytic cycle involves four steps—activation of the first carbon source, reaction with the alkene, activation of the second carbon source, and reductive elimination from a diorgano-TM intermediate (4)

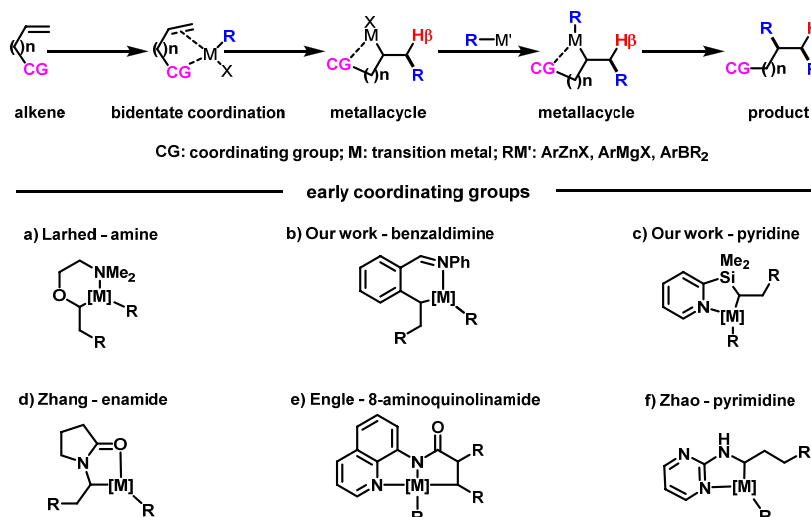
Scheme 2. Structural Variations of Alkenes in Early Reactions



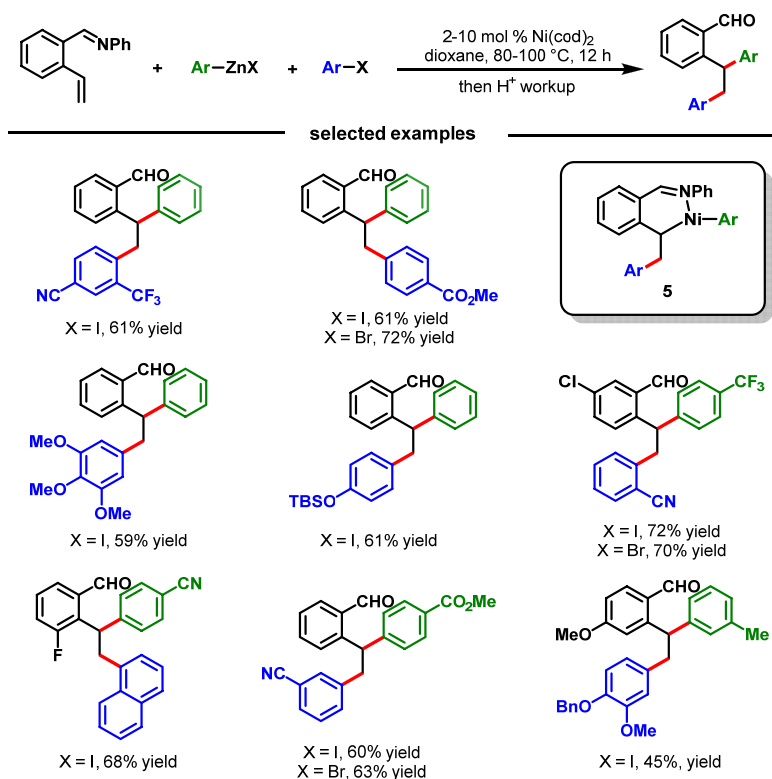
(Scheme 1). However, sequential execution of the four steps is particularly challenging as there are two mainstream chemistries that function as side reactions. The first is the direct coupling between two carbon sources prior to reaction with the alkene.⁷ The second is the Heck reaction after the intermediates (3 and 4) undergo β -H elimination.⁸ Consequently, alkene dicarbofunctionalization reactions require that the rate of the alkene reaction be faster than coupling between the two carbon sources. Also, the rate of activation of the second carbon source and reductive elimination must be faster than β -H elimination. Moreover, controlling the regiochemistry of products is also difficult because the order of addition of the electrophiles and nucleophiles could be reversed. In some cases, intermediate 3 could also undergo a β -H elimination/[M]-H re-insertion step to generate rearranged dicarbofunctionalized products.

Historically, alkene dicarbofunctionalization reactions have been conducted through cross-coupling with organic halides and organometallic reagents using Pd as a catalyst. In these reactions, the predominant tactic has been the use of bicyclic *cis*-alkenes, since the work of Paolo Chiusoli and Catellani in 1982,⁹ to promote alkene insertion, and prevent β -H elimination by creating a geometry with β -H trans to Pd(II) (Scheme 2a).¹⁰ Conjugated dienes have also served as effective substrates for alkene dicarbofunctionalization with Pd.^{11–13} Conjugated dienes promote alkene insertion by strong bidentate coordination, generating π -allyl-Pd(II) intermediates to suppress β -H elimination (Scheme 2b). Alternatively, many reactions have been performed with disubstituted terminal alkenes through cyclization (Scheme 2c).^{14,15} Upon migratory insertion, the disubstituted terminal alkenes generate $C(sp^3)$ -Pd(II) intermediates lacking β -H's. Unfortunately, these substrates were designed to circumvent β -H elimination. Therefore, the scope of the reaction is seriously limited, ultimately restricting its synthetic application. Details of developments and advances of these reactions have recently been reviewed in a number of articles.^{16–24} In this Account, we present our studies on the development of Ni-, Cu-, and Pd-catalyzed dicarbofunctionalization reactions of alkenes that generate $C(sp^3)$ -[M] intermediates containing β -H's, which eliminate constraints on substrate scope. In these studies, we use cross-coupling for bond formation, in which organic halides and organometallic reagents serve as two carbon sources. Other bond-forming approaches, such as reductive coupling,^{25,26} radical reaction^{27–29} and photoredox catalysis,^{30–34} have also remained successful. We illustrate that the β -H- $C(sp^3)$ -[M] intermediates of Ni and Cu are sufficiently stable to enable transmetalation and reductive elimination in cyclization/coupling processes. For more

Scheme 3. Concept of Forming a Transient Metallacycle for Alkene Dicarbofunctionalization



Scheme 4. Imine-Assisted Nickel-Catalyzed Diarylation of 2-Alkenylbenzaldehydes



challenging three-component reactions, we implement Ni catalysts in conjunction with a coordination strategy, facilitating the generation of metallacycles to stabilize $\beta\text{-H-C}(\text{sp}^3)\text{-[M]}$ intermediates.

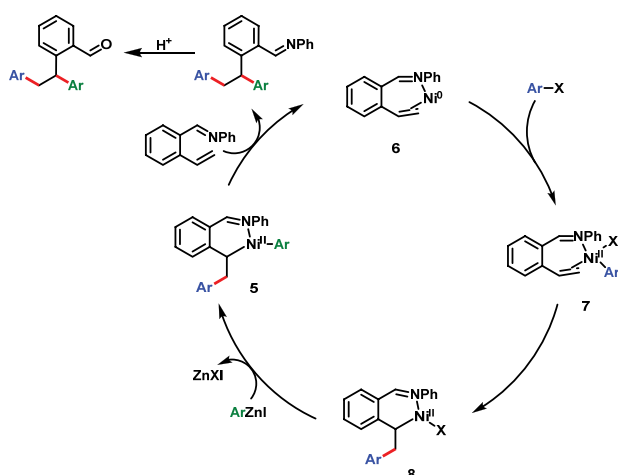
2. THREE-COMPONENT ALKENE DICARBOFUNCTIONALIZATION

2.1. Coordination-Controlled Vicinal Dicarbofunctionalization

Recently, we implemented the concept of forming transient $\beta\text{-H-C}(\text{sp}^3)\text{-metallacycles}$ with a removable coordinating group for alkene difunctionalization with organic halides and organo-

metallic reagents (Scheme 3).³ Our approach relied upon Whitesides et al.'s observation³⁵ that $\beta\text{-H-C}(\text{sp}^3)\text{-platinacycles}$ undergo $\beta\text{-H}$ elimination much slower than acyclic $\beta\text{-H-C}(\text{sp}^3)\text{-Pt(II)}$ complexes. In metallacycles, the TM and $\beta\text{-H}$'s are oriented out of syn-coplanarity due to geometric restriction. We envisioned that alkenyl substrates bearing a heteroatom coordinating group would function as a bidentate ligand. Bidentate coordination would be critical for promoting pseudo-intramolecular migratory insertion of TM-bound alkenes, and for stabilizing postalkene insertion $\beta\text{-H-C}(\text{sp}^3)\text{-[M]}$ intermediates as metallacycles. Previously, Neufeldt and Sanford³⁶ and Toste et al.³⁷ utilized heteroatom coordination for

Scheme 5. Catalytic Cycle via Nickellacycle Formation

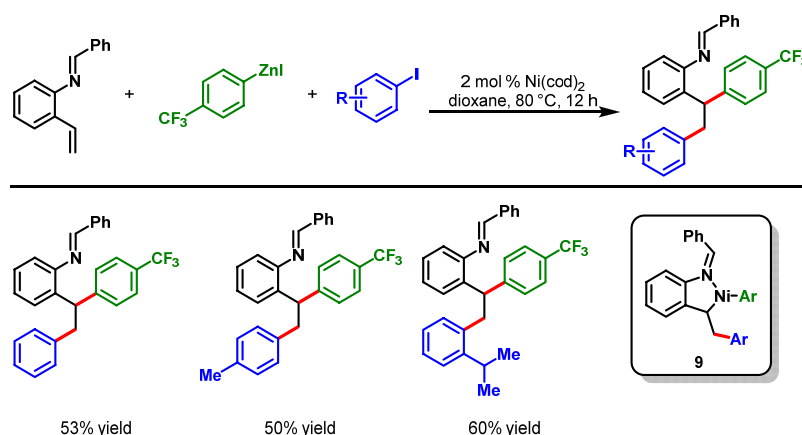


dioxygenation of *O*-allyloximes and fluoroarylation of 2-vinylarenes with Pd catalysts. In 2009, Larhed et al.³⁸ implemented -NMe_2 for a Pd-catalyzed homodiarlylation of an alkene with arylboronic acids (Scheme 3a).

In 2017, we disclosed a $\text{Ni}(\text{cod})_2$ -catalyzed diarylation of 2-alkenylbenzaldehydes with aryl halides and arylzinc reagents (Scheme 4).³ During our work, Zhang et al.,^{39,40} Engle et al.⁴¹ and recently Koh et al.,⁴² and Zhao et al.⁴³ also disclosed similar coordination strategies with enamide, bidentate 8-aminoquinolinamide, and pyrimidine, respectively, for alkene dicarbofunctionalization (Scheme 3d–f). Our benzaldimine substrate was designed to orient both the γ,δ -alkene and the imine groups *syn* to each other. The lateral arene facilitated the formation and stabilization of six-membered nickellacycles (5 and 8) by planarization and rigidification (Scheme 5). This thermodynamic stabilization of transient metallacycles enabled β -H elimination to proceed slower than transmetalation and reductive elimination, as required for alkene difunctionalization.

Our imine-assisted reaction demonstrated an excellent scope with aryl iodides, aryl bromides, aryl triflates, arylzinc reagents, and 2-alkenylbenzaldehydes. The reaction condition was also amenable to the diarylation of 2-alkenylaniline-derived imines (Scheme 6). This latter reaction proceeded with five-membered nickellacycles (9). Unlike 8-aminoquinolinamide, enamide, and pyrimidine, our imine coordinating group was readily removed instantaneously during a simple acid workup.

