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CONSTRUCTION OF CYCLOPENTYL CARBINOLS FROM ω-TOSYLOXY-1-ALKENYL BORONATE ESTERS AND GRIGNARD REAGENTS†

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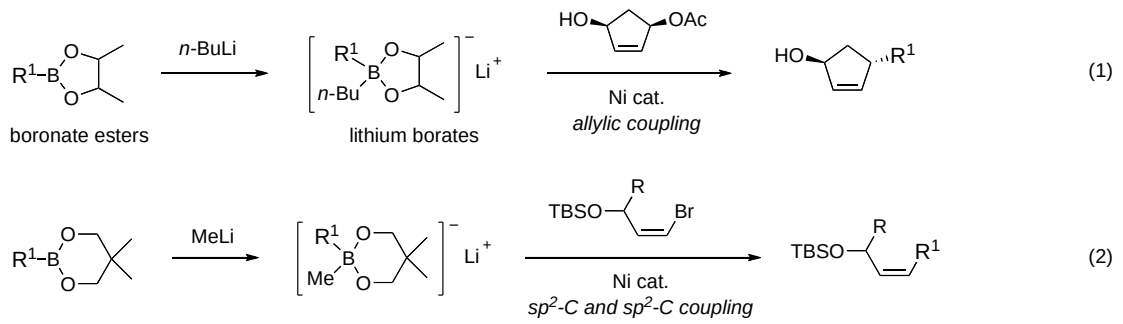
Abstract – Addition of RMgCl (R = *n*-Bu, Ph) to pinacol esters of 6-tosyloxy-1-alkenyl boronic acids at –78 °C gave the borates, which upon warming to room temperature underwent migration of R on boron to C(1) carbon and concomitant ring construction C–C bond formation between C(2) and C(6), eventually producing cyclopentyl alkyl (or aryl) carbinols after oxidative workup of the borane intermediates with 35% H_2O_2. Eight examples are presented and the reaction was applied to construction of a cyclohexyl carbinol.

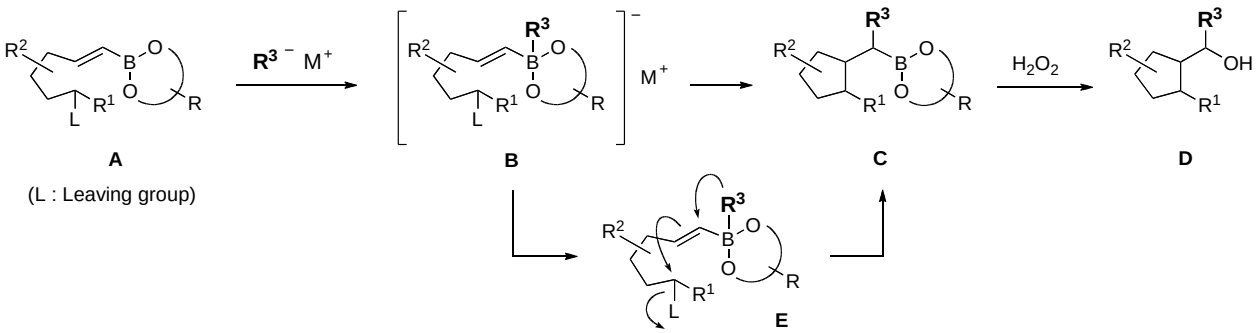
Esters of organoboronic acids with a diol (organoboronate esters) are chemically stable neutral compounds that are easily purified by chromatography and/or by distillation, whereas organoborates derived by reaction with organometallics are reactive anions that undergo coupling reactions with allylic acetates, alkenyl bromides, and aryl halides.[1] Examples of such coupling reactions are shown in eqs (1)[2,3] and (2)[4,5] of Scheme 1.[6] Importantly, low reactivity of the substrates due to steric reasons are compensated by the high reactivity of the borates. We then envisioned another reaction delineated in Scheme 2, in which borate **B** undergoes migration of R^3 to the olefinic carbon and concomitant cyclization as illustrated in **E** to produce cyclopentyl alkyl (or aryl) carbinol **D** after oxidative workup of the borane intermediate **C**. Previously, an anion and a radical, generated at the C-L (L = I, Br) carbon of organoboranes of similar structures to **A**, have been shown to undergo cyclization.[7,8] Herein, we report preliminary results of the migration/cyclization.

