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Catalytic Asymmetric Petasis Reactions of Vinylboronates

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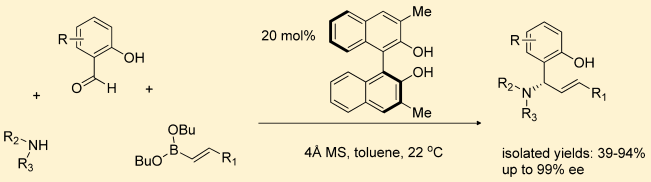
Supporting Information

ABSTRACT: Binaphthol-catalyzed asymmetric Petasis reactions of salicylaldehydes with dibutyl vinylboronates and secondary amines in the presence of 4 Å molecular sieves (MS) afforded products with up to 99% ee in isolated yields of 39−94%. The 99% ee of the product indicated that the reaction by the binaphthol-catalyzed pathway was roughly 500 times faster than the uncatalyzed pathway. NMR experiments (^{1}H and ^{11}B) showed that the amine component played a role in triggering the reaction between the binaphthol catalyst and the vinylboronate in the catalytic reaction sequence. The 4 Å MS enhanced both the rate and enantioselectivity by effective removal of water from the reaction system. A novel rearrangement reaction of the unconjugated allylic amine Petasis reaction product to a conjugated allylic amine was also observed.



INTRODUCTION

Multiple-component Petasis reactions of boronic acids or their esters with amines and aldehydes/ketones afford diverse complex structures in a single step from simple and readily available starting materials.[1] The reaction has been used in the synthesis of amino acids and alcohols,[2] iminocyclitols,[3] natural products,[4] and a drug recently approved for the treatment of multiple sclerosis (Gilenya).[5] The main characteristic of the Petasis reaction is the presence of a hydroxyl or carboxylic acid group proximate to the reacting aldehyde or ketone carbonyl group. This characteristic has been elegantly applied to diastereoselective syntheses of a variety of compounds of interest by taking advantage of the directing effect of the α-hydroxyl group of chiral aldehydes and ketones.[1,3,4] Diastereoselective syntheses have also been demonstrated using readily available chiral amines and boronates of chiral alcohols.[1] These approaches, however, have limited use for the Petasis reactions of salicylaldehydes because of lack of chirality in salicylaldehydes and their lower reactivity.[6]

Despite their potential versatility, few catalytic asymmetric Petasis reactions have been reported.[1] Lou and Schaus reported the first catalytic asymmetric Petasis reaction of glyoxylates with boronates using organocatalyst[7] binaphthols.[8] Later, Takemoto and co-workers reported a thiourea−alcohol conjugate-catalyzed asymmetric Petasis reaction of *N*-aryl-α-imino amides with vinylboronates.[9] Yuan and co-workers recently described catalytic asymmetric Petasis reactions of salicylaldehydes with boronic acids using thiourea−binaphthol conjugates[10] and binaphthols[11] as catalysts. Unfortunately, in addition to the modest ee afforded by the more readily available binaphthol catalysts, both catalytic systems showed low reactivity, with reactions typically taking 1−5 days. The substrate scope of the reaction partner amines was also limited to cyclic secondary amines.[10,11] The poor activity of these reaction systems may be due to either the low reactivity of the intermediates formed from the reactions between boronic acids and binaphthol catalysts or poor catalyst turnover rates.

In contrast to the boronic acids, the corresponding methyl, ethyl, isopropyl, and butyl esters showed significantly higher reactivity and enantioselectivity in a variety of reactions in the presence of binaphthol catalysts. Besides the Petasis reaction with glyoxylates,[8] good reactivity in asymmetric reactions have been shown by aryl-, alkenyl-, and acetylenylboronates with conjugated ketones,[12,13] hemiacetals,[14] and acylimines[15] and by allylboronates with acyl imines,[16] and ketones[17] in the presence of binaphthol catalysts to afford products in good ee and yields. The reactions were usually very slow in the absence of the binaphthol catalysts. To explain the high ee obtained, acyclic[8,14−17] or cyclic[13,18] binaphthol−boronate intermediates formed from reactions between binaphthols and boronates were proposed. These results suggested that the interactions between the binaphthols and boronates not only imparted stereoselectivity but also enhanced the reaction rate. The low catalyst loading required for some reactions suggested that the binaphthol catalysts were readily decoupled from the products once formed and reentered the catalytic cycle.

We have employed a non-stereoselective Petasis reaction of substituted salicylaldehydes with amines and boronic acids in the synthesis of a compound of biological interest.[19] During the development of enantioselective Petasis reaction conditions for the synthesis of the core structure of the compound, we found that binaphthols dramatically increased the rate of Petasis reactions of salicylaldehydes with vinylboronates to afford the chiral amines with high ee in good isolated yields. Herein we disclose the results of this study, which represents the first example of binaphthol-catalyzed asymmetric reactions of salicylaldehydes with vinylboronates and amines.

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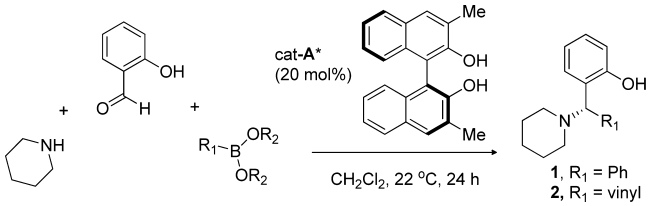
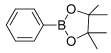
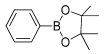
RESULTS AND DISCUSSION

The investigation began with an examination of the reactions of salicylaldehyde with commercially available phenyl- and vinylboronates in the presence of a binaphthol catalyst (cat-**A***) in CH_2Cl_2 at 22 °C (Table 1). For $PhB(OH)_2$ pinacol ester (entry 1), a product yield of <5% was observed after 24 h. Increased conversion (27%) was observed when 4 Å molecular sieves (MS) were added, similar to a previous account for the Petasis reaction of boronic acids.[19] The screening data from Table 1 indicated that vinylboronates were more reactive than the corresponding phenylboronates, and the 76% ee for $(vinyl)B(OBu)_2$ (entry 4), although modest, was worthy of additional investigation. Therefore, the reaction of $(vinyl)B(OBu)_2$ was studied further with the goal of improving the enantioselectivity of the transformation.

Table 1. Reactions of Salicylaldehyde with Commercially Available Aryl- and Vinylboronates[a]



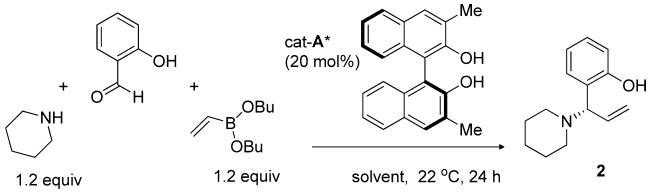
entry	$R_1B(OR_2)_2$	conversion (%)	ee (%)
1		<5	nd[c]
2		27[b]	nd[c]
3		74 (48 h)	34[d]
4		69[b]	nd[c]
5		100	76

[a]Conditions: salicylaldehyde (0.2 mmol), cat-**A*** (0.2 equiv), piperidine (1.2 equiv), boronate (1.2 equiv), CH_2Cl_2 (0.8 mL), 22 °C, 24 h. The conversions and ee were determined by HPLC. [b]The reaction was performed on a 0.8 mmol scale with 4 Å MS (200 mg) added. [c]Not determined. [d]With 4Å MS, conversion and ee (48 h) were 92% and 26%, respectively.

The effect of the solvent on the enantioselectivity of the reaction was explored first. Table 2 shows the ee of **2** obtained from the reaction in six different solvents in the presence of 20 mol % cat-**A***. As the data show, an increase in the ee from 76% in CH_2Cl_2 to 86% in toluene and trifluoromethylbenzene was obtained. A decrease in the ee to 46% was observed in EtOH.

