JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

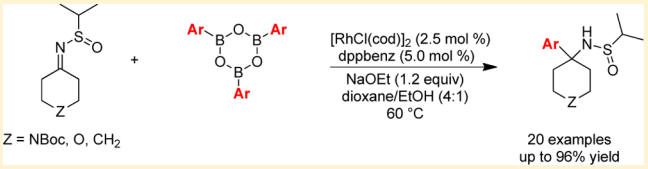
Rh-Catalyzed Addition of Arylboroxines to Cyclic *N*-(Isopropanesulfinyl)ketimines

Hyung Hoon Jung, Andrew W. Buesking, and Jonathan A. Ellman*

Department of Chemistry, Yale University, New Haven, Connecticut 06520-8107, United States

Supporting Information

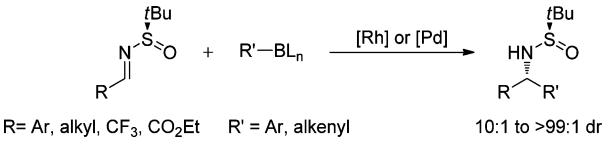
ABSTRACT: Arylboroxines, which are easily accessed by drying commercially available arylboronic acids, are added to *N*-(isopropanesulfinyl)ketimines derived from cyclohexanone, *N*-Boc-piperidin-4-one, and tetrahydropyran-4-one in high yields and with excellent functional group compatibility via rhodium catalysis. These results contrast with additions to the corresponding ketimines incorporating the larger *N*-*tert*-butanesulfinyl group, which give considerably lower yields. Efficient two-step preparation of racemic isopropanesulfinamide from inexpensive isopropyl disulfide and recycling of the isopropanesulfinyl group from the addition products are also described.



INTRODUCTION

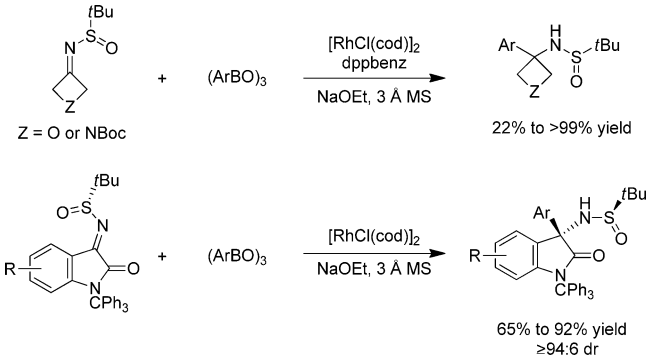
Nucleophilic additions to *N*-(*tert*-butanesulfinyl)imines are among the most extensively used approaches for the synthesis of amines.[1] Transition-metal-catalyzed additions of organoboron reagents to *N*-(*tert*-butanesulfinyl)imines are particularly attractive due to the large number of commercially available, air-stable organoboron reagents and the high functional group compatibility of these transformations.[1,2] While a broad range of amines have been prepared by the addition of aryl- and alkenylboron reagents to *N*-(*tert*-butanesulfinyl)aldimines (Scheme 1),[3,4] only recently have the addition of these reagents to *N*-(*tert*-butanesulfinyl)ketimines been described (Scheme 2).[5,6] However, only *N*-sulfinyl ketimines activated through ring strain and/or electron-withdrawing substituents were reported.

Scheme 1. Previously Reported Additions of Organoboron Reagents to *N*-(*tert*-Butanesulfinyl)aldimines[3,4]



In an effort to broaden the scope of Rh-catalyzed organoboron reagent additions to *N*-sulfinyl ketimines, we sought substrates that were less activated toward nucleophilic attack. Because of increased ring size, imines derived from cyclohexanone, *N*-Boc-piperidin-4-one, and tetrahydropyran-4-one are less electrophilic than previously described *N*-sulfinyl ketimine substrates. Additionally, carbon nucleophile addition products of each of these imines have been extensively used in medicinal chemistry endeavors.[7−9] As a result, we focused on expanding the scope of Rh-catalyzed organoboron reagent additions to racemic imines derived from cyclohexanone, *N*-Boc-piperidin-4-one, and tetrahydropyran-4-one.

Scheme 2. Previously Reported Additions of Organoboron Reagents to Activated *N*-(*tert*-Butanesulfinyl)ketimines[5]



RESULTS AND DISCUSSION

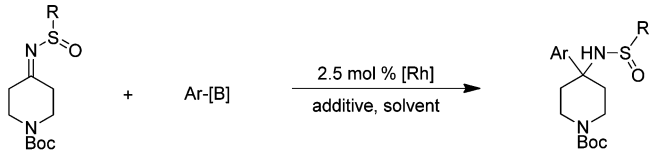
We initiated our study by performing additions to *N*-(*tert*-butanesulfinyl)ketimine **1** under conditions that had previously been determined to be optimal for additions to activated *N*-sulfinyl ketimines, namely, 1.5 equiv of 4-methoxyphenylboroxine with 2.5 mol % of $[RhCl(cod)]_2$ as catalyst, NaOEt as base, and 4:1 dioxane/EtOH as solvent.[5] Unfortunately, product **3** was obtained in a disappointing 36% yield (Table 1, entry 1). Variation of reaction parameters, including boron reagent, base, solvent, temperature, concentration, Rh-precatalyst, and ligands was explored, but a higher yield could not be achieved. Indeed, even the 1,2-diphenylphosphinobenzene (dppbenz) ligand that we had previously identified as an optimal ligand for Rh-catalyzed organoboron reagent additions to *N*-sulfinyl aldimines and ketimines completely abolished reactivity (entries 2 and 3).

Fernandez, Khiar, and co-workers have previously demonstrated that for *N*-sulfinyl imines derived from sterically encumbered

Received: August 1, 2012
Published: October 24, 2012

   dx.doi.org/10.1021/jo301634y | J. Org. Chem. 2012, 77, 9593−9600

Table 1. Optimization of Reaction Conditions[a]



1 (R = *t*Bu)
2 (R = iPr)

3 (R = *t*Bu)
4 (R = iPr)

entry	imine	[Rh] catalyst	Ar[B] (equiv)	additive (equiv)	solvent (ratio)	temp (°C)	yield[b] (%)
1	**1**	$[RhCl(cod)]_2$	$(4\text{-OMePhBO})_3$ (1.5)	NaOEt (1.2)	dioxane/EtOH (4:1)	rt	36
2	**1**	$[RhCl(cod)]_2$, dppbenz		NaOEt (1.2)	dioxane/EtOH (4:1)	rt	0
3	**1**	$[RhCl(cod)]_2$, dppbenz		NaOEt (1.2)	dioxane/EtOH (4:1)	60	<5
4	**2**	$[RhCl(cod)]_2$		NaOEt (1.2)	dioxane/EtOH (4:1)	rt	99
5	**2**	$[RhCl(cod)]_2$	$(4\text{-OMePh})BF_3K$ (3.0)	MeOH (3.0)	dioxane	rt	<5
6	**2**	$[RhCl(cod)]_2$		MeOH (3.0)	dioxane	80	<5
7	**2**	$[RhCl(cod)]_2$, dppbenz		MeOH (3.0)	dioxane	80	<5
8	**2**	$[RhCl(cod)]_2$	$(PhBO)_3$ (1.5)	NaOEt (1.2)	dioxane/EtOH (4:1)	rt	78
9	**2**	$[RhCl(cod)]_2$		NaOEt (1.2)	dioxane/EtOH (4:1)	60	81
10	**2**	$[RhCl(cod)]_2$, dppbenz		NaOEt (1.2)	dioxane/EtOH (4:1)	rt	0
11	**2**	$[RhCl(cod)]_2$, dppbenz		NaOEt (1.2)	dioxane/EtOH (4:1)	60	90
12	**2**	$[RhCl(cod)]_2$, dppbenz	$(PhBO)_3$ (1.0)	NaOEt (1.2)	dioxane/EtOH (4:1)	60	65
13	**2**	$[RhCl(cod)]_2$, dppbenz	$(PhBO)_3$ (2.0)	NaOEt (1.2)	dioxane/EtOH (4:1)	60	91
14	**2**	$[RhCl(cod)]_2$, dppbenz	$PhB(OH)_2$ (4.5)[c]	NaOEt (1.2)	dioxane/EtOH (4:1)	60	70

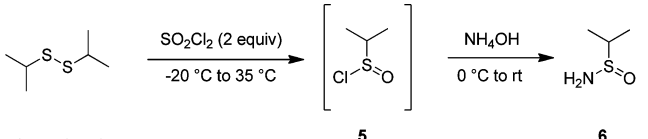
[a]Reactions were performed with 2.5 mol % of rhodium catalyst and when relevant 5 mol % of ligand. The reaction time was 18 h. [b]Yields were determined by ^1H NMR analysis of the crude material relative to 1,3,5-trimethoxybenzene as an external standard. [c]The commercial source of $PhB(OH)_2$ contained 34% w/w boroxine.

carbonyl compounds, additions to *N*-(isopropanesulfinyl)imines can proceed in significiantly higher yields relative to the corresponding more hindered *N*-(*tert*-butanesulfinyl) derivatives.[10] For this reason, we next explored additions to *N*-(isopropanesulfinyl)ketimine **2**. A pronounced increase in reactivity was observed with the addition product **4** obtained in an almost quantitative yield (entry 4).[11] Aryltrifluoroborates were also investigated based upon Hayashi's recent report on their asymmetric addition to sulfonyl ketimines;[6] however, under the reported reaction conditions less than 5% yield was observed (entries 5−7).

