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Ligand-Switchable Directing Effects of Tethered Alkenes in Nickel-Catalyzed Additions to Alkynes

Karen M. Miller and Timothy F. Jamison*

Massachusetts Institute of Technology, Department of Chemistry, Cambridge, Massachusetts 02139

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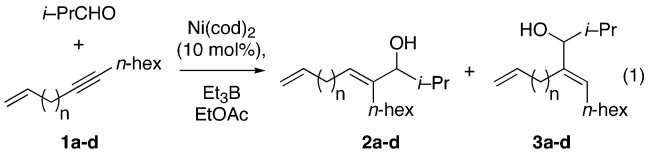
Substrate-directable reactions are a very important class of selective organic transformations.[1] A temporary dative bond between a nonreacting functional group in the starting material and a reagent or catalyst can amplify (or reverse) selectivity by reinforcing (or changing) the low energy conformation of the transition state of the selectivity-determining step. We recently proposed that certain nickel-catalyzed additions to alkynes are directed by a conjugated alkene.[2,3,4] Herein we report not only that a remote, *unconjugated* alkene dictates regioselectivity but also that the sense of regioselectivity can be completely *reversed* (from >95:5 to 5:>95) by a substoichiometric amount of an additive. Simply put, the *degree* of regioselectivity is due entirely to a directing effect of an appropriately placed alkene, and the *sense* of the regioselectivity is due entirely to the presence (or absence) of a phosphine ligand.

In our initial investigations we examined reductive coupling reactions between aldehydes and alkynes with two linear aliphatic groups, one of which posessed a terminal alkene (Table 1, entries 1−4). In all cases a very low yield of the allylic alcohol products was observed in the absence of a phosphine ligand, with one striking exception (entry 3). Remarkably, a tether of three methylene groups (**1c**) provides not only a dramatic increase in reactivity but also complete selectivity for allylic alcohol regioisomer **2c**.

Table 1. Directing Effects of Tethered Alkenes[a]



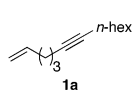
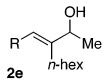
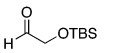
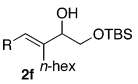
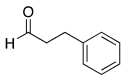
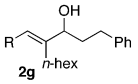
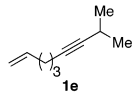
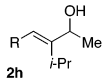
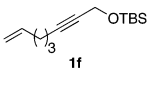
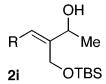
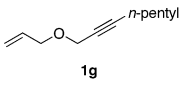
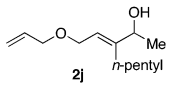
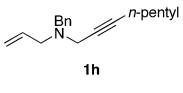
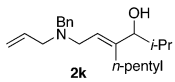
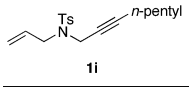
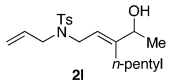
1a-d **2a-d** **3a-d**

entry	alkyne	*n*	yield (%)	regioselectivity (**2**/**3**)[b]
1	**1a**	1	<5	nd
2	**1b**	2	<5	nd
3	**1c**	3	53[c]	>95:5
4	**1d**	4	<5	nd
5	*n*-pentyl−C≡C−*n*-hexyl	n.a.	28[c]	50:50

[a] Standard procedure: The alkyne (0.50 mmol) was added to a 0 °C solution of $Ni(cod)_2$ (0.05 mmol), *i*-PrCHO (1.00 mmol), and Et_3B (1.00 mmol) in EtOAc (0.5 mL), and the solution was allowed to stir 15 h at room temperature. See Supporting Information for details. [b] Determined by ^1H NMR and/or GC. [c] Some alkylative coupling (transfer of Et from Et_3B) also observed.

Because of the marked difference in reactivity and selectivity for one (and only one) tether length, it is very unlikely that the infinitesimal differences in the steric and electronic properties of the alkyne substituents in **1c** are responsible for this effect. Consistent with this notion is a control experiment with the corresponding alkyne lacking the pendant alkene, 1,2-dihydro-**1c** (entry 5). As expected, product yield was significantly diminished, and no regioselectivity was observed.

Table 2. Highly Regioselective, Catalytic Reductive Coupling Reactions Directed by a Remote Alkene[a]

enyne	aldehyde	product	yield, regioselectivity (**2** : **3**)
 **1a**		 **2e**	**69%** (>95:5)
1a		 **2f**	**58%** (>95:5)
1a		 **2g**	**60%** (>95:5)
 **1e**		 **2h**	**64%** (>95:5)
 **1f**		 **2i**	**62%** (>95:5)
 **1g**		 **2j**	**60%** (>95:5)
 **1h**		 **2k**	**62%** (>95:5)
 **1i**		 **2l**	**68%** (>95:5)

[a] See eq 1, Table 1, and Supporting Information. R = $(CH_2)_3CH{=}CH_2$. Regioselectivity determined by ^1H NMR and/or GC.

Table 2 illustrates the scope and utility of this directing effect,[5] and several of the examples deserve further comment. In coupling reactions of *n*-alkyl−C≡C−*i*-Pr alkynes, the steric demand of the *i*-Pr group disfavors the regioisomer corresponding to **2h** (∼1:2 ratio),[2,6] while *n*-alkyl−C≡C−CH_2OTBS alkynes exhibit a 2-fold preference for the regioisomer corresponding to **2i**, attributable to an electron-withdrawing effect of the propargylic oxygen. A tethered alkene, however, is sufficient to override (or reinforce) these "inherent" regioselectivities. Heteroatoms that could compete with the alkene for binding to nickel do not erode regioselectivity but rather augment the versatility of this directable transformation (alkynes **1f**−**i**).

