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Improving Carbene–Copper-Catalyzed Asymmetric Synthesis of α-Aminoboronic Esters Using Benzimidazole-Based Precursors

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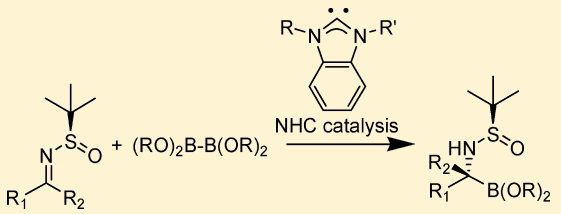
Supporting Information

ABSTRACT: By using a benzimidazole core and N-substitutions to tune the electronic properties of the corresponding N-heterocyclic carbenes, a one-pot protocol for efficient synthesis of α-aminoboronic esters without the need of a glovebox was developed in this work. The starting materials for the transformation can also be extended from aldehydes to ketones. An alternative protocol with short reaction time using preformed carbene–copper chloride is also described.



Recently, the use of α-aminoboronic acid as a key pharmacophore in the design of protease inhibitors has attracted increasing attention. For example, bortezomib is an FDA-approved anticancer drug that contains a C-terminal α-aminoboronic acid moiety and targets 26S proteasome.[1−5] For the development of antidiabetic drugs, α-aminoboronic acid has been incorporated in inhibitors that target dipeptidyl peptidase 4.[6−9] An early stereoselective synthetic method for α-aminoboronic acid, via Matteson's protocol, starts from alkylboronic acid.[10] However, the lack of commercially available alkylboronic acids limits the practical application of this method. A major breakthrough in asymmetric synthesis of α-aminoboronic acid was achieved by the Ellman group. The Ellman protocol utilized Sadighi's catalyst[11] to facilitate direct addition of a boryl group, generated from bis(pinacolato)-diboron (B_2pin_2), to *N*-butanesulfinyl aldimines.[12] Activation of boron reagents for addition to double bonds in either 1,2 and 1,4 fashion has also attracted increased research attention.[13−22] In a related study,[23] α-chloroboronic esters were prepared through catalytic hydrogenation of borolane-substituted vinylic chlorides. A more recent advance for direct borylation of *N*-sulfonyl-protected aldimines used phosphine activation, and stereoselectivity was achieved through chiral phosphines.[24] Although the Ellman method has a great advantage over Matteson's approach in using widely available aldehydes as starting materials to form sulfinyl aldimines and has excellent stereocontrol due to the use of chiral *N*-butanesulfinyl activation/protection, it also has its own drawbacks as the reaction has to be carried out in a glovebox due to the preparation, storage, and handling of Sadighi's catalyst. In continuation to our studies with N-heterocyclic carbenes,[25] we report herein an improved protocol for asymmetric synthesis of α-aminoboronic esters by tuning the properties of NHC catalysts.

Sadighi's catalyst is an imidazole-based N-heterocyclic carbene (NHC)–copper complex (from ligand precursor **2**; see Figure 1). NHCs are widely used as transition metal ligands for catalysis in modern organic synthesis.[26−33] To improve upon Ellman's protocol, we reasoned that tuning the NHC ligand property would most likely lead to efficient catalysts that allow the desired reactions to occur under normal laboratory moisture- and oxygen-free conditions, for example, in a one-pot setting so that one can avoid preparation and storage of the active catalysts. For a given NHC, there are logically two major areas one can modify to achieve significant impact on its electronic properties: one is the substitutions on the nitrogen atoms of the central ring, and the other is the substitution on

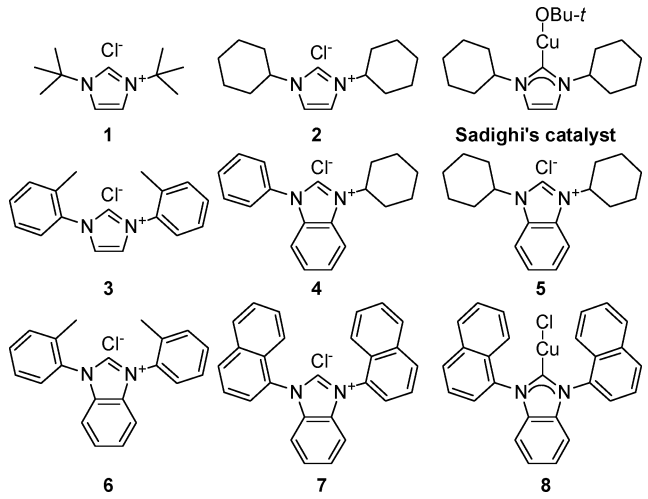


Figure 1. NHC ligand precursors **1**–**7**, Sadighi's catalyst, and NHC–Cu–Cl complex **8**.

