JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

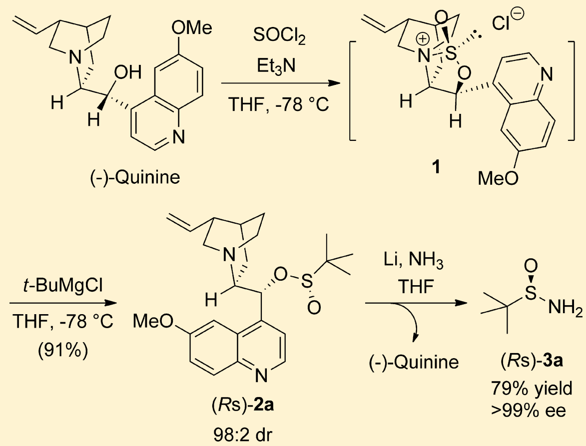
Asymmetric Synthesis of Sulfinamides Using (−)-Quinine as Chiral Auxiliary

Yongda Zhang,* Sampada Chitale, Navneet Goyal, Guisheng Li, Zhengxu S. Han, Sherry Shen, Shengli Ma, Nelu Grinberg, Heewon Lee, Bruce Z. Lu, and Chris H. Senanayake

Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, Ridgefield, Connecticut 06877, United States

Supporting Information

ABSTRACT: A process has been designed and demonstrated for the asymmetric synthesis of sulfinamides using quinine as auxiliary. A variety of chiral sulfinamides including *N*-alkyl sulfinamides with diverse structure were prepared in good yields and excellent enantioselectivity starting from easily available and inexpensive reagents. The auxiliary quinine could be recovered and recycled.



Over the past three decades, chiral sulfinamides such as *p*-toluenesulfinamide and *tert*-butanesulfinamide have been widely exploited and exercised by academia and industry because of their unique roles and importance in the asymmetric synthesis of chiral nitrogen-contained functionalities.[1] The corresponding sulfinylimines, derived from the condensation of sulfinamides with aldehydes and ketones, have been extensively utilized as versatile chiral nitrogen vehicles for synthesis of a variety of chiral amines, including α-branched amines, α- and β- amino acids, 1,2-amino alcohols, 1,3-amino alcohols, aziridines, aminooxetanes, and amino phosphoric acids.[2] Particularly, addition to chiral sulfinketimines has provided an indispensable and reliable tool in modern organic synthesis for preparation of chiral tertiary carbinamines, which are prevalent in natural products, synthetic pharmaceuticals, and catalysts but not accessible from well-developed transition-metal catalyzed asymmetric hydrogenation of imines.[3] Moreover, chiral sulfinamides have been investigated as novel chiral ligands or essential chiral motif in catalyst design to achieve high-level asymmetric induction.[4] Typically, chiral *tert*-butanesulfinamides could be practically prepared via two-step process of an asymmetric catalytic oxidation of *tert*-butyl disulfide and subsequent reaction with an amide anion.[5] In 2002, Senanayake and co-workers reported a modular synthesis of a variety of structurally diverse enantiopure sulfinamides from *N*-sulfonyl-1,2,3-oxathiazolidine-2-oxide agents.[6] Recently, we also developed a new process for the synthesis of chiral sulfinamides using a chiral sulfinyl transfer auxiliary derived from readily available phenylglycine.[7] Considering the vast potential of these chiral sulfinamides as chiral *N*-auxiliaries and ligands, it is highly desirable to further investigate and develop efficient and economic methods for convenient synthesis of chiral sulfinamides with different steric and stereoelectronic characteristics. We envision that will help further realize and expand the potential of chiral sulfinamides in the area of asymmetric organic synthesis.

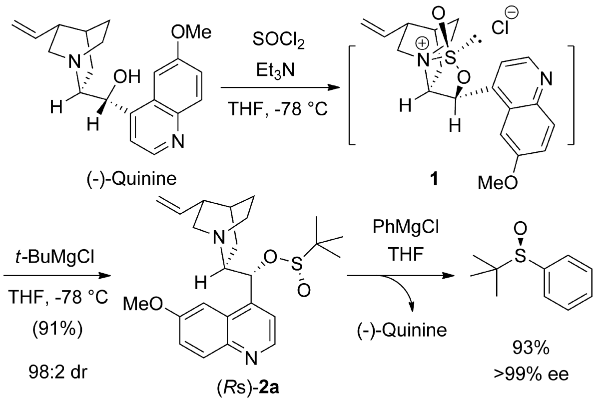
Previously, we reported that chiral sulfoxides could be prepared in excellent enantiopurity and high yields via a pseudo-five-membered ring oxathiazolidine **1** using the inexpensive natural product cinchona alkaloid (−)-quinine as chiral auxiliary (Scheme 1).[8]

We speculated that application of the novel sulfinyl transfer reagent could lead to formation of important chiral sulfinamides by treatment of the resulting chiral sulfinates with suitable amide anions (Scheme 2). Herein, we report our efforts regarding efficient asymmetric synthesis of chiral sulfinamides using inexpensive (−)-quinine as chiral auxiliary.

