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Rhodium-Catalyzed Regiodivergent and Enantioselective Hydroboration of Enamides

Xiao-Yan Bai‡, Wei Zhao‡, Xin Sun and Bi-Jie Li*

Center of Basic Molecular Science (CBMS), Department of Chemistry, Tsinghua University, Beijing, 100084, China

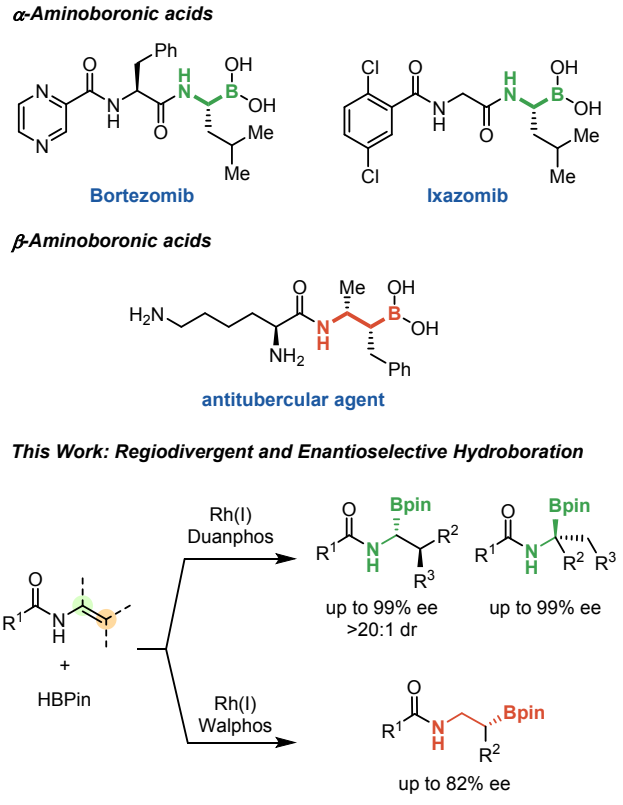
ABSTRACT: Chiral α- and β-aminoboronic acids exhibit unique biological activities. General methods for the synthesis of these bioisosteres of amino acids are highly desirable. We report a facile preparation of these compounds through rhodium-catalyzed regiodivergent and enantioselective hydroboration of enamides. Catalytic asymmetric synthesis of α- and β-aminoboronic esters with high regio-, diastereo-, and enantioselectivities were achieved through effective catalyst control and tuning substrate geometry. Starting from easily available materials, this strategy provides a unified synthetic access to both enantioenriched α-boration and β-boration products. The synthetic utility of these methods was demonstrated by efficient synthesis of an anticancer drug molecule and diverse transformations of the boration products.

1. Introduction

Due to the unique electronic and physicochemical properties, chiral boron-containing compounds have attracted increasing attention in pharmaceutical industry for the development of novel therapeutic agents.[1] These compounds exhibit useful biological activities including antibacterial, anticancer and antiviral activities.[2] In particular, α-aminoboronic acids, bioisosteres of α-amino acids, display distinct utility as reversible covalent inhibitors in a diverse range of therapeutic applications. The successful approval of boronic acid anti-cancer drugs bortezomib, ixazomib and vaborbactam demonstrates the potential of α-aminoboronic acids in drug discovery.[3] On the other hand, β-aminoboronic acids, bioisosteres of β-amino acids, also exhibit substantial potential in medicinal chemistry.[4] For example, β-aminoboronic acid has been identified as a new class of highly selective antimicrobial peptidomimetics that exhibits activity against *Mycobacterium tuberculosis*.[5] Therefore, practical enantioselective methods to access both α-and β-aminoboronic acids are highly desirable in medicinal chemistry (Scheme 1).[6]

Although a number of methods,[7] including Matteson's homologation,[8] lithiation-borylation[9] and borylation of imines with pinacol diborane,[10] have been developed for the synthesis of enantioenriched α-aminoboronic acids,[11] significant limitations remain to be solved. First, very few catalytic asymmetric methods are viable for the preparation of α-alkyl α-aminoboronic esters.[10h,11b] Second, the asymmetric synthesis of chiral α-amino tertiary boronic esters is particularly rare.[12] Recently, Tang's group described an efficient synthesis of chiral α-amino tertiary boronic esters through rhodium-catalyzed protoboration of enamide.[12a] Negishi's group reported a directed lithiation and enantiospecific borylation for the preparation of chiral α-amino tertiary boronic esters.[12b] Both methods were limited to the generation of α-aryl α-aminoboronic esters. Third, with few exceptions,[11g] all these borylation methods generate α-aminoboronic esters with a single stereocenter and are not capable for the synthesis of α-aminoboronic esters containing two adjacent stereocenters. On the other hand, catalytic asymmetric synthesis of β-aminoboronic esters has been developed recently, with strategies that are vastly different from that for the synthesis of α-aminoboronic esters.[13] To the best of our knowledge, none of these existing methods provides a unified entry to both enantioenriched α- and β-aminoboronic esters.[6] General enantioselective methods for the preparation of both α- and β-aminoboronic esters from easily available starting materials remain to be developed.

