Diastereoselective Thiophenol Addition to (S)-N-(α,β-Unsaturated carbonyl)-γ-[(trityloxy)methyl]-γ-butyrolactams

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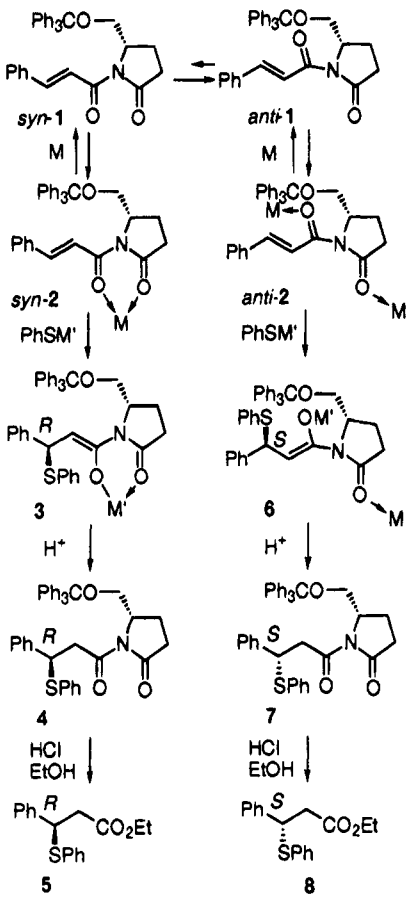
Stereoselective addition of a thiol to an electron deficient olefin to form a sulfur-carbon bond constitutes a key reaction in biosynthesis as well as in chemical synthesis of biologically potent compounds.[1] In spite of its versatility, stereochemical aspects of thiol addition to a chiral olefin have not yet been fully explored.[2] During our studies aimed at the development of stereoselective reactions based on diastereofacial selectivity relationships,[3] we had a chance to examine an asymmetric addition of thiophenol to (*S*)-*N*-cinnamoyl-γ-[(trityloxy)-methyl-γ-butyrolactam (**1**).[4] We describe herein the unprecedented stereochemical aspects of the reaction and highly enantioselective synthesis of β-(phenylthio)carboxylates.

Results and Discussion

It is reasonable to draw a scenario where a metal cation coordinates with the two carbonyl oxygens of **1** to form the *syn*-s-*cis* chelate *syn*-**2**,[5] allowing thiophenol addition from the β-face to give **4**. Lithium thiophenolate attacks preferentially from the β-face of *syn*-**2** (M^+ = Li) avoiding steric repulsion by the (trityloxy)methyl group. Indeed, the reaction of **1** with thiophenol proceeded smoothly in the presence of 0.08 equiv of lithium phenylthiolate in propionitrile at −78 °C for 2 h to afford the addition products **4** and **7** in 91% combined yield. The diastereomeric ratio of **4** and **7** was determined by ^{1}H NMR and HPLC analyses to be 85:15 (70% de) (Table 1, entry 1). Treatment of the diastereomeric mixture with saturated HCl–EtOH[6] under reflux gave (*R*)-ethyl 3-(phenylthio)-3-phenylpropionate **5**[7] of 70% ee in 88% yield, indicating that the major product was **4**.[8]

On the basis of the above result it is reasonable to expect that an increased amount of lithium phenylthiolate would promote formation of *syn*-**2** and improve the diastereoselectivity. Contrary to our expectations, the reaction of **1** in the presence of 1 equiv of lithium thiolate gave **4** and **7** in poor selectivity 48:52 (entry 3). Furthermore, 2 equiv of lithium thiolate in the presence of 2 equiv of thiophenol showed a reverse selectivity, 31:69 (entry 4). It is also noteworthy that the stoichiometry of thiophenol affects the enantioselectivity and the reaction rate.[2] In the absence of an appropriate proton source or in the presence of 2-propanol, the reaction of 2 equiv lithium thiophenolate proceeded sluggishly to afford, after 64 h, the adducts in a ratio of 19:81 (entry 6).[9] We found that 2 equiv of lithium thiolate reacted with **1** in the presence of 2 equiv 2,2,2-trifluoroethanol at −78 °C for 2 h to afford the adducts in the reversed ratio of 15:85 (entry 7). Ethanolysis of the mixture (15:85) gave (*S*)-ethyl 3-(phenylthio)-3-phenylpropionate (**8**) in 72% ee, confirming **7** as the major product. A reversal of diastereofacial differentiation was also observed when a lithium cation trapping agent, kryptofix,[10] was used, affording **4** and **7** in 43:57 (entry 8).



