Chinese Chemical Letters Vol. 16, No. 7, pp 975-978, 2005 975
http://www.imm.ac.cn/journal/ccl.html

Asymmetric Phase-transfer Mediated Epoxidation of α, β-Enones Using Dendritic Catalysts Derived from *Cinchona* Alkaloids

Xu Dong LIU, Xiao Li BAI, Xue Peng QIU, Lian Xun GAO*

State Key Laboratory of Polymer Physics and Chemistry, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Graduate School of the Chinese Academy of Sciences, Changchun 130022

Abstract: Chiral phase-transfer catalysts, derived from *cinchona* alkaloids and Fréchet dendritic wedges up to generation two, have been synthesized. These chiral dendritic molecules have been used as PTCs in the epoxidation of α, β-enones, showing a moderate level of asymmetric induction.

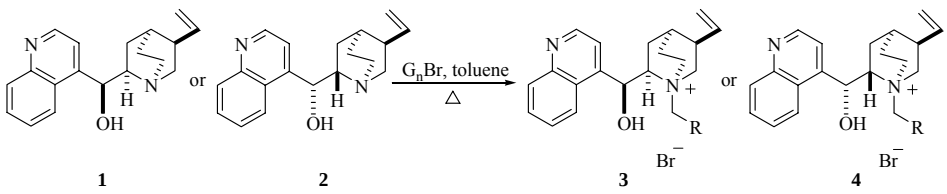
Keywords: Asymmetric epoxidation, phase-transfer catalysis, *cinchona* alkaloids.

Among intermediates in organic synthesis epoxides are the most versatile and as a result the selective epoxidation of alkenes is a major area of research[1]. The epoxides can be easily transformed into a variety of functionalized compounds. For example reductions, rearrangements or ring opening reactions with various nucleophiles give diols, aminoalcohols, allylic alcohols, ketones, polyethers *etc.*. The availability of some epoxides in optically active form has enhanced their use as synthetic intermediates. The development of the enantioselective synthesis of epoxides has been recognized as an important goal in modern organic synthesis[2].

Phase-transfer catalysis is a general green methodology in organic synthesis, and Phase-transfer catalysts (PTCs) are one of the most powerful reagents in chemical transformation, due to they are easy to use, economical and environ-mentally benign[3]. Of all the classes of privileged chiral catalysts[4], *cinchona* alkaloids and their derivatives have proven to be useful in an astonishing varity of important enantioselective transformation[5]. The quinuclidine nitrogen can be quarternized with benzyl halides to give ammonium salts that can serve as useful asymmetric PTCs[6]. Dendrimers[7] are highly branched, fractal macromolecules of defined three-dimensional size, shape, and topology which can be prepared with extremely narrow molecular weight distribution. Dendrimers are due, beyond the aesthetics appeal, to their great potential of applications in biology and materials science. Among the main potential applications of dendrimers, used as catalyst[8] is the most promising one. Here, we reported the synthesis of dendritic *cinchona* alkaloids-derived ammonium salts **3** and **4** which affect

* E-mail: lxgao@ciac.jl.cn

Scheme 1



1 **2** **3** **4**

3a: R = G_0 = $PhCH_2$

3b: R = G_1 , n = 1

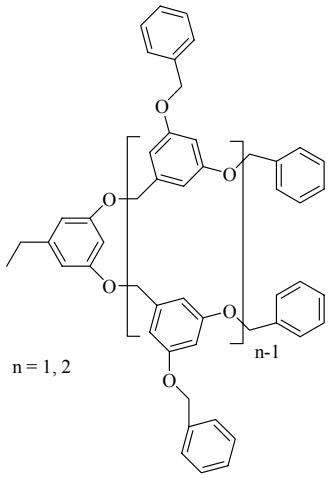
3c: R = G_2 , n = 2

4a: R = G_0 = $PhCH_2$

4b: R = G_1 , n = 1

4c: R = G_2 , n = 2

G_n =



the enantioselectivity due to steric and electronic effects of Fréchet dendritic wedges. They will be used as PTCs in the asymmetric epoxidation of enones[9].

The synthetic route is outlined in **Scheme 1**. **3a** and **4a** were prepared according to the literature[6b]. These Fréchet dendritic wedges were prepared using a convergent approach, involving standard K_2CO_3/18-crown-6 mediated ether formation steps and alcohol to bromide conversions using CBr_4/PPh_3[10]. Cinchonine **1** and cinchonidine **2** were derivatized with Fréchet dendritic wedges up to generation two. The quarternization of the quinuclidine moiety was performed by refluxing benzyl bromide or the corresponding dendritic wedges (as the bromide) with **1** or **2** in toluene. The resulting salts were filtered and washed with toluene, rendering pure derivatives **3b** (91%) and **4b** (62%). **3c** and **4c** were not suitable to recrystallize in toluene due to their high solubility, and purified by flash column chromatograph (SiO_2, CH_2Cl_2 : CH_3OH = 50:1), giving pure **3c** (73%) and **4c** (82%), respectively. All the compounds were characterized and identified by IR, ^1H and MALDITOF mass spectrometry as well as elemental analysis, the results being in full agreement with the proposed structures.