Scheme 1. Aminoboronic Acids by Enamide Hydroboration



Recently, our group reported regio- and enantioselective hydroalkynylations of enamides to produce both α-alkynylation and β-alkynylation products.[14] We surmised whether the enantioselective hydrofunctionalization strategy could be harness to access aminoboronic esters. Specifically, if suitable catalysts could be identified for the regio- and enantioselective hydroboration of enamides, we would be able to directly prepare both enantioenriched α- and β-aminoboronic esters from a common set of starting material (Scheme 1). However, the regiodivergent and enantioselective hydroboration of enamides faces several challenges. First, current enantioselective hydroborations[15] are mostly limited to terminal alkenes,[16] styrenes,[17] and internal alkenes with a coordinating group.[18] Catalytic asymmetric hydroboration of electron-rich olefins is rare.[12a,19] Highly enantioselective hydroboration of multi-substituted enamides with hydroborane is unknown.[20] In addition, very few catalytic systems have been developed for the hydroboration of trisubstituted alkenes to generate two stereocenters[21] or a quaternary stereocenter.[22] Furthermore, suitable catalysts must be identified for the catalytic hydroboration with tunable regioselectivity while maintaining high enantioselectivity.

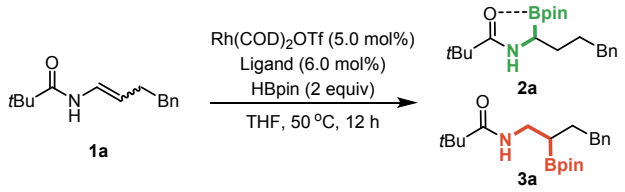
Herein, we report the successful implementation of an unprecedented enamide hydroboration strategy for the regiodivergent synthesis of α- and β-aminoboronic esters. In addition, an efficient rhodium catalyst has been identified for the hydroboration of multi-substituted enamides, generating α-amino tertiary boronic esters and α-aminoboronic esters containing two adjacent stereocenters with high regio-, diastereo- and enantioselectivity. By switching the ligand and olefin geometry, catalytic hydroboration of enamides provides enantioenriched β-aminoboronic esters. Finally, efficient synthesis of an anticancer drug molecule and diverse transformations of the boration products were further demonstrated.

2. Results and Discussion

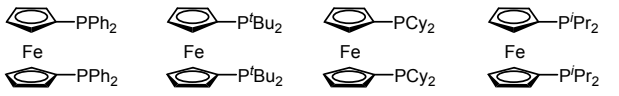
2.1. Reaction Development of Regiodivergent Hydroboration. To verify our hypothesis, catalytic hydroboration of enamide **1a**-*Z* with pinacolborane (HBpin) was conducted to identify a suitable catalyst (Table 1). The catalysts formed from $Rh(COD)_2OTf$ and a series of bisphosphine ligands were tested. When 1,1-bis(diphenylphosphino)ferrocene (DPPF) was used as a ligand, the reaction provided a mixture of α- and β-aminoboronic esters with low selectivity and low yield (entry 1). Thus, a series of DPPF analogues were further tested. The substituents on the ferrocene ligand had a significant impact on the yield and regioselectivity. Similar low yield and low selectivity were obtained with D*t*BuPF as a ligand (entry 2). However, significantly improved selectivity for α-aminoboronic ester was observed with DCyPF ligand, although the yield was moderate (entry 3). When D*i*PrPF was used as the ligand, α-aminoboronic ester was obtained in both high yield and high regioselectivity, even at lower catalyst loading (entry 4). These results indicate that appropriate steric hindrance of the alkyl substituent on the phosphine atom is crucial for both the reactivity and the regioselectivity.

Further experiments were conducted to assess the reactivity of *E*-enamide **1a**-*E*. To our surprise, the regioselectivity was completely reversed under the same conditions, favoring β-boration product (entry 5) (see SI for more details). Thus, this strategy provides access to both α- and β-aminoboronic esters by simply changing the olefin geometry.

