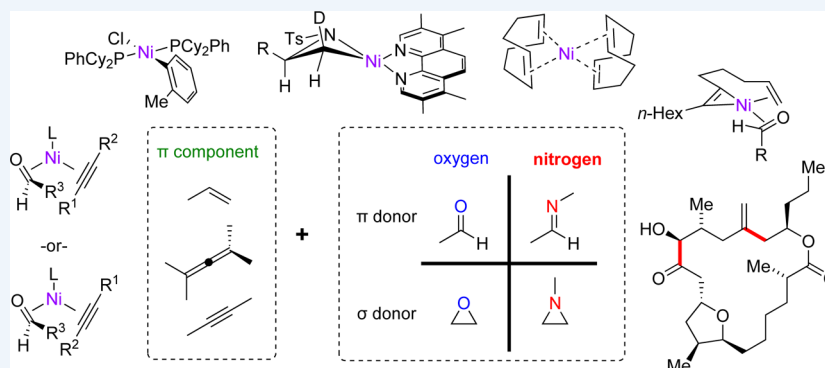


Nickel Catalysis: Synergy between Method Development and Total Synthesis

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CONSPECTUS: Nickel(0) catalysts have proven to be powerful tools for multicomponent coupling reactions in our laboratories over the past 15 years. This interest was originally sparked by the ubiquity of allylic alcohol motifs in natural products, such as (–)-terpestacin, which we envisioned assembling by the coupling of two π components (alkyne and aldehyde) with concomitant reduction. Mechanistic investigations allowed us to elucidate several modes of controlling the regioselectivity and stereoselectivity in the oxidative cyclization, and these insights enabled us to leverage combinations of alkenes and phosphine ligands to direct regioselective outcomes. The initial success in developing the first intermolecular reductive alkyne–aldehyde coupling reaction launched a series of methodological investigations that rapidly expanded to include coupling reactions of alkynes with other electrophilic π components, such as imines and ketones, as well as electrophilic σ components, such as epoxides. Aziridines proved to be more challenging substrates for reductive coupling, but we were recently able to demonstrate that cross-coupling of aziridines and alkylzinc reagents is smoothly catalyzed by a zero-valent nickel/phenanthroline system. Moreover, the enantioselective alkyne–aldehyde coupling and the development of novel P-chiral ferrocenyl ligands enabled the total synthesis of (–)-terpestacin, amphidinolides T1 and T4, (–)-gloeosporone, and pumiliotoxins 209F and 251D.

We subsequently determined that alkenes could be used in place of alkynes in several nickel-catalyzed reactions when a silyl triflate activating agent was added. We reason that such an additive functions largely to enhance the electrophilicity of the metal center by coordination to the electrophilic π component, such that less nucleophilic alkene π donors can undergo productive combination with nickel complexes. This activation manifold was further demonstrated to be effective for alkene–aldehyde couplings. In a related manner, electrophilic promoters were also successfully employed for allylic substitution reactions of allylic carbonates with simple alkenes and in the Mizoroki–Heck reaction of both benzyl and aryl electrophiles. In these instances, it is proposed that counterion exchange from a more strongly coordinating anion to the weakly or noncoordinating triflate counterion enables reaction at an electrophilic Ni(II) center rather than by coordination to one of the coupling components. Mechanistic insights also played an important role in the development of mixed N-heterocyclic carbene/phosphite ligand systems to overcome challenges in regioselective alkene–aldehyde coupling reactions.

We hope that, taken together, the body of work summarized in this Account demonstrates the constructive interplay among total synthesis, methodological development, and mechanistic investigation that has driven our research program.

INTRODUCTION

Natural products are a continual source of inspiration for chemists, particularly for organic chemists engaged in reaction development and methodology. In the early stages of our research program, we were drawn to macrocyclic natural products containing allylic alcohol moieties, such as (–)-ter-

pestacin (**1**) (Figure 1). We envisioned that, in an ideal case, an intramolecular reductive coupling (a field still in its infancy at the time) could be developed to join an alkyne and an aldehyde

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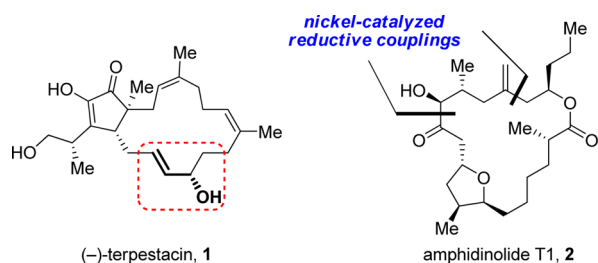


Figure 1. Natural product inspirations for nickel-catalyzed methodology.

to yield this allylic alcohol, simultaneously closing the macrocycle. For this reason we began studying reductive coupling as a tool for C–C bond formation. Additionally, as our program developed, it became clear that a number of other natural products that do not contain allylic alcohols, such as amphidinolide T1 (**2**), could be produced in an analogous fashion after modification of the allylic alcohol formed from such a macrocyclization.

As our investigation into the reductive coupling of alkynes and aldehydes continued, it quickly became clear that many other nucleophilic π components, such as allenes and alkenes, and other electrophilic π components, such as ketones and imines, could be competent substrates in these reactions. Additionally, σ components, such as epoxides, are also able to participate in nickel-catalyzed reductive couplings. This Account describes our journey from inspiration by natural products to the creation of new methods to synthesize these products, the realization of their synthesis, and back again to inventing and improving methodologies with broad applications in organic synthesis.

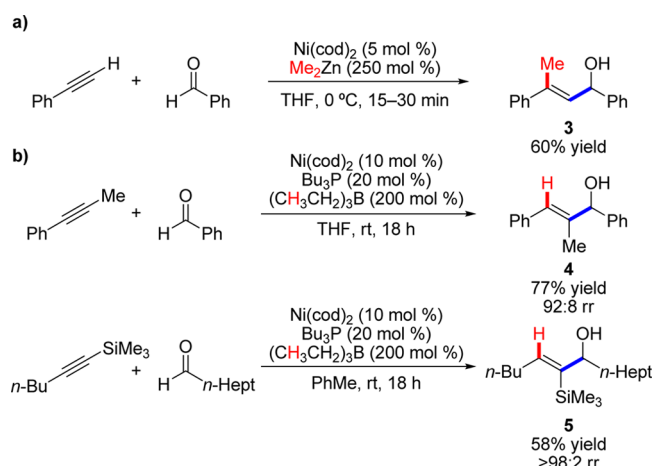
■ REDUCTIVE COUPLING REACTIONS OF ALKYNES

Reductive Coupling of Alkynes and Aldehydes

Nickel(0) complexes have long been privileged catalysts for reactions of alkynes and alkenes, including oligomerization, cyclization, and polymerization.¹ In the late 1990s, new strategies for nickel-catalyzed coupling of two π components to produce a new σ bond between them and a new σ bond with an organometallic reducing agent were being developed, a field later known as reductive coupling.² Although intramolecular reductive cyclizations were well-precedented, the first intermolecular reductive three-component coupling was published by Oblinger and Montgomery³ in 1997 and involved the reaction of alkynes and aldehydes to give allylic alcohols (**3**) (Scheme 1a). However, while the intramolecular coupling reaction conditions could be adjusted to afford either alkylative (C–R bond from the reducing agent) or reductive (C–H bond from the reducing agent) products, intermolecular couplings with alkylzinc reagents provided only alkylative products.

