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Technical Note

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Corey–Itsuno Reduction of Ketones: A Development of Safe and Inexpensive Process for Synthesis of Some API Intermediates

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Supporting Information

ABSTRACT: A safe and inexpensive procedure for asymmetric reduction of ketones using in situ prepared *N,N*-diethylaniline borane (DEANB) and oxazaborolidine catalyst from sodium borohydride, *N,N*-diethylaniline hydrochloride and (*S*)-α,α-diphenylprolinol is described. This protocol is demonstrated successfully to manufacture enantiopure dapoxetine at the plant scale.

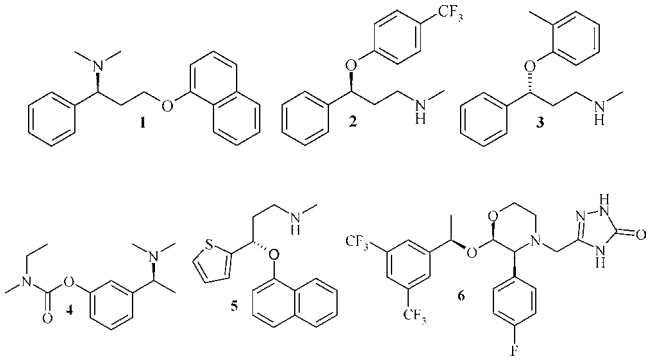
INTRODUCTION

Undoubtedly, asymmetric reduction of prochiral ketones to produce chirally pure alcohols is an extremely important step with wide range of applications in both chemical and pharmaceutical industries. Although many chemical methodologies are reported for this endeavor, the most widely used protocols are biocatalytic,[1] transition metal catalytic,[2] stoichiometric chiral hydride,[3] and oxazaborolidine based asymmetric reduction.[4] The major issues with catalytic asymmetric hydrogenation are the cost of catalysts.[5] Almost all the chiral borane reagents are associated with hazards and when batch is considered with multi kilo scale, the handling of hazardous material becomes a herculean task.

In recent years, Corey's catalytic oxazaborolidine asymmetric reduction has been used quite frequently in pharmaceutical industries particularly for asymmetric reduction of benzylic ketone intermediate.[6a−c] The efficiency of reduction is excellent with guaranteed reproducibility. For better results, reaction must be carried out under anhydrous condition and at 25 ± 5 °C.[6b] However, the original publications of oxazaborolidine encompass the utilization of borane−THF, borane−dimethylsulfide (DMS), or catechol−borane complexes.

To circumvent the use of hazardous borane complexes, protocols to use in situ generated borane by employing R_4NBH_4/CH_3I[7a] or $NaBH_4/CH_2I_2$[7b] reagents are published in literature. Although these methods can avoid hazards, the genotoxic nature of alkyl halides makes these reagents extremely vulnerable to scrutiny from regulatory groups. We believe that, if we can develop a process of oxazaborolidine mediated reduction wherein the use of hazardous and genotoxic reagents could be circumvented while keeping almost the same efficiency, then we could easily and safely scale up the reduction process. The only way to avoid this issue is the use of DEANB[8a] and *N*-*t*-Bu-*N*-trimethylsilylamine−borane complex[8b] which are recognized as industrially favorable reducing agents primarily due to superior storage stability. In addition to high commercial cost, this possesses a serious transportation risk.[9]

A number of drugs such as dapoxetine **1**, fluoxetine **2**, atomoxetine **3**, revastigmine **4**, duloxetine **5**, and aprepitant **6** involve asymmetric reduction of benzylic ketone as a key step to introduce chirality into the drug molecule. Once the envisaged method is successful, other drugs can be brought in to the ambit of this protocol. Dapoxetine is the only drug which has recently been approved in European countries and is under U.S. FDA approval for the treatment of premature ejaculation.[10]



The sole chiral center in dapoxetine has been inducted either by a resolution process or by the asymmetric synthesis.[11] Alt et al. describes one of the best efficient asymmetric synthetic routes which has been utilized to synthesize dapoxetine (Scheme1), and relies on chiraly pure starting material **8** which is converted to dapoxetine in three steps with good yields.[11f] The compound **8** can be prepared by asymmetric reduction of 3-chloropropiophenone **7** using either (+)-DIP-Cl[12a] or oxazaborolidine catalyzed reduction with borane complex with THF,[12b,c] DMS,[12d,e] or using $NaBH_4/ZnCl_2$[12f] or DEANB.[12g]