Scheme 6. Imine-Assisted Nickel-Catalyzed Diarylation of 2-Alkenylanilines

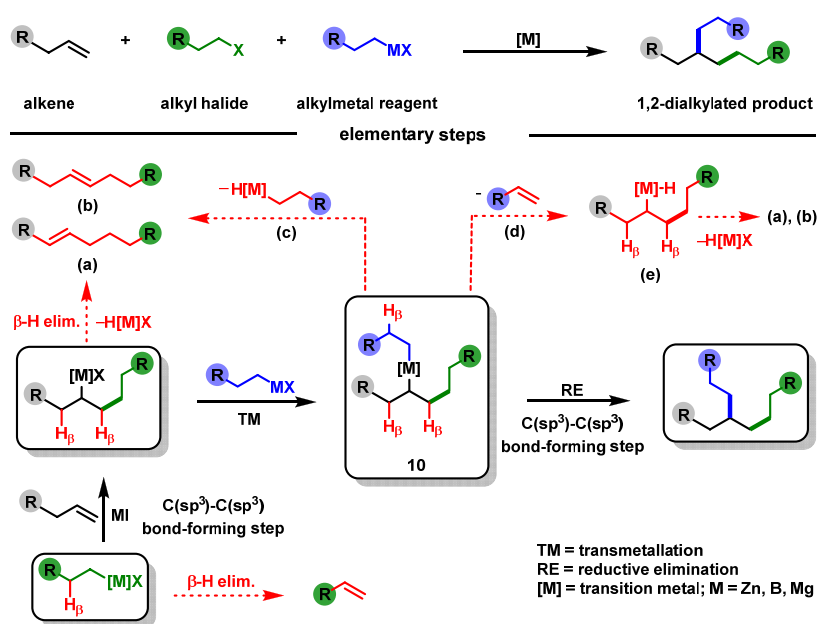


Catalytic alkene difunctionalization with two $\text{C}(\text{sp}^3)$ sources is more challenging than with $\text{C}(\text{sp})$ and $\text{C}(\text{sp}^2)$ sources, as they generate additional $\beta\text{-H-C}(\text{sp}^3)\text{-[M]}$ intermediates (10) during the reaction (Scheme 7). Since the extra $\beta\text{-H-C}(\text{sp}^3)\text{-[M]}$ intermediate makes the reaction more susceptible to β -H elimination, regioselective intermolecular addition of two $\text{C}(\text{sp}^3)$ groups to an alkene remains a serious problem. As such, these reactions are exceptionally rare and inefficient, requiring an excess of reactive $\text{C}(\text{sp}^3)$ sources, high catalyst loadings,⁴⁴ and vinylboron reagents as an alkene source.⁴⁵ In 2020, we reported that 2-alkenylbenzaldehydes were excellent substrates for regioselective dialkylation with benzyl bromides and alkylzinc reagents using $\text{Ni}(\text{cod})_2$ (Scheme 8).⁴⁶ Concomitantly, Koh et al.⁴⁷ disclosed a Ni-catalyzed dialkylation of alkenylquinolinamides with redox active esters. Our dialkylation reaction was highly efficient and could be conducted with 500 ppm catalyst, registering up to 2×10^3 catalytic turnover number (TON) and 165 h^{-1} turnover frequency (TOF) at room temperature. The reaction was also scalable, and proceeded with electronically varied benzyl bromides, alkylzinc reagents, and 2-alkenylbenzaldehydes.

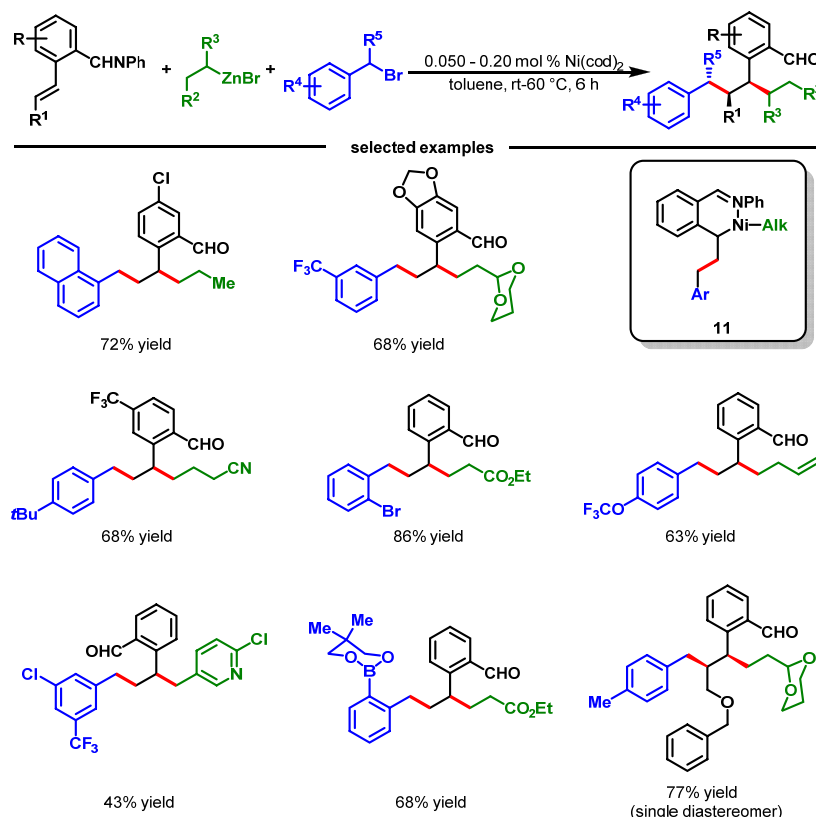
The alkene dialkylation reaction was also effective for the coupling of secondary benzyl bromides and secondary alkylzinc reagents with internal alkenes, and generating products with three contiguous all-carbon secondary stereocenters (Scheme 9). Difunctionalization of internal alkenes with two discrete secondary $\text{C}(\text{sp}^3)$ reagents is a desired reaction that generates branched carbon frameworks with multiple contiguous stereocenters. However, such a process is fundamentally challenging, since internal alkenes are less polarized and more sterically crowded than terminal alkenes. In addition, these reactions require the formation of $\text{C}(\text{sp}^3)\text{-C}(\text{sp}^3)$ bonds between secondary $\text{C}(\text{sp}^3)$ reagents and secondary $\text{C}(\text{sp}^3)\text{-[M]}$ intermediates, which further raises the activation barrier of the transition state due to increased sterics.

In our dialkylation reaction, the *o*-aldehyde remained vital, not only for the generation of an aldimine for coordination, but also as a synthetic handle for further functionalization of the dialkylated products. The dialkylated benzaldimine products could be reduced in situ with NaBH_4 to access advanced secondary arylbenzylamines (Scheme 10). In addition, the reaction could be performed with alkylzinc reagents bearing ester, nitrile, and protected aldehyde groups, wherein the carbonyl α -carbons could be condensed with the *o*-aldehyde to produce tetralenes and benzosuberenes (Scheme 11). Likewise,

Scheme 7. Problems in Metal-Catalyzed Alkene Dialkylolation Reactions



Scheme 8. Imine-Assisted Nickel-Catalyzed Dialkylolation of 2-Alkenylbenzaldehydes

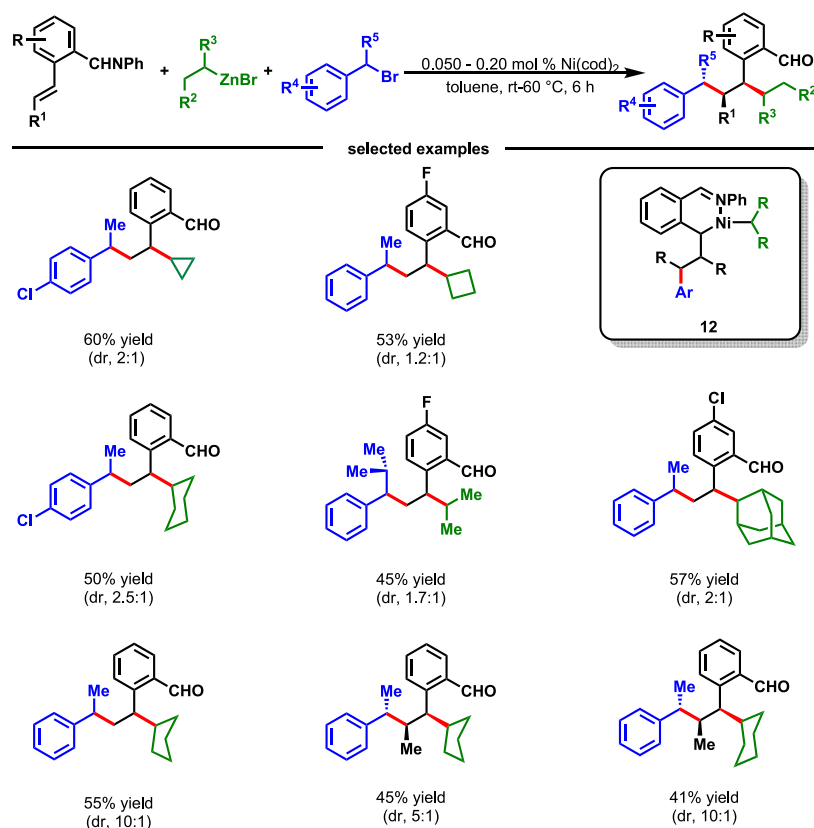


the use of 2-bromobenzyl bromide and 2-(dioxanyl)ethylzinc bromide enabled us to create an arene-studded bicyclo[4.2.2]-decene (14) by the Heck reaction subsequent to dialkylation and cyclization (Scheme 12).

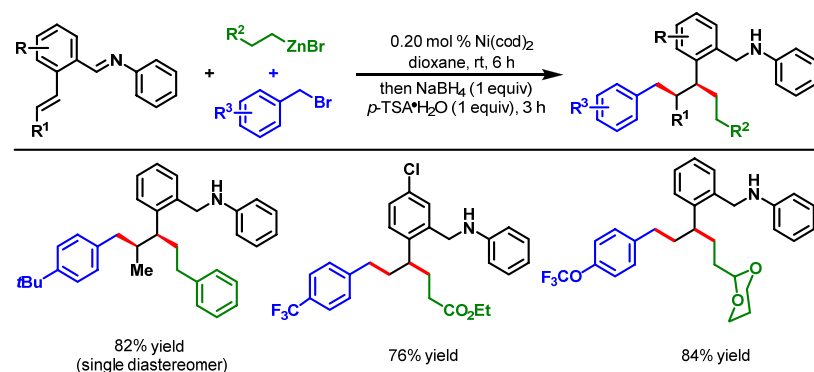
Our Ni-catalyzed alkene difunctionalization method was also amenable to other coordinating groups, in addition to aldimines. In 2018, we disclosed that pyridine could also function as a

coordinating group for regioselective diarylation of alkenes in alkenylpyridylsilanes with aryl halides and arylzinc reagents (Scheme 13).⁴⁸ The reaction required NiBr_2 as a catalyst. However, on the basis of regiochemical outcomes, the reaction is catalyzed by $\text{Ni}(0)$ formed upon in situ reduction of NiBr_2 and proceeds via a pyridine-stabilized five-membered nickellacycle

Scheme 9. Scope with Internal Alkenes, Secondary Halides, and Alkylzinc Reagents



Scheme 10. Rapid Access to Complex Secondary Arylbenzylamines



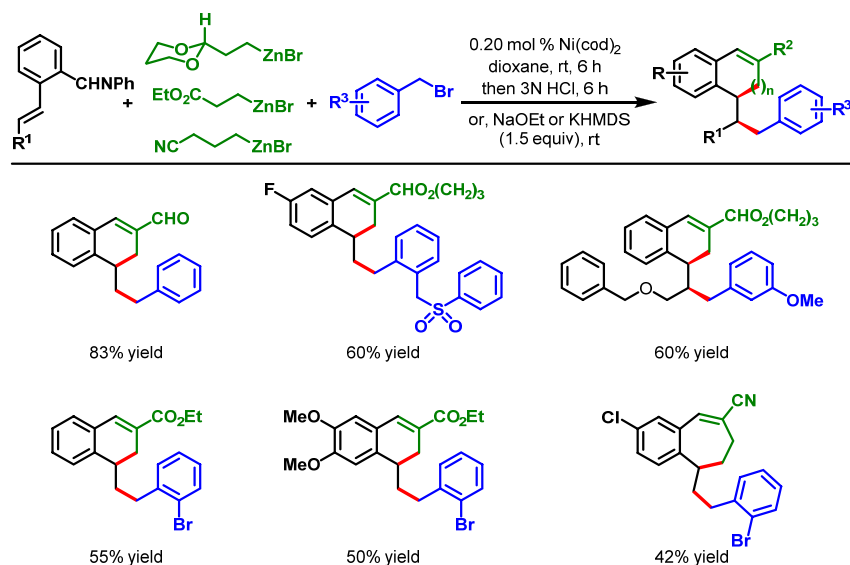
15. The reaction afforded 1,2-diarylethylsilanes, which could be oxidized to 1,2-diarylethanol.

