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# Asymmetric Michael addition of malonates to enones catalyzed by a siloxy amino acid lithium salt

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**Abstract**—Siloxy amino acid lithium salt, *O-tert*-butyldiphenylsilyl L-serine lithium salt, was found to be an effective catalyst for the asymmetric Michael addition reaction of malonates to enones.

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Organocatalysis has come to be recognized as an important synthetic methodology for constructing an enantiomeric carbon center in organic synthesis.<sup>1</sup> In organocatalysis based on the formation of iminiums or enamines from carbonyl compounds with optically active amines, secondary amines, especially L-proline and its derivatives, have generally been employed as catalysts. Within common natural amino acids, however, only a few secondary amino acids are available, while more than 20 types of primary amino acids are readily obtainable from a commercial source. Although the use of primary amines as asymmetric catalysts is quite primitive, several successful works have been published in recent years.<sup>2</sup>

The Michael addition of malonates to  $\alpha,\beta$ -unsaturated carbonyl compounds is one of the most important carbon-carbon bond formation reactions, and many catalytic asymmetric syntheses have been achieved by using amine catalysts,<sup>3</sup> quaternary ammonium catalysts,<sup>4</sup> thiourea catalysts<sup>5</sup> and metal complex catalysts.<sup>6</sup> Zhao and Yang accomplished the reaction of dibenzyl malonate with cyclic or acyclic enones to give Michael adducts in very high yields (up to 99%) with excellent enantioselectivity (up to >99%ee) by using a primary-secondary diamine catalyst derived from L-tryptophan.<sup>3a</sup> To the best of our knowledge, this is one of the most successful reports about a catalytic asymmetric Michael addition of malonates to enones.<sup>3-6</sup> This indicates that primary amines have much potential as asymmetric catalysts as well as secondary amines and may become a leading candidate for asymmetric catalysts in the near future.

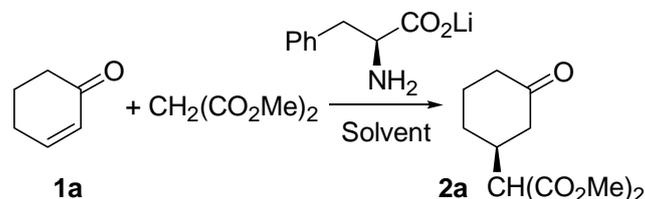
Recently, we reported that a lithium salt of a primary amino acid was an effective catalyst for the asymmetric Michael addition reaction of isobutyraldehyde with nitroalkenes.<sup>7</sup> The reaction is promoted by the formation of an enamine from the catalyst and isobutyraldehyde; that is, the reaction proceeds on the basis of activation of a Michael donor. We then turned our attention to a catalytic asymmetric Michael addition reaction by activation of a Michael acceptor. Thus, we planned the Michael addition reaction of malonates to enones via the formation of imines using a primary amino acid lithium salt as a catalyst. The catalytic use of amino acid alkali metal salts was first reported by Yamaguchi's group in 1991.<sup>3j</sup> They later succeeded in the asymmetric Michael addition of malonates to enones using L-proline rubidium salt.<sup>3g,i</sup> Quite recently, Yamamoto's group reported that asymmetric intramolecular Robinson annulation was catalyzed effectively by a primary amino acid salt.<sup>8</sup>

First, we examined the Michael addition of dimethyl malonate with 2-cyclohexen-1-one (**1a**) in the presence of L-phenylalanine lithium salt, Phe-OLi (Table 1). The reaction proceeded well in a strongly polarized solvent, DMSO or DMF, to give the Michael adduct **2a** with moderate enantioselectivity (Table 1, Entries 1 and 2). The addition of water enhanced the reaction rate and increased the yield of **2a**; however, the enantioselectivity was significantly decreased (Table 1, Entry 3). The Michael addition reaction smoothly proceeded in MeOH; however, the product **2a** was obtained as a racemate (Table 1, Entry 4). As the result of further solvent screening, it was found that the Michael addition reaction did not proceed well in weakly polarized solvents, CH<sub>2</sub>Cl<sub>2</sub>, CHCl<sub>3</sub>, toluene, CH<sub>3</sub>CN, Et<sub>2</sub>O and THF, giving only a trace amount of **2a** due to the low solubility of Phe-OLi in these solvents. To investigate the reaction using an amino acid lithium salt in a weakly polarized solvent, we synthesized a lipophilic amino acid lithium salt, *O*-*tert*-butyldiphenylsilyl L-serine lithium salt [Ser(*O*-TBDPS)-OLi].<sup>9a-d</sup> As shown in Table 2, the Michael addition reaction with Ser(*O*-TBDPS)-OLi could be carried out in various less-polar solvents. A solvent screen revealed that DMSO gave a relatively high yield and that CH<sub>2</sub>Cl<sub>2</sub> and DMF gave better enantioselectivity than the other solvents (Table 2, Entries 1 - 8). After further solvent screening, we found that a 1 : 1 mixed solvent of DMSO and CH<sub>2</sub>Cl<sub>2</sub> gave the best result (Table 2, Entry 9).