Our work commenced with the synthesis of chiral quinine sulfinates, and the results are summarized in the Table 1. All the quinine sulfinates were easily prepared in high yields with excellent diastereoselectivity. In the case of alkyl sulfinate, bulky alkyl Grignard such as *t*-butyl magnesium chloride could be used directly. Typically, the reaction went to completion in less than 0.5 h and gave the desired product **2a** and **2b** in high yield. Formation of symmetric sulfoxides such as di-*tert*-butyl sulfoxide

Received: September 8, 2011
Published: November 29, 2011

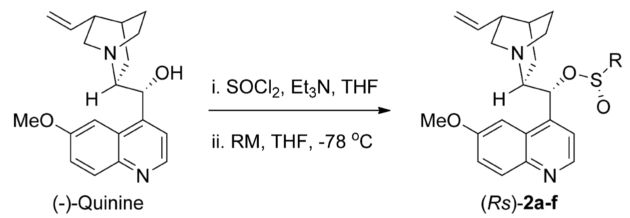
Scheme 1. Asymmetric Synthesis of Chiral Sulfoxides via a Pseudo-Five-Membered Ring Oxathiazolidine

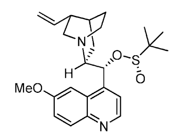
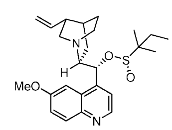
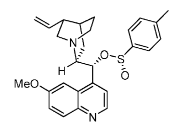
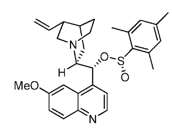
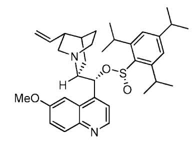
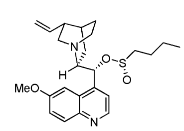


was not observed even in the presence of excessive *t*-butyl magnesium chloride.[10] However, exclusive formation of racemic di(*p*-tolyl)sulfoxide was observed even with 1 equiv of *p*-tolyl magnesium chloride as reported before.[6] The issue was overcome with the use of arylzinc halides, which were easily prepared in situ from aryl Grignard reagents and equal amount of zinc chloride. The resulting quinine sulfinates **2c**, **2d**, and **2e** were prepared in good to high yield with 96:4 diastereoselectivity. To avoid the formation of sulfoxides, in situ generated *n*-BuZnCl was applied also for the synthesis of **2f**. The stereochemistry of the quinine sulfinates **2a–f** at sulfur center was assigned according to the X-ray structure of **2d** (Figure 1). All the products were easily isolated and purified by column chromatography on silica gel.

With chiral quinine sulfinates at hand, we started to investigate the synthesis of chiral sulfinamides. When **2a** was heated with $BnNH_2$ in THF at 70 °C even for 12 h, no sulfinamide **3a** was detected, and **2a** was recovered.[11] No reaction was observed either when the sulfinate **2a** was treated with commercially available metal amides ($LiNH_2$ and $NaNH_2$) at −78 °C in THF. When the reaction mixture was warmed to room temperature overnight, only a small amount of nearly racemic sulfinamide was obtained. Further studies indicated that treatment with bulky LHMDS at −78 °C or aqueous ammonium hydroxide at 23 °C gave no reaction. At this stage, we performed the reaction with Li/NH_3 with THF as cosolvent, which has been extensively utilized for synthesis of sulfinamides. The reaction proceeded immediately and went to completion in 15 min. As shown in Table 2, the *tert*-butanesulfinamide **3a** was prepared in 79% yield and 99% e.e. with stereospecific inversion at sulfur center. In the case of alkyl sulfinate **2b**, the resulting sulfinamide **3b** was obtained with 99% e.e. However, only moderate selectivity was observed when *p*-tolylsulfinate **2c** was treated with Li/NH_3 in THF. Considering the low solubility and slow dissolution of *p*-tolylsulfinate **2c** in THF, we speculated

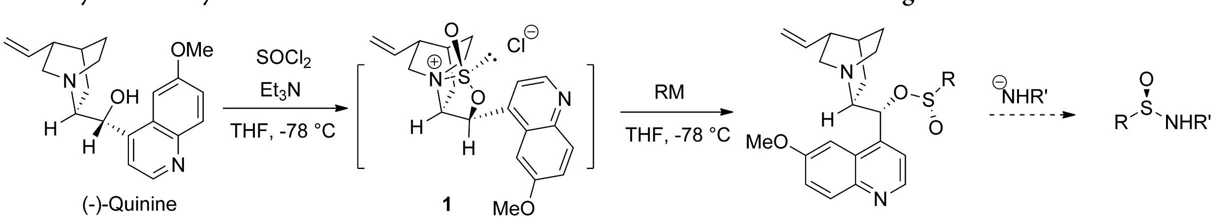
Table 1. Synthesis of Chiral Sulfinates Using (−)-Quinine as Chiral Auxiliaries



entry	RM	product[a]	yield[b] (%)	d.r.[c]
1	*t*-BuMgCl	 (Rs)-**2a**	91	98:2
2	2-Me-2-BuMgCl	 (*R*s)-**2b**	92	96:4
3	*p*-TolylZnCl	 (Rs)-**2c**	76	96:4
4	MesityZnCl	 (*R*s)-**2d**	94	96:4
5	2,4,6-Triisopropyl phenylZnCl	 (*R*s)-**2e**	80	96:4
6	*n*-BuZnCl	 (*R*s)-**2f**	85	96:4

[a]Absolute configurations of **2a–f** were assigned according to X-ray structure of **2e**. [b]Isolated yield after purification by column chromatography. [c]Diastereomeric ratio was determined by HPLC analysis of the crude product.[9]

Scheme 2. Asymmetric Synthesis of Chiral Sulfinamides via a Pseudo-Five-Membered Ring Oxathiazolidine



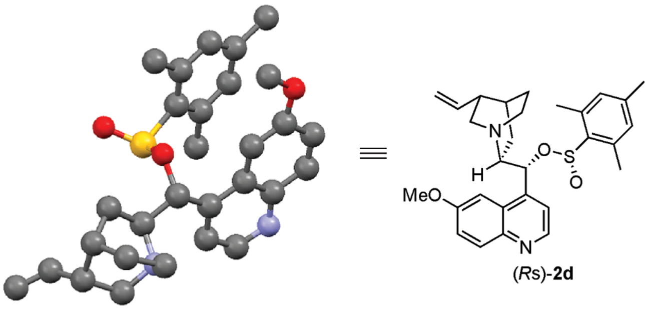
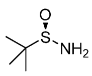
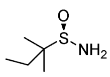
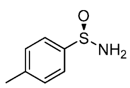
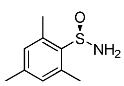
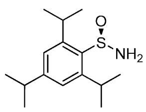
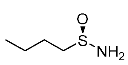


Figure 1. X-ray structure of **2d**. Hydrogen atoms have been omitted for clarity.

