Enantioenriched calcium-complex mediated synthesis of (*S*)-(+)-Fenoprofen

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Abstract

An efficient chiral catalyst for the asymmetric epoxidation of α,β- unsaturated carbonyl compounds is developed utilizing easily available, eco-friendly $CaCl_2$ and chiral ligand. Efficacy of the methodology is extended for the stereoselective synthesis of (S)-Fenoprofen. A survey of ligands indicated that (S)-,6,6'-Diphenyl BINOL-Ca **1e** was the best ligand giving maximum ee (84%) for **4** with excellent yield.

Keywords: Calcium chloride, asymmetric epoxidation, (S)-,6,6'-diphenyl BINOL-Ca, (S)-Fenoprofen

Introduction

Synthesis of optically active non-steroidal anti inflammatory agents (NSAIs) such as 2-aryl propanoic acids are still of commercial importance owing to their wide usage to control the symptoms of ankylosing spondylitis (a form of arthritis), inflammation of the joints and to relieve pain and stiffness caused due to arthritis.[1] It works by blocking the production of a chemical (prostaglandin), which the body produces in response to injury or certain diseases. The majority of these drugs are therapeutically active only in their (*S*)- form.[2] There are several methods to obtain optically pure (*S*)-enantiomer of aryl propanoic acids, which include classical resolution,[3] biocatalysis[4] as well as asymmetric synthesis.[5] Among them, the most impressive synthesis was reported by Lydia carde et. al[6] utilizing silica-adsorbed polyleucine catalyst for the asymmetric epoxidation of enones and extending to the preparation of 2-aryl proponic acid.

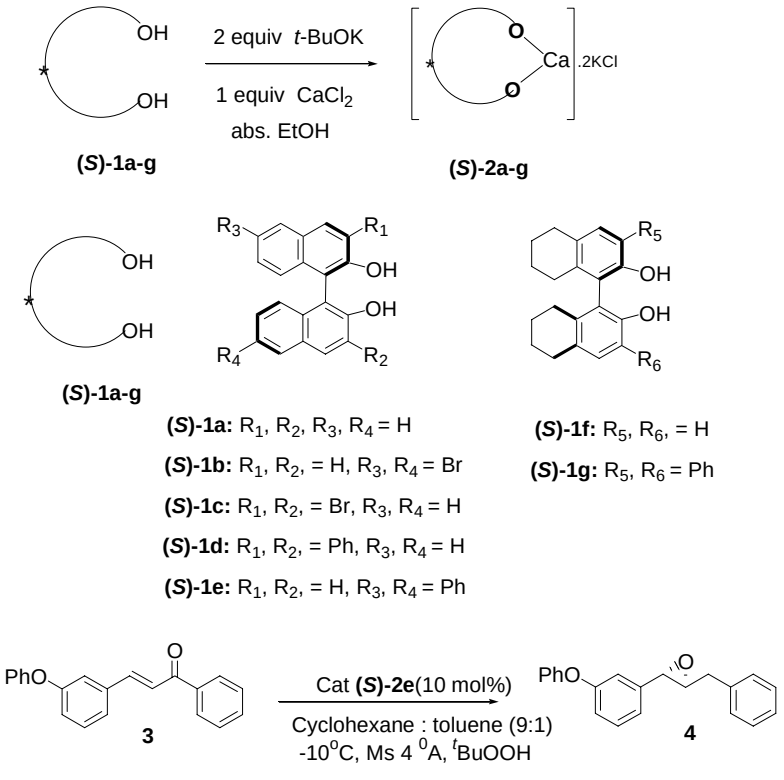
Catalytic asymmetric epoxidation of α,β-unsaturated carbonyl compounds is one of the most important functional group transformations in organic synthesis, for the reason that the corresponding optically active epoxides are potentially useful intermediates in the synthesis of a variety of natural products and pharmaceuticals.[7] In our continuous exploration of the concept of bifunctional catalysis, efforts were directed towards the development of a catalyst calcium-

BINOL that could activate Michael acceptors with high enantiocontrol.[8] The successful demonstration of the enantioenriched catalyst 6,6'-diphenylBINOL-calcium complexes for asymmetric epoxidation of α,β-unsaturated enones prompted us to apply for the total synthesis of (*S*)-(+)-Fenoprofen.

