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COMMUNICATION

Ligand-guided pathway selection in nickel-catalyzed couplings of enals and alkynes†‡

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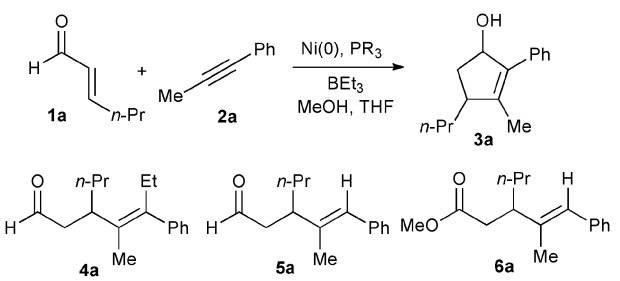
Nickel-catalyzed couplings of enals and alkynes utilizing triethylborane as the reducing agent illustrate a significant dependence on ligand structure. Simple variation of monodentate phosphines allows selective access to alkylative couplings or reductive cycloadditions, while further variation of reaction conditions provides clean access to reductive couplings and redox-neutral couplings.

A broad range of nickel-catalyzed reductive coupling processes have been developed, including procedures that involve couplings of aldehydes, α,β-unsaturated carbonyls, imines, alkynes, dienes, allenes, and nitriles as the reactive π-components.[1] The coupling of enals or enones with alkynes is one of the more extensively studied variants, and within this specific set of substrates, a number of different reaction manifolds have been disclosed, including reductive couplings,[2] reductive cycloadditions,[3] alkylative cycloadditions,[3b] and three-components couplings that proceed without formal substrate reduction.[2d,4] Our prior reports in this area have described modifications in substrates, ligands, reducing agents, additives, solvents, and metal stoichiometry to select between the various possible reaction pathways. To better illustrate the most important features in selecting individual reaction pathways, we describe herein that simple modification of monodentate phosphine structure, while leaving all other reaction variables unchanged, can dramatically alter reaction outcomes. As part of this study, we demonstrate that catalytic alkylative enal-alkyne couplings with organoboranes can also be accessed in addition to the previously reported pathways, and we also disclose that stable, crystalline, electron-rich triarylphosphine ligands can duplicate the reactivity characteristics of the more sensitive and more easily oxidized trialkylphosphine ligands.

To illustrate the unique impact of ligand modifications in enal-alkyne couplings, we examined couplings of aldehyde **1a** and phenylpropyne (**2a**), using 10 mol% $Ni(COD)_2$, 20 mol% of a monodentate phosphine, and 3.0 equiv. of triethylborane, in an 8 : 1 methanol : THF cosolvent system (Scheme 1, Table 1). Under these conditions, [3 + 2] reductive cycloaddition product **3a**, alkylative coupling product **4a**, reductive coupling product **5a**, and ester product **6a** were seen in varying proportions. Our previously reported conditions for [3 + 2] reductive cycloaddition involved PBu_3 as ligand,[3a,b] and under these conditions, cyclopentenol **3a** was obtained in 85% isolated yield as an 87 : 13 mixture of diastereomers (Table 1, entry 1). A series of triarylphosphine ligands were next examined, with an eye towards developing more user-friendly procedures, given the ease of handling these more stable ligands. Couplings with PPh_3 provided mixtures of cyclopentenol **3a** in 46% yield along with alkylative coupling product **4a** in 14% yield and reductive coupling product **5a** in 25% yield (Table 1, entry 2). Use of the bulkier P(1-naphthyl)$_3$ produced alkylative coupling product **4a** in 57% yield along with reductive coupling product **5a** in trace quantities (Table 1, entry 3). Similarly, the use of P(*o*-tol)$_3$ also favored product **4a** in 76% yield, along with 19% isolated yield of **5a** and trace quantities of product **3** (Table 1, entry 4).

