Organocatalytic Enantioselective Synthesis of Chiral Diarylmethylamines from Racemic Alcohols

Min Chen,[+a] Yaodong Han,[+a] Dengke Ma,[+a] Yong Wang[a], Zengwei Lai[a] and Jianwei Sun *[a]

ABSTRACT An organocatalytic approach for direct conversion of racemic diarylmethanols to valuable chiral diarylmethylamines is described. Different from the previously reported elegant "borrowing hydrogen" approach, the present process employs a distinct complementary formal S_N1 strategy. This approach enjoys excellent enantioselectivity, mild conditions, broad scope, and easy product derivatization. Mechanistically, control experiments also provided important insights into some notable features, such as substrate kinetic resolution and reversibility as well as the critical role of the ortho-hydroxy group in the substrate

KEYWORDS amination, asymmetric catalysis, nucleophilic substitution, chirality, organocatalysis

Introduction

Chiral diarylmethylamines are important structural motifs widely present in natural products, pharmaceuticals, and other bioactive molecules of strong relevance to human health (Figure 1).[1] Moreover, they also serve as key chiral backbones of some useful ligands in organic synthesis, such as Ming-Phos developed by Zhang and co-workers.[2] Owning to their ubiquitous versatility, substantial efforts from the synthetic community have been devoted to the efficient assembly of enantioenriched diarylmethylamines in the past two decades.[3] Consequently, a wide variety of catalytic asymmetric approaches have been developed, including kinetic resolution, desymmetrization, aryl addition to imines, and asymmetric hydrogenation, etc.[3] Notably, metal catalysis has been dominant in these reactions. Here we describe a new organocatalytic approach for highly enantioselective synthesis of chiral diarylmethylamines from racemic diarylmethanols.

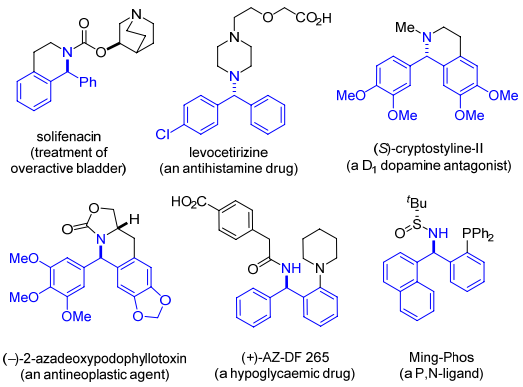
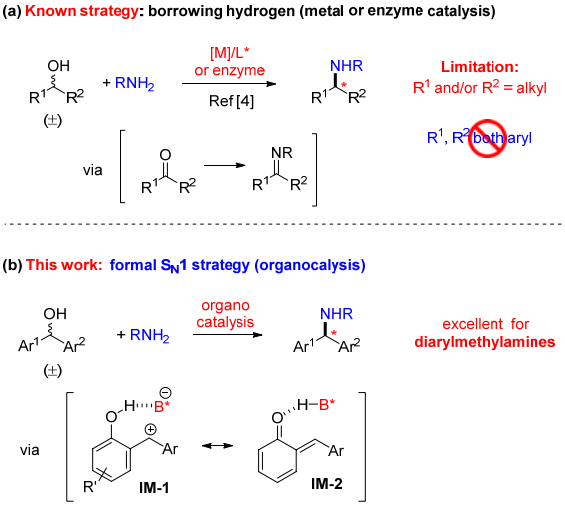


Figure 1 Useful chiral diarylmethylamine derivatives.

Recently, direct asymmetric amination of readily accessible racemic secondary alcohols has been demonstrated to be a highly attractive approach for expedient synthesis of chiral amines (Scheme 1a).[4] Pioneered by Zhao, Dong & Guan, Beller, Zhou, and Turner, etc., these elegant processes via "borrowing hydrogen" strategy proceed very efficiently through an intrinsically well-organized one-pot multistep sequence comprising dehydrogenation to ketone and imine formation followed by asymmetric imine hydrogenation. While such state-of-the-art protocols proved successful for highly enantioenriched methinylamines with alkyl/aryl or sterically biased bis(alkyl) groups (i.e., R^1 and/or R^2 = alkyl), unfortunately, their capability for the synthesis of chiral *diaryl*methylamines (both R^1 and R^2 = aryl) has not been demonstrated so far. This limitation might be due to the challenging steric differentiation of the two aryl groups in the enantiodetermining imine hydrogenation step.

Scheme 1 Catalytic Asymmetric Synthesis of Chiral Amines from Racemic Alcohols.



In the above contexts, it is thus highly desirable to develop a complementary protocol for the analogous direct conversion of racemic diarylmethanols to enantioenriched diarylmethylamines. We hypothesized a completely different approach to address the above limitation. Instead of using "borrowing hydrogen" strategy, we envisioned a formal S_N1 strategy, namely, the reaction will proceed via initial formation of a carbocation, which can be stabilized by the two aryl groups. Furthermore, rather than employing metal or enzymatic catalysis, an organocatalytic approach is employed.

Results and Discussion

In order to differentiate the two aryl groups with subtle steric difference in the C–N bond formation step, here we hypothesized that introduction of a removable hydrogen bonding anchor (e.g., hydroxy group) would be helpful, particularly when hydrogen

[a] The Hong Kong University of Science and Technology (HKUST) Shenzhen Research Institute, Shenzhen, China; Department of Chemistry, HKUST, Clear Water Bay, Kowloon, Hong Kong SAR, China
[+] These authors contributed equally to this work.
E-mail: sunjw@ust.hk

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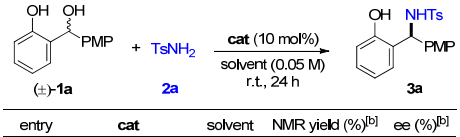
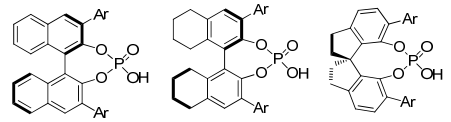
bonding catalysis is employed (Table 1). With this in mind, we started to test our hypothesis with racemic **1a** as the model substrate and *p*-toluenesulfonamide ($TsNH_2$) **2a** as the nucleophile. Chiral phosphoric acids were employed as potential catalyst.[5] Initially, a range of BINOL-derived phosphoric acids were evaluated. Unfortunately, the well-known **TRIP** catalyst **A1** showed no reactivity (Table 1, entry 1), presumably due to the too bulky substituents in the 3,3′-positions. Gratifyingly, variation to other substituents in the BINOL-based catalysts did afford the desired diarylmethylamine **3a**, albeit with moderate efficiency and enantioselectivity (entries 2-4). Among these catalysts, the one with 1-naphthyl substituent was most promising in terms of enantioselectivity. Evaluation of other catalysts indicated that the [H_8]-BINOL-derived analogue **B** could improve the enantioselectivity (64% ee, entry 5).[6] However, the other analogue **C** bearing a spirocyclic backbone proved inferior. Furthermore, 1,2-dichloroethane was found to be the best solvent (entry 7). The reaction did not show reactivity in diethyl ether, presumably due to its competing binding with the acidic catalyst, leading to catalyst deactivation. Subsequent substantial efforts by tuning other reaction parameters, such as using molecular sieves and decreasing reaction temperature and concentration, successfully optimized the reaction and achieved good efficiency and excellent enantioselectivity (entry 13).

