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Nickel-Catalyzed Reductive Alkenylation of Enol Derivatives: A Versatile Tool for Alkene Construction

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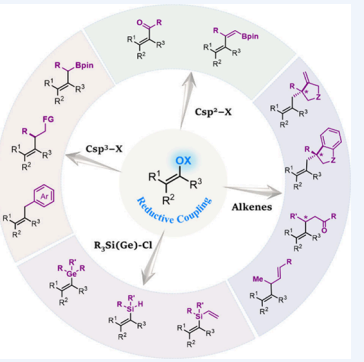
CONSPECTUS: Ketone-to-alkene transformations are essential in organic synthesis, and transition-metal-catalyzed cross-coupling reactions involving enol derivatives have become powerful tools to achieve this goal. While substantial progress has been made in nucleophile−electrophile reactions, recent developments in nickel-catalyzed reductive alkenylation reactions have garnered increasing attention. These methods accommodate a broad range of functional groups such as aldehyde, ketone, amide, alcohol, alkyne, heterocycles, and organotin compounds, providing an efficient strategy to access structurally diverse alkenes. This Account primarily highlights the contributions from our laboratory to this growing field while also acknowledging key contributions from other researchers.



Our early efforts in this area focused on coupling radical-active substrates, such as α-chloroboronates. This method follows the conventional radical chain mechanism, resulting in facile access to valuable allylboronates. Encouraged by these promising results, we subsequently expanded the substrate scope to encompass radical-inactive compounds. By developing new strategies for controlling cross-selectivity, we enabled the coupling of Csp^3 electrophiles (e.g., alcohols and sulfonates), Csp^2 electrophiles (e.g., bromoalkenylboronates and acyl fluorides), and heavier group-14 electrophiles like chlorosilanes and chlorogermanes with alkenyl triflates. These advances have provided efficient synthetic routes to a wide range of valuable products, including aliphatic alkenes, enones, dienylboronates, and silicon- and germanium-containing alkenes. Notably, these methods are particularly effective for synthesizing functionalized cycloalkenes, which are traditionally challenging to obtain through conventional methods involving alkenyl halide or organometallic couplings. We have also extended the scope of enol derivatives from triflates to acetates. These compounds are among the most accessible, stable, cost-effective, and environmentally friendly reagents, while their application in cross-coupling has been hampered by low reactivity and selectivity challenges. We showcased that by the use of a Ni(I) catalyst, alkenyl acetates could undergo reductive alkylation with a broad range of alkyl bromides, yielding diverse cyclic and acyclic aliphatic alkenes.

Furthermore, our work has demonstrated that reductive coupling of enol derivatives with alkenes provides a highly appealing alternative for alkene synthesis. Particularly, this approach offers opportunity to address the regioselectivity challenges encountered in conventional alkene transformations. For instance, achieving regioselective hydrocarbonation of aliphatic 1,3-dienes has been a longstanding challenge in synthetic chemistry. By using a phosphine−nitrile ligand, we developed a nickel-catalyzed reductive alkenylation of 1,3-dienes with alkenyl triflates, delivering a diverse array of 1,4-dienes with high 1,2-branch selectivity (>20:1) while preserving the geometry of the C_3-C_4 double bond. Additionally, our investigations laid the foundation for enantioselective reductive alkenylation methodologies, offering new pathways for constructing enantioenriched diketones as well as complex carbo- and heterocyclic compounds. The introduced alkenyl functionality can be further diversified, enhancing molecular diversity and complexity.

KEY REFERENCES

- Xu, G.-L.; Liu, C.-Y.; Pang, X.; Liu, X.-Y.; Shu, X.-Z. Nickel-Catalyzed Cross-Electrophile Vinyl−Vinyl Coupling: An Approach to Structurally Versatile Dienylboronates. *CCS Chem.* **2022**, *4*, 864−871.[1] *A single nickel catalyst enables Csp^2-Csp^2 coupling between two alkenyl electrophiles, providing an efficient route to synthesize*

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dienylboronates with remarkable structural complexity and molecular diversity.

- He, R.-D.; Bai, Y.; Han, G.-Y.; Zhao, Z.-Z.; Pang, X.; Pan, X.; Liu, X.-Y.; Shu, X.-Z. Reductive Alkylation of Alkenyl Acetates with Alkyl Bromides by Nickel Catalysis. *Angew. Chem., Int. Ed.* **2022**, *61*, e202114556.[2] *Establishing a nickel(I) catalytic system facilitates Csp^2-Csp^3 coupling of alkenyl acetates and alkyl bromides, yielding diverse cyclic and acyclic aliphatic alkenes with excellent functional group compatibility.*
- Pang, X.; Zhao, Z.-Z.; Wei, X.-X.; Qi, L.; Xu, G.-L.; Duan, J.; Liu, X.-Y.; Shu, X.-Z. Regiocontrolled Reductive Vinylation of Aliphatic 1,3-Dienes with Vinyl Triflates by Nickel Catalysis. *J. Am. Chem. Soc.* **2021**, *143*, 4536−4542.[3] *The combination of Ni(0) and a phosphine−nitrile ligand enables a 1,2-branch-selective reductive alkenylation of 1,3-dienes using alkenyl triflates, yielding diverse skipped dienes (1,4-dienes) with a scope complementary to established methods.*
- Qiao, J.-B.; Zhang, Y.-Q.; Yao, Q.-W.; Zhao, Z.-Z.; Peng, X.; Shu, X.-Z. Enantioselective Reductive Divinylation of Unactivated Alkenes by Nickel-Catalyzed Cyclization Coupling Reaction. *J. Am. Chem. Soc.* **2021**, *143*, 12961−12967.[4] *The use of the chiral t-Bu-pmrox ligand in conjunction with $NiBr_2$ enables an enantioselective cross-addition of two alkenyl electrophiles into tethered alkenes, offering a novel approach for synthesizing enantiopure 3-methylene five-membered hetero- and carbocycles.*

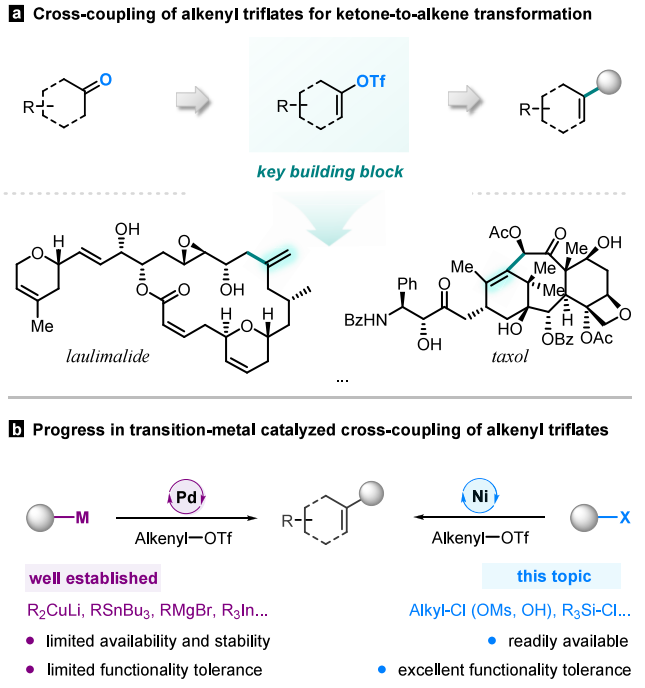
1. INTRODUCTION

Alkenes are fundamental structural motifs present in a wide range of natural products and pharmaceuticals. They also serve as essential intermediates in numerous chemical transformations, facilitating the efficient construction of complex molecular architectures.[5] As a result, developing robust and versatile strategies for alkene synthesis remains a central focus in organic chemistry.

One key strategy for alkene synthesis is the conversion of ketones, which are abundant, versatile, and easily introduced into complex molecules.[6] This transformation is particularly important for the synthesis of natural products and pharmaceuticals. A common approach involves the addition−elimination process, where a nucleophile adds to the ketone, followed by elimination to form the alkene. However, steric hindrance from bulky ketones and nucleophiles often hampers the addition step, and the subsequent dehydration can produce regioisomeric alkene mixtures, complicating selectivity and purification.

A promising alternative is the regioselective transformation of ketones into alkenyl triflates, which undergo transition metal-catalyzed cross-coupling reactions with carbon nucleophiles, offering high regioselectivity and predictability (Scheme 1).[7] Recent advances have enabled the coupling of a variety of carbon nucleophiles (e.g., R_2CuLi, $RSnBu_3$, $RMgBr$, R_3In), leading to structurally diverse alkenes (Scheme 1b, left). This strategy has been especially valuable in the total synthesis of natural products, where alkenyl triflate coupling often serves as a key step.[8] Despite the utility of these methods, the reliance on sensitive organometallic reagents is a notable limitation. These reagents are not only costly and time-consuming to prepare but also pose challenges related to functional group tolerance. This has spurred a growing need for alternative coupling strategies that are more practical and broadly applicable.

Scheme 1. Cross-Couplings of Enol Derivatives for Ketone-to-Alkene Transformation



One promising solution is nickel-catalyzed cross-electrophile coupling, which has emerged as a powerful and versatile approach for C−C bond formation.[9] Unlike traditional organometallic reagents, electrophiles offer a wider range of stable and structurally diverse starting materials. This method allows for the coupling of readily available electrophiles under mild conditions, providing distinct selectivity advantages compared to classical cross-coupling reactions. For a long time, early studies in this area focused on the coupling of organic halides, leveraging a radical chain mechanism where two electrophiles are differentiated by Ni(0) and Ni(I) via two-electron oxidative addition and radical activation, respectively (Scheme 2).[10] Following this strategy, the Weix group successfully demonstrated one example of nickel-catalyzed reductive alkylation of cyclohexenyl triflates with alkyl bromides in 2016.[11]

Building on these foundational studies, our group has explored the potential of nickel-catalyzed reductive coupling of enol derivatives as a versatile method for transforming ketones into alkenes (Scheme 1b, right). However, this approach faces several challenges, including expanding the scope of coupling partners beyond radical-active species such as alkyl halides. Additionally, there is a need to develop more stable and cost-effective enol derivatives to replace triflates, which suffer from poor reactivity and selectivity issues. Integrating cross-electrophile coupling with alkene chemistry holds great promise for expanding molecular diversity, but introduces additional complexities related to chemo-, regio-, and stereoselectivity.

In this account, we summarize our recent efforts in nickel-catalyzed reductive coupling for ketone-to-alkene conversion via enol intermediates. The focus is primarily on progress achieved by our group, with key contributions from other researchers also highlighted. While this review emphasizes the use of enol derivatives and nickel catalysis, it is important to note that significant advances in the coupling of alkenyl halides[12] and the use of cobalt catalysis[13] are also noteworthy, though these topics fall outside the scope of this manuscript.