The reaction was accelerated by cat-**A*** in all solvents. The reactions in the presence of the catalyst were completed in 24 h, except in toluene (91% conversion). The uncatalyzed reactions had significantly lower conversions; only the reaction in CH_2Cl_2 reached completion. Figure 1 shows the conversion rates of salicylaldehyde in three representative solvents. The observed ee values can be qualitatively explained by the differences between the rates of the catalyzed (solid lines) and uncatalyzed (dotted lines) reactions. The low ee obtained in EtOH (46%) was thought to be due to loss of catalytic activity

Table 2. Solvent Effect on the Enantioselectivity of the Binaphthol Catalyzed Petasis Reaction[a]



solvent	CH_2Cl_2	PhMe	EtOAc	$PhCF_3$	EtOH
ee (%)	76	86	84	86	46

[a]Conditions: salicylaldehyde (0.2 mmol), cat-**A*** (0.2 equiv), piperidine (1.2 equiv), $(vinyl)B(OBu)_2$ (1.2 equiv), solvent (0.8 mL), 22 °C, 24 h. The ee values were determined by chiral HPLC, and the conversions were 91−100%.[20]

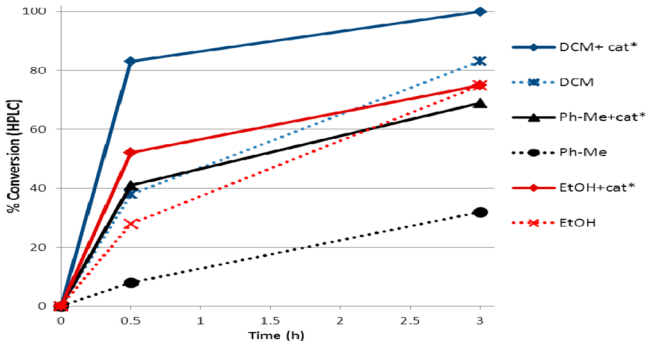


Figure 1. Conversions of salicylaldehyde in three representative solvents in the presence and absence of cat-**A***.

during the reaction, as indicated by the diminishing difference between the conversions for the catalyzed (solid line) and uncatalyzed (dotted line) reactions. The data also showed that the background reaction was significant in all solvents, indicating a potential difficulty in achieving high ee. For prior binaphthol-catalyzed reactions that achieved high ee, the rates of the background reactions seemed negligible under the conditions.[8,13]

The influence of the structure of the catalyst on the enantioselectivity was then examined in the two best reaction solvents (CH_2Cl_2 and toluene), and the results are shown in Table 3. As the data show, in CH_2Cl_2, the methyl group of cat-**A*** provided the optimal size for the 3 and 3′ substituents on the binaphthol, while the smaller hydrogen substituent of cat-**B*** and larger triphenylsilyl substituent of cat-**D*** provided poorer selectivity. In CH_2Cl_2, cat-**F*** was less effective than cat-**A*** and cat-**E***, but in toluene it was as effective as cat-**A*** and cat-**E***. In general, however, higher ee values were obtained in toluene than in CH_2Cl_2 regardless of the catalyst. Therefore, toluene was chosen as the standard solvent for further exploration of the reaction. In toluene, cat-**E***, cat-**F***, and cat-**A*** provided highest but similar ee values; therefore, the reaction was further investigated with only cat-**A*** and cat-**E***.

Molecular sieves have been used in many binaphthol-catalyzed reactions of boronates, and their enhancement of the reaction enantioselectivity was reported for binaphthol-catalyzed allylboration of acyl imines.[16] The positive effects of 4 Å MS on the rate and enantioselectivity of the reaction are shown in Figure 2. Similar results were observed for the reaction using cat-**E***. With the same amount of 4 Å MS, however, slightly higher ee values were obtained with cat-**A***.

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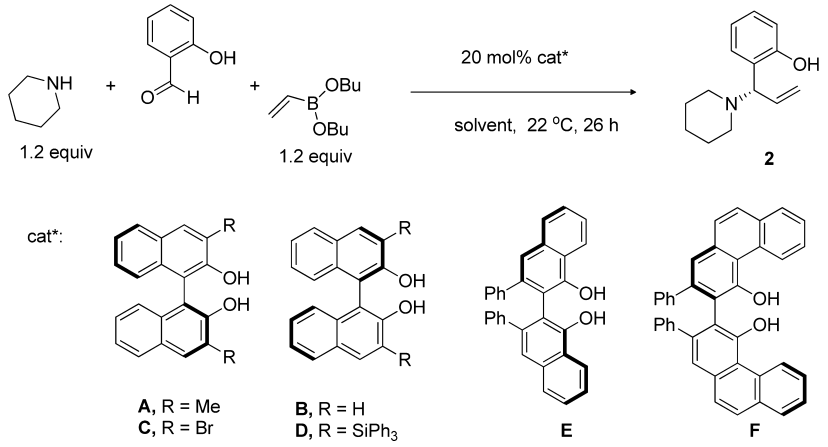
Table 3. Effect of Catalyst Structure on the Enantioselectivity of the Petasis Reaction in CH_2Cl_2 and Toluene[a]



catalyst	cat-**A***	cat-**B***[b]	cat-**C***	cat-**D***[b]	cat-**E***	cat-**F***
ee (%) in CH_2Cl_2	75	−63	44	−12	77	47
ee (%) in PhMe	85	−70	84	−30	90	87

[a]Conditions: salicylaldehyde (0.2 mmol), catalyst (0.2 equiv), piperidine (1.2 equiv), (vinyl)B$(OBu)_2$ (1.2 equiv), solvent (0.8 mL), 22 °C, 26 h. The ee values were determined by chiral HPLC, and the conversions were 91−100% as determined by HPLC. [b]The major product obtained with *R*-configured catalysts was the enantiomer of **2**.

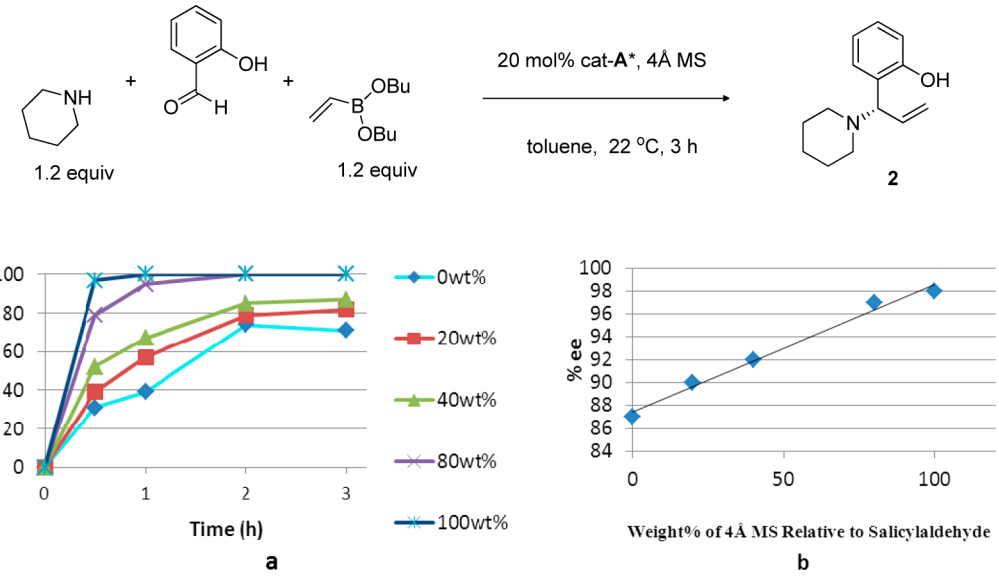
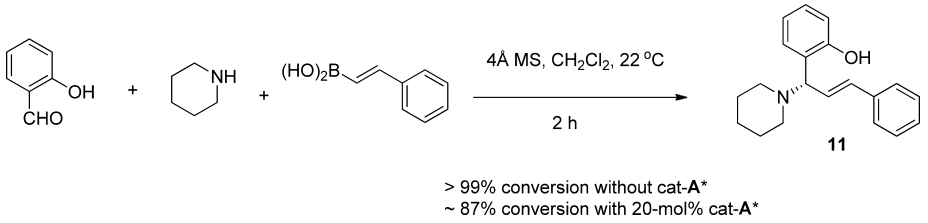


Figure 2. Enhancement of both (a) conversion rate and (b) enantioselectivity by 4 Å MS. Reaction conditions: salicylaldehyde (0.2 mmol), cat-**A*** (0.2 equiv), piperidine (1.2 equiv), (vinyl)B$(OBu)_2$ (1.2 equiv), 4 Å MS, toluene (0.8 mL), 22 °C, 3 h. The conversions and ee values were determined by HPLC.

