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Communication

Synthesis of new C_1-symmetric bis(oxazoline) ligands with a chelating sidearm for stereoselective Mukaiyama aldol condensations

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Abstract

Novel C_1-symmetric bis(oxazoline) ligands with a secondary binding sidearm were prepared in enantiomerically pure form in good yields, in only four steps starting from commercially available reagents. These new chiral ligands were tested in the enantioselective Mukaiyama aldol condensation between the trimethylsilyl keteneacetal of methyl isobutyrate and a non-chelating substrate such as benzaldehyde to afford the product in up to 55% ee.

Keywords: Chiral bis-oxazolines; Copper complexes; Enantioselective catalysis; Mukaiyama aldol condensation; Chelation

1. Introduction

The versatility of chiral bis(oxazolines) to act as ligands in a variety of catalytic enantioselective transformations is well recognised [1]. For example, copper (II) complexes of C_2-symmetric ligand type **1** were shown to be efficient catalysts for several stereoselective C–C bonds formation reactions [2] (see Scheme 1).

However, with these chiral catalytic systems very high enantioselectivities are obtained only by employing substrates which can participate in catalyst chelation. The strict requirement of using a bidentate substrate that contributes in determining a well-defined geometry of the catalyst/substrate complex represents an obvious limitation to the methodology's generality.

The idea to introduce an extra chelating element into the chiral ligand has been recently explored and has led to the development of tris(oxazoline) [3] ligand types **2** (see Scheme 1). The reasons beyond the preparation of this class of molecules were basically to build a deeper chiral concave pocket around the metal center and to synthesize a more stable catalytic system. Alternatively tridentate bis(oxazolinyl)-type ligands have been designed by introducing a donor atom into the link connecting two chiral oxazoline rings [4]. Among the different structures it is worth mentioning Kanemasa's ligand **3** [5], Zhang's bis(oxazolinyl-methyl)amine **4** [6] and specially the "pybox" ligands **5** first developed by Nishiyama [7] (Scheme 1).

However it must be noted that also these tridentate catalytic systems usually promote high enantioselective C–C bond formation reactions with bidentate chelating structures.

2. Results and discussion

In order to overcome this substrate limitation we decided to explore a different approach. The idea was to synthesize a Evan's bis(oxazoline) type **1** ligand but with a chelating sidearm, to afford a structure of type **6**; the new ligand should bind the copper (II) ion following the coordination behaviour of the C_2-symmetric analogs whose complexes geometry has been well studied [8] (see Scheme 2). The active catalytic species has now only one coordination site

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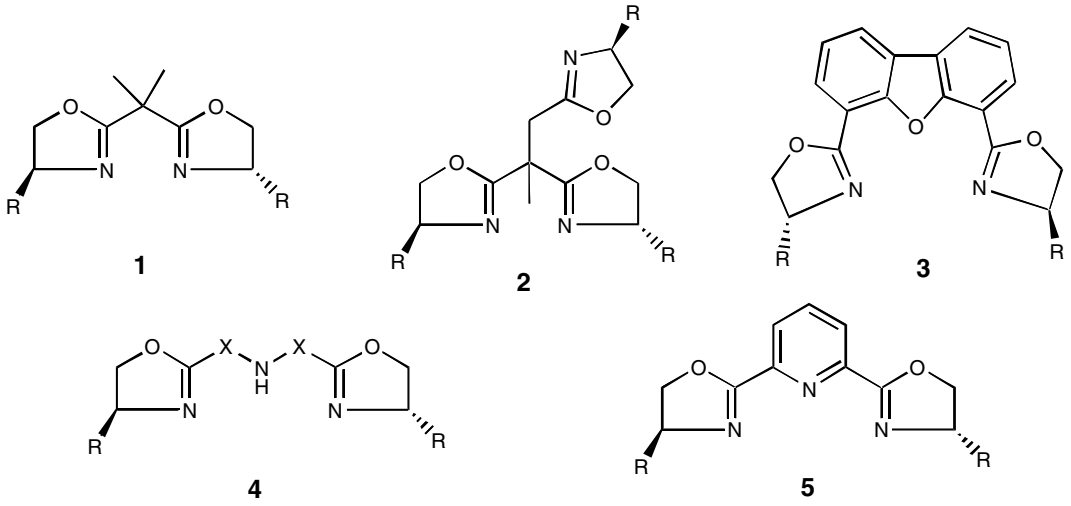


