Cyanoboration

Palladium-Catalyzed Addition of Cyanoboranes to Alkynes: Regio- and Stereoselective Synthesis of α,β-Unsaturated β-Boryl Nitriles

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Much attention has been focused on the development of efficient syntheses of organoboron compounds because of their increasing use in the materials and pharmaceutical sciences.[1] The addition of boron-containing molecules to carbon–carbon multiple bonds is one of the most powerful strategies for the synthesis of organoboron compounds.[2] The process allows the simultaneous introduction into organic molecules of a boryl group and a functional group β to the boryl group regio- and stereoselectively.[3–5]

We have been involved in the development of catalytic addition reactions of boron- and silicon-containing molecules to unsaturated organic compounds.[4,6,7] Our recent interest has focused particularly on the addition of cyanoboranes with a B–CN bond across a carbon–carbon multiple bond to form a C–CN bond and a B–C bond. Although we succeeded recently in the catalytic activation of a B–CN bond in an intramolecular cyanoboration of alkynes, we faced significant difficulties in finding the appropriate reaction conditions for its intermolecular variant with cyanoborane derivatives that had been used in previous studies.[8] It seemed likely that the development of an intermolecular cyanoboration would lead to the efficient synthesis of a wide range of highly substituted α,β-unsaturated nitriles. We report, herein, the intermolecular cyanoboration of alkynes, in which the structure of the cyanoborane has the primary influence on the reactivity and selectivity of the addition.[9]

As reported previously,[8] our attempts at the cyanoboration of alkynes with the bis(dialkylamino) cyanoboranes **1a** and **1b** were unsuccessful. We then turned our attention to cyclic cyanoborane derivatives, such as **1c**–**g**,[10,11] whose reactivities had never been investigated. Representative results of the reactions of **1c**–**g** with 4-octyne (**2a**) are shown in Table 1. We were pleased to find that reactions of the ethylenediamine-derived cyanoboranes **1c** and **1d** afforded the cyanoboration products in moderate yields (Table 1, entries 1 and 2). Only the product of *cis* addition

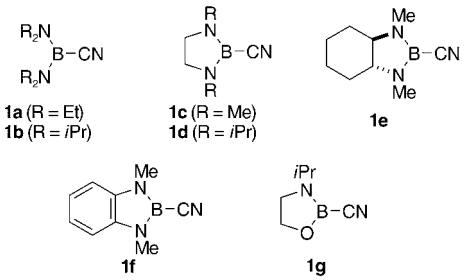
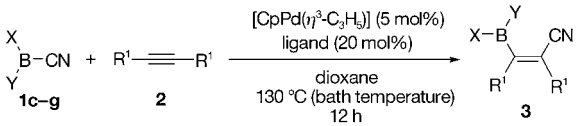


Table 1: Palladium-catalyzed reaction of symmetrical alkynes with cyanoboranes.[a]



Entry	1	Alkyne (R^1)	Ligand	Yield [%]
1	**1c**	**2a** (Pr)	PMe_3	47[b]
2	**1d**	**2a** (Pr)	PMe_3	49[c]
3	**1e**	**2a** (Pr)	PMe_3	81[b]
4	**1e**	**2a** (Pr)	PCy_3	66[b]
5	**1e**	**2a** (Pr)	PMe_2Ph	8[b]
6	**1e**	**2a** (Pr)	PPh_3	0
7	**1f**	**2a** (Pr)	PMe_3	97[b] (87[d])
8	**1g**	**2a** (Pr)	PMe_3	0
9	**1f**	**2b** (Ph)	PMe_3	99[c] (82[d])

[a] The corresponding cyanoborane **1** (0.5 mmol) and alkyne **2** (0.6 mmol) were heated in dioxane (0.5 mL) in the presence of [CpPd(η³-C_3H_5)] (0.025 mmol; Cp is cyclopentadiene) and PMe_3 (0.1 mmol). [b] Yield determined by GC. [c] Yield determined by NMR spectroscopy. [d] Yield of isolated product.

was formed in the cyanoboration reactions. Interestingly, the use of **1e**, which differs from **1c** only in that it has a fused cyclohexane ring, led to the corresponding cyanoboration products in better yields (compare entry 3 with entry 1 of Table 1). A comparison of different phosphine ligands on palladium indicated that trialkylphosphines were more effective than aryl-substituted phosphines (Table 1, entries 4–6). Remarkably, the reaction of the phenylenediamine-derived cyanoborane **1f** afforded the corresponding cyanoboration product almost quantitatively (Table 1, entry 7); the product was isolated by bulb-to-bulb distillation. In contrast, cyanoborane **1g**—derived from an amino alcohol—completely failed to give any addition product (Table 1, entry 8). Under optimal conditions, the reaction of **1f** with diphenylacetylene (**2b**) afforded the corresponding product in high yield (Table 1, entry 9).

