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Asymmetric Synthesis of Protected α-Amino Boronic Acid Derivatives with an Air- and Moisture-Stable Cu(II) Catalyst

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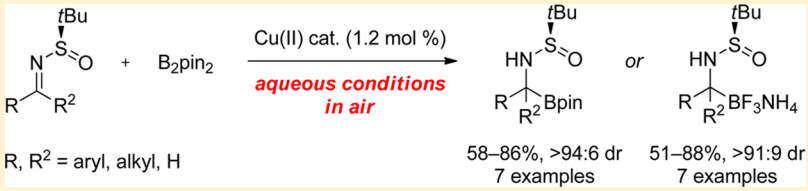
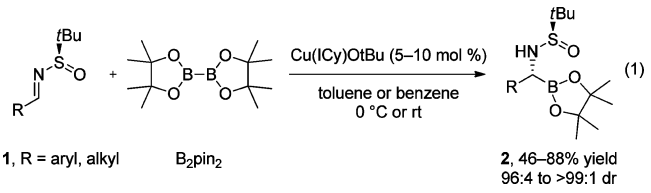
Supporting Information



ABSTRACT: The asymmetric borylation of *N*-*tert*-butanesulfinyl imines with bis(pinacolato)diboron is achieved using a Cu(II) catalyst and provides access to synthetically useful and pharmaceutically relevant α-amino boronic acid derivatives. The Cu(II)-catalyzed reaction is performed on the benchtop in air at room temperature using commercially available, inexpensive reagents at low catalyst loadings. A variety of *N*-*tert*-butanesulfinyl imines, including ketimines, react readily to provide α-sulfinamido boronate esters in good yields and with high stereoselectivity. In addition, this transformation is applied to the straightforward, telescoped synthesis of α-sulfinamido trifluoroborates.

α-Amino boronic acids have significant utility as pharmacophores for protease inhibition as best exemplified by the cancer drug bortezomib (Velcade).[1] More recently, α-amino boronic acid derivatives have also been shown to be competent coupling partners in transition-metal-catalyzed reactions, providing convergent, asymmetric assembly of chiral amine products.[2,3] These applications have inspired the development of a number of methods for the asymmetric synthesis of α-amino boronic acid derivatives.[4−8] We previously reported the Cu(I)-catalyzed asymmetric borylation of *N*-*tert*-butanesulfinyl imines with bis(pinacolato)diboron[9] to provide one of the most efficient asymmetric methods to prepare homochiral α-amino boronic acid derivatives (eq 1).[4,10] However, the utility of this



methodology was limited by the Cu(I) catalyst, which is particularly air- and moisture-sensitive and necessitated use of a glovebox. Thus, we sought to develop a catalyst system with improved stability to air and moisture.

Parallel to our efforts, Sun and co-workers have reported a metal-free, *N*-heterocyclic carbene (NHC) catalyzed method that proceeds open to air and without need for rigorous drying, providing facile entry to α-sulfinamido boronate esters in good yield and with moderate to excellent diastereoselectivity.[6] However, this method suffers from relatively high loading (10 mol %) of 1,3-bis(1-naphthyl)benzimidazolium chloride, which is not commercially available, as the catalyst and provides modest yield and selectivity in the borylation of *N*-*tert*-butanesulfinyl ketimines. We instead chose to develop a Cu(II) catalyst system, in response to a number of recent reports of Cu(II)-catalyzed conjugate borylation, which takes place in water and open to air.[11−15] Herein, we report the first Cu(II)-catalyzed borylation of *N*-*tert*-butanesulfinyl imines for the asymmetric synthesis of protected α-amino boronic acids. The reaction proceeds under aqueous conditions in air at room temperature and consequently is extremely convenient to perform. Moreover, the reaction proceeds at very low loading of $CuSO_4$ and PCy_3 with the ligand introduced as the commercially available and completely air-stable HBF_4 salt.

Our investigation began with the borylation of imine **1a** (Table 1). In water and with picoline as an additive, conditions initially developed by Santos and co-workers for the borylation of α,β-unsaturated ketones and esters,[12] we observed good reactivity but poor diastereoselectivity (entry 1). Using instead a biphasic toluene/H_2O system greatly improved the diastereoselectivity, with a 5:1 toluene/H_2O ratio providing optimal selectivity (entries 2 and 3). Notably, the sense of induction for this transformation was opposite that of our previously reported Cu(I) system.[4] A range of tertiary, secondary, and primary amine additives (e.g., entries 4−6) provided results similar to those observed with 4-picoline. However, only benzylamine afforded marked improvement (entry 7).

Both NHC and phosphorus ligands have previously been utilized in Cu(I)-catalyzed borylations of α,β-unsaturated systems, aldehydes, and imines.[4,10,16−18] Thus, a number of

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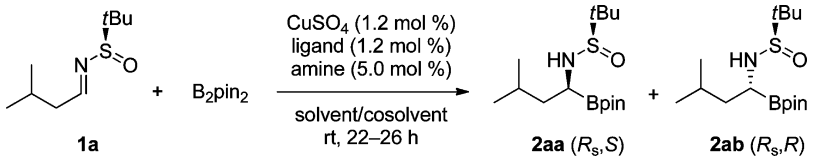
Table 1. Evaluation of Reaction Parameters[a]