Table 1 Condition Optimization[a]



entry	cat	solvent	NMR yield (%)[b]	ee (%)[b]
1	(*R*)-**A1**	DCM	<5	–
2	(*R*)-**A2**	"	35	30
3	(*S*)-**A3**	"	30	–16
4	(*S*)-**A4**	"	45	–48
5	(*R*)-**B**	"	46	64
6	(*R*)-**C**	"	20	–28
7	(*R*)-**B**	DCE	50	72
8	(*R*)-**B**	toluene	62	36
9	(*R*)-**B**	Et_2O	<5	–
10	(*R*)-**B**	CCl_4	49	32
11[c]	(*R*)-**B**	DCE	85	78
12[c,d]	(*R*)-**B**	DCE	85	81
13[c,d,e]	(*R*)-**B**	DCE	85	90



A1: Ar = 2,4,6-^{i}Pr$_3$C$_6$H$_2$
A2: Ar = 9-anthryl
A3: Ar = 9-phenanthryl
A4: Ar = 1-naphthyl

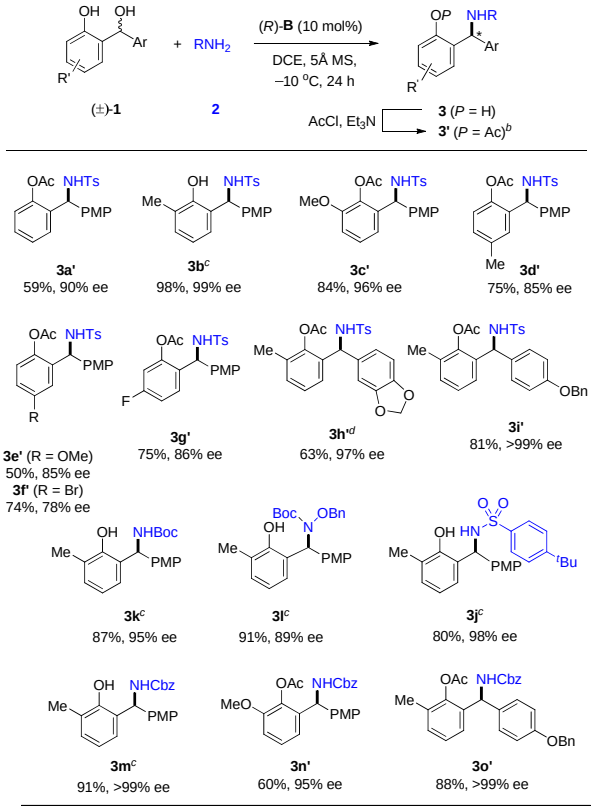
B
Ar = 1-naphthyl

C
Ar = 1-naphthyl

[a] Reaction scale: **1a** (0.05 mmol), **2a** (0.055 mmol), solvent (1 mL). [b] Yield was determined by ^{1}H NMR of the crude reaction mixture using CH_2Br_2 as internal standard. Ee value was determined by HPLC with a chiral column. [c] Run with 0.025 M of **1a**. [d] Run with 5Å MS (20 mg). [e] Run at –10 °C. PMP = *para*-methoxyphenyl.

We next examined the reaction scope (Scheme 2). From readily prepared racemic diarylmethanols, this organocatalytic protocol is applicable to the synthesis of a wide range of chiral diarylmethylamines with excellent enantioselectivity. Different substituents, including electron-donating and electron-withdrawing groups, at different positions of the two aryl moieties did not dramatically influence the good result. It is worth noting that in some cases the free hydroxy group in the product was protected immediately before work-up to minimize erosion of the product optical purity and also simplify purification, as the nucleophile has similar polarity with the product. The mild conditions can tolerate various functional groups. This process is not limited to arenesulfonamide nucleophiles. Other easily deprotectable nitrogen-based nucleophiles, such as $BocNH_2$ and $CbzNH_2$, exhibit equally excellent performance. Secondary amide BocNH(OBn) is also suitable. These results indicate that our process allows straightforward access to other chiral diarylmethylamine analogues by simple modification of the substituents on the nitrogen atom.

Scheme 2 Reaction Scope.[a]

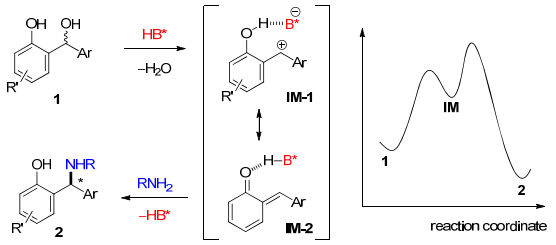


[a] The yield provided is isolated yield. [b] In some cases, the phenol product was protected immediately to minimize erosion of the optical purity during work-up/purification and simplify purification (**3** and **2** have similar R_f values). Reaction conditions: **1** (0.2 mmol), **2** (0.21 mmol), (*R*)-**B** (12.2 mg, 10 mol%), DCE (8 mL), –10 °C, 24 h. [c] Catalyst loading: 15 mol%. [d] Run with 5 equiv. of $TsNH_2$

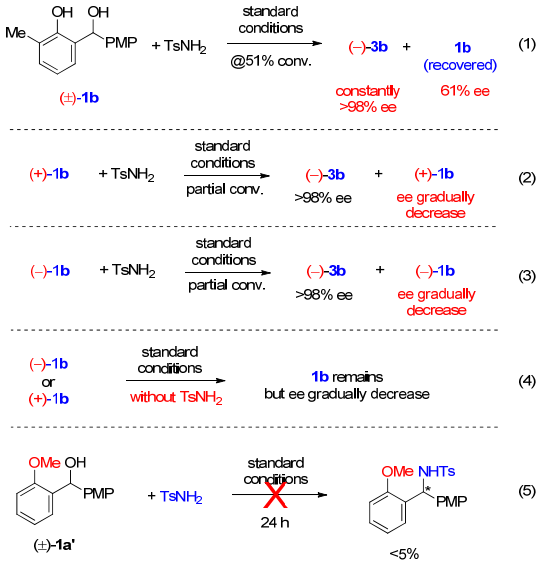
We have proposed a possible mechanism (Scheme 3). In the presence of the acid catalyst, the diarylmethanol undergoes protonation followed by C–O bond cleavage to form carbocation **IM-1**, which is paired with the chiral phosphate anion. The two aryl groups can stabilize this carbocation, thereby decreasing the reaction barrier. Moreover, the interaction of the counter anion with the hydroxy group in the *ortho*-position provides additional stabilization. This stabilization can also be viewed in its resonance form **IM-2**, which is indeed an activated *ortho*-quinone methide. Subsequent addition by the nitrogen nucleophile forms the C–N bond with concomitant stereocontrol. Therefore, the second step is also asymmetric addition of nitrogen nucleophiles to *ortho*-quinone methides, a topic that still remains challenging.[7,8] Asymmetric induction by the chiral anion (in **IM-1**) or hydrogen bonding (in **IM-2**) is critically important. Overall, this whole

process resembles a formal S_N1 process, which is also a challenge in asymmetric catalysis.