The reaction is under kinetic rather than thermodynamic control. Treatment of the mixture of **4** and **7** (15:85) with 0.08 equiv of lithium thiolate and 6 equiv of thiophenol in the presence or absence of trifluoroethanol did not change the ratio, and the recovered mixture was unchanged.

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(6) Basic solvolysis resulted in the concomitant elimination of thiophenol.

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(8) The chiral auxiliary (*S*)-γ-(hydroxymethyl)-γ-butyrolactam was recovered for reuse without racemization.

(9) In the absence of a proton source the reaction should form the enolate **3** or **6** as the initial product, but we could not obtain evidence for their formation. Shono, T.; Matsumura, Y.; Kashimura, S.; Hatanaka, K. *J. Am. Chem. Soc.* **1979**, *101*, 4752. Under the same conditions, an α,β-unsaturated ester does not react and is recovered. Miyata, O.; Shinada, T.; Ninomiya, I.; Naito, T.; Date, T.; Okamura, K.; Inagaki, S. *J. Org. Chem.* **1991**, *56*, 6556.

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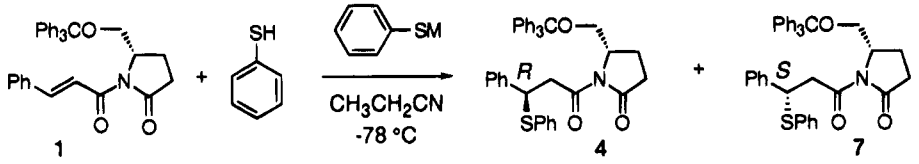
Table 1. Diastereofacial Differentiation in Thiophenol Addition to *N*-Cinnamoyl-γ-[(trityloxy)methyl]-γ-butyrolactam (1)



entry	PhSM/equiv	PhSH/equiv	additive/equiv	time[a]/h	4:7	yield/%
1	Li/0.08	6	none	2	85:15	91
2	Li/0.08	2	none	1	77:23	92
3	Li/1	2	none	1	48:52	98
4	Li/2	2	none	2	31:69	91
5	Li/5	2	none	1	35:65	89
6	Li/2	0	iPrOH/2	64	19:81	85
7	Li/2	0	CF_3CH_2OH/2	1	15:85	84
8	Li/0.08	6	kryptofix/0.2	19	43:57	74
9	MgBr/0.08	6	none	2	90:10	95
10	MgBr/1.5	0	none	60	42:58	82
11	none	6	$Mg(ClO_4)_2$/1	6	85:15	86
12	Li/0.08	6	$Mg(ClO_4)_2$/1	1	99:1	90

[a] The reaction was performed at −78 °C except for entry 8 which was done at rt and entry 11 which was performed at −20 °C for 3 h, followed by 0 °C for 3 h.

The phenylthiolate of magnesium, instead of lithium, easily forms *syn*-**2** and improves the selectivity. As had been expected, the reaction with thiol (6 equiv) in the presence of 0.08 equiv of bromomagnesium thiolate gave **4** and **7** in the improved ratio of 90:10 (entry 9). However, 1.5 equiv of bromomagnesium thiolate in the absence of a proton source again reversed the selectivity, 42:58 (entry 10).[11]

The unexpected dependence of diastereofacial differentiation on the stoichiometry of metal phenylthiolate may be rationalized by the conformational change of **1**. In the presence of more than 1 equiv of metal thiolate, **1** may form *anti*-**2** as an activated chemical species coordinated by two metal ions.[12] On the other hand, in the presence of less than 1 equiv of metal thiolate, **1** would form *syn*-**2**. The reaction takes place from these activated species to afford the corresponding enolate **3** or **6** that is protonated to give **4** or **7** as the major product, respectively. When a lithium cation is trapped by kryptofix, the major reaction occurs from the most stable conformation of **1**, *anti*-**1**,[13] to afford **7** as a major isomer.