With optimal conditions established for the addition of 4-methoxyphenylboroxine, the less reactive phenylboroxine was next investigated. Addition proceeded in 78% yield at rt (entry 8) with heating resulting in miminal improvement (entry 9). The reaction did not proceed at rt in the presence of dppbenz (entry 10), although an excellent yield was obtained upon heating (entry 11). The room temperature results are consistent with previous work on isatin-derived imines that suggests the sterics of dppbenz can actually diminish catalyst reactivity in the case of less reactive substrates;[5] however, for the current class of substrates, this limitation can apparently be overcome upon heating. The number of equivalents of phenylboroxine was also explored. Reactions with just a single equivalent proved detrimental (entry 12), while both 1.5 and 2.0 equiv of phenylboroxine provided similar yields (entries 11 and 13). Finally, using commerical phenylboronic acid under the optimal conditions resulted in a diminished yield (entry 14), a result consistent with previous work with activated *N*-(*tert*-butanesulfinyl)-ketimines.[5]

Before evaluating the scope of Rh-catalyzed arylboroxine additions to *N*-(isopropanesulfinyl)ketimines, we sought to more fully explore their preparation. Ruano has previously reported a two step process for the synthesis of racemic isopropanesulfinamide via NBS oxidation of isopropyl disulfide in MeOH to give methyl isopropylsulfinate followed by addition of lithium bistrimethylsilylamide.[12] By instead oxidizing isopropyl disulfide with sulfuryl chloride to give sulfinyl choride **5**, inexpensive ammonium hydroxide could be used as the amine source to give racemic isopropanesulfinamide (**6**), which was isolated by extraction in 91% overall yield over the two steps (Scheme 3).

Scheme 3. Synthesis of Racemic Isopropanesulfinamide



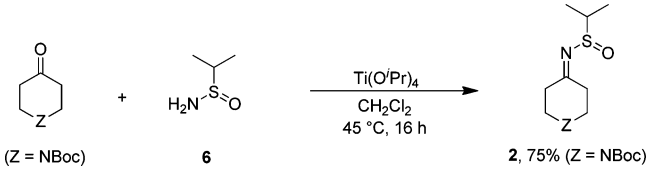
50 mmol scale

5

6
9.78 g, 91%

The subsequent preparation of *N*-isopropanesulfinyl ketimines **2**, **7**, and **9** proceeded in moderate to good yields by condensing **6** with the appropriate ketone using $Ti(O\text{-}i\text{-}Pr)_4$ in CH_2Cl_2 (Scheme 4).

Scheme 4. Preparation of *N*-(Isopropanesulfinyl)ketimines



(Z = NBoc)
(Z = O)
(Z = CH_2)

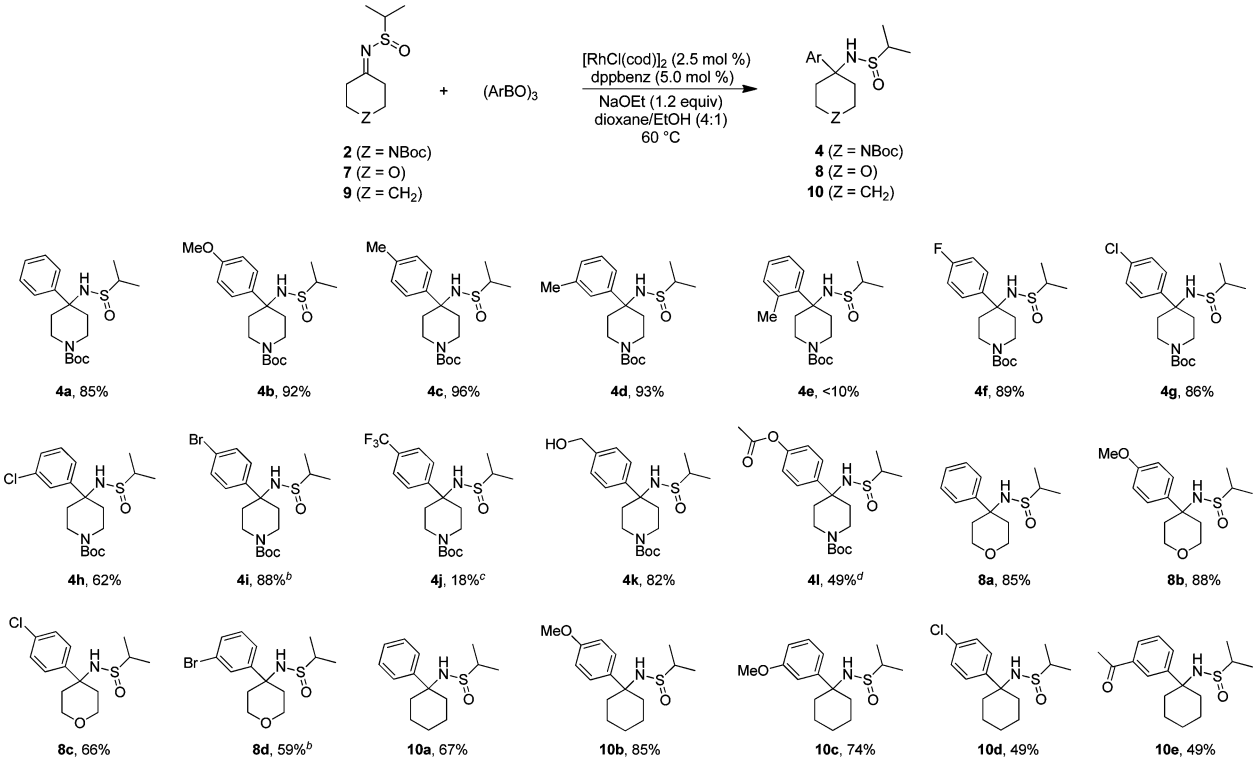
6

2, 75% (Z = NBoc)
7, 62% (Z = O)
9, 56% (Z = CH_2)

The addition of a wide variety of arylboroxines to sulfinyl ketimines **2**, **7**, and **9** was next investigated (Scheme 5). While phenylboroxine showed comparable results whether 1.5 or 2.0 equiv were used, initial investigation of the scope demonstrated

dx.doi.org/10.1021/jo301634y | J. Org. Chem. 2012, 77, 9593−9600

Scheme 5. *N*-(Isopropanesulfinyl)ketimine Addition Reaction Scope[a]

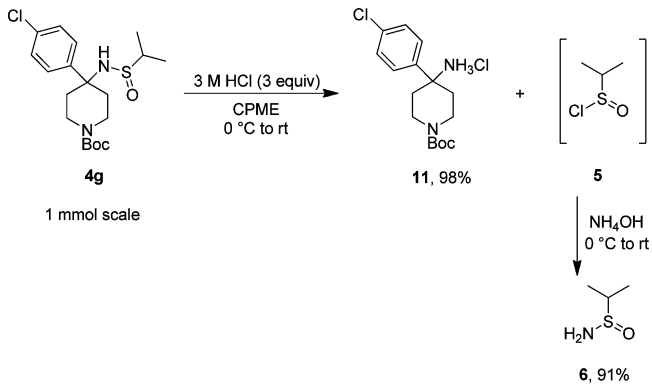


[a]Isolated yields after chromatography. [b]Reaction were performed without added dppbenz. [c]Reaction was performed at 80 °C. [d]Reaction was performed at room temperature in the absence of dppbenz.

that 2.0 equiv of arylboroxine resulted in improved yields for a number of products including **4f** and **4g**. As a result, the reaction scope was evaluated utilizing 2.0 equiv of arylboroxine to provide more general reaction parameters. Electron-neutral and electron-rich aryl boroxines added in good to high yields (e.g., **4a–d**, **8a–b**, and **10a–b**). In contrast, the addition of electron-deficient arylboroxines was less efficient resulting in low (**4j**) to moderate (**10e**) yields. While meta and para substitution was well tolerated (e.g., **4c** and **4d**), ortho-substituted arylboroxines were evaluated but these coupled with poor efficiency (**4e**). The functional group compatibility of the reaction was high with effective couple being observed for arylboroxines incorporating phenyl esters (**4l**), primary alcohols (**4k**), ketones (**10e**), chlorides (**4g**, **4h**, **8c**, and **10d**), fluorides (**4f**), and bromides (**4i** and **8d**). However, for bromo-substituted arylboroxines, coupling was performed without the dppbenz ligand to prevent competitive Rh insertion into the C–Br bond.

