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Catalytic asymmetric epoxidation of allylic alcohols using a renewable hydroperoxide[†]

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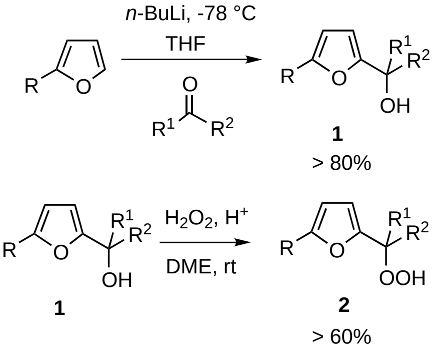
Abstract—Sharpless modified asymmetric epoxidation of allylic alcohols can be successfully performed using an easily accessible and renewable tertiary furyl hydroperoxide in the presence 20 mol% of the chiral $Ti(O\text{-}i\text{-}Pr)_4$/L-DIPT/MS 4 Å system. © 2002 Elsevier Science Ltd. All rights reserved.

Chiral epoxides are important intermediates in organic synthesis and the development of new methodologies for their preparation is a subject of intensive research.[1]

For the epoxidation of allylic alcohols, interesting procedures have been reported using vanadium catalysts and hydroxamic acids derivatives,[2] but the Sharpless protocol with titanium tetraisopropoxide and tartrate esters ligands[3] is still the most employed, furnishing the epoxides with very high enantiomeric excess. Regardless of the metal-catalyzed methodology, the structure of the hydroperoxide[4] plays a significant role in influencing the level of enantioselectivity achievable for this process. As a consequence some investigations have been reported in the literature concerning the employment of structurally different alkyl hydroperoxides.[4,5] It has been observed that tertiary alkyl and aryl hydroperoxides assure the highest ee's in the product. In this respect, for the vanadium-chiral hydroxamic acid methodology, the triphenylmethyl hydroperoxide[2c] proved to be more efficient than the commercial *tert*-butyl hydroperoxide (TBHP). In the catalytic Sharpless epoxidation TBHP and cumene hydroperoxide (CHP) were reported to reproduce the high level of enantioselectivity found under stoichiometric loadings of the chiral catalyst.[3b] Another interesting aspect, scarcely investigated so far, was the employment of optically pure hydroperoxides.[6] Interestingly, if the alkyl hydroperoxide is used in enantiopure form,[7] a cooperative effect of the chiral ligand and hydroperoxide has been observed, but it is difficult to predict the successful combination of both in order to achieve the highest ee in the product.

We previously reported on the synthesis and the reactivity of highly functionalized furyl hydroperoxides[8] as oxygen donors in the Sharpless epoxidation of allylic alcohols. Furthermore, in the same process, racemic secondary hydroperoxides can be kinetically resolved and enantiomerically enriched furyl hydroperoxides and furyl alcohols were isolated. With stoichiometric amounts of the chiral catalyst, high ee's for the epoxides were achieved when using a tertiary furyl hydroperoxide. Unfortunately, when trying substoichiometric amounts of the chiral catalyst a dramatic drop in the enantioselectivity was observed.



Scheme 1.

Keywords: asymmetric epoxidation; alkyl hydroperoxides; titanium; allylic alcohols.

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[†] Dedicated to the memory of Professor Guido Sodano who deceased on June 2001.

0040-4039/02/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
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With the intention of producing an easily accessible class of furyl hydroperoxides[9] to use in asymmetric oxidation processes, very recently, our investigations focused on the synthesis of structurally simple furyl hydroperoxides.[10] We succeeded in our goal with a two-step sequence which allowed us to obtain furyl hydroperoxides of type **2** ($R = Me$, H; $R^1 = H$, Me; $R^2 = $ alkyl, Me) (Scheme 1) with an overall yield ≥50%. Compounds **2** proved to be stable and could be isolated by silica gel chromatography.[11]

The tertiary furyl hydroperoxide **2a** ($R = H$; $R^1 = R^2 = Me$, overall yield 65%), which can be considered a heteroaromatic equivalent of CHP, has been successfully used[12] under catalytic conditions in Uemura's[13] modified procedure of asymmetric sulfoxidation. Then, we thought it would be interesting to study the potential use of this oxidant in the asymmetric epoxidation.

