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Cooperativity of Regiochemistry Control Strategies in Reductive Couplings of Propargyl Alcohols and Aldehydes

Hasnain A. Malik, Mani Raj Chaulagain, and John Montgomery*

Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109-1055

jmontg@umich.edu

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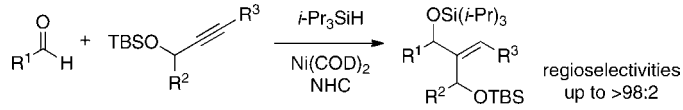
ABSTRACT



The nickel-catalyzed reductive coupling of propargyl alcohols and alkynes proceeds with excellent regiochemical control with an underlying electronic preference that can be supplemented by ligand size effects. The products obtained may be readily converted to substructures that are not directly available by an aldehyde−alkyne reductive coupling. A simple model for how steric and electronic factors are both important in governing regiochemistry in couplings of this type is presented, along with examples of how the effects can combine in either a constructive or destructive manner.

The reductive coupling of aldehydes and alkynes provides a powerful strategy for the preparation of stereodefined allylic alcohols.[1] Numerous strategies either involving stoichiometrically generated, alkyne-derived vinyl organometallic reagents[2] or the catalytic assembly of an allylic alcohol directly from the alkyne[3] have been described. A common issue that plagues intermolecular strategies of this type is the control of regiochemistry in the alkyne insertion. Indeed, controlling regioselectivity is arguably the most challenging task in developing 1,2-difunctionalization reactions of alkynes. The vast majority of regioselective additions to alkynes involve alkynes with a major bias in either the size or the electronic characteristics of the acetylenic substituents.[4] Internal alkynes with only subtle biases between the two acetylenic termini are notoriously difficult substrates for the development of regioselective processes.

In the nickel-catalyzed reductive coupling of aldehydes with electronically biased alkynes, regioselectivities are often

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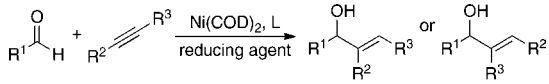
exceptional and are determined predominantly by substrate structure. This outcome is typically seen with terminal, aryl, and silyl alkynes as well as with conjugated enynes and ynamides.[3,5] Internal alkynes without a strong electronic bias, however, often lead to regioisomeric mixtures (Scheme 1).

Scheme 1. Regiocontrol in Aldehyde−Alkyne Reductive Couplings



Of the various reducing agent-ligand combinations reported for nickel-catalyzed intermolecular couplings, Et_3B-mediated couplings with phosphine ligands developed by Jamison and R_3SiH-mediated couplings with *N*-heterocyclic carbene (NHC) ligands from our work are of the broadest scope.[3]

Recently developed strategies that allow regioselective outcomes with nonbiased internal alkynes include ligand size modifications[3d,f] as well as olefin-directed reactions.[3h−k,5] These more recent approaches have the advantage of being tunable, with either regioselectivity outcome being possible depending on experimental setup. Directed reactions are especially effective at exerting regiochemical influences but are limited by the ease with which the directing group can be either removed or converted to a desirable functional group.[6] Herein, using propargyl alcohols as a test case, we describe that subtle electronic influences of an alkyne may be enhanced with protecting group strategies and then matched with ligand size effects to allow excellent control of regiochemistry in aldehyde−alkyne reductive couplings. The predictable synergy of multiple subtle effects often provides highly regioselective couplings that are relatively unselective using standard protocols.

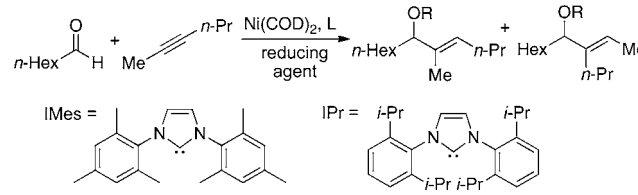
The inherent regioselectivity with unsymmetrical internal alkynes governed by ligand size is illustrated in couplings of 2-hexyne (Table 1).[7] Comparing couplings involving the larger ligand IPr and the smaller IMes using *i*-Pr_3SiH as reducing agent demonstrates that the smaller ligand IMes favors the regioisomer derived from the less hindered alkyne terminus undergoing addition to the aldehyde (entry 1), whereas the larger ligand IPr favors the regioisomer derived from the more hindered alkyne terminus undergoing addition to the aldehyde (entry 2).

