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Rhodium-Catalyzed Borylative Cyclization of 2-Alkynylaryl Isocyanates with Bis(pinacolato)diboron

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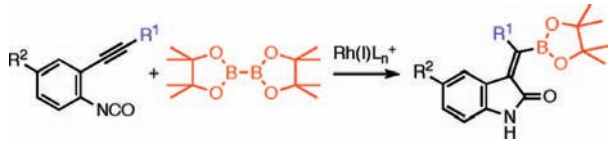
ABSTRACT



2-Alkynylaryl isocyanates reacted with bis(pinacolato)diboron in the presence of a cationic rhodium(I) catalyst to produce borylated 3-alkylideneoxindoles stereoselectively. The carbon−boron linkage formed was further transformed via reactions such as a cross-coupling and a halogenation reaction.

Organoboronic acids and esters have become indispensable reagents in organic synthesis due to their unique reactivity, air-stability, and accessibility.[1] In addition, recent studies on organoboronic acid derivatives have demonstrated their potential as pharmaceutical candidates.[2] Thus, the development of efficient methods for the preparation of organoboronic acid derivatives is currently the subject of intense interest. Transition-metal-catalyzed addition reactions of diboron reagents such as bis(pinacolato)diboron (B_2pin_2) and bis(catecholato)diboron (B_2cat_2) to unsaturated organic compounds presents one of the most useful methods of forming carbon−boron bonds.[3] Not only simple alkynes,[4] allenes,[5] and alkenes,[6] but also bifunctional substrates[7,8] react with diboron reagents. We have recently described the rhodium-catalyzed cyclization reaction of 2-alkynylaryl isocyanates with arylboronic acids.[9] In this reaction, the aryl group on boron is transferred regioselectively onto the alkyne moiety to produce arylated 3-alkylideneoxindoles.[10] In view of the synthetic[11] and medicinal[12] importance of these heterocycles,

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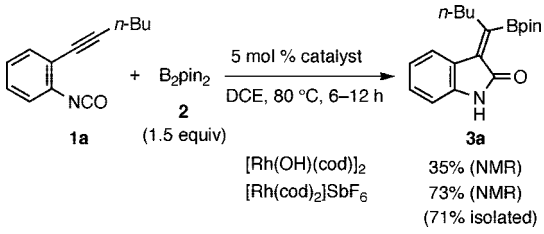
we next tried to incorporate a carbon−boron linkage into the 3-alkylideneoxindole skeleton. We report herein the stereoselective synthesis of borylated 3-alkylideneoxindoles by the rhodium-catalyzed cyclization reaction of 2-alkynylaryl isocyanates with bis(pinacolato)diboron.

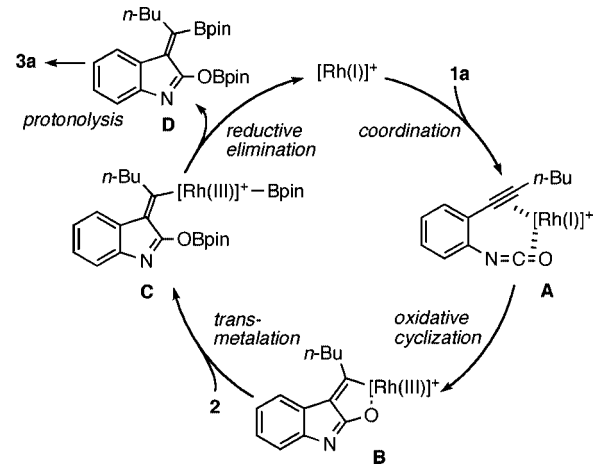
2-(1-Hexynyl)phenyl isocyanate (**1a**, 1.0 equiv) was treated with B_2pin_2 (**2**, 1.5 equiv) in the presence of $[Rh(OH)(cod)]_2$ (5 mol % Rh, cod = cycloocta-1,5-diene) in 1,2-dichloroethane (DCE) at 80 °C for 12 h (eq 1). ^{1}H NMR analysis of the reaction mixture showed that borylated 3-alkylideneoxindole **3a** was formed as a single stereoisomer (E/Z = >20:1,[13] ca. 35% yield). Through this sequence, a carbon−boron bond and a carbon−carbon bond were formed simultaneously. The reaction proceeded more facilely (73% yield by ^{1}H NMR) when the cationic complex $[Rh(cod)]_2SbF_6$ was employed.[14] Although **3a** was labile in solution, expeditious chromatography employing Florisil as the solid phase gave **3a** in 71% yield.[15] Once isolated as a yellow solid, **3a** was relatively stable and could be kept at room temperature for months without any detectable isomerization or decomposition. Whereas bis(neopentyl glycolato)diboron (B_2neo_2) gave the borylated product in a lower yield (50% by ^{1}H NMR), bis(catecholato)diboron was completely inactive under similar reaction conditions.