Scheme 1. Petasis Reactions of a Boronic Acid in the Presence and Absence of cat-A*



Therefore, cat-A* was considered to be the better catalyst for this substrate and was used as the catalyst for additional studies. As the data show, the 4 Å MS not only accelerated the rate (Figure 2a) but also increased the ee of the product **2** (Figure 2b). Further experiments showed that the use of 100−600 wt % 4 Å MS relative to the weight of salicylaldehyde was acceptable, consistently affording product **2** in about 99% ee. The ee increase from 87% to 99% due to addition of 4 Å MS has practical significance because the resulting higher ee may be sufficient for most applications without the need for further

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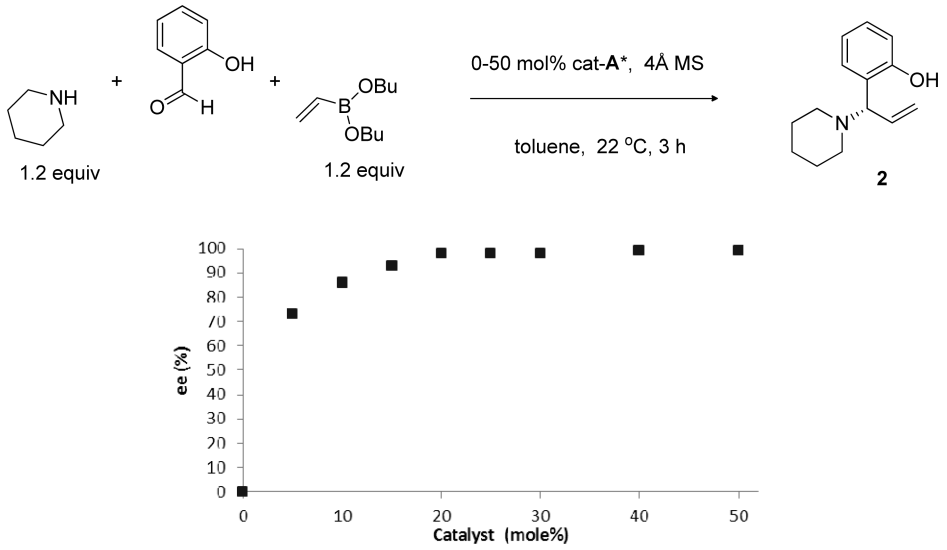
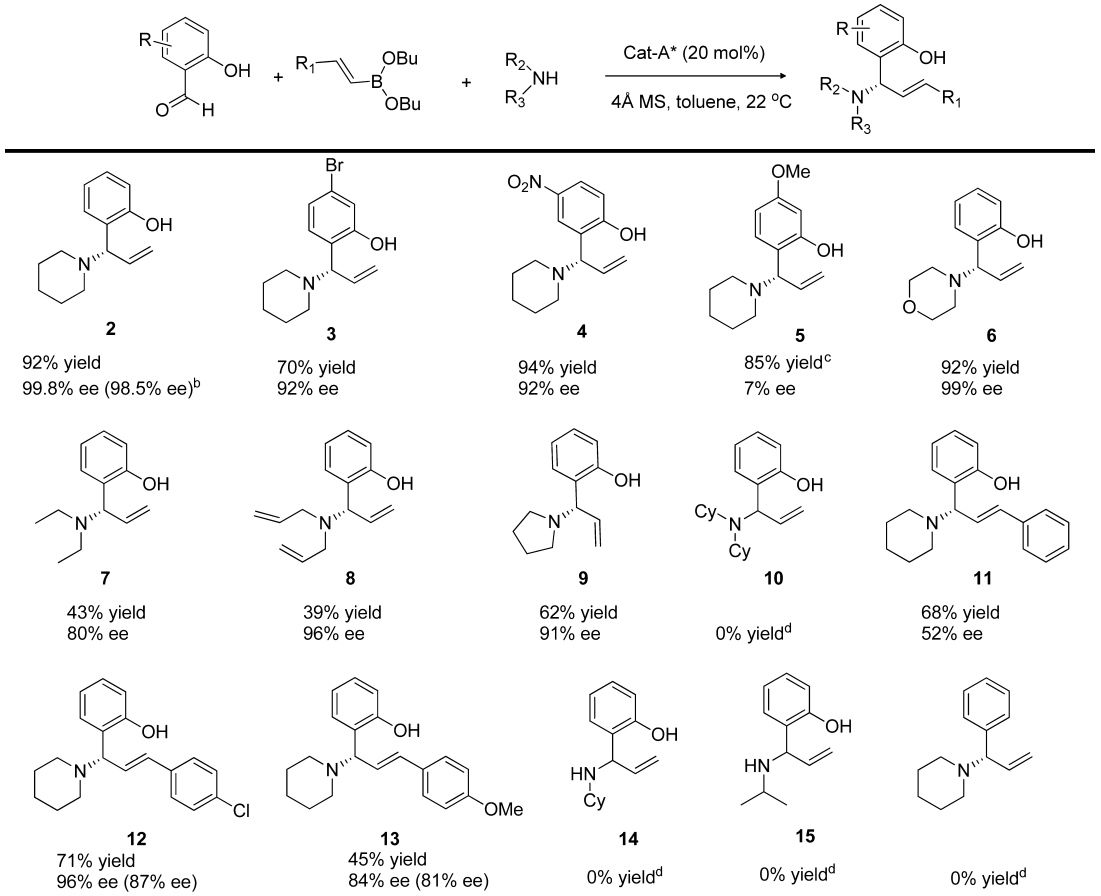


Figure 3. Effect of catalyst loading on the product ee. Reaction conditions: salicylaldehyde (0.2 mmol), cat-**A*** (0.2 equiv), piperidine (1.2 equiv), (vinyl)B(OBu)$_2$ (1.2 equiv), 4 Å MS, toluene (0.8 mL), 22 °C, 3 h. The conversions (95−100%) and ee were determined by HPLC.

Table 4. Scope of the Catalytic Asymmetric Petasis Reaction[a]



[a]Representative conditions for **2**: salicylaldehyde (1.6 mmol), cat-**A*** (0.2 equiv), piperidine (1.2 equiv), (vinyl)B(OBu)$_2$ (1.2 equiv), toluene (6 mL), 4 Å MS (1.6 g), 22 °C, 1.5 h. Yields of isolated products are shown. [b]Values in parentheses are for isolated products. [c]Yield of the crude product after subtraction of residual cat-**A***. [d]No Petasis reaction products were observed.

enrichment. Comparable effects were observed with 3 Å MS. $MgCl_2$ as a drying agent also enhanced the rate and the enantioselectivity of the reaction but was less effective than the 4 Å MS. Na_2SO_4 showed no effect, however.

These results are in agreement with earlier work describing the beneficial effects of 4 Å MS ascribed to their efficient removal of H_2O.[19] The MS may also diminish hydrolysis of the moisture-sensitive boronates to form the corresponding

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boronic acids, which had lower reaction rates in the presence of cat-**A*** and afforded products with low ee.