First, effect of metal cations (M^+) of *n*-Bu-M on the proposed reaction was examined using boronate

† This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

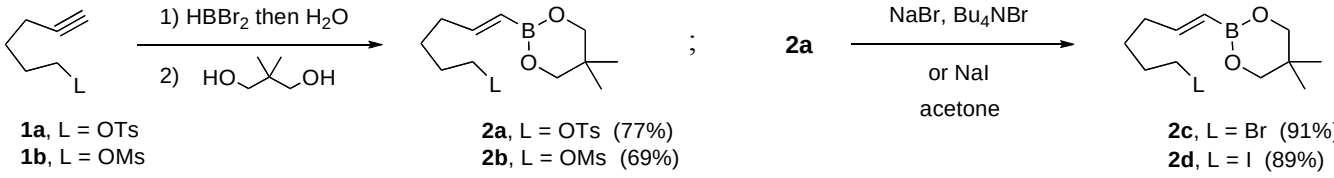


Scheme 1. Previous coupling reactions using lithium borates



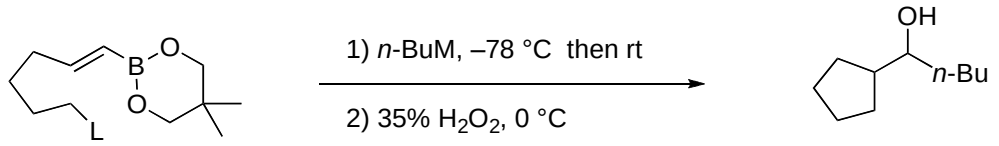
Scheme 2. Formation of cyclopentane ring through migration of R^3 and cyclization on borates **B**

esters **2a**–**d** (L = OTs, OMs, Br, I) possessing a 2,2-dimethylpropane-1,3-diol ligand (examination of diol ligands is described in a later section). The esters **2a** and **2b** were synthesized through hydroboration of acetylenes **1a** and **1b** with $HBBr_2$, hydrolysis, and subsequent esterification of the resulting boronic acid with the diol in good yields. The TsO group in **2a** was replaced by halogen atoms to afford bromide **2c** and iodide **2d**, respectively. Addition of *n*-Bu-M (M = Li, ZnCl, MgCl) to **2a**–**d** were carried out at –78 °C for 30–60 min. The resulting borates were warmed slowly to room temperature and, after stirring overnight, the products were treated with 35% H_2O_2 in order to produce alcohol **3**. As summarized in Table 1, reaction of tosylate **2a** with slightly excess *n*-BuLi (1.2 equiv) in THF and Et_2O gave unidentified products (entries 1, 2). On the other hand, **2a** and excess *n*-BuZnCl (6 equiv) in THF produced the tosylate of 5-hexen-1-ol (entry 3), indicating that the zinc borate was indeed formed, but remained unchanged before the aqueous work up. Next, *n*-BuMgCl (6 equiv) in THF was investigated



Scheme 3. Synthesis of substrates **2a**–**d**

Table 1. Reaction of boronate esters **2a–d** with *n*-Bu-M.



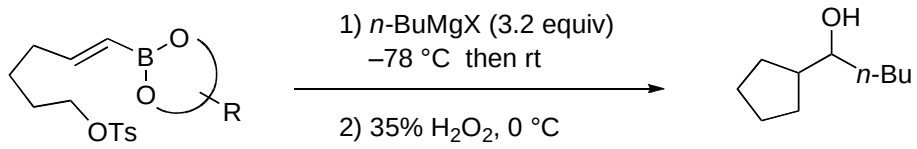
2a–d **3**

entry	substrate	L	*n*-BuM M	*n*-BuM equiv	solvent	yield of **3** (%)
1	**2a**	OTs	Li	1.2	THF	–[a]
2	**2a**	OTs	Li	1.2	Et_2O	–[a]
3	**2a**	OTs	ZnCl	6	THF	–[b]
4	**2a**	OTs	MgCl	6	THF	69[c]
5	**2a**	OTs	MgCl	6	Et_2O	69[c]
6	**2a**	OTs	MgCl	2.5	THF	53[c]
7	**2b**	OMs	MgCl	2.5	THF	41[d]
8	**2c**	Br	MgCl	6	THF	28[d]
9	**2d**	I	MgCl	6	THF	29[d]

[a] A mixture of unidentified compounds was produced. [b] Tosylate of 5-hexen-1-ol was obtained. [c] Isolated yield. [d] Determined by ^{1}H NMR spectroscopy using pyridine as a reference.

to afford the desired alcohol **3** in 69% yield after oxidative workup (entry 4). Reaction in Et_2O proceeded with a comparable yield (entry 5). Use of 2.5 equiv of *n*-BuMgCl in THF resulted in decrease in yield (53%, entry 6). In contrast to tosylate **2a**, mesitylate **2b**, bromide **2c**, and iodide **2d** produced alcohol **3** in lower yields (entries 7–9).

Table 2. Further optimization of the reaction using **2e–g**.

