A Simple Protocol for the One Pot Synthesis of Chiral Secondary Benzylic Alcohols by Catalytic Enantioselective Reduction of Aromatic Ketones

Viviana L. Ponzo, Teodoro S. Kaufman*

Instituto de Química Orgánica de Síntesis -IQUIOS- (CONICET-UNR) and Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Casilla de Correo 991, S2000WAJ Rosario, República Argentina
Fax +54(341)4370477; E-mail: tkaufman@fbioyf.unr.edu.ar

Abstract: A simple and efficient protocol for the one-pot catalytic enantioselective reduction of prochiral aromatic ketones mediated by in situ prepared catalysts derived from (S)-(–)-diphenyl-pyrrolidin-2-yl-methanol, is reported.

Key words: enantioselective reduction, chiral alcohols, oxazaborolidines, chiral catalysts, one-pot reaction

The enantioselective reduction of prochiral ketones to the corresponding secondary alcohols is nowadays a common transformation in organic synthesis and various chiral non-racemic catalysts and reducing agents have been developed for this purpose. The use of optically active oxazaborolidines (OABs) introduced by Itsuno,[1] became an extremely important tool for that purpose since Corey's seminal article of 1987 (CBS process),[2] due to the simplicity of the procedure, its wide range of applicability, high effectiveness and – in certain cases – predictability of the absolute stereochemistry of the product. Several reviews have addressed the capabilities and uses of chiral OABs in catalytic asymmetric organic synthesis;[3] in addition, the usefulness of structurally related compounds such as phosphinamides, phospholidines[4] and sulfonyl (S)-prolinol derivatives[5] as efficient catalysts, working under a similar or related mechanism, has been reported.

Many of the structural and conformational[6] aspects of the OABs' catalytic activity have also been studied[3d] and a wide variety of chiral β-aminoalcohol precursors have been synthesized and functionally tested.[7] On the contrary, a handful of borane carriers, boroxines and boronic acids, specially those commercially available, have been employed as boron sources.[3d,7a,8]

(S)-(–)-Diphenyl-pyrrolidin-2-yl-methanol [(–)-**1**], a β-aminoalcohol derived from natural proline continues to be the most widely used OAB precursor, favored by its commercial availability and the high enantiomeric excesses of products obtained with the catalysts it originates. However, due to its poor backbone flexibility and high steric demand, the elaboration of OABs derived from (–)-**1** usually require conditions including time-consuming operations or relatively expensive reagents,[2,3] which sometimes discourage their preparation, specially in small scale.

Herein, we report a simplified and convenient protocol for the elaboration of OAB catalysts by reaction of (–)-**1** and borane methyl sulfide complex in the presence of an alcohol (Scheme) and its application to the one pot synthesis of chiral secondary benzylic alcohols by catalytic enantioselective reduction of prochiral ketones.
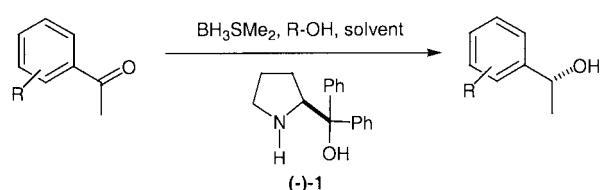
Scheme

The use of alcohols and borate esters in OAB-mediated reductions has some scattered precedents. Alcohols have been added to improve the enantioselectivity in modified OAB-catalyzed reduction protocols,[9] producing alkoxyboranes.[9b] Furthermore, dialkoxyboranes and trialkyl borates have been detected spectroscopically in OAB-mediated reductions[10] and more recently Masui and Shioiri[11] suggested that reaction of β-aminoalcohols with trimethyl borate results in formation of B-methoxy oxazaborolidines, a transformation which was also employed by the group of Andersson for the generation of catalysts from 2-azanorbornane-derived β-aminoalcohols.[12]

Brown has reported an efficient elaboration of borate esters by reaction of alcohols with borane carriers;[13] in addition, the in situ generation and use of OAB catalysts has been recognized as an important factor providing better reproducibility in catalyst's performance.[12b] Therefore, we envisaged that a simple and highly flexible strategy for the in situ obtention of OAB catalysts could result from the combination of Brown's protocol with Masui and Shioiri's observations.

To that end and in order to comparatively evaluate the effect of the nature of the added alcohol on the asymmetry inducing capability of the catalytic system, a series of catalysts were generated employing different primary and secondary alcohols; these catalysts were immediately used for the reduction of 3,4-dimethoxyacetophenone (**2**) as test prochiral ketone, with the results in terms of chemical and optical yields of alcohol (+)-**3**, consigned in Table 1.

The use of an authentic standard of (±)-**3**, obtained by conventional reduction of **2** with sodium borohydride in methanol, allowed the proper qualification of the HPLC separation, employed for assessment of the optical yields of product.

