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Asymmetric Reduction of Acetophenones with $NaBH_4$ in the Presence of Mono-6-(1-methyl-3-imidazolium)-6-deoxy-β-cyclodextrin Tosylate

WEIHUA TANG[1], JIAN TANG[1], SIU-CHOON NG[2] and HARDY SZE ON CHAN[1,*]
[1]*Department of Chemistry, National University of Singapore, 3 Science Drive 3, 117543, Singapore, Singapore;* [2]*Division of Chemical and Biomolecular Engineering, College of Engineering, Nanyang Technological University, 50 Nanyang Avenue, 639798, Singapore, Singapore*

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Abstract

The asymmetric reduction of acetophenone and its derivatives was achieved with sodium borohydride utilizing a novel chiral ionic liquid of β-cylclodextrin (CD), mono-6-(1-methyl-3-imidazolium)-6-deoxy-β-cyclodextrin tosylate (MIM-β-CDOTs). It was found that this chiral β-CD-based ionic liquid could provide higher enantioselectivity for the product alcohols. Moreover, the enantioselectivity of the product alcohols was highly dependent on the structure of prochiral ketones, structure of CD and reduction temperature.

Introduction

Chiral ionic liquids have attracted increasing interest for their potential to chiral discrimination, including asymmetric synthesis and optical resolution of racemates [1–6]. Several types of chiral ionic liquids have been developed involving the imidazole moiety with expensive chiral, alkylated side-chains [1] or chiral anions [7]. Other chiral ionic liquids have been derived from the chiral pool [8], yet only few achieved successful results in chiral discrimination [8]. The application of these salts for the asymmetric reduction of ketones remains unexplored.

Cyclodextrins (CDs) are cyclic oligosaccharides possessing hydrophobic cavities and they mimic enzymes in their capability to bind substrates selectively and catalyze chemical reactions through the formation of reversible host–guest complexes with substrates via non-covalent bonding. Furthermore, CDs with chiral cavitivies can induce asymmetric reactions [9, 10]. The stereoselective reduction of ketones included in β-CD with $NaBH_4$ has been extensively studied [11–13]. However, native β-CD can only present modest enantioselectivity to the product alcohols due to its symmetric structure [14]. Herein, we designed a family of novel cyclodextrin-based chiral ionic liquids, aiming at enhancing the chiral discrimination ability of CDs by changing their symmetric structure [15]. These salts were prepared by launching cations such as alkylimidazolium, alkylpyridinium and ammonium onto the C-6 of cyclodextrins. Their chirality was induced by the chiral environment of cyclodextrins. Though the melting points of these compounds are too high (115–267 °C) for ionic liquid applications as solvent, these cationic cyclodextrins exhibited good enantioseparation ability towards a wide variety of racemates in capillary electrophoresis [16, 17].

Our continuing interest in exploring the chiral recognition ability of these chiral ionic liquids along with studies mentioned above on the asymmetric reduction of prochiral ketones prompted this investigation. Our study was aimed to investigate the possibility of application of our newly-developed CD derivatives for the chiral synthesis of alcohols. Mono-6-(1-methyl-3-imidazolium)-6-deoxy-β-cyclodextrin tosylate (MIM-β-CDOTs) was selected as the model chiral template for the asymmetric reduction of various ketones. The effect of temperature in obtaining better enantioselectivity was examined.

Experimental

General

MIM-β-CDOTs was synthesized in the lab according to the reported procedure [15]. Ketones were obtained from Aldrich (Steinheim, Germany) and used as received. NMR spectra were obtained at Bruker ACF 300 and chemical shifts were reported in ppm relative to TMS, which was used as internal standard. Optical rotation was measured with a JASCO DIP-1000 Digital Polarimeter at 25 °C.