Table 1. Optimization of Rhodium-Catalyzed Hydroboration of Enamide[a]

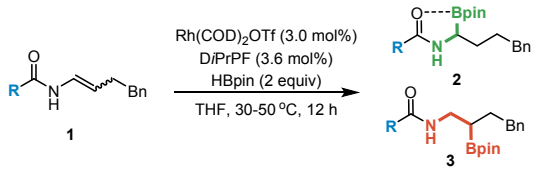


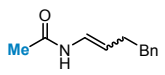
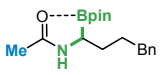
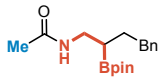
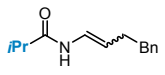
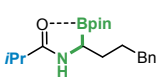
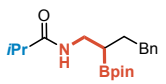
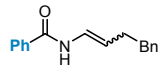
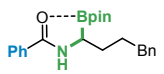
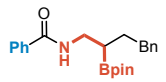
Entry	1a	Ligand	Ratio (α : β)[b]	Yield (%)[c]
1	*Z*	DPPF	3 : 1	12
2	*Z*	D*t*BuPF	1 : 1	13
3	*Z*	DCyPF	36 : 1	53
4[d]	*Z*	D*i*PrPF	18 : 1	83 (75)
5[d]	*E*	D*i*PrPF	1 : 15	94 (88)



[a] Reaction conditions: **1a** (1.0 equiv), HBpin (2.0 equiv), $Rh(COD)_2OTf$ (5.0 mol%), Ligand (6.0 mol%), 50 °C, 12 h. [b] Ratios were determined by GC. [c] Yields were determined by GC using *n*-dodecane as an internal standard. Isolated yield in parenthesis. [d] 3.0 mol% of catalyst.

Table 2. Hydroboration of Enamide[a]



Enamide	α–Boration (from **1**-*Z*)	β-Boration (from **1**-*E*)
 **1b**	 **2b** $\alpha:\beta = 5:1$, 73%	 **3b** $\alpha:\beta = 1:5$, 49%
 **1c**	 **2c** $\alpha:\beta = 5:1$, 66%	 **3c** $\alpha:\beta = 1:7$, 74%
 **1d**	 **2d** $\alpha:\beta > 20:1$, 88%	 **3d** $\alpha:\beta = 1:1$, 24%

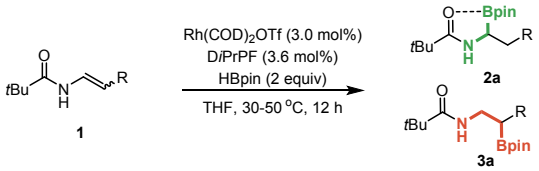
[a] Isolated yields were reported. See SI for details.

Hydroborations with various enamides showed that the substituents on the amide had an influence on the yield and regioselectivity (Table 2). Slightly decreased yields and regioselectivities were obtained in the hydroboration of the acetyl and isobutoyl enamides (**1b** and **1c**). The reaction of a benzoyl substituted *Z*-enamide afforded the α-boration product in 88% yield, while the reaction of *E*-enamide provided the β-boration product in low yield and low selectivity. Thus, the

pivaloyl amide provided the best results in terms of both reactivity and selectivity.

2.2. Scope of Regiodivergent Hydroboration. The scope of the Rh-catalyzed regiodivergent hydroboration of enamides is further demonstrated in Table 3. The reactions occurred with a range of alkyl substituted enamides in good yields and regioselectivity. A series of *Z*- and *E*-enamides were investigated. The *α*-hydroboration products were selectively formed from *Z*-enamides, whereas *β*-hydroboration products were selectively formed from *E*-enamides. Functional groups including alkyl halide (**2h**, **3h**), ester (**2i**, **3i**), carbamate (**2j**, **3j**), silyl ether (**2k**, **3k**), and acetal (**2l-m**, **3l-m**) were all compatible with the reaction conditions. A disubstituted alkene was not tolerated. We further investigated the steric effect of the substrate. For example, when a cyclohexylmethyl substituted substrate was tested, it had little impact on the reactivity and regioselectivity for the hydroboration (**2n**, **3n**). However, while the reaction of an *iso*-propyl substituted *Z*-enamide provided high selectivity for *α*-boration, hydroboration of *E*-enamide generated *α*-boration and *β*-boration products in a 1:1 ratio (**2o, 3o**). These results suggest that the steric effect of the substrate may also affect the regioselectivity. Unlike many other catalyst systems, hydroboration of vinyl enamide did not provide solely *anti*-Markovnikov product (**2p, 3p**). Finally, a free NH group is important for reactivity, as no desired product was observed in the reaction with an *N*-methyl enamide.