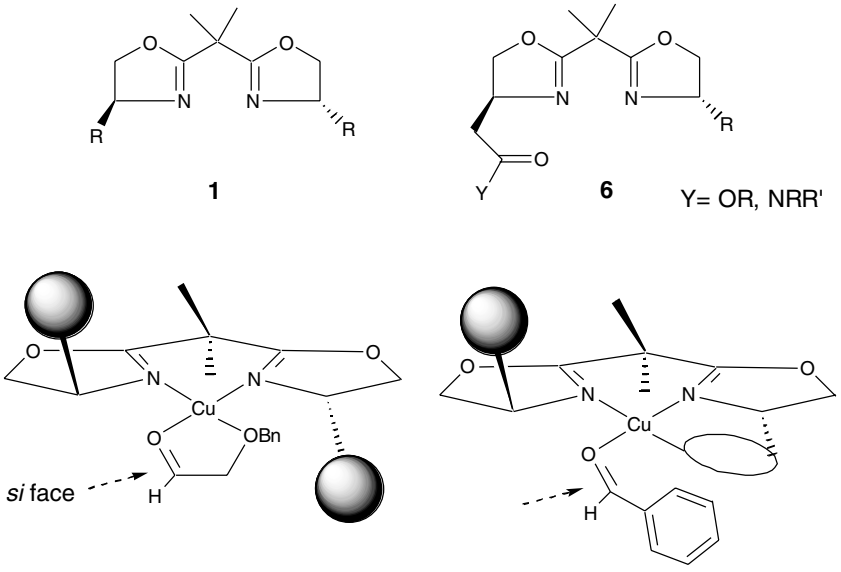
Scheme 1. Oxazoline-type ligands in asymmetric catalysis.

for the substrate that should be attacked by the reagent under the stereocontrol exerted by the substituents at the stereocentres of the oxazoline moieties [9].

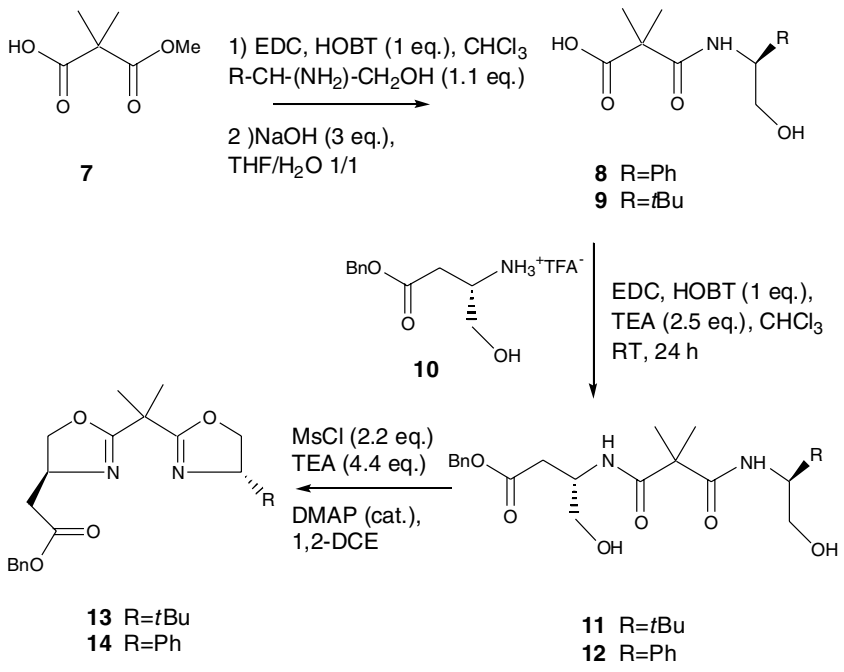
Here, we wish to report the synthesis of new C_1-symmetric bis(oxazoline) ligands with a secondary binding element to be employed in promoting reactions that do not require the use of bidentate substrates. Preliminary studies on the use of these novel chiral ligands in the Mukaiyama aldol condensation of trimethylsilyl keteneacetal of methyl isobutyrate with benzaldehyde will be also described.

