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Catalytic asymmetric hydrogenation of (*Z*)-α-dehydroamido boronate esters: direct route to alkyl-substituted α-amidoboronic esters†

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The direct catalytic asymmetric hydrogenation of (*Z*)-α-dehydroamino boronate esters was realized. Using this approach, a class of therapeutically relevant alkyl-substituted α-amidoboronic esters was easily synthesized in high yields with generally excellent enantioselectivities (up to 99% yield and 99% ee). The utility of the products has been demonstrated by transformation to their corresponding boronic acid derivatives by a Pd-catalyzed borylation reaction and an efficient synthesis of a potential intermediate of bortezomib. The clean, atom-economic and environment friendly nature of this catalytic asymmetric hydrogenation process would make this approach a new alternative for the production of alkyl-substituted α-amidoboronic esters of great potential in the area of organic synthesis and medicinal chemistry.

Since FDA approval of bortezomib[1] for the treatment of multiple myeloma, chiral α-aminoboronic acids have been recognized as key pharmacophores for the design of proteasome inhibitors.[2] The incorporation of chiral α-aminoboronic acid motifs at the C-terminal position of a peptide[3] to develop potential clinical drug candidates has drawn increasing interest[4] (Fig. 1). Meanwhile, chiral α-amidoboronic acids and their derivatives are useful synthetic building blocks for the stereospecific construction of chiral amine compounds.[5] The biological and synthetic value of α-amidoboronates has led to considerable efforts for the development of efficient synthetic methods. However, up to now, limited transition-metal-catalyzed asymmetric approaches have been reported. The widely used strategies to synthesize these compounds are stepwise Matteson homologation/N-nucleophilic replacement,[6] borylation of imines,[7] and alkene functionalization.[8] Recently, two other elegant approaches, Ni-catalyzed decarboxylative borylation of α-amino acid derivatives[9] and enantiospecific borylation of lithiated α-N-Boc species,[10] were reported by the Baran and Negishi groups, respectively. To the best of our knowledge, the majority of the methods relied on either stoichiometric amounts of chiral auxiliaries[6,7a,b] or substrate-control strategies[9] and most of these methods enable the construction of aryl-substituted α-aminoboronates. Enantioselective methods to access unfunctionalized alkyl-substituted α-aminoboronic esters are still rarely developed and so far only two examples have been realized by the Miura[8a] and Scheidt[7f] groups, respectively. Considering that most therapeutically relevant α-amidoboronic acid fragments contain an alkyl subunit and the fact that the options for the synthesis of alkyl-substituted α-amidoboronic esters in an enantioselective manner are still rare, the development of other distinct approaches would be highly desirable. Herein, we report a new alternative to access these compounds by catalytic asymmetric hydrogenation of (*Z*)-α-dehydroamidoboronate esters. With this approach, the desired chiral alkyl-substituted α-amidoboronic esters could be obtained in high yields and generally excellent enantioselectivities (up to 99% yield and 99% ee) with simple purification.

Catalytic asymmetric hydrogenation of olefins is an atom-economic, environmentally friendly and clean process for the

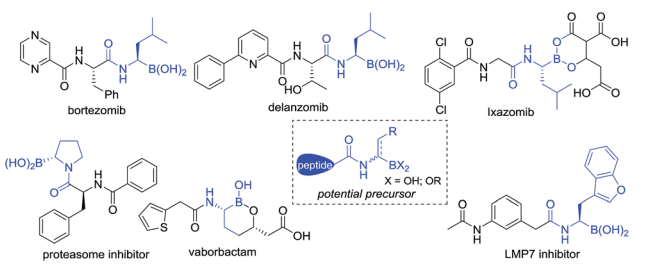

Fig. 1 Selected inhibitors containing chiral alkyl-substituted α-amidoboronic acids.

