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Synthesis of a dicyclobutylideneethane derivative via sequential palladium-catalyzed Miyaura borylation and Suzuki coupling

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Abstract—An efficient synthesis of a dicyclobutylideneethane derivative was achieved using a palladium-catalyzed reaction of a substituted (bromomethylene)cyclobutane with bis(pinacolato)diboron. The reaction mechanism was investigated in detail. The Suzuki cross-coupling reaction of a (bromomethylene)cyclobutane with arylboronic acid was also achieved.

Dicycloalkylideneethanes are 1,3-butadiene derivatives with cycloalkanes at the termini. The synthesis of these strained dienes has drawn much attention in recent years in an effort to understand their properties and behavior in Diels–Alder reactions. Though the syntheses of dicyclopropylideneethane[1] and dicyclopropentylideethane[2] derivatives have been well documented, dicyclobutylideneethanes have not been as accessible. The only synthesis method currently available involves a Wittig reaction between cyclobutylideneacetaldehyde and cyclobutylidenetriphenylphosphorane.[3] However, this approach is hampered by the necessity of preparing the air-sensitive cyclobutylideneacetaldehyde and the low yield of the Wittig condensation. In a continuation of our studies focused on the synthesis of boron neutron capture therapy (BNCT) agents,[4] we prepared boronated 1-aminocyclobutanecarboxylic acids (ACBC) such as **1** (Fig. 1). During the development of **1**, we developed an efficient route to dicyclobutylideneethanes via the reaction of (bromomethylene)cyclobutane **4** with bis(pinacolato)diboron. Recent reports concerning the formation and in situ reactions of (hetero)arylboronic pinacol esters encouraged us to disclose our results.[5]

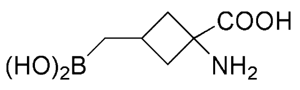

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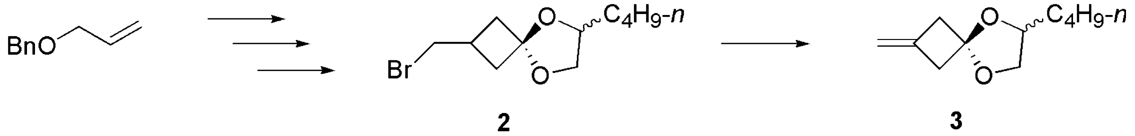
Figure 1.

In developing the synthesis of **1**, we prepared 3-(bromomethyl)cyclobutanone ketal **2** and 3-methyleneclobutanone ketal **3** starting from allyl benzyl ether (Scheme 1).[6] The most popular routes to boronic acids (reactions of Grignard reagents with borate esters,[7] hydroboration of alkenes[8] and dehydrogenative borylation of alkenes[9]) proved problematical due to the presence of the ketal group in **2** and **3**.

We then turned our attention to the newly developed Miyaura borylation[10] reaction, a palladium-catalyzed coupling of an alkenyl halide with bis(pinacolato)diboron. Starting from alkene **3**, alkenyl bromide **4**[11] was prepared in 45% yield in two steps using the



Scheme 1.

Keywords: Suzuki coupling; borylation; synthesis; dicyclobutyldieneethane.

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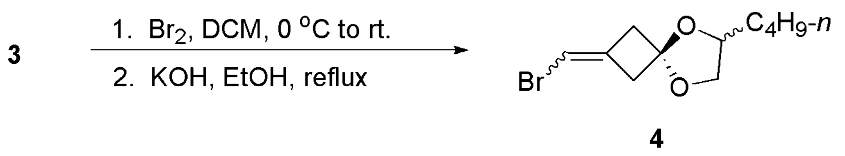
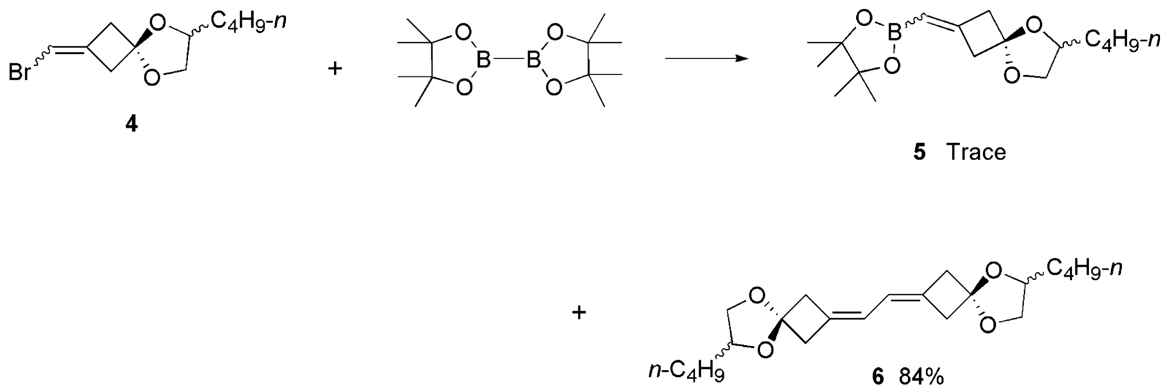


Scheme 2.



