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Microwave-assisted Suzuki–Miyaura cross-coupling of 2-alkyl and 2-alkenyl-benzo-1,3,2-diazaborolanes

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A B S T R A C T

Nitrogen-based boronate esters, such as 2-octyl-benzo-1,3,2-diazaborolane, 2-phenethyl-benzo-1,3,2-diazaborolane, and 2-{(1*E*)-hexenyl}-benzo-1,3,2-diazaborolane have been shown to be suitable coupling partners with arylhalides in microwave accelerated Suzuki cross-coupling reactions. Reaction yields of up to 89% were achieved. The use of a silicon group attached to the nitrogen atom, proved to enhance the reactivity of 2-octyl-benzo-1,3,2-diazaborolane.

1. Introduction

For two decades there has been intense research into the palladium-catalyzed cross-coupling reaction also known as the Suzuki–Miyaura cross-coupling reaction since its discovery by Miyaura, Yanagi, and Suzuki.[1] The Suzuki-coupling methodology has proven to be extremely powerful and versatile in the formation of carbon–carbon bonds,[2a–d] and for the production of building blocks of pharmaceutical importance.[2e–h]

Recently, a number of research groups have focused on the development of new palladium catalyst systems,[3–5] more effective ligands[6] and bases[7] with the aim of enhancing the applicability of the Suzuki type chemistry. Much emphasis has been on investigating the effects of different solvents, additives, ligand[8,9,10a,b] and more recently the use of microwave irradiation.[10c] However, literature precedent accumulated in this area has been based almost exclusively on the utility of boronic acids and boronate esters.[1,2] To date, only a few research groups have directed their attention toward expanding the scope of other potential Suzuki-coupling type organoboranes.[8,11,12] Specifically, nitrogen-based organoboranes have not been investigated in Suzuki–Miyaura chemistry. To the best of our knowledge, only a few publications have been reported on the synthesis of nitrogen-based organoboranes.[13]

We have recently published a new route to the synthesis of nitrogen-based organoboranes via rhodium-catalyzed hydroboration to afford organoboranes in high yields.[14]

The success of our new approach prompted our research into the synthesis of a range of nitrogen-based organoboranes (Table 1) and to explore their respective Pd-mediated coupling reactions with a range of arylhalides as shown in Scheme 1.

2. Results and discussion

Nitrogen-based organoboranes, namely 2-octyl-benzo-1,3,2-diazaborolane **2**, 2-phenethyl-benzo-1,3,2-diazaborolane **3**, and 2-[2-(4-methoxyphenyl)-ethyl]benzo-1,3,2-diazaborolane **4** were synthesized from benzo-1,3,2-diazaborolane **1**, which is readily prepared from commercially available borane–methyl sulfide complex and inexpensive *o*-phenylenediamine, as shown in Table 1. It was interesting to note that **1** was very robust to air and moisture when compared to the widely utilized oxygen analogues benzo-1,3,2-dioxaborolane (catecholborane) and 4,4,6,6-tretramethyl-1,3,2-dioxaborolane (pinacolborane). Benzo-1,3,2-diazaborlane **1** could be handled in an open vessel for several hours without notable oxidation to boric acid.[14]

We were delighted at the ease with which we were able to prepare the novel organoboranes **2**, **3**, and **4** in excellent yields, via Rh(I) catalyzed hydroboration of the corresponding alkenes. Rh(I) catalyzed reactions of similar alkenes with catecholborane have previously been intensively investigated and have been found to lead to a mixture of both internal and terminal products, which is

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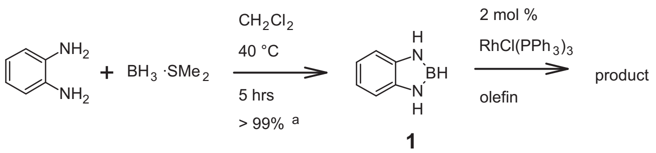
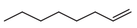
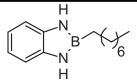
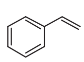
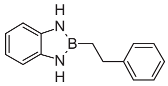
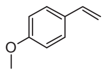
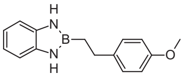
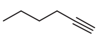
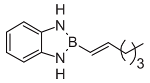
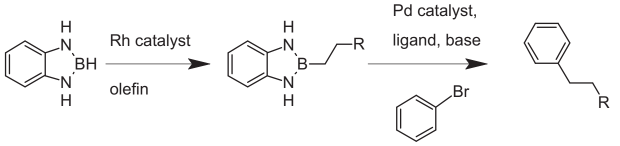
Table 1
$RhCl(PPh_3)_3$-catalyzed synthesis of nitrogen-based organoboranes



Entry	Olefin	Conditions	Product	Yield (%)
1		25 °C, 24 h	 **2**	92[b]
2		40–65 °C, 48 h	 **3**	81[b]
3		40–65 °C, 60 h	 **4**	79[b]
4		10–15 °C $HBBr_2$, 3 h	 **5**	78[b]

[a] ^{11}B NMR spectroscopy was used to monitor the formation of benzo-1,3,2-diazaborolane **1**, the yields are based on ^{11}B NMR spectroscopy.
[b] Isolated yields after flash column chromatography on silica gel. All reactions were conducted under a dry nitrogen atmosphere.



R = $(CH_2)_5CH_3$, Ph, PhOMe

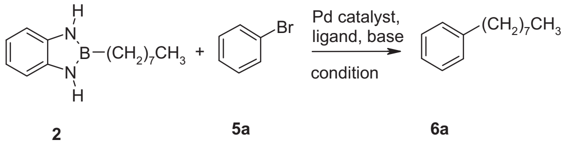
Scheme 1. Rhodium-catalyzed hydroboration and Pd-mediated coupling reactions.

not the case in our study.[15] In addition, our research group has also successfully developed a convenient procedure for the synthesis of 2-alkenyl-benzo-1,3,2-diazaboranes from terminal alkynes without the use of Rh(I) catalyst (Table 1, entry 4).

