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## Catalytic Addition of Simple Alkenes to Carbonyl Compounds Using Group 10 Metals

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### Abstract

Recent advances using nickel complexes in the activation of unactivated monosubstituted olefins for catalytic intermolecular carbon–carbon bond-forming reactions with carbonyl compounds, such as simple aldehydes, isocyanates, and conjugated aldehydes and ketones, are discussed. In these reactions, the olefins function as vinyl- and allylmetal equivalents, providing a new strategy for organic synthesis. Current limitations and the outlook for this new strategy are also discussed.

### Keywords

alkene; transition metal catalysis; carbon–carbon bond formation; carbonyl-ene

## 1 Introduction

Functionalization of simple alkenes has long been a focus in organic chemistry, largely because alkenes are one of the most readily available classes of functional groups.<sup>1</sup> Several indispensable catalytic transformations utilize olefins, such as Ziegler-Natta polymerization, the Wacker oxidation, hydroformylation, epoxidation, hydrometallation, and dihydroxylation, and thereby provide access to several important classes of other functional groups.<sup>2–4</sup> Similarly important technologies are those that functionalize olefins while leaving the olefin intact, such as olefin cross-metathesis and the Heck reaction.<sup>5,6</sup> The resulting functionalized alkenes serve as versatile building blocks for subsequent manipulations. Historically, the most direct methods for the synthesis of allylic and homoallylic alcohols from alkenes and carbonyl compounds are the Prins reaction and carbonyl-ene reaction (Scheme 1).<sup>7,8</sup> These reactions generally form a new carbon–carbon bond at the less substituted carbon of the alkene. Typically, electron-rich alkenes, such as 1,1-disubstituted or trisubstituted olefins, react effectively with small and electron-deficient enophiles, including formaldehyde and glyoxylates. These processes proceed with heating and typically benefit from significant rate enhancement under the action of Lewis acid catalysts.

Considerably less attention has been paid to extending the substrate scope to include electron-rich and sterically demanding aldehydes or less nucleophilic alkenes such as  $\alpha$ -

olefins.<sup>9–12</sup> The typical carbonyl used in the intermolecular Prins reaction to make allylic alcohols is also largely limited to formaldehyde. In short, these traditional technologies are effective for only a small subset of the plethora of possible coupling partners, and are limited to forming new carbon–carbon bonds at the less stabilized position of the alkenes. Consequently, we wished to develop transformations that would bridge these gaps in existing Prins and carbonyl-ene methodology.

Herein we summarize our own efforts in addressing the above deficiencies and highlight several important related discoveries by others. We will focus in particular on recent advances using nickel(0) complexes in the activation of unactivated monosubstituted olefins ( $\alpha$ -olefins) for catalytic intermolecular carbon–carbon bond-forming reactions with carbonyl compounds, such as aromatic and tertiary aliphatic aldehydes, isocyanates, and conjugated aldehydes and ketones.<sup>13</sup> In these reactions, the olefins function as equivalents of vinylmetal and/or allylmetal species, providing a new strategy for organic synthesis. In this Account, we consider “simple alkenes” to be olefins bearing only H or aliphatic substituents, compounds often referred to as “unactivated” or “electronically neutral” alkenes. Thus, reactions employing dienes, enynes, allenes, and olefins functionalized at the vinylic or allylic positions are outside the scope of this account. Because of space limitations and, in general, mechanistic differences, we also do not discuss additions of simple alkenes to carbon monoxide or carbon dioxide.

## 2 Carbonyl-Ene-Type Reactions

### 2.1 Lewis Acid-Catalyzed Reactions Using Group 10 Cationic Complexes

The carbonyl-ene reaction continues to be a powerful C–C bond-forming transformation. Recent developments in the field include asymmetric catalytic methods using chiral Lewis acids. The first catalytic enantioselective variant using a chiral Al-BINOL complex was reported by Yamamoto.<sup>14</sup> Subsequently, Mikami communicated the use of Ti-BINOL complexes as efficient catalysts for the carbonyl-ene reaction.<sup>15</sup> Chiral bis(oxazoline) Cu(II) complexes reported by Evans and co-workers were found to be general and effective catalysts for the reaction of a wide range of unactivated olefins with ethyl glyoxylate, providing the corresponding  $\gamma,\delta$ -unsaturated  $\alpha$ -hydroxy esters in high enantioselectivity.<sup>16</sup> Pioneering work using cationic chiral late transition metal complexes as Lewis acids for the asymmetric carbonyl-ene reaction was also reported by Mikami. For example,  $\{\text{Pd}(\text{CH}_3\text{CN})_2[(S)\text{-Tol-BINAP}]\}(\text{SbF}_6)_2$  was found to be an efficient catalyst for the reaction between ethyl glyoxylate and electron-rich alkenes.<sup>17</sup> Other cationic metal complexes have also been used to catalyze asymmetric carbonyl-ene reactions effectively.<sup>18</sup>

Although high enantioselectivity has been achieved by the systems described above, the development of cationic group 10 metal complexes for carbonyl-ene reactions has gained momentum lately because of growing interest in dynamic asymmetric catalysis.<sup>19</sup> The use of conformationally flexible or meso ligands to either magnify the effect of another chiral ligand or act as the only source of asymmetry in an enantioselective transformation has opened up new opportunities for chiral homoallylic alcohol synthesis. For example, coordination of a diphosphine ligand to a substitutionally inert metal, such as Pt(II), is thought to slow conformational interconversion such that a normally metastable chiral metal-ligand assembly can be used in catalysis. Representative examples included Gagne's  $\delta$ - and  $\lambda$ -[Pt(BIPHEP){(S)-BINOL}], Mikami's axially chiral bis(diphenylphosphino)ferrocene Ni(II) complexes (derived from enantiopure DABN), and Doherty's conformationally flexible NUPHOS diphosphine ligand systems. These catalysts can rival or even outperform the asymmetric glyoxylate-ene reactions achieved with traditional chiral ligands such as BINAP. The ease of preparation and low cost of the diphosphines employed are major motivations for continued development. Other recent

progress in this field includes the use of ionic liquids, and the development of new in situ activation methods for conversion of the diastereopure metal complex to an efficient catalyst without the need for stepwise liberation of the primary chiral source.

Since the first report on using Pd(II)BINOL catalysts in asymmetric carbonyl-ene reactions by Mikami, several groups have demonstrated that the choice of achiral additive can profoundly impact (and improve) the effectiveness of a given chiral catalyst.<sup>20</sup> For example, achiral phenol additives can accelerate reactions employing triflate-based catalysts, possibly by disrupting contact ion pairs and sequestering traces of water.<sup>21</sup> Such acidic phenols may represent a general solution to the frequently encountered problems of undesired counterion coordination and poisoning by water, both of which are often detrimental to catalysis by cationic metal complexes. This strategy has been extended to the reactions between ethyl trifluoropyruvate and various olefins, including less electron-rich monosubstituted olefins, providing a fruitful pathway to chiral homoallylic trifluoromethyl-substituted tertiary alcohol derivatives.

A systematic study has also shown that there is a remarkable difference in reactivity and the reaction pathways observed among group 10 metal-catalyzed carbonyl-ene reactions.<sup>22</sup> Aryl glyoxylates are also good partners for reactions involving 1,1-disubstituted alkenes. The Pd(II) and Pt(II) Lewis acid catalysts bearing BINAP have proven to be water tolerant, and thus highly enantioselective carbonyl-ene reactions of arylglyoxal monohydrate have been documented.<sup>23</sup> More recently, a Ni(II) catalyst system employing a chiral *N,N'*-dioxide ligand was found to be very efficient for carbonyl-ene reactions between  $\alpha$ -methylstyrenes or 2-alkyl-substituted propenes and aromatic or aliphatic glyoxal derivatives, as well as ethyl glyoxylate.<sup>24</sup> Excellent enantioselectivities (up to >99% ee) were obtained.

## 2.2 Reactions Catalyzed by Low-Valent Ni(0) Complexes

The above carbonyl-ene reactions catalyzed by cationic Lewis acid complexes represent a major advance in the field in terms of both efficiency and chiral induction. A wide range of simple alkenes can be used as substrates and are especially selective in carbonyl-ene reactions of glyoxylate esters. Nevertheless, the primary remaining challenge in the carbonyl-ene process is still one of scope. Few carbonyl-ene reactions of aromatic or sterically demanding aldehydes have been reported. The vast majority of carbonyl-ene reactions utilizing  $\alpha$ -olefins are with electron-deficient carbonyl compounds. The most efficient reactants are electron-rich olefins and small and/or highly electron-deficient aldehydes (e.g., chloral, formaldehyde, or glyoxylate esters). In short, current carbonyl-ene technology using cationic metal complexes is effective only within a limited range of possible coupling partners.

