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Highly Selective Catalytic Intermolecular Reductive Coupling of Alkynes and Aldehydes

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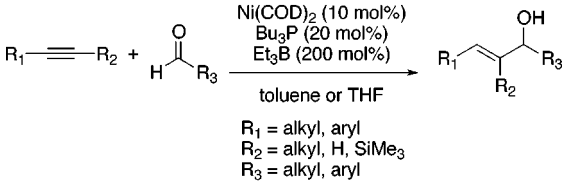
ABSTRACT



Alkynes (internal and terminal) and aldehydes (aromatic and aliphatic) are reductively coupled in a single catalytic reaction to yield di- and trisubstituted allylic alcohols with high stereoselectivity and regioselectivity. In most cases, a 1:1 ratio of alkyne to aldehyde is sufficient for efficient coupling. The yield and regioselectivity are strongly dependent on the phosphine ligand, but the allylic alcohols formed are invariably the products of cis addition to the alkyne.

Transition metal-catalyzed coupling reactions enable convergent synthesis and are among the most efficient methods of assembling complex organic molecules from simpler fragments.[1] Very complex structures have been prepared using an allylic alcohol as the site of fragment coupling,[2] and addition of an alkenylmetal reagent to a carbonyl is a commonly used method that features carbon−carbon bond formation and the creation of a stereogenic center.

Many of the alkenylmetal reagents required for these preparations of synthetically useful allylic alcohols[3] are generated in situ using stoichiometric amounts or excesses of one or more transition metals. For example, the Nozaki−Hiyama−Kishi reaction effects the addition of an alkenyl halide to a carbonyl with a nickel catalyst and an excess of $CrCl_2$, Mn, or Zn.[4] Alternatively, as alkynes are often convenient intermediates, many reliable one-pot methods for effecting their *reductive* coupling with aldehydes to give allylic alcohols have been developed.[5−7] In one approach, an alkyne−metal complex is prepared and then treated with the carbonyl compound.[5] Another commonly used sequence, especially for terminal alkynes, involves stoichiometric

(1) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley: New York, 1997.

(2) For examples in Kishi's palytoxin synthesis, see: Armstrong, R. W.; Beau, J.-M.; Cheon, S. H.; Christ, W. J.; Fujioka, H.; Ham, W.-H.; Hawkins, L. D.; Jin, H.; Kang, S. H.; Kishi, Y.; Martinelli, M. J.; McWorter, W. W.; Mizuno, M.; Nakata, M.; Stutz, A. E.; Talamas, F. X.; Taniguchi, M.; Tino, J. A.; Ueda, K.; Uenishi, J.; White, J. B.; Yonaga, M. *J. Am. Chem. Soc.* **1989**, *111*, 7525.

(3) Reviews: Sigmatropic rearrangements: (a) [2,3]: Brückner, R. Iin *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 6, Chapter 4.6. (b) Hill, R. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 5, Chapter 7.1. (c) [3,3]: Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 5, Chapter 7.2. (d) Directed reactions: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(4) (a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179. (b) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (c) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048. (d) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 2533. (e) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349.

(5) (a) Buchwald, S. L.; Watson, B. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 2544. (b) Van Wagenen, B. C.; Livinghouse, T. *Tetrahedron Lett.* **1989**, *30*, 3495. (c) Takai, K.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1990**, *55*, 1707. (d) Takagi, K.; Rousset, C. J.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 1440. (e) Kataoka, Y.; Miyai, J.; Oshima, K.; Takai, K. Utimoto, K. *J. Org. Chem.* **1992**, *57*, 1973. (f) Takayanagi, Y.; Yamashita, K.; Yoshida, Y.; Sato, F. *J. Chem. Soc., Chem. Commun.* **1996**, 1725.

(6) (a) Oppolzer, W.; Radinov, R. N. *Helv. Chim. Acta* **1992**, *75*, 170. (b) Oppolzer, W.; Radinov, R. N. *J. Am. Chem. Soc.* **1993**, *115*, 1593.

(7) (a) Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197. (b) Wipf, P.; Ribe, S. *J. Org. Chem.* **1998**, *63*, 6454.

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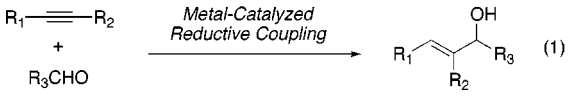
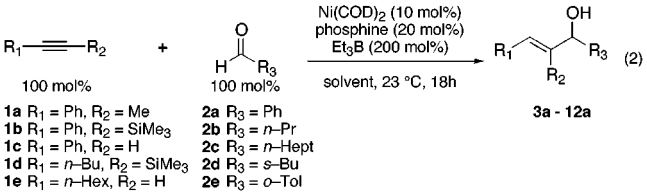
hydroboration,[6] or hydrozirconation,[7] followed by transmetalation and addition of an organic ligand to promote carbonyl addition.

