## Asymmetric Synthesis

## Highly Enantioselective Conjugate Addition of Thioglycolate to Chalcones Catalyzed by Lanthanum: Low Catalyst Loading and Remarkable Chiral Amplification\*\*

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The enantioselective conjugate addition of thiol nucleophiles to electron-deficient olefins is one of the most valuable methods for the synthesis of optically active chiral sulfur compounds, which are widely used in organic and medicinal chemistry.<sup>[1,2]</sup> Since the pioneering works of Hiemstra and Wynberg, and Mukaiyama and co-workers,<sup>[3]</sup> great endeavors have been devoted to the enantioselective sulfa-Michael reaction.<sup>[4,5]</sup> However, the substrate scope was limited to  $\alpha,\beta$ unsaturated imides,<sup>[6]</sup> aldehydes,<sup>[7]</sup> and cyclic enones.<sup>[3a,8]</sup> As for the simple chalcone derivatives, only few examples were documented with restricted substrate scope.<sup>[9]</sup> Additionally thioglycolate, a good alternative sulfur source which is relatively cheap and less toxic<sup>[10]</sup> compared to the other thiol nucleophiles, has not yet been applied in catalytic asymmetric sulfa-Michael reactions. Herein we report a highly efficient catalytic enantioselective conjugate addition of thioglycolate to chalcones using  $N_{N'}$ -dioxide/La(OTf)<sub>3</sub> complexes as the catalyst. Excellent yields (up to 99%) and enantioselectivities (up to 99% ee) were achieved for a wide range of chalcones using a 1 mol% catalyst loading. A remarkably high asymmetric amplification was observed for the reaction, which makes it possible to obtain excellent enantioselectivity of the reaction using a very low enantiomeric excess of the ligand (only 2% ee). The reaction could be additionally performed using a 0.1 mol% to 0.01 mol% catalyst loading, wherein the enantioselectivity of the reaction was maintained.

N,N'-dioxides, which have a sterically and electronically tunable chiral environment, have been applied to many asymmetric syntheses both in our group and the groups of others.<sup>[11,12]</sup> We first examined N,N'-dioxide **L1** which was complexed in situ with various rare-metal salts to catalyze the reaction between chalcone **1a** and methyl thioglycolate (**2a**)

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in CH<sub>2</sub>Cl<sub>2</sub> at 25 °C (Table 1). Different metal complexes promoted the reaction smoothly in 1 hour, but the *ee* values were very low (less than 15 % *ee*, Table 1, entries 1–5).<sup>[13]</sup> A comparatively better metal was La(OTf)<sub>3</sub>, which gave the

**Table 1:** Enantioselective conjugate addition of thioglycolate (2 a,b) to chalcone 1 a catalyzed by N,N'-dioxide–metal complexes.<sup>[a]</sup>

O			L / mastel (1.1. 10 m		COOR <sup>1</sup>
Ph	Ph + H	S <sup>COOR1</sup>	L/metal (1:1; 10 metal (1:1; 10 metal)	Ph *	Ph
1	а	2	solvent, i n	3a,	b
		<b>a</b> : R <sup>1</sup> = Me			
		<b>b</b> : R <sup>1</sup> = Et			
Entry	Ligand	Metal	Solvent	Yield [%] <sup>[b]</sup>	ee [%] <sup>[c]</sup>
1	L1	Yb(OTf)₃	$CH_2Cl_2$	88	4
2	L1	In(OTf)₃	$CH_2Cl_2$	58	0
3	L1	Sc(OTf) <sub>3</sub>	$CH_2Cl_2$	73	12
4	L1	Y(OTf)₃	$CH_2Cl_2$	90	10
5	L1	La(OTf)₃	$CH_2Cl_2$	96	14
6	L2	La(OTf) <sub>3</sub>	$CH_2Cl_2$	69	41
7	L3	La(OTf)₃	$CH_2Cl_2$	56	13
8	L4	La(OTf)₃	$CH_2Cl_2$	94	87
9	L5	La(OTf) <sub>3</sub>	$CH_2Cl_2$	95	92
10	L6	La(OTf)₃	$CH_2Cl_2$	89	91
11	L7	La(OTf)₃	$CH_2Cl_2$	95	75
12	L5	La(OTf)₃	CHCl₃	90	93
13	L5	La(OTf)₃	CHCl <sub>2</sub> CHCl <sub>2</sub>	89	94
14	L5	La(OTf)₃	CH <sub>2</sub> ClCH <sub>2</sub> Cl	96	95
15	L5	La(OTf) <sub>3</sub>	CH <sub>2</sub> ClCH <sub>2</sub> Cl	98	97 <sup>[d]</sup>
16	L5	La(OTf) <sub>3</sub>	CH <sub>2</sub> ClCH <sub>2</sub> Cl	99	97 <sup>[d,e]</sup>
17	L5	La(OTf)₃	CH <sub>2</sub> ClCH <sub>2</sub> Cl	96	94 <sup>[d,e,f]</sup>