The practicality of the addition products was demonstrated by selective cleavage of the isopropanesulfinyl group in **4g** with HCl treatment (Scheme 6). Not only is the desired product **11** readily isolated in almost quantitative yield, but straightforward operations also enable the efficient recovery of the isopropanesulfinyl group via its reconversion to isopropanesulfinamide (**6**).[13] Specifically, treatment of **4g** with greater than 2 equiv of HCl in the acid stable and increasingly popular industrial solvent, cyclopentyl methyl ether (CPME),[14] led to precipitation of the amine hydrochloride **11**, which was isolated in near-quantitative yield and with high purity by simple filtration. The filtrate containing the sulfinyl chloride was then added to ammonium hydroxide to provide sulfinamide **6**, which was also obtained with high purity and excellent yield after straightforward extraction.

Scheme 6. Cleavage and Recycling of Isopropanesulfinyl Group



CONCLUSION

In conclusion, the rhodium-catalyzed additions of arylboroxines to *N*-(isopropanesulfinyl)ketimines derived from cyclohexanone, *N*-Boc-piperidin-4-one, and tetrahydropyran-4-one proceed in high yields with excellent functional group compatibility to provide privileged classes of tertiary carbinamine products. The isopropanesulfinamide is readily prepared using inexpensive starting materials and reagents. Moreover, the isopropanesulfinyl group can be recycled, which adds to the overall efficiency of this tertiary carbinamine synthesis process.

EXPERIMENTAL SECTION

General Experimental Methods. Methylene chloride (CH_2Cl_2), 1,4-dioxane, and cyclopentyl methyl ether (CPME) were dried by passing through an aluminum drying column. Ethanol (EtOH) was

dx.doi.org/10.1021/jo301634y | J. Org. Chem. 2012, 77, 9593–9600

refluxed with activated magnesium for several hours, distilled under nitrogen gas, and stored over MS 3 Å in a nitrogen filled glovebox. Arylboroxines (anhydrous trimers) were readily prepared by heating commercially available arylboronic acids up to 110−130 °C under high vacuum (approximately 0.3 Torr) for 12−18 h; complete conversion to arylboroxine was confirmed by ^{1}H NMR with deuterated dimethyl sulfoxide (DMSO-d_6) as solvent. Powdered molecular sieves (pore size 3 Å) were preheated to 300−350 °C under high vacuum overnight and cooled under dry nitrogen atmosphere. All glassware and magnetic stir bars were dried at 150 °C overnight or flame-dried prior to use. All reagents necessary for addition reactions were stored in a nitrogen-filled glovebox. Reactions were conducted under nitrogen atmosphere unless otherwise specified. Melting points are reported uncorrected. Proton (^{1}H NMR), carbon (^{13}C NMR), and fluorine (^{19}F NMR) nuclear magnetic resonance spectra were recorded on 400 and 500 MHz spectrometers. All ^{19}F NMR experiments utilized proton decoupling. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak or the internal standard tetramethylsilane (TMS) was used as reference values. For ^{1}H NMR: $CDCl_3$ = 7.26 ppm, CD_3OD = 3.31 ppm, TMS = 0.00 ppm. For ^{13}C NMR: $CDCl_3$ = 77.0 ppm, CD_3OD = 49.0 ppm, TMS = 0.00 ppm. Infrared (IR) spectra were collected on a FT-IR spectrometer possessing an ATR attachment with anvil; only partial data are provided. High resolution mass spectra (HRMS) were obtained on a Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer except in the case of ketimine **9**, which was obtained on a time-of-flight (TOF) mass spectrometer.

Isopropanesulfinamide (6). In a 100 mL, three-neck flask with a magnetic stirring bar were placed isopropyl disulfide (8.00 mL, 50.0 mmol, 1.0 equiv) and acetic acid (5.72 mL, 100 mmol, 2.0 equiv). The solution was cooled to −20 °C with stirring; solids formed due to the low melting point of acetic acid. Sulfuryl chloride (12.5 mL, 155 mmol, 3.1 equiv) was slowly added by a syringe over a period of 30 min resulting in slow melting of the solids. The mixture was stirred at −20 °C for 3 h and was allowed to warm to room temperature over a period of 2 h during which evolution of SO_2 (g) and HCl (g) was observed. The reaction mixture was stirred at 35 °C for an additional 1 h and then cooled to 0 °C. Acetyl chloride was removed under a reduced pressure (approximately 0.5 Torr); a vacuum trap was required. The remaining sulfinyl chloride was then dissolved in 80 mL of anhydrous CH_2Cl_2, and the solution was slowly transferred by a cannula to 600 mL of cold 28−30% aqueous NH_4OH solution at 0 °C with vigorous stirring over a period of 1 h. An additional 20 mL of CH_2Cl_2 was added to the reaction flask and then was transferred by cannula to the NH_4OH solution to ensure complete transfer of the sufinyl chloride solution. After the addition was complete, the reaction mixture was stirred overnight open to air during which time much of the ammonia evaporated. The reaction mixture was transferred to a 1 L separatory funnel, the aqueous phase was saturated with NaCl, and then extraction was performed with a solution of 10:1 $CHCl_3$/EtOH (4 × 250 mL). Concentration of the combined organic layers under reduced pressure afforded (±)-isopropanesulfinamide (9.78 g, 91.3 mmol, 91% yield) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.99 (br s, NH_2), 2.73 (sept, J = 6.9 Hz, 1H), 1.28 (d, J = 6.9 Hz, 3H), 1.27 (d, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 54.5, 14.8, 14.7.[12]

General Procedure for the Synthesis of Sulfinyl Ketimines. In a 50 mL, round-bottom flask with a magnetic stirring bar were placed the appropriate ketone and (±)-isopropanesulfinamide. CH_2Cl_2 (10 mL) and then $Ti(O^iPr)_4$ were added at room temperature. The reaction mixture was refluxed (at 45 °C) overnight (ca. 16 h) under a nitrogen atmosphere and then was cooled to room temperature. Conversion was monitored by ^{1}H NMR analysis of aliquots of the reaction mixture diluted with $CDCl_3$. The mixture was poured into a 125 mL Erlenmeyer flask, which contained 50 mL (approx) of satd $NaHCO_3$ (aq) and a long magnetic stirring bar (length = 6.0 cm). The reaction flask was rinsed with 10 mL of CH_2Cl_2, and the rinse was poured into the Erlenmeyer flask. The resulting mixture was vigorously stirred for 20 min (approx) during which time white solids precipitated. The solids were removed by filtration under a reduced pressure through a 60 mL fritted filter funnel (pore size = 20−30 μm and disk size = 6.5 cm) upon which 1.0−1.5 cm (depth) of Celite was added. Additional CH_2Cl_2 (2 × 40 mL) was used to rinse the flask and the pad of Celite. The organic layer of the filtrate was separated, washed with brine, dried over $MgSO_4$, filtered, and concentrated under a reduced pressure. The crude product was purified via flash chromatography on silica gel. Although the imine product did not readily hydrolyze during aqueous workup, imine hydrolysis does occur during purification via chromatography on silica gel. To minimize hydrolysis a short plug of silica gel column (3.0 cm (d) × 10 cm (l)) with constant air-pressure was therefore used.

***N*-(*N*-Boc-4-piperidylidene)isopropanesulfinamide (2).** From 1-Boc-4-piperidone (1.00 g, 5.02 mmol), (±)-isopropanesulfinamide (538 mg, 5.02 mmol), and $Ti(O^iPr)_4$ (3.0 mL, 10 mmol) was obtained ketimine **2** as a slightly yellow solid (1.08 g, 75% yield). R_f = 0.25 (1:1 hexanes/EtOAc). Mp: 63.7−64.3 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.71 (dt, J = 13.2, 6.0, 1H), 3.67−3.53 (m, 3H), 3.09 (ddd, J = 14.9, 6.9, 4.9 Hz, 1H), 2.89 (sept, J = 6.9 Hz, 1H), 2.82 (ddd, J = 14.9, 7.4, 4.9 Hz, 1H), 2.52 (app t, J = 5.3 Hz, 2H), 1.48 (s, 9H), 1.28 (d, J = 6.9 Hz, 3H), 1.27 (d, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 183.1, 154.4, 80.3, 54.1, 39.3, 33.5, 28.3, 14.6, 13.9. IR: 2973, 2930, 1691, 1624, 1416, 1236, 1162, 1075 cm^{-1}. HRMS (ESI): m/z calcd for $C_{13}H_{25}N_2O_3S$ $(M + H)^+$ 289.1580, found 289.1576.

