Pergamon

Tetrahedron Letters 43 (2002) 3601–3604

TETRAHEDRON LETTERS

Synthesis and application in asymmetric copper(I)-catalyzed allylic oxidation of a new chiral 1,10-phenanthroline derived from pinene

Giorgio Chelucci,[a,*] Giovanni Loriga,[b] Gabriele Murineddu[b] and Gerard A. Pinna[b]

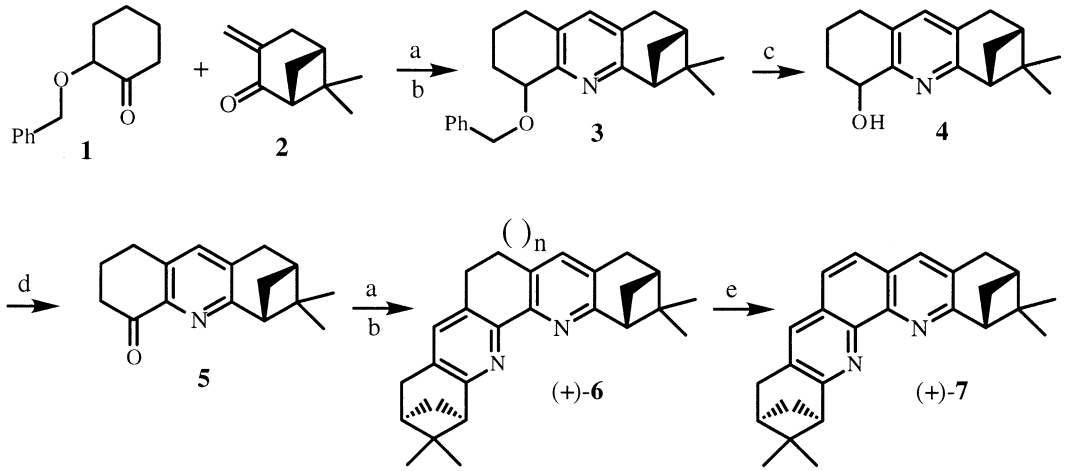
[a]*Dipartimento di Chimica, Università di Sassari, via Vienna 2, I-07100 Sassari, Italy*
[b]*Dipartimento Farmaco Chimico Tossicologico, Università di Sassari, Via Muroni 23, I-07100 Sassari, Italy*

Received 11 October 2001; accepted 14 March 2002

Abstract—A convenient and rapid method for the preparation of chiral C_2-symmetric 1,10-phenanthrolines is reported. As an example of this procedure the synthesis of new 1,10-phenanthroline (+)-**7** and its 5,6-dihydro derivative (+)-**6** from (−)-β-pinene is described. These ligands have been assessed in asymmetric copper(I)-catalyzed allylic oxidation of cycloalkenes affording enantioselectivities up to 71%. © 2002 Published by Elsevier Science Ltd.

Enantioselective reactions based on chiral nitrogen ligands are currently an actively pursued research area and a number of bidentate-nitrogen (N–N) ligands with sp^2-nitrogen donors have been demonstrated to be useful auxiliaries for metal-promoted asymmetric reactions reaching high levels of stereocontrol.[1]

In this contest, there has been considerable work involving the synthesis and application in asymmetric catalysis of 2,2′-bipyridines (bpys) with both C_1-[2] and C_2-symmetry.[3] By contrast, the use of chiral 1,10-phenanthrolines[4] (phens) has been limited to C_1-symmetric derivatives owing to the difficulties associated with the preparation of the C_2-symmetric controupart.[4h,j,k] In fact only one example of this kind of phens has been reported[4h] and used in asymmetric catalysis.[2a]



Scheme 1. (a) LDA, THF, −78°C, 2 h; then **2** from −78°C to slowly rt; (b) AcOH, $AcONH_4$, THF, reflux, 2 h; (c) 10% Pd/C, MeOH, 3 atm; (d) Swern oxidation; (e) 10% Pd/C, decaline, reflux, 3 h.