Table 3. Scope of Rh-Catalyzed Hydroboration of *β*-substituted Enamides[a]



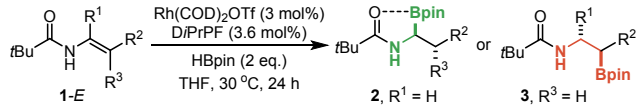
Enamide	α–Boration (from 1-*Z*)	β-Boration (from 1-*E*)
1e	2e α : β = 12 : 1, 61%	3e α : β = 1 : 10, 81%
1f	2f α : β = 11 : 1, 85%	3f α : β = 1 : 10, 88%
1g	2g α : β = 5 : 1, 81%	3g α : β = 1 : 10, 88%
1h	2h α : β = 14 : 1, 56%	3h α : β = 1 : 8, 66%
1i	2i α : β = 7 : 1, 55%	3i α : β = 1 : 10, 72%
1j	2j α : β = 7 : 1, 66%	3j α : β = 1 : >20, 75%
1k	2k α : β = 6 : 1, 81%	3k α : β = 1 : 3, 67%
1l	2l α : β = 13 : 1, 60%	3l α : β = 1 : 12, 87%
1m	2m α : β = 15 : 1, 63%	3m α : β = 1 : 9, 70%
1n	2n α : β = 13 : 1, 80%	3n α : β = 1 : 9, 87%
1o	2o α : β > 20 : 1, 87%	3o α : β = 1 : 1, 30%
1p	2p α : β = 1 : 1, 58%	3p

[a] Isolated yields were reported. See SI for details.

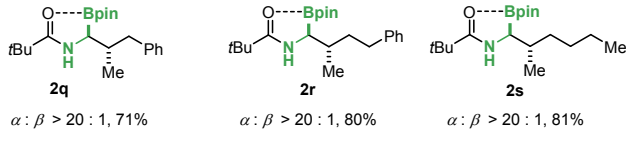
Next we probed the regioselectivity of the hydroboration of disubstituted enamides (Table 4). When *β*,*β*-disubstituted enamides were used, *α*-boration products with two vicinal stereocenters were obtained exclusively (**2q-t**). On the other hand, when α,*β*-disubstituted enamides were tested, *β*-boration products were obtained exclusively (**3w-x**). In all these cases, excellent diastereoselectivities were observed. This stereospecific *syn*-addition provides support against a mechanism involving enamide to imine isomerization followed by imine hydroboration. It appears that in the

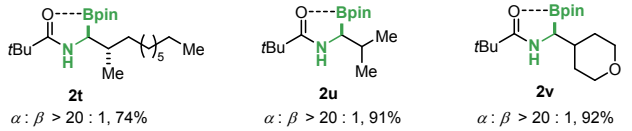
hydroboration of these disubstituted enamides, the steric effect of the substrate overrides the regioselectivity directed by the amide group.

Table 4. Scope of Rh-Catalyzed Hydroboration of Disubstituted Enamides[a]

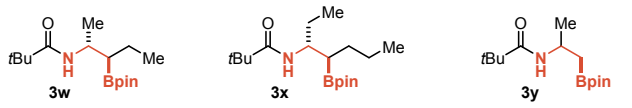


β,β-disubstituted enamide:



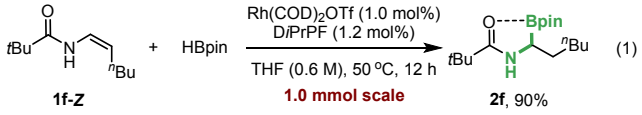


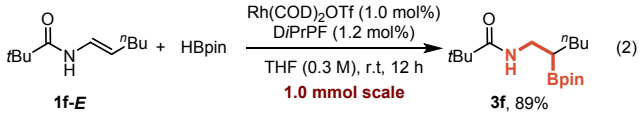
α,β-disubstituted enamide:



[a] Isolated yields were reported. Diastereomeric ratio (dr) >20:1 in all cases. See SI for details.

The catalytic hydroborations can be conducted at larger scale. With 1.0 mol% catalyst, the hydroboration of enamides **1f-*Z*** and **1f-*E*** on 1.0 mmol scale proceeded to completion, affording products **2f** and **3f** in 90% and 89% yield respectively (Eq. 1, 2).





2.3. Origin of Regiodivergence. To understand the origin of the regioselectivity, computational studies were conducted. The reaction starts with the oxidative addition of pinacolborane to an enamide bound rhodium complex (**Int-1**) to afford a boryl rhodium hydride intermediate (**Int-2**). Migratory insertion of the alkene into rhodium hydride generates a rhodacycle with coordination of the carbonyl group. Finally, C-B forming reductive elimination delivers the boration product. The activation free energies of the reaction profile indicate that migratory insertion (**TS-3a** vs **TS-3b**) determines the regioselectivity (Fig. 1). Accordingly, transition state structures for the migratory insertion of *β*-substituted, *β,β*-disubstituted and *α,β*-disubstituted enamides were extensively computed, and the two transition states with lowest activation energies for each substrate were shown in Fig. 2. The stereoisomeric transition state structures with alkene coordination through the opposite face are higher in energy due to steric repulsion (see SI for more details). For all these substrates, the major regioisomer predicted by computation is in good agreement with the experimental observations.

