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## Simplifying Nickel(0) Catalysis: An Air-stable, COD-free Nickel Precatalyst for the Internally-selective Benzylolation of Terminal Alkenes

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### Abstract

The synthesis and characterization of the air-stable nickel(II) complex *trans*-(PCy<sub>2</sub>Ph)<sub>2</sub>Ni(*o*-tolyl)Cl is described in conjunction with an investigation of its use for Mizoroki Heck-type, room temperature, internally-selective coupling of substituted benzyl chlorides with terminal alkenes. This reaction, which employs a terminal alkene as an alkenylmetal equivalent, provides rapid, convergent access to substituted allylbenzene derivatives in high yield and with regioselectivity greater than 95:5 in nearly all cases. The reaction is operationally simple, can be carried out on the bench-top with no purification or degassing of solvents or reagents, and requires no exclusion of air or water during setup. Synthesis of the precatalyst is accomplished through a straightforward procedure that employs inexpensive, commercially available reagents, requires no purification steps, and proceeds in high yield.

### INTRODUCTION

Among the multitude of methods for the synthesis of alkenes, the Mizoroki Heck reaction continues to find frequent use in organic synthesis.<sup>1</sup> Though the first reported couplings of this type employed electron deficient alkenes such as styrenes and acrylates (Scheme 1, eq. 1),<sup>2</sup> there have also been efforts to expand the scope to include electron rich alkenes such as enamides and enol ethers (eq. 2).<sup>3</sup> In contrast to either of those two alkene classes, however, electronically unbiased alkenes such as  $\alpha$ -olefins have seen considerably less attention in the context of the Mizoroki Heck reaction.<sup>3a</sup> In this report, we describe the preparation and use of the first air-stable nickel precatalyst for internally-selective Heck reactions of terminal, electronically unbiased alkenes and benzyl chlorides. The reaction proceeds at room temperature to provide 1,1-disubstituted alkenes and no exclusion of air or moisture is required during the setup of each reaction, nor is drying, degassing, or purification of any reagents required, in stark contrast to what is typically required for nickel(0) catalyzed reactions.

One factor contributing to the historical lack of attention to aliphatic alkenes is likely the difficulty in controlling the regiochemical outcome of such reactions, given that the two carbons of the alkene are not electronically differentiated. Certain privileged alkenes, such as allylic alcohols and amines, are biased significantly enough through electronic and/or

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Supporting Information. Experimental procedures and spectral data (<sup>1</sup>H, <sup>13</sup>C, <sup>31</sup>P as applicable) for all new compounds and X-ray crystallographic data (CIF) for complexes **1** and **4**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

chelation effects to allow for high terminal or internal selectivity, depending on appropriate choice of metal, ligand, and solvent (eq. 3).<sup>4</sup>

However, in addition to our own work in this area,<sup>5</sup> developments from several other laboratories have begun to allow high selectivity for substitution at either the terminal or internal position of unbiased, aliphatic alkenes with aryl electrophiles (eq. 4 and 5).<sup>6</sup> Furthermore, the behavior of benzyl electrophiles in the Mizoroki Heck reaction remains much less well studied than aryl and vinyl electrophiles, despite the inclusion of benzyl halides in Heck's seminal 1972 report.<sup>7</sup> This may be due in part to the propensity for alkene isomerization observed with these types of electrophiles, though a number of methods have indeed been developed employing benzyl halides and benzyl trifluoroacetates as coupling partners, including one enantioselective variant (eq. 6).<sup>8</sup>

As a part of our laboratory's ongoing work in the area of stereo- and regiocontrolled synthesis of alkenes via coupling reactions, we were interested in further developing our previously reported method<sup>5</sup> for the coupling of benzyl chlorides to terminal alkenes catalyzed by Ni(COD)<sub>2</sub> and PCy<sub>2</sub>Ph (COD = 1,5-cyclooctadiene). We sought to make the reaction operationally simpler by removing the need for the use of inert-atmosphere techniques (glove-box or glovebag) to set up each reaction. Furthermore, the cost of Ni(COD)<sub>2</sub> is considerably higher than many Ni(II) sources,<sup>9</sup> its quality from commercial suppliers varies significantly (even between batches from the same supplier), and it has a limited shelf-life if not stored cold and under an inert atmosphere. Of course, the laboratory synthesis of Ni(COD)<sub>2</sub> is well established,<sup>10</sup> but it requires Schlenk or glovebox techniques and does not obviate the need for storage and use under an inert atmosphere. Thus, we sought to reduce the cost and operational complexity of this method by devising an air-stable precatalyst, which would enable this chemistry to be carried out on the benchtop with no use of a glovebox or even any air-free techniques required.

## RESULTS AND DISCUSSION

During early investigations of this reaction, we observed that catalysts comprising the combination of Ni(COD)<sub>2</sub> and PCy<sub>2</sub>Ph effected benzylation of the COD ligands themselves in preference to the intended alkene substrate in some instances. This observation led us to hypothesize that COD was coordinating to nickel with greater affinity than the intended alkene, effectively acting as a competitive inhibitor, causing a rate reduction of the desired transformation. Thus, removing COD from the reaction could allow for a greater turnover frequency and/or a reduced catalyst loading, and potentially allow for the use of more sterically hindered alkenes or even disubstituted alkenes as viable substrates.

A search of the literature brought the stable and isolable, though air-sensitive, complex (PPh<sub>3</sub>)<sub>2</sub>Ni(η<sup>2</sup>-C<sub>2</sub>H<sub>4</sub>) to our attention.<sup>11</sup> This complex is readily synthesized by combining Ni(COD)<sub>2</sub>, PPh<sub>3</sub>, and ethylene in diethyl ether; analogously, (PCy<sub>2</sub>Ph)<sub>2</sub>Ni(η<sup>2</sup>-C<sub>2</sub>H<sub>4</sub>) (**2**) was produced by the combination of Ni(COD)<sub>2</sub>, PCy<sub>2</sub>Ph, and ethylene in ether to form a yellow solid in excellent yield, as illustrated in Scheme 2. We had hoped the additional steric hindrance of PCy<sub>2</sub>Ph (compared to PPh<sub>3</sub>) would endow the complex with greater stability towards oxygen; however, although more tolerant of exposure to oxygen than (PPh<sub>3</sub>)<sub>2</sub>Ni(η<sup>2</sup>-C<sub>2</sub>H<sub>4</sub>), **2** still decomposes in air within a few minutes of exposure, so its use still requires inert-atmosphere techniques.

