Article

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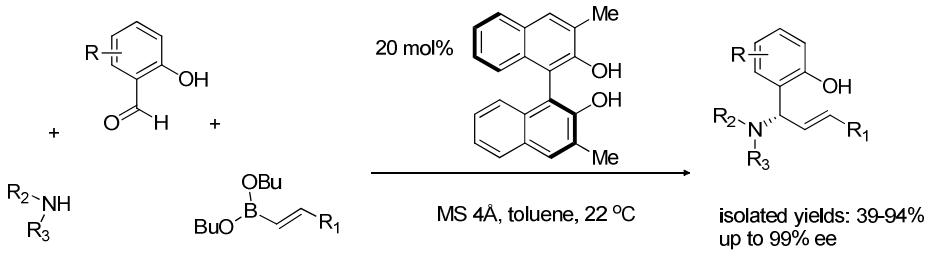


Abstract: Binaphthol catalyzed asymmetric Petasis reactions of salicylaldehydes with dibutyl vinylboronates and secondary amines in the presence of 4Å molecular sieves (MS) afforded products in up to 99% ee and 39−94% isolated yields. The 99% ee of product indicated that the reaction by the binaphthol catalyzed pathway was roughly five hundred times faster than the uncatalyzed pathway. NMR experiments (^{1}H and ^{11}B) showed the amine component played a role in triggering the reaction between the binaphthol catalyst and the vinylboronate in the catalytic reaction sequence. 4Å 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 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 due to 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 the 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 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] aryl-, alkenyl-, and acetylenylboronates have shown good reactivity in asymmetric reactions with conjugated ketones,[1212,13] hemiacetals,[14] and acylimines,[15] as well as 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[12,18] binaphthol-boronate intermediates formed from reactions between binaphthols and boronates were proposed. These results suggested interactions between binaphthols and the boronates not only imparted stereoselectivity, but also enhanced reaction rates. Low catalyst loading required for some reactions suggested that the binaphthol catalysts readily decoupled from the products once formed and reentered the catalytic cycle.

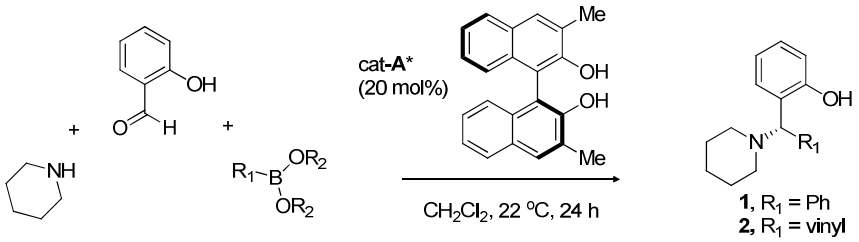
We have employed a non-stereoselective Petasis reaction of substituted salicylaldehydes with amines and boronic acids in the synthesis of a compound of biologic interest.[19] During the development of enantioselective Petasis reaction conditions for synthesis of the core structure of the compound, we found that binaphthols dramatically increased the rate of Petasis reactions of salicylaldehydes with vinylboronates to afford the chiral amines in high ee and 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.

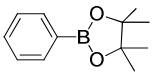
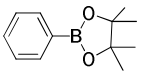
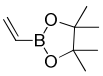
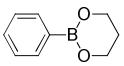
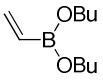
Results and discussion

The investigation began by examining 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 ^oC (Table 1). For $PhB(OH)_2$ pinacol ester (entry 1), < 5% product was observed after 24 h. Increased conversion (27%) was observed when molecular sieves (MS) 4Å 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 $vinylB(OBu)_2$ (entry 4), although modest, was worthy of additional investigation.

Therefore, the reaction of vinylB(OBu)$_2$ was studied further with a goal to improve the enantioselectivity of the transformation.

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



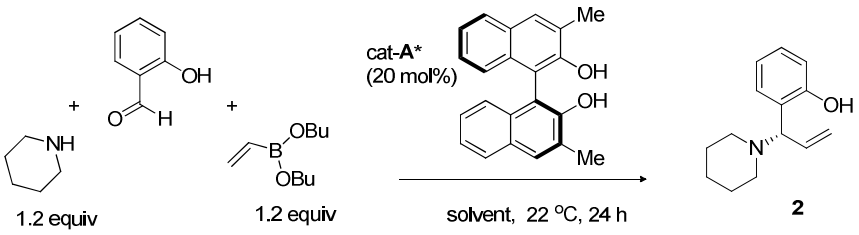
entry	$R_1B(OR_2)_2$	conversion (%)	ee (%)
1		<5	nd[c]
2		27 [b]	nd[c]
3		92 (48 h)	26
4		69[b]	nd[c]
5		100	76

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 ^oC, 24 h. The conversions and ee were determined by HPLC. b. Reactions done at 0.8 mmol scale with 4Å MS (200 mg) added. c. not determined.

The effect of solvents on 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, increase of ee from 76% in CH_2Cl_2 to 86% in toluene and trifluoromethyl benzene was obtained. Decrease of ee to 46% was observed in EtOH.

