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Asymmetric Michael Addition of Malonates to Enones Catalyzed by a Primary β-Amino Acid and Its Lithium Salt

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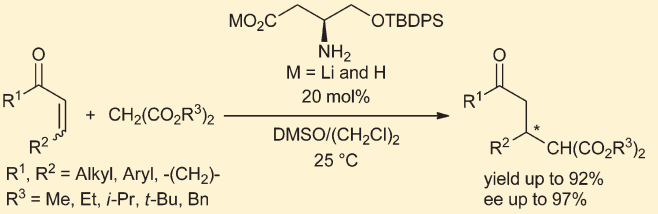
Supporting Information

ABSTRACT: Highly enantioselective Michael addition of malonates to enones was achieved using a mixed catalyst consisting of a primary β-amino acid, *O*-TBDPS (*S*)-β-homoserine, and its lithium salt. Various cyclic and acyclic enones were converted into 1,5-ketoesters in high yields (up to 92%) with high enantioselectivity (up to 97% ee) under mild reaction conditions. Details of synthesis of the catalyst, optimization of the reaction conditions for the Michael addition reaction, and a plausible reaction mechanism are described.



Michael addition reaction of a nucleophile to an α,β-unsaturated carbonyl compound is a strong candidate for the purpose of introducing a substituent into the β-position of the carbonyl group since a large number of examples using various Michael donors and acceptors have been reported. In the case of creating a carbon−carbon bond by the Michael addition reaction, malonates are recognized as useful Michael donors, and a catalytic asymmetric version of the reaction has been achieved using various catalysts including both organocatalysts and organometallic catalysts.[1] As pioneering works in organocatalytic asymmetric Michael addition of carbon nucleophiles to α,β-unsaturated carbonyl compounds,[2] Yamaguchi's group reported that an alkali metal salt of proline efficiently promoted the Michael addition of malonates to enones.[1m−o] In the course of using a primary amino acid as an asymmetric catalyst,[3,4] we recently found that a lithium salt of primary α-amino acid was also an effective catalyst for the asymmetric Michael addition of malonates to enones; however, there was room for improvement in the yields and enantioselectivity of the reaction.[5] To investigate the reaction using a primary amino acid catalyst in more detail, we then planned to employ a β-amino acid as a catalyst because it is known that both yield and enantioselectivity of amino acid catalysis are greatly affected by the position of the amino and carboxyl groups in the catalyst.[6] In this report, we present details of the Michael addition reaction of malonates to enones catalyzed by a primary β-amino acid and its lithium salt (Figure 1).

Initially, lithium salts of 4- and 1-benzyl L-aspartates **1a**,**b** were employed for the asymmetric Michael addition of dimethyl malonate (**2a**) to 2-cyclohexen-1-one (**3a**) to evaluate the difference between an α- and a β-amino acids as catalysts (Table 1, entries 1 and 2). Although the reaction using a β-amino acid salt catalyst **1b** was slow, enantioselectivity was much higher than that in the reaction using an α-amino acid salt catalyst **1a**. Therefore, we decided to employ various β-amino acid lithium salts to carry out a catalyst screen. While esters **1c**,**d** and a dipeptide **1e** gave the Michael adduct **4a** in low to moderate yields (16−42%) with moderate to good enantioselectivity (43−77% ee), a siloxymethyl-substituted β-amino acid salt, *O*-TBDPS (*S*)-β-homoserine lithium salt (**1f**), provided **4a** in a good yield (65%) with high enantioselectivity (82% ee) (Table 1, entry 8). Since the use of siloxymethyl-substituted α- and γ-amino acid salts, **1h**[5] and **1i**, as catalysts resulted in lower enantioselectivity than that from using the β-amino acid salt catalyst **1f**, a β-amino acid moiety was found to be necessary to obtain the Michael adduct with high enantioselectivity (Table 1, entries 9 and 10).[6] Hence, we chose **1f** as a catalyst for further investigations.

