DOI: 10.1002/adsc.201200072

Catalytic Asymmetric Epoxidation of 2-Cyclopentenones

Anna Lee,[a] Corinna M. Reisinger,[a] and Benjamin List[a,*]

[a] Max-Planck-Institut für Kohlenforschung, Kaiser Wilhelm-Platz 1, 45470 Mülheim an der Ruhr, Germany
Fax: (+49)-208-306-2999; e-mail: list@mpi-muelheim.mpg.de

Received: January 26, 2012; Published online: June 5, 2012

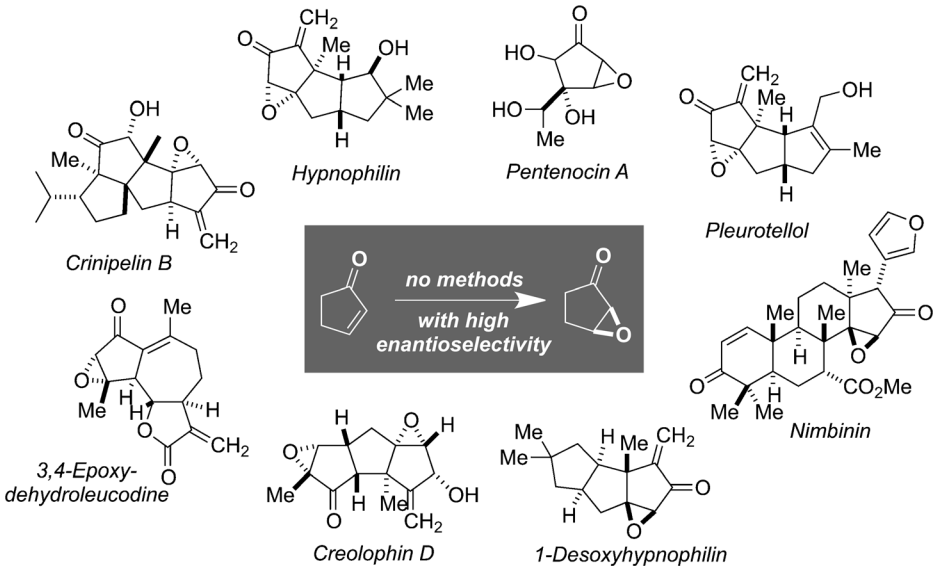
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200072.

Abstract: The first highly efficient asymmetric epoxidation of 2-cyclopentenones has been developed. Using a newly designed and readily available *Cinchona* amine catalyst, 2-cyclopentenones are reacted with hydrogen peroxide to give the corresponding epoxycyclopentanones in high yields and excellent enantioselectivities.

Keywords: asymmetric catalysis; 2-cyclopentenones; epoxidation; organocatalysis; Weitz–Scheffer epoxidation