(5) For rhodium-catalyzed reductive coupling of 1,3-enynes to carbonyl compounds and imines, see: (a) Jang, H.-Y.; Huddleston, R. R.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4664–4668. (b) Kong, J.-R.; Cho, C.-W.; Krische, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 11269–11276. (c) Kong, J.-R.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 718–719. (d) Komanduri, V.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 16448–16449. (e) Hong, Y.-T.; Cho, C.-W.; Skucas, E.; Krische, M. J. *Org. Lett.* **2007**, *9*, 3745–3748.

(6) (a) For site-selective hydrogenations of the products from alkene-directed Ni-catalyzed reactions, see reference 3h. (b) For a general review, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370.

(7) For relevant discussions of ligand size effects, see: (a) Tekavec, T. N.; Arif, A. M.; Louie, J. *Tetrahedron* **2004**, *60*, 7431–7437. (b) Dorta, R.; Stevens, E. D.; Scott, N. M.; Costabile, C.; Cavallo, L.; Hoff, C. D.; Nolan, S. P. *J. Am. Chem. Soc.* **2005**, *127*, 2485–2495.

Table 1. Reductive Couplings of 2-Hexyne[a]



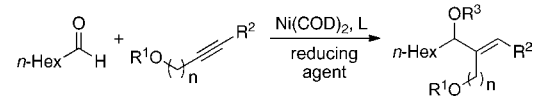
entry	L	reducing agent	yield (%) (regioselectivity)
1	IMes	*i*-Pr_3SiH	83 (67:33)
2	IPr	*i*-Pr_3SiH	84 (20:80)
3	PBu_3	Et_3B	74 (51:49)
4	PCy_3	Et_3B	79 (40:60)
5	P(*t*-Bu)$_3$	Et_3B	67 (38:62)

[a] The catalysts were generated from $Ni(COD)_2$ (12 mol %) in THF. IMes and IPr were generated in situ from the HCl salts and KO-*t*-Bu (10 mol % each), or phosphines were used neat (20 mol %).

Alternatively, reductive couplings involving trialkyl phosphines as ligands and Et_3B as the reducing agent exhibit a smaller regiochemical change with this combination of substrates as the ligand size is varied (entries 3−5). These experiments establish a benchmark for ligand size effects where an electronic bias in the alkyne is largely absent.

Given the wide availability of propargyl alcohols and the utility of the allylic alcohols derived from their couplings, we next examined the performance of propargyl alcohols in reductive couplings with aldehydes (Table 2). A simple propargyl alcohol (2-hexyn-1-ol) underwent *i*-Pr_3SiH-mediated reductive coupling with heptanal using IMes as ligand to favor the product derived from aldehyde coupling with the hy-

Table 2. Optimization of Reductive Couplings of Propargyl Alcohol Derivatives[a]



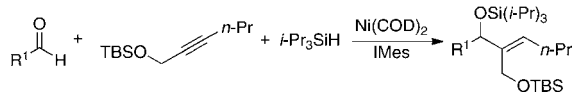
entry	R^1	R^2	n	L	reducing agent	yield (%) (regioselectivity)
1	H	Pr	1	IMes	*i*-Pr_3SiH	92 (80:20)
2	H	Pr	1	IPr	*i*-Pr_3SiH	78 (67:33)
3	H	Pr	1	PCy_3	*i*-Pr_3SiH	80 (67:33)
4	H	Pr	2	IMes	*i*-Pr_3SiH	82 (50:50)
5	Me	Hept	1	IMes	*i*-Pr_3SiH	57 (75:25)
6	*t*-Bu	Hept	1	IMes	*i*-Pr_3SiH	75 (75:25)
7	TBS	Pr	1	IMes	*i*-Pr_3SiH	75 (87:13)
8	TBS	Pr	1	IPr	*i*-Pr_3SiH	86 (71:29)
9	TBS	Pr	1	PBu_3	Et_3B	65 (57:43)
10	TBS	Pr	1	PCy_3	Et_3B	73 (58:42)
11	TBS	Pr	1	P(*t*-Bu)$_3$	Et_3B	71 (53:47)