***N*-(4-Tetrahydropyranylidene)isopropanesulfinamide (7).** From tetrahydro-4*H*-pyran-4-one (923 μL, 9.99 mmol), (±)-isopropanesulfinamide (1.28 mg, 12.0 mmol), and $Ti(O^iPr)_4$ (6.0 mL, 20 mmol) was obtained ketimine **7** as a slightly yellow oil (1.18 g, 62% yield). R_f = 0.30 (EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.95−3.85 (m, 2H), 3.86−3.80 (m, 2H), 3.16−3.09 (m, 1H), 2.91−2.83 (m, 2H), 2.53 (app td, J = 5.7, 2.0 Hz, 2H), 1.27 (d, J = 6.9 Hz, 3H), 1.25 (d, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 182.1, 68.6, 67.5, 54.1, 40.7, 35.1, 14.6, 13.9. IR (thin film): 2966, 2854, 1620, 1381, 1223, 1071, 1030 cm^{-1}. HRMS (ESI): m/z calcd for $C_8H_{16}NO_2S$ $(M + H)^+$ 190.0896, found 190.0894.

***N*-Cyclohexylideneisopropanesulfinamide (9).** From cyclohexanone (1.24 mL, 11.9 mmol), (±)-isopropanesulfinamide (720 mg, 6.72 mmol), and $Ti(O^iPr)_4$ (6.0 mL, 20 mmol) was obtained ketimine **9** as a slightly yellow oil (700 mg, 56% yield). R_f = 0.30 (1:1 hexanes/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.86−2.78 (m, 1H), 2.79 (sept, J = 6.9 Hz, 1H), 2.72−2.64 (m, 1H), 2.39 (app t, J = 6.4 Hz, 2H), 1.82−1.60 (m, 6H), 1.27 (d, J = 6.9 Hz, 3H), 1.23 (d, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.4, 54.0, 40.5, 34.3, 27.8, 27.4, 25.2, 14.6, 14.0. IR: 2932, 2860, 1610, 1448, 1068, 1029 cm^{-1}. HRMS (ESI): m/z calcd for $C_9H_{18}NOS$ $(M + H)^+$ 188.1104, found 188.1133.

General Procedure for the Addition of Arylboroxines to Ketimines 2, 7, and 9. Reactions were set up in a nitrogen-filled glovebox. To a vial (2 dram) containing an *N*-(isopropanesulfinyl)-ketimine substrate (0.20 mmol) and a magnetic stirring bar was transferred a mixture of NaOEt (16 mg, 0.24 mmol), arylboroxine (0.40 mmol), and MS 3 Å powder (200% mass to boroxine) in a solvent mixture of dioxane (0.4 mL) and EtOH (0.2 mL). Subsequently, a heterogeneous orange-colored mixture of $[RhCl(cod)]_2$ (2.5 mg, 5.0 μmol) and dppbenz (4.5 mg, 10 μmol) in dioxane (0.4 mL), which had been initially stirred for 10 min (approx), was added to the reaction vial. The vial was capped, removed from the box, sealed with Parafilm, and placed on a magnetic stir plate. The reaction mixture was stirred at 60 °C for 12−18 h unless otherwise noted. The reaction mixture was then filtered through a short pad of silica gel, which was washed with EtOAc. The filtrate was concentrated under a reduced pressure. The crude product was purified via chromatography on silica gel (hexanes/EtOAc mixture or EtOAc/EtOH mixture).

***N*-4-(*N*-Boc-4-phenylpiperidinyl)isopropanesulfinylamine (4a).** From 58.0 mg (0.201 mmol) of imine **2** and 125 mg (0.401 mmol) of phenylboroxine was obtained 62.5 mg (85% yield) of sulfinylamine **4a** as an off-white solid after purification by silica gel chromatography eluting with 1:1 hexanes/EtOAc followed by 100% EtOAc. R_f = 0.50 (EtOAc). Mp = 120−121 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, J = 7.5 Hz, 2H), 7.38 (t, J = 7.5 Hz, 2H), 7.29 (t, J = 7.5 Hz, 1H), 3.81 (s, NH), 3.63−3.54 (m, 2H), 3.54−3.43 (m, 2H), 2.67 (sept, J = 6.9 Hz, 1H), 2.40−2.32 (m, 1H), 2.24−2.08 (m, 3H), 1.45 (s, 9H), 1.19 (d, J = 6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.7, 143.3, 128.6, 127.7,

dx.doi.org/10.1021/jo301634y | J. Org. Chem. 2012, 77, 9593−9600

126.5, 79.7, 58.3, 55.1, 37.2, 36.9, 28.4, 15.4, 15.3. IR: 3485, 3201, 2973, 2930, 1693, 1424, 1248, 1168, 1031 cm^{-1}. HRMS (ESI): m/z calcd for $C_{19}H_{31}N_2O_3S$ $(M + H)^+$ 367.2050, found 367.2041.

***N*-4-(*N*-Boc-4-(4-methoxyphenyl)piperidinyl)isopropanesulfinylamine (4b).** From 58.0 mg (0.201 mmol) of imine **2** and 161 mg (0.401 mmol) of 4-methoxyphenylboroxine was obtained 73.3 mg (92% yield) of sulfinylamine **4b** as an off-white solid after purification by silica gel chromatography eluting with 1:1 hexanes/EtOAc followed by 100% EtOAc. R_f = 0.40 (EtOAc). Mp =100−101 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 3.81 (s, 3H), 3.71 (s, NH), 3.65−3.58 (m, 1H), 3.54−3.46 (m, 2H), 3.45−3.37 (m, 1H), 2.65 (sept, J = 6.9 Hz, 1H), 2.40−2.32 (m, 1H), 2.20−2.05 (m, 3H), 1.45 (s, 9H), 1.18 (d, J = 6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.9, 154.7, 134.9, 127.9, 113.9, 79.7, 58.0, 55.2, 55.0, 37.5, 37.2, 28.4, 15.4, 15.3. IR: 3483, 3185, 2930, 1688, 1423, 1246, 1165, 1030 cm^{-1}. HRMS (ESI): m/z calcd for $C_{20}H_{33}N_2O_4S$ $(M + H)^+$ 397.2155, found 397.2160.

***N*-4-(*N*-Boc-4-(4-methylphenyl)piperidinyl)isopropanesulfinylamine (4c).** From 58.0 mg (0.201 mmol) of imine **2** and 161 mg (0.401 mmol) of 4-methylphenylboroxine was obtained 73.1 mg (96% yield) of sulfinylamine **4c** as an off-white solid after purification by silica gel chromatography eluting with 1:1 hexanes/EtOAc followed by 100% EtOAc. R_f = 0.55 (EtOAc). Mp = 132−133 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (d, J = 8.2 Hz, 2H), 6.18 (d, J = 8.2 Hz, 2H), 3.72 (s, NH), 3.63−3.57 (m, 1H), 3.57−3.40 (m, 3H), 2.65 (sept, J = 6.9 Hz, 1H), 2.38−2.32 (m, 1H), 2.34 (s, 3H), 2.22−2.06 (m, 3H), 1.45 (s, 9H), 1.19 (d, J = 6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.8, 140.1, 137.4, 129.3, 126.4, 79.7, 58.1, 55.0, 37.3, 37.0, 28.4, 21.0, 15.4, 15.3. IR: 3488, 3202, 2973, 2928, 1692, 1424, 1247, 1166, 1032 cm^{-1}. HRMS (ESI): m/z calcd for $C_{20}H_{33}N_2O_3S$ $(M + H)^+$ 381.2206, found 381.2207.

***N*-4-(*N*-Boc-4-(3-methylphenyl)piperidinyl)isopropanesulfinylamine (4d).** From 58.0 mg (0.201 mmol) of imine **2** and 161 mg (0.401 mmol) of 3-methylphenylboroxine was obtained 70.8 mg (93% yield) of sulfinylamine **4d** as an off-white solid after purification by silica gel chromatography eluting with 1:1 hexanes/EtOAc followed by 100% EtOAc. R_f = 0.55 (EtOAc). Mp = 123−124 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27−7.25 (m, 3H), 7.12−7.09 (m, 1H), 3.74 (s, NH), 3.63−3.53 (m, 2H), 3.53−3.42 (m, 2H), 2.66 (sept, J = 6.9 Hz, 1H), 2.39−2.33 (m, 1H), 2.36 (s, 3H), 2.21−2.08 (m, 3H), 1.45 (s, 9H), 1.19 (d, J = 6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.8, 143.2, 138.1, 128.5, 128.4, 127.3, 123.6, 79.7, 58.3, 55.1, 37.4, 36.9, 28.4, 21.7, 15.4, 15.3. IR: 3483, 3200, 2928, 1688, 1422, 1238, 1159, 1034 cm^{-1}. HRMS (ESI): m/z calcd for $C_{20}H_{33}N_2O_3S$ $(M + H)^+$ 381.2206, found 381.2203.

