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A PRACTICAL, ONE-POT PREPARATION OF DIISOPINOCAMPHEYLCHLOROBORANE

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Abstract: A one-pot preparation of the chiral reducing agent diisopinocampheylchloroborane (Ipc_2BCl) from α-pinene and borane methyl sulfide has been developed. The procedure obviates isolation of the air and moisture sensitive reagent, making it useful for large scale operations. Asymmetric reduction of ketones using the *in situ* prepared Ipc_2BCl is comparable to that using isolated reagent.

The asymmetric reduction of prochiral ketones has recently attracted considerable interest. Several novel methods for conducting chiral reductions have been described in the literature.[1,2] Among these methods is the pioneering work of Midland and Brown which revolutionized the use of chiral boranes in

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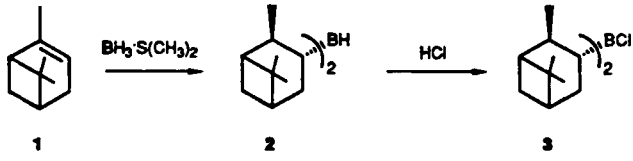
asymmetric synthesis.[3,4] In particular, the use of diisopinocampheylchloroborane has provided the synthetic chemist with an efficient way of performing asymmetric reductions of ketones to provide chiral alcohols. This reagent can be used to reduce both aromatic and α-tertiary aliphatic ketones with good to excellent enantioselectivity.

The utility of diisopinocampheylchloroborane prompted us to develop an efficient and practical procedure for the preparation and use of this reagent. By modification of the existing methodology, we have developed a process which is operationally easier and more practical to carry out, particularly in large scale operation. The previously described preparation involves isolation of the unstable diisopinocampheylborane intermediate 2 and subsequent isolation of sensitive Ipc_2BCl (3) (Scheme I).[4d]

Our procedure is a one-pot process which obviates the need for handling or isolating either of these air

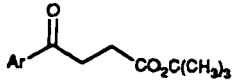


Scheme I

and moisture sensitive reagents. Reaction of (+)-α-pinene (91% ee) with borane methyl sulfide in THF at 0°C for 17 h forms diisopinocampheylborane intermediate 2. Direct addition of a solution of HCl in THF to the Ipc_2BH mixture generates chloroborane 3 *in situ*. Subsequent addition of a ketone substrate leads to asymmetric reduction which is comparable in all respects to reduction using commercial Ipc_2BCl (Table 1). It should be noted that diisopinocampheylborane 2 has been used *in situ* for asymmetric hydroborations;[5] however, chloroborane 3 has not been utilized without first isolating the solid reagent.

We found it interesting that the use of 91% ee (+)-α-pinene *in situ* led to alcohols of essentially the same ee as the use of isolated, optically pure diisopinocampheylchloroborane. We wanted to next examine the effect of lowering the ee of the (+)-α-pinene on the optical purity of the product alcohol. Chloroborane 3 was prepared *in situ* using (+)-α-pinene of varying ee from 98% to 0%. The reagent was then used for chiral reduction of ketoester 7. Our results, summarized in Table 2, show that as the ee of (+)-α-pinene was lowered the optical purity of the alcohol also decreased. However, the relationship between the optical purity of the α-pinene employed and reduction enantioselectivity is non-linear. This

Table 1. A Comparison of *in situ* Ipc_2BCl with Isolated Ipc_2BCl in the Reduction of Ketones

	Ketone	Reduction Method*	Alcohol Yield**	Alcohol ee***
1)	acetophenone	A	97%	94%
	4	B	88%	93%
2)	butyrophenone	A	100%	98%
	5	B	97%	97%
3)	2'-acetonapthone	A	91%	97%
	6	B	90%	97%
4)		A	89%	92%
		B	88%	92%

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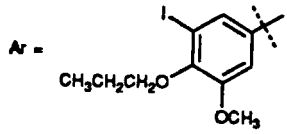


*Method A: commercial Ipc_2BCl; Method B: *in situ* prepared Ipc_2BCl.

**The yield was determined by ^1H NMR using 1,4-dimethoxybenzene as an internal standard except in entry 4 where isolated yields are reported.

***ee's were determined by ^1H NMR analysis of the Mosher ester derivatives.[6]

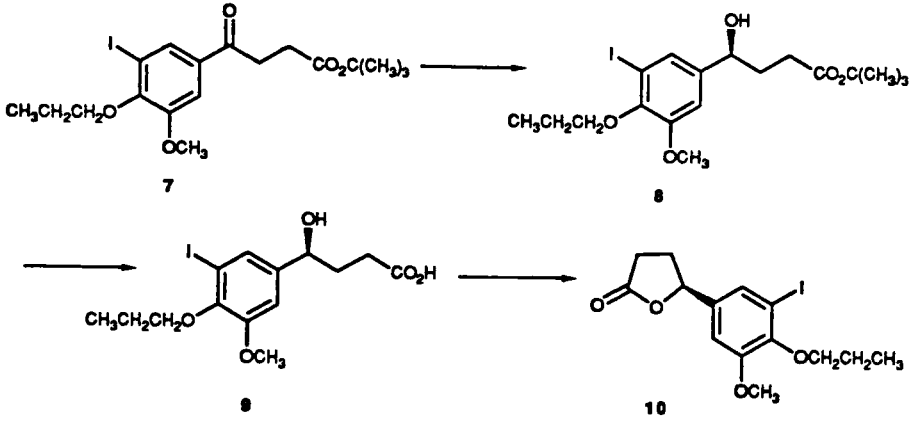
Table 2. Chiral Reduction of Ketoester 7 with Ipc_2BCl Prepared from (+)-α-Pinene of Varying Optical Purity.