After carrying out a solvent screen for Michael addition reaction of **2a** to **3a** with catalyst **1f** (see Supporting Information), we found that a mixed solvent consisting of DMSO and dichloroethane afforded the Michael adduct **4a** with the best enantioselectivity among common organic solvents (Table 2, entry 1). We then attempted to improve the conversion of the Michael addition reaction to increase the yield of **4a**. Results obtained by a screening of additives showed that the addition of a catalytic amount of benzoic or acetic acid greatly increased the yield of **4a** without any loss of enantioselectivity (Table 2, entries 2 and 3). The addition of a weaker or stronger acid or water also increased the yield of **4a**; however, the enantioselectivity was decreased (Table 2, entries 4−6). Since amino acid salt catalyst **1f** is a base, we assumed that the addition of an acid generated an amino acid **1g** in situ by an acid−base equilibrium reaction. This assumption was supported by the fact that Michael addition reaction in the presence of catalyst **1g** and lithium benzoate gave a result similar to that in the presence of catalyst **1f** and benzoic acid

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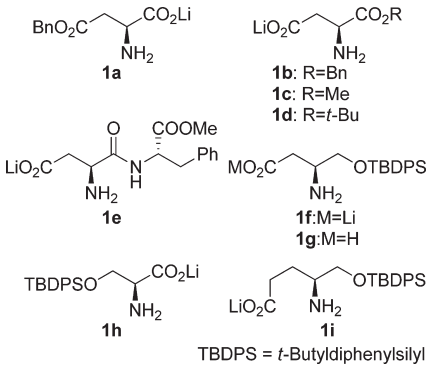
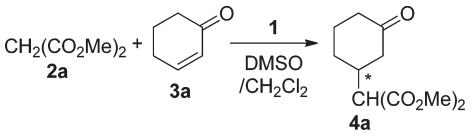


Figure 1. Catalysts used in the Michael addition of malonates to enones.

Table 1. Catalyst Screen for Michael Addition of 2a to 3a[a]



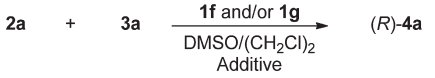
entry	catalyst	yield[b] (%)	ee[c] (%)
1	**1a**	81	63 (*S*)
2	**1b**	22	72 (*R*)
3	**1c**	16	74 (*R*)
4	**1d**	42	43 (*R*)
5	**1e**	25	77 (*R*)
6	**1f**	65	82 (*R*)
7	**1h**	76	69 (*S*)
8	**1i**	70	51 (*R*)

[a] Reactions were carried out with **1** (0.15 mmol), **2a** (0.6 mmol), and **3a** (0.5 mmol) in DMSO/CH_2Cl_2 (1:1, 1 mL) at 25 °C for 24 h. [b] Isolated yield of **4a** based on **3a**. [c] Determined by chiral HPLC analysis. Absolute configurations of **4a** determined by comparison of the specific rotation with that of the literatures are shown in parentheses (see Supporting Information).

(Table 2, entries 2 and 7). Since Michael addition reaction using amino acid catalyst **1g** with other alkali metal (Na, K, Rb, and Cs) salts of benzoic acid or without any additives led to lower yields (except for the reaction with $PhCO_2Na$) and lower enantioselectivity, both amino acid **1g** and its lithium salt **1f** would be necessary to achieve high yield and enantioselectivity (Table 2, entries 8−12). Indeed, a mixed catalyst consisting of **1f** and **1g** afforded the Michael adduct **4a** in good yields with high enantioselectivity (Table 2, entries 13−16). The best molar ratio of **1f** to **1g** was determined to be 1:3 (Table 3, entry 15).

Finally, we examined substrate scope with various malonates and enones (Table 3). Michael addition reaction of **2a** to **3a** was completed within 96 h to give **4a** in 91% yield with 93% ee (Table 3, entry 1). By using moderately bulky malonates, diethyl malonate (**2b**) and diisopropyl malonate (**2c**), Michael adducts **4b,c** were synthesized with slightly better enantioselectivity (95% ee) than that of **2a**, although di-*tert*-butyl malonate (**2d**) was too bulky to react with **3a** (Table 3, entries 2−4). Although the reaction of **2b** with **3a** required 5 days to consume **3a** completely, the reaction time could be reduced to 2 days by increasing the amount of catalyst to 20 mol % from 10 mol % (Table 2, entry 6).