The synthesis of the new ligands follows the classical route that involves the reaction of a dimethyl malonic acid derivative with amino-alcohols to give a bis-amide intermediate that is converted into bis-oxazoline (see Scheme 3). In our synthesis the first step is the EDC- promoted condensation of dimethyl malonic acid monomethylester **7** with (*S*)-phenyl glycinol or (*S*)-*t*-leucinol to afford the amide **8** or **9**, in 81% and 85% yield, respectively. In order to build the oxazoline ring bringing the chelating sidearm we decided to employ the amino alcohol **10**, easily prepared in only three steps from the commercially available 4-benzyl-(*S*)-aspartic acid [10]. After hydrolysis of esters **8** and **9**, the corresponding carboxylic acid amides were condensed to the amino-alcohol **10** to give the corresponding dissimetric bis amides **12** and **11** basically in quantitative yields, as pure compounds without the need of chromatographic purification [11].

Several methodologies were attempted for the closure of bis-amides to the corresponding bis(oxazolines) **13** and **14** [12]. Finally, best results were obtained by reacting **11** and **12** with methansulfonyl chloride and triethylamine to convert them in the corresponding mesylate derivatives which were treated in situ with triethylamine and a catalytic amount of DMAP to afford bis(oxazolines) **13** and



Scheme 2. Novel bis(oxazoline) with a chelating sidearm.



Scheme 3. Synthesis of new bis(oxazoline) ligands **13** and **14**.

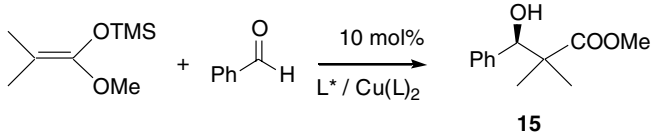
14 in 53% and 45% yields, respectively after chromatographic purification.

Following our interest in studying enantioselective reactions promoted by copper complexes [13] the new enantiomerically pure ligands were tested in the Cu(II) catalysed Mukaiyama aldol condensation [14].

The condensation of the trimethylsilyl keteneacetal of methyl isobutyrate with benzaldehyde was chosen as test reaction, in the presence of 10% of the catalyst [15] (Scheme 4 R = Ph). First, the catalytic ability of Cu(II) trifluoromethane sulfonate complexes was studied (Table 1). After 3 h complexation of $Cu(OTf)_2$ with the bis(oxazoline) ligand, benzaldehyde was added, followed after 15 min by the trimethylsilyl keteneacetal of methyl isobutyrate.

For sake of comparison the reaction was run also in the presence of Evans' bis(oxazoline) type **1** (Scheme 1, R = *t*-Bu) complexed to $Cu(OTf)_2$.

Unfortunately, the results were extremely disappointing. By running the reaction in different temperature conditions the product (*S*)-methyl 2,2-dimethyl-3-hydroxy-3-phenylpropanoate **15** was obtained in good yields but with very low enantioselectivities, comparable to those afforded by bis(oxazoline) **1**.



Scheme 4. Mukaiyama aldol condensation promoted by Cu(II) complexes.

Table 1
Mukaiyama aldol condensation promoted by $Cu(OTf)_2$ complexes

Entry	Ligand	Reaction cond.	Yield[a] (%)	ee (%)[b]
1	**1**	2h, −78 °C; 18 h, RT	43	19
2	**13**	2 h, −78 °C; 18 h, RT	83	11
3	**14**	2 h, −78 °C; 18 h, RT	73	5
4	**1**	20 h, −78 °C	68	24
5	**13**	20 h, −78 °C	58	17

[a] Isolated yields after flash chromatography.
[b] As determined by HPLC on a chiral stationary phase.

