JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

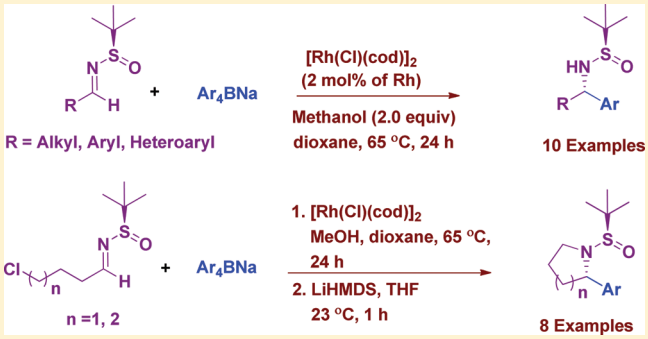
Rhodium-Catalyzed Asymmetric Arylation of *N*-(*tert*-Butanesulfinyl)imines with Sodium Tetraarylborates

Leleti Rajender Reddy,* Aditya P. Gupta,† Eric Villhauer,‡ and Yugang Liu

Chemical and Analytical Development, Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936, United States

Supporting Information

ABSTRACT: A diastereoselective rhodium-catalyzed arylation of *N*-(*tert*-butanesulfinyl)imines with sodium tetraarylborates is described. This method is general for constructing various chiral α-branched amines and 2-substituted pyrrolidines with high diastereoselectivity. A practical asymmetric approach to access chiral amines has been developed involving the use of air-stable Rh catalysts and reagents and in the absence of an external ligand.



INTRODUCTION

Chiral α-branched amines and 2-substituted pyrrolidines are highly important structural motifs in the pharmaceuticals industry[1] and are present in many drugs, drug candidates, and natural products. Some examples are naturally occurring cytokine modulator (−)-cytoxazone,[2] the third-generation antihistamine levocetirizine,[3] the histamine H1-receptor antagonist (*S*)-cetirizine dihydrochloride,[4] the nonpeptide selective opioid receptor agonist SNC80,[5] and the selective Kv1.5 blocker BMS-394136.[6] Therefore, general methods for their asymmetric synthesis are a formidable challenge in synthetic organic chemistry. The stereoselective addition of organmetallic reagents to carbon−heteroatom double bonds represents one of the most straightforward approaches.[7] However, despite recent advances in the synthesis of functionalized Grignard and organlithium reagents, these methods are plagued by inherent functional group instability and modest selectivity.[8] A more functional group tolerant method remains highly desirable. In recent years, transition-metal-catalyzed additions of organboron reagents to carbon−heteroatom double bonds are of increasing interest in organic chemistry.[9] The major limitations associated with these protocols are the difficulties associated with the scale-up,[10] due to moisture-sensitive unstable reagents and catalysts, requiring a glovebox or sealed tube reaction conditions. We reasoned that a simple air-stable catalyst like $[Rh(Cl)(cod)]_2$ would promote the coupling of sodium tetraarylborates with *N*-(*tert*-butanesulfinyl)imines to give α-branched amines and 2-substituted pyrrolidines, which has not been described in the literature to the best of our knowledge.[11−13] Herein, we report a straightforward, scalable, and highly diastereoselective method that provides entry to enantioenriched α-branched amines and 2-substituted pyrrolidines in high yields and in the absence of an exogenous ligand.[14]

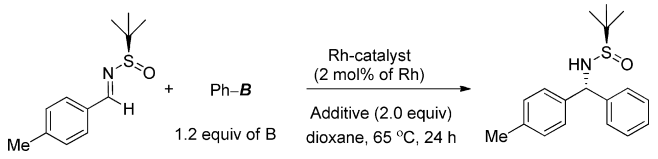
RESULTS AND DISCUSION

Initially, we chose *N*-(*tert*-butanesulfinyl)-4-methylphenylimine (**1a**) as a model substrate and attempted the addition of an air-stable sodium tetraphenylborate **2a** (1.2 equiv) in the presence of air-stable $[Rh(OH)(cod)]_2$ (2 mol % Rh) in dioxane at 65 °C for 24 h. Under these conditions, no reaction was observed, and the starting material was recovered (Table 1, entry 1). No significant improvement was detected when MeOH was used as an additive (Table 1, entry 2). Gratifyingly, 45% of product **3a** was formed with ≥98:2 diastereomeric ratio in the presence of $[Rh(Cl)(cod)]_2$ in dioxane at 65 °C for 24 h (Table 1, entry 3), and similar results were observed with water as an additive (Table 1, entry 4). The best results (95% of product **3a** with ≥98:2 diastereomeric ratio) were obtained by using MeOH as an additive in the presence of $[Rh(Cl)(cod)]_2$ in dioxane at 65 °C for 24 h (Table 1, entries 6), and analogous results (90% of product **3a** with ≥98:2 diastereomeric ratio) were obtained by using EtOH as a additive (Table 1, entries 5). The addition of MeOH or EtOH to the reaction mixture might help the solubility of sodium tetraarylborates.[11] Under these optimal reaction conditions, <10% of **3a** was formed by using phenylboronic acid, phenylboronic acid pinacol ester, or phenylboronic acid MIDA ester as a nucleophile (Table 1, entries 7−9). A somewhat lower yield of **3a** was obtained with potassium tetraphenylboranate (Table 1, entry 10). The structure and absolute configuration of (R_S, *R*)-**3a** was confirmed by comparing the ^{1}H NMR, ^{13}C NMR, and specific rotation data with literature data.[15]

With optimal reaction conditions identified, the scope of the methodology was investigated by phenylation of various *N*-(*tert*-butanesulfinyl)aldimines (Table 2). Interestingly, a large