***N*-4-(*N*-Boc-4-(4-fluorophenyl)piperidinyl)isopropanesulfinylamine (4f).** From 58.0 mg (0.201 mmol) of imine **2** and 147 mg (0.402 mmol) of 4-fluorophenylboroxine was obtained 68.2 mg (89% yield) of sulfinylamine **4f** as an off-white solid after purification by silica gel chromatography eluting with 1:1 hexanes/EtOAc followed by 100% EtOAc. R_f = 0.40 (EtOAc). Mp = 119−121 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46−7.43 (m, 2H), 7.07−7.04 (m, 2H), 3.76 (s, NH), 3.63−3.47 (m, 3H), 3.57−3.40 (m, 1H), 2.68 (sept, J = 6.9 Hz, 1H), 2.36−2.28 (m, 1H), 2.20−2.08 (m, 3H), 1.45 (s, 9H), 1.20 (d, J = 6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.0 (d, J = 246 Hz), 154.7, 139.2 (d, J = 2 Hz), 128.3 (d, J = 9 Hz), 115.4 (d, J = 20 Hz), 79.8, 58.0, 55.1, 37.3, 37.2, 28.4, 15.4, 15.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ −114.56. IR: 3482, 3191, 2972, 1693, 1426, 1248, 1166, 1033 cm^{-1}. HRMS (ESI): m/z calcd for $C_{19}H_{30}FN_2O_3S$ $(M + H)^+$ 385.19557, found 385.19563.

***N*-4-(*N*-Boc-4-(4-chlorophenyl)piperidinyl)isopropanesulfinylamine (4g).** From 58.0 mg (0.201 mmol) of imine **2** and 167 mg (0.402 mmol) of 4-chlorophenylboroxine was obtained 69.3 mg (86% yield) of sulfinylamine **4g** as an off-white solid after purification by silica gel chromatography eluting with 1:1 hexanes/EtOAc followed by 100% EtOAc. R_f = 0.45 (EtOAc). Mp = 102−103 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 8.6 Hz, 2H), 3.79 (s, NH), 3.60 (dt, J = 13.7, 3.2 Hz, 1H), 3.57−3.49 (m, 2H), 3.45−3.37 (m, 1H), 2.68 (sept, J = 6.9 Hz, 1H), 2.33−2.25 (m, 1H), 2.18−2.05 (m, 3H), 1.45 (s, 9H), 1.20 (d, J = 6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.7, 142.1, 133.6, 128.7, 128.0, 79.8, 58.0, 55.2, 37.1, 37.0, 28.4, 15.4. IR: 3480, 3190, 2929, 1687, 1423, 1246, 1163, 1029 cm^{-1}. HRMS (ESI): m/z calcd for $C_{19}H_{30}ClN_2O_3S$ $(M + H)^+$ 401.1660, found 401.1665.

***N*-4-(*N*-Boc-4-(3-chlorophenyl)piperidinyl)isopropanesulfinylamine (4h).** From 58.0 mg (0.201 mmol) of imine **2** and 167 mg (0.402 mmol) of 3-chlorophenylboroxine was obtained 49.8 mg (62% yield) of sulfinylamine **4h** as an off-white solid after purification by silica gel chromatography eluting with 1:1 hexanes/EtOAc followd by 100% EtOAc. R_f = 0.45 (EtOAc). Mp = 147−148 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (s, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 7.27 (d, J = 7.8 Hz, 1H), 3.80 (s, NH), 3.65 (dt, J = 13.6, 5.0 Hz, 1H), 3.61−3.50 (m, 2H), 3.45−3.35 (m, 1H), 2.69 (sept, J = 6.9 Hz, 1H), 2.34−2.26 (m, 1H), 2.20−2.05 (m, 3H), 1.46 (s, 9H), 1.21 (d, J = 6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.7, 145.9, 134.6, 129.8, 127.9, 126.9, 124.7, 79.8, 58.2, 55.2, 37.2, 36.8, 28.4, 15.3. IR: 3488, 3206, 2973, 2929, 1690, 1421, 1247, 1165, 1034 cm^{-1}. HRMS (ESI): m/z calcd for $C_{19}H_{30}ClN_2O_3S$ $(M + H)^+$ 401.1660, found 401.1663.

***N*-4-(*N*-Boc-4-(4-bromophenyl)piperidinyl)isopropanesulfinylamine (4i).** The general reaction procedure was employed except that the dppbenz ligand was not added. From 58.0 mg (0.201 mmol) of imine **2** and 220 mg (0.401 mmol) of 4-bromophenylboroxine was obtained 78.2 mg (88% yield) of sulfinylamine **4i** as an off-white solid after purification by silica gel chromatography eluting with 1:1 hexanes/EtOAc followed by 100% EtOAc. R_f = 0.50 (EtOAc). Mp = 114−115 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 8.6 Hz, 2H), 3.77 (s, NH), 3.64−3.58 (m, 1H), 3.57−3.48 (m, 2H), 3.45−3.38 (m, 1H), 2.68 (sept, J = 6.9 Hz, 1H), 2.32−2.25 (m, 1H), 2.20−2.05 (m, 3H), 1.45 (s, 9H), 1.20 (d, J = 6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.7, 142.7, 131.7, 128.3, 121.8, 79.9, 58.1, 55.2, 37.0, 36.9, 28.4, 15.4. IR: 3484, 3206, 2974, 1684, 1424, 1247, 1163, 1028 cm^{-1}. HRMS (ESI): m/z calcd for $C_{19}H_{30}BrN_2O_3S$ $(M + H)^+$ 447.1136, found 447.1139.

***N*-4-(*N*-Boc-4-(4-(trifluoromethyl)phenyl)piperidinyl)isopropanesulfinylamine (4j).** The general reaction procedure was employed except that the reaction mixture was stirred at 80 °C. From 58.0 mg (0.201 mmol) of imine **2** and 207 mg (0.401 mmol) of 4-(trifluoromethyl)phenylboroxine was obtained 15.6 mg (18% yield) of sulfinylamine **4j** as an off-white solid after purification by silica gel chromatography eluting with 1:1 hexanes/EtOAc followed by 100% EtOAc. R_f = 0.55 (EtOAc). Mp: 90−92 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65−7.58 (m, 4H), 3.87 (s, NH), 3.71 (dt, J = 13.8, 4.6 Hz, 1H), 3.62 (app d, J = 12.6 Hz, 1H), 3.52 (app t, J = 13.8 Hz, 1H), 3.39 (m, 1H), 2.71 (sept, J = 6.9 Hz, 1H), 2.34−2.26 (m, 1H), 2.23−2.08 (m, 3H), 1.46 (s, 9H), 1.22 (d, J = 6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.7, 148.0, 130 (q, J = 32 Hz), 126.9, 125.5 (q, J = 4 Hz), 123.9 (q, J = 270 Hz), 79.9, 58.3, 55.3, 37.0, 36.8, 28.4, 15.4, 15.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.62. IR: 3485, 3191, 2974, 1690, 1424, 1326, 1248, 1164, 1122, 1031 cm^{-1}. HRMS (ESI): m/z calcd for $C_{20}H_{29}F_3N_2O_3SNa$ $(M + Na)^+$ 457.1743, found 457.1728.

***N*-4-(*N*-Boc-4-(4-(hydroxymethyl)phenyl)piperidinyl)isopropanesulfinylamine (4k).** From 58.0 mg (0.201 mmol) of imine **2** and 161 mg (0.401 mmol) of 4-(hydroxymethyl)phenylboroxine was obtained 65.0 mg (82% yield) of sulfinylamine **4k** as an off-white solid after purification by silica gel chromatography eluting with 100% EtOAc followed by 20:1 EtOAc/EtOH. R_f = 0.30 (20:1 EtOAc/EtOH). Mp = 94−95 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 4.67 (d, J = 5.5 Hz, 2H), 3.82 (s, NH), 3.56 (app s, 2H), 3.47 (app s, 2H), 2.66 (sept, J = 6.9 Hz, 1H), 2.37−2.22 (m, 2H), 2.22−2.08 (m, 3H), 1.45 (s, 9H), 1.18 (d, J = 6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.7, 142.5, 140.6, 127.1, 126.6, 79.7, 64.6, 58.1, 55.1, 37.1, 37.0, 28.4, 15.4. IR: 3478, 3222, 2972, 2929, 2870, 1669, 1425, 1248, 1164, 1031 cm^{-1}. HRMS (ESI): m/z calcd for $C_{20}H_{33}N_2O_4S$ $(M + H)^+$ 397.2155, found 397.2160.