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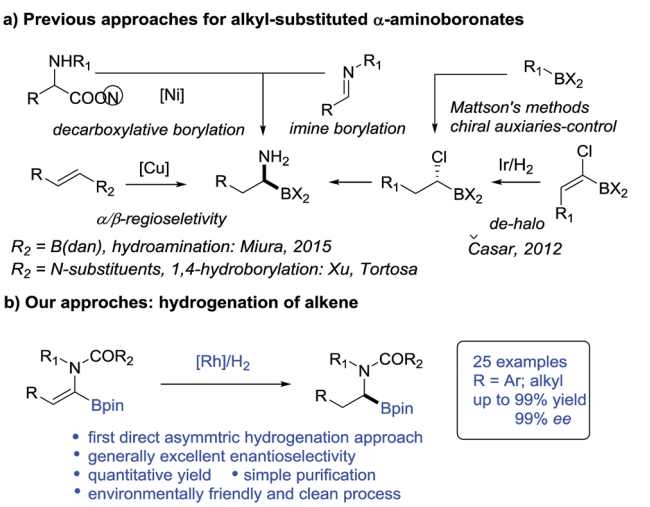
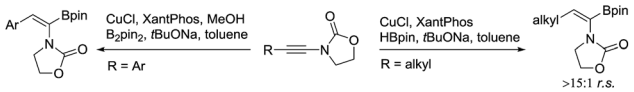
synthesis of valuable pharmaceuticals, agricultural compounds and feedstock chemicals.[11] Recently, hydrogenation of vinylboronic compounds has emerged for the preparation of chiral boronic compounds in a regiodefined manner.[12,13] However, surprisingly α-dehydroamido boronate esters and their derivatives, as elegant precursors to access alkyl-substituted α-amidoboronic compounds, have never been used as substrates in asymmetric hydrogenation and remain a challenging project. To our knowledge, only one efficient hydrogenation approach to (1-halo-1-alkenyl) boronic esters was reported for indirect synthesis of alkyl-substituted α-aminoboronic esters but it was accompanied by inevitable de-halogenated by-products[14] (Scheme 1). Given the catalytic efficiency and atom economy of the hydrogenation method, the development of a new direct hydrogenation approach to construct these important chiral alkyl-substituted α-amidoboronic esters would be very appealing.

The inspiration for our approach to the hydrogenation of α-dehydroamido boronates came from the molecular structures of relevant biologically active inhibitors containing alkyl-substituted α-amidoboronic acid fragments. Due to the limited stability of free α-aminoboronic acids, an electron-withdrawing carboxylic N-substituent is often required.[15] Thus, we envisaged that *N*-carboxyl protected α-dehydroamido boronate esters could serve as a potential precursor for the synthesis of alkyl-substituted α-amidoboronates through Rh-catalyzed asymmetric hydrogenation of the C=C bond[16] (Fig. 1), a strategically distinct approach to the construction of unfunctionalized alkyl-substituted α-amidoboronic esters. However, challenges still remain, including: (1) how to synthesize α-dehydroamido boronates; (2) the facile transmetalation process of the starting materials leading to deboronated by-products in the hydrogenation process;[17] (3) the unknown stability of α-amidoboronic compounds in the presence of a transition-metal catalyst and hydrogen molecules. As part of our continuous efforts to develop efficient hydrogenation approaches to construct valuable motifs,[18] here we present the results of the investigation to address the aforementioned challenges.



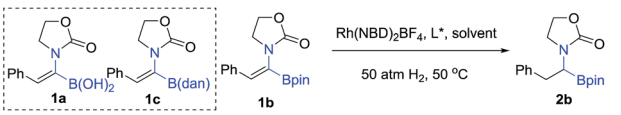
Scheme 1 Approaches towards the synthesis of chiral alkyl-substituted α-aminoboronic esters.