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



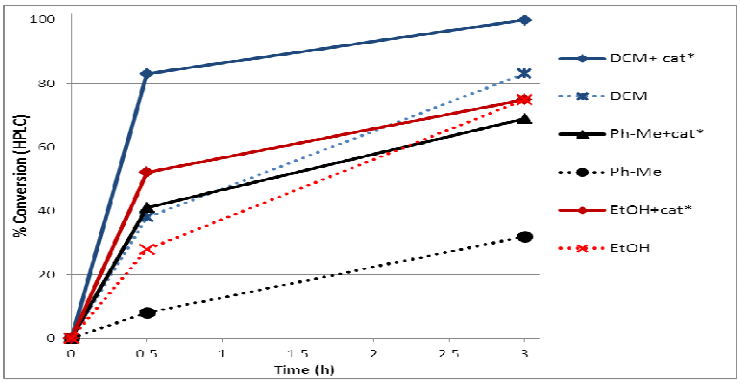
solvent	CH_2Cl_2	PhMe	EtOAc	$PhCF_3$	EtOH
ee (%)	76	86	84	86	46

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

The reaction was accelerated by cat-**A*** in all solvents. The reactions in the presence of the catalyst were completed in 24 h with the exception in toluene (91% conversion). Uncatalyzed reactions had significantly lower conversions; only the reaction in CH_2Cl_2 completed. Figure 1 shows the conversion rates of salicylaldehyde in three representative solvents. The observed ee can be qualitatively explained by the differences between rates of the catalyzed (in solid lines) and uncatalyzed (in dotted lines) reactions. The low ee (46%) obtained in EtOH was thought to be due to loss of catalytic activity during the reaction, as indicated by diminishing difference in conversions between the catalyzed (solid line) and the uncatalyzed (dotted line) reactions. The data also showed that the background reaction was significant in all solvents, indicating a

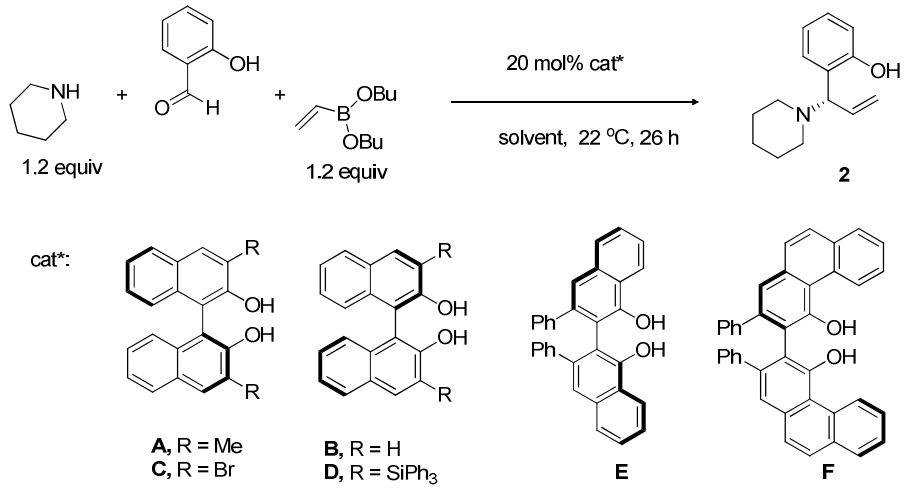
potential difficulty in achieving high ee. For prior binaphthol catalyzed reactions that achieved high ee, the rates of the background reactions seemed negligible under the conditions.[8,13]

Figure 1. Conversions of Salicylaldehyde in Three Representative Solvents in the Presence and Absence of cat-**A***



The influence of the structures of the catalysts 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 of 3 and 3' substituents on the binaphthol while smaller hydrogen of cat-**B*** or larger triphenylsilyl of cat-**D*** substituents 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 was obtained in toluene than in CH_2Cl_2 regardless of the catalysts. Therefore, toluene was chosen as the standard solvent for further exploration of the reactions. In toluene, cat-**E***, **F***, and **A*** provided highest but similar ee; therefore, the reaction was further investigated with only cat-**A*** and **E***.

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



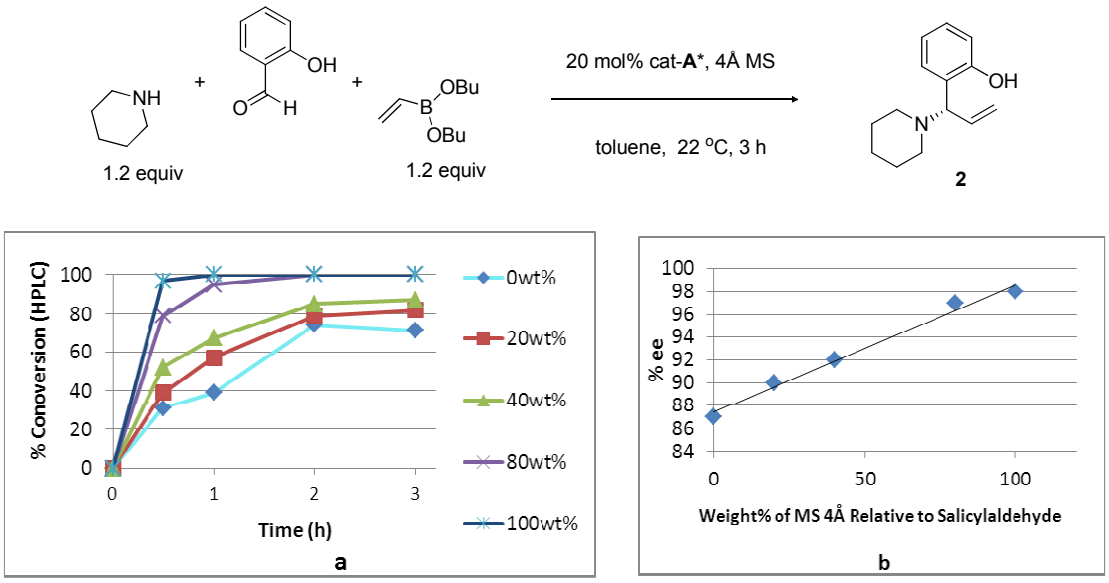
cat*		cat-A*	cat-B*[b]	cat-C*	cat-D*[b]	cat-E*	cat-F*
ee (%)	in CH_2Cl_2	75	-63	44	-12	77	47
	in PhMe	85	-70	84	-30	90	87