Received: November 24, 2011
Published: December 20, 2011

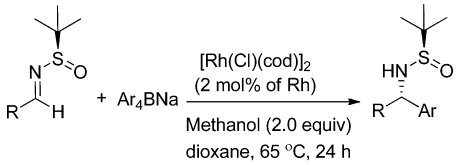
Table 1. Rhodium-Catalyzed Addition of Phenylboron Reagents to 1a: Effect of Catalyst and Nucleophile



entry	Rh catalyst	Ph–B	additive	yield[a] (%)	dr[b]
1	$[Rh(OH)(cod)]_2$	Ph_4BNa	none	0	
2	$[Rh(OH)(cod)]_2$	Ph_4BNa	MeOH	5	≥98:2
3	$[Rh(Cl)(cod)]_2$	Ph_4BNa	none	45	≥98:2
4	$[Rh(Cl)(cod)]_2$	Ph_4BNa	H_2O	50	≥98:2
5	$[Rh(Cl)(cod)]_2$	Ph_4BNa	EtOH	90	≥98:2
6	$[Rh(Cl)(cod)]_2$	Ph_4BNa	MeOH	95	≥98:2
7	$[Rh(Cl)(cod)]_2$	$PhB(OH)_2$	MeOH	8	≥98:2
8	$[Rh(Cl)(cod)]_2$	PhB(MIDA)[c]	MeOH	10	≥98:2
9	$[Rh(Cl)(cod)]_2$	$PhB(OR)_2$[d]	MeOH	6	≥98:2
10	$[Rh(Cl)(cod)]_2$	Ph_4BK	MeOH	72	≥98:2

[a]Isolated yield. [b]The diastereoselectivity was determined by ^1H NMR analysis of crude product. [c]Phenylboronic acid MIDA ester [d](OR)$_2$ = $OCH_2CMe_2CH_2O$.

Table 2. Rhodium-Catalyzed Asymmetric Synthesis of α-Branched Amine[a]



1 **2** **3**

1a: R = 4-MeC_6H_4
1b: R = 4-FC_6H_4
1c: R = 3-FC_6H_4
1d: R = 4-ClC_6H_4
1e: R = 2-naphthyl
1f: R = 2-furyl
1g: R = cC_6H_{11}
1h: R = nC_5H_{11}

entry	1	Ar	product	yield[b] (%)	dr[c]
1	**1a**	Ph (**2a**)	**3a**	95	≥98:2
2	**1b**	**2a**	**3b**	91	≥98:2
3	**1c**	**2a**	**3c**	92	≥98:2
4	**1d**	**2a**	**3d**	95	≥98:2
5	**1e**	**2a**	**3e**	90	≥98:2
6	**1f**	**2a**	**3f**	92	≥98:2
7	**1g**	**2a**	**3g**	93	≥98:2
8	**1h**	**2a**	**3h**	95	≥98:2
9	**1a**	4-FC_6H_4 (**2b**)	**3i**	94	≥98:2
10	**1a**	3-MeC_6H_4 (**2c**)	**3j**	92	≥98:2

[a]All reactions were performed as described in Table 2 on a 2.0 mmol scale, unless otherwise noted. [b]Isolated yield. [c]The diastereoselectivity was determined by ^1H NMR analysis of crude product. The "≥98:2" dr denotes that signals for only one diastereomer were observed.

variety of substituted aromatic *N*-(*tert*-butanesulfinyl)aldimines, such as *p*-fluoro, *m*-fluoro, *p*-methyl, *p*-chloro, α-naphthyl derivatives, reacted cleanly with **2a** leading to the corresponding α-branched amines **3a**–**e** (Table 2, entries 1–5) in excellent yields (90–95%) and high diastereomeric ratios (dr ≥98:2). In the same way, aliphatic *N*-(*tert*-butanesulfinyl)-aldimines such as cyclohexylaldimine **1g** and *n*-hexylaldimine **1h** smoothly reacted with **2a** affording the corresponding α-branched amines **3g** and **3h** (Table 2, entries 7 and 8) in 93% and 95% yield, respectively (dr ≥98:2). The heterocyclic *N*-(*tert*-butanesulfinyl)aldimine **1f** also reacted with **2a** to form amine **3f** (Table 2, entry 6) in 92% yield with dr ≥98:2.

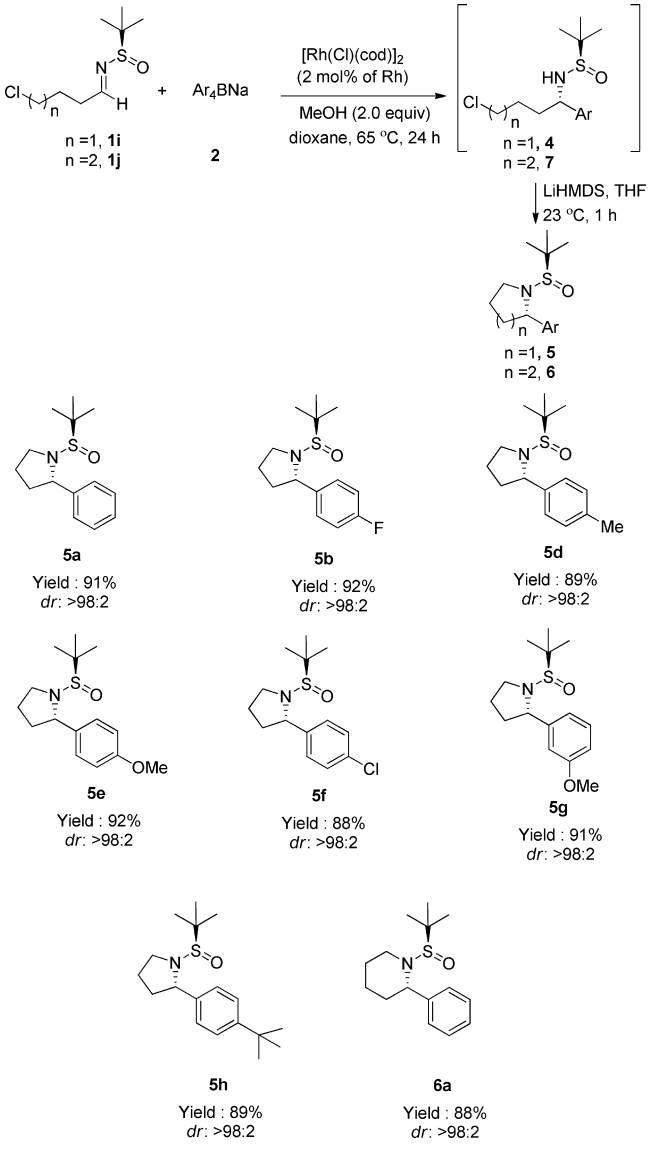
Encouraged by these results, we turned our attention to examining other substituted aromatic borate reagents. Fascinatingly, other substituted aromatic borate reagents, such as sodium tetrakis(*p*-fluorophenyl)borate **2b** or sodium tetrakis-(*m*-methylphenyl)borate **2c**, reacted smoothly with **1a** to obtain the corresponding α-branched amines **3i**–**j** (Table 2, entries 9 and 10) in high yields (90–92%) and high diastereomeric ratios (≥98:2).

