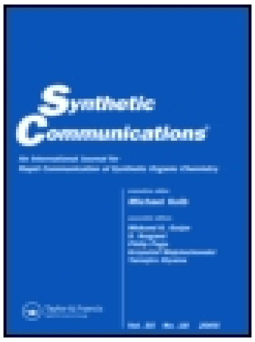

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Gram scale synthesis of alpha-cyanoalkylboronic esters via direct B–B and C–N bond cleavage

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ABSTRACT

A direct metal-free approach for the synthesis of alpha-cyanoalkylboronic esters from bis-diboron ester and azobis-nitrile compound is reported under ambient temperature and pressure via a free radical procedure.

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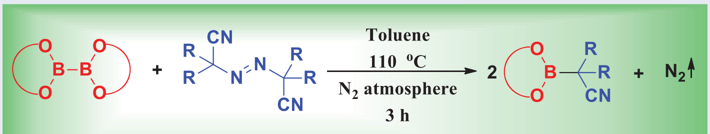
KEYWORDS
Azobis-nitrile; bis-diboron ester; metal-free; radical

GRAPHICAL ABSTRACT



Scalable synthesis of boronic esters
Metal, base and additive free
Stable to air and moisture
No chromatography separation
Simple and practical procedure
Versatile synthetic intermediate

Introduction

Alkylborane or boronate compounds represent an important class of reagents in organic synthesis of bioactive molecules and functional materials,[1–4] which can be converted to a variety of useful building blocks by both catalytic and noncatalytic processes.[5–7] The most common methods to access alkylboranes or boronates are executed by olefin hydroboration[8–10] or by addition of organometallics to borate ester derivatives[11] (i.e. pinBOMe). A more general approach has been the Miyaura borylation-type reaction of alkyl (pseudo)halides,[12,13] and to date, several effective catalyst systems based on palladium,[14] nickel,[15] copper,[16] zinc,[17] manganese,[18] cobalt,[19] platinum,[20] iridium,[21] silver[22] and iron[23] have been reported. Although, these methods have been successful, they usually require strictly anhydrous conditions, and many of them are incompatible with polar or protic groups. There are significantly less methods with metal-free conditions available for the synthesis of alkylboronic esters were encountered.[24–28]

A strategy was developed by Matteson[29] for the synthesis of alkylboronate esters through the coupling of α-haloboronates with organo-lithium or organo-magnesium reagents (Figure 1). To form the desired carbon-carbon bond, this reaction proceeds

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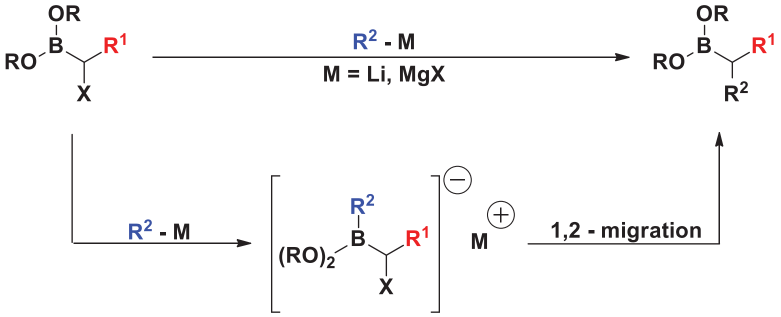


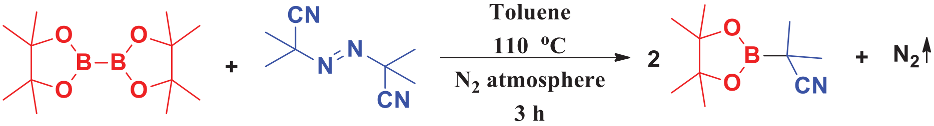
Figure 1. Matteson reaction.

through initial addition of the organometallic nucleophile to the electrophilic boron, followed by a 1,2-migration.

In this report, we describe a high yielding access to alpha-cyanoalkylboronic esters proceeding through B–B and C–N bond cleavage via a free radical procedure.