Table 2. Synthesis of Chiral Sulfinamides Starting from Quinine Sulfinates

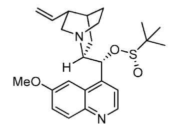
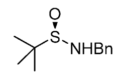
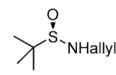
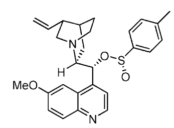
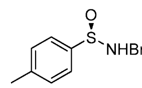
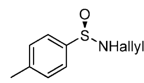
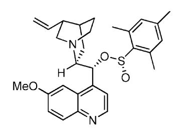
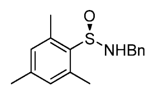
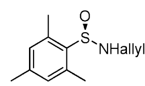
entry	lithium amide	product[a]	yield[b] (%)	e.e.[c]
1	Li/NH_3	 **3a**	79	99%
2	Li/NH_3	 **3b**	71	99%
3	Li/NH_3 LHMDS[d]	 **3c**	92 84	77% 99%
4	Li/NH_3 LHMDS	 **3d**	85 82	70% 98%
5	Li/NH_3	 **3e**	84	99%
6	LHMDS	 **3f**	82 87	56% (23 °C) 96% (-78 °C)

[a]Absolute configurations of **3a**−**f** were deduced from the corresponding sulfinates assuming each nucleophilic substitution inverts the conformation of the sulfinyl center. [b]Isolated yield after purified by column chromatography. [c]Enantiomeric excess was determined by chiral HPLC analysis. [d]DMF was used as solvent.

that byproduct lithium quinine alkoxide could competitively racemize quinine sulfinate. To solve the problem and improve the enantiopurity of the product, more polar DMF was chosen as the solvent for the reaction. The reaction of *p*-tolylsulfinate **2c** with LHMDS in DMF proceeded smoothly and gave the *p*-tolylsulfinamide **3c** with 99% e.e.[12] Excellent enantioselectivity was also obtained when mesityl sulfinate **2d** was treated with LHMDS in THF. The use of Li/NH_3 just gave the product **3d** with moderate enantiopurity. In the case of more bulky 2,4,6-triisopropylphenyl sulfinate **2e**, no reaction was observed when LHMDS was used. However, treatment with Li/NH_3 in THF led to the formation of 2,4,6-triisopropylphenyl sulfinamide **3e** with 99% e.e. and 84% yield. When *n*-butyl sulfinate **2f** was treated with LHMDS at 23 °C, the product **3f** was isolated with 78:22 enantiomeric ratio. The enantioselectivity was improved to 96% e.e. when the reaction was performed at −78 °C.

Chiral *N*-alkyl sulfinamide derivatives have been used as ligands and catalysts and exhibit unique properties in organic transformation[13] but are still not widely explored. We envisioned that chiral *N*-alkyl sulfinamides could be also prepared when our chiral quinine sulfinates were treated with easily prepared lithium alkylamides such as lithium benzylamide. *N*-Alkyl sulfinamides were isolated with excellent enantiopurity and high yield (Table 3). Because of the acidity of NH in the product, at least 2 equiv of lithium amide were used. When *t*-butyl sulfinate **2a** was treated with in situ generated LiNHBn, the reaction proceeded instantaneously even at −78 °C and gave the product **4a** with 88% yield and 99% e.e. The use of LiNHallyl gave *N*-allyl *t*-butylsulfinamide **4b** with 85% yield and 98% e.e. In the case of *p*-tolyl sulfinate **2c**, the product *N*-benzyl *p*-tolylsulfinamide **4c** was obtained in 82% yield and 99% e.e. The treatment of *p*-tolyl sulfinate **2c** with *N*-allyl lithium amide gave the product *N*-allyl *p*-tolylsulfinamide **4d** with 68% yield and 99% e.e. With more sterically hindered mesityl sulfinate **2d**, the reaction with *N*-benzyl lithium amide still proceeded at −78 °C immediately and generated the product *N*-benzyl mesity sulfinamide **4e** with 80% yield and over 99% e.e. In the case of *N*-allyl lithium amide, the product *N*-allyl mesityl sulfinamide **4f** was isolated with 76% yield and 99% e.e.

Table 3. Synthesis of N-alkyl Chiral Sulfinamides Starting from Quinine Sulfinate

entry	sulfinate	product[a]	yield[b] (%)	e.e.[c]
1	 **2a**	 **4a**	88	99%
		 **4b**	85	98%
2	 **2c**	 **4c**	82	99%
		 **4d**	68	99%
3	 **2d**	 **4e**	80	99%
		 **4f**	76	99%

[a]Absolute configurations of **4a**−**f** were deduced from the corresponding sulfinates assuming each nucleophilic substitution inverts the conformation of the sulfinyl center. [b]Isolated yield after purification by column chromatography. [c]Enantiomeric excess was determined by chiral HPLC analysis.

In summary, we have developed and demonstrated a method for the asymmetric synthesis of sulfinamides in high yields and excellent enantioselectivity from chiral quinine sulfinates, which could be easily prepared from cheap and easily available starting material.[14] Moreover, the quinine after the reactions could be recovered and recycled. We believe the expedient route could find wide application in the synthesis of chiral sulfinamides. Further application of these chiral sulfinamides in asymmetric organic synthesis is ongoing and will be reported in near future.

