Published in final edited form as:

J Am Chem Soc. 2010 May 12; 132(18): 6304–6305. doi:10.1021/ja102262v.

A General Strategy for Regiocontrol in Nickel-Catalyzed Reductive Couplings of Aldehydes and Alkynes

Hasnain A. Malik, Grant J. Sormunen, and John Montgomery*

930 N. University Ave., Department of Chemistry, University of Michigan, Ann Arbor, MI 48109-1055

Abstract

A strategy for catalyst-controlled regioselectivity in aldehyde-alkyne reductive couplings has been developed. This strategy is the first where either regiochemical outcome may be selected for a broad range of couplings, without relying on substrate biases or directing effects. The complementary use of small cyclopropenylidene carbene ligands or highly hindered *N*-heterocyclic carbene ligands allows the regiochemical reversal with unbiased internal alkynes, aromatic internal alkynes, conjugated enynes, or terminal alkynes.

The reductive coupling of aldehydes and alkynes has been widely studied as an entry to stereodefined allylic alcohols.¹ While broad scope has been demonstrated for several variants, the control of regiochemistry is consistently a major hurdle.² Indeed, the challenge of controlling regiochemistry plagues nearly every class of alkyne addition reactions. In most classes of addition processes, alkynes that possess either a strong electronic or steric bias often participate with good to excellent regiocontrol, but only a single regiochemical outcome is typically available. Alternatively, alkynes that lack a strong electronic or steric bias generally participate in addition processes with poor regioselectivity. These characteristics generally hold true for aldehyde-alkyne reductive coupling processes. Aromatic alkynes, terminal alkynes, silyl alkynes, ynamides, and conjugated diynes and enynes are among the biased substrate classes that participate in highly regioselective reductive couplings with aldehydes, with a single regiochemical outcome typically being possible.³ Additionally, remote directing functionality such as alkenes and alcohols have proven to be effective in Ni-catalyzed and Ti-promoted variants.^{2,4}

Despite these impressive advances with biased alkynes and directed processes, we envisioned that a strategy for regiochemical control that overrides inherent substrate biases and that does not require installation of a directing functional group would be the ideal solution to regiocontrol in this group of reactions. Previous results from our lab illustrated that regioselectivities may be moderately impacted by ligand structure, but the effects were too small to be broadly useful.⁵ A recent computational study described the minimal impact that

jmontg@umich.edu.

Supporting Information Available: Full experimental details and copies of NMR spectral data (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

ligand structure has on regioselectivity in aldehyde-alkyne reductive couplings with Ni(0)-phosphine catalysts and organoborane reducing agents,⁶ thus highlighting the complexity of designing a ligand-controlled regioselective process. Herein, we describe that carefully selected carbene ligands complexed with nickel provide a general solution to regiocontrol in silane-mediated aldehyde-alkyne reductive couplings with a broad range of alkynes.

Our studies began with an evaluation of ligand effects in reductive couplings of heptaldehyde with 2-hexyne, since this alkyne provides a relatively unbiased case (Table 1).⁷ Initial couplings were evaluated with carbene ligands paired with (*i*-Pr)₃SiH.^{3d} The catalysts were generated in situ, by treating the carbene HCl or HBF₄ salt with Ni(COD)₂ and KO-*t*-Bu in THF. Substantial regiocontrol favoring either product was exerted across the range of ligands examined, although chemical yields were typically poor with less hindered carbenes. As the examples illustrate, ligand **6** (*i*-Pr-BAC), recently developed by Bertrand,⁸ and ligand **3a** (ITol) provided the best selectivities for product **1**, whereas ligands **4b** (SIPr) and **5c**⁹ provided the best selectivities for product **2**.