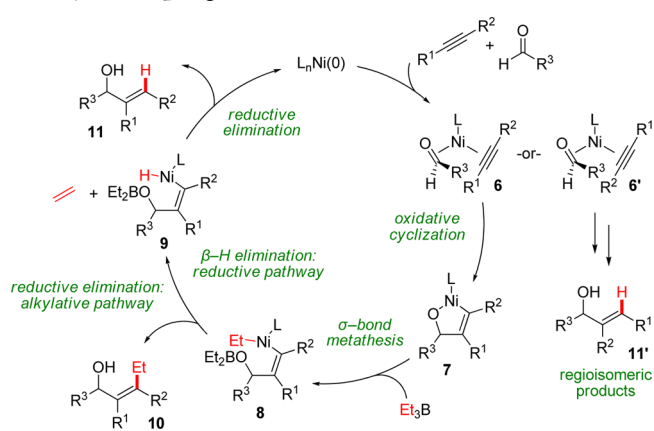
Upon examination of the limitations of the current state of the field, we believed that the value of allylic alcohol products arising from an *intermolecular reductive coupling* (bypassing the traditional need for stoichiometric alkenylmetal reagents) meant that such a transformation would be synthetically and mechanistically interesting. Ultimately, we were able to achieve this goal with the use of alkylboron reducing agents and phosphine ligands (Scheme 1b).⁴ Allylic alcohols were thus produced in high yields and regioselectivities from both aromatic (**4**) and aliphatic aldehydes (**5**).

Scheme 1. Intermolecular (a) Alkylative and (b) Reductive Alkyne–Aldehyde Coupling Reactions



The mechanism for reductive coupling, which was studied using density functional theory (DFT) calculations in an enlightening and fruitful collaboration with Ken Houk, is shown in Scheme 2.⁵ The concerted oxidative cyclization step

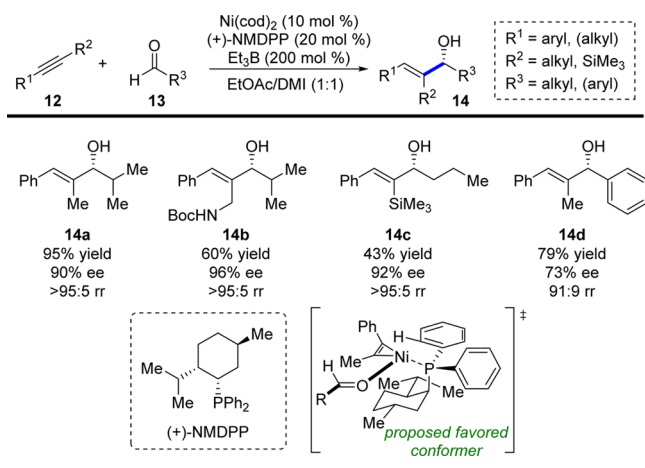
Scheme 2. Mechanism of Reductive and Alkylative Alkyne–Aldehyde Coupling



to form key five-membered nickelacycle **7** explains why only syn addition across the alkyne is always observed. This step is generally considered to be rate-determining and also determines the regioselectivity of the resulting alkene products by the formation of the new C–C bond. The difference between the reductive and alkylative pathways lies in the preference for nickel–alkyl species **8** to undergo β -hydride elimination to form **9** rather than reductive elimination to form **10**. The phosphine ligands employed in our chemistry promote the former. Later, Montgomery showed that reductive couplings could also be accomplished using N-heterocyclic carbene (NHC) ligands with trialkylsilanes as reducing agents.⁶

Since allylic alcohols are useful synthetic intermediates and a widespread motif in natural products, we immediately set out to render these reductive couplings enantioselective. Serendipitously, the very first chiral phosphine ligand that we tested was outstanding and for several years remained optimal: (+)-(neomenthyl)diphenylphosphine (NMDPP) (Scheme 3).⁷ Excellent yields, regioselectivities, and enantioselectivities were achieved for alkyne substrates containing at least one aromatic substituent. The high selectivity is hypothesized to

Scheme 3. Enantioselective Alkyne–Aldehyde Reductive Coupling



originate from the required arrangement of the components in a highly ordered transition state, as depicted in Scheme 3. Later, we synthesized a novel class of P-chiral monodentate ferrocenyl phosphines that were able to accomplish the same coupling using dialkyl alkynes with moderate regio- and enantioselectivities.⁸

Control of Regioselectivity in Alkyne Reductive Coupling

Questions of regioselectivity are inherent in reactions of alkynes. Although good to excellent selectivity could be achieved by varying the electronic nature of the substituents (such as aryl–alkyl alkynes), we wondered whether the use of more general directing groups could secure similarly high levels of selectivity. First, we observed that 1,3-enynes also provided high levels of selectivity, and the resulting dienes (e.g., **15**) could be selectively reduced to give alkyl-substituted allylic alcohols (e.g., **16**) that would otherwise be inaccessible (Scheme 4a).⁹ Moreover, the conjugated alkene preferentially dictates the regioselectivity of the addition, even directly opposite an aryl group. DFT calculations suggested that this intriguing preference may be due to a slightly different oxidative cyclization transition state involving a formal 1,4-attack and a transient η^3 -allylmetal complex (**17**).¹⁰ These 1,3-enyne substrates were also successfully coupled with ketones.¹¹

Next, we decided to investigate whether a remote, tethered alkene could be a suitable directing group. To our surprise, we found not only that the reaction with the aldehyde could be directed to the distal carbon of the alkyne (product A; >95:5 rr)

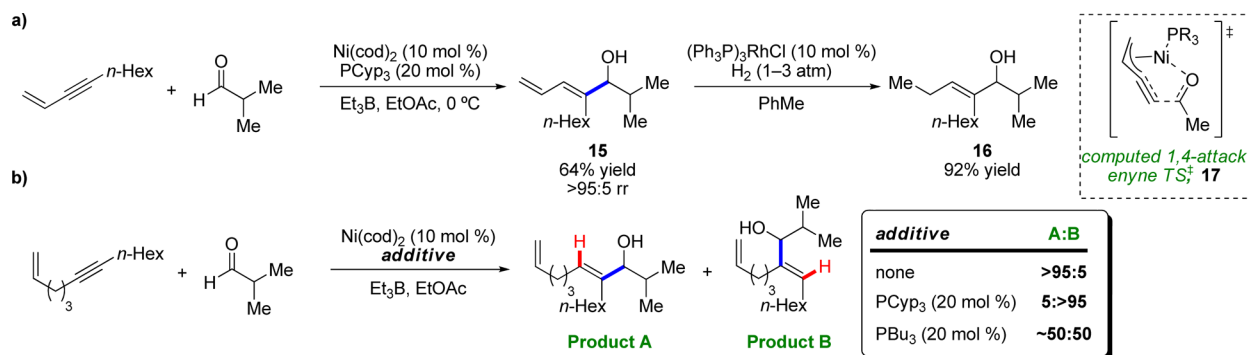
but also that by the addition of tricyclopentylphosphine (PCyp_3) the selectivity could be completely reversed to the proximal carbon (product B; >95:5 rr) (Scheme 4b).¹² Interestingly, addition of a less sterically demanding ligand, tributylphosphine (PBu_3), provided no selectivity (~1:1 rr). To rationalize these results, we considered square-planar intermediate **18**, in which nickel coordinates both the alkyne and tethered alkene, leaving room for one more weakly coordinating ligand (L) (Scheme 5). When no strongly coordinating ligands are present, the aldehyde replaces L (**19**), and the reaction proceeds to form the C–C bond at the carbon atom distal to the tethered alkene (product A). However, when a strongly coordinating phosphine ligand is present, it replaces L (**20a** or **21**). The sterically demanding PCyp_3 disfavors simultaneous coordination of two phosphine ligands, causing the aldehyde to replace the coordinating alkene while preserving the geometry of the complex (**20b**), presumably by an associative mechanism, to eventually produce product B. Less bulky phosphine ligands such as PBu_3 preferentially replace both L and the alkene (**21**), forming products A and B unselectively. These mechanistic proposals were corroborated by examining the product diastereoselectivity using chiral 1,6-enyne substrates.¹³

