Highly Enantioselective Epoxidation of $\alpha$-$\beta$-Unsaturated Ketones Using Amide-Based Cinchona Alkaloids as Hybrid Phase-Transfer Catalysts

Maciej Majdecki,† Agata Tyszka-Gumkowska,† and Janusz Jurczak*

Catalytic enantioselective epoxidation of allylic alcohols, introduced by Sharpless in the 1980s, has been recognized as one of the most significant tools in asymmetric synthesis, since epoxides are considered as versatile building blocks and intermediates in asymmetric organic transformations. This fundamental discovery has significantly expanded over the last 40 years, especially in the field of metal catalysis and organocatalysis. With the growing demand for green and sustainable chemistry, the development of environmentally benign and cheap catalysts remains a great challenge in stereocontrolled organic synthesis. In this area, phase-transfer catalysis (PTC) has become established as a comprehensive method, owing to mild reaction conditions, operational simplicity, and no use of heavy metals. Particular attention in such work has been devoted to the asymmetric epoxidation of $\alpha$-$\beta$-unsaturated ketones as an extension of the pioneering work by Wynberg et al. on epoxidation of $E$-chalcones using quinine salts as catalysts. However, successful examples of highly enantioselective synthesis of epoxycetones still remain few in number. The most representative continuations of Wynberg’s discovery were published in the 1990s by the Lygo and Corey groups. Alternative methods to improving the abilities of Cinchona-based catalysts were presented by the Park and Siva groups, who showed that adding surfactants to reaction mixtures or using ultrasound support increased the enantiomeric excess of products formed. On the other hand, Maruoka et al. introduced efficient, but expensive, BINOL-based catalysts. Furthermore, other types of PTC catalysts, such as macrocyclic compounds, peptides, guanidine salts, prolines, etc., have also been used, albeit without high enantioselectivities.

Despite recent spectacular progress in asymmetric epoxidation of $E$-chalcones, there are several issues that prevent their general applicability. The main disadvantages of the methods discussed are as follows: multistep synthesis of catalysts, high catalyst loading, a frequent necessity to use special techniques, and long reaction times. Therefore, there is a strong need for research on rationally designed and efficient PTC catalysts, especially chiral ones, which meet additional requirements related to the possibility of their reuse. Herein, we report our own approach to enantioselective epoxidation by introducing a readily available and finely tunable library of hybrid Cinchona alkaloid-based catalysts, the potential application of which we have previously demonstrated in studies on alkylation of imino glycine esters.

Received: September 29, 2020
Published: October 28, 2020
enantioselectivity. We postulate that the oxidant/base ratio formation of the reactive HOO−epoxidation of chalcone best solvent for most of these reactions. Finally, we showed that presented in the Supporting Information (Tables S2−S6). The ee values were determined by HPLC analysis using a chiral column Kromasil OD-H or Chiralcel AD-H and OB-H. leading to product with moderate yield 71% and high enantiomeric excess 97% ee. It is worth mentioning the great results obtained for (2E,4E)-1,5-diphenyl-penta-2,4-dien-1-one S18 (95% yield, 96% ee) and α,β-unsaturated ketone S21 containing aliphatic substituent (98% yield, 99% ee). In addition, all epoxides, except P20, can be isolated from organic layer using simple filtration by silica gel pad. Such results indicate a fairly universal character of the developed method, and to the best of our knowledge it is a first example of successful epoxidation such substrates using organocatalysts. The obtained results may indicate a competitive π-stacking effect originating from the phenyl system on the double bond side, which may adversely affect the formation of the diastereomeric complex with the catalyst C5. In order to explain such high selectivity, we obtained monocrystals of C5 by slowly evaporation of its saturated solution in wet acetone. Next, we performed a successful single-crystal X-ray diffraction analysis of catalyst C5 (for details see the Supporting Information), which revealed its distinctive three-dimensional structure (Figure 1).