[a] Unless otherwise noted, reactions were carried out with 0.1 mmol chalcone **1a** and 1.5 equiv methyl thioglycolate (**2a**) in solvent (0.5 mL) at 25 °C for 1 h. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] Reaction at 0 °C. [e] Used 1 mol % catalyst. [f] Used 1.5 equiv ethyl thioglycolate (**2b**). Tf=trifluoromethanesulfonyl.



4290

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product in 96% yield and 14% *ee* (Table 1, entry 5). To improve the enantioselectivity, other chiral N,N'-dioxide ligands were surveyed (Table 1, entries 6–11). Fortunately, when the ligand **L5**, having a bulkier isopropyl group at the *ortho* position of aniline, was used a 92% *ee* was achieved (Table 1, entry 9). As for the chiral backbone moiety of ligand, L-proline-derived N,N'-dioxide **L5** was superior to both **L6** (derived from L-pipecolic acid) and **L7** (derived from L-ramipril acid; Table 1, entry 9 versus entries 10 and 11).

The effects of solvent, reaction temperature, and catalyst loading were also investigated. In changing the solvent from  $CH_2Cl_2$  to  $CH_2ClCH_2Cl$ , the reaction gave the desired product in high yield and enantioselectivity (Table 1, entries 11–14). Up to 97% *ee* and a 98% yield was attained when the reaction was run at 0°C for 1 hour (Table 1, entry 15). Decreasing the catalyst loading from 10 mol% to 1 mol% did not result in loss in either the yield or enantioselectivity (Table 1, entry 16). Furthermore, this process could tolerate air and moisture. Additionally, compound **2b** was also a suitable thiol reagent, as a high yield and enantioselectivity of **3b** could be achieved under the optimized reaction conditions (Table 1, entry 17). The absolute configuration of **3a** was determined by X-ray crystallography to be *R* (Figure 1).<sup>[14]</sup>



*Figure 1.* X-ray crystallographic structure of (*R*)-**3** a. Thermal ellipsoids drawn at 30% probability.

Under the optimized reaction conditions (Table 1, entry 16), the asymmetric conjugate addition of methyl thioglycolate to various chalcones<sup>[15]</sup> were examined to provide the corresponding chiral sulfur compounds **3** in excellent yields and enantioselectivities (Table 2). Neither the electronic nature nor the steric hindrance of the substitution at the aromatic ring ( $\mathbb{R}^2$  or  $\mathbb{R}^3$ ) had any obvious influence upon the enantioselectivity and reactivity (Table 2, entries 1– 13 and 17–23). The naphthyl-substituted derivatives **10** and **1y** proceeded well with **2a**, giving the products **30** and **3y**, respectively, with excellent enantioselectivity (Table 2, entries 14 and 24). The substrate with the bulkier aliphatic  $\mathbb{R}^3$  substituent (such as *tert*-butyl) was more efficient for the

**Table 2:** Substrate scope for catalytic asymmetric conjugate addition of methyl thioglycolate (**2 a**) to chalcones **1**.<sup>[a]</sup>

