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Asymmetric Michael Addition of Ketones to Alkylidene Malonates and Allylidene Malonates via Enamine-Metal Lewis Acid Bifunctional Catalysis

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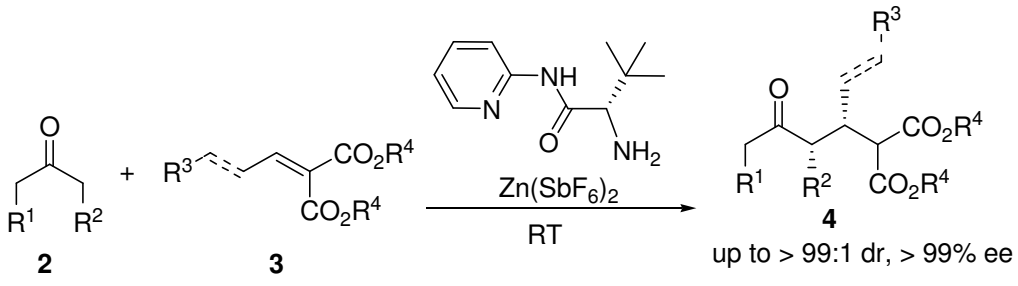
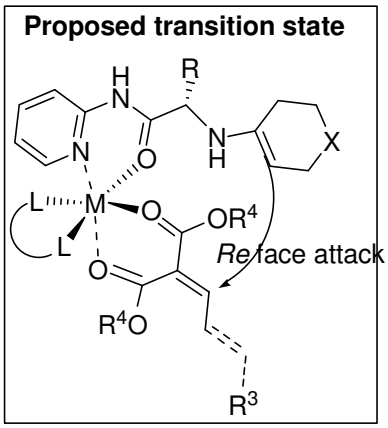
Enamine-metal Lewis acid bifunctional catalysis





Abstract: Novel enamine-metal Lewis acid bifunctional catalysts were successfully applied to the asymmetric Michael addition of ketones to alkylidene malonates, offering excellent stereoselectivity (up to >99% ee and > 99:1 dr). The asymmetric Michael addition of ketones to allylidene malonates was also achieved.

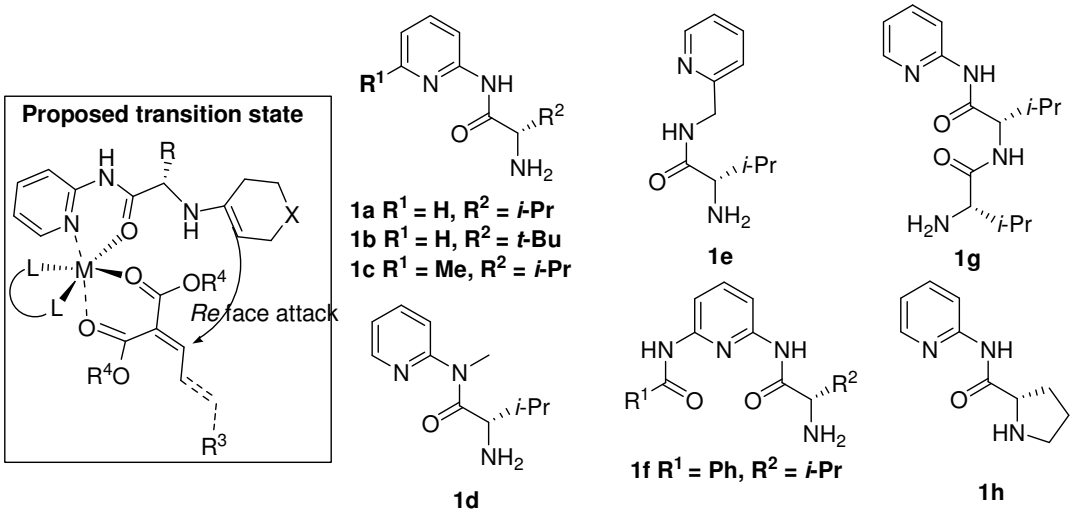
Asymmetric catalysis represents the most efficient and atom-economic tool to build up stereochemical complexity. The development of novel catalytic systems for asymmetric organic transformations has remained a long-lasting interest. In the past decade, the rapid development of organocatalysis has dramatically changed the profile of asymmetric catalysis. In recent years, a new research area involving the combination of the newly developed organocatalysis with the more traditional metal catalysis, although still in its infancy, has emerged as a potentially powerful tool to discover organic transformations

that cannot be accomplished via organocatalysis or metal catalysis independently.[1] This new catalytic approach also offers the opportunity to achieve unprecedented asymmetric organic transformations.[1m]

