

# Chiral amino alcohols via catalytic enantioselective Petasis borono-Mannich reactions

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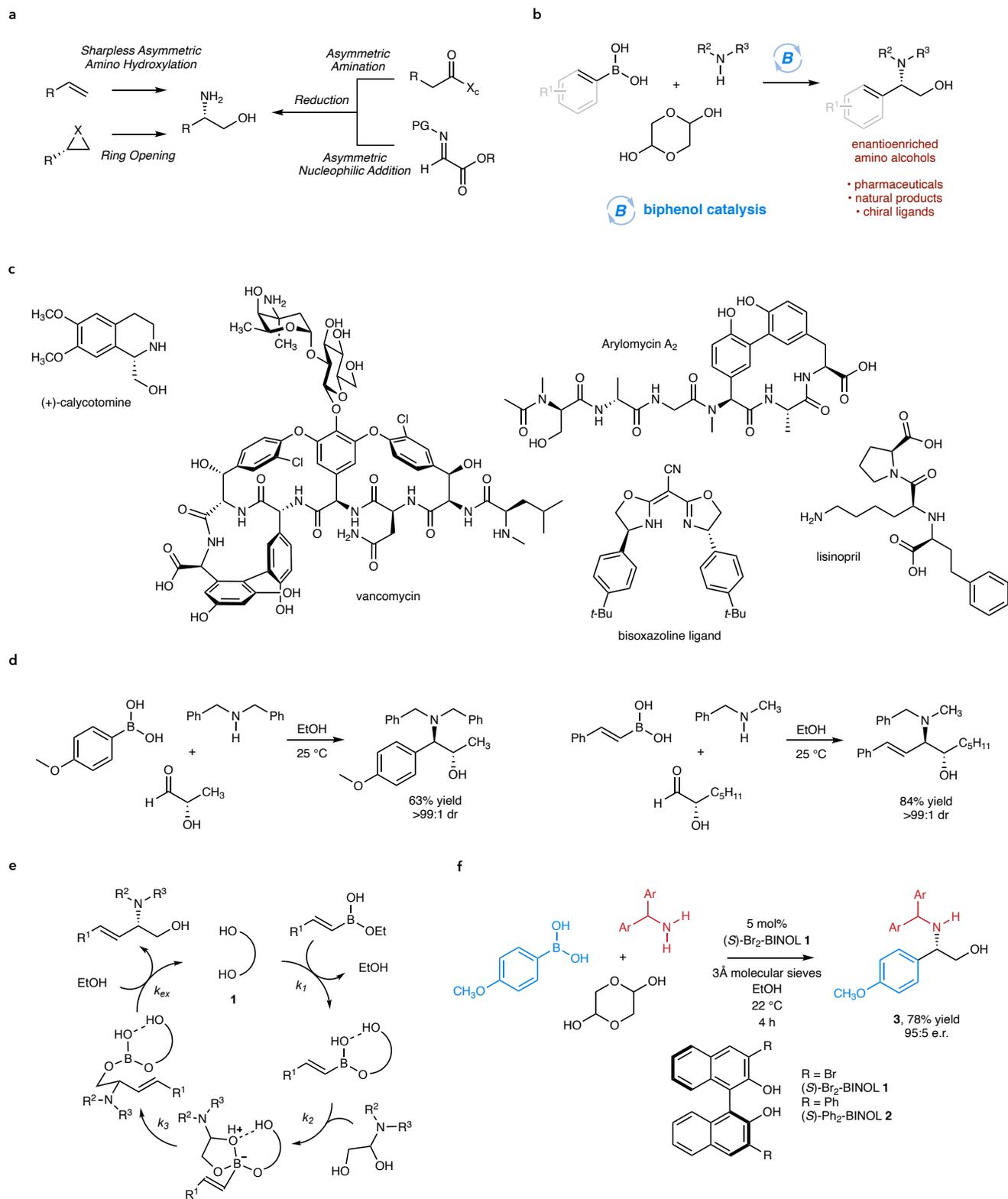
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Chiral amino alcohols are valuable building blocks in the synthesis of drugs, natural products, and chiral ligands used in enantioselective catalysis. The Petasis borono-Mannich reaction is a multicomponent condensation reaction of aldehydes, amines, and boronic acids to afford chiral amines. This report describes a practical, easily scaled, enantioselective Petasis borono-Mannich reaction of glycolaldehyde, with primary or secondary amines, and boronates catalyzed by BINOL-derived catalysts to afford chiral 1,2-amino alcohols in high yields and enantioselectivities. The reactions are executed at room temperature in ethanol or trifluorotoluene using commercially available reagents and leverage an inherently attractive feature of the multicomponent reaction; the ability to use amines and boronates that possess a wide range of structural and electronic properties. Computational modeling of the diastereomeric transition states using DFT calculations identified a non-conventional CH $\cdots$ O interaction as a key feature that selectively stabilizes the transition state leading to the major enantiomer. The enantioselective catalytic reaction exemplifies a truly practical multicomponent condensation to afford 1,2-amino alcohols in highly enantioenriched form.