Finally, it is important to note that other solutions to issues of alkyne regioselectivity in reductive couplings have been reported. Montgomery and co-workers demonstrated that carbene ligands of various steric bulk can be employed to achieve high levels of regioselectivity for both aldehyde reductive coupling product regioisomers.¹⁴ More recently, they disclosed an impressive solution for regiocontrol through alteration of whether the stereodetermining oxidative cyclization is rate-determining or reversible by changing the ligand and silane reducing agent.¹⁵

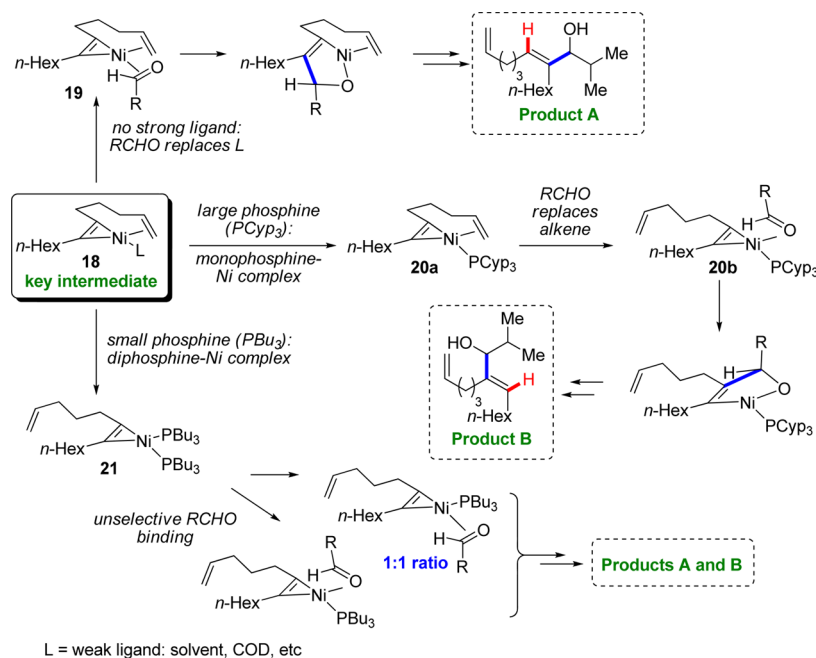
Reductive Coupling of Alkynes and Imines

Intrigued by the success of reductive coupling to provide ready access to allylic alcohols, we were keen to investigate whether alkynes could be coupled with imines to form allylic amines. The reduced electrophilicity of imines provided a challenge and necessitated a complete change in reaction conditions. After extensive investigation, we found that alkylative (rather than reductive) coupling products (e.g., **22**) could be formed in good yields and regioselectivities using protic solvents in combination with electron-rich phosphines and triethylborane (Scheme 6a).¹⁶ Although reductive coupling products were not formed, the scope of the three-component coupling reaction was significantly improved by the use of aryl or vinyl boronic

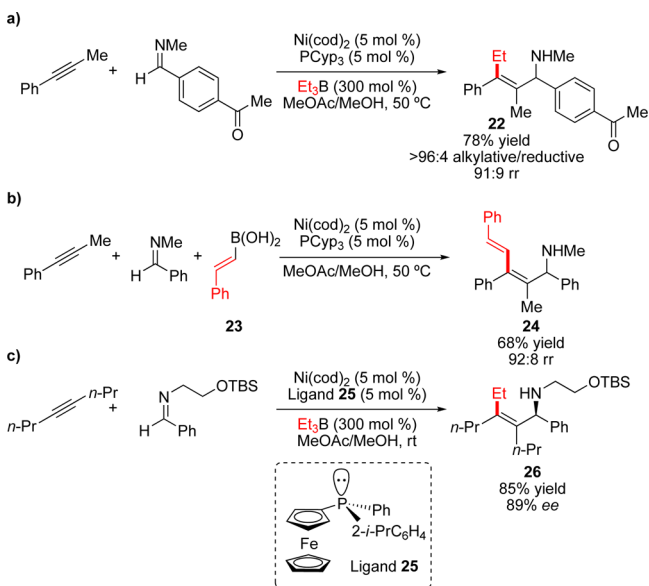
Scheme 4. Alkene Directing Effects in Alkyne–Aldehyde Reductive Coupling Reactions for (a) 1,3-Enynes and (b) Tethered Enynes



Scheme 5. Mechanistic Rationale for the Tethered Alkene Reductive Coupling Regioselectivity



Scheme 6. Selected Examples of Reductive Coupling of Alkynes and Imines Using (a) Borane and (b) Boronic Acid Alkylating Agents; (c) Enantioselective Reductive Coupling of Imines



acids (e.g., **23**) (Scheme 6b). Several years later, Zhou and co-workers determined that reductive coupling products could be formed selectively by using electron-poor *N*-tosylimines, PBu₃, and aprotic solvents.¹⁷

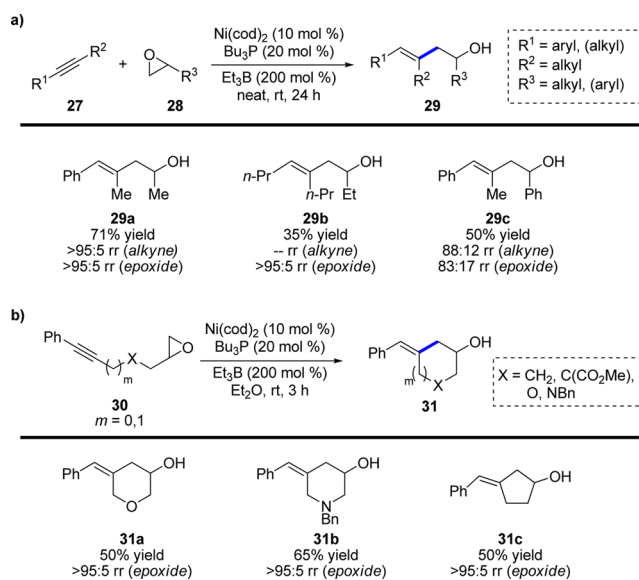
Use of the chiral phosphine (+)-NMDPP, which worked well for the coupling of aldehydes, provided products with only moderate enantioselectivity. Fortunately, when *P*-chiral ferrocenyl phosphine **25** was employed in combination with a removable TBSOCH₂CH₂ protecting group, the resulting alkylative coupling products containing an allylic amine and tetrasubstituted alkene (e.g., **26**) were formed in good yields

with good to excellent regioselectivities and good enantioselectivities (Scheme 6c).¹⁸