a. Conditions: salicylaldehyde (0.2 mmol), cat-**A*** (0.2 equiv), piperidine (1.2 equiv), vinylB$(OBu)_2$ (1.2 equiv), solvent (0.8 mL), 22 °C, 26 h. The conversions were determined by HPLC. The ee were determined by chiral HPLC and the conversions were 91-100%. b. The major product obtained with (*R*) configuration catalysts was the enantiomer of **2**.

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

was considered as the better catalyst for this substrate and was used as the catalyst for additional studies. As the data show, the 4Å MS not only accelerated the rate (Fig. 2a), but also increased

Figure 2. Enhancement of both Conversion Rates (**a**) and Enantioselectivity (**b**) by 4Å MS*



* Conditions: salicylaldehyde (0.2 mmol), cat-**A*** (0.2 equiv), piperidine (1.2 equiv), vinylB(OBu)$_2$ (1.2 equiv), 4Å MS, toluene (0.8 mL), 22 °C, 3 h. The conversions and ee were determined by HPLC.

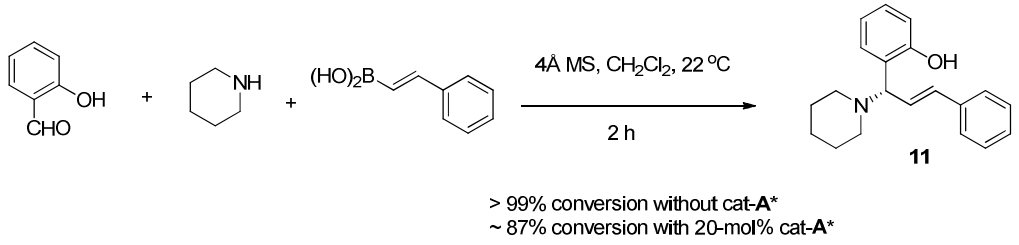
the ee of the product **2** (Fig. 2b). Further experiments showed use of 100−600 wt% 4Å MS relative to the weight of salicylaldehyde was acceptable and afforded product **2** in about 99% ee consistently. The ee increase from 87% to 99% due to addition of the 4Å MS has practical significance because the resulting higher ee may be sufficient for most applications without the need for further enrichment. Aldrich 3Å MS showed comparable effects. Drying agent $MgCl_2$

also enhanced the rate and the enantioselectivity of the reaction, but was less effective than the 4Å MS. Na_2SO_4 showed no effect, however.

These results are in agreement with earlier work describing the beneficial effects of 4Å 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 boronic acids, which had slower reaction rates in the presence of cat-**A*** and afforded products in low ee.

The Petasis reaction of salicylaldehydes with boronic acids in the presence of binaphthol catalysts was slow and provided products in 0−87% ee.[11] Our data indicated rate of the Petasis reaction of salicylaldehyde with boronic acid, styrenylB$(OH)_2$, in the presence of cat-**A*** and 4Å MS was actually slower than in the absence of the catalyst (Scheme 1) and provided lower

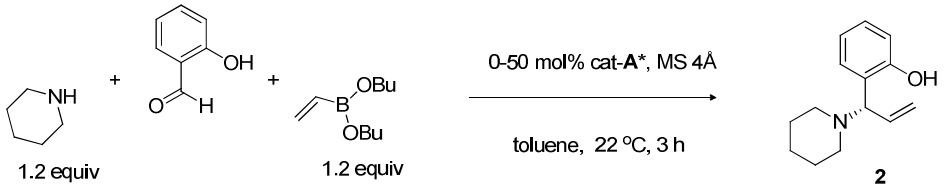
Scheme 1. Petasis Reactions of Boronic Acid in the Presence and Absence of cat-**A***