Our studies established reaction parameters for the dicarbofunctionalization of 2-alkenylbenzaldimines involving six-membered transient nickelacycles. However, the translation of the design principle with 2-alkenylaldimines to linear γ,δ -alkenylimines was infeasible on account of $\text{C}(\text{sp}^3)$ hybridization on the substrate backbone. The six-membered metallacycles (**16** and **17**) would remain in chair conformation, as a fluxional structure, prompting both the imine and alkene to disengage from TMs, imparting low stabilization to the metallacycles (Scheme 14). In addition, fluxionality would permit β -H's to attain *syn*-coplanarity with TMs, causing β -H elimination. Therefore, we hypothesized that difunctionalization of linear γ,δ -alkenylimines would require tinkering with relative kinetic energetics of the migratory insertion, β -H elimination, transmetalation, and reductive elimination steps. Literature reports

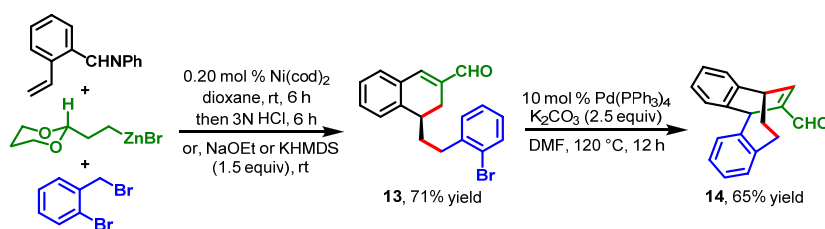
have indicated that Ag salts can abstract halides from ArPdX to generate cationic $[\text{ArPd}(\text{II})]^+$ species and promote both alkene migratory insertion⁴⁹ and transmetalation.⁵⁰ The fast kinetics of migratory insertion and transmetalation are critical to overcome the competing cross-coupling and β -H elimination reactions.

In 2018, we disclosed that catalytic amounts of AgBF_4 or CuX ($\text{X} = \text{I}, \text{BF}_4$) promoted $\text{Ni}(\text{cod})_2$ -catalyzed regioselective γ,δ -diarylation of γ,δ -alkenylketimines with aryl halides and arylzinc reagents (Scheme 15).⁵¹ The reaction worked well with a variety of γ,δ -alkenylketimines, aryl halides, and arylzinc reagents and tolerated a range of functional groups. α -Substituted products were formed as a single diastereomer (racemic), underscoring the potential use of the reaction for stereoselective processes. Such a high degree of stereocontrol could be explained by the formation of a tight pseudochair conformation with the cationic $\text{Ni}(\text{II})$ during migratory insertion.

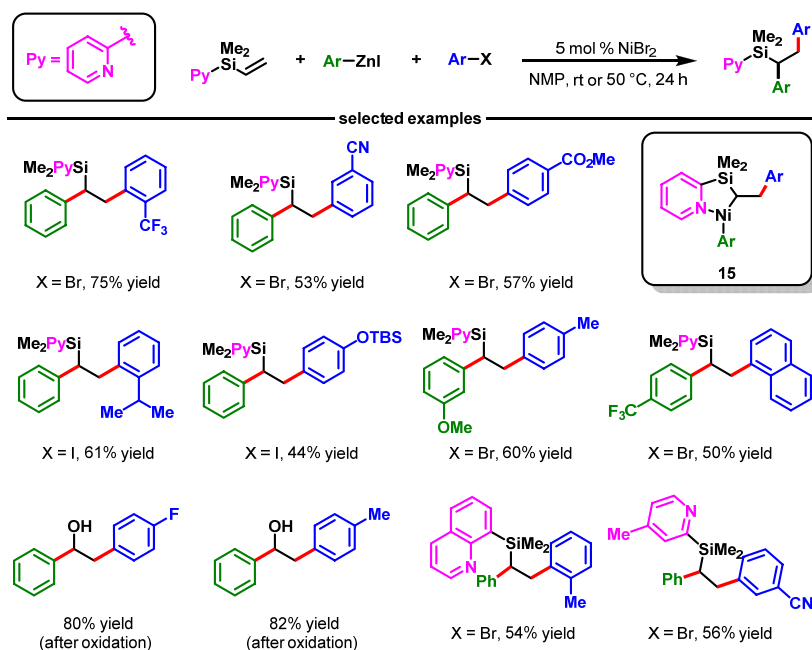
Scheme 11. Rapid Access to Complex Tetralene and Benzosuberene Derivatives



Scheme 12. Rapid Access to Arene-Studded Bicyclo[4.2.2]decene Structures



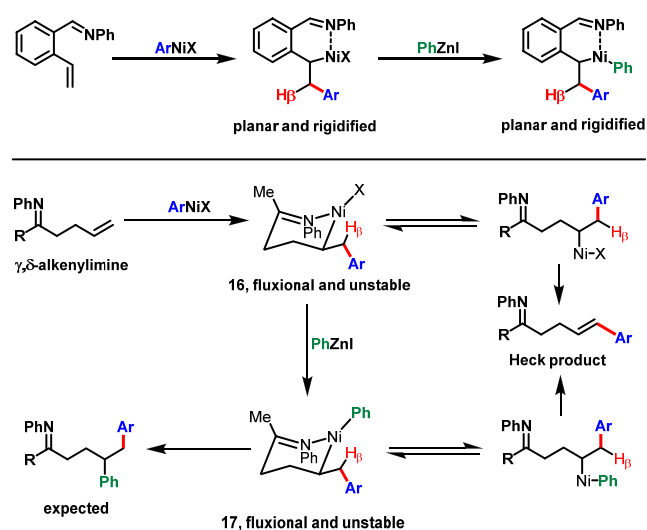
Scheme 13. Pyridine-Assisted Nickel-Catalyzed Diarylation of Vinylpyridylsilanes



Real-time monitoring of the reaction progress by ^{19}F NMR indicated that both AgBF_4 and CuX dramatically increased the rate of alkene diarylation (Figure 1a). In the absence of AgBF_4 or CuX , the reactions generated diarylated products only in 15–30% yields, before terminating in 3 h. Stoichiometric reactions

between $4\text{-FC}_6\text{H}_4\text{ZnI}$ and CuX , and between $4\text{-FC}_6\text{H}_4\text{ZnI}$ and AgBF_4 showed that $[\text{Ar}-\text{Ag}]$ and $[\text{Ar}-\text{Cu}]$ complexes did not form, suggesting that AgBF_4 and CuX did not act as co-transmetalating reagents. Cross-coupling and Heck products were also suppressed in the presence of AgBF_4 and CuX (Figure

Scheme 14. Stability of Planar and Fluxional Six-Membered Metallacycles



1b), indicating that the cationic Ni(II) catalyst promoted migratory insertion faster than cross-coupling and transmetalation faster than β -H elimination.

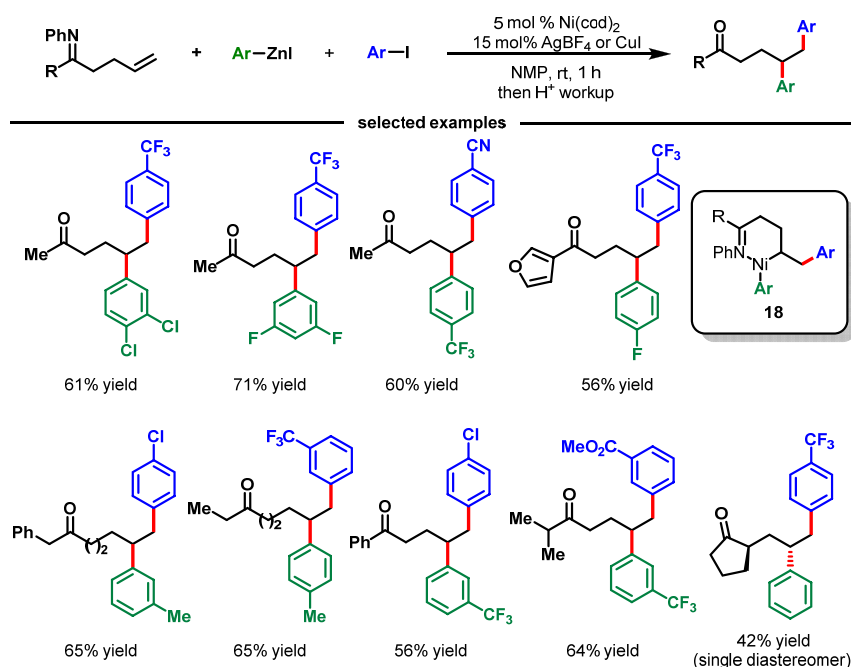
2.2. Coordination-Controlled Homovincinal Dicarbofunctionalization

In alkene difunctionalization, β -H elimination is generally considered a nuisance, and, as such, many strategies such as those outlined in Section 2.1 are employed to overcome this problem. However, recent reports have shown that the process of β -H elimination can also be exploited, to our benefit, to create new bonds at sites that are not generally considered for bond formation.²⁰ Harnessing β -H elimination for alkene difunctionalization strictly depends on the ability of TMs to undergo reversible β -H elimination/alkene hydrometalation.⁵² During hydrometalation, TMs could reside on geminal, allylic, or

remote carbons relative to the original position of alkenes, and generate products with two new bonds at 1,1-, 1,3-, or 1, n -positions (Scheme 16).²⁰ Among these possibilities, dicarbofunctionalization has been mostly observed for 1,1-^{13,53–55} along with limited examples for 1,3-^{43,56,57} and 1, n -positions.^{57–59}

In our efforts to expand the imine-assisted Ni-catalyzed alkene dicarbofunctionalization to γ,δ -alkenylketimines, we observed that a Heck product was consistently generated.⁵⁶ We reasoned that the fluxional six-membered nickelacycle 16 or 17 (Scheme 14) was unable to retain its integrity due to facile β -H elimination. Therefore, the resultant [Ni]–H species was incapable of performing hydronickellation on the alkene intermediate. Upon examining a series of phosphine ligands, we discovered, in 2018, that (PhO)₃P promoted hydronickellation of the resultant alkene intermediate, leading to the formation of γ,δ -diarylation products (Scheme 17).⁵⁶ (PhO)₃P stabilized a thermodynamically stable five-membered nickelacycle 24, generated during the reaction after ring contraction of the initial six-membered nickelacycle 22, via a sequential β -H elimination and alkene hydronickellation process (Scheme 18).

Deuterium labeling at the allylic position of the substrate and a crossover experiment with a putative Heck product indicated that contraction of the six-membered nickelacycle to a five-membered ring proceeded via β -H elimination and alkene hydronickellation and that the [Ni]–H species remained bound to the alkene intermediate during ring contraction (Scheme 19). Metallacycle contraction has been previously proposed for CO deinsertion⁶⁰ and propylene polymerization.⁶¹ Therefore, this unique process has the potential to be further developed to create new bonds at nonclassical alkene sites. Concurrent to our work, Zhao et al.⁴³ also observed a similar phenomenon during difunctionalization of *N*-allyl-2-aminopyrimidine with aryl iodides and arylboronic acids. Our reaction worked with a wide range of γ,δ -alkenylketimines in the presence of electron-deficient triarylphosphite and tris(pyrrolyl)phosphine ligands, and tolerated various functional groups.