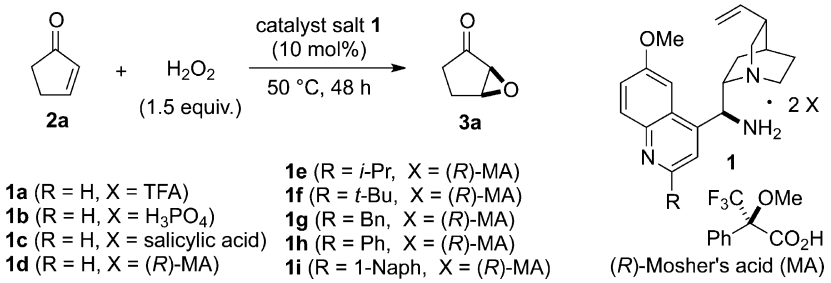
The impact of alkene epoxidation catalysis to modern academic and industrial chemistry can hardly be overstated. In particular, the catalytic enantioselective epoxidation of alkenes has fascinated chemists during the past three decades. Originating from Sharpless' seminal discovery of the catalytic asymmetric epoxidation of allylic alcohols,[1] intensive research to expand the scope of this transformation to other olefin classes began. Important contributions to this endeavour came from Jacobsen,[2] Katsuki,[3] Shi,[4] Juliá and Colonna,[5] Wynberg,[6] Jackson,[7] Enders,[8] Shibasaki,[9] and many more.[10] With the advent of aminocatalysis at the beginning of the last decade,[11] new opportunities for the epoxidation of α,β-unsaturated carbonyl compounds arose and Jørgensen[12] and subsequently MacMillan[13] and our group[14] have developed secondary amine-based catalysts for the asymmetric epoxidation of α,β-unsaturated aldehydes. Recently, our group has expanded the scope of such aminocatalytic epoxidations by introducing powerful *Cinchona*-derived primary amine-catalyzed epoxidations of cyclic and acyclic enones as well as of α-branched, α,β-unsaturated aldehydes.[15] Remarkably though, one substrate class has remained almost entirely unaffected by all previous efforts: *2-cyclopentenones*. To the best of our knowledge, only two attempts for the asymmetric epoxidation of 2-cyclopentenones have been reported: The Laschat group has used an enantiomerically pure peroxide reagent in the epoxidation of 2-cyclopentenone to obtain the product in 31% yield and 12% *ee*.[16] The single published attempt at asymmetric catalysis of this reaction came from our own group using a chiral primary amine salt (DPEN-TRIP) and hydrogen peroxide, giving the epoxide in 33% yield and 78% *ee*.[15a,17] One problem connected to cyclopentenone substrates is their considerable "flatness", rendering them less sensitive to the steric requirements of a chiral catalyst. In fact, asymmetric conjugate additions to 2-cyclopentenones *via* iminium catalysis are considered to be challenging in general.[18] The absence of efficient and highly enantioselective methods for the asymmetric epoxidation of cyclopentenones is particularly poignant in light of the wealth of bioactive natural products possessing a chiral epoxycyclopentanone (for selected examples, see Scheme 1). Here we report a new modified *Cinchona*-derived primary amine catalyst that provides the first solution to this equally important and challenging problem.

Recently, we have introduced a new class of quinoline C-2′-substituted *Cinchona*-derived primary amine catalysts, which are directly accessible *via* protecting group-free addition of an organometallic reagent and *in situ* oxidation. One of these amines enabled us to develop the first catalytic asymmetric Knoevenagel condensation.[19] Encouraged by this work and our continuing interest in aminocatalytic Weitz–Scheffer epoxidations, we wondered how our new catalyst class would perform in the asymmetric epoxidation of cyclopentenones. Initial catalyst evaluation studies are shown in Table 1. We first tested the unmodified quinine-derived aminocatalyst in the presence of different standard acid co-catalysts (**1a**–**1c**). With hydrogen peroxide, these salts converted 2-cyclopentenone **2a** into the corresponding epoxide **3a** in moderate yields and enantioselectivities (entries 1–3). After screening various acid additives, we were pleased to find that (*R*)-Mosher's acid was beneficial to our reaction system. Interestingly, (*R*)-Mosher's acid indeed improved both the yield and enantioselectivity (entry 4). We next evaluated our newly synthesized modified



Scheme 1. Epoxycyclopentanone incorporating natural products and absence of enantioselective 2-cyclopentenone epoxidations.

Table 1. Catalyst evaluation.[a]

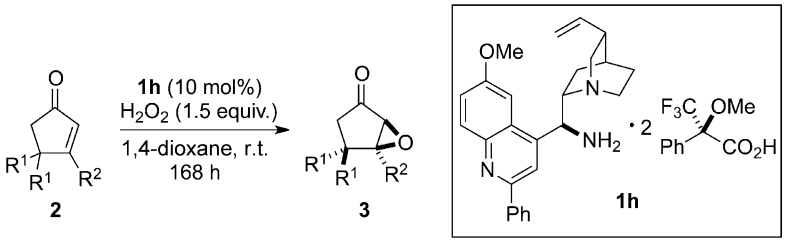


Entry	Catalyst	Yield [%][b]	*e.r.*[c]
1	**1a**	33	87.0:13.0
2	**1b**	50	89.0:11.0
3	**1c**	61	89.0:11.0
4	**1d**	85	91.5:8.5
5[d]	**1d**	88	92.5:7.5
6[d]	**1e**	64	93.0:7.0
7[d]	**1f**	60	83.5:16.5
8[d]	**1g**	60	92.5:7.5
***9*[d]**	***1h***	***90***	***95.0:5.0***
10[d,e]	**1h**	90	94.5:5.5
11[d]	**1i**	60	92.5:7.5

