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Chiral Hydroxytetraphenylene-Catalyzed Asymmetric Conjugate Addition of Boronic Acids to Enones

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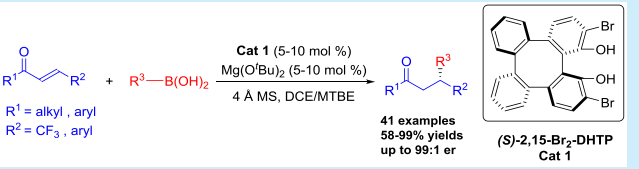
Supporting Information

ABSTRACT: (*S*)-2,15-Br_2-DHTP-catalyzed asymmetric conjugate addition of boronic acids to *β*-trifluoromethyl *α,β*-unsaturated ketones and enones was studied. The reaction afforded the corresponding Michael addition products in moderate to high yields with excellent enantioselectivities (up to 99:1 er). This catalytic system features mild reaction conditions, high efficiency, and tolerance to heteroarylboronic acids.



Asymmetric conjugate addition is an important synthetic method for constructing new C−C bonds.[1] Although transition-metal-catalyzed conjugate additions of boronic acids and their derivatives to *α,β*-unsaturated carbonyl compounds making use of Rh(I), Ir(I), Pd(I), and Cu(I) catalysts have been realized,[2] transition-metal-free conjugate addition reactions are still an important alternative method due to their low toxicity, functional-group tolerance, operational simplicity, and high selectivity.[3,4] After the pioneering study of the nonstereoselective conjugate addition of vinyl boronates to *α,β*-unsaturated ketones was reported by Suzuki and Hara,[5] the Chong group was the first to report the enantioselective conjugate addition of alkynyl boronates to chalcones using 3,3′-disubstituted-BINOL as the catalyst, which was subsequently applied to alkenylboronates and arylboronates.[6] However, alkenylboronic acids afforded lower stereoselectivities, and arylboronic esters required harsh reaction conditions. In 2011, May developed the asymmetric conjugate addition of alkenylboronic acids and alkynylboronic esters to indole-appended enone substrates in the presence of 3,3′-$(C_6F_5)_2$-BINOL and subsequently used heteroaryl and aryl trifluoroborate salts as nucleophiles.[7] In addition, Sugiura used *O*-monoacyltartaric acids as the catalyst for the conjugate addition of alkenylboronic acids to enones to provide only moderate yields and ee values,[8] as compared with those obtained from the reactions catalyzed by chiral biphenol derivatives.

In fluorine chemistry, considerable efforts have been focused on the catalytic asymmetric synthesis of molecules with CF_3-containing stereocenters,[9] because these fluorine-containing molecules can be converted into biologically active compounds.[10] In 2008, Konna and co-workers described the Rh(I)-catalyzed asymmetric conjugate addition of arylboronic acids to *β*-trifluoromethyl *α,β*-unsaturated ketones in the presence of (*S*)-BINAP to give the corresponding addition products in high yields and enantioselectives; however, the selectivities were found to be poor for alkenylboronic acids (one example with 40% ee).[11] In 2014, Pedro reported the first enantioselective conjugate addition of terminal alkynes to *β*-trifluoromethyl enones using a taniaphos-Cu(I) complex as the catalyst, and also achieved the alkynylation of *β*-aryl-*β*-trifluoromethyl enones using diethylzinc and 3,3′-$(C_6F_5)_2$-BINOL with satisfactory enantioselectivities.[12] To date there are very few reports regarding the enantioselective conjugate addition of alkenylboronic acids to *β*-trifluoromethyl enones in high yields and enantioselectivities in the absence of a transition metal catalyst.