Here we report the first *catalytic* method for intermolecular reductive coupling of alkynes and aldehydes (eq 1).[8] Enjoying a broad substrate scope (terminal and internal alkynes; aliphatic and aromatic aldehydes), having many of the hallmarks of an efficient fragment coupling, and exhibiting high stereo- and regioselectivity, this catalytic reaction combines the features of many "tried-and-true" methods of intermolecular reductive couplings of alkynes and aldehydes that use stoichiometric amounts of transition metals.[5−8] A related process is that of Montgomery, who reported a nickel-catalyzed, intermolecular *alkylative* coupling of terminal alkynes and aldehydes that prepares trisubstituted allylic alcohols with a substitution pattern different than that which we obtain.[9] The Montgomery method does not effect intermolecular reductive coupling of alkynes and aldehydes but is useful for the reductive cyclizations of alkynals to give five- or six-membered rings.[9,10]



The technical challenge of this catalytic reaction is its intermolecular nature and the requirement for a stoichiometric reducing agent. The starting materials and products are all subject to reduction, and undesired oligomerization of the alkyne[11] and reductive dimerization (pinacol formation) of the aldehyde[12] can also be competitive. We examined many combinations of transition metal salt, reducing agent, and other additives and indeed found alkyne polymerization and/or simple reduction of the alkyne and/or aldehyde to be the most common undesired reactions.[13] Exceptional in these experiments, however, was the use of a low-valent nickel catalyst along with tricyclohexylphosphine and triethylborane,[14] which afforded the desired allylic alcohol in good yield and high stereoselectivity, but with only moderate regioselection (eq 2 and Table 1, entry 1). In our investigations directed toward improving regioselectivity, we discovered that the phosphine and solvent choices are critical but that the complete (*E*)-selectivity observed in the reaction is invariant (eq 2 and Table 1).[15,16] Notably, smaller trialkylphosphines exhibited the highest regioselectivities (entries 2−3) while larger ones gave the highest yields (entries 1 and 3),[17] with Bu_3P providing the best combination (entries 3−7).[18] In contrast to THF (Table 1, entries 4−5), toluene gave nearly identical results at different temperatures (entries 6 and 7).

Table 1. Effects of Phosphine, Solvent, and Temperature on Intermolecular Reductive Coupling of 1-Phenylpropyne and Aldehydes[a]



entry	aldehyde	phosphine	product	yield[b]	regioselectivity[c]
1	**2a**	Cy_3P	**3a**	76%	77:23
2		Et_3P	**3a**	46%	91:9
3		$(n\text{-Bu})_3P$	**3a**	77%	92:8
4	**2b**	$(n\text{-Bu})_3P$	**4a**	49%	95:5
5[d]		$(n\text{-Bu})_3P$	**4a**	86%	90:10
6[e]		$(n\text{-Bu})_3P$	**4a**	85%	92:8
7[d,e]		$(n\text{-Bu})_3P$	**4a**	88%	92:8

[a] Except where noted, all reactions were conducted using the conditions indicated in eq 2 (initial concentration of alkyne and aldehyde = 0.16 M, Ar atmosphere, THF). [b] Combined isolated yield of regioisomers. [c] Minor regioisomers (**3b**, **4b**) not shown. Regioselectivity was determined either by separation of regioisomers (silica gel chromatography) or with a ^1H NMR spectrum of the product mixture. [d] Reaction conducted at 40 °C. [e] Reaction conducted in toluene.

The efficiency, scope, and high selectivity of this transformation are summarized in Table 2. In most cases, 100 mol % of the alkyne and 100 mol % of the aldehyde are sufficient for good to high yields. No trace of (*Z*) isomer is ever observed,[16] and only one regioisomer can be detected in many cases. Both internal and terminal alkynes can be reductively coupled with aliphatic and aromatic aldehydes, even those possessing moderate steric hindrance (entries 8−10).

The presence of a trimethylsilyl group in the alkyne yields allylic alcohols with near perfect regioselectivity and stereoselectivity in good to high yields (entries 3−4, 6, and 9). The diastereoselectivities obtained in entries 8 and 9 are

(8) Excess SmI_2 effects intermolecular reductive coupling of alkynes and ketones.: Inanaga, J.; Katsuki, J.; Ujikawa, O.; Yamaguchi, M. *Tetrahedron Lett.* **1991**, *32*, 4921.

(9) (a) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065. (b) Review: Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467.

(10) (a) Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 6098. (b) Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **2000**, *122*, 6950. (c) Crowe has reported a Ti-catalyzed alkynal cyclization: Crowe, W. E.; Rachita, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 6787.

(11) Grotjahn, D. B. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: New York, 1995; Vol. 12, Chapter 7.3.

(12) Brettle, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 3, Chapter 2.6.

(13) For example, we tested silanes and boranes in concert with salts of Mg, Cr, Rh, Cu, and Zn.

(14) Trace amounts of desired allylic alcohols were observed using triethylsilane as the reducing agent. For examples of uses of triethylborane in Ni(II)-catalyzed reactions see: (a) Kimura, M.; Ezoe, A.; Shibata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4033. (b) Kimura, M.; Fujimatsu, H.; Ezoe, A.; Shibata, K.; Shimizu, M.; Matsumoto, S.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 397. (c) Kimura, M.; Shibata, K.; Tamaru, Y. *Tetrahedron Lett.* **2000**, *41*, 6789.