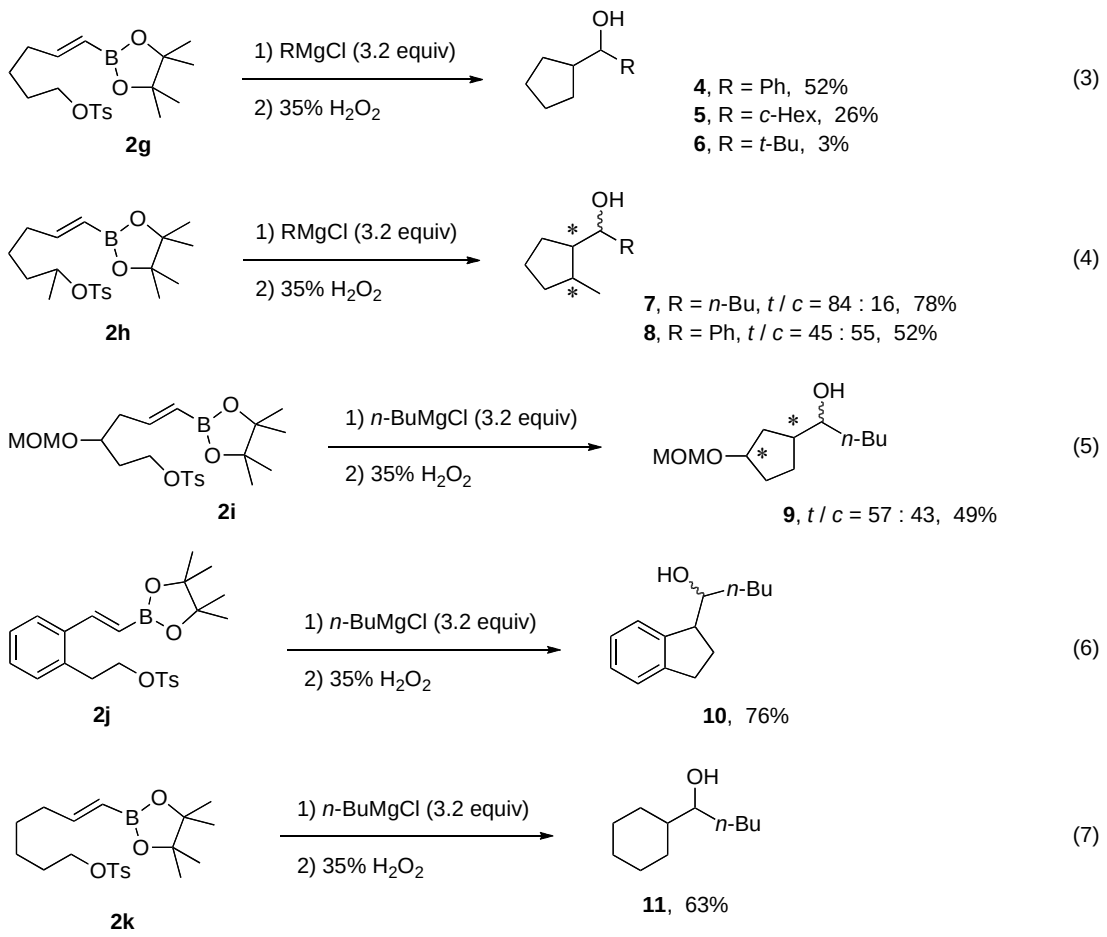


2e–g **3**

entry	substrate	ligand	reagent	yield (%)
1	**2e**	$O(CH_2)_3O$	*n*-BuMgCl	53
2	**2f**	OCH(Me)CH(Me)O	*n*-BuMgCl	58
3	**2g**	$OC(Me)_2C(Me)_2O$	*n*-BuMgCl	74
4	**2g**	$OC(Me)_2C(Me)_2O$	*n*-BuMgBr	48

Further optimization of the reaction was executed with boronate esters **2e–g**, which were prepared by a method similar to **2a**. Reactions with *n*-BuMgX (3.2 equiv) are summarized in Table 2. The pinacol ester **2g** gave product **3** in good yield (entry 3), while **2e** and **2f** showed comparable reactivities to **2a** (entries 1, 2; *cf*. Table 1, entry 6 with 2.5 equiv of BuMgCl). We then tested *n*-BuMgBr, which demonstrated no advantage over *n*-BuMgCl (entry 4).

The conditions developed for the migration/cyclization were applied to various cases to clarify the scope and limitations (Scheme 4). Substrates **2h–j** were synthesized by hydroboration of the corresponding acetylenes with HB(*c*-Hex)$_2$ followed by oxidation of the boranes with Me_3NO and subsequent ligand exchange with pinacol,[9] while **2k** was synthesized through hydroboration with $HBBr_2$ similar to **2a** and **2g**. Reaction of **2g** with PhMgCl (3.2 equiv) afforded **4** in 52% yield, while lower yields were obtained with *c*-HexMgCl and *t*-BuMgCl, indicating a limitation toward steric hindrance at the reagent side (eq 3). On the other hand, bulkiness at the TsO carbon seems less sensitive as indicated by reaction of **2h** with RMgCl (R = *n*-Bu, Ph), giving **7** and **8**, respectively (eq 4). Two more examples are shown in eqs 5 and 6, in which **9** and **10** were formed in moderate to good yields. The reaction was also applicable to cyclohexane ring formation as shown in eq 7.



Scheme 4. Scope and limitations of the reaction

In summary, we have developed a new construction of cyclopentyl alkyl (or aryl) carbinols by reaction of pinacol alkenylboronate esters and RMgCl through migration of R group and cyclization. The stereochemical outcome was, however, controlled little by the existing chiral centers. We are continuing investigation to control the stereochemistry of the reaction.

ACKNOWLEDGEMENTS

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