Treatment of complex **2** with benzyl chloride, Et<sub>3</sub>N, and TESOTf facilitates the benzylation of ethylene to yield allylbenzene and (PCy<sub>2</sub>Ph)<sub>2</sub>Ni(0) (**3**), which is believed to be the catalytically active species.<sup>12</sup> Even at half the catalyst loading (5 mol % instead of 10 mol % employed in our previously published method), the coupling of benzyl chloride with 1-

octene proceeds faster than when Ni(COD)<sub>2</sub> and PCy<sub>2</sub>Ph are used as the catalyst, which we construe as evidence that COD is reducing the rate of reaction. Furthermore, addition of COD to a reaction catalyzed by **2** retards the rate relative to a control experiment in which no COD was added. Thus, we had clearly established the detrimental effect the presence of COD has on this coupling reaction.

These results provide the first definitive evidence showing the COD ligands in Ni(COD)<sub>2</sub> are not innocent in a reaction such as this coupling. Given the widespread use of Ni(COD)<sub>2</sub> as a precursor to homogeneous Ni(0) species in organic synthesis, this result has significant implications for a variety of aspects of nickel catalysis. As researchers continue to seek more highly active catalysts to allow more challenging couplings or lower catalyst loadings, this finding is likely to shape the development of new catalysts and reactions.

Though precatalyst **2** had proven interesting and had provided valuable information regarding the role of COD in the reaction, it still required inert-atmosphere techniques for its synthesis, storage, and usage. As such, we began to examine other possible precatalysts that would possess the same properties, but also tolerate storage under air. A number of complexes of the form *trans*-(PR<sub>3</sub>)<sub>2</sub>Ni(aryl)X (where R = Ph, Cy, Et and X = Cl, Br) have been demonstrated to be air stable with prudent choice of the substituents on the aryl ring, for example when the aryl group is an *o*-tolyl or 2-naphthyl moiety. Though first reported in 1960 by Chatt and Shaw,<sup>13</sup> there have been relatively few reported uses for these complexes.<sup>14</sup>

With this inspiration, we attempted the synthesis of the complex *trans*-(PCy<sub>2</sub>Ph)<sub>2</sub>Ni(*o*-tolyl)Cl (**1**) and determined that it can be conveniently synthesized in a two-step procedure beginning from NiCl<sub>2</sub>·6H<sub>2</sub>O and PCy<sub>2</sub>Ph, followed by addition of one equivalent of *o*-tolylmagnesium chloride to yield **1** as a yellow, diamagnetic, air-stable solid (Scheme 3).<sup>15</sup> Alternatively, the ligand PCy<sub>2</sub>Ph can be easily synthesized from dichlorophenylphosphine and cyclo-hexylmagnesium chloride, which can either be made from chlorocyclohexane or purchased commercially. No purification steps are required in this sequence, making the synthesis of precatalyst **1** remarkably convenient.

Precatalyst **1** as well as the intermediate complex *trans*-(PCy<sub>2</sub>Ph)<sub>2</sub>NiCl<sub>2</sub> (**4**)<sup>16</sup> have both been characterized by single-crystal X-ray diffraction (see thermal ellipsoid representations in Figure 1); **4** adopts a nearly ideal square planar geometry with *trans* stereochemistry. This complex is diamagnetic and air-stable, and can be stored exposed to air at room temperature indefinitely. Likewise, complex **1** assumes a *trans* stereochemistry and square planar geometry, and is stable towards air. The geometry of **4** is somewhat distorted toward a tetrahedral arrangement, as indicated by the observed P Ni P bond angle of 161.7° and Cl Ni C bond angle of 170.4°, both noticeably shy of the ideal 180°.<sup>17</sup>

Upon treatment of complex **1** with an alkene, silyl tri-flate, and base, reduction from the Ni(II) precatalyst to the catalytically-active Ni(0) species occurs within minutes at room temperature. Initially, we hypothesized this to occur by arylation of the alkene as illustrated in Scheme 4; however, 2,2'-dimethylbiphenyl (**6**, 97% yield by GC) is formed rather than styrene **5**. Indeed, treatment of the precatalyst with TMSOTf effects reduction to a nickel(0) species and **6** even in the complete absence of any alkene. This suggests that, following chloride abstraction from **1**, transmetalation with another molecule of **1** to produce **1a** and **1b** occurs. Subsequently, reductive elimination of **6** from complex **1a** is evidently the means by which production of nickel(0) takes place. This in turn suggests that only half of the precatalyst is ultimately reduced presumably the other half is converted to the catalytically-inactive (PCy<sub>2</sub>Ph)<sub>2</sub>Ni(Cl)(OTf) (**1b**), unless reduction of **1b** through another mechanism is concurrently active.<sup>18</sup>

Entry into a nickel(0) manifold from nickel(II) promoted by an additive such as a silyl triflate is unprecedented. In the vast majority of cases, reduction of a nickel(II) species to the catalytically active form is effected in one of 4 ways:<sup>19</sup> (1) by consumption of an organometallic reactant present in the reaction, such as a boronic acid;<sup>20</sup> (2) by an exogenous reductant such as zinc, manganese, or sodium-mercury amalgam, which is added to carry out the reduction by electron transfer; (3) by addition of an organometallic reagent such as AlMe<sub>3</sub>, Et<sub>2</sub>Zn, or MeMgBr, which can effect reduction through two successive transmetalations to yield a dialkylnickel(II) complex, which undergoes reductive elimination to yield an alkane and a nickel(0) species;<sup>21</sup> or (4) by addition of a hydride donor such as DIBAL, methanol, or isopropanol.<sup>22,23</sup> The ability to enter into a nickel(0) catalytic cycle at room temperature and without the use of pyrophoric or strongly basic reagents represents a new and potentially valuable means of entry into nickel(0) species which could be employed for a wide variety of nickel(0)-catalyzed reactions.

Having established the competence of precatalyst **1** for this coupling reaction, we began optimizing the reaction, ultimately arriving at the conditions described in Table 1, with the conditions in entry 4 being chosen as our fully optimized conditions. With our previously published conditions<sup>5</sup> (10 mol % Ni(COD)<sub>2</sub>, 20 mol % PCy<sub>2</sub>Ph, 6 equiv Et<sub>3</sub>N, 1.75 equiv TESOTf) as a starting point, we began by investigating the reaction under solvent-free (neat) conditions, and observed that these conditions performed quite poorly. We attribute this to the low solubility of precatalyst **1** in triethylamine, which causes very slow activation. However, even in toluene, activation of the precatalyst is not facile, as entry 2 highlights: even after 1 hour, only 2 % of product has been produced, and although the reaction ultimately does reach completion, it requires nearly 24 hours to do so. At this time, we also confirmed once more that the addition of COD to the reaction mixture does indeed reduce the rate of reaction (entry 3).