We then synthesized a variety of siloxy amino acid alkali metal salts from L-threonine (Thr), L-tyrosine (Tyr), 4-hydroxy L-proline (Hyp) and L-serine (Ser) to find a suitable catalyst (Table 3).<sup>9</sup> As for an amino acid, Ser and Thr showed better enantioselectivity than did Tyr and Hyp (Table 3, Entries 1-3 and 6). Since Ser gave a better yield of **2a** than did Thr, Ser was selected as a basic amino acid and was used for further modification of the catalyst. Next, we examined the steric effect of the silyl group of Ser(*O*-silyl)-OLi and found that a bulkier silyl group gave better yield and enantioselectivity (TBDPS>TIPS>TBS) (Table 3, Entries 4 - 6). Finally, we examined the effect of alkali metals of Ser(*O*-TBDPS)-OM and found that the enantioselectivity of the reaction greatly depends on the type of

alkali metal (Table 3, Entries 6 - 10).<sup>10</sup> The amino acid Ser(*O*-TBDPS)-OH did not work well as a catalyst and afforded only a trace amount of the Michael adduct (Table 3, Entry 11). Since a lithium salt of Ser(*O*-TBDPS) gave the best result, Ser(*O*-TBDPS)-OLi was selected as the catalyst for the Michael addition of malonates with enones. In addition, a slightly better selectivity was observed when the reaction was carried out in a diluted condition (Table 3, Entry 12).

**Table 1.** Michael addition of dimethyl malonate with **1a** using Phe-OLi.<sup>a</sup>



Entry	Solvent	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	DMSO	64	38
2	DMF	40	45
3	DMSO/H <sub>2</sub> O <sup>d</sup>	86	17
4	MeOH	80	2

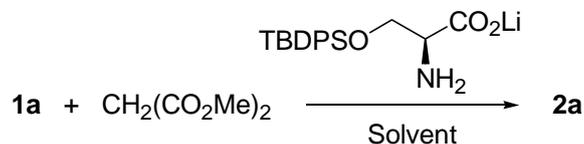
<sup>a</sup> The reaction was carried out with dimethyl malonate (1.0 mmol), **1a** (0.5 mmol) and Phe-OLi (0.1 mmol) in a solvent (1 mL) at 25 °C for 36 h.

<sup>b</sup> Isolated yield of **2a** based on **1a**.

<sup>c</sup> Determined by Chiral HPLC analysis with a Daicel CHIRALPAK AS-H column.

<sup>d</sup> H<sub>2</sub>O (5 mmol) was added.

**Table 2.** Solvent screen for Michael addition of dimethyl malonate with **1a** using Ser(*O*-TBDPS)-OLi.<sup>a</sup>



Entry	Solvent	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	DMSO	76	55
2	DMF	59	65
3	CH <sub>2</sub> Cl <sub>2</sub>	49	65
4	CHCl <sub>3</sub>	44	59
5	Et <sub>2</sub> O	61	58
6	THF	41	60
7	toluene	67	57
8	cyclohexane	69	55
9 <sup>d</sup>	DMSO/CH <sub>2</sub> Cl <sub>2</sub>	76	69
10 <sup>d</sup>	DMF/CH <sub>2</sub> Cl <sub>2</sub>	65	69

<sup>a</sup> The reaction was carried out with dimethyl malonate (0.6 mmol), **1a** (0.5 mmol) and Ser(*O*-TBDPS)-OLi (0.15 mmol) in a solvent (1 mL) at 25 °C for 24 h.

<sup>b</sup> Isolated yield of **2a** based on **1a**.

<sup>c</sup> Determined by Chiral HPLC analysis with a Daicel CHIRALPAK AS-H column.

<sup>d</sup> 1 : 1 mixed solvent of DMSO/CH<sub>2</sub>Cl<sub>2</sub> or DMF/CH<sub>2</sub>Cl<sub>2</sub>.

