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A Selective Transformation of Enals into Chiral γ-Amino Alcohols

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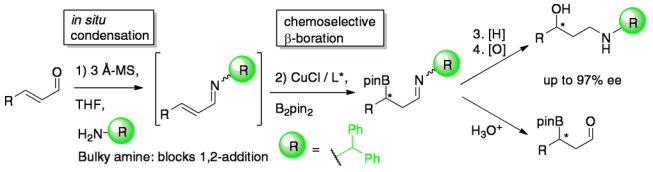
ABSTRACT



A one-pot synthesis of chiral amino alcohols from α,β-unsaturated aldehydes is reported which circumvents competitive 1,2- versus 1,4-boryl addition, by means of using a sterically hindered amine-derived imine. In addition to the complete chemoselectivity, modification of the Cu(I) catalyst with readily available chiral diphosphines, such as (*R*)-DM-BINAP, gave the 1,4-boryl addition products with high levels of asymmetric induction.

Metal and organocatalytic activation of diboron compounds provides the ideal platform to add boryl moieties to α,β-unsaturated carbonyl compounds in a 1,4-fashion (Scheme 1a).[1,2] However, α,β-unsaturated aldehydes suffer from competitive 1,2-boryl addition and, therefore, the synthesis of β-boryl aldehydes is a challenge[3] (Scheme 1b). Copper(I) alkoxides have proven to interact efficiently with B_2pin_2 (bis(pinacolato)diboron) *via* σ-bond metathesis to enhance the chemoselective β-boration of α,β-unsaturated aldehydes.[4] However, the asymmetric induction on the C_β−B bond formation was originally afforded in modest *ee* values when chiral N-heterocyclic carbenes (NHCs) modified Cu(I) salts. The direct activation of B_2pin_2 with chiral NHCs favored the formation of enantioenriched mixtures of β-boryl aldehydes with ee's up to 90% despite large amounts of base and MeOH (30 mol % and 60 equiv respectively) being required.[5] Moreover, this method was limited to β-aryl substituted α,β-unsaturated aldehydes. Alternative approaches to promote the chemoselective 1,4-boryl addition to enals were postulated on the basis of iminium intermediates, in both copper mediated reactions[6] and organocatalytic reactions.[7]

Alternative approaches to promote 1,4-boryl addition to enals were proposed on the basis of using iminium intermediates, in both copper-mediated[6] and organocatalytic reactions.[7] However, only when $CuOTf/PPh_3$ catalyzed the reaction in the presence of a chiral proline-derived cocatalyst could the resulting β-borated product be formed with moderate to high ee (up to 95%) as proved by conversion of the β-boryl aldehyde intermediates into enantioenriched mixtures of homoallylboronates (through Wittig chemistry). However, the use of an organic acid as

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(1) For reviews in metal mediated β-boration, see: (a) Schiffner, J. A.; Müther, K.; Oestreich, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1194. (b) Hartmann, E.; Vyas, D. J.; Oestreich, M. *Chem. Commun.* **2011**, 7917. (c) Lillo, V.; Bonet, A.; Fernández, E. *Dalton Trans.* **2009**, 2899. (d) Dang, L.; Lin, Z.; Marder, T. B. *Chem. Commun.* **2009**, 3987. (e) Mantilli, L.; Mazet, C. *ChemCatChem* **2010**, *2*, 501. (f) Calow, A. D. J.; Whiting, A. *Org. Biomol. Chem.* **2012**, *29*, 5485.

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(3) Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 11036.

(4) (a) Bonet, A.; Lillo, V.; Ramírez, J.; Diaz-Requejo, M.; Fernández, E. *Org. Biomol. Chem.* **2009**, *7*, 1533. (b) Lillo, V.; Prieto, A.; Bonet, A.; Díaz-Requejo, M.; Ramírez, J.; Pérez, P. J.; Fernández, E. *Organometallics* **2009**, *28*, 659.

(5) Wu, H.; Radomkit, S.; O'Brien, J. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 8277.

(6) Ibrahem, I.; Breistein, P.; Córdova, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 12036.