* Author for Correspondence. E-mail: chmcsoh@nus.edu.sg

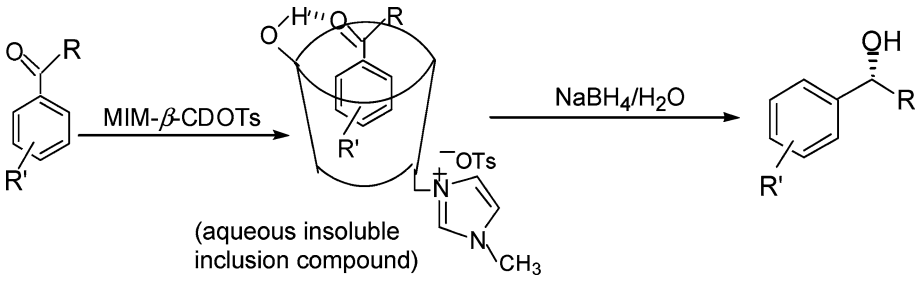


Figure 1. Reduction pathway of substituted acetophenones in the presence of MIM-β-CDOTs.

General procedure for the $NaBH_4$ reduction

The reduction pathway of substituted acetophenones in the presence of MIM-β-CDOTs is depicted in Figure 1. The reductions were performed in a one-pot procedure as reported in literature [11b]. MIM-β-CDOTs (2.74 g, 2.0 mmol) was suspended in 15 ml of 0.1 M aqueous Na_2CO_3 solution. An equimolar amount of ketone in 2 ml of acetonitrile was added and the mixture stirred for a day at fixed temperature (either 0 °C, 20 °C or 35 °C). A 2-fold excess of $NaBH_4$ (0.15 g, 4.0 mmol) was then added and the slurry stirred for further 12 h. After neutralization with 2 M HCl, the mixture was thoroughly extracted with dichloromethane (3×40 ml) and dried over Na_2SO_4. After evaporation of the solvent, the resulting alcohol was purified by flush column (Silica gel, eluent: hexane/EA = 4:1 v/v).

The isolated products were identified by NMR spectra. The absolute configuration was determined from optical rotation data using the reported values of specific rotation. The enantiomeric excess percentages (ee%) were determined by high performance liquid chromatography (HPLC) using the chiral stationary phase (CSP) developed in our lab [18]. In few cases where the alcohols can not be resolved by the selected CSP, the enantiomeric excess (ee) was determined from the reported maximum rotation value of the product alcohol.

Results and discussion

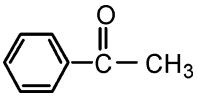
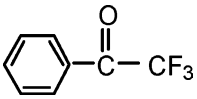
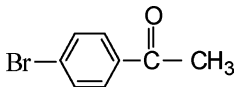
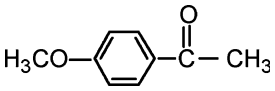
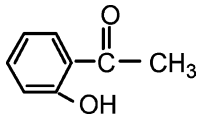
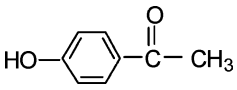
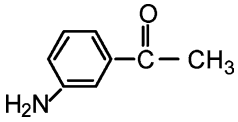
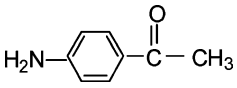
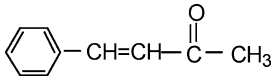
The asymmetric reduction of nine model prochiral ketones was carried out according to the abovementioned procedure. The asymmetric reduction data and the absolute configuration of the resulting secondary alcohols are reported in Table 1. It is evident that MIM-β-CDOTs gave better enantioselectivity to some chiral alcohols in comparison with β-CD [11]. The reduction of ketones of entries 1, 2, 4 were previously performed by suspending β-CD-ketone complexes in $NaBH_4$ aqueous alkaline solution with an optical yield of 3, 24 and 17% respectively [11b, c], whereas the optical yields of the corresponding ketones were improved to 8, 32 and 30% respectively in our study. This indicates that the introduction of methylimidazolium cation onto the rim of β-CD can effectively change its symmetry and stereoselectivivity towards certain guest ketones. In each case the isolated yield of the alcohols ranged between 55 and 88%. In the case of entries 2 and 9, both optical rotation measurement and CSP HPLC were applied to determine the enantiomeric composition and the results agreed well with each other.