In 2006, we reported a general means for catalyzing intermolecular carbonyl-ene-type reactions of several types of compounds that were previously of very limited utility (or in some cases, not feasible) by using a Ni(0)-phosphine system (Table 1). The coupling partners include the most readily available alkenes ( $\alpha$ -olefins), along with several important families of aldehydes (aromatic, heteroaromatic, and tertiary aliphatic aldehydes).<sup>13b</sup> Pivotal to this work was Ogoshi's observation that a Lewis acid facilitated the formation of an oxanickellacycle through intramolecular cyclization of a  $\delta,\omega$ -enal yielding an *allylic* alcohol,<sup>25a</sup> and the first isolation of *homoallylic* alcohol as a minor product in our Ni(0)-catalyzed intermolecular alkene-aldehyde coupling. Further details will be discussed in the next section. The *E* configuration of the homoallylic alcohols in our reaction is favored by a factor of 3–5:1 in all cases of aliphatic  $\alpha$ -olefins examined, while greater than 95:5 *E:Z* selectivity is obtained when allylbenzene is employed. Identical results are obtained when the reaction is performed on a 5-fold larger scale with only 1.5 equivalents of allylbenzene relative to *p*-anisaldehyde.

Apart from the realization of new coupling combinations for homoallylic alcohol product synthesis that previously were unavailable by way of Lewis acid catalyzed carbonyl-ene processes, some observations in our new Ni(0) catalyst system are also noteworthy. First, these are the first catalytic carbonyl-ene-type reactions in which a monosubstituted alkene reacts preferentially over a more substituted double bond.<sup>26</sup> Although 1,1-disubstituted alkenes are among the most effective olefins in Lewis acid-catalyzed carbonyl-ene reactions, they do not undergo coupling to any noticeable degree with the nickel(0) system. Trisubstituted and disubstituted alkenes are similarly unreactive, and coupling products were not detected when methallylbenzene, *cis*-4-octene, and *trans*-4-octene were employed (Scheme 2).

A profound demonstration of this complementary selectivity is illustrated in Scheme 3.<sup>27</sup> When citronellene and benzaldehyde are treated with Me<sub>2</sub>AlCl, only the trisubstituted alkene reacts, and no detectable amount of reaction of the terminal olefin is observed. On the other hand, under the Ni(0)-catalyzed conditions, this selectivity is completely reversed. Products corresponding to reaction of the terminal alkene are the only ones detectable.

Secondly, while we have yet to conduct an exhaustive Hammett analysis, all evidence thus far points to the likelihood that there is a strong dependence of reaction rate upon the electronic nature of the aldehyde. Electron-rich aldehydes are more efficient substrates than those bearing electron-withdrawing substituents. While reactions of benzaldehyde require 48 h at room temperature to reach completion, those involving *p*-anisaldehyde can be complete within 18 h and are generally higher-yielding. Aromatic aldehydes bearing electron-withdrawing substituents, such as *p*-nitrobenzaldehyde, afford no trace of coupling product. It is also notable that heteroaromatic aldehydes are tolerated under our reaction condition, despite the fact that the silyl triflate used in the reaction is highly electrophilic.

Finally,  $\alpha$ -olefins without an allylic hydrogen atom, such as 3,3-dimethyl-1-butene, also coupled with benzaldehyde under our reaction conditions. However, instead of affording the homoallylic alcohol products (via elimination of the methyl group), the Ni-(EtO)PPh<sub>2</sub>-catalyzed reaction gives *trans*-disubstituted allylic alcohol exclusively, complementary to the Prins reaction.

Overall, the above system demonstrated very different substrate scopes and selectivity relative to those observed in the typical Lewis acid-catalyzed carbonyl-ene reaction, suggesting that the nickel species that catalyzes the new alkene-aldehyde coupling reactions above is not functioning simply as a Lewis acid. Indeed, in a set of four control experiments in which Ni(cod)<sub>2</sub>, phosphine ligand, TESOTf, and NEt<sub>3</sub> were each removed from the 1-octene-benzaldehyde coupling reaction, no coupling product was ever detected. The proposed mechanism for the above reaction will be discussed together with that of the closely related Ni(0)-catalyzed allylic alcohol synthesis in a later section.

### 3. Unactivated Monosubstituted Alkenes as Vinyl Metal Equivalents

Monosubstituted olefins form a new carbon-carbon bond with carbonyl compounds at the 1-position in both the carbonyl-ene reaction and the Prins reaction conditions, providing homoallylic alcohols and internal allylic alcohols, respectively. However, recent advances in the Ni(0)-catalyzed coupling reaction showed that the 2-position of the  $\alpha$ -olefin can also be activated highly selectively under appropriate conditions, yielding various terminal allylic alcohols. Conceptually, the  $\alpha$ -olefin here behaves as a 2-vinylmetal equivalent added to the carbonyl group, and provides a new strategy for uniting alkene and carbonyl fragments.

### 3.1 Intramolecular Reactions with Aldehydes and Ketones

Oxidative cyclization involving metal, C=O, and C=C (or C≡C) bonds is one of the mechanisms most often envisioned for transition metal-catalyzed multi-component coupling reactions. Formation of an oxametallacycle through the coupling of simple alkenes and ketones has been observed with several transition metals such as titanium, zirconium and rhodium.<sup>28–30</sup> In 2004, Ogoshi and colleagues directly observed and further confirmed the oxidative cyclization mechanism of an  $\eta^2$ -alkene and  $\eta^2$ -aldehyde on a Ni(0) center. Using 5-hexenal and o-allylbenzaldehyde as substrates, the corresponding oxanickellacycles were formed quantitatively by employing a stoichiometric amount of Ni(0)-phosphine complex.<sup>25a</sup> Subjecting the cyclization product to a CO atmosphere provided the corresponding lactone in quantitative yield. Additionally, the intramolecular oxidative cyclization of a monosubstituted  $\delta,\omega$ -enal on a Ni(0) center can be accelerated by Lewis acids, such as trimethylsilyl triflate.

Later efforts focused on employing  $\delta,\omega$ -enones, such as 2-allylacetophenone or 2-allylbenzophenone, as substrates for oxidative cyclization.<sup>25b</sup> While silyl triflate was unable to facilitate the oxanickellacycle formation even at 60°C, trimethylaluminum was found to be very effective for this purpose. Using this method, intramolecular catalytic allylic alcohol synthesis from an enone was first reported, with a nickel-aluminum dinuclear complex suggested as the key intermediate. Overall, this discovery represents a milestone in the development of catalytic intermolecular coupling.

### 3.2 Intermolecular Reactions with Aldehydes

The first Ni-catalyzed intramolecular alkyne-aldehyde reductive coupling, reported by Montgomery in 1997, and the first intermolecular variant, reported by one of the present authors in 2000, allow for allylic alcohol synthesis starting from simple unsaturated hydrocarbons.<sup>31</sup> Upon careful inspection of those systems, we hypothesized that simple alkenes could take the place of alkynes under non-reductive conditions and therefore provide allylic alcohols in a similar vein. Encouraged both by the value of using simple, inexpensive  $\alpha$ -olefins instead of alkynes as starting materials for catalytic allylic alcohol synthesis, and by Ogoshi's exciting reports on Ni-catalyzed oxidative cyclization, we decided to pursue the intermolecular alkene-aldehyde coupling. At this stage, attempted intermolecular reactions employing styrene or trimethylvinylsilane with benzaldehyde as the coupling partner were reported to be unsuccessful. In addition, in the intermolecular reductive coupling reactions of 1,3- and 1,6-enynes with aldehydes, reaction was observed at the alkyne only. In spite of these observations, we reasoned that the catalytic synthesis of various allylic alcohols should be feasible by employing new conditions that would favor the  $\beta$ -hydride elimination step and subsequent reductive elimination to regenerate the active metal catalyst.