Keywords: 1,10-phenanthrolines; copper complex; allylic oxidation; enantioselectivity.
* Corresponding author. Tel.: +39-79-229539; fax: +39-79-229559; e-mail: chelucci@ssmain.uniss.it

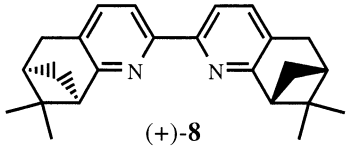
0040-4039/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4039(02)00549-X

Herein, we report a new approach to the synthesis of chiral C_2-symmetric phens describing the preparation of the phen (+)-**7** and of its 5,6-dihydro derivative **6** in which the chiral auxiliary, (−)-β-pinene, is present in the form of a cycloalkeno-condensed substituent in the 2,3- and 8,9-positions of the heterocycle.

The synthesis of phen (+)-**7** begin with racemic 2-benzyloxycyclohexanone **1**[5] (Scheme 1) whose lithium enolate, generated by treatment with LDA (THF, −78°C, 2 h), was treated with (1*R*,5*R*)-3-methylenenopinone (**2**), in turn obtained from (−)-β-pinene,[6] to give by conjugate addition an unisolated 1,5-dicarbonyl intermediate. This intermediate underwent azaanellation with concomitant aromatization ($AcONH_4$, AcOH, reflux, 2 h) to afford the pyridine **3** (23% overall yield). Catalytic hydrogenolysis of this benzyl derivative (Pd/C at 3 atm) gave the carbinol **4** (92%) which was oxidized under Swern conditions to ketone **5** (93%). Starting from this key intermediate, the 5,6-dihydrophen (+)-**6**[7] was prepared by building up the second pyridine ring in a similar manner to that used to prepare **3** from **1** (35% overall yield). Dehydrogenation by using a catalytic amount of palladium on charcoal in refluxing decaline completes the synthesis of (+)-**7**[7] (93%).

Recently, Kocovsky et al. have reported the use of the bipyridine (bpy) (+)-**8** in the asymmetric copper(I)-catalyzed allylic oxidation of cycloalkenes obtaining enantioselectivities up to 62% ee in the case of cycloheptene (75% ee at 0°C).[3a,b] The structure of this bpy is closely related to those of dihydrophen **6** and phen **7**, but a distinct catalytic activity for each of these ligands could be expected as they differ in their coordinating properties. In fact, the five-membered chelate ring resulting from the coordination to the metal of phen **7** is most probably locked in a single conformation, whereas a certain degree of conformational mobility is allowed to the bpy **8** on account of the inherently high flexibility of its backbone. An intermediate situation could be possible to find in the dihydrophen **6** in which the 3,3′-bridge can control the relative orientation of the two pyridine rings and thus influence the shape of the chelating bite-angle.

On the basis of these considerations, it appeared interesting to exploit **6** and **7** as catalysts for the asymmetric copper(I)-catalyzed allylic oxidation of cycloalkenes.[8]

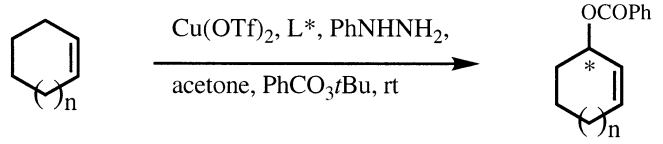


(+)-**8**

The reaction conditions selected to carry out the catalytic oxidation of cycloalkenes were those used by Kocovsky for bpy ligands.[3a,b] The protocol entails the reaction of the ligand with $Cu(OTf)_2$ to give a Cu(II) complex, which is then reduced in situ with phenylhydrazine to the corresponding Cu(I) species.[9] The oxidation reaction is then carried out with *tert*-butyl peroxybenzoate as the oxidant in the presence of the catalyst (1.0 mol%) and of the cycloalkene.[10] The results of the catalytic reactions are reported in Table 1.