■ EXPERIMENTAL SECTION

General Methods. All reactions were run in an oven-dried flask under nitrogen. Unless otherwise noted, reagents were commercially available and used without purification. The racemic sulfinamides were prepared following the literature procedure.[15] Chemical shifts are reported in δ (ppm) relative to TMS in $CDCl_3$ as internal standard (^1H NMR) or the residual $CHCl_3$ signal (^{13}C NMR).

General Experimental Procedure for Synthesis of Quinine Sulfinates. A dry flask fitted with a stir bar was charged with THF (20 mL) under nitrogen. After the solution was cooled to −78 °C, $SOCl_2$ (2.47 mL, 33.9 mmol, 1.1 equiv) was added. Then, a solution of quinine (10 g, 30.8 mmol) and Et_3N (6.44 mL, 46.2 mmol, 1.5 equiv) in THF (80 mL) was added dropwise while the internal temperature was maintained below −70 °C. After 15 min at below −70 °C, organometallic reagent (2.5 equiv) was added while the internal temperature was maintained below −70 °C. After 30 min at below −70 °C, the reaction was then quenched with saturated aqueous NH_4Cl (50 mL). After the mixture was warmed to room temperature, the aqueous layer was extracted with EtOAc (3 × 150 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated. Purification of the crude product by column chromatography on silica gel gave analytically pure product.

Quinine (*R*s)-*tert*-Butylsulfinate 2a.[8] The general procedure above was followed, using quinine (10.0 g, 30.8 mmol), $SOCl_2$ (2.47 mL, 33.9 mmol, 1.1 equiv), Et_3N (6.44 mL, 46.2 mmol, 1.5 equiv), and THF (100 mL). After the reaction mixture was stirred for 15 min below −70 °C, the mixture was further treated with *t*-BuMgCl (77 mL, 77 mmol, 1 M in THF, 2.5 equiv). Column chromatography on silica gel (eluting with 0−5% MeOH in EtOAc) afforded the product **2a** as a pale yellow oil (12.0 g, 91%, >99:1 d.r.).

The known compounds sulfinamide **2a** was isolated as pure sample and the NMR spectra matched the reported compound.[8]

Quinine (*R*s)-1,1-Dimethylpropylsulfinate 2b. The general procedure above was followed, using quinine (10.0 g, 30.8 mmol), $SOCl_2$ (2.47 mL, 33.9 mmol, 1.1 equiv), Et_3N (6.44 mL, 46.2 mmol, 1.5 equiv), and THF (100 mL). After the reaction mixture was stirred for 15 min below −70 °C, the mixture was further treated with 2-methyl-2-butylMgCl (77 mL, 77 mmol, 1 M in ether, 2.5 equiv). Column chromatography on silica gel (eluting with 0−5% MeOH in EtOAc) afforded the product **2b** as a pale yellow oil (12.6 g, 92%, >99:1 d.r.): ^1H NMR (400 MHz, $CDCl_3$) δ 8.71(d, 1H, *J* = 1.6 Hz), 7.98 (dd, 1H, *J* = 3.6 Hz, 9.2 Hz), 7.40−7.30 (m, 3H), 5.79−5.77(m, 1H), 5.65 (bs, 1H), 4.98−4.94 (m, 2H), 3.89 (s, 3H), 3.45 (bs, 1H), 2.97−2.94 (m, 2H), 2.58−2.56 (m, 2H), 2.21 (bs, 1H), 1.99−1.83 (m, 2H), 1.64−1.50 (m, 5H), 1.14 (s, 3H), 1.11 (s, 3H), 0.90 (t, 3H, *J* = 2.4 HZ); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 147.2, 144.8, 143.7, 141.7, 131.7, 126.8, 121.4, 120.2, 114.4, 101.8, 61.6, 60.6, 56.3, 55.4, 42.1, 39.7, 27.8, 27.7, 27.5, 18.6, 18.4, 7.7; HRMS (ES pos.) *m/z* calcd for $C_{25}H_{35}N_2O_3S^+$ (M + H^+) 443.2362, found 443.2372.

Quinine (*R*s)-*p*-Tolylsulfinate 2c.[8] To a solution of 4-methylbenzenemagnesium bromide (77 mL, 1 M in THF) was added a solution of $ZnCl_2$ (145 mL, 0.5 M) in THF at 0 °C. After 0.5 h, the resulting solution was ready for synthesis of sulfinate **2c**.

The general procedure above was followed, using quinine (10.0 g, 30.8 mmol), $SOCl_2$ (2.47 mL, 33.9 mmol, 1.1 equiv), Et_3N (6.44 mL, 46.2 mmol, 1.5 equiv), and THF (100 mL). After the reaction mixture was stirred for 15 min below −70 °C, the mixture was further treated with *p*-MePhZnCl prepared above. Column chromatography on silica gel (eluting with 0−5% MeOH in EtOAc) afforded the product **2c** as a pale yellow oil (10.8 g, 76%, 96:4 d.r.).

The known compounds sulfinamide **2c** was isolated as pure sample and the NMR spectra matched the reported compound.[8]

Quinine (*R*s)-2,4,6-Trimethylbenzenesulfinate 2d. To a solution of 2,4,6-trimethylbenzenemagnesium bromide (77 mL, 77 mmol, 1 M in THF) was added a solution of 0.5 M $ZnCl_2$ (145 mL, 145 mmol) in THF at 0 °C. After 0.5 h, the resulting solution was ready for synthesis of sulfinate **2d**.