Reductive Coupling of Alkynes and Epoxides

After exploring the reductive coupling of various π components, we next sought to study whether one of these π components could be exchanged for an activated σ component. In 2003, we reported the reductive coupling of alkynes with terminal epoxides to afford homoallylic alcohols (**29**) (Scheme 7a).¹⁹ When the reaction was conducted without added solvent, the products were obtained in moderate to good yields. The transformation proceeds with stereospecific syn addition to the alkyne and with excellent regioselectivity for both the alkyne and epoxide. Experiments with enantiomerically enriched epoxides demonstrated, in accordance with the proposed

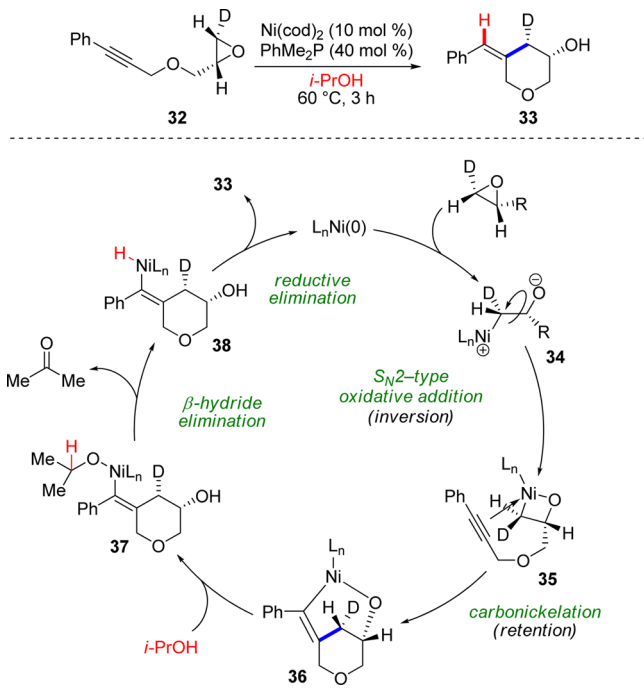
Scheme 7. (a) Inter- and (b) Intramolecular Reductive Couplings of Alkynes and Epoxides



mechanism, that the stereochemistry of the internal C–O bond is preserved in the product. The reaction was also conducted in an intramolecular fashion, which proceeded with excellent endo selectivity (>95:5) in the ring opening regardless of the linking group and ring size formed (Scheme 7b).

In a later study, we demonstrated that the intramolecular reaction could also be performed by employing an inexpensive, air-stable nickel(II) salt as a precatalyst and 2-propanol as the reducing reagent (Scheme 8).²⁰ Deuterium-labeling studies

Scheme 8. Mechanism of the Reductive Coupling Reaction of Alkynes and Epoxides



demonstrated that the terminal carbon of the epoxide undergoes inversion of configuration in the reaction (33). This result, along with the preserved stereochemistry of the epoxide, is indicative of a mechanism involving a nickelaoxetane intermediate (35). Oxidative addition of the terminal epoxide C–O bond with Ni(0) occurs with inversion, by way of nucleophilic ring opening, to afford 35. Next, migratory insertion of the alkyne (with retention) forms 36, and subsequent transmetalation (Et_3B) or protonolysis ($i\text{-PrOH}$) affords 37, which undergoes β -hydride elimination followed by

reductive elimination to release the product and the Ni(0) catalyst.

APPLICATION OF REDUCTIVE COUPLING TO TOTAL SYNTHESIS

Although the discussion thus far has focused on new reaction development, our group has always sought to create methodologies addressing specific unmet needs in complex molecule synthesis. To this end, we have tested our reductive coupling methods in the total synthesis of a number of natural products, particularly in pushing the boundaries of reductive macrocyclizations.

As mentioned in the Introduction, our initial inspiration for pursuing the development of reductive coupling methodology came from the allylic alcohol moiety found in the sesterterpene terpestacin. Indeed, the alkyne–aldehyde reductive coupling reaction allowed us to readily access this motif and rapidly assemble (–)-terpestacin (1) (Scheme 9).²¹ Although dialkyl alkynes such as 39 can present regioselectivity challenges, we were gratified that our P-chiral ferrocenyl phosphine ligands favored the desired diastereo- and regioisomers to produce 41. Moreover, simply by changing the antipode of the ligand, we were afforded complete stereocontrol over the isolated allylic alcohol stereocenter. This allowed us to also access 11-*epi*-terpestacin, whose structure was originally reported to be that of a new natural product, siccanol, via the same synthetic pathway. In fact, we were able to reassign the structure of “siccanol” as being identical to that of (–)-terpestacin.

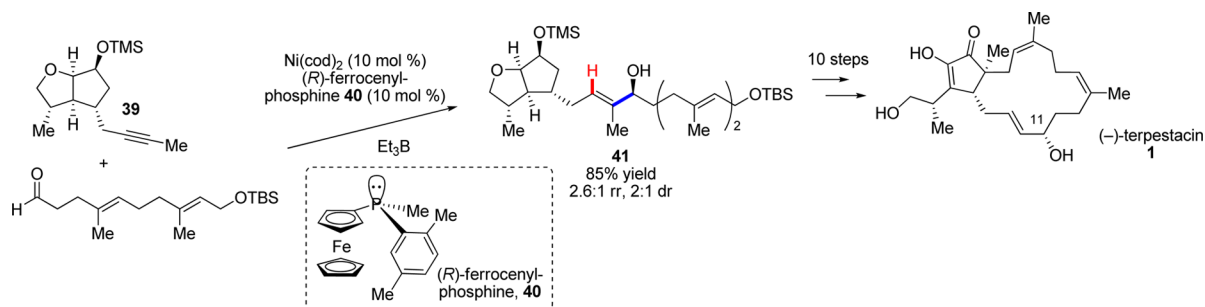
Another molecule whose synthesis was amenable to our developed methods is amphidinolide T1 (2) (Scheme 10).²² In this case, both the homoallylic alcohol and the α -hydroxy ketone motifs were synthesized via reductive coupling of alkynes with an epoxide and an aldehyde, respectively. The transformations proceeded in good yields and diastereoselectivities, including the macrocyclization event that forms the 18-membered-ring product 42, with only a single C13 epimer observed, solely under substrate control. A similar approach allowed us to access the related amphidinolide T4.²³

Additionally, reductive couplings and cyclizations were explored for the synthesis of (+)-acutiphycin (43)²⁴ and have allowed us to achieve the total syntheses of (–)-gloeosporone (44)²⁵ and pumiliotoxins 209F (45) and 251D (46)²⁶ (Figure 2).