To broaden the scope of this method, we investigated the asymmetric synthesis of 2-substituted pyrrolidines under optimal reaction conditions. Reaction of γ-chlorinated *N*-(*tert*-butanesulfinyl)imine **1i** (1 equiv) with **2a** (1.2 equiv) in the

dx.doi.org/10.1021/jo2024224 | J. Org. Chem. 2012, 77, 1095–1100

presence of $[Rh(Cl)(cod)]_2$ (2 mol % Rh) and MeOH (2.0 equiv) in dioxane at 65 °C for 24 h afforded amine **4a** with high diastereomeric ratio (dr ≥98: 2). The crude amine **4a** was converted to the corresponding pyrrolidine **5a** in high yield (91% for two steps) by stirring at room temperature for 1 h in presence of 2.0 equiv of LiHMDS. More importantly, no epimerization occurred during the cyclization. The structure and absolute configuration of (R_S, S)-**5a** was confirmed by comparing the ^{1}H NMR, ^{13}C NMR, and specific rotation data with literature data.[16] In the same way, reaction **1i** with several substituted aromatic borate reagents, such as **2b**, sodium tetrakis(*p*-methylphenyl)borate **2d**, sodium tetrakis(*p*-methoxyphenyl)borate **2e**, sodium tetrakis(*p*-chlorophenyl)-borate **2f**, sodium tetrakis(*m*-methoxyphenyl)borate **2g**, and sodium tetrakis(*p*-*tert*-butylphenyl)borate **2h** gave pyrrolidines **5b**–**g** (Table 3) in high yields (83–89%) and high

Table 3. Rhodium-Catalyzed Asymmetric Synthesis of 2-Substituted Pyrrolidines



diastereomeric ratios (≥98:2). To further extend this methodology, we also examined the asymmetric synthesis of 2-substituted piperidines. Under optimal reaction conditions, δ-chlorinated *N*-(*tert*-butanesulfinyl)imine **1j** was coupled with **2a** and followed by base treatment which afforded piperidine **6a** in high yield (88% for two steps) with high diastereomeric ratio (dr ≥98: 2).

CONCLUSION

In conclusion, we have developed an efficient, highly diastereoselective rhodium-catalyzed asymmetric arylation of *N*-(*tert*-butanesulfinyl)imines with sodium tetraarylborates to afford enantiomerically pure amines and 2-substituted pyrrolidines. This method enables the practical asymmetric synthesis of α-branched amines and 2-substituted pyrrolidines, promoted via air-stable catalyst and reagents and in the absence of external ligand. This method has been found to be effective for a variety of substrates, and extension of this work is currently underway in our laboratory.

EXPERIMENTAL SECTION

General Information. All reactions were performed under dry nitrogen gas in glassware that was flame-dried and equipped with a magnetic stirring bar. Thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm). Flash chromatography was performed using silica gel (40 μm particle size). All compounds were judged pure by TLC analysis (single spot/two solvent systems) using a UV lamp or PMA for detection purposes. ^{1}H and ^{13}C NMR spectra were recorded on an FT-NMR spectrometer at 500 and 125 MHz, respectively. High-resolution mass spectroscopy (HRMS) was carried out in electrospray mode. All reagents were purchased from commercial suppliers and used without further purification. Unless indicated otherwise, the reaction temperatures refer to internal reaction temperatures. Sodium tetraarylborates **2c**–**h**,[17–19] (R_S)-γ-chlorinated *N*-(*tert*-butanesulfinyl)imine (**1i**),[16b] (R_S)-δ-chlorinated *N*-(*tert*-butanesulfinyl)imine (**1j**),[16a] and imines **1a**–**h**[20] were synthesized according to literature procedures.

General Procedure (GP1) for the Synthesis Amines. To a solution of imine **1** (2.0 mmol) in dioxane (5 mL) under nitrogen were added borate **2** (2.4 mmol), methanol (4.0 mmol), and $[Rh(Cl)(cod)]_2$ (2 mol %). The reaction mixture was then stirred at 65 °C for 24 h. After completion, the reaction was allowed to cool to room temperature and diluted with isopropyl acetate (30 mL). The reaction mixture was washed with 20% $KHSO_4$ solution (2 × 30 mL) and water (20 mL). The organic phase was evaporated under vacuum to dryness to obtain the crude product. The crude product was purified by flash column chromatography (silica gel, 10–40% ethyl acetate in heptanes) to afford the pure product **3**.