While substantial changes in regioselectivity of 2-hexyne addition reactions were observed from the above studies, an obvious limitation is the low yield observed with unhindered ligands that favor the formation of product **1**. Extensive experimentation illustrated that the use of BuLi as base and (*t*-Bu)₂SiH₂ as reducing agent provided much improved chemical yields when using ligand **6**, with negligible effect on regioselectivity.¹⁰ Thus, in choosing reaction conditions, the following guidelines may be adopted: To generate products when C-C bond formation at the less hindered alkyne terminus is desired, ligand **3b** (IMes) is a good commercial ligand to employ, and ligand **6** (*i*-Pr-BAC) provides even higher selectivity, especially with internal doubly aliphatic substituted alkynes. To generate products when C-C bond formation at the more hindered alkyne terminus is desired, ligand **4b** (SIPr) is a good commercial ligand to employ, and ligand **5c** provides even higher selectivity, especially with terminal alkynes (*vide infra*).

The above guidelines are illustrated with a broad range of biased and unbiased alkynes (Table 2). Couplings of 2-hexyne with unbranched, branched, or aromatic aldehydes are accomplished with good to excellent regioselectivity for either desired regioisomer **7** or **8** (entries 1–3). Increasing the steric differences between the two alkyne substituents (Me vs *i*-Pr) is cleanly tolerated and provides high regioselectivity for either isomer (entry 4). We next considered the possibility of applying these findings to reductive couplings of alkynes that possess considerable electronic bias, and that typically provide highly regioselective access to only one of the two possible regioisomeric products. We chose to examine aromatic alkynes, conjugated enynes, and terminal alkynes, which uniformly provide highly selective access to regioisomer **7** using previously reported R₃SiH-NHC or Et₃B-PR₃ Ni-catalyzed procedures. Coupling of phenyl propyne with benzaldehyde, as anticipated, provided regioisomer **7** with high selectivity under standard conditions with ligand **3b** (IMes) (entry 5). However, the use of ligand **4** (SIPr) reverses selectivity, favoring regioisomer **8** with 81:19 regioselectivity. We next examined a conjugated enyne, knowing that this substrate class is one of the most biased alkyne classes in reductive couplings.^{3d–f,6} Standard coupling with ligand **3b** (IMes) provided highly selective coupling at the aliphatic substituted alkyne terminus to produce isomer **7** as anticipated (entry 6). However, the use of ligand **4** (SIPr) cleanly reversed selectivity, providing regioisomer **8** with excellent regiocontrol. Finally, three different terminal alkyne-aldehyde combinations were examined (entries 7–9). As anticipated, standard couplings with ligand **3b** (IMes) cleanly and selectively provided the *trans*-1,2-disubstitution pattern (isomer **7**). Unfortunately, this bias could not be overcome with ligand **4** (SIPr), and isomers **7** and **8** were obtained with poor regiocontrol. However the use of ligand **5c** provided an important breakthrough, providing the 1,1-disubstitution pattern (isomer **8**) with excellent regiocontrol, ranging from 12:88 to 5:95 for the three examples studied.¹¹

The simple steric model depicted (Figure 1), wherein reorientation of the alkyne in π -complexes **9** and **10** ultimately governs regiochemistry, provides a possible rationale for the observed regiochemical outcome.¹² This model had previously been presented as part of a synergistic picture to explain how ligand size effects supplement inherent substrate biases.^{5a} However, the current study illustrates that, with careful optimization of ligand structure, the impact of ligand size effects is substantial and can override substrate-derived influences with a broad range of both biased and unbiased alkynes.

In summary, the complementary use of cyclopropenylidene ligands and highly hindered *N*-heterocyclic carbene ligands provides dramatic regiochemical reversal in nickel-catalyzed aldehyde-alkyne reductive couplings. The participation of relatively unbiased internal alkynes or strongly biased terminal alkynes, aryl alkynes, and conjugated enynes provides useful substructures, several of which were previously inaccessible by aldehyde-alkyne reductive coupling. Either regiochemical outcome of the alkyne addition may be selectively accessed with each of these substrate classes. The extent of regiochemical reversal seen across the broad range of alkynes studied rivals that seen for any class of alkyne addition reactions. While improvements in ligand structure can be envisioned to provide further enhancements in selectivity and scope, the above study illustrates the special role that stable carbene ligands can play in governing catalytic reactions that are sensitive to steric controlled regioselection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors wish to acknowledge receipt of NIH grant GM-57014 in support of this work. G.J.S. acknowledges training grant support from NIH grant GM-007767. Mani Raj Chaulagain is thanked for helpful discussions.