Results and discussion

Bis-diboron ester **1a** and azobis-nitrile **2a** were chosen as a substrate for the planned reaction. On exposure, the reaction mixture with dry toluene under nitrogen atmosphere for 3 h delivered the alpha-cyanoalkylboronic esters with a 91% yield with elimination of nitrogen.



1a **2a** **3a**

Reaction conditions: **1a** (6.0 g, 23.63 mmol, 1.0 equiv), **2a** (4.07 g, 24.81 mmol, 1.05 equiv) and dry toluene (90 mL) for 3 h under a nitrogen atmosphere at 110 °C.

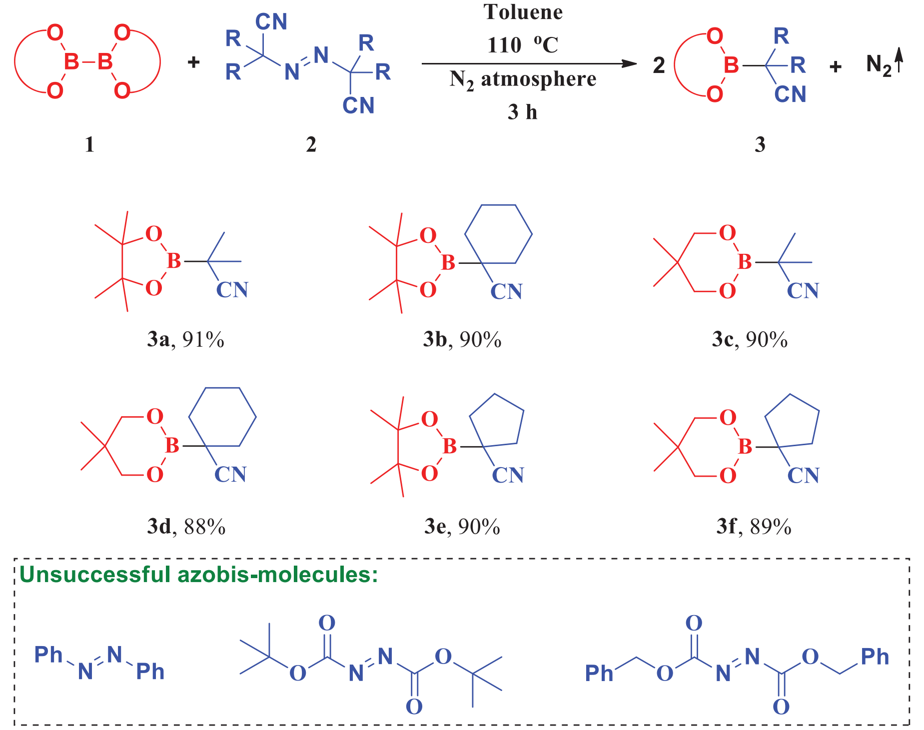
With the above reaction conditions in hand, the scopes of the alpha-cyanoalkylboronic esters were investigated and the results are summarized in Table 1.

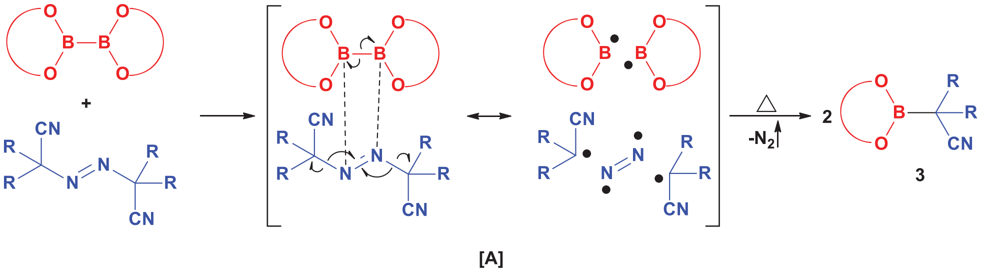
Reaction conditions: **1** (1.0 equiv), **2** (1.05 equiv) and dry toluene for 3 h under a nitrogen atmosphere at 110 °C.

