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Structural Requirements of a Chiral Ligand for the Catalytic Asymmetric Addition of Thiophenol to α,β-Unsaturated Esters

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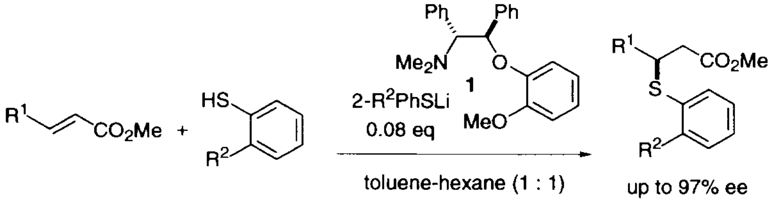
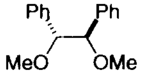
Abstract: The tridentate amino ether ligands **1** and **14** were developed through systematic structural modification of the bidentate diether ligand **2**. The reaction of thiophenol with methyl crotonate was catalyzed by **14** and lithium thiophenolate to afford (*S*)-methyl 3-phenylthiobutanoate in 75% ee and 95% yield.

Enantioselective conjugate addition of thiophenol to α,β-unsaturated carbonyl compounds has been well established to provide a new chiral carbon at the β-position by the use of cinchona alkaloids and proline-derived chiral amines as catalysts.[1] However, these reactions are only limited to activated olefins such as enones and are not applicable to enoates. Exception is the reaction with diisopropyl maleate to afford the adduct in 81% ee and 95% yield at 0 °C after 21 days.[2] As our continuing studies toward enantioselective reactions of organolithiums based on an external chiral ligand,[3,4] we have developed the catalytic asymmetric addition of thiophenol to enoates using lithium thiophenolate as a catalytic nucleophile which has higher reactivity than thiophenol activated by amine.[5] Although rational design of the ligand is a key to the success, much more information on the structural requirements of the ligand is necessary to this goal. We describe herein our systematic approach toward the ligand tuning for the catalytic asymmetric reaction of lithium thiophenolate with enoates.[6]

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The chiral tridentate amino ether 1[7] has been developed after systematic modification of **2** and proved to be useful in the catalytic asymmetric carbon-sulfur bond-forming reaction of 2-trimethylsilylthiophenol with enoates to provide 3-(2-trimethylsilylphenylthio)carboxylates in up to 97% ee.[8] Based on **2** of which versatility has been proved in the asymmetric reaction of organolithiums,[4,9] lithium ester enolates,[10] and lithium phosphonate,[11] investigation of structural requirements of the ligand was carried out in three ways;

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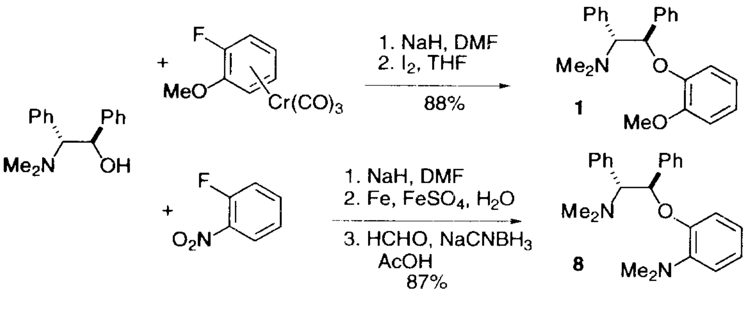
(1) replacement of one methoxy to dimethylamino group, (2) replacement of methoxy to other additional coordinating group, and (3) positional and steric tuning of the two phenyl groups on the chiral centers. As shown in Table 1 and 2, we examined three types of ligand, the first type **2-6** are bidentate ligands, the second **1** and **7-10** are tridentate ligands, the third **11-14** are tridentate ligands having different steric circumstance on the ethylene backbone.

The ligands **1** and **4-8** were prepared by the reaction of (*R*,*R*)-2-dimethylamino-1,2-diphenylethanol with the corresponding fluorides[12,13] as shown in the following selected cases.[14] The ligand **9** was prepared by the reaction with the corresponding tosylate. The ligand **10** was prepared from (*R*,*R*)-1,2-diphenylethane-1,2-diol. The ligands **3**,[15] **11**,[7] **12**,[7] **13**,[7] and **14**[7] were prepared according to the previously reported procedure.