REFERENCES

1. (a) Montgomery J. *Angew. Chem. Int. Ed* 2004;43:3890. (b) Montgomery J, Sormunen GJ. *Metal Catalyzed Reductive C–C Bond Formation: A Departure from Preformed Organometallic Reagents* 2007; Vol. 279:1–23. (c) Moslin RM, Miller-Moslin K, Jamison TF. *Chem. Commun* 2007:4441. (d) Skukcas E, Ngai M-Y, Komanduri V, Krische MJ. *Acc. Chem. Res* 2007;40:1394. [PubMed: 17784728] (e) Bower JF, Kim IS, Patman RL, Krische MJ. *Angew. Chem. Int. Ed* 2009;48:34. (f) Perez LJ, Micalizio GC. *Synthesis* 2008:627. (g) Oppolzer W, Radinov RN. *J. Am. Chem. Soc* 1993;115:1593. (h) Wipf P, Xu W. *Tetrahedron Lett* 1994;35:5197. (i) Kerrigan MH, Jeon S-J, Chen YK, Salvi L, Carroll PJ, Walsh PJ. *J. Am. Chem. Soc* 2009;131:8434. [PubMed: 19476375]
2. For an overview of regiocontrol strategies: Reichard HA, McLaughlin M, Chen MZ, Micalizio GC. *Eur. J. Org. Chem* 2010;391
3. (a) Many examples with aromatic, terminal, and silyl alkynes are described in reference ¹. For ynamides: (b) Saito N, Katayama T, Sato Y. *Org. Lett* 2008;10:3829. [PubMed: 18681448] For diynes: (c) Huddleston RR, Jang HY, Krische MJ. *J. Am. Chem. Soc* 2003;125:11488. [PubMed: 13129338] For enynes: (d) Mahandru GM, Liu G, Montgomery J. *J. Am. Chem. Soc* 2004;126:3698. [PubMed: 15038707] (e) Miller KM, Luanphaisarnnont T, Molinaro C, Jamison TF. *J. Am. Chem. Soc* 2004;126:4130. [PubMed: 15053602] (f) Jang HY, Huddleston RR, Krische MJ. *J. Am. Chem. Soc* 2004;126:4664. [PubMed: 15070383]
4. (a) For ligand-switchable directing effects: Miller KM, Jamison TF. *J. Am. Chem. Soc* 2004;126:15342. [PubMed: 15563136] (b) Bahadoor AB, Flyer A, Micalizio GC. *J. Am. Chem. Soc* 2005;127:3694. [PubMed: 15771493] (c) Bahadoor AB, Micalizio GC. *Org. Lett* 2006;8:1181. [PubMed: 16524298]
5. (a) Malik HA, Chaulagain MR, Montgomery J. *Org. Lett* 2009;11:5734. [PubMed: 19919081] (b) Knapp-Reed B, Mahandru GM, Montgomery J. *J. Am. Chem. Soc* 2005;127:13156. [PubMed:

