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Application of a Rhodium-Catalyzed Addition/ Cyclization Sequence toward the Synthesis of Polycyclic Heteroaromatics

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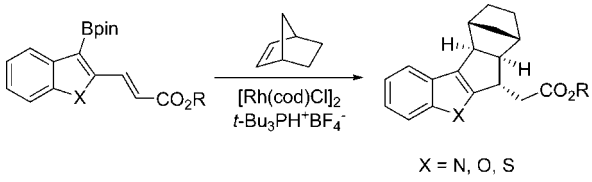
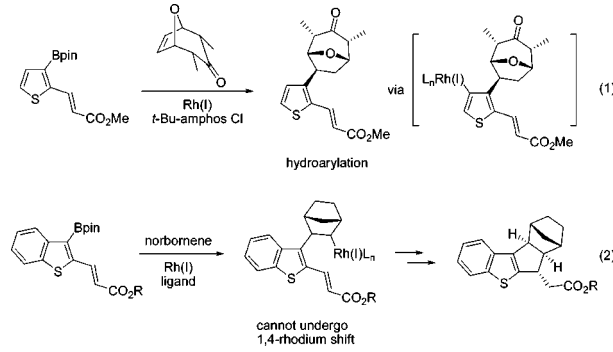


A cascade rhodium-catalyzed addition/cyclization reaction of bifunctional heteroromatic boronate esters to strained bicyclic alkenes has been developed. This method provides an efficient route to generate a variety of polycyclic heteroaromatic molecules containing benzothiophene, benzofuran, and indole moieties.

Rhodium-catalyzed carbon−carbon bond formation reactions have been studied extensively in recent years.[1] The popularity of these methods stems from their wide tolerance of functional groups and the mildness of the reaction conditions. Rhodium-catalyzed carbocyclization reactions have been demonstrated as efficient methods to generate a wide variety of carbocycles through a cascade carborhodation sequence with polyfunctional organoboron reagents.[2−4] We have utilized this approach with ortho-functionalized arylboronate esters to synthesize indanes and indenes;[4a−c] however, extension of this methodology to heteroaromatic boronate esters proved to be problematic.[4b] The unproductive pathway, which led to the noncyclized hydroarylation products, dominated in the reaction, presumably due to the highly favorable rhodium 1,4-migration to C4 of the thiophene moiety (eq 1, Scheme 1).[5,6] To avoid this undesired C−H insertion, we changed the substrate to benzothiophene, which lacks the hydrogen that participates in the rhodium migration (eq 2, Scheme 1). Benzothiophene moieties can be found in a wide variety of pharmaceutical agents and biologically active compounds.[7] By extending this rhodium-catalyzed carbocycle formation reaction to heteroaromatic boronate esters, a new class of polycyclic heterocycles would be available. Herein, we report the synthesis of polycyclic heteroaromatic compounds using ortho-functionalized benzothiophene, benzofuran, and indole boronate esters with strained alkenes under rhodium catalysis.

SCHEME 1. Rhodium-Catalyzed Cascade Addition/ Cyclization Reactions



Benzothiophene boronate ester **1** was prepared from 2-formyl-3-benzothiopheneboronic acid[8] and used for identifying the optimal reaction conditions. The choice of base for this coupling reaction was found to be crucial, as potassium fluoride led to predominantly deboronation of the starting material, while sodium carbonate gave the desired product in good yield. Overall, the optimal conditions were found to use $[Rh(cod)Cl]_2$ as the rhodium source, with a bulky phosphine ligand $(t\text{-Bu})_3P$[9] and sodium carbonate as base in dioxane/water (10:1) solution with norbornene as the coupling partner. At 80 °C, product **3a** was obtained in 84% isolated yield in 3 h (Table 1, entry 1). The stereochemistry of the product was predicted based on analogy to the previous report,[4a,b] which was controlled by the *exo*-carborhodation of the norbornene and followed by the diastereoselective cyclizaton to the Michael acceptor.