The catalytic activity showed by ligands **6** and **7** was greatly dependent on the ring size of the cycloalkene. Thus, the oxidations of cyclopentene, cyclohexene and cycloheptene were complete within <30 min at room temperature giving the corresponding benzoate esters in good yields. It should be noted that the reaction time

Table 1. Asymmetric allylic oxidation of cycloalkanes catalyzed by Cu(I)–L* complexes[a]



9a, n= 0
9b, n= 1
9c, n= 2
9d, n= 3

(S)-(-)-**10a**, n= 0
(S)-(-)-**10b**, n= 1
(S)-(-)-**10c**, n= 2
(S)-(-)-**10d**, n= 3

Entry	Olefin	Ligand	Time (h)	Yield (%)[b]	Ee (%)[c]
1	Cyclopentene	(+)-**6**	0.5	78	47
2	Cyclopentene	(+)-**7**	0.5	86	57
3	Cyclohexene	(+)-**6**	0.5	82	50
4	Cyclohexene	(+)-**7**	0.5	85	53
5	Cycloheptene	(+)-**6**	0.5	81	63
6	Cycloheptene	(+)-**7**	0.5	91	71
7	Cyclooctene	(+)-**6**	168	–	–
8	Cyclooctene	(+)-**7**	168	–	–

[a] The reaction were carried out at room temperature in Me_2CO in the presence of the catalyst (1 mol%), generated in situ by reduction of $Cu(OTf)_2$ with $PhNHNH_2$.[10]
[b] Isolated yields.
[c] Determined by chiral HPLC.[10] The assignment of the absolute configuration is based on the sign of the optical rotation: Ref. 12.

recorded with these alkenes was significantly shorter than most of the catalysts reported so far.[9,11] On the other hand, cyclooctene was substantially unreactive, in fact only a trace of the reaction product was detected after a week.

The stereoselectivity was also dependent on the structure of the cycloalkene. Thus, the enantiomeric excess obtained in the oxidation of cyclopentene and cyclohexene was modest (47–57% ee), while that afforded by cycloheptene was moderately high (63–71% ee).

A comparison among the data obtained with ligands **6**–**8** appear to indicate that the increase of the stiffness of the structure of the ligand passing from the bpy **8** to the phen **7** has a beneficial effect on the enantioselectivity of the reaction. This fact is particularly evident employing cycloheptene as the alkene. In this case the enantiomeric excess of 62% obtained with the bpy **8** was substantially lower than that found with the phen **7** (71% ee).[3a,b]

In summary, we have described a general procedure for the preparation of C_2-symmetric phens preparing the new dyhydrophen (+)-**6** and phen (+)-**7** from (−)-β-pinene. The preliminary results obtained with the [Cu(I)-**7**] complex indicate that phens are good catalysts in asymmetric-catalyzed allylic oxidation of cycloalkenes. Further studies aimed at the synthesis of other C_2-symmetric phens with the hope to obtain a very effective enantioselective catalytic system are in progress.

Acknowledgements

Thanks are due to Mr. Mauro Mucedda for experimental assistance. Financial support by M.U.R.S.T. and by Regione Autonoma Sardegna is gratefully acknowledged.