A plausible reaction mechanism is proposed in Scheme 1; it may be proposed that initially, the two *N*-atom of azobis-molecules coordinate separately with two B-atoms of bis-diboron ester to form the complex (**A**). The azobis-stabilized bis-diboron ester intermediate (**A**) under goes hemolytic cleavage to delivered two molecules of alpha-cyanoalkylboronic esters **3**.[30]

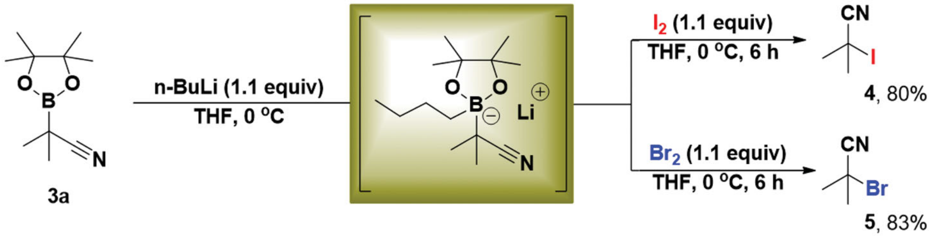
The alpha-cyanoalkylboronic esters **3a** was functionalized with molecular iodine and bromine in the presence of organo-lithium at 0 °C delivering the *tert*-halogenated cyanide compounds **4** and **5** respectively with a good yield. (Scheme 2)

Table 1. Substrate scope for synthesis of alpha-cyanoalkylboronic esters.





Scheme 1. Plausible reaction mechanism.



Scheme 2. Product post-functionalization.

Conclusion

In conclusion, we feel enthusiastic to report a direct way out of preparing a new class of alpha-cyanoalkylboronic esters proceeding through a concomitant radical initiated B–B and C–N bond cleavage. The reaction time is less and the overall yields are satisfactory in all cases. The common hindrances with free radical fragmentation like polymerizations are not visible. The present protocol has been generalized and economic.

Experimental

General procedure (A)

A flame dried (backfilled with nitrogen) two necked 100 mL round-bottomed flask (14/19 joint) was equipped with a 1.5 cm teflon-coated magnetic stir bar. Bis-diboron ester (1.0 equiv) and azobis-nitrile (1.05 equiv) was added, followed by the flask was charged with dry toluene. The flask was immersed in a pre-heated (110 °C) oil bath having a condenser with standard joint (14/19 joint) and nitrogen balloon (Figure 1 in Supporting Information). The mixture was refluxed with stirring for 3 h under nitrogen atmosphere. The resulting colorless solution was allowed to cool down to room temperature (25 °C) overnight. The crystals were found to settle down (Figures 2 and 3 in Supporting Information). The setup was then opened and the solvent was decanted out. The crystals were washed subsequently five times repeatedly with dry hexane (5 × 20 mL) and dried in vacuo (0.80 mm Hg) for 1 h. The resulting colorless crystalline solid delivered the title compound **3** (Figure 4 in Supporting Information for compound **3a**).

*2-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanenitrile (TMBN) (**3a**):* According to the general procedure (A), bis-diboron ester (6.0 g, 23.63 mmol, 1.0 equiv) and azobis-nitrile (4.07 g, 24.81 mmol, 1.05 equiv) and dry toluene (90 mL) were used. The compound was obtained as a colorless crystalline solid and yield 8.39 g (43.01 mmol, 91%). It has the following physical properties: mp 229–235 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) $\delta = 1.27$ (s, 12H), 1.56 (s, 6H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) $\delta = 23.47$, 25.03, 39.37, 83.52, 121.43 ppm; ^{11}B NMR ($CDCl_3$, 128 MHz) $\delta = 30.48$ ppm; **IR** (Neat Film, KBr): 2985, 2236, 1371, 1289, 1126 cm^{-1}. HRMS (ESI) calc'd for $C_{10}H_{18}BNO_2Na$ $[M + Na]^+$: 218.1328, Found: 218.1355.

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