In order to evaluate the efficiency of these derivatives of *cinchona* alkaloids, the nucleophilic epoxidation of α, β-enones to α, β-epoxy ketones (**Scheme 2**) was chosen as a model reaction. A typical procedure[9f] for catalytic asymmetric epoxidation under PTC conditions is as follows: A mixture of enone **5** (0.25 mmol) and PTC (0.0125 mmol) in a biphase-system, dibutyl ether and 30% aqueous H_2O_2 (2.0 mL), was stirred at 0 °C for 20 min. After NaOH (40 mg, 1.0 mmol) was added, the reaction mixture

Scheme 2

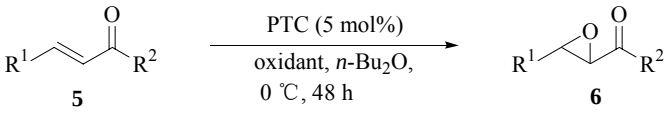


Table 1 Enantioselective epoxidation of α, β-unsaturaed ketones **5** using PTCs **3** and **4** derived from *cinchona* alkaloids

Entry	PTC	Oxidant	Enone	R^1	R^2	Yield (%)	*e.e.* (%)	$[\alpha]_D^{20}$ (*c* 0.1, CH_2Cl_2)
1	**3a**	H_2O_2/NaOH	**5a**	C_6H_5	C_6H_5	78	<2	–4
2	**3b**	H_2O_2/NaOH	**5a**	C_6H_5	C_6H_5	65	14	+20
3	**3c**	H_2O_2/NaOH	**5a**	C_6H_5	C_6H_5	75	8	+15
4	**4a**	H_2O_2/NaOH	**5a**	C_6H_5	C_6H_5	81	<2	–7
5	**4b**	H_2O_2/NaOH	**5a**	C_6H_5	C_6H_5	45	56	–122
6	**4c**	H_2O_2/NaOH	**5a**	C_6H_5	C_6H_5	68	10	–38
7	**3a**	NaClO	**5a**	C_6H_5	C_6H_5	74	21	–47
8	**3b**	NaClO	**5a**	C_6H_5	C_6H_5	62	40	–88
9	**3c**	NaClO	**5a**	C_6H_5	C_6H_5	59	37	–80
10	**4a**	NaClO	**5a**	C_6H_5	C_6H_5	79	7	+15
11	**4b**	NaClO	**5a**	C_6H_5	C_6H_5	72	46	+100
12	**4c**	NaClO	**5a**	C_6H_5	C_6H_5	64	11	+24
13	**4b**	H_2O_2/NaOH	**5b**	4-Cl-C_6H_4	C_6H_5	54	51	–73
14	**4b**	H_2O_2/NaOH	**5c**	4-NO_2-C_6H_4	C_6H_5	92	14	–35
15	**4b**	H_2O_2/NaOH	**5d**	α-naphthyl	C_6H_5	46	58	+48
16	**4b**	H_2O_2/NaOH	**5e**	β-naphthyl	C_6H_5	85	54	–49
17	**4b**	H_2O_2/NaOH	**5f**	C_6H_5	4-CH_3O-C_6H_4	36	61	–53
18	**4b**	H_2O_2/NaOH	**5g**	C_6H_5	4-Cl-C_6H_4	51	58	–130
19	**4b**	H_2O_2/NaOH	**5h**	C_6H_5	4-NO_2-C_6H_4	91	3	+6
20	**4b**	H_2O_2/NaOH	**5i**	C_6H_5	α-naphthyl	72	58	–222

was stirred at 0 °C for 48 h. The mixture was quenched with 1 mol/L HCl (5.0 mL), extracted with ethyl acetate (15 mL × 3), washed with brine, and dried over $MgSO_4$. Removal of the solvent followed by flash column chromatography (SiO_2, petroleum ether: ethyl acetate = 25:1) gave the desired product **6**. Enantiomeric excess was determined by HPLC analysis using CHIRALCEL OD-H. We attempted the catalyst activity of **3** or **4** (**Scheme 2**) using H_2O_2 as oxidant in the presence of NaOH (entries 1-6, **Table 1**) and also tested with oxidant NaClO under the same conditions (entries 7-12, **Table 1**). **4b**/H_2O_2/NaOH gave the best result for the asymmetric epoxidation of **5a** with 56% *e.e.*, as shown in entry 5. **3a**/H_2O_2/NaOH (entry 1) and **4a**/H_2O_2/NaOH (entry 4) were found almost no enantioselectivities and with the increasing generation number of PTC, the enantioselectivities decreased (entries 3, 6, 9 and 12). These results indicated that the substituent effect on PTC is quite important for achieving high