Wong introduced chiral tetraphenylene scaffolds to asymmetric synthesis and achieved good results.[13] Recently, our group has reported the asymmetric allylboration of ketones using (*S*)-2,15-Br_2-DHTP (**Cat 1**, Scheme 1a) as a sufficiently reactive catalyst, affording optically pure tertiary alcohols in moderate to good yields with up to 99% ee (Scheme 1a).[14] These results have led us to believe that the (*S*)-2,15-Br_2-DHTP-catalyzed asymmetric conjugate addition of easy-to-handle boronic acids to *α,β*-unsaturated ketones can be accomplished. Herein, we report our hydroxytetraphenylene-catalyzed approach toward the construction of enantioenriched *β*-trifluoromethyl ketones from boronic acids and *β*-trifluoromethyl-*α,β*-unsaturated ketones (Scheme 1b).

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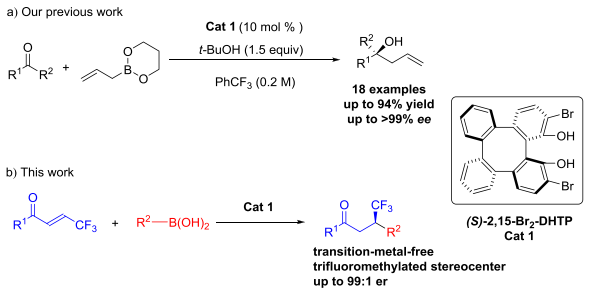
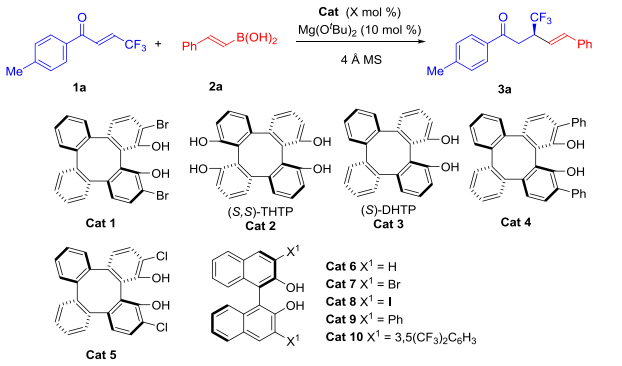
Scheme 1. (*S*)-2,15-Br$_2$-DHTP-Catalyzed Asymmetric Reactions



Initially, the reaction of β-trifluoromethyl α,β-unsaturated ketone **1a** with (*E*)-styrylboronic acid (**2a**) using **Cat 1** as the catalyst in toluene at room temperature was investigated, affording the desired product **3a** in 50% yield with 95.5:4.5 er (entry 1, Table 1). We proposed that the mechanism of the asymmetric conjugate addition of alkenylboronic boronic acids to β-trifluoromethyl enones was similar to that proposed by May,[7a,b] Chong,[6b] and Goodman.[6e] Figure 1a illustrates the proposed mechanism of the reaction of **1a** with **2a** catalyzed by **Cat 1**. **Cat 1** and **2a** first form **A** by losing two water molecules. Then **A** and **1a** form **B** with a tetracoordinated boron atom. **C** is produced by the cleavage of the boron−carbon bond in **B**. **C**, Mg(O^{t}Bu)$_2$, and another **2a** react to produce **D** and **A**. The process of **A** to **C** (red box in Figure 1a) is critical to determining the chirality of the product. To gain molecular insights into the mechanism, we calculated the Gibbs free energy profile along the reaction paths by density functional theory calculations at B3LYP-D3BJ/Def2-SVP level of theory with the C-PCM solvation model (Figure 1b). Computational details are described in the Supporting Information. Path 1 and Path 2 are the paths that produce the desired product **3a** and undesired product, respectively. The isosurface plot of the lowest unoccupied molecular orbital (LUMO) for **A** indicates that the boron atom in **A** acts as a Lewis acid site. The oxygen atom in **1a** can be coordinated to the boron atom in **A**. The overall free energy barrier of Path 1 is 4.28 kcal/mol lower than Path 2, suggesting the desired product **3a** is the more favorable product. Subsequently, various solvents were screened in the presence of 10 mol % of **Cat 1** at 25 °C; DCE was demonstrated to be the optimal solvent (entries 1−6, Table 1). Notably, the addition of Mg(O^{t}Bu)$_2$ and 4 Å MS as additives was critical to accelerate the reaction (Table S1; see Supporting Information).[7a,b] In the absence of Mg(O^{t}Bu)$_2$, the product yield decreased to 30% (entry 7, Table 1). In the absence of 4 Å MS, no product was afforded (entry 8, Table 1). The decrease of the solvent volume to 0.5 mL led to **3a** with a slightly higher enantioselectivity within a shorter reaction time (entry 9, Table 1). Next, various chiral tetraphenylene catalysts **Cat 2**, **Cat 3**, **Cat 4**, and **Cat 5**[15] were examined (entries 10−13, Table 1). However, all these catalysts afforded **3a** in a significantly diminished yield as well as lower enantioselectivities as compared to those of **Cat 1**. These results revealed that substituents on the tetraphenylene frameworks considerably affect selectivities and activities of the catalysts. Bulky, electron-withdrawing groups at positions 2 and 15 of (*S*)-DHTP were found to be imperative for better results. This can be attributed to the fact that electron-withdrawing substituents on the DHTP effectively increase the Lewis acidity of the boron and facilitate co-ordination of the