REDUCTIVE COUPLING OF ALLENES

During the development of multicomponent reductive couplings of alkynes, we questioned whether other types of C–C π bonds could undergo similar transformations. We first

Scheme 9. Total Synthesis of (–)-Terpestacin and 11-*epi*-Terpestacin Using an Enantioselective Alkyne–Aldehyde Reductive Coupling Reaction To Couple Key Fragments



Scheme 10. Total Synthesis of Amphidinolide T1 Leveraging Both Alkyne–Epoxide and Alkyne–Aldehyde Reductive Couplings

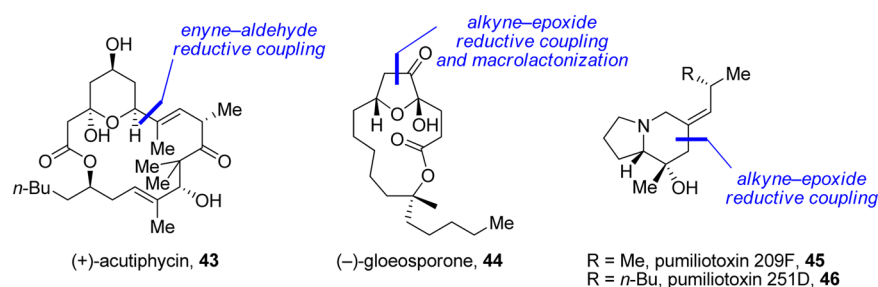
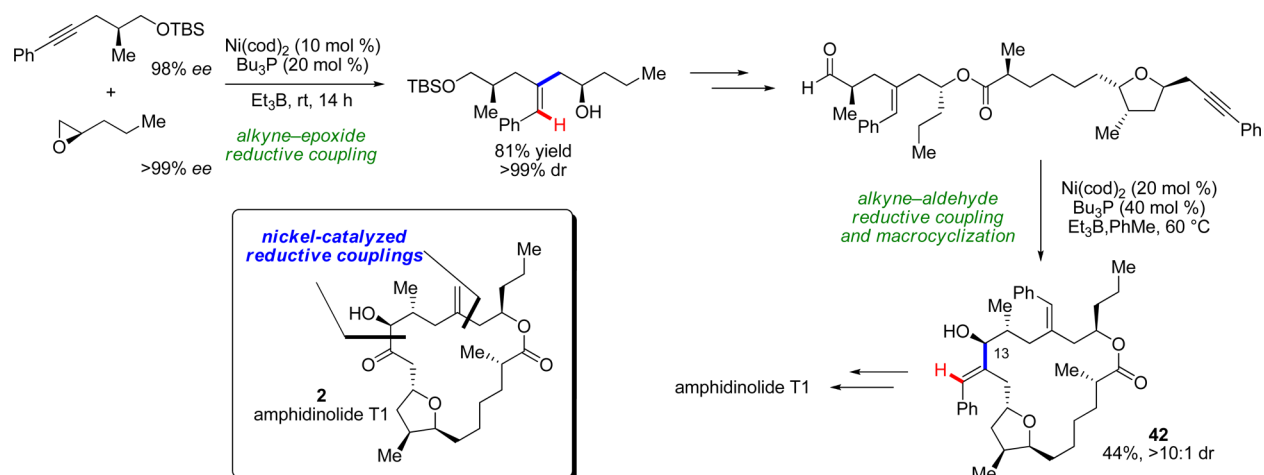
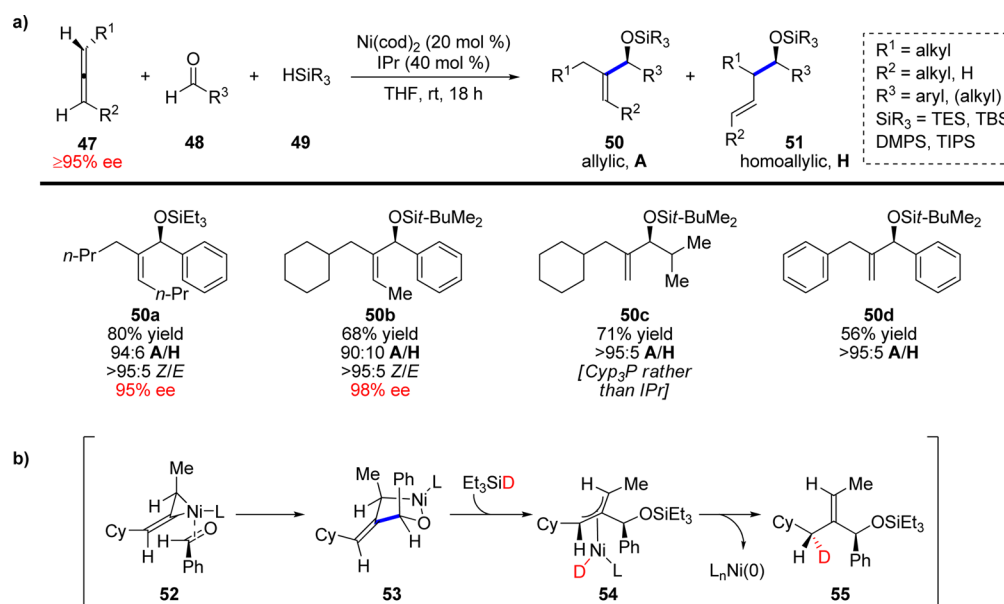


Figure 2. Applications of nickel-catalyzed methods to natural product synthesis.

Scheme 11. (a) Highly Selective Coupling of Allenes, Aldehydes, and Silanes; (b) Proposed Mechanism



decided to study allenenes, and in 2005 we reported a highly stereoselective and regioselective reductive coupling of allenenes, aldehydes, and silanes to furnish allylic alcohol products **50** in moderate to good yields (Scheme 11a).²⁷

Several noteworthy aspects of this transformation deserve further comment. The reaction displays a remarkable site selectivity in which coupling of the least reactive (central sp²-hybridized) carbon atom of allene is observed. Furthermore,

the use of NHC ligands provided complete transfer of enantiomeric purity from the allene to the product. This transfer of axial chirality turned out to be highly ligand-dependent, with aliphatic phosphines, such as PCyp₃, causing significant erosion of the enantiomeric purity. Lastly, the alkene moiety is formed with excellent Z selectivity. This makes the protocol complementary to the previously developed coupling of alkynes and aldehydes, which leads to allylic alcohol products

with excellent *E* selectivity (Scheme 1). The formed *Z* geometry is noteworthy since it corresponds to a syn addition of the aldehyde and the hydride to the more hindered face of the allene (syn to the R^2 substituent). In addition, there appears to be an inherent selectivity for addition across the sterically more hindered double bond of the allene, as shown for products **50b–d**.