Let us consider one of the catalyst molecules as it occurs in a single crystal. The C5 molecule has an aromatic ring stacked in the direction determined by the amide function. Importantly, the arrangement of the phenyl group in the amide arm is nearly perpendicular, this conformational information creating an attractive chiral reaction cavity around the amide function. This

Scheme 1. Scope of Hybrid Cinchona-Based Catalysts

Scheme 2. Asymmetric Epoxidation of α,β-Unsaturated Ketones S1−S21 Using Catalyst C5

“The ee values were determined by HPLC analysis using a chiral column Kromasil OD-H or Chiralcel AD-H and OB-H.”

“...”

Compound C5 allows the desired epoxides to be obtained with high yield (99%) and promising enantiomeric excess (71% ee). Also, reactions with catalysts based on the other Cinchona alkaloids give the desired products with excellent yield, but in racemic form.

Subsequently, we started to optimize the reaction conditions using C5 as the catalyst, and we noted that the ratio of hydrogen peroxide and aqueous solution of NaOH strongly affected the enantioselectivity. We postulate that the oxidant/base ratio affects the rate of hydrogen peroxide decomposition and formation of the reactive HOO− ion. Moreover, instead of toluene we found that a mixture of Et2O/toluene (1:1) was the best solvent for most of these reactions. Finally, we showed that epoxidation of chalcone S1 under the newly found conditions was very efficient and proceeded for 1 h with an excellent enantiomeric excess (99% ee), using only 0.5 mol % of catalyst at 5 °C temperature. Lower catalyst loading resulted in decreased yield and ee value. All details of the optimization process are presented in the Supporting Information (Tables S2−S6).

Under such optimal conditions we examined the reactivity and selectivity of α,β-unsaturated ketones S1−S21 as shown in Scheme 2.

All of the epoxides P1−P21 were obtained from the corresponding substrates S1−S21 with both excellent yield and excellent enantioselectivity. For substrates S1−S13, with various electron-differentiating substituents on the carbonyl group side, no significant changes in the extremely high selectivities (95−99% ee) were observed. Due to lower solubility of epoxides P6, P10, and P12 in the diethyl ether, reactions should be carried out longer (up to 48 h). Slightly lower enantiomeric excesses were noted for epoxidation of E-chalcones with an electron-differentiating substituents in the phenyl ring on the double bond side S14−S17. In those four cases, achievement of complete conversion required the use of 1 mol % of the catalyst and the reactions were carried out in toluene (P13−P16 marked green, Scheme 2), but we noted very high yields and ee values (92−99%, 90−96% ee). With more challenging substrates S18−S21 we performed the epoxidation reactions with 3 mol % of the catalyst C5 and also in these cases we choose toluene as an optimal solvent (P18−P21 marked purple, Scheme 2). Epoxidation of S20 was conducted 72 h

“The ee values were determined by HPLC analysis using a chiral column Kromasil OD-H or Chiralcel AD and OB-H.”

“We obtained a successful single-crystal X-ray diffraction analysis of catalyst C5 (for details see the Supporting Information), which revealed its distinctive three-dimensional structure (Figure 1).
strongly implies that the expected hydrogen-bonding interaction would indeed bring an enone inside the cavity to provide an ideal proximity to the hydrogen peroxide ion. This hypothesis is supported by studies with N-methylated catalyst C5 in which we obtained a racemic epoxide P1. Our proposed model of the transition state (Figure 2) posits that the chalcone substrate is stabilized by the hydrogen bond from the amide function of a catalyst.

A key element determining the high enantioselection of the reaction is the phenyl ring from the amide arm which has a π-π stacking interaction with the β-phenyl group of substrate. Such interactions block one of the E-chalcone faces. Moreover, the hydroxyl group of the catalyst forms an ionic pair with the hydrogen peroxide ion (HOO\(^-\)) via hydrogen bond. Consequently, the hydrogen peroxide can reach the β-carbon atom of an enone exclusively from above to afford the αS,βR-product of epoxidation.