In contrast to the general preference for product **4a** when using substituted triarylphosphines, the use of P(*p*-methoxyphenyl)$_3$ and P(2,4,6-trimethoxyphenyl)$_3$ afforded cyclopentenol **3a** as the major product, in 72% and 79% yields respectively (Table 1, entries 5 and 6). Diastereoselectivities were slightly lower than observed with PBu_3 and PPh_3. Examination of more hindered trialkylphosphines PCy_3 and P(*t*-Bu)$_3$ afforded lower conversions (Table 1, entries 7 and 8) although a new product, methyl ester **6a**, was observed in moderate quantity when PCy_3 was employed. As described below, mechanistic considerations in the production of ester **6a** suggested a simple modification for optimization of this product.

Obtaining the [3 + 2] reductive cycloaddition products using a stable triarylphosphine ligand (Table 1, entry 6) provides a



Scheme 1 Products from enal-alkyne couplings under reductive conditions.

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‡ Electronic supplementary information (ESI) available: Experimental details and copies of NMR spectra. See DOI: 10.1039/c2cc17073f

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Table 1 Ligand effects in reductive couplings[a]

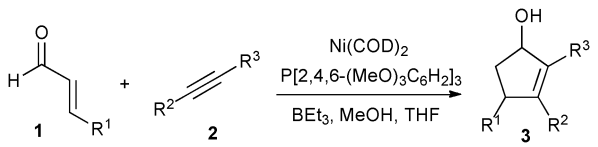
Entry	Ligand	% **3a** (dr)[b]	% **4a**	% **5a**	% **6a**
1	PBu_3	85 (87 : 13)			
2	PPh_3	46 (87 : 13)	14	25	
3	P(1-naphthyl)$_3$		57	<10	
4	P(*o*-tol)$_3$	<10	76	19	
5	P[4-(MeO)C$_6$H$_4$]$_3$	72 (65 : 35)	<10	<10	
6	P[2,4,6-(MeO)$_3$C$_6$H$_2$]$_3$	79 (36 : 64)			
7	PCy_3			12	45
8	P(*t*-Bu)$_3$	<10	17	18	

[a] Conditions: Ni(COD)$_2$ (10 mol%), PR_3 (20 mol%), Et_3B (3.0 equiv), MeOH/THF (8 : 1), rt. Isolated yields shown. [b] Diastereomeric ratio of **3a** is reported as *cis* : *trans* ratio.

useful preparative simplification over the previously reported use of PBu_3. Additionally, the use of a hindered triarylphosphine such as P(*o*-tolyl)$_3$ to obtain product **4a** involving ethylation during the coupling process (Table 1, entry 4) has not been previously reported. Therefore, a brief examination of the scope of these two proceses was examined (Table 2 and 3). First, the efficiency of [3 + 2] reductive cycloadditions employing P[2,4,6-trimethoxyphenyl]$_3$ as ligand was examined (Table 2). Using β-substituted enal **1a**, couplings with symmetrical (Table 2, entries 1-2), unsymmetrical (Table 2, entry 3), and terminal alkynes (Table 2, entry 4) were successful, albeit with low levels of diastereocontrol. Additionally, an alkyne possessing an unprotected hydroxyl could be effectively coupled (Table 2, entry 5). Couplings with acrolein, however, proceeded only in low yield (Table 2, entry 6).

Alkylative couplings with ethyl transfer were briefly examined using P(*o*-tol)$_3$ as ligand. Using β-substituted enal **1a**, couplings with phenylpropyne and diphenylacetylene were effective (Table 3, entries 1 and 2). A coupling of acrolein with diphenylacetylene proceeded in moderate yield (Table 3, entry 3). Additionally using a simple non-aromatic alkyne was effective (Table 3, entry 4). Alkylative couplings of enals or enones with alkynes were previously reported with organozinc,[5] organozirconium,[6] organostannane,[7] organoaluminum,[8] and alkenylborane reagents,[9] but to our knowledge the corresponding process with simple trialkyl boranes has not been previously reported. Triethylborane more commonly functions as a reducing

