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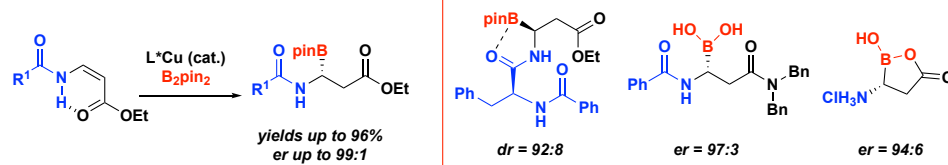
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Copper-Catalyzed Enantioselective Synthesis of β -Boron β -Amino Esters

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Abstract: In this report, the enantioselective, copper-catalyzed borylation of β -amidoacrylates is disclosed. A broad variety of biologically important α -aminoboronates has been prepared with consistently high levels of enantiocontrol, using an inexpensive copper catalyst and a commercially available chiral ligand. The method can be applied to the synthesis of novel boron-containing dipeptides and hemiboronates.

Chiral α -aminoboronic acids have become an important class of biologically active compounds, notably due to their use as proteasome inhibitors.^[1] The α -aminoboronic acid motif is present in the approved anticancer drugs bortezomib (Velcade®) and ixazomib (Ninlaro®) or in phase I/II candidates such as Delanzomib (Figure 1). Additionally, these structures have also been used as intermediates for the synthesis of enantiomerically enriched amines or amino alcohols.^[2]

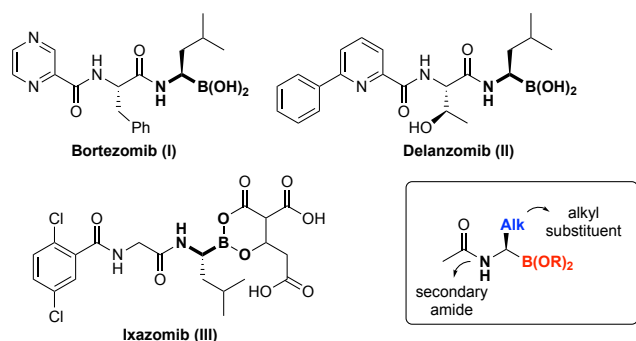
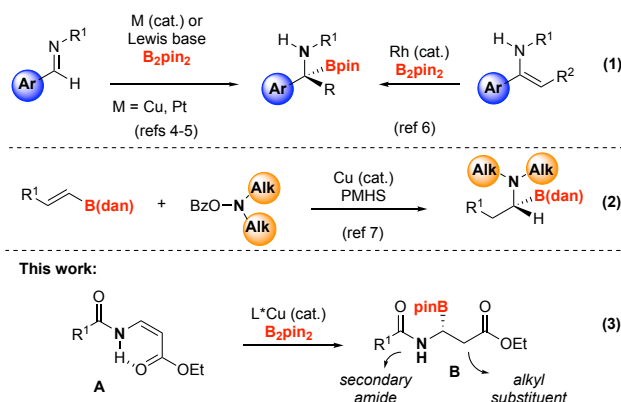


Figure 1. Biologically active α -aminoboronates

Despite their biological relevance and synthetic interest, the asymmetric synthesis of α -aminoboronates has been mostly based on diastereoselective methods that involve the use of stoichiometric amounts of chiral auxiliaries.^[3] Although a few effective catalytic methods have been reported, they still present structural limitations (Scheme 1). For instance, the metal-catalyzed^[4] and metal-free borylation^[5] of imines and enamines^[6] only allow the preparation of aryl-substituted α -aminoboronates (Scheme 1, eq 1). Alternatively, the copper-catalyzed hydroamination of alkenes overcomes this restriction, but only compounds with dialkylamino groups can be prepared (Scheme 1, eq 2).^[7] However, α -aminoboronates shown in Figure 1 have

two structural features in common: a secondary amide with an amino acid residue and an alkyl substituent α to the aminoboronate moiety. Therefore, we realized that the development of catalytic asymmetric methods to introduce these two structural motifs simultaneously remains an important unmet challenge.