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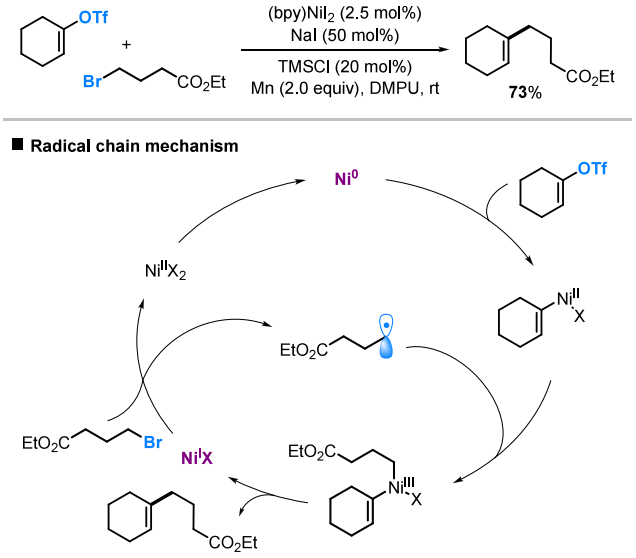
Scheme 2. Seminal Investigation (Weix, 2016)[a]



[a]Alkenyl−OTf (2.0 mmol) and alkyl−Br (2.0 mmol) were used. Reproduced from ref 10 and with permission from ref 11. Copyright 2013 American Chemical Society and 2016 Wiley-VCH, respectively.

2. REACTIONS OF ALKENYL TRIFLATES AND RADICAL-ACTIVE ELECTROPHILES

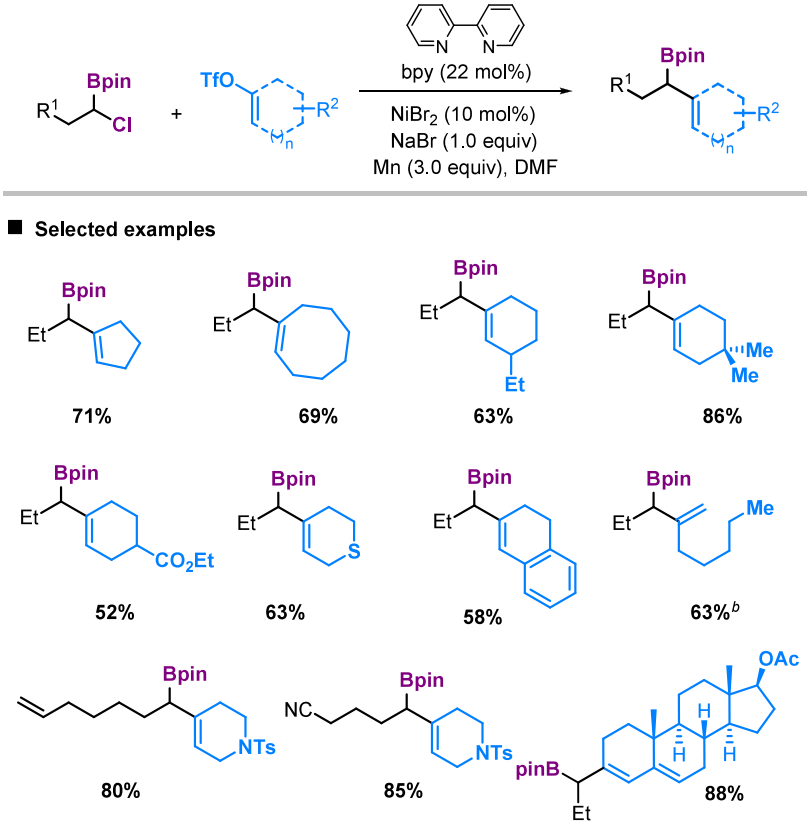
Allylboronates are important building blocks frequently used in organic synthesis. Traditionally, they have been prepared through methods such as the boration of allylic substrates, hydroboration of 1,3-dienes and allenes, or the coupling of alkenyl−M reagents with α-chloroboronates.[14] However, these approaches are primarily effective for producing acyclic allylboronates. We hypothesized that the reductive coupling of cyclic alkenyl triflates with α-chloroboronates could offer a new route to access cyclic allylboronates.

Given that α-chloroboronates possess both nucleophilic and electrophilic sites, we proposed that the C−Cl bond could be radically activated, generating a stable α-boron radical.[15] This radical could then follow the aforementioned radical chain process to afford the desired coupling product. Indeed, when treating alkenyl triflates and α-chloroboronates with common reductive conditions, cyclic allylboronates were obtained in good yields (Scheme 3).[16] The reaction proceeds under mild conditions, demonstrating broad substrate compatibility and functional group tolerance.

The ready availability of alkenyl triflates from ketones makes this approach ideal for the divergent modification of biologically active compounds (Scheme 4). The reaction is operable on gram-scale, and the versatile reactivity of allylboronates allows for divergent transformations such as hydration, vinylation, and addition reactions.

The radical chain mechanism has enabled the development of asymmetric reactions. By employing a chiral bis(oxazoline) ligand, the Reisman group achieved an enantioselective alkenylation of α-chlorosilanes, enabling the synthesis of chiral allylic silanes (Scheme 5).[17]

Scheme 3. Reductive Coupling of Alkenyl Triflates and α-Chloroboronates[a]



[a]Alkenyl−OTf (0.2 mmol) and α-chloroboronates (0.36 mmol) were used. [b]4,7-Diphenyl-1,10-phenanthroline was used instead of bpy. Reproduced from ref 16. Copyright 2020 American Chemical Society.

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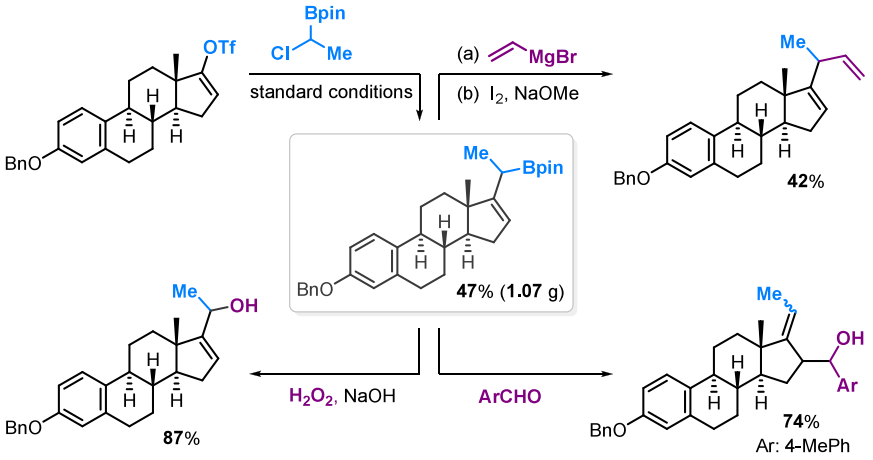
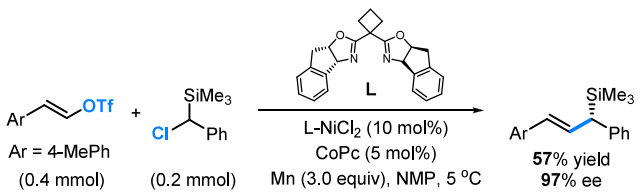
Scheme 4. Gram-Scale Reaction and Derivation of Allylboronates[a]



[a]Reproduced from ref 16. Copyright 2020 American Chemical Society.

Scheme 5. Enantioselective Reductive Coupling of Alkenyl Triflates and α-Chlorosilane (Reisman)[a]



[a]Reproduced from ref 17. Copyright 2017 American Chemical Society.

3. REACTIONS OF ALKENYL TRIFLATES AND RADICAL-INACTIVE ELECTROPHILES

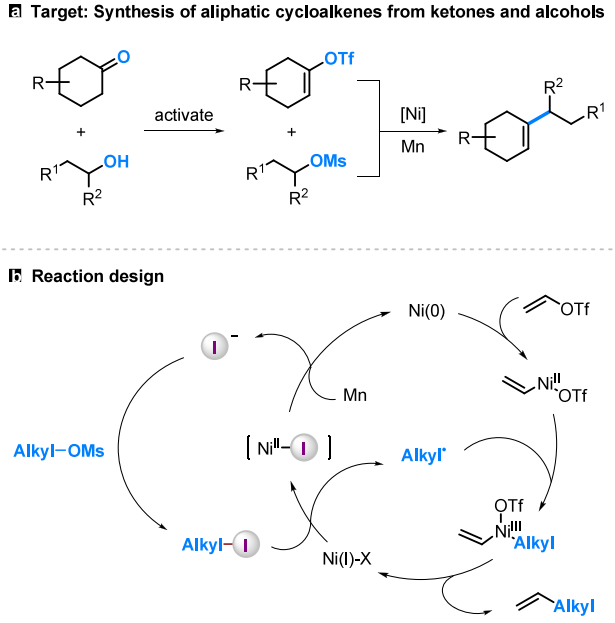
Early work in nickel-catalyzed cross-electrophile coupling relied heavily on radical-chain mechanisms, requiring radical-active substrates like alkyl halides. However, many compounds that are not radical-active remain largely untapped for these reactions. Expanding the substrate scope to include these compounds is highly important but presents a significant challenge, and the following section outlines our efforts to address this.

3.1. Radical-Inactive Csp^3 Electrophiles

Aliphatic cycloalkenes are important structural motifs in numerous natural products and pharmaceuticals. While traditional coupling methods provide routes to construct these structures, the inherent reactivity and availability of cyclic alkenyl and alkyl metals make the synthesis of highly functionalized or secondary alkyl-substituted cycloalkenes particularly challenging.[7] Furthermore, reductive couplings involving alkenyl halides are predominantly effective for acyclic alkenes.[12] We wondered the potential of synthesizing aliphatic cycloalkenes from ketones and alcohols via the coupling of their derivatives, such as alkenyl triflates and alkyl mesylates (Scheme 6a). If successful, this approach could leverage the abundance of these two compounds in both natural and synthetic products, expanding the method's applicability.

The challenge in achieving this target arises from the distinct reactivity of the two electrophiles. While alkenyl triflates are highly reactive in oxidative addition to Ni(0), unactivated alkyl mesylates are among the most challenging substrates in cross-coupling.[18] Additionally, the C−OMs bonds are resistant to

Scheme 6. Reaction Design for Constructing Aliphatic Cycloalkenes from Ketones and Alcohols[a]



[a]Reproduced from ref 19. CC BY-NC 3.0.

homolysis, which is necessary to generate carbon radicals for radical-chain reactions. Indeed, in our initial studies, alkenyl triflates typically converted to alkenyl−H and dimers, while alkyl mesylates remained unreacted.[19] To address this, we introduced a halide-exchange cycle by applying a catalytic amount of iodide, which in situ converts alkyl−OMs to the more reactive alkyl−I (Scheme 6b). This species then engages in coupling with alkenyl triflates through a radical-chain mechanism.

Using this approach, we were able to synthesize a wide range of primary and secondary aliphatic cycloalkenes from ketones and alcohols (Scheme 7).[19] The reaction proceeds under mild conditions and tolerates a broad array of functional groups, including alcohols, aldehydes, ketones, amides, esters, alkynes, alkenes, heterocycles, organotin, and organosilicon compounds. This catalytic iodide-mesylate exchange also enhances cross-selectivity compared to alkyl iodides.