[a] The catalysts were generated from $Ni(COD)_2$ (12 mol %) in THF. IMes and IPr were generated in situ from the HCl salts and KO-*t*-Bu (10 mol % each), or phosphines were used neat (20 mol %).

droxymethyl-substituted alkyne terminus in 4:1 regioselectivity (entry 1). The identical conditions using IPr or PCy_3 as ligand afforded the same product in 2:1 regioselectivity (entries 2 and 3). Using IMes as ligand, a homopropargylic alcohol underwent coupling with 1:1 regioselectivity (entry 4), suggesting that the modest regiocontrol in couplings of propargyl alcohols is derived from an inductive bias rather than via direct coordination of the hydroxyl group to nickel. Upon further examination of couplings using IMes as ligand, protection of the propargyl alcohol as the Me or *t*-Bu ether resulted in an erosion of regioselectivity (entries 5 and 6) in comparison to leaving the hydroxyl unprotected, but protection as the TBS (*tert*-butyldimethylsilyl) ether improved regioselectivity to 7:1 (entry 7). Use of more bulky IPr as ligand in this latter case resulted in erosion of regioselectivity (entry 8). To further evaluate the effectiveness of phosphine complexes in impacting regioselectivity, we examined several phosphine−Et_3B combinations and found that only minimal regiochemical bias was observed (entries 9−11). Therefore, the TBS ether−IMes combination using *i*-Pr_3SiH as reducing agent was the optimal set of conditions for maximizing regioselectivity with this pair of substrates (entry 7).

Given the potential utility of reductive couplings of simple silyloxymethyl-substituted alkynes with aldehydes, a variety of couplings were examined using *i*-Pr_3SiH as reducing agent and IMes as ligand (Table 3). Couplings of a branched and an unbranched aldehyde proceeded with 7:1 regioselectivity (entries 1 and 2), and couplings of benzaldehyde derivatives or furaldehyde (entries 3−5) proceeded in 10:1 regioselectivity. α-Silyloxyaldehydes were also excellent participants, with couplings proceeding in excellent yields and regioselectivities ranging from 11:1 to >98:2 (entries 6 and 7).

Table 3. Scope of Reductive Couplings of Propargyl Alcohol Derivatives[a]

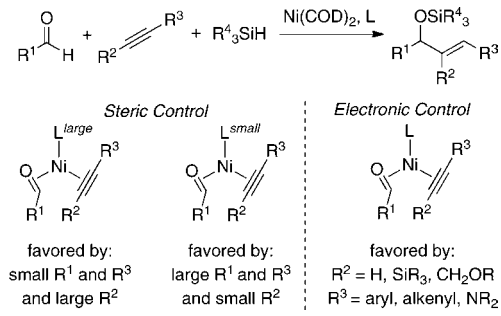


entry	R^1	yield (%) (regioselectivity)	(anti:syn)
1	Hex	75 (87:13)	
2	*c*-Hex	87 (87:13)	
3	Ph	85 (91:9)	
4	*p*-$(CH_3CO)C_6H_4$	83 (91:9)	
5	Furyl	82 (91:9)	
6	$CH_3(CH_2)_4$(TBSO)CH	74 (>98:2)	(75:25)
7	$CH_3(CH_2)_4$(TIPSO)CH	75 (92:8)	(80:20)

[a] The catalysts were generated from $Ni(COD)_2$ (12 mol %) in THF. IMes and IPr were generated in situ from the HCl salts and KO-*t*-Bu (10 mol % each), or phosphines were used neat (20 mol %).

As the examples above illustrate, regiocontrol derived from variation in size of the NHC ligand is somewhat subtle (Table 1). Electronic biases of simple propargyl alcohols are similarly modest (Table 2, entries 1−2). However, proper choice of protecting groups and ligands can result in preparatively useful levels of regiocontrol in relatively unbiased cases (Table 3). Significantly, a simple model that combines the predictive influences of ligand sterics and of substrate electronic and steric biases may now be formulated based on examples from the current study and previous work[3] (Scheme 2).