Scheme 1. Enantioselective catalytic approaches to α -aminoboronates

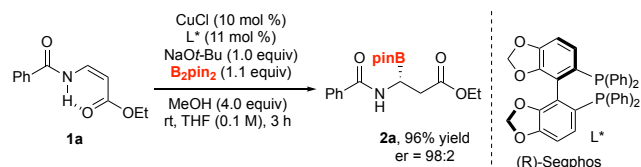


To address this task, we turned our attention to *Z*-enamides of type **A** as potential precursors of α -aminoboronates **B** through an enantioselective copper-catalyzed borylation (Scheme 1, eq 3). We reasoned that the hydrogen bond between the N-H and the carbonyl could provide a rigid template for the development of an effective asymmetric transformation. Additionally, *Z*-enamides can be easily prepared as single stereoisomers. The products would be a novel class of α -aminoboronates that contain the two structural motifs present in biologically active compounds: the secondary amide moiety and an alkyl substituent with a functional group susceptible to further functionalization. Moreover, from a biological point of view, they could also benefit from being β -amino acid derivatives.^[8] Importantly,

the transformation would represent the first copper-catalyzed borylation of a β -amidoacrylate.^{[9],[10]}

To test our hypothesis, we prepared enamide **1a** through palladium-catalyzed addition of benzamide to ethyl propiolate.^[11] We next examined the copper-catalyzed borylation^[12] of **1a** in the presence of a variety of chiral phosphines.^[13] Enamide **1a** was treated in THF, at room temperature, with CuCl (10 mol %), B₂pin₂ (1.1 equiv), NaOt-Bu (1 equiv), MeOH (4 equiv) and 11 mol % of a chiral ligand. After some optimization, we found that (*R*)-Segphos provided the highest yield and the best enantiomeric ratio (Scheme 2).

Scheme 2. Optimized copper-catalyzed borylation



One of the main challenges we encountered during the reaction optimization was the moderate stability of compound **2a** on silica gel. Although the ¹H NMR of the crude products showed clean conversion, **2a** was consistently obtained in low yields. Standard deactivation of the silica gel with trimethylamine did not work. After significant effort, we found that it was essential to deactivate the silica gel with 30 weight % of water to obtain high yields.

We next explored the scope of the method with different Z-enamides (Table 1). Aryl enamides with electron-donating (Table 1, entry 2) and electron-withdrawing groups in the *para*, *meta* and *ortho* positions (Table 1, entries 3-6) afforded α -aminoboronates **2b-2f** in high yields and excellent enantiomeric ratios. Heteroaromatic substituted enamides, with coordinating atoms such as sulfur and nitrogen, were also suitable substrates for the borylation. Importantly, alkyl amides such as **2i** and *N*-Boc protected α -aminoboronate **2j** could be also prepared with excellent stereoselectivity (Table 1, entries 9-10). Finally, we were pleased to find that this catalytic system also worked when we substituted the ester moiety for a peptide bond (Table 1, compounds **2k, 2l**).^[14] On the contrary, the enantiomeric excess dropped down significantly when ketones were tested. Finally, using 5 mol % of CuCl, we observed lower yields in most cases.

Next, we tested the present catalytic system with a more challenging substrate such as **1m** (Scheme 3), with a phenyl alanine fragment structurally close to the anticancer agent bortezomib **1** (Scheme 1). Using the standard reaction conditions and (*R*)-DM-Segphos as a chiral ligand, the borylated product **2m** was obtained with moderate dr,

Table 1. Substrate scope of Z-enamides **1**

entry ^[a]	product	er ^[b]	yield (%) ^[c]
1		98:2	96

2		96:4	77
3		96:4	68
4		95:5	71
5		96:4	76
6		91:9	69
7		95:5	76
8		96:4	60
9		94:6	67
10		97:3	49
11 ^[e]		>99:1	67
12 ^[d,e]		97:3	96

^[a] Reaction conditions: **1** (0.2 mmol), B₂pin₂ (0.22 mmol, 1.1 equiv), NaOt-Bu (1.0 equiv), CuCl (10 mol %), **L2** (11 mol %), MeOH (0.8 mmol, 4.0 equiv), THF (0.1 M).