We then examined unsymmetrical alkynes that bear both an aryl and an alkyl group at their sp-hybridized carbon atoms. The reaction of **1c** with 1-phenylpropyne (**4a**) resulted in the formation of the cyanoboration products with moderate regioselectivity (Table 2, entry 1). The regioselectivity was improved significantly to 95:5 with **1d**, which has bulky isopropyl groups on the nitrogen atoms (Table 2, entry 2). The major product was assigned as the isomer in which the cyano

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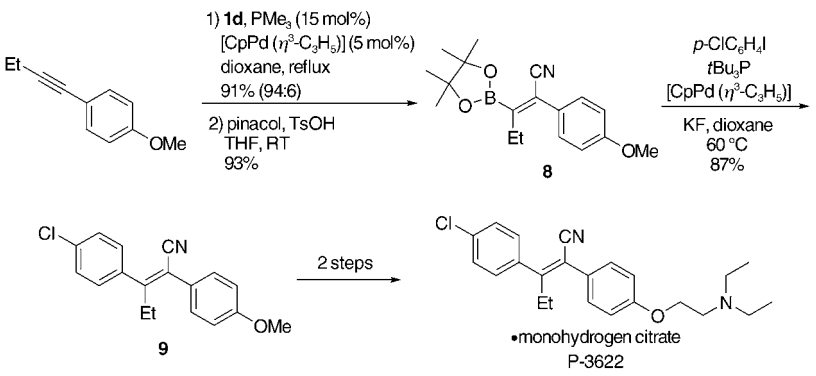
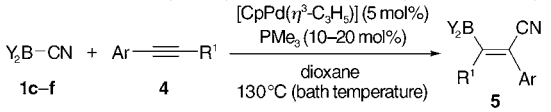
group is attached to the carbon atom α to the aryl group. The reactions of **4a** with the other methyl-substituted cyanoboranes **1e** and **1f** were moderately regioselective (Table 2, entries 3 and 4). High regioselectivities were observed for the cyanoboration of other aryl–alkyl acetylenes with **1d** (Table 2, entries 5–11). There may be a tendency for alkynes that bear a bulky aryl group to give rise to particularly high regioselectivities (Table 2, entries 8–10).

The reaction of 1-octyne with **1d** in the presence of a PMe_3/Pd^0 catalyst afforded the corresponding product **7d** in 74% yield as an



Scheme 1. Formal synthesis of the potential squalene synthetase inhibitor P-3622. Ts = *p*-toluenesulfonyl.

Table 2: Palladium-catalyzed cyanoboration of unsymmetrical alkynes.[a]

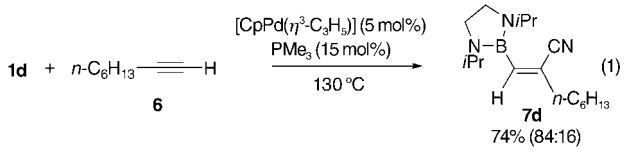


1c–f 4 5

Entry	1	Alkyne (Ar, R^1)	Yield [%][b]	Product ratio[c]
1	**1c**	**4a** (Ph, Me)	77	85:15
2	**1d**	**4a** (Ph, Me)	94	95:5
3	**1e**	**4a** (Ph, Me)	97	83:17
4	**1f**	**4a** (Ph, Me)	96	83:17
5	**1d**	**4b** (Ph, Bu)	89	95:5
6	**1d**	**4c** (*p*-$EtO_2CC_6H_4$, Bu)	72	88:12
7	**1d**	**4d** (*p*-$CF_3C_6H_4$, Me)	81	93:7
8	**1d**	**4e** (*o*-$CH_3C_6H_4$, Bu)	59	98:2
9	**1d**	**4f** (*o*-$MOMOC_6H_4$, Bu)	80	99:1
10	**1d**	**4g** (1-Naph, Me)	72	99:1
11	**1d**	**4h** (2-Naph, Bu)	61	91:9

[a] The corresponding cyanoborane **1** (0.5 mmol) and alkyne **4** (0.6 mmol) were heated in dioxane (0.1–0.5 mL) in the presence of [CpPd(η³-C_3H_5)] (5 mol%) and PMe_3 (0.05–0.1 mmol) unless otherwise noted. [b] Yield of isolated product. [c] Regioisomeric ratio determined by GC and ^{1}H NMR spectroscopy. MOM = methoxymethyl, Naph = naphthyl.

84:16 mixture of regioisomers [Eq. (1)]. The regioselectivity of the reaction was critically affected by the bulkiness of the cyanoborane: The use of **1c** instead of **1d** resulted in a 6:4 ratio of product regioisomers.



This new cyanation protocol offers a route to fully substituted α,β-unsaturated nitriles, whose regio- and stereoselective synthesis has often proved difficult. We have completed a convenient synthesis of the potential squalene synthetase (SQS) inhibitor P-3622[12] by applying a palladium-catalyzed intermolecular cyanoboration as a key step (Scheme 1). Cyanoboration of 1-(4-methoxyphenyl)-1-butyne with cyanoborane **1d**, followed by exchange of the diamine ligand on the boron atom for a pinacol ligand, afforded the corresponding 2-boryl-1-cyanoalkene **8** with good regioselectivity. Suzuki–Miyaura coupling of **8** with *p*-chloroiodobenzene gave **9**, which was converted into the SQS inhibitor P-3622 and some related compounds.[13,14]

Further optimization of the catalytic system, the synthetic application of the products, and the expansion of the scope of the cyanoboration reaction are now being investigated in our laboratory.

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[10] **Caution!** The handling cyanoboranes requires special care to avoid inhalation of hydrogen cyanide, which may be generated by the hydrolysis of the cyanoboranes. Although the cyanoboranes can be handled in air for short periods, for example, to be weighed out, all operations should be carried out in a fume hood.

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