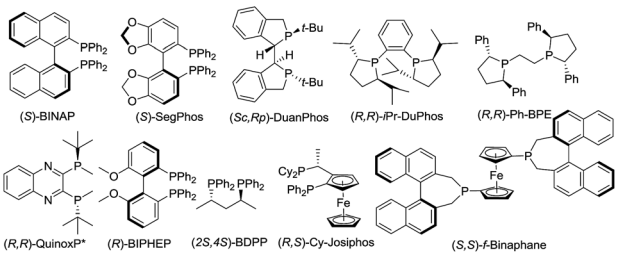
Scheme 2 Synthetic route to (*Z*)-α-dehydroamino boronates.

The desired aryl-substituted (*Z*)-α-dehydroamido boronates could be obtained by Cu-catalyzed regioselective hydroborylation of ynamide according to a previous report.[19] However, different α/β-regioselectivity was observed for the preparation of alkyl-substituted (*Z*)-α-dehydroamido boronate esters and a new synthetic route was developed (Scheme 2, see the ESI† for details). Of note, (*Z*)-α-dehydroamido boronate esters should be purified with deactivated silica gel,[7c] or else protodeborylation would occur readily with flash chromatography.

Table 1 Condition optimization for catalytic asymmetric hydrogenation of **1**[a]



Entry	Sub	Ligand	Conv.[b] (%)	ee[c] (%)
1[d]	**1a**	(*Rc*,Sp)-*DuanPhos*	89	n.d.
2[e]	**1b**	(*Rc*,Sp)-DuanPhos	>99	98
3	**1c**	(*Rc*,Sp)-DuanPhos	n.r.	n.d.
4	**1b**	(*R*,*R*)-QuinoxP*	>99	97
5	**1b**	(*S*)-SegPhos	>99	17
6	**1b**	(*S*)-BINAP	>99	10
7	**1b**	(*R*,*R*)-^{i}Pr-DuPhos	>99	3
8	**1b**	(*R*,*S*)-Cy-JosiPhos	>99	14
9	**1b**	(*R*)-BIPHEP	>99	−30
10	**1b**	(*R*,*R*)-Ph-BPE	>99	−86
11	**1b**	(*S*,*S*)-*f*-Binaphane	>99	61
12	**1b**	(2*S*,4*S*)-BDPP	>99	59
13[e,f,g]	**1b**	(*Rc*,Sp)-DuanPhos	>99(99)	99

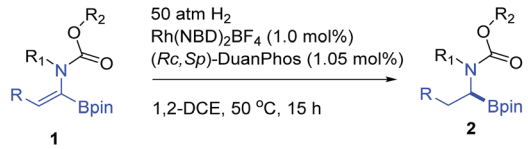


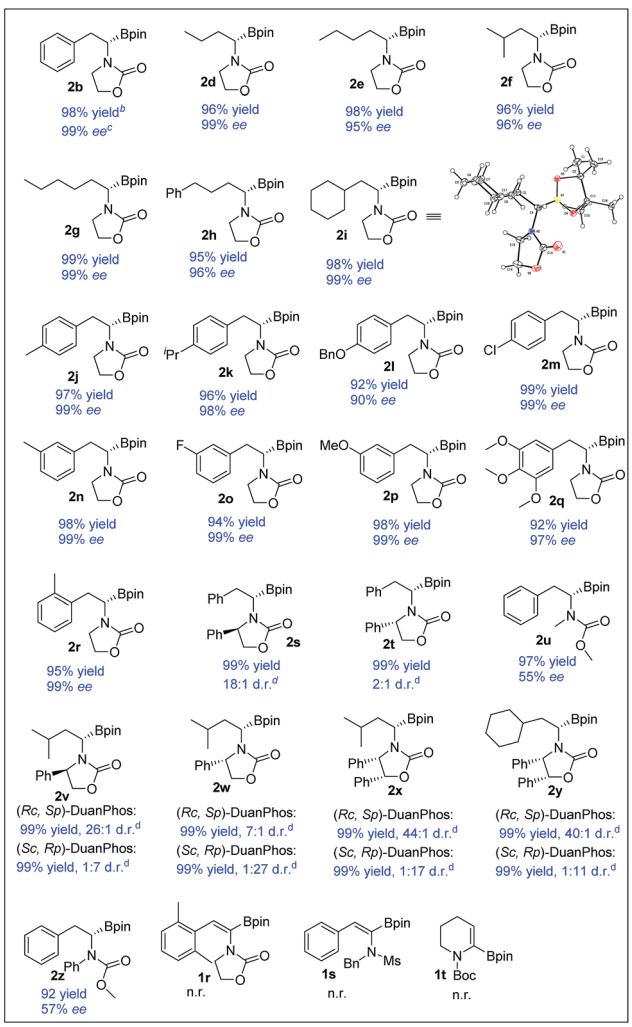
[a] Unless otherwise mentioned, the reactions were performed with **1** (0.1 mmol), $Rh(NBD)_2BF_4$ (10 mol%), and a ligand (11 mol%) in 1.0 mL THF at 50 °C for 15 h. [b] Determined by crude ^{1}H NMR. [c] Determined with chiral HPLC. [d] The reaction was performed in ^{i}PrOH. [e] $Rh(NBD)_2BF_4$ (1.0 mol%) and ligand (1.05 mol%) were used. [f] Isolated yield in parentheses. [g] 1,2-DCE was used as the solvent. Pin = 2,3-dimethyl-2,3-butanediol; dan = 1,8-diaminonaphthalene.