The results of a set of coupling reactions employing an organophosphine were especially surprising and provide significant insight into the mechanistic framework of not only these directed reactions but also nickel-catalyzed reductive coupling reactions of alkynes in general (eq 2).[7] In contrast to the experiments summarized in Table 1 (no phosphine), alkynes **1a**, **1b**, and **1d** (*n* = 1,

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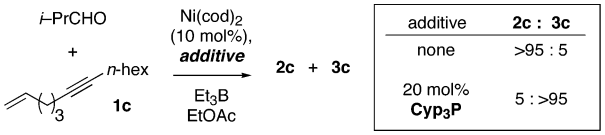
2, and 4, respectively) did undergo coupling with *i*-PrCHO when tricyclopentylphosphine (Cyp_3P)[2,8] was employed, but in a non-regioselective fashion (75% yield (54:46), 84% (47:53), and 50% (50:50), respectively). However, with three carbon−carbon single bonds between the alkene and the alkyne (**1c**), remarkably high regioselectivity was observed as before, but in this case with complete preference for the *other* regioisomer (**3c**, 45% yield).[9] A control experiment using 1,2-dihydro-**1c** also provided further evidence for a temporary dative interaction between the remote alkene and the metal center (77% (50:50)).

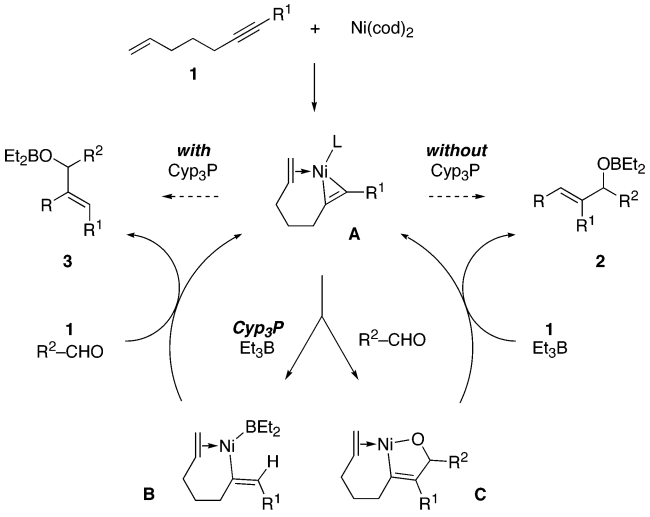


additive	2c : 3c
none	>95 : 5
20 mol% **Cyp_3P**	5 : >95

(2)

Our explanation of these observations is that the directed reactions herein proceed by fundamentally *distinct* mechanisms (Scheme 1). Intermediate **A** is consistent with the studies of Pörschke, who showed that 1,6-heptadiene and 1,6-heptadiyne chelate nickel in three-coordinate, approximately trigonal planar complexes in the solid state and in solution.[10] The exclusive formation of regioisomer **3** when Cyp_3P is employed can be explained by installation of the alkenyl H prior to carbon−carbon bond formation. Oxidative addition of a Ni−ligand complex into a carbon−boron bond of Et_3B and directed hydrometalation would give alkenyl−nickel species **B** that undergoes carbonyl addition.

Scheme 1



Conversely, in the absence of Cyp_3P, the formation of regioisomer **2** is best accounted for by reversing the order of events (C−C bond formation prior to alkenyl H introduction) possibly by way of oxanickellacyclopentene (**C**).[11,12,13]

Although directing effects of tethered alkenes have been demonstrated in other metal-mediated reactions,[14] the only other examples in which the sense of the effect was reversed by an additive are Pd-catalyzed enyne isomerizations reported by Trost.[15] However, high regioselectivity was observed in only one direction (≥15:1 vs 1:2.5), and the reversal was not the result of two different alkene-directed mechanisms, but rather preferential binding to Pd of the additive over the tethered olefin that was responsible for the directing effect.

Montgomery's recent crossover labeling experiments elegantly demonstrated that the pathways operating in related coupling reactions depend strongly on the ligand used.[3a] The experiments in this work not only resonate with the ligand-dependence observed by Montgomery, but they also provide the first strong evidence for *which mechanism* is operating in each case, carbon−carbon bond formation prior to hydrometalation or vice versa.

The results of the studies described here have several other important ramifications. A chiral tether between the alkyne and alkene or alkene-containing ligands themselves may impart high stereo- and/or regioselectivity in these reactions.[16,17] These areas and the use of ligand-switchable directed reactions in target-oriented synthesis are under current investigation.

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Supporting Information Available: Experimental procedures and data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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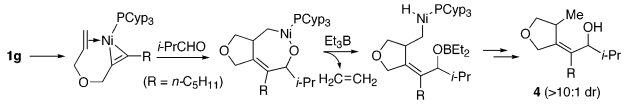
(5) Aromatic aldehydes are of considerably reduced efficacy. An extended reaction time (40 h) was required for a 26% yield (>95:5 regioselectivity) in a coupling between **1h** and PhCHO. See Supporting Information.
(6) Colby, E. A.; Jamison, T. F. *J. Org. Chem.* **2003**, *68*, 156−166.
(7) Details in Supporting Information.
(8) Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1364−1367.
(9) Alkynes with a heteroatom in the tether (**1g**−**i**) primarily afford products of phosphine-promoted carbocyclization (i.e., not allylic alcohols **2j**−**l** or **3j**−**l**). Under investigation is the scope of this process, which, as shown below, may arise from a species akin to **A** (Scheme 1). See also Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 1286−1288.



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