Alkene Hydroamination

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Regioselective, Asymmetric Formal Hydroamination of Unactivated Internal Alkenes

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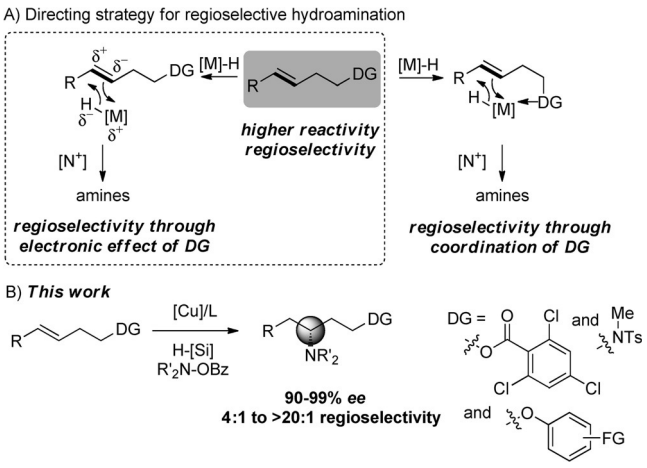
Abstract: *We report the regioselective and enantioselective formal hydroamination of unsymmetrical internal alkenes catalyzed by a copper catalyst ligated by DTBM-SEGPHOS. The regioselectivity of the reaction is controlled by the electronic effects of ether, ester, and sulfonamide groups in the homoallylic position. The observed selectivity underscores the influence of inductive effects of remote substituents on the selectivity of catalytic processes occurring at hydrocarbyl groups, and the method provides direct access to various 1,3-aminoalcohol derivatives with high enantioselectivity.*

Additions to alkenes are a fundamental class of reaction,[1] but the hydrofunctionalization of internal alkenes is challenging because of the low reactivity of internal alkenes and the difficulty of controlling the regioselectivity and stereoselectivity of addition of the H–X bond. Directed[2] hydrogenations[3] have been developed in which binding of the catalyst to the functional group controls the face of addition to which the alkene occurs, and this concept has been extended to directed hydrofunctionalizations, such as hydrosilyation,[4] hydroboration,[5] and hydroacylation,[6] in which a polar substituent controls the carbon to which the functional group is bound in the product. Although basic functional groups bind to the catalyst in some classes of directed addition reactions, the electronic properties of the polar group could control the regioselectivity of olefin functionalization in other cases, particularly the palladium-catalyzed oxidative functionalization of alkenes.[7]

Although the hydroamination of alkenes has been widely studied,[8] hydroaminations with alkenes containing directing groups are limited.[9] Our group has reported the hydroamination of internal α,β-unsaturated esters and nitriles,[10] and β-substituted vinylarenes,[11] but the reactivity and regioselectivity of the reactions of these substrates is dominated by conjugation of the alkene to the carbonyl or arene substituents. The transition-metal-catalyzed hydroamination of unconjugated alkenes directed by a functional group is limited to a single set of reactions of *N*-allyl imines.[9,12]



Scheme 1. Regioselective hydroamination of unactivated internal alkenes.

The hydroamination of alkenes has been investigated with many classes of catalyst and reagents. The intramolecular addition of the N–H bonds of amines to alkenes has been reported with complexes of many transition metals, and reactions catalyzed by those of the late transition metals occur with high compatibility for functional groups.[13] Recently, Miura[14] and Buchwald[15] showed independently that the intermolecular reaction of a hydride from a silane and an electrophilic amino ($^{+}NR_2$) group from a hydroxylamine derivative, rather than the N–H bond of an amine, gives rise to the products from formal hydroamination[16] of vinylarenes and later 1,1-disubstituted alkenes.[17] During the course of our study on directed hydroamination of internal alkenes, Buchwald also reported reactions of symmetrical internal alkenes, as well as two unsymmetrical alkenes bearing unfunctionalized alkyl groups.[18] However, three equivalents of internal olefins were required to achieve high yields, making the utility of this method for reactions of valuable alkenes limited.