Hoberg first demonstrated that various oxanickellacycles could be prepared intermolecularly in high yield from the corresponding Ni(0)-ligand complex, ethylene or  $\alpha$ -olefins, and CO<sub>2</sub> or isocyanates in the early 1980s,<sup>32–34</sup> and we decided to start our own investigation by employing ethylene and  $\alpha$ -olefins as the alkene components. In 2005, our group reported the first *catalytic intermolecular aldehyde-alkene coupling* yielding allylic alcohol by using ethylene, aldehydes and silyl triflate under very mild conditions,<sup>13a</sup> shortly after Ogoshi's first catalytic intramolecular ketone-alkene coupling reaction using an enone and AlMe<sub>3</sub>.<sup>25b</sup> At only 1 atm of ethylene pressure and room temperature, our system allowed the synthesis of various allylic alcohols in good to excellent yield from aromatic aldehydes and tertiary aldehydes such as pivaldehyde (Table 2). The use of both tris(*ortho*-methoxyphenyl)phosphine ligand and triethylamine were crucial to the success of this coupling. It appears that a balance of the nucleophilicity, basicity, and steric bulk of the



amine base is required for the coupling to occur efficiently. As an additional advantage, multiple common silyl triflates can be used in the coupling reaction, providing orthogonal protection of the hydroxyl group when necessary.

$\alpha$ -Olefins can also be used as a substrate for the allylic alcohol-forming reaction with aldehydes. A new carbon-carbon bond is formed at the 2-position of the  $\alpha$ -alkenes when dicyclohexylphenylphosphine is used as a ligand, although the yield is moderate (50%) and a small amount of homoallylic alcohol is also observed.

After extensive study and optimization, we found that both allylic and homoallylic products can be synthesized in good to excellent yield and selectively, depending on the nature of supporting phosphine ligands and (to a lesser extent) the substrates employed. We propose that both the homoallylic and allylic product formation share a similar mechanistic framework (Scheme 4). The proposed mechanism involves the formation of oxanickellacycles from a nickel(0) phosphine complex and the substrates, followed by a *syn*- $\beta$ -hydride elimination (in analogy to the Heck reaction), affording the coupling product and a nickel-hydride species. Finally, a subsequent base-promoted reductive elimination of the triflic acid from the nickel center could regenerate the nickel(0) catalyst. Note that a base-mediated  $\beta$ -elimination of the oxanickellacycle via an E2-like mechanism cannot be completely ruled out. The unusual *trans*-disubstituted allylic product **A'** formed in some cases presumably was synthesized via formation of the typical oxanickellacycle for homoallylic alcohol synthesis, followed by the *syn*-elimination of the *endo* $\beta$ -hydrogen in an open structure.

The interactions of nickel with the ligand, alkene, and aldehyde govern oxanickellacycle assembly, and the ratio of the two possible oxanickellacycles in turn determines the product selectivity. In general, the oxanickellacycle in which steric interactions between the ligand, alkene, and aldehyde substituents are minimized will be formed preferentially. For a given substrate combination, the ratio of the oxanickellacycles is determined by a combined effect of the electronic properties and the cone angle of the phosphine ligands.<sup>35</sup> High homoallylic to allylic alcohol ratios (**H:A**) can be achieved by using less electron-rich phosphines with small cone angles, such as (EtO)Ph<sub>2</sub>P. Conversely, high **A:H** ratios can be obtained by using more electron-rich phosphines with large cone angles, such as Cy<sub>2</sub>PhP. Scheme 5 shows the profound ligand effect on **H:A** ratio observed with 1-octene and benzaldehyde as representative substrates. The stretching frequency ( $\nu$  CO, cm<sup>-1</sup>) of the terminal CO of CpFe(CO)-LCOMe shown along the *x*-axis is a measure of the  $\sigma$ -electron-donating ability to a metal center, with less electron-donating ligands generally having a higher stretching frequency. This served as a useful guideline for us to optimize selectivities and yields for the synthesis of both homoallylic and allylic alcohols using  $\alpha$ -olefins. Nevertheless, phosphine ligands with even larger cone angle (such as Cy<sub>3</sub>P or bidentate ligands) or with lower electron-donating ability (such as (EtO)<sub>2</sub>PPh) are not effective, affording low coupling yield even with prolonged reaction time.

The scope and relative reactivity of the aldehyde component discovered in the Ni(0)-catalyzed homoallylic alcohol synthesis correlate well to that observed in the synthesis of allylic alcohols from  $\alpha$ -olefins. However, there are significant differences in alkene substrate scope between the two reactions (Table 3). While employing non-linear  $\alpha$ -olefins does not affect the coupling yield and does not lower the **H:A** ratio severely in the Ni-(EtO)PPh<sub>2</sub> system, when we use Ni-Cy<sub>2</sub>PPh to favor allylic product synthesis, branching of the olefin (especially at the allylic position) significantly lowers the yield and/or the **A:H** ratio. For example, vinylcyclohexane gives only 5% yield of allylic product with benzaldehyde. Highly sterically demanding  $\alpha$ -olefins without allylic hydrogen, such as 3,3-dimethyl-1-butene, are not converted to the typical allylic alcohol products at all.

Overall, the selectivity and the substrate scope for allylic alcohol synthesis from sterically more demanding substrates remained far from satisfactory. Despite our use of a bulky, electron-rich phosphine, a general method for high **A:H** selectivity was still lacking. In 2007, however, we were able to remedy that deficiency by exploiting a synergistic relationship between a strong  $\sigma$ -donor and a strong  $\pi$ -acceptor.

Our proposed model for determining the product distribution suggested that ligands featuring a sterically demanding environment and strong electron-donating properties should be good potential candidates for favoring a high **A:H** ratio. Based on this hypothesis, *N*-heterocyclic carbene (NHC) ligands were screened, with favorable preliminary results.<sup>36</sup> We found that the reaction using the NHC ligand IPr was highly selective for the allylic product, even when an  $\alpha$ -branched alkene (vinylcyclohexane) was used. However, the reaction did not appear to proceed catalytically.

The side products isolated from these stoichiometric reactions provided important leads as to how to render the reaction catalytic. The product of hydrosilylation (reduction) of the aldehyde was isolated in roughly the same amount as desired coupling product. In addition, hydrovinylation products from the alkene were formed in significantly greater quantities in the NHC-mediated reaction relative to the previous phosphine ligand systems (Scheme 6).<sup>37,38</sup>

We suspected that both the formation of side products and lack of catalysis might be caused by the fact that the electron-rich NHC ligand retards formal reductive elimination of triflic acid, necessary to regenerate a Ni(0) species. Stalling the catalytic cycle results in accumulation of a [Ni(NHC)H](OTf) species, which is responsible for the side reactions.

With this idea in mind, we first attempted to solve the problem by employing a stronger organic and/or inorganic base. Bases including K<sub>2</sub>CO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub>, diisopropylethylamine, pyridine, 2,6-lutidine, *N*-methylmorpholine, *N*-methylpyrrolidine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were examined to facilitate the reductive elimination. However, this strategy did not prove successful. Although deprotonation of a H-Metal-X species by a base is a common mechanism for restoring zero-valent metal in the Pd-catalyzed Heck reaction, Ni(0) species are presumably more difficult to regenerate in this fashion.<sup>6,39,40</sup> Therefore, we needed to consider an alternative means to restore the catalytic cycle.

Approaches employing electron-deficient alkenes to withdraw electron density from metal center, or using organophosphorus compounds to introduce sterically unfavorable interactions, to facilitate the reductive elimination processes have been reported in the literature.<sup>41–44</sup> Nevertheless, in our nickel(0)-catalyzed alkene-aldehyde coupling system, these approaches could have fatal flaws related to functional group compatibility and reaction pathway competition, respectively.

Indeed, using *m*-CF<sub>3</sub>-styrene as an additive led to some catalytic turnover, but coupling product derived from this additive was also obtained in a significant amount. Facilitating the elimination by adding sterically demanding bulky phosphines (Cy<sub>2</sub>PPh) did not work. Employing triphenylphosphine, phosphinite and phosphonate showed marginal catalytic efficiency, but these ligands' direction toward the homoallylic pathway eroded the high **A:H** selectivity provided by the NHC.

Based on the findings of previous studies and our own results in this area, we decided to employ a phosphorus additive that featured strongly electron-accepting character and did not promote the homoallylic alcohol-forming pathway. Finally, triphenylphosphite, a good  $\pi$ -electron acceptor with a small cone angle, was found to be a good companion for this

reaction. Use of triphenylphosphite in conjunction with the NHC renders the reaction catalytic without eroding the high allylic alcohol selectivity. Presumably, this is due to the reduction of electron density at coordinatively unsaturated Ni, which makes removal of the Ni-H species and regeneration of the Ni(0) catalyst more efficient (Scheme 6). The amount of side products resulting from hydrosilylation of the aldehyde (reduction) and hydrovinylation were dramatically diminished.