The general procedure above was followed, using quinine (10.0 g, 30.8 mmol), $SOCl_2$ (2.47 mL, 33.9 mmol, 1.1 equiv), Et_3N (6.44 mL, 46.2 mmol, 1.5 equiv), and THF (100 mL). After the reaction mixture was stirred for 15 min below −70 °C, the mixture was further treated with mesityl ZnCl prepared above. Column chromatography on silica gel (eluting with 0−5% MeOH in EtOAc) afforded the product **2d** as a pale yellow oil (14.2 g, 94%, 96:4 d.r.): ^1H NMR (400 MHz, $CDCl_3$) δ 8.72 (bs, 1H), 7.99 (dd, 1H, *J* = 3.6 Hz, 9.2 Hz), 7.46 (bs, 1H), 7.34 (m, 1H), 7.24 (m, 1H), 6.72−6.70 (m, 2H), 5.79−5.73 (m, 2H), 4.96−4.90 (m, 2H), 3.86 (s, 3H), 3.33 (bs, 1H), 3.00−2.95 (m, 2H), 2.58−2.52 (m, 2H), 2.48 (s, 6H), 2.20−2.18 (m, 4H), 1.79 (bs, 2H), 1.65 (bs, 1H), 1.49−1.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 147.4, 144.6, 143.5, 142.2, 141.7, 138.3, 137.4, 131.9, 130.7, 126.5, 121.6, 119.9, 114.5, 101.5, 80.6, 60.1, 56.8, 55.6, 42.4, 39.8, 27.7, 27.6, 24.1, 21.1, 19.2; HRMS (ES pos.) *m/z* calcd for $C_{29}H_{35}N_2O_3S^+$ (M + H^+) 491.2362, found 491.2368.

Quinine (*R*s)-2,4,6-Triisopropylbenzenesulfinate 2e. To a solution of 2,4,6-triisopropylbenzenemagnesiumbromide (77 mmol) was added a solution of 0.5 M $ZnCl_2$ (145 mL, 145 mmol) in THF at 0 °C. After 0.5 h, the resulting solution was ready for synthesis of sulfinate **2e**.

The general procedure above was followed, using quinine (10.0 g, 30.8 mmol), $SOCl_2$ (2.47 mL, 33.9 mmol, 1.1 equiv), Et_3N (6.44 mL, 46.2 mmol, 1.5 equiv), and THF (100 mL). After the reaction mixture was stirred for 15 min below −70 °C, the mixture was further treated with 2,4,6-triisopropylbenzeneZnCl (2.5 equiv) prepared above. Column chromatography on silica gel (eluting with 0−5% MeOH in EtOAc) afforded the product **2e** as a pale yellow oil (14.2 g, 80%, 96:4 d.r.): ^1H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, 1H, *J* = 4.4 Hz), 8.04 (d, 1H, *J* = 9.2 Hz), 7.54 (bs, 1H), 7.39−7.33 (m, 2H), 7.06 (s, 2H), 5.90 (bs, 1H), 5.80−5.75 (m, 1H), 4.90−4.93 (m, 2H), 3.91 (s, 3H), 3.40 (bs, 1H), 3.02−2.85 (m, 3H), 2.65−2.54 (m, 2H), 2.23 (bs, 1H), 1.81−1.45 (m, 5H), 1.23−1.17 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 153.3, 148.8, 147.5, 144.8, 143.3, 141.7, 138.1, 131.9, 126.7, 122.7, 121.6, 120.0, 114.5, 101.4, 81.3, 59.7, 56.7, 55.7, 42.4, 39.9, 34.4, 28.2, 27.6, 24.8, 24.1, 23.7; HRMS (ES pos.) *m/z* calcd for $C_{35}H_{47}N_2O_3S^+$ (M + H^+) 575.3301, found 575.3305.

Quinine (*R*s)-*n*-Butylsulfinate 2f. To a solution of 0.5 M $ZnCl_2$ (77 mL, 38.5 mmol) in THF was added a solution of *n*-BuLi (15.4 mL, 38.5 mmol, 2.5 M in hexane) at 0 °C. After 0.5 h, the resulting solution was ready for synthesis of sulfinate **2f**.

The general procedure above was followed, using quinine (5.0 g, 15.4 mmol), $SOCl_2$ (2.02 g, 16.95 mmol, 1.1 equiv), Et_3N (3.22 mL, 23.1 mmol, 1.5 equiv), and THF (50 mL). After the reaction mixture was stirred for 15 min below −70 °C, the mixture was further treated with *n*-BuZnCl (2.5 equiv) prepared above. Column chromatography on silica gel (eluting with 0−5% MeOH in EtOAc) afforded the product **2f** as a pale yellow oil (5.68 g, 86%, 99:1 d.r.): ^1H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, 1H, *J* = 4.5 Hz), 8.04 (d, 1H, *J* = 9.1 Hz), 7.50 (d, 1H, *J* = 4.5), 7.39−7.34 (m, 2H), 5.95 (d, 1H, *J* = 5.5 Hz), 5.78 (m, 1H), 5.0−4.96 (m, 2H), 3.96 (s, 3H), 3.34 (m, 1H), 3.15 (bs, 1H), 3.05 (m, 1H), 2.73−2.61 (m, 4H), 2.29 (bs, 1H), 1.88−1.54 (m, 7H), 1.36−1.30 (m, 2H), 0.85 (t, 3H, *J* = 7.32 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 147.4, 144.7, 143.5, 141.4, 132.0, 126.4, 121.8, 120.0, 114.7, 101.3, 78.4, 60.1, 57.3, 56.7, 55.8, 42.6, 39.6, 27.6, 27.5, 23.8, 23.2, 21.9, 13.6; HRMS (ES pos.) *m/z* calcd for $C_{24}H_{33}N_2O_3S^+$ (M + H^+) 429.2206, found 429.2221.