Scheme 15. Imine-Assisted Nickel-Catalyzed γ,δ -Diarylation of γ,δ -Alkenylketones

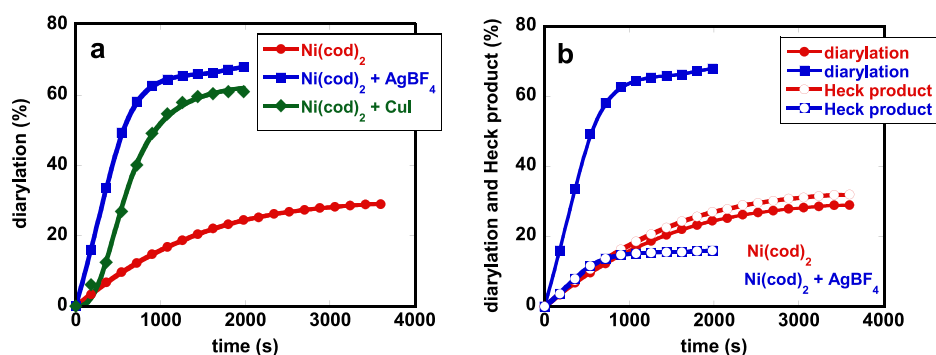
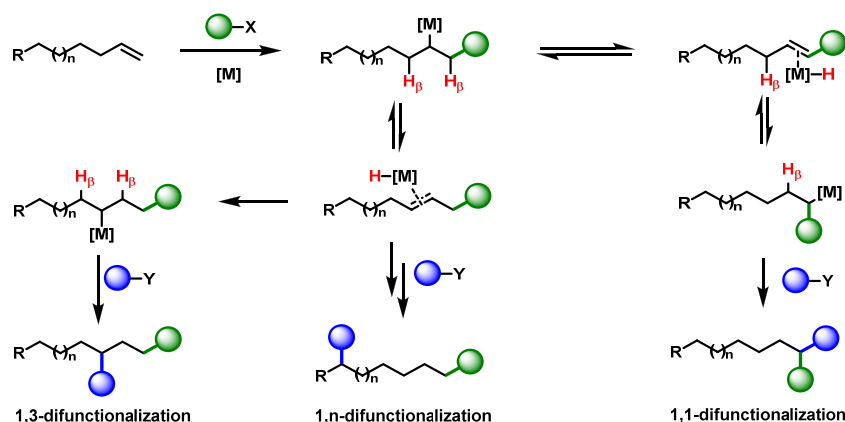
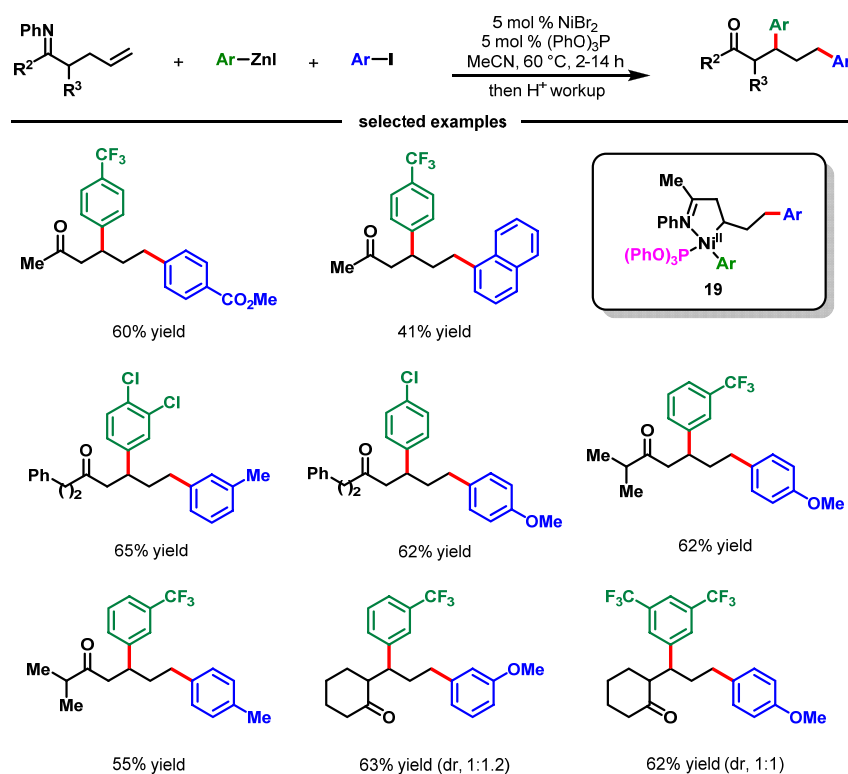


Figure 1. (a) Effects of AgBF₄ and CuI cocatalyst on alkene diarylation. (b) Effect of AgBF₄ on diarylation and the Heck product.

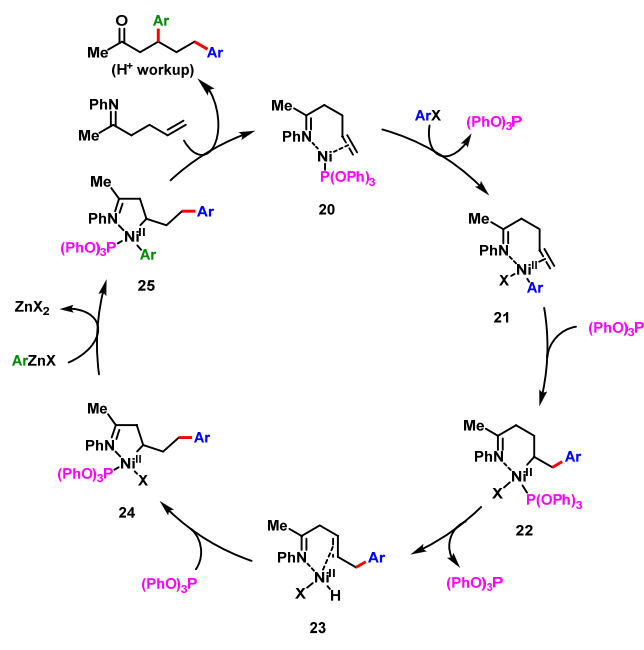
Scheme 16. 1,1-, 1,3-, or 1,*n*-Difunctionalizations via β -H Elimination/Hydrometallation



Scheme 17. Imine-Assisted Nickel-Catalyzed β,δ -Diarylation of γ,δ -Alkenylketones via the Contraction of Transient Nickellacycles



Scheme 18. Catalytic Cycle for Alkene Diarylation by the Nickellacycle Contraction Process



The discovery above indicated that strong coordinating groups, such as imine and pyrimidine, could be crucial to trigger ring contraction and stabilize five-membered nickellacycles. However, we hypothesized that metallacycle contraction could be more readily executed by weak coordination, in contrast to strong binding; since the fluxional six-membered metallacycle is more susceptible to undergo β -H elimination due to fast ligand dissociation. This possibility would open a completely new scope for metallacycle contraction because any simple functional group could participate in the process. On the basis of this idea, we disclosed a NiCl_2 -catalyzed β,δ -alkenylarylation of γ,δ -alkenyl- α -cyanocarboxylic esters with alkenyl triflates and arylzinc reagents (Scheme 20).⁵⁶ In this reaction, a simple cyanoester group promoted nickellacycle contraction and stabilized five-membered nickellacycles. Our reaction proceeded with terminal and internal alkenes and furnished complex aliphatic α -cyanoesters. The α -cyanoester products could be selectively hydrolyzed to access α -cyanocarboxylic acids, dicarboxylic acids, dicarboxylic acid monoamides, monocarbox-

ylic acids, nitriles, and spirolactones, further attesting to the reaction's wide synthetic applicability (Scheme 21).

The reaction was unique because the products were formed with regioreversal for the addition of alkenyl triflates and arylzinc reagents. Therefore, this reaction was transmetalation-initiated, contrary to oxidative addition-initiated, which is the most common reaction initiation pathway. On the basis of the product regiochemistry, and additional control, deuterium-labeling, and crossover experiments, we proposed that the reaction proceeds via a Ni(I)-catalyzed metallacycle contraction process (Scheme 22). This catalytic cycle ensues with a combination of cationic, neutral, and anionic speciation and with a high fidelity of the alkene intermediate binding to the $[\text{Ni}]$ -H species during ring contraction. The requirement for a weak organic base (4-PhPy) and a cationizing agent (KPF_6) supports a possible reversible step to generate a cationic Ni(I) species 28 to initiate transmetalation with an arylzinc reagent, and further stabilize the β -H- $\text{C}(\text{sp}^3)$ - $[\text{Ni}]$ intermediate 32 as an enolate-bound metallacycle.

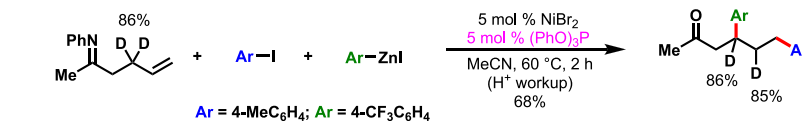
2.3. Electronically-Controlled Vicinal Dicarbofunctionalization

Three-component alkene dicarbofunctionalization without heteroatom coordination suffers seriously from the β -H elimination issue. When alkenyl-OTf is used, the resultant β -H elimination products proceed with hydrometallation to generate π -allylpalladium(II) intermediates and eventually furnish 1,1-difunctionalized products.¹³ Since Takai's Cr-mediated work in 1998,⁶² stabilization of alkylmetal species as π -allylmetal intermediates has served as fodder for developing vicinal dicarbofunctionalization in conjugated dienes.^{11–13} An analogous reaction scenario can be anticipated with alkenylarenes, in which the electronically polarized alkene can enhance reactivity and regiocontrol, and the native arene can stabilize the resultant migratory insertion intermediate as a π -benzylmetal species.^{63,64} Consequently, alkenylarenes have always been at the forefront for alkene dicarbofunctionalization since Kambe's Cp_2TiCl_2 -catalyzed dialkylation in 1998;⁶⁴ although, the general scope has so far been surprisingly limited.

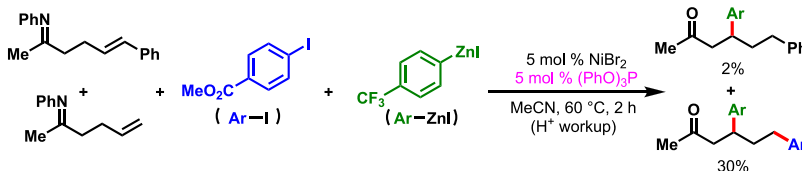
In 2018, our laboratory developed a Ni-catalyzed three-component alkylarylation of alkenylarenes with alkyl halides and arylzinc reagents, which generated 1,1-diaryllalkane products (Scheme 23).² The reaction was achieved via the formation of two $\text{C}(\text{sp}^3)$ - $\text{C}(\text{sp}^3)$ and $\text{C}(\text{sp}^3)$ - $\text{C}(\text{sp}^2)$ bonds. Concurrently, a similar Ni-catalyzed diarylation of alkenylarenes with aryl halides and arylboronic esters was disclosed by Brown et al.,⁶⁵

Scheme 19. Deuterium Labeling and Crossover Experiments

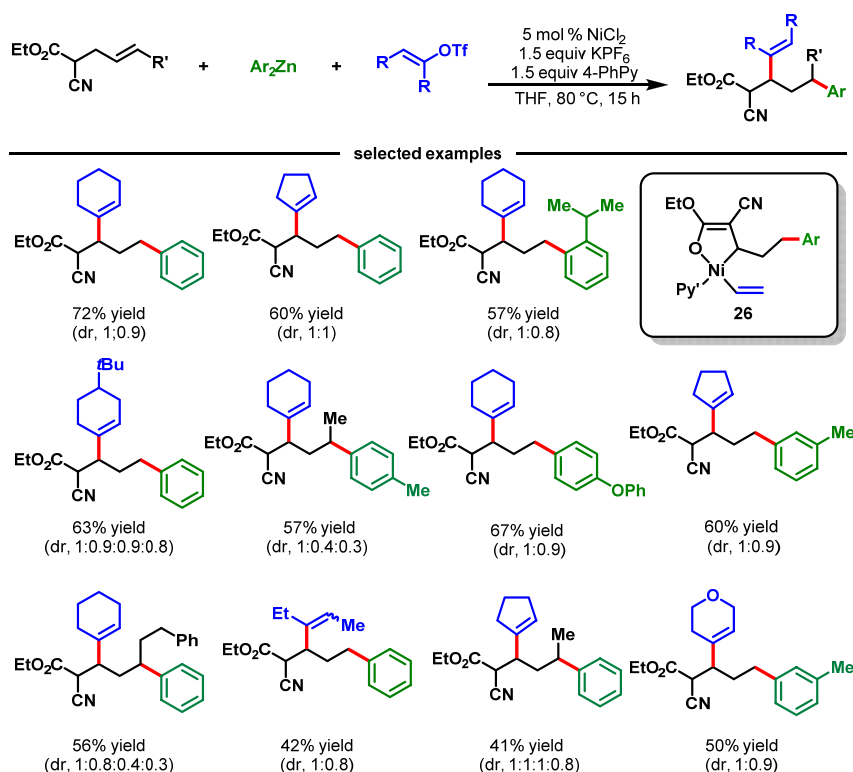
a) Deuterium-Labeling Experiment



b) Crossover Experiment



Scheme 20. Carbonyl-Assisted Nickel-Catalyzed β,δ -Alkenylarylation of γ,δ -Alkenyl- α -cyanoesters via the Contraction of Transient Nickellacycles



which created two $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^2)$ bonds. Our reaction tolerated various functional groups on alkenylarenes, alkyl halides, and arylzinc reagents. The reaction could be conducted with primary, secondary, and even tertiary alkyl halides. The coupling of primary and secondary alkyl halides was performed with NiBr_2 as a catalyst, while that of tertiary alkyl halides required $(\text{Ph}_3\text{P})_2\text{NiCl}_2$.