Results and Discussion

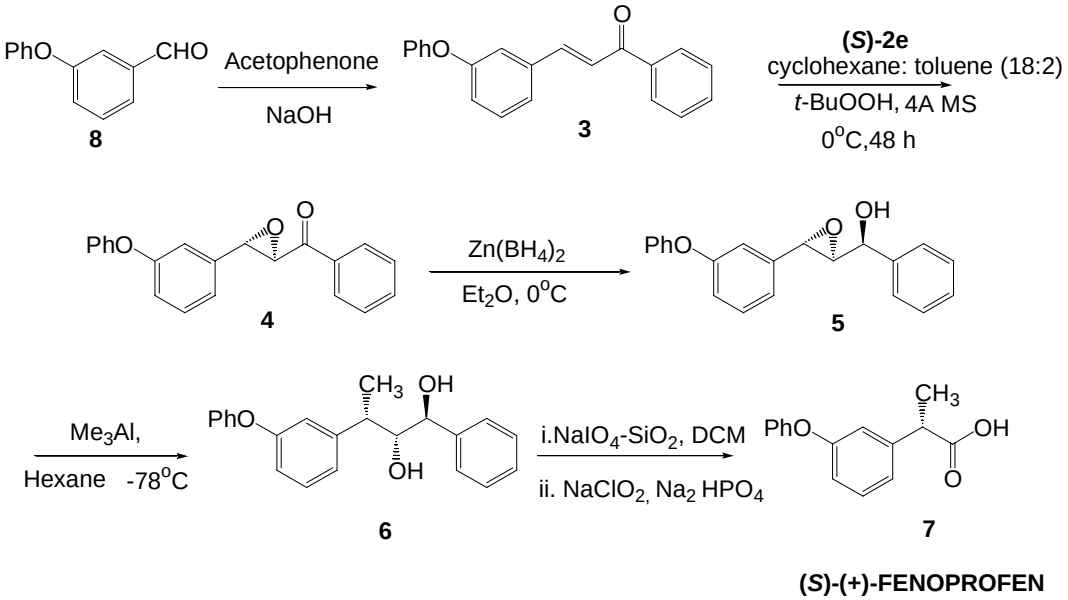
We thus report on the design and the utilization of bifunctional chiral calcium complexes prepared from the calcium chloride and substituted optically active BINOL derivatives for the epoxidation reaction of chalcones. This methodology of asymmetric epoxidation using chiral enantioenriched calcium complexes was successfully extended to the synthesis of pharmacological active compound pursuing a short, practical synthesis of anti-inflammatory drug (*S*)-(+)-Fenoprofen.

In an effort to enhance the enantioselectivity of the epoxy ketone (**4**), various factors were investigated.[9] An array of various substituted BINOL ligands as catalyst were studied (Scheme1) and the ligand of choice was **1e** giving maximum enantioselectivity.



Scheme 1

Our strategy was based on catalytic asymmetric epoxidation of chalcone to generate a chiral epoxide **4**, a key intermediate for the synthesis of fenoprofen. Thus, the epoxidation of *m*-phenoxy chalcone **3** was carried out using 10 mol% of 6,6'-diphenylBINOL[10] **(*S*)-2e** with 1.5 equivalent of TBHP and 4A MS in a solvent mixture of cyclohexane:toluene 9:1 at -10°C afforded the required chiral epoxy ketone **4** in 85% yield and 84:16 selectivity.[11] In an effort to increase the enantioselectivity during the epoxidation process molecular sieves were added portion-wise and chalcone was added using a syringe pump. Dramatic enhancement in the ee's was observed on adopting these two precautions. Further, the enantioselectivity of the epoxide **4** was enriched to 96% by one crystallization in the solvent mixture of hexane:DCM. The epoxy ketone **4** was reduced with zinc borohydride at 0°C to give the corresponding epoxy alcohol **5** as major diastereomer in high yield (82%) accompanying minor diastereoisomer, which was separated by column chromatography. As anticipated, the pure diastereoisomer **5** was alkylated by ring opening using trimethylaluminium in hexane at 0°C to give diol **6** with retention of stereochemistry at C-3 carbon with a selectivity of 98:2. The optically active diol **6** was subjected to two stage oxidation processes resulted in the final product **7**. The diol **6** was initially oxidized using sodium periodate-silica gel followed by further oxidation using sodium chlorite and sodium dihydrogen phosphate, afforded (*S*)-(+)-Fenoprofen **7** in 76% yield over the two steps with 95% (+ 45.3 [lit[13] + 45.7 (*c* 1, $CHCl_3$)]) enantioselectivity (Scheme 2). The absolute stereochemistry was assigned by correlating the compounds with those reported in the literature.