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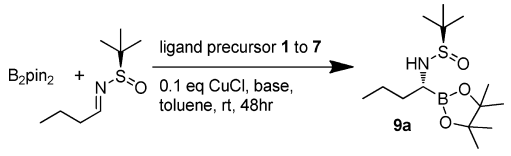
the central N-heterocyclic ring itself. Therefore, we chose to investigate precursors (**1**–**7**) by varying (a) either an alkyl or an aromatic substitution on the nitrogen and/or (b) a benzimidazole central ring to alter the electronic features of carbenes when generated with base treatment. Initial screening of reaction conditions with B_2pin_2 is summarized in Table 1.

Table 1. Screening NHCs for One-Pot Synthesis of α-Aminoboronic Esters



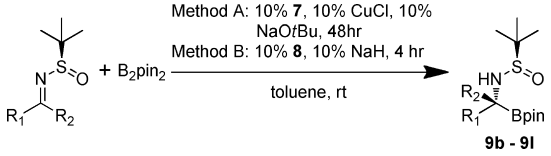
entry	ligand precursor	base	yield[a]
1	0.1 equiv of **1**	0.1 equiv of NaOtBu	none
2	0.1 equiv of **2**	0.1 equiv of NaOtBu	none
3	0.1 equiv of **2**	0.2 equiv of NaOtBu	18%
4	0.1 equiv of **3**	0.1 equiv of NaOtBu	23%
5	0.1 equiv of **3**	0.2 equiv of NaOtBu	45%
6	0.1 equiv of **4**	0.1 equiv of NaOtBu	65%
7	0.1 equiv of **5**	0.1 equiv of NaOtBu	none
8	0.1 equiv of **6**	0.1 equiv of NaOtBu	52%
9	0.1 equiv of **7**	0.1 equiv of NaOtBu	88%

[a]Isolated yield at 2 mmol scale.

In Ellman's original report, benzene was the optimal solvent. Using toluene led to a significant drop in yields. However, considering the disadvantages of benzene and in anticipation that our new catalyst may improve the reaction sufficiently, we tested the reactions in less toxic toluene. As shown in Table 1, the imidazole-based ligand precursor **2** corresponding to the original Sadighi's catalyst did not produce desirable results under our screening conditions with 1 equiv of base. When 2 equiv of base was used to facilitate the generation of Sadighi's catalyst, a low yield of 18% was achieved without the use of a glovebox to isolate the pure catalytic agent. An NHC precursor with an imidazole core and two aromatic N-substitutions (**3**) gave moderate product yields depending on the amount of base used (23–45%, entries 4 and 5). NHC precursor **5** with a benzimidazole core and two *N*-cyclohexyl substitutions did not perform well either. A benzimidazole core plus at least one N-aromatic substitution (precursors **4**, **6**, and **7**) gave better outcomes with precursor **7** producing desirable yields in toluene. From this initial screening, it can be concluded that aromatic substitution on at least one nitrogen atom in the NHC is critical for efficient catalysis in this one-pot protocol. A fused benzene ring to the imidazole core also improves catalytic efficiency.

