Pergamon

Tetrahedron Letters 41 (2000) 4251–4255

TETRAHEDRON LETTERS

Aryl and vinyl cyclopropanes through the in situ generation of *B*-cyclopropyl-9-BBN and its Suzuki–Miyaura coupling

John A. Soderquist,* Ramon Huertas† and Gisela Leon-Colon‡

Department of Chemistry, University of Puerto Rico, Rio Piedras, PR 00931-3346, Puerto Rico

Received 20 March 2000; accepted 6 April 2000

Abstract

Dihydroboration of propargyl bromide with 9-BBN-H followed by treatment of the adduct with aqueous sodium hydroxide affords the hydroxy(cyclopropyl)borate complex (**1**), which undergoes efficient palladium-catalyzed cross-coupling to produce a variety of aryl and vinyl cyclopropanes (**2**) in good to excellent yields.

The palladium-catalyzed coupling of organic halides or triflates with organoboranes under basic conditions (Suzuki–Miyaura coupling) provides a highly versatile method for the construction of new carbon–carbon bonds which tolerates many functional groups.[1] Of the recent new applications of this process, its versatility in the synthesis of substituted cyclopropanes is particularly interesting because their vinyl and aryl derivatives undergo many unusual transformations which have significant synthetic value.[2] To date, all of the reported coupling procedures involve the use of cyclopropylboronic acid derivatives (i.e. *c*-PrB(OR)$_2$) normally requiring high temperatures, long reaction times and/or large amounts of Pd catalyst to be effective.[3] Moreover, these processes are not well-suited to the synthesis of simple mono-substituted cyclopropanes.

Several years ago, we found that when 9-BBN-based organoborane processes produce intermediate alkoxy- or hydroxyborate complexes (e.g. **1**), these mixtures can be used directly in efficient Suzuki–Miyaura couplings, thereby avoiding completely the necessity to isolate the organoborane intermediate.[4] Unfortunately, neither cyclopropyllithium nor Grignard reagents in ether produce such complexes from *B*-MeO-9-BBN with the 1:1 stoichiometry.[5] However, we envisaged a very simple direct synthesis of **1** from the dihydroboration of propargyl bromide with 2 equivalents of 9-BBN-H followed by Brown's based-induced cyclization.[7] We expected the Suzuki–Miyaura coupling of **1** with vinyl and aryl bromides to provide a very convenient route to **2**.

* Corresponding author.

† US Department of Education GAANN Pre-Doctoral Fellow.

‡ Present address: Department of Chemistry, University of Puerto Rico, Bayamon, PR.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00605-5