The above results turned our attention to the possibility of further improving our reaction. After confirming the stability of catalyst C5 under PTC-epoxidation conditions, we decided to investigate the possibility of its reuse. Scheme 3 presents our concept of conducting 10 epoxidation cycles under subsequent conditions. The chalcone S1, in the presence of 1 mol % of catalyst C5, was used for the first reaction cycle.

After completion of the reaction, another portion of hydrogen peroxide and aqueous NaOH, accompanied by chalcone S1 were added (the second cycle). This procedure was repeated after each reaction cycle in order to maintain full conversion of the reaction. Thus, we were able to carry out epoxidation of chalcone S1 on a 5 g scale, after 10 reaction cycles, and the product was obtained in total with 97% yield and >99% ee. Note that during eight reaction cycles, the model catalytic reaction did not lose any efficiency or enantioselectivity; however, we terminated the experiment after the tenth cycle due to the slightly lowering of the conversion (to 97%). Given that the epoxidation reaction is very clean, after isolation of the desired product P1, we were also able to recover the catalyst C5 from a postreaction mixture with 99% efficiency, simply by precipitating it with the addition of diethyl ether. Given these advantages, the discussed procedure is an excellent solution for epoxidation on a multigram scale, as only 0.1 mol % of the catalyst was used, based on the final amount of the product obtained. Note that when such catalyst loading under classical batch conditions (without sequential addition of reagents) was used, the products were obtained in the form of a racemate with low yield. Such high efficiency of sequential addition of reagents is observed due to the continuous presence of 1 mol % of catalyst in the reaction mixture, which does not lose its activity over time or in the presence of the product.

In summary, we have developed an efficient method for the preparation of enantiomerically pure epoxyketones using hybrid amide-based Cinchona alkaloids as catalysts under PTC conditions. The low loading (0.5 mol %) of highly effective catalysts allowed us to obtain a wide range of such chiral epoxyketones with very high yields and with excellent enantioselectivity (up to 99% and 99% ee, respectively). To the best of our knowledge, these are unique results as compared to those obtained with application of known catalysts, while maintaining such low catalyst loading. Additionally, for the first
time we presented the possibility of reusing *Cinchona* derivatives in the synthesis of optically pure epoxy ketones by follow-up epoxidation cycles without adding a fresh portion of catalyst between subsequent reactions. This approach could be highly valuable in the synthesis of potential building blocks in the field of medicinal, agrochemical, and material chemistry on a large scale. Further work on applying our catalyst library to asymmetric epoxidation with other enones is in progress.

**ASSOCIATED CONTENT**

| Supporting Information |
|------------------------|
| The Supporting Information is available free of charge at [https://pubs.acs.org/doi/10.1021/acs.orglett.0c03272](https://pubs.acs.org/doi/10.1021/acs.orglett.0c03272). |

**REFERENCES**

We acknowledge Poland’s National Science Centre (Project 2016/21/B/ST5/03352) for financial support.

**ACKNOWLEDGMENTS**

The authors declare no competing financial interest.

**AUTHOR INFORMATION**

**Corresponding Author**

Janusz Jurczak — Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warsaw, Poland; orcid.org/0000-0002-0351-6614; Email: jurczak_group@icho.edu.pl

Complete contact information is available at: [https://pubs.acs.org/doi/10.1021/acs.orglett.0c03272](https://pubs.acs.org/doi/10.1021/acs.orglett.0c03272)

**Author Contributions**

M.M. and A.T.-G. contributed equally.

**Notes**

The authors declare no competing financial interest.

**REFERENCES**

(1) (a) Katsuki, T.; Sharpless, K. B. The first practical method for asymmetric epoxidation. *J. Am. Chem. Soc.* 1980, 102, 5974–5976. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masumune, H.; Sharpless, K. B. Catalytic asymmetric epoxidation and kinetic resolution: modified procedures including in situ derivatization. *J. Am. Chem. Soc.* 1987, 109, 5765–5780.