Intriguingly, changing the reaction solvent to di-chloromethane facilitated rapid activation of the catalyst and a greatly accelerated coupling, requiring only 4 hours for the reaction to reach complete conversion (cf. entries 2 and 4), which corresponds approximately to a five-fold rate enhancement. At present, we are unaware of any nickel(0)-catalyzed cross-couplings carried out in a solvent of dichloromethane, making this reaction unique in that regard.<sup>24,25</sup> The change from toluene to CH<sub>2</sub>Cl<sub>2</sub> also allows for a reduction of the excess of alkene required (cf. entries 4–9). In toluene, changing from 5 to 2 equiv of alkene caused a marked decrease in the yield, even after 24 hours of reaction time (92% vs. 54%). However, in CH<sub>2</sub>Cl<sub>2</sub>, changing from 5 to 2 equiv of alkene ultimately affords the product in only a slightly diminished yield (96 vs. 84%), though the reaction rate is decreased. As the excess further decreases, however, the yield begins to drop considerably, ultimately to 68% when a 1:1 stoichiometry of benzyl chloride and alkene is used.

Also interesting is the marked reduction in yield observed when Hunig's Base (Et<sup>t</sup>Pr<sub>2</sub>N) is used instead of tri-ethylamine (cf. entries 4 and 11). Though of similar thermodynamic basicity, this likely suggests that the sterically less hindered Et<sub>3</sub>N is capable of deprotonating the nickel hydride (formed after β-hydride elimination Scheme 7, *vide infra*) much more efficiently.

Prior to beginning this optimization process, one of the changes we investigated was whether the use of dried and degassed solvents and reagents is necessary to obtain satisfactory results. Preliminary trials showed that using reagents and solvents "as received" had no negative effects on the yield of the reaction, however a direct comparison was carried out to rigorously verify this observation. As the comparison between entries 4 and 12 indicates, the reaction does appear to proceed more rapidly when purified and degassed reagents are employed, but ultimately the same yield is achieved in both cases. We attribute

this difference in rate to the oxygen mediated decomposition of some portion of the catalyst when unpurified reagents are employed, causing the effective catalyst loading to be slightly less than the nominal loading.<sup>26</sup> Having verified the absence of negative effects, we opted to carry out the remainder of the optimization without purification or degassing of any reagents, taking the conditions described in entry 4 as our optimized conditions.

Having satisfactorily optimized the conditions for the coupling reaction, we next examined the scope of the reaction, the results of which are shown in Scheme 5. Several aspects are noteworthy: first, the reaction is highly selective for the branched product over the linear product across a wide variety of electronically and sterically differentiated benzyl chlorides and alkenes. The selectivity, described by the ratio between the branched product and the sum of all other isomers observed, is greater than 95:5 in nearly all instances, which not only indicates an intrinsically high selectivity for the branched product over the linear product, but it also shows that isomerization of the product after its formation is extremely minimal.<sup>27</sup>

Substitution in the *ortho*, *meta*, and *para* positions of the benzyl chloride is well tolerated, including fluorine, chlorine, bromine, and iodine substituents (ex. **11**, **12**, **14**, **15**, **17**). Some addition of nickel into the C I bond was observed, but the yield of the corresponding desired product (**11**) was not significantly diminished. The tolerance of aryl halides is a significant feature of this method, since this enables the construction of halogen-substituted allylbenzene derivatives, which can then be directly used in further cross-coupling reactions, if desired. Oxidative addition of Ni(0) phosphine complexes into aryl fluorides,<sup>28</sup> chlorides,<sup>29</sup> bromides, and iodides<sup>30</sup> is well established, so the excellent chemoselectivity of the oxidative addition into the benzyl  $sp^3C$  Cl bond in preference to the  $sp^2C$  X bonds suggests the former occurs significantly faster than the latter.

As examples **23**, **27**, **29**, and **31** demonstrate, primary alkyl chlorides, bromides, and tosylates are all tolerated again, this speaks to the excellent chemoselectivity of the oxidative addition into the benzyl  $sp^3C$  Cl bond in preference to primary  $sp^3C$  Cl,  $sp^3C$  Br, and  $sp^3C$  OTs bonds. As with their aryl counterparts, oxidative addition by nickel(0) into these types of bonds is well documented.<sup>31</sup> Construction of these 1° alkyl electrophiles could prove useful, whether it be for nucleophilic substitution reactions, cross couplings, or in the preparation of nucleophilic organometallic reagents such as Grignard, organolithium, or organozinc reagents.

Additionally, as a part of our efforts to increase the convenience and flexibility of this method, we also explored the use of alternative silyl triflate additives. In the majority of cases, TMSOTf can be used in place of the more expensive TESOTf with no detrimental effects, though there are some instances in which the greater Lewis acidity of TMSOTf compared to that of TESOTf causes partial decomposition of substrates. Likewise, TBSOTf is also a competent silyl triflate additive for this reaction. Given the interchangeability of these additives, researchers may find it convenient to be able to use any of these silyl triflates, depending on what is readily available.

Using these three different silyl triflate additives, we demonstrated that in situ protection of free alcohols, carboxylic acids, and amines is possible on both the alkene and benzyl chloride coupling partners, directly yielding protected alcohols (**12**, **22**), phenols (**24**), and following aqueous workup, free carboxylic acids (**21**) and amines (**25**). As illustrated by example **17**, allyltrimethylsilane is a competent alkene coupling partner, though some protodesilylation does occur (ca. 15%). In this particular example, the protodesilylated material was separable by column chromatography, allowing clean isolation of **17**, though in modest yield.

Also of considerable interest is the marked unreactivity of styrenes compared to  $\alpha$ -olefins, as evidenced by the formation of **18** in high yield from 4-vinylbenzyl chloride and 3-butenylbenzene with no observable reaction at the styrene. Gratifyingly, sulfur-containing functional groups, such as sulfones (**19**, **26**) and benzothiophene (**27**) are tolerated with no apparent poisoning of the catalyst. Lastly, methylene acetals (**26**, **29**) are compatible with the reaction conditions.

While most reactions proceed in good to excellent yield, a reduction in yield typically results from substitution on the *ortho* positions of the benzyl chloride or substitution adjacent to the olefin. Examples **8**, **9**, **14**, **28** demonstrate this trend, since all four are obtained in a lower yield than substrates containing similar functional groups, but connected in different positions. Additionally, there are several other specific conditions which greatly reduce the yield of the reaction, or in some cases, completely prevent product formation. Such examples are outlined in Chart 1.