Table 2. Additive Screen for Michael Addition Reaction of 2a to 3a in the Presence of Catalyst 1f and/or 1g[a]



entry	catalyst	additive	yield[b] (%)	ee[c] (%)
1	**1f**	none	43	90
2	**1f**	$PhCO_2H$	69	92
3	**1f**	CH_3CO_2H	70	92
4	**1f**	p-$NO_2C_6H_4OH$	55	87
5	**1f**	p-$CH_3C_6H_4SO_3H$	77	78
6	**1f**	H_2O[d]	54	87
7	**1g**	$PhCO_2Li$	73	93
8	**1g**	$PhCO_2Na$	76	74
9	**1g**	$PhCO_2K$	59	43
10	**1g**	$PhCO_2Rb$	64	44
11	**1g**	$PhCO_2Cs$	65	33
12	**1g**	none	26	13
13	**1f**/**1g** (3:1)	none	61	92
14	**1f**/**1g** (1:1)	none	71	93
15	**1f**/**1g** (1:3)	none	76	93
16	**1f**/**1g** (1:6)	none	74	90

[a] Unless otherwise mentioned, the reactions were carried out with **1f** and/or **1g** (total 0.05 mmol), **2a** (1.0 mmol), **3a** (0.5 mmol), and an additive (0.05 mmol) in DMSO/$(CH_2Cl)_2$ (1:2, 1 mL) at 25 °C for 24 h. [b] Isolated yield of **4a** based on **3a**. [c] Determined by chiral HPLC analysis. [d] 0.5 mmol of H_2O was added.

We then employed other cyclic enones as substrates. Reaction of 2-cyclohepten-1-one (**3b**) was also successfully completed within 2 days to give Michael adduct **4f** in 89% yield with 97% ee, while the reaction with 2-cyclopenten-1-one (**3c**) was very slow and provided Michael adduct **4g** in 61% yield after 7 days (Table 3, entries 7 and 8).[1a,g,l] Acyclic enones were then subjected to the reaction conditions. Benzalacetone (**3d**), 4-phenyl-3-buten-2-one, was found to be a good substrate to provide Michael adduct **4h** in a good yield (92%) with high enantioselectivity (86% ee) (Table 3, entry 9). Other 4-aryl-3-buten-2-ones, (*E*)-4-(furan-2-yl)- (**3e**) and (*E*)-4-(thiophen-2-yl)-3-buten-2-one (**3f**), also gave similar results, and the corresponding Michael adducts **4i** (88%, 90% ee) and **4j** (86%, 85% ee) were successfully obtained (Table 3, entries 10 and 11). Although a 4-alkyl-3-buten-2-one, (*E*)-3-octen-2-one (**3g**), required longer reaction time, Michael adduct **4k** was obtained in a good yield with high enantioselectivity (Table 3, entry 12). Unfortunately, chalcone (**3h**), an aryl vinyl ketone, was found to be an unsuitable substrate for the present reaction conditions since a large amount of **3h** was recovered after carrying out the reaction for 7 days (Table 3, entry 13).

A plausible reaction mechanism of Michael addition reaction of **2a** to **3a** catalyzed by a mixed catalyst **1f**/**1g** is depicted in Scheme 1. Since the use of amino acid **1g** as a sole catalyst gave the Michael adduct **4a** in a low yield with very low enantioselectivity (Table 2, entry 12), amino acid lithium salt **1f** would favorably react with **3a** to form carbinolamine **I**. Probably, amino acid **1g** converted the carbinolamine **I** into carbinolamine **II** by an acid−base equilibrium reaction to promote the formation of imine **III** since dehydration of carbinolamine generally proceeds smoothly in a weak acidic condition. Then malonate **2a** was added to the imine **III** from the less hindered side to generate

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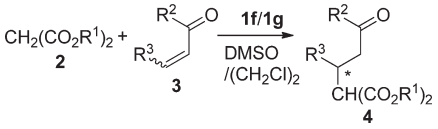
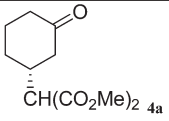
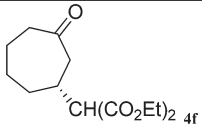
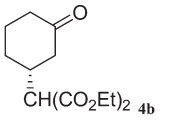
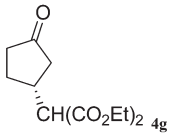
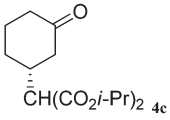
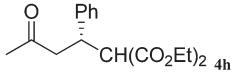
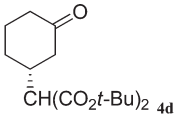
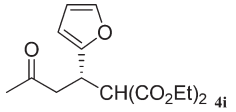
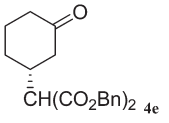
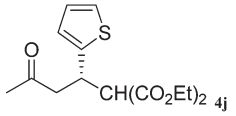
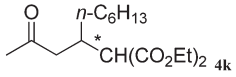
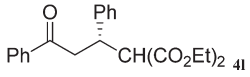
Table 3. Substrate Scope[a]



