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Vanadium-Catalyzed Asymmetric Oxidation of Sulfides Using Schiff Base Ligands Derived from β-Amino Alcohols with Two Stereogenic Centers

Yinuo Wu,[a] Juntao Liu,[a] Xingshu Li,*[a] and Albert S. C. Chan[a]

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Novel Schiff base ligands derived from β-amino alcohols with two stereogenic centers were prepared and used in the preparation of optically pure sulfoxides by using aqueous hydrogen peroxide as the oxidant. A variety of sulfides were smoothly converted into the corresponding sulfoxides catalyzed by the chiral vanadium–Schiff base complex. Good yields (>80 %) with excellent enantioselectivities (>99 % *ee*) were obtained in most cases.

Introduction

Enantiopure sulfoxides are valuable chiral auxiliaries that are useful in organic synthesis as well as in the preparation of biologically active compounds.[1] The catalytic asymmetric oxidation of sulfides is a convenient method for the preparation of these valuable compounds.[2] Among all the oxidants that have been used in asymmetric oxidation, aqueous hydrogen peroxide (H_2O_2) is the most attractive, as it is both economical and environmentally benign. These unique features have stimulated the development of practical procedures for the asymmetric oxidation of sulfides with hydrogen peroxide as the oxidant in recent years.[3] In 1995, Bolm et al. revealed that catalysts prepared in situ from $VO(acac)_2$ and Schiff bases effectively catalyzed the oxidation of sulfides to sulfoxides by using hydrogen peroxide as the oxidant with good enantioselectivity.[4,5] The low catalyst loading (1 % equiv.) and the use of inexpensive hydrogen peroxide as the oxidant made it particularly attractive for large-scale industrial applications. Many ligands and improved methods were also developed on the basis of the protocol outlined by Bolm. Berkessel et al. developed (*S*)-*t*-leuciol-based Schiff base ligands from chiral salicylic aldehydes.[6] Skarzewski et al. introduced Schiff bases with a phenyl substituent at C^3 of salicylaldehyde.[7] Anson et al. reported that a vanadium–chiral Schiff base complex derived from 3,5-diiodosalicylaldehyde and (*S*)-*t*-leucinol was effective in the vanadium-catalyzed oxidation of alkyl aryl sulfides.[8] Ahn described the application of sterically hindered chiral Schiff base ligands that were prepared from chiral *t*-leucinol and aldehydes derived from binol for the oxidation of sulfides.[9]

In recent years, some other metal catalysts were also investigated for asymmetric sulfoxidation. Bolm found that an iron catalyst formed in situ by mixing $Fe(acac)_3$ and Schiff bases could efficiently catalyze this reaction.[10] By adding some acids or carboxylates into the catalyst system, the enantioselectivity increased to 66–96 %.[11] Strukul reported the chiral platinum diphosphane complex catalyzed oxidation of sulfides in water with surfactants.[12] Very recently, Katsuki et al. performed highly enantioselective sulfoxidation (up to 96 %*ee*) in water by using a Fe(salalen) complex.[13] They also carried out the reaction by using a chiral Al(salalen) complex in the presence of a phosphate buffer. Very high *ee* values were obtained for aryl methyl sulfides (99 %*ee*), but relatively lower enantioselectivities were also observed for phenyl ethyl sulfide (90 %*ee*) and benzyl methyl sulfide (80 % *ee*).[14]

Kinetic resolution of racemic sulfoxides or the oxidation/kinetic resolution of prochiral sulfides for the preparation of enantiomerically pure sulfoxides were also developed. Uemura et al. demonstrated an accompanying kinetic resolution of the sulfoxide enantiomers following the asymmetric oxidation of sulfides in 1993.[15] Scettri et al. reported the preparation of sulfoxides by the method of Uemura with furyl hydroperoxide as the oxidant.[16] Chan et al. described an improved method in which initial oxidation at 0 °C followed by resolution at 25 °C allowed the isolation of sulfoxides in excellent enantioselectivities.[17] Jackson et al. successfully developed vanadium-catalyzed sulfur oxidation/kinetic resolution for the synthesis of chiral sulfoxides in chloroform.[18] Zeng et al. combined enantioselective sulfoxidation with concomitant kinetic resolution to produce chiral sulfoxides with vanadium–Schiff base complexes derived from phenylalaninol or isoleucinol as the catalyst; moderate yields (40.6 %) and up to 99 %*ee* were obtained by using H_2O_2 (2.0 equiv.) as the oxidant.[19]