*(R)-2-Methyl-N-[(R)-Phenyl(p-tolyl)methyl]propane-2-sulfinamide (**3a**).* Following the general procedure (GP1), the reaction of imine **1a** (0.450 g, 2.0 mmol) with borate **2a** (0.82 g, 2.4 mmol) afforded pyrrolidine **3a** (0.57 g, 95%) as a white solid: mp = 58–59 °C; $[\alpha]^{20}_D$ = −65.9 (*c* 0.8, $CHCl_3$); ^{1}H NMR (501 MHz, $CDCl_3$) δ ppm 7.40 (d, *J* = 7.25 Hz, 2 H), 7.29–7.34 (m, 2 H), 7.21–7.27 (m, 3 H), 7.12 (d, *J* = 8.20 Hz, 2 H), 5.61 (d, *J* = 2.52 Hz, 1 H), 3.68 (d, *J* = 1.89 Hz, 1 H), 2.30 (s, 3 H), 1.25 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 141.5, 139.8, 129.5, 128.5, 127.8, 127.2, 61.9, 55.8, 22.7, 21.0; HRMS (EI) calcd for $C_{18}H_{24}NOS$ [M + H] 302.1579, found 302.1582.

*(R)-2-Methyl-N-[(R)-phenyl(p-fluorophenyl)methyl]propane-2-sulfinamide (**3b**).* Following the general procedure (GP1), the reaction of imine **1b** (0.455 g, 2.0 mmol) with borate **2a** (0.82 g, 2.4 mmol) afforded pyrrolidine **3b** (0.55 g, 91%) as a white solid: mp = 65–66 °C; $[\alpha]^{20}_D$ = −70.8 (*c* 1.2, $CHCl_3$); ^{1}H NMR (501 MHz, $CDCl_3$) δ ppm 7.22–7.42 (m, 7 H), 6.90–7.04 (m, 2 H), 5.62 (d, *J* = 2.84 Hz, 1 H), 3.72 (d, *J* = 2.84 Hz, 1 H), 1.24 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 163.2, 161.2, 141.1, 138.6, 138.5, 134.2, 129.0 (d, *J* = 8.25 Hz,), 127.8, 115.7 (d, *J* = 21.08 Hz,), 61.6, 55.9, 22.6; HRMS (EI) calcd for $C_{17}H_{21}NOSF$ [M + H] 306.1328, found 306.1330.

*(R)-2-Methyl-N-[(R)-phenyl(m-fluorophenyl)methyl]propane-2-sulfinamide (**3c**).* Following the general procedure (GP1), the

dx.doi.org/10.1021/jo2024224 | J. Org. Chem. 2012, 77, 1095–1100

reaction of imine **1c** (0.455 g, 2.0 mmol) with borate **2a** (0.82 g, 2.4 mmol) afforded pyrrolidine **3c** (0.56 g, 92%) as a viscous oil: $[\alpha]^{20}_{D}$ = −52.3 (*c* 1.1, $CHCl_3$); ^{1}H NMR (501 MHz, $CDCl_3$) δ ppm 7.38 (d, *J* = 7.25 Hz, 2 H), 7.28−7.34 (m, 2 H), 7.21−7.27 (m, 2 H), 7.14−7.19 (m, 1 H), 7.05−7.10 (m, 1 H), 6.86−6.93 (m, 1 H), 5.62 (d, *J* = 3.15 Hz, 1 H), 3.84 (d, *J* = 2.84 Hz, 1 H), 1.23 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 163.9, 161.9, 145.2, 140.8, 130.4 (d, *J* = 8.25 Hz,), 128.7, 127.9, 127.2, 123.0, 114.7 (d, *J* = 21.08 Hz,), 114.2 (d, *J* = 22.9 Hz,),, 61.8, 55.9, 22.6; HRMS (EI) calcd for $C_{17}H_{21}NOSF$ [M + H] 306.1328, found 306.1326.

*(R)-2-Methyl-N-[(R)-phenyl(p-chlorophenyl)methyl]propane-2-sulfinamide (**3d**).* Following the general procedure (GP1), the reaction of imine **1d** (0.485 g, 2.0 mmol) with borate **2a** (0.82 g, 2.4 mmol) afforded pyrrolidine **3d** (0.61 g, 95%) as a pale yellow solid: mp = 78−80 °C; $[\alpha]^{20}_{D}$ = −64.1 (c 0.9, $CHCl_3$); ^{1}H NMR (501 MHz, $CDCl_3$) δ ppm 7.19−7.45 (m, 9 H), 5.61 (d, *J* = 3.15 Hz, 1 H), 3.70 (d, *J* = 2.52 Hz, 1 H), 1.24 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 141.2, 140.9, 129.0, 128.7, 127.8, 61.7, 55.9, 22.6; HRMS (EI) calcd for $C_{17}H_{21}NOSCl$ [M + H] 322.1032, found 322.1033.

*(R)-2-Methyl-N-[(R)-phenyl(2-naphthyl)methyl]propane-2-sulfinamide (**3e**).* Following the general procedure (GP1), the reaction of imine **1e** (0.518 g, 2.0 mmol) with borate **2a** (0.82 g, 2.4 mmol) afforded pyrrolidine **3e** (0.60 g, 90%) as a viscous oil: $[\alpha]^{20}_{D}$ = −75.3 (*c* 0.6, $CHCl_3$); ^{1}H NMR (501 MHz, $CDCl_3$) δ ppm 7.70−7.83 (m, 4 H), 7.37−7.51 (m, 5 H), 7.32 (t, *J* = 7.57 Hz, 2 H), 7.18−7.27 (m, 1 H), 5.80 (d, *J* = 2.52 Hz, 1 H), 3.84 (d, *J* = 2.52 Hz, 1 H), 1.25 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 141.2, 140.0, 133.3, 132.9, 128.8, 128.6, 128.1, 127.8, 127.7, 126.4, 126.2, 126.0, 125.3; HRMS (EI) calcd for $C_{21}H_{24}NOS$ [M + H] 338.1579, found 338.1571.