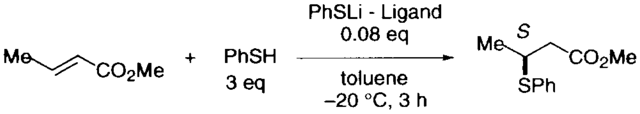
The reaction of thiophenol (3 eq) with methyl crotonate was examined with 0.08 eq of lithium thiophenolate and 0.1 eq of **2** in toluene at –20 °C for 3 h. On the contrary to our expectation, (*S*)-methyl 3-phenylthiobutanoate[16] was obtained in only 6% ee (Table 1). The ligand **3** with a dimethylamino group of much powerful coordinating ability afforded the nearly racemic product. Then, the methoxy group of **3** was changed to more bulky phenoxy group, **4**, affording (*R*)-product in 29% ee. The 4-methoxyphenoxy ligand **5**, which has higher coordinating ability than **4** by the 4-methoxy activation, gave 21% ee. The 2-methylphenoxy ligand **6**, which has coordinating ability weaker than **4** and **5** due to steric reason, gave 10% ee.

We next examined tridentate ligands. Modification of the phenoxy moiety of bidentate **4** was proved to be successful. The 2-methoxyphenoxy ligand **1** gave (*S*)-ester in 71% ee. The 2-amino- and 2-dimethylaminophenoxy ligands **7** and **8** also gave (*S*)-ester, but in 20 and 34% ees, respectively. Although the ligand **9** is the tridentate ligand, it gave only 2% ee, indicating the necessity of the 2-methoxyphenoxy moiety. The importance of the dimethylamino group in **1** is shown by the methoxy version **10** that gave 22% ee.

It is worthy to note that tridentate ligands **1**, **7**, **8**, and **10** gave (*S*)-ester, whereas bidentate ligands **4-6** gave (*R*)-ester. The change in the sense of enantiofacial selection is attributable to the change of complex mode, that is, the ligands **1**, **7**, **8**, and **10** are tridentate ligands for the lithium to satisfy its tetravalency and form a bicyclic [3.3.0] complex.

Next we examined effect of the two phenyl groups at the chiral carbons of **1** (Table 2). The ligand **11**, which lacks one phenyl group on the carbon bearing dimethylamino group, gave 63% ee. The ligand **12**, which lacks also one phenyl group on the carbon attached by 2-methoxyphenoxy group, gave 50% ee. Superiority of **1** to **11** and **12** is attributable to the presence of two phenyl groups in *trans*-manner. Thus, the ligand **13**, placing two phenyl groups in *cis*-manner, gave the nearly racemic ester. Placing a methyl in place of one phenyl group of **1** gave the comparable 75% ee as shown by the reaction of **14**.

Table 1. Asymmetric Reaction of Thiophenol with Methyl Crotonate Catalyzed by Ligands **1** - **10**



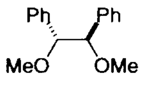
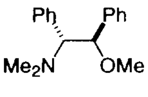
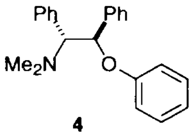
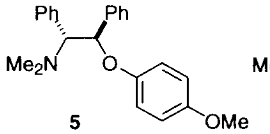
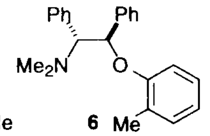
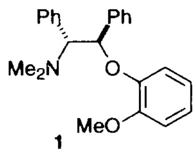
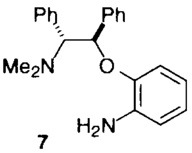
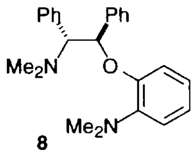
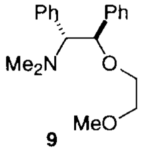
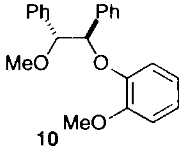
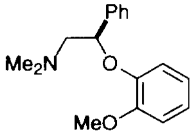
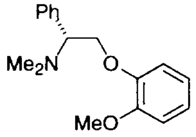
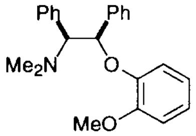
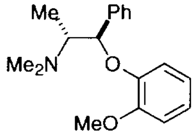
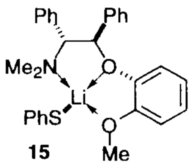
Bidentate ligands					
	2	**3**	**4**	**5**	**6**
yield/%	92	85	99	90	99
ee/%	6	1	*ent*-29	*ent*-21	*ent*-10
Tridentate ligands					
	1	**7**	**8**	**9**	**10**
yield/%	99	99	99	98	81
ee/%	71	20	34	2	22

