Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 3095–3098

TETRAHEDRON: *ASYMMETRY*

Reversal of enantioselection in an aldol reaction catalyzed by sterically congested bis(oxazoline)–Cu(II) complexes

Hirofumi Matsunaga, Yasuhiro Yamada, Tsukasa Ide, Tadao Ishizuka and Takehisa Kunieda *

Faculty of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honmachi, Kumamoto 862-0973, Japan

Received 28 June 1999; accepted 23 July 1999

Abstract

The use of sterically congested C_2-symmetrical bis(oxazoline) ligands with methylene and ethylene spacers between the oxazoline rings results in the reversal of the enantioselection for aldol reactions catalyzed by bis(oxazoline)–Cu(II) complexes. © 1999 Elsevier Science Ltd. All rights reserved.

An increasing number of papers have appeared, directed at the design and development of efficient chiral catalysts for enantioselective asymmetric syntheses and this field is now one of the most challenging areas of organic chemical research. The high potential of chiral bis(oxazoline) ligand–metal catalysts in a wide variety of asymmetric synthesis has been extensively documented since the 1990s.[1] Chiral C_2-symmetrical bis(oxazoline) ligands are available in great structural diversity and the spacer moieties between the oxazoline rings are primarily responsible for the 'bite' angle of the bidentate ligands, which considerably influences the chiral environment at the catalytic site, thus effecting the efficiency and enantioselectivity of a reaction.[2] However, few studies have been reported for reactions catalyzed by bis(oxazoline) ligands in which the spacer length between the oxazoline rings clearly plays a key role in determining the stereochemical course of the reaction.[2,3]

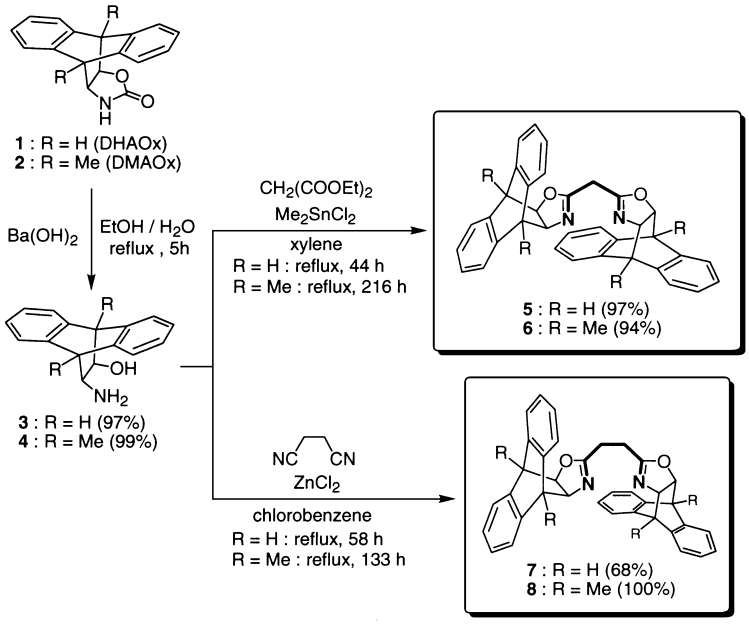
In this paper, we describe a new class of sterically congested and conformationally rigid chiral bis(oxazoline) ligands with methylene and ethylene spacers between the oxazoline rings, from which the derived Cu(II)-complexes serve as catalysts in asymmetric aldol reactions, resulting in the reversal of enantioselectivity, depending on six- and seven-membered chelate sizes.