References

1. Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159.
2. (a) Chelucci, G.; Gladiali, S.; Sanna, M. G.; Brunner, H. *Tetrahedron: Asymmetry* **2000**, *11*, 3419; (b) Chelucci, G.; Gladiali, S.; Saba, A.; Sanna, G.; Soccolini, F. *Tetrahedron: Asymmetry* **2000**, *11*, 3427; (c) Chelucci, G.; Pinna, G. A.; Saba, A. *Tetrahedron: Asymmetry* **1998**, *9*, 531; (d) Collomb, P.; von Zelewsky, A. *Tetrahedron: Asymmetry* **1998**, *9*, 3911; (e) Duboc-Toia, C.; Ménage, S.; Lambeaux, C.; Fontecave, M. *Tetrahedron Lett.* **1997**, *38*, 3727; (f) Chelucci, G.; Cabras, M. A.; Botteghi, C.; Basoli, C.; Marchetti, M. *Tetrahedron: Asymmetry* **1996**, *7*, 885; (g) Chen, C.; Tagami, K.; Kishi, Y. *J. Org. Chem.* **1995**, *60*, 5386.
3. (a) Malkov, A. V.; Baxandale, I. R.; Bella, M.; Langer, V.; Fawcett, J.; Russell, D. R.; Mansfield, D. J.; Valko, M.; Kocovsky, P. *Organometallics* **2001**, *20*, 673; (b) Malkov, A. V.; Bella, M.; Langer, V.; Kocovsky, P. *Org. Lett.* **2000**, *2*, 3047; (c) Wong, H. L.; Tian, Y.; Chan, K. S. *Tetrahedron Lett.* **2000**, *41*, 7723; (d) Rios, R.; Liang, J.; Lo, M. M.-C.; Fu, G. C. *Chem. Commun.* **2000**, 377; (e) Chelucci, G.; Culeddu, N.; Saba, A.; Valenti, R. *Tetrahedron: Asymmetry* **1999**, *10*, 3537; (f) Fletcher, N. C.; Keene, F. R.; Ziegler, M.; Stoeckli-Evans, H.; Viebrock, H.; von Zelewsky, A. *Helv. Chim. Acta* **1996**, *79*, 119; (g) Ito, K.; Yoshitake, M.; Katsuki, T. *Tetrahedron* **1996**, 3905; (h) Ito, K.; Katsuki, T. *Chem. Lett.* **1994**, 1857; (i) Chelucci, G.; Falorni, M.; Giacomelli, G. *Tetrahedron* **1992**, *48*, 3653; (j) Ito, K.; Tabuchi, S.; Katsuki, T. *Synlett* **1992**, 575; (k) Ito, K.; Tabuchi, S.; Katsuki, T. *Tetrahedron Lett.* **1992**, 575; (l) Bolm, C.; Zehnder, M.; Bur, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 205.
4. (a) Gladiali, S.; Chelucci, G.; Madadu, M. T.; Gastaut, M. G.; Thummel, R. P. *J. Org. Chem.* **2001**, *66*, 400; (b) Chelucci, G.; Pinna, G. A.; Saba, A.; Sanna, G. *J. Mol. Catal. A* **2000**, *159*, 423; (c) Chelucci, G.; Saba, A.; Sanna, G.; Soccolini, F. *Tetrahedron: Asymmetry* **2000**, *11*, 3427; (d) Chelucci, G.; Thummel, R. P. *Synth. Commun.* **1999**, *29*, 1665; (e) O'Neill, D.; Helquist, P. *Org. Lett.* **1999**, *1*, 1659; (f) Riesgo, E. C.; Credi, A.; De Cola, L.; Thummel, R. P. *Inorg. Chem.* **1998**, *37*, 2145; (g) Chelucci, G.; Saba, A. *Tetrahedron: Asymmetry* **1998**, *9*, 2575; (h) Peña-Cabrera, E.; Norrby, P.-A.; Sjgören, M.; Vitagliano, A.; De Felice, V.; Oslob, J.; Ishii, S.; O'Neill, D.; Åkermark, B.; Helquist, P. *J. Am. Chem. Soc.* **1996**, *118*, 4299; (i) Gladiali, S.; Pinna, L.; Delogu, G.; De Martin, S.; Zassinovich, G.; Mestroni, G. *Tetrahedron: Asymmetry* **1990**, *1*, 635; (j) Kandzia, C.; Steckhan, E.; Knoch, F. *Tetrahedron: Asymmetry* **1993**, *4*, 39; (k) Chelucci, G.; Falorni, M.; Giacomelli, G. *Tetrahedron* **1992**, *48*, 3653; (l) Gladiali, S.; Chelucci, G.; Soccolini, F.; Delogu, G.; Chessa, G. *J. Organomet. Chem.* **1989**, *370*, 285; (m) Gladiali, S.; Chelucci, G.; Chessa, G.; Delogu, G.; Soccolini, F. *J. Organomet. Chem. C* **1987**, *327*, 15.
5. Wu, Y.-J.; Ding, W.-L.; Du, C.-X. *Tetrahedron: Asymmetry* **1998**, *9*, 4035.
6. Gianini, M.; Von Zelewsky, A. *Synthesis* **1996**, 702.
7. All compounds showed satisfactory spectroscopic and analytical data. Compound (+)-**6**: mp 116–118°C; $[\alpha]_D^{20}$ +111.5 (*c* 1.1 $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.26 (s, 2H), 3.29 (t, 2H, $J=5.7$ Hz); 3.00–279 (m, 8H); 2.69 (m, 2H); 2.29 (m, 2H); 1.40 (s, 6H); 1.30 (d, 2H, $J=9.6$ Hz); 0.69 (s, 6H). Compound (+)-**7**: mp 104–106°C; $[\alpha]_D^{20}$ +68.2 (*c* 1.2 $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.91 (s, 2H); 7.63 (s, 2H), 3.58 (t, 2H, $J=5.7$ Hz); 3.17 (m, 4H); 2.80 (m, 2H); 2.28 (m, 2H); 1.46 (s, 6H); 1.42 (d, 2H, $J=9.9$ Hz); 0.71 (s, 6H).
8. (a) Katsuki, T. In Jacobsen, E. N.; Pfaltz, A., Yamamoto, H., Eds.; *Asymmetric C–H Oxidation in Comprehensive Asymmetric Catalysis*; Springer: Berlin, 1999; Vol. 2, Chapter 21, pp. 791–802; (b) Kohmura, Y.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 3941 and references cited therein.
9. (a) Sekar, G.; DattaGupta, A.; Singh, V. K. *J. Org. Chem.* **1998**, *63*, 2961; (b) Koswer, E. M. *Acc. Chem. Res.* **1971**, *4*, 193.
10. Typical procedure for allylic oxidation: a solution of the ligand (0.06 mmol) and $Cu(OTf)_2$ (18 mg, 0.05 mmol) in acetone (4 ml) was stirred under a nitrogen atmosphere at 20°C for 1 h. Phenylhydrazine (5.9 ml, 0.06 mmol) was