In our opinion, in situ preparation and subsequent use of DEANB in reduction step is the most viable approach. Various methods are available in the literature for in situ preparation of DEANB which are summarized below. Schubert and Lang synthesized pure DEANB by vacuum distillation of crude DEANB which is produced from *N,N*-diethylaniline hydrochloride **10** and $Zn(NH_3)_4(BH_4)_2$ in pyridine.[13a] The other noteworthy methods to produce DEANB involve the use of $NaBH_4/BF_3$[13b] and $NaBH_4/Me_2SO_4$[13c] along with *N,N*-

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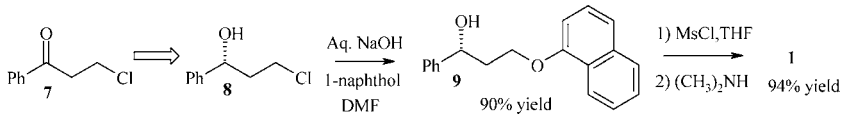
Scheme 1

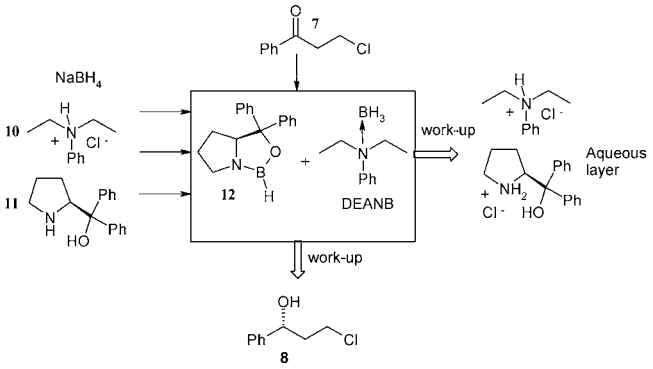


diethylaniline. The use of $Zn(NH_3)_4(BH_4)_2$, BF_3, and Me_2SO_4 is not advisable for large-scale commercial production of API due to cost and hazard.

RESULTS AND DISCUSSION

The procedures for synthesis of less reactive aliphatic amine borane and pyridine borane from $LiAlH_4$ or $NaBH_4$ and respective amine hydrochloride[14a,b] are reported, which have not been explored for preparation of more reactive DEANB. Herein, we report, for the first time, the preparation of DEANB from **10** and $NaBH_4$ and its in-situ use in asymmetric reduction of prochiral ketones, using (*S*)-*α*,*α*-diphenylprolinol **11** catalyst to produce some API intermediates on a large scale (Scheme 2).

Scheme 2



Initially, DEANB was prepared by addition of solid powder of **10** into a suspension of sodium borohydride in dimethoxyethane followed by asymmetric reduction of prochiral ketone in the same pot (Table 1, entry 1). Subsequently, we realized that addition of solid powder of **10** may not be a safe practice at large scale because of the evolution of flammable hydrogen gas. Therefore, **10** was dissolved in dichloromethane and this solution was added to the suspension of sodium borohydride in a slow stream at ambient temperature without changing other reaction parameters (Table 1, entry 2).

The dimethoxyethane solvent was replaced in the reaction with dichloromethane and THF, but there was no conversion observed (Table 1, entries 3–4). When the addition sequence of **10** and **11** was changed, adding **11** before **10** (Table 1, entry 5), the reaction was found incomplete and also enantioselectivity was low (80%). The equimolar ratio of **10** and sodium borohydride must be maintained (Table 1, entries 6–8) for better enantioselectivity.

To explore the application of our approach further, some prochiral ketones having different functional groups were studied (Table 2). Good enantioselectivity was observed with prochiral ketones **7**, **13**, **14**, **16**, and **18** (Table 2, entries 1–5), whereas ketones **20** and **22** (Table 2, entries 6–7) yielded corresponding alcohols with poor enantioselectivity.