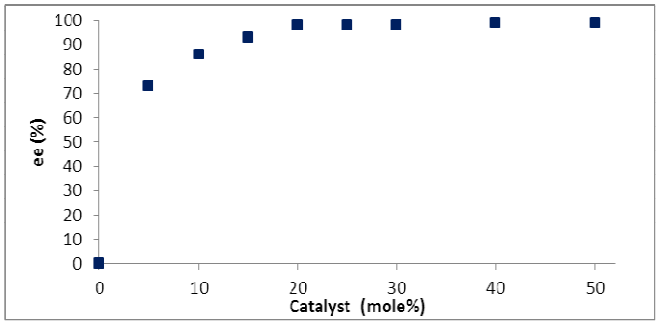


enantioselectivity (<40% ee) than its dibutyl ester (52% ee). HPLC monitoring revealed that the reaction of the boronic acid reached 91% conversion in 30 min and completed in 2 h without cat-**A***. In the presence of the catalyst, the reaction stalled after 30 min. In contrast, the catalytic reaction of dibutyl ester of the boronic acid was significantly faster than the uncatalyzed and completed in less than 30 min. These results suggested the 4Å MS also eliminated the negative effect of the boronic acid by preventing its formation from hydrolysis of the corresponding boronate.

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

Figure 3. Effect of Catalyst Loading on Product ee*

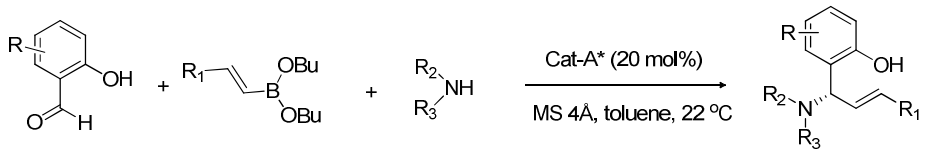


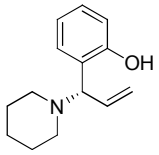
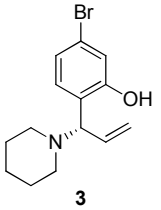
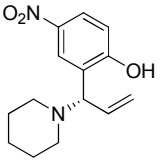
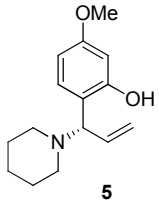
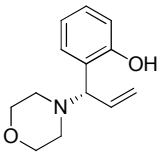
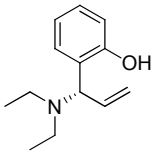
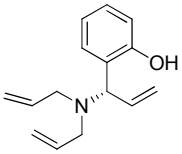
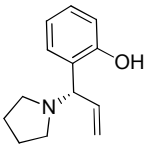
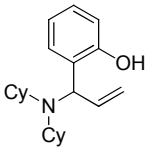
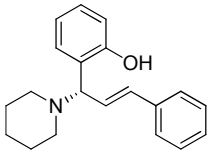
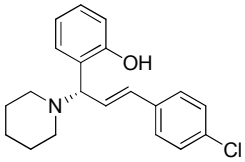
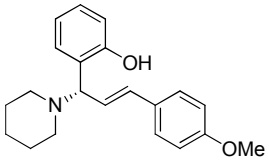
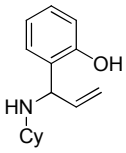
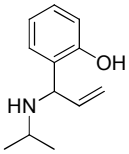
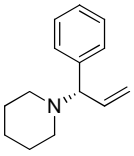


*Conditions: salicylaldehyde (0.2 mmol), cat-**A*** (0.2 equiv), piperidine (1.2 equiv), vinylB(OBu)$_2$ (1.2 equiv), 4Å MS, toluene (0.8 mL), 22 °C, 3 h. The conversions (95-100%) and ee were determined by HPLC.

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 the products (**6**−**11**) in good yields and ee. To our delight, participation of acyclic secondary amines showed the reaction had broader generality for amine reaction partner compared to the binaphthol-thiourea and binaphthol catalyzed reactions of boronic acids systems, where only cyclic secondary amines participated in the reaction.[10,11]

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



 **2** 92% yield 99.8% ee (98.5% ee)[b]	 **3** 70% yield 92% ee	 **4** 94% yield 92% ee	 **5** 85 %[c] 7% ee	 **6** 92% yield 99% ee
 **7** 43% yield 80% ee	 **8** 39% yield 96% ee	 **9** 62 % yield 91 % ee	 **10** 0% yield[d]	 **11** 68 % yield 52% ee
 **12** 71 % yield 96% ee (87% ee)	 **13** 45% yield 84% ee (81% ee)	 **14** 0% yield[d]	 **15** 0% yield[d]	 0% yield[d]

a. Representative conditions for **2**: salicylaldehyde (1.6 mmol), cat-A* (0.2 equiv), piperidine (1.2 equiv), vinylB(OBu)$_2$ (1.2 equiv), toluene (6 mL), 4Å MS (1.6 g), 22 ^{o}C, 1.5 h. The yields were for isolated products. b. Values in parentheses are for isolated products. c. Yield of crude product after subtracting residual cat-**A***. d. No Petasis reaction products were observed.

Two reactions run using primary amines, cyclohexylamine and isopropylamine, respectively, however did not provide the desired products (**14** and **15**). HPLC analysis showed that >75% of

the starting salicylaldehyde remained after 3 days for both reactions. This result was 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 deficient, neutral, and rich aryl substituents on the 2-position of the vinyl also reacted to afford products **11**−**13**. The reaction worked well for electron neutral and deficient salicylaldehydes to give products **2**–**4** in good yields and ee.