An ester moiety at the *ortho* position appears to completely prevent catalytic turnover; intriguingly, this functional group is well-tolerated in the 4-position of the aromatic ring, suggesting it may be interfering with the catalytic cycle through chelation to the nickel center after oxidative addition. Substitution of both the 2- and 6- positions of the benzyl chloride with fluorine (**34**) prevents product formation, leading to exclusive formation of the homocoupled product 1,2-bis(2,6-difluorophenyl)ethane. However, 2,4-difluorobenzyl chloride (**30** and **32**) is a competent substrate, indicating that the combination of the steric hindrance *and* the electron poor nature of 2,6-difluorobenzyl chloride is problematic, especially given that 2,4,6-trimethylbenzyl chloride is a competent substrate (**28**). Additionally, 4-(chloromethyl)pyridine (**34**, as the HCl salt) does not provide any product; it is unclear if this is due to reaction with the silyl triflate or because the nitrogen is able to coordinate to nickel, disrupting the catalytic cycle. Finally, 4-(chloromethyl)-*N,N*-dimethylbenzamide (**36**) did not provide any of the desired product, likely due to reaction of the amide with the silyl triflate.

A number of alkenes also provided very little or no product; allyl phenyl ether (**37**) underwent coupling, but also reacts with TESOTf, as does the coupling product, both of which decomposed to a significant extent. Diene **38** decomposed under the reaction conditions, and the rate of reaction of cyclohexene (**39**) was extremely low, with only traces of product formed, even after 48 hours of reaction time.

The profound selectivity for reaction with terminal, electronically unbiased alkenes in preference to styrenes (as evidenced by example **18**) is a surprising and interesting outcome, which we felt warranted further investigation. As shown in Scheme 6, the reaction between benzyl chloride and 1-octene proceeded in high yield as expected; the analogous reaction with styrene, however, provided **40** in only 8% yield. Of further interest is the regiochemical outcome of the reaction with styrene: though not as selective as with aliphatic alkenes, substitution at the internal position is still favored in a 78:22 ratio. To date, the highest regioselectivity reported for styrene is 40:60 in favor of the linear product, making this a significant improvement from a theoretical standpoint, despite the low yield.<sup>32</sup>

During NMR spectroscopic characterization of complex **1**, we observed that dissolution in CD<sub>2</sub>Cl<sub>2</sub> caused the solution to take on a markedly red color compared to the pure yellow color observed in benzene. This difference is also reflected in the NMR spectra of the complex in C<sub>6</sub>D<sub>6</sub> compared to CD<sub>2</sub>Cl<sub>2</sub>: the <sup>31</sup>P NMR spectrum in C<sub>6</sub>D<sub>6</sub> shows only a single peak at 16.1 ppm, whereas the spectrum in CD<sub>2</sub>Cl<sub>2</sub> shows three signals one at 15.0 ppm, corresponding to **1**, as well as a signal at 3.1 ppm for free PCy<sub>2</sub>Ph and one downfield signal at 44.9 ppm, presumably (PCy<sub>2</sub>Ph)Ni(*o*-tolyl)Cl or a CD<sub>2</sub>Cl<sub>2</sub> adduct thereof (spectra are

included in Supporting Information). On this basis, it is reasonable to suggest that dichloromethane promotes or stabilizes dissociation of one PCy<sub>2</sub>Ph ligand, which we hypothesize is necessary during the course of the reaction to allow coupling to occur, as outlined in the proposed mechanism (Scheme 7).

The proposed mechanism begins with reduction of the precatalyst **1** to the NiL<sub>2</sub> species **41** (via the mechanism presented in Scheme 4), followed by rapid oxidative addition to yield **42**, which is in equilibrium with **42'**. Abstraction of chloride by the silyl triflate yields cationic nickel species **43**, which facilitates alkene coordination to yield **44**.<sup>33</sup> This species undergoes β-migratory insertion with the indicated regiochemistry to produce **45**, with nickel bonded to the less substituted of the two carbons comprising the alkene. The migratory insertion step is likely irreversible, and it also determines the regiochemical outcome of the reaction: insertion as shown (**44** to **45**) will ultimately provide the branched (desired) product, whereas insertion with the opposite regiochemistry will lead to formation of the linear product.

Following migratory insertion, β-hydride elimination to form nickel hydride **46** takes place. Product release, ligand association, and deprotonation by Et<sub>3</sub>N complete the catalytic cycle. One commonly observed side product (**43'**), formed by the formal protonation of benzyl nickel species **43**, is often produced in small quantities during the course of the reaction. As the concentration of alkene decreases, the equilibrium between **43** and **44** shifts more toward **43**, which results in a higher concentration of **43** at any given time, causing reduction product **43'** to be formed in greater amounts. We suspect this is the root cause for the decrease in yield observed as the amount of alkene used in the reaction is reduced or when more sterically hindered alkenes are used.

We hypothesize that the principal factor responsible for formation of the branched product in preference to the linear product is the steric differentiation of the two ends of the alkene, which manifests itself as a difference in energy between the incipient 1° C Ni and 2° C Ni bond formed during migratory insertion (**44** to **45**). The less hindered 1° C Ni bond is lower in energy, and as such, the transition state leading to its formation is also lower in energy. The uniformly high selectivity observed across a range of electronically diverse substrates supports this hypothesis, suggesting that electronic factors are of secondary importance in determining the regiochemical outcome of the migratory insertion, and thus of the reaction. The comparison between styrene and an aliphatic olefin (Scheme 6) further supports this hypothesis: while the branched product is still the major product, the selectivity is indeed reduced compared to electronically unbiased alkenes.

## CONCLUSIONS

In summary, we have developed a convenient protocol for the internally-selective benzylation of terminal alkenes using the air-stable precatalyst *trans*-(PCy<sub>2</sub>Ph)<sub>2</sub>Ni(*o*-tolyl)Cl (**1**). This precatalyst is easily prepared from commercially available NiCl<sub>2</sub> · 6H<sub>2</sub>O, PCy<sub>2</sub>Ph, and *o*-tolylmagnesium chloride in a high-yielding, two-step procedure, and can be stored open to air at room temperature with no measurable loss of purity or activity. Furthermore, all reagents used in the reaction can be used “as received” with no purification or even any degassing necessary. The reaction is tolerant of substitution on both the benzyl chloride and alkene coupling partners, allowing rapid access to a wide variety of substituted allylbenzene derivatives. Additionally, this study has provided useful information regarding the commonly employed nickel(0) source Ni(COD)<sub>2</sub>, demonstrating that the COD ligands are not innocent under all circumstances. This finding has wider implications for the field of nickel(0) catalysis, where Ni(COD)<sub>2</sub> is frequently used as a precursor to a variety of Ni(0)