Î	> + +	1-2 n	10 <b>I% L5</b> /	La(OTf) <sub>3</sub> (1	i:1) ↓	s∕_cooch₃
R² 💛	∩R³ T F	IS COOCH3	CH <sub>2</sub> CICH	H₂CI, 0 °C	$\rightarrow R^2 \checkmark$	*`R³
1		2a				3
Entry	1	$R^{2}$ , $R^{3}$	<i>t</i> [h]	Prod.	Yield [%] <sup>[b]</sup>	ee [%] <sup>[c]</sup>
1	la	Ph, Ph	1	(R)- <b>3 a</b>	99	97(R)
2	1c	Ph, 4-MeC <sub>6</sub> H₄	2	3 c	99	97
3	1 d	Ph, 2-MeOC <sub>6</sub> H <sub>4</sub>	2	3 d	99	98
4	1e	Ph, 3-MeOC <sub>6</sub> H <sub>4</sub>	1	3 e	99	97
5	1 f	Ph, 4-MeOC <sub>6</sub> H <sub>4</sub>	1	3 f	95	97
6	1g	Ph, 2-ClC <sub>6</sub> H <sub>4</sub>	1	3 g	99	97
7	1h	Ph, 3-ClC <sub>6</sub> H₄	1	3 h	99	97
8	1i	Ph, 4-ClC <sub>6</sub> H₄	1	3 i	99	97
9	1j	Ph, $4\text{-FC}_6\text{H}_4$	1	3 j	94	97
10	1 k	Ph, 4-BrC <sub>6</sub> H <sub>4</sub>	1	3 k	92	96
11	11	Ph, 3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	1	31	99	99
12	1 m	Ph, 4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	1	3 m	95	96
13	1n	Ph, 4-PhC <sub>6</sub> H₄	1	3 n	99	99
14	1o	Ph, 2-naphthyl	1	3 o	99	95
15	1p	Ph, CH₃	1	3 p	97	80 <sup>[d]</sup>
16	1 q	Ph, <i>t</i> -butyl	2	3 q	99	97
17	lr 🛛	4-MeC <sub>6</sub> H <sub>4</sub> , Ph	1	3 r	99	96
18	1 s	4-MeOC <sub>6</sub> H <sub>4</sub> , Ph	2	3 s	96	96
19	1t	2-MeOC <sub>6</sub> H <sub>4</sub> , Ph	1	3t	97	96
20	lu	4-FC <sub>6</sub> H <sub>4</sub> , Ph	1	3 u	99	98
21	1 v	4-ClC <sub>6</sub> H <sub>4</sub> , Ph	1	3 v	99	98
22	1w	4-BrC <sub>6</sub> H <sub>4</sub> , Ph	1	3 w	95	98
23	1x	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> , Ph	1	3 x	97	96
24	1у	2-naphthyl, Ph	1	3 y	99	96
25	1z	2-furyl, Ph	1	3 z	96	95
26	1 aa	2-furyl, 2-furyl	4	3 aa	85	90 <sup>[d]</sup>
27	1 ab	CH <sub>3</sub> , Ph	4	3 ab	86	72 <sup>[e]</sup>

[a] Unless otherwise noted, reactions were carried out with 1 mol% L5/ La (OTf)<sub>3</sub> (1:1), 0.2 mmol chalcones 1, and 1.5 equiv methyl thioglycolate (2a) in ClCH<sub>2</sub>CH<sub>2</sub>Cl (0.5 mL) at 0°C for 1–4 h. [b] Yield of isolated product. [c] Determined by HPLC analysis, and the absolute configuration of 3 a was determined by X-ray crystallographic analysis. [d] Used 10 mol% catalyst. [e] Used 2 mol% catalyst.

reaction (Table 2, entry 16 versus 15). In addition, the current catalyst system was also efficient for the heteroaromatic substrates, which provided the corresponding adducts in up to 95% ee and 96% yield (Table 2, entries 25 and 26). When benzalacetone was employed, moderate results were also obtained (Table 2, entry 27). Notably, the conjugate addition of other thiols (such as *t*BuSH, EtSH, PhSH, and PhCH<sub>2</sub>SH) to chalcone 1a was also tested under the optimized reaction conditions, but only trace products could be detected. These experimental phenomena indicated 2a might be activated by coordination to the catalyst at the carbonyl group.<sup>[16]</sup> Consequently, the rigid enones 4a and 4b were subjected to the reaction (Scheme 1), and excellent results were maintained with up to 95% ee and 93:7 d.r. To the best of our knowledge, most of them represented the best results for sulfa-Michael reaction using chalcone derivatives as the acceptor to date.