Scheme 3 Proposed Mechanism.

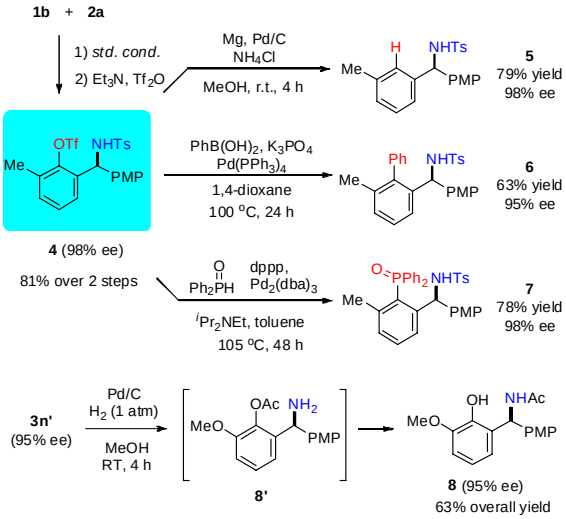


To help understand the mechanism, we carried out a series of control experiments. We carefully monitored the reaction of racemic **1b** under the standard conditions. At partial conversions, product **3b** was generated with constantly high enantiomeric excess (ee). In contrast, the ee value of **1b** (originally racemic) changed over time during the progress of the reaction, indicating substrate kinetic resolution (Eq 1). Next, enantiopure substrate **1b** was prepared and subjected to the standard conditions to further probe the reversibility of the first step. As shown in Eqs 2-3, both (+)-**1b** and (–)-**1b** led to product (–)-**3b** with the same absolute configuration, indicating that it is not the substrate, but the catalyst configuration that determines the product stereochemistry. This is consistent with the proposed mechanism involving loss of substrate stereochemical information in the carbocation intermediate. Furthermore, in these two experiments, the substrate ee values gradually decreased (see SI for more details), suggesting that the first step is reversible. Indeed, in the absence of a nucleophile, gradual racemization of **1b** was also observed upon treatment with the catalyst, but without obvious conversion to any intermediate or byproduct (Eq 4). Based on these observations, a qualitative reaction coordinate diagram is proposed (Scheme 3), showing that the first step is an equilibrium thermodynamically favoring substrate, and the second step is rate-limiting. Finally, for comparison, substrate **1a'** bearing an *ortho*-methoxy group (instead of OH) was subjected to the standard reaction protocol. Unfortunately, essentially no desired C–N bond formation product was observed (Eq 5). This observation further confirmed that the initial design to take advantage of this free hydroxy group for hydrogen bonding is crucial for effective enantiocontrol and attainable reaction barrier.



We carried out some derivatizations to demonstrate the product utility. In particular, it would be ideal if the free *ortho*-hydroxy anchor can be easily removed or converted, although diarylmethylamines containing such a hydroxy group are already useful structures themselves (e.g., Betti base).[9] Gratifyingly, triflation of the phenol motif in the product can work efficiently in a one-pot operation immediately after the standard protocol, furnishing aryl triflate **4** in good yield (Scheme 4). Subsequent reduction led to successful removal of the triflate moiety to form **5** in good yield. The triflate can also undergo cross-coupling to form biaryl **6**. Finally, palladium-catalyzed phosphonylation gave phosphine oxide **7**, which is poised for further reduction to form a chiral P,N ligand, a highly analogous structure to Ming-Phos (shown in Scheme 1).[2] Furthermore, the Cbz group in proudct **3n'** can be easily deprotected to form free amine **8'**, which easily underwent intramolecular acyl shift to give amide **8**. Notably, in all these reactions, the enantiomeric excess remained excellent.

Scheme 4 Product Transformations.



Conclusions

In summary, we have developed the first organocatalytic approach for direct conversion of racemic diarylmethanols to valuable chiral diarylmethylamines. It represents an excellent complement to the elegant metal-catalyzed "borrowing hydrogen" approach for chiral amine synthesis, with regard to both mechanism and scope. By proper design of the substrate as well as careful optimization of the catalytic system, the intermolecular C–N bond formation process provides expedient access to a range of chiral diarylmethylamines with excellent efficiency and enantioselectivity. The mild conditions tolerate a diverse set of functional groups. Mechanistically, a series of control experiments provided important insights into some key features of the distinct formal S_N1 pathway, such as substrate kinetic resolution and reversible first step. The presence of the *ortho*-hydroxy group in the substrate is critically important for achieving both high chemical efficiency and excellent asymmetric induction via hydrogen bonding. Finally, the enantioenriched diarylmethylamines products are important precursors to other useful chiral molecules.

Experimental

General information All air moisture sensitive reactions were conducted in oven-dried glassware under nitrogen atmosphere using dry solvents. Flash column chromatography was performed over silica gel (230-400 mesh) purchased from Qindao Puke Co., China. Anhydrous diethyl ether, dichloromethane, toluene, and tetrahydrofuran were purified by Innovative® solvent purification system. Chloroform, tetrachloromethane, methanol, 1,4-dioxane, and dichloroethane (DCE) were purchased from Sigma-Aldrich® and used as received. ^{1}H and ^{13}C NMR were collected on a Bruker AV 400 MHz NMR spectrometer using residue solvent peaks as an internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm, DMSO-d_6 at 2.50 ppm; ^{13}C NMR: $CDCl_3$ at 77.2 ppm, DMSO-d_6 at 39.5 ppm).

General procedure for the catalytic asymmetric synthesis of diarylmethylamines 3

At −10°C, to a 20-mL vial charged with a mixture of the alcohol **1** (0.2 mmol), the amine **2** (0.21 mmol), 5Å molecular sieves (80 mg), and DCE (8 mL). Next, a solution of the catalyst (*R*)-**B** (12.2 mg, 10 mol%) in DCE (0.2 mL) was added. The reaction mixture was stirred at −10°C for 24 h. Upon completion, the reaction mixture was warmed to room temperature and concentrated. The crude product was purified by silica gel column chromatography to afford the desired product **3**.