Real-time monitoring of the reaction between 4-fluorophenylzinc bromide and $\text{NiBr}_2\cdot\text{DME}$ by ^{19}F NMR suggested that $\text{Ni}(\text{II})$ was reduced in situ to $\text{Ni}(\text{0})$ and that the latter was the catalytically active species. We also performed competition studies between primary, secondary, and tertiary alkyl bromides ($3^\circ > 2^\circ > 1^\circ$) and between alkyl iodide, bromide, and chloride ($\text{I} > \text{Br} > \text{Cl}$) (Scheme 24). The outcomes indicated that the reaction was initiated by a rate-limiting halogen-atom abstraction via inner-sphere SET from $\text{Ni}(\text{0})$ to alkyl halides. The presence of carbon-centered radicals (**34** and **35**) was also supported by a radical clock experiment and the isolation of a dimeric product **37** from a catalytic reaction. The rate-limiting alkyl halide activation was also supported by a competition study between electronically biased arylzinc reagents that showed no product selectivity, and our further quantitative kinetic studies examining rate dependence and reaction order. Overall, the complete catalytic cycle involved $\text{Ni}(\text{0})$, $\text{Ni}(\text{I})$, and $\text{Ni}(\text{II})$ speciation (Scheme 25) and proceeded via a rate-limiting halogen-atom abstraction by inner-sphere SET, followed by carbon-centered radical addition to alkene, recombination of benzylic radical with $\text{Ni}(\text{I})$, transmetalation, and, finally, reductive elimination.

In 2020, we reported that alkyl halides could be replaced with α -halocarbonyl compounds as $\text{C}(\text{sp}^3)$ sources to difunctionalize alkenylarenes to access γ,δ -diarylcarbonyl compounds (Scheme

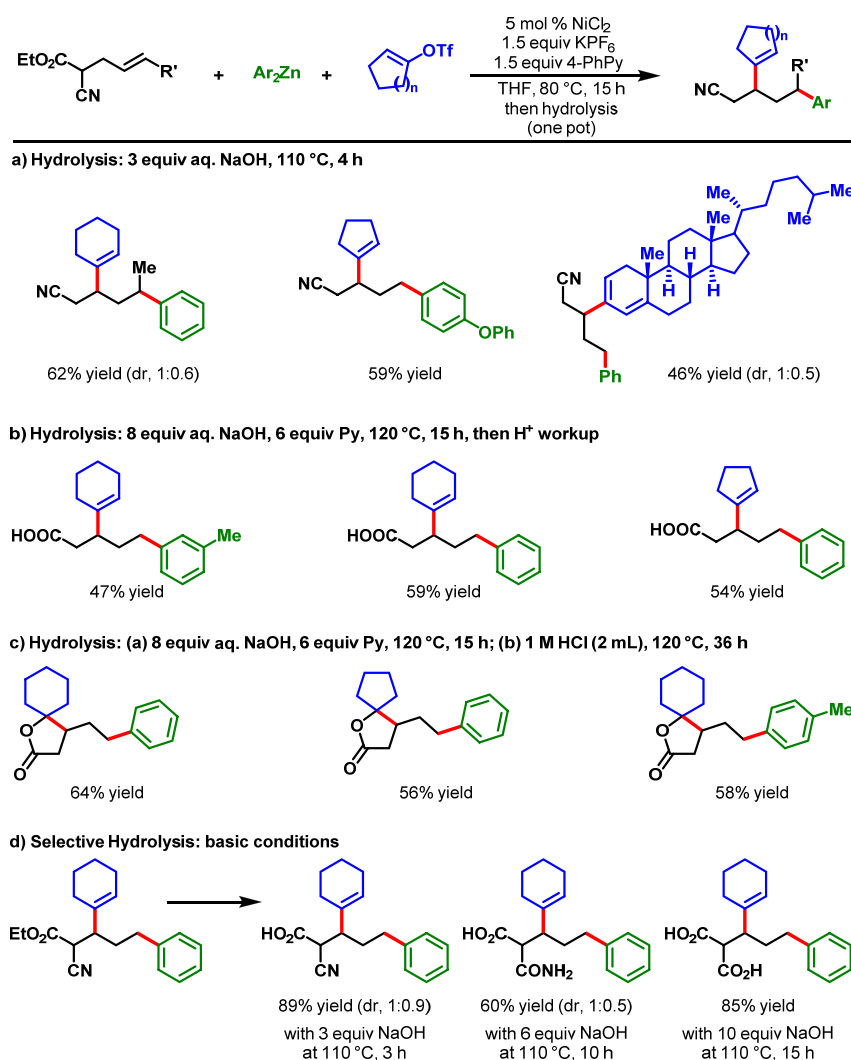
26).⁶⁶ Although this reaction could be conducted under otherwise identical conditions developed for alkylarylation using NiBr_2 as the catalyst, $\text{Ni}(\text{cod})_2$ proved to be more competent, furnishing products in higher yields. Examination of the reaction scope revealed that variously substituted alkenylarenes could be difunctionalized with primary, secondary, and tertiary α -halocarboxylic esters, and electronically varied aryl/heteroarylzinc reagents. α -Halolactones and α -haloketones also participated in the reaction, although the scope was somewhat limited.

The reaction also tolerated internal alkenes, which were difunctionalized with absolute regioselectivity and good diastereoselectivity. Cyclic internal alkenes, such as indenones, proceeded with high diastereoselectivity ($>10:1$) affording trans-stereoisomers as the major products. Preliminary mechanistic studies with a radical clock and TEMPO, as a radical trap, indicated that the reaction generated a stable α -carbon radical. This radical could be intercepted with TEMPO and electronically polarized intermolecular alkenes in alkenylarenes but was unable to undergo radical cyclization onto an electronically unbiased tethered alkene. On the basis of these studies, we presume that the catalytic cycle is analogous to that for alkylarylation described in Scheme 25.

3. TWO-COMPONENT ALKENE DICARBOFUNCTIONALIZATION

Two-component alkene dicarbofunctionalization reactions are conducted through cyclization/coupling in which an alkene is tethered to an organic electrophile or nucleophile. In these reactions, the alkylmetal species generated upon cyclization is intercepted by a second carbon source; creating five- and six-membered carbo- and heterocycles. Cyclization/coupling is

Scheme 21. Rapid Access to Synthetically Appealing Precursors



entropically favored for migratory insertion, which, along with intramolecular alkene activation, helps to overcome cross-coupling.

Pd-catalyzed cyclization/coupling is the most studied alkene dicarbofunctionalization reaction. However, β -H elimination still dominates the outcome of these reactions. Consequently, the reactions were compelled to employ disubstituted terminal alkenes,^{14,15} which generated $\text{C}(\text{sp}^3)\text{-Pd}(\text{II})$ intermediates lacking β -H's. Tour and Negishi⁶⁷ and Suzuki et al.²⁸ independently demonstrated that the use of alkenes predestined for β -H elimination was also possible for cyclization/coupling. Recently, Alexanian et al. observed analogous reactivity with a $\text{Mn}_2(\text{CO})_{10}$ catalyst.²⁹ However, such reactions required a combination of photolytic conditions amenable to the formation of carbon-centered radicals and capture by CO. Last year, Glorius et al. disclosed that a photoexcited Pd catalyst could also accomplish cyclization/coupling reactions of alkenes prone to cause β -H elimination via carbon-centered radicals.²⁷

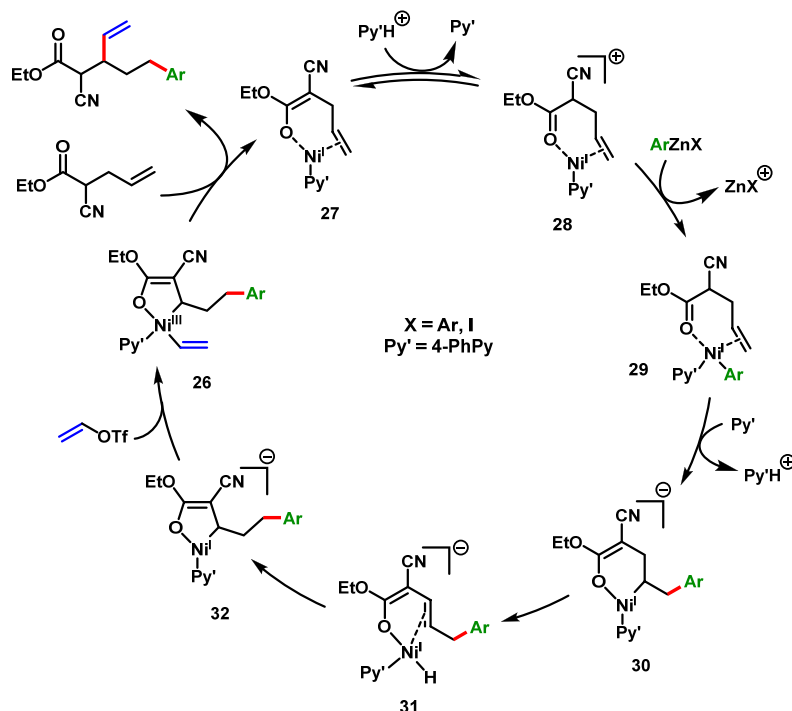
In 2017, we attempted Pd-catalyzed cyclization/coupling of alkenyl carboxamides with intramolecular enolates as nucleophiles (Scheme 27).⁶⁸ To our surprise, our studies showed that $\text{Pd}(\text{dba})_2$ could catalyze such reactions to generate 1,3,4-trisubstituted pyrrolidinones, products that could arise from the

interception of $\beta\text{-H-C}(\text{sp}^3)\text{-Pd}(\text{II})$ species with ArI. In 1987, Balme et al. also developed a similar Pd-catalyzed cyclization/coupling of alkenyl dicarbonyl compounds bearing an enolizable α -hydrogen (DMSO, $\text{p}K_a \sim 13$).⁶⁹ Our reaction could employ alkenyl carboxamides bearing an enolizable α -hydrogen with a much higher $\text{p}K_a$ (DMSO, ~ 27), and various electronically modified ArI's. Recently, Newhouse et al. also disclosed a similar cyclization/coupling of alkenyl carbonyl compounds with aryl electrophiles using a Ni catalyst.⁷⁰ Likewise, Wolfe et al. reported a (BrettPhos)Pd-catalyzed cyclization/coupling of alkene-tethered ArX and alkenyl-OTf in which malonates functioned as nucleophiles.⁷¹

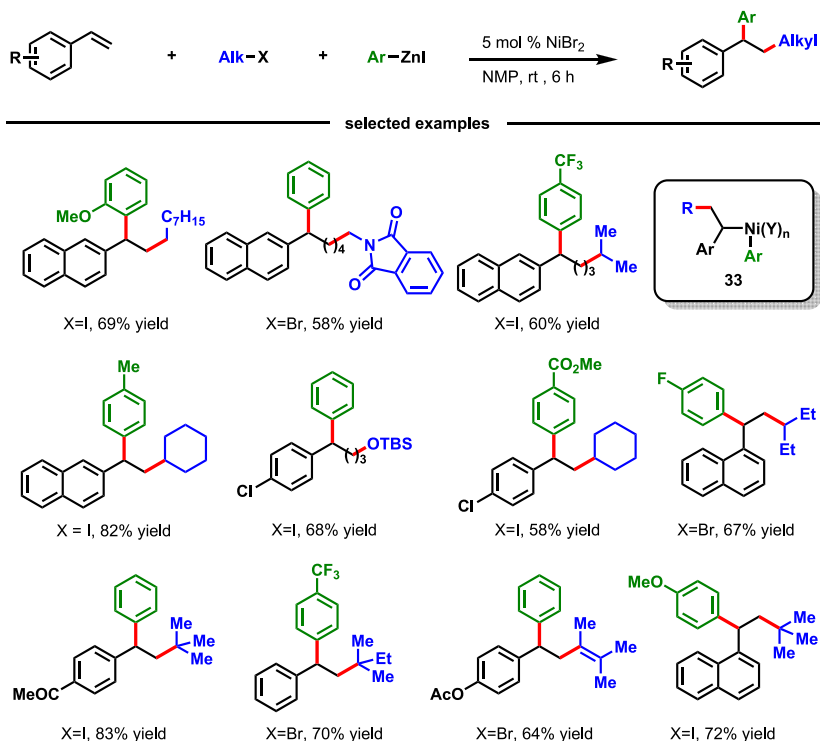
Puzzled by the observation of zero to minute amounts of Heck products, we monitored the progress of the reaction over time (Scheme 28). The experiment immediately revealed that $\beta\text{-H-C}(\text{sp}^3)\text{-Pd}(\text{II})$ intermediates, generated upon migratory insertion of alkenes to $\text{ArPd}(\text{II})$, indeed underwent β -H elimination to form Heck products as reaction intermediates. In the presence of K_3PO_4 , the styryl group in the Heck product **40** would undergo in situ base-promoted conjugate addition with the internal enolate to furnish final products.