We examined the scope of this reaction by screening a variety of strained alkenes. Benzonorbornene **2b** gave the desired product in excellent yield (Table 1, entry 2). Norbornadiene **2c**

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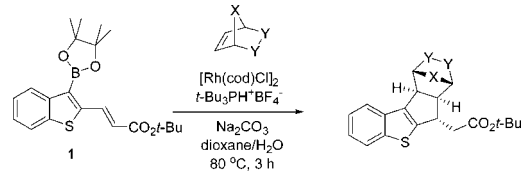
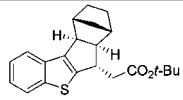
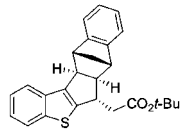
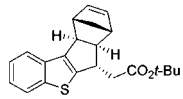
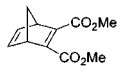
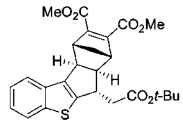
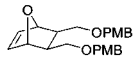
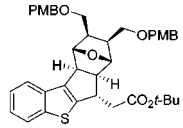
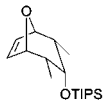
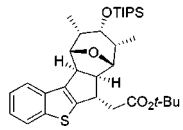
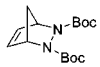
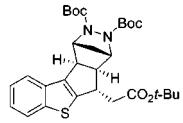
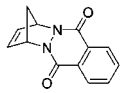
TABLE 1. Screening of Strained Bicyclic Alkenes as Coupling Partners[a]

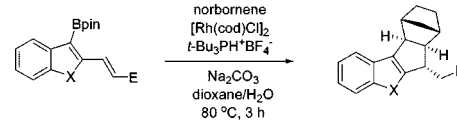


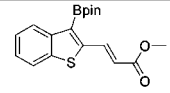
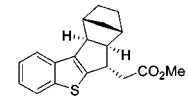
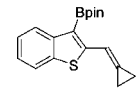
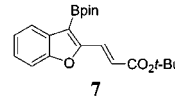
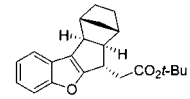
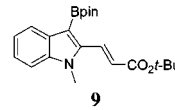
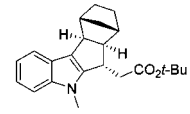
entry	alkene	product	yield (%)[b]
1	 **2a**		**3a**, 84
2	 **2b**		**3b**, 98
3	 **2c**		**3c**, 76
4	 **2d**		**3d**, 84
5	 **2e**		**3e**, 88
6	 **2f**		**3f**, 62
7	 **2g**		**3g**, 61
8	 **2h**	---	N.R.

[a] All reactions were run under the following conditions: **1** (0.20 mmol, 1.0 equiv), **2** (0.20−0.38 mmol, 1.0−1.9 equiv), $[Rh(cod)Cl]_2$ (0.006 mmol, 3 mol %), t-$Bu_3PH^+BF_4^-$ (0.012 mmol, 6 mol %), Na_2CO_3 (0.40 mmol, 2 equiv) in 3.0 mL of dioxane and 0.3 mL of H_2O. [b] Isolated by column chromatography.

could potentially give the double addition product. However, we found that careful control of stoichiometry could lead to monocyclized product **3c** (entry 3). Reacting with norbornadiene derivative **2d** showed the coupling occurred selectively on the electron-rich, unsubstituted double bond (entry 4). Oxabicyclic alkenes such as **2e** and **2f**, which tend to ring-open under rhodium-catalyzed conditions,[10] were found to be compatible and afforded the corresponding products with no ring-opening observed (entries 5 and 6). The nitrogen-containing strained alkene **2g** was also tested and gave an interesting diazabicyclic product in moderate yield (entry 7). Surprisingly, the extension of nitrogen-containing alkene to **2h** was not successful. Under

TABLE 2. Screening of Different Heteroaromatic Boronate Esters[a]



entry	boronate ester	product	yield (%)[b]
1	 **4**		**5**, 76
2	 **6**	---	N.R.
3	 **7**		**8**, 22[c]
4	 **9**		**10**, 45

[a] All reactions were run under the following conditions: **1** (0.20 mmol, 1.0 equiv), norbornene (0.24 mmol, 1.2 equiv), $[Rh(cod)Cl]_2$ (0.006 mmol, 3 mol %), t-$Bu_3PH^+BF_4^-$ (0.012 mmol, 6 mol %), Na_2CO_3 (0.40 mmol, 2 equiv) in 3.0 mL of dioxane and 0.3 mL of H_2O. [b] Isolated by column chromatography. [c] Yield obtained with 3 equiv of norbornene (0.60 mmol).

the standard reaction conditions, no desired product was obtained, presumably due to the low solubility of the diazabicyclic alkene **2h** (entry 8).