Herein we report that high enantioselectivity can be achieved in the asymmetric Sharpless epoxidation employing the tertiary hydroperoxide **2a**, but more importantly the level of asymmetric induction is maintained high using catalytic conditions.

Some preliminary runs, under stoichiometric conditions, were carried out in order to evaluate the reactivity and the efficiency of the tertiary furyl hydroperoxide **2a** in the asymmetric epoxidation of allylic alcohols (Table 1).

Geraniol and *trans* 2-methyl-3-phenyl-prop-2-en-1-ol were epoxidized in high yield and ee as shown, respectively, in entries 1 and 2. It has been reported that the order of addition of the reagents and in particular the allylic alcohol and the alkyl hydroperoxide, can affect the enantioselectivity.[3] When the oxidant **2a** was added before geraniol in the experimental procedure, a reduced yield and slightly lower ee were observed (entry 3).

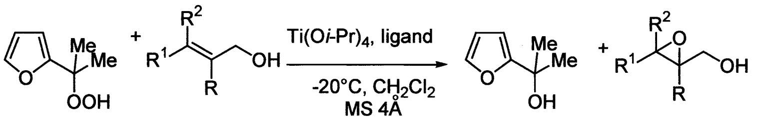
Hence having proved successful under stoichiometric conditions, hydroperoxide **2a** was reacted in the presence of catalytic molar loadings of Ti(O-*i*-Pr)$_4$/L-DET 0.20/0.30 with respect to **3** (Table 2).

A catalytic procedure is highly desirable for different reasons: Lewis acid sensitive epoxides can be synthesized in higher yields, easier isolation work up is needed and less consuming reagents protocol can be applied.

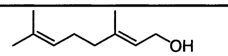
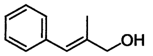
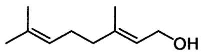
We were delighted to observe that the level of asymmetric induction was still high when 20 mol% of the chiral catalyst was employed for the epoxidation of geraniol (entry 1). L-Diisopropyl tartrate (L-DIPT) turned out to be a better ligand than L-DET, in fact, a significant improvement of ee was observed for 2,3-epoxygeraniol (entry 2). A variety of double bond substituted allylic alcohols treated under catalytic conditions, using L-DIPT as ligand, were converted to the epoxides in good yield and very high ee. In some examples the ee measured was higher than the one obtained with the use of TBHP/L-DET[3b] (entry 4). Not surprisingly, the epoxidation of nerol (entry 7) furnished the epoxide with moderate ee.

In the Sharpless epoxidation, *cis* allylic alcohols react slowly compared to *trans* allylic alcohols, moreover,

Table 1. Asymmetric epoxidation with **2a** under stoichiometric conditions[a]

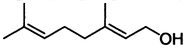
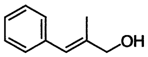
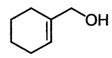
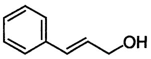
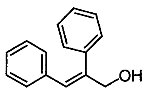
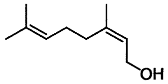


2a **3** **1a** **4**

Entry	**3**	Ligand	Time (h)	Yield **4**%[b]	E.e. **4**%[c,d]
1		L-DET	2.5	80	95
2		"	2.5	90	>98[e]
3[e]		"	3.5	69	92

[a] *Typical experimental procedure*: to a solution of dry CH$_2$Cl$_2$ (6 mL) at –10°C and under argon atmosphere, are added activated MS 4Å (40%wt based on allylic alcohol), Ti(O*i*-Pr)$_4$ (1 mmol), L-DET (1.25 mmol), **3** (1 mmol) dissolved in CH$_2$Cl$_2$ (2 mL). The stirred mixture is then cooled to –20°C for 20 minutes. Then **2a** (1.1 mmol) dissolved in CH$_2$Cl$_2$ (2 mL) is added. After completion of the reaction water (5 mL) is added and a vigorous stirring is mantained at rt for 1h. The resulting gel is filtered over celite and thoroughly washed with CH$_2$Cl$_2$, then dried over Na$_2$SO$_4$. The filtered organic solution is concentrated under vacuum to 20 ml and 5% NaOH solution (6.5 mL) is added and stirring is mantained for 30 min at rt, then the organic phase is extracted with saturated brine and dried over Na$_2$SO$_4$. The solvent was removed by evaporation under vacuum and the crude reaction mixture is purified by flash chromatography to afford the pure epoxide. [b] Isolated yield. [c] Determined by ^{1}H-NMR shift experiments[3b] on the acetylated epoxide with Eu(hfc)$_3$. [d] The absolute configuration of the epoxides resulted the same reported by the use of TBHP by comparison of $[\alpha]_D$. [e] Determined by ^{1}H-NMR analysis of the derived MTPA ester[3b] in C$_6$D$_6$. [e] In this reaction **2a** was added before **3**.