The scope of this synergistic NHC/phosphite effect and new {Ni(IPr)[P(OPh)<sub>3</sub>]}-catalyzed transformation are summarized in Table 4. Particularly noteworthy is that an **A:H** selectivity of greater than 20:1 was finally observed in all cases examined. The range of suitable alkene substrates was also far broader than that found in our previous Ni-phosphine-catalyzed processes. We attribute this improvement to the sterically demanding and highly electron-donating nature of the IPr ligand, which better differentiates the energetics between formation of the two oxanickellacycles. The more electron-rich nickel center also facilitates oxidative cyclization of challenging substrates (Scheme 7).

In summary, this work represents a rare example of using an additive *other* than an electron-deficient alkene or sterically demanding phosphine to accelerate reductive elimination in a catalytic reaction. Remarkably, IPr and the phosphite are compatible with one another in this two-ligand system, and neither seems to interfere with the role of the other. For this reason in particular, this phosphite-NHC combination may have several other applications and broader implications in NHC-metal-catalyzed transformations. For example, other reactions that rely upon the reductive elimination of H-X from H-M-X, or of R<sup>1</sup>-M-R<sup>2</sup> in general, such as the Heck reaction or catalytic cross coupling reactions, may also enjoy a similar accelerating effect by the use of a phosphite. While an electron-deficient alkene may not be appropriate for the Heck reaction, an organophosphite may be a good alternative.

### 3.3 Synthesis of Acrylamides with Isocyanates

With the aim of broadening the scope of simple alkenes as nucleophiles in carbon-carbon bond-forming reactions, we became interested in expanding the scope of electrophiles with which simple alkenes could be coupled. Methodologies for the selective coupling of  $\alpha$ -olefins and isocyanates to provide acrylamides have potential applications in the field of polymer science. Poly(acrylamides) have been extensively studied for their properties as temperature-sensitive aqueous microgels.<sup>45</sup> The monomers are commonly prepared by reaction of (meth)acryloyl chloride with the corresponding amine.<sup>46</sup> By comparison, direct synthesis of these unsaturated amides from alkenes and isocyanates would afford monomers with a greater variety of substitution patterns of the polymer backbone and avoid the formation of byproducts such as chloride salts.

Nevertheless, Baker and Holdsworth found that addition reactions of simple alkenes (e.g. trimethylethylene and propylene) to phenyl isocyanate in the presence of a Lewis acid (SnCl<sub>4</sub>) did not provide acrylamides. The proposed mechanism and the experimental evidence suggest that the reaction may involve the formation of an  $\beta,\gamma$ -unsaturated amide intermediate, but this did not undergo isomerization to yield acrylamides in significant amount, and the corresponding triphenylbiurets were isolated as final products instead.

Hoberg first demonstrated the synthesis of *N*-phenylacrylamide from phenyl isocyanate and ethylene using Ni(0) with trialkylphosphine ligands as a catalyst. A variety of other olefins, both activated and unactivated, have been reported to react with phenyl isocyanate with Ni(0) and phosphine ligands. While the major product is the *trans*-disubstituted  $\alpha,\beta$ -unsaturated amide, the 1,1-disubstituted acrylamide was observed in two cases, though in low yield as a minor product (3 and 13 % yield). Hoberg proposed that the reaction proceeds via an azanickellacyclopentanone intermediate, which then undergoes  $\beta$ -hydride elimination.



Presumably, the alkene substituent would be on the carbon adjacent to Ni in the relevant nickellacycle in order to obtain 1,2-disubstituted  $\alpha,\beta$ -unsaturated amides.

Encouraged by our initial success in employing a NHC as a directing ligand for nickellacycle formation in the alkene-aldehyde system, we wondered whether we could selectively synthesize 1,1-disubstituted acrylamides effectively, using a NHC to alter the regioselectivity of azanickellacyclopentanone formation. We surmised that replacing the phosphine ligands by a bulky NHC ligand might help to direct the olefin substituent away from the metal center in a similar way (Scheme 8).

Indeed, use of a NHC ligand favors products with the opposite sense of regioselectivity compared to those obtained when phosphine ligands are used. In the presence of catalytic Ni(0) and the NHC ligand IPr, C–C bond formation was observed to form selectively at the 2-position of the olefin, providing a new preparation of 1,1-disubstituted acrylamides. Also, by simply adding an acid treatment step, the free amides can be obtained from the initial *N*-*tert*-butyl products.<sup>48</sup>

The scope of the reaction appears to be limited to bulky, electron-rich alkyl isocyanates (Table 5). However, as in our work with aldehydes, reactions occurred at the (ostensibly) least activated alkenes. When reacted with cyclohexyl isocyanate, 10 mol % of Ni(cod)<sub>2</sub>, and 10 mol % of IPr in toluene in a sealed tube at 60 °C for 18–24 h, methylenecyclohexane and cyclohexene afforded coupling products in less than 10% yield. No product was observed with *trans*-4-octene under identical conditions. A common side reaction is oligomerization of the isocyanate, which may be catalyzed by free NHC ligands in solution, as reported recently by Louie.<sup>49,50</sup> The NHC ligand seems to play an important role in favoring reaction at the more substituted position of the alkene. In this reaction, we again can utilize a simple alkene as the functional equivalent of a 2-vinylmetal reagent.

The alkene–isocyanate coupling is unique among the systems we have examined to date, in that it does not require activation by a third component, such as a Lewis acid, to proceed. Also, the reductive elimination of the product to regenerate the catalytic cycle can proceed without the assistance of a base and/or phosphite. The high coupling yields and the fact that no significant amount of alkene hydrovinylation product was observed suggest that the Ni–H species can be removed readily at higher temperature. An alternative explanation is that isocyanate may also function as a promoter for reductive elimination, similar to the electron-deficient styrene or the phosphite mentioned previously.

### 3.4 Conjugate Addition to $\alpha,\beta$ -Unsaturated Aldehydes and Ketones

Conjugate additions, discovered over a century ago, continue to be one of the most utilized organic reactions.<sup>51–53</sup> For this reason, we next investigated the addition of simple alkenes to electrophilic conjugated systems. Lewis acid-catalyzed addition of an electron-rich alkene to an  $\alpha,\beta$ -unsaturated carbonyl, such as acrolein or methyl vinyl ketone, represents a powerful application of the ene reaction for carbon–carbon bond formation. Depending on the reaction conditions, the resulting  $\delta,\omega$ -unsaturated carbonyl compounds may undergo a further intramolecular reaction between the newly formed alkene and the carbonyl group, providing a cyclization product. In order to synthesize  $\gamma,\delta$ -unsaturated carbonyl compounds from conjugate aldehydes or ketones, vinylmetal nucleophiles are typically used.<sup>54,55</sup> Earlier technology employed organolithium, Grignard, or organocopper reagents; more recently, organozinc and organoboron compounds have significantly enhanced the functional group compatibility of this transformation. Nevertheless, an organometallic or organometalloid reagent is required for these methods (Scheme 9).

Recent reported advances in Ni-catalyzed alkene–alkene coupling reactions (e.g. hydrovinylation), the wide variety of Ni-catalyzed conjugate addition reactions reported by Montgomery, and our initial work using simple alkenes as vinyl- and allylmetal equivalents suggested to us that the catalytic addition of simple unactivated olefins to conjugate systems should be feasible under optimized conditions.<sup>56</sup> Indeed, in the presence of Ni catalyst, the simple olefins take the place of organometallic reagents and add to enals and aromatic or heteroaromatic enones successfully, with the aid of silyl triflate as accelerator (Table 6). Again, an alkene functions as a vinylmetal surrogate in this carbon–carbon bond-forming process. Various enolsilanes were isolated in moderate to good yield, and in most cases the transformation gives rapid access to enolsilanes with high olefin stereoselectivity. Besides  $\alpha$ -methylene carbonyl compounds, (*E*)-2-methyl cinnamaldehyde has also been tested for the coupling with ethylene. However, in this case the chemoselectivity is reversed, favoring 1,2-addition to the carbonyl (1,2:1,4 ~3:2). This result suggests that the reaction is sensitive to substitution at the  $\beta$ -position of the enophile.