The Petasis reaction of salicylaldehydes with boronic acids in the presence of binaphthol catalysts was slow and provided products with 0−87% ee.[11] Our data indicated that the Petasis reaction of salicylaldehyde with the boronic acid (styrenyl)B-$(OH)_2$ in the presence of cat-**A*** and 4 Å MS was actually slower than that in the absence of the catalyst (Scheme 1) and provided lower enantioselectivity (<40% ee) than the reaction with the dibutyl ester of this acid (52% ee). HPLC monitoring revealed that the reaction of the boronic acid reached 91% conversion in 30 min and was complete in 2 h without cat-**A***. In the presence of the catalyst, the reaction stalled after 30 min. In contrast, the catalytic reaction of the dibutyl ester of the boronic acid was significantly faster than the uncatalyzed one and was complete in less than 30 min. These results suggested that the 4 Å MS also eliminated the negative effect of the boronic acid by preventing its formation via hydrolysis of the corresponding boronate.

The optimal amount of cat-**A*** for the reaction of salicylaldehyde with (vinyl)B$(OBu)_2$ and piperidine in toluene in the presence of 4 Å MS was determined experimentally. The results showed that the ee of **2** reached a plateau at around 98% ee with ∼20 mol % cat-**A*** (Figure 3).

The substrate scope of the reaction was explored with a variety of reaction partners, and the results are shown in Table 4. The data were obtained using the reaction conditions optimized for compound **2**, and the yields were not optimized. Cyclic and acyclic secondary amines (except $HNCy_2$) participated in the reaction, providing products **6**−**11** in good yields and ee. To our delight, the participation of acyclic secondary amines showed that the reaction had broader generality for the amine reaction partner compared with the binaphthol−thiourea- and binaphthol-catalyzed reactions of boronic acid systems, in which only cyclic secondary amines participate.[10,11]

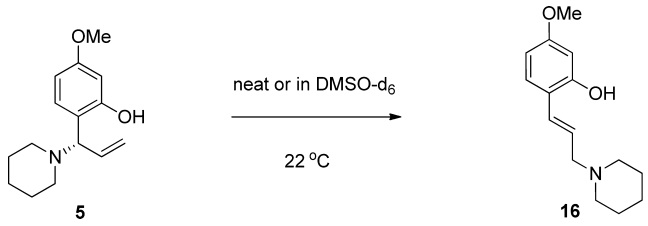
Two reactions run using primary amines (cyclohexylamine and isopropylamine), however, did not provide the desired products (**14** and **15**, respectively). HPLC analysis showed that >75% of the starting salicylaldehyde remained after 3 days for both reactions. These results are consistent with the observation that primary amines did not participate in the Petasis reaction of salicylaldehydes with either boronic acids[21] or boronates.[22] The vinylboronates with electron-neutral, -deficient, and -rich aryl substituents at the 2-position of the vinyl group also reacted to afford products **11**−**13**, respectively. The reaction worked well for electron-neutral and -deficient salicylaldehydes to give products **2**−**4** in good yields and ee.

With an electron-donating methoxy group on salicylaldehyde, the Petasis reaction went to completion in <30 min; however, analysis showed that the chiral purity of **5** was ∼7% ee. In addition, purification of **5** by silica gel column chromatography was hampered by an apparent lack of stability. The ^{1}H NMR spectrum of crude **5** obtained after aqueous workup showed fairly pure **5** containing ∼20 mol % cat-**A***. However, chromatographic isolation gave **5** in very low yield (the yield in Table 4 was based on crude **5** after subtraction of residual cat-**A*** content). In a separate experiment, pure **5** was obtained from the uncatalyzed reaction without a chromatographic purification. These results indicated that the reaction of 4-methoxysalicylaldehyde was fast and clean. The observed low ee was due to either the low stereoselectivity of the reaction or instability of the stereogenic center of **5**.

Discrepancies in the ee values determined in situ and after isolation (e.g., compounds **11**−**13**; Table 4) indicated that partial racemization of the stereogenic center occurred during isolation. Erosion of the ee was also observed upon holding samples of isolated products. For instance, a change of ee for **2** from 98.5% to 96.9% was observed after it was held in a vial at 22 °C for 4 days. Adding NEt*i*Pr$_2$ had no effect upon the ee erosion of **2**, but adding TFA did accelerate the ee erosion. The racemization of compound **2** in the reaction mixture at 22 °C without isolation was relatively slow, however. No change in ee after 48 h and a slight decrease (∼0.2%) after 5 days were observed. At lower temperatures (0−5 °C), **2** was chemically stable for at least 4 months as determined by NMR analysis.

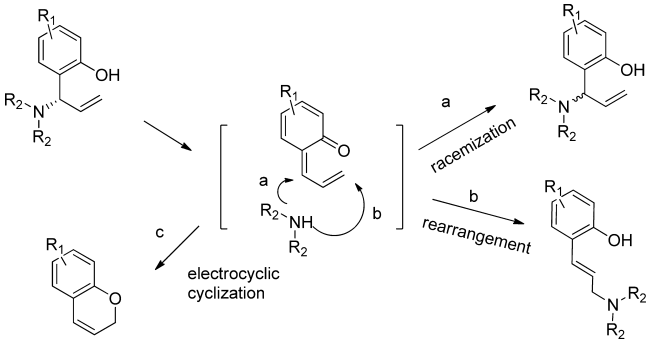
The racemic product **5** (oil) obtained from the uncatalyzed reaction was cleanly converted into a new solid compound, **16**, at 22 °C in 2 days. An NMR sample of **5** in DMSO-d_6 was also converted into **16**, and the ^{1}H NMR spectrum showed that **16** was the only product. ^{1}H and ^{13}C NMR and HRMS data indicated that **16** was a rearrangement product of **5** (Scheme 2).

Scheme 2. Rearrangement Reaction of Compound 5



The rearrangement of **5** and racemization of the compounds discussed above may occur through a quinone methide intermediate (Scheme 3), which was suggested[23] as an

Scheme 3. Possible Mechanism for the Racemization, Rearrangement, and Cyclization Reactions



intermediate in the formation of 2*H*-chromenes from aryl allylic amines.[24] The quinone methide can react with the amine eliminated during its formation, resulting in racemization (pathway a) or linear rearrangement products such as **16** (pathway b). It may also undergo an electrocyclization[25] to give the 2*H*-chromene (pathway c), which may alternatively be formed through an anionic cyclization mechanism as proposed previously.[24] The mechanism, substrate scope, and application of this rearrangement reaction are under investigation and will be reported separately.

The *S* configuration of **2** obtained using (*S*)-cat-**A*** was determined by using vibrational circular dichroism (VCD),[26]

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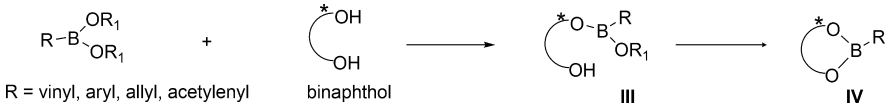
Scheme 4. Ligand Exchange Reaction between Binaphthols and Boronates



