3,5-Bis(perfluorodecyl)phenylboronic Acid as an Easily Recyclable Direct Amide Condensation Catalyst

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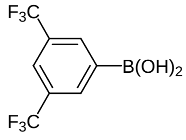
Abstract: 3,5-Bis(perfluorodecyl)phenylboronic acid has been synthesized based on the direct coupling of perfluorodecyl iodide with 1,3-diiodobenzene. This new boronic acid is shown to be a "green" catalyst for the direct amide condensation reaction by virtue of the strong electron-withdrawing effect and the immobility in the fluorous recyclable phase of the perfluorodecyl group.

Key words: arylboronic acids, recycle, direct amide condensation, green chemistry, fluorous bi-phasic catalysis



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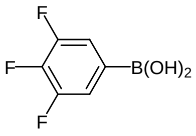

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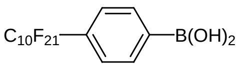

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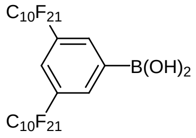

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Arylboronic acids bearing electron-withdrawing substituents at the aryl group behave as water-, acid-, and base-tolerant thermally stable Lewis acids and can be easily handled in air. We have succeeded in enhancing the catalytic activities of a chiral acyloxyborane (CAB) derived from 2,6-di(isopropoxy)benzoyltartaric acid and borane·THF, Corey's chiral oxazaborolidine catalyst derived from *N*-(*p*-toluenesulfonyl)-*(S)*-tryptophan and borane·THF, and the Brønsted acid-assisted chiral Lewis acid (BLA) derived from chiral tetrol and borane·THF by a modified method using 3,5-bis(trifluoromethyl)phenylboronic acid (**1**) instead of borane•THF.[1–3] Moreover, we have found that **1** and 3,4,5-trifluorophenylboronic acid (**2**) are highly effective catalysts for the amide condensation of amines (1 equiv) and carboxylic acids (1 equiv).[4] To the best of our knowledge, this is the first example of a catalytic and direct amide condensation which does not require excess amounts of substrates.

Most of the above homogeneous catalytic reactions require relatively large quantities of arylboronic acid catalysts (1~20 mol%), and trace amounts of the catalysts must be removed from the reaction products. This has hampered the application of this methodology to large-scale syntheses. Recently, the concept of fluorous bi-phasic catalysis (FBC) was introduced as an environmentally benign recycling process.[5–7] In this paper, we describe a convenient and high-yielding route to phenylboronic acids **3** and **4** bearing perfluorinated ponytails based on the direct coupling of fluoroalkyl iodides with halobenzenes and their catalytic and recyclable application in a direct amide condensation.

Cross-coupling of fluoroalkyl iodides with iodoaromatic compounds to give fluoroalkyl-substituted aromatics in the presence of copper was reported by McLoughlin and Thrower more than three decades ago.[8] Prompted by this early finding, we attempted the synthesis of perfluoroalkylated phenylboronic acids **3** and **4** (Scheme). Treatment of 4-iodoanisole (**5**) and perfluorodecyl iodide in DMSO (120 °C, 40 h) gave the substituted anisole **6** in 90% yield.[9] Compound **6** was converted to **7** by demethylation with boron tribromide (70% yield) and subsequent triflation with triflic anhydride (>99% yield). The palladium-catalyzed cross-coupling of triflate **7** with bis(pinacolato)diboron yielded the corresponding arylboronate **8** in 81% yield.[10a] Finally, **8** was converted to **3**[11] in 70% yield by treatment with boron tribromide. Thus, the new boronic acid **3** was prepared from **5** in five steps. In a similar manner, 3,5-bis(perfluorodecyl)phenylboronic acid (**4**)[12] was prepared from 1,3-diiodobenzene (**9**) in four steps: copper-mediated coupling of **9** with perfluorodecyliodide, electrophilic aromatic bromination of **10** with *N*-bromosuccinimide (NBS),[13] palladium-catalyzed cross-coupling of arylbromide **11** with bis(pinacolato)diboron,[10b] and deprotection of **12** with boron tribromide.