*(R)-2-Methyl-N-[(R)-phenyl(2-furyl)methyl]propane-2-sulfinamide (**3f**).* Following the general procedure (GP1), the reaction of imine **1f** (0.4 g, 2.0 mmol) with borate **2a** (0.82 g, 2.4 mmol) afforded pyrrolidine **3f** (0.51 g, 92%) as a viscous oil: $[\alpha]^{20}_{D}$ = −41.2 (*c* 1. 0, $CHCl_3$); ^{1}H NMR (501 MHz, $CDCl_3$) δ ppm 7.19−7.50 (m, 6 H), 6.29 (dd, *J* = 3.15, 1.89 Hz, 1 H), 6.10 (d, *J* = 3.15 Hz, 1 H), 5.62 (d, *J* = 3.78 Hz, 1 H), 3.89 (d, *J* = 3.15 Hz, 1 H), 1.22 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 154.4, 142.6, 139.0, 128.5, 128.2, 110.3, 107.9, 56.7, 55.9, 22.5; HRMS (EI) calcd for $C_{15}H_{20}NO_2S$ [M + H] 278.1215, found 278.1208.

*(R)-2-Methyl-N-[(S)-phenyl(cyclohexyl)methyl]propane-2-sulfinamide (**3g**).* Following the general procedure (GP1), the reaction of imine **1g** (0.4 g, 2.0 mmol) with borate **2a** (0.82 g, 2.4 mmol) afforded pyrrolidine **3g** (0.448 g, 93%) as a viscous oil: ^{1}H NMR (501 MHz, $CDCl_3$) δ ppm 7.18−7.37 (m, 5 H), 4.14 (dd, *J* = 7.25, 2.52 Hz, 1 H), 3.52 (d, *J* = 1.58 Hz, 1 H), 1.89 (d, *J* = 12.61 Hz, 1 H), 1.71−1.81 (m, 1 H), 1.55−1.70 (m, 3 H), 1.38−1.50 (m, 1 H), 1.20−1.30 (m, 1 H), 1.18 (s, 9 H), 0.96−1.14 (m, 2 H), 0.78−0.93 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 140.7, 128.4, 128.02, 127.3, 64.0, 55.4, 44.5, 29.9, 29.4, 26.2, 22.5; HRMS (EI) calcd for $C_{17}H_{27}NOS$ [M + H] 294.1892, found 294.1885.

*(R)-2-Methyl-N-[(S)-1-phenylhexyl]propane-2-sulfinamide (**3h**).* Following the general procedure (GP1), the reaction of imine 1 h (0.4 g, 2.0 mmol) with borate **2a** (0.82 g, 2.4 mmol) afforded pyrrolidine **3h** (0.533 g, 95%) as a viscous oil: ^{1}H NMR (501 MHz, $CDCl_3$) δ ppm 7.17−7.37 (m, 5 H), 4.24−4.44 (m, 1 H), 3.38 (d, *J* = 1.89 Hz, 1 H), 1.69−1.86 (m, 2 H), 1.21−1.41 (m, 6 H), 1.15 (s, 9 H), 0.75−0.93 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 142.1, 128.3, 127.6, 127.4, 59.2, 55.4, 38.8, 31.5, 25.6, 22.5, 22.3, 13.9; HRMS (EI) calcd for $C_{16}H_{28}NOS$ [M + H] 282.1892, found 282.1887.

*(R)-2-Methyl-N-[(S)-p-fluorophenyl(p-tolyl)methyl]propane-2-sulfinamide (**3i**).* Following the general procedure (GP1), the reaction of imine **1a** (0.450 g, 2.0 mmol) with borate **2b** (0.94 g, 2.4 mmol) afforded pyrrolidine **3i** (0.599 g, 94%) as a viscous oil: ^{1}H NMR (501 MHz, $CDCl_3$) δ ppm 7.37 (dd, *J* = 8.51, 5.36 Hz, 2 H), 7.19−7.30 (m, 2 H), 7.13 (d, *J* = 7.88 Hz, 2 H), 7.00 (t, *J* = 8.67 Hz, 2 H), 5.59 (d, *J* = 2.21 Hz, 1 H), 3.67 (d, *J* = 1.58 Hz, 1 H), 2.31 (s, 3 H), 1.25 (s, 9 H); ^{13}C NMR (125 MHz, *CDCl*$_3$) δ ppm 163.1, 161.2, 139.5, 137.7, 137.2, 129.6, 129.0 (d, *J* = 7.33 Hz,), 127.0, 115.4 (d, *J* = 21.08 Hz), 61.1, 55.8, 22.6, 21.04; HRMS (EI) calcd for $C_{18}H_{23}NOSF$ [M + H] 320.1484, found 320.1487.

*(R)-2-Methyl-N-[(S)-m-tolyl(p-tolyl)methyl]propane-2-sulfinamide (**3j**).* Following the general procedure (GP1), the reaction of imine **1a** (0.450 g, 2.0 mmol) with borate **2b** (0.90 g, 2.4 mmol) afforded pyrrolidine **3j** (0.58 g, 92%) as a viscous oil: ^{1}H NMR (501 MHz, $CDCl_3$) δ ppm 7.29 (d, *J* = 8.20 Hz, 2 H), 7.09−7.23 (m, 5 H), 7.04 (d, *J* = 6.94 Hz, 1 H), 5.56 (d, *J* = 2.21 Hz, 1 H), 3.66 (d, *J* = 1.58 Hz, 1 H), 2.32 (s, 3 H), 2.30 (s, 3 H), 1.25 (s, 98 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 142.6, 138.5, 138.4, 137.3, 129.2, 128.7, 128.1, 127.9, 127.8, 124.1, 61.9, 55.8, 22.7, 21.4, 21.1; HRMS (EI) calcd for $C_{19}H_{26}NOS$ [M + H] 316.1735, found 316.1738.