General Experimental Procedure for Synthesis of Chiral Sulfinamides 3a, 3b, and 3e. A 250 mL three-neck flask fitted with a stir bar and temperature probe was charged with anhydrous liquid ammonia (50 mL) at −78 °C. After a few crystals of $Fe(NO_3)_3$ (50 mg) were added to the flask, Li wire was added in portions (0.22 g, 31.0 mmol) while the temperature was maintained at −45 °C. The reaction mixture was stirred at −45 °C for 2 h and then cooled to −78 °C (dark brown-gray suspension formed). A solution of quinine sulfinate (3.1 mmol) in THF (6 mL) was then added to the reaction mixture dropwise over a period of 45 min. After 15 min, solid NH_4Cl (1.1 g) was added to the reaction mixture in portions to quench the reaction. The reaction mixture was then warmed slowly to room temperature. After water (10 mL) was added slowly into the flask, EtOAc (15 mL) was added to extract the product. The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated. Purification of the crude product by column chromatography on silica gel gave analytically pure product.

The known compounds sulfinamides **3a**, **3b**, **3e** were isolated as pure samples, which showed NMR spectra matching the reported compounds.[6,7]

(*R*s)-4-Methylbenzenesulfinamide 3c.[6,7] A 50 mL three-neck flask fitted with a stir bar and temperature probe was charged with quinine (*R*s)-*p*-tolylsulfinate **2c** (0.5 g, 1.08 mmol) in DMF (7 mL). LiHMDS (1.1 mL, 1.08 mmol, 1.0 equiv, 1 M in THF) was then added to the reaction mixture at room temperature dropwise. After 30 min, the reaction was then quenched with water (5 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were extracted with water (3 × 15 mL) and brine (1 × 15 mL), dried over Na_2SO_4, and concentrated. Purification of the crude product by column chromatography (0.5% Et_3N in EtOAc) on silica gel gave (*R*)-*p*-tolylsulfinamide **3c** as a white solid (105 mg, 84%).

The known compound sulfinamide **3c** was isolated as pure sample, which showed NMR spectra and enantiomeric purity matching the reported compound.[6,7]

(*R*s)-2,4,6-Trimethylbenzenesulfinamide 3d.[7] A 50 mL three-neck flask fitted with a stir bar and temperature probe was charged with quinine (*R*s)-mesitylsulfinate **2d** (0.35 g, 0.71 mmol) in THF (4.5 mL). LiHMDS (0.71 mL, 1.0 equiv, 1 M in THF) was then added to the reaction mixture at room temperature dropwise. After 30 min, the reaction was then quenched with water (5 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated. Purification of the crude product by column chromatography (0.5% Et_3N in EtOAc) gave (*R*s)-2,4,6-trimethylbenzenesulfinamide **3d** as a white crystal (107 mg; 82%).

The known compound sulfinamide **3d** was isolated as pure sample, and the NMR spectra matched the reported compound.[7]

(*R*s)-*n*-Butylsulfinamide 3f. A 50 mL three-neck flask fitted with a stir bar and temperature probe was charged with a solution of quinine (*R*s)-*n*-butylsulfinate **2f** (5 g, 11.7 mmol) in THF (10 mL). LiHMDS (11.7 mL, 1.0 equiv, 1 M in THF) was then added to the solution at −78 °C dropwise. After 10 min, the reaction was quenched with water (10 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated. Purification of the crude product by column chromatography (0.5% MeOH in EtOAc) gave (*R*s)-*n*-butylsulfinamide **3f** as a solid (1.23 g; 87%, 98:2 e.r.): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37 (bs, 2H), 2.83−2.71 (m, 2H), 1.75−1.64 (m, 2H), 1.54−1.40 (m, 2H), 0.96 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 57.2, 24.9, 21.8, 13.7; HRMS (ES pos.) *m*/*z* calcd for $C_4H_{12}NOS^+$ (M + H$^+$) 122.0634, found 122.0639. Chiral HPLC conditions: Chiralpak AD-H, 4.6 × 250 mm, 5 μm; 97:3 heptane/ethanol, 1.0 mL/min; 220 nm; (*R*)-**3f**, t_R = 29.13 min; (*S*)-**3f**, t_R = 32.55 min.

General Experimental Procedure for Synthesis of *N*-Alkyl Chiral Sulfinamides. A solution of the corresponding amine (5.09 mmol, 5 equiv) in anhydrous THF (5 mL) was cooled to −78 °C. Then, *n*-BuLi (4.5 equiv) was added slowly at the same temperature. After 45 min, a solution of quinine sulfinate (1.02 mmol) in THF (5 mL) was added to the reaction mixture at −78 °C. After 10 min, the reaction mixture was quenched with aqueous ammonium chloride (10 mL). The product was extracted with ethyl acetate (20 mL). The aqueous layer was extracted using ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Purification of the crude product by column chromatography on silica gel (20−30% EtOAc in hexane) gave analytically pure product.

(*R*s)-*N*-Benzyl-2-methylpropane-2-sulfinamide 4a.[16] 88% yield: $[\alpha]^{22}_D$ −29.3 [*c* 1.27, $CHCl_3$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.28 (m, 5H), 4.30 (dd, 2H, *J* = 4.8, 13.8 Hz), 3.52 (s, 1H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 128.5, 128.0, 127.6, 55.9, 49.4, 22.6. Chiral HPLC conditions: Chiralpak AD-H, 4.6 × 250 mm, 5 μm; 94:6 heptane/ethanol, 1.5 mL/min; 220 nm; (*S*)-**4a**, t_R = 16.74 min; (*R*)-**4a**, t_R = 23.31 min.