All of the evaluated alcohols showed good to excellent performances. Reaction conditions, however, required fine tuning for the best performance to be achieved; a temperature of 34 ºC was found to be optimal for the reduction and no significant differences were observed between toluene and THF as solvents. Repeated tests indicated that in small scale reactions, lower alcohols (entries 1 and 2) were outperformed by their higher molecular weight congeners, which furnished better and more repeatable results. This seems to be in line with a previous publication in which MeOH and EtOH as additives gave comparatively poorer results.[9a] On the other hand, the catalyst derived from *n*-octanol showed one of the best performances; unfortunately, however, its exact structure could not be unveiled because in agreement with a previous report, attempts to isolate this catalyst met with failure due to its instability.[11]

Interestingly, in spite of Brown's report indicating that the reaction of secondary alcohols with borane does not achieve completion at room temperature,[13] reductions carried out with catalysts derived from cyclohexanol and 2-propanol (entries 3 and 6) were almost quantitative, provided (+)-**3** with excellent enantiomeric excesses and were not appreciably slower than those which employed OABs derived from primary alcohols.

Table 1 Reduction of 3,4-Dimethoxyacetophenone (**2**) with Catalysts Derived from (–)-**1**, Formed in the Presence of Various Alcohols
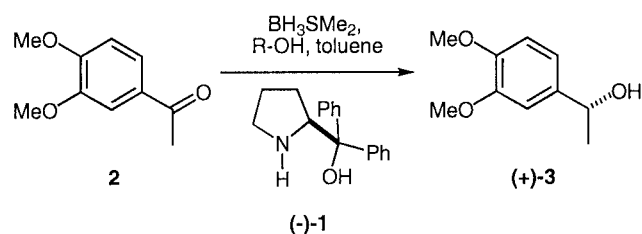
Entry	Alcohol[a]	Yield (%)[b]	ee (%)[c]
1	MeOH	100	90
2	MeCH$_2$OH	90	90
3	MeCH(OH)Me	90	97
4	Me(CH$_2$)$_3$OH	100	96
5	Me(CH$_2$)$_7$OH	98	97
6	Cyclohexanol	93	96

[a] 10 mol% of (–)-**1** were employed.
[b] Isolated yield after flash column chromatography.
[c] Determined by HPLC with a Chiralcel OD column; mobile phase: hexane/2-propanol (9:1) at 0.5 mL/min.

Encouraged by these results and in order to further test the catalytic performance of the so generated catalysts, a set of aromatic ketones carrying various substituents was submitted to this enantioselective reduction under standarized conditions. In a typical and representative procedure, a flame-dried 10 mL flask was charged with toluene (1 mL) and a 2 M solution of BH$_3$·SMe$_2$ in SMe$_2$ (0.075 mL, 0.15 mmol) under an argon atmosphere. This was dropwise treated with dry *n*-octanol (0.063 mL, 0.40 mmol) and the reaction mixture was stirred for 1 hour at 34 ºC, when a solution of (–)-**1**[14] (28 mg, 0.11 mmol) in anhydrous toluene (1 mL) was added to the thus formed borate ester. After stirring for 1 hour at 34 ºC, more BH$_3$·SMe$_2$ in SMe$_2$ (0.55 mL, 1.1 mmol) was added, followed by slow injection (1 h) via syringe pump of a solution of ketone **2** (200 mg, 1.1 mmol) in toluene (1 mL). When judged completed by TLC analysis, the reaction was quenched with 1 N HCl (5 mL) and extracted with EtOAc (3 × 15 mL). The extracts were successively washed with saturated NaHCO$_3$ (5 mL) and brine (5 mL), dried with Na$_2$SO$_4$, concentrated under reduced pressure and chromatographed furnishing (+)-**3** (198 mg, 98%; ee = 97%, by chiral HPLC), as a colorless oil.

The results, summarized in Table 2, evidence that regardless of the nature of the functional group or the substitution pattern, the reactions were highly enantioselective for the tested acetophenones. The secondary alcohol obtained in entry 3 was recently employed as a key intermediate for an enantioselective total synthesis of 1-*S*-(–)-salsolidine.[15] As expected, in the case of 3,4-dimethoxy phenylacetone (entry 9), very low induction was observed.[9b]

In conclusion, this work demonstrated the efficiency and usefulness of a simplified protocol for the one pot catalytic enantioselective reduction of prochiral ketones, featuring a facile in situ preparation of oxazaborolidines by reaction of BH$_3$·SMe2, an alcohol and (–)-**1**.
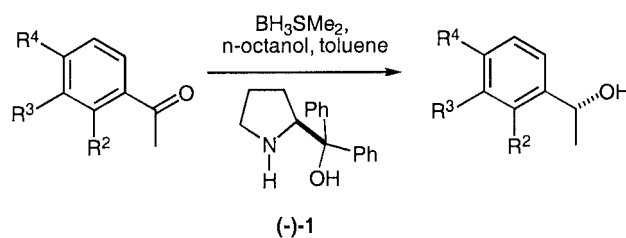
The protocol is simple, versatile, easy to be carried out in small scale and isolation of air and moisture sensitive oxazaborolidine species is not required. The use of readily available chemicals constitutes an additional attractive favoring the adoption of this methodology.

