



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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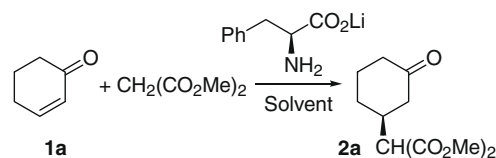
Organocatalysis has been recognized as an important synthetic methodology for constructing an enantiomeric carbon center in organic synthesis.¹ In organocatalysis based on the formation of iminiums or enamines from carbonyl compounds with optically active amines, secondary amines, especially *L*-proline 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.²

The Michael addition of malonates to α,β -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,³ quaternary ammonium catalysts,⁴ thiourea catalysts,⁵ and metal complex catalysts.⁶ 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.^{3a} They explained that the reaction proceeds via the iminium catalysis: the primary amine moiety activates an enone via the formation of an iminium ion and the secondary amine moiety activates a malonate. To the best of our knowledge, this is one of the most successful reports about a catalytic asymmetric Michael addition of malonates to enones using organocatalysts or metal catalysts.^{3–6} 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.⁷ 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.^{3j} They later succeeded in the asymmetric Michael addition of malonates to enones using *L*-proline rubidium salt.^{3g,i} Quite recently, Yamamoto's group reported that asymmetric intramolecular Robinson annulation was catalyzed effectively by a primary amino acid salt.⁸

Table 1
Michael addition of dimethyl malonate with **1a** using Phe-OLi^a



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

^a 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.

^b Isolated yield of **2a** based on **1a**.

^c Determined by Chiral HPLC analysis with a Daicel CHIRALPAK AS-H column.

^d H₂O (5 mmol) was added.

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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 high-polar 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 low-polar solvents, CH₂Cl₂, CHCl₃, toluene, CH₃CN, Et₂O, 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 low-polar solvent, we synthesized a lipophilic amino acid lithium salt, *O*-tert-butylidiphenylsilyl L-serine lithium salt [Ser(*O*-TBDPS)-OLi].^{9a–d} As shown in Table 2, the Michael addition reaction with Ser(*O*-TBDPS)-OLi could be carried out in various low-polar solvents. The reactions were carried out with 30 mol % of catalyst to consume substrates satisfactory. A solvent screen revealed that DMSO gave a relatively high yield and that CH₂Cl₂ 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 CH₂Cl₂ 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).⁹ As for an amino acid, Ser and Thr showed better enantioselectivity than Tyr and Hyp (Table 3, entries 1–3 and 6). Since Ser gave a better yield of **2a** than 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).¹⁰ 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

Table 2
Solvent screen for Michael addition of dimethyl malonate with **1a** using Ser(*O*-TBDPS)-OLi^a

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

^a 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.

^b Isolated yield of **2a** based on **1a**.

^c Determined by Chiral HPLC analysis with a Daicel CHIRALPAK AS-H column.

^d 1:1 mixed solvent of DMSO/CH₂Cl₂ or DMF/CH₂Cl₂.

Table 3
Optimization of siloxy amino acid alkali metal^a

Entry	Catalyst ^b	Yield ^c (%)	ee ^d (%)
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 ^e	Ser(<i>O</i> -TBDPS)-OLi	59	70
13 ^f	Ser(<i>O</i> -TBDPS)-OLi	73	62

^a The reaction was carried out with dimethyl malonate (0.6 mmol), **1a** (0.5 mmol), and a catalyst (0.15 mmol) in DMSO/CH₂Cl₂ (1:1, 1 mL) at 25 °C for 24 h.

^b TBDPS = *tert*-butyldiphenylsilyl, TIPS = *tri*-*iso*-propylsilyl, TBS = *tert*-butyldimethylsilyl.

^c Isolated yield of **2a** based on **1a**.

^d Determined by Chiral HPLC analysis with a Daicel CHIRALPAK AS-H column.

^e The reaction was carried out in DMSO/CH₂Cl₂ (1:1, 5 mL).

^f The reaction was carried out in DMSO/CH₂Cl₂ (1:1, 0.5 mL).

selectivity was observed when the reaction was carried out in a diluted condition (Table 3, entry 12).

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-*iso*-propyl 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

Table 4
Michael addition of various malonates with enones using Ser(*O*-TBDPS)-OLi^a

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

^a The reaction was carried out with a malonate (*n* equiv), **1** (0.5 mmol), and Ser(*O*-TBDPS)-OLi (0.15 mmol) in DMSO/CH₂Cl₂ (1:1, 5 mL) at 25 °C for 72 h.

^b Isolated yield of **2** based on **1**.

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

^d The reaction was carried out for 96 h.

^e The reaction was carried out for 7 days.

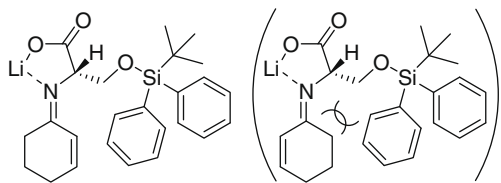


Figure 1. Plausible reaction intermediate.

amount of di-*iso*-propyl malonate to 2 equiv 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).¹¹ 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.

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,^{2a,c} 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.

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*-TBBDPS)-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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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.033.

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