The asymmetric conjugate addition of carbon-centered nucleophiles to electron-deficient olefins is one of the most important carbon–carbon bond forming reactions in constructing enantioenriched carbon skeletons in natural products and biologically active compounds. The organocatalytic enantioselective conjugate addition of aldehydes and ketones to electron-deficient alkenes, such as nitrostyrenes, α, β-unsaturated aldehydes, and enones, have been extensively investigated.[2] In contrast, the asymmetric conjugate addition of aldehydes and ketones to alkylidene malonates are much less studied.[3] The first organocatalytic asymmetric Michael addition of ketones to alkylidene malonates was achieved by the Barbas group in 2001, giving only 24% yield and 65% *ee* for cyclohexanone.[3b] Considerable progress has been made on this reaction by several groups in recent years, and higher yields and enantioselectivity have been obtained for cyclohexanone.[3c-f] However, large excess of ketones, neat conditions and/or elevated temperature are still required to complete the reaction. In particular, the conjugate addition of cyclopentanone to alkylidene malonates results in low stereoselectivity and yields, and still remains a challenge.[3b-c, 3e-f] In consideration of this reaction, we feel that the enamine-metal Lewis acid bifunctional catalysts developed in our laboratory might be a good fit for this reaction.[1l, 4] The metal Lewis acid can activate alkylidene malonates through chelating to the metal (Fig. 1); the bifunctional nature of the catalysts can also convert an intermolecular reaction into a much more efficient intramolecular-like reaction; in addition, the bifunctional nature can also enhance stereoselectivity of the reaction.

Herein, we wish to report the first examples of asymmetric Michael addition of ketones catalyzed by enamine-metal Lewis acid bifunctional catalysts. The first examples of asymmetric Michael addition of ketones to allylidene malonates are also presented.[5]

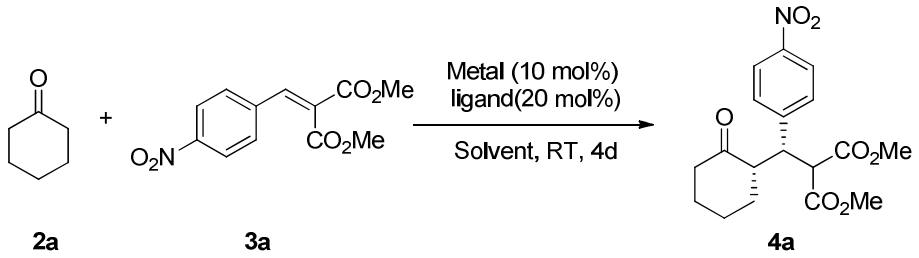
Figure1. Proposed Transition State of Asymmetric Michael Addition via Enamine-metal Lewis Acid Bifunctional Catalysis and the Structure of the Ligands



We initially conducted metal screening using ligand **1a** for the asymmetric Michael addition of cyclohexanone (**2a**) to dimethyl 2-(4-nitrobenzylidene)malonate (**3a**) in THF at room temperature. We were delighted to find out that some metal salts examined displayed activity (Table 1, entries 1–4, for more details see Supporting Information). $Zn(OTf)_2$ showed exceptionally good activity and high stereoselectivity (99% yield, >99:1 *dr*, 93% *ee*). Similar reaction carried out in CH_3CN also gave high ee and good yield (entry 5). In order to obtain optimal conditions for this reaction, we also screened other ligands modified from **1a** (Fig. 1). We reasoned that a ligand with a longer tether might match better for the Michael addition due to the longer distance between the electrophilic and the nucleophilic centers, as compared with aldol reaction. Compounds