entry	solvent/cosolvent	base	ligand	yield[b] (%)	dr[c] (2aa:2ab)
1[d]	H_2O	4-picoline	none	41	1:1
2	1:5 toluene/H_2O	4-picoline	none	34	5:1
3	5:1 toluene/H_2O	4-picoline	none	29	>9:1
4	5:1 toluene/H_2O	Et_3N	none	35	>9:1
5	5:1 toluene/H_2O	piperidine	none	27	>9:1
6	5:1 toluene/H_2O	$CyNH_2$	none	38	>9:1
7	5:1 toluene/H_2O	$BnNH_2$	none	51	>9:1
8	5:1 toluene/H_2O	$BnNH_2$	ICy·HBF_4	46	4:1
9	5:1 toluene/H_2O	$BnNH_2$	$P(OPh)_3$	85 (46[e])	95:5
10[f]	5:1 toluene/H_2O	$BnNH_2$	$P(OPh)_3$	0[g]	
11	5:1 toluene/H_2O	none	$P(OPh)_3$	4	>9:1
12	5:1 toluene/H_2O	$BnNH_2$	PCy_3	94	10:90
13	5:1 toluene/H_2O	$BnNH_2$	$POCy_3$	31	92:8
14	5:1 toluene/H_2O	$BnNH_2$	PCy_3·HBF_4	89 (84[e])	6:94
15[h]	5:1 toluene/H_2O	$BnNH_2$	PCy_3·HBF_4	84	6:94
16[f]	5:1 toluene/H_2O	$BnNH_2$	PCy_3·HBF_4	0[g]	
17	5:1 toluene/H_2O	none	PCy_3·HBF_4	92	6:94
18	5:1 toluene/H_2O	none	PEt_3·HBF_4	16	15:85
19	5:1 toluene/H_2O	none	$PtBu_3$·HBF_4	66	5:95

[a]Reagents and conditions: **1a** (1.0 equiv), B_2pin_2 (2.0 equiv), $CuSO_4$ (1.2 mol %), ligand (1.2 mol %), amine (5.0 mol %) in solvent (0.42 M). [b]Determined by ^1H NMR of crude material relative to 1,3,5-trimethoxybenzene as an external standard. [c]Based on ^1H NMR of crude material. [d]Reaction time of 3 h. [e]Isolated yield after column chromatography. [f]Reaction conducted in the absence of $CuSO_4$. [g]No product observed by ^1H NMR. [h]Reaction conducted with $CuSO_4$ (0.6 mol %), PCy_3·HBF_4 (0.6 mol %), and $BnNH_2$ (2.5 mol %).

potential ligands were next evaluated (entries 8–19). The NHC that we previously employed in our Cu(I)-catalyzed imine borylation[4] failed to improve the yield and resulted in diminished diastereoselectivity (entry 8). However, phosphorus ligands demonstrated more promising results, with $P(OPh)_3$ providing the α-sulfinamido boronate ester with excellent conversion and good diastereoselectivity (entry 9).[19] From a mechanistic perspective, both $CuSO_4$ and $BnNH_2$ were essential; reactions conducted without either of these components resulted in no more than trace product (entries 10 and 11).

Among the commercially available phosphines evaluated, the electron-rich phosphine PCy_3 afforded the highest yield and diastereoselectivity (entry 12). Still, variability in yield and stereoselectivity was observed for this ligand likely due to its contamination with phosphine oxide,[20] which could diminish the yield and erode the diastereoselectivity (entry 13). Therefore, the commercially available, air-stable HBF_4 salt served as the more convenient ligand source (entry 14). It is noteworthy that the sense of induction for this addition was opposite that observed with $P(OPh)_3$ (entry 9), which highlights the importance of the phosphorus ligand for controlling asymmetric induction. Because diastereomer **2ab** was more stable than diastereomer **2aa** to chromatographic isolation (compare entries 9 and 14), we chose to employ PCy_3·HBF_4 in further studies.

A number of experiments were conducted to probe the $CuSO_4$/PCy_3·HBF_4 catalyst system. First, a comparable yield and selectivity of **2ab** were obtained when the catalyst loading was dropped 2-fold to 0.6 mol % (entry 15). Consistent with this high catalyst activity, variable but significant background reaction (15–51% yield, ≥95:5 dr) was observed in the absence of exogenous $CuSO_4$. However, rigorous exclusion of trace copper as well as other metal contaminants by use of new vials, stir bars, and high-purity water (total ion concentration 30 ppb) demonstrated that addition of $CuSO_4$ is important for achieving an effective catalyst system (entry 16).[21] Although benzylamine was necessary when $P(OPh)_3$ was employed (entry 11), it was not essential for the PCy_3·HBF_4 system (entry 17). However, in exploration of the scope, benzylamine proved beneficial particularly in the borylation of more challenging substrates (vida infra). The less and more hindered electron-rich trialkylphosphine salts PEt_3·HBF_4 and $PtBu_3$·HBF_4 were also investigated but exhibited lower selectivity and/or yield (entries 18 and 19).[22]

Finally, varying the ligand to copper ratio established that ≥1:1 stoichiometry is optimal (Table 2). Using excess copper resulted in comparable yield but diminished diastereoselectivity (entry 1) likely arising from the competitive ligand-free reaction. When excess ligand was employed, the yields and selectivity remained comparable to those observed with a 1:1 ratio (entries 2–4).

The scope of the reaction with respect to the *N*-*tert*-butanesulfinyl imine substrates was next explored (Table 3). A variety of alkyl imines reacted readily under the optimized conditions to afford the desired α-sulfinamido boronate esters; products possessing α- and β-branching (**2ab** and **2b**) as well as linear alkyl chains (**2c**) could be prepared in good yield and with high diastereoselectivity. Highlighting the functional group compatibility of this method, a carboxybenzyl-protected amine was compatible with the reaction conditions (**2d**). Aryl imines also reacted readily under these conditions, with para and ortho

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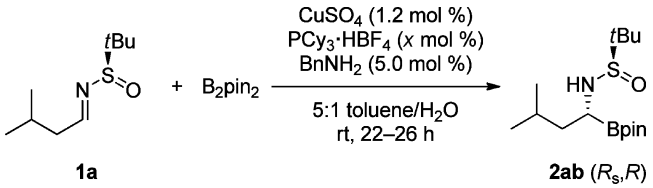
Table 2. Effect of the Ligand:Cu(II) Ratio[a]



1a **2ab** (R_s,R)

entry	$CuSO_4$/PCy_3	yield[b] (%)	dr[c]
1	2:1	89	75:25
2	1:1	88	94:6
3	1:2	89	93:7
4	1:4	91	95:5

[a]Reagents and conditions: **1a** (1.0 equiv), B_2pin_2 (2.0 equiv), $CuSO_4$ (1.2 mol %), PCy_3·HBF_4 (0.76–4.8 mol %), $BnNH_2$ (5.0 mol %) in solvent (0.42 M). [b]Determined by ^{1}H NMR of crude material relative to 1,3,5-trimethoxybenzene as an external standard. [c]Based on ^{1}H NMR of crude material.