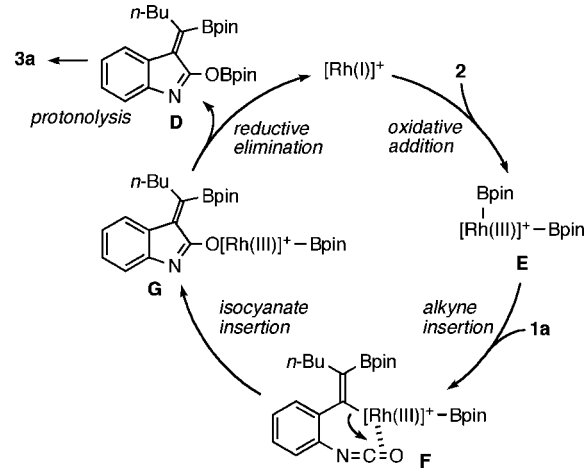
(1)

We propose that the reaction takes place through the pathway outlined in Scheme 1. The substrate **1a** binds to rhodium(I) to generate the chelate complex **A**, which then forms the oxa-rhodacycle **B** by oxidative cyclization.[16] A subsequent reaction of **B** with B_2pin_2 (**2**) produces the boryl−rhodium(III) species **C**. Finally, reductive elimination from **C** affords the diboryl intermediate **D** along with the starting cationic rhodium(I) species to complete the catalytic cycle. Protonolysis of **D** occurs during aqueous workup to give **3a**. It should be noted, however, that another mechanism is also conceivable, which involves oxidative addition of the B−B bond onto a cationic rhodium(I) complex furnishing a diboryl−rhodium(III) intermediate **E**,[17] sequential addition onto the alkyne moiety and the isocyanate moiety, and reductive elimination (Scheme 2).[18]

Scheme 1. Proposed Reaction Pathway (I)



Scheme 2. Proposed Reaction Pathway (II)



The use of other 2-alkynylaryl isocyanates **1** was also examined, with the results being listed in Table 1. Primary

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(13) The stereochemistry of the exocyclic double bond was assigned by a difference nOe study.

(14) The results with other catalysts (NMR yield/%): $[Rh(cod)_2]BF_4$ (36%), $[Rh(cod)_2]PF_6$ (35%), $[Rh(cod)_2]ClO_4$ (60%), $[Rh(cod)_2]$BARF (45%), $[Rh(cod)(MeCN)_2]SbF_6$ (56%), $[Rh(bpy)(cod)]SbF_6$ (trace), $[Ir(cod)_2]$BARF (8%), $[Ir(cod)(MeCN)_2]$BARF (7%).

(15) The borylated products **3** could be further purified by recrystallization. See the Supporting Information for details.

(16) A related rhodacycle intermediate is assumed for the Rh(I)-catalyzed Pauson−Khand-type reaction of 2-alkynylaryl isothiocyanates: Saito, T.; Nihei, H.; Otani, T.; Suyama, T.; Furukawa, N.; Saito, M. *Chem. Commun.* **2008**, 172.