Even running the reaction at lower temperature did not produce any appreciable improvement as the enantioselectivity was not significantly increased [16]. It is interesting to observe that both new ligands **13** and **14** promoted the reaction at room temperature with better yields than ligand **1** (entries 1–3, Table 1), suggesting maybe an enhanced stabilization of the catalytically active complex at room temperature.

The catalytic behaviour of $Cu(SbF_6)_2$ as copper (II) source [17] was then investigated (Scheme 4, R = Ph, L = SbF_6).

At low temperature the new ligands **13** and **14** promoted the reaction once again in better yields than ligand **1** (entries 1 and 2 vs. entry 3). When the reaction was run for 2 h at −78 °C and allowed to rinse to room temperature for 18 h the enantioselectivity increased up to 41% ee, always maintaining a very good chemical efficiency (entries 4 and 5, Table 2).

Since the trend seemed to suggest better performances of the catalysts at room temperature the aldol condensation was run at 25 °C for 20 h; in these conditions the ligand

Table 2
Mukaiyama aldol condensation promoted by $Cu(SbF_6)_2$ complexes

Entry	Ligand	Reaction cond.	Yield[a] (%)	ee (%)[b]
1	**1**	20 h, −78 °C	63	5
2	**13**	20 h, −78 °C	64	7
3	**14**	20 h, −78 °C	81	15
4	**13**	2 h, −78 °C; 18 h, RT	85	21
5	**14**	2 h, −78 °C; 18 h, RT	87	41
6	**13**	20 h, RT	69	23
7	**14**	20 h, RT	71	55
8[c]	**14**	20 h, RT	72	53
9[d]	**14**	20 h, RT	75	55

[a] Isolated yields after flash chromatography.
[b] As determined by HPLC on a chiral stationary phase.
[c] 20% of catalyst was used.
[d] 50% of catalyst was used.

14 promoted the reaction in slightly lower yields but with enantioselectivity up to 55% ee (entry 7, Table 2) [18]. Increased catalyst loading did not allow to improve the enantioselectivity (entries 8–9). The reaction of a non-aromatic aldehyde was also performed; the silyl keteneacetal addition to hydrocinnamaldehyde (Scheme 4, R = $PhCH_2CH_2$) in the same conditions of entry 5 lead to the aldol product in similar yield but lower enantioselectivity (65% yield, 39% ee) [19].

It must be noted that the copper (II) counterion plays an important role; it has been already demonstrated that the stereochemical outcome may be heavily influenced by the presence or the absence of the counterion in the ligand/copper complex [20]. A different geometry of the two complexes **14**/$Cu(OTf)_2$ and **14**/$Cu(SbF_6)_2$ might be responsible for the different stereochemical efficiency [21].

3. Conclusions

In conclusion the synthesis of new enantiomerically pure C_1-symmetric bis(oxazolines) with a secondary binding element has been successfully developed [22]. The new chiral ligands should allow the promotion of stereoselective reactions with substrates that do not require the presence of a chelating element.

In these preliminary studies on the Mukaiyama aldol condensation of trimethylsilyl keteneacetal of methyl isobutyrate with benzaldehyde the product has been obtained in very good chemical yields and with an ee up to 55%. Although the level of enantioselectivity is quite modest, the new C_1-symmetric bis(oxazolines) have shown a certain ability in stereodirecting the aldol reaction and represent an interesting starting point for further developments in order to improve the stereoselectivity of such catalytic reactions.

4. Experimental

General: ^1H NMR spectra were recorded at 300 MHz in chloroform-*d* ($CDCl_3$) unless otherwise stated, and were referenced to tetramethylsilane (TMS) at 0.00 ppm. ^{13}C NMR spectra were recorded at 75 MHz and were referenced to 77.0 ppm in $CDCl_3$. Optical rotations were measured at the Na-D line in a 1 dm cell at 22 °C. IR spectra were recorded on thin film or as a solution in CH_2Cl_2.