A possible explanation for these observed selectivities was provided by a deuterium-labeling study (Scheme 11b). When DSiEt_3 was used, deuterium incorporation occurred with excellent diastereoselectivity (>19:1) at a single site (**55**). On the basis of this result, the reaction is proposed to proceed via complex **52**, where $\text{Ni}(0)$ coordinates to the less hindered allene face and least sterically congested alkene. The aldehyde would then coordinate opposite to the methyl substituent. Insertion of the aldehyde forms metallacycle **53**, which after σ -bond metathesis with the silane is believed to afford η^3 -allylnickel complex **54**. Next, reductive elimination occurs to form the least congested alkene, accounting for the location of the deuterium incorporation.

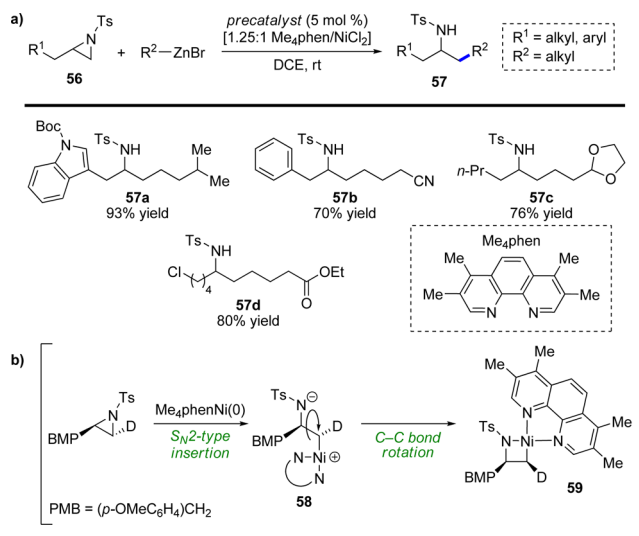
CROSS-COUPLING OF AZIRIDINES

During our investigation of reductive coupling reactions, we became interested in the application of aziridines as σ -bond electrophiles. Despite numerous attempts, we have not been able to develop a reductive coupling of aziridines and alkynes to form homoallylic amines. However, we and others have recently developed highly selective nickel-catalyzed coupling reactions of aziridines with organozinc reagents (Scheme 12a).

Seminal work by Hillhouse demonstrated that (bpy)Ni(0) complexes undergo oxidative insertion into the terminal position of aliphatic monosubstituted aziridines to form stable, isolable azanickelacyclobutane complexes.²⁸ Despite this intriguing discovery, no nickel-catalyzed cross-coupling reactions of aziridines were developed until Huang and Doyle²⁹ reported a Negishi-type reaction in 2012. In that study, they showed that styrene-derived *N*-tosylaziridines undergo regioselective coupling with aliphatic organozinc reagents at the more reactive benzylic position. Subsequently, less reactive aliphatic *N*-tosylaziridines were successfully coupled by using an *N*-sulfonyl group containing an unsaturated ester at the 2-position of the arylsulfonyl group.³⁰ Although the catalytic system displayed excellent reactivity, the method provided only moderate regioselectivity and furnished the products as a mixture of inseparable isomers.

Inspired by the pioneering studies of Hillhouse and the successful development of a catalytic coupling reaction by Doyle, we were able to develop a highly selective (>20:1 rr) and efficient coupling of aliphatic *N*-tosylaziridines with aliphatic organozinc reagents that affords sulfonamide products **57** in good to excellent yields (Scheme 12a).³¹ Furthermore, we developed an air-stable nickel(II)chloride/ligand precatalyst that can be handled and stored outside a glovebox, thus avoiding the use of air-sensitive $\text{Ni}(\text{cod})_2$. Finally, through examination of catalytic intermediates for competency and deuterium-labeling studies, we were able to devise a likely mechanism for this transformation. First, the nickel(0) catalyst, generated from the precatalyst by two consecutive transmetalation and reductive elimination reactions, undergoes insertion into the least hindered, terminal C–N bond of the aziridine to form azanickelacyclobutane **59**. The oxidative insertion proceeds via an $\text{S}_{\text{N}}2$ -type mechanism (inversion) followed by C–C bond rotation (**58**) and ring closure to form

Scheme 12. (a) Highly Regioselective Cross-Coupling of *N*-Tosylaziridines and Alkylzinc Reagents; (b) Proposed Mechanism for Azanickelacyclobutane Formation



59 (Scheme 12b), similar to the mechanism of epoxide oxidative addition shown in Scheme 8. Subsequent transmetalation with the organozinc reagent and reductive elimination releases product **57** (as a ZnBr adduct).