Entry	Michael adduct **4**	Time (d)	Yield[b] (%)	ee[c] (%)	Entry	Michael adduct **4**	Time (d)	Yield[b] (%)	ee[c] (%)
1	 **4a**	4	91	93, (*R*)	7	 **4f**	2[e]	89	97, (*R*)
2	 **4b**	5	91	95, (*R*)	8	 **4g**	7[e]	61	73, (*R*)
3	 **4c**	3	85	95, (*R*)	9	 **4h**	3[e]	92	86, (*S*)
4	 **4d**	7	47[d]	86, (*R*)	10	 **4i**	3.5[e]	88	90, (*S*)
5	 **4e**	3	92	92, (*R*)	11	 **4j**	3.5[e]	86	85, (S)
6	**4b**	2[e]	91	95, (*R*)	12	 **4k**	6[e]	69	85
					13	 **4l**	7[e]	36[f]	10, (*S*)

[a] Unless otherwise mentioned, the reactions were carried out with a mixed catalyst **1f**/**1g** (1:3, 0.05 mmol), **2** (1.0 mmol), and **3** (0.5 mmol) in DMSO/$(CH_2Cl)_2$ (1:2, 0.5 mL) at 25 °C. [b] Isolated yield of **4** based on **3**. [c] Determined by chiral HPLC analysis. Absolute configurations of **4** determined by comparison of the specific rotation with that of the literatures are shown in parentheses (see Supporting Information). [d] Conversion: 83%. [e] The amount of catalyst was increased to 0.1 mmol. [f] Conversion: 40%.

imine **IV**. Finally, hydration of the imine **IV** provided the Michael adduct **4a** and catalyst **1f**/**1g**.

In summary, we found that a mixed catalyst consisting of a primary β-amino acid, *O*-TBDPS β-homoserine, and its lithium salt was an effective catalyst for Michael addition reaction of malonates to enones to give various 1,5-ketoesters in good yields with high enantioselectivity.

EXPERIMENTAL SECTION

Materials. Enones and malonates were used after purification by distillation or column chromatography. 4-Benzyl L-aspartate, 1-benzyl L-aspartate, 1-methyl L-aspartate, 1-*t*-butyl L-aspartate, and aspartame were commercially available. Their lithium salts **1a**−**e** were prepared by treatment with lithium hydroxide according to the literature.[1m] *O-tert*-Butyldiphenylsilyl L-serine was synthesized according to the literature[7] and converted into its lithium salt **1h**.

Synthesis of *O-tert*-Butyldiphenylsilyl (*S*)-β-Homoserine (1g). To a mixture of $NaHCO_3$ (4.20 g, 50 mmol), H_2O (100 mL), and THF (50 mL) was added 4-benzyl L-aspartate (4.46 g, 20 mmol). After cessation of gas evolution, benzyl chloroformate (3.75 g, 22 mmol) was added dropwise. After stirring for 1 h at room temperature, the resulting reaction mixture was washed with Et_2O (50 mL × 2) and acidified to pH 2 with aq 1 N HCl. The obtained cloudy solution was extracted with ethyl acetate (50 mL × 3). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained white solid was washed with hexane and dried in air to give 4-benzyl *N*-benzyloxycarbonyl L-aspartate [Z-Asp(OBn)-OH][8,9] in 98% yield (7.00 g, 19.6 mmol). In a round-bottomed flask, trimethyl borate (6.7 mL, 60 mmol) was added to a solution of Z-Asp(OBn)-OH (7.14 g, 20 mmol) in dry THF (80 mL)

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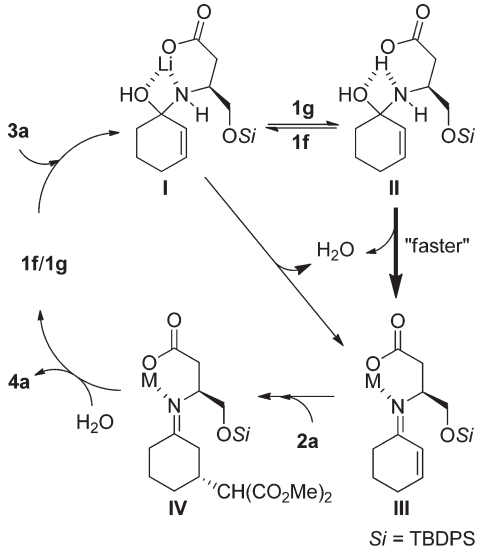
Scheme 1. Plausible Reaction Mechanism