Based on our results, we proposed a general mechanistic framework, with the sequence of events based largely on a crystal structure of a 1,3-diene and benzaldehyde with Ni-phosphine reported by Ogoshi (Scheme 10, c.f.  $\alpha,\beta$ -unsaturated carbonyls and alkenes with Ni-phosphine).<sup>25c</sup> The bulky substituents on the enophile 1- and 2-position tend to point away from each other to minimize unfavorable steric interactions during and after the oxidative cyclization step with the alkene component. This, together with the more energetically favorable chair-like chelation to the Ni centre allowed in this organization (**A**), accounts for the observed enolsilane geometry. The superior performance of electron-rich enals and enones is consistent with the fact that reaction with silyl triflate is a critical step in the cycle. Another possibility, suggested by the stoichiometric coupling reactions of allylnickel with enal (or enone), is that the silyl triflate and enal (or enone) first combine, and that the resulting species (**B**) then undergoes coupling with the alkene.

Styrene and  $\alpha$ -olefins both add to the conjugate system, but with opposite regioselectivity with respect to the alkene. When using an  $\alpha$ -olefin such as 1-octene as a substrate with 2-hexylacrolein, coupling at the olefin 2-position is favored. Since there are a greater number of general methods for the preparation of 1-alkenyl organometallics (e.g. hydrometalation of terminal alkynes), the fact that 1-octene functions as a 2-alkenyl organometallic reagent highlights a particularly useful aspect of this reaction. In contrast, in the reaction of styrene with enals or enones, carbon–carbon bond formation occurs exclusively at the 1-position of the styrenyl olefin. The contrasting regioselectivity in these two cases may be attributed to the avoidance of steric repulsion between the Ni-phosphine complex and the alkene substituent, and the electronic stabilization offered by the formation of a benzylic Ni species, respectively.

There appears to be a delicate balance between the desired reaction pathway and side reactions for various ligand-substrate combinations. In this reaction, the enophiles are also vulnerable to direct nucleophilic attack by ligand or base. This may result in non-productive conversion of substrates or lower the desired reaction rate, and therefore the choice of ligand and base was found to be extremely critical for this reaction. PBU<sub>3</sub>, CyPPh<sub>2</sub>, and Cy<sub>3</sub>P are the most effective ligands for the couplings using ethylene, 1-octene, and styrene, respectively. However, we did not observe any obvious phosphine structure-reactivity relationship in the screening. IPr and bipyridine were not suitable as ligands for this coupling reaction.

Overall, this transformation is a rare example of selective conjugate addition of a vinyl equivalent to an unsaturated aldehyde. Typically in such reactions 1,2-addition is favored, or complex mixtures are afforded. The products of this reaction are of particular interest

because obtaining a defined enolsilane configuration is the key for a wide range of enantioselective transformations.<sup>57</sup> For instance, enolsilanes can be converted to carbonyl compounds with quaternary stereogenic centers in the  $\alpha$ -position, in many cases with very high enantioselectivity.<sup>58,59</sup> The nickel-catalyzed conjugate addition reaction provides rapid access to synthetically useful tri- and tetrasubstituted enolsilanes that would be difficult to prepare with high selectivity via standard enolization of an acyclic aldehyde or ketone. Additionally, the mono-substituted alkene present in the product when ethylene is used as a coupling partner is an excellent tether for subsequent olefin cross-metathesis. By combining conjugate addition of ethylene with cross-metathesis, products that are regiocomplementary to those obtained from nickel-catalyzed conjugate addition reaction with aliphatic, monosubstituted alkenes can be accessed.

#### 4 Intramolecular Insertion of Alkenes to Cyclobutanones

Another major advance in the Ni(0)-catalyzed addition of alkenes to carbonyl compounds was reported by Murakami and Ashida (Scheme 11).<sup>60</sup> A Ni(0) catalyst provides benzobicyclo[2.2.2]octenones from the corresponding 3-styrylcyclobutanones via an intramolecular alkene-cyclobutanone coupling, forming two new carbon-carbon bonds regioselectively. This can be contrasted to results obtained with a Rh(I) catalyst, which provides benzobicyclo[3.2.1]octenones from the same starting materials. Tricyclohexylphosphine was found to be the most effective ligand for the nickel-catalyzed reaction, which can be carried out without the use of Lewis acidic additives at 100°C. Substrates having an  $\alpha$ - or  $\beta$ -methyl group on the styrene moiety and those with an additional substituent on the  $\beta$ -position of the cyclobutanone are also tolerated. However, structures like 2-styrylcyclobutanone and 3-(but-3-enyl)-3-phenylcyclobutanone do not undergo the coupling reaction under similar conditions.

The nickel(0)-catalyzed alkene-aldehyde coupling reactions discussed above, as well as previous studies on the intermolecular variant using alkynes, provide the basis for the proposed mechanism. Oxidative cyclization between the cyclobutanone and styrene to form an oxanickellacycle is proposed as the first key step. Next, the four-membered ring derived from the cyclobutanone is then opened by  $\beta$ -carbon elimination, regenerating the carbonyl. Subsequent reductive elimination of the carbocycle from the nickel center turns over the catalytic cycle. Formation of an alternative oxanickellacycle at the styrene  $\beta$ -position would result in a more sterically demanding intermediate, and this may account for the complete regioselectivity of the alkene insertion process.

#### 6 Limitations and Outlook

Recent advances in the group 10 metal-catalyzed addition of simple alkenes to carbonyl compounds represent a significant breakthrough in joining these two readily accessible fragments. These not only provide new alternatives to traditional methodologies, but also expand the scope to several challenging coupling partners previously of very limited or nonexistent utility. The range of new products obtained further reveals the advantages of using chemical feedstocks such as simple alkenes as primary starting materials in place of stoichiometric amounts of vinyl- and allylmetal reagents. We envision that the methods described herein will offer conceptual and practical advantages for organic synthesis.

This account has focused on our recent results in the area of Ni(0)-catalyzed coupling of simple alkenes and carbonyl compounds. Unlike the related transition metal-catalyzed reductive coupling reactions developed by our group and others, the nickel-catalyzed coupling of olefins and carbonyl compounds is not an overall reductive process. Additions of ethylene and unactivated mono-substituted alkenes to various aromatic, heteroaromatic, and tertiary aliphatic aldehydes, isocyanates, and conjugated aldehydes or ketones are now

possible, yielding allylic and homoallylic alcohols, acrylamides, and stereodefined enolsilanes, respectively. Having demonstrated the feasibility of using  $\alpha$ -olefins as both allyl- and vinylmetal equivalents in the carbon-carbon bond forming reactions described, our current efforts include expanding the scope and the utility of the process. Numerous other potential coupling partners and analogs may await discovery.

Nevertheless, significant aspects of the mechanistic proposals for these systems have been based on fragmentary data and analogy. In this vein, much more work is needed before we can understand the Ni(0)-catalyzed processes completely. Several other significant challenges still need to be addressed before the full potential of using simple alkenes as starting materials is realized in the context of the transformations described herein.

The major side reactions in these Ni(0)-catalyzed coupling reactions are the hydrovinylation and isomerization of olefins, and the pinacol coupling and hydrosilylation of aldehydes. These reactions may diminish the effectiveness of the transformation. A more selective and efficient system that could allow catalyst loadings would also be favorable.

The combination of silyl triflates and  $\text{NEt}_3$  was optimal for assisting the Ni(0)-catalyzed carbon-carbon bond-forming reactions at low temperature. Although we focused on aromatic systems, which have not been fully utilized in typical carbonyl-ene technology, the extension of the scope to other simple carbonyls is always attractive. However, enolizable carbonyl compounds are not tolerated in this system; under these conditions, silyl enol ethers, which are not active in the multi-component coupling, are formed. Only in a few cases employing ethylene is the coupling reaction fast enough to compete with aldehyde enolization to give the allylic alcohol product in moderate yield.

While excellent enantioselectivities for conventional Lewis acid-catalyzed carbonyl-ene reactions have been achieved by using various chiral cationic metal complexes, the asymmetric coupling between monosubstituted olefins and electron-rich aldehydes yielding chiral homoallylic and allylic alcohol products remains elusive at this stage. Development of asymmetric variants of these transformations would be an extremely valuable continuation of the advances so far made in this field.

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Kristin D. Schleicher was born in Winfield, IL and raised in Naperville, IL and Danville, CA. She received her undergraduate degree in Chemistry from Stanford University in 2005. She is currently pursuing graduate studies in the laboratory of Professor Timothy F. Jamison at MIT, where her research has focused on the use of nickel catalysis in method development and natural product synthesis.