We previously developed the sterically congested and conformationally rigid chiral 2-aminoalcohols, **3** and **4**, which are derived from the corresponding 2-oxazolidinone auxiliaries, **1** and **2**, as promising chiral sources, and whose 'roofed' structures would be expected to play a key part in the construction of highly congested and well-ordered asymmetric spaces.[4] Thus, the sterically congested chiral bis(oxazoline) ligands (**5**–**8**) were prepared by the ring-opening of the polycyclic 'roofed' 2-oxazolidinone auxiliaries, (+)-**1** (DHAOx) and (+)-**2** (DMAOx), to give the conformationally rigid aminoalcohols, followed by

* Corresponding author. E-mail: tkuni@gpo.kumamoto-u.ac.jp

PII: S0957-4166(99)00306-7

condensation with diethyl malonate and succinonitrile with the aid of Me_2SnCl_2[5] and $ZnCl_2$[6] catalysts, respectively (Scheme 1). The reactions proceeded smoothly to give the bis(oxazoline) ligands, mostly in yields in excess of 90%.[7,8]



Scheme 1.

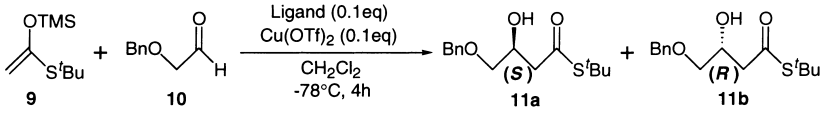
Evans and co-workers have extensively investigated the Mukaiyama aldol reactions of silylketene acetals derived from *t*-butyl thioacetate **9** and benzyloxyacetoaldehyde **10**, which are effectively catalyzed by bis(oxazoline)–Cu(II)-derived complexes.[9] This well documented reaction was selected as a probe to explore the influence of chelate size on the selectivity of our bis(oxazoline) ligands.

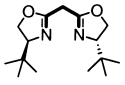
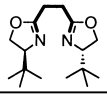
Thus, benzyloxyacetoaldehyde was treated with the trimethylsilyl enolate of the thioester in the presence of catalysts (0.1 equiv.) derived from the bis(oxazoline) ligands and $Cu(OTf)_2$ at −78°C for 4 h, as described by Evans et al. As shown in Table 1, the use of the ligand **5** with a methylene spacer resulted in the preferential formation of the (*R*)-isomer in 92% ee, while the ligand with an ethylene spacer **7** gave the (*S*)-isomer (80% ee) preferentially. A similar trend for the reversal of the enantioselectivity was observed with the more congested ligands **6** and **8**, although the selectivity was moderate. The *tert*-leucinol-derived bis(oxazoline) ligands with methylene and ethylene spacers were similarly explored for the sake of comparison. The bis(*t*-butyl-oxazoline) ligand with methylene spacer **12** gave the (*R*)-isomer in 64% ee,[10] while the ethylene spacer ligand **13** was nearly ineffective.

The reversal of enantiofacial selectivity observed can be rationalized by taking into account the geometrical change in aldehyde coordination in the equatorial-equatorial to the apical-equatorial positions on the pyramidal metal geometry, which is dependent on the ring size of the chelates (Fig. 1). Such a geometrical change in the bis(oxazoline)–metal catalysts has a precedent and has extensively been discussed by Evans et al.[11] Alternatively, the reversed selectivity can be explained by the tetrahedral and square planar geometries of the transition Cu(II)-complexes, as in the hypothesis proposed by Jørgensen et al.[12] The former rationalization appears to be more likely, based on the small differences in the ESR spectra of the bis(oxazoline) **5**- and **7**-Cu(II)–aldehyde complexes.[13]

Thus, the transition metal complexes derived from **5** and **7** adopt the pyramidal geometries **14** and **15**,

Table 1
Enantioselective aldol reactions catalyzed by bis(oxazoline)–Cu(OTf)$_2$ complexes



Entry	Ligand	Yield(%)[a]	11a : 11b[b]	(%e.e.)
1	**5**	49	1 : 24	(92)
2	**6**	42	1 : 3.3	(54)
3	**7**	46	9 : 1	(80)
4	**8**	42	3.2 : 1	(52)
5	 **12**	68	1 : 4.6	(64)
6	 **13**	5	1 : 1	(0)

a) Isolated yields.
b) Ratios determined by HPLC analysis (DAICEL CHIRALCEL OD-H).

respectively, as depicted in Fig. 1. The silyl enol ether preferentially attacks the aldehyde from the less hindered enantio-faces to give the (*R*)- and the (*S*)-isomers from **14** and **15**, respectively.