General procedure for the catalytic asymmetric synthesis of diarylmethylamines 3'

At −10 °C, to a 20-mL vial charged with a mixture of the alcohol **1** (0.2 mmol), the amine **2** (0.21 mmol), 5Å molecular sieves (80 mg), and DCE (8 mL). Next, a solution of the catalyst (*R*)-**B** (12.2 mg, 10 mol%) in DCE (0.2 mL) was added. The reaction mixture was stirred at −10 °C for 24 h. After that, DCM (8 mL) was added to the vial, and the reaction mixture was cooled to −78 °C. Then, triethylamine (1.0 mmol, 150 μL) and acetyl chloride (0.8 mmol, 80 μL) were added sequentially. The mixture was stirred at the same temperature for 2 h. Upon completion, the reaction mixture was warmed to room temperature and concentrated. The crude product was purified by silica gel column chromatography to afford the desired product **3'**.

(*S*)-2-((4-Methoxyphenyl)(4-methylphenylsulfonamido)methyl)phenyl acetate **(3a')** was prepared (purified by column chromatography, eluent: Et_2O/hexanes = 2:3 to 1:1) as a white solid (50.5 mg, 59% yield, 90% ee). $[\alpha]_D^{25}$ = −5.8 (*c* = 1.0, $CHCl_3$). HPLC analysis of the product: Daicel CHIRALPAK® AD-H column; 30% *i*-PrOH in hexanes; 1.0 mL/min; retention times: 12.05 min (minor), 19.12 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 2H), 7.25 – 7.21 (m, 1H), 7.12 – 7.10 (m, 3H), 7.05 (d, *J* = 1.2 Hz, 1H), 7.03 – 6.97 (m, 3H), 6.71 (d, *J* = 8.8 Hz, 2H), 5.68 (d, *J* = 8.0 Hz, 1H), 5.26 (d, *J* = 8.0 Hz, 1H), 3.74 (s, 3H), 2.36 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 159.2, 148.2, 143.3, 137.6, 132.4, 131.7, 129.5, 129.2, 128.8, 128.4, 127.3, 126.0, 123.5, 114.0, 56.7, 55.4, 21.7, 20.9. IR (neat, cm^{-1}) 3276, 2957, 2923, 1713, 1511, 1377, 1159. HRMS (CI+) calculated for $C_{23}H_{22}NO_5S$ $[M–H]^+$: 424.1219, found: 424.1222.

(*S*)-*N*-((2-Hydroxy-3-methylphenyl)(4-methoxyphenyl)methyl)-4-methyl benzenesulfonamide (3b) was prepared (purified by column chromatography, eluent: Et_2O/hexanes = 2:3 to 1:1) as a pale yellow solid (77.9 mg, 98% yield, 99% ee). $[\alpha]_D^{25}$ = −10.0 (*c* = 1.0, $CHCl_3$). HPLC analysis of the product: Daicel CHIRALPAK® AD-H column; 15% *i*-PrOH in hexanes; 1.0 mL/min; retention times: 16.00 min (minor), 16.87 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.3 Hz, 2H), 7.07 (dd, *J* = 8.5, 2.3 Hz, 4H), 6.97 (d, *J* = 6.6 Hz, 1H), 6.78 – 6.72 (m, 3H), 6.68 (t, *J* = 7.5 Hz, 1H), 5.63 (d, *J* = 8.2 Hz, 1H), 5.44 (d, *J* = 8.2 Hz, 1H), 5.36 (s, 1H), 3.75 (s, 3H), 2.33 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 151.5, 143.1, 136.8, 131.7, 130.4, 129.1, 128.2, 127.3, 127.1, 125.7, 124.5, 120.4, 113.8, 58.7, 55.3, 21.4, 15.6. IR (neat, cm^{-1}) 3431, 3289, 2926, 1603, 1441, 1250, 1150, 1028.HRMS (MALDI) calculated for $C_{22}H_{23}NO_4SK$ $[M+K]^+$: 436.0985, found: 436.0975.

(*S*)-2-Methoxy-6-((4-methoxyphenyl)(4-methylphenylsulfonamido)methyl) phenyl acetate **(3c')** was prepared (purified by column chromatography, eluent: Et_2O/hexanes = 1:1) as a pale yellow oil (69.5 mg, 84% yield, 96% ee). $[\alpha]_D^{25}$ = −8.1 (*c* = 1.0, $CHCl_3$). HPLC analysis of the product: Daicel CHIRALPAK® AD-H column; 50% *i*-PrOH in hexanes; 1.0 mL/min; retention times: 7.94 min (minor), 16.45 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 7.02 – 6.96 (m, 3H), 6.81 (d, *J* = 0.8 Hz, 1H), 6.72 – 6.68 (m, 3H), 5.67 (d, *J* = 87.0 Hz, 1H), 5.64 – 5.62 (m, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 2.34 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 159.0, 151.5, 143.0, 137.5, 134.0, 131.6, 129.3 (2C), 128.3, 127.2, 126.4, 120.2, 113.8, 111.7, 56.3, 56.0, 55.3, 21.5, 20.4. IR (neat, cm^{-1}) 3277, 2973, 2937, 1768, 1610, 1512, 1161. HRMS (CI+) calculated for $C_{24}H_{25}NO_6S$ $[M^+]$: 455.1403, found: 455.1396.

(*S*)-2-((4-Methoxyphenyl)(4-methylphenylsulfonamido)methyl)-4-methyl phenyl acetate **(3d')** was prepared (purified by column chromatography, eluent: Et_2O/hexanes = 2:3 to 1:1) as a white solid (66.0 mg, 75% yield, 85% ee). $[\alpha]_D^{25}$ = −7.7 (*c* = 1.0, $CHCl_3$). HPLC analysis of the product: Daicel CHIRALPAK® AD-H column; 30% *i*-PrOH in hexanes; 1.0 mL/min; retention times: 8.87 min (major), 10.35 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.02 – 6.97 (m, 3H), 6.86 – 6.81 (m, 2H), 6.70 (d, *J* = 8.4 Hz, 2H), 5.71 – 5.67 (m, 1H), 5.63 (d, *J* = 8.4 Hz, 1H), 3.72 (s, 3H), 2.34 (s, 3H), 2.13 (s, 3H). 2.00 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 159.0, 145.8, 143.0, 137.6, 135.5, 131.8, 131.6, 129.6, 129.3, 129.1, 128.2, 127.2, 123.0, 113.9, 56.7, 55.3, 21.5, 20.8 (2C).IR (neat, cm^{-1}) 3276, 2956, 2925, 1763, 1511, 1192, 1158. HRMS (CI+) calculated for $C_{24}H_{24}NO_5S$ $[M–H]^+$: 438.1375, found: 438.1374.