Next, we carried out reactions of various malonates with enone **1a** to examine the steric effects of malonates (Table 4, Entries 1 - 5). The reaction of dimethyl and diethyl malonate with **1a** gave the Michael adduct **2a** (77%, 69%ee) and **2b** (61%, 76%ee), respectively (Table 4, Entries 1 and 2). A moderately bulky malonate, di-*isopropyl*

malonate, afforded the Michael adduct **2d** in 69% yield with 80%ee; however, di-*tert*-butyl malonate was found to be too bulky to react with **1a** (Table 4, Entries 4 and 5). By increasing the amount of di-*iso*-propyl malonate to 2 equivalents to enone **1a**, the yield of **2d** was improved to 83% without a significant loss of selectivity (Table 4, Entry 6). The Michael addition reaction of di-*iso*-propyl malonate with **1a** was completed within 96 h to give the product **2d** in 92% yield with 79%ee (Table 4, Entry 8). Cycloheptenone (**1b**) also gave the Michael adduct **2e** in a good yield with high enantioselectivity (96%, 87%ee) (Table 4, Entry 9). Although the reaction of cyclopentenone (**1c**) was not completed within 7 days, moderate selectivity was observed (Table 4, Entry 10).<sup>11</sup> Michael addition reactions of acyclic enones, benzalacetone (**1d**) and chalcone (**1e**) with di-*iso*-propyl malonate proceeded slowly to afford the products **2g** (63%, 70%ee) and **2h** (47%, 10%ee) with polar by-products, respectively (Table 4, Entries 11 and 12). Probably, chalcone could not efficiently form an imine with the catalyst.

**Table 3.** Optimization of siloxy amino acid alkali metal salts<sup>a</sup>

$$\mathbf{1a} + \text{CH}_2(\text{CO}_2\text{Me})_2 \xrightarrow[\text{DMSO/CH}_2\text{Cl}_2]{\text{Catalyst}} \mathbf{2a}$$

Entry	Catalyst <sup>b</sup>	Yield <sup>c</sup> (%)	ee <sup>d</sup> (%)
1	Thr( <i>O</i> -TBDPS)-OLi	65	68
2	Tyr( <i>O</i> -TBDPS)-OLi	80	44
3	Hyp( <i>O</i> -TBDPS)-OLi	73	44
4	Ser( <i>O</i> -TBS)-OLi	52	59
5	Ser( <i>O</i> -TIPS)-OLi	63	67
6	Ser( <i>O</i> -TBDPS)-OLi	76	69
7	Ser( <i>O</i> -TBDPS)-ONa	68	43
8	Ser( <i>O</i> -TBDPS)-OK	76	29
9	Ser( <i>O</i> -TBDPS)-ORb	77	16
10	Ser( <i>O</i> -TBDPS)-OCs	77	26
11	Ser( <i>O</i> -TBDPS)-OH	trace	-
12 <sup>e</sup>	Ser( <i>O</i> -TBDPS)-OLi	59	70
13 <sup>f</sup>	Ser( <i>O</i> -TBDPS)-OLi	73	62

<sup>a</sup> The reaction was carried out with dimethyl malonate (0.6 mmol), **1a** (0.5 mmol) and a catalyst (0.15 mmol) in DMSO/CH<sub>2</sub>Cl<sub>2</sub> (1:1, 1 mL) at 25 °C for 24 h.

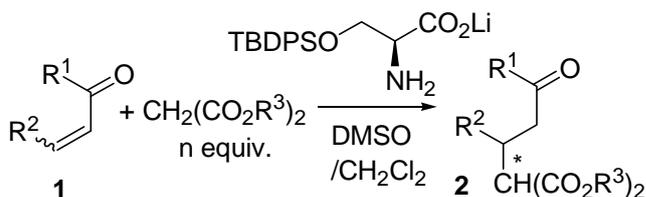
<sup>b</sup> TBDPS=*tert*-butyldiphenylsilyl, TIPS=*tri-iso*-propylsilyl, TBS=*tert*-butyldimethylsilyl.

<sup>c</sup> Isolated yield of **2a** based on **1a**.

<sup>d</sup> Determined by Chiral HPLC analysis with a Daicel CHIRALPAK AS-H column.

<sup>e</sup> The reaction was carried out in DMSO/CH<sub>2</sub>Cl<sub>2</sub> (1:1, 5 mL).