Herein, we disclose our results that the formal hydroamination of internal alkenes containing an oxygen or nitrogen substituent in the homoallylic position occurs with high regioselectivity and enantioselectivity, and without the need for excess olefin (Scheme 1B). The observed regioselectivity results from the electronic effect of the substituent on the alkene, rather than direct coordination of the functionality to the metal. These results suggest that the inductive effects of remote electronegative groups on regioselectivity can be large enough to cause regioselectivity at an alkene to be high,[7] much like they are large enough to influence the

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site-selectivity for C–H bond functionalization on a saturated hydrocarbyl substituent.[19] This chemistry provides a simple route to highly enantioenriched 1,3-aminoalcohol derivatives, which are prevalent in natural products and pharmaceuticals[20] and are useful synthetic building blocks.[21]

To probe the effect of functional groups on the regioselectivity for the formal hydroamination of internal alkenes, we first investigated the reaction of *trans*-3-hexenyl benzyl ether (**1a**) with diethoxymethylsilane (DEMS) and *N*,*N*-dibenzyl-*O*-benzoyl hydroxylamine (Table 1, entry 1). The

Table 1: Evaluation of directing groups for regioselective hydroamination.[a]

Entry	R Group	Conversion[b] (%)	Yield[b] (%)	P:D[c]	*ee*[d]
1	Bn (**1a**)	55	50	3.3:1[e]	–
2	PMB (**1b**)	48	46	3.2:1[e]	–
3	4-CF_3-$C_6H_4CH_2$ (**1c**)	56	52	3.6:1[e]	–
4	Bz (**1d**)	>95	39	7.1:1	99
5	$BzCl_3$[f] (**1e**)	90	84	9.0:1	97
6	C_6F_5 (**1f**)	90	81	7.6:1	97
7	4-Br-C_6H_4 (**1g**)	84	83	4.6:1	94
8	Ts (**1h**)	<5	0	–	–

[a] Reaction conditions: **1** (0.05 mmol), **2** (0.10 mmol, 2 equiv), Cu(PPh$_3$)H (10 mol%) and (*S*)-DTBM-SEGPHOS (11 mol%) in THF (0.14 mL), rt, 84 h; [b] Determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard; [c] Proximal:distal ratio was determined by analysis of the ^{1}H NMR spectra of the crude reaction mixture; [d] Determined by SFC for the major isomer; [e] Determined by GC; [f] $BzCl_3$ = 2,4,6-trichlorobenzoyl.

reaction of these reagents in the presence of 10 mol% Cu(PPh$_3$)H and 11 mol% (*S*)-DTBM-SEGPHOS[22] in THF at room temperature for 84 h gave the hydroamination products in moderate yield and regioselectivity (50% yield, 3.3:1 regioselectivity). Modification of the electronic properties of the aryl group on the benzyl ether from electron-rich *p*-methoxy benzyl ether **1b** to electron-poor *p*-trifluoromethyl benzyl ether **1c** did not alter the yield or regioselectivity significantly. However, the regioselectivity was slightly higher for the reaction of the more electron-poor **1c** (entry 3).

Thus, this formal hydroamination was conducted on an internal alkene bearing a more electron-withdrawing benzoyl group (**1d**). The regioselectivity of the reaction of the homoallylic benzoate was clearly higher than that for reaction of the homoallylic ethers (**1a**–**1c**). However, the yield for reaction of the benzoate was lower, owing to competing reduction of the ester in both the starting material (**1d**) and the corresponding hydroamination products.

To suppress the competing reduction, we studied reactions of benzoates bearing substituents at the *ortho* positions. Indeed, the reaction of an internal olefin bearing a 2,4,6-trichlorobenzoyl group (**1e**) afforded the hydroamination products in high yield, with high regioselectivity and without formation of the competing reduction product. Moreover, this reaction occurred with excellent enantioselectivity.

Reactions of alkenes containing other electron-deficient groups, such as phenyl ethers (**1f**, **1g**) and a tosylate (**1h**) were also studied. The reactions of the olefins bearing phenyl ether groups formed the addition product in higher yield and regioselectivity than those of reactions of olefins bearing alkyl ether groups. The yield and regioselectivity of reactions of alkenes bearing more electron-deficient phenyl ethers were higher than those of reactions of alkenes bearing less electron-deficient phenyl ethers (**1f** vs. **1g**). However, the removal of the phenyl ether group requires harsh conditions, rendering it impractical for controlling the regioselectivity of the hydroamination. The alkene bearing a tosylate group reacted to less than 5% conversion (**1h**).

The scope of the reactions of alkenes containing the 2,4,6-trichlorobenzoyl group is summarized in the top section of Table 2. Alkenes containing ethyl-, isopropyl-, *tert*-butyl-, and cyclohexyl substituents (**3a**–**3d**) underwent hydroamination in good isolated yields with consistently high regioselectivity and excellent enantioselectivity. The alkenes with branching α to the alkene formed a single constitutional isomer, but the most hindered alkene bearing a *tert*-butyl group reacted in slightly lower yield than those with secondary alkyl substituents at this position. Methyl-substituted alkene (**3e**) underwent the reaction in low yield, but the lower yield was due to the lack of conversion, rather than formation of side products.