It is notable that most of the screening conditions only involve the use of 1 equiv of base to generate NHC from the precursor; as a consequence, Sadighi's catalyst (NHC–copper *t*-butoxide) or its benzimidazole analogues may not form significantly during the reaction (although one may not completely rule out this possibility due to the heterogeneous nature of the reaction). To investigate if NHC–Cu chloride could catalyze the reaction as it may be the most likely intermediate in our 1 equiv base protocol, we isolated such

Table 2. Additional Examples of α-Aminoboronic Esters Using Two Protocols



entry	R_1	R_2	product	yield[a] (method)	dr[b]
1	$(CH_3)_3C-$	H	**9b**	86% (A) 89% (B)	>99:1
2	$(CH_3)_2CHCH_2-$	H	**9c**	89% (A) 90% (B)	99:1
3	(4-MeO-Ph) $CH_2O(CH_2)_3-$	H	**9d**	83% (A) 85% (B)	>99:1
4	$PhCH_2-$	H	**9e**	85% (A) 88% (B)	98:2
5	(4-F-Ph)CH_2-	H	**9f**	88% (A) 91% (B)	99:1
6	4-Me-Ph–	H	**9g**	82% (A) 84% (B)	>99:1
7	4-Cl-Ph–	H	**9h**	79% (A) 86% (B)	>99:1
8	4-MeO-Ph–	H	**9i**	80% (A) 85% (B)	99:1
9	naphtha-2-yl–	H	**9j**	75% (A) 83% (B)	98:2
10	Ph–	CH_3	**9k**	48% (A) 56% (B)	71:29
11	CH_3CH_2-	CH_3	**9l**	66% (A) 75% (B)	74:26

[a]Isolated yield in 2 mmol scale reaction. [b]Diastereomeric ratio measurements are described in the main text.

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species (compound **8** from precursor **7**, Figure 1) in a glovebox. However, incubation of **8** with diboron and an aldimine did not lead to the formation of the desired product. The product was only formed with the addition of more base (additional 1 or more equiv to NHC) including a non-nucleophilic base such as NaH. This certainly ruled out the formation of the Sadighi's catalyst but may suggest that, if a catalytic intermediate such as NHC−Cu−B(pin) is formed,[11,12,22] base activation of diboron is still required. More detailed studies of the reaction mechanism are currently underway. One significant difference between the NHC−Cu chloride protocol and our one-pot protocol is that using preformed NHC−Cu chloride and additional base allowed the entire reaction can to be complete in a few hours rather than 48 h in the one-pot protocol. Isolated yields using the two methods are very similar (in 2 mmol scale for **9a**, 88% for one-pot and 92% for preformed **8** with NaH).

Additional examples of asymmetric synthesis of α-aminoboronic esters are listed in Table 2, using precursor **7** to generate NHC in situ for the one-pot 48 h protocol (method A) or using preformed **8** for a 4 h protocol (method B). These examples cover a wide variety of functional groups in the *N-tert*-butanesulfinyl aldimine substrates. Entries 1−5 cover aliphatic aldimines. For those substrates, using either protocol gave comparable results with yields generally in the 80−90% range. Entries 6−9 cover aromatic substrates. In these cases, using method B with preformed NHC−Cu chloride and shorter reaction time produced slightly better results. Although the overall yields are slightly worse than with aliphatic substrates, we did not suffer much significant loss in product stability as reported by the Ellman group.[12] Entries 10 and 11 cover substrates derived initially from ketones rather than aldehydes with moderate yields (48−75%). Ellman's initial report did not cover ketimine substrates, although one would expect the catalytic system to work with ketimines with less efficiency due to the lower electrophilic properties of ketimines than aldimines. We now confirmed this with experimental data.

Similar to the original Ellman report, the stereoselectivity of this NHC−Cu-catalyzed reaction was high for aldimine substrates. We measured the diastereoselectivity ratio of the reaction using the method reported by the Ellman group.[12] For all aldimine substrates (entries 1−9), the diastereoselectivity ratios are greater than 98:2. For the two ketimine substrates (entries 10 and 11), the diastereoselectivity ratios dropped to around 70:30 in the worst case. This drop in stereospecificity with ketimine substrates was not unexpected as the size difference between the two groups on a ketimine moiety would be smaller than that of an aldimine.

In summary, by changing the electronic properties of NHC as a ligand to a copper complex, we were able to find new benzimidazole-based NHC precursors that allow the establishment of a simplified one-pot protocol for the NHC−copper-catalyzed asymmetric synthesis of α-aminoboronic esters without the use of a glovebox to isolate the catalytic agent. This new procedure is applicable to a range of aromatic and aliphatic *N*-sulfinyl aldimine or ketimine substrates, which can be generated from widely available aldehydes or ketones. We expect the new NHC precursors will offer improved access to α-aminoboronic esters in drug discovery and industrial applications.