enantioselectivity. According to these results, we examined the generality in this asymmetric epoxidation through the substrate effect, as shown in entries 13-16. PTC **4b** acts as an effective catalyst, as expected, and the desired products were obtained with moderate enantioselectivities except for substrate **5c**. The substituent effect at position R^2 in the enone substrates (entries 17-20) was also investigated. As shown in **Table 1**, the results suggest that a range of different groups can be tolerated at position R^2 in the enone substrates.

In summary, dendritic *cinchona* alkaloids ammonium salts were synthesized and applied to asymmetric epoxidation as phase-transfer catalysts. PTC **4b** shows to be a good PTC catalyst giving a moderate level of asymmetric induction. Further studies into the variation of the molecular structure to improve enantioselectivity are underway.

References

1. (a) J. G. Smith, *Synthesis*, **1984**, 629; (b) C. Bonini, G. Righi, *Synthesis*, **1994**, 225.
2. (a) M. J. Porter, J. Skidmore, *Chem. Commun.*, **2000**, 1215; (b) B. S. Lane, K. Burgess, *Chem. Rev.*, **2003**, *103*, 2457; (c) Z. G. Zhang, X. Y. Wang, C. Sun, H. C. Shi, *Chin. J. Org. Chem.*, **2004**, *24*, 7.
3. M. Makosza, *Pure Appl. Chem.*, **2000**, *72*, 1399.
4. T. P. Yoon, E. N. Jacobsen, *Science*, **2003**, *299*, 1691.
5. K. Kacprzak, J. Gawroński, *Synthesis*, **2001**, 961.
6. (a) R. Helder, J. C. Hummelen, R. W. P. M. Laane, J. S. Wiering, H. Wynberg, *Tetrahedron Lett.*, **1976**, *21*, 1831; (b) M. J. O'Donnell, S. D. Wu, J. C. Huffman, *Tetrahedron*, **1994**, *50*, 4507; (c) B. Lygo, P. G. Wainwright, *Tetrahedron Lett.*, **1997**, *38*, 8595; (d) E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.*, **1997**, *119*, 12414.
7. (a) H. M. Tan, Y. J. Luo, *Dendritic Polymers*, Chem Ind Press, Beijing, **2002**; (b) M. Fischer, F. Vogtle, *Angew. Chem., Int. Ed. Engl.*, **1999**, *38*, 884; (c) A. W. Bosman, H. M. Janssen, E. W. Meijer, *Chem. Rev.*, **1999**, *99*, 1665; (d) S. M. Grayson, J. M. J. Fréchet, *Chem. Rev.*, **2001**, *101*, 3819.
8. (a) D. Astruc, F. Chardac, *Chem. Rev.*, **2001**, *101*, 2991; (b) R. V. Heerbeek, P. C. J. Kamer, P. W. N. M. Leeuwen, J. N. H. Reek, *Chem. Rev.*, **2002**, *102*, 3717; (c) X. D. Tang, Q. Z. Zhang, D. Q. Wang, Q. F. Zhou, *Chin. J. Org. Chem.*, **2003**, *23*, 238.
9. For recent results on asymmetric epoxidation of enones promoted *cinchona* alkaloids-derived ammonium salts, see (a) B. Lygo, P. G. Wainwright, *Tetrahedron Lett.*, **1998**, *39*, 1599; (b) S. Arai, H. Tsuge, T. Shioiri, *Tetrahedron Lett.*, **1998**, *39*, 7563; (c) E. J. Corey, F. Y. Zhang, *Org. Lett.*, **1999**, *1*, 1287; (d) B. Lygo, P. G. Wainwright, *Tetrahedron*, **1999**, *55*, 6289; (e) B. Lygo, D. C. M. To, *Tetrahedron Lett.*, **2001**, *42*, 1343; (f) S. Arai, H. Tsuge, M. Oku, M. Miura, T. Shioiri, *Tetrahedron*, **2002**, *58*, 1623.
10. C. J. Hawker, J. M. J. Fréchet, *J. Am. Chem. Soc.*, **1990**, *112*, 7638.

Received 16 Augest, 2004