[a] *Reaction conditions*: **2a** (0.1 mmol), hydrogen peroxide (50% aqueous solution, 0.15 mmol), catalyst **1** (0.01 mmol), acid co-catalyst (0.02 mmol), 1,4-dioxane (0.4 mL).
[b] Determined by GC-MS.
[c] Determined by GC analysis on a chiral stationary phase.
[d] Reaction was carried out for 168 h at room temperature.
[e] (*S*)-Mosher's acid was used.

catalysts **1e**–**1i** in the presence of (*R*)-Mosher's acid (entries 6–11). Excitingly, of these salts, phenyl-modified catalyst **1h** gave product **3a** in 90% yield and high enantioselectivity (*er* = 95:5) (entry 9). Using (*S*)-Mosher's acid instead of its (*R*)-enantiomer did not diminish catalyst reactivity and only slightly reduced the enantiomeric ratio (entry 10).

Table 2. Substrate scope.[a]



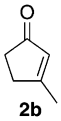
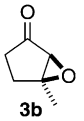
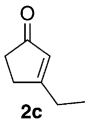
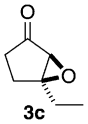
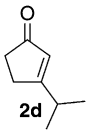
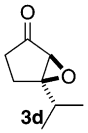
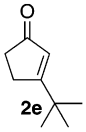
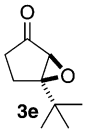
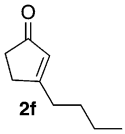
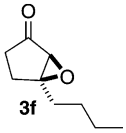
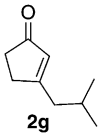
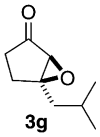
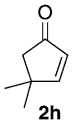
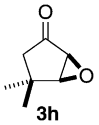
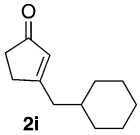
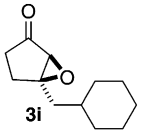
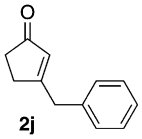
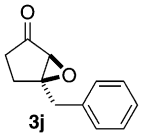
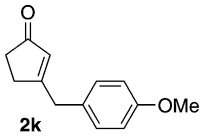
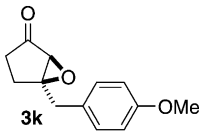
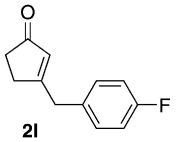
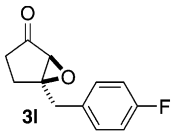
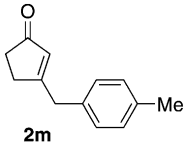
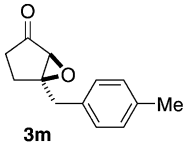
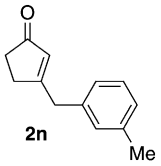
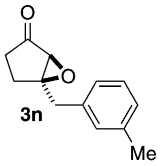
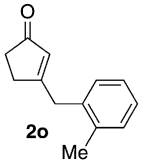
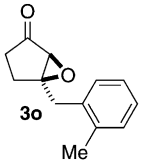
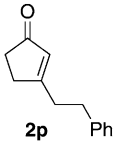
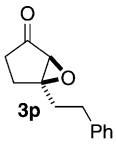
Entry	Substrate	Product	Yield [%][b]	*er* [%][c]
1	 **2a**	 **3a**	87	95:5
2	 **2b**	 **3b**	89	95.5:4.5
3	 **2c**	 **3c**	85	96:4
4	 **2d**	 **3d**	86	95.5:4.5
5	 **2e**	 **3e**	65	96:4
6	 **2f**	 **3f**	90	95.5:4.5
7	 **2g**	 **3g**	90	96:4
8	 **2h**	 **3h**	90	96.5:3.5
9	 **2i**	 **3i**	88	95.5:4.5
10	 **2j**	 **3j**	84	97.5:2.5