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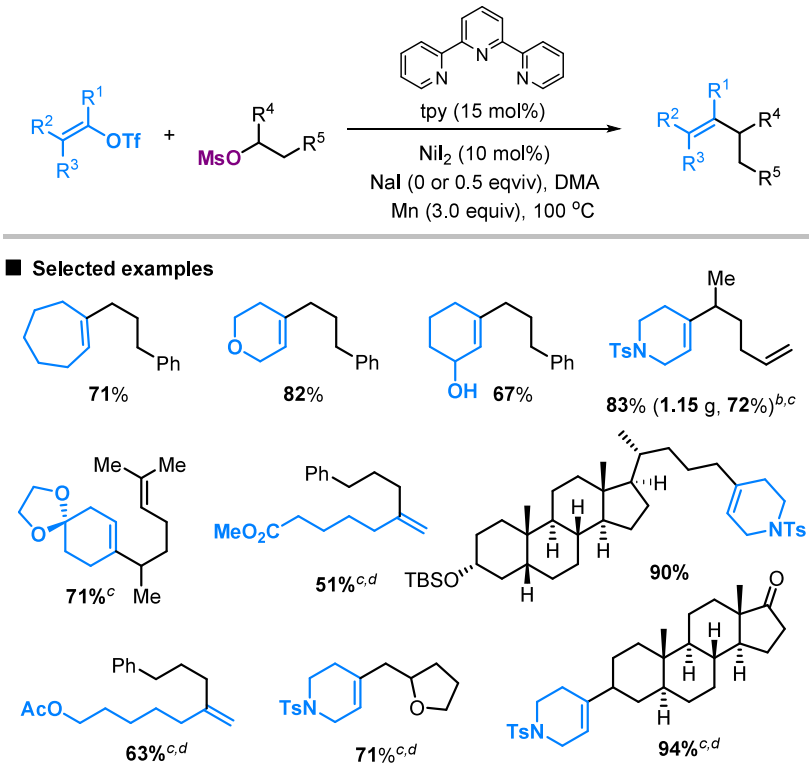
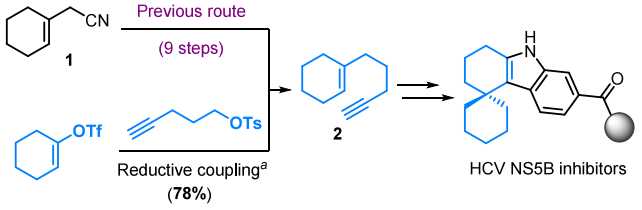
Scheme 7. Reductive Coupling of Alkenyl Triflates and Alkyl Sulfonates[a]



[a]Alkenyl−OTf (0.2 mmol) and alkyl−OMs (0.36 mmol) were used. [b]Gram-scale reaction. [c]NaI (0.5 equiv) was used. [d]Alkyl−OTS was used. Reproduced from ref 19. CC BY-NC 3.0.

Scheme 8. Synthetic Application of Reductive Coupling of Alkenyl Triflates and Alkyl Sulfonates



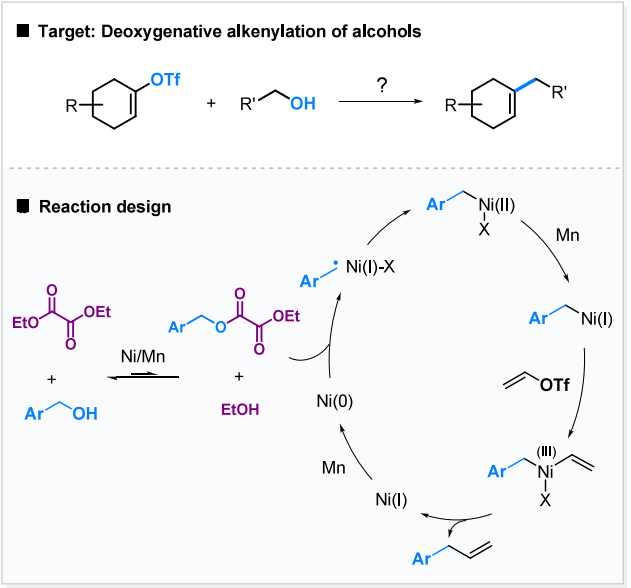
[a]Conditions as shown in Scheme 7, but NaI (0.5 equiv) and 40 °C were used. Reproduced from ref 19. CC BY-NC 3.0.

Scheme 8 highlights the method's efficiency in synthesizing biologically active molecules. Enyne **2**, a key intermediate in the synthesis of HCV NS5B inhibitors, previously required nine steps from nitrile **1**.[20] The reductive coupling now allows for its one-step synthesis from simpler starting materials.

The use of readily available alkyl mesylates as coupling partners broadens the scope and efficiency of olefin synthesis. However, this protocol requires the prefunctionalization of alcohols with RSO_2Cl, which limits the tolerance of nucleophilic functionalities in alcohols due to the sensitivity of these reagents. Ideally, alcohols would be used directly, but the aliphatic C−OH bond is highly inert to nickel catalysis either via one- or two-electron oxidative addition (Scheme 9a).[21]

Our strategy leverages the slow transesterification between oxalates and alcohols (Scheme 9b). Dialkyl oxalates are inexpensive, stable feedstock chemicals that are compatible with most functional groups. We found that these compounds undergo slow transesterification with primary alcohols under reductive nickel-catalyzed conditions.[22] Additionally, we observed that benzyl oxalates are highly reactive toward Ni(0) and can be activated via radical mechanisms. We hypothesized that radical oxidative addition to Ni(0) would generate benzyl-Ni(II), which, upon reduction by Mn, would form benzyl-Ni(I). This species could then undergo oxidative addition with alkenyl triflates, followed by reductive elimination to yield the deoxygenative coupling product.

Scheme 9. Reaction Design for Deoxygenative Alkenylation of Alcohols



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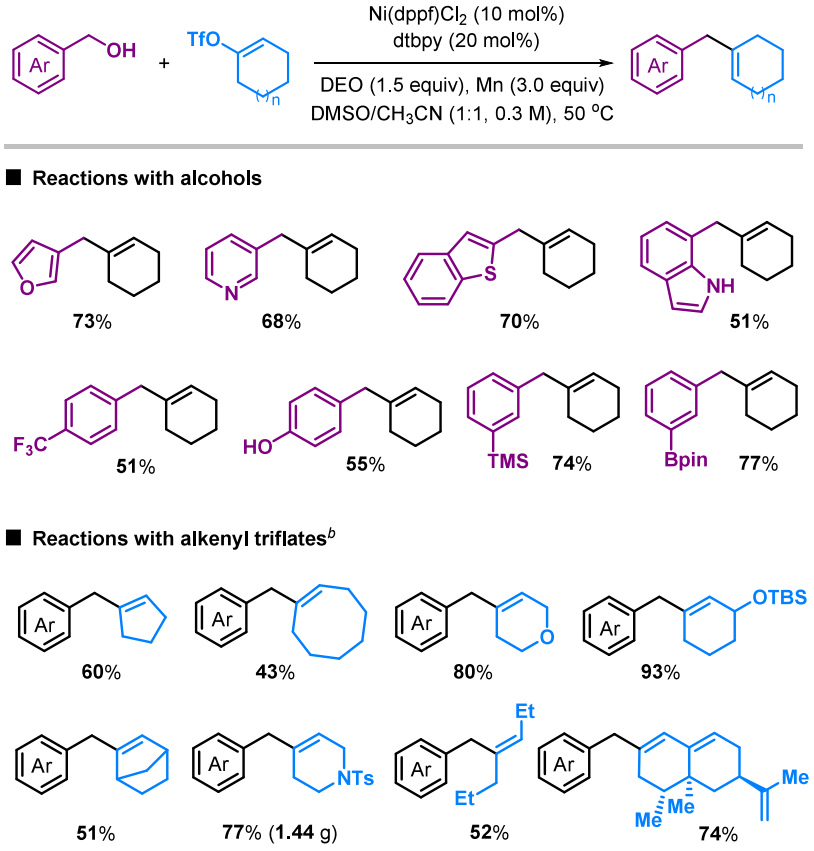
Scheme 10. Deoxygenative Reductive Coupling of Alkenyl Triflates and Benzyl Alcohols[a]



[a]Alkenyl−OTf (0.3 mmol) and benzyl−OH (0.2 mmol) were used. [b]Ar = 4-MeS-Ph.

Based on this concept, we developed a nickel-catalyzed dynamic kinetic reductive coupling between alkenyl triflates and benzyl alcohols, using diethyl oxalate (DEO) (1.5 equiv) as an activator (Scheme 10).[23] This method offers a new route for synthesizing allylarenes, key structural motifs in many natural products. While current reductive coupling methods mainly produce acyclic alkenes from alkenyl bromides, this approach uniquely yields versatile cyclic alkenes. A wide range of benzylic alcohols and alkenyl triflates were effectively coupled, with functional groups such as phenols, indoles, heterocycles, and boronic esters being tolerated. However, due to the slow transesterification rate, the reaction remains inefficient for secondary alcohols.

Aside from our work, the Gong group developed a Ni-catalyzed reductive coupling of α-pivaloyloxy glycine with alkenyl triflates by employing in situ conversion of radical-inactive α-pivaloyloxy glycine into reactive α-iodoglycine or iminium esters. This method facilitates the synthesis of α-alkenyl amino acids.[24]

3.2. Coupling with Csp^2 Electrophiles

While Csp^3−Csp^2 coupling of alkenyl triflates is commonly used to produce aliphatic alkenes from ketones, their coupling with Csp^2 electrophiles could offer access to conjugated alkenes, which are vital in organic synthesis. However, Csp^2 electrophiles are generally radical-inactive and exhibit similar reactivity to alkenyl triflates toward nickel. Developing cross-electrophile Csp^2−Csp^2 alkenylation reactions is challenging. We hypothesized that steric and coordination effects of the substrates could help control cross-selectivity, and this section highlights our preliminary findings.

Dienylboronates are a key class of building blocks with broad applications in the synthesis of biologically active natural products. Traditional methods, such as hydroboration or alkene metathesis of enynes, yield dienylboronates with the boron atom anti to the second alkene.[25] While cross-coupling of bromovinylboronates can synthesize *syn* isomers, they require alkenyl metals (R−M, M = Zn, B, Sn, Zr). We explored the possibility of synthesizing dienylboronates from ketones via the reductive coupling of alkenyl triflate intermediates (Scheme 11a). If successful, this approach would provide a more convenient and synthetically appealing route.

Our reaction design is outlined in Scheme 11b.[1] Despite alkenyl triflates typically being more reactive than bromides in oxidative addition, our control experiments show that bromovinylboronates react more efficiently with Ni(0) than triflates. We attribute this to the coordination of the Bpin group to nickel, which influences selectivity. Reduction of this Ni(II) complex could form a boron-substituted alkenyl-Ni(I) species, which undergoes a second oxidative addition with alkenyl triflates, leading to cross-coupling. We propose that the Bpin group's coordination will prevent homocoupling with sterically hindered bromovinylboronates and enhance cross-selectivity.