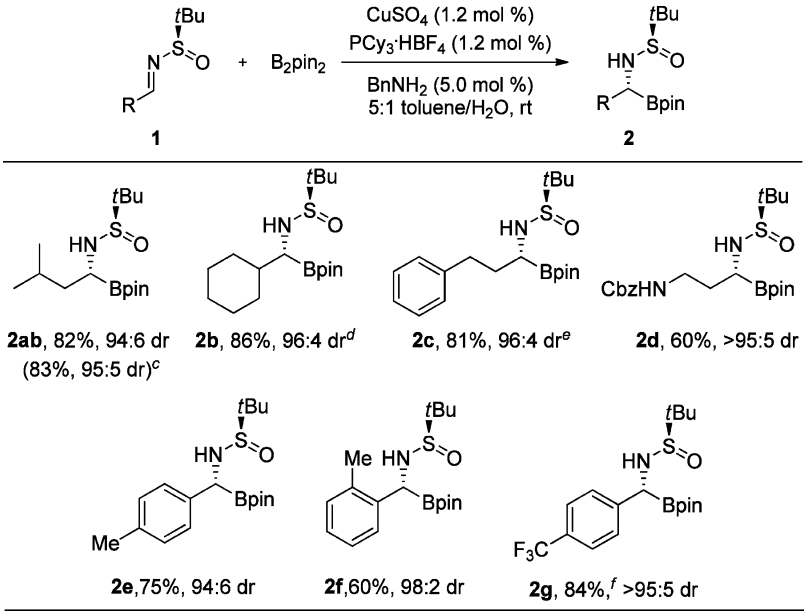
substitution being well tolerated (**2e** and **2f**, respectively). Finally, the reaction tolerated the electron-deficient trifluoromethyl substituent (**2g**). For boronate ester **2g**, the NMR rather than an isolated yield is reported as a measure of reaction efficiency because highly electron-deficient benzyl boronate esters partially degrade during chromatographic isolation.[4]

Given the improved stability of trifluoroborates over the corresponding boronate esters[23−25] and our interest in α-sulfinamido trifluoroborates as coupling partners in transition-metal-catalyzed reactions,[3] we also developed a telescoped synthesis of these reagents employing the newly developed Cu(II) catalyst system (Table 4). Importantly, all steps in this process are tolerant of aqueous conditions and can be set up on the benchtop in air. The trifluoroborates **3a**, **3b**, and **3c** could be isolated in yields comparable to those of the corresponding boronate esters (see Table 3, compounds **2ab**, **2e**, and **2f**). Additionally, electron-rich and electron-poor functionalities, including the methoxy, chloro, and trifluoromethyl groups, were compatible with this reaction sequence, providing the products in good yield and selectivity (**3d**−**3f**). While electron-rich **3d** was isolated in moderate yield, the corresponding potassium salt **3d′** was isolated in excellent yield via precipitation, demonstrating that chromatographic isolation and not poor reactivity was responsible for the diminished yield of this ammonium trifluoroborate. Additionally, the trifluoromethyl-substituted trifluoroborate (**3f**), which was not stable to chromatographic isolation as the corresponding boronate ester (**2g**), could be isolated in good yield.

N-tert-Butanesulfinyl ketimines also react readily at higher concentration (1.2 M compared to 0.42 M), and this method represents the first highly diastereoselective borylation of this substrate class. Dialkyl *N-tert*-butanesulfinyl ketimine **4a** could be readily borylated to provide the protected α,α-disubstituted α-amino boronate ester **5a** in moderate yield but with good selectivity (Scheme 1). Additionally, α,α-disubstituted α-amino trifluoroborate **6** could be synthesized in good yield and excellent diastereoselectivity (Scheme 2). Notably, in the absence of $BnNH_2$, a significantly lower yield of **6** was observed due to poor conversion to intermediate **5b** in the borylation step.

In conclusion, we have developed an air- and moisture-tolerant Cu(II) catalyst system for the borylation of *N-tert*-butanesulfinyl imines. The borylation of aldimines occurs at low catalyst loadings (1.2 mol %) and provides α-amino boronic acid derivatives in good yield and stereoselectivity. In addition, the corresponding α-sulfinamido trifluoroborates can be prepared in good yield through a telescoped sequence. Finally, we have demonstrated the first highly diastereoselective borylation of *N-tert*-butanesulfinyl ketimines to provide access

Table 3. Substrate Scope of the Cu(II)-Catalyzed Borylation[a,b]



1 **2**

2ab, 82%, 94:6 dr (83%, 95:5 dr)[c] **2b**, 86%, 96:4 dr[d] **2c**, 81%, 96:4 dr[e] **2d**, 60%, >95:5 dr

2e,75%, 94:6 dr **2f**,60%, 98:2 dr **2g**, 84%,[f] >95:5 dr

[a]Reagents and conditions: **1** (1.0 equiv), B_2pin_2 (2.0 equiv), $CuSO_4$ (1.2 mol %), PCy_3·HBF_4 (1.2 mol %), $BnNH_2$ (5.0 mol %) in 5:1 toluene/H_2O (0.42 M). [b]Unless noted, isolated yield of mixture of diastereomers after column chromatography. Diastereomeric ratio determined by ^{1}H NMR of the crude product. [c]Reaction conducted without $BnNH_2$; see the Experimental Section for details. [d]Reaction conducted from 0 °C to rt; see the Experimental Section for details. [e]Diastereomeric ratio determined upon isolation. [f]Determined by ^{1}H NMR relative to 1,3,5-trimethoxybenzene as an external standard. Product could not be isolated via silica gel chromatography.