Scheme 3. *Reagents and conditions:* $PdCl_2(PPh_3)_2 \cdot 2PPh_3$ (5 mol%); PhOK (1.5 equiv.); toluene (3 mL); 50°C.

reported procedures[12] (Scheme 2). Alkenyl bromide **4** exhibits characteristic resonances at δ 135,5 and 98.9 ppm in the ^{13}C NMR spectrum. The rigid spiro conformation in **4** leads to four different resonances (46.3; 46.0, 45.0; 44.7 ppm) for the two secondary cyclobutyl carbon atoms.

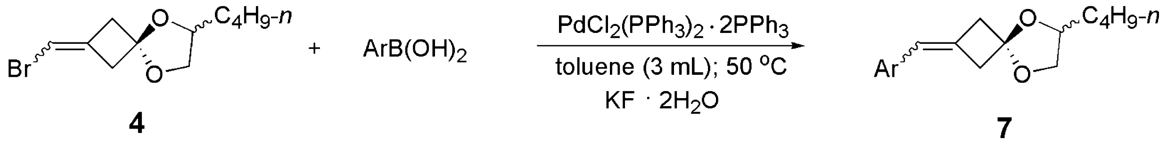
Under typical Miyaura conditions (5 mol% $PdCl_2(PPh_3)_2 \cdot 2PPh_3$ and 1.5 equivalents of PhOK in toluene at 50°C),[10c] the reaction of **4** with 1.1 equivalent of bis(pinacolato)diboron afforded only a trace of the anticipated alkenylboronic ester **5**. However, dicyclobutylideneethane **6** was obtained in 84% isolated yield (Scheme 3).[13] Diene **6** exhibits a characteristic olefinic singlet at δ 5.84 ppm in the ^1H NMR and four resonances at 45.2, 44.9, 43.7, 43.4 ppm in the ^{13}C NMR spectrum. Since the precursor (bromomethylene)cyclobutane can be readily prepared from cyclobutanone,[12,14] this route to dicyclobutylideneethane is quite attractive.

There are three mechanistic pathways which could lead to diene **6**: homocoupling of alkenyl bromide **4**,[15] homocoupling of the in situ generated alkenylboronic ester **5**,[16] and Suzuki cross-coupling of alkenyl bromide **4** with in situ generated alkenyl boronic ester **5**.

In order to determine which pathway is active, we carried out a series of experiments. Reaction of alkenyl bromide **4** in the absence of the diboron ester but in the presence of the catalyst system did not generate diene **6**, which rules out simple homocoupling of the alkenyl bromide. Reaction of alkenyl bromide with excess diboron ester (10 equiv.) produced boronic ester **5** in significant yields, but **6** did not form. We then found that a substoichiometric quantity of the diboron ester (0.55 equiv.) was sufficient for the complete consumption of alkenyl bromide and led to good yields of the diene. Based on these observations, diene **6** is formed via the Miyaura borylation of the alkenyl bromide followed by Suzuki cross coupling of the product boronic ester with the remaining alkenyl bromide.

Suzuki cross-coupling reactions of various alkenyl bromides with boronic acids have been extensively studied.[17] To the best of our knowledge Suzuki reactions of highly strained (bromomethylene)cyclobutane have not been reported. With alkenyl bromide **4** in hand, we decided to investigate its cross-coupling reaction with arylboronic acids. Using PhOK as the base and $PdCl_2(PPh_3)_2 \cdot 2PPh_3$ as catalyst in toluene at 50°C, the reaction produced a mixture of cross-coupling product **7** and alkene **3** (the reduction product of the alkenyl bromide **4**). Though many palladium-catalyzed ring-opening reactions of cyclobutane have been reported,[18] under our reaction conditions the highly strained methylenecyclobutane moiety was unreactive. After careful examination of a variety of bases, $KF \cdot 2H_2O$ was found to be most effective. Apparently it suppresses the formation of alkene **3** and the reaction affords the cross-coupling product **7** in good yield (Scheme 4).

In summary, we have developed a high yield method for preparing a dicyclobutylideneethane derivative via sequential Miyaura borylation and Suzuki cross-coupling reactions of a (bromomethylene)cyclobutane. The reaction mechanism was identified. The reaction provides a novel and general synthetic strategy to a variety of symmetric dicycloalkylideethanes. The Suzuki cross-coupling of highly strained (bromomethylene)-cyclobutane derivative with arylboronic acid was also investigated.



Ar: 4-methylbenzyl 75%; 1-naphthyl 85%; 4-acetobenzyl 73%

Scheme 4.

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