Communications to the Editor

Steric Tuning of Reactivity and Enantioselectivity in Addition of Thiophenol to Enoates Catalyzed by an External Chiral Ligand

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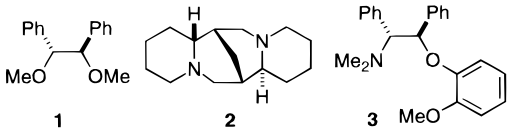
The addition of a thiol to an electron-deficient olefin to form a sulfur−carbon bond constitutes a key reaction in biosynthesis as well as in chemical synthesis of biologically potent compounds.[1] The asymmetric additions of thiols to conjugated unsaturated carbonyl compounds bonded covalently by chiral auxiliary have been well-documented to give the adducts with high level of diastereoselectivity.[2] The enantioselective reactions have also been developed with the use of chiral amine catalysts.[3] Especially, cinchona alkaloids[4] and proline-derived chiral amines[5] were shown to be good catalysts that form stereochemically ordered complexes with substrates and thiols. In spite of impressive progress, catalytic asymmetric addition of a thiol to a prochiral olefin has not yet reached at the satisfactory level. The asymmetric synthesis with use of chiral olefins has the drawback, from a chemical economic viewpoint, of requiring at least an equal amount of chiral auxiliary.[6] The chiral amine-catalyzed reactions require reactive olefins and relatively high temperature to promote the reaction because of poor reactivity of thiol activated by an amine. We describe herein that a combination of lithium thiophenolate and an external chiral ligand catalyzes asymmetric addition reaction of thiophenol with enoates to give the addition products in high enantioselectivity, overcoming the above drawbacks.[7]

We have been involved in the asymmetric reactions of organolithiums or lithium ester enolates with imines or enoates under control of chiral ether or amino ether ligands, giving the chiral products.[8] On the basis of these studies on asymmetric reactions of lithiated carbonucleophiles, lithium thiophenolate, and chiral compounds **1**−**3** were chosen as the nucleophile and representative chiral ligands, respectively.



1 **2** **3**

It is reasonable to draw a scenario that lithium thiophenolate has a nucleophilic reactivity higher than amine-activated thiol, and the lithium cation coordinates with the two or three heteroatoms of **1**−**3** to form a chiral chelate,[9] allowing asymmetric addition of thiophenol. Indeed, the reaction of thiophenol (**5a**, 3 equiv) with methyl crotonate (**4**) proceeded smoothly in the presence of 0.08 equiv of lithium thiophenolate and 0.1 equiv of **1**[8,9] in toluene at −20 °C for 2 h to afford (*S*)-methyl 3-phenylthiobutanoate (**6a**)[10] in 92% yield. The ee was determined by chiral stationary phase HPLC (Daicel Chiralcel-OD) to be 6%. The reaction mediated by (−)-sparteine (**2**)[11] gave (*S*)-**6a** in 15% ee and 85% yield after 3 h at −20 °C. Fortunately, we found that the chiral amino ether **3**[12] gave (*S*)-**6a** in a reasonably good ee of 71% and 99% yield after 3 h at −20 °C. In the absence of lithium thiophenolate the reaction mediated by **3** is sluggish, giving **6a** in 0.5% yield after 6 days at room temperature. Although the enantioselectivity is unsatisfactory, these reactions indicate the higher reactivity of lithium thiophenolate than that of amine-activated thiophenol.

To improve the enantioselectivity, the reaction with **3** was allowed to cool at −60 °C for 47 h to give (*S*)-**6a** in 74% ee, but in 55% yield. The reaction did not proceed at −78 °C. These unsatisfactory results clearly indicate that lithium thiophenolate itself requires much more activation. Thus, the size of 2-substituent of thiophenol (**5**) was found to exert profound effects on the reactivity as well as enantioselectivity (Table 1). It is interesting that both reactivity and enantioselectivity increased along with the increase of the size of 2-substituent. The most bulky compound 2-*tert*-butylthiophenol (**5d**) reacted with **4** within 1 h at −20 °C, giving **6d** in 90% ee and 99% yield. These favorable and size-dependent effects of 2-substit-

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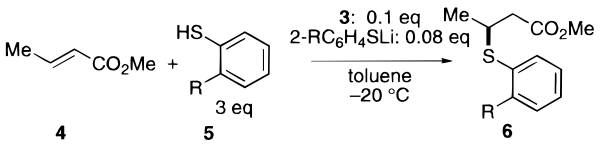
Table 1. 2-Substituent Effects of **5** on Reactivity and Enantioselectivity