Table 1. Optimization of the Reaction Conditions[a]



Entry	Cat (mol %)	Solvent	t (h)	T (°C)	Yield (%)[b]	er[c]
1	**Cat 1** (10)	$PhCH_3$	36	30	50	95.5:4.5
2	**Cat 1** (10)	CH_2Cl_2	45	25	78	97.1:2.9
3	**Cat 1** (10)	THF	45	25	<10	–
4	**Cat 1** (10)	MTBE	48	25	30	95.2:4.8
5	**Cat 1** (10)	$PhCF_3$	48	25	82	97.3:2.7
6	**Cat 1** (10)	DCE	40	25	90	97:3
7[d]	**Cat 1** (10)	DCE	40	25	30	97:3
8[e]	**Cat 1** (10)	DCE	40	25	N.R.	–
9[f]	**Cat 1** (10)	DCE	30	25	88	97.2:2.8
10[f]	**Cat 2** (10)	DCE	40	25	11	83.7:16.3
11[f]	**Cat 3** (10)	DCE	40	25	5	78:22
12[f]	**Cat 4** (10)	DCE	40	25	30	96.7:3.3
13[f]	**Cat 5** (10)	DCE	48	25	32	95.5:4.5
14[f]	**Cat 6** (10)	DCE	48	25	6	42.9:57.1
15[f]	**Cat 7** (10)	DCE	48	25	19	10.2:89.8
16[f]	**Cat 8** (10)	DCE	72	25	14	5.9:94.1
17[f]	**Cat 9** (10)	DCE	48	25	10	17.3:82.7
18[f]	**Cat 10** (10)	DCE	72	25	12	9:91
19[f]	**Cat 1** (10)	DCE	84	0	38	98:2
20[f]	**Cat 1** (10)	DCE	20	60	92	96.3:3.7
21[f]	**Cat 1** (5)	DCE	72	25	74	96.8:3.2
22[f]	**Cat 1** (20)	DCE	46	25	88	97.7:2.3

[a]Reaction conditions: β-trifluoromethyl enone **1a** (0.1 mmol), (*E*)-styrylboronic acid **2a** (0.12 mmol), catalyst (0.01 mmol), Mg(O^{t}Bu)$_2$ (0.01 mmol), 4 Å MS (50 mg), and 1.0 mL of dry solvent were stirred under N_2. [b]Isolated yield. [c]The er values were determined by chiral HPLC analysis. [d]Without Mg(O^{t}Bu)$_2$. [e]Without 4 Å MS. [f]With 0.5 mL of DCE.