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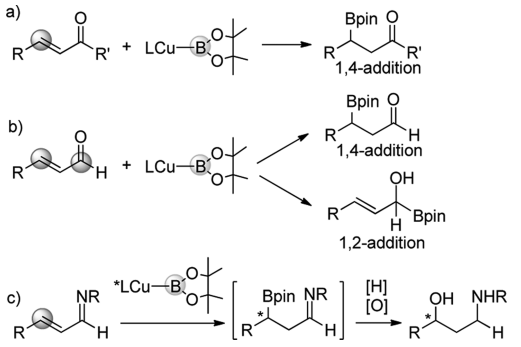
10.1021/ol4022029

an additive (2-fluorobenzoic acid) was required to accelerate the catalytic cycle of the iminium ion formation and to provide the chemoselective 1,4-addition.

Scheme 1. Illustrative Copper-Mediated Bpin Addition to α,β-Unsaturated Ketones, Aldehydes, and Aldimines



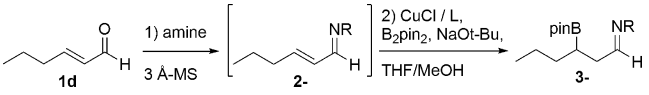
In our ongoing research to establish new methods to reach γ-amino alcohols using one-pot protocols, through organoboron intermediates,[8] we recently established a highly chemoselective Cu-catalyzed β-boration of *in situ* formed enone and enal-derived imines, with subsequent C=N reduction and C−B oxidation.[9] Furthermore, the four steps were efficiently carried out without isolation of intermediates, and the substrate scope was open to β-alkyl and β-aryl substituted α,β-unsaturated aldehydes. We focus now on the enantioselective version of this straightforward method to establish a new protocol to induce enantioselectivity through the use of chiral phosphines that modify the Cu(I) catalytic system (see Scheme 1c).

The advantage of using α,β-unsaturated aldimines as substrates to be borylated is based on complete chemoselectivity on the 1,4-addition as a result of steric hindrance of the C=NR bond versus C=O (Table 1). We performed a comparative study of chemoselective β-boration of 2-hexenal **1d** and the β-boration of the corresponding imines, formed *in situ* by condensation with benzhydrylamine, benzylamine, *p*-MeO-benzylamine, and *n*-butylamine. Subsequent hydrolysis of the β-borated imines (Scheme 2) thus provided the β-borated aldehyde with higher chemoselectivity than the direct β-boration of 2-hexenal. In the β-boration of the α,β-unsaturated imine formed from *n*-butylamine, the chemoselectivity dropped significantly, probably due to the reduced steric hindrance around the C=N bond (Table 1, entry 5).

We found that benzhydrylamine provided sufficient steric hindrance to guarantee the complete chemoselective β-boration of 2-hexenal. For that reason, we moved to β-aryl substituted enals to explore the viability of this method, and indeed, we could follow the *in situ* formation of imine **2a** derived from cinnamaldehyde **1a** and benzhydrylamine, using ReactIR (see Figure 1).

(8) Solé, A.; Gulyas, H.; Whiting, A.; Fernandez, E. *Adv. Synth. Catal.* **2011**, *353*, 376–384.
(9) Calow, A. D. J.; Batsanov, A. S.; Fernández, E.; Solé, C.; Whiting, A. *Chem. Commun.* **2012**, *48*, 11401–1403.

Table 1. Comparative β-Boration of α,β-Unsaturated 2-Hexenal and the Corresponding Aldimines[a]



entry	L	amine	conv (%)[b]	β-borated **3-** (%)
1	PPh_3	–	99	63
2	"	NH_2CH_2Ph	99	99
3	"	$NH_2CH_2p\text{-}C_6H_4OMe$	99	99
4	"	NH_2CHPh_2	99	99
5	"	$NH_2C_4H_9$	99	75

[a] A 0.25 mmol scale reaction: 2.00 mmol (1:1, amine/enal) were stirred in THF (8 mL) and 3 Å-MS (2.0 g) for 16 h, after which a 1 mL aliquot was transferred to a Schlenk tube (under Ar) containing Cu(I) salt (3 mol %), PPh_3 (6 mol %), NaOt-Bu (9 mol %), and B_2pin_2 (1.1 equiv). After 5 min, MeOH (2.5 equiv) was added to the solution and the reaction was stirred for 6 h. [b] Determined by ^1H NMR.