The experiments in Scheme 12 were designed to test the coordination effect of the Bpin group.[1] When a noncoordinative *tert*-butyl group (**3**, *syn*/*anti* = 1:1.3) was used, the reaction yielded an *anti*-selective product **4**. However, bromovinylboronate **5** (syn/anti = 1:1) exhibited a reversed selectivity, yielding compound **6** in 82% with a syn/anti ratio >20:1. We hypothesize

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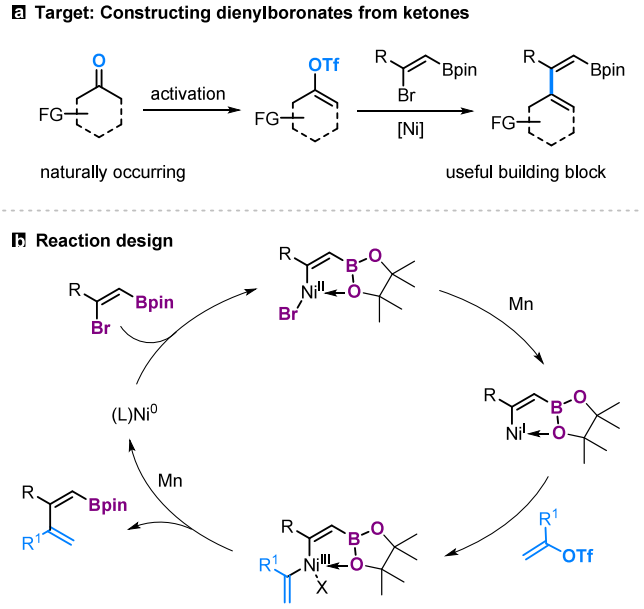
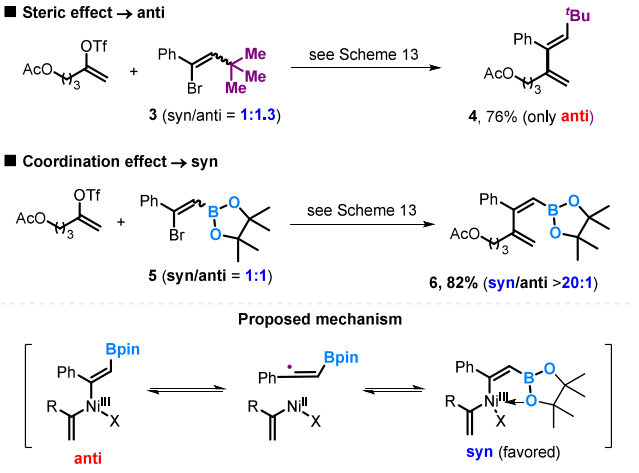
Scheme 11. Reaction Design for Construction Dienylboronates from Ketones[a]



[a]Reproduced from ref 1. Copyright 2021 Chinese Chemical Society.

Scheme 12. Insight into the Coordination Effect of the Bpin Group[a]



[a]Alkenyl triflate (0.3 mmol) and alkenyl bromides (0.2 mmol) were used, and NMR yields are given. Reproduced from ref 1. Copyright 2021 Chinese Chemical Society.

that stereoconvergent coupling is driven by reversible homolytic cleavage of the Ni−C bond, followed by recombination of alkenyl−$Ni^{II}X$ and alkenyl radicals. The boronate's coordination enhances *syn*-selectivity.

Scheme 13 illustrates selected examples that were produced through reductive alkenyl−alkenyl coupling between alkenyl triflates and bromovinylboronates. A wide range of cyclic, acyclic, and highly functionalized dienylboronates were synthesized with high stereoisomeric selectivity (>20:1), complementing existing methods. This approach is tolerant of various functional groups, including alkyl chlorides, esters, protected alcohols, silyl ethers, amides, and phosphonates.

Dienylboronates are versatile intermediates that enable divergent synthesis through key transformations (Scheme 14). Their boronate and diene groups allow for Suzuki−Miyaura cross-coupling (**7** and **8**) and Diels−Alder cycloadditions (**9**). Additionally, the boronate can be easily transformed into other functional groups, such as potassium trifluoroborate (**10**) and bromide (**11**). Oxidation of dienylboronates yields enal **12**, further expanding their utility.

The scope of Csp^2 coupling partners can be expanded to include acyl fluorides for the synthesis of enones (Scheme 15).[26] Enones are key structural motifs in many pharmaceuticals and biologically active natural products and serve as foundational intermediates for various reactions. Traditional methods for enone synthesis often require preformation of alkenyl or acyl metallic reagents. In contrast, this approach enables the direct construction of enone frameworks at acid and ketone sites via the reductive coupling of acyl fluorides and alkenyl triflates. Unlike acyl chlorides, acyl fluorides exhibit superior stability, allowing for easy isolation by organic extraction and flash chromatography on silica gel.[27] The reaction proceeds under mild conditions and demonstrates broad compatibility with various cyclic alkenyl triflates and acyl fluorides. Given the frequent occurrence of acid and ketone groups in pharmaceuticals and biologically active compounds, this method provides a valuable tool for late-stage functionalization.

Control experiments indicate that alkenyl triflates are significantly more reactive than acyl fluorides toward Ni(0), suggesting the initial formation of an alkenyl-Ni(II)−X species, which subsequently couples with the acyl fluoride.[26] However, the exact reason why the in situ-formed alkenyl−Ni(I) species preferentially reacts with acyl fluorides over alkenyl triflates remains unclear. It is possible that differences in the coordination ability of the electrophiles to the Ni(I) intermediate influence this selectivity.

Apart from our work, significant progress has been made in alkenylative Csp^2−Csp^2 couplings.[28] For example, the Weix group developed a dual palladium and nickel catalysis system, enabling highly selective cross-coupling between alkenyl bromides and triflates (Scheme 16a).[28a] Reductive alkenyl−alkenyl coupling has also been employed as a key step in the construction of the tetracyclic core of batrachotoxin (Scheme 16b).[28b]

3.3. Group-14 Element Electrophiles: Chlorosilanes and Chlorogermanes

Bioisosteric substitutions are a key strategy in medicinal chemistry, often employed to modify molecular properties and optimize drug candidates. Silicon and germanium, as heavier group-14 elements, are frequently considered bioisosteres of carbon. Over the years, their incorporation in place of carbon in biologically active molecules has been studied, showing promising results in altering activity profiles and enhancing metabolic stability.[29] This approach expands the chemical space in drug discovery, providing new opportunities for optimizing therapeutic molecules.

However, introducing silicon and germanium into the backbone of biologically active molecules remains a challenge due to the limited availability of effective C−Si(Ge) bond-forming methodologies.[30] Currently, the most reliable reactions for C−Si(Ge) bond formation involve the nucleophilic substitution of R_3Si−Cl and R_3Ge−Cl using Grignard reagents (R−MgX). The high reactivity and availability issues with Grignard reagents, however, limit the practicality of this approach. Given that ketones are readily available functional groups, developing a method for introducing silicon and

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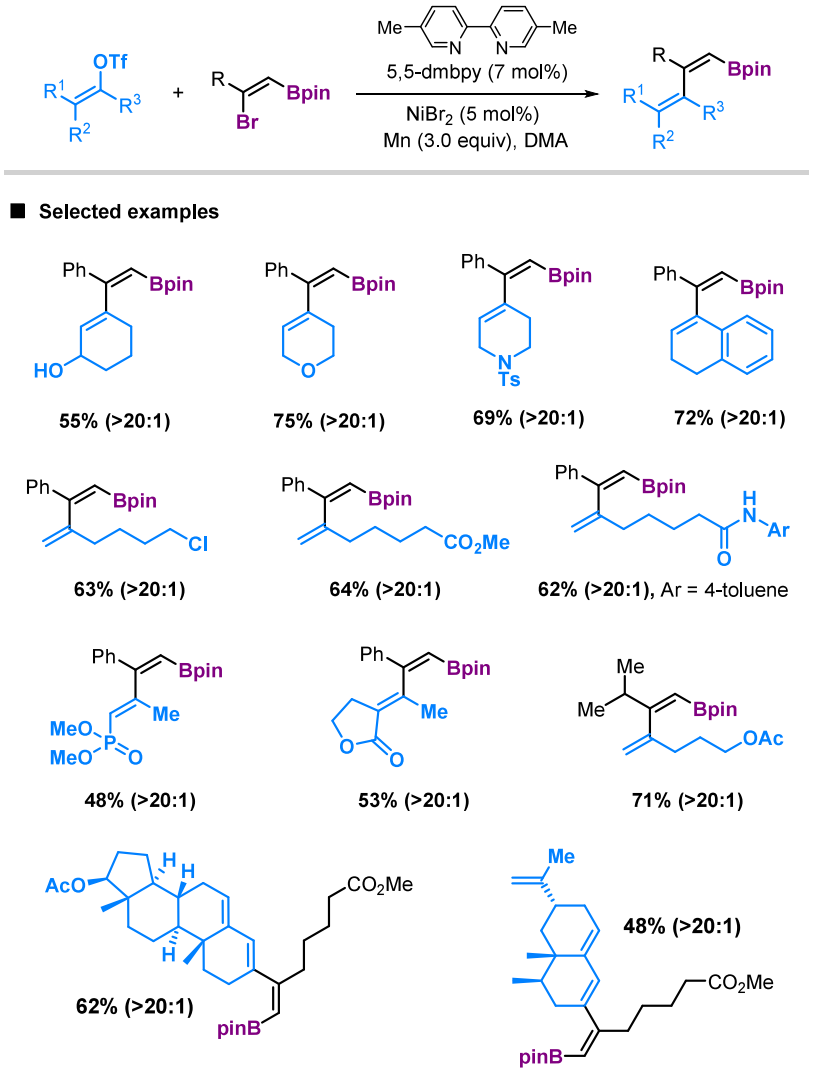
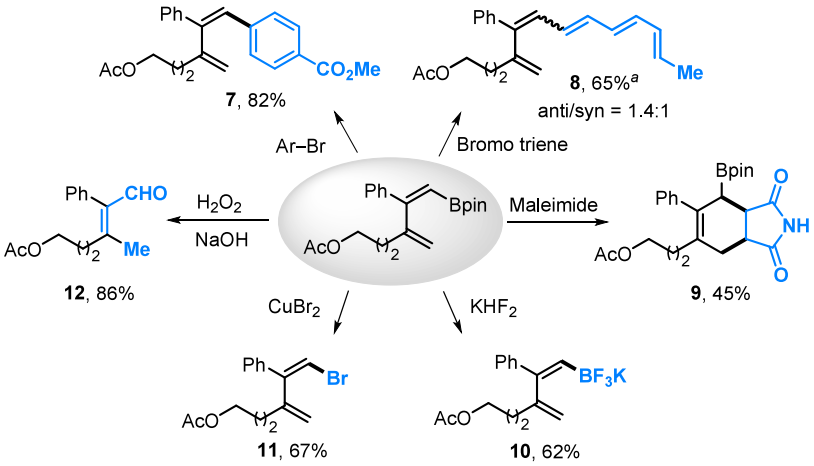
Scheme 13. Reductive Coupling of Alkenyl Triflates and Boron-Substituted Alkenyl Bromides[a]



[a]Alkenyl−OTf (0.3 mmol) and bromovinylboronates (0.2 mmol) were used. Reproduced from ref 1. Copyright 2021 Chinese Chemical Society.

