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Sterically congested 'roofed' 2-thiazolines as new chiral ligands for copper(II)-catalyzed asymmetric Diels–Alder reactions

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Abstract—Newly introduced chiral 'roofed' 2-thiazolines, prepared from sterically congested, conformationally rigid chiral 2-aminothiols, function as efficient chiral ligands for the asymmetric Diels–Alder reaction of cyclopentadiene and 3-acryloyl-2-oxazolidinone.

The development of chiral ligands for asymmetric catalytic reactions is a subject of considerable interest in the field of asymmetric synthesis.[1] To date, a large number of chiral ligands have been reported and, chiral oxazolines in particular, have played a key role as efficient ligands for variety types of catalytic asymmetric reactions.[2]

However, sulfur analogs, thiazolines, are less well-known[3–6] and only a few examples have been reported for asymmetric catalytic reactions such as allylic alkylation,[3] hydrosilylation,[4] and cyclopropanation[5] in which thiazoline–metal complexes are used.

Considering the difference in atomic character between oxygen and sulfur, such as atomic radius, electronegativity, bond length and bond angle, the chelating behavior of such compounds toward metal ions between oxazolines and corresponding thiazolines would be expected to be quite different. Actually, Masson and co-workers reported that the catalytic activity of a certain bis(thiazoline) was superior to the corresponding bis(oxazoline), giving a higher ee value for a palladium-catalyzed allylic alkylation.[3b] Therefore, further exploration of the 'thiazoline' as a chiral ligand appears to be warranted.

We recently developed some chiral 'roofed' 2-thiazolidinones, which are conformationally rigid and sterically bulky, by the thermal [4+2] cycloaddition of a simple 5-membered heterocycle, 2-thiazolone, to cyclic dienes followed by optical resolution.[7] These compounds have proven to be excellent chiral auxiliaries for asymmetric C–C bond formation, including α-alkylations of carbonyl compounds[7] and β-conjugate additions. The excellent stereoselectivities obtained in these reactions prompted us to apply this unique skeleton to the preparation of a new type of chiral 'roofed' 2-thiazoline ligands and to test them for catalytic asymmetric reactions as chiral ligands.

In this letter, we report on some sterically congested 'roofed' 2-thiazolines as new chiral ligands for Cu(II)-catalyzed asymmetric Diels–Alder reactions, leading to excellent *endo*/*exo* ratio and *endo*-enantioselectivity compared to the corresponding chiral 'roofed' 2-oxazoline ligand.

Starting from the 'roofed' *cis*-2-aminothiol **2**, readily obtained from the chiral 2-thiazolidinone **1** by hydrolytic ring cleavage with $Ba(OH)_2$ in ethanol under reflux, three types of new 'roofed' thiazoline ligands, bis(thiazoline) **5**,[8] pyridylthiazoline **6**,[9] and (2-diphenylphosphino)phenylthiazoline **7**,[10] were prepared in one or two steps following the general procedure for the preparation of oxazoline ligands (Scheme 1).[2]

Similarly, (2-diphenylphosphino)phenyloxazoline **10**,[11] the analog of **7**, was synthesized from the 'roofed' *cis*-2-aminoalcohol **8** (Scheme 2).[12]