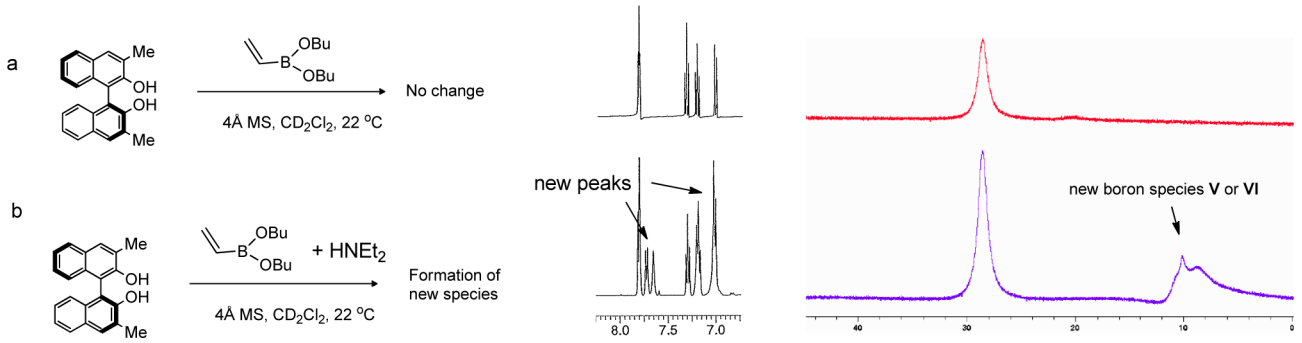
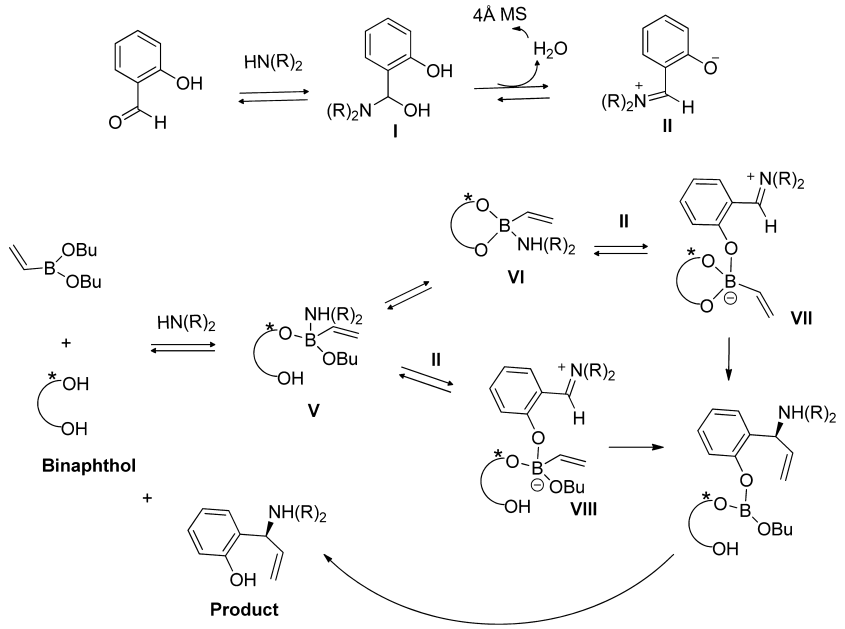


Figure 4. ^{1}H and ^{11}B NMR spectra of the reaction mixtures of cat-**A*** and (vinyl)$B(OBu)_2$ and $HNEt_2$. (a) Partial ^{1}H NMR and ^{11}B NMR spectra of the reaction mixture of cat-**A*** (1.0 equiv), (vinyl)$B(OBu)_2$ (1.0 equiv), and 4 Å MS in CD_2Cl_2 at 22 °C taken after the mixing was completed. (b) Partial ^{1}H NMR and ^{11}B NMR spectra of the reaction mixture of cat-**A*** (1.0 equiv), (vinyl)$B(OBu)_2$ (1.0 equiv), $HNEt_2$ (1.0 equiv), and 4 Å MS in CD_2Cl_2 at 22 °C taken after the mixing was completed. It should be noted that the ^{1}H NMR spectra of both reaction mixtures remained unchanged over 24 h except for the appearance of similar weak new signals.

Scheme 5. Proposed Mechanism



and that of **11** was determined on the basis of chiral HPLC analysis and comparison of its sign of optical rotation with literature data.[10] The *R* enantiomer of **2** was obtained in 98% ee with the *R* enantiomer of cat-**A***, as determined by chiral HPLC analysis. The absolute configurations of the other compounds in Table 4 were assigned by analogy.

The mechanism for the rate acceleration[27] of this catalytic Petasis reaction is not entirely clear. Acyclic (**III**) and cyclic (**IV**) types of structures formed from reactions between binaphthols and boronates have been proposed to explain the observed enantioselectivity of many reactions (Scheme 4).[12−18] Formation of **III** with a vinylboronate was reported on the basis of NMR and MS studies.[14] Our ^{1}H and ^{11}B NMR experiments showed that the reaction between cat-**A*** and (vinyl)$B(OBu)_2$ in CD_2Cl_2 in the presence of 4 Å MS (Figure 4a) to generate either acyclic **III** or cyclic **IV** was very slow[28] compared with the overall rate of the catalytic Petasis reaction, which was complete in <20 min in a NMR tube under the same conditions. Addition of salicylaldehyde did not affect the reaction between cat-**A*** and (vinyl)$B(OBu)_2$ in 24 h.[29]

However, addition of $HNEt_2$ resulted in the immediate appearance of new ^{1}H signals in the aromatic region (6.8−8.0 ppm) (Figure 4b). The spectra of the mixture remained the same over 24 h. Signals of $HNEt_2$ in the ^{1}H NMR spectra were broad, suggesting coordination of $HNEt_2$ to (vinyl)$B(OBu)_2$. New ^{11}B signals at 10.1 and 8.8 ppm in addition to the peak for (vinyl)$B(OBu)_2$ at 28.6 ppm were also detected from the mixture (Figure 4b). These data indicated formation of tetrahedral boron complexes[30] from the reaction. ^{1}H and ^{11}B NMR experiments showed that there was no change in the

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spectrum for (vinyl)B(OBu)$_2$ and HNEt$_2$ in CD_2Cl_2 in the presence of 4 Å MS at 22 °C in 24 h.[31]

These NMR observations prompted us to propose the reaction mechanism shown in Scheme 5. In this mechanism, HNEt$_2$ reacts with salicylaldehyde to form iminium **II**, a proposed key intermediate for the Petasis reaction,[19] through aminal **I**. HNEt$_2$ also activates and participates in the reaction between cat-**A*** and (vinyl)B(OBu)$_2$ to form reactive intermediate **V** or **VI**, which then leads to the cyclic (**VII**) or acyclic (**VIII**) intermediate, respectively. Migration of the vinyl group in **VII** or **VIII** affords the Petasis product boron complex, which gives the final product after aqueous workup. Each step of this catalytic reaction sequence is faster than the rate-limiting step of the uncatalyzed pathway, resulting in the overall rate acceleration. The criticality of the −OH group of salicylaldehyde indicated in the mechanism was confirmed when PhCHO did not react under the same conditions. The structures of **V**−**VIII** and the mechanism for the rate acceleration of this catalytic Petasis reaction, particularly the role of the amine components, are the subject of further studies whose results will be reported in due course.

CONCLUSION

A novel and highly enantioselective catalytic asymmetric Petasis reaction of salicylaldehydes with secondary amines and vinylboronates has been achieved using a binaphthol/molecular sieves catalytic system. The amine component of the reaction also plays a role in activating the reaction between cat-**A*** and (vinyl)B(OBu)$_2$.

EXPERIMENTAL SECTION

General. All reagents, catalysts, and solvents were purchased from commercial sources and used as received. Both (*S*)- and (*R*)-3,3′-dimethyl-1,1′-binaphthalene-2,2′-diol catalysts were purchased from Astar Pharma. Molecular sieves (4 Å, activated, 2.5 μm, powdered) were purchased from Aldrich. NMR spectra were recorded at 400 MHz for ^{1}H and at 100 MHz for ^{13}C. Chemical shifts are expressed as δ values in parts per million using TMS or the residual signals of the solvents as the internal standard. High-resolution mass spectra were acquired using an FT ICR instrument. HPLC data were collected with UV detection at 214 nm or as specified using a Sunfire column (C18, 3.5 μm, 150 mm × 4.6 mm) and mobile phases A (water with 0.1% TFA) and B (acetonitrile with 0.1% TFA) with a linear gradient from 30 to 70% B in 15 min at a flow rate of 1 mL/min. The products were isolated by flash chromatography with a CH_2Cl_2/IPA gradient eluent.