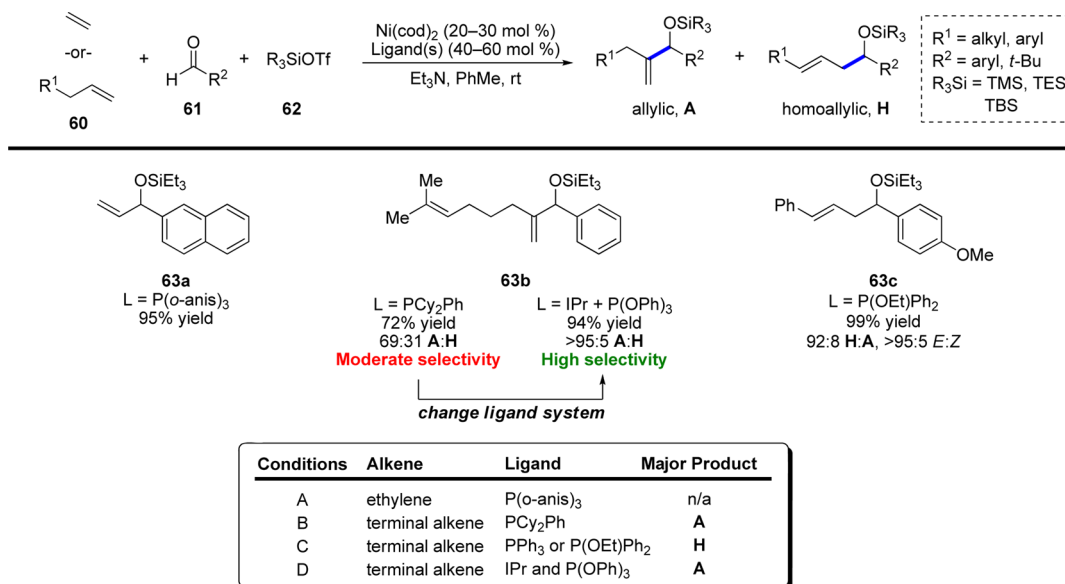
ALKENES AS NUCLEOPHILES

Coupling Reactions of Alkenes and Aldehydes

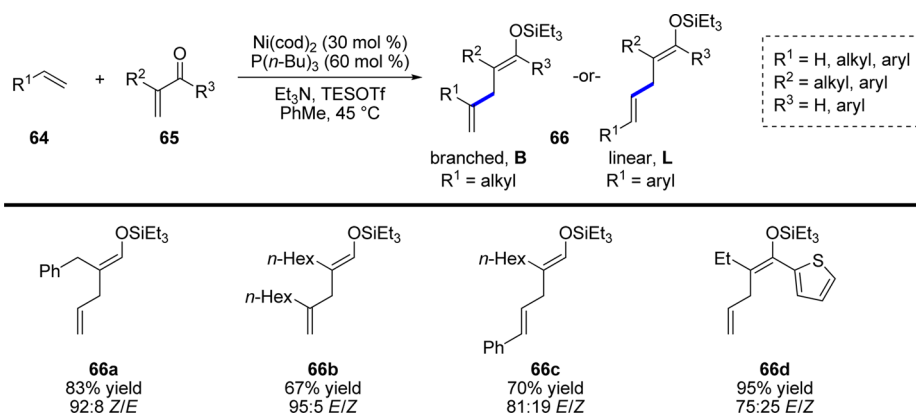
Throughout the course of our work with alkynes and allenes, we aimed to extend these methods to other types of π nucleophiles, particularly alkenes. These investigations bore their first fruit in 2005, when we disclosed our first example of a nickel-catalyzed alkene–aldehyde coupling (Scheme 13). Closely related to both the carbonyl–ene and Prins reactions, this multicomponent reaction couples terminal olefins (including ethylene), aldehydes, and silyl triflates to form silyl-protected allylic³² or homoallylic alcohols.³³ In contrast to prototypical carbonyl–ene chemistry, less substituted alkenes, such as ethylene and terminal alkenes, are more reactive coupling partners than di-, tri-, and tetrasubstituted alkenes. The key component in this reaction is the highly electrophilic silyl triflate promoter. A number of groups, for example that of Tamaru,³⁴ have demonstrated the important role that Lewis acid additives, such as Et_2Zn and Et_3B , play in the activation of weakly electrophilic π components. Subsequently, Ogoshi demonstrated that silyl triflate additives can also fulfill this role and can allow even poor external nucleophiles, such as alkenes, to react with the electrophilic nickel species more easily.³⁵

Ultimately, three distinct reaction protocols were devised to enable the selective synthesis of either the allylic (**A**, or branched) or homoallylic (**H**, or linear) isomer.³⁶ Initially, $\text{P}(o\text{-anis})_3$ was found to be an outstanding ligand for ethylene (Scheme 13, conditions A, **63a**). However, monosubstituted alkenes required a different ligand for successful reaction, favoring the allylic product (conditions B, **63b**). Unfortunately, the yields were only moderate, and the selectivity for the allylic product was generally not better than $\sim 2:1$. Subsequently, conditions were developed that afforded the homoallylic products in good yield with excellent selectivity (conditions C, **63c**). However, despite having devised methods to provide

Scheme 13. Nickel-Catalyzed Carbonyl–Ene Reaction



Scheme 14. Nickel-Catalyzed Conjugate Addition of Alkenes to Enals and Enones



both the allylic and homoallylic products, the selectivity for the allylic product remained inadequate, so we returned to this reaction to attempt to improve the selectivity. Extensive optimization and mechanistic investigation were reported after the two initial communications,³⁷ and the results of this investigation suggested that nickel complexes containing NHC ligands, such as IPr, were competent to support the early steps of the coupling reaction with excellent allylic selectivity, but that catalytic turnover did not take place. Thus, a campaign was initiated to turn NHC-ligated nickel complexes into viable catalysts.³⁸

Ultimately, we determined that the catalytic cycle was likely stalling subsequent to β -hydride elimination. Studies by Yamamoto and co-workers³⁹ had demonstrated that difficult reductive eliminations could be induced by the coordination of an electron-deficient alkene to the metal center. The addition of 3-trifluoromethylstyrene slightly improved the yield of the desired product, prompting us to examine other π -accepting ligands that could fulfill the same role; indeed, $\text{P}(\text{OPh})_3$ was identified as an extremely effective additive. The combination of $\text{Ni}(\text{cod})_2$, IPr, and $\text{P}(\text{OPh})_3$ (Scheme 13, conditions D) provided the desired silyl-protected allylic alcohol products in excellent yields with essentially perfect A:H selectivity. Intriguingly, both $\text{P}(\text{OPh})_3$ and IPr are incapable of catalyzing

the reaction, yet the combination of these ligands forms the ideal catalyst system. We believe that this results from the fact that IPr coordinates much more strongly to nickel and that it is not until the IPr–nickel hydride has formed that $\text{P}(\text{OPh})_3$ can coordinate to nickel, eventually resulting in reductive elimination and catalyst turnover.

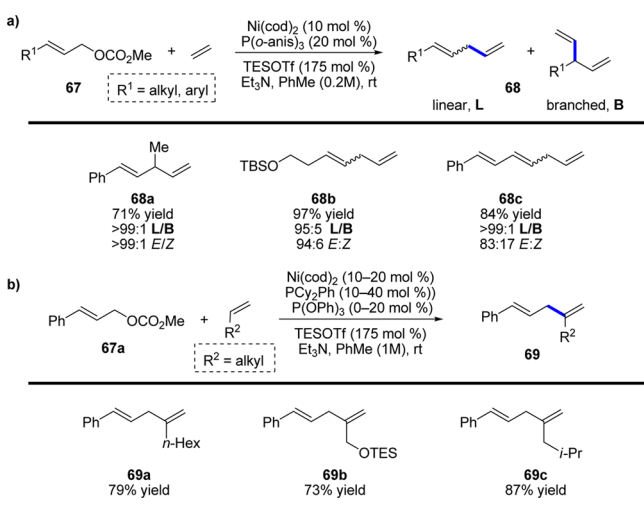
Coupling Reactions of Alkenes and Enones

An extension of this work was subsequently developed in which the alkene could act as an alkenylmetal equivalent as before, but instead of 1,2-addition to the carbonyl, 1,4-addition across an enone or enal (**65**) could be effected (Scheme 14).⁴⁰ The position of reactivity on the alkene is determined by the identity of R^1 : an alkyl group causes reaction at the internal position (**66b**), whereas an aryl group reverses the reactivity to form a linear product (**66c**).

Allylic Substitution Reactions

After demonstrating the use of alkenes as nucleophiles in conjugate additions, we sought to examine a reaction that could instead provide skipped dienes (1,4-dienes) more generally. We envisioned an allylic substitution reaction with simple alkenes as a way to obtain these valuable products, and our initial efforts found that allylic carbonates (**67**), as well as several other allylic substrates, react smoothly with ethylene (Scheme 15a) and

Scheme 15. Allylic Substitution Reactions of (a) Ethylene and (b) Terminal Aliphatic Alkenes



terminal alkenes (Scheme 15b). The reaction produces 1,4-dienes in good yield with outstanding selectivity for linear (as opposed to branched) products, for 1,4-dienes instead of isomerized 1,3-dienes, and for *E* rather than *Z* alkene isomers (68a–c).⁴¹ Additionally, when terminal alkenes were used, excellent selectivity for reaction at the internal position of the alkene was obtained (69a–c).