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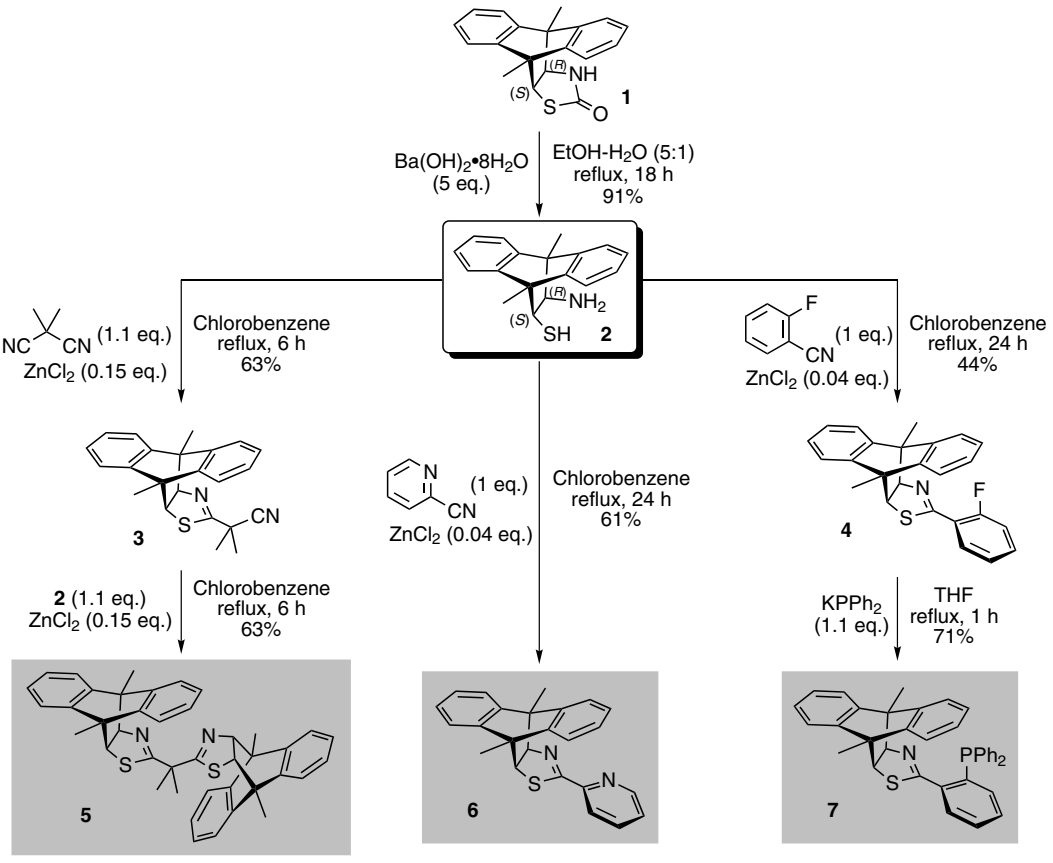
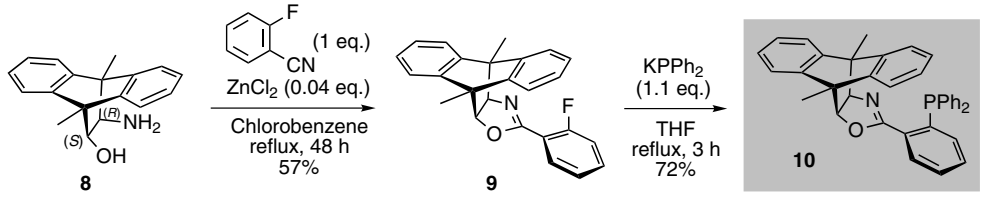


Scheme 1.

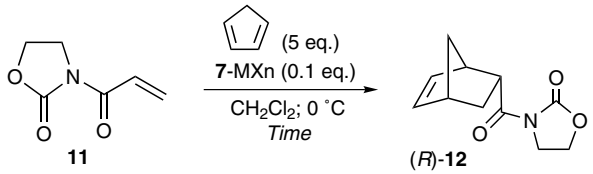


Scheme 2.

The enantioselective Diels–Alder reaction has been extensively studied and chiral oxazoline–Cu(II) complexes have proven to be efficient chiral Lewis acids for this reaction system.[1,2] However, the use of a chiral thiazoline as a chiral ligand for the same reaction has not been examined. Therefore, we chose chiral Cu(II) Lewis acid-catalyzed enantioselective Diels–Alder reactions as a model reaction for the evaluation of the chiral thiazoline ligands **5**–**7**.

In a typical procedure, the thiazoline–copper(II) complex was prepared by mixing 0.1 equiv of thiazoline ligand with an equivalent amount of $Cu(OTf)_2$ in CH_2Cl_2 for 30 min at room temperature under argon atmosphere. After the addition of 3-acryloyl-2-oxazolidinone **11** to the catalyst solution and stirring for 30 min, 5 equiv of cyclopentadiene were added followed by stirring at 0 °C. The consumption of the substrate **11** was monitored by TLC. After the usual work-up, the crude product was purified by silica gel column chromatography to yield the corresponding [4+2] cycloadducts. The

Table 1. Asymmetric Diels–Alder reaction of *N*-acryloyl-2-oxazolidinone **11** and cyclopentadiene catalyzed by various copper(II) salts



11 (*R*)-**12** *endo* (*R*)

Entry	MX_n	Time (h)	Yield[a] (%)	$\sum endo:\sum exo$[b]	*endo* % ee[b]
1	$CuCl_2$	12	94	90:10	4 (*R*)
2	$Cu(acac)_2$	9	88	94:6	5 (*R*)
3	$Cu(OTf)_2$	1	92	87:13	76 (*R*)
4	$Cu(ClO_4)_2$	9	92	87:13	41 (*R*)
5	$Cu(SbF_6)_2$	0.5	97	91:9	63 (*R*)

[a] Isolated yields.
[b] Determined by HPLC.

endo/*exo* ratio and *endo*% ee was determined by HPLC (Daicel CHIRALCEL OD-H).