Scheme 14. Diverse Transformation of Dienylboronate



[a]Bromotriene (5:1 stereoisomers) was used. Reproduced from ref 1. Copyright 2021 Chinese Chemical Society.

germanium at the ketone position could provide a valuable tool for bioisosteric substitution, though this remains unexplored (Scheme 17a). We wondered whether the reductive coupling of enol intermediate with R_3Si-Cl and R_3Ge-Cl could offer a solution.[31]

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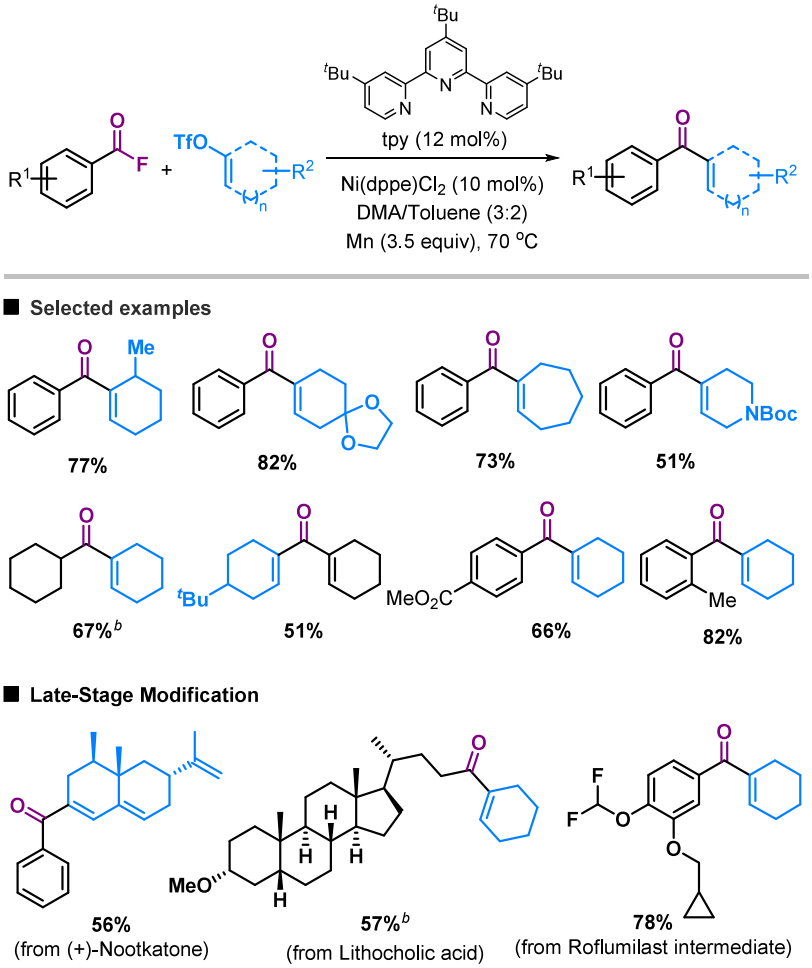
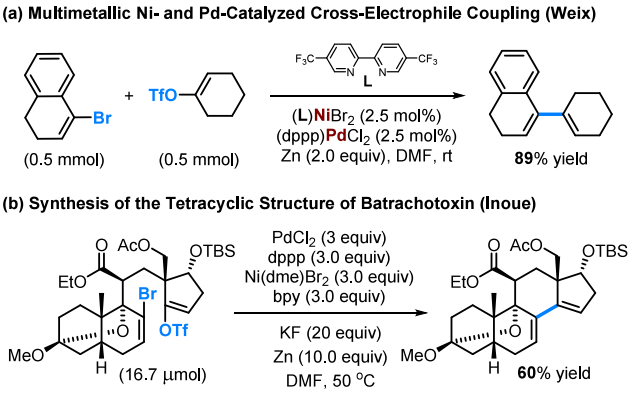
Scheme 15. Reductive Coupling of Alkenyl Triflates and Acyl Fluorides[a]



[a]Alkenyl−OTf (0.2 mmol) and acyl fluorides (0.3 mmol). [b]Tpy (15 mmol %) was used. Reproduced from ref 26. Copyright 2019 American Chemical Society.

Scheme 16. Other Notable Achievements in Reductive Alkenylative Csp^2−Csp^2 Coupling[a]



[a]Reproduced from refs 28a and 28b. Copyright 2018 and 2017, respectively, American Chemical Society.

The challenge stems from the high bond dissociation energies of Si−Cl (113 kcal/mol for Me_3Si−Cl) and Ge−Cl (107 kcal/mol for Me_3Ge−Cl) compared to alkyl halides (e.g., 83.7 kcal/mol for CH_3−Cl).[32] This makes direct radical activation by transition metals extremely difficult. However, since Si−Cl and Ge−Cl bonds are polarized, leading to highly electrophilic silicon and germanium centers, we hypothesized that an in situ-formed alkenyl−Ni(I) intermediate could undergo an S_N2-type oxidative addition to activate R_3Si−Cl and R_3Ge−Cl (Scheme 17b). This would then be followed by reductive elimination to yield the desired coupling products.

In 2020, we established the first reductive C−Si coupling using vinyl chlorosilanes as coupling partners, where the vinyl group proved to be essential (Scheme 18a,b).[33] Attempts to couple common chlorosilanes without the vinyl group resulted in no C−Si bond formation (Scheme 18a). We hypothesize that the steric bulk of these species hinders their effective coordination to the nickel center. In contrast, the vinylsilicon unit shows a strong tendency to coordinate with transition metals (TM), as the d-p_{π^*}-d interaction between the silicon atom, C = C bond, and TM enhances the thermal stability of the vinylsilane−TM complex.[34]

This protocol provides a straightforward method for introducing the (vinyl)silyl moiety at the ketone position, enabling the efficient synthesis of unsymmetric dialkenylsilanes with high molecular diversity and complexity (Scheme 18b). These compounds have potential applications in organic synthesis and materials science, and the versatility of the alkene group allows for further functionalization.

Expanding the scope beyond vinyl chlorosilanes has been a key focus. Recently, we demonstrated that less sterically hindered chlorohydrosilanes can also serve as effective coupling partners

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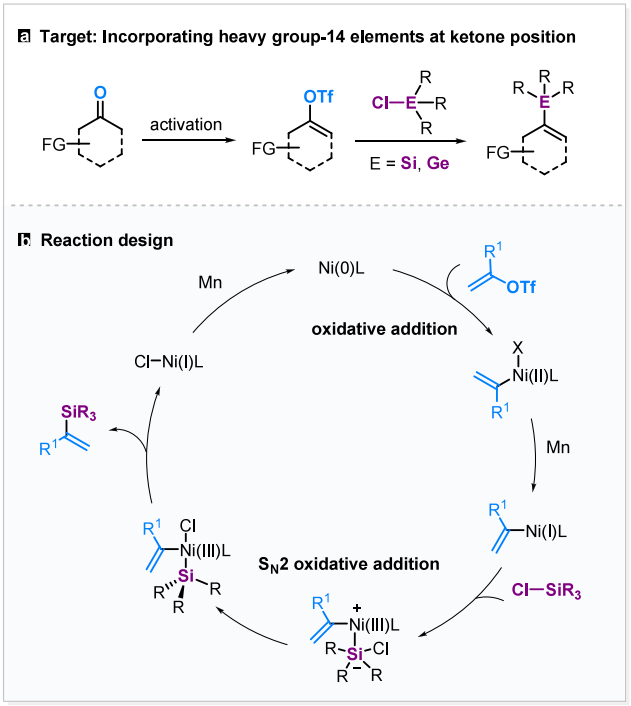
Scheme 17. Reaction Design for Introducing Heavy Group-14 Elements at the Ketone Position



(Scheme 18c).[35] Conventionally, the Si−H bond of H−Si(R)$_2$−Cl is selectively cleaved by low-valent transition metals. However, under reductive nickel catalysis, we showed that the stronger, more polarized Si−Cl bond can be selectively activated, leading to the formation of structurally versatile alkenyl hydrosilanes. Both cyclic and acyclic alkenyl triflates coupled efficiently, with broad functional group tolerance, including protected alcohols, esters, ketals, heterocycles, alkyl chlorides, and amides.

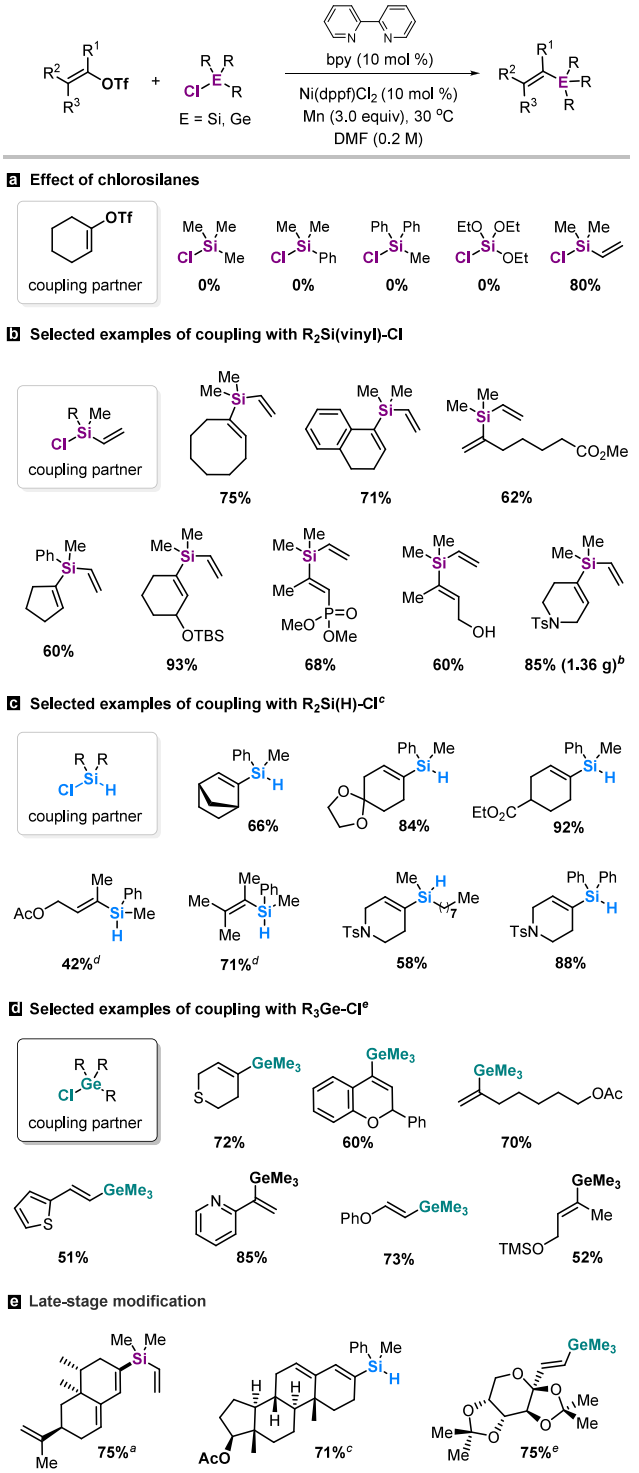
Unlike chlorosilanes, common chlorogermanes such as Me$_3$Ge−Cl and Me$_2$Ge(Ph)−Cl readily undergo nickel-catalyzed reductive coupling with alkenyl triflates (Scheme 18d).[36] We believe that the larger atomic radius of germanium reduces steric hindrance compared to silicon, allowing R$_3$Ge−Cl to more easily coordinate to the nickel center. This approach successfully accommodates both cyclic and acyclic alkenylgermanes and can be scaled up to gram quantities without loss of efficiency.

The reductive coupling approach offers a practical method for incorporating silicon and germanium into biologically active molecules, with the added advantage that the alkene and hydrosilane groups provide opportunities for further structural modifications of the resulting building blocks (Scheme 18e).