Although a great deal of progress has been made in asymmetric sulfoxidation, effective catalyst systems and

[a] School of pharmaceutical science, Sun Yat-Sen University, Guangzhou 510006, P. R. China
Fax: +86-20-3994-3050
E-mail: lixsh@mail.sysu.edu.cn
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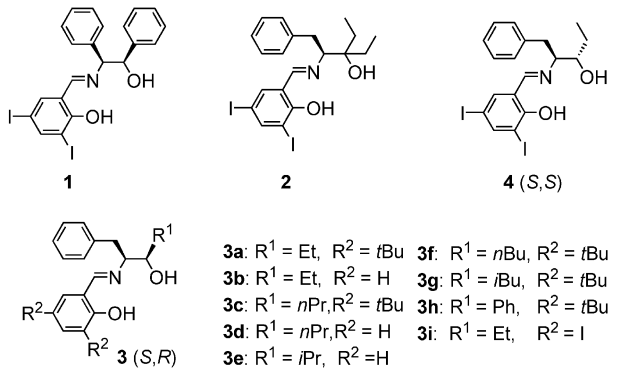
practical procedures providing high yields and excellent enantioselectivities are still highly desirable. Herein, we report a highly enantioselective vanadium–Schiff base catalyst system that consists of $VO(acac)_2$ and Schiff bases derived from β-amino alcohols with two stereogenic centers for the preparation of optically pure sulfoxides with the use of aqueous hydrogen peroxide as the oxidant.

Chiral β-amino alcohols and their derivatives are important ligands in asymmetric synthesis including the enantioselective catalytic borane reduction of prochiral ketones,[20] enantioselective addition of dialkylzinc,[21] asymmetric hydrogen transfer from alcohols to ketones,[22] and other asymmetric reactions.[23] Generally, there are many differences in activity and enantioselectivity between the various amino alcohols. Gau et al. prepared a series of *N*-sulfonylated β-amino alcohols with one and two stereogenic centers and examined their application in asymmetric trialkylaluminum additions, diethylzinc additions, and trimethylsilylcyanation to aldehydes.[24] Their results showed that ligands with two stereogenic centers are better than those with only one stereogenic center. With regard to modifications of Schiff base ligands derived from amino alcohols for the enantioselective oxidation of sulfides, previous work mainly focused on different β-amino alcohols with one stereogenic center or on substitutions of the salicylaldehyde moiety.[8] We wish to investigate the structural influence of the β-amino alcohol moiety, especially those with two stereogenic centers, to find a highly efficient catalyst system for this reaction. Because phenylalanine is a very cheap, commercially available material that can be modified to different target products with routine procedures,[25,26] we chose it as the starting material for the screening of the amino alcohols with two stereogenic centers for the enantioselective oxidation of sulfides.

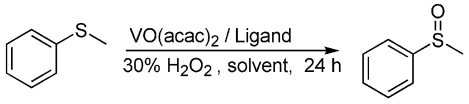
Results and Discussion

In a preliminary screening of Schiff base ligands with two stereogenic centers, we carried out the vanadium-catalyzed oxidation of thioanisole in CH_2Cl_2 with H_2O_2 (1.1 equiv.) as the oxidant. When Schiff base **1**, derived from a commercially available amino alcohol, was used as the ligand, good yield with moderate enantioselectivity was obtained (83% yield, 43%*ee*). With the expectation that the enantioselectivity might be substantially influenced by structural changes in the ligands, we prepared Schiff base ligand **2** and ligands **3a**–**i** (Scheme 1) according to a literature method for evaluation.[25,26] Ligand **2**, derived from a β-amino alcohol with one stereogenic center, afforded poor enantioselectivity (3%*ee*). In contrast, ligand **3a**, derived from a β-amino alcohol with two stereogenic centers, gave the desired product with enhanced enantioselectivity (61%*ee*) at room temperature. Inspired by this result, we investigated other ligands of this family (i.e., **3b**–**i**) and found that ligand **3i** afforded nearly quantitative yield with 67%*ee*. To investigate the effect of the stereochemistry of the Schiff base ligands on the enantioselectivity of the product, we also prepared ligand **4** (Scheme 1), a diastereomer of ligand **3i**, according to a literature method.[27] Under the same reaction conditions, ligand **4** afforded the product in moderate yield but with poor enantioselectivity (Table 1, Entry 12; 78% yield, 5%*ee*).