Enantioenriched chiral amino alcohols are used in the synthesis of natural products<sup>1</sup>, pharmaceutically active molecules<sup>2</sup>, and ligands employed in enantioselective catalysis<sup>3</sup>. Access to these valuable building blocks via enantioselective synthesis include the asymmetric aminohydroxylation<sup>4</sup>, asymmetric ring opening of epoxides<sup>5</sup> and aziridines<sup>6</sup>, the asymmetric amination of chiral enolates<sup>7</sup>, and nucleophilic addition to chiral imines<sup>8</sup> (Fig. 1a). Notably, in the synthesis of vancomycin (Fig. 1c) and related natural products<sup>9</sup> Evans developed an asymmetric amination of oxazolidinones<sup>10</sup>, Nicolaou utilized the Sharpless asymmetric dihydroxylation subsequently converting the diol to the 1,2-amino alcohol<sup>11</sup>, and Boger elegantly implemented the Sharpless asymmetric aminohydroxylation<sup>12</sup>. Each of these methods were used to make key aryl glycines necessary for the route sought by each group. Another method to access chiral aryl glycinols is the nucleophilic addition of metal arenes to chiral imines best illustrated by use of the Ellman chiral sulfoxamine<sup>13</sup>. The need to access chiral aryl glycines and aryl glycinols is



**Figure 1 | Synthesis and utility of chiral 1,2-amino alcohols.** a, Enantioselective synthesis of 1,2-amino alcohols. b, Asymmetric multi-component Petasis borono-Mannich reaction catalyzed by chiral biphenols. c, Natural products, pharmaceuticals, and chiral ligands that can be derived from chiral 1,2-amino alcohols. d, Substrate-directed Borono-Mannich reaction described by Petasis in 1998. e, Proposed catalytic cycle for enantioselective Petasis borono-Mannich reaction catalyzed by chiral biphenols. f, Enantioselective multi-component Petasis borono-Mannich Reaction. e.r. = enantiomeric ratio. Ar = 4-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>. Ph = C<sub>6</sub>H<sub>5</sub>. Bn = C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>.

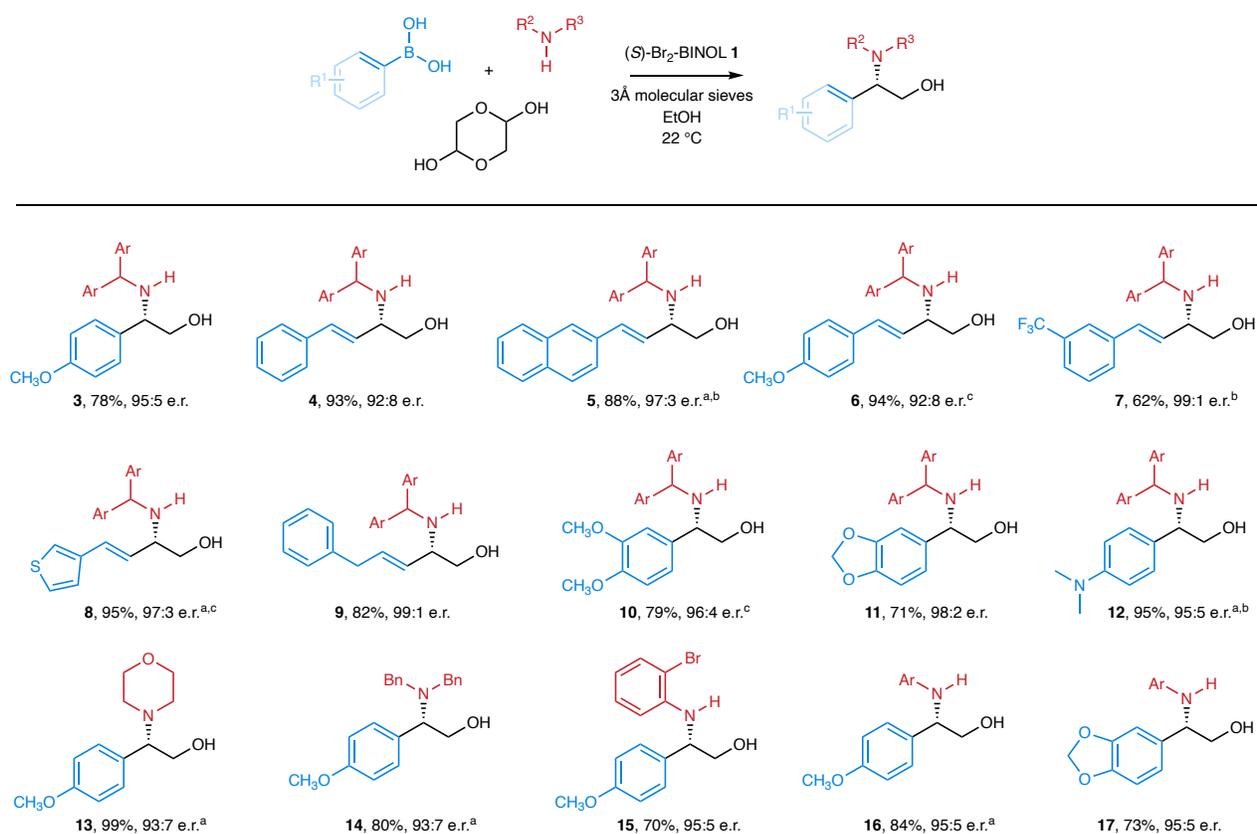
highlighted more recently in the syntheses of the arylomycins (Fig. 1c) by Dufour<sup>14</sup>, Smith and Heise at Genentech<sup>15</sup>, and by the Baran lab<sup>16</sup>. In each synthetic approach, a lengthy synthesis of a functionalized hydroxy aryl glycine suitable for use in the synthetic route was performed in multiple steps from the commercially available hydroxyphenyl glycine. Chiral aryl glycinols are also used for the synthesis of chiral bisoxazolines<sup>17</sup> (Fig. 1c), a class of metal binding ligands widely employed in enantioselective catalysis and recently used by Fu and MacMillan in the development of an asymmetric alkylation of amino acids using photoredox and nickel catalysis<sup>18</sup>. These are just a few examples that illustrate the importance of amino alcohols in synthesis and provide an indication of the impact that a practical and scalable method for the synthesis of chiral 1,2-amino alcohols will have on different areas of synthesis.