Scheme 2. Predictive Model for Regiocontrol



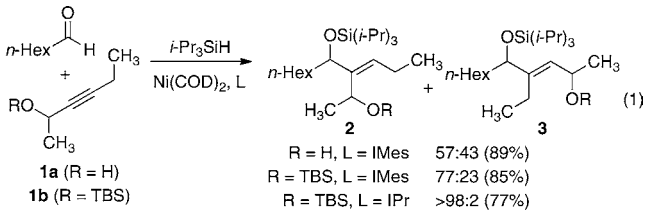
The formation of a nickel metallacycle intermediate is typically invoked in reactions of this type,[3a,b,8] and we envision that the inductive influence of the silyloxy group is responsible for the regioselectivity bias of couplings of protected propargyl alcohols. The observations that homopropargyl alcohols proceed with very poor selectivity (Table 2, entry 4) and that silyl-protected propargyl alcohols proceed with higher regioselectivities than unprotected propargyl alcohols (Table 2, compare entries 1 and 7) both suggest that hydroxyl direction via coordination to nickel is not responsible for the effect.[9] As depicted, electronic and/or steric biases of the alkyne can combine in either a constructive or destructive manner with ligand sterics, and one must consider the characteristics of the aldehyde, alkyne, and ligand in order to predict the regiochemical outcome. For simplicity, steric and electronic biases are illustrated separately in the predictive model, but there is clear synergy between the effects (Scheme 2).

Whereas the substructures examined in Table 3 are best optimized using IMes as ligand, the predictive model (Scheme 2) suggests that the best ligand choice for a particular coupling will depend on a complete evaluation of multiple factors. The cooperative nature of steric and electronic control features is illustrated by couplings of substituted propargyl alcohols **1a** and **1b** (eq 1). Initial couplings with substrate **1a** and IMes as ligand provide a 1.3:1 mixture of regioisomers **2** and **3**. Protection as the TBS ether **1b** maximizes the inductive influences to afford a 3.3:1 mixture of regioisomers **2** and **3**. Steric influences are then maximized by matching substrate **1b** with IPr as ligand to afford product **2** with >98:2 regioselectivity. Importantly, these substantial changes in regioselectivity can be predicted by considering the simple model (Scheme 2), wherein matching

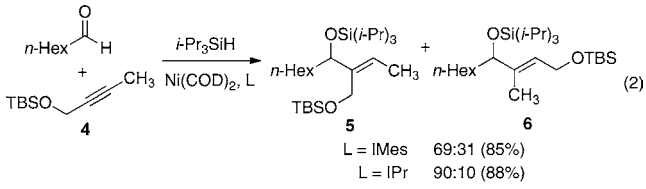
(8) (a) For a recent computational study: McCarren, P. R.; Liu, P.; Cheong, P. H.-Y.; Jamison, T. F.; Houk, K. N. *J. Am. Chem. Soc.* **2009**, *131*, 6654–6655. (b) For metallacycle isolation, see: Ogoshi, S.; Arai, T.; Ohashi, M.; Kurosawa, H. *Chem. Commun.* **2008**, 1347–1349.

(9) For representative examples of hydroxyl-directed reductive couplings, see: (a) Qun, L. G.; Kim, S.-H.; Lee, J. C.; Cha, J. K. *Angew. Chem., Int. Ed.* **2002**, *41*, 2160. (b) Ryan, J.; Micalizio, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 2764. (c) Chen, M. Z.; Micalizio, G. C. *Org. Lett.* **2009**, *11*, 4982.

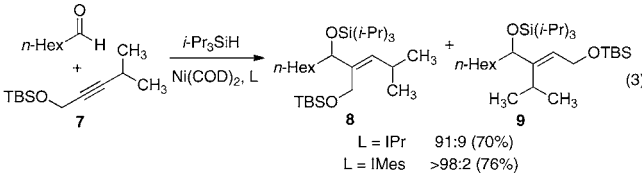
steric and electronic influences synergistically maximizes regioselectivity.



Similarly, a reductive coupling of protected 2-butyn-1-ol (**4**) with heptanal proceeds with modest regioselectivity using IMes as ligand to afford a 2.2:1 mixture of products **5** and **6** (eq 2). However, synergy of electronic and steric biases is predicted by the use of a large ligand in this case, and the use of IPr as ligand generates product **5** with 9:1 regioselectivity.