Scheme 1. Ligands for asymmetric oxidation of sulfides.

Table 1. Influence of chiral ligands on the enantioselectivity of the asymmetric oxidation of thioanisole.[a]



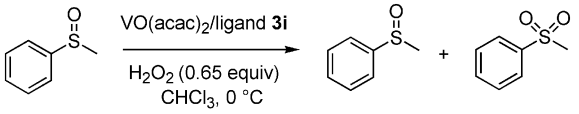
Entry	Ligand	Yield [%][b]	*ee* [%][c] and configuration[d]
1	**1**	83	43 (*S*)[d]
2	**2**	85	3 (*S*)
3	**3a**	97	61 (*S*)
4	**3b**	87	53 (*S*)
5	**3c**	97	47 (*S*)
6	**3d**	80	30 (*S*)
7	**3e**	59	6 (*S*)
8	**3f**	98	38 (*S*)
9	**3g**	54	8 (*S*)
10	**3h**	97	44 (*S*)
11	**3i**	98	67 (*S*)
12	**4**	78	5 (*R*)

[a] All reactions were carried out with 30% H_2O_2 (1.1 equiv.) for 24 h under ambient conditions. H_2O_2 (30.34%) was titrated by using an iodometric method. [b] Isolated yield. [c] Determined by HPLC analysis with a chiralcel OD-H column. [d] Absolute configuration determined by comparison of the optical rotation with the literature value.

The result indicated that *syn* diastereomer **3i** (*S*,*R*) exerted a stronger chiral discrimination effect than *anti* diastereomer **4** (*S*,*S*) in the reaction. The solvent effect of the $VO(acac)_2$/**3i** system was examined. Methanol and THF gave the product with very low *ee* values (5 and 6%*ee*, respectively), and toluene afforded a moderate yield and enantioselectivity. Because chloroform was another good solvent for this reaction and there were some examples showing more efficient kinetic resolution in this solvent,[18] ligands **3a**–**i** were also examined in chloroform at 0 °C. The results showed that ligand **3i** was still the best ligand under these reaction conditions (82% yield and 84%*ee* were obtained by using 1.1 equiv. 30% H_2O_2 as the oxidant). As some thioanisole (starting material) still remained and no

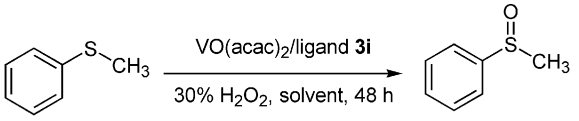
sulfone was found in the reaction system, it appeared that no kinetic resolution took place under these reaction conditions.

We also investigated the kinetic resolution of racemic phenyl methyl sulfoxide in chloroform with the use of 0.65 equiv. of H_2O_2 as the oxidant and VO(acac)$_2$/**3i** as the catalyst (Scheme 2). When the reaction was carried out at 0 °C for 48 h, 50% conversion with 73%*ee* was obtained (S = 13.8). The result implied that a higher ratio of hydrogen peroxide in the asymmetric oxidation of sulfide would be favorable for the *ee* values. We then adjusted the ratio of hydrogen peroxide/sulfide to 1.20, and obtained 91% yield with 89%*ee* under the same reaction conditions. Good yield (81%) with very high enantioselectivity (up to 99%*ee*) were obtained with 1.35 equiv. of H_2O_2 as the oxidant. The results showed that chloroform was the best choice of solvent with VO(acac)$_2$/**3i** as catalyst at 0 °C, and the optimal ratio of hydrogen peroxide to sulfide was 1.35. It could be concluded that the highly efficient asymmetric oxidation and the following kinetic resolution gave good chemical yield and excellent enantioselectivity when the oxidant was used in excess. In contrast, it was found that a lower temperature was favorable for higher chemical yields and *ee* values. When the reaction temperature was lowered to –10 °C, the *ee* value of the product was found to further increase to 95% (Table 2, Entry 5).