In the 1990's Petasis reported the borono-Mannich reaction of alpha-hydroxy-aldehydes, amines, and boronic acids in a novel and interesting approach to provide access to chiral 1,2-amino alcohols<sup>19</sup>. The reaction was highly diastereoselective using chiral hydroxy aldehydes giving rise to stereochemically well-defined anti-1,2-amino alcohols (Fig. 1d). Since the initial reaction described by Petasis<sup>20</sup>, the reaction has been extensively used in synthesis<sup>21</sup>, however, an enantioselective version of the reaction has proved to be elusive<sup>22</sup>. In our continuing efforts to develop enantioselective boronate reactions catalyzed by ligand exchange we have described the enantioselective Petasis borono-Mannich reaction of ethyl glyoxylate with amines and vinyl boronic acids catalyzed by VAPOL<sup>23</sup>. While the reaction is one of the first examples of an enantioselective Petasis borono-Mannich reaction, the reaction was less than ideal for practical access to the chiral amino ester products requiring relatively high catalyst loadings at low temperatures. Given the value of chiral 1,2-amino alcohols as synthons, we sought to develop an enantioselective Petasis borono-Mannich reaction of achiral alpha-hydroxy aldehydes to afford amino alcohols<sup>24</sup> (Fig. 1b). We envisaged an enantioselective reaction of glycol aldehyde, amines, and boronates catalyzed by chiral biphenols; a mode of enantioselective boronate activation developed by us and others. Since our initial report, chiral biphenols have been used in enantio- and diastereoselective Petasis borono-Mannich reactions but in very specific contexts providing a narrow selection of building blocks afforded from the reaction<sup>25</sup>. In developing an enantioselective Petasis borono-Mannich reaction with glycol aldehyde we sought to leverage the ability to use different amine and boronate coupling partners to maximize the diversity of products afforded from the reaction; in so doing, developing an attractive method to provide access to valuable chiral synthons. Herein, we report a highly enantioselective Petasis borono-Mannich reaction affording chiral 1,2-amino alcohols under practical and operationally simple reaction conditions.

## Results and discussion

Our experiments started by using diethyl boronate esters in the reaction with amines and glycol aldehyde dimer catalyzed by (*S*)-3,3'-Br<sub>2</sub>-BINOL **1**. The reaction generally worked well for electron rich boronates affording the Mannich product in good yields and enantioselectivities. The drawback to using boronate esters in the reaction is the added synthetic step to first make the boronate ester from the corresponding commercially available boronic acid. We postulated that the reaction could be performed using the boronic acid in ethanol to facilitate the catalyst exchange process (Fig. 1e), both at the catalyst coordination step, but also at the end of the reaction to liberate the catalyst, a process we have