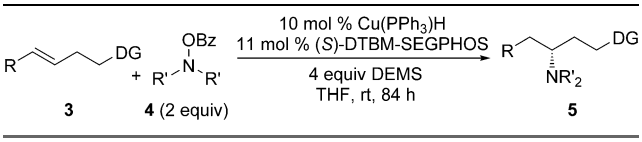
A series of functional groups are tolerated. Reactions of alkenes in substrates containing a silyl ether (**3f**) occur at the alkene, although lower regioselectivity (4.1:1) was observed, perhaps because the functional groups counterbalance the electronic influence of the homoallylic ester. Site-selective hydroamination of a non-conjugated diene occurred at the alkene proximal to the ester over the alkene distal to the ester (**3h**). Internal alkenes containing a phenyl ether unit **3k**–**3o** (evaluated due to their facile synthesis) reacted in the presence of halogens on the arene of the ether, as well as ketals and heteroarenes.

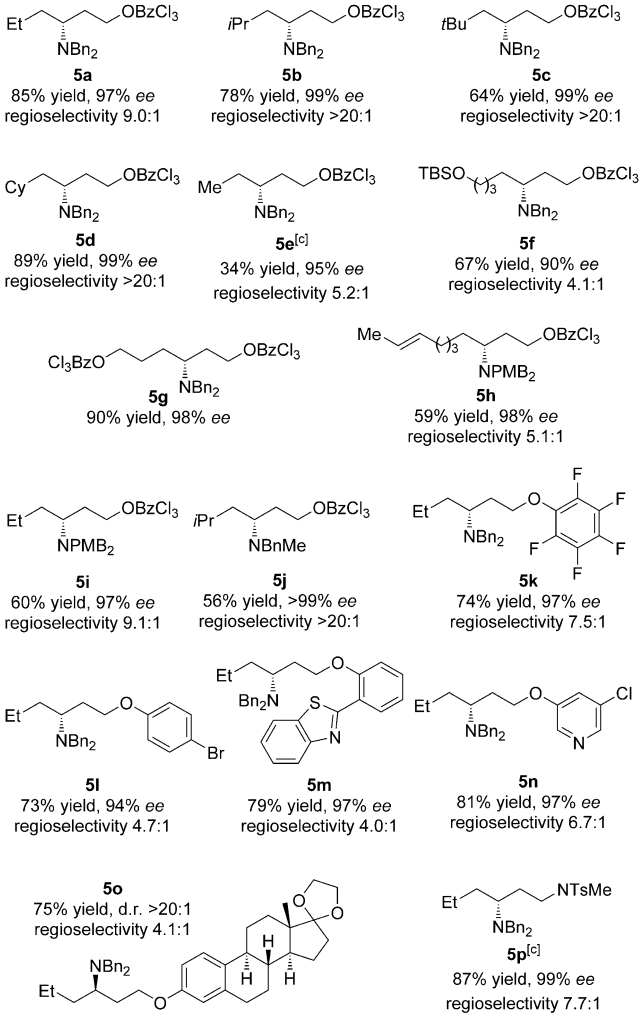
This reaction was found to be very sensitive to the substituents at nitrogen of the *O*-benzoylhydroxylamine. *N*,*N*-dibenzyl- and *N*-benzyl-*N*-alkyl-*O*-benzoylhydroxylamines underwent hydroamination in good yields (**5j**, **5k**) and high regioselectivity, but the reaction of an *N*,*N*-dialkyl-*O*-benzoylhydroxylamine provided the product in low yield.[23]

Furthermore, to expand the scope of functionalized alkenes that undergo this formal hydroamination, we found that substrates (**3p**) that contain functionality connected at the homoallylic position by heteroatoms other than oxygen, also underwent hydroamination in high yield with good regioselectivity and excellent enantioselectivity. This method provides access to enantioenriched 1,3-diamine derivatives.