***N*-4-(*N*-Boc-4-(4-acetoxyphenyl)piperidinyl)isopropanesulfinylamine (4l).** The general reaction procedure was employed except that the dppbenz ligand was not added and the reaction mixture was stirred at room temperature. From 58.0 mg (0.201 mmol) of imine **2** and 195 mg (0.401 mmol) of 4-acetoxyphenylboroxine was obtained

dx.doi.org/10.1021/jo301634y | J. Org. Chem. 2012, 77, 9593−9600

41.7 mg (49% yield) of sulfinylamine **4l** as an off-white solid after purification by silica gel chromatography eluting with 1:1 hexanes/EtOAc followed by 100% EtOAc. R_f = 0.45 (EtOAc). Mp = 104−105 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H), 3.79 (s, NH), 3.64−3.47 (m, 3H), 3.47−3.39 (m, 1H), 2.68 (sept, J = 6.9 Hz, 1H), 2.35−2.28 (m, 1H), 2.29 (s, 3H), 2.18−2.09 (m, 3H), 1.45 (s, 9H), 1.20 (d, J = 6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.2, 154.7, 150.0, 141.0, 127.7, 121.5, 79.8, 58.2, 55.1, 37.3, 37.0, 28.4, 21.1, 15.4, 15.3. IR: 3484, 3220, 2973, 1758, 1686, 1424, 1365, 1199, 1164, 1030 cm^{-1}. HRMS (ESI): m/z calcd for $C_{21}H_{32}N_2O_5SNa$ $(M + Na)^+$ 447.1924, found 447.1902.

***N*-4-(4-Phenyltetrahydropyranyl)isopropanesulfinylamine (8a).** From 38.0 mg (0.201 mmol) of imine **7** and 125 mg (0.401 mmol) of phenylboroxine was obtained 45.5 mg (85% yield) of sulfinylamine **8a** as an off-white solid after purification by silica gel chromatography eluting with 100% EtOAc followed by 20:1 EtOAc/EtOH. R_f = 0.30 (20:1 EtOAc/EtOH). Mp = 64−65 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, J = 7.5 Hz, 2H), 7.39 (t, J = 7.5 Hz, 2H), 7.30 (d, J = 7.5 Hz, 1H), 3.94 (ddd, J = 11.9, 8.1, 3.1 Hz, 1H), 3.83 (ddd, J = 12.0, 8.1, 3.1 Hz, 1H), 3.82 (s, NH), 3.77 (ddd, J = 11.9, 6.3, 3.7 Hz, 1H), 3.67 (ddd, J = 12.0, 6.3, 3.7 Hz, 1H), 2.68 (sept, J = 6.9 Hz, 1H), 2.50−2.43 (m, 1H), 2.29−2.15 (m, 3H), 1.19 (d, J = 6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.6, 128.6, 127.7, 126.5, 64.1, 64.0, 57.5, 55.1, 38.2, 37.7, 15.4, 15.3. IR: 3447, 3204, 2960, 2929, 2868, 1447, 1420, 1160, 1030 cm^{-1}. HRMS (ESI): m/z calcd for $C_{14}H_{22}NO_2S$ $(M + H)^+$ 268.1366, found 268.1361.

***N*-4-(4-(4-Methoxyphenyl)tetrahydropyranyl)isopropanesulfinylamine (8b).** From 38.0 mg (0.201 mmol) of imine **7** and 161 mg (0.401 mmol) of 4-methoxyphenylboroxine was obtained 52.4 mg (88% yield) of sulfinylamine **8b** as an off-white solid after purification by silica gel chromatography eluting with 100% EtOAc followed by 10:1 EtOAc/EtOH. R_f = 0.25 (20:1 EtOAc/EtOH). Mp = dec over 150 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, J = 8.9 Hz, 2H), 6.90 (d, J = 8.9 Hz, 2H), 3.92 (ddd, J = 11.3, 7.6, 1.4 Hz, 1H), 3.86 (s, NH), 3.84−3.78 (m, 1H), 3.81 (s, 3H), 3.78−3.72 (m, 1H), 3.67−3.62 (m, 1H), 2.67 (sept, J = 6.9 Hz, 1H), 2.47−2.41 (m, 1H), 2.25−2.13 (m, 3H), 1.19 (d, J = 6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.9, 135.3, 127.9, 113.8, 64.2, 64.0, 57.1, 55.2, 55.0, 38.4, 38.0, 15.6, 15.4. IR: 3445, 3203, 2965, 1464, 1189, 1101, 1028 cm^{-1}. HRMS (ESI): m/z calcd for $C_{15}H_{24}NO_3S$ $(M + H)^+$ 298.14714, found 298.14713.

***N*-4-(4-(4-Chlorophenyl)tetrahydropyranyl)isopropanesulfinylamine (8c).** From 38.0 mg (0.201 mmol) of imine **7** and 167 mg (0.402 mmol) of 4-chlorophenylboroxine was obtained 41.6 mg (69% yield) of sulfinylamine **8c** as an off-white solid after purification by silica gel chromatography eluting with 100% EtOAc followed by 20:1 EtOAc/EtOH. R_f = 0.35 (20:1 EtOAc/EtOH). Mp =103.6−104.4 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H), 3.92 (ddd, J = 11.9, 8.3, 3.0 Hz, 1H), 3.84−3.75 (m, 2H), 3.81 (s, NH), 3.70−3.66 (m, 1H), 2.68 (sept, J = 6.9 Hz, 1H), 2.41(ddd, J = 13.9, 8.3, 3.5 Hz, 1H), 2.23−2.14 (m, 3H), 1.20 (d, J = 6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.4, 133.6, 128.7, 128.0, 63.9, 63.7, 57.2, 55.2, 38.0, 37.8, 15.4, 15.3. IR: 3446, 3192, 2957, 2867, 1493, 1095, 1035, 1014 cm^{-1}. HRMS (ESI): m/z calcd for $C_{14}H_{21}ClNO_2S$ $(M + H)^+$ 302.0976, found 302.0977.

***N*-4-(4-(3-Bromophenyl)tetrahydropyranyl)isopropanesulfinylamine (8d).** The general reaction procedure was employed except that the dppbenz ligand was not added. From 38.0 mg (0.201 mmol) of imine **7** and 220 mg (0.401 mmol) of 3-bromophenylboroxine was obtained 41.2 mg (59% yield) of sulfinylamine **8d** as an off-white solid after purification by silica gel chromatography eluting with 20:1 CH_2Cl_2/EtOH. R_f = 0.25 (20:1 EtOAc/EtOH). Mp: = 107.8−108.4 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 (t, J = 1.8 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.26 (t, J = 8.0 Hz, 1H), 3.93 (ddd, J = 11.9, 8.6, 3.0 Hz, 1H), 3.84 (s, NH), 3.83−3.77 (m, 2H), 3.72−3.67 (m, 1H), 2.70 (sept, J = 6.9 Hz, 1H), 2.41 (ddd, J = 13.9, 8.6, 3.8 Hz, 1H), 2.25−2.12 (m, 3H), 1.22 (d, J = 6.9 Hz, 3H), 1.21 (d, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.5, 130.8, 130.1, 129.9, 125.2, 122.8, 63.9, 63.7, 57.3, 55.2, 38.1, 37.5, 15.4, 15.3. IR: 3450, 3200, 2959, 2868, 1466, 1241, 1207, 1103, 1026 cm^{-1}. HRMS (ESI): m/z calcd for $C_{14}H_{21}BrNO_2S$ $(M + H)^+$ 348.0451, found 348.0452.

***N*-(1-Phenylcyclohexyl)isopropanesulfinylamine (10a).** From 38.5 mg (0.200 mmol) of imine **9** and 125 mg (0.401 mmol) of phenylboroxine was obtained 35.8 mg (67% yield) of sulfinylamine **10a** as an off-white solid after purification by silica gel chromatography eluting with 1:1 hexanes/EtOAc followed by 100% EtOAc. R_f = 0.20 (1:1 hexanes/EtOAc). Mp: = 99.6−100.2 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 7.26 (t, J = 8.2 Hz, 1H), 3.76 (s, NH), 2.63 (sept, J = 6.9 Hz, 1H), 2.36−2.29 (m, 1H), 2.16−2.06 (m, 2H), 2.04−1.97 (m, 1H), 1.78−1.72 (m, 1H), 1.65−1.38 (m, 5H), 1.17 (d, J = 6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.6, 128.3, 127.1, 126.8, 59.8, 55.0, 38.9, 37.4, 25.4, 22.6, 22.3, 15.5, 15.2. IR: 3445, 3186, 2929, 2859, 1448, 1035 cm^{-1}. HRMS (ESI): m/z calcd for $C_{15}H_{24}NOS$ $(M + H)^+$ 266.1573, found 266.1568.

