Diisopinocampheylhaloboranes as Stereoselective Reducing Agents

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Chiral diisopinocampheylchloroborane (dIpc2BCl and lIpc2BCl)1 has proven to be extremely efficient for the chiral reduction of aralkyl ketones,2,4,5 α-tertiary alkyl ketones,3,4 and α,β-acetylenic ketones.6 In addition to that, the reagent appears to be an excellent chemo- and regioselective reducing agent in the reduction of carbonyl compounds.7-9 Most organic functional groups, except for aldehydes, ketones2-9 and epoxides,10 are compatible with the reagent.8 Moreover, the ready availability of both the enantiomers (naturally occurring), simple reaction conditions, easy workup procedure, and complete recovery of the chiral auxiliary α-pinene10 make this reagent especially attractive. The mechanism of the reduction is explained via a cyclic boatlike transition state.4,7-9 This fascinating reagent attracted us to investigate its general reducing characteristics in details. In the course of exploration of its selectivity, we found that dIpc2BCl reduces cyclic ketones in a considerable degree of stereoselectivity. Such results led us to consider the role of both isopinocampheyl moiety (Ipc-) and halogen substituent in Ipc2BX in the stereoselective reduction of cyclic ketones: the steric size of halogen atom might play an important role in such a reduction. Accordingly, we examined a series of diisopinocampheylhaloboranes (Ipc2BX, where X = Cl, Br, I), as the stereostructure of isopinocampheyl group being fixed, for their stereoselectivity in the reduction of representative monocyclic and bicyclic ketones.11

As Table 1 shows, the halogen substituent in dIpc2BX plays an important role in the selective reduction of typical cyclic ketones as expected. The stereoselectivity increased dramatically with increasing steric size of the substituent. For example, in the reduction of 4-methylcyclohexanone at −30 °C dIpc2BCl affords 74% cis-4-methylcyclohexanol, the less stable isomer. However, the introduction of the bromo group instead of chloro one exerts a tremendous stereoselectivity enhancement (to 91.5%). Furthermore, the stereoselectivity of the iodo derivative reaches up to 98%. Generally, the bromo derivative achieves a relatively very high stereoselective reduction, compared to other results done by several conventional reagents. However, the iodo derivative appears to be a really ideal stereoselective reducing agent, showing an essentially 100% selectivity in the reduction of representative cyclic ketones at −30 °C. It is noteworthy to note that lIpc2BCl, prepared from (−)-α-pinene, shows a similar selectivity as dIpc2BCl does. On the other hand, the selectivity achieved by dlIpc2BBr, prepared from a racemate of α-pinene, is significantly lower than that by dIpc2BBr. For example, in the reduction of norcamphor at 0 °C dlIpc2BBr gave endo-norborneol in an essentially 100% selectivity, whereas dlIpc2BBr afforded the less stable isomer in a ratio of 76%.

Although Ipc2BI, particularly among Ipc2BX, achieves an essentially 100% stereoselectivity in the reduction of cyclic ketones, the reagent possesses a drawback in producing alcohols. The yields of alcohols in the reduction of cyclic ketones with Ipc2BI were significantly low. Several experiments with varying reaction conditions (i.e., an increase in the ratio of reagent to ketone, a longer reaction time, or an increase in the concentration of reagent) were carried out in order to increase the yields of alcohols: no significant increase in the yield was realized and the starting ketone was recovered. It is believed that the hydride transfer from the isopinocampheyl group of Ipc2BI competes with the iodide transfer from Ipc2BI to the carbonyl carbon; the iodinated product is then converted into the starting ketone upon hydrolysis.

Ipc2BI, particularly among Ipc2BX, achieves an essentially perfect stereoselective reduction of representative cyclic ketones to afford the less stable alcohol isomers exclusively. The disadvantage of this reaction as a preparative method is the low yield of the alcohol product and, hence, the use of excess reactants is necessary to obtain...
**Notes**