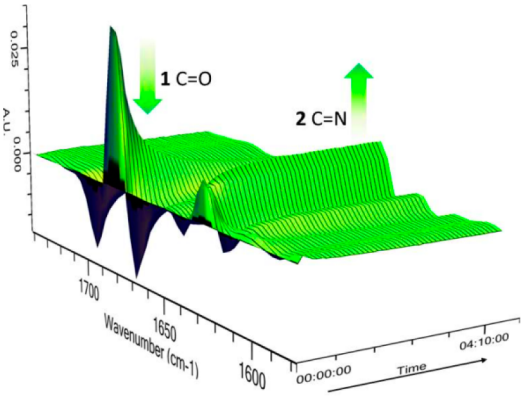
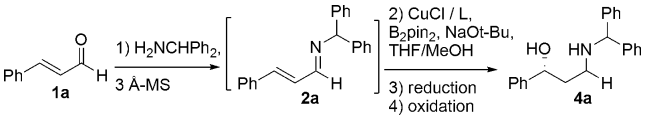


Figure 1. ReactIR plot of the *in situ* reaction of cinnamaldehyde and benzhydrylamine to give the corresponding α,β-unsaturated imine.

Imine **2a** was formed *in situ*, and without isolation, we conducted the Cu/PPh_3 mediated β-boration. This again proved that the competitive 1,2 boryl addition was no longer observed (Table 2, entry 1) and the β-borated imine was then subjected to reduction and oxidation *in situ* to give the corresponding γ-amino alcohol **4a**. With these results in hand, we subjected the model substrate **1a** to the one-pot enantioselective β-boration through the intermediate imine **2a**. When BINAP **L1** (Figure 2) or Tol-BINAP **L2** were used, high conversions into the desired product **4a** were observed (85 and 95% yields, respectively) with moderate enantioselectivity (ee's 72 and 71%, respectively, Table 2, entries 2 and 3). Furthermore, when (*R*)-DM-BINAP **L3** was employed, the corresponding γ-amino alcohol (*R*)-**4a** was formed in excellent conversion (95%) and ee (97%, Table 2, entry 4). The absolute configuration was determined by X-ray crystallography of the corresponding 1,3-oxazine derived from **4a**

Table 2. Enantioselective β-Boration of Cinnamaldehyde **2** through the Imine Intermediate **2a**[a]



entry	L	conv (%)[b] **4a**	IY(%) **4a**	ee (%)[c]
1	PPh_3	99	62	–
2	**L1**	85	53	72 (*R*)
3	**L2**	95	64	71 (*R*)
4	**L3**	95	50	97 (*R*)
5	**L4**	95	45	80 (*R*)
6	**L5**	95	86	58 (*R*)
7	**L6**	27	–	97 (*R*)

[a] A 0.50 mmol scale reaction: 2.00 mmol (1:1, amine/enal) were stirred in THF (8 mL) and 3 Å-MS (2.0 g) for 3–9 h (see Supporting Information for imine formation), after which a 2 mL aliquot was transferred to a Schlenk tube (under Ar) containing Cu(I) salt (3 mol %), PPh_3 (6 mol %) or diphosphine (3 mol %), NaOt-Bu (9 mol %), and B_2pin_2 (1.1 equiv). After 5 min, MeOH (2.5 equiv) was added to the solution, and the reaction was stirred for 16 h. $NaBH_4$ (1.50 mmol) was added, followed by the dropwise addition of MeOH (1 mL). The mixture was stirred for 3 h, followed by the removal of solvent under reduced pressure. THF (3 mL) was added to the resulting residue, followed by NaOH (0.30 mL, w/v 20%) and H_2O_2 (0.13 mL, w/v 35%), and the solution was heated to reflux for 1 h. The product was obtained after SiO_2 column chromatography. [b] Determined by ^1H NMR, with some percentage of substrate not transformed. [c] Determined by chiral HPLC on the resulting O/N diacetate (see Supporting Information).

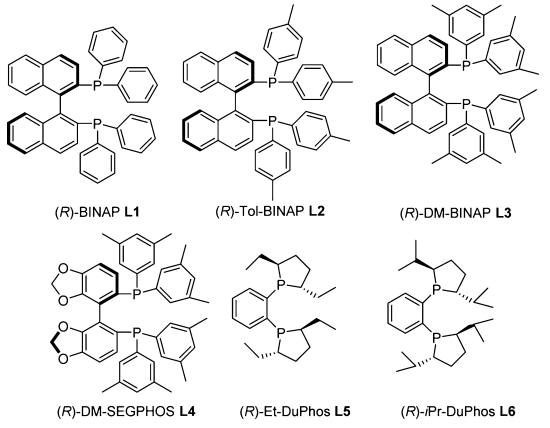
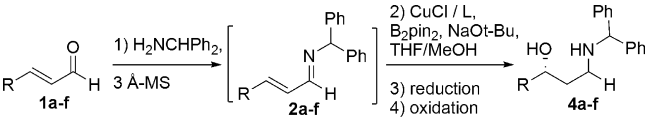


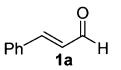
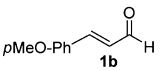
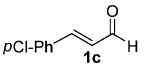
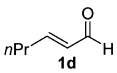
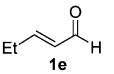
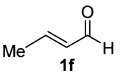
Figure 2. Chiral phosphine ligands, **L1**–**6**.