***N*-(1-(4-Methoxyphenyl)cyclohexyl)isopropanesulfinylamine (10b).** From 38.5 mg (0.200 mmol) of imine **9** and 161 mg (0.401 mmol) of 4-methoxyphenylboroxine was obtained 50.2 mg (85% yield) of sulfinylamine **10b** as an off-white solid after purification by silica gel chromatography eluting with 1:1 hexanes/EtOAc followed by 100% EtOAc. R_f = 0.45 (EtOAc). Mp = 88.6−89.4 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 3.81 (s, 3H), 3.71 (s, NH), 2.61 (sept, J = 6.9 Hz, 1H), 2.34−2.28 (m, 1H), 2.13−2.06 (m, 2H), 2.00−1.93 (m, 1H), 1.78−1.72 (m, 1H), 1.63−1.38 (m, 5H), 1.17 (d, J = 6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.5, 136.4, 128.1, 113.5, 59.4, 55.1, 54.9, 39.1, 37.7, 25.4, 22.6, 22.4, 15.5, 15.2. IR: 3448, 3185, 2931, 2860, 1452, 1248, 1182, 1034 cm^{-1}. HRMS (ESI): m/z calcd for $C_{16}H_{26}NO_2S$ $(M + H)^+$ 296.1679, found 296.1669.

***N*-(1-(3-Methoxyphenyl)cyclohexyl)isopropanesulfinylamine (10c).** From 38.5 mg (0.200 mmol) of imine **9** and 161 mg (0.401 mmol) of 4-methoxyphenylboroxine was obtained 43.7 mg (74% yield) of sulfinylamine **10c** as an off-white solid after purification by silica gel chromatography eluting with 1:1 hexanes/EtOAc followed by 100% EtOAc. R_f = 0.45 (EtOAc). Mp = 113−114 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (t, J = 8.2 Hz, 1H), 7.09 (d, J = 8.2 Hz, 1H), 7.06 (s, 1H), 6.80 (dd, J = 8.2, 2.4 Hz, 1H), 3.81 (s, 3H), 3.76 (s, NH), 2.61 (sept, J = 6.9 Hz, 1H), 2.32−2.25 (m, 1H), 2.15−2.03 (m, 2H), 2.03−1.97 (m, 1H), 1.80−1.73 (m, 1H), 1.65−1.36 (m, 5H), 1.18 (d, J = 6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.5, 146.5, 129.2, 119.1, 113.3, 111.9, 59.8, 55.1, 54.9, 39.0, 37.4, 25.4, 22.6, 22.2, 15.4, 15.3. IR: 3455, 3188, 2931, 2859, 1451, 1243, 1037 cm^{-1}. HRMS (ESI): m/z calcd for $C_{16}H_{26}NO_2S$ $(M + H)^+$ 296.1679, found 296.1668.

***N*-(1-(4-Chlorophenyl)cyclohexyl)isopropanesulfinylamine (10d).** From 38.5 mg (0.200 mmol) of imine **9** and 167 mg (0.402 mmol) of 4-chlorophenylboroxine was obtained 29.4 mg (49% yield) of sulfinylamine **10d** as an off-white solid after purification by silica gel chromatography eluting with 1:1 hexanes/EtOAc. R_f = 0.60 (EtOAc). Mp = 128−129 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, J = 8.7 Hz, 2H), 7.31 (d, J = 8.7 Hz, 2H), 3.75 (s, NH), 2.63 (sept, J = 6.9 Hz, 1H), 2.28−2.22 (m, 1H), 2.14−2.07 (m, 1H), 2.06−1.95 (m, 2H), 1.79−1.72 (m, 1H), 1.65−1.52 (m, 3H), 1.52−1.36 (m, 2H), 1.18 (d, J = 6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.3, 133.0, 128.4, 128.3, 59.4, 55.0, 38.8, 37.5, 25.3, 22.5, 22.2, 15.4, 15.3. IR: 3460, 3200, 2928, 2859, 1494, 1451, 1033, 1010 cm^{-1}. HRMS (ESI): m/z calcd for $C_{15}H_{23}ClNOS$ $(M + H)^+$ 300.1183, found 300.1176.

***N*-(1-(3-Acetylphenyl)cyclohexyl)isopropanesulfinylamine (10e).** From 38.5 mg (0.200 mmol) of imine **9** and 176 mg (0.402 mmol) of 3-acetylphenylboroxine was obtained 30.2 mg (49% yield) of sulfinylamine **10e** as an off-white solid after purification by silica gel chromatography eluting with 1:1 hexanes/EtOAc followed by 100% EtOAc. R_f = 0.30 (EtOAc). Mp = 97−98 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (s, 1H), 7.85 (d, J = 7.7 Hz, 1H), 7.73 (d, J = 7.7 Hz, 1H), 7.46 (t, J = 7.7 Hz, 1H), 3.88 (s, NH), 2.67 (sept, J = 6.9 Hz, 1H), 2.61 (s, 3H), 2.34−2.27 (m, 1H), 2.22−2.15 (m, 1H), 2.08−2.03 (m, 2H), 1.83−1.75 (m, 1H), 1.67−1.55 (m, 3H), 1.55−1.45 (m, 1H), 1.45−1.37 (m, 1H), 1.20 (d, J = 6.9 Hz, 3H), 1.19 (d, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.1, 145.9, 137.1, 131.6, 128.5, 127.3, 126.6, 59.7, 55.1, 38.6, 37.5, 26.7, 25.2, 22.3, 22.1, 15.4, 15.3.

dx.doi.org/10.1021/jo301634y | J. Org. Chem. 2012, 77, 9593−9600

IR: 3457, 3184, 2931, 2860, 1681, 1450, 1257, 1036 cm^{-1}. HRMS (ESI): m/z calcd for $C_{17}H_{26}NO_2S$ $(M + H)^+$ 308.1679, found 308.1672.

4-(*N*-Boc-4-(4-chlorophenyl)piperidinyl)amine Hydrochloride (11). To a cooled solution of sulfinyl amide **3g** (401.0 mg, 1.00 mmol) in CPME (10 mL) at 0 °C was slowly added a 3 M HCl solution in CPME (1.0 mL, 3.00 mmol) over 10 min under a dry nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 30 min, allowed to warm to room temperature, and then stirred for an additional 1−2 h. While no solid was formed at 0 °C, a white solid precipitated at room temperature. Complete consumption of the starting material was monitored by TLC analysis. The white solid was filtered through a finely fritted filter funnel with a moderate positive pressure of nitrogen gas. The solid was then washed with CPME (10 mL). The filter funnel was directly placed under reduced pressure for 1 h. The disk of white solid on the filter funnel was transferred to a preweighed vial and was placed under a high vacuum (ca. 0.5 Torr) overnight to afford the amine hydrochloride **11** (340.5 mg, 98% yield) as a white powder. Mp = 212.8−213.4 °C. ^{1}H NMR (500 MHz, D_2O): δ 7.60 (d, J = 9.0 Hz, 2H), 7.57 (d, J = 9.0 Hz, 2H), 4.00−3.88 (m, 2H), 3.02−2.92 (m, 2H), 2.65 (dm, J = 13.7 Hz, 2H), 2.08 (ddd, J = 13.7, 11.1, 4.1 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR (125 MHz, D_2O): δ 156.1, 135.0, 133.8, 129.5, 128.4, 82.1, 56.0, 40.0 (br), 32.9, 27.5. IR: 2867, 1696, 1514, 1405, 1392, 1166 cm^{-1}. HRMS (ESI): m/z calcd for $C_{32}H_{47}Cl_2N_4O_4$ $(2M - HCl_2)^+$ 621.2969, found 621.2957.

