Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Molecular Catalysis A: Chemical 216 (2004) 7–12
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
www.elsevier.com/locate/molcata

Highly diastereoselective epoxidation of cholest-5-ene derivatives catalyzed by polymer-supported manganese(III) porphyrins

Can-Ping Du, Zheng-Kai Li, Xiang-Min Wen, Jiang Wu, Xiao-Qi Yu*, Meng Yang, Ru-Gang Xie[1]

Department of Chemistry, Sichuan Key Laboratory of Green Chemistry and Technology, Sichuan University, Chengdu 610064, PR China

Received 18 August 2003; received in revised form 17 November 2003; accepted 1 December 2003

Available online 19 March 2004

Abstract

Manganese(III) 5,10,15-tris(tolyl)-20-(4-hydroxyphenyl) porphyrin covalently attached to Merrifield's peptide resin (MPR) was prepared. The catalysts exhibit high reactivity and β-selectivity toward the epoxidation of cholest-5-ene derivatives with PhIO. Under mild reaction conditions, the catalyst was consecutively reused four times without detectable catalyst leaching and gave over 90% epoxide yield and over 99% β-selectivity.

Keywords: Diastereoselective epoxidation; Cholest-5-ene derivatives; Supported metalloporphyrins

1. Introduction

There is a considerable interest in developing metalloporphyrin catalysts for epoxidation of unfunctionalized alkenes [1–5]. Most of the studies have been focused on the relationship between the porphyrin structure and the corresponding catalytic efficiency, or the promising application of these catalytic systems [6–13]. In recent years, the emphasis has been put on the catalyst stability and reuse [14–20]. At the same time, β-epoxidation of Δ^5-steroids has attracted a growing attention; the 5β,6β-epoxidation are less accessible than corresponding 5α, 6α-isomers owing to the C(10)-angular methyl group of Δ^5-steroids [21,22]. Some success in β-epoxidation of Δ^5-steroids has been achieved by using metal-based oxidants, e.g. chromium, manganese, or iron tetraphenylporphyrin/iodosobenzene [23], vanadium or molybdenium catalyst/alkyl hydroperoxides [24], iron(III) or titanium(III) acetylacetonates/hydrogen peroxide [25], ruthenium(IV) tetramestylporphyrin or ruthenium(II) bioxazoline complex/molecular oxygen [26–28], potassium permanganate/metal sulfates [29,30], metal nitrates [31], or sodium perborate [32]. The major drawbacks of these methods are that some catalysts of metal complexes are not easy to be prepared and are not stable and cannot be reused.

Recently, heterogenized manganese porphyrin catalysts have been used to catalyze the epoxidation of general alkenes [33,34]. There were numerous reports on their attachment to insoluble polymer supports including surface-modified mesoporous molecular sieve (MCM-41) [35,36], the Merrifield's peptide resin (MPR) [14–18] and the polyethylene glycol (PEG) [19] to give heterogeneous catalysts. These heterogenized metalloporphyrin catalyst were used to catalyze the transform action of general alkenes to epoxides with high efficiency and epoxide selectivity, and the reuse experiments reveal neither significant catalyst leaching nor deactivation. However these catalysts have never been used to catalyze the diastereoselective epoxidation of natural products. Following line of this research, the results obtained in the highly diastereoselective epoxidation of cholest-5-ene derivatives with PhIO catalyzed by polymer-supported manganese(III) porphyrins are reported.

2. Results and discussion

Since ruthenium porphyrins have been attached to solid supports through a covalent linkage showing high

* Corresponding author. Tel.:+86-28-85415886; fax: +86-28-85412285.
E-mail address: schemorg@mail.sc.cninfo.net (X.-Q. Yu).
[1] Co-corresponding author.