Synthesis of bis(oxazoline) ***14***: To a stirred solution of bis-amide **12** (0.44 g, 1 mmol) and triethylamine (0.63 mL, 4.4 mmol) in 1,2-dichloroethane (5 cm^3) kept under nitrogen and cooled at 0 °C, mesyl chloride (0.18 mL, 2.2 mmol) was added dropwise. The mixture was stirred at RT for 2 h. A solution of triethylamine (0.63 mL, 4.4 mmol) and a catalytic amount of DMAP in 1,2-dichloroethane (2 mL) was added dropwise and the reaction mixture was allowed to stir at 50 °C for 40 h. The organic phase was concentrated under vacuum to give the crude product, that was purified by chromatography with a 6:4 CH_2Cl_2:AcOEt mixture as eluant. The product (0.18 g, 0.45 mmol, 45% yield) was a pale yellow thick oil that solidified on standing in the freezer. It had $[\alpha]D^{22}$ −27.4 (*c* 0.4 in CH_2Cl_2). Anal. Calc. for $C_{24}H_{26}N_2O_4$ requires: C, 70.92; H, 6.45; N, 6.89. Found: C, 71.05; H, 6.51; N, 6.95%. IR(DCM): *v* 1712, 1655, 1265 cm^{-1} ^1H NMR (300 MHz, $CDCl_3$): δ 7.30–7.20 (m, 10 H), 5.16 (m, 1H), 5.10 (s, 2H), 4.55 (t, $J = 6.5$ Hz, 1H), 4.45 (m, 2H), 4.15 (m, 2H), 2.92 (dd, $J = 3.5$ Hz, $J = 12.5$ Hz, 1H), 2.48 (dd, $J = 5.5$ Hz, $J = 12.5$ Hz, 1 H), 1.55 (s, 3H), 1.52 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 170.1, 169.8, 142.3, 140.0, 131.1, 130.0, 128.6, 128.0, 127.7, 127.5, 127.0, 126.5, 75.4, 73.0, 69.4, 66.5, 62.5, 40.1, 39.0, 24.4, 24.2.

Aldol condensation: To a stirred solution of Box **14** (0.020 g, 0.05 mmol) in dry CH_2Cl_2 (2.0 cm^3) $CuCl_2$ (0.007 g , 0.05 mmol) was added and the mixture stirred at 23 °C for 3 h. $Ag(SbF_6)$ (0.034 g, 0.1 mmol) was added and the mixture stirred at 23 °C for 12 h. To the complex thus obtained benzaldehyde (0.05 mL, 0.5 mmol) was added first and after 15 min the silyl keteneacetal (0.16 mL, 0.80 mmol) was added too. After the mixture was stirred for 20 h at 23 °C, the organic phase was concentrated under vacuum and the residue was purified by flash chromatography with a hexanes:AcOEt 8:2 mixture as eluant to afford the product (*S*)-**15** as a white solid; m.p. 70–71 °C (lit.: [19] 71–72 °C). The ee was established by HPLC analysis on a Chiralpak AD column, flow rate 0.8 cm^3/min, $\lambda = 210$ nm; hexane:ethanol 95:5; t_R: 14.3 min (minor) and 20.4 min (major). The product had ^1H NMR data identical to those reported [23].

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References

[1] A.K. Ghosh, P. Mathivanan, J. Cappiello, Tetrahedron: Asymmetry 9 (1998) 1–45.

[2] (a) D.A. Evans, T. Rovis, J.S. Johnson, Pure Appl. Chem 71 (1998) 1407–1421;
(b) K.A. Jorgensen, M. Johannsen, S. Yao, H. Audrian, J. Thorhauge, Acc. Chem. Res. 32 (1999) 605–619;
(c) D.A. Evans, J.S. Johnson, Acc. Chem. Res 33 (2000) 325–345;
(d) H.A. McManus, P.J. Guiry, Chem. Rev. 104 (2004) 4151.

[3] (a) J. Zhou, Y. Tang, J. Am Chem. Soc 124 (2002) 9030–9031;
(b) S. Bellemin-Laponnaz, L.H. Gade, Angew. Chem., Int. Ed. 41 (2002) 3473–3475.

[4] H.A. McManus, P.J. Guiry, J. Org. Chem 67 (2002) 8566–8573.

[5] V. Kanemasa, Y. Oderatoshi, S. Sakaguchi, H. Yamamoto, J. Tanaka, E. Wada, D.P. Curran, J. Am. Chem. Soc. 120 (1998) 3074–3083.