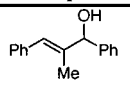
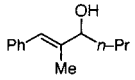
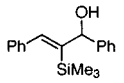
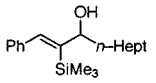
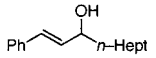
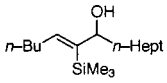
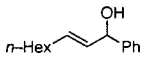
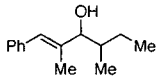
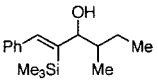
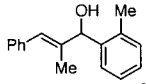
(15) Identity established by comparison with known compounds and/or by appropriate NOE NMR experiments. See Supporting Information. Similar regioselectivity trends were observed with terminal alkynes.

(16) As the Cahn−Ingold−Prelog priority of Si is higher than that of C, the allylic alcohol products in entries 3, 4, 6, and 9 (Table 2) are assigned the (*Z*) configuration. As in all other cases, they are nevertheless the products of cis addition to the alkyne.

(17) While Ph_3P afforded trace amounts of allylic alcohol, neither $(t\text{-Bu})_3P$ nor BINAP was an effective additive in these reactions.

(18) Equivalent results are obtained with the less expensive "tributylphosphine" (contains isomers) as with the more expensive "tri-*n*-butylphosphine" (isomerically pure). The former was used in all subsequent experiments.

Table 2. Intermolecular Catalytic Reductive Couplings of Internal and Terminal Alkynes with Aromatic and Aliphatic Aldehydes[a]

entry	alkyne	aldehyde	major product		yield,[b] regioselectivity[c]
1[d]	**1a**	**2a**		**3a**	77% (92:8)
2	**1a**	**2b**[e]		**4a**	85% (92:8)
3[d,f]	**1b**[e]	**2a**		**5a**	49% (>98:2)
4	**1b**	**2c**		**6a**	89% (>98:2)
5[g]	**1c**[e]	**2c**		**7a**	45% (>98:2)
6	**1d**	**2c**		**8a**	58% (>98:2)
7[d]	**1e**[e]	**2a**		**9a**	76% (96:4)
8[f]	**1a**	**2d**		**10a**	41% (94:6) (66:34 dr)
9[f]	**1b**	**2d**		**11a**	31% (>98:2) (58:42 dr)
10	**1a**	**2e**		**12a**	83% (93:7)

[a] Except where noted, all reactions were conducted using the conditions indicated in eq 2 (1 mmol of alkyne, 1 mmol of aldehyde, toluene, Ar atmosphere). [b] Combined isolated yield of regioisomers. [c] Minor regioisomers (**3b**−**12b**) not shown. Regioselectivity (**a**:**b**) was determined either by separation of regioisomers (silica gel chromatography) or with a ^{1}H NMR spectrum of the product mixture. [d] THF used as solvent. [e] 200 mol % used. [f] Reaction conducted under reflux. [g] Reaction conducted at 0 °C.

comparable to that obtained in a related alkenylzinc addition to the same aldehyde.[19] That neither acetophenone nor 3-pentanone undergoes reductive coupling suggests applications of this method in site-selective fragment coupling reactions.

Highly selective, of wide scope, and using commercially available catalysts and reagents, this catalytic transformation joins two common functional groups by effecting a reduction and an intermolecular carbonyl addition reaction without undesired reductions of either the aldehyde or the alkyne. As a 1:1 ratio of alkyne to aldehyde is sufficient for high-yielding reductive couplings in most cases, this reaction may also find use in joining late-stage intermediates in complex molecule synthesis,[20] with the concomitant benefits of creating a highly substituted alkene and a stereogenic center.[21] Our efforts in these and related areas are ongoing.[22]

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Supporting Information Available: Experimental procedures and physical, spectrometric, and chromatographic properties of compounds **3**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Hydrozirconation of **1b**, transmetalation with $ZnMe_2$, and addition to **2d** affords **10a** as a 64:36 ratio of diastereomers. See Supporting Information and ref 6a.

(20) See ref 10 for examples of Ni-catalyzed reductive alkynal cyclizations in natural product synthesis.

(21) Access to enantiomerically enriched allylic alcohols is possible in two catalytic reactions by combining this method with an efficient kinetic resolution. (a) Sharpless asymmetric epoxidation (review): Johnson, R. A.; Sharpless, K. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 7, Chapter 3.2. (b) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492. (c) Vedejs, E.; Daugulis, *J. Am. Chem. Soc.* **1999**, *121*, 5813. (d) Bellemin-Laponnaz, S.; Tweddell, J.; Ruble, J. C.; Breitling, F. M.; Fu, G. C. *J. Chem. Soc., Chem. Commun.* **2000**, 1009.

(22) Elucidation of the mechanism of this transformation will require further experiments, as irreversible hydrometalation of the alkyne does not occur in the absence of aldehyde and no substrate conversion occurs in the absence of Et_3B (see Supporting Information). See also refs 9 and 10 for discussions of possible mechanisms of related intramolecular reactions using Et_3SiH as the reducing agent and ref 14 for discussions of the role of Et_3B in Ni(II)-catalyzed reactions.