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Homologations of boronate esters: the first observation of sequential insertions

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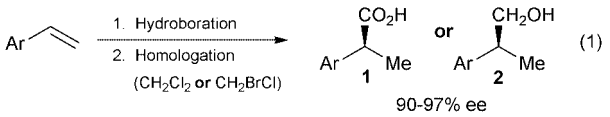
By employing dibromo or diiodomethane as halomethyllithium precursors, the *in situ* double and triple homologation of boronate esters has been obtained for the first time.

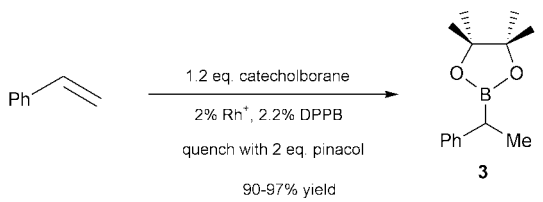
Homologation reactions of boronate esters and other borane species have been well explored, most notably by Brown *et al.*[1] and Matteson *et al.*[2] We have recently reported a variant in which the chirality is introduced *catalytically via* a Rh–binap-mediated hydroboration with catechol borane.[3,4] Homologation of the intermediate boronate ester with CH_2Cl_2 or CH_2BrCl in the presence of Bu^nLi yields either 2-arylpropionic acids **1** or 2-arylpropanols **2** respectively [eqn. (1)]. This asymmetric hydroboration–homologation (AHH) reaction was used in the synthesis of enantiomerically enriched 2-arylpropionic acids, such as Ibuprofen™ [eqn. (1)].



(1)

During our study of the latter reaction, we were intrigued by the observed chemoselectivity. In both cases, the products of the homologation reaction, prior to oxidation, are also boronate esters and might be expected to undergo homologation themselves. The boronate ester resulting from homologation with $LiCHCl_2$ is sufficiently distinct from the starting boronate ester **3** [eqn. (2)] by virtue of the chlorine substituent. However, the boronate ester from homologation with $LiCH_2Cl$ **7** [eqn. (5)] should be susceptible to further homologation. Despite this fact, no such sequential homologation with halomethane reagents has been reported to the best of our knowledge. Brown *et al.* have reported a ring-expansive sequential homologation reaction using halomethane reagents, in which the halomethane reagent was added in successive portions after isolation of the previously generated boracycle.[5] Shea *et al.*[6] have reported that sulfur ylides can homologate triorganoboranes sequentially in the same pot to yield long chain aliphatic alcohols after oxidation but such a reaction has not been observed with boronate esters. We wish to report that by adjusting the leaving group ability of the halomethane reagent, double and triple homologations can be achieved.

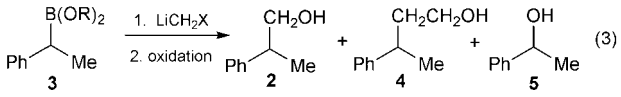
Using our standard protocol, boronate ester **3** is generated by hydroboration of styrene with catechol borane in the presence of $[Rh(cod)_2]^+BF_4^-$ and dppb,† followed by transesterification with pinacol which permits isolation of the boronate ester by chromatography [eqn. (2)].[4]



(2)

Treatment of **3** with $LiCH_2Cl$ provided, after oxidation, the expected product **2** (Table 1).‡§ The nature of the halogen which is transmetallated to generate $LiCH_2Cl$ has little effect on the outcome of the homologation. Thus ICH_2Cl gave 79% homologation while $BrCH_2Cl$ gave 88%. However, the nature of the leaving group was significant. Using $BrCH_2Br$ as the precursor to the homologation reagent, a new product **4** was observed which resulted from the incorporation of two CH_2 units. Diiodomethane also gave the product of double homologation, but with lower overall conversion (entry 4). This is presumably due to the decreased stability of $LiCH_2I$.[7] (Note that any unreacted boronate ester **3** is converted into **5** after oxidation with $NaOH/H_2O_2$.) Although the amount of the doubly homologated alcohol could be increased by increasing the amount of $LiCH_2Br$ (see below), no double homologation was observed with $LiCH_2Cl$ even when it was used in excess (entry 5).