^[b] The er was determined by chiral HPLC. ^[c] Isolated yield. ^[d] 1.5 equiv of B₂pin₂ was used. ^[e] The reaction time was 12 h.

revealing a possible mismatched scenario (Scheme 4). Indeed, the use of (*S*)-DM-Segphos, provided the matched diastereomer **2m'** with improved diastereomeric ratio.

Scheme 3. Synthesis of boron-containing dipeptides

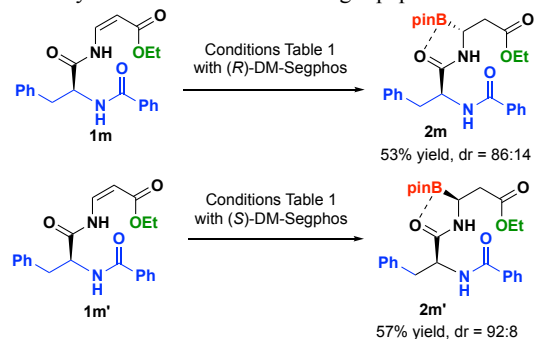


Table 2. Substrate scope of *E*-enamides **3**

entry ^[a]	product	er ^[b]	yield (%) ^[c]
1 ^[d]		96:4	68
2 ^[e]		95:5	70
3 ^[e]		95:5	65
4 ^[e]		92:8	56
5 ^[d]		95:5	73
6 ^[e]		91:9	70
7 ^[e,f]		95:5	65
8 ^[e]		91:9	59
9 ^[d]		91:9	38

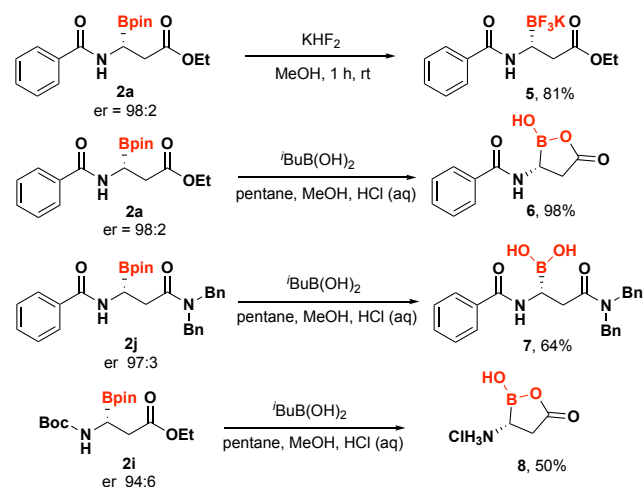
^[a] Reaction conditions: **3** (0.2 mmol), B₂pin₂ (0.22 mmol, 1.1 equiv), NaOt-Bu (1.0 equiv), CuCl (10 mol %), **L2** (11 mol %), MeOH (0.8 mmol, 4.0 equiv), THF (0.1 M).

^[b] The er was determined by chiral HPLC. ^[c] Yield of isolated **4**. ^[d] The reaction time was 4 h. ^[e] The reaction time was 12 h. ^[f] The reaction was performed at -20 °C.