A model study was conducted in order to optimize the conditions for Suzuki–Miyaura coupling reactions. In this study 2-octyl-benzo-1,3,2-diazaborolane **2** was reacted with bromobenzene as a substrate (Table 2). This reaction was repeated several times varying commonly used Suzuki-coupling reagents (Table 2, entries 1–7), however, all attempts failed to improve the coupling reaction in yields greater than ca. 5%. Changing the solvent to THF and allowing the reaction to reflux for 48 h gave a moderately improved yield of 30% (Table 2, entry 8).

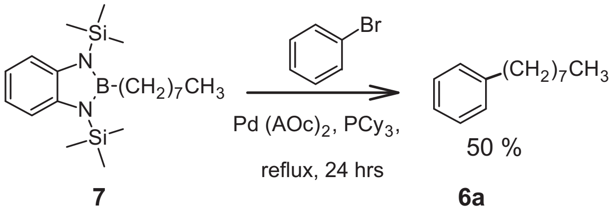
The low reactivity of **2** was attributed to the reduced Lewis acidity of the boron atom, due to pronounced overlap of the nitrogen lone pair of electrons into the vacant p_z-boron orbital. In order to enhance the reactivity of this species, it was envisaged that the introduction of a silicon hetero-atom α to the nitrogen would diminish this orbital overlap. Consequently, 2-octyl-1,3-bis-trimethylsilanyl-benzo-1,3,2-diazaborole **7** (Scheme 2) was synthesized. As anticipated, **7** was more reactive than **2** giving ca. 50% of **6a** when treated similarly to entry 8 of Table 2. Despite the increased reactivity, **7** was also more susceptible to oxidation during purification which made it difficult to work with.

Table 2
Pd-catalyzed coupling reaction of bromobenzene with 2-octyl-benzo-1,3,2-diazaborolane, optimum condition survey



Entry	Catalyst	Base	Ligand	Condition	Yield[a] (%)
1	$Pd(PPh_3)_4$	Aq Na_2CO_3	None	A	0
2	$Pd(PPh_3)_4$	Aq K_2CO_3	None	A	0
3	$Pd(PPh_3)_4$	K_2CO_3	None	A[b]	2
4	$Pd(PPh_3)_4$	K_2CO_3	None	B	2
5	$Pd(OAc)_2$	K_2CO_3	PPh_3	A[b]	5
6	$Pd(OAc)_2$	K_2CO_3	PPh_3	B	2
7	$Pd(OAc)_2$	$K_3PO_4 \cdot H_2O$	PCy_3	A[b]	0
8	$Pd(OAc)_2$	$K_3PO_4 \cdot H_2O$	PCy_3	A[c]	30
9	$Pd(OAc)_2$	$K_3PO_4 \cdot H_2O$	PCy_3	B[d]	50
10	$Pd(OAc)_2$	$K_3PO_4 \cdot H_2O$	PCy_3	C	88

Reaction conditions: (A) 1.0 equiv of **2**, 1.0 equiv of bromobenzene, 3.0 equiv of base, benzene, 4 mol % $Pd(PPh_3)_4$ or $Pd(OAc)_2$, reflux for 24 h. (B) Same as (A) but DMF was used and the mixture was capped in a closed vessel and irradiated with 100 W of microwave energy for 1 h. (C) Solvent free, 4 mol % $Pd(OAc)_2$, and 8 mol % PCy_3 was used, closed vessel 50 W microwave irradiation, 5 min.
[a] Isolated yields after flash column chromatography on silica gel.
[b] DMF used instead.
[c] 48 h reflux in THF.
[d] 2 h reflux in THF.



Scheme 2. Coupling reaction of silylated diazaborolane **7**.

Further investigations with 2-octyl-benzo-1,3,2-diazaborolane **2** incorporating the use of $K_3PO_4 \cdot H_2O$, PCy_3, $Pd(OAc)_2$ in conjunction with microwave irradiation afforded a slightly higher yield of 50% in 2 h (Table 2, entry 9) compared to conventional heating (ca. 30% in 48 h; Table 2, entry 8). The reaction yields were improved significantly to 88% when solvent free conditions were employed, furthermore, reaction completion was reached in only 5 min with microwave irradiation (Table 2, entry 10).

Having achieved optimal reaction conditions (Table 2, entry 10), we investigated the utility of diazaborolane **2**, **3**, and **5** with different arylhalides (X=Cl, Br, and I) in order to assess the scope and the limitations of such unusual Suzuki-coupling partners. The results obtained are summarized in Table 3. Working with optimized reaction conditions, diazaborolane **2** afforded the coupled-product **6b** in low 35% yield with an electron donating substituted substrate (Table 3, entry 2), however, an appreciably high yield of 89% was achieved with a more conjugated substrate (Table 3, entry 3). An arylhalide bearing an electron-withdrawing substituent reacted moderately with diazaborolane **3** in toluene affording the cross-coupled product **6d** in 57% yield (Table 3, entry 4). A solvent free cross-coupling reaction of diazaborolane **3** with bromobenzene furnished **6e** in 79% (Table 3, entry 5).

Applying the same optimal reaction conditions to couple diazaborolane **5** to different arylhalides, however, failed to give the coupled-product in excellent yields. Under these conditions, the coupling reaction of diazaborolane **5** with 9-bromoanthracene and *p*-bromonitrobenzene afforded the desired product in 34% and 64%,