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A Convenient and Economical Method for the Preparation of DIP-Chloride™ and Its Application in the Asymmetric Reduction of Aralkyl Ketones

Mangzhu Zhao*, Anthony O. King, Robert D. Larsen, Thomas R. Verhoeven and Paul J. Reider

Process Research Department, Merck Research Laboratories, Merck & Co. Inc., P.O. Box 2000, Rahway, NJ 07065, USA

Abstract: A convenient and economical in situ preparation of DIP-Chloride™ from $NaBH_4$, BCl_3 and α-pinene is described. Its application in the asymmetric reduction of representative aralkyl ketones is presented. © 1997 Elsevier Science Ltd.

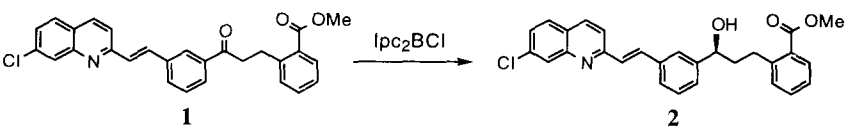
Asymmetric synthesis is especially important for the pharmaceutical industry due to the often dramatic differences in the pharmacological behaviors of enantiomers. *B*-Chlorodiisopinocampheylborane (Ipc_2BCl or DIP-Chloride™) has been demonstrated to be an excellent reagent for the asymmetric reduction of aralkyl ketones[1]. In this paper, we wish to report a new, convenient and economical method for the preparation of DIP-Chloride from $NaBH_4$, BCl_3 and α-pinene.

DIP-Chloride™ can be prepared by several reported methods. The first method[1c] developed by H. C. Brown entails reaction of BH_3•SMe_2 with α-pinene followed by treatment of the resultant Ipc_2BH with HCl to give Ipc_2BCl. The second method[2] involves reaction of BH_2Cl•SMe_2 and α-pinene to prepare Ipc_2BCl directly. However, both BH_3•SMe_2 and BH_2Cl•SMe_2 are expensive and environmentally unfriendly particularly on an industrial scale. Therefore, other alternatives for the preparation of Ipc_2BCl were investigated.

Since $NaBH_4$ is one of the cheapest sources of hydride, we examined its use in the preparation of the chiral reducing agent Ipc_2BCl. It is well known that BH_3 can be prepared *in situ* from $NaBH_4$ and BF_3 etherate. It has also been reported by H. C. Brown[3] that reaction of α-pinene with the *in situ* generated BH_3 gives Ipc_2BH. We found that treatment of the Ipc_2BH prepared in this manner with BCl_3 instead of HCl also gave Ipc_2BCl (eq. 1). In this method all of the hydrides in $NaBH_4$ are used and the formation of H_2 gas is avoided.

$$NaBH_4 + \alpha\text{-pinene} \xrightarrow{BF_3{\cdot}Et_2O} Ipc_2BH \xrightarrow{BCl_3} Ipc_2BCl \qquad \text{(eq. 1)}$$

However, we found that this protocol was particularly sensitive to overcharge of $NaBH_4$. With 20% overcharge of $NaBH_4$, the enantiomeric purity of the chiral alcohol **2**[2b] decreased from 95% to ~30% ee (eq. 2).



1 **2** (eq. 2)

Since $NaBH_4$ itself does not reduce ketone **1** under the reaction conditions (–20 °C, THF), we suspected that reduction of the substrate by the BH_3 and/or BH_2Cl generated from excess $NaBH_4$ and BCl_3 was responsible for the poor enantioselectivity. Whereas ~10% α-pinene remains under normal conditions, no α-pinene was detected in this case. Addition of sufficient α-pinene should trap these borane species and cure this problem. Indeed, the reaction proceeded with high enantioselectivity (93–95%) when 20% excess α-pinene was added even with 20% overcharge of $NaBH_4$. The above observation also implied that BH_3 or BH_2Cl could be prepared directly from $NaBH_4$ and BCl_3 without the mediation of BF_3 etherate. As a matter of fact, addition of a BCl_3 solution in heptane to a mixture of $NaBH_4$ and α-pinene in diglyme at –10 °C followed by warming to 40 °C gave the Ipc_2BCl directly (eq. 3). Substituting diglyme with DME, in order to facilitate the recovery of the solvents and α-pinene, presented no problem. The procedure failed completely in THF or diethyl ether, however. Although it has been reported that Ipc_2BCl can be prepared from $LiBH_4$ and BCl_3 in diethyl ether[4], the high cost of $LiBH_4$ limits its use on a commercial scale.