General Procedure (GP2) for the Synthesis 2-Substituted Pyrrolidines. To a solution of amine **1** (2.0 mmol) in dioxane (5 mL) under nitrogen were added borate **2** (2.2 mmol), methanol (4.0 mmol) and $[Rh(Cl)(cod)]_2$ (2 mol %). The reaction mixture was then heated at reflux at 65 °C for 24 h. After completion, the reaction was allowed to cool to room temperature and diluted with isopropyl acetate (30 mL). The reaction mixture was washed with 20% $KHSO_4$ solution (2 × 30 mL) and water (20 mL). The organic phase was evaporated under vacuum to dryness to obtain the crude product **4**. The crude product was taken in 10 mL of THF, followed by addition of LiHMDS (4.0 mmol) at 23 °C and stirred for 1 h at at 23 °C. On completion, the reaction was quenched with saturated NH4Cl solution (20 mL) and ethyl acetate (20 mL). The organic layer was then separated, washed with water and dried under vacuum to give crude product. The crude product was purified by flash column chromatography (silica gel, 10−40% ethyl acetate in heptanes) to afford the pure product **5**.

*(S)-1-((R)-2-Methylpropane-2-sulfinyl)-2-phenylpyrrolidine (**5a**).* Following the general procedure (GP2), the reaction of γ-chloro *N*-sulfinylimine **1i** (0.418 g, 2.0 mmol) with borate **2a** (0.82 g, 2.4 mmol) and followed by LiHMDS (4.0 mL, 4.0 mmol, 1.0 mL in THF) afforded pyrrolidine **5a** (0.455 g, 91%) as a viscous liquid: $[\alpha]^{25}_{D}$ = −120.1 (*c* 1.1, $CHCl_3$); ^{1}H NMR (501 MHz, $CDCl_3$) δ ppm 7.16−7.37 (m, 5 H), 4.64 (t, *J* = 7.25 Hz, 1 H), 3.84−3.95 (m, 1 H), 2.90−3.06 (m, 1 H), 2.16−2.33 (m, 1 H), 1.70−2.07 (m, 3 H), 1.10 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 143.3, 128.2, 127.2, 69.3, 57.2, 42.1, 35.9, 26.3, 23.8; HRMS (EI) calcd for $C_{14}H_{22}NOS$ [M + H] 252.1439, found 252.1432.

*(S)-1-((R)-2-Methylpropane-2-sulfinyl)-2-(p-fluorophenyl)-pyrrolidine (**5b**).* Following the general procedure (GP2), the reaction of γ-chloro *N*-sulfinylimine **1i** (0.418 g, 2.0 mmol) with borate **2b** (0.94 g, 2.4 mmol) and followed by LiHMDS (4.0 mL, 4.0 mmol, 1.0 mL in THF) afforded pyrrolidine **5b** (0.49 g, 92%) as a viscous liquid: $[\alpha]^{25}_{D}$ = −123.2 (*c* 1.2, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.18−7.34 (m, 2 H), 6.87−7.07 (m, 2 H), 4.54−4.70 (m, 1 H), 3.83−3.97 (m, 1 H), 2.90−3.03 (m, 1 H), 2.15−2.30 (m, 1 H), 1.66−2.04 (m, 3 H), 1.09 (s, 9 H);^{13}C NMR (125 MHz, *CDCl*$_3$) δ ppm 163.2, 160.6, 138.9, 128.8 (d, *J* = 8.25 Hz,), 115.5 (d, *J* = 21.08 Hz,),, 68.5, 57.2, 42.0, 36.0, 26.3, 23.6; HRMS (EI) calcd for $C_{14}H_{21}NOSF$ [M + H] 270.1322, found 270.1319.

*(S)-1-((R)-2-Methylpropane-2-sulfinyl)-2-(p-methylphenyl)-pyrrolidine (**5d**).* Following the general procedure (GP2), the reaction of γ-chloro *N*-sulfinylimine **1i** (0.418 g, 2.0 mmol) with borate **2d** (0.955 g, 2.4 mmol) and followed by LiHMDS (4.0 mL, 4.0 mmol, 1.0 mL in THF) afforded pyrrolidine **5d** (0.47 g, 89%) as a white solid: mp = 62−65 °C; $[\alpha]^{25}_{D}$ = −145.0 (*c* 1.5, MeOH); ^{1}H NMR (501 MHz, $CDCl_3$) δ ppm 7.14−7.20 (m, 2 H), 7.05−7.14 (m, 2 H), 4.60 (t, *J* = 7.41 Hz, 1 H), 3.81−3.95 (m, 1 H), 2.89−3.04 (m, 1 H), 2.32 (s, 3 H), 2.22 (dd, *J* = 11.19, 4.89 Hz, 1 H), 1.68−2.04 (m, 3 H), 1.10 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 140.2, 136.7, 128.9, 127.1, 69.0, 57.1, 42.0, 35.9, 26.3, 23.8, 21.0; HRMS (EI) calcd for $C_{15}H_{24}NOS$ [M + H] 266.1573, found 266.1570.