Table 2. Asymmetric epoxidation with **2a** under catalytic conditions[a]

Entry	3	Ligand	Time (h)	Yield 4%[b]	E.e. 4%[c,d]
1		L-DET	22	45	85
2	"	L-DIPT	21	58	91
3		"	27	87	97
4		"	21	64	96
5		"	27	69	98
6		"	28	54	90
7		"	25	56	73

[a] *Typical experimental procedure*: the procedure is the same as in the stoichiometric conditions, but the volumes of CH_2Cl_2 are: (1 mL) at the beginning, then **3** is dissolved in CH_2Cl_2 (750 μL) and finally **2a** is added dissolved in CH_2Cl_2 (1 mL). [b] Isolated yield. [c] Determined by ^{1}H-NMR analysis of the derived MTPA ester. [d] See note d in Table 1.

considerably lower ee's for the corresponding *cis* epoxides are reported.[4]

In conclusion, furyl hydroperoxide **2a** can be considered an efficient oxidant in the asymmetric Sharpless epoxidation of allylic alcohols.

The enantioselectivity is maintained high under catalytic loadings of the chiral catalyst and the epoxides are generally obtained with ee's >90%. This modified procedure of catalytic Sharpless epoxidation is an example of resource-saving protocol. Unlike cumyl alcohol, which is a side-product of the epoxidation when using CHP as oxidant, the furyl alcohol **1a** (Table 1) can be recovered by flash chromatography and recycled as starting material for the synthesis of hydroperoxide **2a** according to Scheme 1.

Acknowledgements

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References

1. (a) Katsuki, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, 1999; Vol. II, Chapter 18.1; (b) Jacobsen, E. N., Wu, M. F. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, 1999; Vol. II, Chapter 18.2.
2. (a) Michaelson, R.; Palermo, R. E.; Sharpless, K. B. C. *J. Am. Chem. Soc.* **1977**, *99*, 1990; (b) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059; (c) Murase, N.; Hoshino, Y.; Oishi, M.; Yamamoto, H. *J. Org. Chem.* **1999**, *64*, 338; (d) Hoshino, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 10452; (e) Bolm, C.; Kühn, T. *Synlett* **2000**, *6*, 899.
3. (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974; (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
4. (a) Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; p. 247; (b) Rossiter, B. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; p. 193.
5. Adam, W.; Korb, M. N. *Tetrahedron: Asymmetry* **1997**, *8*, 1131.
6. Aoki, M.; Seebach, D. *Helv. Chim. Acta* **2001**, *84*, 187 and references cited therein.
7. Bolm, C.; Beckmann, O.; Kühn, T.; Palazzi, C.; Adam, W.; Rao, P. B.; Saha-Möller, C. R. *Tetrahedron: Asymmetry* **2001**, *12*, 2441.
8. (a) Lattanzi, A.; Iannece, P.; Scettri, A. *Tetrahedron Lett.* **1999**, *40*, 3899; (b) Lattanzi, A.; Bonadies, F.; Scettri, A. *Tetrahedron: Asymmetry* **1997**, *8*, 2141.
9. The synthesis of highly functionalized furyl hydroperoxides used as oxygen donors in Ref. 8b requires four synthetic steps.
10. Massa, A.; Palombi, L.; Scettri, A. *Tetrahedron Lett.* **2001**, *42*, 4577.
11. It should be reminded that alkyl hydroperoxides are a class of organic compounds which are generally difficult to synthesize with good yields (>50%) and which suffer fast decomposition. Indeed, only some of them are chemically and termically stable to be isolated by common chromatographic protocols and then successfully employable in metal-catalyzed oxidations.
12. Massa, A.; Lattanzi, A.; Siniscalchi, F.; Scettri, A. *Tetrahedron: Asymmetry* **2001**, *12*, 2775.
13. Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 4529.