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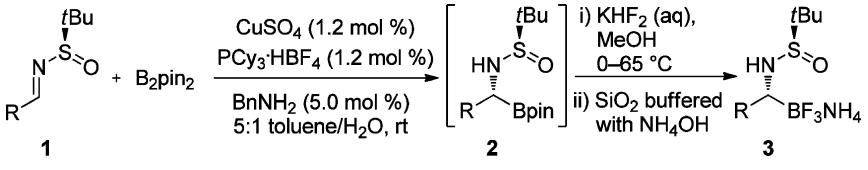
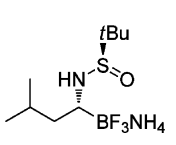
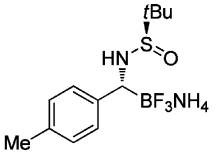
Table 4. Substrate Scope for the Telescoped Synthesis of α-Sulfinamido Trifluoroborates[a,b]



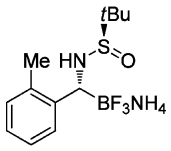
1 2 3



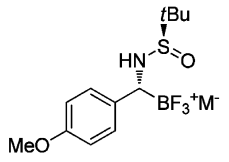
3a, 87%, 94:6 dr



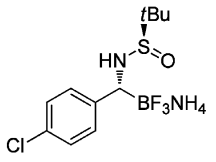
3b, 88%, 94:6 dr (85%, 94:6 dr)[c]



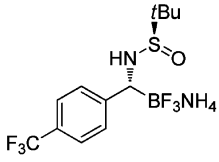
3c, 62%, >95:5 dr



M = NH_4 **3d**, 51%, 91:9 dr
K **3d'**, 78%, 91:9 dr[d]



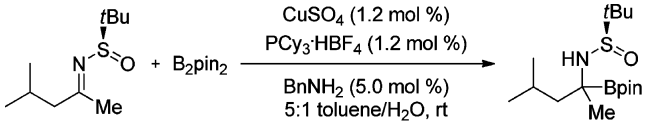
3e,78%, 97:3 dr



3f,73%, >95:5 dr

[a]For detailed reaction conditions, see the Experimental Section. [b]Isolated yield of mixture of diastereomers after column chromatography. Diastereomeric ratio determined by ^{1}H NMR of the crude boronate ester. [c]Reaction conducted without $BnNH_2$; see the Experimental Section for details. [d]Product isolated as the potassium trifluoroborate via precipitation.

Scheme 1. Borylation of a Dialkyl *N*-*tert*-Butanesulfinyl Ketimine



4a **5a**, 58%, 94:6 dr

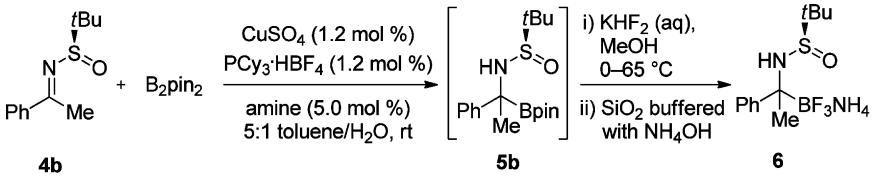
to the corresponding trisubstituted organoboron compounds in good to moderate yield and with good selectivity.

EXPERIMENTAL SECTION

General Experimental Methods. Unless otherwise noted, imine substrates **1** were prepared using previously reported methods.[26,27] Bis(pinacolato)diboron was recrystallized from pentane prior to use. Toluene was passed through a column of activated alumina under nitrogen; it could be collected and stored on the benchtop in a glass bottle for >1 month without the reactivity being affected. All other reagents were obtained from commercial suppliers and used without further purification. Aqueous solutions of $CuSO_4$ were prepared from $CuSO_4{\cdot}5H_2O$ and deionized water. Unless noted, all reactions were set up on the benchtop and were *not* set up under an inert atmosphere or using dried glassware. Reactions conducted in 1 dram vials were capped with polypropylene caps equipped with PTFE/silicone septa. Unless noted, diastereomeric ratios were determined by ^{1}H NMR of the crude boronate ester. Products were isolated as a mixture of diastereomers. NMR spectra were obtained at room temperature. Chemical shifts are reported in parts per million relative to the peak for $CHCl_3$ (7.26 ppm for ^{1}H and 77.2 ppm for ^{13}C) or DMSO (2.50 ppm for ^{1}H and 39.5 ppm for ^{13}C). C_6F_6 (−162.5 ppm in DMSO-d_6) was used to standardize ^{19}F NMR chemical shifts. ^{11}B NMR spectra in DMSO-d_6 are reported uncorrected. IR spectra were collected on an FT-IR spectrometer possessing an ATR attachment with an anvil; only partial data are provided. Melting points are reported uncorrected. High-resolution mass spectrometry (HRMS) was performed using electrospray ionization (ESI) on a time-of-flight (TOF) mass spectrometer.

*(R,E)-Benzyl (3-((tert-Butanesulfinyl)imino)propyl)carbamate (**1d**).* The reaction was conducted in flame-dried glassware under an inert atmosphere. A round-bottom flask was charged with a magnetic stir bar, 3-[(benzyloxycarbonyl)amino]propionaldehyde (0.251 g, 1.21 mmol), (*R*)-(+)-*tert*-butanesulfinamide (0.29 g, 2.4 mmol), pyridinium *p*-toluenesulfonate (17.5 mg, 0.0696 mmol), and magnesium sulfate (0.74 g, 6.1 mmol). CH_2Cl_2 (2.4 mL) was then added, and the resulting suspension was stirred rapidly for 17 h. The reaction mixture was then filtered through Celite, rinsing with CH_2Cl_2. The resulting solution was concentrated under reduced pressure. Purification by flash chromatography (silica gel, 30% EtOAc/CH_2Cl_2) afforded imine

Scheme 2. Telescoped Synthesis of an α,α-Disubstituted α-Sulfinamido Trifluoroborate



4b **5b** **6**

With $BnNH_2$ 84%, >95:5 dr
Without $BnNH_2$ 11%, >95:5 dr

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1d (0.329 g, 88%) as a clear oil. Analytical data were consistent with those of previous literature reports.[28]

