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Chiral phenanthrolines as ligands for Cu(I)-catalyzed asymmetric allylic oxidation

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Abstract

A number of chiral 1,10-phenanthrolines (phens) have been assessed in asymmetric Cu(I)-catalyzed allylic oxidation of cyclohexene. Very effective copper-phen catalysts are obtained only when these ligands bear at least a substituent close to the reactive site of the catalyst. Enantioselectivity up to 36% was obtained.

Keywords: Chiral 1,10-phenanthrolines; Copper complex; Allylic oxidation reaction; Enantioselectivity

1. Introduction

The allylic oxidation of olefins with peresters in the presence of copper salts to give allylic esters (known as the Kharasch–Sosnovsky reaction) [1,2] can represent an allylic alcohol synthesis since the allylic esters can easily be converted into the corresponding alcohols by saponification or reduction methods. Copper complexes of nitrogen-containing chiral ligands are becoming the catalysts of choice for the enantioselective version of this reaction [3].

However, though with nitrogen ligands moderately good enantioselectivities have been obtained, especially in the case of cyclic olefins, a practical catalytic system of high efficiency is still to be developed. In fact, most of catalysts reported to date often require several days to allowed the completion of the reaction [4–7].

Kocovsky et al. have recently reported that Cu(I)-complexes of the chiral C_2-symmetric 2,2′-bipyridines (bpys) **1**–**3** (Scheme 1) are very effective catalysts in this process [8,9]. Though the obtained enantioselectivity did not exceed 75% ee, these catalysts needed to convert the starting material a very short reaction time ($\leq$30 min at room temperature) which is significantly shorter than most of catalysts reported so far [4–7]. The results obtained with ligand **1** have been attributed to the stabilization of the copper geometry halfway between square planar (favoured by Cu(II)) and tetrahedral (favoured by Cu(I)).

In our research efforts aimed at the application of chiral pyridine derivatives to asymmetric catalysis, we have successful applied both bpys and 1,10-phenanthrolines (phens) to several catalytic processes [10–12]. These two kinds of ligands have in several cases showed different catalytic activity and stereoselectivity which have been ascribed to the different conformational mobility induced in the catalyst by the heterocyclic template [13–15]. The five-membered chelate ring resulting from the coordination to the

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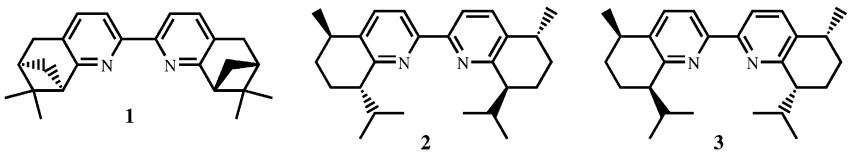


Scheme 1.

metal of these ligands is most probably locked in a single conformation in the case of phen derivatives, whereas a certain degree of conformational freedom is allowed to bpy ligands in account of the inherently flexibility of this backbone.

On the basis of the above considerations, we became interested to determine the potentiality of phen based ligands in metal-catalyzed allylic oxidation of olefins.

In this paper we report the results obtained with a number of chiral phens in asymmetric copper Cu(I)-catalyzed allylic oxidation of cyclohexene.

2. Results and discussion

The reaction conditions selected to carry out the catalytic oxidation are those used by Kocovsky for bpy ligands [8,9]. 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. The oxidation reaction is then carried out with *tert*-butyl-peroxybenzoate in the presence of the catalyst (1.0 mol%) and of cyclohexene. This alkene is used as a representative substrate to compare the catalytic activity and stereodifferentiating ability of the examined ligands (Scheme 2).

Starting our investigation, we assessed the unsubstituted phens **6** (Scheme 3) to probe the catalytic activity of Cu(I)–phen complexes. This phen gave a copper-species devoid of any catalytic activity (no reaction product was detected after one week). This surprising result prompted us to examine the related bpys **7** (Scheme 3). Also in this case no reaction occurred.

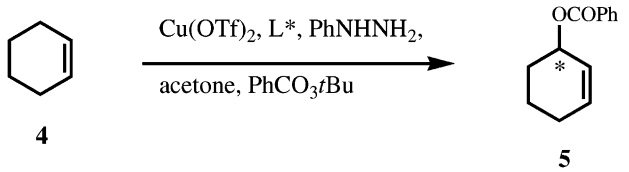
These results suggested that the substituents on the two pyridine rings of the C_2-symmetric bpys **1**–**3** could be responsible for their particular reactivity. As an attempt to verify this hypothesis, we tested the bpys **8** and **9**, both derived from pinene (Scheme 3). The former is the C_1-symmetric correspondant of **1**, while the latter is its regioisomer bearing the same cycloalkeno group fused in the 4,5-positions of the bpy framework.

While ligand **8** provided an effective catalyst, consuming the *tert*-butyl-peroxybenzoate in 30 min, its isomer **9** was unreactive.