4 **5** **6**

5	R	time (h)	yield (%)	ee (%)[a]
a	H	3	99	71
b	Me	2	93	79
c	*i*-Pr	2	99	85
d	*t*-Bu	1	99	90
e	TMS	1	97	88

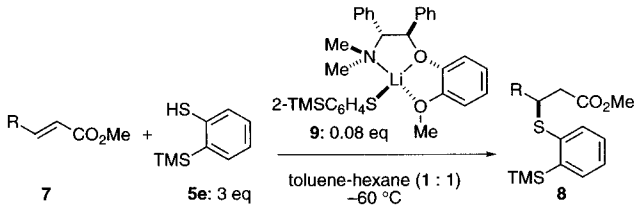
[a] The absolute configuration was determined to be *S* for **6a**,[10] **b**,[15] and **e**[10] by specific rotation and tentatively assigned by analogy for **6c**,**d**.

uents are attributable to both inhibition of solvation of the thiolate anion[13] and formation of the sterically defined monomeric chelated structure where the lithium cation is coordinated by the three heteroatoms of the tridentate ligand **3** as shown in **9**. This situation is supported by the crystal structure of 2-substituted thiophenolates.[14] 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.

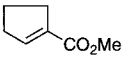
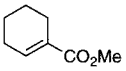
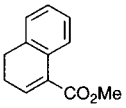
We then turned our attention to 2-(trimethylsilyl)thiophenol (**5e**)[16] as a nucleophile, equivalent to an activated thiophenol **5a**. The reaction of **5e** (3 equiv) with **4** (**7**: R = Me) in the presence of 0.08 equiv of lithiated **5e** and 0.1 equiv of **3** in toluene proceeded at −20 °C for 1 h, affording (*S*)-**6e** in 88% ee and 97% yield. The reaction at −78 °C for 120 h in toluene−hexane (1:1) gave (*S*)-**6e** (**8**: R = Me) in 97% ee and 99% yield (Table 2). The chiral ligand **3** was recovered quantitatively for reuse. Treatment of (*S*)-**6e** with triflic acid[17] at room temperature for 10 min gave the protodesilylated ester (*S*)-**6a** of 97% ee in 99% yield.

Some of the results obtained using **5e** in toluene−hexane (1:1) are summarized in Table 2. The reaction of acyclic *trans*-enoates **7** (R = Me, Et, Pr, Bu, *i*-Bu, $PhCH_2$) generally affords **8** in high ee. Exception is the enoates bearing a branched side

Table 2. Asymmetric Addition of 2-$TMSC_6H_4SH$ **5e** to Methyl Enoates **7**



7 **5e**: 3 eq **8**

R	time (h)		yield (%)	ee (%)[a]	*R/S*
Me	120[b]		99	97	*S*[c]
Et	18		99	93	
Pr	30		99	93	
i-Pr	55		66	77	
Bu	30		99	94	
i-Bu	30		93	94	
Ph	72[d]		78	70	*R*[e]
$PhCH_2$	30		98	95	
	33	*cis*	82	96	1*S*,2*S*[f]
		trans	10	92	
	60[g]	*cis*	84	83	
	72[h]	*cis*	96	81	1*S*,2*S*[i]

[a] Ee was determined by chiral stationary phase HPLC. [b] −78 °C. [c] Reference 10. [d] −40 °C. [e] Reference 18. [f] Reference 19. [g] −20 °C. [h] **5a** was used instead of **5e** at −70 °C in toluene. [i] Reference 20.

chain (**7**, R = *i*-Pr) or phenyl group (R = Ph) at the 3-position, giving relatively lower ee's.

Cyclopentenecarboxylate was converted to the corresponding *cis* adduct[1g] in high ee, whereas 6-membered enoates gave *cis* products in relatively lower ee's.

The absolute configuration of **8** was determined in four of the 11 different cases among shown in Table 2, and the sense of asymmetric induction is the same. The attack of thiol takes place from the top face of **7**.

The stereochemistry is determined at the addition step of lithium thiophenolate to enoate. Treatment of racemic **8** (R = Me) under the asymmetric reaction conditions, 3 equiv of **5e**, 0.08 equiv of lithium thiolate, and 0.1 equiv of **3** in toluene−hexane (1:1) at −20 °C for 3 h, recovered racemic **8**. On the other hand, **8** (R = Me), with 90% ee, was treated with 3 equiv of **5e** and 0.08 equiv of thiolate with recovery of **8** of unchanged ee of 90%. These results indicate that kinetic control is operative in the asymmetric addition reaction.

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Supporting Information Available: Details of the experimental procedure, characterization data and determination of the absolute configuration (20 pages). See any current masthead page for ordering information and Internet access instructions.

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