complexes. More detailed studies of the mechanism of activation of precatalyst **1** and of the mechanism of the coupling reaction are underway.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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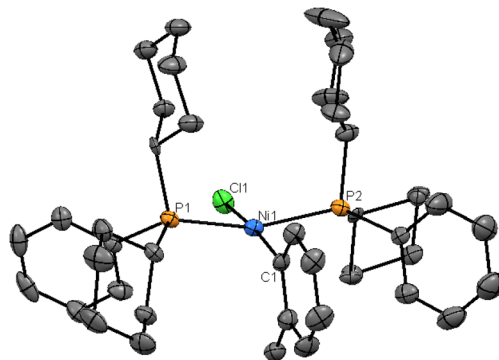
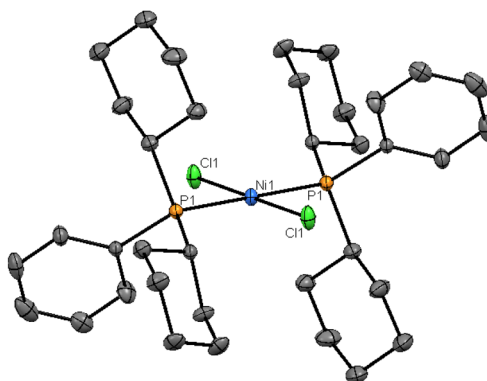
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- Based on prices from Strem Chemicals, Inc., Ni(COD)<sub>2</sub> is approximately 200 times more expensive than NiCl<sub>2</sub>·6H<sub>2</sub>O on a mole for mole basis, or ca. 80 times more expensive than Ni(acac)<sub>2</sub> hydrate.
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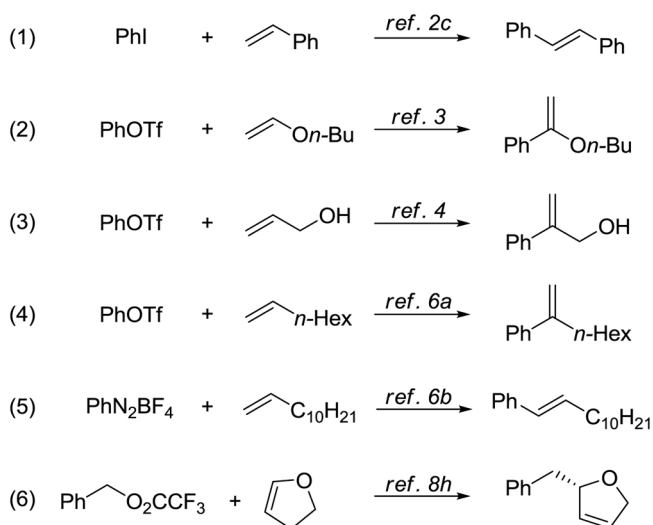
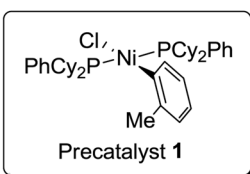
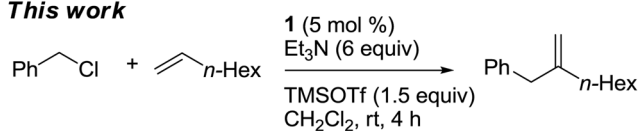
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12. It is likely that  $(PCy_2Ph)_2Ni(0)$  exists in solution coordinated to solvent or allylbenzene, rather than as a discrete species. There is evidence that 2-coordinate nickel(0) species do exist in solution, but only with very large NHC ligands such as IPr. For an example, see Louie J, Gibby JE, Farnworth MV, Tekavec TN. *J Am Chem Soc.* 2002; 124:15188–15189. [PubMed: 12487590]
13. Chatt J, Shaw BL. *J Chem Soc.* 1960:1718–1729. Further examples can be found in Cross RJ, Wardle R. *J Chem Soc A.* 1970:840–845. Cassar L, Ferrara S, Foá M. *Adv Chem Ser. American Chemical Society Washington, DC* 1974; 132:252–273. Brandsma L, Vasilevsky SF, Verkrujjsse HD. *Application of Transition Metal Catalysts in Organic Synthesis.* Springer New York 1998:3–4.
14. For a selection of some recent examples, see Chen C, Yang LM. *Tet Lett.* 2007; 48:2427–2430. Gao CY, Yang LM. *J Org Chem.* 2008; 73:1624–1627. [PubMed: 18198889] Lanni EL, Locke JR, Gleave CM, McNeil AJ. *Macromolecules.* 2011; 44:5136–5145. Zhang N, Hoffman DJ, Gutsche N, Gupta J, Percec V. *J Org Chem.* 2012; 77:5956–5964. [PubMed: 22712768] Leowanawat P, Zhang N, Safi M, Hoffman DJ, Fryberger MC, George A, Percec V. *J Org Chem.* 2012; 77:2885–2892. [PubMed: 22369478]
15. During the course of these studies, a sample of **4** was allowed to stand open to the atmosphere at room temperature for 4 months. No change in the  $^1H$ ,  $^{13}C$ , or  $^{31}P$  NMR spectra was observed, nor was the sample observed to be hygroscopic, and reactions run using precatalyst that had been allowed to stand for several months showed no difference from reactions run using freshly-prepared precatalyst.
16. The synthesis of  $trans-(PCy_2Ph)_2NiCl_2$  was first reported in 1967, and it has been used sporadically in the years since. However, no crystal structure has been obtained, nor has the complex been characterized by NMR spectroscopy. For the first reported synthesis, see Masahiro U, Yves C, Gilles L. *C R Seances Acad Sci, Ser C.* 1967; 265:103–106. a more rigorous characterization of the complex and a number of related complexes was carried out: Stone PJ, Zvi D. *Inorg Chim Acta.* 1970; 5:434–438.
17. Due to the disorder in the position of the *o*-tolyl moiety, the value of the Cl Ni C bond angle is uncertain. Possible values range from 166.5° to 170.4°.
18. A control experiment using 5 mol % of  $trans-(PCy_2Ph)_2NiCl_2$  as the precatalyst produced a trace of product (<1%), whereas a control experiment with no catalyst added produced no product; this suggests that it is possible for  $trans-(PCy_2Ph)_2NiCl_2$  to mediate this reaction, though evidently not in a catalytic fashion.
19. An excellent overview of these techniques is provided in Rosen BM, Quasdorf KW, Wilson DA, Zhang N, Resmerita AM, Garg NK, Percec V. *Chem Rev.* 2011; 111:1346–1416. [PubMed: 21133429]
20. (a) Tamao K, Sumitani K, Kiso Y, Zembayashi M, Fujioka A, Kodama S-i, Nakajima I, Minato A, Kumada M. *Bull Chem Soc Jpn.* 1976; 49:1958–1969. (b) Quasdorf KW, Tian X, Garg NK. *J Am Chem Soc.* 2008; 130:14422–14423. [PubMed: 18839946]
21. Wolfe JP, Buchwald SL. *J Am Chem Soc.* 1997; 119:6054–6058. (b) Other mechanisms of reduction are possible: the use of *n*-BuLi as the reductant yields a mixture of *n*-butane, 1-butene, and *n*-octane. A discussion of this topic is found in ref. 19.
22. For selected examples of MeOH and *i*-PrOH as reducing agents in Ni-catalyzed coupling reactions, see Herath A, Li W, Montgomery J. *J Am Chem Soc.* 2008; 130:469–471. [PubMed: 18081296] Li W, Herath A, Montgomery J. *J Am Chem Soc.* 2009; 131:17024–17029. [PubMed: 19883082] Phillips JH, Montgomery J. *Org Lett.* 2010; 12:4556–4559. [PubMed: 20843015] Beaver MG, Jamison TF. *Org Lett.* 2012; 13:4140–4143. [PubMed: 21718038]
23. A number of reductive couplings catalyzed by iridium and ruthenium have been reported using isopropanol as the terminal reductant. Bower JF, Skucas E, Patman RL, Krische MJ. *J Am Chem Soc.* 2007; 129:15134–15135. [PubMed: 18020342] Bower JF, Patman RL, Krische MJ. *Org Lett.* 2008; 10:1033–1035. [PubMed: 18254642] Shibahara F, Bower JF, Krische MJ. *J Am Chem Soc.* 2008; 130:6338–6339. [PubMed: 18444617] Patman RL, Chaulagain MR, Williams VM, Krische MJ. *J Am Chem Soc.* 2009; 131:2066–2067. [PubMed: 19173651]