The relationship between the enantiomeric excess of the ligand **L5** and the product **3a** was investigated. A remarkably strong positive nonlinear effect<sup>[17]</sup> was observed for the sulfa-Michael reaction (Figure 2). The reaction could even achieve excellent enantioselectivity (94% *ee*) using **L5** having only a

Communications



Scheme 1. Asymmetric sulfa-Michael addition to rigid enones 4a and 4b using methyl thioglycolate (2a).



Figure 2. Chiral amplification in the sulfa-Michael Reaction of 1 a with 2a catalyzed by L5/La(OTf)<sub>3</sub>.

2% ee. The product (S)-3a was also obtained in 95% ee by using a catalyst derived from a ligand at very low enantiomeric excess (-2% ee). Such a phenomenon was universally presented in various chalcones (Table 3). The remarkable asymmetric amplification makes it possible to achieve high enantioselectivity (up to 98% ee) in the reaction by using L5 having a low ee value. The remarkably strong positive nonlinear effect implied that the reaction occurred in the presence of polymeric La species. The heterochiral La complex was easily formed and showed extremely low or even no catalytic activity for the reaction. Though the exact catalytically active catalyst is unclear, it is believed that the catalytically active intermediates had provided an excellent chiral environment for the reaction.

In light of the remarkable asymmetric amplification, we

additionally tested the application of the current catalyst system to prepare (R)-3a on large scale using low catalytic loading (Scheme 2). By using only 0.1 mol% of L5/ La(OTf)<sub>3</sub>, product (R)-3a was obtained in excellent yield (98%) and 94% ee. Notably, the catalyst loading was additionally lowered to 0.01 mol%, and the excellent enantioselectivity (93% ee) was maintained.<sup>[18]</sup>

In summary, we have developed an efficient asymmetric conjugate addition of chal-

cone derivates with thioglycolate catalyzed by a chiral L5/La(OTf)<sub>3</sub> complex. This method represents a rare example of the highly efficient asymmetric synthesis of the optically active chiral sulfur compounds in the presence of 1 mol% of [La<sup>III</sup>(L5)] (up to 99% ee). Additionally, excellent enantioselectivity (93% ee) was maintained when using a 0.01 mol% catalyst loading (on 4.165 g scale), which highlighted the potential value of the catalyst system.

Table 3: Catalytic asymmetric conjugate addition of methyl thioglycolate (2a) to chalcones 1 using 2% ee catalyst  $L5/La(OTf)_3$ .<sup>[a]</sup>

0 ℝ <sup>2</sup>	R <sup>3+</sup> H	HS  COOCH <sub>3</sub>	<b>5</b> (2% ee)/La nL CH <sub>2</sub> CICH <sub>2</sub>	a(OTf) <sub>3</sub> (1:1) CI, 0 °C R <sup>2</sup>	s COO R <sup>3</sup> 3
Entr	y 1	$R^{2}, R^{3}$	Prod.	Yield [%] <sup>[b]</sup>	ee [%] <sup>[c]</sup>
1	la	Ph, Ph	(R)- <b>3</b> a	95	94(R)
2	1a	Ph, Ph	(S)-3a	93	95(S) <sup>[d]</sup>
3	1 f	Ph, 4-MeOC <sub>6</sub> H₄	3 f	83	90
4	1i	Ph, 4-CIC <sub>6</sub> H <sub>4</sub>	3 i	99	94
5	11	Ph, $3 - NO_2C_6H_4$	31	88	98
6	10	Ph, 2-naphthyl	3 o	99	93
7	1r	4-MeC <sub>6</sub> H <sub>4</sub> , Ph	3 r	89	84
8	lu	4-FC <sub>6</sub> H₄, Ph	3 u	99	93
9	1 v	4-ClC₅H₄, Ph	3 v	99	94
10	1 y	2-furyl, Ph	3 z	92	85

[a] Unless otherwise noted, reactions were carried out with 1 mol% nonenantiopure L5 (2% ee)/La(OTf)<sub>3</sub> (1:1), 0.2 mmol chalcones 1, and 1.5 equiv methyl thioglycolate **2a** in CICH<sub>2</sub>CH<sub>2</sub>Cl (0.5 mL) at 0 °C for 2 h. [b] Yield of isolated product. [c] Determined by HPLC analysis and the absolute configuration was determined by X-ray crystallographic analysis. [d] Used 1 mol% non-enantiopure L5  $(-2\% ee)/La(OTf)_3$  (1:1).