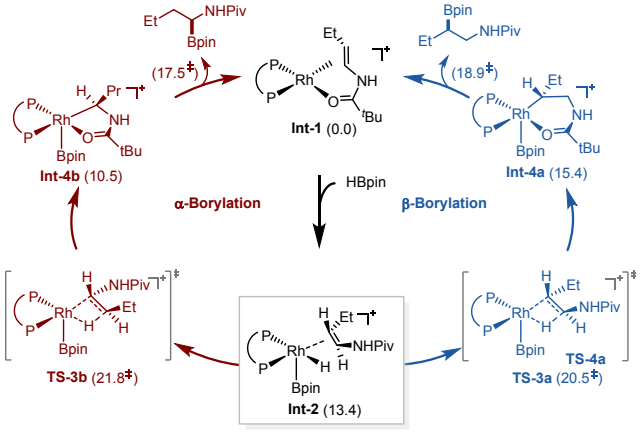


Fig. 1. Reaction pathways for hydroboration.

Analysis of the transition state structures provides insight into the origin of regioselectivity. One *iso*-propyl group on the ligand is in close proximity with the substrate. This repulsive interaction determines the orientation of the enamide during migratory insertion. For example, the *iso*-propyl group has more repulsion with the alkyl group of the enamide in **TS-6a**, **TS-7a** and **TS-8b** than that with the hydrogen in **TS-6b**, **TS-7b** and **TS-8a**. The *iso*-propyl group experience repulsion with hydrogen atom in both **TS-5a** and **TS-5b**, and consequently the energy difference between **TS-5a** and **TS-5b** is not as significant as that in **TS-6**, **TS-7** and **TS-8**. However, this repulsion is more severe in **TS-5b** because the hydrogen in **TS-5b** is closer to the ligand. These computational results indicate that the repulsive interaction of the ligand with the substrate during migratory insertion is crucial for controlling the regioselectivity of the hydroboration.

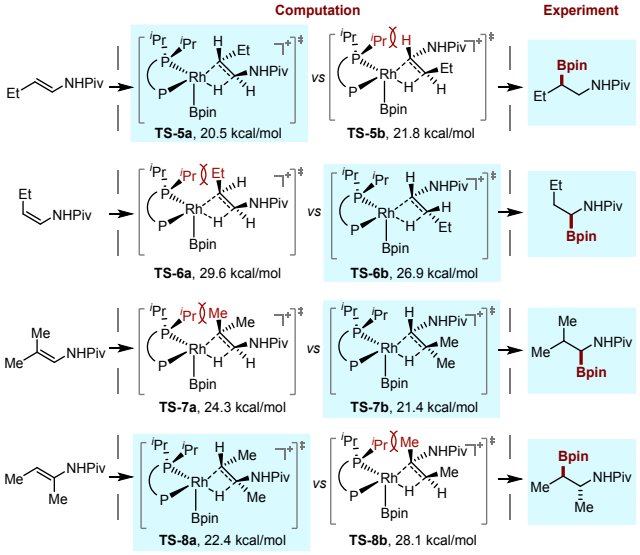
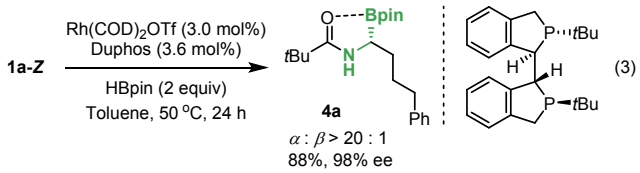


Fig. 2. Computed energies for migratory insertions.

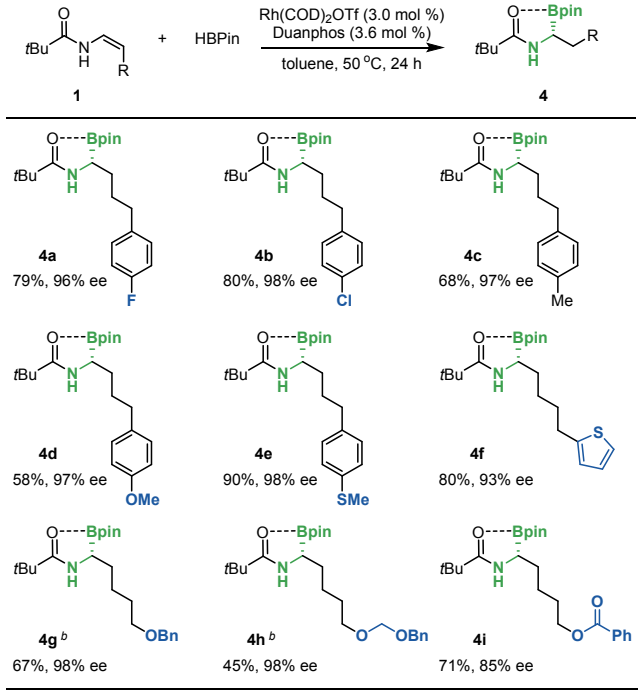
2.4. Enantioenriched *α*-Aminoboronic Esters. Further effort was directed towards the development of enantioselective hydroborations of enamide. In the presence of $Rh(COD)_2OTf$ as a catalyst precursor, a series of chiral