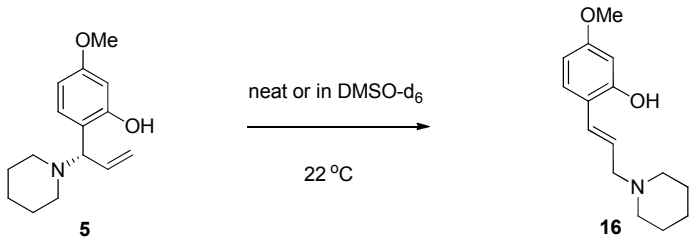
With the electron donating group MeO- on salicylaldehyde, the Petasis reaction went to completion in < 30 min; however, analysis showed the chiral purity of **5** was ~7% ee. In addition, purification of **5** by silica gel column chromatography was hampered by an apparent lack of stability. A ^{1}H-NMR spectrum of crude **5** obtained after aqueous work-up 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 subtracting residual cat-**A***content). In a separate experiment, pure **5** was obtained from the un-catalyzed reaction without a chromatographic purification. These results indicated the reaction of 4-MeO-salicylaldehyde was fast and clean. The observed low ee was either due to the low stereoselectivity of the reaction or instability of the stereogenic center of **5**.

Discrepancies in the ee determined *in situ* and after isolation, for examples compounds **11**–**13** (Table 4), indicated 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 holding it in a vial at 22 ^{o}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 ^{o}C without isolation was relatively slow, however. No change of ee in 48 h and a slight decrease (~ 0.2%) after 5

days were observed. At lower temperature (0−5 °C) **2** was chemically stable for at least 4 months based on NMR analysis.

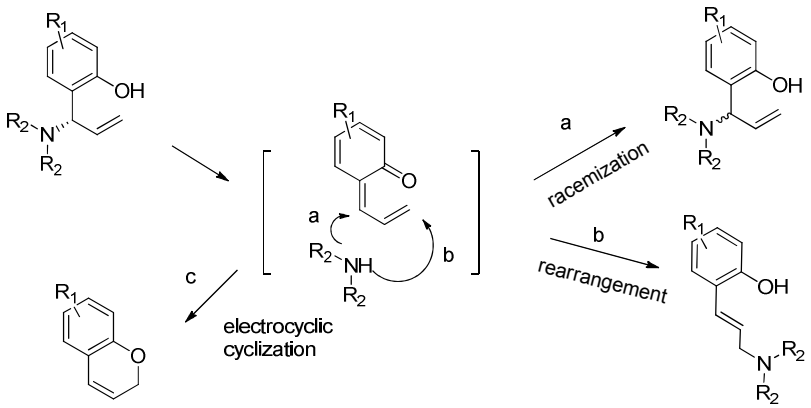
Racemic product **5** (oil) obtained from the un-catalyzed reaction cleanly converted into a new solid compound (**16**) at 22 °C in 2 days. An NMR sample of **5** in DMSO-*d6* also converted into **16** and the ^{1}H-NMR spectrum showed **16** was the only product. ^{1}H- and ^{13}C-NMR, HRMS data indicated **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 intermediate in the formation of *2H*-chromenes from aryl allylic amines.[24] The quinone methide can react with the amine eliminated during its formation resulting in racemization (pathway a) and the linear rearrangement products (pathway b), such as **16**. It may also undergo an electrocyclization[25] (pathway c) to give the *2H*-chromenes, 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.

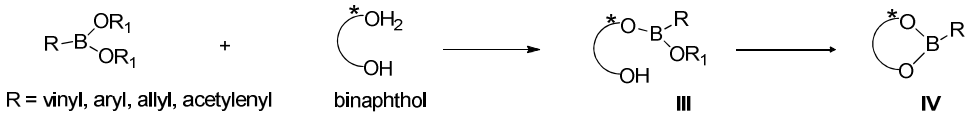
Scheme 3. Possible Mechanism for the Racemization, Rearrangement, and Cyclization Reactions



The (*S*) configuration of **2** obtained using (*S*)-cat-**A*** was determined by using vibrational circular dichroism (VCD)[26] and that of **11** was determined on the basis of chiral HPLC analysis and its sign of optical rotation comparing with literature data.[10] The (*R*) enantiomer of **2** was obtained in 98% ee with (*R*) enantiomer of cat-**A*** based on chiral HPLC analysis. The absolute configurations of the other compounds in Table 5 were assigned by analogy.