We first investigated the catalytic activities of arylboronic acids **1**−**4** (5 mol%), which promote the model reaction of 4-phenylbutyric acid (1 equiv) with 3,5-dimethylpiperidine (1 equiv) in toluene at azeotropic reflux with removal of water (4-Å molecular sieves in a Soxhlet thimble) for 1 h, and its recovery by extraction with fluorous solvents (Table 1). As expected, 3,5-bis(perfluorodecyl)phenylboronic acid **4** was more active than 4-(perfluorodecyl)phenylboronic acid **3**, and was recovered in quantitative yield by extraction with perfluoromethylcyclohexane. Although **1** and **2** were more active than **4**, they could not be recovered by extraction with any fluorous solvents. The amide condensation proceeded cleanly in the presence of 5 mol% of **4**, the desirable amide was obtained in 95% yield by azeotropic reflux for 15 h. In addition, the corresponding *N*-benzylamide was obtained in quantitative

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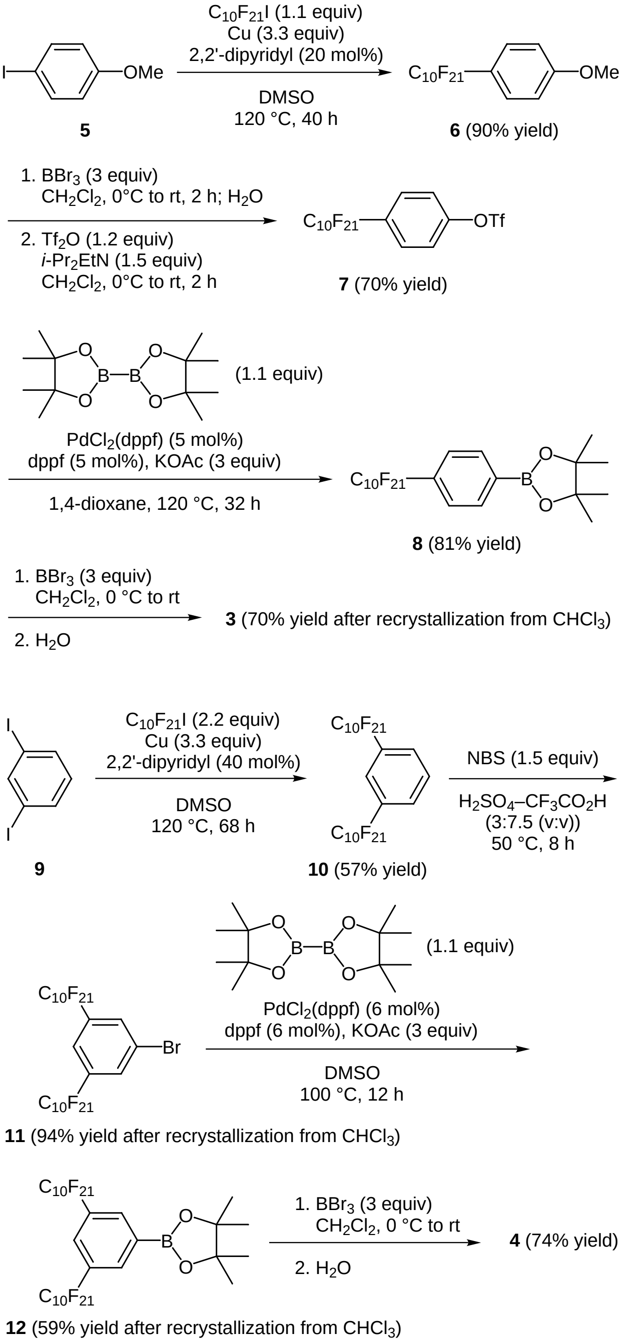
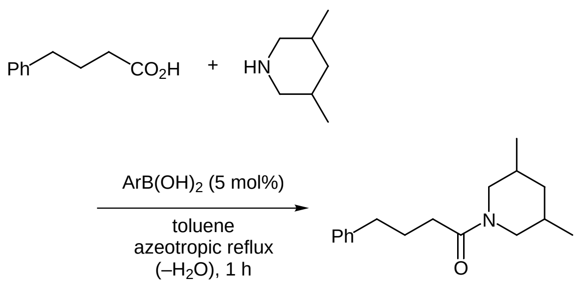