References

(1) Hirao, A.; Itsuno, S.; Nakahama, S.; Yamazaki, N. *J. Chem. Soc., Chem. Commun.* **1981**, 315.
(2) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.
(3) (a) Singh, V. K. *Synthesis* **1992**, 605. (b) Martens, J.; Wallbaum, S. *Tetrahedron: Asymmetry* **1992**, *3*, 1475. (c) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763. (d) Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1987.

Table 2 Chemical Yields, Optical Yields and Optical Rotation Data of the Chiral Secondary Alcohols Obtained by Reduction of their Corresponding Ketones with the Catalyst Derived from (–)-**1** and *n*-Octanol

Entry	Starting Ketone/Product			Yield (%)[a]	ee (%)[b]	$[\alpha]_D$[c]
	R^2	R^3	R^4			
1	H	H	H	98	97.5	+ 52.0 (c = 1.0)
2	H	MeO	MeO	98	97	+ 40.5 (c = 1.1)
3	H	MeO	AcO	99	97	+ 70.8 (c = 1.8)
4	H	MeO	HO	98	97.5	+ 41.2 (c = 0.8)
5	MeO	H	MeO	99	90	+ 24.6 (c = 0.9)
6	H	H	NO_2	97	95	+ 39.1 (c = 0.8)
7	H	NH_2	H	99	95	+ 45.6 (c = 1.2)
8	H	H	Br	98	97	+ 32.1 (c = 0.8)
9	*R*-1-(3,4-dimethoxy-phenyl-2-propanol)[d]			96	25	–

[a] Isolated yield after flash column chromatography.

[b] Determined by HPLC with a Chiralcel OD column; mobile phase: hexane/2-propanol (9:1) at 0.5 – 1.0 mL/min.

[c] All measurements were made in $CHCl_3$, employing a Jasco DIP 1000 photopolarimeter; concentrations are expressed in g/dL.

[d] 3,4-Dimethoxy-phenylacetone was employed as starting material.

(4) (a) Gamble, M. P.; Studley, J. R.; Wills, M. *Tetrahedron Lett.* **1996**, *37*, 2853. (b) Gamble, M. P.; Smith, A. R.; Wills, M. *J. Org. Chem.* **1998**, *63*, 6063. (c) Buono, G.; Chiodi, O.; Wills, M. *Synlett* **1999**, 377.

(5) Yang, G.-S.; Hu, J.-B.; Zhao, G.; Ding, Y.; Tang, M.-H. *Tetrahedron: Asymmetry* **1999**, *10*, 4307.

(6) (a) Manju, K.; Trehan, S. *Tetrahedron: Asymmetry* **1998**, *9*, 3365. (b) Fujisawa, T.; Onogawa, Y.; Shimizu, M. *Tetrahedron Lett.* **1998**, *39*, 6019.

(7) (a) Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Turner, J. E. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. *J. Org. Chem.* **1991**, *56*, 751. (b) Jones, T. K.; Mohan, J. J.; Xavier, L. C.; Blacklock, T. J.; Mathre, D. J.; Sohar, P.; Jones, E. T. T.; Reamer, R. A.; Roberts, F. E.; Grabowski, E. J. *J. Org. Chem.* **1991**, *56*, 763. (c) Fujisawa, T.; Onogawa, Y.; Shimizu, M. *Tetrahedron Lett.* **1998**, *39*, 6019. (d) Nevalainen, V. *Tetrahedron: Asymmetry* **1991**, *2*, 827; and references cited therein.

(8) (a) Cho, B. T.; Ryu, M. H. *Bull. Korean Chem. Soc.* **1994**, *15*, 1027. (b) Hong, Y.; Nie, X.; Zepp, C. M. *Tetrahedron Lett.* **1994**, *35*, 6631. (c) Caze, C. *React. Funct. Polymers* **1995**, *26*, 85.

(9) (a) Shi, Y.-J.; Cai, D.; Dolling, U.-H.; Douglas, A. W.; Tschaen, D. M.; Verhoeven, T. R. *Tetrahedron Lett.* **1994**, *35*, 6409. (b) Tschaen, D. M.; Abramson, L.; Cai, D.; Desmond, R.; Dolling, U.-H.; Frey, L.; Karady, S.; Shi, Y.-J.; Verhoeven, T. R. *J. Org. Chem.* **1995**, *60*, 4324.

(10) Salunkhe, A. M.; Burkhardt, E. R. *Tetrahedron Lett.* **1997**, *38*, 1523.

(11) Masui, M.; Shioiri, T. *Synlett* **1997**, 273.

(12) (a) Pinho, P.; Guijarro, D.; Andersson, P. G. *Tetrahedron* **1998**, *54*, 7897. (b) Brandt, P.; Andersson, P. G. *Synlett* **2000**, 1092.

(13) Brown, C. A.; Krishnamurthy, S. *J. Org. Chem.* **1978**, *43*, 273.

(14) Kaufman, T. S.; Ponzo, V. L.; Zinczuk, J. *Org. Prep. Proc. Int.* **1996**, *28*, 487.

(15) Ponzo, V. L.; Kaufman, T. S. *Tetrahedron Lett.* **1995**, *36*, 9105.