boron to the carbonyl oxygen of the enone. Interestingly, commercially available catalysts (*R*)-BINOL **Cat 6**, (*R*)-3,3′-Br$_2$-BINOL **Cat 7**, (*R*)-3,3′-I$_2$-BINOL **Cat 8**, (*R*)-3,3′-Ph$_2$-BINOL **Cat 9**, and **Cat 10** bearing two 3,5-bis(trifluoromethyl)phenyl groups exhibited poorer catalytic effects (entries 14−18, Table 1). Furthermore, with the decrease of the reaction temperature to 0 °C and the extension of the reaction time to 84 h, **Cat 1** gave a lower yield with a slightly higher er (entry 19, Table 1). Moreover, slightly diminished product enantioselectivities were observed at 60 °C (entry 20, Table 1). Finally, the catalyst loading was decreased to 5 mol %, affording the desired product in moderate yield with good er (entry 21, Table 1). However, the increase in the catalyst loading to 20 mol % did not achieve a significantly better result (entry 21, Table 1). Thus, the optimal reaction conditions are therefore **1a** (0.1 mmol) and **2a** (0.12 mmol) in the presence of **Cat 1** (0.01 mmol, 10 mol %), 4 Å MS (50 mg), and

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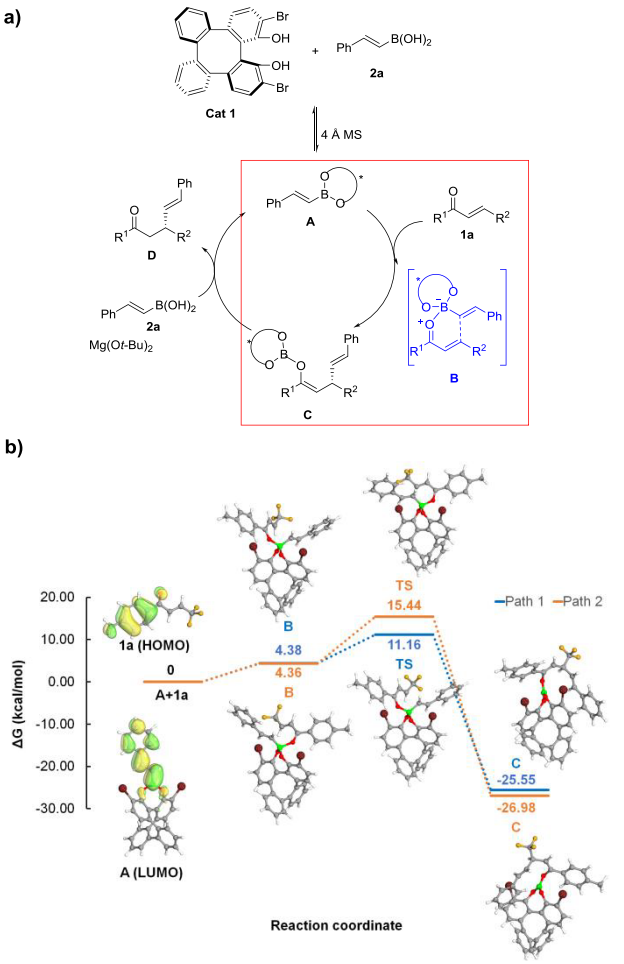
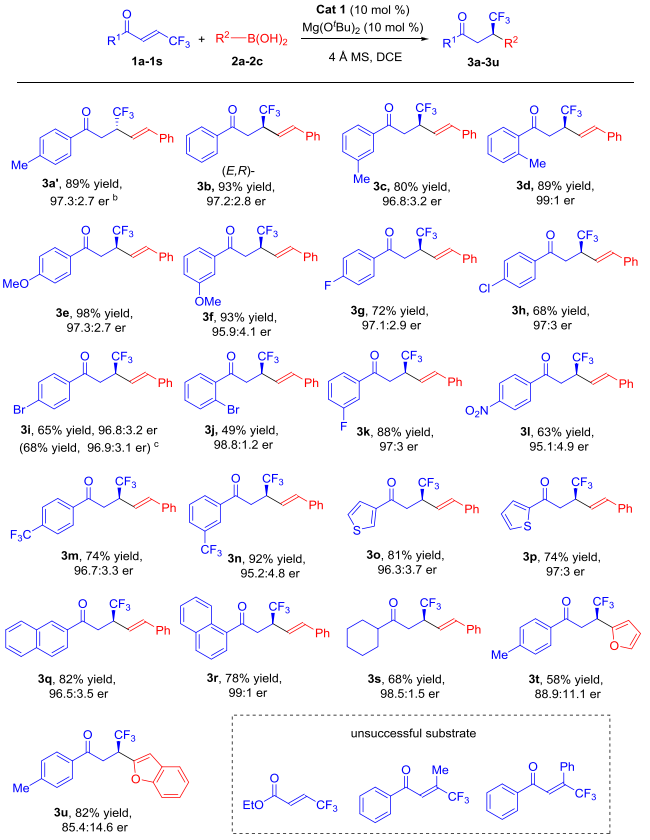