**Table 1 | Enantioselective Petasis Borono-Mannich Reaction in Ethanol**

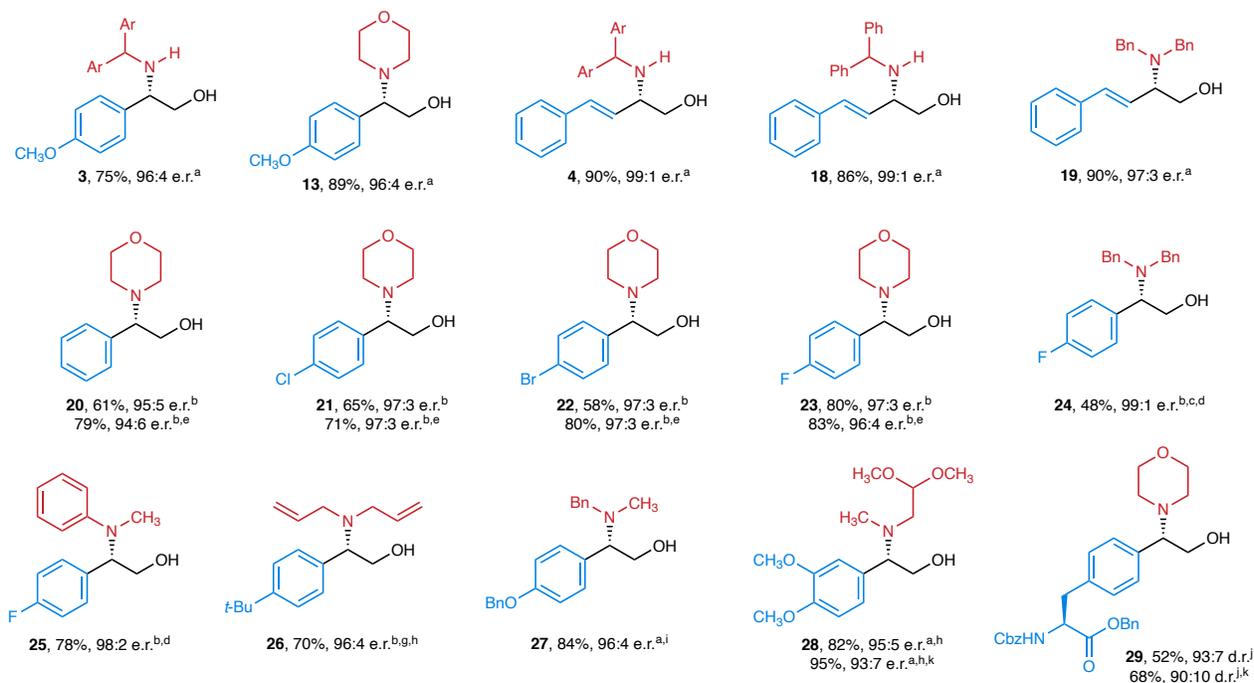
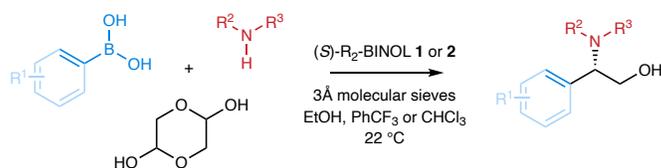


Boronic acid (1.3 mmol, 1.3 equiv), glycolaldehyde dimer (0.50 mmol, 0.5 equiv), amine (1.0 mmol, 1.0 equiv), (S)-Br<sub>2</sub>-BINOL **1** (0.05 mmol, 0.05 equiv), and 3Å molecular sieves (500 mg) were added to a reaction flask with a stir bar. The mixture was suspended in EtOH (2.5 mL) and stirred at room temperature for 16 hours. <sup>a</sup>0.10 equiv **1**. <sup>b</sup>Diethyl boronate was used in the reaction. <sup>c</sup>In 1 mL EtOH. e.r. = enantiomeric ratio. Ar = 4-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>. Bn = C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>.

demonstrated to be important in the overall catalytic cycle<sup>26</sup>. Indeed, by using molecular sieves in ethanol with *para*-methoxyphenyl boronic acid, catalytic (*S*)-3,3'-Br<sub>2</sub>-BINOL **1**, glycol aldehyde dimer, and bis(4-methoxyphenyl)methanamine, the corresponding 1,2-amino alcohol **3** was obtained in 78% isolated yield and 95:5 enantiomeric ratio (e.r.) at room temperature (Fig. 1f). The reaction conditions proved to be general for electron rich boronic acids with the benzhydryl amine (Table 1, amino alcohols **4** - **17**). In some cases, higher catalyst loadings were required (**8**, **12**, **14**, **16**), but still afforded the desired product in good yields (>50% yield) and high enantioselectivities (≥95:5 e.r.). An undesired pathway that can sometimes be a challenge in the Petasis borono-Mannich reaction is the direct Mannich product of the amine and aldehyde component; a competing pathway observed when using 2°-amines (dibenzylamine, **14**) resulting in lower yields of the desired amino alcohol. The direct Mannich reaction pathway can be mitigated by using higher catalyst loadings, increasing the rate of the desired Petasis borono-Mannich reaction. In addition, the use of diethyl boronates in the reaction also increases the rate of the desired Petasis Mannich reaction affording the product in yields and selectivities commensurate with reactions using the boronic acid (**5**, **7**, **12**). For electron rich, highly nucleophilic boronates reaction conditions were identified that afforded the enantioenriched 1,2-amino alcohols in high enantioselectivities.