4. REACTIONS OF ALKENYL ACETATES

While alkenyl triflates have been the primary focus, there is increasing interest in extending this approach to more stable and environmentally friendly enol derivatives.[37] Alkenyl acetates are particularly appealing in this regard, but their application in cross-electrophile coupling has been hampered by low reactivity and selectivity challenges.[38] Initially, we addressed the selectivity issue by using unreactive ammonium salts to couple with alkenyl acetates.[39] However, this strategy was only effective for benzylic substrates. Expanding the alkyl electrophiles to more common but reactive alkyl halides presents greater synthetic appeal, but it introduces significant selectivity problems.

Scheme 18. Reductive Coupling of Alkenyl Triflates with Group-14 Element Chlorides[a]



[a]Alkenyl−OTf (0.2 mmol) and R$_3$Si−Cl (0.6 mmol) were used. [b]Gram-scale reaction. [c]Ni(OTf)$_2$ (10 mol %), bpy (15 mol %), Mn (2.0 euiv), DMF, 35 °C. [d]Ni(dppe)Cl$_2$ (10 mol %), dmbpy (15 mol %) in DMA at 0 °C. [e]Alkenyl−OTf (0.2 mmol), R$_3$ Ge−Cl (0.3 mmol), NiCl$_2$ (10 mol %), MeO$_2$C-terpy (12 mol %), Mn (3.0 equiv), DMF, 30 °C. Reproduced with permission from refs 33, 35, and 36. Copyright 2020, 2022, and 2021, respectively, Wiley-VCH.

Indeed, our initial attempts led predominantly to alkyl halide-derived byproducts, while the alkenyl acetates remained

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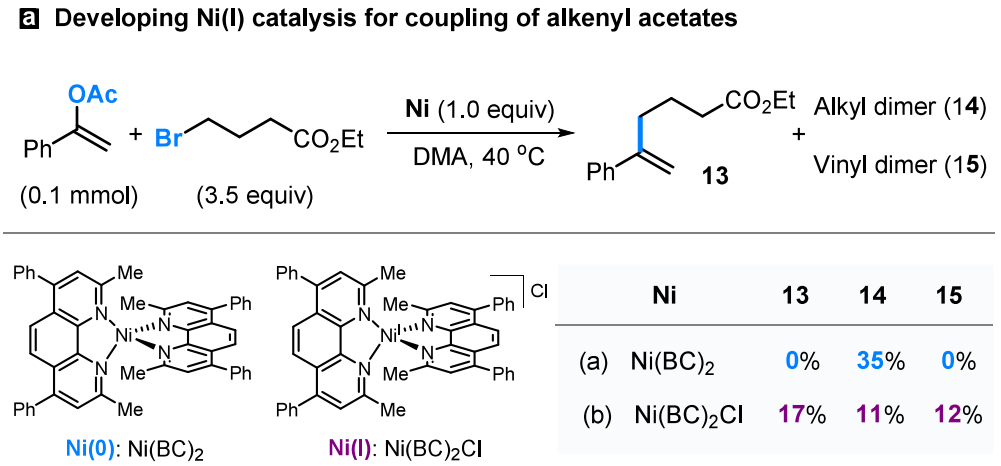
Scheme 19. Developing Ni(I) Catalysis for Coupling Alkenyl Acetates with Alkyl Bromides[a]



[a]Reproduced with permission from ref 2. Copyright 2021 John Wiley and Sons.

unreacted.[2] We determined that these catalytic systems typically generate Ni(0) species, which preferentially activate alkyl halides over alkenyl acetates (Scheme 19a, entry a). This observation prompted us to explore the use of a Ni(I) species, $Ni(BC)_2Cl$, capable of activating both coupling partners and delivering the desired cross-coupling product (Scheme 19a, entry b). Further investigation revealed that treating $NiBr_2$(diglyme) (10 mol %) and 5,5′-dmbpy (15 mol %) with Zn in DMA generates exclusively Ni(I) species. Under these conditions, we successfully achieved the reductive alkenylation of alkyl bromides with alkenyl acetates. The updated radical chain mechanism is outlined in Scheme 19b: oxidative addition of the alkenyl acetate to Ni(I) forms a Ni(III) species, which is subsequently reduced to alkenyl-Ni(II). This intermediate combines with an alkyl radical, and reductive elimination then produces the desired product.

This method efficiently couples a variety of (hetero)aryl-substituted alkenyl acetates (Scheme 20).[2] Cyclic alkenyl acetates yield β-alkyl-substituted cyclic enones, ranging from five- to seven-membered rings. A broad scope of primary, secondary, cyclic, and acyclic alkyl bromides are also well-tolerated. The mild reaction conditions facilitate the synthesis of structurally diverse alkenes, bearing functional groups that are typically sensitive to Grignard reagents, such as alkyl−Cl, RCON−H, R−CN, and R−CHO, as well as terminal alkenes, skipped dienes, alkylsilanes, ketones, mesylates, and phenols. Notably, cyclic enone **16** serves as a key building block for synthesizing biologically active compounds like α-acoradiene, isoitalicene, and γ-curcumene.

5. REACTIONS INVOLVING ALKENES

Alkenes are a versatile class of readily available starting materials. Developing a reductive alkenylation strategy involving alkenes could significantly enhance molecular and structural diversity in ketone-to-alkene synthesis. Additionally, introducing a reductive coupling method into alkene chemistry may offer new opportunities to address the selectivity and scope limitations associated with conventional alkene transformations.

5.1. Reductive Alkenylation of Alkenes

Catalytic hydrocarbonation of 1,3-dienes has emerged as a powerful tool for divergent synthesis. These reactions typically

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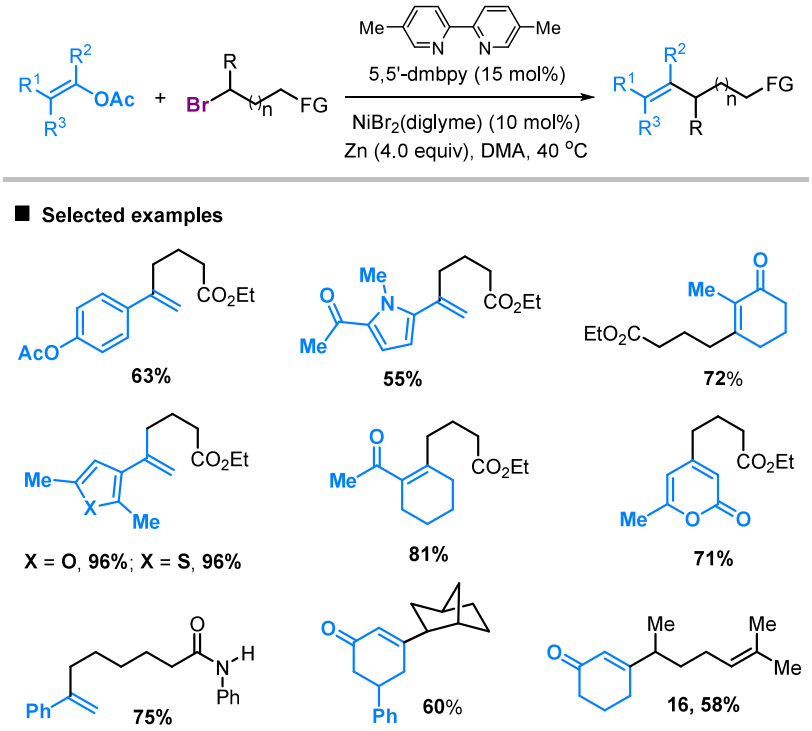
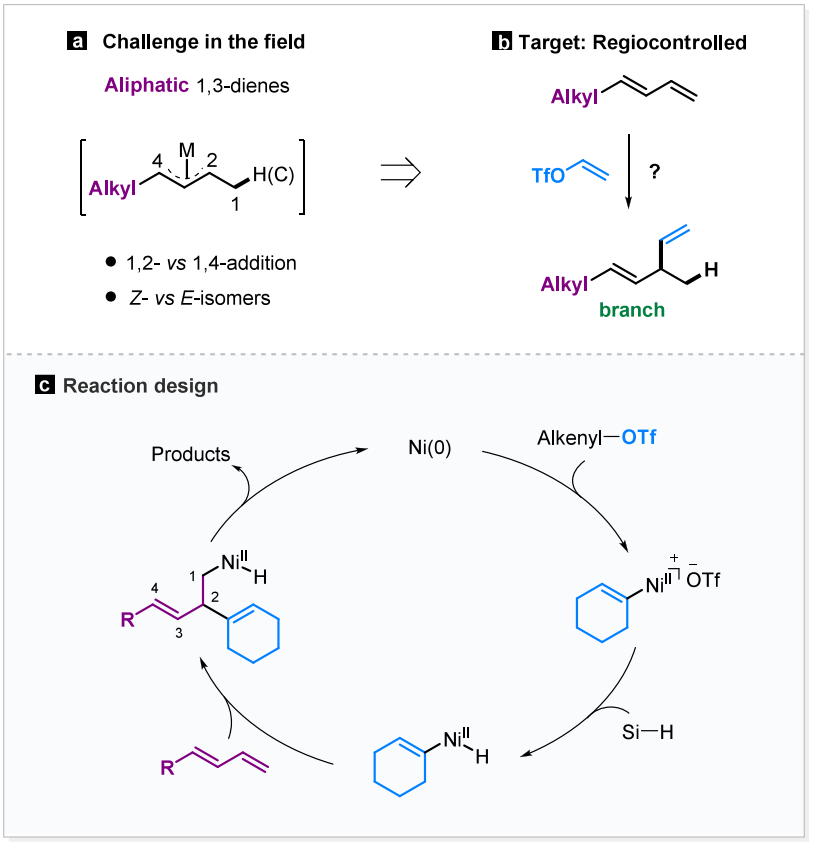
Scheme 20. Reductive Coupling of Alkenyl Acetates and Alkyl Bromides



[a]Alkenyl−OAc (0.2 mmol) and alkyl−Br (0.7 mmol) were used. Reproduced with permission from ref 2. Copyright 2021 Wiley-VCH.