Reports of catalytic reactions⁷ have shown that $\beta\text{-H-C}(\text{sp}^3)\text{-[M]}$ intermediates of first row late TMs are slower to undergo β -

Scheme 22. Catalytic Cycle for Alkene Alkenylarylation by the Nickellacycle Contraction Process



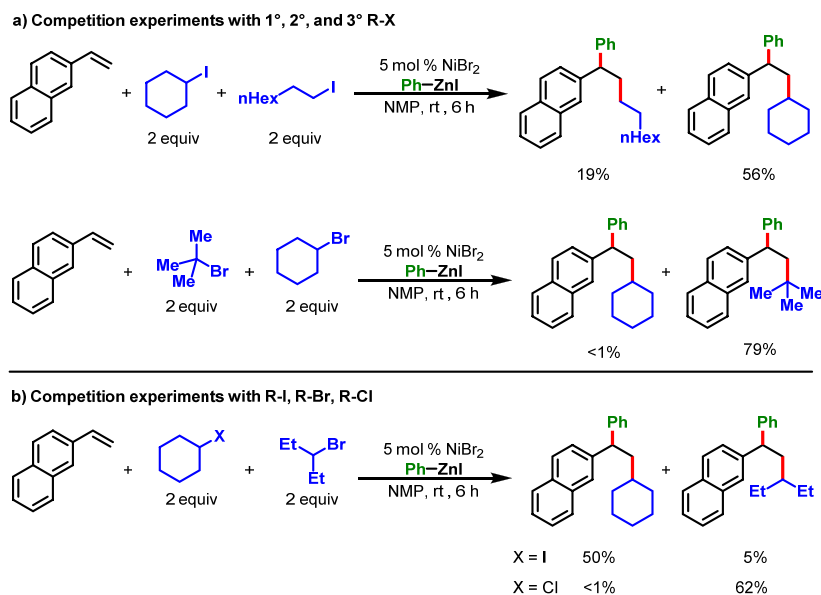
Scheme 23. Nickel-Catalyzed Alkylarylation of 2-Alkenylarenes



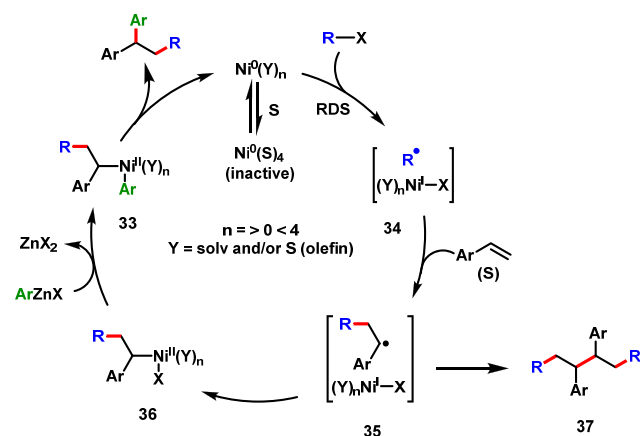
H elimination than $\beta\text{-H-C}(\text{sp}^3)\text{-Pd}(\text{II})$ species. In 1994, Delgado et al. demonstrated that a stoichiometric amount of $\text{Ni}(\text{cod})_2$ could catalyze cyclization/coupling of alkene-tethered vinyl bromides amenable to generate $\beta\text{-H-C}(\text{sp}^3)\text{-[Ni]}$ intermediates.⁷² Although, their stabilization was attributed to intramolecular nitrogen coordination. In 2001, Oshima et al. demonstrated that $(\text{dppe})\text{CoCl}_2$ was an effective catalyst to perform cyclization/coupling of alkene-tethered alkyl halides

with ArMgX .⁷³ In 2007, Cárdenas et al. disclosed that $(\text{pybox})\text{NiCl}_2$ could overcome even more challenging cyclization/coupling of alkene-tethered alkyl halides with alkylzinc reagents.⁷⁴ The overall observation of successful examples unequivocally substantiates the notion that the first row TMs are great catalysts for alkene dicarbofunctionalization involving $\beta\text{-H-C}(\text{sp}^3)\text{-[M]}$ intermediates.

Scheme 24. Competition Experiments



Scheme 25. Catalytic Cycle for Nickel-Catalyzed Alkene Alkylarylation



In 2017, we demonstrated that Cu(I) salts could catalyze cyclization/coupling of alkene-tethered organozinc reagents with aryl/heteroaryl iodides (Scheme 29).⁴ The reaction furnished a wide range of complex carbocyclic and N,O-heterocyclic products containing cyclopentyl, pyrrolidinyl, furanyl, dihydrofuranyl, indanyl, and indolinyl cores in excellent diastereoselectivity. Prior to our work, Cong and Fu⁷⁵ and You and Brown,⁷⁶ in 2014, also disclosed similar cyclization/coupling of alkenyl-aryl-9-BBN.

Analysis of the products generated and the stereoselectivity observed during organozinc synthesis, under radical conditions, highlighted different scenarios for cyclization of alkenes tethered to alkyl and arylzinc reagents. In alkenylalkylzinc reagents, the radical cyclization ensued in situ during alkylzinc preparation, and the resultant cyclized alkylzinc species underwent transmetalation with Cu(I) during the catalytic reaction to generate $\beta\text{-H-C}(\text{sp}^3)\text{-[Cu]}$ intermediates (Scheme 30). In contrast, alkenylarylzinc reagents remained mostly intact during arylzinc synthesis and participated in radical cyclization during the Cu-catalyzed reaction (Scheme 31). This resulted in the formation

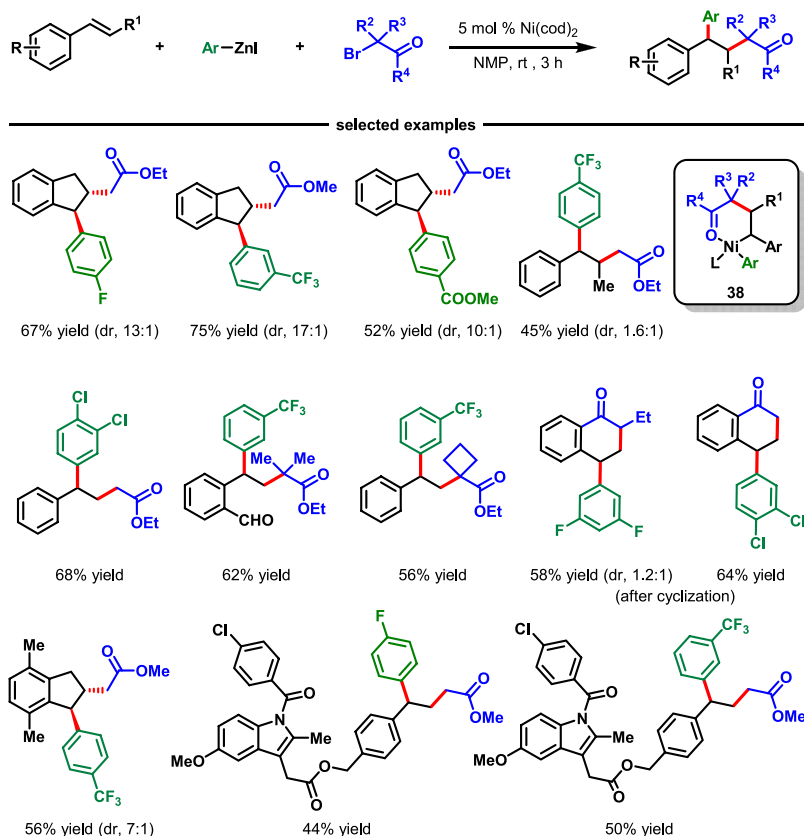
of $\beta\text{-H-C}(\text{sp}^3)\text{-[Cu]}$ intermediates for subsequent reaction with aryl halides.

The Cu-catalyzed reaction illustrated the synthetic aptitude of cyclization/coupling to generate rapidly complex carbo- and heterocycles. The reaction was also amenable for cyclization/coupling with heterocyclic arenes. However, the reaction scope remained largely limited to electron-deficient and heteroaryl iodides. In order to surmount this shortcoming, we switched the tethering of alkenes from alkylzinc reagents to alkyl halides and developed a NiBr_2 -catalyzed cyclization/coupling in which arylzinc reagents supplied the arene component (Scheme 32).⁷⁷ The reaction required terpyridine as a ligand. The (terpy)Ni-catalyzed cyclization/coupling proceeded in high diastereoselectivity and tolerated a number of sensitive functional groups and molecules with racemizable stereocenters. One of the appealing outcomes of the Ni-catalyzed reaction, that is complementary to the Cu-catalyzed process, is the access to (arylmethyl)carbo- and heterocyclic scaffolds containing electron-rich arenes, structural cores that are ubiquitous in various lignan natural products.⁷⁸ The reaction proceeded via a SET process involving carbon centered radicals for cyclization (Scheme 33).²¹

4. APPLICATIONS

The robustness of a chemical method is measured against its potential in the synthesis of complex natural products and bioactive molecules.⁷⁹ Since the development of metal-catalyzed alkene dicarbofunctionalization reactions has been relatively dormant for almost four decades, their vetting against long-established synthetic protocols has not been thoroughly investigated. Yet, the potential of alkene dicarbofunctionalization through cyclization/coupling was realized early on in the rapid synthesis of complex natural products. In 1994, Balme and Bouyssi described the total synthesis of a sesquiterpene, $(\pm)\text{-D}^{9(12)}$ capnellene,⁸⁰ through cyclization/coupling of α -allyl-dicarboxylic esters with organic halides.⁶⁹

In 2018, we scrutinized our Ni-catalyzed cyclization/coupling for the concise synthesis of six lignan natural products with three different structural frameworks.⁷⁷ In 2014, Cong and Fu also synthesized a dihydrobenzofuran core of fasiglifam via a Ni-

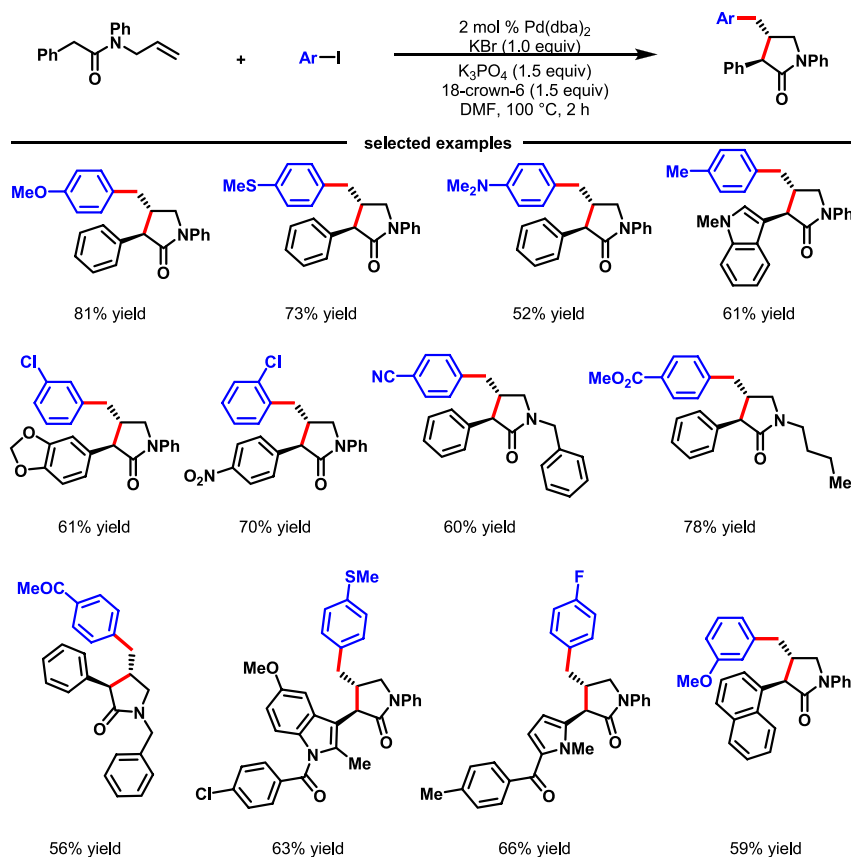
Scheme 26. Nickel-Catalyzed α -Carbonylalkylarylation of 2-Alkenylarenes

catalyzed cyclization/coupling of alkenylaryl-9-BBN.⁷⁵ Recently, Diao et al. utilized Ni-catalyzed reductive cyclization/coupling to prepare a key intermediate toward the synthesis of an epoxide hydrolase inhibitor.²⁶ Our target lignan natural products contain a di(arylmethyl)butyrolactone core and display a wide range of biological activity.⁷⁸ We accessed the 3-arylmethylbutyrolactone intermediates (**63** and **64**) required for ($\pm$)-kusunokinin (**65**), ($\pm$)-dimethylmatairesinol (**66**), ($\pm$)-burshehnerin (**67**), and ($\pm$)-yatein (**68**), through cyclization/coupling of 1-(1-(allyloxy)-2-iodoethoxy)butane (**62**) with corresponding arylzinc reagents, followed by the Jones oxidation (Scheme 34). The butyrolactone derivatives could be generated in a one-pot, two-step process in gram-scale quantities. These butyrolactone intermediates were subsequently converted to the natural products upon reaction with corresponding benzyl bromides.