Formation of *syn*-**2** may be possible by using a more positive metal cation. For example, magnesium perchlorate alone promotes the reaction in the absence of metal phenylthiolate to afford, after 3 h at −20 °C and 3 h at 0 °C, **4** and **7** in a ratio of 85:15 (entry 11). Upon addition of magnesium perchlorate in the presence of 0.08 equiv of lithium thiolate at −78 °C the reaction of **1** with thiophenol gave a mixture of **4** and **7** in a ratio of 99:1 in 90% yield (entry 12). It is quite interesting in that even 2 equiv of magnesium perchlorate provided the same level of high diastereoselectivity, indicating formation of *syn*-**2** ($M = Mg^{2+}$) instead of *anti*-**2**.[14]

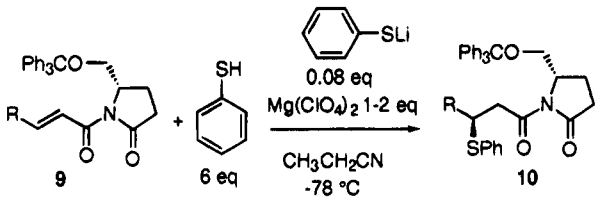
(11) Contrary to this observation, it has been reported that an organomagnesium is superior to an organolithium in formation of the *syn-s-cis* chelate and promotes a copper-catalyzed, highly diastereoselective, 1,4-addition to chiral enecarbonyl compounds. Tomioka, K.; Suenaga, T.; Koga, K. *Tetrahedron Lett.* **1986**, *27*, 369. Li, G.; Patel, D.; Hruby, V. *Tetrahedron: Asymmetry* **1993**, *4*, 2315.

(12) Contrary to our observation, appropriate stoichiometry of Lewis acid has been proposed to form the *syn-s-cis* chelate. Castellino, S.; Dwight W. J. *J. Am. Chem. Soc.* **1993**, *115*, 2986.

(13) A Cache calculation (MM and MOPAC) indicates that the *anti* conformation is more stable than the *syn* form by ca. 2 kcal.

(14) Formation of *syn*-**2** by magnesium perchlorate was confirmed by NMR analysis. The results will be reported elsewhere.

Table 2. Asymmetric Addition of Thiophenol to 9 Giving 10



entry	R	time/h	de[a]/%	yield/%
1	Me	0.5	86	90
2	iPr	3	96[b]	91
3	Bu	1	89[b]	71
4	Ph	1	98	90
5	CO_2Me	2	70	64

[a] The absolute configuration at the newly created asymmetric center of the major isomer was determined by converting to the known compounds (R = Me: Griesbeck, A.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1326. R = Ph: ref 8. R = CO_2Me: Yamashita, H.; Mukaiyama, T. *Chem. Lett.* **1985**, 363). [b] The absolute configuration was assigned by analogy.

Highly stereoselective addition of thiophenol to other chiral olefins confirmed the general applicability of the conditions (Table 2). The products were converted to the corresponding ethyl β-(phenylthio)carboxylates of high ee by treatment with saturated HCl-EtOH under reflux.

Experimental Section

General Procedure for Addition Reaction of Thiophenol (Table 2, Entry 4). To thiophenol (0.3 mL, 1.5 mmol) was added a hexane solution of butyllithium (0.03 mL, 0.04 mmol) at 0 °C. After the mixture was stirred for 10 min, propionitrile (2 mL) was added. A solution of **1**[4] (243 mg, 0.5 mmol) and $Mg(ClO_4)_2$ (112 mg, 0.5 mmol) in propionitrile (3 mL) was added to the above solution at −78 °C. The whole solution was stirred at −78 °C for 1 h and then treated with saturated NH_4Cl (10 mL). The mixture was extracted with CH_2Cl_2 (20 mL × 3). The combined extracts were washed with 10% KOH (10 mL × 2), and saturated NaCl (10 mL × 2) and dried over Na_2SO_4. Concentration followed by silica gel column chromatography (benzene) gave a mixture of **4** and **7** (268 mg, 90%). Chiral HPLC analysis (Daicel AD, hex:iPrOH = 20:1, 0.7 mL/min) showed the diastereomer ratio to be 99:1.

(*S*)-*N*-[(*R*)-3-Phenyl-3-(phenylthio)propanoyl]-5-[(trityloxy)methyl]-2-pyrrolidinone (4). ^1H NMR (270 MHz/$CDCl_3$) δ 1.82−1.98 (2H, m), 2.39 (1H, ddd, J = 3.9, 9.0, 17.8 Hz), 2.89