Boronates possessing less nucleophilic character proved more challenging. The reactions would not proceed in ethanol. However, we knew that polar, aprotic, non-coordinating solvents serve as excellent reaction solvents for catalytic boronate reactions<sup>27</sup>. With this understanding of boronate reactivity in mind, we used a solvent mix of ethanol and trifluorotoluene that would facilitate the boronate-BINOL exchange process and promote the Mannich reaction. Trifluorotoluene is a more practical alternative to chlorinated solvents<sup>28</sup>, and while chloroform also works in the reaction, trifluorotoluene is preferred for reactions run in industrial settings<sup>29</sup>. The Petasis borono-Mannich reaction worked equally as well using a 10:1 mixture of trifluorotoluene:ethanol under the catalytic conditions (Table 2; amino alcohols **3**, **4** & **18**) in comparison to using ethanol alone. This solvent mixture proved important for less reactive aryl boronic acids (Table 2; **20** – **25**). The Mannich reactions worked equally as well using chloroform rather than trifluorotoluene, affording the desired amino alcohols in commensurate yields and enantioselectivities (Table 2; **20** – **23**). The *tert*-butylphenyl boronic acid similarly performed well in the Mannich reaction with diallyl amine to afford the amino alcohol **26** in good isolated yields and enantioselectivities (96:4 e.r.). The Mannich reaction of *p*-benzyloxyphenyl boronic acid afforded the corresponding amino alcohol **27** in 96:4 e.r., a building block that could potentially be used in the synthesis of the arylomycins. The reaction of dimethoxyphenyl boronic acid with methylamino acetaldehyde dimethyl acetal afforded the corresponding amino alcohol **28** in excellent yields and good enantioselectivities, an amino alcohol used in the synthesis of (+)-calycotomine<sup>30</sup> (Fig. 1c). The reaction proceeded well in both trifluorotoluene and chloroform ethanol mixtures. Lastly, we sought to evaluate the reaction using more functionalized boronic acid nucleophiles. The Mannich reaction of the Cbz-protected phenylalanine benzyl ester derived boronic acid with morpholine afforded the amino alcohol **29** in 93:7 diastereomeric ratio (d.r.) and 52% isolated yield using trifluorotoluene and ethanol. The reaction in chloroform and ethanol resulted in a 9:1 d.r. and 68% isolated yield. These results are notable given the existing stereocenter, albeit remote, and hydrogen bond donors and acceptors already present in the boronic acid nucleophile. In summary, the use of polar solvent mixtures of trifluorotoluene or

**Table 2 | Enantioselective Petasis Borono-Mannich Reaction**



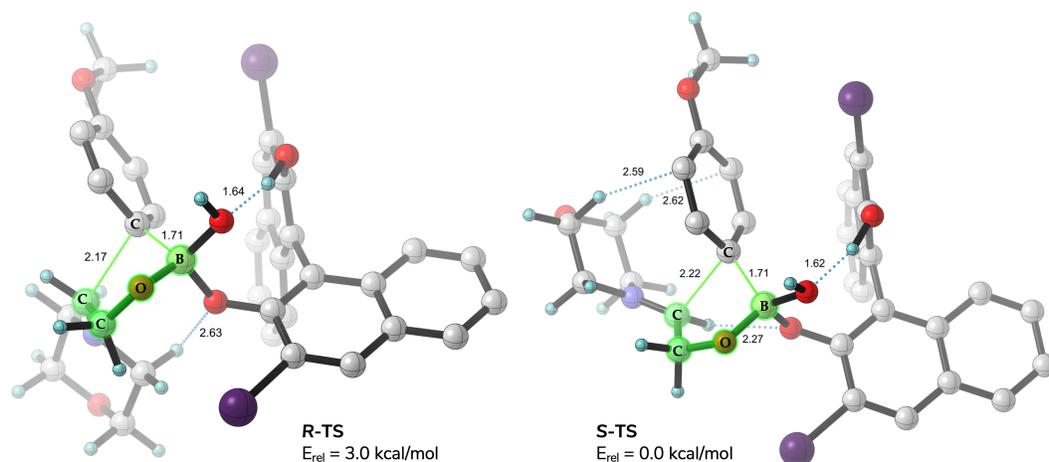
<sup>a</sup>Boronic acid (1.3 mmol, 1.3 equiv), glycolaldehyde dimer (0.50 mmol, 0.5 equiv), amine (1.0 mmol, 1.0 equiv),  $(S)$ -Br<sub>2</sub>-BINOL **1** (0.05 mmol, 0.05 equiv), and 3Å molecular sieves (500 mg) were added to a reaction flask with a stir bar. The mixture was suspended in trifluorotoluene (2.2 mL) and EtOH (0.3 mL) and stirred at room temperature for 16 hours. <sup>b</sup>Boronic acid (1.5 mmol, 1.5 equiv), glycolaldehyde dimer (1.0 mmol, 1.0 equiv), amine (1.0 mmol, 1.0 equiv),  $(S)$ -Ph<sub>2</sub>-BINOL **2** (0.15 mmol, 0.15 equiv), and 3Å molecular sieves (500 mg) were added to a reaction flask with a stir bar. The mixture was suspended in trifluorotoluene (2.2 mL) and EtOH (0.3 mL) and stirred at room temperature for 2 hours. <sup>c</sup>Run at 50 °C. <sup>d</sup>Run for 16 hours. <sup>e</sup>The mixture was suspended in chloroform (2.2 mL) and EtOH (0.3 mL) and stirred at room temperature for 16 hours. <sup>f</sup>The mixture was suspended in trifluorotoluene (1.8 mL) and EtOH (0.7 mL) and stirred from 0 °C to room temperature over 4 hours. <sup>g</sup>0.07 equiv **2**. <sup>h</sup>0.12 equiv **1** for 4 hours. <sup>i</sup>Boronic acid (0.2 mmol, 1.3 equiv), glycolaldehyde dimer (0.17 mmol, 1.0 equiv), amine (0.17 mmol, 1.0 equiv),  $(S)$ -Ph<sub>2</sub>-BINOL **2** (0.016 mmol, 0.09 equiv), and 3Å molecular sieves (88 mg) were added to a reaction flask with a stir bar. The mixture was suspended in trifluorotoluene (0.4 mL) and EtOH (0.1 mL) and stirred at room temperature for 16 hours. <sup>k</sup>Chloroform was used instead of trifluorotoluene. e.r. = enantiomeric ratio. Ar = 4-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>, Ph = C<sub>6</sub>H<sub>5</sub>, Bn = C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>.