Representative Procedure for the Preparation of Racemic Samples: Preparation of Racemic 5-Methoxy-2-(1-(piperidin-1-yl)allyl)phenol (5). To a magnetically stirred mixture of 4-methoxy-2-hydroxybenzaldehyde (121 mg, 0.8 mmol), 4 Å molecular sieves (0.8 g), and dibutyl vinylboronate (211 μL, 0.96 mmol, 1.2 equiv) in toluene (6 mL) was added piperidine (96 μL, 0.97 mmol, 1.2 equiv). The mixture was stirred at 22 °C for 20 h (until completion as determined by HPLC analysis) and then filtered through a Celite bed. The Celite bed was washed with toluene. The combined filtrates were washed with dilute brine (three times), dried over anhydrous Na_2SO_4, filtered, and concentrated on a rotary evaporator to give product **5** as an oil (166 mg, 84% yield). The purity and structure of **5** were verified by ^{1}H NMR analysis. All other racemic samples prepared by this procedure were confirmed by ^{1}H NMR analysis and used for the development of the chiral HPLC methods without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.77 (br, 1H), 6.74 (d, *J* = 8.28 Hz, 1H), 6.30 (d, *J* = 2.26 Hz, 1H), 6.24 (dd, *J* = 2.51, 8.28 Hz, 1H), 5.80−5.96 (m, 1H), 5.06−5.22 (m, 2H), 3.84 (d, *J* = 9.54 Hz, 1H), 3.65 (s, 3H), 2.22−2.78 (m, 4H), 1.44−1.65 (m, 4H), 1.28−1.43 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 156.8, 133.2, 127.0, 116.7, 115.3, 103.2, 100.1, 71.7, 53.4, 49.2, 24.3, 22.5; ESI-HRMS calcd for $C_{15}H_{22}NO_2$ $[M + H]^+$ 248.16541, found 248.16438.

Representative Procedure for Catalytic Asymmetric Petasis Reactions: Preparation of (*S*)-2-(1-(Piperidin-1-yl)allyl)phenol (2). To a magnetically stirred mixture of 2-hydroxybenzaldehyde (195.4 mg, 1.6 mmol), (*S*)-3,3′-dimethyl-1,1′-binaphthalene-2,2′-diol (100.6 mg, 0.32 mmol, 0.2 equiv), 4 Å molecular sieves (1.60 g), and dibutyl vinylboronate (423 μL, 1.92 mmol, 1.2 equiv) in toluene (6 mL) was added piperidine (192 μL, 1.94 mmol, 1.2 equiv). The mixture was stirred at 22 °C for 1.5 h and then filtered through a Celite bed (Note: The reaction was first monitored by HPLC after 30 min of reaction time, and the data showed that the reaction was complete. For some reactions below, the first HPLC analysis was done after 24 h.) The Celite bed was washed with toluene. The product in the filtrate had 99% ee as determined by HPLC analysis (Chiralcel OD-H column, eluent *n*-hexane containing 0.1% HNEt$_2$, flow rate = 0.8 mL/min, 35 °C, signal detection at 280 nm): t_{major} = 12.1 min, 99.4%; t_{minor} = 16.8 min, 0.6%. The combined filtrates were washed with dilute brine (three times), dried over anhydrous Na_2SO_4, filtered, and concentrated on a rotary evaporator. The residue was isolated by flash chromatography, and the fractions containing product **2** were combined and concentrated on a rotary evaporator to give **2** as a colorless oil (317 mg, 91% yield). The *S* configuration of **2** was determined using VCD.[26] The enantiomeric excess was 98.4% ee as determined by HPLC (same method as above): t_{major} = 11.8 min, 99.2%; t_{minor} = 16.0 min, 0.8%. $[\alpha]_{546}^{26}$ = +248° (*c* = 0.10, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.48 (br s, 1H), 7.04−7.13 (m, 1H), 7.00 (dd, *J* = 1.25, 7.53 Hz, 1H), 6.65−6.78 (m, 2H), 5.94 (td, *J* = 9.69, 17.00 Hz, 1H), 5.30 (dd, *J* = 1.63, 16.94 Hz, 1H), 5.21 (dd, *J* = 2.01, 10.04 Hz, 1H), 4.08 (d, *J* = 9.54 Hz, 1H), 2.27−2.53 (m, 4H), 1.47−1.64 (m, 4H), 1.34−1.46 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.7, 135.6, 128.2, 128.2, 125.0, 118.8, 118.4, 115.8, 71.9, 50.7, 25.6, 23.8; ESI-HRMS calcd for $C_{14}H_{20}NO$ $[M + H]^+$ 218.15394, found 218.15401.

The *R* enantiomer of **2**, (*R*)-2-(1-(piperidin-1-yl)allyl)phenol, was made with (*R*)-cat-**A*** using the same procedure. The enantiomeric excess was 98% ee based on chiral HPLC analysis: t_{major} = 14.6 min, 99.3%; t_{minor} = 11.2 min, 0.7%.

*(S)-5-Bromo-2-(1-(piperidin-1-yl)allyl)phenol (**3**).* 4-Bromo-2-hydroxybenzaldehyde (321.6 mg, 1.6 mmol), (*S*)-3,3′-dimethyl-1,1′-binaphthalene-2,2′-diol (100.6 mg, 0.32 mmol, 0.2 equiv), 4 Å molecular sieves (1.60 g), and dibutyl vinylboronate (423 μL, 1.92 mmol, 1.2 equiv) in toluene (6 mL), piperidine (192 μL, 1.94 mmol, 1.2 equiv), 22 °C, 24 h. 92% ee by HPLC analysis (Chiralcel OD-H column, eluent *n*-hexane containing 0.1% HNEt$_2$, flow rate = 0.8 mL/min, 35 °C, signal detection at 280 nm): t_{major} = 10.1 min, 96%; t_{minor} = 11.9 min, 4%. Oil (330 mg, 70% yield). $[\alpha]_{546}^{26}$ = +239° (*c* = 0.054, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.83−7.00 (m, 3H), 5.90 (td, *J* = 9.60, 16.94 Hz, 1H), 5.32 (dd, *J* = 1.63, 16.94 Hz, 1H), 5.25 (dd, *J* = 1.76, 10.04 Hz, 1H), 4.12 (d, *J* = 9.29 Hz, 1H), 2.29−2.52 (m, 4H), 1.47−1.61 (m, 4H), 1.32−1.45 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.2, 135.0, 129.9, 124.7, 121.5, 120.6, 119.0, 118.4, 70.8, 50.5, 25.5, 23.7; ESI-HRMS calcd for $C_{14}H_{19}BrNO$ $[M + H]^+$ 296.06445, found 296.06453.

*(S)-4-Nitro-2-(1-(piperidin-1-yl)allyl)phenol (**4**).* 4-Nitro-2-hydroxybenzaldehyde (267.4 mg, 1.6 mmol), (*S*)-3,3′-dimethyl-1,1′-binaphthalene-2,2′-diol (100.6 mg, 0.32 mmol, 0.2 equiv), 4 Å molecular sieves (1.60 g), and dibutyl vinylboronate (423 μL, 1.92 mmol, 1.2 equiv) in toluene (6 mL), piperidine (192 μL, 1.94 mmol, 1.2 equiv), 22 °C, 24 h. 92% ee by HPLC (Chiralcel OD-H column, eluent 99:1:0.1 hexanes/IPA/HNEt$_2$, flow rate = 0.8 mL/min, 35 °C, signal detection at 280 nm): t_{major} = 12.4 min, 96%; t_{minor} = 13.9 min, 4%. Oil (393 mg, 94%). $[\alpha]_{546}^{26}$ = +183° (*c* = 0.093, MeOH); ^{1}H NMR (400 MHz, DMSO- d_6) δ 8.02 (dd, *J* = 2.76, 9.04 Hz, 1H), 7.93 (d, *J* = 2.76 Hz, 1H), 6.78 (d, *J* = 9.04 Hz, 1H), 6.00 (td, *J* = 9.73, 16.94 Hz, 1H), 5.32−5.53 (m, 2H), 4.47 (d, *J* = 9.29 Hz, 1H), 2.48−2.68 (m, 4H), 1.51−1.66 (m, 4H), 1.34−1.48 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.4, 137.9, 133.1, 125.2, 124.7, 124.4, 121.2, 116.8, 70.1, 50.0, 25.0, 23.2; ESI-HRMS calcd for $C_{14}H_{19}N_2O_3$ $[M + H]^+$ 263.13902, found 263.13906.