We further expanded the scope of our method to *N*-Boc-protected *E*-enamides **3**, with an alkyl substituent and a removable protecting group on the nitrogen (Table 2). Gratifyingly, our catalytic system proved to be robust despite the significant structural changes. *N*-Boc protected benzylic (**4a-4b**) and heterobenzylic (**4c-4d**) derivatives were prepared in good yields and high enantiomeric ratio, with the opposite configuration at the aminoboro stereocenter compared to compounds **2**.^[15] Simple alkyl chains on the nitrogen (**4e**) as well as β-carboxylate groups (**4f**) were also tolerated. *E*-Enamides with a benzylic ester were also suitable substrates for the copper-catalyzed borylation, affording compounds **4g** and **4h** in good yields and high stereocontrol. Finally, α-aminoboronate **4i** was prepared in

moderate yield, showing that the benzoyl group on the nitrogen is less efficient for the *E*-enamide series

To provide compounds more suitable for biological applications, we removed the pinacol ester moiety (Scheme 4). Treatment of α-aminoboronate **2a** with KHF₂ afforded trifluoroborate salt **5** in excellent yield. Interestingly, hydrolysis of the pinacol boronic ester in **2a** resulted in formation of hemiboronate **6**. However, when the same hydrolysis conditions were applied to amide **2j**, boronic acid **7** was obtained in good yield. Importantly, *N*-Boc protected derivative **2i** was transformed into primary α-aminoboronate **8**.

Scheme 4. Removal of the pinacol ester

Finally, we performed DFT calculations to gain insight into the mechanism of the reaction and to account for the observed stereoselectivity (Figure 2). We started from Cu(I)-boryl complex **C**, using (*R*)-Segphos and (*S*)-Segphos as ligands, and enamide **E**. We introduced a methyl group at the enamide instead of an ethyl group to simplify the calculation. The reaction begins with the initial endothermic complexation of chiral copper-boryl complex **C** and enamide **E**. Two metal-η²-alkene complexes are initially formed, with **Complex-S** resulting slightly lower in energy than **Complex-R**. The borylation reaction is a highly exoergic (-26.9 kcal mol⁻¹) and, therefore, irreversible process (Figure 2). Consequently, the enantioselectivity of the process is kinetically controlled in the insertion step. Two transition states for the boryl cupration (**TS-R** and **TS-S**) were located and permitted the calculation of the corresponding activation energies for the formation of both enantiomers. Importantly, calculated **TS-R** showed a 9.7 Kcal mol⁻¹ lower energetic barrier than **TS-S** (Figure 2), consistent with the formation of the observed major enantiomer using ligand (*R*)-**L2**.^[16] Finally, once the C-B bond and the stereochemistry has been defined, the copper is stabilized forming a copper enolate. These results suggest the insertion as the rate-limiting step, as well as the enantiodetermining step.

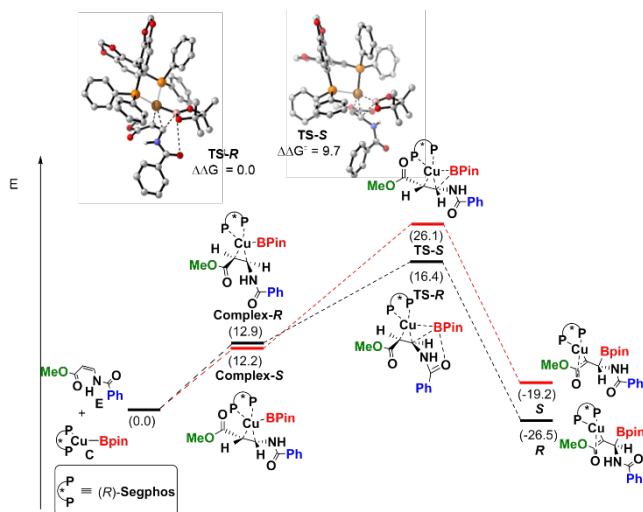


Figure 2. Energy profile for the enantioselective borylation process. M06-2X/6-31G(d,p)-cc-pVDZ-DK(Cu)-SMD(THF)//B3LYP/6-31G(d)-cc-pVDZ-DK(Cu)-SMD(THF). C-H bonds were omitted for clarity. All energies in kcal mol⁻¹. For more detail, see Supporting Information.

In summary, we have developed a novel catalytic approach for the preparation of enantiomerically enriched α -aminoboronates. Our method has proven to be general for a wide variety of substrates, including the preparation of boryl containing dipeptides, using an inexpensive copper catalyst and a commercially available chiral ligand. Biological studies of the prepared compounds are underway.