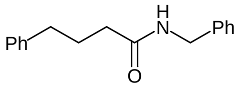
Scheme

Table 1 Catalytic Activities and Recovery of Arylboronic Acid for Direct Amide Condensation



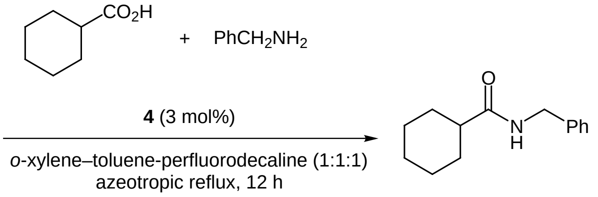
ArB(OH)$_2$	Yield of amide (%)[a]	Recovery of ArB(OH)$_2$ (%)[b]
1	59	0
2	60	0
3	39	57
4	47 (95)[c]	>99
PhB(OH)$_2$	23	0
–[d]	<2	–

[a] Isolated yield. [b] Extraction with perfluoromethylcyclohexane. [c] Yield after heating at azeotropic reflux for 15 h is indicated in parenthesis. [d] No catalyst was added.



99% yield, >99% recovery of **4**
[Reaction conditions: **4** (2 mol%), toluene, azeotropic reflux for 4 h]

Table 2 Recovery and Reuse of **4** in the Recyclable Fluorous Immobilized Phase[a]



Cycle[a]	1	2	3	4	5[c]
Conversion (%)[b]	>99 (99)	>99	>99	>99 (98)	>99 (99)

[a]Reaction conditions (See Scheme 2): **4** (0.03 mmol), cyclohexanecarboxylic acid (1 mmol), benzylamine (1 mmol), o-xylene (2.5 mL), toluene (2.5 mL), and perfluorodecaline (2.5 mL). After the reaction, a solution of the amide in the upper phase was decanted and the catalyst **4** in the lower phase was recycled successively. [b]Values in parentheses refer to the isolated yields. [c]Catalyst **4** was recovered in 98% yield from the perfluorodecalin phase.

yield by heating 4-phenylbutyric acid with benzylamine in the presence of 2 mol% of **4** under azeotropic reflux conditions for 4 h.

Based on the above results, the recyclable use of **4** was examined for direct amide condensation (Table 2 and Figure 1).[14] The reaction of cyclohexanecarboxylic acid and benzylamine in a 1:1:1 mixture of *o*-xylene, xylene, and perfluorodecalin was carried out under azeotropic reflux conditions with removal of water for 12 h in the presence of 3 mol% of **4**.[15] After cooling to ambient temperature, the two heterogeneous phases were separated to give the corresponding amide in quantitative yield. Catalyst **4** was completely recovered and reused in the recyclable fluorous immobilized phase.

Catalyst **4** was insoluble in toluene and *o*-xylene at room temperature even in the presence of carboxylic acids, amines, and amides. However, the amide condensation catalyzed by **4** proceeded homogeneously under reflux conditions. To demonstrate this advantage of **4** with respect to solubility,[16] we attempted to reuse **4** (5 mol%) 10 times for the amide condensation reaction of cyclohexanecarboxylic acid with benzylamine (Table 3 and Figure 2).[17] After heating the reaction mixture at reflux with removal of water for 3 h, the mixture was allowed to stand at ambient temperature for 1 h to precipitate **4**. The liquid phase of the resultant mixture was decanted and the residual solid catalyst **4** was reused without isolation. No loss of activity was observed for the recovered catalyst, and 26% of **4** remained in the flask in the 10th reaction. This means that 88% of **4** was retained in each cycle. The total isolated yield of the amide which was obtained in ten reactions was 96%. Moreover, pure compound **4** could be recovered in 97% yield as a white solid from the above reaction mixture by filtration and washing with toluene.[17]