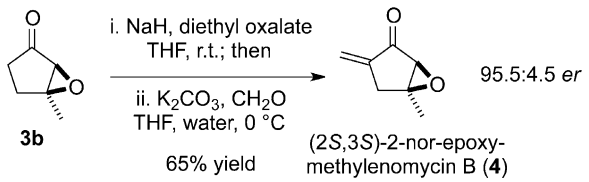
Table 2. (Continued)

Entry	Substrate	Product	Yield [%][b]	*er* [%][c]
11	 **2k**	 **3k**	82	97.5:2.5
12	 **2l**	 **3l**	80	97.5:2.5
13	 **2m**	 **3m**	80	97.5:2.5
14	 **2n**	 **3n**	78	97.5:2.5
15	 **2o**	 **3o**	65	98:2
16	 **2p**	 **3p**	84	96:4

[a] **2** (0.2 mmol), hydrogen peroxide (50% aqueous solution, 0.3 mmol), catalyst **1h** (0.02 mmol), (*R*)-Mosher's acid (0.04 mmol), 1,4-dioxane (0.8 mL).
[b] Yield of isolated product.
[c] Determined by GC analysis on a chiral stationary phase.

It turned out that catalyst **1h** is a fairly general catalyst that can be used in the epoxidation of various substituted 2-cyclopentenones under optimized conditions (Table 2). For example, methyl (entry 2) and linear alkyl chains at the 3-position are tolerated very well (entries 3 and 6). But even cyclopentenones that possess branched alkyl groups such as *i*-Pr, *i*-Bu, or *t*-Bu at this critical position furnish the corresponding epoxides in good yields and high enantioselectivities (entries 4, 5, 7, 9 and 16). The robustness of our reaction to sterical hindrance is further illustrated with the smooth conversion of substrate **2h** containing a quaternary center within the ring adjacent to the reacting carbon atom (entry 8). Excellent enantioselectivities were also obtained with 3-benzyl-substituted cyclopentenones (entries 10–15). Both electron-deficient (entry 12) and electron-rich (entries 11 and 13) aromatic substituents gave the desired products in excellent enantioselectivities. Furthermore, *ortho*-, *meta*- and *para*-substituted arenes can all be used with similarly high efficiency (entries 13–15).

To illustrate the synthetic utility of our reaction, we synthesized the highly potent antibacterial epoxide **4** (Scheme 2) This compound [(2*S*,3*S*)-2-nor-epoxy-methylenomycin B] has been discovered in the context of structure/activity elucidations of the methylenomycins and displays particularly strong antibacterial activity against *E. coli* and *B. subtilis*.[20] The intro-



Scheme 2. First asymmetric synthesis of antibacterial agent (2*S*,3*S*)-2-nor-epoxy-methylenomycin B (**4**).

duction of the methylene functionality at C-5 was achieved through a straightforward one-pot procedure. Our approach represents the first asymmetric synthesis of epoxide **4**, which was obtained from product **3b** without loss of enantiomeric purity.

In conclusion, the first highly efficient and general asymmetric epoxidation of 2-cyclopentenones has been developed. Our approach is based on iminium ion catalysis using a newly developed modified *Cinchona* amine catalyst. Various enones gave the desired products in good to excellent enantioselectivities and high yields using H_2O_2 as highly practical and economic oxidant. Remaining challenges include the use of α-branched enones and β-aryl-substituted cyclopentenones, which remained essentially unaffected under our conditions. We expect to be able to addressing these limitations through careful mechanistic studies, which are currently ongoing in our laboratory. As a prelude to future applications, we illustrated the relevance of our method with a concise synthesis of the highly potent antibacterial epoxide **4** and we expect the true potential of our method to be revealed in the context of more complex natural product syntheses.

