Catalytic Coupling Reactions

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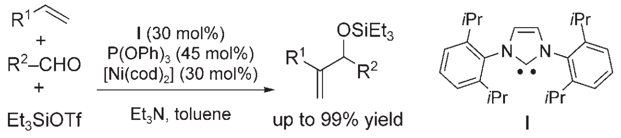
# Highly Selective Coupling of Alkenes and Aldehydes Catalyzed by [Ni(NHC){P(OPh)$_3$}]: Synergy between a Strong σ Donor and a Strong π Acceptor**

*Chun-Yu Ho and Timothy F. Jamison**

Recently we described two new nickel-catalyzed, three-component coupling reactions involving α-olefins, aldehydes, and silyl triflates.[1] The appropriate choice of ligand favors the production of either allylic (A) or homoallylic (H) alcohol derivatives, both of which are synthetically useful intermediates.[2] In these studies we achieved greater than 95:5 H/A selectivity using EtOPPh$_2$ or Ph$_3$P, but a general method for with high A/H selectivity has remained elusive.

Herein we describe a solution to this deficiency and document a synergistic relationship between substoichiometric amounts of a strong σ donor [**I**, (IPr) Eq. (1), Tf = trifluoromethanesulfonyl, cod = cycloocta-1,5-diene] and a strong π acceptor (PhO)$_3$P. We believe that this phenomenon is the result of attenuation of the strong electron-donating ability of **I** by the electron-withdrawing phosphine (PhO)$_3$P at a specific point in the catalytic cycle that consequently accelerates reductive elimination. This new strategy may have many broader applications in certain metal-catalyzed reactions, for example, the Heck reaction.[3]

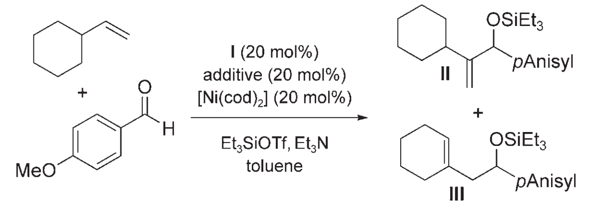


In preliminary investigations of imidazolinyl-derived NHC ligands (NHC = N-heterocyclic carbene) in these transformations, we found that **I** was exceptionally selective for the allylic product (Table 1, entry 1), even when a rather encumbered alkene (vinylcyclohexane) was used.[4] With our previous phosphine-based system, α-branched alkenes afforded only traces of allylic product **II**. However, these reactions did not appear to proceed catalytically. An additional complication was that significant quantities of two side products were also observed, resulting from hydrosilylation of the aldehyde (reduction) and hydrovinylation.[5]

We surmised that both problems (product distribution and no discernable catalytic mechanism) might have a common cause (Scheme 1): Formal reductive elimination of triflic acid (HOTf) from **3** to regenerate a Ni$^0$ species (for example, **1**) is likely retarded by the electron-rich ligand **I**.[3b,c,6] Stalling the catalytic cycle at this point would result in an accumulation of a [Ni(NHC)H](OTf) species **3** which is responsible for the aforementioned side reactions. Our first attempts to render this process catalytic involved the use of stronger organic and/or inorganic bases to facilitate reductive elimination. Unfortunately, this strategy summarily failed, perhaps because **I** is a very strong σ donor.[7]

We thus required an alternative means to rescue the catalytic cycle and considered the possibility of shunting **3** into a different manifold to make reductive elimination more facile (Scheme 1). As the pioneering investigations of Yama-