(2) (a) Seayad, J.; List, B. Asymmetric organocatalysis. *Org. Biomol. Chem.* 2005, 3, 719–724. (b) Hughes, D. L. Asymmetric Organocatalysis in Drug Development—Highlights of Recent Patent Literature. *Org. Process Res. Dev.* 2018, 20, 574–584. (c) Carlone, A.; Bernardi, L. Enantioselective organocatalytic approaches to active pharmaceutical ingredients — selected industrial examples. *Phyto. Sci. Rev.* 2019, 4, 20180097.

(3) See (a) Goryczkni Smith, J. Synthetically Useful Reactions of Epoxides. *Synthesis* 1984, 629–656. (b) Lauret, C. Epoxy ketones as versatile building blocks in organic synthesis. *Tetrahedron: Asymmetry* 2001, 12, 2359–2383. (c) Marico-Contelles, J.; Molina, M. T.; Anjum, S. Naturally Occurring Cyclohexane Epoxides: Sources, Biological Activities, and Synthesis. *Chem. Rev.* 2004, 104, 2857. (d) Miyasita, K.; Imanishi, T. Syntheses of Natural Products Having an Epoxyquinone Structure. *Chem. Rev.* 2005, 105, 4515–4536.

(4) (a) Besse, P.; Veschambre, H. Chemical and biological synthesis of chiral epoxides. *Tetrahedron* 1994, 50, 8885–8897. (b) Xia, Q.-H.; Ge, H. Q.; Ye, C. P.; Liu, Z. M.; Su, K. X. Advances in Homogeneous and Heterogeneous Catalytic Asymmetric Epoxidation. *Chem. Rev.* 2005, 105, 1603–1662. (c) Wang, Ch.; Yamamoto, H. Asymmetric Epoxidation Using Hydrogen Peroxide as Oxidant. *Chem. - Asian J.* 2015, 10, 2056–2068.

(5) (a) Adam, W.; Saha-Möller, C. R.; Ganeshpura, P. A. Synthetic Applications of Nonmetal Catalysts for Homogeneous Oxidations. *Chem. Rev.* 2001, 101, 3499–3548. (b) Kelly, D. R.; Roberts, S. M. Oligopeptides as catalysts for asymmetric epoxidation. *Biopolymers* 2006, 84, 74–89. (c) Wong, O. A.; Shi, Y. Organocatalytic Asymmetric Epoxidation of Olefins Catalyzed by Chiral Ketones and Iminium Salts. *Chem. Rev.* 2008, 108, 3958–3987. (d) Lattanzi, A. Non-covalent Organocatalytic Approach in the Asymmetric Epoxidation of Electron-Poor Alkenes: Recent Developments Frontiers of Green Catalytic Selective Oxidations; Springer: Singapore, 2019. (e) Triandafillidi, I.; Tzaras, D. I.; Kokotos, Ch. G. Green Organocatalytic Oxidative Methods using Activated Ketones. *ChemCatChem* 2018, 10, 2521–2535.

(6) (a) Tavakolian, M.; Vahdat-Kajeh, S.; Asgari, S. Recent Advances in Solvent-Free Asymmetric Catalysis. *ChemCatChem* 2019, 11, 2943–2977. (b) Bryliakov, K. P. Catalytic Asymmetric Oxidations with the Environmentally Benign Oxidants H. *Chem. Rev.* 2017, 117, 11406–11459.