Timothy F. Jamison was born in San Jose, CA and grew up in neighboring Los Gatos, CA. He received his undergraduate education at the University of California, Berkeley. A six month research assistantship at ICI Americas in Richmond, CA under the mentorship of Dr William G. Haag was his first experience in chemistry research. Upon returning to Berkeley, he joined the laboratory of Prof. Henry Rapoport and conducted undergraduate research in his group for nearly three years, the majority of which was under the tutelage of William D. Lubell (now at the University of Montreal). A Fulbright Scholarship supported ten months of research in Prof. Steven A. Benner's laboratories at the ETH in Zurich, Switzerland, and thereafter he undertook his PhD studies at Harvard University with Prof. Stuart L. Schreiber. He then moved to the laboratory of Prof. Eric N. Jacobsen at Harvard University, where he was a Damon Runyon-Walter Winchell postdoctoral fellow. In July 1999, he began his independent career at MIT, where his research program focuses on the development of new methods of organic synthesis and their implementation in the total synthesis of natural products.

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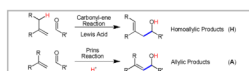
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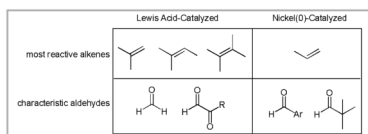
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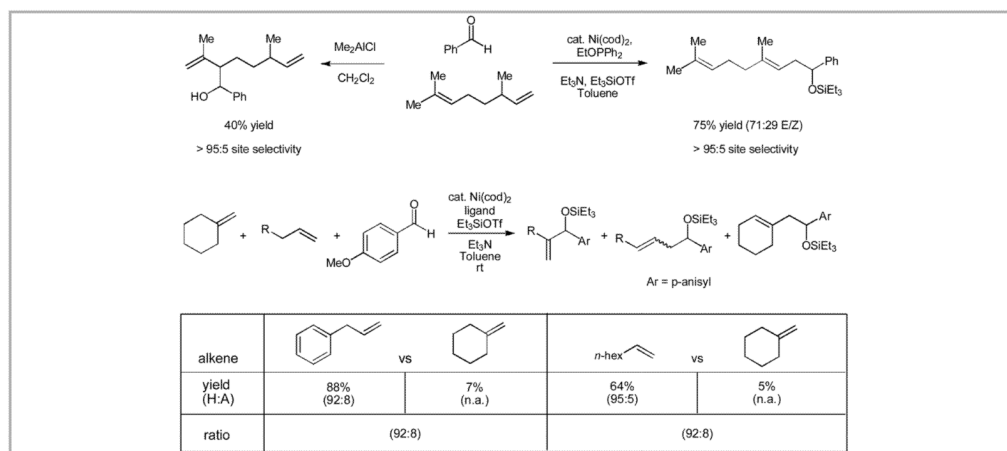




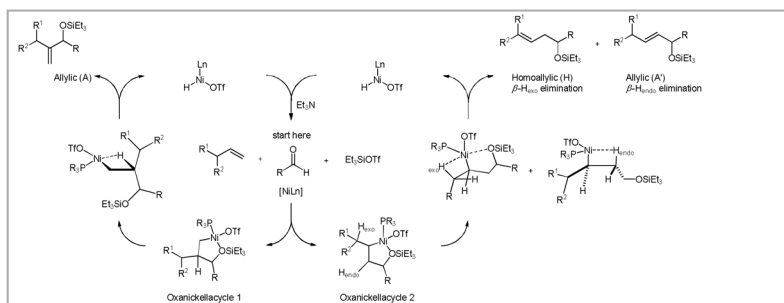
**Scheme 1.**  
Traditional Methods of Synthesis of Homoallylic and Allylic Alcohols from Simple Alkenes and Aldehydes: Carbonyl-Ene and Prins Reactions



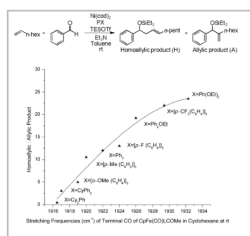
**Scheme 2.**  
Complementarity of Catalytic Alkene Addition to Aldehyde



**Scheme 3.**  
Intra- and Intermolecular Competition Experiments Using  $\alpha$ -Olefins Versus 1,1-Disubstituted Alkenes Under Ni(0) Catalysis.



**Scheme 4.**  
Proposed Mechanism for the Ni(0)-Catalyzed Synthesis of Homoallylic and Allylic Alcohol Products

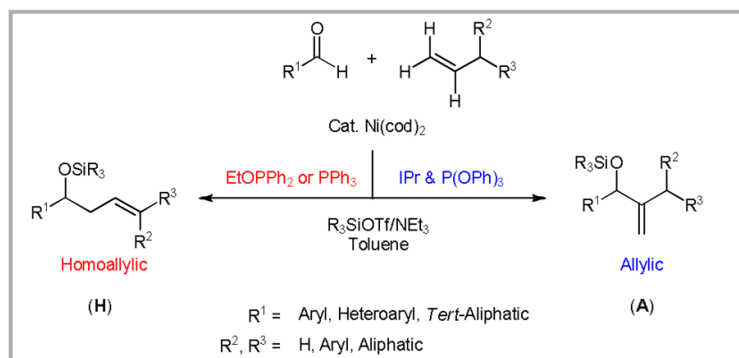


**Scheme 5.**  
Ligand Effect on Coupling Product Selectivity

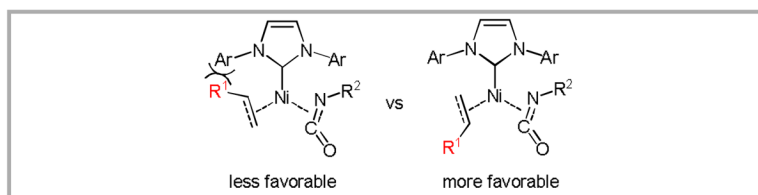




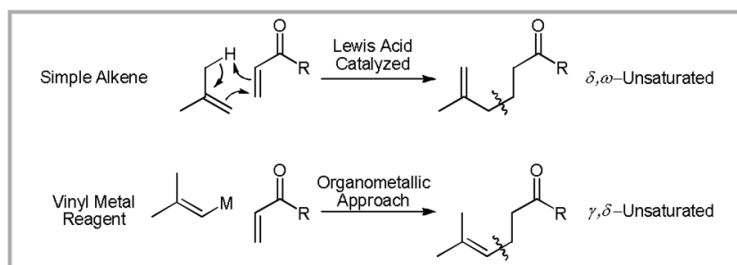
**Scheme 6.**  
Proposed Mechanism for Highly Selective Coupling of Alkenes and Aldehydes Catalyzed by Ni(NHC)P(OPh)<sub>3</sub>: Synergy between a Strong  $\sigma$ -Donor and a Strong  $\pi$ -Acceptor



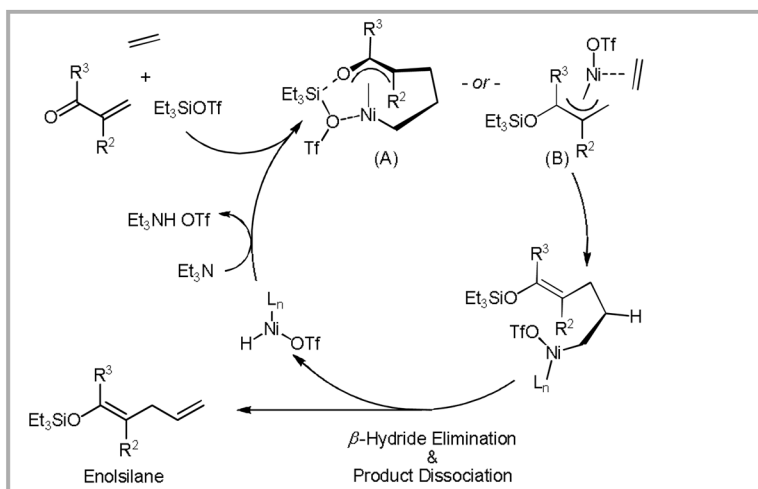
**Scheme 7.**  
 Highly Selective Synthesis of Homoallylic or Allylic Alcohols: Ligand-Controlled Ni(0)-Catalyzed Coupling of  $\alpha$ -Olefins, Aldehydes and Silyl Triflates