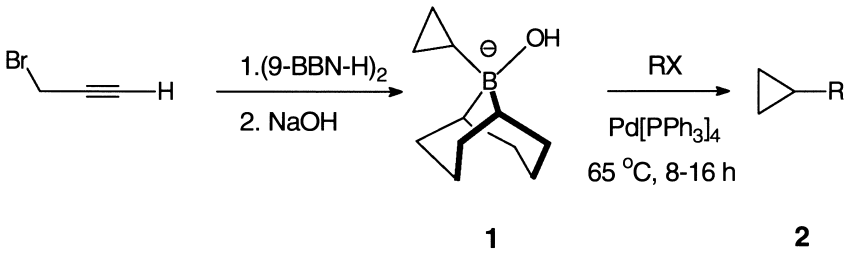


Table 1
Representative aryl and vinyl cyclopropanes from **1**

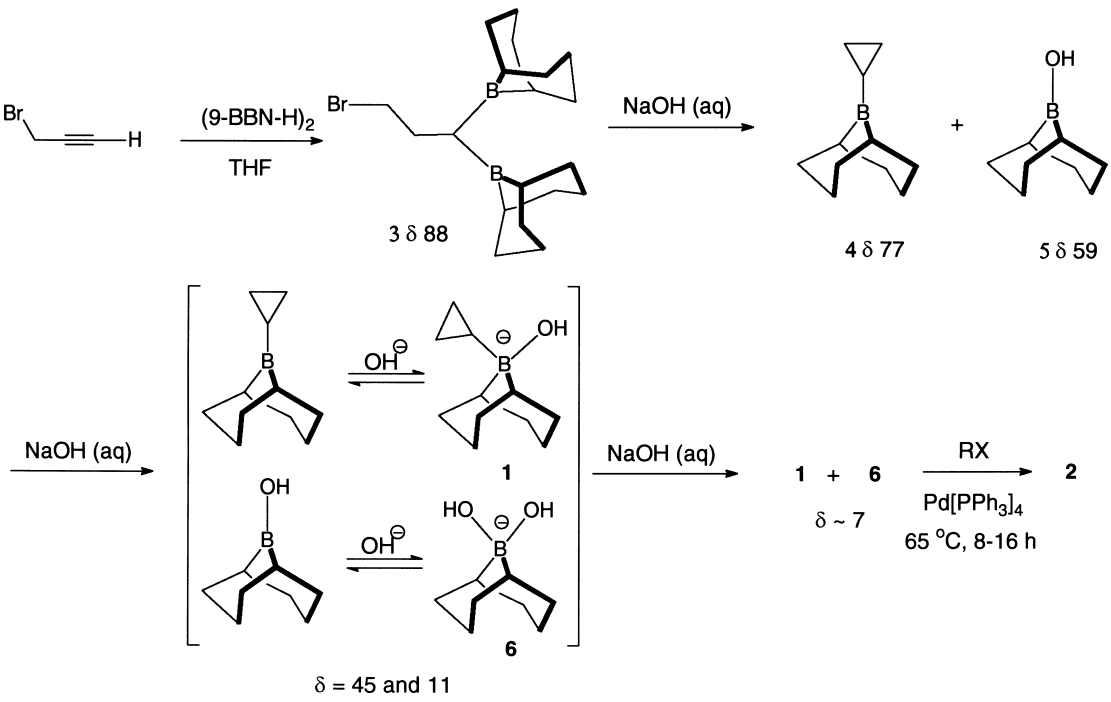
Entry	R	Product	Yield (%)[a]
1	Ph	**2a**	61
2	*m*-C_6H_4(Me)	**2b**	63
3	*o*-C_6H_4(OMe)	**2c**	92(99)[b]
4	*o*-C_6H_4(CHO)	**2d**	79
5	C(Ph)=CH_2	**2e**	84
6	β-naphthyl	**2f**	85
7	*cis*-CH=CHBu	**2g**	68 (>99% Z)[c]
8	*trans*-CH=CHBu	**2h**	60 (>99% E)[c]
9	PhCH=C<	**2i**	58

[a] Isolated yields of analytically pure materials. [b] GC yield (*vs.* internal standard). [c] Isomeric purity.

This methodology proved to be remarkably general for the synthesis of the cyclopropyl derivatives **2** (R = aryl, vinyl) proceeding smoothly to completion in 8–16 h at 65°C with isolated product yields ranging from 60–92% (Table 1).[8] Moreover, no detectable isomerization was observed in the vinylic derivatives and even a 1,1-bis-cyclopropylalkene (**2i**) was prepared from its *gem*-dibromide precursor. The process also tolerates sensitive functionality (e.g. CHO) in the aryl coupling partner (i.e. Table 1, entry 4).

We chose to examine our new process in more detail through ^{11}B NMR analysis (Scheme 1). As reported,[7a] the dihydroboration of propargyl bromide with 9-BBN-H (δ 27, dimer) proceeds smoothly to produce the 1,1-diboryl adduct **3**[7] which is cyclized with NaOH (1 equiv.) to the desired **4** together with *B*-OH-9-BBN (**5**).[9] Through ^{11}B NMR analysis, we conclude that, with the addition of a second equivalent of base, these compete for hydroxide forming an equilibrium mixture of **4** and **5** and their hydroxyborate complexes, **1** and **6**, consistent with our earlier observations with *B*-Hx-9-BBN/**5** mixtures.[9] With the addition of a third equivalent of base, the formation of both **1** and **6** is essentially complete, also consistent with the related behavior of *B*-Hx-9-BBN/**5** mixtures.[9]

For comparison purposes, we also carried out several representative couplings employing **4** to determine whether or not the presence of **5** had a deleterious effect on the overall process (Table 2). However, our results reveal that using **4** to generate **1** does not appear to have any advantages over the far more convenient in situ process. We also included an alkynyl derivative (**2j**) to extend the scope of the general process observing that the alkynyl bromide couples rapidly at 25°C.



Scheme 1.

Table 2
Representative aryl, alkynyl and vinyl cyclopropanes from **4**

Entry	R	Product	Yield (%)[a]	Rxn Time (h)/Temp (°C)
1	Ph	**2a**	65	4, 65
2	PhC≡C	**2j**	80	4, 25
3	*p*-C_6H_4(OMe)	**2k**	56	8, 65
4	C(Ph)=CH_2	**2e**	61	24, 25
5	PhCH=C<	**2i**	36	3, 65
6	*cis*-CH=CH(C_9H_{19}-*n*)	**2l**	32	4, 65

[a] Isolated yields of analytically pure materials.