In order to check the feasibility of our hypothesis, three substrates were prepared with $Rh(NBD)_2BF_4$ and examined and our group prepared (*Rc*,*Sp*)-DuanPhos under 50 atm hydrogen pressure (Table 1). Gratifyingly, substrate **1b** reacted smoothly to provide the desired product **2b** in high yield and enantioselectivity (>99% conv., 98% ee, entry 2) whilst the reaction with substrate **1a** yielded a mixture of deborylation products and **1c** did not work at all (entries 1 and 3). Of note, we did not observe deborylation products with **1b** under the current reaction conditions and we did not select (*Z*)-α-dehydroamido boronic acid **1a** as the model substrate because of its poor solubility in most solvents. Then, a variety of chiral diphosphine ligands were investigated along with $Rh(NBD)_2BF_4$ and the results are shown in Table 1. In most cases, the reaction proceeded smoothly to furnish the desired products and the best results were obtained when (*Rc*,*Sp*)-DuanPhos was used as the ligand (entries 2 and 4–12). Poor results were obtained with axially bidentate phosphine ligands (entries 5, 6 and 9). (*R*,*R*)-QuinoxP* and (*R*,*R*)-Ph-BPE also gave good conversion with a slightly decreased ee whilst (*R*,*R*)-^{i}Pr-DuPhos exhibited poor results (entries 4, 7 and 10). Subsequent solvent screening revealed that the desired products could be obtained in most of the solvents and 1,2-DCE was the best solvent. (Entry 13, see the ESI†).