(7) For recent reviews on asymmetric phase-transfer catalysis, see: (a) O’Donnell, M. The Enantioselective Synthesis of α-Amino Acids by Phase-Transfer Catalysis with Achiral Schiff Base Esters. *Acc. Chem. Res.* 2004, 37, 506. (b) Jew, S.-s.; Park, H.-b. *Cinchona*-based phase-transfer catalysts for asymmetric synthesis. *Chem. Commun.* 2009, 14, 7090–7103. (c) Maruoka, K. Highly practical amino acid and alkyloid synthesis using designer chiral phase transfer catalysts as high-performance organocatalysts. *Chem. Rev.* 2010, 10, 254–259. (d) Shirakawa, S.; Maruoka, K. Recent developments in asymmetric phase-transfer reactions. *Angew. Chem., Int. Ed.* 2013, 52, 4312–4348. (e) Tan, J.; Yasuda, N. Contemporary Asymmetric Phase Transfer Catalysis: Large-Scale Industrial Applications. *Org. Proces. Rev. Dev.* 2015, 19, 1731–1746.

(8) For selected examples, see: (a) Lattanzi, A. Enantioselective Epoxidation of αβ-Enones Promoted by αα-Diphenyl-l-prolinol as Bifunctional Organocatalyst. *Org. Lett.* 2005, 7, 2579–2582. (b) Li, Y.; Liu, X.; Yang, Y.; Zhao, G. 4-Substituted-αα-diaryl-prolinols Improve the Enantioselective Catalytic Epoxidation of αβ-Enones. *J. Org. Chem.* 2007, 72, 288–291. (c) Bondicz, B. P.; Urushima, T.; Ishikawa, H.; Hayashi, Y. Asymmetric Epoxidation of αα-Substituted Acroleins Catalyzed by Diphenylprolinyl Silyl Ether. *Org. Lett.* 2010, 12, 5434–5437.

(9) For selected examples see: (a) Chu, Y. Y.; Liu, X. H.; Li, W.; Hu, X. L.; Lin, L. L.; Feng, X. M. Asymmetric catalytic epoxidation of αβ-unsaturated carbonyl compounds with hydrogen peroxide: Additive-free and wide substrate scope. *Chem. Sci.* 2013, 3, 1996–2000. (b) Wang, B.; Miao, C.; X.; Wang, S. F.; Xia, C. G.; Sun, W. Manganese Catalysts with C1-Symmetric N4 Ligand for Enantioselective Epoxidation of Olefins. *Chem. - Eur. J.* 2012, 18, 6750–6753. (c) Nishikawa, Y.; Yamamoto, H. Iron-Catalyzed Asymmetric Epoxidation of ββ-Disubstituted Enones. *J. Am. Chem. Soc.* 2011, 133, 8432–8435. (d) Qian, Q.; Tan, Y.; Zhao, B.; Feng, T.; Shen, Q.; Yao, Y. Asymmetric Epoxidation of Unsaturated Ketones Catalyzed by Heterobimetallic Rare Earth-Lithium Complexes Bearing Phenoxy-Functionalized Chiral Diphenylprolinol Ligand. *Org. Lett.* 2014, 16, 4516–4519. (e) Zeng, C.; Yuan, D.; Zhao, B.; Yao, Y. Highly Enantioselective Epoxidation of αβ-Unsaturated Ketones Catalyzed by Rare-Earth Amides [{(MeSi)2N}2Re(E-C)LI(THF)], with Phenoxy-Functionalized Chiral Diphenylprolinol Org. Lett. 2015, 17, 2242–2245. (10) (a) Reisinger, C. M.; Wang, X.-W.; List, B. Catalytic Hydroxyperoxidation of αβ-Unsaturated Ketones: An Approach to Enantiopure Peroxyhemiketals, Epoxides, and Aldols. *Angew. Chem.*
(b) Kawai, H.; Okusu, S.; Yuan, Z.; Tokunaga, E.; Yamano, A.; Shiro, M.; Shibata, N. Enantioselective synthesis of epoxides having a tetrasubstituted trifluoromethylated carbon center: methylhydrazine-induced aerobic epoxidation of β,β-disubstituted enones. *Angew. Chem., Int. Ed.* 2013, 52, 2221–2225.

(11) Hummelen, J. C.; Wynberg, H. Alkaloid assisted asymmetric synthesis IV additional routes to chiral epoxides. *Tetrahedron Lett.* 1978, 19, 1089–1092.