chloroform with ethanol enabled the use of less nucleophilic boronic acids in the asymmetric Petasis borono-Mannich reaction.

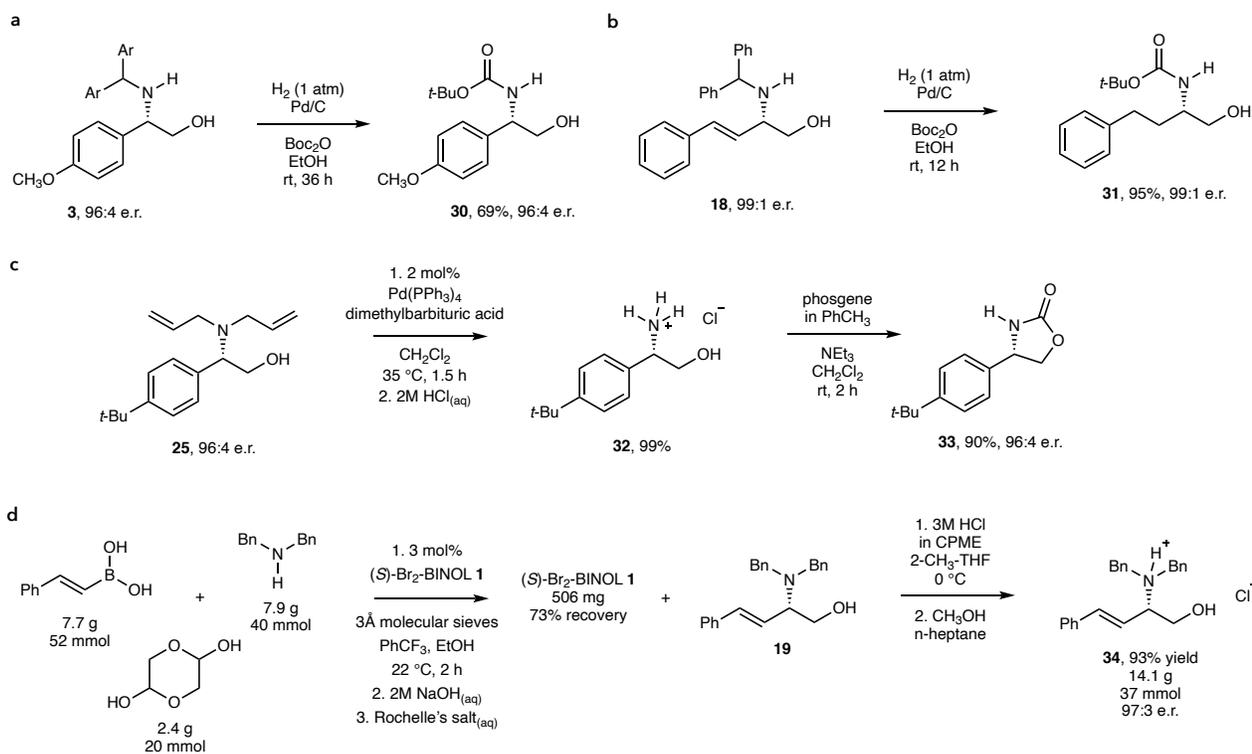
Computational modeling experiments were performed to evaluate the key factors mediating the observed selectivity. The enantioselectivity-determining step in the chiral biphenol catalyzed three component Petasis-borono-Mannich reaction of glycolaldehyde, morpholine, and *p*-methoxyboronic acid most likely proceeds via a tetracoordinate boronate intermediate<sup>31</sup> formed by reaction of the iminium ion from condensation of morpholine and glycolaldehyde, *p*-methoxyboronic acid, and one of the hydroxyl groups of (*S*)-Br<sub>2</sub>-BINOL **1**. We modeled the intramolecular transfer of the aryl group from the anionic boron to the iminium carbon of this intermediate using B97-D<sup>32</sup>/Def2-SVP<sup>33</sup> calculations as executed in Gaussian '16<sup>34</sup>. Single-point energy calculations were performed using  $\omega$ B97X-D<sup>35</sup>/Def2-TZVP<sup>33</sup> with a PCM solvent model<sup>36</sup> for ethanol for all computed transition structures (TS). Relative free energy barriers presented in the manuscript are extrapolated Gibbs free energies obtained by adding the free energy correction from the B97-D/Def2-SVP optimization to the high-level single point energy calculation. The free energies were corrected using Grimme's quasi rigid rotor-harmonic oscillator (qRRHO) approach, which raises vibrational frequencies that are below 100 cm<sup>-1</sup> to 100 cm<sup>-1</sup><sup>37</sup>.