Experimental Section

General Remarks

For detailed experimental procedures, spectral data and characterization see the Supporting Information.

Typical Experimental Procedure for the Catalytic Asymmetric Epoxidation of 2-Cyclopentenones

The catalyst **1h** (0.02 mmol, 0.1 equivalent) and (*R*)-Mosher's acid (0.04 mmol, 0.2 equivalents) were dissolved in 1,4-dioxane (0.8 mL) at room temperature. 2-Cyclopentenone **2** (0.2 mmol) was added, and 5 min later 50% aqueous hydrogen peroxide (0.3 mmol, 1.5 equivalents) was added at the same temperature. After stirring for 168 h, the reaction mixture was poured into water (10 mL) and extracted with diethyl ether (3×15 mL). The organic fractions were dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel (*n*-pentane/diethyl ether, 50:50) afforded the products as pale yellow oils.

Acknowledgements

Generous support from the Max-Planck-Society and the Fonds der Chemischen Industrie (Kekulé fellowship to C.M.R) is gratefully acknowledged.

References

[1] T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.
[2] W. Zhang, J. L. Loebach, S. R. Wilson, E. N. Jacobsen, *J. Am. Chem. Soc.* **1990**, *112*, 2801–2803.
[3] R. Irie, K. Noda, Y. Ito, N. Matsumoto, T. Katsuki, *Tetrahedron Lett.* **1990**, *31*, 7345–7348.
[4] a) Y. Tu, Z. X. Wang, Y. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 9806–9807; b) Z. X. Wang, S. M. Miller, O. P. Anderson, Y. Shi, *J. Org. Chem.* **1999**, *64*, 6443–6458.
[5] S. Juliá, J. Guixer, J. Masana, J. Rocas, S. Colonna, R. Annuziata, H. Molinari, *J. Chem. Soc. Perkin Trans. 1* **1982**, 1317–1324.
[6] H. Wynberg, B. Greijdanus, *J. Chem. Soc. Chem. Commun.* **1978**, 427–428.
[7] O. Jacques, S. J. Richards, R. F. W. Jackson, *Chem. Commun.* **2001**, 2712–2713.
[8] D. Enders, J. Zhu, G. Raabe, *Angew. Chem.* **1996**, *108*, 1827–1829; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1725–1728. This elegant enone epoxidation utilizes oxygen as the oxidant and (over)stoichiometric amounts of diethyl zinc and *N*-methylpseudoephedrine as chiral reagent.
[9] M. Bougauchi, S. Watanabe, T. Arai, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1997**, *119*, 2329–2330.
[10] a) B. Lygo, P. G. Wainwright, *Tetrahedron Lett.* **1998**, *39*, 1599–1602; b) B. Lygo, P. G. Wainwright, *Tetrahedron* **1999**, *55*, 6289–6300; c) E. J. Corey, F. Y. Zhang, *Org. Lett.* **1999**, *1*, 1287–1290; d) A. Lattanzi, A. Russo, *Tetrahedron* **2006**, *62*, 12264–12269; e) C. Zheng, Y. Li, Y. Yang, H. Wang, H. Cui, J. Zhang, G. Zhao, *Adv. Synth. Catal.* **2009**, *351*, 1685–1691.
[11] a) B. List, *Synlett* **2001**, 1675–1686. For reviews on aminocatalysis, see: b) B. List, *Acc. Chem. Res.* **2004**, *37*, 548–557; c) B. List, *Chem. Commun.* **2006**, 819–824; d) G. Lelais, D. W. C. MacMillan, *Aldrichimica Acta* **2006**, *39*, 79–87; e) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569; f) A. Erkkilä, I. Majander, P. Pihko, *Chem. Rev.* **2007**, *107*, 5416–5470; g) S. Bertelsen and K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178–2189; h) B. List, *Angew. Chem.* **2010**, *122*, 1774–1779; *Angew. Chem. Int. Ed.* **2010**, *49*, 1730–1734.
[12] T. B. Poulsen, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 6964–6965.
[13] S. Lee, D. W. C. MacMillan, *Tetrahedron* **2006**, *62*, 11413–11424.
[14] X. Wang, B. List, *Angew. Chem.* **2008**, *120*, 1135–1138; *Angew. Chem. Int. Ed.* **2008**, *47*, 1119–1122.
[15] a) X. Wang, C. M. Reisinger, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 6070–6071; b) C. M. Reisinger, X. Wang, B. List, *Angew. Chem.* **2008**, *120*, 8232–8235; *Angew. Chem. Int. Ed.* **2008**, *47*, 8112–8115; c) O. Lifchits, C. M. Reisinger, B. List, *J. Am. Chem. Soc.* **2010**, *132*, 10227–10229. For other iminium catalytic epoxidations, see: d) H. Sundén, I. Ibrahem, A. Córdova, *Tetrahedron Lett.* **2006**, *47*, 99–103; e) X. Lu, Y. Liu, B. Sun, B. Cindric, L. Deng, *J. Am. Chem. Soc.* **2008**, *130*, 8134–8135; f) C. Sparr, W. B. Schweizer, H. M. Senn, R. Gilmour, *Angew. Chem.* **2009**, *121*, 3111–3114; *Angew. Chem. Int. Ed.* **2009**, *48*, 3065–3068; g) J. Li, N. Fu, L.