Scheme 21. Reaction Design for Branch-Selective Reductive Alkenylation of Aliphatic 1,3-Dienes



proceed through η^3-π-allylmetal intermediates, with regioselectivity primarily influenced by the electronic and steric properties of the diene substrate (Scheme 21a).[40] However, in the case of aliphatic 1,3-dienes, where electronic factors are absent, the

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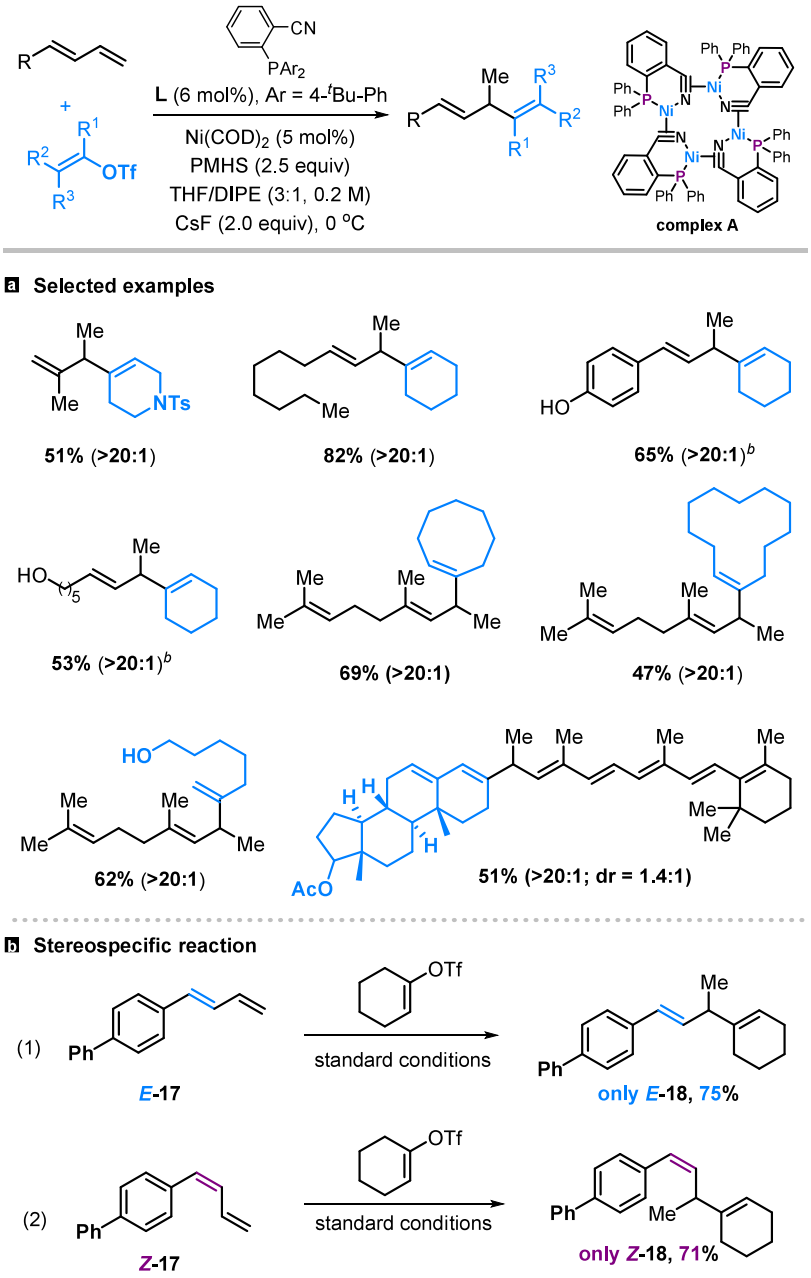
Scheme 22. Reductive Alkenylation of 1,3-Dienes with Alkenyl Triflates[a]



[a]Alkenyl−OTf (0.2 mmol) and dienes (0.36 mmol) were used. [b]TBAF (0.2 mmol) was added after 48 h to cleave the O−Si bond formed in situ. Reproduced from ref 3. Copyright 2021 American Chemical Society.

reaction often produces complex mixtures of 1,2- and 1,4-adducts, along with *Z*/*E* isomers. Achieving regioselective hydrocarbonation of aliphatic 1,3-dienes remains a long-standing challenge.

We hypothesized that a reductive coupling protocol could provide a solution, enabling the formation of a branch-selective alkenylation product.[3] The reaction design, as outlined in Scheme 21c, involves the oxidative addition of an alkenyl−OTf to Ni(0), yielding alkenyl-Ni(II)−OTf. This intermediate reacts with Si−H to form an alkenyl-Ni(II)−H species. Regioselective migratory insertion of the 1,3-diene into the alkenyl-Ni(II)−H bond, followed by reductive elimination, produces the desired product.

While migratory insertion generally favors the formation of a stabilized allylmetal intermediate, we hypothesized that ligand sterics could reverse the selectivity.[41] After numerous trials, we discovered that phosphine-nitrile ligands enabled the reaction to bypass the conventional η^3-π-allylnickel intermediate pathway, yielding skipped dienes with excellent branch selectivity (>20:1) (Scheme 22).[3] Nitrogen, phosphine, and phosphinooxazoline ligands either provided low efficiency or poor regioselectivity. Although the exact role of the phosphine-nitrile ligand remains unclear, its combination with $Ni(COD)_2$ resulted in a catalytically active tetrameric complex **A**.

A wide range of substrates, including simple butadiene, aliphatic and aromatic 1,3-dienes, and highly conjugated polyenes, showed excellent reactivity with alkenyl triflates

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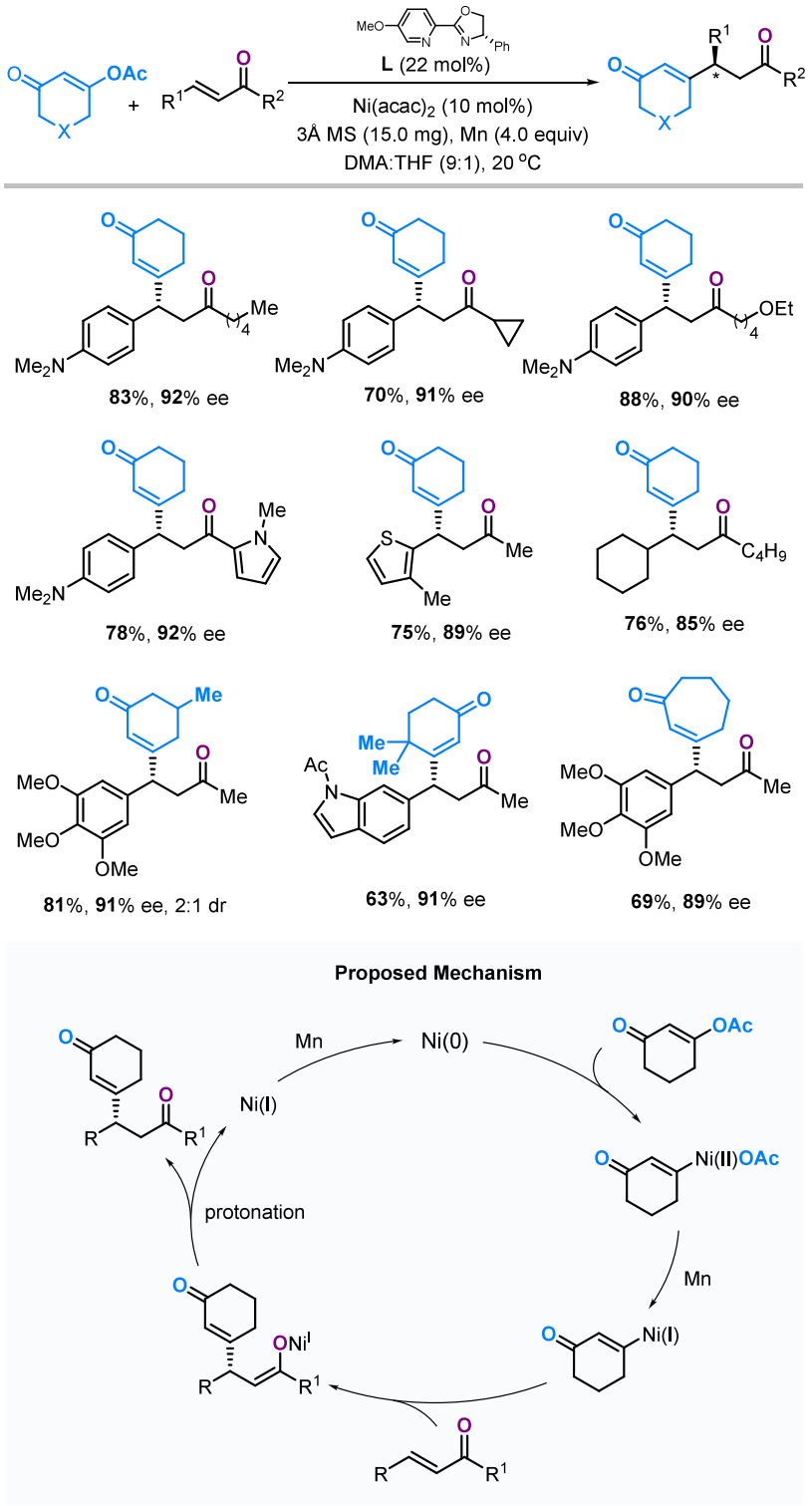
Scheme 23. Nickel-Catalyzed Enantioselective Reductive Conjugate Alkenylation of α,β-Enones with Keto Alkenyl Acetates[a]



[a]Alkenyl−OAc (0.6 mmol) and α,β-enones (0.2 mmol) were used. Adapted with permission from ref 42. Copyright 2024 Science China Press.

(Scheme 22a). Both cyclic and acyclic alkenyl triflates were successfully incorporated. This approach enables the conjugation of two biologically active units to form complex polyene molecules.

Control experiments utilizing *E*-**17** and *Z*-**17** exclusively produced *E*-**18** and *Z*-**18** in yields of 75% and 71%, respectively (Scheme 22b). These results clearly show that the reaction proceed through a mechanism bypassing a π-allylnickel intermediate.

Following our success in regioselective alkenylation, we turned our focus to enantioselective transformations. Alkenyl acetates were explored for this purpose, though they had not previously been applied in asymmetric synthesis. To overcome the challenges of low reactivity and stereoselectivity, we employed

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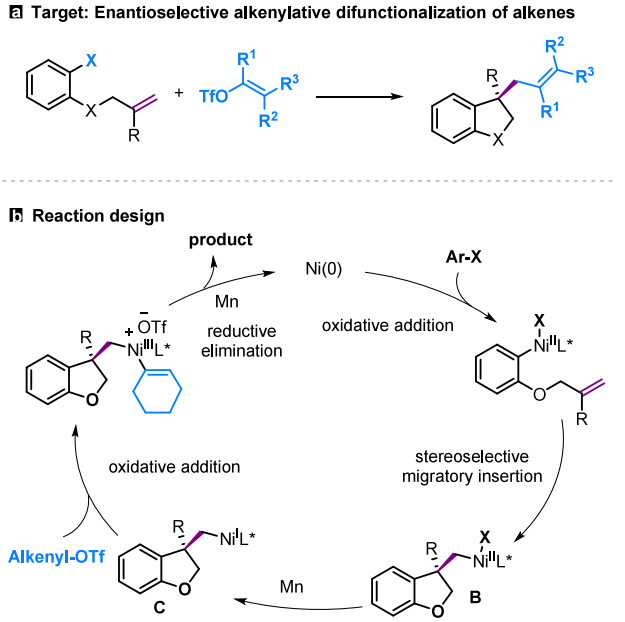
Scheme 24. Reaction Design for Enantioselective Arylalkenylation of Tethered Alkenes[a]



[a]Reproduced from ref 46. Copyright 2019 American Chemical Society.