(1H, ddd, J = 10.3, 10.8, 17.8 Hz), 3.09 (1H, dd, J = 2.7, 10.0 Hz), 3.46 (1H, dd, J = 5.7, 17.2 Hz), 3.51 (1H, dd, J = 3.5, 10.0 Hz), 3.80 (1H, dd, J = 9.0, 17.2 Hz) 4.27 (1H, m), 4.72 (1H, dd, J = 5.7, 9.0 Hz), 7.10–7.20 (25H, m); ^{13}C NMR (67.5 MHz/$CDCl_3$) δ 21.0, 33.0, 43.1, 48.6, 56.6, 63.7, 87.0, 127.1, 127.6, 127.9, 128.3, 128.5, 128.8, 133.2, 134.3, 141.2, 143.6, 170.7, 176.3; IR (Nujol) 1725, 1680 cm^{-1}; EIMS m/z 597 (M), 354 (M − Tr), 243 (Tr). Anal. Calcd for $C_{39}H_{35}NO_3S$: C, 78.39; H, 5.86; N, 2.34. Found: C, 78.15; H, 5.68; N, 2.22.

Table 1, Entry 7. To thiophenol (21 mg, 0.2 mmol) was added a hexane solution of butyllithium (0.13 mL, 0.2 mmol) at 0 °C. After the mixture was stirred for 10 min, propionitrile (1 mL) and trifluoroethanol (0.015 mL, 0.2 mmol) were added. A solution of **1** (48 mg, 0.1 mmol) in propionitrile (1 mL) was added to the above solution at −78 °C. The whole solution was stirred at −78 °C for 1 h and then treated with saturated NH_4Cl (10 mL). The mixture was extracted with CH_2Cl_2 (20 mL × 3). The combined extract was washed with 10% KOH (10 mL × 2), and saturated NaCl (10 mL × 2) and dried over Na_2SO_4. Concentration followed by silica gel column chromatography (benzene) gave a mixture of **4** and **7** (50 mg, 84%). Chiral HPLC analysis (Daicel AD, hex:iPrOH = 20:1, 0.7 mL/min) showed the diastereomer ratio to be 15:85.

This mixture was converted to the corresponding (*S*)-ethyl ester by ethanolysis in 83% yield, which showed $[\alpha]^{25}_D$ −98.5 (*c* 0.95, $CHCl_3$). Chiral HPLC analysis (Daicel OD, hex:iPrOH = 60:1, 0.4 mL/min) showed 72%ee.

(*S*)-*N*-[(*S*)-3-Phenyl-3-(phenylthio)propanoyl]-5-[(trityloxy)methyl]-2-pyrrolidinone (7): ^{1}H NMR (270 MHz/$CDCl_3$) δ 1.77–2.10 (2H, m), 2.43 (1H, ddd, J = 2.0, 7.8, 17.8 Hz), 2.86 (1H, ddd, J = 9.7, 9.7, 17.8 Hz), 3.07 (1H, dd, J = 2.4, 9.7 Hz), 3.42 (1H, dd, J = 3.8, 9.7 Hz), 3.57 (1H, dd, J = 6.8, 17.8 Hz), 3.68 (1H, dd, J = 7.3, 17.8 Hz), 4.37 (1H, m), 4.78 (1H, dd, J = 6.8, 7.3 Hz), 7.05–7.40 (25H, m).

General Procedure for Ethanolysis. (*R*)-Ethyl 3-Phenyl-3-(phenylthio)propanoate (5). A mixture of **4** and **7** (97:3, 95% de, 155 mg, 0.26 mmol) in $CHCl_3$ 0.8 mL was added to a 6.5 M solution of HCl in EtOH 0.8 mL and the whole solution was stirred under reflux for 13 h. The solution was diluted with EtOH-$CHCl_3$ (1:1, 5 mL), neutralized with $NaHCO_3$, and stirred at rt for 1.5 h. Filtration followed by concentration afforded a yellow oil 144 mg. Purification by silica gel column chromatography (Hex/$CHCl_3$ 5:2) gave the corresponding ester (52.5 mg, 88%) and recovered lactam (18 mg, 60%). HPLC (Daicel chiralcel OD, Hex/iPrOH 60:1, 0.4 mL/min) showed 95% ee: $[\alpha]^{25}_D$ +138.3 (*c* 0.8, $CHCl_3$) (lit.[8] $[\alpha]_D$ +129.5 (*c* 1.48, $CHCl_3$)); ^{1}H NMR (270 MHz/$CDCl_3$) δ 1.15 (3H, t, J = 6.0 Hz), 2.93 (2H, d, J = 7.5 Hz), 4.04 (2H, q, J = 6.0 Hz), 4.66 (1H, t, J = 7.5 Hz), 7.12–7.41 (10H, m); IR (film) 1740 cm^{-1}.

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Supporting Information Available: Characterization data (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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