ligands were tested in the hydroboration of enamides **1a**-*Z* with pinacolborane (see SI for more details). Eventually, Duanphos[23] was identified as an efficient ligand, promoting the hydroboration of enamide **1a**-*Z* to afford *α*-hydroboration product **4a** with high regio- and enantioselectivity (Eq. 3). The absolute configuration of the product was determined by comparison of the optical rotation with authentic sample.



The scope of the Rh-catalyzed enantioselective hydroboration of *Z*-enamides is demonstrated in Table 5. Enantioenriched *α*-aminoboronic esters were selectively formed from *Z*-enamides. The reactions occurred with a range of alkyl substituted enamides in good yields and high regio- and enantioselectivities. Both electron-withdrawing (**4a**-**4b**) and electron-donating (**4c**-**4e**) groups on the phenyl ring were tolerated. Functional group including thiophene, benzyl ether, acetal and ester were all compatible with the reaction conditions (**4f**-**4i**).

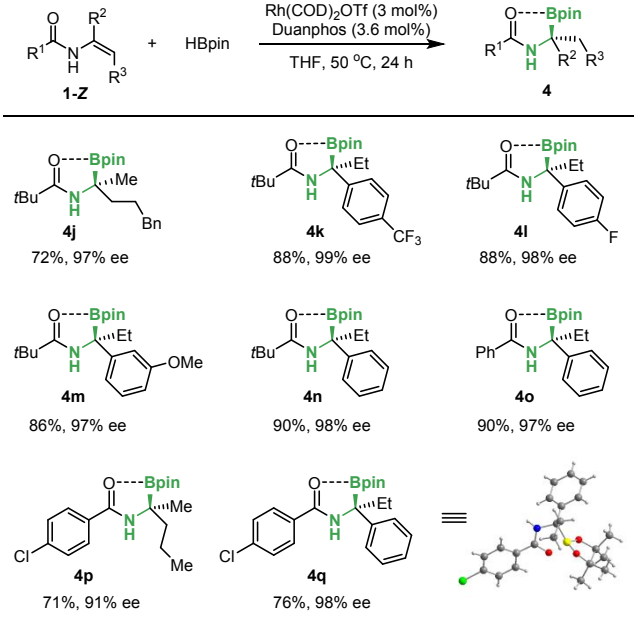
Table 5. Scope of Asymmetric Hydroboration of 1,2-Disubstituted *Z*-Enamides[a]



[a] Isolated yields were reported. The ee values were determined by HPLC on a chiral stationary phase. See SI for details. [b] 5 mol% Rh catalyst.

Next we probed the asymmetric hydroboration of disubstituted enamides. When *α,β*-disubstituted enamides were tested, α-boration products with a quaternary stereocenter were obtained exclusively with high enantioselectivity (Table 6). With this catalyst, the catalyst control overrides the steric control, which is in contrast with that observed in the racemic reaction. Several aryl or alkyl substituted enamides were tolerated in the reaction (**4j-4q**). The absolute configuration was determined by X-ray structure of **4q**.

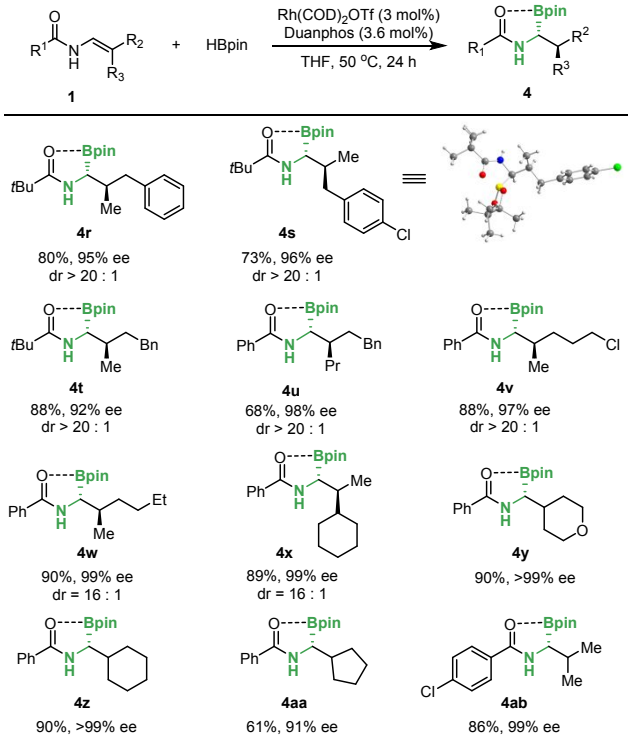
Table 6. Scope of Asymmetric Hydroboration of α,β-Disubstituted Enamides[a]