(12) (a) Lygo, B.; Wainwright, P. G. Asymmetric phase-transfer mediated epoxidation of α,β-unsaturated ketones using catalysts derived from Cinchona alkaloids. *Tetrahedron Lett.* 1998, 39, 1599–1602. (b) Lygo, B.; To, D. C. M. Improved procedure for the room-temperature asymmetric phase-transfer mediated epoxidation of α, β-unsaturated ketones. *Tetrahedron Lett.* 2001, 42, 1343–1346. (c) Lygo, B.; Gardiner, S. T.; McLeod, M. C.; To, D. C. M. Diastereoe- and enantioselective synthesis of α,β-epoxyketones using aqueous NaOCl in conjunction with dihydrocinchonidine derived phase-transfer catalysis at room temperature. Scope and limitations. *Org. Biomol. Chem.* 2007, 5, 2283–2290.

(13) Corey, E. J.; Zhang, F.-Y. Mechanism and conditions for highly enantioselective epoxidation of α, β-enones using charge-accelerated catalysis by a rigid quaternary ammonium salt. *Org. Lett.* 1999, 1, 1287–1290.

(14) Jew, S.-s.; Lee, J.-H.; Jeong, B.-S.; Kim, M. J.; Lee, Y.-J.; Lee, J.; Choi, S.-H.; Lee, K.; Lah, M.-S.; Park, H.-g. Highly Enantioselective Epoxidation of 2,4-Diarylenones by Using Dimeric Cinchona Phase-Transfer Catalysts: Enhancement of Enantioselectivity by Surfactants. *Angew. Chem., Int. Ed.* 2005, 44, 1383–1385.

(15) Sivamani, J.; Ashokkumar, V.; Sadhasivam, V.; Duraimurugan, K.; Siva, A. Ultrasonic assisted dimeric cinchona based chiral phase transfer catalysts for highly enantioselective synthesis of epoxidation of α,β-unsaturated ketones. *RSC Adv.* 2014, 4, 60293–60299.

(16) Ooi, T.; Ohara, D.; Tamura, M.; Maruoka, K. Design of New Chiral Phase-Transfer Catalysts with Dual Functions for Highly Enantioselective Epoxidation of α,β-Unsaturated Ketones. *J. Am. Chem. Soc.* 2004, 126, 6844–6845.

(17) (a) Bakó, T.; Bakó, P.; Keglevich, G.; Bombicz, P.; Kubinyi, M.; Pál, K.; Bodor, S.; Makó, A.; Tőke, L. Phase-transfer catalyzed asymmetric epoxidation of chalcones using chiral crown ethers derived from d-glucose, d-galactose, and d-mannitol. *Tetrahedron: Asymmetry* 2004, 15, 1589–1595. (b) Hori, K.; Tamura, M.; Tani, K.; Nishiwaki, N.; Ariga, M.; Tohda, Y. Asymmetric epoxidation catalyzed by novel azacrown ether-type chiral quaternary ammonium salts under phase-transfer catalytic conditions. *Tetrahedron Lett.* 2006, 47, 3115–3118. (c) Yoo, M.-S.; Kim, D. G.; Ha, W. M.; Jew, S.-s.; Park, H.-g.; Jeong, B.-S. Synthesis of (αR,βS)-epoxyketones by asymmetric epoxidation of chalcones with Cinchona phase-transfer catalysts. *Tetrahedron Lett.* 2010, 51, 5601.

(18) (a) Majdecki, M.; Niedbala, P.; Jurczak, J. Amide-Based Cinchona Alkaloids as Phase-Transfer Catalysts: Synthesis and Potential Application. *Org. Lett.* 2019, 21, 8085–8090. (b) Majdecki, M.; Niedbala, P.; Jurczak, J. Synthesis of C2 Hybrid Amide-Based PTC Catalysts and Their Comparison with Saturated Analogues. *ChemistrySelect* 2020, 5, 6424–6429.