1381-1169/$ – see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.molcata.2003.12.039

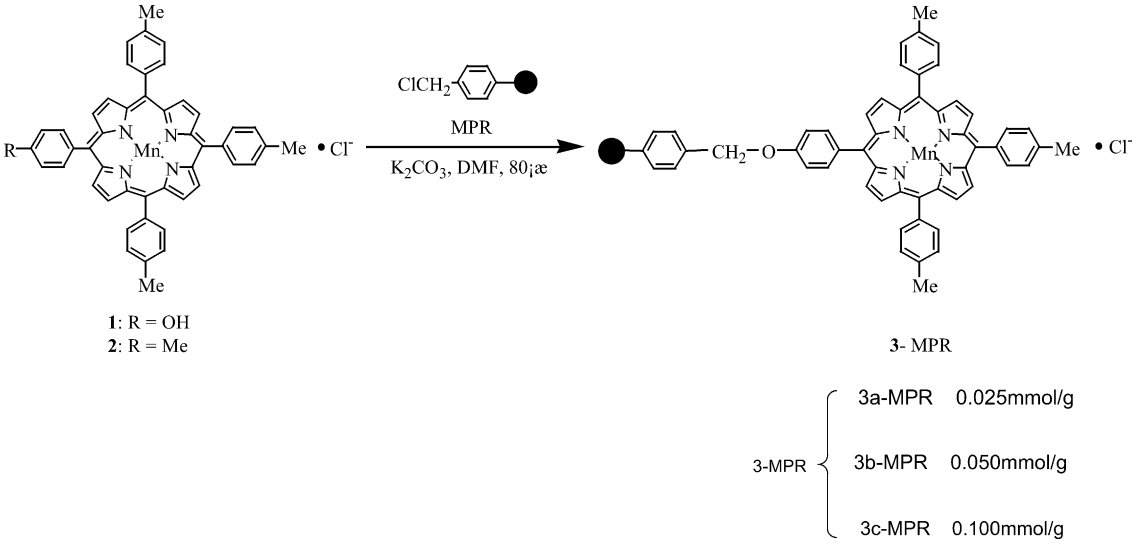


Fig. 1. Synthesis of manganese porphyrins covalently immobilised onto Merrifield's peptide resin.

diastereoselectivity and high stability in epoxidation of glycal and α-aminoalkyl alkene. [14–17], we are interested in attaching manganese porphyrin to a solid support through a covalent linkage forming stable catalysts as depicted in Fig. 1. The polymer-supported manganese(III) porphyrins were found more efficient for cholest-5-ene derivatives epoxidation (93% yield) than those obtained with soluble Mn-porphyrins **2**. In the reused experiments, the supported catalysts are clearly superior to the corresponding soluble Mn-porphyrins, resulting in better yields.

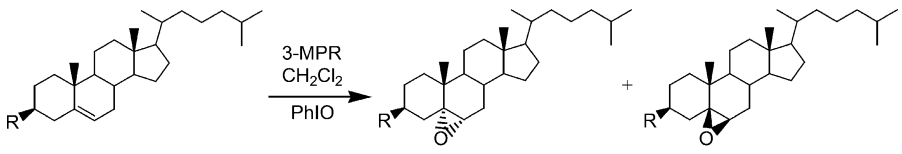
The unsymmetrically 5,10,15-tris(tolyl)-20-(4-hydroxyphenyl)porphyrin was readily prepared via a "one-pot" reaction of the corresponding aldehydes and pyrrole. Subsequent reaction with $Mn(OAc)_2{\cdot}4H_2O$ in refluxing DMF afforded manganese(III) porphyrin **1** in high yields.

Attachment of manganese(III) porphyrin to Merrifield's peptide resin (abbreviated here as MPR) was achieved in high yields (81%) by treating **1** and MPR in DMF at 80 °C for 6 h in the presence of anhydrous potassium carbonate (Fig. 1). The excellent solvation and swelling of MPR in certain organic solvents, such as dichloromethane and *N*,*N*-dimethylformamide (DMF) may allow metalloporphyrins to be attached not only at the surface of the polymer bead but also within the interior of the cross-linked polymer matrix. Consequently, there is a possibility of achieving a high selectivity by supporting sterically unencumbered manganese porphyrins onto MPR as a result of the unique microenvironment constituted by the porphyrin macrocycle and the polymer matrix. The resulting heterogenized catalysts are designated as **3a**–**c**, which were prepared by changing the amount of **1** used in Fig. 1.

