

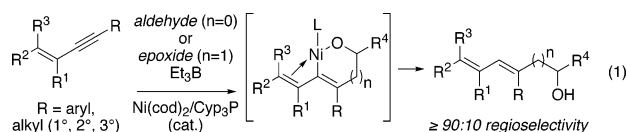
## Alkene-Directed, Nickel-Catalyzed Alkyne Coupling Reactions

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As carbon–carbon double bonds can be transformed into a vast array of other functional groups, alkenes are among the most important and versatile organic compounds. While many simpler alkenes are commodity chemicals, those that are highly substituted are generally less available.<sup>1</sup> The controlled addition of two groups across an alkyne triple bond is an important strategy for the synthesis of these olefins,<sup>1d</sup> and low-valent nickel complexes catalyze several of these transformations.<sup>2</sup> In intermolecular cases, regioselectivity, one of the chief challenges in all alkyne addition reactions, is generally governed by electronic and/or steric differences between the two alkyne substituents.<sup>3,4</sup> We now report a new strategy for selective olefin synthesis, whereby a transient interaction between a conjugated alkene and a transition metal<sup>5</sup> dramatically enhances reactivity and uniformly directs regioselectivity (eq 1, Table 1).



In Ni-catalyzed coupling reactions of alkynes of the general form Ar–C≡C–alkyl the regioselectivity is generally very high (>95:5), favoring carbon–carbon bond formation distal to the aromatic group.<sup>3d,g–i</sup> It was therefore quite unexpected that an electronically similar and smaller vinyl group caused a *complete reversal* in the sense of regioselectivity, favoring C–C bond formation *proximal* to the aryl substituent (entry 1). This regioselectivity is also opposite that observed by Montgomery in intramolecular aldehyde–enyne couplings.<sup>6,7,8</sup>

The alkene substituent not only imparts exquisite regioselectivity but, as demonstrated by *t*-Bu–C≡C–CH=CH<sub>2</sub> (**1b**, entry 2), also provides a remarkable increase in reactivity. Other alkynes with *tert*-alkyl substituents (*t*-Bu–C≡C–alkyl and Ar–C≡C–*t*-Bu) do not undergo reductive coupling under similar conditions.<sup>9</sup> Of even further significance is that few examples of catalytic carbon–carbon bond-forming reactions of *tert*-alkyl–C≡C–R alkynes are known,<sup>3a,10</sup> and in *none* of these, Ni-catalyzed or otherwise, is C–C bond formation favored *adjacent* to a *tert*-alkyl group.<sup>11</sup>

The directing ability of the alkene depends neither on the nature or size of the other alkyne substituent (aryl, alkyl (1°, 2°, 3°)) nor on the degree of alkene substitution (entries 1–9). Terminal epoxides also undergo coupling<sup>3i</sup> in similarly high regioselectivity and with retention of configuration (entries 10–11). The availability of epoxides in >99% ee<sup>12</sup> makes this strategy attractive for preparing enantiomerically pure 3,5-dienols. It is also noteworthy that the product dienes do not react with another molecule of aldehyde<sup>2,13</sup> or epoxide under these conditions.

The dramatic enhancement of reactivity (e.g., entry 2) and the invariant sense and degree of regioselectivity (in particular the complete turnover vs Ph, entry 1) are not consistent with a purely steric and/or electronic phenomenon. Conversely, these trends

**Table 1.** Alkene-Directed, Nickel-Catalyzed Coupling Reactions of Alkynes with Aldehydes and Epoxides<sup>a</sup>

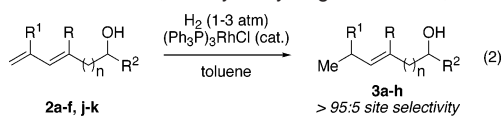
entry	enyne	diene	yield (%)	regioselectivity <sup>b</sup>
1			71	95:5
2 <sup>c</sup>			69	>95:5
3 <sup>c</sup>			63	>95:5
4			64	>95:5
5			64	>95:5
6			71	95:5
7			89	95:5
8			79	90:10
9 <sup>c</sup>			88	95:5
10 <sup>d</sup>			50 <sup>e</sup>	>95:5
11 <sup>d</sup>			51 <sup>e</sup>	>95:5

<sup>a</sup> See eq 1. Standard procedure (see Supporting Information): To a solution of Ni(cod)<sub>2</sub> (0.05 mmol), tricyclopentylphosphine (Cyp<sub>3</sub>P) (0.10 mmol), and Et<sub>3</sub>B (1.0 mmol) in EtOAc (0.5 mL) at 0 °C were added *i*-PrCHO (1.0 mmol) and the enyne (0.5 mmol). Upon consumption of the enyne, purification by chromatography provided dienes **2a–2k**. <sup>b</sup> Regioselectivity determined by <sup>1</sup>H NMR. <sup>c</sup> (+)-Neomenthylidiphenylphosphine used as ligand. <sup>d</sup> Bu<sub>3</sub>P and (+)-octene oxide (>99% ee) used in place of Cyp<sub>3</sub>P and *i*-PrCHO. EtOAc omitted. <sup>e</sup> Yield over two steps.