% ee of (+)-α-pinene	% ee of alcohol
98	90
91	89
83	87
75	82
62	81
42	68
26	50
15	25
0	0

implies that formation of the meso-isomer ((+)(-)-Ipc_2BCl) is disfavored with respect to either (+)(+)Ipc_2BCl or (-)(-)Ipc_2BCl.[7] Alternatively, the meso-isomer may react at an appreciably slower rate.

We have applied our procedure using 91% ee pinene to a series of aromatic ketones (Table 1). Although the chiral reductions proceed in good yield by NMR assay, isolation of the pure alcohol is difficult for some of the simple aromatic ketones (4,5). This is due to both the excess α-pinene and the isopinocampheol, generated on oxidative work-up, which can only be removed by repeated distillation and/or chromatography.[8] This is

a significant deterrent for using Ipc_2BCl in large scale chiral reductions. We have found that Ipc_2BCl finds greater utility in the asymmetric reduction of ketone substrates which contain an ester functionality. In these cases, the ester can be hydrolyzed after reduction and extracted into the aqueous layer. The



neutral pinene-related byproducts can then be easily removed. We have demonstrated this method using ketoester 7 and have prepared multi kilogram quantities of chiral lactone 10 in support of our work on platlet activating factor antagonists. Details regarding this work will be disclosed in a separate article.[9,10]

Experimental

General

α-Pinene, borane methyl sulfide complex and (-)-β-diisopinocampheylchloroborane were purchased from

Aldrich Chemical Company. Reagent grade solvents which had been dried over molecular sieves were used. All reactions were carried out under a nitrogen atmosphere and were monitored for consumption of starting material by TLC or analytical HPLC. The enantiomeric excess of each alcohol was determined by ^{1}H NMR (300 MHz) analysis of the corresponding Mosher esters.[6]

In Situ Preparation of Ipc_2BCl and Acetophenone Reduction

Borane methyl sulfide (2.48 mL, 0.028 mol) and 5 mL of THF were cooled to 0°C under nitrogen. (+)-α-Pinene (91% ee)(9.79 mL, 0.062 mol) was added dropwise over 10 min maintaining the temperature at ≤5°C. A white precipitate formed in ∿1 h at 0°C. After stirring for 2 h, the resulting slurry was aged for 18 h at 0-5°C. A 9.0M solution of HCl in THF (3.1 mL, 0.028 mol) was added dropwise over ∿15 min. CAUTION: H_2 gas is evolved during the addition. The clear solution of chloroborane was aged an additional 15 min and acetophenone (1.92 mL, 0.0165 mol) was added over ∿5 min. After 23 h at 0°C, TLC showed no starting material. Water (4.0 mL) followed by 30% H_2O_2 (7.0 mL) was added dropwise maintaining the temperature of the reaction mixture at ≤20°C. CAUTION: H_2O_2 addition is very exothermic! The reaction mixture was diluted with ethyl acetate (75 mL) and water (25 mL). The organic extract was washed successively with water (50 mL),

saturated sodium bicarbonate (2 x 50 mL) and brine (2 x 50 mL) and dried over sodium sulfate. The solvent was removed *in vacuo* to provide a colorless oil. The yield was determined to be 88% by ^{1}H NMR using 1,4-dimethoxybenzene as an internal standard. The enantiomeric excess was 93% as determined by ^{1}H NMR analysis of the Mosher ester derivative.

Preparation of lactone 10 from ketoester 7

In situ diisopinocampheylchloroborane was prepared as described above. To the clear solution of chloroborane was added ketoester 7 (7.29 g, 0.016 mol) dissolved in THF (5 mL) dropwise over ~10 min. The reaction was monitored by analytical HPLC. After 24 h at 0°C, water (6.6 mL) methanol (20 mL), and 5M NaOH (23 mL) were successively added to the reaction mixture maintaining the temperature at ≤15°C. The solution was warmed to ambient temperature and aged for 2 h (HPLC showed no hydroxyester starting material). The orange solution was poured into methyl t-butyl ether (125 mL) and saturated sodium bicarbonate (50 mL). The aqueous layer was back extracted with MTBE (90 mL). The alkaline aqueous layer was acidified to pH 2 with 2N HCl, and then extracted with toluene (2 x 100 mL).

Pyridinium p-toluenesulfonate (40 mg) was added to the combined toluene extracts and the solution was heated to 70°C under vacuum. After 1 h, HPLC showed no

hydroxyacid 9. The solution was cooled to ambient temperature and washed with saturated sodium bicarbonate (100 mL) and 5% aq sodium chloride (100 mL). The solvent was removed in vacuo to give crude lactone 10 as a yellow solid. The ee was determined to be 88% by ^{1}H NMR (300 MHz) using (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol.

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