We also screened several different electron-withdrawing groups on the benzothiophene boronate esters. Changing from a *tert*-butyl to methyl ester gave **5** in comparable yield to **3a** (Table 2, entry 1). We hoped that use of a methylenecyclopropane-containing boronate ester **6** would enable addition, followed by fragmentation of the methylenecyclopropane.[11,12] However, **6** failed to react, perhaps due to the lack of electron withdrawing group on the alkene (entry 2). Other heteroaromatic boronate esters such as benzofuran **7** and indole **9** were also examined. The corresponding polycyclic heteroaromatic products were obtained in low to moderate yield (entries 3 and 4). Increasing the amount of norbornene to 3 equiv only led to a slightly higher yield of **8** (22%). The major side products of entries 3 and 4 were identified as the deboronated alkenyl heterocycles.

In summary, we have developed an efficient method to synthesize a series of polycyclic heteroaromatic compounds as an extension of previously reported rhodium-catalyzed cascade addition reactions. The unproductive pathway arising from a rhodium 1,4-shift could be excluded by using the bifunctional benzothiophene boronate esters. Among the examined het-

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eroaromatic boronate esters, benzothiophene shows the highest reactivity and gave the desired product in moderate to excellent yields.

Experimental Section

General Procedure for Rhodium-Catalyzed Cascade Addition/Cyclization Reactions. A solution of 0.3 mL of water and 3 mL of dioxane in a 5-mL 2-necked round-bottomed flask was purged with argon and stirred for 10 min at 25 °C. $[Rh(cod)Cl]_2$ (3.0 mg, 0.006 mmol), tri-*tert*-butylphosphonium tetrafluoroborate (3.5 mg, 0.012 mmol), and sodium carbonate (42.4 mg, 0.40 mmol) were added to the solution, which was then stirred at 25 °C for 10 min. To the bright yellow solution was added the alkene **2** (0.20−0.38 mmol), followed by addition of the boronate ester (0.20 mmol) and the reaction mixture was stirred at 80 °C for 3 h. The reaction was quenched with brine, and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried with $MgSO_4$, filtrated, and concentrated in vacuo. The crude material was then purified by column chromatography on silica gel.

Benzothiophene 3a (Table 1, entry 1): white solid, mp 78−81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.34−7.29 (m, 1H), 7.26−7.21 (m, 1H), 3.35−3.28 (m, 1H), 3.16 (d, J = 7.2 Hz, 1H), 2.60 (dd, J = 15.6, 7.4 Hz, 1H), 2.52 (dd, J = 15.6, 7.6 Hz, 1H), 2.46 (d, J = 3.9 Hz, 1H), 2.46 (d, J = 3.9 Hz, 1H), 2.42 (dd, J = 7.0, 2.2 Hz, 1H), 1.68−1.51 (m, 2H), 1.49 (s, 9H), 1.44−1.36 (m, 1H), 1.29−1.20 (m, 2H), 1.07 (dt, J = 10.1, 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 146.4, 145.5, 141.7, 134.5, 124.0, 123.5, 123.3, 121.4, 80.7, 58.4, 50.0, 45.8, 43.3, 42.7, 39.6, 33.1, 28.9, 28.5, 28.1; IR (neat) 2949, 2870, 1726, 1455, 1432, 1392, 1366, 1294, 1249, 1151, 1018, 937, 849, 752, 731 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{26}O_2S$ [M^+] 354.1654, found 354.1661.

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Supporting Information Available: Experimental procedures and spectroscopic characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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