Zhang, P. Zhou, S. Luo, J-P. Cheng, *Eur. J. Org. Chem.* **2010**, 6840–6849; h) B. P. Bondzic, T. Urushima, H. Ishikawa, Y. Hayashi, *Org. Lett.* **2010**, *12*, 5434–5437. For a catalytic asymmetric peroxidation of α,β-unsaturated ketones, see: i) YX. Lu, B. Sun, B. Cindric, L. Deng, *J. Am. Chem. Soc.* **2008**, *130*, 8134–8135.

[16] M. Kienle, W. Argyrakis, A. Baro, S. Laschat, *Tetrahedron Lett.* **2008**, *49*, 1971–1974.

[17] For a catalytic asymmetric aziridination of cyclic enones including 2-cyclopentenones using *Cinchona*-derived amine catalyststs, see: F. D. Vincentiis, G. Bencivenni, F. Pesciailoi, A. Mazzanti, G. Bartoli, P. Galzerano, P. Melchiorre, *Chem. Asian J.* **2010**, *5*, 1652–1656.

[18] a) S. Hanessian, V. Pham, *Org. Lett.* **2000**, *2*, 2975–2978; b) C. E. T. Mitchell, S. E. Brenner, S. V. Ley, *Chem. Commun.* **2005**, 5346–5348; c) D. Perdicchia, K. A. Jørgemsen, *J. Org. Chem.* **2007**, *72*, 3565–3568; d) V. Wascholowski, K. R. Knudsen, C. E. T. Mitchell, S. V. Ley, *Chem. Eur. J.* **2008**, *14*, 6155–6165; e) P. Li, S. Wen, F. Yu, Q. Liu, W. Li, Y. Wang, X. Liang, J. Ye, *Org. Lett.* **2009**, *11*, 753–756; f) N. Mase, M. Fukasawa, N. Kitagawa, F. Shibagaki, N. Noshiro, K. Takabe, *Synlett* **2010**, 2340–2344; g) M. Yoshida, K. Hirama, M. Narita, S. Hara, *Symmetry*, **2011**, *3*, 155–164.

[19] A. Lee, A. Michrowska, S. Sulzer-Mosse, B. List, *Angew. Chem.* **2011**, *123*, 1745–1748; *Angew. Chem. Int. Ed.* **2011**, *50*, 1707–1710.

[20] K. Tonari, K. Sameshima, *J. Jpn. Oil Chem. Soc.* **2000**, *49*, 583–590.