[a] Isolated yields were reported. The ee values were determined by HPLC on a chiral stationary phase. See SI for details.

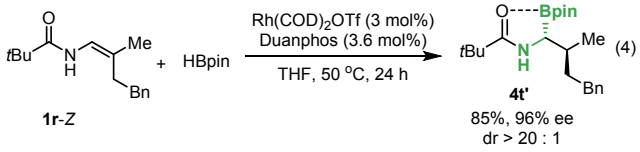
We further tested the asymmetric hydroboration of *β,β*-disubstituted enamides (Table 7). Under these conditions, *α*-boration products with two adjacent stereocenters were obtained exclusively. In all these cases, excellent diastereoselectivities were observed (**4r-4ab**), owing to the stereospecificity of the catalytic hydroboration process. The absolute configuration was determined by X-ray structure of **4s**. These results showed that the stereospecific *syn*-addition ensures the complete diastereoselectivity and the effective catalyst control gives rise to the high enantioselectivity.

Table 7. Scope of Asymmetric Hydroboration of β,β-Disubstituted Enamides[a]

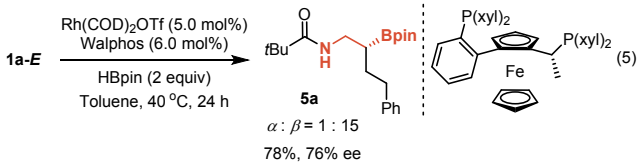


[a] Isolated yields were reported. The ee values were determined by HPLC on a chiral stationary phase. See SI for details.

The stereospecific *syn*-addition of the catalytic hydroboration allows the diastereoselectivity of the product to be tuned by simply changing the geometry of the enamide. Indeed, hydroboration of *Z*-enamide **1r**-*Z* generated the other diastereomer of **4t** (Eq. 4). Therefore, all four possible stereoisomers of **4t** could be obtained through the hydroboration process by switching the olefin geometry and the ligand configuration.

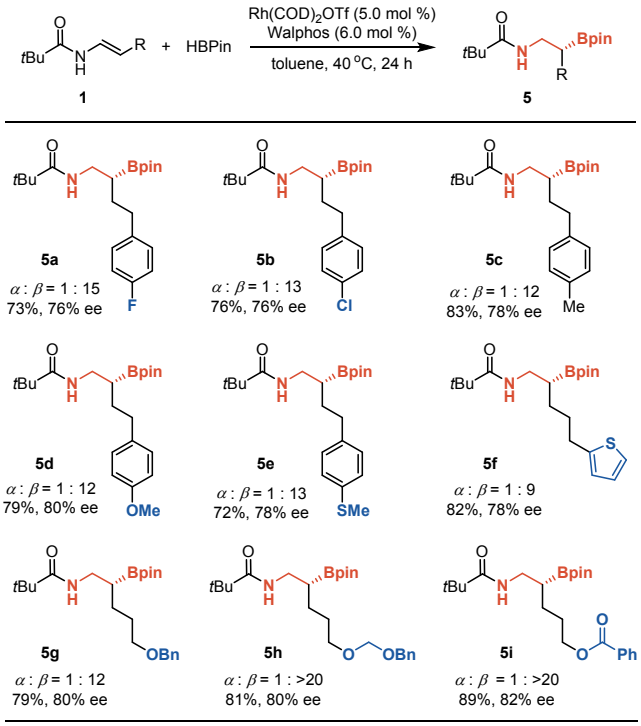


2.5. Enantioenriched β-Aminoboronic Esters. With a method for enantioselective *α*-hydroboration established, we sought to identify a catalyst for enantioselective *β*-hydroboration. For the hydroboration of *E*-enamide **1a**-*E*, Walphos was found to be the best ligand so far, delivering the *β*-hydroboration product in good regio- and enantioselectivity (Eq. 5).



A series of *β*-substituted *E*-enamides were tested under these conditions (Table 8). The enantioenriched *β*-hydroboration products were selectively formed. The reactions occurred with a range of alkyl substituted enamides in good yields and enantioselectivities. Both electron-withdrawing and electron-donating groups on the phenyl ring were tolerated (**5a-5e**). Functional group including thiophene, benzyl ether, acetal and ester did not interfere with the catalyst (**5f-5i**). Hydroboration of disubstituted enamides did not proceed under these conditions so far.