*Pinacol (S)-1-((R)-tert-Butanesulfinamido)-3-methylbutylboronate (**2aa**).* To a 1 dram vial equipped with a magnetic stir bar were added a solution of $P(OPh)_3$ in toluene (0.10 mL, 100 mM, 6.0 μmol), aqueous $CuSO_4$ (0.20 mL, 30 mM, 6.0 μmol), and benzylamine (2.7 μL, 25 μmol), sequentially. The vial was capped, and the catalyst mixture was stirred for 10 min. The vial was uncapped, and a solution of aldimine **1a** (94.7 mg, 0.500 mmol) in toluene (0.90 mL) and then bis(pinacolato)diboron (254 mg, 1.00 mmol, 1.2 equiv) were added. The vial was recapped, and the mixture was stirred rapidly for 22 h. The reaction mixture was diluted with EtOAc and filtered through a deactivated silica gel plug (100:35 SiO_2/H_2O) eluting with EtOAc. The resulting solution was concentrated under reduced pressure. The crude material was purified by *rapid* column chromatography on deactivated silica gel (100:35 silica/H_2O) eluting with 5−15% EtOAc/CH_2Cl_2 to provide **2aa** as a clear oil (73.0 mg, 46%). IR: 2956, 1365, 1331, 1143, 1067 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.45 (d, J = 4.5 Hz, 1H), 3.07 (m, 1H), 1.77 (m, 1H), 1.46 (m, 2H), 1.24 (s, 12H), 1.20 (s, 9H), 0.89 (d, J = 6.6 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 84.2, 55.4, 41.4, 24.9, 24.8, 24.7, 22.8, 22.7, 22.2. HRMS: m/z calcd for $C_{15}H_{33}BNO_3S$ $[M + H]^+$, 318.2269; found, 318.2245.

General Procedure for Borylation of *N*-*tert*-Butanesulfinyl Aldimines. To a 1 dram vial charged with $PCy_3{\cdot}HBF_4$ (2.2 mg, 6.0 μmol, 1.2 mol %) and equipped with a magnetic stir bar were added toluene (0.10 mL), aqueous $CuSO_4$ (0.20 mL, 30 mM, 6.0 μmol, 1.2 mol %), and benzylamine (2.7 μL, 25 μmol, 5.0 mol %), sequentially. The vial was capped, and the catalyst mixture was stirred for 10 min. The vial was uncapped, and then toluene (0.90 mL), the appropriate aldimine (0.500 mmol, 1.0 equiv), and bis(pinacolato)diboron (254 mg, 1.00 mmol, 2.0 equiv) were added. The reaction vial was recapped, and the reaction mixture was stirred rapidly for 20−24 h. The reaction mixture was diluted with EtOAc and filtered through a deactivated silica gel plug (100:35 SiO_2/H_2O) eluting with EtOAc. The resulting solution was concentrated under reduced pressure. The product was isolated by *rapid* silica gel chromatography on deactivated silica gel (100:35 SiO_2/H_2O) using EtOAc/CH_2Cl_2 mixtures. Products were visualized on TLC via UV and CMA or $KMnO_4$ stain. CMA stain was prepared by dissolving ammonium molybdate (25 g) and $Ce(SO_4)_2$ (5 g) in H_2O (450 mL) and then *slowly* adding concd H_2SO_4 (50 mL).

*Pinacol (R)-1-((R)-tert-Butanesulfinamido)-3-methylbutylboronate (**2ab**).* The general procedure was followed with aldimine **1a** (95.1 mg, 0.502 mmol). The crude material was purified by column chromatography on deactivated silica gel eluting with 10−20% EtOAc/CH_2Cl_2 to yield the desired product **2ab** as a white solid (131 mg, 82%). Analytical data were consistent with those of previous literature reports.[4]

Without Benzylamine. The general procedure was followed with aldimine **1a** (94.7 mg, 0.500 mmol) except benzylamine was not added. The crude material was purified by column chromatography on deactivated silica gel eluting with 10−20% EtOAc/CH_2Cl_2 to yield the desired product **2ab** as an off-white solid (132 mg, 83%). Analytical data were consistent with those of previous literature reports.[4]

*Pinacol (R)-1-((R)-tert-Butanesulfinamido)-cyclohexylmethylboronate (**2b**).* The general procedure was followed with (*R*,*E*)-*N*-(cyclohexylmethylene)-2-methylpropane-2-sulfinamide (**1b**) (106 mg, 0.494 mmol) except the vial was placed in a 0 °C bath before addition of B_2pin_2. The bath was allowed to come to room temperature over the course of the reaction. The crude material was purified by column chromatography on deactivated silica gel eluting with 15% EtOAc/CH_2Cl_2 to yield the desired **2b** product as a white solid (146 mg, 86%). Analytical data were consistent with those of previous literature reports.[4]

*Pinacol (R)-1-((R)-tert-Butanesulfinamido)-2-phenylpropylboronate (**2c**).* The general procedure was followed with (*R*,*E*)-2-methyl-*N*-(3-phenylpropylidene)propane-2-sulfinamide (**1c**) (119 mg, 0.500 mmol). The crude material was purified by column chromatography on deactivated silica gel eluting with 15−25% EtOAc/CH_2Cl_2. Mixed fractions were combined and purified by a second column eluting with 15−25% EtOAc/CH_2Cl_2. The desired product **2c** was isolated as a white solid (149 mg, 81%). Analytical data were consistent with those of previous literature reports.[4]

*Pinacol (R)-3-(((Benzyloxy)carbonyl)amino)-1-((R)-tert-butanesulfinamido)propylboronate (**2d**).* The general procedure was followed with aldimine **1d** (195 mg, 0.628 mmol) and bis(pinacolato)diboron (321 mg, 1.26 mmol). The catalyst and solvent were scaled accordingly: aqueous $CuSO_4$ (0.25 mL, 30 mM, 7.5 μmol), $PCy_3{\cdot}HBF_4$ (2.8 mg, 7.5 μmol), benzylamine (3.4 μL, 31 μmol), and toluene (1.23 mL). The crude material was purified by column chromatography on deactivated silica gel eluting with 30−50% EtOAc/CH_2Cl_2 to yield the desired product **2d** as a light brown oil (169 mg, 60%). IR: 3283, 2977, 1704, 1141, 1041 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.38−7.25 (m, 5H), 5.47 (s, 1H), 5.12 (d, J = 12.3 Hz, 1H), 5.05 (d, J = 12.3 Hz, 1H), 3.47−3.26 (m, 3H), 3.11 (dd, J = 13.9, 6.6 H z, 1H), 2.03−1.95 (m, 1H), 1.90−1.76 (m, 1H), 1.24 (s, 15H), 1.20 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.6, 136.9, 128.5, 128.1, 128.0, 84.4, 66.6, 56.2, 41.4 (br), 38.7, 32.8, 25.1, 24.7, 22.7. HRMS: m/z calcd for $C_{42}H_{70}B_2N_4NaO_{10}S_2^+$ $[2M + Na]^+$, 899.4612; found, 899.4599.