These results indicate that bpy ligands dot not require the presence of C_2-symmetry to afford catalytically active copper–bpy complexes but, on the other hand, point out that an essential feature for this kind of ligands is to have a substituent as close as possible to the reactive side of the catalyst, that is to say to the heterocyclic nitrogen.

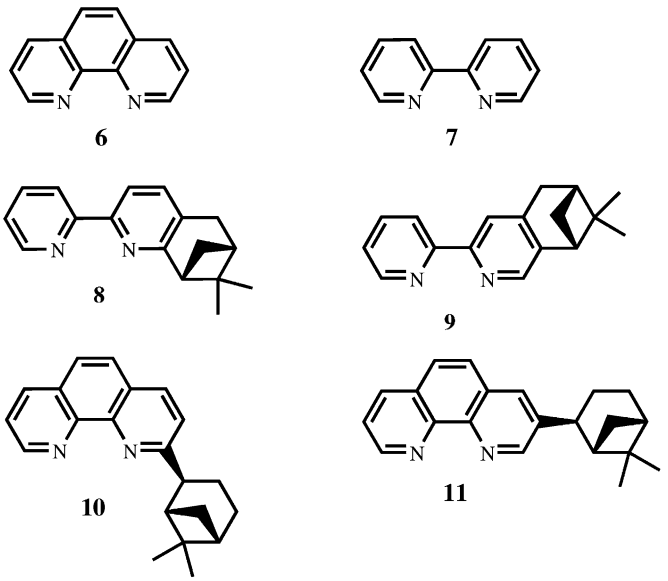
At this point, we again devoted our attention to phen ligands. In order to verify that phens follow the trend observed with bpys, we checked the ligands **10** and **11** bearing the 2,2-dimethylnorpinan-2-yl unit as the common chiral pendant at the 2- and 3-positions, respectively, of the heterocycle (Scheme 3). As expected, whereas the 3-substituted phen **11** was not able to provide an effective copper-complex (no reaction product was detected after a week), the copper-species derived from the corresponding 2-substituted isomer converted completely the starting material in less than 24 h.

Taking into account these results, for a better understanding of the scope of phen ligands in the



4 **5**

Scheme 2.



Scheme 3.

copper-catalyzed allylic oxidation, we decided to further pursued our study of this reaction including also the chiral phens **12**–**17**. All these ligands share a chiral framework, derived from natural occurring compounds, fused in the 2,3-positions of the heterocycle. They are the two phens **12** and **13** prepared from (+)-nopinone and (+)-camphor, respectively; the four phens **14a**–**d** derived from (−)-pinocarvone and the three phens **15**–**17** obtained from steroids. The structures and configurations of these ligands, prepared according to reported procedures, are depicted in Scheme 4.

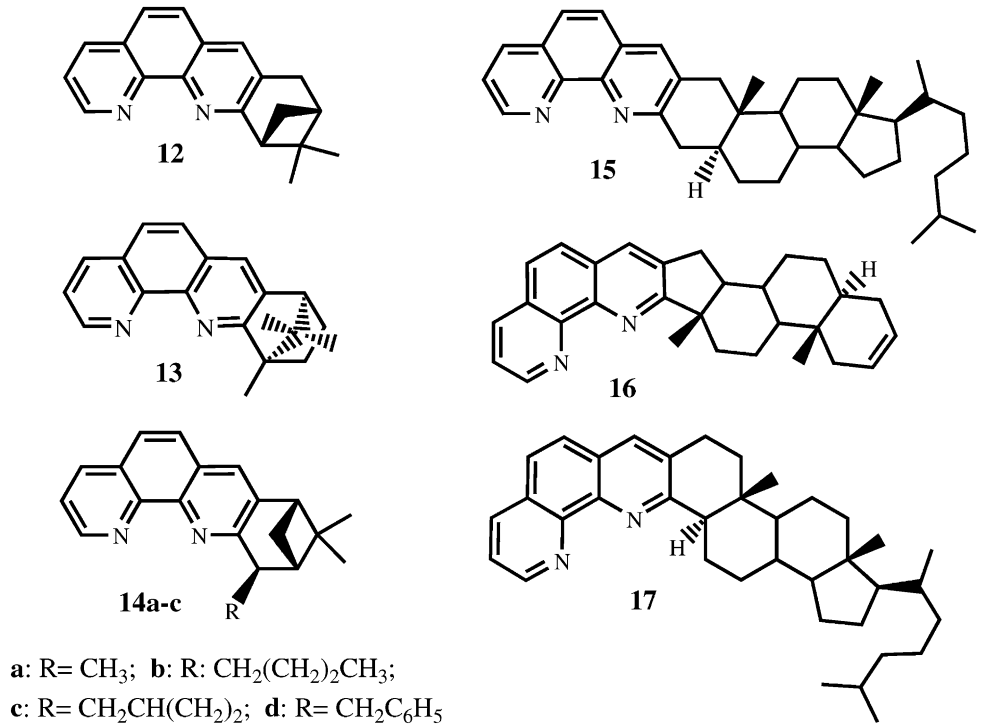
All examined phens displayed good catalytic activity affording the cyclohexenyl benzoate (**5**) in satisfactory yields. The reaction was in any case complete in less than 60 min and a very short reaction time (15 min) was observed with ligands **15** and **16**.