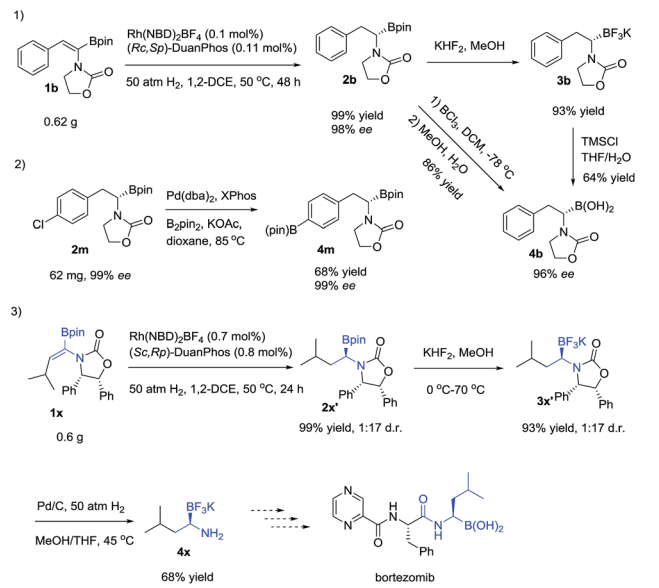
With the optimized reaction conditions in hand, a series of (*Z*)-α-dehydroamido boronate esters were tested and the results are summarized in Table 2. All the substrates reacted smoothly to give the corresponding alkyl-substituted α-amidoboronates in high yields with good to excellent enantioselectivities (**2b**, **2d–2r**, and **2u**, 99% yield, 57–99% ee). Alkyl-substituted (*Z*)-α-dehydroamido boronate esters were well tolerated in the current reaction, providing the corresponding α-amidoboronates in high yields and excellent enantioselectivities (**2d–2i**, 99% yield, 96–99% ee). Aryl-substituted (*Z*)-α-dehydroamido boronate esters with electron-donating (**2j–l**, **2n** and **2p–r**) and withdrawing (**2m** and **2o**) substituents could also give the desired products in excellent yield with excellent enantioselectivities (90–99% ee). The *ortho*-methyl-substituted substrate **1r** reacted smoothly to give the desired product with excellent enantioselectivity, but the 2,6-dimethyl-substituted substrate **1z** could not react at all. Functional groups such as ether, halo and benzyl were well tolerated in the current reaction (**2k**, **2l**, **2m** and **2o–q**). Replacement of the N-substituents with acyclic carbamate was also tolerated but with a decreased ee (**2u** and **2z**). Substrates containing a chiral oxazolidin-2-one unit bearing bulky Ph-substituents around the nitrogen and oxygen were also

Table 2 Substrate scope.[a,b,c]





[a] Unless otherwise mentioned, the reactions were performed with **1** (0.1 mmol), $Rh(NBD)_2BF_4$ (1.0 mol%), and a ligand (1.05 mol%) in 1.0 mL 1,2-DCE at 50 °C under 50 atm H_2 for 15 h. [b] Isolated yield. [c] Determined with chiral HPLC. [d] Determined by crude ^{1}H NMR.



Scheme 3 Scale-up synthesis and synthetic utility.

competent, yielding the desired products with good to excellent diastereoselectivities (**2s**, **2t**, and **2v–y**). Of note, the substrate **1s** bearing an N-Ms substituent and the cyclic substrate **1t** did not work in the current reaction. The absolute configuration of generated α-amidoboronates was assigned as (*S*) by X-ray crystallographic analysis of **2i** (Scheme 3).[20]

To demonstrate the utility of the products, a scale-up reaction (0.62 g) was successfully performed with 0.1 mol% catalytic loading, giving **2b** in 99% yield and 98% ee, and **2b** could be easily transformed to a more stable α-amidoborate **3b** with KHF_2,[6d,21] followed by hydrolysis with TMSCl to yield α-amido boronic acid **4b** in 46% yield,[22] which could also be obtained from **2b** by treating it with BCl_3 in 84% yield, without loss of the optical purity.[8b] **2m** could easily be transformed to **4m** in 68% yield by a Pd-catalyzed borylation reaction. Meanwhile, after hydrogenation of **1x** to **2x′** and transformation of **2x′** to its trifluoroborate derivative **3x′**, removal of the benzyl group of **3x′** with Pd/C under hydrogenation conditions[23] yielded the primary α-aminoborate **4x** in 62% yield in three steps, which could serve as a potential precursor[15] to synthesize bortezomib.

