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A New Directed Synthesis of Enol Borates from *gem*-Borazirconocene Alkanes, and their Regioselective Conversion to α-Bromo Ketones

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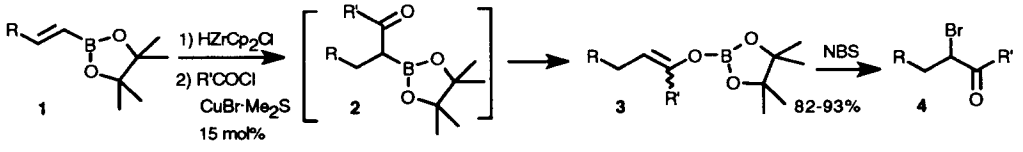
Abstract: Reaction of acid chlorides and gem-borazirconocene alkanes produces enol borates by rearrangement of α-bora ketones. Reaction of the enol borates with NBS occurs with complete regioselectivity to give unsymmetrical α–bromo ketones.

Boron enolates are useful intermediates in organic synthesis and as such have received much attention.[1] They undergo the very useful aldol condensation, giving products of high diastereoselectivity.[2] Where appropriate, enantioselectivities are also high.[3] In addition, boron enolates undergo several other useful reactions such as halogenation,[4] conversion to enolate ions,[5] ready hydrolysis,[6] and an interesting enantioselective Ireland-Claisen rearrangement.[7] While most of the efforts for the preparation of boron enolates have centered on borinates, C=C-OBR$_2$, several syntheses of enol borates have appeared in the literature. Thus, Gennari reported the preparation of enol borates from ketones and 2-chloro-1,3,2-dioxaborolane,[8] or by exchange between a silyl enol ether and 2-chloro-1,3,2-dioxaborolane.[9] Hoffmann has oxidized 1-alkenyl boronates with trimethylamine-N-oxide.[10] More recently, he has tried low-temperature reaction of lithium enolates with 2-chloro-1,3,2-dioxaborolane.[11] But these methods are limited. In this communication we offer a different approach for the synthesis of enol borates, and as an example of their utility, their regioselective conversion to α-bromo ketones.

Scheme 1. Directed Formation of Enol Borates and their Conversion to α–Bromo Ketones



We have been demonstrating the synthetic usefulness of *gem*-borazirconocene alkanes.[12] They are readily available from alkynes by a hydroboration/hydrozirconation sequence. The utility of *gem*-borazirconocene alkanes lies in the very different reactivities of the Zr-C and B-C bonds. To date, all reactions involving *gem*-borazirconocenes proceed initially with cleavage of the Zr-C bond, thus allowing complete control of bond formation. Zirconocene chloroalkanes react with acid chlorides to give ketones.[13] In the case of *gem*-borazirconocene alkanes, a similar reaction would lead to α-bora ketones. Owing to the very favorable driving force of B-O bond formation, we reasoned that the α-bora ketones, **2** should undergo spontaneous rearrangement to enol borates, **3.** Thus, when **1a** was reacted with acetyl chloride, enol borate **3a** was produced and isolated. The *E/Z* ratio, 6:1, was determined from the vinylic hydrogens (δ 4.97 and 4.62) or from the methyl groups (δ 1.80 and 1.82). However, for the moment our concern is not with the aldol reaction or the geometry of the enol borates. α–Bromo ketones are useful intermediates in the pharmaceutical industry.[14] However, unsymmetrical α-bromo ketones are difficult to prepare. Hooz has demonstrated that enol borinates undergo regioselective halogenation.[4] Therefore, taken together directed enol boration of *gem*-borazirconocene alkanes followed by regioselective bromination should offer an attractive approach to the preparation of synthetically useful unsymmetrical α-bromo ketones. That this indeed is the case is illustrated in Scheme 1.

A typical procedure is the preparation of **4a**: A suspension of $HZrCp_2Cl$ (312 mg, 1.21 mmol) in CH_2Cl_2 (2 ml) was stirred at ambient temperature under an atmosphere of argon. A solution of (E)-pinacol 1-octenylboronic ester (230 mg, 0.97 mmol) in CH_2Cl_2 (2 ml) was added. After the cloudy reaction mixture turned to a clear yellow solution, 25 mg of $CuBr{\cdot}SMe_2$ was added, followed by acetyl chloride (142 mg, 1.8 mmol). When the yellow color of the reaction mixture disappeared (usually 4-8 hr), 323 mg of N-bromosuccinimide was added. The reaction mixture was stirred for 30 min. Evaporation of the solvent, extraction of the resulting residue with hexanes (3 x 4 ml), and concentration of the combined extracts provided an oil which was purified by chromatography (hexanes:ether 95:5) leading to analytical pure **4a** (208 mg, 89%). ^1H NMR δ 4.22 (dd, 1H), 2.35 (s, 3H), 2.05-1.87 (m, 2H), 1.51-1.22 (m, 10H), 0.89 (t, 3H). ^{13}C NMR δ 202.2, 54.5, 33.6, 31.7, 29.0, 28.9, 27.3, 26.0, 22.6, 14.0. EI-MS: m/z (relative intensity) 236/234 (M^+, 1), 193/191 (1), 155 (6), 138/136 (100).

Table 1. Preparation of α-Bromo Ketones[a]

Entry	R in Scheme 1	R'	Product	^{1}H NMR δ CHBr (dd, $^3J_{H...H}$ /Hz)	^{13}C NMR δ CHBr	Yield, %[b]
1	n-hexyl	Me	**4a**	4.22 (8.1, 6.7)	54.5	89
2	n-butyl	n-Pr	**4b**	4.24 (8.1, 6.5)	53.8	93
3	cyclopentyl	Me	**4c**	4.25 (8.1, 6.6)	53.8	91
4	3-chloropropyl	Me	**4d**	4.23 (8.2, 6.2)	53.7	85
5	3-phenylpropyl	Me	**4e**	4.20 (8.1, 6.4)	54.1	90
6	phenyl	Me	**4f**	4.48 (7.5)[c]	53.2	82
7	t-butyl	Me	**4g**	4.32 (8.6, 4.8)	50.4	83
8	cyclopentyl	Ph	**4h**	5.17 (7.3)[c]	46.4	91

The one-pot reaction was run in a 1:1.2:1.5:1.5 ratio of alkenyl boronate, $HZrCp_2Cl$, R'COCl, NBS, respectively. [b]Isolated yields based on alkenylboronates. All structures are consistent with ^{1}H NMR, ^{13}C NMR and MS spectra. [c]Overlapping doublets.

The yields of **4** are excellent and are summarized in Table 1. The reaction works well for primary, secondary and tertiary R groups (Scheme 1). The totally directed bromination of what amounts to n-pentyl n-propyl ketone (Table 1, entry 2) is exemplary. The reaction also works with aryl groups (Table 1, entry 8), though of course, no problem of directed bromination would be expected here. Indeed, we have found that the reaction when done with freshly recrystalized NBS gives essentially analytically pure samples. Thus, we have a very general one-pot procedure for obtaining α-bromo ketones from alkenyl boronates and acid chlorides.

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