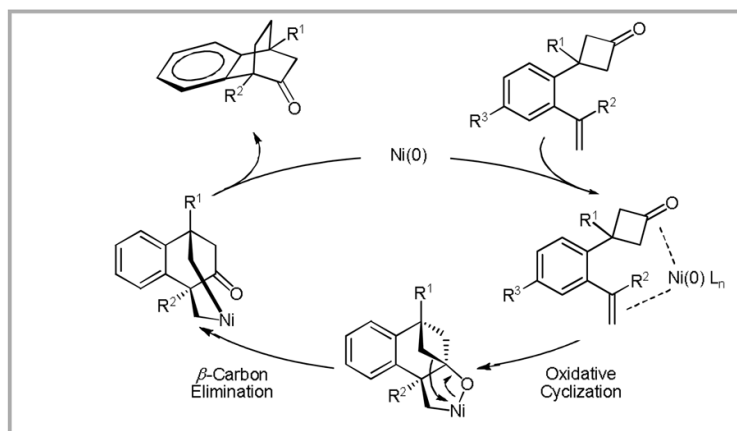
**Scheme 8.**  
Proposal for IPr-Controlled Azanickellacycle Formation



**Scheme 9.**  
Traditional Approaches for Synthesis of  $\delta,\omega$ - or  $\gamma,\delta$ -Unsaturated Carbonyl Compounds  
Using Lewis Acid-Catalyzed Conditions and Organometallic Reagents




**Scheme 10.**  
Proposed Mechanism for the Ni(0)-Catalyzed, Highly Selective Alkene Addition to Conjugate Systems



**Scheme 11.**  
Proposed Mechanism for the Ni(0)-Catalyzed Intramolecular Coupling of 3-Styrylcyclobutanones

Table 1

Nickel(0)-Catalyzed, Carbonyl-Ene-Type Reactions of Monosubstituted Olefins<sup>a</sup>


Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Yield % <sup>b</sup>	H:A	E:Z <sup>b</sup>
1 <sup>d</sup>	H	H	Ph	73 (89:11)		n.a.
2	<i>n</i> -Pent	H	Ph	85 (95:5)		75:25
3 <sup>e</sup>	<i>n</i> -Pent	H	Ph	72 (>95:5)		75:25
4 <sup>e</sup>	<i>n</i> -Pent	H	<i>p</i> -Anisyl	85 (>95:5)		75:25
5 <sup>e</sup>	<i>n</i> -Pent	H	<i>p</i> -Cl(C <sub>6</sub> H <sub>4</sub> )	37 (>95:5)		74:26
6	<i>n</i> -Pent	H	2-Naphthyl	88 (>95:5)		70:30
7	<i>n</i> -Pent	H	2-( <i>N</i> -Me-Indole)	56 (>95:5)		83:17
8 <sup>f</sup>	<i>n</i> -Pent	H	<i>t</i> -Bu	64 (>95:5)		78:22
9	Ph	H	Ph	86 (92:8)		>95:5
10	Ph	H	<i>x</i> -MeO(C <sub>6</sub> H <sub>4</sub> )	( <i>o</i> -) 78 (92:8)		>95:5
				( <i>m</i> -) 98 (92:8)		>95:5
				( <i>p</i> -) 99 (92:8)		>95:5
				( <i>p</i> -) 98 (92:8)		>95:5
11 <sup>f</sup>	Ph	H	2-Naphthyl	88 (95:5)		>95:5
12	Ph	H	2-( <i>N</i> -Me-Indole)	57 (>95:5)		>95:5
13	Ph	H	<i>t</i> -Bu	65 (>95:5)		78:22
14	Bn	H	<i>p</i> -Anisyl	91 (92:8)		69:31
15	<i>i</i> -Pr	H	Ph	82 (>95:5)		81:19
16	Me	Me	Ph	95 (86:14) <sup>g</sup>		n.a.
17	-(C <sub>5</sub> H <sub>10</sub> -)		Ph	99 (75:25) <sup>h</sup>		n.a.
18 <sup>i</sup>	-	-	Ph	14 (<5:95) <sup>h</sup>		>95:5



<sup>a</sup>Standard procedure: (entries 1–8, 15–18): To a solution of Ni(cod)<sub>2</sub> (0.1 mmol) and EtOPPh<sub>2</sub> (0.2 mmol) in toluene (2.5 mL) at 23 °C under Ar were added the alkene (0.5 mL), triethylamine (3.0 mmol), the aldehyde (0.5 mmol), and Et<sub>3</sub>SiOTf (0.875 mmol). The mixture was stirred 48 h at room temperature and purified by chromatography (SiO<sub>2</sub>). Entries 9–14: Ph<sub>3</sub>P was used in place of EtOPPh<sub>2</sub>.

<sup>b</sup>Yields were determined by <sup>1</sup>H NMR using DMF as a standard.

<sup>c</sup>A here refers to terminal allylic products formed by coupling at alkene 2-position, see reference 13b for details.

<sup>d</sup>Propene (1 atm) was used in place of Ar.

<sup>e</sup>Reaction time 18 h.

<sup>f</sup>Reaction temperature 35 °C.

<sup>g</sup>Fivefold larger reaction scale.

<sup>h</sup>A here refers to internal disubstituted allylic products formed by coupling at alkene 1-position.

<sup>i</sup>3,3-dimethylpropene was used as alkene substrate.

Table 2

Nickel(0)-Catalyzed Coupling of Ethylene, Aldehydes, and Silyl Triflates<sup>a</sup>

Entry	R <sup>1</sup>	Yield %
1	Ph	82
2	<i>p</i> -tol	88
3	<i>o</i> -tol	93
4	<i>p</i> -Anisyl	95
5	2-Naphthyl	95
6 <sup>b</sup>	2-Naphthyl	60
7 <sup>c</sup>	2-Naphthyl	67
8	2-( <i>N</i> -Me-Indole)	80
9	2-Furyl	38
10 <sup>d</sup>	<i>p</i> -CF <sub>3</sub> (C <sub>6</sub> H <sub>4</sub> )	25
11 <sup>d</sup>	<i>p</i> -COOMe(C <sub>6</sub> H <sub>4</sub> )	34
12	<i>t</i> -Bu	70
13	<div style="text-align: center; border: 1px solid black; padding: 5px; width: fit-content; margin: 0 auto;"> </div>	81
14 <sup>e</sup>	Cy	25 (34) <sup>f</sup>

<sup>a</sup>Standard procedure: Ni(cod)<sub>2</sub> (0.1 mmol) and (*o*-Anisyl)<sub>3</sub>P (0.2 mmol) were dissolved in 2.5 mL toluene under argon. Ethylene (balloon, 1 atm) was substituted for argon. Triethylamine (3 mmol) the aldehyde (100 mol%, 0.5 mmol), and Et<sub>3</sub>SiOTf (0.875 mmol) were added. The reaction mixture was stirred 6–18 h at 23 °C.

<sup>b</sup>Et<sub>3</sub>SiOTf was replaced by Me<sub>3</sub>SiOTf.

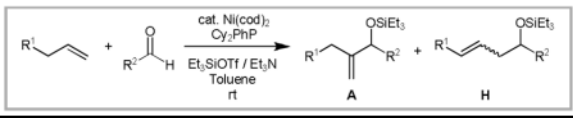
<sup>c</sup>Et<sub>3</sub>SiOTf was replaced by TBDMSSiOTf.

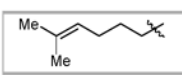
<sup>d</sup>Stirred at room temperature for 30 h.

<sup>e</sup>Yields determined by <sup>1</sup>H NMR using DMF as a standard.

<sup>f</sup>Conducted under 2 atm of ethylene.

Table 3

Preparation of Allylic Alcohol Products from Nickel(0)-Catalyzed Alkene–Aldehyde Couplings<sup>a</sup>


Entry	R <sup>1</sup>	R <sup>2</sup>	Yield % (A:H) <sup>b</sup>
1 <sup>c,d</sup>	Me	2-Naphthyl	82 (84:16)
2	<i>n</i> -Hex	Ph	70 (71:29)
3 <sup>c</sup>	Me	<i>p</i> -Anisyl	95 (82:18)
4	Ph	2-( <i>N</i> -Me-Indole)	56 <sup>e</sup> (80:20)
5	<i>i</i> -Bu	Ph	62 (71:29)
6		Ph	72 (71:29)
7	Cy	Ph	5

<sup>a</sup>Standard procedure: Ni(cod)<sub>2</sub> (0.1 mmol), Cy<sub>2</sub>PhP (0.2 mmol) were dissolved in 2.5 mL toluene. Excess alkene, triethylamine (3 mmol), the aldehyde (100 mol%, 0.5 mmol), and Et<sub>3</sub>SiOTf (0.875 mmol) were added. The reaction mixture was stirred 18 h at 23 °C.

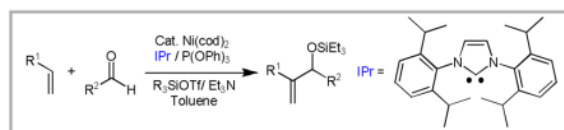
<sup>b</sup>Ratios were determined by <sup>1</sup>H NMR of the crude reaction mixture.