Scheme 2

In conclusion, the efficiency of the catalytic epoxidation process developed has been demonstrated by its application towards the synthesis of (*S*)-Fenoprofen. The enantioselective epoxidation of *m*-phenoxy chalcone is the primary step for the synthesis of (*S*)-Fenoprofen. The concise simple synthesis resulted fenoprofen in its biologically active form as a *S*-enantiomer in

46.9 % overall yield from chiral epoxy ketone **4f**. The asymmetric epoxidation process developed is applicable to several substituted chalcones thus, providing a rapid, high yielding and easy route leading to the synthesis of various optically active 2-aryl propanoic acids, a group of non-steroidal anti-inflammatory drugs. The route to (*S*)-*m*-phenoxyphenyl propanoic acid described here is simple, economical, efficient and high yielding.

Experimental Section

General procedure for the asymmetric epoxidation of enones

***trans*-2,3-Epoxy-3-(3-phenoxyphenyl)-1-phenylpropan-1-one (4)**

A mixture of 6,6'-diphenylBINOL **(*S*)-2e** (657 mg, 1.5 mmol), potassium *tert*-butoxide (337 mg, 3.0 mmol) in abs. EtOH (40 ml) were stirred under argon for 0.5 h. The ethanol was evaporated under reduced pressure and to the residue, solid $CaCl_2$ (99%) (166.3 mg, 1.5 mmol) was added. The combined components were dried under vacuum (10 mm Hg, 15 min.) followed by the addition of abs. EtOH (40 ml) to give a white color suspension. After being stirred for 3 h at ambient temperature, ethanol was evaporated under reduced pressure to obtain a white solid powder. To this solid complex, cyclohexane (117 ml) and toluene (13 ml) were added sequentially and allowed to stir for 3 h. The 4A MS powder (900 mg, activated at 260-280^{o}C/10 mm Hg, 3 h) was added to the reaction mixture. After cooling it to -10^{o}C, TBHP (6.7 ml, 22.5 mmol, 3.3 M solution in toluene) was added. After 15 min, a 1.5 M toluene solution of chalcone **3** (4.5 g in 10 ml toluene, 15.0 mmol) was added via a syringe pump (0.33ml/h) over a period of 30 h at -10^{o}C. Additional 4A MS (4 x 900 mg portion) was added to the reaction mixture portion-wise at an interval of 5 h. After completion of the addition, the reaction mixture was stirred for an additional 10 h maintaining the same temperature. The reaction mixture was quenched with saturated NH_4Cl solution (50 ml) and extracted with ethyl acetate (2 × 100 ml). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (Silica gel 60-120 Mesh, 6% EtOAc: Hexane) to give epoxy ketone **4** as a white solid.

Yield: 4.02 g, 85%. mp: 74 - 76^{o}C. $[\alpha]_D^{25}$: -194 (*c* 1, $CHCl_3$).

Enantiomeric excess was determined by chiral stationary phase HPLC analysis. (DAICEL Chiralpak AD-H, hexane/2-propanol, 95:5) t_r = 17.95 min (minor), t_r = 21.15 min (major) detection at 254 nm.

IR (KBr): 2875, 1695, 1245 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.02 (d, *J* = 1.92 Hz, 1 H), 4.16 (d, *J* = 1.92 Hz, 1 H), 6.92-7.18 (m, 6 H), 7.27-7.62 (m, 6 H), 7.95- 8.05 (d, *J* = 8.00 Hz, 1 H). EIMS: 316 (M^+). Anal. Calcd. for $C_{21}H_{16}O_3$: C, 79.73; H, 5.10; Found: C, 80.02; H, 5.29.