Conclusions

In summary, we have presented a strategically distinct alternative for the direct synthesis of chiral alkyl-substituted α-amidoboronates by Rh-catalyzed asymmetric hydrogenation. A series of (*Z*)-α-dehydroamido boronate esters could be hydrogenated to the corresponding alkyl-substituted α-amidoboronic esters in excellent yields with generally excellent enantioselectivities. The boronic acid derivatives and the potential precursor of bortezomib could be facilely obtained with this approach. Additional asymmetric transformations of the alkyl-substituted α-amidoboronates are underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 (*a*) R. C. Kane, P. F. Bross, A. T. Farrell and R. Pazdur, *Oncologist*, 2003, **8**, 508; (*b*) J. Adams and M. Kauffman, *Cancer Invest.*, 2004, **22**, 304; (*c*) R. C. Kane, R. Dagher, A. Farrell, C.-W. Ko, R. Sridhara, R. Justice and R. Pazdur, *Clin. Cancer Res.*, 2007, **13**, 5291.

2 Selected reviews, see: (*a*) L. R. Dick and P. E. Fleming, *Drug Discovery Today*, 2010, **15**, 243; (*b*) S. J. Baker, J. W. Tomsho and S. J. Benkovic, *Chem. Soc. Rev.*, 2011, **40**, 4279; (*c*) W. Yang, X. Gao and B. Wang, *Med. Res. Rev.*, 2003, **23**, 346.

3 (*a*) M. D. Valery, Q. Abed Al Aziz and S. Morris, *Mini-Rev. Med. Chem.*, 2004, **4**, 1001; (*b*) D. S. Matteson, *Med. Res. Rev.*, 2008, **28**, 233; (*c*) L. J. Milo, J. H. Lai, W. Wu, Y. Liu, H. Maw, Y. Li, Z. Jin, Y. Shu, S. E. Poplawski, Y. Wu, D. G. Sanford, J. L. Sudmeier and W. W. J. Bachovchin, *Med. Chem.*, 2011, **54**, 4365; (*d*) N. Micale, K. Scarbaci, V. Troiano, R. Ettari, S. Grasso and M. Zappalá, *Med. Res. Rev.*, 2014, **34**, 1001.

4 Selected reviews and examples, see: (*a*) S. J. Baker, C. Z. Ding, T. Akama, Y.-K. Zhang, V. Hernandez and Y. Xia, *Future Med. Chem.*, 2009, **1**, 1275; (*b*) L. Han, Y. Wen, R. Li, B. Xu, Z. Ge, X. Wang, T. Cheng, J. Cui and R. Li, *Bioorg. Med. Chem.*, 2017, **25**, 4031; (*c*) K. Markus, H. Oliver, H. Philipp and B. Michaul, PCT Int. Appl., WO 2016050359 A1, 2016; (*d*) B. D. Dorsey, M. Iqbal, S. Chatterjee, E. Menta, R. Bernardini, A. Bernareggi, P. G. Cassarà, G. D. Arasmo, E. Ferretti, S. D. Munari, A. Oliva, G. Pezzoni, C. Allievi, I. Strepponi, B. Ruggeri, M. A. Ator, M. Williams and J. P. Mallamo, *J. Med. Chem.*, 2008, **51**, 1068; (*e*) B. A. Teicher and J. E. Tomaszewski, *Biochem. Pharmacol.*, 2015, **96**, 1; (*f*) A. Rentsch, D. Landsberg, T. Brodmann, L. Bülow, A. Girbig and M. Kalesse, *Angew. Chem., Int. Ed.*, 2013, **52**, 5450; (*g*) D. Chauhan, Z. Tian, B. Zhou, D. Kuhn, R. Orlowski, N. Raje, P. Richardson and K. C. Anderson, *Clin. Cancer Res.*, 2011, **17**, 5311.

5 (*a*) T. Awano, T. Ohmura and M. Suginome, *J. Am. Chem. Soc.*, 2011, **133**, 20738; (*b*) T. Ohmura, T. Awano and M. Suginome, *J. Am. Chem. Soc.*, 2010, **132**, 13191; (*c*) T. Ohmura, T. Awano and M. Suginome, *Chem. Lett.*, 2009, **38**, 664; (*d*) T. Ohmura, K. Miwa, T. Awano and M. Suginome, *Chem.—Asian J.*, 2018, **13**, 2414.