2.1. Cholest-5-ene derivatives epoxidation with PhIO catalyzed by 3-MPR

Preliminary examinations of the catalytic behavior of **3a**–**c** toward epoxidation of cholesteryl acetate with PhIO revealed that the catalysts **3a**–**c** can efficiently catalyze the transform action of Δ^5-steroids to the corresponding epoxides in high yield. Two stereoisomers of epoxide from Δ^5-steroids, α- and β-stereoisomer, are shown in Scheme 1. The results of the reaction with **4a** as a substrate are summarized in Table 1.

As shown in Table 1, the conversions of the substrate varied directly with reaction temperature. The best conversion was found when the reaction was carried out in CH_2Cl_2 at room temperature for 72 h with **3b**-MPR as a catalyst. When the reaction temperature increased to 40 °C, the conversion decreased with no significant change of the amount of β-stereoisomer. Three catalyst with different **1** loadings



a:R= AcO; b:R=TsO; c:R= PhCOO; d:R= MsO; e:R= Cl

Scheme 1.

Table 1
The major influence factors on the epoxidation of 4a[a]

Entry	Temperature (°C)	Reaction time (h)	Catalyst	Conversion[b] (%)	Stereoisomer[c] (%)	
					α	β
1	0	72	**3b**-MPR	10	24	76
2	RT	72	**3b**-MPR	57	33	67
3	30	72	**3b**-MPR	43	36	64
4	40	72	**3b**-MPR	36	39	61
5	RT	24	**3b**-MPR	32	36	64
6	RT	48	**3b**-MPR	44	38	62
7	RT	96	**3b**-MPR	49	42	58
8	RT	120	**3b**-MPR	46	31	69
9	RT	72	**3a**-MPR	32	34	66
10	RT	72	**3c**-MPR	46	12	88

[a] All the reaction were carried out in CH_2Cl_2 for 72 h, catalyst: oxidant:substrate = 1:1500:1250 (molar ratio). No axial ligand was used.
[b] Conversion and yield were determined by ^{1}H NMR (400 MHz) based on the amount of substrate.
[c] The ratio of β/α was determined by ^{1}H NMR according to previous literature [37].

(0.025, 0.050, 0.100 mmol/g) designated as **3a**-, **3b**- and **3c**-MPR, respectively, were used to catalyze the epoxidation of Δ^5-steroids. It was found that all of the conversions were similar but β-stereoisomer of the epoxide products varied from 66 to 67 and 88% (entries 2,9,10).

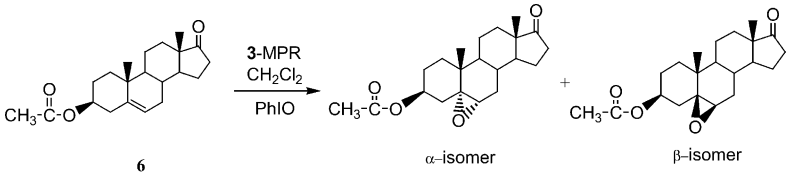
The most striking features of the catalytic epoxidations with manganese porphyrins are the remarkable improvement of the rate, chemo- and stereoselectivity of the reaction by addition of pyridine or imidazole derivatives in the reaction mixture. These ligands are efficient co-catalysts in the epoxidation of alkenes with manganese porphyrins as catalyst. In this study, imidazole or *N*-methylimidazole were used as an axial ligand respectively in the epoxidation at room temperature for 72 h with **3c**-MPR as a catalyst and **4a** (0.3 mmol) as a substrate. The results are shown in Table 2. It was found that some ligands perpendicular complexed to the plane of the catalyst **3**-MPR could improve the catalyst activity and gave the conversion of substrate **4a** 100 and 86%, respectively (entries 2 and 3). Moreover, the β-stereo isomer of these reactions was more than 99%. The conversions and β-selectivities rapidly decrease with the increase of the amount of the axial ligand. When the ratio of axial ligand with catalyst is 1:20, the conversion drops to 34% and the β-selectivity of epoxide is 27% (entry 4). The influence of the axial ligand on the catalytic epoxidation reaction has been studied by several research groups [38], who reported that mono-ligated Mn(P)L species (P represents porphyrin and L is describes the axial ligand) is the most reactive in the formation of the high valent metallo-oxo complex, while the non-coordinated species Mn(P) and the bis-ligated $Mn(P)L_2$ are poorly reactive and not reactive, respectively. When the axial ligand is much more than the amount of complex, Mn(P)L will react with another axial ligand to form the bis-ligated structure to inhibit the catalytic ability of metalloporphyrin.