24. It is known that Ni(COD)<sub>2</sub> reacts with CH<sub>2</sub>Cl<sub>2</sub> at room temperature to form Ni particles and free COD: Miller JS, Pokhodnya KI. *J Mater Chem.* 2007; 17:3585–3587. Likewise, (bpy)Ni(COD) and Ni(PEt<sub>3</sub>)<sub>4</sub> have been shown to react with geminal dihalides such as dichloromethane: Takahashi S, Suzuki Y, Hagihara N. *Chem Lett.* 1974:1363–1366. Eisch JJ, Qian Y, Singh M. *J Organomet Chem.* 1996; 512:207–217.
25. Protocols for the Ni-catalyzed difunctionalization of CH<sub>2</sub>Cl<sub>2</sub> have been reported, though it is not believed that Ni(0) is involved. See Csok Z, Vechorkin O, Harkins SB, Scopelliti R, Hu XL. *J Am Chem Soc.* 2008; 130:8156–8157. [PubMed: 18528995] Vechorkin O, Hu XL. *Angew Chem, Int Ed.* 2009; 48:2937–2940. Vechorkin O, Csok Z, Scopelliti R, Hu XL. *Chem Eur J.* 2009; 15:3889–3899. [PubMed: 19229933]
26. A reaction carried out using 1 mol % of precatalyst **4** and unpurified reagents provided a 0% yield of the desired product, suggesting that the amount of dissolved oxygen in the reagents is sufficient to destroy all of the catalyst.
27. Nickel hydrides (such as complex **47**, Scheme 7) are known to isomerize alkenes, which can under some circumstances cause a small amount of isomerization of the starting alkene to form the corresponding cis- or trans-2-alkene. In these instances, between 0 and 5% of the recovered starting alkene is isolated as this isomer. For a recent example of a nickel hydride used for alkene isomerization, see Lim HJ, Smith CR, RajanBabu TV. *J Org Chem.* 2009; 74:4565. [PubMed: 19441793]
28. For an example of a Ni(0)-catalyzed cross-coupling reaction of an unactivated aryl fluoride, see Tobisu M, Xu T, Shimasaki T, Chatani N. *J Am Chem Soc.* 2011; 133:19505–19511. [PubMed: 22023167]
29. A room-temperature, nickel(0) catalyzed Suzuki-Miyaura reaction of unactivated aryl chlorides has been described: Tang ZY, Hu QS. *J Org Chem.* 2006; 71:2167–2169. [PubMed: 16497011]
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31. Tamaru, Y., editor. *Modern Organonickel Chemistry*. Vol. Chapter 2. Wiley-VCH; Weinheim: 2005.
32. See references 3a d.
33. Based on the observation that the rate of the reaction is dependent on the concentration of alkene and the observation that the amount of side product **43'** formed increases at lower alkene concentrations, we hypothesize that **43** is the resting state of the catalyst.

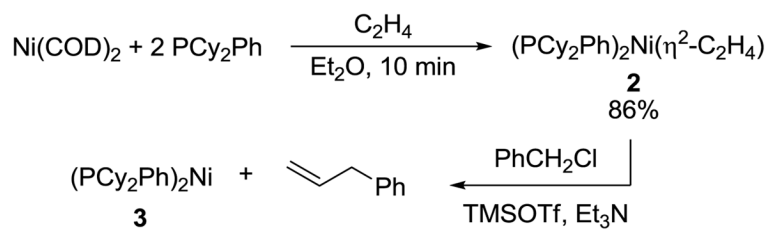
*trans*-(PCy<sub>2</sub>Ph)<sub>2</sub>Ni(*o*-tolyl)Cl (**1**)*trans*-(PCy<sub>2</sub>Ph)<sub>2</sub>NiCl<sub>2</sub> (**4**)**Figure 1. Thermal Ellipsoid Representations of Nickel Complexes 1 and 4**

Thermal ellipsoid representations of *trans*-(PCy<sub>2</sub>Ph)<sub>2</sub>Ni(*o*-tolyl)Cl (**1**, top) and *trans*-(PCy<sub>2</sub>Ph)<sub>2</sub>NiCl<sub>2</sub> (**4**, bottom) with ellipsoids at 50% probability level. Hydrogen atoms and disorder on ligands not shown for clarity; see Supporting Information for full representations, including disorder.

**This work**

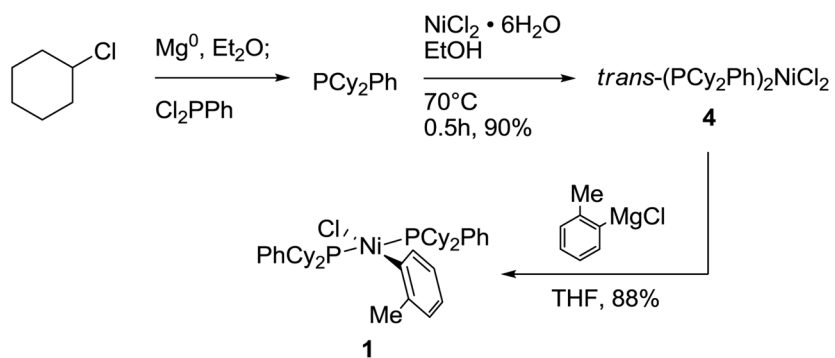
- Air-stable
- Simple to synthesize
- Highly active