ASSOCIATED CONTENT

Experimental procedures, compound characterization data, analytic details for all enantiomerically enriched products and crystal structural data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

the authors declare no competing financial interest.

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REFERENCES

- [1] a) Andres, P.; Ballano, G.; Calaza, M. I.; Cativiela, C. *Chem. Soc. Rev.* **2016**, *45*, 2291. b) Gentile, M.; Offidani, M.; Vigna, E.; Corvatta, L.; Recchia, A. G.; Morabito, L.; Morabito, F.; Gentili, S. *Expert Opin. Invest. Drugs* **2015**, *24*, 1287. c) Gozhina, O. V.; Svendsen, J. S.; Lejon, T. J. *Pept. Sci.* **2014**, *20*, 20. d) Rentsch, A.; Landsberg, D.; Brodmann,

- T.; Buelow, L.; Girbig, A.-K.; Kalesse, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 5450. e) Das, B. C.; Thapa, P.; Karki, R.; Schinke, C.; Das, S.; Kambhampati, S.; Banerjee, S. K.; Van Veldhuizen, P.; Verma, A.; Weiss, L. M.; Evans, T. *Future Med. Chem.* **2013**, *5*, 653. f) Roemmele, R. C.; Christie, M. A. *Org. Process Res. Dev.* **2013**, *17*, 422. g) Gallerani, E.; Zucchetti, M.; Brunelli, D.; Marangon, E.; Noberasco, C.; Hess, D.; Delmonte, A.; Martinelli, G.; Böhm, S.; Driessen, C.; De Braud, F.; Marsoni, S.; Cereda, R.; Sala, F.; D'Incalci, M.; Sessa, C. *Eur. J. Cancer* **2013**, *49*, 290. h) Smoum, R.; Rubinstein, A.; Dembitsky, V. M.; Srebnik, M. *Chem. Rev.* **2012**, *112*, 4156. i) Dick, L. R.; Fleming, P. E. *Drug Discovery Today* **2010**, *15*, 243. j) Gracia, S. R.; Gaus, K.; Sewald, N. *Future Med. Chem.* **2009**, *1*, 1289.
- [2] a) Ohmura, T.; Awano, T.; Sugimoto, M. *J. Am. Chem. Soc.* **2010**, *132*, 13191. b) Awano, T.; Ohmura, T.; Sugimoto, M. *J. Am. Chem. Soc.* **2011**, *133*, 20738. c) Buesking, A. W.; Ellman, J. A. *Chem. Sci.* **2014**, *5*, 1983.
- [3] a) Matteson, D. S.; Sadhu, K. M. *J. Am. Chem. Soc.* **1981**, *103*, 5241. b) Beenen, M. A.; An, C.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 6910. c) Buesking, A. W.; Bacauanu, V.; Cai, I.; Ellman, J. A. *J. Org. Chem.* **2014**, *79*, 3671. d) Xie, J.-b.; Luo, J.; Winn, T. R.; Cordes, D. B.; Li, G. *Beilstein J. Org. Chem.* **2014**, *10*, 746. e) He, Z.; Zajdlík, A.; Denis, J. D. St.; Assem, N.; Yudin, A. K. *J. Am. Chem. Soc.* **2012**, *134*, 9926. f) Zajdlík, A.; Wang, Z.; Hickey, J. L.; Aman, A.; Schimmer, A. D.; Yudin, A. K. *Angew. Chem. Int. Ed.* **2013**, *52*, 8411.
- [4] a) Hong, K.; Morken, J. P. *J. Am. Chem. Soc.* **2013**, *135*, 9252. b) Zhang, S. S.; Zhao, Y.-S.; Tian, P.; Lin, G.-Q. *Synlett* **2013**, *24*, 437. c) Wang, D.; Cao, P.; Wang, B.; Jia, T.; Lou, Y.; Wang, M.; Liao, J. *Org. Lett.* **2015**, *17*, 2420.
- [5] Sole, C.; Gulyas, H.; Fernández, E. *Chem. Commun.* **2012**, *48*, 3769.
- [6] Hu, N.; Zhao, G.; Zhang, Y.; Liu, X.; Li, G.; Tang, W. *J. Am. Chem. Soc.* **2015**, *137*, 6746.
- [7] Nishikawa, D.; Hirano, K.; Miura, M. *J. Am. Chem. Soc.* **2015**, *137*, 15620.
- [8] Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219.