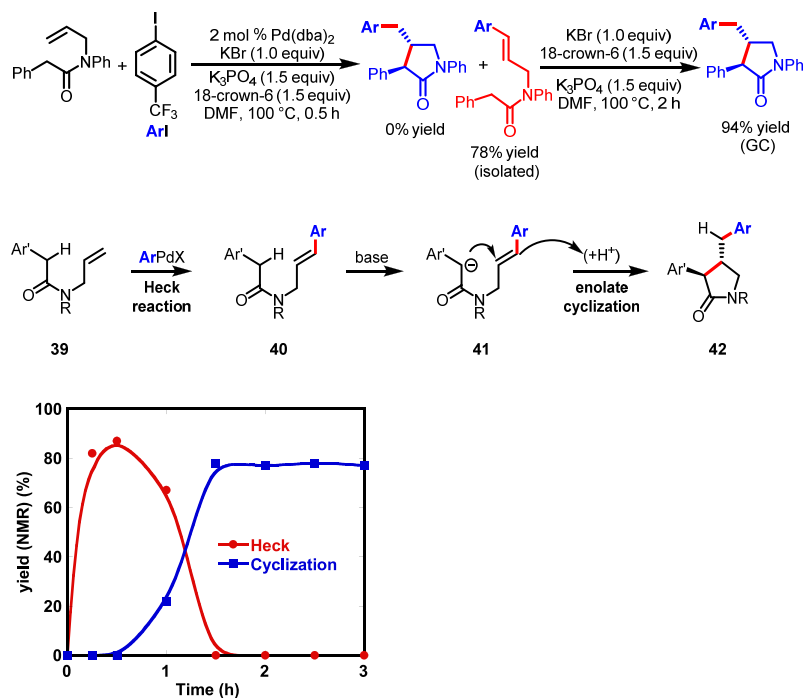
The 3-arylmethylbutyrolactone derivatives also serve as intermediates for more complex lignan natural products, including ($\pm$)-dimethylretrodendrin (**69**) and ($\pm$)-collinusin (**73**). For example, 3-(3,4-dimethoxybenzyl)butyrolactone **63** could be condensed with 3,4-dimethoxybenzaldehyde followed by Friedel–Crafts cyclization to synthesize ($\pm$)-dimethylretrodendrin (**69**) in high yield and excellent diastereoselectivity (Scheme 34). The carbonylbutyrolactone **72** necessary for the synthesis of ($\pm$)-collinusin (**73**) was also accessed in a concise manner following the same one-pot, two-step process beginning with a (2-aryloxy)aryl zinc reagent **71** (Scheme 35). Through this synthesis, we demonstrated the astonishing efficiency and practicality of our new method, as the synthesis of similar lignan products required several steps to construct the dihydronaphthofuranone core.⁷⁸

The application of three-component alkene dicarbonylation in the synthesis of natural products/bioactive molecules remains extremely scarce. We recently applied our Ni-catalyzed alkylarylation of alkenylarenes to synthesize a potential 5-lipoxygenase activating protein (FLAP) inhibitor **75** along with a few of its analogs (Scheme 36) and a regioisomer (Scheme 37).⁸¹ The bioactive compound is constructed on a 1,1-diaryllalkane framework, which has broadly shown bioactivity against FLAP, lung cancer, breast cancer, and brain cancer.^{82–84} In particular, in 2012, the Merck Research Laboratory reported the FLAP inhibitory activity of compound **75**, which they synthesized in 12 steps.⁸² In contrast, we were able to successfully synthesize the same potential FLAP inhibitor **75** in just five steps by using our Ni-catalyzed alkylarylation reaction. Concomitantly, Brown et al. also synthesized *rac*-lasofoxifene through a Ni-catalyzed alkenylarene diarylation reaction.⁶⁵

The required alkenylarene **74** was conveniently synthesized through four steps from commercially available 2-bromo-4-nitrobenzoic acid methyl ester. The alkenylarene **74** was subjected to Ni-catalyzed alkylarylation with *t*BuI and PhZnI to yield the potential FLAP inhibitor **75** in 65% yield. Since our Ni-catalyzed alkylarylation was used at the last step in the synthetic sequence, we were also able to synthesize additional analogs of the potential FLAP inhibitor (**76–79**) with the same alkenylarene intermediate **74**. A transposition of the *O*-quinolinyl group on the central arene also enabled us to synthesize the FLAP inhibitor's regioisomer **81** in just four steps from the commercially available 2-bromo-5-methoxybenzoic acid methyl ester (Scheme 37). Similarly, we applied our Ni-catalyzed regioselective α -carbonylalkylarylation reaction to the

Scheme 27. Palladium-Catalyzed Cyclization/Coupling of *N*-Allylcarboxamides

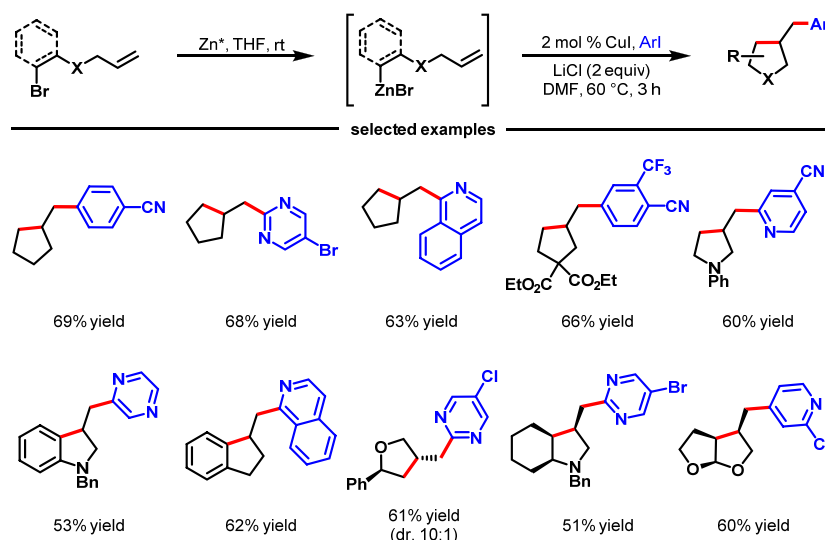
Scheme 28. Reaction Kinetic Profile and Mechanism



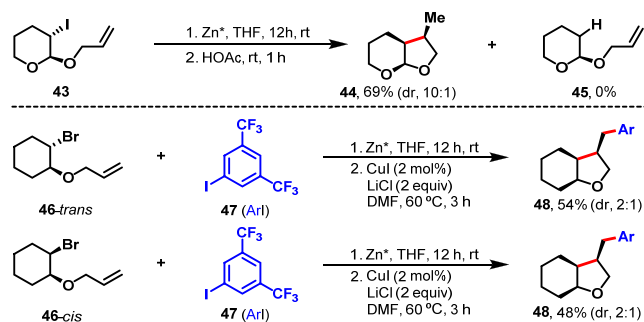
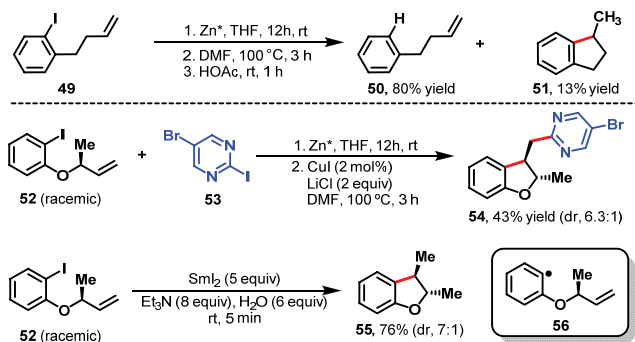
rapid synthesis of different aryltetralone derivatives.⁶⁶ This ability enabled us to synthesize dichlorophenyltetralone **82**, a known synthetic precursor to a commercial antidepressant drug, sertraline-HCl (Zoloft) **83** (Scheme 38).⁸⁵

In another synthetic application, we applied our $\text{Ni}(\text{cod})_2$ -catalyzed diarylation of 2-alkenylbenzaldehydes with aryl halides and arylzinc reagents to synthesize 9-arylmethylantracene derivatives (Scheme 39).⁸⁶ We found that the *o*-aldimine group

Scheme 29. Copper-Catalyzed Cyclization/Coupling of Alkenyl Organozinc Reagents



Scheme 30. Radical Cyclization during the Preparation of Alkenyl Alkylzinc Reagents

Scheme 31. Radical Cyclization during CuI- and SmI₂-Catalyzed Reactions

was a synthetic bonus in this reaction, since it could be condensed with the proximal arene by acid-catalyzed in situ deaminative aromatization to generate functionalized anthracenes. This method illustrated a new three-component approach to synthesize 9-arylmethylanthracene derivatives.

5. CONCLUSION AND OUTLOOK

As described in this Account, alkene dicarbofunctionalization with organic halides and organometallic reagents is emerging as a formidable method to construct complex molecules rapidly

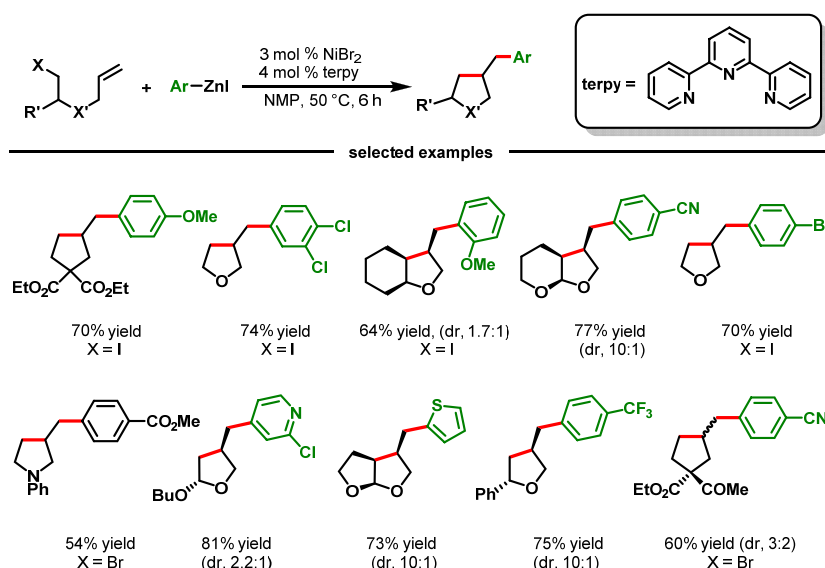
from readily available chemicals. Early discoveries were limited, as the methods relied on bicyclic and disubstituted terminal alkenes to circumvent the β -H elimination issue from the inevitable $C(sp^3)-[M]$ intermediates generated during the reaction. Recent studies have shown that alkenes that generate $C(sp^3)-[M]$ intermediates bearing β -H's can now be difunctionalized without suffering from β -H elimination. The immense success and the current rise in alkene dicarbofunctionalization lends credit to the fundamental understanding of the nature of β -H- $C(sp^3)-[M]$ intermediates and their susceptibility toward β -H elimination. In particular, studies have shown that β -H- $C(sp^3)-[M]$ species of first row late metals are more resistant to β -H elimination than those of Pd and that these species can be intercepted as coordination-assisted transient metallacycles to bestow further stability to them. These two factors, collectively or individually, have contributed to the tremendous success of alkene dicarbofunctionalization through both entropically driven cyclization/coupling and more intractable three-component reactions in some of the most common organic molecules, including, aryl and alkyl halides, organometallics, aromatics, and carbonyl compounds. However, general chemical space is yet to be fully revealed, and a number of challenges, including an expanding scope to simple alkenes without coordinating groups, solving regioselectivity issues, and developing enantioselective variations, are still to be met. New catalytic systems and ligand discoveries will likely address these challenges in the future. In addition, the rapid rise in the method development has not parlayed into the synthetic output of complex natural products and bioactive molecules, which could serve as a touchstone for the method's promise. Some optimism is on the horizon with the synthesis of a few natural products, pharmaceuticals, and bioactive molecules, from us and others. We anticipate that this field will soon grow exponentially and live up to synthetic chemists' expectations to assemble complex molecules expeditiously.