The lowest energy TSs for aryl transfer from the boronate to either the *re*-face (**R-TS**) or the *si*-face (**S-TS**) of the iminium ion were identified after a rigorous conformational exploration (Fig. 2). Both TSs are characterized by (a) covalent attachment of the catalyst to boron via one of the phenolic oxygen atoms of catalyst, and (b) a strong intramolecular H-bonding interaction between the proton of the other phenolic group of the catalyst and an OH group attached to the boron (1.64 Å in **R-TS** and 1.62 Å in **S-TS**). This intimate association of the catalyst to the reaction transition state allows for enantio-differentiation by distinctly different catalyst-substrate and substrate-substrate interactions. In the lowest energy TS leading to the *S*-enantiomer (**S-TS**), there is a moderately strong CH $\cdots$ O interaction (2.27 Å) between the iminium CH and the catalyst phenolic oxygen that is attached to the boron<sup>38</sup>. Additionally, there are two CH- $\pi$  interactions between the protons  $\alpha$  to the nitrogen in the morpholine ring and the  $\pi$ -system of the electron-rich migrating aryl anion (2.59 Å and 2.62 Å in **S-TS**)<sup>39</sup>. The transfer of the aryl group from boron to the iminium carbon occurs via a 5-membered envelope-like TS (**S-TS**, highlighted in green) – with the migrating carbon atom representing the top of the envelope flap.

In contrast, the lowest-energy TS leading to the *R*-enantiomer (**R-TS**) proceeds via a 5-membered envelope-like TS where the boron atom is at the top of the envelope flap. This conformation places the other four atoms of the envelope in a plane, resulting in destabilizing eclipsing interactions between the bulky morpholine substituent on the iminium carbon and the other substituents on the adjacent carbon atoms in the 5-membered TS (**R-TS**, highlighted in green). Intriguingly, both the CH $\cdots$ O and the CH- $\pi$  interactions that stabilize **S-TS** (*vide supra*) are absent in **R-TS**. The only stabilizing interaction in **R-TS** is a weak non-covalent between the proton  $\alpha$  to the nitrogen in the morpholine ring and the phenolic oxygen attached to the boron (2.63 Å). The forming C-C bond distance in **R-TS** is 2.17 Å, which corresponds to a later transition state than **S-TS** where the corresponding distance is 2.22 Å. The superior transition state stabilization of **S-TS** makes it 3.0 kcal/mol lower than **R-TS** in free energy. This translates to a predicted enantiomeric ratio of 99.4 : 0.6 at 22 °C, which is in reasonable agreement with experiment



**Figure 2** | Lowest energy transition structures leading to both enantiomers calculated using  $\omega$ B97X-D/Def2-TZVP PCM(ethanol)//B97-D/Def2-SVP level of theory. Transition state stabilization of **S-TS** makes it 3.0 kcal/mol lower than **R-TS** in free energy.



**Figure 3** | a, One step diarylmethyl deprotection and Boc protection of **3** via palladium-catalyzed hydrogenation (5 mole % Pd loading). b, One step benzhydryl deprotection, Boc reprotection, and olefin reduction of **18** using palladium-catalyzed hydrogenation at (5 mole % Pd loading). c, Two step palladium-catalyzed allyl deprotection of **25** and subsequent synthesis of chiral oxazolidinone **33**. d, Extractive purification sequence for scalable production of enantioenriched amino alcohol in the absence of column chromatography. (*S*)-Br<sub>2</sub>-BINOL **1** is recovered by pH adjustment of an initial basic extraction followed by extraction of the pH adjusted aqueous layer. Crude **19** was suspended in 2-CH<sub>3</sub>-THF followed by treatment with HCl, initially forming an amorphous solid precipitate. The amorphous solid was dissolved by the addition of methanol and a filterable solid was precipitated via a solvent exchange with *n*-heptane using rotary evaporation. e.r. = enantiomeric ratio. Ar = 4-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>. Ph = C<sub>6</sub>H<sub>5</sub>. Bn = C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>.