EXPERIMENTAL SECTION

Purification of Raw Materials. Toluene was refluxed with sodium under argon before use. CuCl was dissolved in concentrated hydrochloric acid and then recrystallized from the solution after water was added.

Representative Procedure with Ligand Precursor 7 for Product 9a. (Method A): Under argon, ligand precursor **7** (81 mg, 0.2 mmol) was mixed with CuCl (20 mg, 0.2 mmol) and NaOBu-*t* (19 mg, 0.2 mmol) in 10 mL of toluene. The mixture was stirred at room temperature for 4 h, during which time the reaction solution turned from colorless to green then to light black color. To this were then added in one portion a solution of *N-tert*-butylsulfinyl butaldimine (350 mg, 2.0 mmol) and bis(pinacolato)diboron (559 mg, 2.2 mmol) in 10 mL of toluene. The reaction was stirred under argon at room temperature for 48 h. Then the solution was diluted with 30 mL of ethyl acetate and quenched with saturated K_2CO_3 solution. After separation and washing the aqueous layer with ethyl acetate (2 × 30 mL), the combined organic solution was dried over anhydrous Na_2SO_4 and then concentrated. Purification using water-inactivated silica gel (CH_2Cl_2/MeOH as eluent) gave **9a** as colorless oil: 533 mg (yield 88%); ^{1}H NMR (400 MHz, CD_3OD, δ) 2.97 (t, J = 7.2 Hz, 1H), 1.66 (m, 2H), 1.45 (m, 2H), 1.29 (d, J = 3.2 Hz, 12H), 1.23 (s, 9H), 0.96 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD, δ) 83.9, 55.9, 43.4, 35.3, 23.9, 23.6, 21.6, 19.6, 13.1; MS (ESI-TOF) m/z 304.2 $[M + H]^+$; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{14}H_{31}BNSO_3$ 304.2112; found 304.2117.

Preparation of Catalyst 8.[34] In a nitrogen-filled glovebox, a round-bottomed flask equipped with a Teflon-coated stir bar was charged with copper(I) chloride (1.30 g, 13.13 mmol) and sodium *tert*-butoxide (1.20 g, 12.53 mmol). Tetrahydrofuran (100 mL) was added, and the mixture was stirred for 2 h. 1,3-Bis(2,6-dinaphthyl)-imidazolinium chloride[25] (4.87 g, 12 mmol) was added, and the mixture was stirred for an additional 12 h. The mixture was filtered through Celite, washed with dichloromethane (5 × 30 mL), and then transferred out of glovebox to dry in vacuo to give the title complex (4.77g, 85%). Final product was transferred back and stored in the glovebox: ^{1}H NMR (400 MHz, DMSO-d_6, δ) 8.31 (d, J = 8.4 Hz, 2H), 8.25 (dd, J_1 = 4.8 Hz, J_2 = 8.0 Hz, 2H), 8.14 (d, J = 7.2 Hz, 1H), 8.03 (d, J = 6.8 Hz, 1H), 7.84 (m, 2H), 7.73 (m, 2H), 7.64 (m, 4H), 7.41 (m, 2H), 7.14 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, δ) 135.1, 134.5, 133.7, 133.6, 131.0, 131.0, 129.7, 129.5, 129.2, 129.1, 128.6, 128.4, 127.7, 127.7, 127.2, 127.1, 126.4, 126.4, 125.6, 125.5, 122.8, 122.6, 112.8. Anal. Calcd for $C_{27}H_{18}ClCuN_2$: C, 69.08; H, 3.86. Found: C, 68.94; H, 3.99.