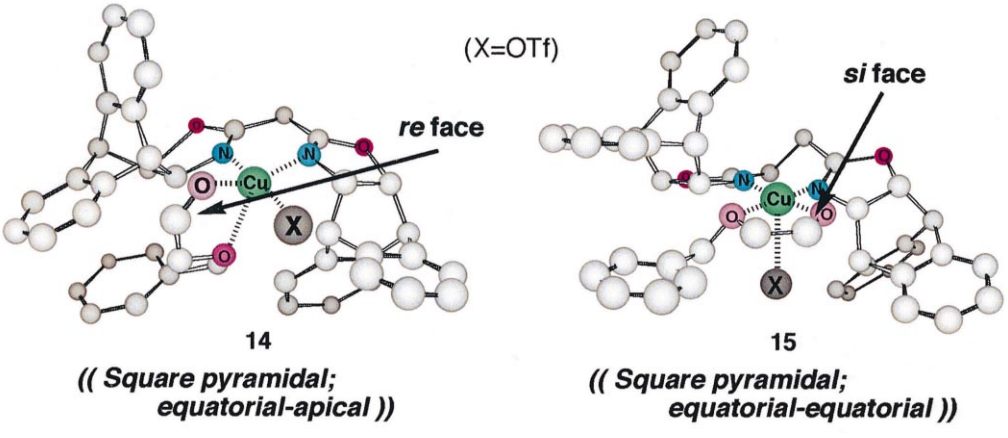
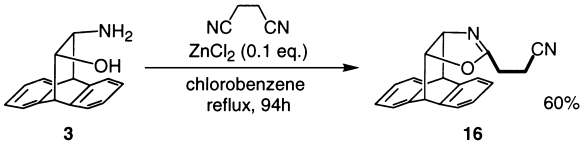


Figure 1. [14]

The results herein suggest that, in the case of an aldol reaction catalyzed by bis(oxazoline)–Cu(II) complexes, the spacer length between the sterically congested oxazoline rings has a considerable effect on the chiral environment at the catalytic site, thus resulting in the reversal of enantioselection. Further study is now under way.