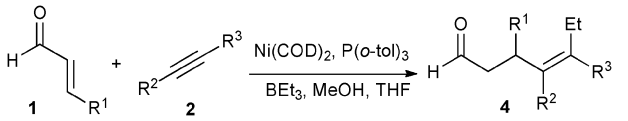
Table 2 Examination of [3 + 2] reductive cycloadditions[a]



Entry	R^1	R^2	R^3	% **3** (dr)
1	*n*-Pr	Et	Et	51 (48 : 52)[b]
2	*n*-Pr	Ph	Ph	70 (53 : 47)[b]
3	*n*-Pr	Me	Ph	79 (36 : 64)[b]
4	*n*-Pr	H	Ph	71 (64 : 36)[c]
5	*n*-Pr	$(CH_2)_3OH$	Ph	65 (62 : 38)[c]
6	H	Me	Ph	31

[a] Conditions: Ni(COD)$_2$ (10 mol%), P[2,4,6-(MeO)$_3$C$_6$H$_2$]$_3$ (20 mol%), Et_3B (3.0 equiv), MeOH/THF (8 : 1), rt. Isolated yields shown. [b] Diastereomeric ratio of **3a** is reported as *cis* : *trans* ratio. [c] Stereochemistry of the diastereomeric mixture was not determined.

Table 3 Examination of alkylative couplings[a]



Entry	R^1	R^2	R^3	% **4**
1	*n*-Pr	Me	Ph	76
2	*n*-Pr	Ph	Ph	52
3	H	Ph	Ph	53
4	*n*-Pr	Et	Et	57

[a] Conditions: Ni(COD)$_2$ (10 mol%), P(o-tol)$_3$ (20 mol%), Et_3B (3.0 equiv), MeOH/THF (8 : 1), rt. Isolated yields shown. Only a single regio- and stereoisomer was observed.

agent with H-atom transfer in reactions of this type,[1c,10] although ethyl transfer was previously described in imine-alkyne couplings.[11]

We interpret the ligand effects described above (Table 1) by the following analysis (Scheme 2). Following the production of metallacycle intermediate **7**,[12] enolate protonation occurs to generate common intermediate **8**. The use of a small basic phosphine (PBu_3) allows direct addition of the vinyl nickel fragment to the coordinated aldehyde of **8** while electronically disfavoring ethyl transfer to **9** due to the strong σ-donating capability of the ligand. This addition produces cyclopentenol derivative **10** leading to product **3a**. By employing less basic aryl phosphines, ethyl transfer to **9** is facilitated, and reductive elimination to produce **4a** occurs. While PPh_3 provides a mixure of products **3a** and **4a**, the increased sterics of P(*o*-tol)$_3$ and P(1-naphthyl)$_3$ disfavor addition to the aldehyde and provide superior entries to product **4a**. In contrast, P(*p*-methoxyphenyl)$_3$ and P(2,4,6-trimethoxyphenyl)$_3$ are considerably more σ-donating than the other triarylphosphines, and these ligands duplicate the electronic biases of PBu_3, favoring the production of cyclopentenol **3**. It is noteworthy that these electron-rich triaryl phosphines display the crystallinity and stability of other triaryl phosphines, and provide considerable practical advantanges over the use of more sensitive trialkyl phosphines.

While simple variation of phosphine structure does not allow efficient production of products **5a** and **6a**, one can readily visualize solutions to these optimizations according to the mechanistic analysis described above. These previously-reported advances complement the ligand control strategies reported in this contribution and are summarized here to provide a complete analysis of the products described in Scheme 1. Using Et_3B with a protic solvent medium, the generation of product **5** could not be readily optimized. However, by employing a trialkylsilane as the reducing agent in an aprotic solvent, metallacycle **13** is converted directly to intermediate **14**, which does not release the electrophilic aldehyde (Scheme 3). Additionally, direct transfer of a hydrogen atom from the silane removes the complexity of C–Et *vs.* C–H reductive elimination. Therefore, the enol silane **15** (corresponding to product **5a**) is obtained by this procedure.[2c]