Figure 1. (a) Proposed catalytic mechanism. (b) Calculated relative Gibbs free energy profile along reaction coordinates, structures of intermediates and transition states, and isosurface plots of the highest occupied molecular orbital (HOMO) for **1a** and the lowest unoccupied molecular orbital (LUMO) for **A**.

Scheme 2. Substrate Scope of *β*-Trifluoromethyl *α,β*-Unsaturated Ketones[a]



[a]Unless otherwise noted, reactions were carried out with *β*-trifluoromethyl enones **1a**−**1t** (0.1 mmol, 1.0 equiv), (*E*)-styrylboronic acid **2a**−**2c** (0.12 mmol, 1.2 equiv), **Cat 1** (0.01 mmol, 10 mol %), $Mg(O^tBu)_2$ (0.01 mmol), and 4 Å MS (50 mg) in 0.5 mL of dry DCE at 25 °C under N_2 for 24−48 h. Isolated yield. The er values were determined by chiral HPLC analysis. [b]With (*R*)-2,15-Br_2-DHTP (0.01 mmol, 10 mol %). [c]With **Cat 1** (0.02 mmol, 20 mol %).

$Mg(O^tBu)_2$ (0.01 mmol, 10 mol %) in dry DCE (0.5 mL) at 25 °C (entry 9, Table 1).

With the optimal reaction conditions in hand, the substrate scope of *β*-trifluoromethyl *α,β*-unsaturated ketones **1a**−**1s** was investigated (Scheme 2). When the enantiomer of **Cat 1** (*R*)-2,15-Br_2-DHTP was utilized in the reaction, the corresponding product **3a′** was obtained in 89% yield with 97.3:2.7 er. In the case of substrate **2b**, desired product **3b** was generated in 93% yield with 97.2:2.8 er, and the result was considerably better than that reported previously ((*E,S*)-**3b′**: 66% yield, 78% ee; (*E,R*)-**3b**: 70% yield, 40% ee).[12a,11a] All reactions of *β*-trifluoromethyl *α,β*-unsaturated ketones bearing either electron-donating or electron-withdrawing groups on the phenyl ring were performed, leading to the formation of the corresponding products in moderate to high yields with excellent enantioselectivities (90−98% ee). Halides, Me, OMe, CF_3, and nitro groups on the *ortho*, *para*, or *meta* position of the phenyl ring were tolerated under the standard reaction conditions (Scheme 2, **3c**−**3n**), albeit diminished yields for products **3i** and **3j** were noted. In addition, heteroaromatic thiophene *α,β*-unsaturated ketones **2o** and **2p** and ring-fused naphthyl *α,β*-unsaturated ketones **2q** and **2r** afforded the corresponding products in good yields with excellent er values (Scheme 2, **3o**−**3r**). The use of alkyl-substituted substrate **2s** afforded the desired product **3s** in 68% yield with 98.5:1.5 er. These results reveal that the substituents on the *β*-trifluoromethyl-*α,β*-unsaturated ketones do not significantly affect the stereoselectivities of products. Unfortunately, relevant reactions involving ethyl 4,4,4-trifluorocrotonate, *β*-methyl *β*-trifluoromethyl *α,β*-unsaturated ketone, or *β*-phenyl *β*-trifluoromethyl *α,β*-unsaturated ketone were unsuccessful. Furthermore, effects of alternative boronic acids were examined for the reaction with substrate **1a**. Thus, furanboronic acid **2b** and benzofuranboronic acid **2c** exhibited acceptable reactivities, affording products **3t** and **3u** with good enantioselectivities, respectively. Arylboric acids were unreactive under our reaction conditions. These findings reveal that structures of boronic acids lead to a significant impact on reactivities and enantioselectivities of these catalytic reactions. The absolute configuration of **3b** was determined to be (*E,R*) by comparison of chiral HPLC data and specific rotation values reported in the literature.[11a,12a] Accordingly, the *R*-configuration was assigned to the remainder of the expected products **3** by assuming a uniform stereochemical pathway.