Table 2
The influence of axial ligand on the epoxidation of cholesteryl acetate[a]

Entry	n[b]	Conversion (%)	Stereoisomer (%)	
			α	β
1	1	32	<1	>99
2	10	100	<1	>99
3	10	86[c]	<1	>99
4	20	34	73	27
5	40	26	58	42
6	60	20	52	48
7	80	8	68	32
8	100	7	62	38

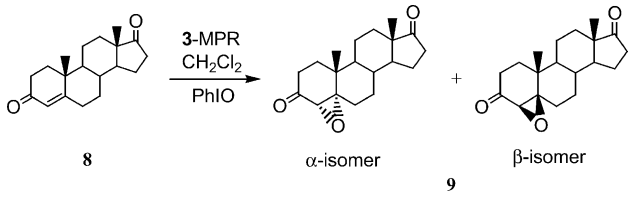
[a] Reaction conditions: all the reaction were carried out in CH_2Cl_2 at room temperature for 72 h with **4a** (0.3 mmol) as substrate, **3c**-MPR as catalyst, imidazole as axial ligand, catalyst: oxidant: substrate 1: 1500:1250 (molar ratio).
[b] n = axial ligand(mol)/catalyst (mol).
[c] *N*-methylimidazole as axial ligand.

Taking the imidazole as an axial ligand with a 10:1 molar ratio based on catalyst, the reaction of substrates **4a**–**4d** provided more than 99% of conversion and β-stereoisomer product in 90% epoxide yield (entries 1–4) (Scheme 2). Although the reaction of **4e** and **6** also gave more than 99% of β-stereoisomer, conversion were 56 and 94%. The epoxide



6 7

Scheme 2.



Scheme 3.

Table 3
Cholest-5-ene derivatives epoxidation with PhIO catalyzed by **3c**-MPR

Entry	Substrate	Conversion (%)	Epoxide yield (%)	Stereoisomer (%)	
				α	β
1	4a	>99	92	<1	>99
2	4b	>99	93	<1	>99
3	4c	>99	90	<1	>99
4	4d	>99	90	<1	>99
5	4e	56	48	<1	>99
6	6	94	81	<1	>99
7	8	23	91	<1	>99

All reactions were carried out with substrate (0.3 mmol), catalyst (3c-MPR) and axial ligand (*N*-methylimidazole) in CH_2Cl_2at room temperature for 72 h. Catalyst:axial ligand:oxidant:substrate 1:10:1500:1250 (molar ratio).

yields from **4e** and **6** are 48 and 81%, respectively (entries 5 and 6). Although the epoxidation of α,β-unsaturated ketones can also be efficiently catalyzed by other metal complexes or polypeptides [39], very few reports deal with the epoxidation of such substrates catalyzed by metalloporphyrins. Moreover, the reaction of 4-androstene-3,17-dione **8** possessing α,β-unsaturated ketone structure shown in Scheme 3 was also carried out in the same manner. It gave 23% of conversion and more than 99% of β-stereoisomer product (entry 7).