We first examined the counteranion effect of the copper(II) salts for the chiral Lewis acid derived from (2-diphenylphosphino)phenylthiazoline **7** and the Cu(II) salts (Table 1). All reactions proceeded well to give the corresponding *endo*/*exo* mixture of cycloadducts in 12 h and triflate led to the highest enantioselectivity of *endo*-product (entry 3). The highest reaction rate occurred with hexafluoroantimonate but the enantioselectivity was lower than that for triflate (entry 5).

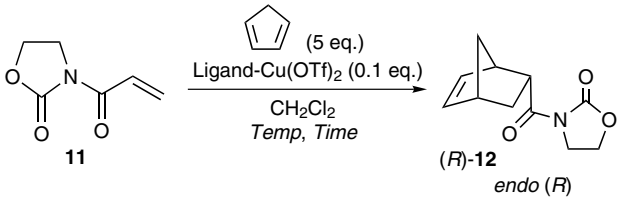
Table 2 summarizes the enantioselective Diels–Alder reaction of substrate **11** with cyclopentadiene in the presence of a chiral Lewis acid derived from $Cu(OTf)_2$ and various thiazoline ligands **5**–**7** and the oxazoline ligand **10**.

Contrary to the acceptable result for (2-diphenylphosphino)phenylthiazoline **7**, the bis(thiazoline) ligand **5**, and the pyridylthiazoline ligand **6** gave low enantioselectivities (entries 1–3). In the case of **7**, a decrease in the reaction temperature led to an increase in the *endo*/*exo* ratio and enantioselectivity. The best results, a 97:3 *endo*/*exo* ratio and 92% ee, was achieved at a temperature of −60 °C (entry 4). It is interesting to note that the results for (2-diphenylphosphino)phenyloxazoline **10**, the analog of phosphinothiazoline **7**, were inferior to **7** at 0 °C and at −60 °C (entries 5 and 6).

The mechanism we propose for the 'roofed' (2-diphenylphosphino)phenyloxazoline **10**-Cu(II)-catalyzed asymmetric Diels–Alder reaction is depicted in Figure 1.[13] Thus, in the equilibrium of square planar phosphinooxazoline–Cu(II)–dienophile complexes, **13B** is favored over **13A** because of the steric repulsion between the acryloyl group and the phenyl substituent on the phosphine moiety in **13A**. Cyclopentadiene attacks the acryloyl dienophile from the *Si*-face, the site opposite the 'roof' moiety, in an *endo* fashion in **13B** preferentially to give the (2*R*)-*endo* cycloadduct (*R*)-**12** as the major product.

While the precise mechanism for the 'roofed' (2-diphenylphosphino)phenylthiazoline **7**-Cu(II)-catalyzed asymmetric Diels–Alder reaction is not clear,[14] the most plausible structures of the phosphinothiazoline **7** and corresponding phosphinooxazoline **10**, the longer bond length of C–S (1.76–1.81 Å)[15] than C–O

Table 2. Asymmetric Diels–Alder reaction of *N*-acryloyl-2-oxazolidinone **11** and cyclopentadiene catalyzed by chiral ligand–$Cu(OTf)_2$ complexes



Entry	Ligand	Temp (°C)	Time (h)	Yield [a] (%)	$\sum endo:\sum exo$ [b]	*endo* % ee [b]
1	**5**	0	3	97	87:13	2 (*R*)
2	**6**	0	24	88	91:9	16 (*S*)
3	**7**	0	1	92	87:13	76 (*R*)
4	**7**	−60	36	81	97:3	92 (*R*)
5	**10**	0	0.5	95	76:24	57 (*R*)
6	**10**	−60	24	94	84:16	73 (*R*)

[a] Isolated yields.
[b] Determined by HPLC.

