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

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ABSTRACT

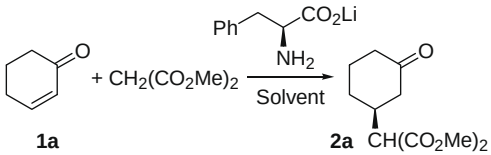
Siloxy amino acid lithium salt, *O-tert*-butyldiphenylsilyl L-serine lithium salt, was found to be an effective catalyst for the asymmetric Michael addition reaction of malonates to enones.

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_2O[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] H_2O (5 mmol) was added.

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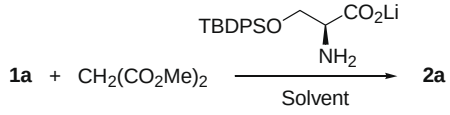
First, we examined the Michael addition of dimethyl malonate with 2-cyclohexen-1-one (**1a**) in the presence of L-phenylalanine lithium salt, Phe-OLi (Table 1). The reaction proceeded well in a high-polar solvent, DMSO or DMF, to give the Michael adduct **2a** with moderate enantioselectivity (Table 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, CH_2Cl_2, $CHCl_3$, toluene, CH_3CN, Et_2O, 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*-butyldiphenylsilyl 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 CH_2Cl_2 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_2Cl_2 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 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

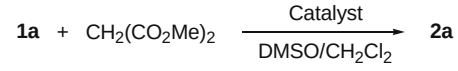
Table 2
Solvent screen for Michael addition of dimethyl malonate with **1a** using Ser(*O*-TBDPS)-OLi[a]



Entry	Solvent	Yield[b] (%)	ee[c] (%)
1	DMSO	76	55
2	DMF	59	65
3	CH_2Cl_2	49	65
4	$CHCl_3$	44	59
5	Et_2O	61	58
6	THF	41	60
7	Toluene	67	57
8	Cyclohexane	69	55
9[d]	DMSO/CH_2Cl_2	76	69
10[d]	DMF/CH_2Cl_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/CH_2Cl_2 or DMF/CH_2Cl_2.

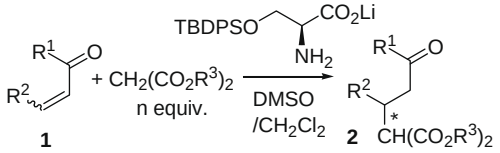
Table 3
Optimization of siloxy amino acid alkali metal[a]



Entry	Catalyst[b]	Yield[c] (%)	ee[d] (%)
1	Thr(*O*-TBDPS)-OLi	65	68
2	Tyr(*O*-TBDPS)-OLi	80	44
3	Hyp(*O*-TBDPS)-OLi	73	44
4	Ser(*O*-TBS)-OLi	52	59
5	Ser(*O*-TIPS)-OLi	63	67
6	Ser(*O*-TBDPS)-OLi	76	69
7	Ser(*O*-TBDPS)-ONa	68	43
8	Ser(*O*-TBDPS)-OK	76	29
9	Ser(*O*-TBDPS)-ORb	77	16
10	Ser(*O*-TBDPS)-OCs	77	26
11	Ser(*O*-TBDPS)-OH	Trace	—
12[e]	Ser(*O*-TBDPS)-OLi	59	70
13[f]	Ser(*O*-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/CH_2Cl_2 (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/CH_2Cl_2 (1:1, 5 mL).
[f] The reaction was carried out in DMSO/CH_2Cl_2 (1:1, 0.5 mL).

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**	*iso*-Pr	1.2	69, **2d**	80 (*S*)
5		**1a**	*tert*-Bu	1.2	Trace	—
6		**1a**	*iso*-Pr	2.0	83, **2d**	79 (*S*)
7		**1a**	*iso*-Pr	3.0	88, **2d**	76 (*S*)
8[d]		**1a**	*iso*-Pr	2.0	92, **2d**	79 (*S*)
9[d]		$(CH_2)_4$, **1b**	*iso*-Pr	2.0	96, **2e**	87 (*S*)
10[e]		$(CH_2)_2$, **1c**	*iso*-Pr	2.0	47, **2f**	55 (*S*)
11[e]	Me	*trans*-Ph, **1d**	*iso*-Pr	2.0	63, **2g**	70 (*R*)
12[e]	Ph	*trans*-Ph, **1e**	*iso*-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/CH_2Cl_2 (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.

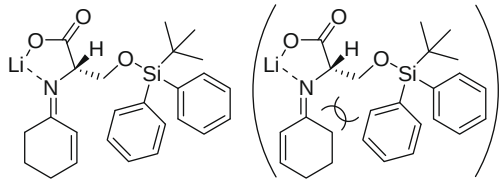


Figure 1. Plausible reaction intermediate.

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*-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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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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