According to a recent review [20], the driving forces contributive to the inclusion complexation of cyclodextrins include electrostatic interactions, van der Waals bonding, hydrophobic interactions, hydrogen bonding, release of conformational strain, etc. In our case, a methylimidazolium cation was attached on C6 of β-CD rim. Therefore, the driving forces would be a little different from those between neutral β-CD and ketones when the inclusion complex between MIM-β-CDOTs and ketones was formed. For example, electrostatic interactions including ion–dipole and dipole–dipole interactions can be formed not only between CD and the ketones but between the methylimidazolium cation and ketones. This difference in electrostatic interaction may account for the improved enantioselectivity of MIM-β-CDOTs.

The extent of asymmetric reduction and the absolute configuration of the product alcohols were highly dependent upon the structure of prochiral ketones. Thus, comparing the structures of ketones of entries 1 and 2, one could suggest that the enantioface selectivity was remarkably increased by introducing fluorine atoms in place of hydrogens in the methyl group of acetophenone (ee 8% and 32% for entry 1 and 2, respectively). The effect of substituent in the benzene ring on the enantioselective reduction of acetophenone with $NaBH_4$ in the presence of β-CD was previously investigated by Ernard [11c]. Generally, the presence of substituents induced higher enantioselectivities than that obtained for acetophenone probably due to stronger host–guest interactions in the former case (Table 1). Moreover, for *p*-derivatives, the enantioface selectivity was governed by a combination of steric hindrance and hydrophobic interactions with hydrogen bonding of the carbonyl group to the hydroxyls of CD.

As indicated in Table 1, the optical yields of the product alcohols significantly increased upon decreasing the reaction temperature, i.e. 14% yield (0 °C) and 10%

Table 1. Asymmetric reduction of ketones in the presence of MIM-β-CDOTs

Entry	Ketone	CDs	Alcohols		
			Isolated yield (%)	[α] (solvent)	Optical yield (ee%)
1		β-CD [11b]	82	1.4(CH_2Cl_2)	3[c] (*R*)
		MIM-β-CDOTs	86	3.5(CH_2Cl_2)	8[c] (*R*)
2		β-CD [11b]	89	3.5(C_6H_6)	24[c] (*S*)
		MIM-β-CDOTs	83	4.7(C_6H_6)	32[c], 34[d] (*S*)
3		β-CD [11c]	60	/	17 (*S*)
			88	1.6(CH_2Cl_2)	5.9[d] (*S*)
		MIM-β-CDOTs	83 [a]	2.7(CH_2Cl_2)	10[d] (*S*)
			82 [b]	3.1(CH_2Cl_2)	14[d] (*S*)
4		β-CD [11c]	58	/	17 (*S*)
			87	1.2(CH_2Cl_2)	25[d] (*S*)
		MIM-β-CDOTs	84[a]	2.8(CH_2Cl_2)	30[d] (*S*)
			75[b]	4.5(CH_2Cl_2)	41[d] (*S*)
5		MIM-β-CDOTs	78	2.0(CH_2Cl_2)	16[d]
			73[a]	3.5(CH_2Cl_2)	28[d]
6		MIM-β-CDOTs	74	5.7(CH_2Cl_2)	NA
7		MIM-β-CDOTs	55	8.0(CH_2Cl_2)	NA
8		MIM-β-CDOTs	63	3.5(CH_2Cl_2)	NA
9		MIM-β-CDOTs	87	3.0(MeOH)	31[c], 27[d] (*R*)

Conditions: Reduction of ketones was carried out at 35 °C unless specified.
(a). reduction temperature 20 °C; (b). reduction temperature 0 °C; (c). calculation based on the reported maximum rotation value: +44.86 (CH_2Cl_2) for *R*-1-phenylethanol [19a]; +14.76 (C_6H_6) for *S*-1-phenyl-2,2,2-trifluoroethanol [19b]; +9.75 (MeOH) for *R*-4-phenyl-3-buten-2-ol [19c]; (d). ee (%) determined by HPLC analysis with the chiral column (0.46 cm × 25 cm) packed with mono(6^A-N-allylamino-6^A-deoxy)per-phenylcarbamoylated-cyclodextrin using hexane/propan-2-ol (97:3) as eluent at a flow rate of 1.0 ml/min using UV detection (254 nm).