Scheme 2. Kinetic resolution of racemic sulfides.

Table 2. Optimization of reaction conditions for the VO(acac)$_2$/**3i**-catalyzed asymmetric oxidation of thioanisole.[a]

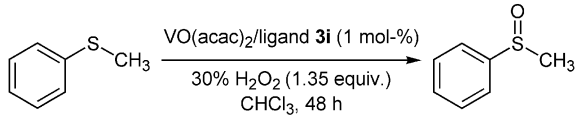


Entry	Solvent	T (°C)	H_2O_2 [equiv.]	Yield [%][b]	*ee* [%][c]
1	$CHCl_3$	r.t.	1.1	89	66
2	CH_2Cl_2	0	1.1	93	54
3	$CHCl_3$	0	1.1	82	84
4	$CHCl_3$	0	1.2	93	89
5	$CHCl_3$	–10	1.2	91	95
6	$CHCl_3$	0	1.3	86	97
7	$CHCl_3$	0	1.35	81	99

[a] All reactions were carried out with VO(acac)$_2$ (1 mol-%) and ligand **3i** (1 mol-%) for 48 h. [b] Isolated yields. [c] Determined by HPLC analysis with a chiralcel OD-H column. The absolute configuration (S) was determined by comparison of the optical rotation with the literature value.

Under the optimal reaction conditions, expanding the scope of the catalyst system to other alkyl aryl sulfides was performed, and the results are listed in Table 3. All substrates gave high yields, and in most cases the enantioselectivities were higher than 99% (Table 3, Entries 1–9). Interestingly, phenyl ethyl sulfide, which usually gave relatively lower enantioselectivities than methyl aryl sulfides in other excellent catalyst systems,[15] gave 84% yield with 99%*ee*. The results of other alkyl aryl sulfides were also examined. Even in the case of naphthyl butyl sulfide, which contains a larger alkyl group, an excellent *ee* value of 98% was achieved.

Table 3. Substrate generality for VO(acac)$_2$/**3i**-catalyzed asymmetric oxidation of sulfides in chloroform.[a]



Entry	Ar	R	Yield [%][b]	*ee* [%][c]
1	Ph	Me	81	99 (S)[d]
2	Ph	Et	84	99 (S)
3	*p*-ClC_6H_5	Me	83	99 (S)
4	*p*-$CH_3C_6H_5$	Me	85	99 (S)
5	*p*-BrC_6H_5	Me	81	>99 (S)
6	*p*-$MeOC_6H_5$	Me	84	>99 (S)
7	2-naphthyl	Me	85	99 (S)
8	2-naphthyl	Et	81	>99 (S)
9	2-naphthyl	*n*Pr	80	>99
10	2-naphthyl	*n*Bu	81	98

[a] All reactions were carried out with VO(acac)$_2$ (1 mol-%) and ligand **3i** (1 mol-%) for 48 h under ambient conditions. [b] Isolated yields. [c] Determined by HPLC analysis with a chiralcel OD-H column. [d] Absolute configuration determined by comparison of the optical rotation with the literature value.

To the best of our knowledge, among all the catalyst systems used for the asymmetric oxidation of sulfides with hydrogen peroxide as the oxidant, this catalyst system is the best in terms of good yield and excellent enantioselectivity.

Conclusions

Novel Schiff bases derived from β-amino alcohols with two stereogenic centers have been established as highly effective chiral ligands for the production of chiral sulfoxides. A variety of sulfides were converted into the corresponding sulfoxides smoothly with good yields and excellent enantioselectivities. The easy preparation of the ligands from natural amino acids and their excellent performance make them good choices for practical applications. Further studies on the scope of this reaction are under way.

Experimental Section

General Procedure for Asymmetric Oxidation of Sulfides: A test tube was charged with VO(acac)$_2$ (0.01 mmol), chiral ligand **3i** (0.015 mmol) and $CHCl_3$ (2 mL). The mixture was stirred for 0.5 h at room temperature. The sulfide substrate (1 mmol) was then added, and the mixture was stirred for another 10 min. After the solution was cooled to 0 °C, 30% H_2O_2 (1.1 equiv.) was slowly added. The mixture was stirred smoothly (200 rpm) at 0 °C for 48 h, and the reaction was monitored by TLC. After the reaction

was complete, the aqueous layer was separated off, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (30% ethyl acetate in petroleum ether) to give the desired product. The enantiomeric excess was determined by chiral HPLC on a chiralcel OD-H column [hexane/isopropyl alcohol (9:1); 0.5 mL min^{-1}, 254 nm].