Table 1 Observation of single and double homologation



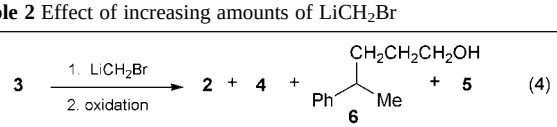
(3)

Entry	Reagent precursor	Homologation reagent	Equiv.	Single insertion **2**[a]	Double insertion **4**	Unreacted **5**
1	$BrCH_2Cl$	$LiCH_2Cl$	1.1	88%	0%	12%
2	ICH_2Cl	$LiCH_2Cl$	1.1	79%	0%	21%
3	$BrCH_2Br$	$LiCH_2Br$	1.1	74%	15%	11%
4	ICH_2I	$LiCH_2I$	1.1	43%	17%	40%
5	$BrCH_2Cl$	$LiCH_2Cl$	2.0	83%	0%	17%

[a] Relative ratios determined by integration of appropriate resonances in NMR; NMR yield calculated by use of internal standard is within several percent of quoted ratios.

Using dibromomethane as the candidate for further study, the effect of increasing the amount of the homologating reagent was examined. As shown in Table 2, the percentage of doubly homologated alcohol **4** which was formed in the reaction increased when the amount of $LiCH_2Br$ was increased above 1 equivalent. A significant increase was not, however, observed as the amount of $LiCH_2Br$ was increased further. It should be noted that a 5–10% variance was generally observed in the relative ratios reported in Table 2, which may be attributable to

Table 2 Effect of increasing amounts of $LiCH_2Br$



(4)

Entry	Equiv. of $LiCH_2Br$	Single insertion **2**[a]	Double insertion **4**	Triple insertion **6**	Unreacted **5**
1	1.1	74%	15%	0%	11%
2	2.0	34%	34%	10%	22%
3	4.0	29%	40%	10%	21%
4	6.0	35%	28%	7%	31%
5	10.0	22%	30%	19%	29%

[a] Relative ratios determined by integration of appropriate resonances in NMR; NMR yield calculated by use of internal standard is within several percent of quoted ratios.

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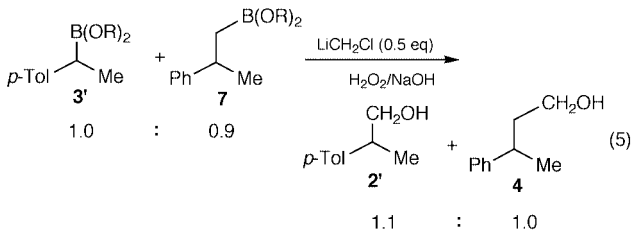
differences in rates of addition of Bu^nLi, especially as we attempted to generate increasing amounts of $LiCH_2Br$. At these higher loadings, we also observed alcohol **6**, resulting from incorporation of *three* CH_2 units. One interesting trend which can be gleaned from Table 2 is that as the amount of $LiCH_2Br$ used is increased, there is a concomitant increase in the amount of alcohol **5** resulting from unreacted starting material (compare entry 1 with 4 and 5).

This observation led us to postulate that homologated boronate esters such as **7** were more reactive than the seondary boronate esters **3**. This reactivity difference could be rationalized by the different steric requirements of **3** *cf.* primary homologated derivatives such as **7**. To test this hypothesis, we prepared and isolated **7** and also prepared boronate ester **3′** by hydroboration of *p*-methylstyrene. A *ca.* 1 : 1 mixture of **7** and **3′** was then treated with $LiCH_2Cl$ [eqn. (5)]. This homologating reagent was chosen for two reasons. Firstly, its use would obviate complications due to double homologations observed with $LiCH_2Br$; and secondly, as $LiCH_2Cl$ is the least reactive of the homologating reagents, it would presumably be the best probe of reactivity differences.