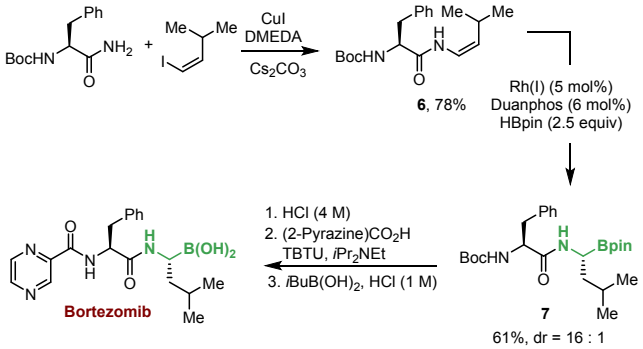
Table 8. Scope of Asymmetric Hydroboration of 1,2-Disubstituted *E*-Enamides[a]



[a] Isolated yields were reported. The ee values were determined by HPLC on a chiral stationary phase. See SI for details.

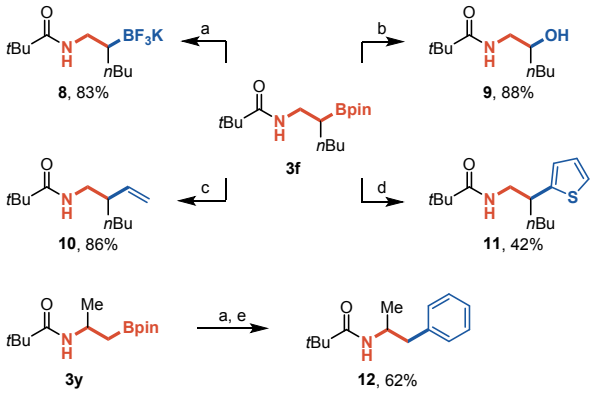
2.6. Synthetic Application. To demonstrate the practicability of these methods, asymmetric synthesis of Bortezomib was conducted (Scheme 2). Hydroboration of enamide **6,** obtained through Cu-catalyzed C-N coupling, gave the hydroboration product **7** with high diastereoselectivity. Following the literature method,[10a] compound **7** was transformed to Bortezomib through a sequence of deprotection, amidation and hydrolysis. This method provided a straightforward synthesis of the drug molecule from easily available starting materials.

Scheme 2. Synthesis of Bortezomib.



In addition, the *β*-boronic ester provided a useful handle for various further functionalizations (Scheme 3).[24] For example, Treatment of **3f** with KHF_2 provided the corresponding potassium trifluoroborate salt **8** in 83% yield. Oxidation, alkenylation and heteroarylation of **3f** generated *β*-hydroxyl amide **9**, homoallylic amide **10** and *β*-aryl amide **11**, respectively.[25,26] Additionally, *β*-boronic ester **3y** underwent Suzuki coupling to deliver the arylation product **12** in two steps with 62% yield.[27]

Scheme 3. Synthetic Transformation of *β*-Aminoboronic Esters.



Reaction conditions: (a) KHF_2, MeOH/H_2O, r.t. (b) $NaBO_3{\cdot}4H_2O$, THF/H_2O, r.t. (c) (i) Vinylmagnesium bromide, THF, -78 °C, (ii) I_2, MeOH, -78 °C to 0 °C. (d) (i) Thiophene, *n*BuLi, THF, -78 °C, (ii) NBS, THF, -78 °C to r.t. (e) PhBr, $Pd(OAc)_2$, Ad_2PnBu, Cs_2CO_3, toluene/H_2O, 100 °C.

3. Conclusion

In summary, we have developed a rhodium-catalyzed regiodivergent and stereoselective hydroboration of enamides. The regioselectivity of the hydroboration could be tuned by simply changing the olefin geometry. Computational studies revealed the origin of this unusual selectivity. In addition, we have achieved enantioselective hydroborations of enamides to access both *α*- and *β*-aminoboronic esters. Particularly, chiral *α*-amino tertiary boronic esters and *α*-aminoboronic esters containing two adjacent stereocenters have been synthesized with high regio- and enantioselectivities, which would be otherwise challenging to prepare. Furthermore, our methods enabled the efficient synthesis of a drug molecule with short synthetic steps. The boration products underwent diverse transformations to afford valuable building blocks. Further mechanistic studies are currently ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization of new compounds and spectroscopic data are provided in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

bijieli@mail.tsinghua.edu.cn

Notes

The authors declare no competing financial interests.

Author Contributions

‡These authors contributed equally.

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