References

1. For reviews, see: Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1–45.
2. Bedekar, A. V.; Koroleva, E. B.; Andersson, P. G. *J. Org. Chem*. **1997**, *62*, 2518–2526.
3. For recent examples, see: (a) Davies, I. W.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett*. **1996**, *37*, 1725–1726. (b) Denmark, S. E.; Stavenger, R. A.; Faucher, A.-M.; Edwards, J. P. *J. Org. Chem*. **1997**, *62*, 3375–3389.
4. (a) Kimura, K.; Sugiyama, E.; Ishizuka, T.; Kunieda, T. *Tetrahedron Lett*. **1992**, *33*, 3147–3150. (b) Imado, H.; Ishizuka, T.; Kunieda, T. *Tetrahedron Lett*. **1995**, *36*, 931–934. (c) Hashimoto, N.; Kawamura, S.; Ishizuka, T.; Kunieda, T. *Tetrahedron Lett*. **1996**, *37*, 9237–9240. (d) Hashimoto, N.; Ishizuka, T.; Kunieda, T. *Heterocycles* **1997**, *44*, 189–192. (e) Yokoyama, Y.; Ishizuka, T.; Ohmachi, N.; Kunieda, T. *Tetrahedron Lett*. **1998**, *39*, 4847–4850. (f) Hashimoto, N.; Ishizuka, T.; Kunieda, T. *Tetrahedron Lett*. **1998**, *39*, 6317–6320.
5. Masamune, S.; Lowenthal, R. E. *Tetrahedron Lett*. **1990**, *31*, 6005–6008.
6. Bolm, C.; Weickhardt, K.; Zehnder, M.; Ranff, T. *Chem. Ber*. **1991**, *124*, 1173–1180.
7. **5**: Mp 249°C (from acetonitrile), $[\alpha]_D$ −7.6 (*c* 1.00, $CHCl_3$), ^{1}H NMR (500 MHz/$CDCl_3$) δ: 2.27 (2H, s), 4.45 (2H, dd, *J*=3.7, 9.2 Hz), 4.53 (2H, d, *J*=3.7 Hz), 4.56 (2H, d, *J*=3.7 Hz), 4.78 (2H, dd, *J*=3.7, 9.2 Hz), 7.04–7.32 (16H, m). **6**: Mp 232°C (from EtOH), $[\alpha]_D$ −25.9 (*c* 1.00, $CHCl_3$), ^{1}H NMR (500 MHz/$CDCl_3$) δ: 1.97 (6H, s), 2.02 (6H, s), 2.25 (2H, s), 4.14 (2H, d, *J*=9.2 Hz), 4.45 (2H, d, *J*=9.2 Hz), 7.05–7.34 (16H, m). **7**: Mp>300°C (from acetonitrile), $[\alpha]_D$ +59.0 (*c* 1.00, $CHCl_3$), ^{1}H NMR (500 MHz/$CDCl_3$) δ: 1.35–1.49 (4H, m), 4.44 (2H, dd, *J*=3.7, 8.5 Hz), 4.53 (2H, d, *J*=3.7 Hz), 4.55 (2H, d, *J*=3.7 Hz), 4.75 (2H, dd, *J*=3.7, 8.5 Hz), 7.06–7.32 (16H, m). **8**: Mp>300°C (from EtOH), $[\alpha]_D$ +52.4 (*c* 1.00, $CHCl_3$), ^{1}H NMR (500 MHz/$CDCl_3$) δ: 1.27–1.47 (4H, m), 1.97 (6H, s), 2.03 (6H, s), 4.12 (2H, d, *J*=9.2 Hz), 4.42 (2H, d, *J*=9.2 Hz), 7.08–7.33 (16H, m).
8. The condensation proceeded smoothly with 0.05–0.1 equiv. molar amounts of Lewis acids except for the bis(oxazoline) **7**. $ZnCl_2$ (0.5 equiv.) was used for compound **7**, while smaller amounts of $ZnCl_2$ (0.1 equiv.) gave 2-cyanoethyloxazoline **16** (mp 167°C) as the major product (Scheme 2).



Scheme 2.

9. Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc*. **1996**, *118*, 5814–5815.
10. Evans et al. obtained 91% ee by use of the bis(oxazoline) ligand with a dimethylmethylene spacer.[8]
11. (a) Evans, D. A.; Olhava, E. J.; Johnson, J. S.; Janey, J. M. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 3372–3375. (b) Evans, D. A.; Johnson, J. S.; Burgey, C. S.; Campos, K. R. *Tetrahedron Lett*. **1999**, *40*, 2879–2882. (c) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Connell, B. T. *J. Am. Chem. Soc*. **1999**, *121*, 669–685.
12. Johannsen, M.; Jørgensen, K. A. *J. Org. Chem*. **1995**, *60*, 5757–5762.
13. The $g_\perp$, $g_\parallel$ and $A_\parallel$ values for the ESR spectra (9.4 GHz) are as follows: **5**-Cu$(OTf)_2$−**10**: $g_\perp$=2.07, $g_\parallel$=2.33, $A_\parallel$=159.6G; **7**-Cu$(OTf)_2$−**10**: $g_\perp$=2.08, $g_\parallel$=2.33, $A_\parallel$=146.3G. These values are almost identical with those of a known square pyramidal complex.[11c]
14. This figure was depicted by Chem 3D® (CambridgeSoft Corp.).