The success of this remarkably simple coupling is wholly consistent with our recent mechanistic data which supports the intermediacy of hydroxyborate complexes such as **1** in alkylborane couplings leading to B→C alkyl group transfer through a hydroxo μ_2-bridged intermediate (Fig. 1).[9] Alkyl group couplings occur with retention of configuration and this has also been observed for the cyclopropylboronate systems.[3] For 9-BBN derivatives, hydroxyborate complexes (**1**) are

readily formed which not only effectively deliver the hydroxide to L_2RPdBr, but also lead directly to the key intermediate which is required for the transmetallation to occur.[9] Normally, alkyl group couplings are very slow with boronate derivatives.[10] This is consistent with their lower Lewis acidities which prevents hydroxide from being transported to the palladium via a hydroxyborate complex. Thus, this hydrolysis step becomes rate-limiting even with borinates such as **7**. However, while the transmetallation step is faster for **7** than is this hydrolysis, this may not be true for alkylboronates.

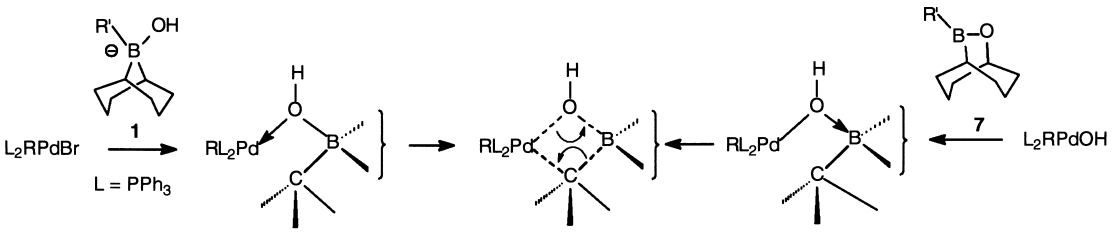


Figure 1. Approaches to the four-centered transition state for B→Pd alkyl group transfer

In summary, by taking full advantage of the formation of the hydroxy(cyclopropyl)-9-BBN complex **1** through a simple hydroboration/base-induced cyclization sequence, the key borane partner for the cyclopropylation of aryl and vinyl bromides was achieved. Its cross-coupling with a variety of these substrates provides a remarkably simple entry to **2** under milder conditions than is possible employing boronate ester or acid precursors.

Acknowledgements

The support of NIH (S06GM8102) and the US Department of Education GAANN Program (P200A70219-97A) is gratefully acknowledged.

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5. Addition of *c*-PrLi[6a] to MeO-9-BBN in ether at –78°C gives **5** and LiOMe while *c*-PrMgBr[6b] produces a ~1:1 mixture of MeO-9-BBN and MgBr[(*c*-Pr)$_2$-9-BBN] (δ –20).

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8. General procedure: To 9-BBN-H (1.35 g, 11.1 mmol) in 5 mL of dry THF was added propargyl bromide (0.66 g, 5.6 mmol) and the mixture was refluxed for 2 h. After cooling to room temperature, a previously degassed aqueous solution of NaOH (5.5 mL of 3 M, 16.5 mmol) was added and stirring was continued for 1 h. This mixture was transferred to a second flask containing *p*-$MeOC_6H_4Br$ (0.91 g, 4.9 mmol) and $Pd(PPh_3)_4$ (0.172 g, 0.15 mmol) in dry THF (10 mL). After refluxing for 8 h, the reaction was quenched with water (10 mL) and extracted with pentane (5×5 mL). The combined organic extracts were washed with 3 M NaOH (5×10 mL) and water (20×10 mL (removes THF)) and elueted through silica gel (70–230) with pentane:ether (98:2). Concentration of the filtrate in vacuo furnished 0.66 g of **2c** (92%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.02 (dt, $J=9.3$, 2.5 Hz, 2H), 6.81 (dt, $J=9.8$, 2.5 Hz, 2H), 3.78 (s, 3H), 1.86 (m, 1H), 0.90 (m, 2H), 0.62 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 135.9, 126.8, 113.7, 55.3, 14.6, 8.5; IR (neat) 3080, 3000, 2930, 2840, 1620, 1585, 1520, 1470, 1460, 1445, 1300, 1250, 1180, 1110, 1030; MS *m*/*z* (relative abundance) 148 ($M^{+\cdot}$, 100), 147 (75), 133 (62), 117 (53), 105 (48), 91 (49).
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