Representative Procedure with Preformed 8 for Product 9a. (Method B): In a glovebox filled with nitrogen, *N-tert*-butylsulfinyl butaldimine (350 mg, 2.0 mmol) was mixed with bis(pinacolato)-diboron (559 mg, 2.2 mmol), complex **8** (94 mg, 0.2 mmol), and NaH (5 mg, 0.2 mmol) in 10 mL of toluene. The reaction vessel was sealed and then transferred out of the glovebox. The reaction was stirred at room temperature for 4 h. Then the solution was diluted with 30 mL of ethyl acetate and quenched with saturated K_2CO_3 solution. After separation and washing the aqueous layer with ethyl acetate (2 × 30 mL), the combined organic solution was dried over anhydrous Na_2SO_4 and then concentrated. Purification using water-inactivated silica gel (CH_2Cl_2/MeOH as eluent) gave **9a** as colorless oil: 558 mg (yield 92%).

Representative Procedure for the Determination of Diastereomeric Ratio of Product 9a. Compound **9a** was dissolved in dioxane in an oven-dried vial equipped with a Teflon-coated stir bar under nitrogen. Freshly distilled MeOH (10 equiv) was added to the solution, followed by the dropwise addition of 4.0 M HCl in dioxane (1 equiv). The reaction mixture was stirred at rt for 45 min to 1 h before it was directly concentrated under reduced pressure. The resulting amine hydrochloride salt was triturated with a 2:1 mixture of hexanes to Et_2O. The amine hydrochloride (1.0 equiv) was then dissolved in CH_2Cl_2 and cooled to 0 °C. DIPEA (4.0 equiv) was then added followed by the addition of >99% ee (+) or >99% (−) MTPA chloride (~2.0 equiv), and the resulting mixture was stirred for 1 h at 0 °C. The reaction mixture was diluted with EtOAc and then washed with 1 N sodium bisulfate. The organic layer was then washed with 1 N $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated. Diastereomeric ratios were determined by ^{19}F NMR of

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the unpurified material,[35,36] dr > 99:1, and the diastereomeric ratio was determined by ^{19}F NMR (376 MHz, DMSO-d_6): (*R*)-MTPA derivative of major diastereomer δ = −68.42, minor diastereomer δ = −68.56.

9b: White solid; 545 mg (yield 86%); mp 98.6−100.7 °C (method A); 564 mg (yield 89%) (method B); dr > 99:1; ^{19}F NMR (376 MHz, DMSO-d_6) (*R*)-MTPA derivative of major diastereomer δ = −68, minor diastereomer δ = −68.16; ^{1}H NMR (400 MHz, DMSO-d_6, δ) 4.31 (d, *J* = 8.0 Hz, 1H), 2.54 (d, *J* = 8.0 Hz, 1H), 1.22 (d, *J* = 2.4 Hz, 12H), 1.10 (s, 9H), 0.93 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6, δ) 83.9, 56.2, 54.1, 34.2, 28.1, 25.2, 24.9, 22.9; MS (ESI-TOF) *m*/*z* 318.2 [M + H]$^+$; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{33}BNSO_3$ 318.2269; found 318.2266.

9c: White solid; 564 mg (yield 89%); mp 153.4−154.9 °C (method A); 570 mg, (yield 90%) (method B); dr = 99:1; ^{19}F NMR (376 MHz, DMSO-d_6) (*R*)-MTPA derivative of major diastereomer δ = −68.51, minor diastereomer δ = −68.56; ^{1}H NMR (400 MHz, DMSO-d_6, δ) 4.67 (d, *J* = 6.0 Hz, 1H), 2.80 (dd, J_1 = 8.0 Hz, J_2 = 14.4 Hz, 1H), 1.67 (m, 1H), 1.41 (m, 2H), 1.19 (d, *J* = 5.2 Hz, 12H), 1.09 (s, 9H), 0.86 (dd, J_1 = 6.8 Hz, J_2 = 2.4 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6, δ) 83.7, 55.6, 42.2, 25.4, 25.1, 24.8, 23.1, 23.1, 23.0; MS (ESI-TOF) *m*/*z* 318.2 [M + H]$^+$; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{33}BNSO_3$ 318.2269; found 318.2274.