***Table 1:*** Evaluation of additives in the coupling reactions mediated by [Ni(IPr)].



| Entry[a] | Additive | Conv. [%][b] | Yield **II** [%][b,c] | Yield **III** [%][b] |
|---|---|---|---|---|
| 1 | none | 55 | 18 (33) | 0 |
| 2 | $m$(CF$_3$)C$_6$H$_4$C=CH$_2$ | 79 | 39 (49) | 0 |
| 3 | CyPPh$_2$ | 61 | 19 (31) | 0 |
| 4 | PPh$_3$ | 100 | 34 (34) | 44 |
| 5 | EtOPPh$_2$ | 100 | 34 (34) | 37 |
| 6 | (EtO)$_2$PPh | 84 | 30 (35) | 29 |
| 7 | P(OBu)$_3$ | 68 | 32 (47) | 9 |
| **8** | **P(OPh)$_3$** | **59** | **45 (76)** | **0** |
| 9 | P(OPh)$_3$[d] | 7 | 0 (0) | 0 |

[a] See the Supporting Information for details. [b] Determined by $^1$H NMR analysis (relative to an external standard (CH$_3$NO$_2$)). [c] Values in parentheses are yields based on conversion of aldehyde. [d] Without added ligand **I**.

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[*] Dr. C.-Y. Ho, Prof. T. F. Jamison
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, MA 02139 (USA)
Fax: (+1) 617-324-0253
E-mail: tfj@mit.edu

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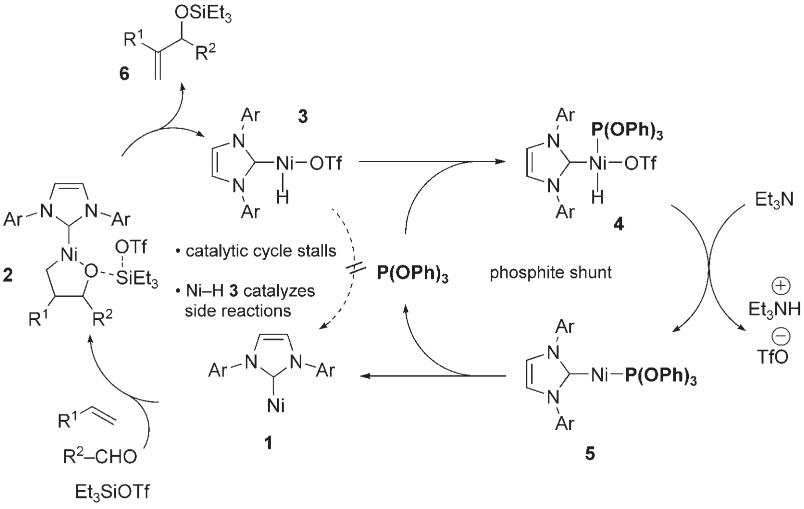

***Scheme 1.*** Proposed Mechanism.

moto et al. had demonstrated that electron-poor alkenes dramatically accelerate the reductive elimination of R′–R″ from species of the general form R′–Ni–R″ by decreasing the electron density at the metal center,[8] we examined the effect of these electron-poor olefins on the reaction.

With *meta*-trifluoromethylstyrene and a catalyst loading of 30 mol %, we observed a 39 % yield of the desired coupling product (Table 1, entry 2), but coupling products derived from the added styrene were also observed in the reaction.[9a–c] Nevertheless, catalysis had been achieved for the first time, and we expanded our search to include electron-withdrawing phosphorus-containing compounds to avoid undesired coupling reactions between the additive and the aldehyde.[10]

We were mindful of the fact that this approach could very well have a fatal flaw related to ligand compatibility. In previous studies we found electron-poor phosphinites, among others, disfavored the formation of allylic alcohol derivatives and, as mentioned above, were in fact superior to all other additives for high H/A selectivity.[11] Thus, the electron-deficient additive could erode or overturn the high A/H selectivity provided by ligand **I**.

Table 1 summarizes the results of these studies. Moderately electron-donating phosphines such as CyPPh$_2$ (Cy = cyclohexyl) proved ineffective (Table 1, entry 3). Substoichiometric amounts of certain electron-poor phosphines (relative to CyPPh$_2$) provided marginal catalytic activity (Table 1, entries 4–6). Unfortunately, a significant amount of the undesired homoallylic alcohol derivative **III** was observed, presumably because of the competing homoallylic-favoring reaction, the potential pitfall mentioned above.