Much to our surprise, in the presence of a limiting quantity of $LiCH_2Cl$ (50%), boronate esters **7** and **3′** gave equal amounts of homologated products **4** and **2′** (19 and 21% respectively) indicating no difference in the reactivity of the secondary and primary boronate esters under these conditions. It should be noted that the introduction of the *para* methyl substituent will skew the results somewhat as it alters the electronic nature of the migrating group. An isotopically labeled analog of **3** is currently being prepared and the results of this study will be reported in due course. Experiments are also underway to elucidate the reason for the remarkable differences in the reactivity of $LiCH_2Cl$ and $LiCH_2Br$.

In conclusion, we have shown that the homologation of boronate esters derived from the hydroboration of styrene and its derivatives can be carried out in a sequential, one-pot manner depending on the nature of the homologating reagent used. Homologation with $LiCH_2Cl$ yields only the product of single homologation regardless of the number of equivalents used, and $LiCH_2Br$ yields the doubly homologated product even at 1 equivalent loading. Increasing the amount of this reagent leads to the incorporation of three CH_2 units in a single reaction.

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Notes and references

† cod = Cycloocta-1,5-diene, dppb = 1,4-bis(diphenylphosphino)butane. Note that the asymmetric version of this reaction employs binap [2,2'-bis(diphenylphosphino)-1,1'-binapthyl]. See ref. 4 for appropriate experimental procedures.

‡ The following procedure is representative. *Double homologation with* $LiCH_2X$: in a 10 mL flame dried round bottomed flask, (1-phenethyl)pinacolboronate **3** (229.8 mg, 1.0 mmol) and $BrCH_2Br$ (0.077 mL, 1.1 mmol) were dissolved in 2.0 mL of THF. After cooling to −78 °C using a N_2/isopropyl alcohol bath (bath temperature monitored by a low temp. thermometer), Bu^nLi (2.17 M in hexane, 0.50 mL, 1.1 mmol) was added dropwise over 15 min to the center of the flask with vigorous stirring. The reaction mixture was then allowed to warm gradually to room temperature overnight under N_2. The solvent was removed *in vacuo*, and the resulting residue diluted with 10 mL of saturated aqueous NH_4Cl. The aqueous layer was extracted with light petroleum (bp 30–60 °C, 20 mL × 4), and the combined organic layers dried over $MgSO_4$. After filtration and removal of solvent *in vacuo*, crude (1-phenylpropyl)pinacolboronate (231 mg) **7** was obtained.

Boronate ester **7**, (231 mg), was dissolved in 10 mL of diethyl ether, 2.0 mL of methanol and 4.0 mL of 1 M NaOH (8.0 mmol). The flask was flushed with nitrogen and 0.285 mL of H_2O_2 (30% w/v in H_2O, 2.27 mmol) was added slowly at room temperature. The reaction mixture was left at room temperature under N_2 overnight. The ether layer was separated and the aqueous layer washed with diethyl ether (20 mL × 3). The combined organic layers were dried over $MgSO_4$. After filtration and removal of solvent *in vacuo*, a mixture of 1-phenethanol **5** (11%), 2-phenylpropanol **2** (74%) and 3-phenylbutanol **4** (15%) was obtained. The ratio was determined by 400 MHz ^1H NMR. The NMR yields (11, 74 and 15%, respectively) of the aforementioned products were determined by integration of the peaks of interest *vs*. added internal standard (*p*-nitrotoluene).

§ For spectral data of compound **2**, see ref. 4; compound **4** is commercially available (Aldrich); and for compound **6**, the data are as follows: ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.19 (m, 5H, C_6H_5), 3.62 (t, *J* 6.8 Hz, 2H, CH_2OH), 2.72 (m, 1H, C*H*), 1.70–1.63 (m, 2H, $CH_2CH_2CH_2$), 1.55–1.40 (m, 2H, $CH_2CH_2CH_2$), 1.28 (d, *J* 7.2 Hz, 3H, CH_3), 1.18 (br s, 1H, O*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 128.6, 127.2, 126.2, 63.3, 40.0, 34.6, 31.2, 22.6.

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