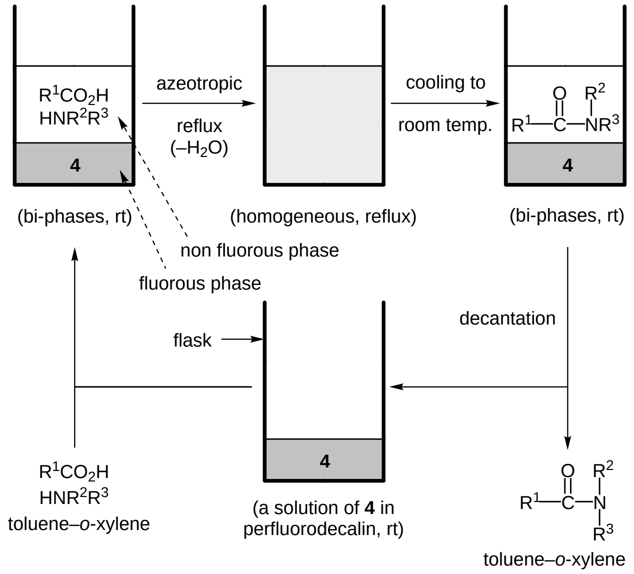


Figure 1 Recycling of **4** in the recyclable fluorous immobilized phase

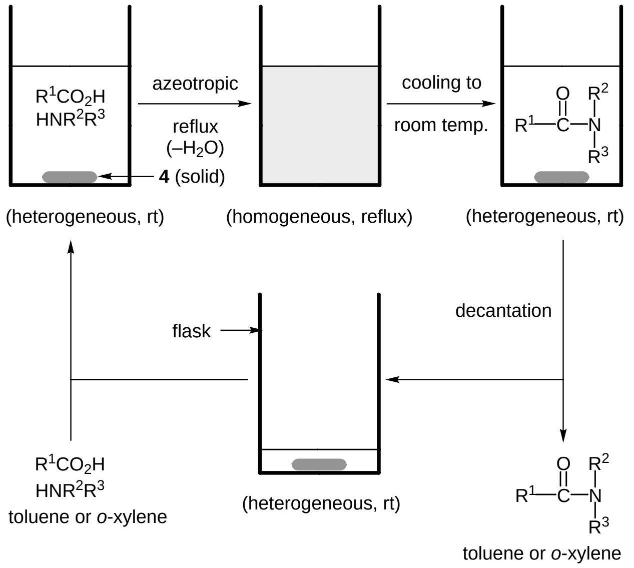
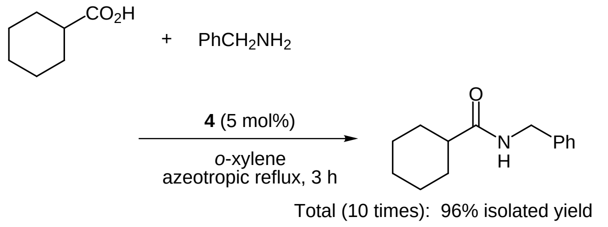


Figure 2 Recovery of **4** by decantation and its reuse without isolation

Table 3 Reuse of Catalyst **4** for the Amide Condensation of Cyclohexanecarboxylic Acid with Benzylamine.[a]



Use of 4[a]	1	2	3	4	5	6	7	8	9	10
Conversion (%)	>99	>99	>99	>99	99	>99	>99	>99	>99	>99

[a] Reaction conditions: **4** (0.05 mmol), cyclohexanecarboxylic acid (1 mmol), benzylamine (1 mmol), xylene (5 mL). After the reaction, the solution was decanted and the residual catalyst **4** was reused without isolation (see, Scheme 2). [b] Recovered catalyst **4** was used successively (Use 2, 3, 4,.)

In conclusion, we have shown that 3,5-bis(perfluorodecyl)phenylboronic acid **4** is a "green" catalyst by virtue of the electron-withdrawing effect and the immobility in the fluorous recyclable phase of the perfluorodecyl group. In addition, it is noteworthy that **4** was simply recovered by filtration without using any fluorous solvents. Perfluorodecyl groups on **4** increased precipitation properties in nonfluorous organic solvents. We believe that direct amide condensation catalyzed by a reusable boronic acid **4** may be useful as an environmentally and industrially ideal condensation method in the near future.