However, highly electron-deficient phosphite ligands were found to be very efficient additives (Table 1, entries 7 and 8). Not only did triphenylphosphite render the system catalytic, but it also completely suppressed formation of the homoallylic by-product ($^1$H NMR, limit of detection approx. 2 %). Furthermore, hydrosilylation of the aldehyde was not observed and the amount of alkene hydrovinylation was dramatically reduced.

It should be emphasized that both **I** and (PhO)$_3$P were necessary for catalysis, the absence of one results in either no product (**I** absent) or no turnover (phosphite absent). Thus, unlike other electron-poor phosphorus additives, (PhO)$_3$P did not erode the allylic selectivity, perhaps because it did not promote the reaction on its own (Table 1, entry 9).

The scope of this synergistic NHC/phosphite effect and new [Ni(IPr)]-catalyzed transformation are summarized in Table 2. Particularly noteworthy is that an A/H selectivity of greater than 20:1 was observed in all cases examined. Also, the range of suitable alkene substrates was far broader than that found in our previous Ni–phosphine-catalyzed processes.[1]

Anisaldehydes substituted in the *para*, *ortho*, and *meta* positions proved to be good-to-excellent substrates (Table 2, entries 1–4). Bulky silyl triflates such as TBDMSOTf (TBDMS = *tert*-butyldimethylsilyl) could also be used as activating reagents (Table 2, entry 2). Styrenes, which readily underwent self-hydrovinylation in our earlier studies, became competent starting materials in the presence of the phosphite (Table 2, entry 5).

Allylbenzene and homoallylbenzene both displayed excellent selectivity (Table 2, entries 6 and 7), despite a reduced reaction rate. Sterically demanding α-branched substrates underwent highly regioselective coupling (Table 2, entries 8–10). Similarly, coupling reactions of β-branched alkenes with the phosphite additive also showed a marked increase in A/H selectivity (Table 2, entry 11). A trisubstituted double bond was found to be inert, thus enabling its use as a masked functional group for subsequent modification (Table 2, entry 12).

Benzaldehyde and 2-naphthaldehyde also showed good reactivity and high A/H ratios (Table 2, entries 13 and 14). A chlorine atom attached to the aldehyde was tolerated (Table 2, entries 15 and 16), but the reaction rate was much slower, and the side reactions of hydrosilylation and hydrovinylation became significant. Furfural was found to behave similarly (Table 2, entry 17).

We believe the high selectivity for the allylic alcohol and the broader range of substrates tolerated in this new reaction system are related to the sterically demanding and highly electron-donating nature of the ligand **I** (Scheme 1). The ligand not only orients the substituents of the alkene and aldehyde away from the Ni center, but also accelerates the oxidative coupling (**1** to **2**).

Conversely, the downside of this latter effect is perhaps that, in the absence of the phosphite additive, reductive elimination is much more difficult for the same reason that oxidative addition is more facile. Thus, we propose that the phosphite promotes this step in the catalytic cycle by reducing the electron density at a coordinatively unsaturated Ni center. A complex such as **4** (Scheme 1) would be expected to undergo reductive elimination to **5** more readily than would **3** to **1**.

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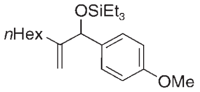
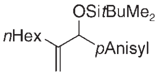
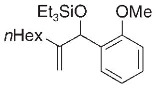
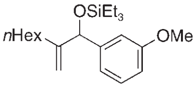
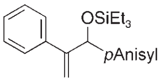
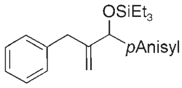
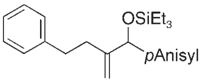
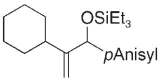
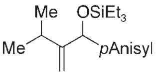
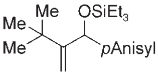
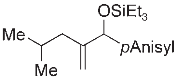
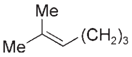
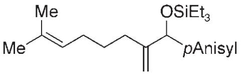
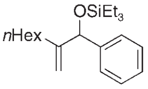
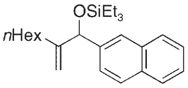
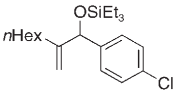
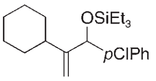
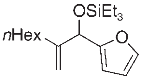
*Table 2:* Alkene–aldehyde coupling reactions catalyzed by [Ni(**I**){P(OPh)$_3$}].