(*R*s)-*N*-Allyl-2-methylpropane-2-sulfinamide 4b.[12] 85% yield: $[\alpha]^{22}_D$ −66.0 [*c* 4.77, $CHCl_3$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96−5.86 (m, 1H), 5.29−5.14 (m, 2H), 3.84−3.67 (m, 2H), 3.21 (s, 1H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.3, 117.2, 128.0, 55.8, 48.2, 22.6; HRMS (ES pos.) *m*/*z* calcd for $C_7H_{16}NOS^+$ (M + H$^+$) 162.0947, found 162.0950. Chiral HPLC conditions: Chiralpak AD-H, 4.6 × 250 mm, 5 μm; 97:3 heptane/ethanol, 1.5 mL/min; 220 nm; (*R*)-**4a**, t_R = 6.49 min; (*S*)-**4a**, t_R = 7.74 min.

(*R*s)-*N*-Benzyl-4-methylbenzenesulfinamide 4c.[17] 82% yield: $[\alpha]^{22}_D$ −15.4 [*c* 1.59, $CHCl_3$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, 2H, *J* = 8.5 Hz), 7.34−7.24 (m, 7H), 4.30 (t, 1H, *J* = 5.5 Hz), 4.24 (dd, 1H, *J* = 4.9, 13.1 Hz), 3.90 (q, 1H, *J* = 7.1 Hz), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 140.8, 137.8, 129.6, 128.7, 128.3, 127.7, 126.0, 44.6, 21.3; HRMS (ES pos.) *m*/*z* calcd for $C_{14}H_{16}NOS^+$ (M + H$^+$) 246.0947, found 246.0957. Chiral HPLC conditions: Chiralpak AD-H, 4.6 × 250 mm, 5 μm; 94:6 heptane/ethanol, 1.5 mL/min; 220 nm; (*R*)-**4c**, t_R = 5.75 min; (*S*)-**4c**, t_R = 7.94 min.

(*R*s)-*N*-Allyl-4-methylbenzenesulfinamide 4d.[18] 68% yield: $[\alpha]^{22}_D$ −122.8 [*c* 1.79, $CHCl_3$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, 1H, *J* = 8.4 Hz), 7.27 (d, 1H, *J* = 8.4 Hz), 5.83 (m, 1H), 5.18 (dd, 1H, *J* = 1.6, 17.2 Hz), 5.09 (d, 1H, *J* = 10.4 Hz), 4.14 (1H, bs), 3.68 (m, 1H), 3.40 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 1412, 134.9, 129.8, 126.1, 117.5, 42.9, 21.5; HRMS (ES pos.) *m*/*z* calcd for $C_{10}H_{14}NOS^+$ (M + H$^+$) 196.0791, found 196.0797. Chiral HPLC conditions: Chiralpak AD-H, 4.6 × 250 mm, 5 μm; 94:6 heptane/ethanol, 1.5 mL/min; 220 nm; (*S*)-**4d**, t_R = 5.58 min; (*R*)-**4d**, t_R = 10.02 min.

(*R*s)-*N*-Benzyl-2,4,6-trimethylbenzenesulfinamide 4e.[19] 80% yield: $[\alpha]^{22}_D$ −141 [*c* 0.62, $CHCl_3$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.24 (m, 5H), 6.84 (s, 2H), 4.39−4.27 (m, 3H), 2.56 (s, 6H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 137.1, 136.3, 135.9, 129.8, 127.6, 127.2, 126.7, 47.4, 19.9, 18.5; HRMS (ES pos.) *m*/*z* calcd for $C_{16}H_{20}NOS^+$ (M + H$^+$) 274.1260, found 274.1272; HRMS (ES pos.) *m*/*z* calcd for $C_{16}H_{20}NOS^+$ (M + H$^+$) 274.1260, found 274.1272. Chiral HPLC conditions: Chiralpak AS-H, 4.6 × 250 mm, 5 μm; 97:3 heptane/ethanol, 1.0 mL/min; 220 nm; (*S*)-**4e**, t_R = 16.74 min; (*R*)-**4e**, t_R = 18.30 min.

(*R*s)-*N*-Allyl-2,4,6-trimethylbenzenesulfinamide 4f. 76% yield: $[\alpha]^{22}_D$ −191 [*c* 1.75, $CHCl_3$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (s, 2H), 5.98−5.87 (m, 1H), 5.29−5.12 (m, 2H), 4.16 (t, 1H, *J* = 6.3 Hz), 3.86−3.73 (m, 2H), 2.56 (s, 6H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 137.5, 136.7, 134.9, 130.8, 117.4, 47.4, 20.9, 19.4; HRMS (ES pos.) *m*/*z* calcd for $C_{12}H_{18}NOS^+$ (M + H$^+$) 224.1103, found 224.1118. Chiral HPLC conditions: Chiralpak AS-H, 4.6 × 250 mm, 5 μm; 94:6 heptane/ethanol, 1.0 mL/min; 220 nm; (*R*)-**4f**, t_R = 10.78 min; (*S*)-**4f**, t_R = 13.0 min.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR of all new compounds and crystal data for **2d**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yongda.zhang@boehringer-ingelheim.com.

■ REFERENCES

(1) (a) Ruano, J. L. G.; Aleman, J.; Cid, M. B.; Fernandez-Ibanez, A.; Mesestro, M. C.; Martin, M. R.; Martin-Castro, A. M. In *Organosulfur Chemistry in Asymmetric Synthesis*; Toru, T., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 2008; p 55. (b) Senanayake, C. H.; Han, Z.; Krishnamurthy, D. In *Organosulfur Chemistry in Asymmetric Synthesis*; Toru, T., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 2008; p 234. (c) Senanayake, C. H.; Krishnamurthy, D.; Lu, Z.-H.; Han, Z.; Gallou, I. *Aldrichimica Acta* **2005**, *38* (3), 93. (d) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869. (e) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (f) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600. (g) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003.