(*S*)-4-Methoxy-2-((4-methoxyphenyl)(4-methylphenylsulfonamido)methyl) phenyl acetate **(3e')** was prepared (purified by column chromatography, eluent: Et_2O/hexanes = 1:1) as a yellow oil (45.6 mg, 50% yield, 85% ee). $[\alpha]_D^{25}$ = +7.7 (*c* = 1.0, $CHCl_3$). HPLC analysis of the product: Daicel CHIRALPAK® AD-H column; 50% *i*-PrOH in hexanes; 1.0 mL/min; retention times: 12.45 min (minor), 33.18 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 1H), 6.73 – 6.70 (m, 3H), 6.57 (d, *J* = 3.2 Hz, 1H), 5.61 (d, *J* = 8.0 Hz, 1H), 5.42 (d, *J* = 8.0 Hz, 1H), 3.73 (s, 3H), 3.64 (s, 3H), 2.35 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 159.2, 157.2, 143.3, 141.5, 137.6, 133.1, 131.5, 129.5, 128.3, 127.3, 124.2, 114.3, 114.0, 113.7, 56.8, 55.6, 55.4, 21.6, 20.8. IR (neat, cm^{-1}) 3276, 2935, 1763, 1511, 1180, 1159, 1035. HRMS (CI+) calculated for $C_{24}H_{25}NO_6S$ $[M^+]$: 455.1403, found: 455.1391.

(*S*)-4-Bromo-2-((4-methoxyphenyl)(4-methylphenylsulfonamido)methyl) phenyl acetate **(3f')** was prepared (purified by column chromatography, eluent: Et_2O/hexanes = 2:3 to 1:1) as a pale yellow oil (74.2 mg, 74% yield, 78% ee). $[\alpha]_D^{25}$ = +1.12 (*c* = 1.0, $CHCl_3$). HPLC analysis of the product: Daicel CHIRALPAK® AD-H column; 30% *i*-PrOH in hexanes; 1.0 mL/min; retention times: 11.83 min (minor), 15.14 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.30 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.16 – 7.12 (m, 3H), 6.99 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 1H), 6.73 (d, *J* = 8.8 Hz, 2H), 5.79 (d, *J* = 8.4 Hz, 1H), 5.66 (d, *J* = 8.0 Hz, 1H), 3.74 (s, 3H), 2.39 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 159.2, 147.0, 143.5, 137.2, 134.1, 131.8, 131.4, 130.9, 129.5, 128.2, 127.1, 125.1, 119.0, 114.1, 56.4, 55.3, 21.6, 20.7. IR (neat, cm^{-1}) 3278, 2975, 1768, 1512, 1162. HRMS (CI+) calculated for $C_{23}H_{22}BrNO_5S$ $[M^+]$: 503.0402, found: 503.0411.

(*S*)-5-Fluoro-2-((4-methoxyphenyl)((4-methylphenyl)sulfonamido)methyl) phenyl acetate **(3g')** was prepared (purified by column chromatography, eluent: Et_2O/hexanes = 2:3 to 1:1) as a white solid (86.5 mg, 75% yield, 86% ee). $[\alpha]_D^{25}$ = −9.4 (*c* = 1.0, $CHCl_3$). HPLC analysis of the product: Daicel CHIRALPAK® AD-H column; 30% *i*-PrOH in hexanes; 1.0 mL/min; retention times:

11.59 min (minor), 15.75 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.0 Hz, 2H), 7.09 (t, *J* = 9.2 Hz, 3H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.80 – 6.71 (m, 2H), 6.70 (d, *J* = 8.4 Hz, 2H), 5.71 – 5.63 (m, 2H), 3.72 (s, 3H), 2.35 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 161.9 ($J_{C\text{-}F}$ = 248.4 Hz), 159.0, 148.6 (d, $J_{C\text{-}F}$ = 10.9 Hz), 143.2, 137.4, 131.3, 129.9 (d, $J_{C\text{-}F}$ = 9.4 Hz), 129.3, 128.3 (d, $J_{C\text{-}F}$ = 3.6 Hz), 128.1, 127.1, 113.90, 112.7 (d, $J_{C\text{-}F}$ = 21.2 Hz), 111.1 (d, $J_{C\text{-}F}$ = 24.7 Hz), 56.0, 55.2, 21.4, 20.7. ^{19}F NMR (376Hz, $CDCl_3$) δ −112.1. IR (neat, cm^{-1}) 2931, 1752, 1602, 1502, 1204, 1150, 1015, 665. HRMS (MALDI) calculated for $C_{23}H_{22}FNO_4SNa$ [M+Na^+]: 466.1100, found: 466.1058.

(*S*)-2-(Benzo[d][1,3]dioxol-5-yl(4-methylphenylsulfonamido) methyl)-6-methylphenyl acetate **(3h')** was prepared (purified by column chromatography, eluent: Et_2O/hexanes = 2:3 to 1:1) as an orange solid (50.7 mg, 63% yield, 97% ee). $[\alpha]_D^{25}$ = −14.3 (*c* = 1.0, $CHCl_3$). HPLC analysis of the product: Daicel CHIRALPAK® AD-H column; 50% *i*-PrOH in hexanes; 1.0 mL/min; retention times: 9.70 min (minor), 21.18 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.4 Hz, 2H), 7.11 – 7.07 (m, 3H), 6.97 – 6.91 (m, 2H), 6.60 – 6.54 (m, 3H), 5.86 (d, *J* = 7.2 Hz, 2H), 5.60 (d, *J* = 7.6 Hz, 1H), 5.50 (d, *J* = 7.6 Hz, 1H), 2.35 (s, 3H), 2.15 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 147.8, 147.1, 143.2, 137.5, 133.4, 132.6, 131.5, 130.8, 129.3, 127.3 (2C), 126.6, 126.1, 120.8, 108.1 (2C), 101.2, 56.9, 21.6, 20.6, 16.5. IR (neat, cm^{-1}) 3274, 2957, 2920, 1762, 1488, 1162. HRMS (CI+) calculated for $C_{24}H_{23}NO_6S$ [M^+]: 453.1246, found: 453.1268

(*S*)-2-((4-(Benzyloxy)phenyl)((4-methylphenyl)sulfonamido)m ethyl)-6-methylphenyl acetate **(3i')** was prepared (purified by column chromatography, eluent: Et_2O/hexanes = 1:2) as a pale yellow solid (83.5 mg, 81% yield, >99% ee). $[\alpha]_D^{25}$ = −8.8 (*c* = 1.0, $CHCl_3$). HPLC analysis of the product: Daicel CHIRALPAK® AD-H column; 50% *i*-PrOH in hexanes; 1.0 mL/min; retention times: 15.06 min (minor), 33.25 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.2 Hz, 2H), 7.43 – 7.37 (m, 4H), 7.35 - 7.30 (m, 1H), 7.13 – 7.06 (m, 3H), 7.00 (d, *J* = 8.6 Hz, 2H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.83 – 6.75 (m, 2H), 5.66 (d, *J* = 7.7 Hz, 1H), 5.34 (s, 1H), 4.99 (s, 2H), 2.36 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 158.2, 146.9, 143.0, 137.5, 136.8, 132.6, 131.7, 131.5, 130.6, 129.2, 128.6, 128.4, 128.0, 127.5, 127.1, 126.8, 126.7, 125.9, 114.7, 70.0, 21.5, 20.4, 16.4. IR (neat, cm^{-1}) 3033, 2924, 1757, 1507, 1210, 1157, 1012, 665. HRMS (MALDI) calculated for $C_{30}H_{29}NO_5SK$ [M+K^+]: 554.1404, found: 554.1437.