Supporting Information (see footnote on the first page of this article): Preparative methods and characterization of the chiral ligands; procedures for asymmetric oxidation of sulfides; NMR spectra and HPLC behavior of the products; $[\alpha]_D$ values and absolute configurations.

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[1] a) H. Pellissier, *Tetrahedron* **2006**, *62*, 5559–5601; b) I. Fernández, N. Khiar, *Chem. Rev.* **2003**, *103*, 3651–3706; c) S. A. Blum, R. G. Bergman, J. A. Ellman, *J. Org. Chem.* **2003**, *68*, 150–155; d) S. Renfrey, J. Featherstone, *Nat. Rev. Drug Discov.* **2002**, *1*, 175; e) P. Renaud, M. Gerster, *Angew. Chem. Int. Ed.* **1998**, *37*, 2562–2579; f) M. C. Carreño, *Chem. Rev.* **1995**, *95*, 1717–1760.

[2] a) H. B. Kagan, T. O. Luukas, "Catalytic Asymmetric Sulfide Oxidations" in *Transition Metals for Organic Synthesis* (Eds.: M. Beller, C. Bolm), 2nd ed., Wiley-VCH, Weinheim, Germany, **2004**, vol. 2, pp. 479–495; b) C. Bolm, *Coord. Chem. Rev.* **2003**, *237*, 245–256.

[3] For some examples of asymmetric sulfoxidation with the use of H_2O_2 as terminal oxidant, see: a) C. Drago, L. Caggiano, R. F. W. Jackson, *Angew. Chem. Int. Ed.* **2005**, *44*, 7221–7223; b) J. Legros, C. Bolm, *Chem. Eur. J.* **2005**, *11*, 1086–1092; c) J. Sun, C. Zhu, Z. Dai, M. Yang, Y. Pan, H. Hu, *J. Org. Chem.* **2004**, *69*, 8500–8503; d) D. J. Weix, J. A. Ellman, *Org. Lett.* **2003**, *5*, 1317–1320; e) V. V. Thakur, A. Sudalai, *Tetrahedron: Asymmetry* **2003**, *14*, 407–410; f) T. Miyazaki, T. Katsuki, *Synlett* **2003**, 1046–1048; g) C. Ohta, H. Shimizu, A. Kondo, T. Katsuki, *Synlett* **2002**, 161–163; h) B. Saito, T. Katsuki, *Tetrahedron Lett.* **2001**, *42*, 3873–3876; i) P. B. Page, J. P. Heer, D. Bethell, B. L. Lund, *Phosphorus Sulfur Silicon Relat. Elem.* **1999**, 153–154; P. B. Page, J. P. Heer, D. Bethell, B. L. Lund, *Phosphorus Sulfur Silicon Relat. Elem.* **1999**, 247–258.

[4] C. Bolm, F. Bienewald, *Angew. Chem.* **1995**, *107*, 2883–2885; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2640–2642.

[5] C. Bolm, G. Schlingloff, F. Bienewald, *J. Mol. Catal. A* **1997**, *117*, 347–350.

[6] A. H. Vetter, A. Berkessel, *Tetrahedron Lett.* **1998**, *39*, 1741–1744.

[7] a) J. Skarzewski, E. Ostrycharz, R. Siedlecka, *Tetrahedron: Asymmetry* **1999**, *10*, 3457–3461; b) J. Skarzewski, E. Ostrycharz, R. Siedlecka, M. Zielinska-Blajet, B. Pisarski, *J. Chem. Res.* **2001**, 263–264.

[8] B. Pelotier, M. S. Anson, I. B. Campbell, S. J. F. Macdonald, G. Priem, R. F. W. Jackson, *Synlett* **2002**, 1055–1060.

[9] Y. C. Jeong, S. Choi, Y. D. Hwang, K. H. Ahn, *Tetrahedron Lett.* **2004**, *45*, 9249–9252.

[10] J. Legros, C. Bolm, *Angew. Chem.* **2004**, *116*, 4321–4324; *Angew. Chem. Int. Ed.* **2004**, *43*, 4225–4228.

