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# Use of (±)-Isopinocampheyldichloroborane for the Efficient Synthesis of Unsymmetrical Ketones via Stepwise Hydroboration of Alkenes.

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***Abstract:*** A convenient, one-pot synthesis of unsymmetrical ketones has been developed making use of the *in situ* reduction - hydroboration reactions of readily prepared and stable (±)-isopinocampheyldichloroborane.

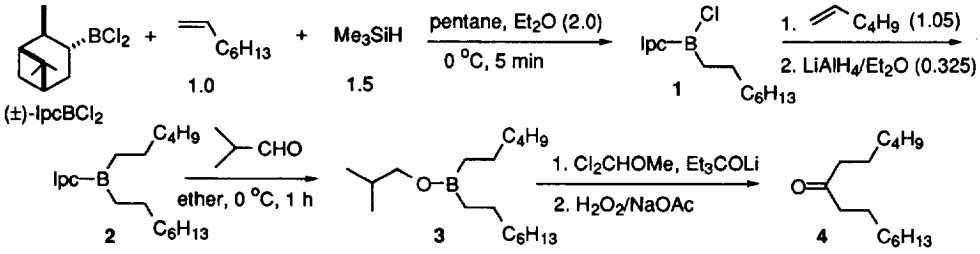
Stepwise hydroboration of two different alkenes followed by replacement of the boron by a carbonyl group constitutes one of the important routes for the synthesis of unsymmetrical ketones. Various stepwise hydroborating agents reported in the literature for this purpose include $BHBr_2{\cdot}SMe_2$,[2] thexylchloroborane (ThxBHCl),[3] 2,4,6-triisopropylphenylborane ($TripBH_2$)[4] and mesitylborane.[5] However, many of them suffer from significant disadvantages such as multistep preparation, limited stability, high susceptibility to reaction conditions etc. We herein report the use of the readily prepared, stable (±)-isopinocampheyldichloroborane [(±)-$IpcBCl_2$] to achieve a highly efficient synthesis of unsymmetrical ketones via stepwise hydroboration of alkenes.

During the past several years, we have developed a number of reagents based on α-pinene as the chiral auxiliary.[6] Some of these reagents include $Ipc_2BH$, $IpcBH_2$, $Ipc_2BAll$, $Ipc_2BCl$ (Ipc = isopinocampheyl). In view of the ability of compounds of the type $IpcBR_2$ to undergo ready and quantitative elimination of α-pinene on treatment with aldehydes[7] to give the corresponding borinates which in turn can be converted by the DCME reaction[8] into the corresponding ketones in high yield, we decided to explore the possibility of developing a stepwise hydroboration methodology utilizing a reagent based on (±)-α-pinene.

We envisaged a sequential *in situ* reduction - hydroboration of (±)-$IpcBCl_2$[9] in the presence of two different alkenes as a route to the desired mixed trialkylboranes. Alkyldichloroboranes are known to give dialkylchloroboranes via an *in situ* reduction - hydroboration reaction when treated with $Me_3SiH$ and alkenes in pentane.[10] However, the reaction of (±)-$IpcBCl_2$ with 1-octene in pentane at room temperature proved to be quite slow even in the presence of a considerable excess (6 equiv) of $Me_3SiH$. Recently, during our investigation of the use of preformed and *in situ* generated IpcBHX (X=Cl, Br, I), new reagents for the asymmetric hydroboration of prochiral alkenes[11], we had observed that the use of ether instead of pentane as the solvent, achieved a remarkable accelerating effect on the *in situ* reduction - hydroboration reaction of $IpcBCl_2$ with $Me_3SiH$ and alkenes. Therefore, we reexamined the reaction of (±)-$IpcBCl_2$ with $Me_3SiH$ and 1-octene in ether. Indeed, the reaction was almost instantaneous even at 0 °C. Unfortunately, a small amount of dihydroboration product accompanied the desired monohydroboration product **1**. Gratifyingly, when the

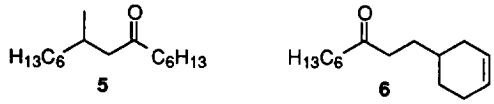
same reaction was carried out in pentane in the presence of 2 equivalents of ether, the hydroboration was still fast, while the $^{11}B$ NMR showed the formation of the required dialkylchloroborane **1** ($\delta$ 76, $^{11}B$ NMR) free from any other boron species (Scheme 1). Remarkably, even when 2 equiv of $Me_3SiH$ were used, equally clean monohydroboration was achieved.