(1*S*,2*S*,3*S*)-2,3-Epoxy-3-(3-phenoxyphenyl)-1-phenylpropan-1-ol (5). To the cooled ether solution (120 ml, 0^{o}C) of **29** (4 g, 12.6 mmol) was added $Zn(BH_4)_2$[14](30 ml, 4.41 mmol) under nitrogen atmosphere. After stirring for 4h, the reaction mixture was quenched with saturated NH_4Cl at the same temperature. The aqueous layer was extracted with EtOAc. The combined

organic layer was dried and evaporated. The residue was purified through column chromatography (Silica gel 60-120 Mesh; 5% EtOAc : Hexane) to give **5** as viscous liquid which solidifies slowly. mp 63-65°C. Yield: 3.3 g, 82%.IR : 3425, 1223, 890 cm^{-1}.$[\alpha]_D^{25}$: -15.0 (*c* 1, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.33 (br s, 1 H), 3.25 (dd, *J* = 2.98, 2.0, 1 H), 4.1 (d, *J* = 2.0, 1H), 4.94 (d, *J* = 2.98, 1 H), 6.87-7.93 (m, 14 H). ^{13} C-NMR (75 MHz, $CDCl_3$): δ 54.9, 64.7, 71.5, 116.2, 118.4, 120.8, 123.6, 126.9, 128.6, 128.9, 129.9, 138.7, 138.9, 156.9, 157.6. EI-MS: 318, 212, 183, 105, 77. **HRMS** Calculated 318.12558 Found 318.12516.

(1*S*,2*R*,3*S*)-1,1-Dihydroxy-3-(3-phenoxyphenyl)-1-phenyl-butane (6). To a cooled DCM solution (22 ml, -78°C) of **5** (3.3 g, 10.3 mmol) was added a 2.5 M hexane solution of trimethyl aluminum (12.5 ml, 30.9 mmol). The reaction mixture was gradually warmed to room temperature and then quenched with saturated NH_4Cl (30 ml). The aqueous layer was extracted with EtOAc. The combined organic layer was dried and evaporated. The residue was purified through column chromatography (Silica gel 60-120 mesh; 7% EtOAc: Hexane) to give **6** as viscous liquid, which slowly solidifies. mp 81-82°C; Yield: 3.11 g, 90%. IR : 3613, 3072, 3030, 1605, 1658 cm^{-1}. $[\alpha]_D^{25}$: + 63.0 (*c* 1, $CHCl_3$).^{1}H-NMR (300 MHz, $CDCl_3$): δ 128 (d, *J* = 7.15, 3 H), 1.85 (br s, 1 H), 2.21 (br s, 1 H), 2.70 (m, 1 H), 3.95 (dd, *J* = 6.6, 5.3, 1 H), 4.5 (d, *J* = 5.3,1 H), 6.8-7.3 (m, 14 H). ^{13} C-NMR (75 MHz, $CDCl_3$): δ 16.5, 41.3, 75.2, 78.6, 116.7, 118.5, 118.9, 122.6, 123.2, 127.6, 128.3, 128.9, 129.8, 140.6, 146.5, 157.8, 157.8. EI-MS: 334, 227, 197, 108, 77. **HRMS** Calculated 334.15689 Found 334.15678.

(*S*)-(+)-Fenoprofen. To a vigorously stirred suspension of silica gel supported $NaIO_4$ reagent[15] (10 g) in DCM (5 ml) was added a solution of **6** (3.1 g, 9.2 mmol) in DCM (25 ml) at room temperature and stirred for 1 h. The mixture was filtered through sintered funnel and washed with chloroform. The organic layer was evaporated. The crude product was subjected to further oxidation process. Sodium chlorite dissolved in 20% aqueous sodium hydrogendiphosohate was added to crude product dissolved in 20 ml *tert*- butanol at 23°C. The reaction mixture was stirred for 1h at the same temperature. The reaction mixture was extracted with EtOAc and the organic layer was washed with 8% aq.NaH_2PO_4, dried and evaporated. The residue was purified through column chromatography (silica gel 60–120 Mesh; Hexane : EtOAc 6/4) to obtain acid **7** as a viscous oil.