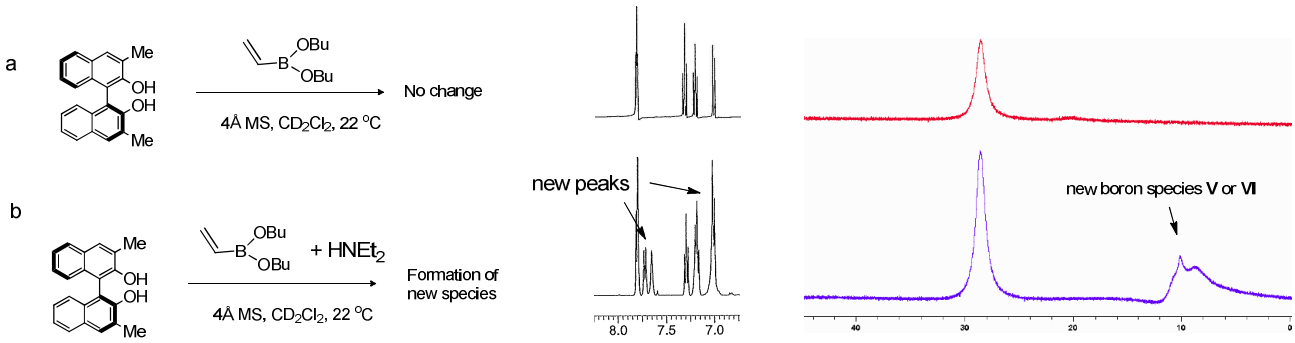
The mechanism for the rate acceleration[27] of this catalytic Petasis reaction is not entirely clear. Acyclic (**III**) and cyclic (**IV**) types of structures formed from reactions between binaphthols and boronates were proposed to explain the observed enantioselectivity of many reactions (Scheme 4).[12-18] Formation of **III** with a vinylboronate was reported based on NMR and MS studies.[14] Our ^{1}H- and ^{11}B -NMR experiments showed that the reaction between cat-**A*** and vinylB(OBu)$_2$ in CD_2Cl_2 in the presence of 4Å MS (a, Fig. 4) 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 the cat-A* and vinylB(OBu)$_2$ in 24 h.[29]

Scheme 4. Ligand Exchange Reaction between Binaphthols and Boronates



However, addition of $HNEt_2$ resulted in immediate appearance of new ^1H signals in the aromatic region (6.8−8.0 ppm) (b, Fig. 4). The spectra of the mixture remained the same over 24 h. Signals of $HNEt_2$ in the ^1H-NMR spectra were broad suggesting coordination of $HNEt_2$ to

Figure 4. ^1H− and ^{11}B−NMR Spectra of the Reaction Mixtures of cat-**A*** and Vinyl$B(OBu)_2$ and $HNEt_2$

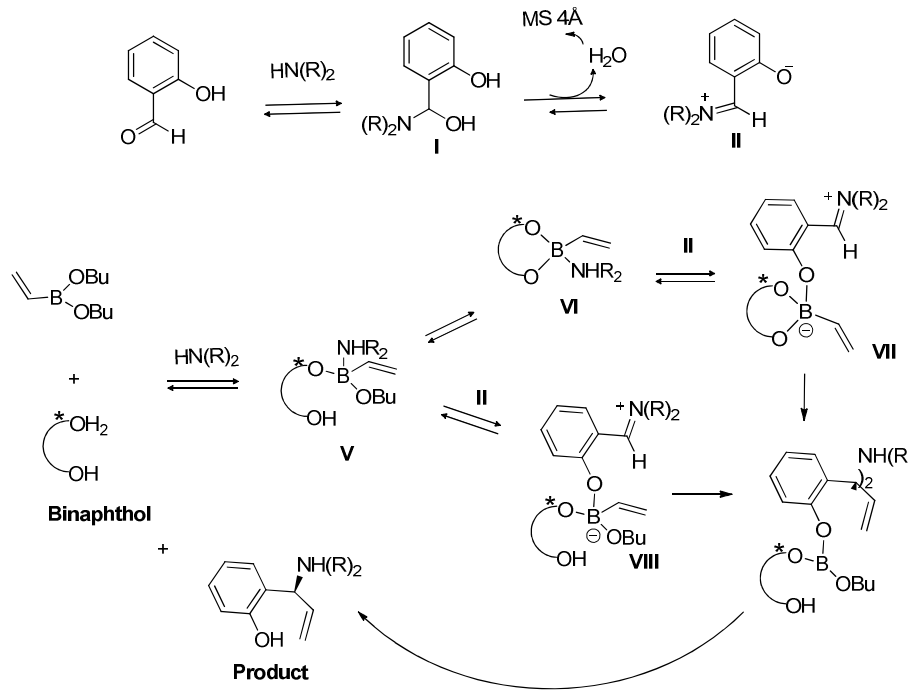


a. Partial ^1H NMR and ^{11}B NMR spectrum of the reaction mixture of cat-**A*** (1.0 equiv), vinyl$B(OBu)_2$ (1.0 equiv), and 4Å MS in CD_2Cl_2 at 22 °C taken after the mixing was completed. b. Partial ^1H NMR and ^{11}B NMR spectrum of the reaction mixture of cat-**A*** (1.0 equiv), vinyl$B(OBu)_2$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

vinylB(OBu)$_2$. New ^{11}B signals at 10.1 and 8.8 ppm in addition to the peak of vinylB(OBu)$_2$ at 28.6 ppm were also detected from the mixture (b, Fig. 4). These data indicated formation of tetrahedral boron complexes[30] from the reaction. ^{1}H and ^{11}B NMR experiments showed there was no change in spectrum between vinylB(OBu)$_2$ and HNEt$_2$ in CD_2Cl_2 in the presence of 4Å MS at 22 ^{o}C in 24 h.[31]

These NMR observations prompted us to propose a reaction mechanism shown in Scheme 5. In this mechanism, HNEt$_2$ reacts with salicylaldehyde to form iminium **II**, a proposed key intermediate for Petasis reaction,[19] through aminal **I**. HNEt$_2$ also activates and participates in the

Scheme 5. Proposed Mechanism



reaction between cat-**A*** and vinylB(OBu)$_2$ to form reactive intermediates **V** or **VI**, which then lead to the cyclic (**VII**) or acyclic (**VIII**) intermediates, respectively. Migration of the vinyl

group in **VII** and **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 and results 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 and will be reported on in due course.