Recycling of Sulfinyl Moiety To Yield Isopropansulfinamide (6). The filtered CPME solution from above was slowly transferred into a 28−30% aqueous ammonium hydroxide solution (approximately 4.0 N) (5 mL) at 0 °C with rapid stirring over 30 min. The mixture was stirred for 30 min at 0 °C and then was allowed to warm to room temperature with stirring for an additional 1 h. The mixture was concentrated by rotary evaporation at 40 °C (water bath temperature). Residual CPME and water were then removed under a high vacuum (approximately 0.5 Torr) to afford a crude *N*-isopropanesulfinamide as a yellow solid. The crude sulfinamide was redissolved with 10 mL of CH_2Cl_2, filtered through a finely fritted filter funnel, and washed with CH_2Cl_2 (2 × 10 mL). The filtrate was concentrated under a reduced pressure to afford a pale white solid, which was further purified by washing with a cold solution of hexanes/EtOAc (10:1) (2 × 2 mL) to regenerate analytically pure *N*-isopropanesulfinamide (98 mg, 91% yield).[12]

■ ASSOCIATED CONTENT

Supporting Information

Spectroscopic data of all new compounds shown in Schemes 3−6. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jonathan.ellman@yale.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the NSF (CHE-1049571). We also thank Dr. T. T. Lam and Edward Voss from the FT-ICR Mass Spectrometry Resource of the Keck Biotechnology Resource Laboratory for the HRMS data/results obtained.

■ REFERENCES

(1) For reviews on *N*-*tert*-butanesulfinyl imine chemistry, see: (a) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600. (b) Ferreira, F.; Botuha, C.; Chemla, F.; Perez-Luna, A. *Chem. Soc. Rev.* **2009**, *38*, 1162.

(2) For several reviews discussing the advantages of organoboron reagents, see: (a) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062. (b) Suzuki, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6723. (c) Marques, C. S.; Burke, A. J. *ChemCatChem* **2011**, *3*, 625. (d) Lautens, M.; Fagnou, K. *Chem. Rev.* **2003**, *103*, 169. (e) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(3) For Rh-catalyzed organoboron reagent additions to *N*-(*tert*-butanesulfinyl)aldimines, see: (a) Weix, D. J.; Shi, Y.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 1092. (b) Bolshan, Y.; Batey, R. A. *Org. Lett.* **2005**, *7*, 1481. (c) Beenen, M. A.; Weix, D. J.; Ellman, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 6304. (d) Truong, V. L.; Pfeiffer, J. Y. *Tetrahedron Lett.* **2009**, *50*, 1633. (e) Brak, K.; Ellman, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 3850. (f) Brak, K.; Ellman, J. A. *J. Org. Chem.* **2010**, *75*, 3147. (g) Reddy, L. R.; Gupta, A. P.; Villhauer, E.; Liu, Y. *J. Org. Chem.* **2012**, *77*, 1095.

(4) For Pd-catalyzed additions to *N*-(*tert*-butanesulfinyl)aldimines, see: Dai, H.; Lu, X. *Org. Lett.* **2007**, *9*, 3077.

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

(6) For Rh-catalyzed asymmetric additions of organoboron reagents to *N*-sulfonylketimines, see: (a) Shintani, R.; Takeda, M.; Tsuji, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 13168. (b) Shintani, R.; Takeda, M.; Soh, Y.-T.; Ito, T.; Hayashi, T. *Org. Lett.* **2011**, *13*, 2977. (c) Nishimura, T.; Noishiki, A.; Tsui, G. C.; Hayashi, T. *J. Am. Chem. Soc.* **2012**, *134*, 5056.

(7) For additions to *N*-(*tert*-butanesulfinyl)imines derived from cyclohexanone, see: (a) McMahon, J. P.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 1645. (b) Plettenburg, O.; Hofmeister, A.; Kadereit, D.; Peukert, S.; Ruf, S.; Loehn, M.; Monecke, P.; Schiffer, A.; Kannt, A.; Kohlmann, M. WO 2008077554, 2008; *Chem. Abstr.* **2008**, 2008:804743. (c) Plettenburg, O.; Lorenz, K.; Goerlitzer, J.; Loehn, M.; Biscarrat, S.; Jeannot, F.; Duclot, O. WO 2008077556, 2008; *Chem. Abstr.*, **2008**, 2008:804060. (d) Traverse, J.; Leong, W. W.; Miller, S. P.; Albaneze-Walker, J.; Hunter, T. J.; Wang, L.; Liao, H.; Arasappan, A.; Trzaska, S. T.; Smith, R. M.; Lekhal, A.; Bogen, S. L.; Kong, J.; Bennett, F.; Njoroge, F. G.; Poirier, M.; Kuo, S.-C.; Chen, Y.; Matthews, K. S.; Demonchaux, P.; Ferreira, A. WO 2011014494, 2011; *Chem. Abstr.* **2011**, 2011:145223. (e) Velazquez, F.; Sannigrahi, M.; Bennett, F.; Lovey, R. G.; Arasappan, A.; Bogen, S.; Nair, L.; Venkatraman, S.; Blackman, M.; Hendrata, S.; Huang, Y.; Huelgas, R.; Pinto, P.; Cheng, K.-C.; Tong, X.; McPhail, A. T.; Njoroge, F. G. *J. Med. Chem.* **2010**, *53*, 3075. (f) Bennett, F.; Lovey, R. G.; Huang, Y.; Hendrata, S.; Saksena, A. K.; Bogen, S. L.; Liu, Y.-T.; Njoroge, F. G.; Venkatraman, S.; Chen, K. X.; Sannigrahi, M.; Arasappan, A.; Girijavallabhan, V. M.; Velazquez, F. WO 2005087731, 2005; *Chem. Abstr.* **2005**, 2005:1026933. (g) Shiau, T. P.; Houchin, A.; Nair, S.; Xu, P.; Low, E.; Najafi, R.; Jain, R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1110. (h) Bogen, S. L.; Arasappan, A.; Velazquez, F.; Blackman, M.; Huelgas, R.; Pan, W.; Siegel, E.; Nair, L. G.; Venkatraman, S.; Guo, Z.; Doll, R.; Shih, N.-Y.; Njoroge, F. G. *Bioorg. Med. Chem.* **2010**, *18*, 1854.

(8) For additions to *N*-(*tert*-butanesulfinyl)imines derived from *N*-Boc-piperidin-4-one, see: (a) Deu, E.; Leyva, M. J.; Albrow, V. E.; Rice, M. J.; Ellman, J. A.; Bogyo, M. *Chem. Biol.* **2010**, *17*, 808. (b) Davies, T. G.; Garrett, M. D.; Boyle, R. G.; Collins, I. WO 2007125321, 2007; *Chem. Abstr.* **2007**, 2007:1275232. (d) Berdini, V.; Boyle, R. G.; Saxty, G.; Walker, D. W.; Woodhead, S. J.; Wyatt, P. G.; Caldwell, J.; Collins, I.; Da Fonseca, T. F. WO 2006046024, 2006; *Chem. Abstr.* **2006**, 2006:411957. (e) Alvaro, G.; Castiglioni, E.; Marasco, A. WO 2009133135, 2009; *Chem. Abstr.* **2009**, 2009:1363320.

(9) For additions to *N*-(*tert*-butanesulfinyl)imines derived from tetrahydropyran-4-one, see: (a) John, V.; Maillard, M.; Tucker, J. WO 2005087752, 2005; *Chem. Abstr.*, **2005**, 2005:1021744. (b) John, V.; Hom, R.; Sealy, J.; Aquino, J.; Probst, G.; Tung, J.; Fang, L. WO 2005070407, 2005; *Chem. Abstr.* **2005**, 2005:696731. (c) Nitta, A.; Fujii, H.; Sakami, S.; Nishimura, Y.; Ohyama, T.; Satoh, M.; Nakaki, J.; Satoh, S.; Inada, C.; Kozono, H.; Kumagai, H.; Shimamura, M.; Fukazawa, T.; Kawai, H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5435.

(10) (a) Fernández, I.; Valdivia, V.; Gori, B.; Alcudia, F.; Àlvarez, E.; Khiar, N. *Org. Lett.* **2005**, *7*, 1307. (b) Fernández, I.; Valdivia, V.; Khiar, N. *J. Org. Chem.* **2008**, *73*, 745.

(11) The corresponding *N*-(propanesulfinyl)imine was also initially explored; however, under all conditions tested, the yields for the Rh-catalyzed addition were lower than those obtained for the *N*-(isopropanesulfinyl)imine.
(12) García Ruano, J. L.; Alemán, J.; Fajardo, C.; Parra, A. *Org. Lett.* **2005**, *7*, 5493.
(13) For previous reports on the recycling of the *tert*-butanesulfinyl group, see: Wakayama, M.; Ellman, J. A. *J. Org. Chem.* **2009**, *74*, 2646.
(14) For leading references on CPME, see: (a) Antonucci, V.; Coleman, J.; Ferry, J. B.; Johnson, N.; Mathe, M.; Scott, J. P.; Xu, J. *Org. Process Res. Dev.* **2011**, *15*, 939. (b) Watanabe, K.; Yamagiwa, N.; Torisawa, Y. *Org. Process Res. Dev.* **2007**, *11*, 251.