2.2. Catalyst stability and reuse

The covalent attachment of metalloporphyrin **1** to the polymer support indeed makes the resulting supported manganese porphyrin **3**-MPR a highly stable catalyst for the epoxidation of cholest-5-ene derivatives. The stability of the supported catalyst **3c**-MPR was studied in repeated epoxidation of cholesteryl acetate with PhIO. The catalyst was removed at the end of the reaction, washed and reused in a repeated epoxidation. Under the conditions shown in Table 3, the catalyst **3c**-MPR was consecutively reused four times without detectable catalyst leaching or a significant loss of epoxide yield and a decrease of β-selectivity (Table 4). In contrast, unsupported manganese porphyrin **2** was bleached and had no catalytic activity after one time use. It shows that immobilization of manganese porphyrins remarkably enhances their stability.

Table 4
The results of **3c**-MPR reused in the epoxidation of cholesteryl acetate

Reused times	Conversion (%)	Epoxide yield (%)	β-Selectivity (%)
1	>99	92	>99
2	>99	90	>99
3	>99	92	>99
4	>99	91	>99

The reaction condition is the same as in Table 3.

3. Experimental

3.1. General

Merrifield's peptide resin (Aldrich, 2% cross-linked, 200–400 mesh, ~2 mmol Cl/g) and $Mn(OAc)_2{\cdot}4H_2O$ were used as received. The cholest-5-ene derivatives used as substrates were commercially available from Sigma and Aldrich. Reaction solvents were distilled before use according to standard procedures. PhIO was prepared by the Sultzman's method [40]. 5,10,15-Tris(4-tolyl)-20-(4-hydroxyphenyl)porphyrin was synthesized according to the reported procedure [41].

^{1}H NMR spectra were measured on a Varian INOVA-400 spectrometer (400 MHz) by using tetramethylsilane (TMS) as an internal standard, with the chemical shifts relative to TMS. UV-Vis spectra were measured on a Shimadzu UV-240 spectrophotometer. The manganese content in **3**-MPR were determined on a Perkin-Elmer 3110 flame atomic absorption spectrometer.

3.2. Preparation of mangnese porphyrin *1*

A mixture of $Mn(OAc)_2{\cdot}4H_2O$ (200 mg) and the corresponding free base porphyrin (200 mg) in DMF (50 ml) was vigorously stirred at 80 °C under nitrogen for 8 h. The resulting green solution was poured into saturated solution of NaCl; the green solid was collected by filtration, washed thoroughly with water, loaded on an alumina column. Some other impurities were removed by using $CHCl_3/(CH_3)_2CO$ = 5:2 (v/v) as the eluent. The green band containing the desired product was collected. Removal of the solvent followed by recrystallization of the residual solid from chloroform/*n*-hexane (1:6, v/v) afforded complex **1** as green purple crystals. Yield 86%, m.p. > 300 °C. UV-Vis ($CHCl_3$): λ_{max} 480 nm (Soret). Mn content: 7.48% (Calcd.: 7.22%).

3.3. Preparation of polymer-supported mangnese porphyrin catalysts *3*-MPR. A typical procedure

To a solution of **3** (0.1 mmol) in DMF (30 ml) were added Merrifield's peptide resin (1.0 g) and anhydrous potassium carbonate (0.5 g). The mixture was vigorously stirred at 80 °C for 4 h under a nitrogen atmosphere. After cooling the green resin was collected by filtration, washed thoroughly with water, ethanol, and chloroform, and dried in vacuo at

room temperature for several hours. This procedure gave the catalyst **3c**-MPR. The catalysts **3a**- and **3b**-MPR were prepared in a similar manner by using a smaller amount of **1**, respectively. The contents of **1** in **3a**-, **3b** or **3c**-MPR were calculated from the manganese contents in the heterogenized catalysts determined by atomic absorption spectroscopy.