exhibit all the hallmarks of directed reactions<sup>14</sup> and can be explained by complexation of the alkene to the metal center during the regioselectivity-determining step.<sup>5,15</sup>

In conjunction with a rhodium-catalyzed, site-selective hydrogenation (eq 2, Table 2), the above couplings address two general problems observed in catalytic additions to alkynes, namely control of regioselectivity with unsymmetrical dialkylacetylenes (alkyl–C≡C–alkyl)<sup>16</sup> and inaccessibility of disfavored regioisomers. Wilkinson's catalyst [(Ph<sub>3</sub>P)<sub>3</sub>RhCl] under H<sub>2</sub> smoothly converted dienes **2a–f** into allylic alcohols **3a–f** (entries 1–6)<sup>17,18</sup> and dienes **2j–k** into homoallylic alcohols **3g–h** (entries 7–8).<sup>19,20</sup>

Substrate-directed reactions are of tremendous importance to selective chemical synthesis.<sup>14</sup> In the case of Ni-catalyzed alkyne-coupling reactions, an alkenyl group dramatically enhances reactiv-

**Table 2.** Site-Selective, Catalytic Hydrogenation of 1,3-Dienes<sup>a</sup>

entry	diene	R	R <sup>1</sup>	n	R <sup>2</sup>	alkenol	yield (%)
1	<b>2a</b>	Ph	H	0	<i>i</i> -Pr	<b>3a</b>	80
2	<b>2b</b>	<i>t</i> -Bu	H	0	<i>i</i> -Pr	<b>3b</b>	83
3	<b>2c</b>	Cy	H	0	<i>i</i> -Pr	<b>3c</b>	87
4	<b>2d</b>	<i>i</i> -Pr	H	0	<i>i</i> -Pr	<b>3d</b>	76
5	<b>2e</b>	<i>n</i> -Hex	H	0	<i>i</i> -Pr	<b>3e</b>	92
6	<b>2f</b>	Et	Me	0	<i>i</i> -Pr	<b>3f</b>	96
7 <sup>b</sup>	<b>2j</b>	Et	Me	1	<i>n</i> -Hex	<b>3g<sup>c</sup></b>	94
8 <sup>b</sup>	<b>2k</b>	<i>i</i> -Pr	H	1	<i>n</i> -Hex	<b>3h<sup>c</sup></b>	85

<sup>a</sup> See eq 2. Standard procedure (see Supporting Information): A solution of the diene (0.12 mmol) and RhCl(PPh<sub>3</sub>)<sub>3</sub> (12 μmol) in toluene (1 mL) was stirred under H<sub>2</sub> until the diene was consumed. Purification (chromatography) provided alkenols **3a–3h**. <sup>b</sup> TBS ether of alcohol used; see Table 1. <sup>c</sup> TBS ether isolated in >99% ee.

ity and completely controls regioselectivity, (Table 3), enabling the regiocontrolled preparation of highly substituted, synthetically useful 1,3-dienes.<sup>2,13</sup> A novel, site-selective hydrogenation yields allylic and homoallylic alcohols that cannot be obtained in high regioselectivity (or at all) from the corresponding alkynes with these methods.<sup>3d,g–i</sup> Finally, the alkene-directing effect presented herein may be of broad utility in catalytic reactions of alkynes, a possibility that we are currently investigating.

**Table 3.** Effects of Alkene Directing Groups on Regioselectivity and Reactivity in Nickel-Catalyzed Alkyne Coupling Reactions<sup>a</sup>

reference alkynes (not alkene-directed)	alkene-directed (this work)	effect of alkenyl group
		reverses regioselectivity
		increases reactivity – and – controls regioselectivity
		circumvents poor regioselectivity

<sup>a</sup> Numbers indicate typical regioselectivity (Table 1 and refs 3d, g–i).

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**Note Added in Proof.** Recently Montgomery reported two examples of intermolecular, nickel-catalyzed, enyne-aldehyde reductive coupling reactions that proceed with the same sense of regioselectivity as that which we observe (Table 1). See

Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698–3699.

**Supporting Information Available:** Experimental procedures and data for compounds **1a–e**, **1g–i**, **2a–k**, and **3a–h** (PDF). This information is available free of charge via the Internet at <http://pubs.acs.org>

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