<sup>f</sup> The reaction was carried out in DMSO/CH<sub>2</sub>Cl<sub>2</sub> (1:1, 5 mL).

**Table 4.** Michael addition of various malonates with enones using Ser(*O*-TBDPS)-OLi.<sup>a</sup>

Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	n / equiv.	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1		(CH <sub>2</sub> ) <sub>3</sub> , <b>1a</b>	Me	1.2	77, <b>2a</b>	69 ( <i>S</i> )
2		<b>1a</b>	Et	1.2	61, <b>2b</b>	76 ( <i>S</i> )
3		<b>1a</b>	Bn	1.2	77, <b>2c</b>	66 ( <i>S</i> )
4		<b>1a</b>	<i>iso</i> -Pr	1.2	69, <b>2d</b>	80 ( <i>S</i> )
5		<b>1a</b>	<i>tert</i> -Bu	1.2	trace	-
6		<b>1a</b>	<i>iso</i> -Pr	2.0	83, <b>2d</b>	79 ( <i>S</i> )
7		<b>1a</b>	<i>iso</i> -Pr	3.0	88, <b>2d</b>	76 ( <i>S</i> )
8 <sup>d</sup>		<b>1a</b>	<i>iso</i> -Pr	2.0	92, <b>2d</b>	79 ( <i>S</i> )
9 <sup>d</sup>		(CH <sub>2</sub> ) <sub>4</sub> , <b>1b</b>	<i>iso</i> -Pr	2.0	96, <b>2e</b>	87 ( <i>S</i> )
10 <sup>e</sup>		(CH <sub>2</sub> ) <sub>2</sub> , <b>1c</b>	<i>iso</i> -Pr	2.0	47, <b>2f</b>	55 ( <i>S</i> )
11 <sup>e</sup>	Me	<i>trans</i> -P h, <b>1d</b>	<i>iso</i> -Pr	2.0	63, <b>2g</b>	70 ( <i>R</i> )
12 <sup>e</sup>	Ph	<i>trans</i> -P h, <b>1e</b>	<i>iso</i> -Pr	2.0	47, <b>2h</b>	10 ( <i>R</i> )

<sup>a</sup> The reaction was carried out with a malonate (n equiv.), **1** (0.5 mmol) and Ser(*O*-TBDPS)-OLi (0.15 mmol) in DMSO/CH<sub>2</sub>Cl<sub>2</sub> (1:1, 5 mL) at 25 °C for 72 h.

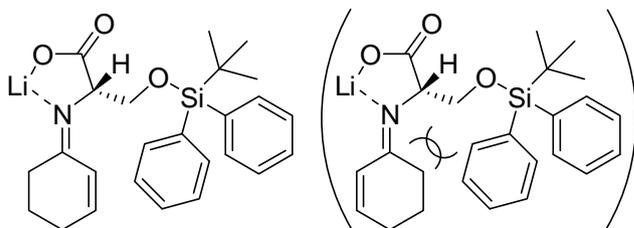
<sup>b</sup> Isolated yield of **2** based on **1**.

<sup>c</sup> Determined by Chiral HPLC analysis with a Daicel CHIRALPAK AS-H or AD-H column. Absolute configuration of **2** is shown in parentheses.

<sup>d</sup> The reaction was carried out for 96 h.

<sup>e</sup> The reaction was carried out for 7 days.

A plausible reaction intermediate for the Michael addition reaction using **1a** is shown in Figure 1. As previously reported for imine-based primary amine catalysis,<sup>2a,c</sup> the present Michael addition of malonates with enones also proceeds via the formation of imine. Although (*E*)- and (*Z*)-stereoisomers of imine can be formed, a relatively bulky methylene group comes to the less-hindered side rather than the vinyl group. The Lewis acidic lithium cation coordinates with the nitrogen atom of imine to reduce the electron density of the β-carbon and to hold the side chain of the amino acid on the *Re*-face of the imine. Therefore, a malonate attacks from the *Si*-face of the imine to give (*S*)-Michael adduct selectively. Probably, a small and Lewis acidic lithium cation can coordinate more strongly with the nitrogen atom than can other alkali metal cations.

**Figure 1.** Plausible reaction intermediate

In summary, we found that a primary amino acid lithium salt worked as a catalyst for the asymmetric Michael addition of malonates to enones. A lipophilic amino acid lithium salt, Ser(*O*-TBDPS)-OLi, was

found to be an effective catalyst, and various 1,5-ketoesters were synthesized in good yields with moderate to high enantioselectivity.

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