In our experimental protocol, crystalline solid powder of **10** with water content 0.08% was synthesized from *N*, *N*-diethylaniline and hydrogen chloride gas in Me-*t*-Bu ether as a solvent. A water content of 0.23% was observed during preparation of **10** in plant scale and there was no impact on enantioselectivity (Table 2, entry 1). A nitrogen sweep was maintained to remove the hydrogen gas evolved during addition of **10** in reaction mass (Scheme 2). After completion of the reaction, 2-butanone was added to the reaction mass to destroy excess of borane complex and then **8** was extracted with toluene. Toluene layer was washed with dilute hydrochloric acid solution to remove **10**. In early stages of experimentation, dichloromethane was used as a solvent for extraction of the products, but removal of **10** was difficult from dichloromethane layer with dilute hydrochloric acid solution wash. Enhancement of chiral purity of **8** was attempted by crystallization from *n*-hexane, but this was not practiced due to the yield loss of 20–40%. Therefore, during manufacturing at plant scale, a concentrated solution of **8** in toluene was used in the next step to give dapoxetine. Though **8** was obtained with a chiral purity ranging from 85 to 95%, enrichment of chiral purity to >99.8% was observed during conversion of dapoxetine free base to the corresponding hydrochloride.

Table 1. Asymmetric Reduction of 3-Chloropropiophenone at Various Conditions Using 10, $NaBH_4$, and 11[a]

entry	solvent	conversion[b]	**10**/$NaBH_4$ molar ratio	% ee (*R* isomer)[c]
1	DME	>95%	1.0	92[d]
2	DME	>95%	1.0	95
3	dichloromethane	no reaction	1.0	--
4	THF	no reaction	1.0	--
5	DME	<70%	1.0	80[e]
6	DME	>95%	1.03	95
7	DME	>95%	1.1	84
8	DME	>95%	0.95	74

[a]Reaction condition: A solution of **10** (water content: 0.08%) in dichloromethane was added slowly to a suspension of $NaBH_4$ in a solvent at 25–30 °C and stirred for 4 h. Then, **11** (5 mol %) was added to the above solution and further stirred for 3 h. Then, a solution of **7** in dichloromethane was added for 2–3 h at 25 to 30 °C. After 12 h stirring, the reaction mass was analyzed for chiral purity on HPLC. [b]Reaction progress was monitored by TLC. [c]Absolute configuration was assigned by comparison of retention time with reference standard on chiral HPLC. [d]Solid powder of **10** was added in reaction mass instead of dichloromethane solution. [e]**11** was added before addition of **10**.

CONCLUSION

In summary, we present here a cost-effective, safe, and easy to scale up protocol for asymmetric reduction of prochiral ketones yielding chiral alcohol intermediates useful for synthesis of aprepitant, rivastigmine, and a number of selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake Inhibitors (SNRIs).

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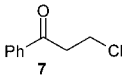
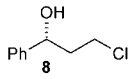
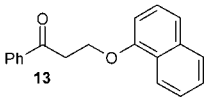
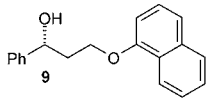
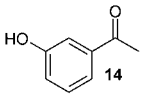
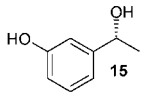
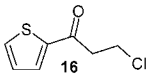
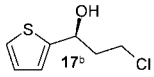
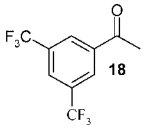
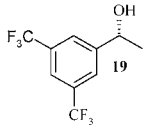
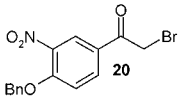
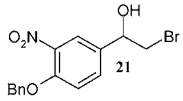
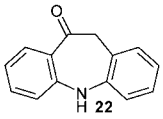
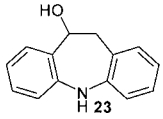
Table 2. Asymmetric Reduction of Prochiral Ketones

entry	prochiral ketones	chiral alcohol	% yield	% ee	intermediate of
1	 7	 8	96	95[a]	dapoxetine, fluoxetine & atomoxetine
2	 13	 9	80	98	dapoxetine
3	 14	 15	95	86	rivastigmine
4	 16	 17[b]	90	91	duloxetine
5	 18	 19	88	85[c]	aprepitant
6	 20	 21	-[d]	12	arformoterol
7	 22	 23	-[d]	17	eslicarbazepine

[a]Ahmed-Omer et al. reports 92% ee using DEANB in flow reactor.[12g] [b]Antipode of **11** was used. [c]Brands et al. reports 95% ee using DEANB in Me-*t*-Bu ether as a solvent at −10 to 0 °C.[15] [d]Incomplete conversion was observed on TLC. Detailed experimental condition given in Experimental Section and in Supporting Information.