(see Figure 3). The use of a similar bidentate ligand (*R*)-DM-SEGPHOS **L4** with the CuCl catalyst also accomplished the formation of **4a** with high conversion but lower enantioselectivity (80% ee, Table 2, entry 5).

Chiral Et-DuPHOS **L5** and Pr-DuPHOS **L6** gave a spread of results depending on the bulky substituents, while the Cu(I)/Et-DuPHOS **L5** system provided high conversion but with the lowest ee (58%, Table 2, entry 6). In contrast, the Cu(I)/*i*-Pr-DuPHOS **L6** catalytic system

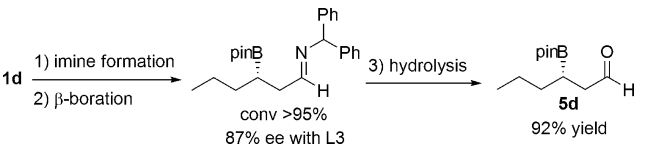
Table 3. Substrate Scope of the Enantioselective β-Boration of α,β-Unsaturated Aldehydes *in Situ* Condensed with Benzhydrylamine[a]



entry	substrate	L	conv **4**-(%)[b]	IY **4**-(%)	ee (%)[c]
1		PPh_3	95	62	---
		L3	95	50	97
2		PPh_3	95	61	---
		L3	95	90	90
3		PPh_3	95	71	---
		L3	95	59	90
4		PPh_3	95	50	---
		L3	95	59	87
5		PPh_3	79	42	---
		L3	95	65	76
6		PPh_3	95	78	---
		L3	95	88	80

[a] Same reaction conditions as those shown in Table 2. [b] Determined by ^1H NMR, with some percentage of substrate not transformed. [c] Determined by chiral HPLC on the resulting O/N diacetate (see Supporting Information).

Scheme 2. Access to Enantioenriched β-Boryl Aldehyde **5d** *via* Imine Hydrolysis



afforded a high ee (97%), but with low conversion (27%, Table 2, entry 7).

Due to the low cost and ready availability of the (*R*)-DM-BINAP **L3**, we applied the optimized one-pot reaction to a variety of enals with varying β-substituents (alkyl and aryl), as shown in Table 3. To our delight, substrates **1a**–**f** were transformed into the analogous γ-amino alcohols **4a**–**f** in excellent conversion and ee's, which were all readily determined by derivatization to the analogous O/N-diacetates.

In summary, we have reported an efficient and highly enantioselective route for the one-pot conversion of enals to γ-amino alcohols in up to 97% ee. The key to the success of this procedure is an *in situ* imine formation using a sufficiently sterically demanding amine to ensure complete

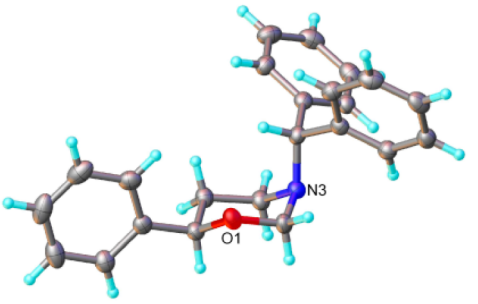


Figure 3. X-ray structure of the analogous 1,3-oxazine of **4a** used to determine the absolute stereochemistry.

chemoselectivity in the subsequent β-boration step. This novel and straightforward approach enables the use of enal-derived aldimines that had previously only undergone 1,2-boryl addition to now undergo selective 1,4-addition of the nucleophilic copper-boryl species. While this approach allows the subsequent transformation of the borylation products to γ-amino alcohols, this protocol also opens up the way for asymmetric borylation of unsaturated aldehydes by simple hydrolysis of the corresponding borylated aldimines. Further studies in this area will be reported in due course.

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Supporting Information Available. Full experimental details, characterization data for all products, ReactIR and X-ray crystallographic and CIF information. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.