6 Reviews and selected examples, see: (*a*) D. S. Matteson, *Chem. Rev.*, 1989, **89**, 1535; (*b*) D. S. Matteson, *Acc. Chem. Res.*, 1988, **21**, 294; (*c*) D. S. Matteson and M. Debesh, *J. Am. Chem. Soc.*, 1980, **102**, 7588; (*d*) D. S. Matteson and K. M. Sadhu, *J. Am. Chem. Soc.*, 1981, **103**, 5241.

7 (*a*) M. A. Beenen, C. An and J. A. Ellman, *J. Am. Chem. Soc.*, 2008, **130**, 6910; (*b*) A. W. Buesking, V. Bacauanu, I. Cai and J. A. Ellman, *J. Org. Chem.*, 2014, **79**, 3671; (*c*) K. Hong and J. P. Morken, *J. Am. Chem. Soc.*, 2013, **135**, 9252; (*d*) S. Zhang, Y. Zhao, P. Tian and G. Lin, *Synlett*, 2013, **4**, 437; (*e*) D. Wang, P. Cao, B. Wang, T. Jia, Y. Lou, M. Wang and J. Liao, *Org. Lett.*, 2015, **17**, 2420; (*f*) C. B. Schwamb, K. P. Fitzpatrick, A. C. Brueckner, H. C. Richardson, P. H. Cheong and K. A. Scheidt, *J. Am. Chem. Soc.*, 2018, **140**, 10644.

8 (*a*) D. Nishikawa, K. Hirano and M. Miura, *J. Am. Chem. Soc.*, 2015, **137**, 15620; (*b*) N. Hu, G. Zhao, Y. Zhang, X. Liu, G. Li and W. Tang, *J. Am. Chem. Soc.*, 2015, **137**, 6746; (*c*) L. Chen, X. Zou, H. Zhao and S. Xu, *Org. Lett.*, 2017, **19**, 3676; (*d*) A. López, T. B. Clark, A. Parra and M. Tortosa, *Org. Lett.*, 2017, **19**, 6272; (*e*) L. Chen, J.-J. Shen and S. Xu, *Chem. Sci.*, 2018, **9**, 5855.

9 C. Li, J. Wang, L. M. Barton, S. Yu, M. Tian, D. S. Peters, M. Kumar, A. W. Yu, K. A. Johnson, A. K. Chatterjee, M. Yan and P. S. Baran, *Science*, 2017, **356**, 1045.

10 Q. Qi, X. Yang, X. Fu, S. Xu and E. Negishi, *Angew. Chem., Int. Ed.*, 2018, **57**, 15138.

11 Selected reviews and examples, see: (*a*) F. Glorius, *Org. Biomol. Chem.*, 2005, **3**, 4171; (*b*) S. Werkmeister, J. Neumann, K. Junge and M. Beller, *Chem.–Eur. J.*, 2015, **21**, 12226; (*c*) T. Zell and D. Milstein, *Acc. Chem. Res.*, 2015, **48**, 1979; (*d*) J.-H. Xie, S.-F. Zhu and Q.-L. Zhou, *Chem. Rev.*, 2011, **111**, 1713; (*e*) Y.-G. Zhou, *Acc. Chem. Res.*, 2007, **40**, 1357; (*f*) R. H. Morris, *Acc. Chem. Res.*, 2015, **48**, 1494; (*g*) Z. Zhang, N. A. Butt and W. Zhang, *Chem. Rev.*, 2016, **116**, 14769; (*h*) W. Liu, B. Sahoo, K. Junge and M. Beller, *Acc. Chem. Res.*, 2019, **51**, 1858.

12 Rh-catalysed asymmetric hydrogenation of vinylboronic compounds, see: (*a*) J. B. Morgan and J. P. Morken, *J. Am. Chem. Soc.*, 2004, **126**, 15338; (*b*) W. J. Moran and J. P. Morken, *Org. Lett.*, 2006, **8**, 2413; (*c*) G. Liu, A. Li, X. Qin, Z. Han, X.-Q. Dong and X. Zhang, *Adv. Synth. Catal.*, 2019, **361**, 2844. Ni-catalysed example: Z. Han, G. Liu, X. Zhang, A. Li, X.-Q. Dong and X. Zhang, *Org. Lett.*, 2019, **21**, 3923.