(2) Examples of α-branched amines synthesis: (a) Ellman, J. A.; Kochi, T. *J. Am. Chem. Soc.* **2004**, *126*, 15652. Examples of amino acids: (b) Davis, F. A.; Zhang, Y. *Tetrahedron Lett.* **2009**, *50*, 5205. Examples of amino alcohols: (c) Akindele, T.; Yamamoto, Y.; Maekawa, M.; Umeki, H.; Yamada, K.-I.; Tomioka, K. *Org. Lett.* **2006**, *8*, 5729. (d) Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 6518. Examples of *N*-contained heterocycles: (e) Denolf, B.; Leemans, E.; Kimpe, N. D. *J. Org. Chem.* **2007**, *72*, 3211. Examples of amino phosphonates: (f) Chen, Q.; Yuan, C. *Synthesis* **2007**, *24*, 3779. Examples of aminooxetanes: (g) Hamzik, P, J.; Brubaker, J. D. *Org. Lett.* **2010**, *12*, 1116.

(3) See examples of synthesis of chiral amines by hydrogenation: Fleury-Brégeot, N.; de la Fuente, V.; Castillón, S.; Claver, C. *ChemCatChem* **2010**, *2*, 1346.

(4) See examples: (a) Owens, T. D.; Frederick J. Hollander, F. J.; Oliver, A. G.; Ellma, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 1539. (b) Kimmel, K. L.; Robak, M. T.; Ellman, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 8754. (c) Robak, M. T.; Trincado, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 15110. (d) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science* **2010**, *327*, 986. (e) Solà, J.; Revés, M.; Riera, A.; Verdaguer, X. *Angew. Chem., Int. Ed.* **2007**, *46*, 5020.

(5) (a) Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011. (b) Weix, D. J.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 1317. (c) Weix, D. J.; Ellman, J. A. *Org. Synth.* **2005**, *82*, 157. (d) Enzyme-catalyzed resolution of *N*-acyl arylsulfinamides: Savile, C. K.; Magloire, V. P.; Kazlauskas, R. J. *J. Am. Chem. Soc.* **2005**, *127*, 2104.

(6) Han, Z.; Krishnamurthy, D.; Paul Grover, P.; Fang, Q. K.; Senanayake, C. H. *J. Am. Chem. Soc.* **2002**, *124*, 7880.

(7) Han, Z.; Meyer, A. M.; Xu, Y.; Zhang, Y.; Busch, R.; Shen, S.; Grinberg, N; Lu, B. Z.; Krishnamurthy, D.; Senanayake, C. H. *J. Org. Chem.* **2011**, *76*, 5480.

(8) (c) Lu, B. Z.; Jin, F.; Zhang, Y.; Wu, X.; Wald, S. A.; Senanayake, C. H. *Org. Lett.* **2005**, *7*, 1465. Examples of the use of quinine as a catalytic chiral sulfinyl transfer reagent, see: (a) Peltier, H. M.; Evans, J. W.; Ellman, J. A. *Org. Lett.* **2005**, *7*, 1733. (b) Shibata, N.; Matsunaga, M.; Fukuzumi, T.; Nakamura, S.; Toru, T. *Synlett.* **2005**, *11*, 1699.

(9) HPLC conditions: column Halo C8, 4.6 × 150 mm, 2.7 μm particle size, column temperature at 25 °C, mobile phase A (0.2% H_3PO_4 in water), mobile phase B (acetonitrile), flow rate 1.2 mL min^{-1}, gradient program 30% B to 70% B in 6 min, to 85% B in 1 min, to 98% B in 0.5 min, hold at 98% B for 1.5 min, λ = 220 nm. The samples for HPLC were diluted with MeOH.

(10) Control experiment indicated that isolated **2a** was stable even at room temperature in the presence of *t*-butylmagnesium chloride.

(11) Ruano, J. L. G.; Parra, A.; Yuste, F.; Mastranzo, V. M. *Synthesis* **2008**, *2*, 311.

(12) Our primary studies indicated that the reaction with the minor isomer was much slower than the major isomer. With 96:4 d.r. sulfinate **2c**, the corresponding sulfinamide **3c** was isolated with 99% e.e. when the reaction was quenched once the major isomer disappeared by HPLC. However, the reaction eventually gave **3c** with 96:4 e.r with elongation time.

(13) (a) Achard, T.; Benet-Buchholz, J.; Riera, A.; Verdaguer, X. *Organometallics* **2009**, *28*, 480. (b) Ji, Y.; Riera, A.; Verdaguer, X. *Org. Lett.* **2009**, *11*, 4346. (c) Mellah, M.; Voituriez, A.; Schulz, E. *Chem. Rev.* **2007**, *107*, 5133. (d) Beck, E. M.; Hyde, A. M.; Jacobsen, E, N. *Org. Lett.* **2011**, *13*, 4263.

(14) The other enantioisomers *Ss*-sulfinamides could be synthesized in the same way using quinidine as auxiliary.

(15) Brak, K.; Barrett, K. T.; Ellman, J. A. *J. Org. Chem.* **2009**, *74*, 3606.

(16) Brun, S.; Parera, M.; Pla-Quintana, A.; Roglans, A.; León, T.; Achard, T.; Solà, J.; Verdaguer, X.; Riera, A. *Tetrahedron* **2010**, *66*, 9032.

(17) Revés, M.; Achard, T.; Solà, J.; Riera, A.; Verdaguer, X. *J. Org. Chem.* **2008**, *73*, 7080.

(18) Kunio, H.; Takashi, W. *Heterocycles* **2001**, *54*, 73–76.

(19) Gölz, H.; Glatz, B.; Has, G.; Helmchen, G.; Muxfeldt, H. *Angew. Chem.* **1977**, *89*, 742.