(*S*)-4-(*tert*-Butyl)-*N*-((2-hydroxy-3-methylphenyl)(4-methoxyp henyl)methyl) benzenesulfonamide **(3j)** was (purified by column chromatography, eluent: Et_2O/hexanes = 1:2) as a white solid (69.5 mg, 80% yield, 98% ee). $[\alpha]_D^{25}$ = −20.9 (*c* = 1.0, $CHCl_3$). HPLC analysis of the product: Daicel CHIRALPAK® AD-H column; 15% *i*-PrOH in hexanes; 1.0 mL/min; retention times: 10.64 min (minor), 11.49 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.50 (m, 2H), 7.26 – 7.20 (m, 2H), 7.10 – 7.04 (m, 2H), 6.92 (d, *J* = 7.3 Hz, 1H), 6.76 – 6.68 (m, 3H), 6.63 (t, *J* = 7.5 Hz, 1H), 5.64 (s, 2H), 5.49 (s, 1H), 3.74 (s, 3H), 2.10 (s, 3H), 1.27 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 155.4, 150.9, 135.9, 130.9, 129.8, 127.6, 126.7, 126.3, 124.8 (2C), 123.7, 119.7, 113.1, 58.1, 54.6, 34.3, 30.4, 15.0. IR (neat, cm^{-1}) 3290, 2962, 1600, 1506, 1154, 1024, 648. HRMS (MALDI) calculated for $C_{25}H_{29}NO_4SNa$ [M+Na]$^+$: 462.1715, found: 462.1709.

tert-Butyl(*S*)-((2-hydroxy-3-methylphenyl)(4-methoxyphenyl) methyl)carbamate (**3k**) was prepared (purified by column chromatography, eluent: hexanes/EtOAc = 8:1 to 4:1) as an orange solid (59.8 mg, 87% yield, 95% ee). $[\alpha]_D^{25}$ = −44.5 (*c* = 1.0, $CHCl_3$). HPLC analysis of the product: Daicel CHIRALPAK® AD-H column; 10% *i*-PrOH in hexanes; 1.0 mL/min; retention times: 10.00 min (major), 11.12 min (minor) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.7 Hz, 2H), 7.05 (d, *J* = 6.8 Hz, 1H), 6.91 – 6.84 (m, 2H), 6.79 – 6.70 (m, 2H), 6.11 (d, *J* = 9.2 Hz, 1H), 5.42 (d, *J* = 8.7 Hz, 1H), 3.80 (s, 3H), 2.26 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1, 156.0, 152.1, 131.9, 129.6, 127.9, 127.3, 125.7, 125.1, 119.3, 113.2, 80.1, 54.7 (2C), 27.7, 15.6. IR (neat, cm^{-1}) 3423, 3180, 2928, 1660, 1501, 1243, 1156, 1033, 768. HRMS (CI+) calculated for $C_{20}H_{25}NO_4$ [M^+]: 343.1784, found: 343.1777.

tert-Butyl(*S*)-(benzyloxy)((2-hydroxy-3-methylphenyl)(4-met hoxyphenyl) methyl)carbamate **(3l)** was prepared (purified by column chromatography, eluent: Et_2O/hexanes = 1:5) as a pale yellow oil (81.8 mg, 91% yield, 89% ee). $[\alpha]_D^{25}$ = −6.8 (*c* = 1.0, $CHCl_3$). HPLC analysis of the product: Daicel CHIRALPAK® AD-H column; 5% *i*-PrOH in hexanes; 1.0 mL/min; retention times: 13.29 min (major), 13.97 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.7 Hz, 2H), 7.29 – 7.21 (m, 3H), 7.11 (d, *J* = 7.5 Hz, 1H), 7.06 (dd, *J* = 7.3, 2.1 Hz, 2H), 7.01 (d, *J* = 7.5 Hz, 1H), 6.91 – 6.84 (m, 2H), 6.79 (t, *J* = 7.6 Hz, 1H), 6.42 (s, 1H), 6.29 (s, 1H), 4.50 (d, *J* = 11.8 Hz, 2H), 3.80 (s, 3H), 2.24 (s, 3H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 156.9, 152.6, 134.7, 130.7, 129.8, 129.6, 129.1, 128.7, 128.5, 128.3, 125.4, 124.4, 119.9, 113.9, 82.4, 78.6, 64.1, 55.3, 28.2, 16.2. IR (neat, cm^{-1}) 3404, 2973, 1682, 1510, 1247, 1163, 749. HRMS (CI+) calculated for $C_{27}H_{31}NO_5$ [M^+]: 499.2202, found: 499.2214.

Benzyl(*S*)-((2-hydroxy-3-methylphenyl)(4-methoxyphenyl)me thyl) carbamate **(3m)** was prepared (purified by column chromatography, eluent: Et_2O/hexanes = 1:2) as a yellow oil (68.7 mg, 91% yield, >99% ee). $[\alpha]_D^{25}$ = −31.7 (*c* = 1.0, $CHCl_3$). HPLC analysis of the product: Daicel CHIRALPAK® IC column; 10% *i*-PrOH in hexanes; 1.0 mL/min; retention times: 14.48 min (major), 18.63 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 5H), 7.19 (d, *J* = 8.5 Hz, 2H), 7.07 (dd, *J* = 7.4, 0.7 Hz, 1H), 6.90 (d, *J* = 7.4 Hz, 1H), 6.88 – 6.82 (m, 2H), 6.82 – 6.76 (m, 1H), 6.57 (br s, 1H), 6.18 (d, *J* = 8.9 Hz, 1H), 5.85 (d, *J* = 9.1 Hz, 1H), 5.13 (dd, *J* = 28.2, 12.2 Hz, 2H), 3.79 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 156.2, 156.2, 151.7, 135.4, 131.9, 129.7, 128.0, 127.62, 127.58, 127.5, 127.3, 126.0, 119.7, 113.3, 66.8 (2C), 54.6, 15.4. IR (neat, cm^{-1}) 3332, 3026, 2949, 1964, 1505, 1237, 1032, 747. HRMS (CI+) calculated for $C_{23}H_{23}NO_4$ [M^+]: 377.1627, found: 377.1627.