Table 2. Asymmetric Reaction of Thiophenol with Methyl Crotonate Catalyzed by Ligands **11** - **14**

				
	11	**12**	**13**	**14**
yield/%	93	91	94	95
ee/%	63	50	*ent*-2	75

It became apparent that, for the external chiral ligand in the conjugate addition reaction of thiophenol with crotonate, tridentate ligand is the favorite, and furthermore, two groups on the ethylene bridge are arranged in *trans* placement. These results indicate the existence of bicyclo[3.3.0] complex **15** as active species in the reaction.[17]

Further studies toward structure tuning of the ligand based on **15** for improvement of the reaction efficiency are in progress in our laboratories.



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References and Notes

1. Wynberg, H.; Greijdanus, B. *J. Chem. Soc., Chem. Commun.* **1978**, 427-428; Kobayashi, N.; Iwai, K. *J. Am. Chem. Soc.* **1978**, *100*, 7071-7072; Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417-430; Shibasaki, M.; Nishida, A.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1982**, 1324-1325; Suzuki, K.; Ikegawa, A.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3277-3282.
2. Yamashita, H.; Mukaiyama, T. *Chem. Lett.* **1985**, 363-366.
3. Tomioka, K. *Synthesis* **1990**, 541-549; Noyori, R. *Asymmetric Catalysis in Organic Synthesis* John Wiley and Sons, Inc. New York, 1994; Denmark, S. E.; Nicaise, O. J.-C. *J. Chem. Soc., Chem. Commun.* **1996**, 999-1004.
4. Shindo, M.; Koga, K.; Tomioka, K. *J. Am. Chem. Soc.* **1992**, *114*, 8732-8733.
5. Enantioselective activation of thiol by means of metalation is quite rare. Iida, T.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 4783-4784; Manickam, G.; Sundararajan, G. *Tetrahedron: Asymmetry* **1997**, *8*, 2271-2278.
6. An inclusion complex of chiral host with cycloalkenone has been used in enantioselective asymmetric reaction of thiol, which needs an equivalent amount of chiral host. Toda, F.; Tanaka, K.; Sato, J. *Tetrahedron: Asymmetry* **1993**, *4*, 1771-1774.
7. Okuda, M.; Tomioka, K. *Tetrahedron Lett.* **1994**, *35*, 4585-4586. The synthesis of **1** was improved as shown in the text.
8. Nishimura, K.; Ono, M.; Nagaoka, Y.; Tomioka, K. *J. Am. Chem. Soc.* in press.
9. Mizuno, M.; Kanai, M.; Iida, A.; Tomioka, K. *Tetrahedron,* **1997**, *53*, 10699-10708; Asano, Y.; Iida, A.; Tomioka, K. *Tetrahedron Lett.* **1997**, *38*, 8973-8976; Amurrio, D.; Khan, K.; Kündig, E. P. *J. Org. Chem.* **1996**, *61*, 2258-2259.
10. Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060-2061.
11. Mizuno, M.; Fujii, K.; Tomioka, K. *Angew. Chem.* in press.
12. Davies, S. G.; Hume, W. E. *Tetrahedron Lett.* **1995**, *36*, 2673-2674.
13. Beugelmans, R.; Bigot, A.; Zhu, J. *Tetrahedron Lett.* **1994**, *35*, 5649-5652.
14. All new compounds described herein were fully characterized by spectroscopic and analytical data.
15. Inoue, I.; Shindo, M.; Koga, K.; Kanai, M.; Tomioka, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2527-2533.
16. The ee was determined by chiral stationary phase HPLC (Daicel Chiralcel-OD). The absolute configuration was determined by specific rotation. Puzicha, G.; Lévai, A.; Szilágyi, L. *Monatsch. Chem.* **1988**, *119*, 933-944.
17. It was reported by X-ray crystallography that lithium thiophenolate forms a polymer containing an infinite Li-S chain, and the lithium is coordinated by two external pyridine molecules. On the other hand, lithium 2-methylthiophenolate forms a monomeric crystal containing a lithium coordinated by three external pyridine ligands. Banister, A. J.; Clegg, W.; Gill, W. R. *J. Chem. Soc., Chem. Commun.* **1987**, 850-852; Sigel, G. A.; Power, P. P. *Inorg. Chem.* **1987**, *26*, 2819-2822.