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(11) **3**: white solid; mp 166 °C; IR (KBr) 3600−3200 (OH), 1406, 1375, 1345, 1240, 1210, 1150 cm; ^{1}H NMR ($CDCl_3$, 300 MHz, 55 °C) δ 7.63 (d, *J* = 9.3 Hz, 1H), 7.90 (d, *J* = 9.3 Hz, 1H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −128.17 (s, 3F), −124.61 (s, 2F), −123.51 (s, 10F), −123.06 (s, 2F), −111.91 (s, 2F), −83.33 (s, 2F). Anal. Calcd for $C_{16}H_6F_{21}BO_2$: C, 30.03; H, 0.94. Found: C, 30.09; H, 0.89.

(12) **4**: white solid; mp 166 °C; IR (KBr) 1375, 1841, 1293, 1225, 1150, 1096, 899 cm^{-1} (The OH stretching freuency for **4** was not observed probably because the sample contained varying amounts of boronic anhydride); ^{1}H NMR ($CDCl_3$, 300 MHz, 55 °C) δ 7.90 (s, 1H), 8.12 (s, 2H); ^{19}F NMR ($CDCl_3$, 282 MHz, 55 °C) δ −127.09 (s, 6F), −123.70 (s, 4F), −122.78 (s, 20F), −122.15 (s, 4F), −112.04 (t, *J* = 15.2 Hz, 4F), −81.96 (t, *J* = 9.0 Hz, 4F). Anal. Calcd for $C_{26}H_5F_{42}BO_2$: C, 26.97; H, 0.44. Found: C, 27.01; H, 0.35.

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(14) **Typical procedure for the direct amide condensation (Table 2 and Figure 1).** A dry, 10-mL round-bottom flask fitted with a stirring bar and 15-mL pressure-equalized addition funnel (containing a cotton plug and ca. 2 g of 4 Å molecular sieves (pellets) and functioning as a Soxhlet extractor) surmounted by a reflux condenser was charged with cyclohexanecarboxylic acid (128.2 mg, 1.0 mmol), benzylamine (109.2 µL, 1.0 mmol), and **4** (34.7 mg, 0.03 mmol) in *o*-xylene (2.5 mL) and perfluorodecaline (2.5 mL). The mixture was heated at azeotropic reflux with removal of water to provide a homogeneous solution. After 3 h, the resulting mixture was cooled to ambient temperature, and phase separation occurred immediately. The organic phase was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluant: hexane-ethyl acetate = 3:1) to give the corresponding amide (215 mg, 0.99 mmol, 99% yield). The spectral data for the amide is in agreement with data previously reported by us.[4a] The fluorous phase containing the catalyst **4** was recovered and could be used for further experiments.

(15) Perfluorodecaline was not miscible with a single non-fluorous solvent, toluene or *o*-xylene, even under reflux conditions.

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(17) **Typical procedure for the direct amide condensation (Table 3 and Figure 2).** A dry, 10-mL round-bottom flask fitted with a stirring bar and a 5-mL pressure-equalized addition funnel (containing a cotton plug and ca. 2 g of 4 Å molecular sieves (pellets) and functioning as a Soxhlet extractor) surmounted by a reflux condenser was charged with cyclohexanecarboxylic acid (128.2 mg, 1.0 mmol), benzylamine (109.2 µL, 1.0 mmol), and **4** (57.9 mg, 0.05 mmol) in *o*-xylene (5 mL). The mixture was heated at azeotropic reflux with removal of water to provide a homogeneous solution. After 3 h, the resulting mixture was cooled to ambient temperature to precipitate **4**. After 1 h, the liquid phase of the resultant mixture was decanted and the residual solid catalyst **4** was reused without isolation. Catalyst **4** remained in the flask in the 10th reaction. Liquid phases which were obtained in each reactions were combined, concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluant: hexane-ethyl acetate = 3:1) to give the corresponding amide (2.08 g, 9.6 mmol, 96% yield). The spectral data for the amide is in agreement with data previously reported by us.[4a] **Typical Procedure for Recovering of 4.** After completing the above reaction (one cycle), the resulting mixture was cooled to ambient temperature to precipitate **4**. After 1 h, the resultant mixture was diluted with toluene (3 mL), and **4** was separated by filtration, washed with toluene (2 mL), and dried under vacuum (1 torr) to recover **4** (56.0 mg, 97% yield) as a pure white solid.

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