$$NaBH_4 + \alpha\text{-pinene} \xrightarrow[\text{diglyme or DME}]{BCl_3} Ipc_2BCl \qquad \text{(eq. 3)}$$

The procedure for the preparation of Ipc_2BCl is described as follows: To a 250-mL round-bottomed flask was added sodium borohydride (1.89 g, 50 mmol). Dimethoxyethane (30 mL) and (*R*)-(+)-α-pinene (85% ee, 31.6 mL, 200 mmol) were added under nitrogen and the mixture was cooled to –10 °C. A solution of boron trichloride (52.5 mL, 1.0 M in heptane) was added at a rate such that the temperature of the reaction mixture did not exceed 10 °C (15 min.). The mixture was stirred at 10 °C for 15 min., room temperature for 1 h and then 40 °C for 1 h to give the chiral reducing agent Ipc_2BCl.

Using the Ipc_2BCl prepared in this manner for the reduction of oxo ester **1** afforded the hydroxy ester **2** in essentially quantitative yield and 94–97% ee. The optical purity can be easily upgraded to >99.5% ee by crystallization. To a slurry of oxo ester **1** (25.08g, 55 mmol) in THF (200 mL) at –25 °C was added the Ipc_2BCl prepared above. The mixture was aged at –25 °C for 5 h, then 0 °C for 1 h and then quenched with PhCHO (15 mL). The reaction mixture was heated to 40 °C to release all of the α-pinene then poured into 31% K_2CO_3 (80 mL) at rt. with vigorous stirring. The organic layer was separated and washed with brine (40 mL). After concentrating the organic layer to 1/3 of its original volume, water was added (3 mL) followed by heptane (120 mL) at 50 °C. The mixture was cooled to rt. and aged for 2 h. Filtration followed by washing the product cake (5/1 heptane/THF) and drying, afforded 24.6 g of the hydroxy ester **2** as its monohydrate (93% yield, >99.5% ee).

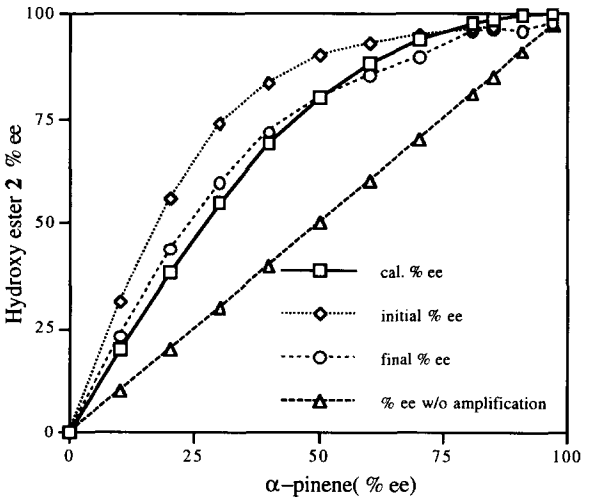
Next, we examined the effectiveness of the *in situ* prepared Ipc_2BCl for the asymmetric reduction of a number of aralkyl ketones (see the table). It is clear that the *in situ* prepared Ipc_2BCl from 85% ee α-pinene gives comparable results to pure Ipc_2BCl prepared from 98% ee α-pinene. It is interesting that 2-methoxy acetophenone is reduced much faster than acetophenone (entry 5), while the 3- and 4-methoxy isomers and 3,4-dimethoxy acetophenone are reduced much more slowly (entry 6–8). This indicates that the reaction rate is more affected by chelation than by electronic effect.