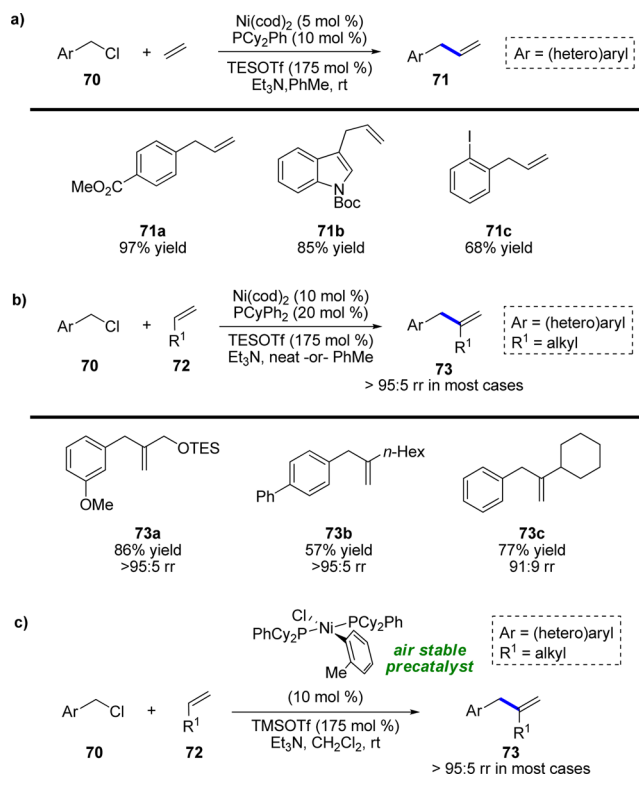
The Mizoroki–Heck Reaction

Having demonstrated the use of terminal alkenes as alkenylmetal equivalents, we became interested in one of the classic examples of such a reaction, the Mizoroki–Heck reaction (MHR). Often grouped more closely with cross-coupling, the MHR is mechanistically quite similar to allylic substitution reactions and is an indispensable means to synthesize alkenes. Under conditions closely related to those for allylic carbonates, the desired allylbenzenes (71) were obtained in outstanding yields from a wide range of substituted benzyl chlorides and ethylene (Scheme 16a).⁴² Fortunately, only a slight change to the conditions was necessary to allow successful reaction with terminal alkenes, yielding substituted allylbenzenes (73) with outstanding regioselectivity for reaction at the internal position of the alkene (>95:5 branched/linear in almost all cases; Scheme 16b).

Subsequently, we decided to investigate monosubstituted alkenes as substrates in more detail and improve the method with respect to practicality and cost (Scheme 16c).⁴³ A critical enabling factor was the development of an air-stable Ni(II) precatalyst for this reaction, which was crucial because it alleviated the need to use expensive and highly air-sensitive Ni(cod)₂. This change allows all of the reactions to be set up entirely without the use of a glovebox or even any air-free techniques, which greatly simplifies the use of this chemistry. This investigation significantly expanded the substrate scope and systematically examined the functional group compatibility of the reaction, as well as substituting TMSOTf for the far more expensive TESOTf. These air-stable Ni σ -aryl precatalysts were further explored in subsequent studies and can be prepared from numerous ligands.⁴⁴

Following the success of the benzylic MHR, we sought to examine related reactions in which this catalyst system could be applicable. One logical extension was to examine aryl electrophiles rather than benzyl electrophiles. Obtaining the

Scheme 16. Mizoroki–Heck Benzoylation of (a) Ethylene and (b) Terminal Alkenes and (c) the Development of an Air-Stable Ni(II) Precatalyst



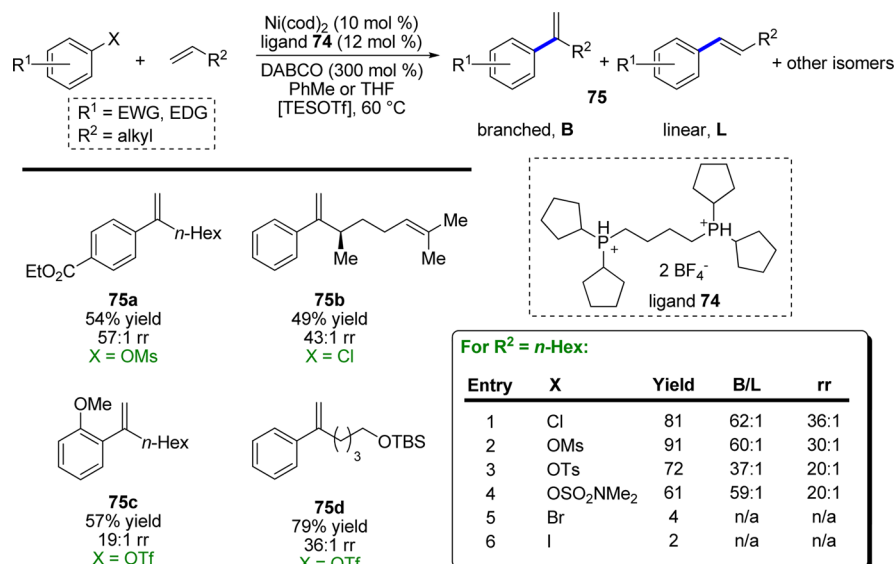
branched product of an MHR with electronically unbiased alkenes was, at the time, an open problem in this field⁴⁵ and therefore piqued our interest.

Unfortunately, the developed conditions, as well as many related conditions, generally performed poorly with aryl chlorides and triflates instead of benzyl chlorides. Moving from benzyl to aryl electrophiles, although a subtle change, removes the possibility for η^3 -allylnickel intermediates, and thus, a distinct ligand sphere is required. Indeed, bidentate phosphine ligands proved to be essential and, in combination with the appropriate base, provided the desired branched styrene products in good yield with excellent regioselectivity of >95:5 for the branched product relative to all of the other isomers produced (Scheme 17).⁴⁶ Importantly, aryl electrophiles other than triflates could also be employed in the reaction when TESOTf was also added to perform a counterion exchange and intercept a common Ni–OTf species.

CONCLUSIONS

Though our interest in nickel catalysis initially arose from the utility of reductive coupling reactions to reach structural motifs such as allylic alcohols found in many natural products, the breadth of methodology developed in our group over the past 15 years has far outstripped our initial plans. We were successfully able to couple readily available alkynes with π donors, such as aldehydes and imines, as well as σ donors, in the form of epoxides, to furnish ubiquitous allylic alcohols and amines and homoallylic alcohols, respectively. One clear omission, and a place for future developments, lies in the reductive coupling reactions of aziridines to afford homoallylic amines. However, we were able to develop a nickel-catalyzed

Scheme 17. Branch-Selective Mizoroki–Heck Arylation of Terminal Aliphatic Alkenes



cross-coupling reaction of aziridines, demonstrating that oxidative addition, at least, is feasible.

In addition, we have expanded the range of π components for nickel-catalyzed coupling reactions beyond alkynes to allenes and alkenes. Coupling of alkenes in particular has proven extremely fruitful, not only with aldehydes as coupling partners but with allylic, benzylic, and aryl electrophiles as well. We foresee that many of the modes of reactivity and mechanistic insights gained over the course of our studies will add to the current exciting developments in the field of nickel catalysis. For instance, leveraging many of the different oxidation states that are readily available to nickel⁴⁷ could provide access to distinct modes of activity in addition to those displayed by the Ni(0)/Ni(II) catalytic cycles discussed in this Account. For these reasons, we eagerly look forward to contributing to new developments within the field of nickel catalysis.

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Notes

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