- [9] For representative examples of enantioselective 1,4 copper-catalyzed borylations: a) Hornillos, V.; Vila, C.; Otten, E.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2015**, *54*, 7867. b) Kobayashi, S.; Xu, P.; Endo, T.; Ueno, M.; Kitanosono, T. *Angew. Chem. Int. Ed.* **2012**, *51*, 12763. c) Molander, G. A.; Wisniewski, S. R.; Hosseine-Sarvari, M. *Adv. Synth. Catal.* **2013**, *355*, 3037. d) Burns, A. R.; Gonzalez, J. S.; Lam, H. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 10827. e) Moure, A. L.; Gomez Arrayas, R.; Carretero, J. C. *Chem. Commun.* **2011**, *47*, 6701. f) Lee, J. C.; McDonald, R.; Hall, D. G. *Nat. Chem.* **2011**, *3*, 894. g) Fernandez, E.; Gulyas, H.; Sole, C.; Mata, J. A.; Tatla, A.; Whiting, A. *Chem. Eur. J.* **2011**, *17*, 14248. h) O'Brien, J. M.; Lee, K.-S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10630. i) Chen, I.-H.; Yin, L.; Itano, W.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 11664. j) Lillo, V.; Prieto, A.; Bonet, A.; Diaz-Requejo, M. M.; Ramirez, J.; Perez, P. J.; Fernandez, E. *Organometallics* **2009**, *28*, 659. k) Lee, E.; Yun, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 145.
- [10] During the preparation of this manuscript, Xu *et al.* reported a related transformation (published online June 21, 2017): Chen, L.; Zou, X.; Zhao, H.; Xu, S. *Org. Lett.* **2017**, *19*, 3676. Most of the examples reported by Xu contain α -aminoboronates with disubstitution on the nitrogen. However, our catalytic system is general for the preparation of α -aminoboronates that contain a secondary amide, which is an important feature in biologically active compounds. Both methods are, therefore, complementary.
- [11] Panda, N.; Mothkuri, R. *J. Org. Chem.* **2012**, *77*, 9407.
- [12] For our previous work on copper-catalyzed borylations, see: a) Guisan-Ceinos, M.; Parra, A.; Martin-Heras, V.; Tortosa, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 6969. b) Jarava-Barrera, C.; Parra, A.; López, A.; Cruz-Acosta, F.; Collado-Sanz, D.; Cárdenas, D. J.; Tortosa, M. *ACS Cat.* **2016**, *6*, 442. c) Parra, A.; Amenós, L.; Guisan-Ceinos, M.; López, A.; Garcia-Ruano, J. L.; Tortosa, T. *J. Am. Chem. Soc.* **2014**, *136*, 15833. d) Alfaro, R.; Parra, A.; Alemán, J.; Garcia-Ruano, J. L.;

Tortosa, M. *J. Am. Chem. Soc.* **2012**, *134*, 15165. e) Tortosa, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 3950.

[13] See Supporting Information for details.

[14] CCDC 1514307 contains the supplementary crystallographic data for compound **2b**. The crystal structure of **2b** shows a dative bond between the carbonyl oxygen of the amide and the boron atom. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html.

[15] The absolute configuration for the *E*-enamide series was established for compound **4l** by comparison of its optical rotation with that of the product of benzylation of **2a**. See Supporting Information for details.

[16] For a stereochemical model see Supporting Information.