- 16173738] (c) Chaulagain MR, Sormunen G, Montgomery J. J. Am. Chem. Soc 2007;129:9568. [PubMed: 17628066] (d) Oblinger E, Montgomery J. J. Am. Chem. Soc 1997;119:9065.
6. (a) Liu P, McCarren P, Cheong PHY, Jamison TF, Houk KN. J. Am. Chem. Soc 2010;132:2050. [PubMed: 20095609] (b) Huang WS, Chan J, Jamison TF. Org. Lett 2000;2:4221. [PubMed: 11150204]
7. For regioselectivity in imine-alkyne couplings: Barchuk A, Ngai MY, Krische MJ. J. Am. Chem. Soc 2007;129:8432. [PubMed: 17571894]
8. (a) Lavallo V, Canac Y, Donnadiou B, Schoeller WW, Bertrand G. Science 2006;312:722. [PubMed: 16614171] (b) Kuchenbeiser G, Donnadiou B, Bertrand G. J. Organomet. Chem 2008;693:899. [PubMed: 19255609] (c) Schoeller WW, Frey GD, Bertrand G. Chem. Eur. J 2008;14:4711.
9. Ligand **5c** is available as the racemate by the procedure employed. (a) For development of the general structural motif: Funk TW, Berlin JM, Grubbs RH. J. Am. Chem. Soc 2006;128:1840. [PubMed: 16464082] (b) For the synthesis of a precursor of **5c**: Mercer GJ, Sturdy M, Jensen DR, Sigman MS. Tetrahedron 2005;61:6418.
10. For the role of base structure in deprotonation of **6**: Lavallo V, Ishida Y, Donnadiou B, Bertrand G. Angew. Chem. Int. Ed 2006;45:6652.
11. For alternate access to the 1,1-disubstituted isomer: Takai K, Sakamoto S, Isshiki T, Kokumai T. Tetrahedron 2006;62:7534.
12. For discussions of ligand size effects: (a) Tekavec TN, Arif AM, Louie J. Tetrahedron 2004;60:7431. (b) Dorta R, Stevens ED, Scott NM, Costabile C, Cavallo L, Hoff CD, Nolan SD. J. Am. Chem. Soc 2005;127:2485. [PubMed: 15725003] (c) Ragone F, Poater A, Cavallo L. J. Am. Chem. Soc 2010;132:4249. [PubMed: 20205432]

Figure 1.
Ligand Steric Control of Regiochemistry.

Table 1

Ligand Effects in Couplings of 2-Hexyne.

entry	L·HX	Regioselectivity (1:2)	% Yield
1	3a	87:13	18
2	6	86:14	29
3	5a	75:25	22
4	3b	67:33	83
5	4a	61:39	73
6	3c	44:56	64
7	5b	29:71	86
8	3d	20:80	84
9	4b	7:93	85
10	5c	6:94	69

L·HX =

3a, R = *p*-tolyl**4a**, R = mesityl**3b**, R = mesityl**4b**, R = 2,6-di-isopropylphenyl**3c**, R = adamantyl**3d**, R = 2,6-di-isopropylphenyl **5c** (R = 2,6-diisopropylphenyl)

Table 2

Ligand-Controlled Regioselectivity Reversal.

entry	R ¹	R ²	R ³	7:8 (% yield) ^a	7:8 (% yield) ^a
1	<i>n</i> -Hex	Me	<i>n</i> -Pr	A, 88:12 (78)	B, 7:93 (85)
2	<i>c</i> -Hex	Me	<i>n</i> -Pr	A, 82:18 (75)	B, 5:95 (91)
3	Ph	Me	<i>n</i> -Pr	A, 84:16 (72)	B, 2:>98 (86)
4	Ph	Me	<i>i</i> -Pr	A, 97:3 (85)	B, 10:90 (89)
5	Ph	Me	Ph	C, >98:2 (84)	B, 19:81 (99)
6	<i>n</i> -Hex	Me	<i>c</i> -Hexenyl	C, 97:3 (99)	B, 9:91 (77)
7	Ph	H	CH ₂ OTBS	C, 93:7 (88)	D, 15:85 (86)
8	Ph	H	<i>n</i> -Hex	C, 97:3 (82)	D, 12:88 (71)
9	<i>n</i> -Hex	H	<i>i</i> -Pr	C, >98:2 (74)	D, 5:95 (76)

^a Conditions: A L·HX = **6**, BuLi, (*t*-Bu)₂SiH₂; B L·HX = **4b**, KO-*t*-Bu, (*i*-Pr)₃SiH; C L·HX = **3b**, KO-*t*-Bu, (*i*-Pr)₃SiH or Et₃SiH; D L·HX = **5c**, BuLi, Et₃SiH. Ligand structures are given in Table 1.