(20 °C) in entry 3, 41% yield (0 °C) and 30% (20 °C) in entry 4, and 28% (20 °C) in entry 5. This indicates that a pre-equilibrium between the substrate and MIM-β-CDOTs has been attained in this case and this might be helpful in increasing the enantioface selectivity. This observation is consistent with that reported by Park [11b].

It is interesting to note that the absolute configurations of the product alcohols obtained by MIM-β-CDOTs are the same as those by β-CD [11]. This may be explained by the inclusion of the guest ketones. Due to the steric hindrance of the large imidazolium moiety at the narrow rim of CD, the aromatic groups of the ketones have to insert into the CD cavity from the secondary hydroxyl side, which is the prevailing pattern of insertion of aromatic group of guest molecules in the presence of β-CD. Some representative chromatograms of product alcohols are depicted in Figure 2.

In conclusion, the chiral discrimination ability of MIM-β-CDOTs was examined in the asymmetric reduction of prochiral ketones. The newly designed salt gave enhanced enantioselectivity in comparison with the parent β-CD. Further investigations on the influence of temperature and substituents on the enantioselective reduction of acetophenones will be reported elsewhere.

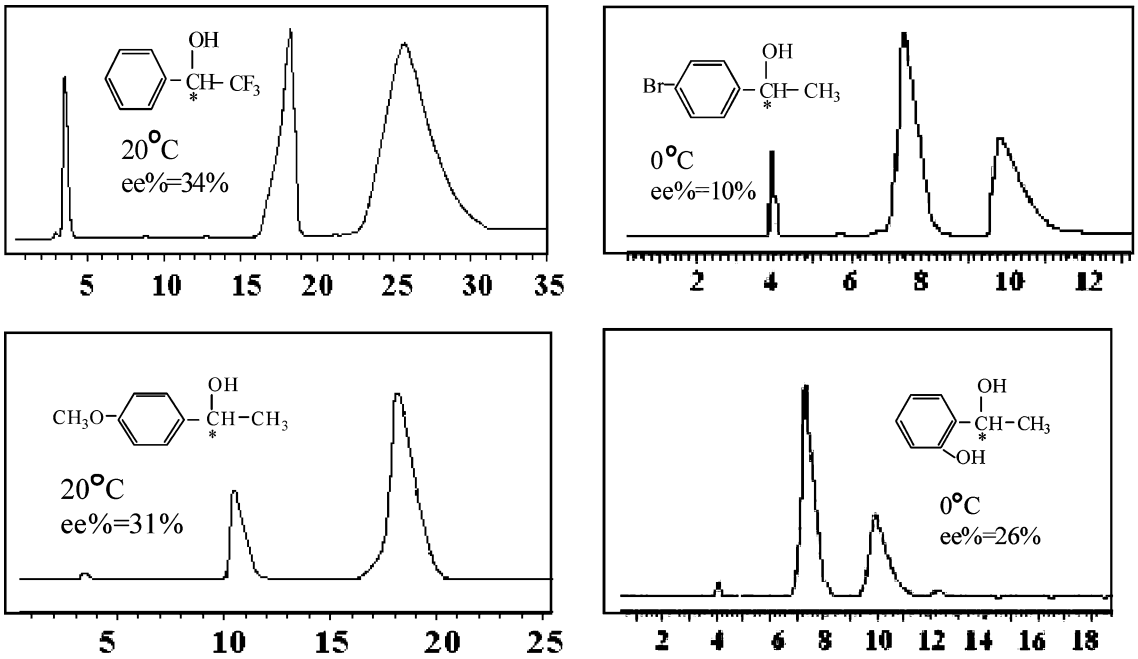


Figure 2. Representative chromatograms for some product alcohols on the CSP column. Conditions: buffer hexane/propan-2-ol (97:3), flow rate: 1.0 ml/min, UV detector: $\lambda = 254$ nm.