| Entry[a] | Alkene (R$^1$) | Product | Conv. [%][b] | Yield [%][b,c] |
|---|---|---|---|---|
| 1 | *n*Hex |  | 95[d] | 96 |
| 2 | *n*Hex |  | 92[d,e] | 82 |
| 3 | *n*Hex |  | 80 | 75 |
| 4 | *n*Hex |  | 86 | 98 |
| 5 | Ph |  | 69 | 84 |
| 6[d] | PhCH$_2$ |  | 75 | 99 |
| 7 | PhCH$_2$CH$_2$ |  | 88 | 99 |
| 8 | Cy |  | 100 | 96 |
| 9[f,g] | *i*Pr |  | 100 | 93 |
| 10[g,h] | *t*Bu |  | 32 | 41 |
| 11 | *i*Bu |  | 100 | 99 |
| 12 |  |  | 100 | 94 |
| 13 | *n*Hex |  | 95 | 96 |
| 14 | *n*Hex |  | 74 | 99 |
| 15[h] | *n*Hex |  | 88 | 73 |
| 16 | Cy |  | 66 | 32 |
| 17[h,i] | *n*Hex |  | 100 | 36 |

[a] See the Experimental Section and the Supporting Information for details. [b] Determined by integration ($^1$H NMR spectroscopy) relative to an external standard (CH$_3$NO$_2$). [c] Based on conversion. [d] 150 mol% of alkene used. [e] *t*BuMe$_2$SiOTf used in place of Et$_3$SiOTf. [f] 1 mL of alkene used. [g] Reaction carried out in a sealed tube. [h] 40 mol% of catalyst used. [i] Reaction carried out at room temperature.

While many electron-deficient olefins have been used as additives for similar purposes, this study represents a rare example of using an additive other than an alkene in this manner in a catalytic reaction.[9,12] Remarkably, **I** and the phosphite are compatible with one another in this two-ligand system, neither seems to impede 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 (M = metal, X = for example, halide, triflate, sulfonate), particularly in the Heck reaction, or of R′–M–R″ in general, such as catalytic cross-coupling reactions, may also enjoy an accelerating effect by the use of a phosphite.[13] While an electron-deficient alkene may not be appropriate, as it may react in the Heck reaction, an organophosphite may, in contrast, be compatible. We are currently exploring such possibilities.

## Experimental Section

General Procedure (see the Supporting Information for examples): In a glove box, [Ni(cod)$_2$] (30 mol%), 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (**I**, 30 mol%), and a stirrer bar were added to an oven-dried test tube (10 mL). The tube was sealed with a rubber septum, removed from the glove box, and connected to an Ar line. The catalyst mixture was dissolved in degassed toluene (3 mL) under Ar and stirred for 1 h at room temperature. The alkene (500 mol% or indicated amount), triethylamine (600 mol%), aldehyde (0.25 mmol, 100 mol%), and triphenylphosphite (45 mol%) were added sequentially. Triethylsilyl triflate (175 mol%) was added dropwise, and the mixture was stirred for 48 h at 35 °C. After cooling the mixture to room temperature, it was diluted with diethyl ether (5 mL) and stirred for 30 min in open air. The resulting mixture was filtered through a short plug of silica gel and rinsed with 20% EtOAc/hexane (50 mL). The solvent was removed under reduced pressure, and purification

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by flash chromatography ($SiO_2$, 1% EtOAc in hexane) afforded the product.

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