*3.4. Procedure for PhIO epoxidation of cholest-5-ene derivatives catalyzed by **3c**-MPR*

All the epoxidation reactions were carried out in a sealed vial or flask under nitrogen. A mixture of cholest-5-ene derivative (0.3 mmol), PhIO (0.36 mmol), and **3c**-MPR (1.8 mg) in dichloromethane was stirred at 40 °C. When the reaction was complete, as revealed by TLC analysis, the mixture was filtered, and the filtrate was evaporated in vacuo to remove the solvent. The spectra data of the residue are identical with those of the enantiomer of α- or β-configuration reported in the literature [37]. Conversions and yields were determined by ^{1}H NMR (400 MHz) in the presence of trans-stilbene as internal standard and based on the amount of cholest-5-ene derivatives.

*3.5. Reuse of **3c**-MPR catalyst for epoxidation of **4a***

Catalyst **3c**-MPR was used to do the reuse experiment with the general procedure described above. At the end of the epoxidation reaction, the catalyst was recovered by filtration and briefly dried under reduced pressure. In all cases, the filtrate was colorless, and the UV-Vis spectrum revealed the absence of porphyrin species. The epoxidation reaction was repeated by employing the recovered catalyst, fresh **4a** and PhIO under the same conditions. The conversions and yields were determined by ^{1}H NMR (400 MHz) in the presence of trans-stilbene as internal standard and based on the amount of **4a**.

4. Conclusion

We have developed an efficient and relatively-environmentally friendly method for epoxidation of cholest-5-ene derivatives in very good yields (93%) and high selectivity (β/α > 99%). The reaction requires imidazole as an axial ligand and a stable and reusable catalyst such as **3c**-MPR. The catalysts **3**-MPR are robust toward the epoxidation reactions of cholesteryl acetate. Moreover, four times reuse of the catalyst **3c**-MPR in the epoxidation of cholesteryl acetate provided no significant decrease of epoxide yield and β-selectivity.

Acknowledgements

We would like to thank National Natural Science Foundation of China (No. 20272039) and a grant from Education Ministry of China for Returnee.