[6] Y. Jiang, Q. Jiang, X. Zhang, J. Am. Chem. Soc. 120 (1998) 3817–3818.

[7] (a) H. Nishiyama, Y. Itoh, H. Matsumoto, S.-B. Park, K. Itoh, J. Am. Chem. Soc. 116 (1994) 2223–2224;
(b) D.A. Evans, Z.K. Sweeney, T. Rovis, J.S. Tedrow, J. Am. Chem. Soc. 123 (2001) 12095–12096, and references cited.

[8] D.A. Evans, M.C. Kozlowski, J.A. Murry, C.S. Burgey, K.R. Campos, B.T. Connell, R. Staples, J. Am Chem. Soc. 121 (1999) 669–685;
D.A. Evans, J.A. Murry, M.C. Kozlowski, J. Am Chem. Soc. 118 (1996) 5814.

[9] For a recent report about the use of secondary binding sites for the asymmetric cyclopropanation of furans see M. Schinnerl, C. Bohm, M. Seitz, O. Reiser, Tetrahedron: Asymmetry 14 (2003) 765–771.

[10] A.B. Maude, A.P. Mehrotra, D. Gani, J. Chem. Soc. Perkin Trans. I (1997) 2513–2522.

[11] All the new products were fully characterized and show spectral data in agreement with the proposed structure.

[12] Other combinations such as tosyl chloride/triethylamine or the use of Burgess reagent gave the product in lower yields or did not work at all.

[13] A. Puglisi, M. Benaglia, R. Annunziata, A. Bologna, Tetrahedron Lett. 44 (2003) 2947–2951;
S. Orlandi, M. Benaglia, F. Cozzi, Tetrahedron Lett. 45 (2004) 1747–1749;
M. Benaglia, D. Negri, G. Dell'Anna, Tetrahedron Lett. 45 (2004) 8705–8708;
S. Orlandi, F. Colombo, M. Benaglia, Synthesis (2005) 1689–1692;
F. Colombo, M. Benaglia, S. Orlandi, F. Usuelli, J. Org. Chem. 71 (2006) 2064–2070.

[14] For a PEG-supported bis(oxazoline)-copper(II) promoted reaction in water see M. Benaglia, M. Cinquini, F. Cozzi, G. Celentano, Org. Biomol. Chem. 2 (2004) 3401–3407.

[15] For the same reaction promoted by bis(oxazoline)-copper (II) complexes in aqueous solvents see S. Kobayashi, S. Nagayama, T. Busujiama, Tetrahedron 55 (1999) 8739–8746.

[16] At −78 °C ligand 14/ $Cu(OTf)_2$ complex catalysed the reaction in 41% yield basically without stereoselection.

[17] D.A. Evans, G.S. Peterson, J.S. Johnson, D.M. Barnes, K.R. Campos, K.A. Woerpel, J. Org. Chem. 63 (1998) 4541–4544.

[18] In our hands the $Cu(SbF_6)$/ligand **1** complex at RT promoted the reaction with 7% ee. The result seems to suggest that the addition of a sidearm in the ligand has some beneficial effect on the enantioselectivity of the process. In this sense the figure of Scheme 2 represents a very preliminary working model that accounts for the formation of the product (*S*)-15.

[19] At the present based on these preliminary results it would be premature to invoke the presence of π–π interactions.

[20] For a discussion on the stereochemical models for bis(oxazolines) copper(II) complexes see Refs. [8,2c].

[21] Several issues have to be addressed: for example the copper coordination of a C_1-symmetric bis(oxazoline) might bring about the formation of two different complexes; our working hypothesis is that for steric reasons one should be favoured over the other; of course also the control of the approach of the aldehyde is another point that deserves further studies. Preliminary attempted NMR studies showed the presence of more than one species in solution.

[22] For other catalysts prepared following the same design principles see: J. C-D. Le, B.L. Pagenkopf, Org. Lett. 6 (2004) 4097.

[23] F. Fringuelli, O. Piermatti, F. Pizzo, J. Org. Chem. 60 (1995) 7006–7009.