To assess whether the chiral catalyst could control the diastereoselectivity for the hydroamination of chiral alkenes, we conducted the reaction of enantiopure internal alkene **6** bearing a stereogenic center at the site of the homoallylic benzoate (Table 3). The reaction of **6** catalyzed by the copper

Table 2: Scope of regioselective hydroamination of unactivated internal alkenes.[a,b]

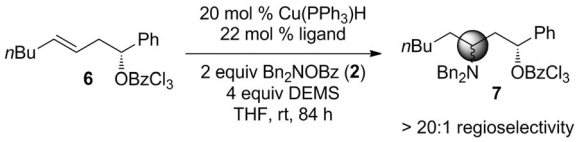




[a] Reaction conditions: **3** (0.2 mmol), **4** (0.4 mmol), $Cu(PPh_3)H$ (10 mol%) and (*S*)-DTBM-SEGPHOS (11 mol%) in THF (0.2 mL), rt, 84 h; [b] Regioselectivity and diastereoselectivity were determined by analysis of the ^1H NMR spectrum of the crude reaction mixture; [c] $Cu(PPh_3)H$ (15 mol%) and (*S*)-DTBM-SEGPHOS (17 mol%) used.

complex ligated by either (*S*)-DTBM-SEGPHOS or (*R*)-DTBM-SEGPHOS formed the addition products with excellent diastereoselectivity (>20:1 and 11:1, respectively) and regioselectivity (>20:1). The configuration at the carbon bearing the amino group was controlled by the configuration of the catalyst. When the reaction was conducted with *rac*-DTBM-SEGPHOS as the ligand, a d.r. of 4:1 in favor of the 1,3-*syn*-aminoester was observed. This result indicates that reaction of the (*R*)-substrate catalyzed by the (*S*)-DTBM-SEGPHOS complex is faster than the reaction of this substrate catalyzed by the (*R*)-DTBM-SEGPHOS complex. We have not identified an achiral phosphine that catalyzes the

Table 3: Study of diastereoselectivity of hydroamination of a chiral homoallylic ester.

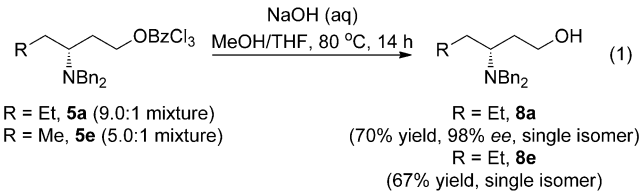


Entry	Ligand	Product	Yield[a]	d.r.[b]
1	(*S*)-DTBM-SEGPHOS	**7a**	55%	>20:1
2	(*R*)-DTBM-SEGPHOS	**7b**	20%	11:1
3	rac-DTBM-SEGPHOS	**7a**	(35%)	4:1

[a] Isolated yields. Yield in parenthesis refers to NMR yields using 1,3,5-trimethoxybenzene as internal standard. [b] Determined by analysis of ^1H NMR spectroscopy.

reaction to determine the inherent substrate bias on the diastereoselectivity.

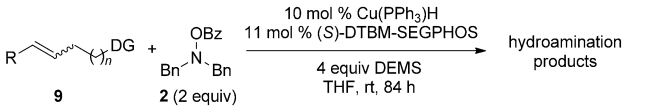
The 2,4,6-trichlorobenzoate groups of the hydroamination products (**5a** and **5e**) can be removed under saponification conditions. The corresponding 1,3-aminoalcohols (**8a** and **8e**) were obtained as single isomers in high yield with high enantiomeric excess [Eq. (1)].

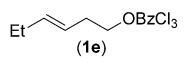
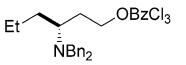
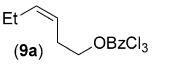
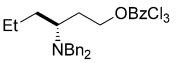
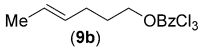
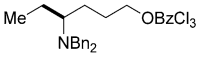
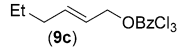
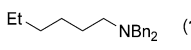


To gain insight into the effects of the structure of the substrate on the observed regioselectivity, we conducted reactions of a series of substrates that vary in the geometry and position of the alkene (Table 4). The *cis*-alkene (**9a**) underwent hydroamination in low yield and with low enantioselectivity, but did react with high regioselectivity. The substrate **9b** in which the alkene is positioned one carbon further away from the directing group underwent hydroamination with poor regioselectivity (1.2:1) and low yield (24%). Allylic benzoate **9c** underwent S_N2' addition of hydride and subsequent hydroamination to afford the terminal amine (**10c**) in nearly quantitative yield.