*(S)-1-((R)-2-Methylpropane-2-sulfinyl)-2-(p-methoxyphenyl)-pyrrolidine (**5e**).* Following the general procedure (GP2), the reaction of γ-chloro *N*-sulfinylimine **1i** (0.418 g, 2.0 mmol) with borate **2e** (1.05 g, 2.4 mmol) and followed by LiHMDS (4.0 mL, 4.0 mmol, 1.0 mL in THF) afforded pyrrolidine **5e** (0.518 g, 92%) as a white solid: mp = 60−62 °C; $[\alpha]^{25}_{D}$ = −122.0 (*c* 1.2, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.19−7.24 (m, 2 H), 6.81−6.88 (m, 2 H), 4.55−4.60 (m, 1 H), 3.81−3.92 (m, 1 H), 3.79 (s, 3 H), 2.90−3.01 (m, 1 H),

dx.doi.org/10.1021/jo2024224 | *J. Org. Chem.* 2012, 77, 1095−1100

2.13−2.24 (m, 1 H), 1.91−2.03 (m, 1 H), 1.71−1.92 (m, 2 H), 1.08 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 158.7, 135.0, 128.3, 113.6, 68.6, 57.0, 55.1, 41.9, 35.9, 26.3, 23.8; HRMS (EI) calcd for $C_{15}H_{24}NO_2S$ [M + H] 282.1528, found 282.1530.

*(S)-1-((R)-2-Methylpropane-2-sulfinyl)-2-(p-chlorophenyl)-pyrrolidine (**5f**).* Following the general procedure (GP2), the reaction of γ-chloro *N*-sulfinylimine **1i** (0.418 g, 2.0 mmol) with borate **2f** (1.10 g, 2.4 mmol) and followed by LiHMDS (4.0 mL, 4.0 mmol, 1.0 mL in THF) afforded pyrrolidine **5f** (0.525 g, 92%) as a white solid: mp = 74−76 °C; $[\alpha]^{25}_D$ = −110.5 (*c* 1.2, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.13−7.40 (m, 4 H), 4.51−4.71 (m, 1 H), 3.83−3.97 (m, 1 H), 2.89−3.11 (m, 1 H), 2.17−2.31 (m, 1 H), 1.64−2.06 (m, 3 H), 1.10 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 141.8, 132.9, 128.6, 128.4, 68.6, 57.2, 42.1, 36.0, 26.3, 23.8; HRMS (EI) calcd for $C_{14}H_{21}NOSCl$ [M + H] 286.1032, found 286.1034.

*(S)-1-((R)-2-Methylpropane-2-sulfinyl)-2-(m-methoxyphenyl)-pyrrolidine (**5g**).* Following the general procedure (GP2), the reaction of γ-chloro *N*-sulfinylimine **1i** (0.418 g, 2.0 mmol) with borate **2g** (1.05 g, 2.4 mmol) and followed by LiHMDS (4.0 mL, 4.0 mmol, 1.0 mL in THF) afforded pyrrolidine **5g** (0.51 g, 91%) as a white solid: mp = 45−46 °C; $[\alpha]^{25}_D$ = −152.8 (*c* 1.2, MeOH); ^{1}H NMR (501 MHz, $CDCl_3$) δ ppm 7.18−7.29 (m, 1 H), 6.72−6.94 (m, 3 H), 4.63 (t, *J* = 7.09 Hz, 1 H), 3.86−3.98 (m, 1 H), 3.80 (s, 3 H), 2.88−3.11 (m, 1 H), 2.24 (dd, *J* = 11.03, 5.36 Hz, 1 H), 1.68−2.05 (m, 3 H), 1.12 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 159.6, 145.0, 129.3, 119.5, 112.9, 112.4, 69.2, 57.2, 55.1, 42.1, 35.8, 26.2, 23.8; HRMS (EI) calcd for $C_{15}H_{24}NO_2S$ [M + H] 282.1528, found 282.1524.

*(S)-1-((R)-2-Methylpropane-2-sulfinyl)-2-(p-tert-butylphenyl)-yrrolidine (**5h**).* Following the general procedure (GP2), the reaction of γ-chloro *N*-sulfinyl imine **1i** (0.418 g, 2.0 mmol) with borate **2h** (1.3 g, 2.4 mmol) and followed by LiHMDS (4.0 mL, 4.0 mmol, 1.0 mL in THF) afforded pyrrolidine **5h** (0.55 g, 89%) as a white solid: mp = 48−50 °C; $[\alpha]^{25}_D$ = −113.1 (*c* 1.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.33 (d, *J* = 8.34 Hz, 2 H), 7.21 (d, *J* = 8.34 Hz, 2 H), 4.64 (t, *J* = 6.95 Hz, 1 H), 3.79−3.96 (m, 1 H), 2.88−3.03 (m, 1 H), 2.13−2.28 (m, 1 H), 1.70−2.07 (m, 3 H), 1.32 (s, 9 H), 1.11 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 150.0, 140.1, 126.7, 125.1, 69.0, 57.2, 42.0, 35.8, 34.4, 31.4, 26.2, 23.9; HRMS (EI) calcd for $C_{18}H_{30}NOS$ [M + H] 308.2043, found 308.2041.

*(S)-1-((R)-2-Methylpropane-2-sulfinyl)-2-phenylpiperidine (**6a**).* Following the general procedure (GP2), the reaction of δ-chloro *N*-sulfinylimine **1j** (0.445 g, 2.0 mmol) with borate **2a** (0.82 g, 2.4 mmol) and followed by LiHMDS (4.0 mL, 4.0 mmol, 1.0 mL in THF) afforded pyrrolidine **6a** (0.46 g, 88%) as a white solid: mp = 48−51 °C; $[\alpha]^{25}_D$ = +114.1 (*c* 1.0, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.40 (d, *J* = 8.20 Hz, 2 H), 7.38 (t, *J* = 7.72 Hz, 2 H), 7.21−7.28 (m, 1 H), 4.67 (t, *J* = 4.10 Hz, 1 H), 3.28 (dd, *J* = 8.04, 3.31 Hz, 2 H), 2.15−2.24 (m, 1 H), 2.00−2.10 (m, 1 H), 1.55−1.71 (m, 4 H), 1.42−1.51 (m, 1 H), 1.14 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 140.2, 128.5, 127.4, 126.6, 58.7, 31.2, 25.6, 23.0, 20.4; HRMS (EI) calcd for $C_{15}H_{24}NOS$ [M + H] 266.1579, found 266.1569.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rajender.leleti@novartis.com.