(*S*)-2-((((Benzyloxy)carbonyl)amino)(4-methoxyphenyl)methy l)-6-methoxy phenyl acetate **(3n')** was prepared (purified by column chromatography, eluent: hexanes/EtOAc = 4:1 to DCM/EtOAc = 20:1) as a pale yellow oil (52.3 mg, 60% yield, 95% ee). $[\alpha]_D^{25}$ = −12.3 (*c* = 1.0, $CHCl_3$). HPLC analysis of the product: Daicel CHIRALPAK® AD-H column; 15% *i*-PrOH in hexanes; 1.0 mL/min; retention times: 36.21 min (minor), 38.32 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 5H), 7.19 – 7.11 (m, 3H), 6.91 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 3H), 6.11 (d, *J* = 8.2 Hz, 1H), 5.43 (d, *J* = 7.2 Hz, 1H), 5.11 (s, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 158.9, 155.5, 151.7, 137.9, 136.4, 135.3, 132.5, 128.5, 128.2 (2C), 128.0, 126.7, 119.8, 113.9, 111.8, 67.0, 56.1, 55.3, 53.6, 20.3. IR (neat, cm^{-1}) 2944, 1764, 1707, 1508, 1169, 1029, 732. HRM**S** (CI+) calculated for $C_{25}H_{25}NO_6$ [M^+]:435.1682, found: 435.1662.

(*S*)-2-((((Benzyloxy)carbonyl)amino)(4-(benzyloxy)phenyl)me thyl)-6-methylphenyl acetate **(3o')** was prepared (purified by column chromatography, eluent: Et_2O/hexanes = 1:2) as a white solid (87.2 mg, 88% yield, >99% ee). $[\alpha]_D^{25}$ = −2.1 (*c* = 1.0, $CHCl_3$). HPLC analysis of the product: Daicel CHIRALPAK® AD-H column; 50% *i*-PrOH in hexanes; 1.0 mL/min; retention times: 17.41 min (major), 20.03 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.40 (m, 3H), 7.39 – 7.29 (m, 7H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 3H), 7.04 (d, *J* = 6.9 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 2H), 6.10 (d, *J* = 7.8 Hz, 1H), 5.34 (s, 1H), 5.12 (s, 2H), 5.04 (s, 2H), 2.14 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 158.1, 155.5, 147.5, 136.9, 136.4, 134.0, 132.9, 131.6, 130.7, 128.62, 128.55, 128.3, 128.2, 128.1, 128.0, 127.5, 126.2, 114.9, 114.6, 70.0, 67.0, 53.7, 20.3, 16.5. IR (neat, cm^{-1}) 3032, 2940, 1708, 1505, 1211, 1162, 735. HRMS (MALDI) calculated for $C_{31}H_{29}NO_5$ [M^+]: 495.2046, found: 495.1954.

(*S*)-2-((4-Methoxyphenyl)(4-methylphenylsulfonamido)methyl)-6-methyl phenyl trifluoromethanesulfonate **(4)**. At –10 °C, to a flask charged with a mixture of the alcohol **1b** (244.4 mg, 1.0 mmol), $TsNH_2$ (1.2 mmol, 205 mg), 5Å molecular sieves (500 mg), and DCE (20 mL). Next, a solution of the catalyst (*R*)-**B** (30.5 mg, 10 mol%) in DCE (0.5 mL) was added slowly. The reaction mixture was stirred at –10 °C for 24 h. After that, anhydrous DCM (20 mL) was added to the flask, and the reaction mixture was cooled to –78 °C. Then triethylamine (6.0 mmol, 604 mg) and trifluoromethanesulfonic anhydride (4.0 mmol, 672 uL) were added sequentially. The mixture was stirred at the same temperature for 2 h before it was filtered through a pad of celite, which was washed with DCM (40 mL). The filtrate was concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography to afford triflate **4** as white foam (426 mg, 81% yield, 98% ee). $[\alpha]_D^{25}$ = −4.70 (*c* = 1.0, $CHCl_3$). HPLC analysis of the product: Daicel CHIRALPAK® AD-H column; 30% *i*-PrOH in hexanes; 1.0 mL/min; retention times: 5.72 min (minor), 8.58 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 6.8 Hz, 1H), 7.22 – 7.14 (m, 4H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.71 (d, *J* = 8.8 Hz, 2H), 5.92 (d, *J* = 7.2 Hz, 1H), 5.50 (d, *J* = 7.2 Hz, 1H), 3.72 (s, 3H), 2.39 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4 (2C), 144.4, 143.6, 137.0, 135.1, 132.2, 131.9, 131.5, 129.6, 128.8, 128.7, 127.53, 127.45, 114.1, 55.4, 55.2, 21.7, 17.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.2. IR (neat, cm^{-1}) 3268, 2975, 1512, 1334, 1160, 1139, 881. HRMS (CI+) calculated for $C_{23}H_{22}F_3NO_6S_2$ [M^+]: 529.0841, found: 529.0839.

(*S*)-*N*-((4-Methoxyphenyl)(m-tolyl)methyl)-4-methylbenzene sulfonamide **(5)**. At room temperature, a 10-mL flask was charged with trifluoromethane sulfonate **4** (53.0 mg, 0.1 mmol), magnesium turnings (24 mg, 1 mmol), palladium on carbon (26.5 mg, 50 wt%), ammonium chloride (53.5 mg, 1.0 mmol) and methanol (2 mL). The mixture was stirred under nitrogen at room temperature for 4 h. Then it was filtered through a pad of silica gel. The silica gel was washed with EtOAc (3×20 mL). The filtrate was concentrated, and the crude product was purified by silica gel column chromatography (eluent: Et_2O/hexanes = 1:3) to afford pure **5** as a white solid (30.1 mg, 79% yield, 98% ee). $[\alpha]_D^{25}$ = −12.0 (*c* = 1.0, $CHCl_3$). HPLC analysis of the product: Daicel CHIRALPAK® AD-H column; 30% *i*-PrOH in hexanes; 1.0 mL/min; retention times: 8.36 min (minor), 9.09 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.14 – 7.03 (m, 3H), 7.01 – 6.97 (m, 3H), 6.90 – 6.86 (m, 2H), 6.74 – 6.71 (m, 2H), 5.49 (d, *J* = 7.2 Hz, 1H), 5.28 (d, *J* = 7.2 Hz, 1H), 3.74 (s, 3H), 2.38 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 143.2, 140.8, 138.3, 137.7, 133.1, 129.4, 128.8, 128.6, 128.3, 128.1, 127.4, 124.5, 114.0, 61.0, 55.4, 21.6, 21.5. IR (neat, cm^{-1}) 3277, 2957, 2925, 1512, 1159. HRMS (CI+) calculated for $C_{22}H_{23}NO_3S$ [M^+]: 381.1399, found: 381.1393.