### Table 1. Stereoselective Reduction of Representative Cyclic Ketones with Ipc₂BX in Pentane

<table>
<thead>
<tr>
<th>ketone</th>
<th>temp.</th>
<th>ratio of less stable isomer (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>yield of alcohol (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ratio of less stable isomer (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>yield of alcohol (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ratio of less stable isomer (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>yield of alcohol (%)&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>2-methylcyclohexanone</td>
<td>25</td>
<td>0 34 99</td>
<td>93.5 86</td>
<td>98 99.9</td>
<td>94 55</td>
<td>55 60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>−30</td>
<td>47 95</td>
<td>&gt;99.9 84</td>
<td>&gt;99.9</td>
<td>&gt;99.9</td>
<td>45 50</td>
<td></td>
</tr>
<tr>
<td>3-methylcyclohexanone</td>
<td>25</td>
<td>0 89(85)&lt;sup&gt;b&lt;/sup&gt; 99(86)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>89.5 80</td>
<td>98(98)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>50(60)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>65 80</td>
<td></td>
</tr>
<tr>
<td></td>
<td>−30</td>
<td>92 95</td>
<td>94 80</td>
<td>99.9</td>
<td>45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-methylcyclohexanone</td>
<td>−30</td>
<td>74 99</td>
<td>91.5 70</td>
<td>98</td>
<td>55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-ethylcyclohexanone</td>
<td>0</td>
<td>80 75</td>
<td>87 64</td>
<td>98(65)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>56(60)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>80 91</td>
<td></td>
</tr>
<tr>
<td>3,3,5-trimethylcyclohexanone</td>
<td>0</td>
<td>97 100</td>
<td>98</td>
<td>&gt;99.9</td>
<td>90</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>−30</td>
<td>98 99</td>
<td>99</td>
<td>&gt;99.9</td>
<td>86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>norcamphor</td>
<td>25</td>
<td>0 91(92)&lt;sup&gt;e&lt;/sup&gt; 95(100)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>&gt;99.9(76)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>&gt;99.9(99.9)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>60(65)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td></td>
<td>−30</td>
<td>95.5 90</td>
<td>&gt;99.9</td>
<td>98(99.9)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>50(52)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>camphor</td>
<td>25</td>
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<td>98</td>
<td>45</td>
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<tr>
<td></td>
<td>−30</td>
<td>81 72</td>
<td>&gt;99.9(97)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>65(60)&lt;sup&gt;g&lt;/sup&gt;</td>
<td>&gt;99.9</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td></td>
<td>−30</td>
<td>99.5 70</td>
<td>&gt;99.9</td>
<td>60</td>
<td>&gt;99.9(99.9)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>30(32)&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
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</table>

<sup>a</sup>Reagents were prepared from (+)-α-pinene (98% ee), except where otherwise indicated. <sup>b</sup>A 2 : 1 ratio for reagent (1.25 M) : ketone was utilized; reacted for 24 h with Ipc₂BCl, and 48 h with Ipc₂BBr or Ipc₂BI. <sup>c</sup>Data obtained using Ipc₂BX prepared from (−)-α-pinene (98% ee). <sup>d</sup>Data obtained using Ipc₂BX prepared from (±)-α-pinene. <sup>e</sup>A 4 : 1 ratio for reagent : ketone was utilized. <sup>f</sup>A solution of 3.3 M was used. <sup>g</sup>Reacted for 7 days.

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**Experimental Section**

Techniques for handling air-sensitive compounds have been previously described. <sup>12</sup> <sup>1</sup>B NMR was recorded on 300-MHz Bruker instrument. GC analysis was done on a Hewlett-Packard 5790A gas Chromatograph having a flame ionization detector, integrated with a Hewlett-Packard 3390 integrator/plotter. GC columns, 1/8 in. × 12 ft, were packed with 10% Carbowax 20 M on Supelcoport (100-120 mesh) or 15% THEED on Supelcoport (100-120 mesh).

Borane-methyl sulfide (BMS) and α-pinene (98% ee) were obtained from the Aldrich Chemical Co. The ketones were obtained from the Aldrich Chemical Co. or Fluka Chemie AG and were used as received. Anhydrous ethereal hydrogen chloride and hydrogen bromide were prepared by using a Brown automatic gasimeter.

**Preparation of Diisopinocampheylborane (Ipc₂BX).** <sup>14</sup>

The procedure for preparation of Ipc₂BCl is illustrative. Diisopinocamphylborane (Ipc₂BH), prepared from (+)-α-pinene (220 mmol) and BMS (100 mmol) in THF (96 mL) at 0° by the reported procedure, <sup>13</sup> was suspended in diethyl ether (EE; 50 mL) in a 250-mL round-bottom flask containing a magnetic stirring bar and fitted with a septum-capped sidearm and a connecting tube. Dry HCl in EE (1 equiv, calculated for the amount of Ipc₂BH) was added. After being stirred for 15 min at −78°, the reaction mixture was warmed to 0° and stirred at that temperature until all of the solid dissolved and gas evolution ceased. The EE was pumped off and 50 mL of pentane was added. <sup>11</sup>B NMR showed a singlet at δ 75 ppm. Similarity, Ipc₂BBr was prepared by using dry HBr in EE. <sup>11</sup>B NMR of a solution of Ipc₂BBr in pentane showed a singlet at δ 74 ppm.

**Stereoselective Reductions.** The following procedure was used to explore the stereoselectivity of these reagents. In an oven-dried, 10 mL round-bottom flask equipped with a septum-capped sidearm and a magnetic stirring bar was placed 3.2 mL of a 1.25 M solution of Ipc₂BI in pentane (4.0 mmol). The flask was maintained at −30° by a bath. To this flask was added 0.23 g of 2-methylcyclohexanone (2 mmol) and the mixture was stirred for 48 h at −30°. The reaction mixture was then quenched by addition of 5 mL of 3 M...
NaOH. The organoborane was oxidized by treatment with 1.4 mL of 30% H₂O₂. The aqueous layer was saturated with anhydrous K₂CO₃ and the organic layer was separated and dried. GC analysis revealed the presence of 50% 2-methylcyclohexanol containing > 99.9% of the cis isomer and a trace of trans isomer.

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References

1. The superscripts ‘d’ and ‘l’ indicate that the reagents are derived from (+)- and (−)-α-pinene, respectively: Joshi, N. N.; Srebnik, M.; Brown, H. C. J. Am. Chem. Soc. 1988, 110, 6246.
14. See also the other preparation procedure: Brown, H. C.; Ramachandran, P. V.; Chandrasekharan, J. Heteroatom Chem. 1995, 6, 117.