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

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 (4Å, activated, 2.5 μm, powdered) were purchased from Aldrich. NMR spectra were recorded for ^{1}H NMR at 400 MHz, for ^{13}C NMR at 100 MHz. Chemical shifts are expressed as δ (ppm) values using TMS or the residual signals of the solvents as the internal standard. High resolution mass spectra were acquired using FT ICR. HPLC data were collected with UV detection at 214 nm or as specified using Sunfire column (C18, 3.5 μm, 150 x 4.6 mm) and mobile phase A: water with 0.1% TFA and B: acetonitrile with

0.1% TFA; a linear gradient from 30-70% B in 15 min; flow rate 1 mL per minute. The products were isolated by flash chromatography with CH_2Cl_2-IPA gradient eluent.

Representative procedure for 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-hydroxy-benzaldehyde (121 mg, 0.8 mmol), molecular sieves 4Å (0.8 g), and dibutyl vinylboronate (211 μL, 0.96 mmol, 1.2 equiv) in toluene (6 mL) was added piperidine (96 uL, 0.97 mmol, 1.2 equiv). The mixture was stirred at 22 ºC for 20 h (until completion by HPLC analysis), and filtered through a Celite® bed. The Celite® bed was washed with toluene. The combined filtrates were washed with dilute brine (3 times) and 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 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 the catalytic asymmetric Petasis reactions. Preparation of **(*S*)-2-(1-(piperidin-1-yl)allyl)phenol** (**2**). To a magnetically stirred mixture of 2-hydroxy-benzaldehyde (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), molecular sieves 4Å (1.60 g), dibutyl vinylboronate (423 μL, 1.92 mmol, 1.2 equiv) in toluene (6 mL) was added piperidine (192 uL, 1.94 mmol, 1.2 equiv). The mixture

was stirred at 22 ºC for 1.5 h and filtered through a Celite® bed (Note: The reaction was first monitored by HPLC at 30 min reaction time and the data showed 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 by HPLC analysis (Chiralcel OD-H column, eluent *n*-hexane containing 0.1% $HNEt_2$, flow rate 0.8 mL/min, 35 ^oC, 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 (3 times) and 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 rotary evaporator to give **2** as a colorless oil (317 mg, 91% yield). The (*S*) configuration of **2** was determined by using VCD (see next section of this experimental below). 98.4% ee by HPLC (same method as above), t_{major}=11.8 min, 99.2%; t_{minor} = 16.0 min, 0.8%. $[\alpha]_{546}^{26}$ = +248^o (c = 0.10, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.48 (brs., 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 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% 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-hydroxy-benzaldehyde (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), molecular sieves 4Å (1.60 g), dibutyl vinylboronate (423 μL, 1.92 mmol, 1.2 equiv) in toluene (6 mL), piperidine (192 uL, 1.94 mmol, 1.2 equiv), 22 ºC, 24 h. er: 92% ee by HPLC analysis (Chiralcel OD-H column, eluent *n*-hexane containing 0.1% $HNEt_2$, flow rate 0.8 mL/min, 35 ^oC, 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^o (c = 0.054, MeOH); ^1H 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-hydroxy-benzaldehyde (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), molecular sieves 4Å (1.60 g), dibutyl vinylboronate (423 μL, 1.92 mmol, 1.2 equiv) in toluene (6 mL), piperidine (192 uL, 1.94 mmol, 1.2 equiv), 22 ºC, 24 h. 92% ee by HPLC (Chiralcel OD-H column, eluent hexanes/IPA/$HNEt_2$ (99/1/0.1), flow rate 0.8 mL/min, 35 ^oC, 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^o (c = 0.093, MeOH); ^1H 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.

(*S*)-5-Methoxy-2-(1-(piperidin-1-yl)allyl)phenol (5). 4-Methoxy-2-hydroxy-benzaldehyde (243 mg, 1.6 mmol), (*S*)-3,3'-dimethyl-1,1'-binaphthalene-2,2'-diol (100.6 mg, 0.32 mmol, 0.2

equiv), molecular sieves 4Å (1.60 g), dibutyl vinylboronate (423 μL, 1.92 mmol, 1.2 equiv) in toluene (6 mL), piperidine (192 uL, 1.94 mmol, 1.2 equiv), 22 ºC, 1 h. 7% ee by HPLC (Chiralcel OD-H column, eluent hexanes/isopropanol/diethylamine (99/1/0.1), flow rate 0.8 mL/min, 35 ^{o}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 subtracting residual catalyst based on NMR analysis). The characterization data of this compound were obtained with a racemic sample immediately after it was made (see data above in procedure for preparation of racemic samples).