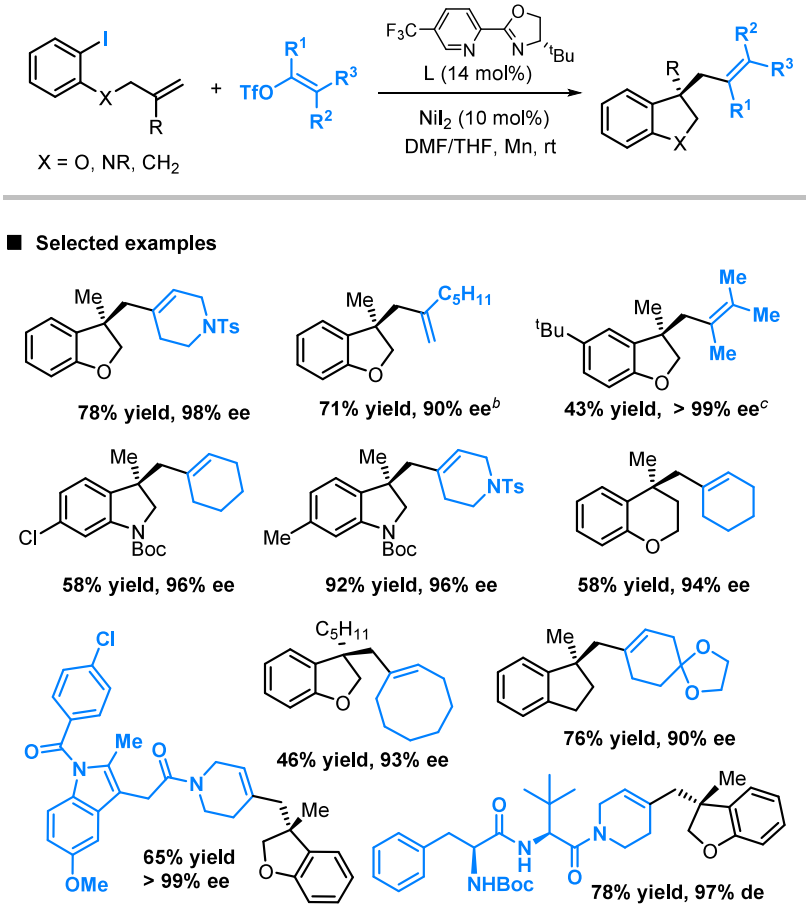
the electron-rich Pyrox ligand, 5-MeOPyrox. Using this system, we achieved reductive conjugate addition of keto alkenyl acetates to α,β-enones with high enantioselectivity (Scheme 23).[42] This method enables the incorporation of keto alkenyl groups into α,β-enones, providing access to a class of enantioenriched unsaturated diketones that are otherwise difficult to synthesize.[43] The enantioselective addition of alkenyl-Ni(I) into α,β-enones to form an enolate intermediate was proposed as a key step in the mechanism.

5.2. Enantioselective Reductive Alkenylative Dicarbofunctionalization of Unactivated Alkenes

Asymmetric reductive dicarbofunctionalization of alkenes offers a valuable strategy for producing enantioenriched architectures.[44] Specifically, reactions of tethered alkenes with R−X and alkenyl triflates can result in the formation of chiral carbo- and heterocyclic frameworks containing alkene groups, which are suitable for further molecular modification (Scheme 24a).[45]

The reaction design is depicted in Scheme 24b. First, oxidative addition of Ar−X to Ni(0) forms Ar-Ni(II)−X, which then undergoes enantioselective migratory insertion into the alkene, yielding an enantioenriched complex **B**. Following reduction by Mn, the resulting Ni(I) complex **C** engages in a second oxidative addition with alkenyl triflates. Reductive elimination ultimately provides the desired product. The coordination of the tethered alkene to nickel may help achieving the necessary chemoselectivity.

Scheme 25. Enantioselective Arylalkenylation of Tethered Alkenes with Aryl Iodides and Alkenyl Triflates



[a]Alkenyl−OTf (0.2 mmol), alkenes (0.2 mmol) were used. [b]Reaction in THF. [c]Reaction in DMF. Reproduced from ref 46. Copyright 2019 American Chemical Society.

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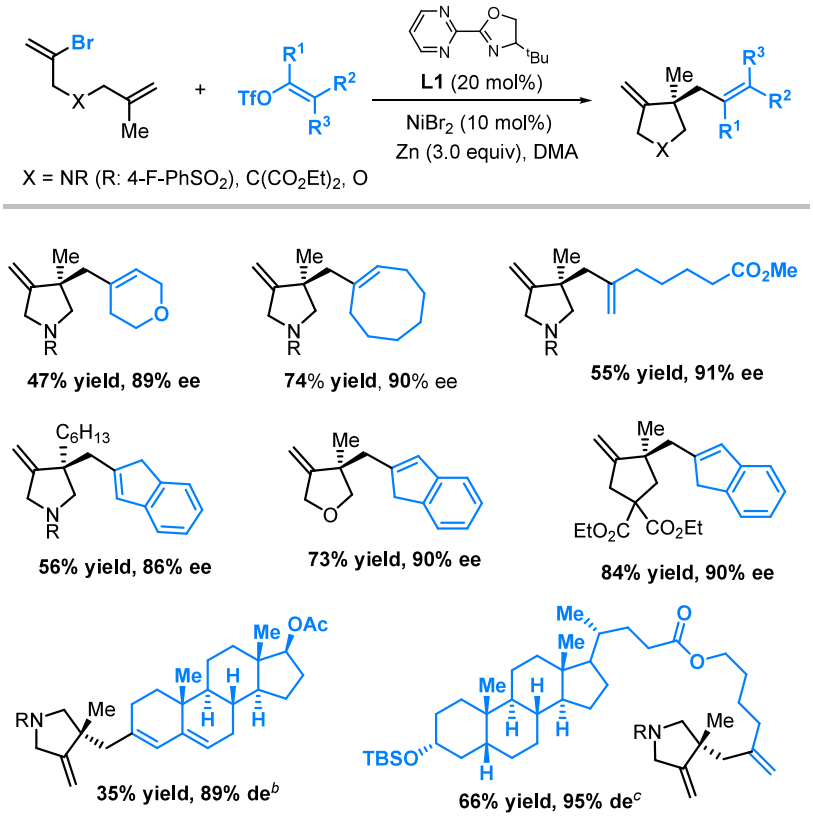
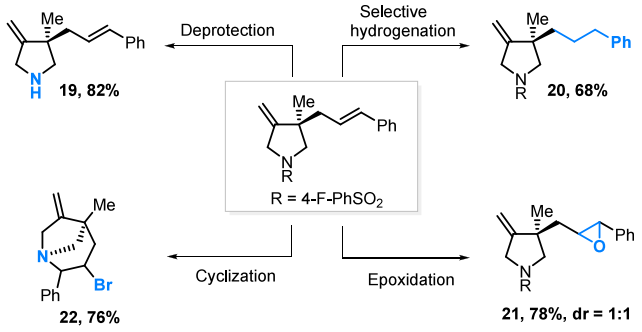
Scheme 26. Enantioselective Dialkenylation of Tethered Alkenes with Alkenyl Bromides and Triflates



[a]Alkenyl−OTf (0.3 mmol) and alkenes (0.2 mmol) were used. [b]ligand **L2** was used. [c]ligand **L3** was used. Reproduced from ref 4. Copyright 2021 American Chemical Society.

Scheme 27. Derivatization of Product[a]



[a]Reproduced from ref 4. Copyright 2021 American Chemical Society.

In 2019, we reported an enantioselective reductive arylalkenylation of unactivated alkenes using a nickel catalyst and a chiral Pyrox ligand (Scheme 25).[46] This method facilitates the synthesis of a variety of biologically significant chiral molecules, such as dihydrobenzofurans, indolines, and indanes. The introduced alkenyl group can undergo further transformations, thereby enhancing the molecular diversity and complexity of the products.

Generally, cross-electrophile difunctionalization of alkenes requires aryl-tethered substrates with rigid aromatic rings to enhance selectivity.[9d,47] Recently, we extended this methodology to nonaromatic substrates, showing that chiral *t*-Bu-Pyrox and 3,5-difluoro-Pyrox ligands enable high enantioselectivity in dialkenylation of alkenes (Scheme 26).[4] This advancement allows for the synthesis of enantioenriched 3-methylene five-membered hetero- and carbocycles, structures that are challenging to obtain through conventional methods. The ready availability of alkenyl triflates further enhances the efficiency of this approach in incorporating enantioenriched five-membered rings into complex molecules.

The resulting products can undergo further diversification (Scheme 27). For example, the sulfonyl group can be removed to generate cyclic amine **19**. The two alkenes can be selectively transformed through hydrogenation and epoxidation, yielding compounds **20** and **21**, respectively. Additionally, a tandem deprotection and cyclization sequence produces polycyclic compound **22** as a single isomer in 76% yield.

6. CONCLUSION

The readily available nature of ketone functionality make ketone-to-alkene transformation particularly valuable for molecule synthesis. Nickel-catalyzed reductive alkenylation of enol derivatives presents a promising approach to achieving this transformation. These methods are notable for their high functional group compatibility, providing access to structurally diverse alkenes, especially cyclic alkenes, with many of them difficult to access otherwise.

In the context of a classic radical chain mechanism, alkenyl triflates couple effectively with α-chloroboronates to form allylboronates. Further research has explored expanding the scope to include a wider range of radical-inactive coupling partners. In situ activation strategies, such as halide exchange and oxalate transesterification, have been employed to achieve deoxygenative alkenylation of alkyl mesylates and benzyl alcohols, producing versatile aliphatic alkenes. The use of double

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Acc. Chem. Res. XXXX, XXX, XXX−XXX

oxidative addition has enabled efficient Csp^2-Csp^2 alkenylation of bromoalkenylboronates and acyl fluorides, facilitating access to dienylboronates and enones. Additionally, sequential oxidative addition and S_N2 oxidative addition strategies have proven effective for coupling alkenyl triflates with chlorosilanes and chlorogermanes, expanding the scope to include heavier group-14 elements. Efforts have also been made to broaden the range of enol derivatives from triflates to more environmentally friendly, cost-effective, but less reactive acetates.

Reductive alkenylation involving alkenes presents an attractive alternative for producing alkenes with enhanced structural and molecular diversity. For instance, branch-selective reductive alkenylation of 1,3-dienes with alkenyl triflates allows access to various 1,4-dienes, while enantioselective reductive alkenylation of enones produces enantioenriched unsaturated diketones. Asymmetric cross-coupling of tethered alkenes with Csp^2-X and alkenyl triflates offers an efficient route to construct enantioenriched carbo- and heterocyclic structures, with ligands playing a crucial role in controlling regio- and stereoselectivity.

Despite these advances, several challenges remain to improve the practicality of this approach. Expanding the scope of coupling partners to include readily available compounds, especially those derived from naturally occurring functionalities and feedstock chemicals, holds great promise. The use of cost-effective and stable alkenyl coupling partners such as enol acetates is particularly appealing, though research in this area is still in its infancy. Reductive alkenylation has the potential to address the regioselectivity challenges associated with conventional alkene transformations, but its full potential remains to be realized. Continued development of asymmetric methodologies is expected to further advance the synthesis of enantioenriched alkenes.

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Author Contributions

†Z.-Z.Z. and P.G. contributed equally. CRediT: **Zhen-Zhen Zhao** visualization, writing - original draft; **Peng Guo** visualization, writing - original draft; **Xiaobo Pang** writing - review & editing; **Xing-Zhong Shu** conceptualization, funding acquisition, supervision, writing - review & editing.

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Notes

The authors declare no competing financial interest.

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Xiaobo Pang received her Master's and Ph.D. degrees from Lanzhou University. She was appointed at Lanzhou University in 2024, where she is a tenure-track professor.

Xing-Zhong Shu received his Ph.D. degree from Lanzhou University in 2010. He then moved to the University of Wisconsin-Madison to conduct postdoctoral research with Professor Weiping Tang. In 2012 he joined F. Dean Toste's group at the University of California-Berkeley as a postdoctoral researcher. He was appointed at Lanzhou University in 2015, where he is a Full Professor of Chemistry.

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