Notes

[†]Summer Intern (2010 and 2011): Undergraduate Student from New York University, New York, NY 10012.

[‡]Summer Intern (2010): Undergraduate Student from University of Chicago, Chicago, IL 60637.

■ ACKNOWLEDGMENTS

We thank Dr. Mahavir Prashad, Dr. Prasad Kapa, and Dr. Ravinder Raju for valuable suggestions.

■ REFERENCES

(1) (a) Over 5000 compounds containing these pharmacophores are currently in advanced stages of biological testing: *MDL Drug Data Report*; MDL Information Systems, Inc.: San Leandro, CA, 2010. (b) Elbein, A.; Molyneux, R. I. In *Alkaloids, Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; John Wiley: New York, 1990. (c) *The Alkaloids: Chemistry and Biology*; Cordell, G. A, Ed.; Academic Press: San Diego, 2000; Vol. *54*.

(2) (a) Kakeya, H.; Morishita, M.; Kobinata, K.; Osono, M.; Ishizuka, M.; Osada, H. *J. Antibiot.* **1998**, *51*, 1126. (b) Kakeya, H.; Morishita, M.; Koshino, H.; Morita, T.; Kobayashi, K.; Osada, H. *J. Org. Chem.* **1999**, *64*, 1052.

(3) (a) Grant, J. A.; Riethuisen, J.-M.; Moulaert, B.; DeVos, C. *Ann. Allergy Asthma Immunol.* **2002**, *88*, 190. (b) Day, J. H.; Ellis, A. K.; Rafeiro, E. *Drugs Today* **2004**, *40*, 415. (c) Walsh, G. M. *Curr. Med. Chem.* **2006**, *13*, 2711.

(4) Opalka, C. J.; D'Ambra, T. E.; Faccone, J. J.; Bodson, G.; Cossement, E. *Synthesis* **1995**, 766.

(5) Calderon, S. N.; Rothman, R. B.; Porreca, F.; Flippen-Anderson, J. L.; McNutt, R. W.; Xu, H.; Smith, L. E.; Bilsky, E. J.; Davis, P.; Rice, K. C. *J. Med. Chem.* **1994**, *37*, 2125.

(6) Lloyd, J.; Finlay, H. J.; Vacarro, W.; Hyunh, T.; Kover, A.; Bhandaru, R.; Yan, L.; Atwal, K.; Conder, M. L.; Jenkins-West, T.; Shi, H.; Huang, C.; Li, D.; Sun, H.; Levesque, P. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1436.

(7) (a) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (b) Côté, A.; Boezio, A. A.; Charette, A. B. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5405. (c) Hermanns, N.; Dahmen, S.; Bolm, C.; Bräse, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3692−3694. (d) Akullian, L. C.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4244−4247. (e) Li, S.-W.; Batey, R. *Chem. Commun.* **2004**, 1382.

(8) (a) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302. (b) Nájera, C.; Yus, M. *Curr. Org. Chem.* **2003**, *7*, 867.

(9) Asymmetric Rh(I)-catalyzed arylboron additions to imines: (a) Kuriyama, M.; Soeta, T.; Hao, X.; Chen, Q.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 8128. (b) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584. (c) Richard, B. C.; Jagt, P.; Toullec, P. Y.; Geerdink, D.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2789. (d) Duan, H.; Jia, Y.; Wang, L.; Zhou, Q. *Org. Lett.* **2006**, *8*, 2567. (e) Wang, Z. Q.; Feng, C. G.; Xu, M. H.; Lin, G. Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336. (f) Trincado, M.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 5623.

(10) (a) Anderson, N. G. *Practical Process Research & Development*; Academic Press: San Diego, 2000. (b) Repic, O. *Principles of Process Research and Chemical Development in the Pharmaceutical Industry*; John Wiley & Sons, Inc.: New York, 1998.

(11) Shintani, R.; Takeda, M.; Tsuji., T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 13168.

(12) Jung, H. H.; Buesking, A. W.; Ellman, J. A. *Org. Lett.* **2011**, *13*, 3912.

(13) (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (b) Ellman, J. A. *Pure Appl. Chem.* **2003**, *75*, 39. (c) Senanayake, C. H.; Krishnamurthy, D.; Lu, Z.-H.; Han, Z.; Gallou, I. *Aldrichim. Acta* **2005**, *38*, 93. (d) Daniel, M.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869. (e) Lin, G.-Q.; Xu, M.-H.; Zhong, Y.-W.; Sun, X.-W. *Acc. Chem. Res.* **2008**, *41*, 831. (f) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600.

(14) Bolshan, Y.; Batey, R. A. *Org. Lett.* **2005**, *7*, 1481.

(15) (a) Weix, D. J.; Shi, Y.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 1092. (b) Plobeck, N.; Powell., D. *Tetrahedron: Asymmetry* **2002**, *13*, 303.

(16) (a) Reddy, L. R.; Das, S. G.; Liu, Y.; Prashad, M. *J. Org. Chem.* **2010**, *75*, 2236. (b) Reddy, L. R.; Prashad, M. *Chem. Commun.* **2010**, *46*, 222. (c) Leemans, E.; Mangelinckx, S.; De Kimpe, N. *Chem. Commun.* **2010**, *46*, 3122.
(17) Shintani, R.; Takeda, M.; Tsuji, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 13168.
(18) Shintani, R.; Tsutsumi, Y.; Nagaosa, M.; Nishimura, T.; Hayashi, T. *J. Am. Chem. Soc.* **2009**, *131*, 13588.
(19) Shintani, R.; Isobe, S.; Takeda, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 3795.
(20) Liu, G.-C.; Cogan, C. A.; Owens, T. D.; Tang, T. P.; Ellman, J. *J. Org. Chem.* **1999**, *64*, 1278.