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*(S)-5-Methoxy-2-(1-(piperidin-1-yl)allyl)phenol (**5**).* 4-Methoxy-2-hydroxybenzaldehyde (243 mg, 1.6 mmol), (*S*)-3,3′-dimethyl-1,1′-binaphthalene-2,2′-diol (100.6 mg, 0.32 mmol, 0.2 equiv), 4 Å molecular sieves (1.60 g), and dibutyl vinylboronate (423 μL, 1.92 mmol, 1.2 equiv) in toluene (6 mL), piperidine (192 μL, 1.94 mmol, 1.2 equiv), 22 °C, 1 h. 7% ee by HPLC (Chiralcel OD-H column, eluent 99:1:0.1 hexanes/isopropanol/diethylamine, flow rate = 0.8 mL/min, 35 °C, signal detection at 280 nm): t_{major} = 10.6 min, 54%; t_{minor} = 11.3 min, 46%. Oil (183 mg, crude, containing 20 mol %, 85% yield after subtraction of residual catalyst based on NMR analysis). The characterization data for this compound were obtained with a racemic sample immediately after it was made (see the data in Representative Procedure for the Preparation of Racemic Samples).

Compound **5** was not stable (0−22 °C) and was cleanly converted into a new solid compound, (*E*)-5-methoxy-2-(3-(piperidin-1-yl)prop-1-en-1-yl)phenol (**16**), at 22 °C in 2 days. Characterization data of **14** are provided below.

*(E)-5-Methoxy-2-(3-(piperidin-1-yl)prop-1-en-1-yl)phenol (**16**).* Pure compound **16** (solid) was obtained from racemic 5-methoxy-2-(1-(piperidin-1-yl)allyl)phenol (**5**) when it was left on the bench at 22 °C for ∼2 days and then slurried in EtOAc and dried. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.53 Hz, 1H), 6.55−6.69 (m, 1H), 6.29−6.52 (m, 3H), 3.75 (s, 3H), 3.17 (d, *J* = 6.78 Hz, 2H), 2.32−2.71 (m, 4H), 1.62−1.78 (m, 4H), 1.37−1.58 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 155.9, 129.5, 129.4, 124.8, 117.7, 105.5, 102.2, 62.7, 55.2, 54.3, 25.3, 24.2; ESI-HRMS calcd for $C_{15}H_{22}NO_2$ $[M + H]^+$ 248.16541, found 248.16430.

*(S)-2-(1-Morpholinoallyl)phenol (**6**).* 2-Hydroxybenzaldehyde (195.0 mg, 1.6 mmol), (*S*)-3,3′-dimethyl-1,1′-binaphthalene-2,2′-diol (100.6 mg, 0.32 mmol, 0.2 equiv), 4 Å molecular sieves (1.60 g), and dibutyl vinylboronate (423 μL, 1.92 mmol, 1.2 equiv) in toluene (6 mL), morpholine (168 μL, 1.92 mmol, 1.2 equiv), 22 °C, 24 h. 99% ee by HPLC (Chiralcel OD-H column, eluent 99:1:0.1 hexanes/IPA/$HNEt_2$, flow rate = 0.8 mL/min, 35 °C, signal detection at 280 nm): t_{major} = 12.9 min, 99.5%; t_{minor} = 14.2 min, 0.5%. Oil (324 mg, 92%). $[\alpha]^{26}_{546}$ = +212° (*c* = 0.11, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 6.99−7.18 (m, 2H), 6.65−6.85 (m, 2H), 5.91 (td, *J* = 9.60, 16.94 Hz, 1H), 5.30 (dd, *J* = 1.51, 16.82 Hz, 1H), 5.17 (dd, *J* = 1.76, 10.04 Hz, 1H), 4.07 (d, *J* = 9.29 Hz, 1H), 3.60 (t, *J* = 4.64 Hz, 4H), 2.24−2.53 (m, 4H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 155.8, 136.7, 128.5, 128.2, 125.0, 119.2, 118.0, 115.7, 70.7, 66.2, 50.8; ESI-HRMS calcd for $C_{13}H_{18}NO_2$ $[M + H]^+$ 220.13325, found 220.13325.

*(S)-2-(1-(Diethylamino)allyl)phenol (**7**).* 2-Hydroxybenzaldehyde (195.0 mg, 1.6 mmol), (*S*)-3,3′-dimethyl-1,1′-binaphthalene-2,2′-diol (100.6 mg, 0.32 mmol, 0.2 equiv), 4 Å molecular sieves (1.60 g), and dibutyl vinylboronate (423 μL, 1.92 mmol, 1.2 equiv) in toluene (6 mL), diethylamine (199 μL, 1.92 mmol, 1.2 equiv), 22 °C, 24 h. 80% ee by HPLC analysis (Chiralcel OD-H column, eluent *n*-hexane containing 0.1% $HNEt_2$, flow rate = 0.8 mL/min, 35 °C, signal detection at 280 nm): t_{major} = 10.7 min, 90.0%; t_{minor} = 14.1 min, 10%. Oil (140 mg, 43%). $[\alpha]^{26}_{546}$ = −15° (*c* = 0.075, MeOH); ^{1}H NMR (400 MHz, DMSO- d_6) δ 7.06−7.14 (m, 1H), 7.00 (d, *J* = 6.78 Hz, 1H), 6.74 (dt, *J* = 0.88, 7.47 Hz, 1H), 6.69 (d, *J* = 8.03 Hz, 1H), 5.96 (td, *J* = 9.79, 17.07 Hz, 1H), 5.26−5.42 (m, 2H), 4.45 (d, *J* = 9.29 Hz, 1H), 2.59−2.73 (m, 2H), 2.45−2.56 (m, 2H), 1.02 (t, *J* = 7.15 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.2, 134.4, 128.2, 128.0, 125.3, 119.2, 118.7, 115.8, 66.9, 42.4, 11.5; ESI-HRMS calcd for $C_{13}H_{20}NO$ $[M + H]^+$ 206.15394, found 206.15399.

*(S)-2-(1-(Diallylamino)allyl)phenol (**8**).* 2-Hydroxybenzaldehyde (195.0 mg, 1.6 mmol), (*S*)-3,3′-dimethyl-1,1′-binaphthalene-2,2′-diol (100.6 mg, 0.32 mmol, 0.2 equiv), 4 Å molecular sieves (1.60 g), and dibutyl vinylboronate (423 μL, 1.92 mmol, 1.2 equiv) in toluene (6 mL), diallylamine (239 μL, 1.94 mmol, 1.2 equiv), 22 °C, 24 h. 96% ee by HPLC (Chiralcel OD-H column, eluent *n*-hexane containing 0.1% $HNEt_2$, flow rate = 0.8 mL/min, 35 °C, signal detection at 280 nm): t_{major} = 10.0 min, 98.0%; t_{minor} = 13.3 min, 2%. Oil (144 mg, 39%). $[\alpha]^{26}_{546}$ = +3.7° (*c* = 0.054, MeOH); ^{1}H NMR (400 MHz, DMSO- d_6) δ 10.86 (s, 1H), 7.02−7.15 (m, 2H), 6.70−6.79 (m, 2H), 5.91−6.06 (m, 1H), 5.84 (tdd, *J* = 6.59, 10.32, 16.91 Hz, 2H), 5.25−5.36 (m, 2H), 5.10−5.24 (m, 4H), 4.49 (d, *J* = 9.29 Hz, 1H), 3.01−3.25 (m, 4H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 156.6, 134.9, 134.1, 128.3, 128.2, 125.2, 119.1, 119.0, 118.8, 115.8, 65.6, 51.7; ESI-HRMS calcd for $C_{15}H_{20}NO$ $[M + H]^+$ 230.15394, found 230.15400.