then added. After 10 min, the cycloalkene was added, followed by the dropwise addition of *tert*-butyl peroxybenzoate (0.2 ml, 1.0 mmol). The progress of reaction was monitored by TLC (hexane/ethyl acetate = 9/1). Disappearance of the peroxyester indicated the completion of the reaction. The solvent was removed under vacuum and the residue taken up with CH_2Cl_2 (15 ml). The organic solution was washed successively with a saturated aqueous $NaHCO_3$ solution, brine and finally with water. The organic solution was dried over anhydrous Na_2SO_4 and the solvent was evaporated. The residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate = 20/1). The enantiomeric excess was determined by HPLC: (a) 2-cyclopenten-1-benzoate: (Chiralcel OD-H; hexane/isopropanol = 99.8/0.2, flow 1.0 ml/min, temperature 25°C); retention time: 18.6 min [(*R*)-2-cyclopentenyl-1-benzoate] and 18.1 min [(*S*)-2-cyclopentenyl-1-benzoate]. (b) 2-Cyclohexenyl-1-benzoate (Chiralcel OJ; hexane, flow 0.3 ml/min, temperature 25°C); retention time: 32.6 min [(*R*)-2-cyclohexenyl-1-benzoate] and 35.3 min [(*S*)-2-cyclohexenyl-1-benzoate]. (c) 2-Cycloheptenyl-1-benzoate (Chiralcel OJ; hexane/isopropanol = 99.7/0.3, flow 0.5 ml/min, temperature 25°C); retention time: 17.5 min [(*R*)-2-cycloheptenyl-1-benzoate] and 18.1 min [(*S*)-2-cycloheptenyl-1-benzoate].

11. (a) Andrus, M. B.; Asgari, D. *Tetrahedron* **2000**, *56*, 5775; (b) Kohmura, Y.; Katsuki, T. *Tetrahedron Lett*. **2000**, *41*, 3941; (c) Gokhale, A. S.; Minidis, A. B. E.; Phaltz, A. *Tetrahedron Lett*. **1995**, 361831.
12. Kawasaki, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 6337.