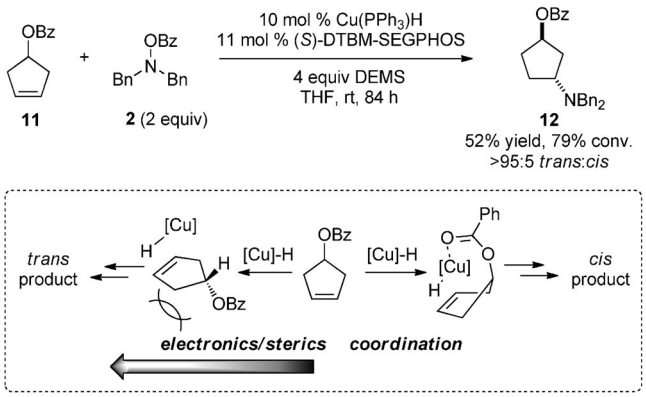
While the higher regioselectivity with substrates containing more electron-withdrawing and less basic substituents than with less electron-withdrawing and more basic substituents suggest that the regioselectivity of hydroamination arises from the electronic effects of the directing group, we sought less equivocal data on the origin of the regioselectivity. To distinguish between regioselectivity derived from the electronic effects of the proximal polar group and regioselectivity derived from direct coordination to the catalyst, we conducted the hydroamination of cyclopentene **11** (Scheme 2). If

Table 4: Effect of olefin position and geometry on the hydroamination.[a]



Entry	Substrate	Product		NMR yield (conv.), *ee* regioselectivity
1	 (**1e**)		(**5a**)	84% (90%), 97% *ee* regioselectivity 9.0:1
2	 (**9a**)		(**10a**)	15% (16%), 67% *ee* regioselectivity 9.0:1
3	 (**9b**)		(**10b**)	24% (28%) regioselectivity 1.2:1
4	 (**9c**)		(**10c**)	97% (100%)

[a] Yield and conversion were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

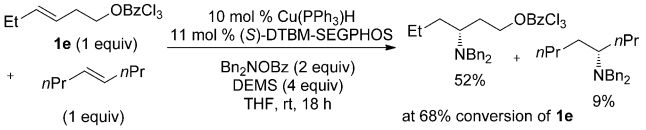


Scheme 2. Probe of origin of regioselectivity.

the regioselectivity occurs by coordination of the benzoate to the copper catalyst, insertion of the alkene would occur predominantly on the same face of the alkene as the directing group. This selectivity, followed by stereoretentive[15,24] electrophilic amination, would provide the *cis*-aminoester. If the regioselectivity occurs by an influence of the electronic properties of the polar group without direct coordination of the ester to the catalyst, the copper hydride would preferentially approach the alkene on the face opposite the ester unit, to avoid steric repulsions between the group and the catalyst. In this scenario, subsequent stereoretentive electrophilic amination would provide the *trans*-aminoester.

The hydroamination of **11** afforded the *trans* product exclusively (52% yield). Thus, coordination of the directing group to the copper hydride intermediate during the alkene insertion step is unlikely and the stereoselectivity for reaction of this substrate is consistent with a model for regioselectivity of the acyclic substrates owing to inductive effects.

Finally, to test whether the 2,4,6-trichlorobenzoate simply leads to selectivity or increases the reactivity of the substrate, we conducted the reaction with a combination of *trans*-4-octene and **1e**. The reaction was conducted under the standard conditions at partial conversion (68% of **1e**, 18 h) to gauge the relative reactivity (Scheme 3; see the Supporting Information for details).[25] This experiment showed that alkene **1e** reacts significantly faster than *trans*-4-octene.



Scheme 3. Relative reactivity of homoallylic benzoate **1e** and *trans*-4-octene.

In summary, we report the hydroamination of unsymmetrical internal alkenes with excellent enantioselectivity and regioselectivity controlled by synthetically valuable substituents that impart an electronic effect on the alkene. The 2,4,6-trichlorobenzoate group controls the regioselectivity and activates the alkene towards hydroamination, and it can be removed easily to afford synthetically useful enantioenriched 1,3-aminoalcohols. Studies on the cyclic substrate **11** support our hypothesis that the regioselectivity originates from the electronic and steric effects on the alkene. Evaluation of suitable directing groups for hydroamination reactions by the addition of the N–H bonds of the amines to alkenes are currently underway in our laboratory.

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Keywords: electronic effects · enantioselectivity · hydroamination · regioselectivity · unactivated internal olefins

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[25] Reactions conducted as a more conventional competition with excess of the alkene lead to reduction of the hydroxylamine as a major side pathway.

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