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

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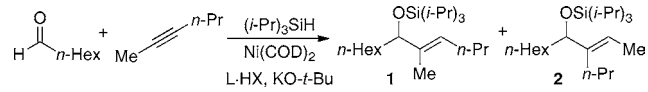
The reductive coupling of aldehydes and alkynes has been widely studied as an entry to stereodefined allylic alcohols.[1] While broad scope has been demonstrated for several variants, the control of regiochemistry is consistently a major hurdle.[2] Indeed, the challenge of controlling regiochemistry 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 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.

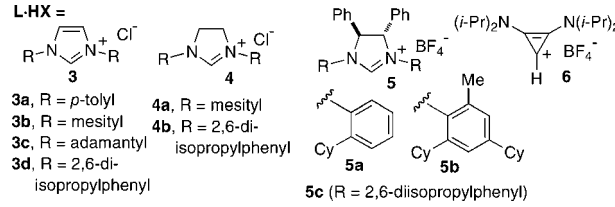
Our studies began with an evaluation of ligand effects in reductive couplings of heptaldehyde with 2-hexyne, since this alkyne provides a relatively unbiased case (Table 1).[7] Initial couplings were evaluated with carbene ligands paired with (*i*-Pr)$_3$SiH.[3d] The catalysts were generated in situ, by treating the carbene HCl or HBF$_4$ 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

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



favor the formation of product **1**. Extensive experimentation illustrated that the use of BuLi as base and (*t*-Bu)$_2$SiH$_2$ 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 R$_3$SiH−NHC or Et$_3$B−PR$_3$ Ni-catalyzed pro-

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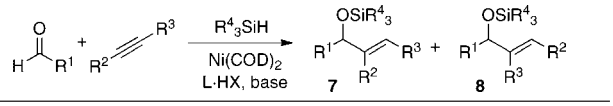
Table 2. Ligand-Controlled Regioselectivity Reversal



entry	R^1	R^2	R^3	**7**:**8** (% yield)[a]	**7**:**8** (% yield)[a]
1	*n*-Hex	Me	*n*-Pr	**A**, 88:12 (78)	**B**, 7:93 (85)
2	*c*-Hex	Me	*n*-Pr	**A**, 82:18 (75)	**B**, 5:95 (91)
3	Ph	Me	*n*-Pr	**A**, 84:16 (72)	**B**, 2:>98 (86)
4	Ph	Me	*i*-Pr	**A**, 97:3 (85)	**B**, 10:90 (89)
5	Ph	Me	Ph	**C**, >98:2 (84)	**B**, 19:81 (99)
6	*n*-Hex	Me	*c*-Hexenyl	**C**, 97:3 (99)	**B**, 9:91 (77)
7	Ph	H	CH_2OTBS	**C**, 93:7 (88)	**D**, 15:85 (86)
8	Ph	H	*n*-Hex	**C**, 97:3 (82)	**D**, 12:88 (71)
9	*n*-Hex	H	*i*-Pr	**C**, >98:2 (74)	**D**, 5:95 (76)

[a] Conditions: **A**: L·HX = **6**, BuLi, $(t\text{-Bu})_2SiH_2$; **B**: L·HX = **4b**, KO-*t*-Bu, $(i\text{-Pr})_3SiH$; **C**: L·HX = **3b**, KO-*t*-Bu, $(i\text{-Pr})_3SiH$ or Et_3SiH; **D**: L·HX = **5c**, BuLi, Et_3SiH. Ligand structures are given in Table 1.

cedures. 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

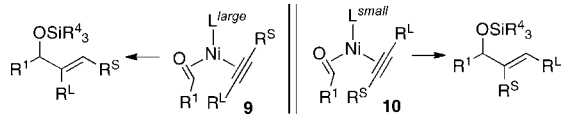


Figure 1. Ligand steric control of regiochemistry.

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.

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

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