at 0 °C. After stirring for 10 min at 0 °C, borane dimethylsulfide complex (12 mL, 120 mmol) was added, and the whole reaction mixture was stirred for 2 h at room temperature. Then H_2O (100 mL) and saturated aq $NaHCO_3$ (100 mL) were successively added carefully, and the resulting solution was extracted with ethyl acetate (100 mL × 3). The combined organic phase was washed with a diluted aq NaCl (made from 10 mL of H_2O and 100 mL of saturated aq NaCl), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude product was purified by column chromatography (silica gel; hexane/ethyl acetate 1:1) to give *N*-benzyloxycarbonyl (*S*)-*β*-homoserine benzyl ester [Z-Asp(OBn)-ol][10] in 66% yield (4.53 g, 13.2 mmol). To a solution of Z-Asp(OBn)-ol (4.53 g, 13.2 mmol) in DMF (25 mL) were successfully added at 0 °C imidazole (0.9 g, 13.2 mmol) and *t*-butyldiphenylchlorosilane (3.63 g, 13.2 mmol). After stirring for 14 h at room temperature, the resulting solution was poured into saturated aq NH_4Cl (100 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic phase was washed with saturated aq NaCl (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude product was purified by column chromatography (silica gel; hexane/ethyl acetate 3:1) to give *N*-benzyloxycarbonyl *O*-*t*-butyldiphenylsilyl (*S*)-*β*-homoserine benzyl ester in 89% yield (6.79 g, 11.7 mmol). *N*-Benzyloxycarbonyl *O*-*t*-butyldiphenylsilyl (*S*)-*β*-homoserine benzyl ester (2.91 g, 5 mmol) was dissolved in MeOH (40 mL), and the solution was added on Pd/C (10%, 300 mg) under nitrogen atmosphere in a round-bottomed flask. After the atmosphere in the flask was replaced with hydrogen, the reaction mixture was stirred for 18 h under hydrogen atmosphere at room temperature. Pd/C was filtered with Celite, and the filtrate was concentrated under reduced pressure. The obtained white solid was washed with H_2O and hexane successively and dried in air to give pure *O*-*t*-butyldiphenylsilyl (*S*)-*β*-homoserine (**1g**) in 79% yield (1.41 g, 3.95 mmol) as a white solid: mp 154−155 °C; $[\alpha]^{19}_D$ = −13.7 (*c* = 1.0, MeOH), δ_H (CD_3OD) 1.09 (9H, s), 2.43−2.53 (2H, m), 3.53−3.58 (1H, m), 3.70−3.81 (2H, m), 7.41−7.70 (10H, m); δ_C (CD_3OD) 20.0, 27.3, 36.3, 52.2, 65.1, 129.0, 131.2, 131.3, 133.68, 133.71, 136.71, 136.73, 177.3; ν (KBr)/cm^{-1} 1594 (C═O); HR ESI-MS calcd for $C_{20}H_{27}NO_3Si$ + Na (M + Na) 380.1652, found M^+ + Na, 380.1653.

Preparation of a Mixed Catalyst 1f/1g (1:3). In a vial, ground LiOH monohydrate (42 mg, 1 mmol) was added to a solution of **1g** (1.43 g, 4 mmol) in MeOH (4 mL) at 0 °C. After stirring overnight at room temperature, the reaction mixture was concentrated under reduced pressure. The obtained white solid was ground well and dried in vacuo. The obtained powder was used as a mixed catalyst **1f**/**1g** (1:3).