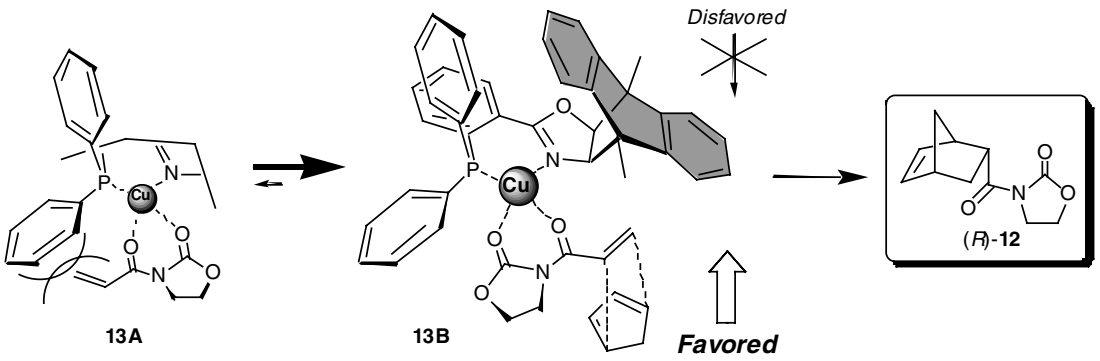


Figure 1.

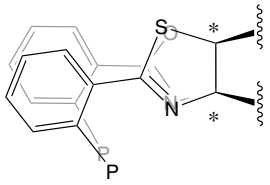


Figure 2. Plausible structure of phosphinothiazoline (black) and phosphinooxazoline (gray) (superimposed for comparison).

(1.34–1.45 Å)[16] and the narrower bond angle of C–S–C (94.5 °)[15] than C–O–C (111.2 °),[16] may cause difference in the position of the phosphine moiety. These structural and positional changes of phosphinothiazoline **7** may induce the improvement of the *endo*/*exo* ratio and *endo* enantioselectivity than phosphinooxazoline ligand **10** (Fig. 2).

In conclusion, we demonstrate a new and novel chiral 'roofed' (2-diphenylphosphino)phenylthiazoline **7**, which functions as an efficient chiral ligand in the asymmetric Diels–Alder reaction of cyclopentadiene and 3-acryloyl-2-oxazolidinone. Further trials are currently in progress.

Acknowledgments

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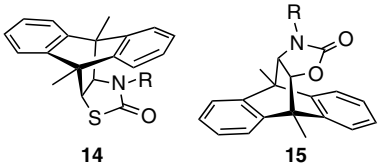
References and notes