**Scheme 1.**  
Regiochemistry of the Mizoroki Heck Reaction

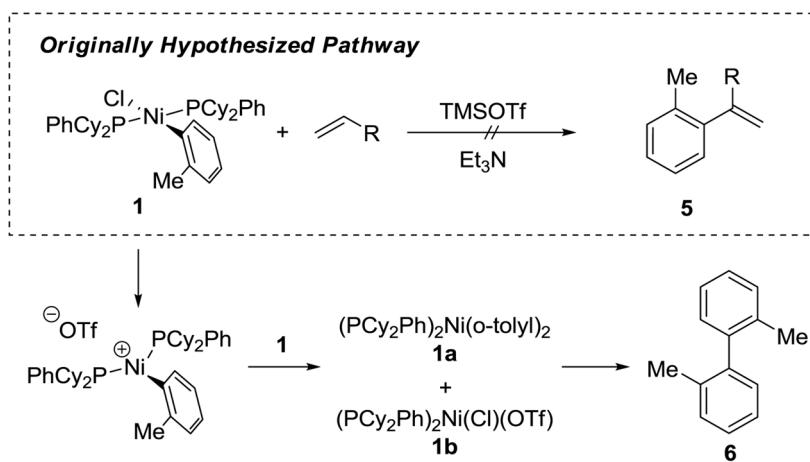


**Scheme 2. Synthesis of  $(\text{PCy}_2\text{Ph})_2\text{Ni}(\eta^2\text{-C}_2\text{H}_4)$**

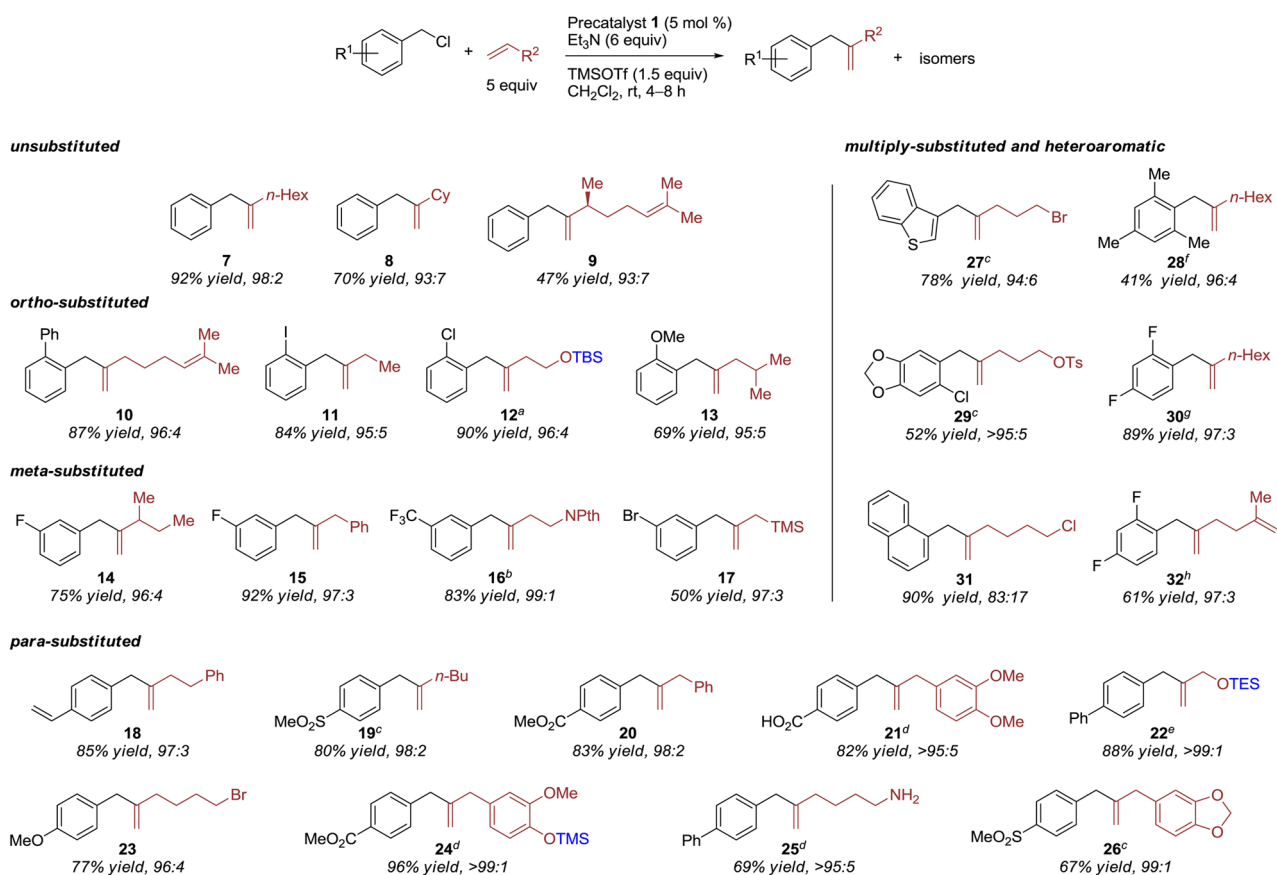
Complex **3** was not isolated; its yield was determined indirectly to be >98% based on the amount of allylbenzene formed (measured by GC).



**Scheme 3.**  
Synthesis of *trans*-(PCy<sub>2</sub>Ph)<sub>2</sub>Ni(*o*-tolyl)Cl



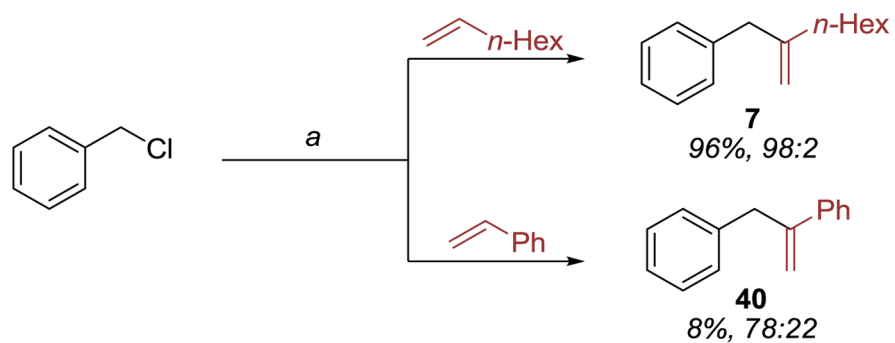
**Scheme 4.**  
Activation of Precatalyst 1