*Pinacol (R)-((R)-tert-Butanesulfinamido)(4-methylphenyl)-methylboronate (**2e**).* The general procedure was followed with (*R*,*E*)-2-methyl-*N*-(4-methylbenzylidene)propane-2-sulfinamide (**1e**) (112 mg, 0.500 mmol). The crude material was purified by column chromatography on deactivated silica gel eluting with 5−15% EtOAc/CH_2Cl_2. Mixed fractions were combined and purified by a second column eluting with 5−15% EtOAc/CH_2Cl. The desired product **2e** was isolated as a white solid (132 mg, 75%). Analytical data were consistent with those of previous literature reports.[10]

*Pinacol (R)-((R)-tert-Butanesulfinamido)(2-methylphenyl)-methylboronate (**2f**).* The general procedure was followed with (*R*,*E*)-2-methyl-*N*-(2-methylbenzylidene)propane-2-sulfinamide (**1f**) (112 mg, 0.502 mmol). The crude material was purified by column chromatography on deactivated silica gel eluting with 5−15% EtOAc in CH_2Cl_2. Mixed fractions were combined and purified by a second column on deactivated silica gel eluting with 2.5%−10% EtOAc/CH_2Cl_2 to yield the desired product **2f** as a white solid (106 mg, 60%). Mp: >80 °C dec. IR: 2983, 1344, 1139, 1064 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, J = 7.2 Hz, 1H), 7.19−7.13 (m, 1H), 7.13−7.10 (m, 2H), 4.48 (d, J = 3.9 Hz, 1H), 3.50 (d, J = 3.9 Hz, 1H), 2.37 (s, 3H), 1.22 (s, 9H), 1.18 (s, 6H), 1.14 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 138.5, 135.8, 130.6, 127.8, 126.8, 126.3, 84.3, 56.4, 43.8 (br), 24.8, 24.4, 22.8, 19.9. HRMS: m/z calcd for $C_{18}H_{31}BNO_3S^+$ $[M + H]^+$, 352.2112; found, 352.2137.

General Procedure for the Telescoped Synthesis of α-Sulfinamido Trifluoroborates. *Cu(II)-Catalyzed Borylation.* To a 1 dram vial charged with $PCy_3{\cdot}HBF_4$ (2.2 mg, 6.0 μmol, 1.2 mol %) and equipped with a magnetic stir bar were added toluene (0.10 mL), aqueous $CuSO_4$ (0.20 mL, 30 mM, 6.0 μmol, 1.2 mol %), and benzylamine (2.7 μL, 25 μmol, 5.0 mol %), sequentially. The vial was capped, and the catalyst mixture was stirred for 10 min. The vial was uncapped, and then toluene (0.90 mL), the appropriate aldimine (0.500 mmol, 1.0 equiv), and bis(pinacolato)diboron (254 mg, 1.00 mmol, 2.0 equiv) were added. The reaction vial was recapped, and the reaction mixture was stirred rapidly for 20−24 h. The reaction mixture was diluted with EtOAc and filtered through a silica gel plug (100:35 silica/H_2O) eluting with EtOAc. The resulting solution was concentrated under reduced pressure to afford the crude boronate ester.

Trifluoroborate Formation. To a 100 mL round-bottom flask containing the crude boronate ester and a magnetic stir bar was added MeOH (5.0 mL). The resulting solution was cooled to 0 °C, and aqueous KHF_2 (1.8 mL, ∼4.5M, 8.1 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and then heated to 65 °C. The reaction mixture was stirred for 1 h and subsequently cooled to room temperature. The reaction mixture was concentrated by rotary evaporation and then high vacuum overnight. The resulting solid was triturated with acetone (∼45 mL) to remove inorganic salts, and the filtrate was concentrated by rotary evaporation. The ammonium trifluoroborate was isolated by silica gel chromatog-

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raphy using CH_2Cl_2/MeOH/NH_4OH mixtures and visualized on TLC by UV and $KMnO_4$ stain.

*Ammonium (R)-1-((R)-tert-Butanesulfinamido)-3-methylbutyltrifluoroborate (**3a**).* The general procedure was followed with aldimine **1a** (95.1 mg, 0.502 mmol). The crude trifluoroborate was purified by silica gel chromatography eluting with 99:10:1 to 44:10:1 CH_2Cl_2/MeOH/NH_4OH to yield the desired product **3a** as a white solid (121 mg, 87%). Mp: >90 °C dec. IR: 3267, 2952, 1449, 992, 929 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6): δ 7.08 (br s, 4H), 3.27 (d, J = 7.1 Hz, 1H), 2.09 (s, 1H), 1.90−1.80 (m, 1H), 1.26−1.19 (m, 1H), 1.17−1.06 (m, 1H), 1.03 (s, 9H), 0.81 (d, J = 6.6 Hz, 3H), 0.79 (d, J = 6.6 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 55.0, 44.0, 24.2, 24.0, 22.3, 22.2.[24] ^{19}F NMR (376 MHz, DMSO-d_6): major, δ −145.5; minor, δ −146.3. ^{11}B NMR (128 MHz, DMSO-d_6): δ 3.57. HRMS: m/z calcd for $C_9H_{24}BF_2N_2OS^+$ $[M - F]^+$, 257.1665; found, 257.1692.