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References

1. J. Howarth, K. Hanlon, and P. Mccormac: *Tetrahedron Lett*. **38**, 3097 (1997).
2. Y. Ishida, H. Miyauchi, and K. Saigo: *Chem. Commun*. **19**, 2240 (2002).
3. E.G. Yanes, S.R. Gratz, M.J. Baldwin, S.E. Robinson, and A.M. Stalcup: *Anal. Chem*. **73**, 3838 (2001).
4. J.L. Anderson and D.W. Armstrong: *Anal. Chem*. **75**, 4851 (2003).
5. D.W. Armstrong, L.F. He, and Y.S. Liu: *Anal. Chem*. **71**, 3873 (1999).
6. E.G. Yanes, S.R. Gratz, and A.M. Stalcup: *Analyst* **125**, 1919 (2000).
7. M.J. Earle, P.B. McCormac, and K.R. Seddon: *Green Chem*. **1**, 23 (1999).
8. P. Wasserscheid, A. Bösmann, and C. Bolm: *Chem. Commun*. **3**, 200 (2002).
9. K. Takahashi: *Chem. Rev*. **98**, 2013 (1998).
10. L.R. Reddy, N. Bhanumathi, and K.R. Rao: *Chem. Commun*. **20**, 2321 (2000).
11. R. Fornasier, F. Reniero, P. Scrimin, and U. Tonellato: *J. Org. Chem*. **50**, 3209 (1985); (b) K.K. Park, W.-J. Sim, and J.W. Park: *J. Incl. Phenom. Mol. Recog. Chem*. **27**, 41 (1997); (c) A. Deratani and E. Renard: *Chirality* **6**, 658 (1994).
12. A. Schlatter, M.K. Kundu, and W.-D. Woggon: *Angew. Chem. Int. Ed*. **43**, 6731 (2004); (b) M.A. Reddy, N. Bhanumathi, and K.R. Rao: *Chem. Commun*. **19**, 1974 (2001); (c) Y. Kawajiri and N. Motohashi: *J. Chem. Soc., Chem. Commun*. 1336 (1989); (d) T. Maraldo and A. Deratani: *Minutes of the fifth International Symposium on Cyclodextrins*, Paris, 659 (1990).
13. F. Toda and T. Shigemasa: *Carbohydr. Res*. **192**, 363 (1989); (b) W.-S. Chung, N.J. Turro, J. Silver, and W.J. Le Noble: *J. Am. Chem. Soc*. **112**, 1202 (1990); (c) G. Mehta, F.A. Khan, and K.A. Lakshmi: *Tetrahedron Lett*. **33**, 7977 (1992).
14. C.J. Easton and S.F. Lincoln: *Chem. Soc. Rev*. **25**, 163 (1996).
15. I.W. Muderawan, T.-T. Ong, W.-H. Tang, D.J. Young, C.-B. Ching, and S.-C. Ng: *Tetrahedron Lett*. **46**, 1747 (2005).
16. W.-H. Tang, T.-T. Ong, and S.-C. Ng: *Electrophoresis* **26**, 3125 (2005).
17. W.-H. Tang, I.W. Muderawan, T.-T. Ong, and S.-C. Ng: *Anal. Chim. Acta* **546**, 119 (2005).
18. X.-H. Lai and S.-C. Ng: *Tetrahedron Lett*. **44**, 2657 (2003).
19. U. Nagai, T. Shishido, R. Chiba, and H. Mitsuhashi: *Tetrahedron* **21**, 1701 (1965); (b) H.M.D. Peters, M.H. Feigl, and S. Mosher: *J. Org. Chem*. **33**, 4245 (1968); (c) J. Buckingham (ed.), *Dictionary of Organic Compounds*, Vol. 5, (5th edn), Chapman and Hall, New York (1982) p. 4609.
20. L. Liu and Q.-X. Guo: *J. Incl. Phenom. Mol. Recog. Chem*. **42**, 1 (2002).