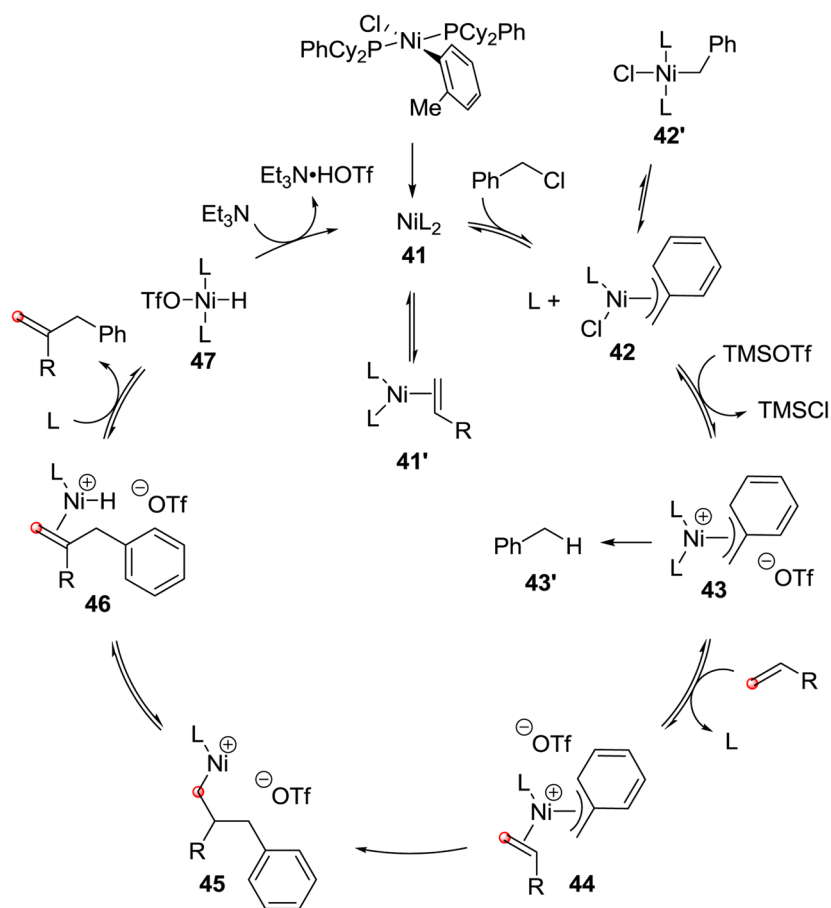
### Scheme 5. Substrate Scope of the Nickel-catalyzed Coupling of Benzyl Chlorides to Terminal Alkenes

Yields listed are isolated yields. Ratios reported represent the ratio of the major (branched) product to the sum of all other isomers as determined by GC. Ratios reported as >95:5 were determined by NMR. <sup>a</sup> TBSOTf and 3 equiv 3-buten-1-ol used in place of TMSOTf. <sup>b</sup> 3 equiv alkene used. <sup>c</sup> TESOTf used in place of TMSOTf. <sup>d</sup> Excess TMSOTf used to effect in situ protection. <sup>e</sup> TESOTf and 3 equiv allyl alcohol used in place of TMSOTf. <sup>f</sup> Ratio was 78:22 prior to purification. The linear and branched products were separable by column chromatography. <sup>g</sup> Reaction carried out on 10 mmol scale. <sup>h</sup> Product contained an inseparable byproduct (ca. 10% by mass) formed by the oligomerization of 2-methyl-1,5-hexadiene.



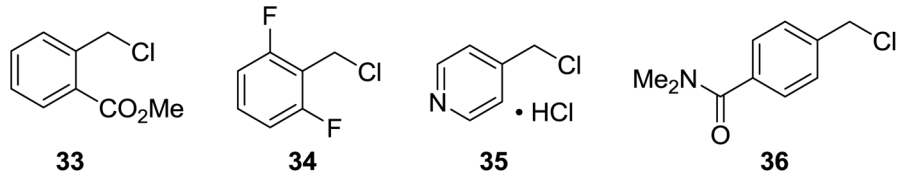
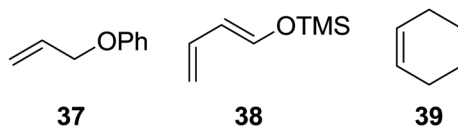
**Scheme 6. Comparison of Styrene and  $\alpha$ -olefins**

<sup>a</sup> Reaction conditions: precatalyst **1** (5 mol %), 5 equiv alkene (1-octene or styrene), Et<sub>3</sub>N (6 equiv), TMSOTf (1.5 equiv), 2 M in CH<sub>2</sub>Cl<sub>2</sub>. Yields and ratios determined by GC.



**Scheme 7. Hypothesized Mechanism**

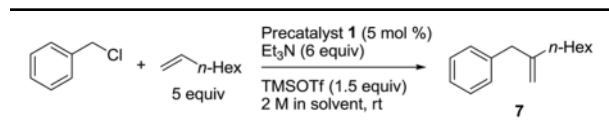
Migratory insertion (**44** to **45**) occurs to form the new nickel carbon bond to the less substituted carbon of the alkene, which is marked with for emphasis.

**Benzyl chlorides****Alkenes**

**Chart 1.**  
Substrates that did not provide the desired benzylation products.

Table 1

## Optimization of reaction parameters



entry	Change from above conditions	% Yield at time (h)		
		1	3	24
1	Neat	1	3	11
2	PhMe	2	40	92
3	PhMe, 10 mol % 1,5-COD added	2	16	76
<b>4</b>	<b>CH<sub>2</sub>Cl<sub>2</sub></b>	<b>51</b>	<b>68</b>	<b>96</b>
5	CH <sub>2</sub> Cl <sub>2</sub> , 2 equiv 1-octene	35	52	84
6	CH <sub>2</sub> Cl <sub>2</sub> , 1.3 equiv 1-octene	21	40	79
7	CH <sub>2</sub> Cl <sub>2</sub> , 1 equiv 1-octene	19	38	68
8	PhMe, 3.5 equiv 1-octene	1	11	73
9	PhMe, 2 equiv 1-octene	1	8	54
10	CH <sub>2</sub> Cl <sub>2</sub> , TESOTf inst. TMSOTf	48	65	95
11	CH <sub>2</sub> Cl <sub>2</sub> , Et <sup>t</sup> Pr <sub>2</sub> N instead of Et <sub>3</sub> N	2	6	12
12	Purified and degassed reagents <sup>a</sup>	59	76	95

All yields were determined by gas chromatography against a calibrated internal standard. All reagents were used "as received" except where explicitly stated. Many reactions were complete prior to 24 hours, but were run for the full 24 hours for comparison purposes.

<sup>a</sup> liquid reagents and solvents were dried over a suitable drying agent and distilled, followed by three cycles of freeze-pump-thaw degassing.