Since $Me_3SiH$ was not able to achieve the hydridation of **1** required for the second hydroboration, we investigated the hydridation of **1** with $LiAlH_4$ in the presence of a slight excess (1.05 equiv) of 1-hexene at various temperatures (–25 °C, 0 °C and rt) and in different solvents (ether, pentane, ether-pentane) to find conditions which provided negligible amount of scrambling. The best results were realized by simply adding 1.3 times the theoretical amount[12] (i.e. 1.3 x 0.25 equiv) of $LiAlH_4$ (as a 1.0 M solution in ether) to the reaction mixture produced in the first hydroboration step in presence of 1.05 equiv of 1-hexene at 0 °C. The product produced is exclusively trialkylborane **2** ($\delta$ 83, $^{11}B$ NMR).



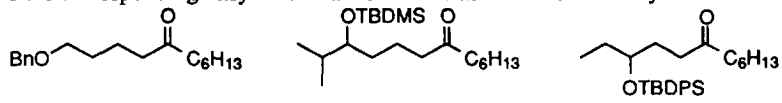

Scheme 1

The elimination of $\alpha$-pinene from **2** with isobutyraldehyde[7] gave borinate **3** ($\delta$ 53, $^{11}B$ NMR) which on DCME reaction[8] followed by $H_2O_2$ oxidation gave the required unsymmetrical ketone **4** in 93% yield (GC). The amount of scrambling in this synthesis, represented by the amounts of symmetrical ketones produced *viz.* dihexyl and dioctyl ketones, was less than 5%. We confirmed the effectiveness of this methodology by applying it for the synthesis of two more ketones **5** and **6** which showed that alkenes containing substituents in the 2-position, as well as alkenes with an internal double bond can be successfully utilized in this methodology (Table 1).



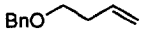
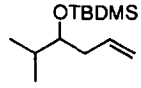
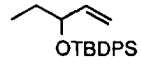

The fact that the reduction - hydroboration of (±)-$IpcBCl_2$ proceeds efficiently even in the presence of a complexing solvent such as ether, and is almost instantaneous even at 0 °C, prompted us to explore the applicability of this protocol in the case of alkenes containing an ether functionality in the structure. The results are presented in Table 1. In the case of the benzyl protected homoallylic alcohol (entry 4), although the first hydroboration gave the required monohydroboration product exclusively, some cleavage of the protecting group occurred in the second step, resulting in a decreased (60%) yield of ketone **7**. However, no cleavage of the protecting group was observed when a TBDMS-protected homoallylic alcohol (entry 5) was employed for the synthesis of the unsymmetrical ketone **8**. Surprisingly, the TBDMS protecting group was not successful for allyl alcohol. In this case, the first hydroboration took place readily, as before, but the product dialkylchloroborane was not stable and had undergone considerable cleavage of the TBDMS group, as

evidenced by the presence of borinate (δ 53) in the $^{11}B$ NMR taken after 10 min at 0 °C. Fortunately, when the protecting group was changed to *tert*-butyldiphenylsilyl (TBDPS) group (entry 6), no such problem was encountered and the corresponding unsymmetrical ketone **9** was obtained in 79% yield.




**7** **8** **9**

Table 1. Synthesis of Unsymmetrical Ketones by Stepwise Hydroboration Using (±)-IpcBCl$_2$

| Entry | First Alkene | Second Alkene | Product[a,b] | % Yield |
|---|---|---|---|---|
| 1 | 1-octene | 1-hexene | **4** | 93[c] |
| 2 | 2-methyl-1-pentene | 1-hexene | **5** | 85[c] |
| 3 | 1-hexene | 4-vinyl-1-cyclohexene | **6** | 82[c] |
| 4 |  | 1-hexene | **7** | 60[d] |
| 5 |  | 1-hexene | **8** | 81[d] |
| 6 |  | 1-hexene | **9** | 79[d] |

[a] ≤ 5% symmetrical ketones were also formed in the reaction. [b] All new compounds were characterized by $^1H$, $^{13}C$ NMR and elemental analysis. [c] GC yield. [d] Yield of pure isolated ketone.

In conclusion, we have developed a new efficient stepwise hydroboration methodology based on the use of (±)-IpcBCl$_2$ for the synthesis of unsymmetrical ketones.[13] Notable features of this methodology include: 1. (±)-IpcBCl$_2$ is a liquid which can be prepared in one step in almost quantitative yield from inexpensive (±)-α-pinene and can be stored under a nitrogen atmosphere for extended periods of time without any deterioration. 2. All the steps in this methodology can be carried out in one pot in a matter of 10-12 h. 3. The unsymmetrical ketones are obtained in high overall yields. Currently, we are exploring the application of this methodology for the synthesis of optically active spiroketals.