References

[1] B. Meunier, Chem. Rev. 92 (1992) 1411.
[2] J.P. Collman, X.M. Zhang, V.J. Lee, E.S. Uffelman, J.I. Brauman, Science 261 (1993) 1404.
[3] F. Montanari, L. Casella (Eds.), Metalloporphyrins Catalyzed Oxidations, Kluwer, Dordrecht, 1994.
[4] A.M.R. Gonsalves, M.M. Pereira, J. Mol. Catal. A: Chem. 113 (1996) 209.
[5] D. Dolphin, T.G. Traylor, L.Y. Xie, Acc. Chem. Res. 30 (1997) 251.
[6] R. Saladino, R. Bernini, E. Mincione, P. Tagliatesta, T. Boschi, Tetrahedron Lett. 37 (1996) 2647.
[7] P. Tagliatesta, R. Bernini, C. Crestini, D. Monti, T. Boschi, E. Mincione, R. Saladino, J. Org. Chem. 64 (1999) 5361.
[8] R. Saladino, P. Carlucci, C. Crestini, D. Monti, T. Boschi, P. Tagliatesta, Nucleosides Nucleotides 18 (1999) 1123.
[9] A. Thellend, P. Battioni, W. Sanderson, D. Mansuy, Synthesis (1997) 1387.
[10] N. Ito, T. Etoh, H. Hagiwara, M. Kato, Synthesis (1997) 153.
[11] J.A.S. Cavaleiro, G.M.S.F.C. Nascimento, M.G.P.M.S. Neves, M.T. Pinto, A.J.D. Silvestre, M.G.H. Vicente, Tetrahedron Lett. 37 (1996) 1893.
[12] R.R.L. Martins, M.G.P.M.S. Neves, A.J.D. Silvestre, A.M.S. Silva, J.A.S. Cavaleiro, J. Mol. Catal. A: Chem. 137 (1999) 41.
[13] R.R.L. Martins, M.G.P.M.S. Neves, A.J.D. Silvestre, M.M.Q. Simoes, A.M.S. Silva, A.C. Tome, J.A.S. Cavaleiro, P. Tagliatesta, C. Crestini, J. Mol. Catal. A: Chem. 172 (2001) 33.
[14] X.-Q. Yu, J.-S. Huang, W.-Y. Yu, C.-M. Che, J. Am. Chem. Soc. 122 (2000) 5337.
[15] J.-S. You, Y.-F. Xiao, X.-Q. Yu, A.-X. Cheng, Z.-W. Lan, Chin. J. Chem. 14 (1996) 303.
[16] X.-Q. Yu, Z.-W. Lan, T.-X. Wei, J.-S. You, H.-M. Zhao, Chin. Chem. Lett. 6 (1995) 149.
[17] J.-S. You, X.-Q. Yu, Y.-F. Xiao, Y.-L. Wu, Z.-W. Lan, Chin. Chem. Lett. 7 (1996) 329.
[18] X.-Q. Yu, T.-X. Wei, Z.-W. Lan, J.-S. You, H.-M. Zhao, J. Mol. Catal. (Chin.) 9 (1995) 242.
[19] J.-L. Zhang, C.-M. Che, Org. Lett. 4 (2002) 1911.
[20] Nestler, K. Severin, Org. Lett. 3 (2001) 3907.
[21] D.N. Kirk, M.P. Hartshorn, in: C. Eabron, N.B. Chapman (Eds.), Steroid Reaction Mechanism, Elsevier, London, 1968, p. 69.
[22] G.J. Matthews, A. Hassner, in: J. Fried, J.A. Edwards (Eds.), Organic Reactions in Steroid Chemistry, vol. 2, Van Nostrand Reinhold, New York, 1972, p. 1.
[23] T. Muto, J. Umehara, H. Masumori, T. Miura, M. Kimura, Chem. Pharm. Bull. 33 (1985) 4749.
[24] K.B. Sharpless, R.C. Michaelson, J. Am. Chem. Soc. 95 (1973) 6136.
[25] M. Tohmam, T. Tomita, M. Kimura, Tetrahedron Lett. (1973) 4359.
[26] J.-C. Marchon, R. Ramasseul, J. Chem. Soc. Chem. Commun. (1988) 298.
[27] J.-C. Marchon, R. Ramasseul, Synthesis (1989) 389.
[28] V. Kesavan, S. Chandrasekaran, J. Org. Chem. 63 (1998) 6999.
[29] M.S. Syamala, J. Das, S. Baskaran, S. Chandrasekaran, J. Org. Chem. 57 (1992) 1928.
[30] E.J. Parish, S. Li, J. Org. Chem. 61 (1996) 5665.
[31] J.A.R. Slavador, M.L. Sae Melo, A.S. Campos Neves, Tetrahedron Lett. 37 (1996) 687.
[32] J.R. Hanson, N. Terry, C. Uyanik, J. Chem. Res.(s) (1998) 50.
[33] P. Battioni, J.-P. Lallier, L. Barloy, D. Mansuy, J. Chem. Soc. Chem. Commun. (1989) 1149.
[34] H.C. Sacco, Y. Iamamoto, J.R.L. Smith, J. Chem. Soc. Perkin Trans. 2 (2001) 181.

[35] C.-J. Liu, S.-G. Li, W.-Q. Pang, C.-M. Che, Chem. Commun. (1997) 65.
[36] C.-J. Liu, W.-Y. Yu, S.-G. Li, C.-M. Che, J. Org. Chem. 63 (1998) 7364.
[37] D. Yang, G.-S. Jiao, Chem. Eur. J. 6 (2000) 3517.
[38] M.J. Gunter, P. Turner, J. Mol. Catal. A Chem. 66 (1991) 14.
[39] (a) S. Julia, J. Masana, J.C. Vega, Angew. Chem. Int. Ed. Engl. 19 (1980) 929;
(b) L. Pu, Tetrahedron: Asymmetry 9 (1998) 1457.
[40] H. Sultzman, J.G. Sharefkin, Org. Syn. Coll. 5 (1973) 658.
[41] R.G. Little, J.A. Anton, P.A. Loach, J.A. Ibers, J. Heterocycl. Chem. 12 (1975) 343.