EXPERIMENTAL SECTION

Ketones **7**, **14**, **18**, and **20** were purchased from commercial suppliers (Jiangsu Danyang Huasheng Chem China, Unilex Exports India, Tradmax pharmaceuticals China, and Chengdu Pharmaceuticals, respectively); ketone **22** was prepared by hydrolysis of oxcarbazepine; and **16** was prepared as per reported procedure.[16] The moisture content was <0.1% in raw materials except *N*, *N*-diethylaniline hydrochloride (water content <0.25%).

Preparation of *N*, *N*-Diethylaniline Hydrochloride (10). To a stirred solution of *N*, *N*-diethylaniline (10 kg, 67 mol) in Me-*t*-Bu ether (30 L), hydrogen chloride gas was purged in to the reaction mass slowly until reaching a pH of 1.5 at 10−15 °C and the reaction mass was stirred for 2 h at the same temperature. Reaction mass was filtered, and the solid residue was washed with Me-*t*-Bu ether (10 L) and dried under vacuum at 60−70 °C for 12 h. Vacuum was released under nitrogen and **10** (11.82 kg, 95.32% yield) was unloaded into bags. Water content by KF = 0.15%, assay by titration = 99.9%.

Preparation of (*R*)-(+)-3-Chloro-1-pheny-L-propanol (8). To a stirred solution of sodium borohydride (1.2 kg, 31.72 mol) in DME (24 L), a solution of **10** (6.0 kg, 32.31 mol, water content: 0.23%) in dichloromethane (9.0 L) was added slowly at 20−30 °C in 3 h and the reaction mass was stirred for 3 h. Nitrogen sweep was maintained in the reactor to displace hydrogen through flame arrestor vent. **11** (0.45 kg, 1.77 mol) was dissolved in dichloromethane (0.6 L) and the resulting solution was added to the reaction mass under stirring at 25−30 °C. The above reaction mixture was stirred for 1 h at 25−30 °C. A solution of **7** (6.0 kg, 35.58 mol, water content: 0.06%) prepared in dichloromethane (9.0 L) was added to the reaction mass slowly in 3 h and stirred for 6 h at 25−30 °C. The completion of the reaction was monitored by HPLC (**7** = 0.03%) and chiral purity of reaction mass was checked by HPLC (94.5% ee). To the reaction mass, 2-butanone (6.0 L) was added and stirred for 1 h, followed by the addition of toluene (18.0 L), water (30.0 L), and concentrated hydrochloric acid (1.8 L) and stirred for 30 min at 20−30 °C. The layers were separated. The aqueous layer was further extracted with toluene (12.0 L). The two toluene extracts were combined and washed with a solution of concentrated hydrochloric acid (1.8 L) in water (12.0 L) followed with water (12.0 L) and concentrated under vacuum to obtained solution of **8** (9 L). For analysis purpose, reaction mass aliquot (10 mL) was removed and concentrated under vacuum, and after chloroform stripping, solid residue (6.45 g) was obtained with 95.85% yield, $[\alpha]^{25}_{D}$ = +24.22° (*c* = 1 in $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.25 (m, 5H, Ar), 4.96−4.92 (m, 1H, C***H***OH) 3.76−3.53 (m, 2H, CH_2), 2.28−2.05 (m, 2H, CH_2), 1.97 (s, 1H, O***H***). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.36, 128.35, 127.57, 125.60, 70.89, 41.43, 41.08. The obtained SOR[17] and ^{1}H NMR[12g] were in conformity with the literature. Enantiomeric excess was determined by chiral HPLC on a chiralcel OJ-H (4.6 × 250 mm, 5 μm) column eluting with *n*-hexane/ethanol (90:10) at 1.5 mL min^{-1} flow rate and λ = 210 nm. Retention times were 14.63 and 15.69 min for (*S*) and (*R*) enantiomers, respectively. (Synthesis of dapoxetine hydrochloride from solution of **8** in toluene is included in Supporting Information.)

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■ ASSOCIATED CONTENT

Supporting Information

Chiral HPLC chromatograms, ^{1}H NMR, and ^{13}C NMR spectra for **8**. Procedure for preparation of **1**, **9**, **13**, **15**, **17**, **19**, **21**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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