It should be emphasized that 85% ee α-pinene was used instead of the expensive 97% ee material to take advantage of the asymmetric amplification reported from our labs.[2b,5] The enantiomeric purity of the chiral alcohols obtained were as high as 97% ee with Ipc_2BCl prepared from 85% ee α-pinene. To rationalize this asymmetric amplification, we have proposed the following hypothesis:[2b,5] a) the ratio of (+,+)/(+,–)/(–,–)Ipc_2BCl formed is in accordance to statistics. b) (+,–) isomer is essentially unreactive.

c) (+,+) and (–,–) isomers give perfect asymmetric induction. If all these assumptions hold true, then 70% ee (+)-α-pinene (+/– = 85/15) should give the Ipc_2BCl in the following proportions: (+,+)/(+,–)/(–,–) = 72/26/2. The maximum % ee for the reduction would be 94.5%. This agrees very well with the experimental result (93% ee for the reduction of **1**). Reduction of the oxo ester **1** with Ipc_2BCl prepared from racemic α-pinene also supported this hypothesis. In this case, the reaction essentially stopped after ~50% conversion at –20 °C and proceeded further only very slowly.

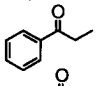
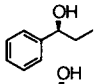
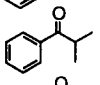
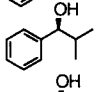
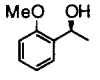
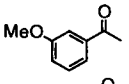
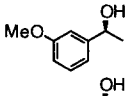
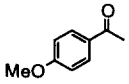
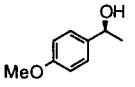
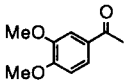
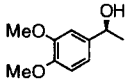
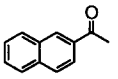
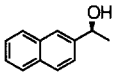
However, a closer examination revealed significant deviation from the calculation based on the above hypothesis (see the graph). The initial enantiomeric purity of **2** (at 10-20% conversion) was even better than the maximum values calculated especially with ~30% ee α-pinene. It was particularly striking that the initial % ee of **2** was as high as 90% using Ipc_2BCl from 50% ee α-pinene, whereas the calculation indicated 80%. Even with 30% ee α-pinene, the initial % ee of **2** was as high as 74% while calculation indicated only 55%. As expected, the enantioselectivity decreased gradually with the progress of the reaction. This decrease is due to the fact that the (+,–)-Ipc_2BCl, although much less active than the (+,+) or (–,–) isomers, reduces the ketone slowly and non stereoselectively. As the active reagents are gradually depleted, the relative contribution from the (+,–)-Ipc_2BCl increases resulting in lower enantioselectivity. Coincidentally, the final % ee (18 h at –25 °C with 10–20% excess of the ketone **1**) came fairly close to the calculation. The reason for the large deviation of the initial % ee from the calculation is not clear. But Kagan's recent paper[7] offers evidence that the non random formation of the three Ipc_2BCl species may be responsible for the observed non linear effect since mixtures of independently prepared (+,+)/(–,–) Ipc_2BCl do exhibit linearity between the % ee of the Ipc_2BCl and the reduction products.

Graph. Calculated and experimental % ee of hydoxy ester **2**



In conclusion, we have developed a very convenient and economical method for the preparation of Ipc_2BCl from $NaBH_4$, BCl_3 and α-pinene. The *in situ* prepared reagent has been demonstrated to be as effective as pure Ipc_2BCl for the reduction of aralkyl ketones. Additionally, by taking advantage of the asymmetric amplification, up to 97% ee of the chiral alcohols can be obtained by using cheap 85% ee α-pinene instead of the much more expensive 98% material.

Table. Asymmetric Reduction of Aralkyl Ketones

entry	substrate	conditions	product	yield	% ee
1		-25 °C, 6 h		95.3 (72)	96 (97)
2		-25 °C, overnight		100 (62)	99 (97)
3[c]		-25 °C, 6 days		81.7 (68)	89(90)
4[c]		-25 °C, 2 days		88.1 (70)	88 (87)
5		-25 °C, 1 h		100	97 (92)
6		-25 °C, 18 h		93.9	95
7		-25 °C, 23 h (91% conversion)		90.7	87
8		-25 °C, 1 day		94.6	94
9		-25 °C, 15 h		93.8 (90)	94 (98)
10[c]		-25 °C, 2 days		94.6 (85)	93 (91)

a) Authentic sample of the racemic alcohols were obtained from reduction of the corresponding ketones by $NaBH_4$ or purchased commercially. The configurations of the products are based on the prediction according to the literature. b) The yield and % ee in parentheses were the results reported by H. C. Brown[1a,6] with 98% ee Ipc_2BCl. All other yields and % ee were determined by HPLC with reverse phase column (Zorbax SB-Phenyl) and normal phase chiral columns (Chiralcel OD, OB or OJ), respectively. c) Ipc_2BCl amount was doubled to speed up the reaction.

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