We also optimized the reaction conditions with *trans*-chalcone **4a** and (*E*)-styrylboronic acid (**2a**), and the desired product **5a** was obtained in 99% yield with 98.1:1.9 er using 5 mol % **Cat 1** (Table S2; see Supporting Information). The

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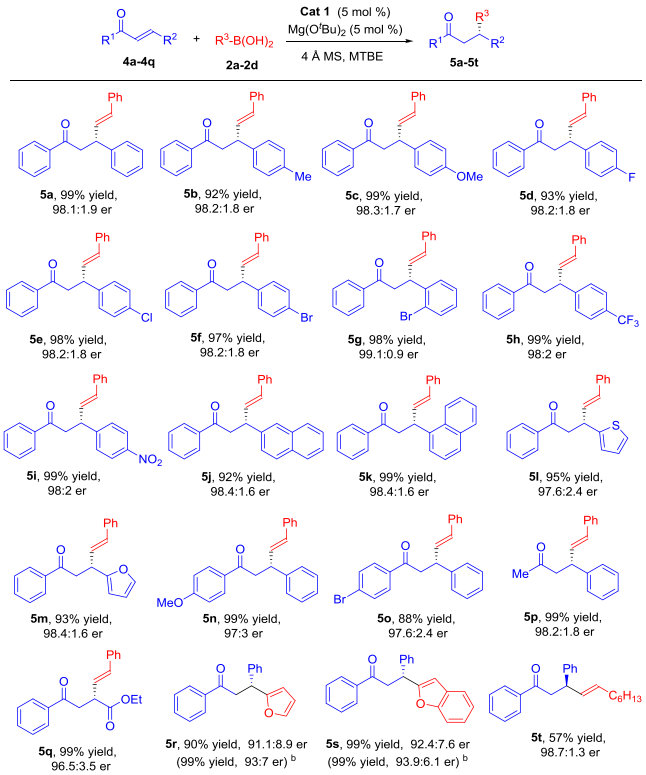
substrate scope of enones **4b**–**4q** was then evaluated (Scheme 3). Initially, chalcones carrying β-aryl groups with diverse

Scheme 3. Substrate Scope of Enones[a]