[11] J. Legros, C. Bolm, *Angew. Chem.* **2003**, *115*, 5645–5647; *Angew. Chem. Int. Ed.* **2003**, *42*, 5487–5489.

[12] A. Scarso, G. Struku, *Adv. Synth. Catal.* **2005**, *347*, 1227–1234.

[13] H. Egami, T. Katsuki, *J. Am. Chem. Soc.* **2007**, *129*, 8940–8941.

[14] T. Yamaguchi, K. Matsumoto, B. Saito, T. Katsuki, *Angew. Chem. Int. Ed.* **2007**, *46*, 4729–4731.

[15] N. Komatsu, M. Hashizume, T. Sugita, S. Uemura, *J. Org. Chem.* **1993**, *58*, 7624–7626.

[16] A. Massa, F. R. Siniscalchi, V. Bugatti, A. Lattanzi, A. Scettri, *Tetrahedron: Asymmetry* **2002**, *13*, 1277–1283.

[17] X. Jia, X. Li, L. Xu, Y. Li, Q. Shi, T. Au-Yeung, C. Yip, X. Yao, A. Chan, *Adv. Synth. Catal.* **2004**, *346*, 723–726.

[18] C. Drago, L. Caggiano, R. F. W. Jackson, *Angew. Chem. Int. Ed.* **2005**, *44*, 7221–7223.

[19] Q. Zeng, H. Wang, T. Wang, Y. Cai, W. Weng, Y. Zhao, *Adv. Synth. Catal.* **2005**, *347*, 1933–1936.

[20] a) S. Itsuno, M. Nakano, K. Miyazaki, H. Masuda, K. Ito, A. Hirao, S. J. Nakahama, *J. Chem. Soc. Perkin Trans. 1* **1985**, 2039; b) E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553; c) E. J. Corey, M. Azimioata, S. Sarshar, *Tetrahedron Lett.* **1992**, *33*, 3435–3438; d) L. Deloux, M. Screbnik, *Chem. Rev.* **1993**, *93*, 763–784; e) D. J. Ager, I. Prakash, D. R. Schaad, *Chem. Rev.* **1996**, *96*, 835–875; f) J. Martens, I. Reiners, *Tetrahedron: Asymmetry* **1997**, *8*, 27–28; g) E. J. Corey, C. J. Helal, *Angew. Chem. Int. Ed.* **1998**, *37*, 1986–2012.

[21] a) M. Kitamura, S. Suga, K. Kawai, R. Noyori, *J. Am. Chem. Soc.* **1986**, *108*, 6071–6072; b) M. Kossenjans, J. Martens, *Tetrahedron: Asymmetry* **1998**, *9*, 1409–1417.

[22] a) J. Takehara, S. Hashiguch, A. Fuji, S. I. Inoue, T. Ikariya, R. Noyori, *Chem. Commun.* **1996**, *2*, 233–234; b) K. Soai, T. Hayasaka, S. Ugajin, *J. Chem. Soc., Chem. Commun.* **1989**, *8*, 516–517.

[23] a) K. Tomioka, M. Shindo, K. Koga, *Chem. Pharm. Bull.* **1989**, *34*, 1120–1122; b) A. Ando, T. Shoir, *J. Chem. Soc., Chem. Commun.* **1987**, *9*, 656–658.

[24] a) J. You, H. Gau, M. C. K. Choi, *Chem. Commun.* **2000**, *19*, 1963–1964; b) J. You, S. Hsieh, H. Gau, *Chem. Commun.* **2001**, *17*, 1546–1547; c) J. You, M. Shao, H. Gau, *Tetrahedron: Asymmetry* **2001**, *12*, 2971–2975.

[25] G. Jalce, M. Seck, X. Franck, R. Hocquemiller, B. Figadere, *J. Org. Chem.* **2004**, *69*, 3240–3241.

[26] M. T. Reetz, M. W. Drewes, A. Schmitz, *Angew. Chem.* **1987**, *99*, 1186–1188; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1141–1143.

[27] J. M. Andres, R. Barrio, M. A. Martinez, R. Pedrosa, A. Perez-Encabo, *J. Org. Chem.* **1996**, *61*, 4210–4213.

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