*Ammonium (R)-((R)-tert-Butanesulfinamido)(4-methylphenyl)methyltrifluoroborate (**3b**).* The general procedure was followed with **1e** (112 mg, 0.500 mmol). The crude trifluoroborate was purified by silica gel chromatography eluting with 99:10:1 to 44:10:1 CH_2Cl_2/MeOH/NH_4OH to yield the desired product **3b** as a white solid (137 mg, 88%). Analytical data were consistent with those of previous literature reports.[3]

Without Benzylamine. The general procedure was followed with aldimine **1e** (112 mg, 0.500 mmol) except benzylamine was not added during the Cu(II)-catalyzed borylation. The crude trifluoroborate was purified by silica gel chromatography eluting with 99:10:1 to 44:10:1 CH_2Cl_2/MeOH/NH_4OH to yield the desired product **3b** as a white solid (132 mg, 85%). Analytical data were consistent with those of previous literature reports.[3]

*Ammonium (R)-((R)-tert-Butanesulfinamido)(2-methylphenyl)methyltrifluoroborate (**3c**).* The general procedure was followed with **1f** (111 mg, 0.497 mmol). The crude trifluoroborate was purified by silica gel chromatography eluting with 99:10:1 to 44:10:1 CH_2Cl_2/MeOH/NH_4OH to yield the desired product **3c** as a white solid (95.3 mg, 62%). Analytical data were consistent with those of previous literature reports.[3]

*Ammonium (R)-((R)-tert-Butanesulfinamido)(4-methoxyphenyl)methyltrifluoroborate (**3d**).* The general procedure was followed with (*R*,*E*)-*N*-(4-methoxybenzylidene)-2-methylpropane-2-sulfinamide (**1g**) (121 mg, 0.506 mmol). The crude trifluoroborate was purified by silica gel chromatography eluting with 99:10:1 to 44:10:1 CH_2Cl_2/MeOH/NH_4OH to yield the desired product **3d** as a white solid (84.1 mg, 51%). Mp: >70 °C dec. IR: 3275, 2965, 1510, 1441, 1243, 970 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 7.08 (apparent d, J = 8.2 Hz, 6H), 6.71 (d, J = 8.5 Hz, 2H), 3.98 (d, J = 5.0 Hz, 1H), 3.69 (s, 3H), 3.21 (s, 1H), 1.07 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 156.2, 139.7, 127.8, 112.4, 55.3, 54.9, 22.1.[29] ^{19}F NMR (376 MHz, DMSO-d_6): δ −145.4. ^{11}B NMR (128 MHz, DMSO-d_6): δ 2.94. HRMS: m/z calcd for $C_{12}H_{22}BF_2N_2O_2S^+$ $[M - F]^+$, 307.1458; found, 307.1462.

*Potassium (R)-((R)-tert-Butanesulfinamido)(4-methoxyphenyl)methyltrifluoroborate (**3d′**).* The general procedure was followed with **1g** (479 mg, 2.00 mmol) and bis(pinacolato)diboron (1.02 g, 4.00 mmol). The catalyst, reagents, and solvent were scaled accordingly: aqueous $CuSO_4$ (0.80 mL, 30 mM, 24 μmol), $PCy_3{\cdot}HBF_4$ (8.7 mg, 24 μmol), benzylamine (10.9 μL, 0.100 mmol), toluene (4.0 mL), KHF_2 (7.1 mL, ∼4.5 M, 32 mmol), and MeOH (20 mL). The crude trifluoroborate was dissolved in CPME (22 mL), pentane (50 mL), and acetone (10 mL). The volatile components of the solvent were removed by rotary evaporation. To the remaining solution was added pentane (50 mL), resulting in the precipitation of a white solid. The solid was collected via filtration with a fine-fritted funnel, washing with pentane (3 × 30 mL). Until the final wash, the entirety of the solvent was not allowed to pass through the frit; doing so resulted in the formation of an oily solid, which was difficult to manipulate. Upon evaporation of trace solvent, the product **3d′** was obtained as a powdery, white solid (542 mg, 78%). Analytical data were consistent with those of previous literature reports.[3]

*Ammonium (R)-((R)-tert-Butanesulfinamido)(4-chlorophenyl)methyltrifluoroborate (**3e**).* The general procedure was followed with (*R*,*E*)-*N*-(4-chlorobenzylidene)-2-methylpropane-2-sulfinamide (**1h**) (123 mg, 0.505 mmol). The crude trifluoroborate was purified by silica gel chromatography eluting with 99:10:1 to 44:10:1 CH_2Cl_2/MeOH/NH_4OH to yield the desired product **3e** as a white solid (130 mg, 78%). Mp: >90 °C dec. IR: 3272, 2967, 1440, 976 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 7.23−7.14 (m, 4H), 7.08 (br s, 4H), 4.13 (d, J = 5.2 Hz, 1H), 3.29 (s, 1H), 1.08 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 147.0, 128.5, 128.0, 126.7, 55.5, 22.1.[29] ^{19}F NMR (376 MHz, DMSO-d_6): δ −145.6. ^{11}B NMR (128 MHz, DMSO-d_6): δ 2.68. HRMS: m/z calcd for $C_{11}H_{19}BClF_2N_2OS^+$ $[M - F]^+$, 311.0968; found, 311.0956.

*Ammonium (R)-((R)-tert-Butanesulfinamido)(4-(trifluoromethyl)phenyl)methyltrifluoroborate (**3f**).* The general procedure was followed with (*R*,*E*)-*N*-(4-(trifluoromethyl)benzylidene)-2-methylpropane-2-sulfinamide (**1i**) (123 mg, 0.505 mmol) except the Cu(II)-catalyzed borylation was worked up after 1 h. The crude trifluoroborate was purified by silica gel chromatography eluting with 99:10:1 to 44:10:1 CH_2Cl_2/MeOH/NH_4OH to yield the desired product **3f** as a white solid (135 mg, 73%). Mp: >130 °C dec. IR: 3283, 2968, 1322, 996, 845 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 7.47 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.11 (br s, 4H), 4.23 (d, J = 5.0 Hz, 1H), 3.42 (s, 1H), 1.09 (s, 9H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 153.36, 127.19, 125.0 (q, J = 272 Hz), 124.4 (q, J = 32 Hz), 123.7 (q, J = 4.5 Hz), 55.61, 22.12.[29] ^{19}F NMR (376 MHz, DMSO-d_6): δ −60.1 (s, 3F), −145.6 (br s, 3F). ^{11}B NMR (128 MHz, DMSO-d_6): δ 2.74. HRMS: m/z calcd for $C_{12}H_{15}BF_5NNaOS^+$ $[M - NH_4F + Na]^+$, 350.0780; found, 350.0755.