9d: Colorless oil; 729 mg (yield 83%) (method A); 746 mg (yield 85%) (method B); dr > 99:1; ^{19}F NMR (376 MHz, DMSO-d_6) (*R*)-MTPA derivative of major diastereomer δ = −68.55, minor diastereomer δ = −68.63; ^{1}H NMR (400 MHz, DMSO-d_6, δ) 7.24 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 4.77 (d, *J* = 6.4 Hz, 1H), 4.36 (s, 2H), 3.74 (s, 3H), 3.36 (m, 2H), 2.76 (d, *J* = 6.4 Hz, 1H), 1.57 (m, 4H), 1.19 (d, *J* = 2.8 Hz, 12H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6, δ) 159.1, 131.1, 129.5, 114.1, 83.8, 71.9, 69.7, 55.4, 55.5, 42.4, 29.8, 27.1, 25.1, 24.8, 23.1; MS (ESI-TOF) *m*/*z* 440.2 [M + H]$^+$; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{39}BNSO_5$ 440.2637; found 440.2640.

9e: Colorless oil; 597 mg (yield 85%) (method A); 618 mg (yield 88%) (method B); dr = 98:2; ^{19}F NMR (376 MHz, DMSO-d_6) (*R*)-MTPA derivative of major diastereomer δ = −68.34, minor diastereomer δ = −68.45; ^{1}H NMR (400 MHz, DMSO-d_6, δ) 7.24 (m, 5H), 4.83 (d, *J* = 5.2 Hz, 1H), 3.07 (m, 1H), 2.95 (m, 1H), 2.79 (m, 1H), 1.10 (s, 15H), 1.04 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6, δ) 139.2, 129.6, 128.6, 126.7, 83.8, 55.7, 55.4, 43.6, 25.1, 24.7, 23.0; MS (ESI-TOF) *m*/*z* 352.2 [M + H]$^+$; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{31}BNSO_3$ 352.2112; found 352.2118.

9f: Light yellow oil; 649 mg (yield 88%) (method A); 672 mg (yield 91%) (method B); dr = 99:1, ^{19}F NMR (376 MHz, DMSO-d_6) (*R*)-MTPA derivative of major diastereomer δ = −68.41, minor diastereomer δ = −68.49; ^{1}H NMR (400 MHz, DMSO-d_6, δ) 7.25 (dd, J_1 = 8.4 Hz, J_2 = 6.0 Hz, 2H), 7.10 (dd, J_1 = 9.2 Hz, J_2 = 2.4 Hz, 2H), 4.90 (d, *J* = 5.6 Hz, 1H), 3.05 (m, 1H), 2.92 (m, 1H), 2.78 (m, 1H), 1.11 (s, 6H), 1.08 (s, 9H), 1.04 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6, δ) 161.3, 135.4, 131.4, 115.2, 83.8, 55.7, 43.8, 38.2, 25.1, 24.7, 23.0; MS (ESI-TOF) *m*/*z* 370.2 [M + H]$^+$; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{30}BNSO_3F$ 370.2018; found 370.2015.

9g: Colorless oil; 576 mg (yield 82%) (method A); 590 mg (yield 84%) (method B); dr > 99:1; ^{19}F NMR (376 MHz, DMSO-d_6) (*R*)-MTPA derivative of major diastereomer δ = −68.21, minor diastereomer δ = −68.71; ^{1}H NMR (400 MHz, DMSO-d_6, δ) 7.20 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 5.33 (d, *J* = 4.2 Hz, 1H), 4.01 (d, *J* = 4.2 Hz, 1H), 2.27 (s, 3H), 1.13 (s, 15H), 1.10 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6, δ) 138.2, 135.7, 129.2, 127.6, 84.0, 56.1, 46.8, 24.9, 24.5, 23.2, 21.1; MS (ESI-TOF) *m*/*z* 352.2 [M + H]$^+$; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{31}BNSO_3$ 352.2112; found 352.2110.

9h: White solid; 586 mg (yield 79%); mp 85.6−87.5 °C (method A); 638 mg (yield 86%) (method B); dr > 99:1; ^{19}F NMR (376 MHz, DMSO-d_6) (*R*)-MTPA derivative of major diastereomer δ = −68.58, minor diastereomer δ = −68.89; ^{1}H NMR (400 MHz, DMSO-d_6, δ) 7.36 (m, 4H), 5.57 (d, *J* = 5.6 Hz, 1H), 4.08 (d, *J* = 5.6 Hz, 1H), 1.14 (s, 15H), 1.12 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6, δ) 104.7, 131.3, 129.4, 128.5, 84.3, 56.2, 46.8, 24.9, 24.5, 23.1; MS (ESI-TOF) *m*/*z* 372.2 [M + H]$^+$; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{28}BNSClO_3$ 372.1566; found 372.1574.