*(S)-2-(1-(Pyrrolidin-1-yl)allyl)phenol (**9**).* 2-Hydroxybenzaldehyde (195.0 mg, 1.6 mmol), (*S*)-3,3′-dimethyl-1,1′-binaphthalene-2,2′-diol (100.6 mg, 0.32 mmol, 0.2 equiv), 4 Å molecular sieves (1.60 g), and dibutyl vinylboronate (423 μL, 1.92 mmol, 1.2 equiv) in toluene (6 mL), pyrrolidine (162 μL, 1.94 mmol, 1.2 equiv), 22 °C, 24 h. 91% ee by HPLC (Chiralcel OD-H column, eluent *n*-hexane containing 0.1% $HNEt_2$, flow rate = 0.8 mL/min, 35 °C, signal detection at 280 nm): t_{major} = 11.9 min, 95.5%; t_{minor} = 14.2 min, 4.5%. Oil (200 mg, 62%). $[\alpha]^{26}_{546}$ = +228° (*c* = 0.054, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.07 (br s, 1H), 7.02−7.14 (m, 2H), 6.64−6.79 (m, 2H), 5.90−6.06 (m, 1H), 5.26 (dd, *J* = 1.38, 16.94 Hz, 1H), 5.07 (dd, *J* = 1.76, 10.04 Hz, 1H), 4.00 (d, *J* = 8.78 Hz, 1H), 2.35−2.62 (m, 4H), 1.63−1.84 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.1, 138.0, 128.1, 127.9, 126.2, 118.9, 116.3, 115.6, 70.9, 51.4, 23.0; ESI-HRMS calcd for $C_{13}H_{18}NO$ $[M + H]^+$ 204.13829, found 204.13831.

*(S,E)-2-(3-Phenyl-1-(piperidin-1-yl)allyl)phenol (**11**).* This compound is the enantiomer of a known compound.[10] 2-Hydroxybenzaldehyde (195 mg, 1.6 mmol), (*S*)-3,3′-dimethyl-1,1′-binaphthalene-2,2′-diol (100.6 mg, 0.32 mmol, 0.2 equiv), 4 Å molecular sieves (1.60 g), and dibutyl phenylvinylboronate (499 mg, 1.92 mmol, 1.2 equiv) in toluene (6 mL), piperidine (192 μL, 1.94 mmol, 1.2 equiv), 22 °C, 24 h. 52% ee by HPLC (Chiralpak AD-H column, eluent 97:3:0.1 *n*-hexane/EtOH/diethylamine, flow rate = 0.8 mL/min, 35 °C, signal detection at 280 nm): t_{major} = 6.3 min, 76%; t_{minor} = 6.9 min, 24%. Oil (321 mg, 68%) that turned into a solid in the refrigerator. $[\alpha]^{26}_{546}$ = +44° (*c* = 0.054, MeOH).

*(S,E)-2-(3-(4-Chlorophenyl)-1-(piperidin-1-yl)allyl)phenol (**12**).* 2-Hydroxybenzaldehyde (69 mg, 0.56 mmol), (*S*)-3,3′-dimethyl-1,1′-binaphthalene-2,2′-diol (35.5 mg, 0.11 mmol, 0.2 equiv), 4 Å molecular sieves (0.2 g), and dibutyl 4-chlorophenylvinylboronate (200 mg, 0.68 mmol, 1.2 equiv) in toluene (2 mL), piperidine (68 μL, 0.68 mmol, 1.2 equiv), 22 °C, 1.5 h. 96% ee by HPLC (Chiralpak AD-H column, eluent 97:3:0.1 *n*-hexane/EtOH/$HNEt_2$, flow rate = 1.0 mL/min, 35 °C, signal detection at 280 nm): t_{major} = 5.5 min, 98%; t_{minor} = 9.7 min, 2%. Oil (169 mg, 91%) that turned into a solid in the refrigerator. $[\alpha]^{26}_{546}$ = +50° (*c* = 0.046, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (d, *J* = 8.53 Hz, 2H), 7.37 (d, *J* = 8.28 Hz, 2H), 7.02−7.14 (m, 2H), 6.62−6.81 (m, 3H), 6.44 (dd, *J* = 9.54, 15.81 Hz, 1H), 4.26 (d, *J* = 9.29 Hz, 1H), 2.35−2.58 (m, 4H), 1.48−1.66 (m, 4H), 1.32−1.46 (m, 2H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 156.6, 135.1, 132.0, 131.2, 128.5, 128.3, 128.3, 128.2, 128.1, 125.1, 118.9, 115.8, 70.8, 50.8, 25.6, 23.7; ESI-HRMS calcd for $C_{20}H_{22}ClNO$ $[M + H]^+$ 328.14627, found 328.14637.

*(S,E)-2-(3-(4-Methoxyphenyl)-1-(piperidin-1-yl)allyl)phenol (**13**).* 2-Hydroxybenzaldehyde (28 mg, 0.23 mmol), (*S*)-3,3′-dimethyl-1,1′-binaphthalene-2,2′-diol (14.5 mg, 0.046 mmol, 0.2 equiv), 4 Å molecular sieves (0.4 g), and dibutyl 4-methoxyphenylvinylboronate (80 mg, 0.28 mmol, 1.2 equiv) in toluene (0.9 mL), piperidine (28 μL, 0.28 mmol, 1.2 equiv), 22 °C, 1 h. 84% ee by HPLC (Chiralcel OD-H column, eluent 97:3:0.1 *n*-hexane/EtOH/$HNEt_2$, flow rate = 0.7 mL/min, 35 °C, signal detection at 280 nm): t_{major} = 7.2 min, 92% (area); t_{minor} = 7.6 min, 8%. Oil (40 mg, 43%) that turned into a solid in the refrigerator. $[\alpha]^{26}_{546}$ = +0.85° (*c* = 0.117, MeOH); ^{1}H NMR (400 MHz, DMSO- d_6) δ 11.64 (br s, 1H), 7.40 (d, *J* = 8.78 Hz, 2H), 7.07 (dq, *J* = 1.63, 7.74 Hz, 2H), 6.88 (d, *J* = 8.78 Hz, 2H), 6.68−6.76 (m, 2H), 6.60 (d, *J* = 15.81 Hz, 1H), 6.24 (dd, *J* = 9.54, 15.81 Hz, 1H), 4.22 (d, *J* = 9.54 Hz, 1H), 3.74 (s, 3H), 2.38−2.60 (m, 4H), 1.49−1.60 (m, 4H), 1.37−1.47 (m, 2H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 158.9, 156.7, 132.2, 128.8, 128.2, 128.0, 127.6, 125.5, 124.5, 118.8, 115.7, 113.9, 71.2, 55.0, 50.7, 25.6, 23.7; ESI-HRMS calcd for $C_{21}H_{26}NO_2$ $[M + H]^+$ 324.19581, found 324.19585.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Procedures, characterization data, ^{1}H and ^{13}C NMR spectra, and chiral HPLC chromatograms of the new compounds and

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^{1}H and ^{11}B NMR spectra for mechanistic studies. 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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