(*S*)-4-Amino-5-*tert*-butyldiphenylsiloxy Valeric Acid Litium Salt (1i). 5-Benzyl L-glutamate was synthesized by a modified procedure of the literature method.[11] In a round-bottomed flask, benzyl alcohol (12 g, 110 mmol) was added to a mixture of L-glutamic acid (14.7 g, 100 mmol), concd H_2SO_4 (9.8 g) and H_2O (6.5 mL), and the whole reaction mixture was stirred for 45 min at 70 °C. Then water was removed from the flask under reduced pressure for 4 h at 70 °C. The resulting syrup was poured into a 500 mL beaker containing $NaHCO_3$ (16.8 g, 200 mmol) and H_2O (50 mL) at 0 °C, and the remaining syrup in the flask was washed off with cold water (30 mL). After the combined reaction mixture was left standing overnight at room temperature, a precipitated white solid was collected by filtration and recrystallized from H_2O. The obtained white solid was washed with ethyl acetate to give 5-benzyl L-glutamate in 33% yield (7.88 g, 33 mmol). Z Protection (86%), reduction of carboxyl group (60%), TBDPS protection (74%), and removal of benzyl and Z groups (82%) were performed by the same procedure for the synthesis of **1g** to give (*S*)-4-amino-5-*t*-butyldiphenylsiloxy valeric acid (pre-**1i**): mp 126−127 °C; $[\alpha]^{19}_D$ = +18.5 (*c* = 1.0, MeOH), δ_H ($CDCl_3$) 1.02 (9H, s), 1.60−1.87 (2H, m), 2.20−2.40 (2H, m), 3.17−3.22 (1H, m), 3.68 (2H, d, *J* = 5.4 Hz), 7.31−7.62 (10H, m); δ_C ($CDCl_3$) 19.2, 25.8, 26.8, 34.6, 53.5, 64.7, 127.8, 129.9, 132.55, 132.59, 135.51, 135.54, 179.1; ν (KBr)/cm^{-1} 1577 (C═O); HR ESI-MS calcd for $C_{21}H_{29}NO_3Si$ + Na (M + Na) 394.1809, found M^+ + Na, 394.1805. Treatment with pre-**1i** with lithium hydroxyde[1m] gave the title compound **1i**.

Typical Procedure for the Michael Addition of Malonates 2 to Enones 3. In a 7 mL vial, **2b** (160 mg, 1 mmol) was added to a solution of a mixed catalyst **1f**/**1g** (1:3, 36 mg, 0.1 mmol) and **3a** (48 mg, 0.5 mmol) in DMSO/$(CH_2Cl)_2$ (1:2, 0.5 mL) at 25 °C. After the reaction mixture was stirred for 48 h at 25 °C, saturated aq NaCl (1 mL) was added to the vial and extracted with Et_2O (1.5 mL × 4). The combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. (*R*)-3-[Bis(ethoxycarbonyl)methyl]cyclohexanone (**4b**)[12a,b] was isolated by column chromatography (silica gel, hexane/Et_2O 1:1) in 91% yield (116 mg, 0.455 mmol) as oil. The enantioselectivity was determined by HPLC analysis (95% ee). The absolute configuration was determined by comparison of the specific rotation with that of the literature: δ_H ($CDCl_3$) 1.26−1.30 (6H, t × 2, *J* = 7.2 Hz), 1.46−1.56 (1H, m), 1.62−1.74 (1H, m), 1.95−1.98 (1H, m), 2.05−2.11 (1H, m), 2.22−2.31 (2H, m), 2.38−2.59 (3H, m), 3.30 (1H, d, *J* = 7.9 Hz), 4.18−4.24 (4H, q × 2, *J* = 7.2 Hz).

4-[Bis(ethoxycarbonyl)methyl]-2-decanone (4k): δ_H ($CDCl_3$) 0.87 (3H, t, *J* = 7.1 Hz), 1.25−1.38 (16H, m), 2.14 (3H, s), 2.51 (1H, dd, *J* = 6.7, 17.1 Hz), 2.65−2.69 (1H, m), 2.75 (1H, dd, *J* = 5.3, 17.1 Hz), 3.53 (1H, d, *J* = 5.5 Hz), 4.180 (2H, q, *J* = 7.1 Hz), 4.184 (2H, q, *J* = 7.1 Hz); δ_C ($CDCl_3$) 14.15, 14.18, 22.7, 27.0, 29.3, 30.4, 31.8, 32.3, 33.6, 45.4, 54.1, 61.3, 61.4, 168.9, 169.1, 207.7; ν(neat)/cm^{-1} 1751, 1730 (C═O); HR ESI-MS calcd for $C_{17}H_{30}O_5$ + Na (M + Na) 337.1986, found: M^+ + Na, 337.1992.

Spectroscopic data of **4a**,[12a,b] **4b**,[12a,b] **4c**,[1m,12a] **4d**,[12c] **4e**,[1f,12c,12d] **4f**,[12a] **4g**,[12a,b] **4h**,[1k,12a,12d] **4i**,[1g] **4j**,[1g] and **4l**[1k,12e,12f] are in agreement with the published data.

■ ASSOCIATED CONTENT

Supporting Information. Solvent screen for Michael addition of **2a** to **3a** with catalyst **1f**, specific rotation and HPLC data of **4**, and NMR spectra of **1g**, pre-**1i**, and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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