9i: Colorless oil; 587 mg (yield 80%) (method A); 624 mg (yield 85%) (method B); dr = 99:1; ^{19}F NMR (376 MHz, DMSO-d_6) (*R*)-MTPA derivative of major diastereomer δ = −68.53, minor diastereomer δ = −68.80; ^{1}H NMR (400 MHz, DMSO-d_6, δ) 7.23 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.27 (d, *J* = 5.2 Hz, 1H), 3.99 (d, *J* = 5.2 Hz, 1H), 3.72 (s, 3H), 1.13 (s, 15H), 1.11 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6, δ) 158.4, 133.1, 128.9, 114.1, 84.0, 56.1, 55.5, 46.8, 24.9, 24.5, 23.1; MS (ESI-TOF) *m*/*z* 368.2 [M + H]$^+$; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{31}BNSO_4$ 368.2061; found 368.2054.

9j: Colorless oil; 581 mg (yield 75%) (method A); 642 mg (yield 83%) (method B); dr = 98:2; ^{19}F NMR (376 MHz, DMSO-d_6) (*R*)-MTPA derivative of major diastereomer δ = −68.38, minor diastereomer δ = −68.45; ^{1}H NMR (400 MHz, DMSO-d_6, δ) 8.08 (m, 1H), 7.92 (m, 1H), 7.80 (m, 1H), 7.66 (m, 1H), 7.53 (m, 4H), 5.55 (d, *J* = 5.6 Hz, 1H), 4.76 (d, *J* = 5.6 Hz, 1H), 1.18 (s, 9H), 1.08 (d, *J* = 9.6 Hz, 12H); ^{13}C NMR (100 MHz, DMSO-d_6, δ) 137.6, 133.7, 130.8, 129.0, 127.2, 126.2, 126.0, 125.3, 123.9, 84.3, 56.3, 43.8, 24.9, 24.5, 23.2; MS (ESI-TOF) *m*/*z* 388.2 [M + H]$^+$; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{31}BNSO_3$ 388.2112; found 388.2120.

9k: Colorless oil; 318 mg (yield 48%) (method A); 371 mg (yield 56%) (method B); dr = 71:29; ^{19}F NMR (376 MHz, DMSO-d_6) (*R*)-MTPA derivative of major diastereomer δ = −68.81, minor diastereomer δ = −69.16; ^{1}H NMR (400 MHz, DMSO-d_6, δ) 7.40 (m, 2H), 7.31 (m, 2H), 7.18 (m, 1H), 5.18 (s, 0.34H), 5.15 (s, 0.51H), 1.64 (s, 1.22H), 1.58 (s, 1.78H), 1.20 (s, 9H), 1.16 (s, 12H), 1.13 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6, δ) 146.2, 146.1, 128.3, 128.2, 127.2, 126.3, 126.2, 84.4, 84.2, 56.7, 55.8, 25.0, 24.9, 24.9, 24.6, 24.4, 23.4, 23.2; MS (ESI-TOF) *m*/*z* 352.2 [M + H]$^+$; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{31}BNSO_3$ 352.2112; found 352.2119.

9l: Colorless oil; 374 mg (yield 66%) (method A); 425 mg (yield 75%) (method B); dr = 74:26; ^{19}F NMR (376 MHz, DMSO-d_6) (*R*)-MTPA derivative of major diastereomer δ = −68.64, minor diastereomer δ = −68.88; ^{1}H NMR (400 MHz, DMSO-d_6, δ) 4.34 (s, 0.65H), 1.63 (m, 1H), 1.51 (m, 1H), 1.21 (d, *J* = 3.2 Hz, 12H), 1.13 (m, 12H), 0.84 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ) 84.1, 55.4, 32.7, 25.1, 24.9, 24.0, 23.0, 22.2; MS (ESI-TOF) *m*/*z* 304.2 [M + H]$^+$; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{31}BNSO_3$ 304.2112; found 304.2105.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General methods and NMR spectra of all compounds. 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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