Compound **5** is not stable (0 − 22 ^{o}C) and cleanly converted into a new solid compound **14**, (*E*)-5-methoxy-2-(3-(piperidin-1-yl)prop-1-en-1-yl)phenol, at 22 ^{o}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 bench at 22 ^{o}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-Hydroxy-benzaldehyde (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), molecular sieves 4Å (1.60 g), dibutyl vinylboronate (423 μL, 1.92 mmol, 1.2 equiv) in toluene (6 mL), morpholine (168 uL, 1.92 mmol, 1.2 equiv), 22 ºC, 24 h. 99% ee by HPLC (Chiralcel OD-H

column, eluent hexanes/IPA/$HNEt_2$ (99/1/0.1), 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%). $[\alpha]_{546}^{26}$ = +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-Hydroxy-benzaldehyde (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), molecular sieves 4Å (1.60 g), dibutyl vinylboronate (423 μL, 1.92 mmol, 1.2 equiv) in toluene (6 mL), diethylamine (199 uL, 1.92 mmol, 1.2 equiv), 22 ºC, 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%). $[\alpha]_{546}^{26}$ = -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-Hydroxy-benzaldehyde (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), molecular sieves 4Å (1.60 g), dibutyl vinylboronate (423 μL, 1.92 mmol, 1.2 equiv) in toluene (6 mL),

diallylamine (239 uL, 1.94 mmol, 1.2 equiv), 22 ºC, 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 ^oC, signal detection at 280 nm), t_{major} = 10.0 min, 98.0%; t_{minor} = 13.3 min, 2%. Oil (144 mg, 39%). $[\alpha]_{546}^{26}$ = +3.7^o (c = 0.054, MeOH); ^1H 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-Hydroxy-benzaldehyde (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), molecular sieves 4Å (1.60 g), dibutyl vinylboronate (423 µL, 1.92 mmol, 1.2 equiv) in toluene (6 mL), pyrrolidine (162 uL, 1.94 mmol, 1.2 equiv), 22 ºC, 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 ^oC, signal detection at 280 nm), t_{major} = 11.9 min, 95.5%; t_{minor} = 14.2 min, 4.5%. Oil (200 mg, 62%). $[\alpha]_{546}^{26}$ = +228^o (c = 0.054, MeOH); ^1H 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-Hydroxy-benzaldehyde (195 mg, 1.6 mmol), (*S*)-3,3'-dimethyl-1,1'-binaphthalene-2,2'-diol (100.6 mg, 0.32 mmol, 0.2 equiv), molecular sieves 4Å (1.60 g), dibutyl

phenylvinylboronate (499 mg, 1.92 mmol, 1.2 equiv) in toluene (6 mL), piperidine (192 uL, 1.94 mmol, 1.2 equiv), 22 ºC, 24 h. 52% ee by HPLC (Chiralpak AD-H column, eluent *n*-hexane/EtOH/diethylamine: 97/3/0.1, flow rate 0.8 mL/min, 35 ^{o}C, signal detection at 280 nm), t_{major} = 6.3 min, 76%; t_{minor} = 6.9 min, 24%. Oil (321 mg, 68%) turned into a solid in refrigerator. $[\alpha]_{546}^{26}$ = +44^{o} (c = 0.054, MeOH).

(*S,E*)-2-(3-(4-Chlorophenyl)-1-(piperidin-1-yl)allyl)phenol (12). 2-Hydroxy-benzaldehyde (69 mg, 0.0.56 mmol), (*S*)-3,3'-dimethyl-1,1'-binaphthalene-2,2'-diol (35.5 mg, 0.11 mmol, 0.2 equiv), molecular sieves 4Å (0.2 g), dibutyl 4-chlorophenylvinylboronate (200 mg, 0.68 mmol, 1.2 equiv) in toluene (2 mL), piperidine (68 uL, 0.68 mmol, 1.2 equiv), 22 ºC, 1.5 h. 96% ee by (Chiralpak AD-H column, eluent *n*-hexane/EtOH/$HNEt_2$: 97/3/0.1, flow rate 1.0 mL/min, 35 ^{o}C, signal detection at 280 nm), t_{major} = 5.5 min, 98%; t_{minor} = 9.7 min, 2%. Oil (169 mg, 91%) turned into a solid in refrigerator. $[\alpha]_{546}^{26}$ = +50^{o} (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-Hydroxy-benzaldehyde (28 mg, 0.23 mmol), (*S*)-3,3'-dimethyl-1,1'-binaphthalene-2,2'-diol (14.5 mg, 0.046 mmol, 0.2 equiv), molecular sieves 4Å (0.4 g), dibutyl 4-methoxyphenylvinylboronate (80 mg, 0.28 mmol, 1.2 equiv) in toluene (0.9 mL), piperidine (28 uL, 0.28 mmol, 1.2 equiv), 22 ºC, 1 h. er: 84 by HPLC (Chiralcel OD-H column, eluent *n*-hexane/EtOH/$HNEt_2$: 97/3/0.1, flow rate 0.7 mL/min, 35 ^{o}C, signal detection at 280 nm), t_{major} = 7.2 min, 92% (area); t_{minor} = 7.6min, 8%. Oil (40 mg,

43%) turned into a solid in refrigerator. $[\alpha]_{546}^{26}$ = +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.

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Supporting Information Available. Procedures, characterization data, ^{1}H/^{13}C NMR spectra, chiral HPLC chromatograms of the new compounds; ^{1}H/^{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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