Yield: 1.7 g, 76%. IR (KBr): 2700-3100, 1720 cm^{-1}. $[\alpha]_D^{25}$: [lit.[13] + 45.7 (*c* 1, $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.36 (d, *J* = 7.0, 3 H), 3.5 (q, 1 H), 6.79-7.31 (m, 9 H), 8.40 (br s, 1 H). ^{13} C-NMR (75 MHz, $CDCl_3$): δ 18.2, 45.75, 117.6, 118.9, 119.0, 122.6, 123.4, 129.7, 142.3, 157.6, 157.8, 180.8. EI-MS: 242.

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References

1. Sonawane, H. R.; Bellur, S. N.; Ahuja, A. R.; Kulkarni, D. G. *Tetrahedron: Asymmetry* **1992**, *3*, 163.
2. Hutt, A. J.; Caldwell. *J. Clin. Pharmacology* **1984**, *9*, 371.
3. (a) Chang, C. S.; Tsai, S.W.; Lin, L. N. *Tetrahedron: Asymmetry* **1998**, *9*, 2799. (b) Charushin, V. N.; Krasnov, V. P.; Levit, G. L.; Korolyova, M. A.; Chupakin, O. N.; Kim, M. H.; Lee, H. S.; Park, Y. J. *Tetrahedron: Asymmetry* **1999**, *10*, 2691.
4. Chen, C. C; Tsai, S.W.; Villeneuve, P. *J. Mol Cat B: Enzy,* In Press, Corrected Proof,Available online 17 May 2005.
5. Ishibashi, H.; Maeki, M.; Yagi, J.; Ohba, M.; Kanai, T. *Tetrahedron* **1999**, *55*, 6075.
6. Carde, L.; Davies, H.; Geller, T.P.; Roberts, S. M. *Tetrahedron: Asymmetry* **1999**, *40*, 5421.
7. (a) Noyori, R. *Asymmetric Catalysis In Organic Synthesis*; John Wiley: NewYork, 1994. (b) Ojima, I. *Catalytic Asymmetric Synthesis*, 2nd Edn., Wiley-VCH, Inc: New York, 2000. **(**c) Morrison, J. D. *Asymmetric Synthesis*, Vol 5; *Chiral Catalysis*; Academic Press: New York. (d) Morrison, J. D.; Mosher, S. H. *Asymmetric Organic Reaction;* Prentice-Hall: Englewood Cliff, New Jersey, 1972. (e). Lauret, C. *Tetrahedron: Asymmetry* **2001**, *12*, 2329. (b). Roberts, S.; Skidmore, J. *Chem. Br*. **2000**, 31 (f). Porter, M. J.; Skidmore, J. *Chem. Commun*. **2000**, 1215.
8. (a) Kumaraswamy, G.; Sastry, M. N. V.; Jena, N. *Tetrahedron* **2001**, *42*, 8515. (b) Kumaraswamy, G.; Sastry, M. N. V.; Jena, N.; Ravikumar, K.; Vairamani, M. *Tetrahedron: Asymmetry* **2003**, *14*, 3797.
9. Solvent and temperature has no substantial effect on the epoxidation reaction.
10. While isolating product **4**, the ligand (*S*)-(+)- 6,6'Diphenyl BINOL **1e** was also eluted through column chromatography and optical purity was found to be 99%.
11. Several epoxides were prepared under optimized conditions and the enantioselectivity obtained were ranging from 68-89% with quantitative yields.
12. (a) Chen, R.; Qian, C.; de Vries, J. *Tetrahedron Lett.* **2001**, *42*, 6819. (b) Chen, R.; Qian, C.; de vries, J. *Tetrahedron Lett.* **2001**, *57*, 9837.
13. Marshall, W. J.; Eli Lilly and Company, *Fr. Demande* 2 015 728; 1970. *Chem. Abstr.* **1971**, 75, 48707m.
14. Reetz, M. T.; Maier, W. F. *Angew. Chem., Int. Ed.* **1978**, *17*, 48.
15. Zhong, Y. L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622.