(*S*)-*N*-((4-Methoxyphenyl)(6-methyl-[1,1'-biphenyl]-2-yl)methyl)-4-methyl benzenesulfonamide **(6)**. Under N_2, a 4-mL vial was charged with trifluoromethanesulfonate **4** (53.0 mg, 0.1 mmol), phenylboronic acid (13.4 mg, 0.11 mmol), potassium phosphate (31.8 mg, 0.15 mmol), $Pd(PPh_3)_4$ (2.9 mg, 2.5 mol%) and degassed 1,4-dioxane (0.5 mL). The vial was sealed and stirred at 100 °C for 24 h. Upon completion, the mixture was cooled to room temperature, diluted with Et_2O (1.0 mL) and water (1.0 mL). The layers were separated. The aqueous layer was extracted by Et_2O (3×1.0 mL). The combined organic layers were washed with water (10 mL) and brine (5 mL), then dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by silica gel column chromatography (eluent: Et_2O/hexanes = 2:3) to afford pure **6** as a white solid (29.0 mg, 63% yield, 95% ee). $[\alpha]_D^{25}$ = −15.6 (*c* = 1.0, $CHCl_3$). HPLC analysis of the product: Daicel CHIRALPAK® OD-H column; 15% *i*-PrOH in hexanes; 1.0 mL/min; retention times: 8.94 min (minor), 11.76 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 15.5 Hz, 2H), 7.32 – 7.27 (m, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.12 – 7.08 (m, 6H), 6.60 (m, 3H), 6.54 (d, *J* = 7.6 Hz, 1H), 5.25 (d, *J* = 5.6 Hz, 1H), 4.81 (d, *J* = 6.0 Hz, 1H), 3.72 (s, 3H), 2.40 (s, 3H), 1.94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 143.3, 140.7, 139.2, 138.8, 136.8, 133.3, 129.9, 129.5, 129.2, 129.0, 128.7, 128.2, 127.6, 127.5, 127.2, 124.7, 113.9, 58.3, 55.4, 21.7, 21.0. IR (neat, cm^{-1}) 3277, 2957, 2924, 1511, 1159. HRMS (EI+) calculated for $C_{28}H_{27}NO_3S$ [M^+]: 457.1712, found: 457.1710.

(*S*)-*N*-((2-(Diphenylphosphoryl)-3-methylphenyl)(4-methoxyphenyl)methyl) -4-methylbenzenesulfonamide **(7)**. Under N_2, a 4-mL vial was charged with trifluoromethanesulfonate **4** (140 mg, 0.264 mmol), diphenylphosphine oxide (106 mg, 0.528 mmol), redistilled *N*,*N*-diisopropylethylamine (100 μL, 0.60 mmol), 1,3-bis(diphenylphosphino)propane (12 mg, 10 mol%), $Pd_2(dba)_3$ (11 mg, 5.0 mol%) and degassed toluene (1.5 mL). The vial was sealed and stirred at 105 °C for 48 h. Upon completion, the mixture was cooled to room temperature, and directly subject to silica gel column chromatography (eluent: Et_2O/hexanes = 3:1 to 1:1) to afford pure **7** as a white solid (120 mg, 78% yield, 98% ee). $[\alpha]_D^{25}$ = −48.3 (*c* = 1.0, $CHCl_3$). HPLC analysis of the product: Daicel CHIRALPAK® IC column; 40% *i*-PrOH in hexanes; 1.0 mL/min; retention times: 40.47 min (minor), 44.28 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 - 7.54 (m, 3H), 7.50 - 7.36 (m, 3H), 7.34 - 7.24 (m, 6H), 7.23 - 7.11 (m, 4H), 7.11 - 7.04 (m, 1H), 6.79 (d, *J* = 8.8 Hz, 2H), 6.48 (s, 1H), 6.35 (d, *J* = 8.8 Hz, 2H), 3.58 (s, 3H), 2.35 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 149.4 (d, *J* = 7.3 Hz), 142.7 (d, *J* = 10.9 Hz), 142.4, 133.2, 132.0 (d, *J* = 2.5 Hz), 131.9 (d, *J* = 11.1 Hz), 131.7 (d, *J* = 10.1 Hz), 131.4, 131.4 (d, *J* = 5.6 Hz), 131.1 (d, *J* = 10.3 Hz), 129.2, 128.5 (d, *J* = 12.2 Hz), 128.4, 128.2 (d, *J* = 12.4 Hz), 127.2, 127.1 (d, *J* = 96.4 Hz), 112.8, 55.0, 25.4, 25.3, 21.5. ^{31}P NMR (162 MHz, $CDCl_3$) δ 33.3. IR (neat, cm^{-1}) 3270, 2973, 1511, 1438, 1115. HRMS (CI+) calculated for $C_{34}H_{32}NO_4PS$ [M^+]: 581.1790, found: 581.1780.

(*S*)-*N*-((2-hydroxy-3-methoxyphenyl)(4-methoxyphenyl)methyl)acetamide (**8**). Under H_2 atmosphere (H_2 balloon, 1 atm), to an oven-dried Schlenk tube were added Pd/C (10 wt%, 13 mg), **3n'** (56.9 mg, 0.13 mmol) and MeOH (3 mL). The reaction mixture was stirred at room temperature for 4 h, and it was filtered through a short pad of celite (eluent: DCM/MeOH = 1:1). After evaporation, the crude product was purified by preparative thin layer chromatography on silica gel (eluent: DCM/MeOH = 20:1) to afford pure product **8** as a white solid (24.8 mg, 63% yield, 95% ee). $[\alpha]_D^{25}$ = +1.6 (*c* = 0.5, $CHCl_3$). HPLC analysis of the product: Daicel CHIRALPAK® AD-H column; 15% *i*-PrOH in hexanes; 1.0 mL/min; retention times: 22.43 min (major), 27.66 min (minor). ^{1}H NMR (400 MHz, acetone-d_6) δ 7.76 (s, 1H), 7.75 (s, 1H), 7.27 - 7.19 (m, 2H), 6.96 - 6.88 (m, 2H), 6.88 - 6.77 (m, 3H), 6.53 (d, *J* = 8.8 Hz, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 2.00 (s, 3H). ^{13}H NMR (100 MHz, acetone-d_6) δ 169.8, 160.2, 149.1, 145.4, 136.4, 130.6, 129.8, 121.6, 120.7, 115.0, 111.7, 57.1, 56.2, 52.6, 23.8. IR (neat, cm^{-1}) 3332, 2960, 2927, 1725, 1685, 1260. HRMS (CI+) calculated for $C_{17}H_{19}NO_4$ [M^+]: 301.1314, found: 301.1320.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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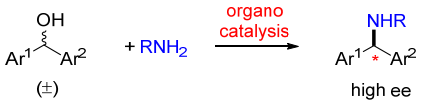
Organocatalytic Enantioselective Synthesis of Chiral Diarylmethylamines from Racemic Alcohols



Min Chen,[+] Yaodong Han,[+] Dengke Ma,[+] Yong Wang, Zengwei Lai and Jianwei Sun*

An organocatalytic approach for direct conversion of racemic diarylmethanols to valuable chiral diarylmethylamines is described. Different from the previously reported elegant "borrowing hydrogen" approach, the present process employs a distinct formal S_N1 strategy, thereby leading to complementary features on reaction scope and catalytic system. This new approach enjoys excellent enantioselectivity, mild conditions, broad scope, and easy derivatization of products. Mechanistically, control experiments also provided important insights into some notable features, such as substrate kinetic resolution and reversibility as well as the critical role of the ortho-hydroxy group in the substrate.