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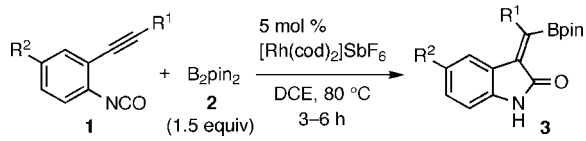
(18) Although the reaction in DCE-d_4 was monitored by ^{1}H NMR, no possible intermediate was detected.

Table 1. Rh(I)-Catalyzed Cyclization Reaction of **1** with Bis(pinacolato)diboron (**2**)[a]



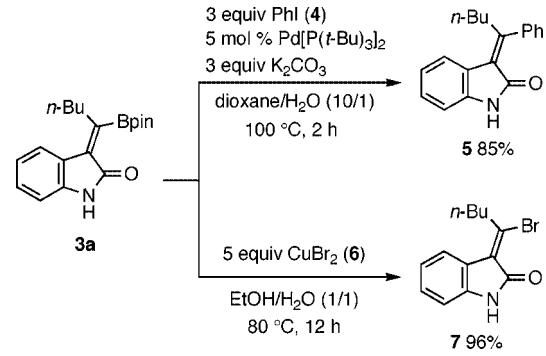
entry	**1**	R^1	R^2	**3**	yield (%)[b]
1	**1b**	Et	H	**3b**	74
2	**1c**	*n*-Pr	H	**3c**	77
3	**1d**	*i*-Pr	H	**3d**	86
4	**1e**	*t*-Bu	H	**3e**	31[c]
5	**1f**	Ph	H	**3f**	70[c]
6	**1g**	4-$MeOC_6H_4$	H	**3g**	67[c]
7	**1h**	4-BrC_6H_4	H	**3h**	74[c]
8	**1i**	3-thienyl	H	**3i**	54[c]
9	**1j**	*n*-Bu	Cl	**3j**	74
10	**1k**	*n*-Bu	OMe	**3k**	65
11	**1l**	*n*-Bu	CO_2Et	**3l**	78

[a] Conditions: **1** (0.125 mmol), **2** (0.188 mmol), $[Rh(cod)_2]SbF_6$ (6.3 μ mol, 5 mol %) in DCE (1.5 mL) at 80 °C for 3−6 h under Ar unless otherwise noted. [b] ^1H NMR yield using toluene as an internal standard; an average of two experiments. [c] $[Rh(cod)_2]SbF_6$ (12.6 μmol, 10 mol %).

and secondary alkyl groups were suitable substituents on the alkyne (entries 1−3). However, the reaction of *tert*-butyl-substituted alkyne **1e** failed to reach completion and the product **3e** was obtained in only 31% yield (entry 4). The terminal alkyne substrate gave a complex mixture. Aryl- and thienyl-substituted substrates **1f**−**1i** successfully participated in the reaction (entries 5−8). A range of functional groups including chloro, methoxy ether, and ester were tolerated on the aryl group of **1** (entries 9−11).

The synthetic utility of the isolated borylated 3-alkylideneoxindole **3a** (*E*/*Z* = >20:1) was demonstrated by further functional-group transformations shown in Scheme 3. The Suzuki−Miyaura cross-coupling reaction with iodobenzene (**4**) was executed using $Pd[P(t\text{-}Bu)_3]_2$ as the catalyst to give the phenylated 3-alkylideneoxindole **5** in 85% yield without

Scheme 3. Synthetic Application of the Borylated 3-Alkylideneoxindole **3a**



a loss of geometrical purity (*E*/*Z* = 1:>20).[19] Treatment of **3a** with $CuBr_2$ (**6**) resulted in the formation of brominated 3-alkylideneoxindole **7** in 96% yield again with retention of stereochemistry (*E*/*Z* = 1:20).[20]

In summary, we have developed a new borylative cyclization reaction with wide functional-group tolerance. The sequence results in the stereoselective incorporation of a boryl group on the exocyclic double bond of 3-alkylideneoxindoles. Studies addressing the synthetic scope of the cyclization reaction and the pharmacological properties are ongoing.

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Supporting Information Available: Experimental details and spectra data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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