(96:4 e.r. for **13**). Finally, the  $\Delta G^\ddagger$  for *S*-TS is 19.2 kcal/mol with respect to separate starting materials – a value that is consistent with the facility of the reaction at 22 °C.

The enantioenriched amino alcohol products of the Petasis Borono-Mannich reaction are readily manipulated as building blocks for use in synthesis (Fig. 3 a – c). The 4,4'-dimethoxydiphenylmethane group of amino alcohol **3** was selectively cleaved via palladium-catalyzed hydrogenolysis, and protected as the *t*-butylcarbamate in good yields (**30**, 69% yield) using a one-pot procedure<sup>40</sup>. Similarly, amino alcohol **18** underwent olefin hydrogenation, benzhydryl hydrogenolysis, and *t*-butylcarbamate formation in excellent yields (**31**, 95% yield). Hydrogenation of the olefin occurs rapidly, rendering an intermediate with the desired benzhydryl C-N bond to be cleaved by hydrogenolysis, ultimately resulting in facile removal of the benzhydryl group and formation of the carbamate. Palladium-mediated allyl deprotection<sup>41</sup> of **25** proceeded in quantitative yields to afford **32** as the amine hydrochloride salt after workup (Fig. 3c). The salt was converted directly to the oxazolidone **33** in the presence of phosgene and amine base<sup>42</sup>. In each case, exposure to palladium did not racemize the benzylic or allylic amine stereocenter or otherwise degrade enantioenrichment.

We demonstrated the scalability of the method by running the reaction on a 40 mmol scale, employing extractive purification techniques, and use of industrially appropriate solvents, ultimately minimizing the need for chromatographic separations (Fig. 3d). The Petasis borono-Mannich reaction chosen to illustrate the ability to produce multi-gram quantities of enantioenriched amino alcohols was the reaction of styrenylboronic acid and dibenzylamine with glycolaldehyde dimer. The reaction proceeded well using just 3 mole % biphenol catalyst **1** and after filtration of the molecular sieves and dilution with 2-CH<sub>3</sub>-THF, the catalyst and excess boronic acid were removed by aqueous NaOH extraction. Catalyst recovery was accomplished by adjusting the pH to 8 using aqueous HCl and extraction with *tert*-butyl methyl ether (TBME). The TBME extract was washed with aqueous Rochelle's salt to remove any remaining boronic acid. After concentration, a silica plug was used for final purification of the catalyst (73% recovery). The 2-CH<sub>3</sub>-THF solution containing amino alcohol was dried and concentrated under reduced pressure to render crude **19** as a viscous oil. The freebase oil was suspended in 2-CH<sub>3</sub>-THF and treated with dry HCl in cyclopentyl methyl ether (CPME) initially forming a white suspension that was brought into solution by the addition of anhydrous methanol. Solvent exchange with n-heptane was accomplished using rotary evaporation affording pure **34** as a solid (14.1 g, 93% yield) recovered after filtration. The enantiomeric ratio of the recovered HCl salt was 97:3 demonstrating that the reaction can easily be scaled to multigram quantities without compromising the enantioselectivity of the reaction.

In summary, we have developed an enantioselective Petasis borono-Mannich reaction of glycol aldehyde, amines, boronic acids or boronate esters, catalyzed by chiral biphenols. The reaction is executed under ambient conditions using solvents easily amenable to academic and industrial settings. We ultimately worked to achieve a mix and stir procedure that readily provides access to valuable chiral building blocks in enantioenriched form. We were able to use electron deficient and electron rich boronates with 1°, 2°, and aryl amines in an attempt to leverage the multi-component nature of the Petasis borono-Mannich reaction. Computational modeling of the diastereomeric transition states illustrates a two CH- $\pi$  interactions between the moderately acidic protons  $\alpha$  to the nitrogen in the morpholine ring

and the  $\pi$ -system of the electron-rich migrating aryl anion leading to a preferred **S-TS** transition state 3.2 kcal/mol lower than **R-TS** in free energy. Finally, the reaction was scaled to afford multigram quantities of the enantioenriched amino alcohol product using an extractive workup procedure eliminating the need for column chromatography. Our hope is that the method will be used by the community as a practical method for accessing chiral amino alcohols for use as building blocks in synthesis.

### **Dedication**

Dedicated to Professor Eric N. Jacobsen on the occasion of his 60<sup>th</sup> birthday.

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### **Competing Interests**

The authors report no competing financial interests in connection with this research.

### **Author Contributions**

J.A.K. and K.E.K. equally contributed to the experimental design and experimental execution. Preliminary experimental work was performed by R.D. and P.N.M. Computational experiments were performed by V.W.. M.J.V. designed computational experiments and wrote and participated in the preparation of the manuscript. S.E.S. designed experiments, wrote and coordinated the preparation of the manuscript.

**Supplementary Information** is available for this paper.

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