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9. (±)-IpcBCl$_2$ (δ 62, $^{11}$B NMR) was conveniently prepared in 90% yield in one step from (±)-α-pinene and BCl$_3$ using Me$_3$SiH[10] and purified by distillation (liquid, b.p. 60-5 °C/0.2 mm Hg). It showed no detectable change in $^1$H and $^{13}$C NMR even after 4 months at rt when stored under nitrogen atmosphere.
10. (a) Soundararajan, R. ; Matteson, D. S. *J. Org. Chem.* **1990**, *55*, 2274. (b) Soundararajan, R. ; Matteson, D. S. *Organometallics* **1995**, *14*, 4157.
11. Dhokte, U. P.; Kulkarni, S. V.; Brown, H. C. unpublished results.
12. The reason for adding 1.3 times the theoretical amount of LiAlH$_4$ is the fact that Me$_3$SiCl formed in the first step also reacts with LiAlH$_4$ but at a much slower rate than that of the dialkylchloroborane **1**. It reacts with any excess LiAlH$_4$ added and thus prevents the decomposition of required trialkylborane **2** to dialkylboranes and borohydrides.
13. Typical procedure: To a stirred solution of (±)-IpcBCl$_2$ (2.19 g, 10.0 mmol) in pentane (8.0 mL) and ether (2.09 mL, 20.0 mmol) at 0 °C was added 4-(*tert*-butyldimethylsiloxy)-5-methyl-1-hexene (2.28 g, 10.0 mmol). To this solution was immediately added precooled (–78 °C) Me$_3$SiH (1.11 g, 15.0 mmol) via a double ended needle. After 10 min, 1-hexene (0.88 g, 10.5 mmol) was added followed by LiAlH$_4$ (1.0 M solution in ether, 3.25 mL, 3.25 mmol). After 5 min at 0 °C, the reaction mixture was allowed to come to rt, volatiles removed under water aspirator vacuum, the residue diluted with ether (10.0 mL), cooled to 0 °C, isobutyraldehyde (0.86 g, 12.0 mmol) was added and the reaction mixture was stirred for 1 h. After removing the volatiles under water aspirator vacuum at rt, the residue was dissolved in THF (10.0 mL) and cooled to –10 °C. To this solution was added α,α-dichloromethyl methyl ether (2.87 g, 25.0 mmol) followed by a dropwise addition of Et$_3$COLi (25.0 mmol, prepared by reaction of Et$_3$COH and BuLi) over a period of 10 min. After stirring for 30 min at this temperature, it was allowed to come to rt (LiCl precipitated out) and stirred for 2 h. The reaction mixture was then concentrated to half its volume, diluted with EtOH (5.0 mL) and subjected to oxidation by adding of 3M NaOAc (10.0 mL), 30% H$_2$O$_2$ (4.5 mL, 40.0 mmol) and heating at 70 °C for 2 h with vigorous stirring. It was then diluted with ether (40.0 mL) and the organic layer was washed with water (2 X 25 mL), dried over anhyd MgSO$_4$ and concentrated to remove the solvents. After removal of Et$_3$COH and other low boiling impurities from the reaction mixture by heating at 100 °C in an oil bath under water aspirator vacuum (12 mm Hg), the product was distilled at 0.2 mm Hg in a Kugelrohr apparatus to give crude ketone 3-(*tert*-butyldimethylsiloxy)-2-methyl-7-tridecanone (**8**) in about 90% purity. It was further purified by flash column chromatography (98:2 hexane:ethyl acetate) to give pure **8** as a colorless oil (2.77 g, 81%): $^1$H NMR δ 3.43 (q, *J* =5.4 Hz, 1 H), 2.38 (t, *J* = 7.5 Hz, 4 H), 1.44 - 1.78 (m, 5 H), 1.22-1.40 (m, 8 H), 0.80-0.92 (m, 18 H), 0.033 (s, 3 H), 0.028 (s, 3 H); $^{13}$C NMR δ 211.40, 76.62, 43.06, 42.99, 42.75, 32.64, 31.64, 28.96, 25.95, 23.86, 22.52, 20.00, 18.16, 18.01, 17.67, 14.04, –4.26, –4.47; Anal. Calcd for C$_{20}$H$_{42}$O$_2$Si: C, 70.11; H, 12.36. Found: C, 70.36; H, 12.37.

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