*Pinacol 1-((R)-tert-Butanesulfinamido)-4-methylpentyl-2-boronate (**5a**).* To a 1 dram vial charged with $PCy_3{\cdot}HBF_4$ (2.2 mg, 6.0 μmol) were added toluene (35 μL), aqueous $CuSO_4$ (67 μL, 90 mM, 6.0 μmol), and benzylamine (2.7 μL, 25 μmol), sequentially. The vial was capped, and the catalyst mixture was stirred for 10 min. The vial was uncapped, and then ketimine **4a** (102 mg, 0.500 mmol) in toluene (0.30 mL) and bis(pinacolato)diboron (254 mg, 1.00 mmol) were added. The reaction vial was recapped, and the reaction mixture was stirred rapidly for 24 h. The reaction mixture was diluted with EtOAc and filtered through a deactivated silica gel plug (100:35 SiO_2/H_2O) eluting with EtOAc. The resulting solution was concentrated under reduced pressure. The crude product was purified by *rapid* silica gel chromatography on deactivated silica gel (100:35 SiO_2/H_2O) eluting with 0−10−20% EtOAc/CH_2Cl_2 to yield the desired product **5a** as a clear oil (95.9 mg, 58%). IR: 2955, 1325, 1136, 1065, 833 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.64 (s, 1H), 1.78−1.69 (apparent d, J = 11.2 Hz, 2H), 1.45 (dd, J = 14.9, 9.7 Hz, 1H), 1.38 (s, 3H), 1.24 (s, 12H), 1.20 (s, 9H), 0.89 (d, J = 6.3 Hz, 3H), 0.86 (d, J = 6.3 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 84.4, 55.9, 47.5, 26.9, 25.0, 24.83, 24.77, 24.2, 23.0, 22.8. HRMS: m/z calcd for $C_{16}H_{35}BNO_3S^+$ $[M + H]^+$, 332.2425; found, 332.2397. To ascertain the diastereomeric ratio, the authentic diastereomers were prepared as previously described.[30] Diagnostic peaks in ^1H NMR (600 MHz, $CDCl_3$): major, δ 3.66 (s, 1H, NH) 1.38 (s, 3H, CH_3); minor, δ 3.24 (s, 1H, NH), 1.31 (s, 3H, CH_3).

*Ammonium 1-((R)-tert-Butanesulfinamido)-1-phenylethyltrifluoroborate (**6**).* To a 1 dram vial charged with $PCy_3{\cdot}HBF_4$ (2.2 mg, 6.0 μmol) and equipped with a magnetic stir bar were added toluene (35 μL), aqueous $CuSO_4$ (67 μL, 90 mM, 6.0 μmol), and benzylamine (2.7 μL, 25 μmol, 5.0 mol %), sequentially. The vial was capped, and the catalyst mixture was stirred for 10 min. The vial was uncapped, and then ketimine **4b** (112 mg, 0.500 mmol) in toluene (0.30 mL) and bis(pinacolato)diboron (254 mg, 1.00 mmol) were added. The reaction vial was recapped, and the reaction mixture was stirred rapidly for 24 h. The reaction mixture was diluted with EtOAc and filtered through a deactivated silica gel plug (100:35 SiO_2/H_2O) eluting with EtOAc. The resulting solution was concentrated under reduced pressure to afford the crude boronate ester. To a 100 mL round-bottom flask containing the crude boronate ester and a magnetic stir bar was added MeOH (5.0 mL). The resulting solution was cooled to 0 °C, and aqueous KHF_2 (1.8 mL, ∼4.5 M, 8.1 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and then heated to 65 °C. The reaction mixture was stirred for 1 h and subsequently cooled to room temperature. The

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reaction mixture was concentrated by rotary evaporation and then high vacuum overnight. The resulting solid was triturated with acetone (~45 mL) to remove inorganic salts, and the filtrate was concentrated by rotary evaporation. The crude trifluoroborate was purified by silica gel chromatography eluting with 99:10:1 to 44:10:1 CH_2Cl_2/MeOH/NH_4OH to yield the desired product **6** as a white solid (130 mg, 84%).

Without Benzylamine. The aforementioned procedure was followed with ketimine **4b** (112 mg, 0.500 mmol) except benzylamine was not added during the Cu(II)-catalyzed borylation. The crude trifluoroborate was purified by silica gel chromatography eluting with 99:10:1 to 44:10:1 CH_2Cl_2/MeOH/NH_4OH to yield the desired product **6** as a white solid (17.0 mg, 11%). Mp: >70 °C dec. IR: 3266, 2964, 1443, 1167, 978, 701 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 7.30 (d, J = 7.9 Hz, 2H), 7.17−7.04 (m, 6H), 6.95 (t, J = 7.2 Hz, 1H), 3.76 (s, 1H), 1.48 (s, 3H), 1.07 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 149.9, 127.4, 126.3, 123.2, 54.5, 24.9, 22.6.[29] ^{19}F NMR (376 MHz, DMSO-d_6): δ −151.4. ^{11}B NMR (128 MHz, DMSO-d_6): δ 3.06. HRMS: m/z calcd for $C_{12}H_{19}BF_2NOS^+$ $[M - NH_4F + H]^+$, 274.1243; found, 274.1244.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectroscopic data for all compounds shown in Tables 3 and 4 and Schemes 1 and 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(19) Isolation of boronate ester **2aa** was possible, but a low isolated yield was obtained due to the apparent instability of this diastereomer to silica gel chromatography.

(20) In commercial PCy_3 that had been stored on the benchtop, a signal corresponding to $POCy_3$ was observed by ^{31}P NMR.

(21) A number of other commercially available Cu(II) salts (e.g., $CuCl_2$, $Cu(OAc)_2$, and CuO) were also investigated as copper sources, and while many were capable of catalyzing the reaction, none proved superior to $CuSO_4$.

(22) Stoichiometry of the $CuSO_4$/$PtBu_3$ system was also evaluated. Improved yield but comparable diastereoselectivity was observed with a 1:2 ratio of $CuSO_4$/$PtBu_3$·HBF_4 (78%, 6:94 dr).

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