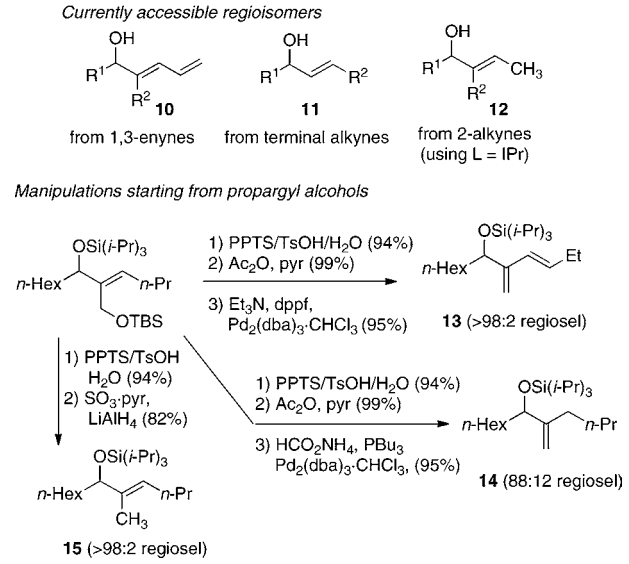


As a final illustration, if one reverses the relative size of the alkyne substituents, as seen in alkyne **7**, the ligand steric model predicts that a smaller ligand would favor the major product **8** (eq 3). Indeed, in this instance, couplings using IPr as ligand are quite selective (10:1), but the use of the smaller ligand IMes provides exceptional regiocontrol (>98:2) over the alternate regioisomer **9**. The optimized choice of ligand in each of these examples (eq 1−3) may be readily predicted from the model presented above (Scheme 2).



As noted above, a limitation of any substrate-controlled strategy for product selection is the ease with which the controlling functionality may be converted into a desired product. Propargyl alcohols are especially valuable in this respect. For example, the products of the type described in Table 3 may be converted to three classes of compounds that currently cannot be directly accessed in high regioselectivity by a nickel-catalyzed silane-mediated aldehyde-alkyne reductive coupling. A protecting group swap from TBS to acetate may be followed by Pd(0)-catalyzed conversion to diene **13**,[10a] which is the opposite regioisomer from that directly accessed by 1,3-enyne reductive couplings (compound **10**).[10b] The same acetate may also be subjected to a Pd(0)-catalyzed reductive transposition to afford product **14**,[10c] which is the opposite regioisomer from that derived from a terminal alkyne reductive couplings (compound **11**). Finally, TBS deprotection may be directly followed by a sulfonylation/reduction procedure[10d] to directly afford product **15**, which is the opposite regioisomer from that preferentially obtained from reductive couplings of 2-alkynes using IPr as ligand (compound **12**, Table 1, entry 2; Scheme 3).

Scheme 3. Post-Coupling Manipulations



In summary, highly regioselective nickel-catalyzed reductive couplings of propargyl alcohol derivatives and aldehydes have been developed. This work addresses strategies to control the regiochemistry in alkyne insertions; an issue that plagues nearly every intermolecular metal-catalyzed process involving alkynes. The interplay of steric and electronic considerations in nickel-catalyzed reductive couplings provides a predictable strategy for controlling regiochemistry for a variety of substrate combinations, including couplings of propargyl alcohols. In comparing a variety of phosphines and NHCs as ligands, the NHCs examined are best able to exert steric influences in controlling regiochemistry. For a number of desirable regiochemical outcomes that are elusive by direct coupling strategies, the derivatization of propargyl alcohol-derived products provides an indirect but effective alternative. The examination of different classes of NHCs that exert even greater regiochemical biases with a range of alkynes is in progress.

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

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(10) (a) Takacs, J. M.; Lawson, E. C.; Clement, F. *J. Am. Chem. Soc.* **1997**, *119*, 5956–5957. (b) For an exception, see ref 9c. (c) Tsuji, J.; Mandai, T. *Synthesis* **1996**, 1–24. (d) Corey, E. J.; Achiwa, K. *J. Org. Chem.* **1969**, *34*, 3667–3668.