13 Ir-catalyzed asymmetric hydrogenation of vinylboronic compounds, see: (*a*) A. Ganić and A. Pfaltz, *Chem.–Eur. J.*, 2012, **18**, 6724; (*b*) A. Paptchikhine, P. Cheruku, M. Engman and P. G. Andersson, *Chem. Commun.*, 2009, **45**, 5996.

14 (*a*) I. G. Smilović, E. Casas-Arcé, S. J. Roseblade, U. Nettekoven, A. Zanotti-Gerosa, M. Kovačevič and Z. Časar, *Angew. Chem., Int. Ed.*, 2012, **51**, 1014; (*b*) S. J. Roseblade, I. G. Smilović and Z. Časar, *Tetrahedron*, 2014, **70**, 2654; (*c*) S. J. Roseblade, E. Casas-Arcé, U. Nettekoven, I. G. Smilović, A. Zanotti-Gerosa and Z. Časar, *Synthesis*, 2013, **45**, 2824.

15 S. Touchet, F. Carreaux, G. A. Molander, B. Carboni and A. Bouillon, *Adv. Synth. Catal.*, 2011, **353**, 3391.

16 C. R. Landis and J. Halpern, *J. Am. Chem. Soc.*, 1987, **109**, 1746.

17 (*a*) G. He, Q. Zhang, H. Huang, S. Chen, Q. Wang, D. Zhang, R. Zhang and H. Zhu, *Eur. J. Org. Chem.*, 2013, 6979; (*b*) E. M. Simmons, B. Mudryk, A. G. Lee, Y. Qiu, T. M. Razler and Y. Hsiao, *Org. Process Res. Dev.*, 2017, **21**, 1659.

18 Selected reviews and examples, see: (*a*) W. Zhang, Y. Chi and X. Zhang, *Acc. Chem. Res.*, 2007, **40**, 1278; (*b*) G.-Q. Chen, B.-J. Lin, J.-M. Huang, L.-Y. Zhao, Q.-S. Chen, S.-P. Jia, Q. Yin and X. Zhang, *J. Am. Chem. Soc.*, 2018, **140**, 8064; (*c*) X. Tan, S. Gao, W. Zeng, S. Xin, Q. Yin and X. Zhang, *J. Am. Chem. Soc.*, 2018, **140**, 2024.

19 Here, an incorrect Cu-catalyzed regioselective hydroborylation of alkyl-substituted ynamides was observed in the reference: G. He, S. Chen, Q. Wang, H. Huang, Q. Zhang, D. Zhang, R. Zhang and H. Zhu, *Org. Biomol. Chem.*, 2014, **12**, 5945. Thus, we developed a new synthetic route using alkyl-substituted (*Z*)-α-dehydroamido boronate esters and on the gram-scale the reaction worked smoothly to yield the desired products.

20 CCDC 1897699 ((*S*)-**2i**) contains the supplementary crystallographic data for this paper.†

21 V. Bagutski, A. Ros and V. K. Aggarwal, *Tetrahedron*, 2009, **65**, 9956.

22 S. R. Inglis, E. C. Y. Woon, A. L. Thompson and C. J. Schofield, *J. Org. Chem.*, 2010, **75**, 468.

23 (*a*) O. Tamura, M. Hashimoto, Y. Kobayashi, T. Katoh, K. Nakatani, M. Kamada, I. Hayakawa, T. Akiba and S. Terashima, *Tetrahedron Lett.*, 1992, **33**, 3487; (*b*) P. B. D. Ranslow, L. S. Hegedus and C. D. L. Rios, *J. Org. Chem.*, 2004, **69**, 105.