<sup>c</sup>1 atm propene (balloon) was used.

<sup>d</sup>Naphthaldehyde (100 mol%) was mixed with Ni(cod)<sub>2</sub> and Cy<sub>2</sub>PhP before the addition of toluene.

<sup>e</sup>Yields were determined by <sup>1</sup>H NMR using DMF as a standard.

Table 4

[(IPr)Ni(0){P(OPh)<sub>3</sub>}] Catalyzed Alkene–Aldehyde Coupling Reactions<sup>a</sup>

Entry	R <sup>1</sup>	R <sup>2</sup>	Conversion % <sup>b</sup>	Yield % <sup>b,c</sup>
1 <sup>d</sup>	<i>n</i> -Hex	<i>p</i> -Anisyl	95	96
2 <sup>d,e</sup>	<i>n</i> -Hex	<i>p</i> -Anisyl	92	82
3	<i>n</i> -Hex	<i>o</i> -Anisyl	80	75
4	<i>n</i> -Hex	<i>m</i> -Anisyl	86	98
5	Ph	<i>p</i> -Anisyl	69	84
6 <sup>d</sup>	Bn	<i>p</i> -Anisyl	75	99
7	BnCH <sub>2</sub>	<i>p</i> -Anisyl	88	99
8	Cy	<i>p</i> -Anisyl	100	96
9 <sup>f,g</sup>	<i>i</i> -Pr	<i>p</i> -Anisyl	100	93
10 <sup>g,h</sup>	<i>t</i> -Bu	<i>p</i> -Anisyl	32	41
11	<i>i</i> -Bu	<i>p</i> -Anisyl	100	99
12		<i>p</i> -Anisyl	100	94
13	<i>n</i> -Hex	Ph	95	96
14	<i>n</i> -Hex	2-Naphthyl	74	99
15 <sup>h</sup>	<i>n</i> -Hex	<i>p</i> -Cl(C <sub>6</sub> H <sub>4</sub> )	88	73
16	Cy	<i>p</i> -Cl(C <sub>6</sub> H <sub>4</sub> )	66	32
17 <sup>h,i</sup>	<i>n</i> -Hex	2-Furyl	100	36

<sup>a</sup>Standard condition: IPr (0.075 mmol), Ni(cod)<sub>2</sub> (0.075 mmol) were dissolved in degassed toluene (3 mL). The catalyst mixture was under argon and stirred at room temperature for 1 hour. Alkene (1.25 mmol or indicated amount), triethylamine (1.5 mmol), aldehyde (0.25 mmol, 100 mol%), triphenylphosphite (0.11 mmol) were then added sequentially to the reaction mixture. Triethylsilyltriflate (0.44 mmol) was added to the reaction mixture dropwise, and the mixture was stirred 48 h at 35°C.

<sup>b</sup>Determined by integration (<sup>1</sup>H NMR) relative to an external standard (CH<sub>3</sub>NO<sub>2</sub>).

<sup>c</sup>Based on conversion.

<sup>d</sup>150 mol% of alkene used.

<sup>e</sup>*t*-BuMe<sub>2</sub>SiOTf used in place of Et<sub>3</sub>SiOTf.

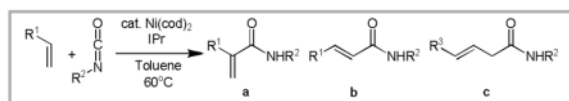
<sup>f</sup>1 mL of alkene used.

<sup>g</sup>Reaction carried out in a sealed tube.

<sup>h</sup>40 mol% of catalyst used.

<sup>i</sup>Reaction carried out at room temperature.

Table 5

Nickel(0)-Catalyzed Coupling of Alkenes and Isocyanates<sup>a</sup>

Entry <sup>a</sup>	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Yield % <sup>b</sup> a; b; c
1	<i>n</i> -Hex	Cy	-	79; 14; 0
2	<i>n</i> -Hex	<i>t</i> -Bu	-	74; 17; 0
3	Cy	<i>t</i> -Bu	-	91; 0; 0
4 <sup>c</sup>	CH <sub>2</sub> <i>i</i> -Pr	Cy	-	74; 5; 0
5 <sup>c</sup>	Bn	Cy	Ph	65; 8; 22
6 <sup>c</sup>	Bn	<i>t</i> -Bu	Ph	83; 1 <sup>d</sup> ; 5 <sup>d</sup>
7 <sup>c</sup>		Cy	-	86; 0; 0
8		Cy	-	74; 13; 0
9		<i>t</i> -Bu	-	70; 2; 0
10		<i>t</i> -Bu	-	65; 9; 0

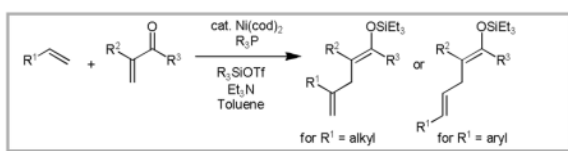
<sup>a</sup>Standard conditions: In a sealed tube, Ni(cod)<sub>2</sub> (0.05 mmol), IPr (0.05 mmol), were dissolved in 0.5 mL toluene. 1-octene (0.5 mmol), isocyanate (1.0 mmol) were then added under Ar(g), the tube was sealed and stirred at 60 °C for 18–24 h.

<sup>b</sup>Isolated yields.

<sup>c</sup>Reaction was run using 2 mL of toluene.

<sup>d</sup>Isolated as a mixture of **b** and **c**, with relative ratios determined by <sup>1</sup>H NMR.

Table 6

Ni(0)-Catalyzed Conjugate Addition Reactions of Alkenes<sup>a</sup>

Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Yield % ( <i>E:Z</i> ) <sup>b</sup>
1	H	Me	H	52 (95:5)
2	H	<i>n</i> -Hex	H	76 (95:5)
3 <sup>c</sup>	H	<i>n</i> -Hex	H	58 (95:5)
4 <sup>d</sup>	H	<i>n</i> -Hex	H	64 (95:5)
5	H	Bn	H	83 (8:92)
6 <sup>e,f</sup>	H		H	97 (7:93)
7	H	Me	Ph	90 (95:5)
8	H	<i>n</i> -Pr	Ph	94 (90:10)
9 <sup>d</sup>	H	<i>n</i> -Pr	Ph	86 (90:10)
10	H	<i>i</i> -Pr	Ph	78 (13:87)
11 <sup>g</sup>	H	Ph	Ph	70 n.d.
12 <sup>h</sup>	H	Me	<i>p</i> -Anisyl	94 (91:9)
13	H	<i>n</i> -Bu	2-Furyl	95 (75:25)
14	H	Et	2-Thienyl	95 (75:25)
15 <sup>f</sup>	<i>n</i> -Hex	<i>n</i> -Hex	H	67 <sup>i</sup> (95:5)
16 <sup>f</sup>	Ph	<i>n</i> -Hex	H	70 (81:19)
17 <sup>f</sup>	H	Me	<i>p</i> -Anisyl	55 (91:9)

<sup>a</sup>Standard conditions (entries 1–11): Et<sub>3</sub>N (1.5 mmol) and the enal or enone (0.25 mmol) were added to a solution of Ni(cod)<sub>2</sub> (0.075 mmol) and Bu<sub>3</sub>P (0.15 mmol) in toluene (1.5 mL) at 23°C under ethylene (1 atm). Triethylsilyltriflate (0.44 mmol) was added dropwise at 0°C. The mixture was stirred for 48 h at 45°C and purified by chromatography (SiO<sub>2</sub>). In some cases CyPPh<sub>2</sub> (Cy=cyclohexyl; entry 15) or tricyclopentylphosphine (entries 16,17) was used in place of Bu<sub>3</sub>P.

<sup>b</sup>Determined by <sup>1</sup>H NMR spectroscopy.

<sup>c</sup>Ethylene pressure was 2 atm.

<sup>d</sup>Fourfold larger scale (1 mmol enal used).

<sup>e</sup>The enal was added over 48 h.

<sup>f</sup>Reaction time 72 h; a lower yield was obtained after a 24 h reaction time.

<sup>g</sup>A dihydropyran from the hetero-Diels-Alder reaction of 2 equiv of enone was isolated (13%).

<sup>h</sup>Reaction time 24 h.



<sup>i</sup> Combined yield of conjugate additions from alkene 2- and 1-position, with a 79:21 ratio.