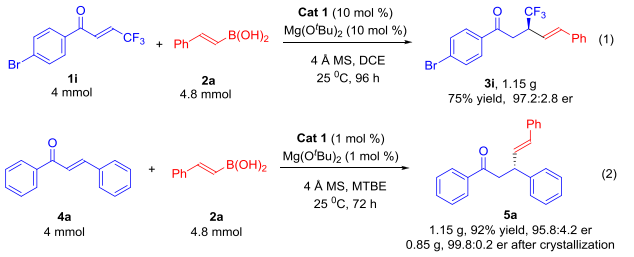


[a]Unless otherwise noted, enones **1a**–**1q** (0.1 mmol), boronic acid **2a**–**2d** (0.12 mmol), **Cat 1** (0.005 mmol, 5 mol %), $Mg(O^tBu)_2$ (0.005 mmol, 5 mol %), 4 Å MS (100 mg), and dry MTBE (1.0 mL) were stirred at 25 °C under N_2. Isolated yield. The er values were determined by chiral HPLC analysis. [b]With **Cat 1** (0.1 mmol, 10 mol %).

substituents were examined. Various electron-donating groups (OMe, Me) and electron-withdrawing groups (F, Cl, Br, CF_3, NO_2) on the phenyl ring were well tolerated, delivering adducts in excellent yields and enantioselectivities (**5b**–**5i**, 92–99% yields, 96–98% ee). Moreover, phenyl-type enones bearing a fused ring and heteroaromatic ring at the β-position were also applicable, affording the corresponding products with excellent results (**5j**–**5m**). Then, enones bearing α'-aryl groups with different substituents (OMe, Br) were allowed to react with (*E*)-styrylboronic acid (**2a**) to give the expected products in good yields and er values (**5n** and **5o**). Of particular note is that enone **4p** bearing a methyl group and enone **4q** bearing an ester group both reacted with boronic acid **2a** smoothly, and the desired products **5p** and **5q** were obtained in quantitative yields with 98.2:1.8 and 96.5:3.5 er, respectively. Finally, this catalytic reaction also worked well with other boronic acids, such as furanboronic acid **2b**, benzofuranboronic acid **2c**, and alkenylboronic acid **2d**. In the case of **2b** and **2c**, the corresponding reactions provided the desired products **5r** and **5s** in excellent yields with 91.1:8.9 and 92.4:7.6 er under the standard reaction condition, while the er values increased to 93:7 and 93.9:6.1 when the catalyst loading was increased to 10 mol %. Product **5t** was afforded in 57% yield with 98.7:1.3 er, and the moderate yield is likely due to the lower reactivity of alkenylboronic acid **2d** as compared with that of **2a**. All results in our system were better than those reported by Sugiura.[8a] The configuration of all products was assigned by comparison with that reported in literature.

To confirm the scalability of the current protocol, a gram-scale reaction of β-trifluoromethyl α,β-unsaturated ketone **1i** (4 mmol) with (*E*)-styrylboronic acid (**2a**) (4.8 mmol) was carried out, affording product **3i** in an isolated yield of 75% with 97.2:2.8 er (eq 1, Scheme 4). A gram-scale reaction of

Scheme 4. Gram-Scale Reactions



enone **4a** with boronic acid **2a** in the presence of **Cat 1** (1 mol %) and $Mg(O^tBu)_2$ (1 mol %) was also conducted. To our delight, 1.15 g of product **5a** was obtained in 92% yield with 95.8:4.2 er, and after crystallization, 0.85 g of **3a** was afforded with 99.8:0.2 er (eq 2, Scheme 4). After the reaction, **Cat 1** was easily recovered by flash column chromatography, which can be reused without loss of activity.

In summary, we have developed an asymmetric conjugate addition of boronic acids to α,β-unsaturated ketones catalyzed by (*S*)-2,15-Br_2-DHTP under mild reaction conditions. Enantioenriched products bearing a trifluoromethylated stereocenter were obtained in moderate to high yields and good to excellent enantioselectivities (up to 99:1 er). In addition, heteroarylboronic acids were tolerated under these reaction conditions, and gram-scale reactions were achieved without loss of enantioselectivities. Additional investigations to extend the scope to other substrates and applications of the resulting products are underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01637.

Experimental details; computational details; copies of ^1H, ^{13}C, ^{19}F NMR spectra; and chromatograms of racemic and optically active products (PDF)

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Notes

The authors declare no competing financial interest.

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