For the production of compound **6a**, the mechanistic scheme above (Scheme 2) illustrates that methanol addition to **8**, followed by a formal 1,5 shift of the hemiacetal proton of **12** leads to the production of compound **6a** without involvement of an external reducing agent. Therefore, simple omission of the reducing agent

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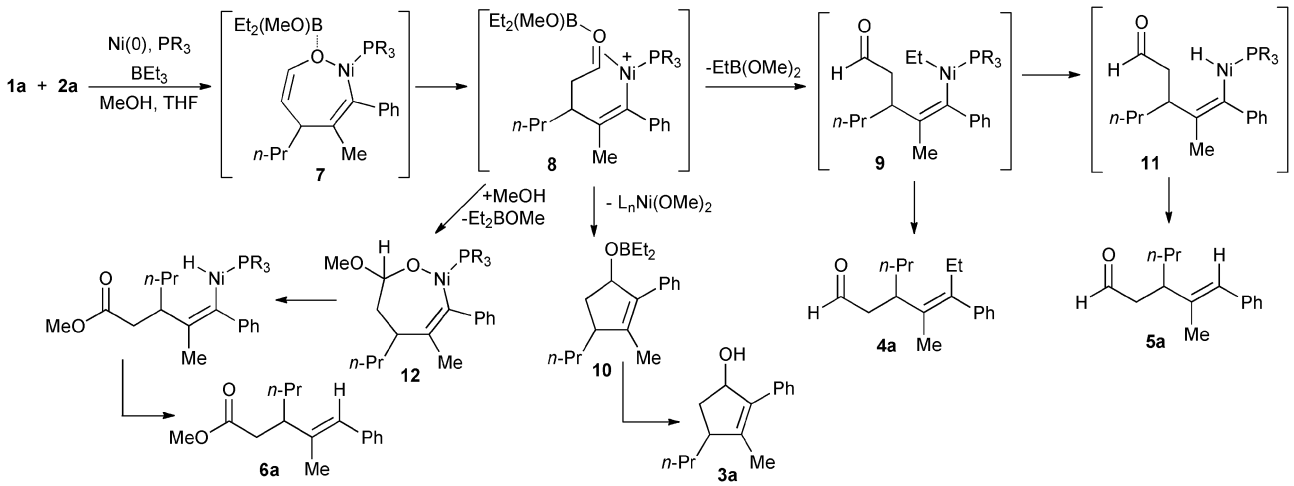
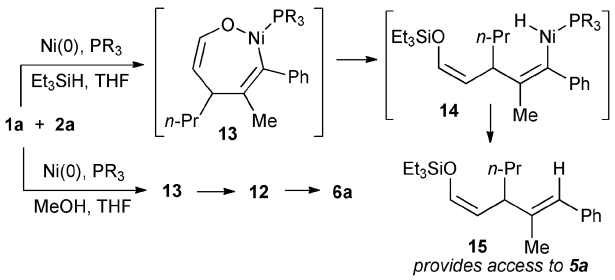


Scheme 2 Mechanistic rationale for ligand control in enal-alkyne couplings.



Scheme 3 Alternate pathways for accessing products **5a** and **6a**.

(BEt_3) allows clean production of the methyl ester product **6a**, likely involving the intermediacy of **13** and **12** (Scheme 3).[4,13] Formation of product **6a** was futher optimized by the use of *N*-heterocyclic carbene ligands.[4]

In conclusion, an interesting array of cyclic and acyclic products are obtained by the nickel-catalyzed coupling of enals and alkynes. Simple variation of ligand structure has a major impact on the reaction outcome, and a mechanistic scheme formulated allowed rational optimization of each of the possible reaction outcomes. A noteworthy feature of this study is the use of stable electron-rich triaryl phosphines that serve as a convenient replacement for more sensitive trialkylphosphines in reductive cycloadditions.

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