AUTHOR INFORMATION

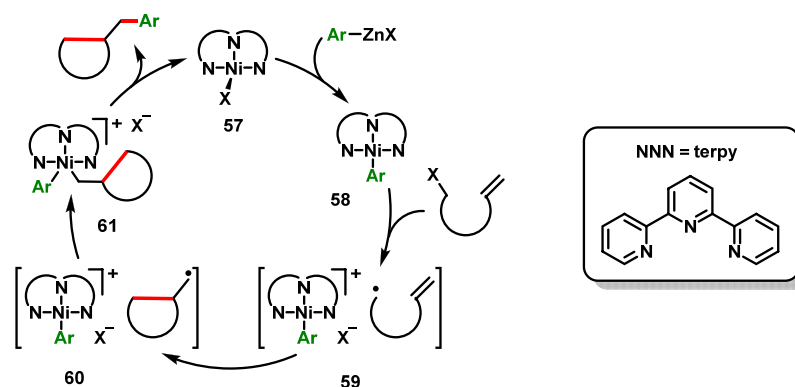
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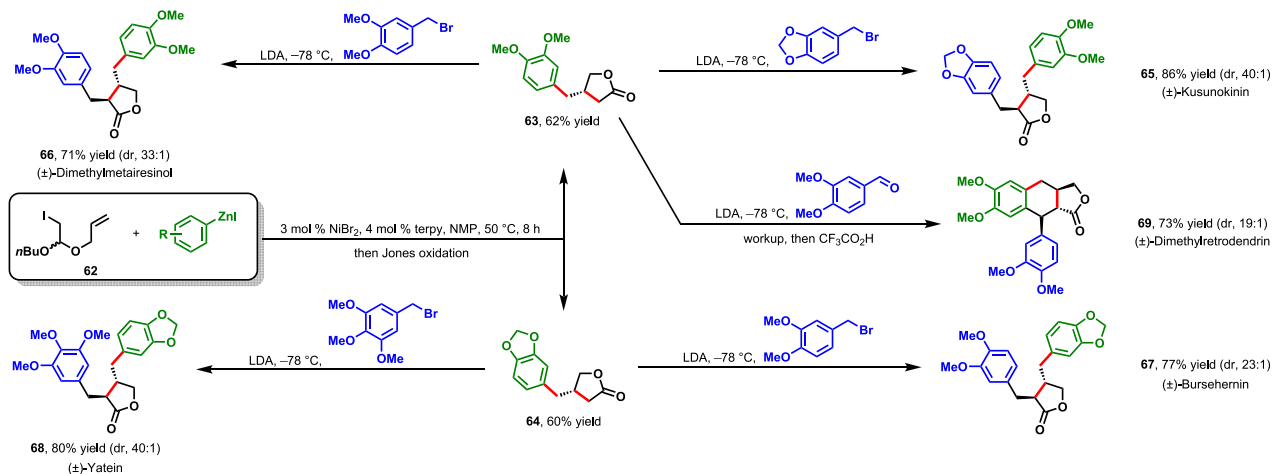
Scheme 32. (Terpy)Ni-Catalyzed Cyclization/Coupling of Alkenyl Alkyl Halides



Scheme 33. Catalytic Cycle for the (terpy)Ni-Catalyzed Cyclization/Coupling Reaction



Scheme 34. Concise Synthesis of (±)-Kusunokinin, (±)-Dimethylmatairesinol, (±)-Bursehernin, (±)-Dimethylretrodendrin, and (±)-Yatein via Nickel-Catalyzed Cyclization/Coupling

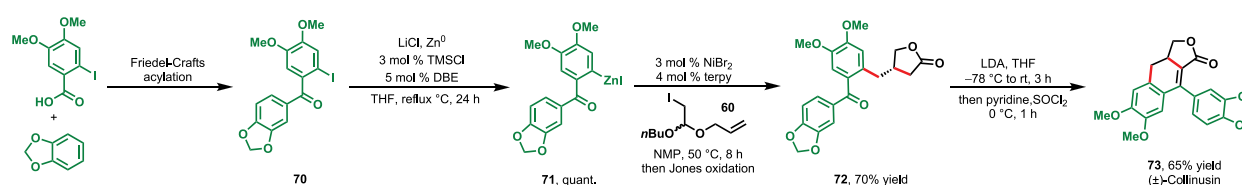


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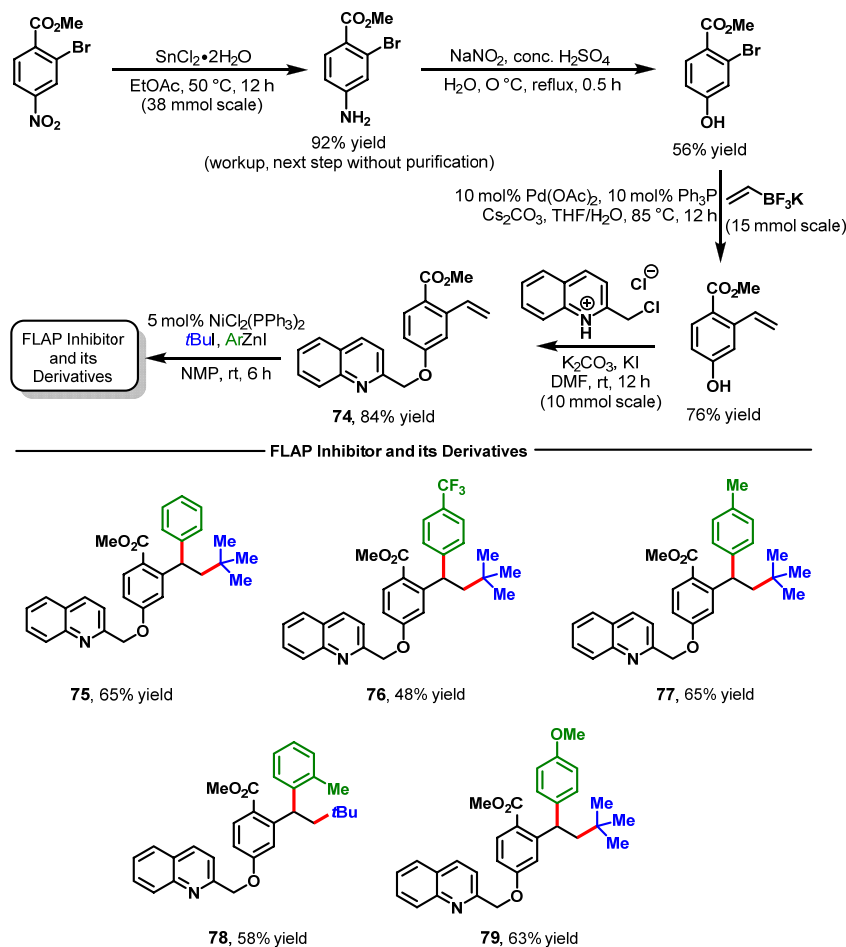
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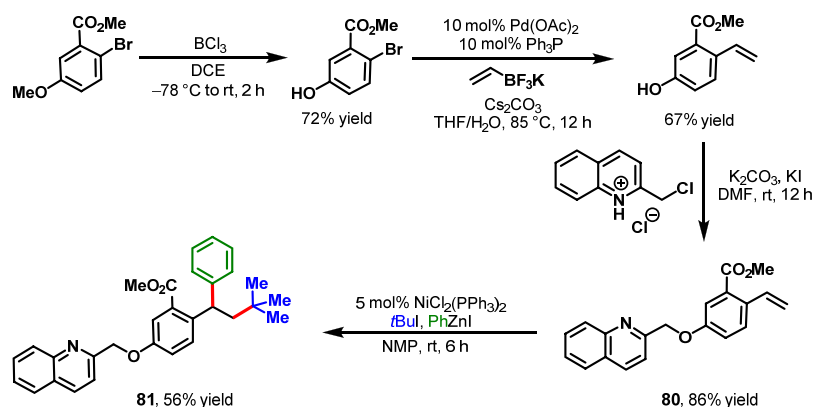
Scheme 35. Concise Synthesis of (±)-Collinsin via Nickel-Catalyzed Cyclization/Coupling



Scheme 36. Synthesis of a Potential FLAP Inhibitor and Its Derivatives via Nickel-Catalyzed Alkene Alkylarylation

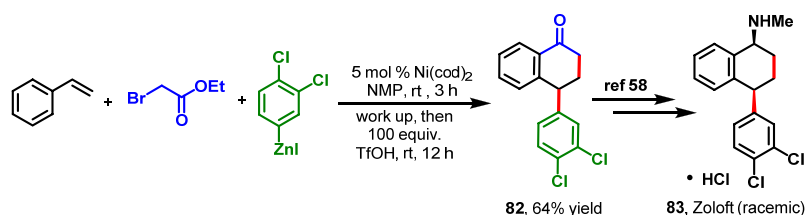


Scheme 37. Synthesis of a Regioisomer of the Potential FLAP Inhibitor via Nickel-Catalyzed Alkene Alkylarylation

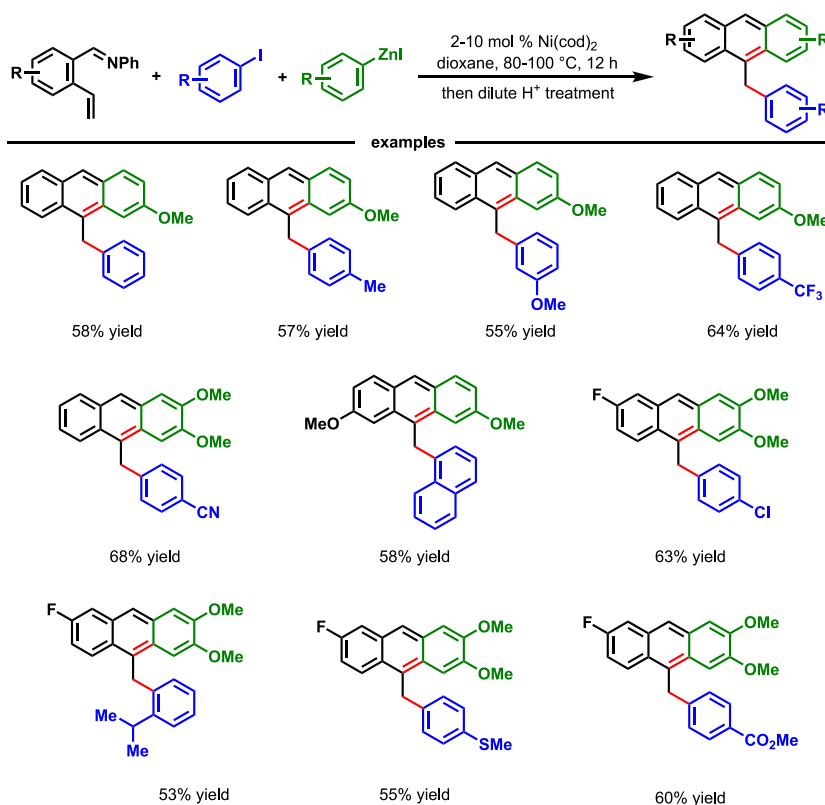


Complete contact information is available at:

<https://pubs.acs.org/10.1021/acs.accounts.1c00329>

Scheme 38. Synthesis of Zoloft Precursor via Nickel-Catalyzed Alkene α -Carbonylalkylation

Scheme 39. Synthesis of 9-Arylmethylantracene Derivatives via a Nickel-Catalyzed Three-Component Alkene Diarylation Reaction



Notes

The authors declare no competing financial interest.

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