Meanwhile, a strong positive nonlinear effect was observed in this catalyst system, and the substrate scope was additionally expanded to chalcones using a 2% ee catalyst at a 1 mol% catalyst loading. Additional investigations into the mechanism of the asymmetric induction<sup>[19]</sup> and the extension of the methodology to other types of additions are ongoing.

## **Experimental Section**

General experimental procedure: The mixture of ligand L5 (1.2 mg, 0.002 mmol), La(OTf)<sub>3</sub> (1.2 mg, 0.002 mmol), and chalcone **1a** (41.6 mg, 0.2 mmol) in CH<sub>2</sub>ClCH<sub>2</sub>Cl (0.5 mL) was stirred at 35 °C for 0.5 h, cooled to 0°C, and then methyl thiolglycolate 2a (0.3 mmol) was added. After the reaction was completed as determined by TLC,

			x mol% L5/La(OTf) <sub>3</sub> (1:1) y mL CH <sub>2</sub> ClCH <sub>2</sub> Cl	O S COOCH <sub>3</sub>	
	1a	2a	0 °C, 1 h	(R)- <b>3a</b>	
0.1	0.417 g (0.02 mol)	0.45 mL	y = 0.5	98% yield, 94% ee 0.62 g	
0.01	4.165 g (0.2 mol)	4.50 mL	y = 1.5	53% yield, 93% <i>ee</i> 3.33 g	

Scheme 2. Scaled-up reaction under low catalyst loading.

x =

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the mixture was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 6:1) to afford the desired product 3a in 99% yield with 97% *ee*.

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- [13] We also investigated the ligand L5 complexed in situ with Sc(OTf)<sub>3</sub> and Y(OTf)<sub>3</sub> in the catalysis of the reaction in 0.5 mL CH<sub>2</sub>Cl<sub>2</sub> at room temperature. The product was obtained in 25% *ee* and 76% yield using L5–Sc(OTf)<sub>3</sub>, and 1% *ee* and 88% yield using L5–Y(OTf)<sub>3</sub>.
- [14] CCDC 759697 (3a) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www. ccdc.cam.ac.uk/data\_request/cif.
- [15] Several other kinds of enones were also used, although most of the reactions proceeded smoothly, the sulfa-Michael products were afforded with poor *ee* values (see the Supporting Information).
- [16] For direct proof of the proposed activation, we investigated the reaction using ESI-MS. The sample was prepared from thiogly-colate and L5–La(OTf)<sub>3</sub> (1:1). The spectrum of the sample revealed ions at m/z 1163.5153, corresponding to the signals for enolate intermediates [L5 + La(OTf)<sub>2</sub> + 2a]<sup>+</sup>.
- [17] a) C. Girard, H. B. Kagan, Angew. Chem. 1998, 110, 3088; Angew. Chem. Int. Ed. 1998, 37, 2922; b) H. B. Kagan, Adv. Synth. Catal. 2001, 343, 227; c) D. G. Blackmond, Acc. Chem. Res. 2000, 33, 402; d) Y. Yuan, X. Li, J. Sun, K. L. Ding, J. Am. Chem. Soc. 2002, 124, 14866; e) T. Satyanarayana, S. Abraham, and H. B. Kagan, Angew. Chem. 2009, 121, 464; Angew. Chem. Int. Ed. 2009, 48, 456.
- [18] Chalcone 1a (4.165 g) is not soluble in 0.5 mL CH<sub>2</sub>ClCH<sub>2</sub>Cl, therefore it was dissolved in 1.5 mL of warm CH<sub>2</sub>ClCH<sub>2</sub>Cl at 50 °C. As a result, the concentration of the catalyst system was decreased, leading to a lower yield. P. J. Walsh, H. M. Li, C. A. Parrodi, *Chem. Rev.* 2007, 107, 2503.
- [19] A proposed working model is described in the Supporting Information.

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