1. For a review, see: *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999.
2. For reviews, see: (a) Ghosh, A. K.; Mathivanan, P.; Capellio, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1–45; (b) Braunstein, P.; Naud, F. *Angew. Chem., Int. Ed.* **2001**, *40*, 680–699; (c) Wong, G. S. K.; Wu, W. 2-Oxazolines. In *Chemistry of Heterocyclic Compounds*; Palmer, D. C., Ed.; John Wiley & Sons: New York, 2004, pp 331–528, Part B, Chapter 5; (d) Ghosh, A.; Bilcer, G.; Fidanze, S. Chiral Bis(oxazolines). In *Chemistry of Heterocyclic Compounds*; Palmer, D. C., Ed.; John Wiley & Sons: New York, 2004, pp 529–594, Part B, Chapter 5.
3. (a) Abrunhosa, I.; Gulea, M.; Levillain, J.; Masson, S. *Tetrahedron: Asymmetry* **2001**, *12*, 2851–2859; (b) Abrunhosa, I.; Gulea, M.; Delain-Bioton, L.; Gaumont, A.-C.; Gulea, M.; Masson, S. *Tetrahedron* **2004**, *60*, 9263–9272; (c) Fu, B.; Do, D.-M.; Xia, Q. *Synthesis* **2004**, 221–226.
4. Helmchen, G.; Krotz, A.; Ganz, K.-T.; Hansen, D. *Synlett* **1991**, 257–259.
5. (a) Ikehira, H. Jpn. Kokai Tokkyo Koho JP 09194432 A2, 1997; (b) Ikehira, H. Jpn. Kokai Tokkyo Koho JP 11124373 A2, 1999.
6. Tárraga, A.; Molina, P.; Curiel, D.; Bautista, D. *Tetrahedron: Asymmetry* **2002**, *13*, 1621–1628.
7. Hoshimoto, S.; Matsunaga, H.; Kunieda, T. *Chem. Pharm. Bull.* **2000**, *48*, 1541–1544.
8. Compound **5**: colorless crystals, mp 209–210 °C (from EtOH); $[\alpha]_D$ −26.7 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.55 (3H, s), 1.85 (3H, s), 2.16 (3H, s), 3.93 (1H, d, J = 9.2 Hz), 3.93 (1H, d, J = 9.2 Hz), 7.08–7.39 (8H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.8, 17.7, 26.2, 45.7, 46.9, 47.1, 62.4, 87.8, 121.2, 122.0, 122.9, 123.3, 125.1, 125.5, 126.0, 126.2, 141.9, 142.5, 144.5, 145.2, 173.5. Anal. Calcd for $C_{41}H_{38}N_2S_2$: C, 79.06; H, 6.15; N, 4.50. Found: C, 79.10; H, 6.11; N, 4.34.
9. Compound **6**: colorless crystals, mp 198–199 °C (from CH_2Cl_2–EtOH); $[\alpha]_D$ −73.4 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.98 (3H, s), 2.31 (3H, s), 4.20 (1H, d, J = 9.8 Hz), 5.08 (1H, d, J = 9.8 Hz), 7.01–8.50 (12H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.8, 17.7, 45.8, 47.1, 61.0, 89.5, 121.2, 121.3, 122.0, 123.6, 125.0, 125.5, 125.6, 126.2, 126.3, 136.3, 141.9, 142.5, 144.7, 145.5, 149.0, 151.1, 169.0. Anal. Calcd for $C_{24}H_{20}N_2S$: C, 78.13; H, 5.47; N, 7.60. Found: C, 78.13; H, 5.38; N, 7.61.
10. Compound **7**: colorless crystals, mp 219–220 °C (from EtOH); $[\alpha]_D$ −175.6 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.79 (3H, s), 1.92 (3H, s), 4.06 (1H, d, J = 9.8 Hz), 4.86 (1H, d, J = 9.8 Hz), 6.79–7.34 (22H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.2, 17.9, 45.7, 46.8, 62.8, 89.6, 121.1, 122.0, 123.0, 123.3, 125.1, 125.6, 126.0, 126.2, 128.0, 128.1, 128.1, 128.2, 128.3, 129.6, 129.8, 129.9, 133.7, 133.9, 134.0, 134.6, 137.1, 137.3, 137.8, 138.0, 138.9, 139.1, 141.8, 142.5, 144.8, 145.3, 165.1. Anal. Calcd for $C_{37}H_{30}NPS$: C, 80.55; H, 5.48; N, 2.54. Found: C, 80.34; H, 5.52; N, 2.42.
11. Compound **10**: colorless crystals, mp 237–238 °C (from hexane–CH_2Cl_2); $[\alpha]_D$ −52.5 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.79 (3H, s), 1.92 (3H, s), 4.06 (1H, d, J = 9.8 Hz), 4.86 (1H, d, J = 9.8 Hz), 6.79–7.34 (22H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.2, 17.9, 45.7, 46.8, 62.8, 89.6, 121.1, 122.0, 123.0, 123.3, 125.1, 125.6, 126.0, 126.2, 128.0, 128.1, 128.1, 128.2, 128.3, 129.6, 129.8, 129.9, 133.7, 133.9, 134.0, 134.6, 137.1, 137.3, 137.8, 138.0, 138.9, 139.1, 141.8, 142.5, 144.8, 145.3, 165.1. Anal. Calcd for $C_{37}H_{30}NPS$: C, 80.55; H, 5.48; N, 2.54. Found: C, 80.34; H, 5.52; N, 2.42.
12. Hashimoto, N.; Ishizuka, T.; Kunieda, T. *Heterocycles* **1997**, *44*, 189–192.
13. (a) Sagasser, I.; Helmchen, G. *Tetrahedron Lett.* **1998**, *39*, 261–264; (b) Hiroi, K.; Watanabe, K. *Tetrahedron: Asymmetry* **2002**, *13*, 1841–1843.
14. Unfortunately, we have no clear structural data such as X-ray crystallography and a clear NMR spectrum of phosphinothiazoline **7**–Cu(II) complex. Further attempts to collect such data are ongoing.
15. Cited from X-ray crystallographic data of compound **14**.[7]
16. Cited from X-ray crystallographic data of compound **15** Kimura, K.; Murata, K.; Otsuka, K.; Ishizuka, T.; Haratake, M.; Kunieda, T. *Tetrahedron Lett.* **1992**, *33*, 4461–4464.



14 **15**