The stereoselectivity was depending from the structure of the ligand. The reaction with both phen **12** and bpy **8**, incorporating the same chirogenic element, gave negligible enantioselectivities (2 and 3% ee, respectively). On the other hand, a low but definite enantiomeric excess was obtained with the phen **13** (8% ee).

In the series of ligands **14a**–**c**, a modest enantiomeric excess was obtained with the phens **14a**,**b** (19–21% ee) bearing small substituents (methyl and butyl) onto the carbon adjacent to the heterocyclic ring, whereas more bulky substituents (*i*-butyl, benzyl) reduced the stereoselectivity significantly (8–10% ee). These results appear to indicate that the stereochemistry of the reaction is basically dictated by the stereocentre at the C11 and that the presence of a demanding substituent onto this carbon creates a mismatching stereotopic relationship with the dimethyl groups on the bridge.

Among ligands **15**–**17**, incorporating a steroid moiety, the best performing ligand was the phen **16** which gave an enantioselectivity of 36% ee. This is the best stereochemical outcome afforded by the C_1-symmetric phens examined in this study (Table 1).

In conclusion, this preliminary investigation points out that bpys and phens can provide effective copper-catalysts only when these ligands possess at least a substituent close to the heterocyclic nitrogen. Moreover, the results obtained with Cu(I)–phen complexes show that these are good catalysts in asymmetric catalyzed allylic oxidation of cyclohexene providing a reaction rate which is the shortest, to date, for this kind of transformation. This study demonstrates that the presence of C_2-symmetry for this kind of ligands is not an essential feature to obtain catalytically active copper complexes and on the other hand suggests that the presence of this topological property is necessary



Scheme 4.

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

Entry	Ligand	Reaction time	Yield (%)[b]	ee (%)[c]	Configuration[d]
1	**6**	7 days	0	–	–
2	**7**	7 days	0	–	–
3	**8**	30 min	79	3	*S*
4	**9**	7 days	0	–	–
5	**10**	24 h	75	20	*R*
6	**11**	7 days	0	–	–
7	**12**	30 min	74	2	*S*
8	**13**	<60 min	85	8	*S*
9	**14a**	30 min	87	19	*S*
10	**14b**	30 min	84	21	*S*
11	**14c**	30 min	79	8	*S*
12	**14d**	30 min	88	10	*S*
13	**15**	15 min	77	8	*R*
14	**16**	15 min	87	36	*S*
15	**17**	30 min	82	21	*R*

[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 $Cu(OTf)_2$–L* complex with $PhNHNH_2$.
[b] Isolated yields.
[c] Determined by HPLC on a chiral column.
[d] The assignement of the absolute configuration is based on the sign of the optical rotation: [16].

to obtain an effective enantioselective catalytic system. Further studies aimed at the synthesis of C_2-symmetric phens are currently in progress in our laboratory.

3. Experimetal section

3.1. Materials

(6*R*,8*R*)-6,8-Methano-7,7-dimethyl-2-(pyridin-2-yl)-5,6,7,8-tetrahydroquinoline (**8**) [5], (6*R*,8*R*)-6,8-methano-7,7-dimethyl-2-(pyridin-2-yl)-5,6,7,8-tetrahydro isoquinoline (**9**) [17], 2-(6,6-dimethylnorpinan-2-yl)(1,10)phenanthroline (**10**) [18], 3-(6,6-dimethylnorpinan-2-yl)(1,10)phenanthroline (**11**) [19], (9*R*,11*R*)-9,11-methano-10,10-dimethyl-8,9,10,11-tehydrobenzo(b)(1,10)phenanthroline (**12**) [20], (8*R*,11*R*)-11,12,12-trimethyl-8,11-methano-8,9,10,11-tehydrobenzo(b)(1,10)phenanthroline (**13**) [21], (8*S*,10*S*,11*R*)-8,10-methano-9,9,11-trimethyl-8,9,10,11-tetrahydrobenzo(b)(1,10)phenanthroline (**14a**) and the corresponding (8*S*,10*S*,11*R*)-11-butyl- (**14b**), (8*S*,10*S*,11*R*)-11-(2-methylpropyl) (**14c**) and (8*S*,10*S*,11*R*)-11-benzyl derivatives (**14d**) [10], 5a-cholesta(2,3-b)(1,10)phenanthroline (**15**) [22], 5α-androstadieno(17,16-b)(1,10) phenanthroline (**16**) [22] and 5α-cholesta(4,3-b)(1,10) phenanthroline (**17**) [12] were prepared following literature procedures.

3.2. 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, cyclohexene (5 mmol) 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 = 20/1). 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 (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).

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