1e and **1g** were prepared for this purpose. As it turned out, both **1e** and **1g** showed significantly decreased activity (entries 9 & 11), indicating the importance of the distance between the functional groups for bifunctional catalysts. The attachment of a methyl group either at the 6 position of pyridine (**1c**) or on the nitrogen of amide (**1d**) did not facilitate the reaction (entries 7 & 8). When tridentate ligand **1f** was used in this reaction, the reaction gave good yield but only in moderate enantioselectivity (entry 10); ligand **1h** derived from proline did not show activity for this reaction (entry 12). Counter anion effect was observed in this reaction. $Zn(SbF_6)_2$ displayed higher stereoselectivity than $Zn(OTf)_2$ and $Zn(ClO_4)_2$ (entries 4, 13 & 14). When the isopropyl group in **1a** was replaced with a *tert*-butyl group (**1b**), excellent stereoselectivity (> 99:1 dr and >99% *ee*) was obtained with high yield in both THF and CH_3CN (entries 15 & 17). Lowering cyclohexanone to 5 equivalents in conjunction with increased loading of the catalyst (15 mol%) did not affect the stereoselectivity and activity of the reaction (entries 15-17). Slightly better result was obtained by adding 1 equivalent of hexafluoroisopropanol (HFIP, entry 16). Control experiments carried out with ligand (**1b**) or metal ($Zn(OTf)_2$) only did not show any activity, demonstrating the bifunctional nature of these catalysts (entries 18 and 19). The absolute configuration (*S*, *S*) of the product was determined by comparison with literature,[3d] matching well with the proposed transition state (Fig. 1), which features enamine attack from the *re*-face of the malonate.

Table 1. Screening of Conditions



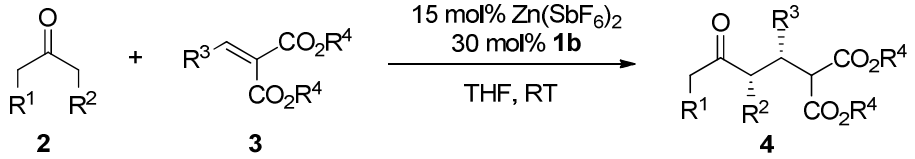
2a **3a** **4a**

entry[a]	metal	ligand	solvent	yield[b] (%)	*dr*[c]	*ee*[c] (%)
1	$Cu(OTf)_2$	**1a**	THF	trace	-	-
2	$Co(ClO_4)_2$•$6H_2O$	**1a**	THF	64	94:6	95
3	$Y(OTf)_3$	**1a**	THF	64	70:30	24
4	$Zn(OTf)_2$	**1a**	THF	99	>99:1	93
5	$Zn(OTf)_2$	**1a**	CH_3CN	89	>99:1	97
6	$Zn(OTf)_2$	**1b**	THF	93	>99:1	93
7	$Zn(OTf)_2$	**1c**	THF	trace	-	-
8	$Zn(OTf)_2$	**1d**	THF	trace	-	-
9	$Zn(OTf)_2$	**1e**	THF	trace	-	-
10	$Zn(OTf)_2$	**1f**	THF	90	>99:1	50
11	$Zn(OTf)_2$	**1g**	THF	trace	-	-
12	$Zn(OTf)_2$	**1h**	THF	0	-	-
13	$Zn(ClO_4)_2$	**1a**	THF	64	>99:1	95
14	$Zn(SbF_6)_2$	**1a**	THF	95	>99:1	97
15[d]	$Zn(SbF_6)_2$	**1b**	THF	91 (87)	>99:1	>99
16[d,e]	$Zn(SbF_6)_2$	**1b**	THF	99 (95)	>99:1	>99
17[d]	$Zn(SbF_6)_2$	**1b**	CH_3CN	92	>99:1	>99
18	$Zn(OTf)_2$		THF	0	-	-
19	-	**1b**	THF	0	-	-

[a]Unless noted, reactions were carried out with 0.1 mmol of **3a**, 1.0 mmol of cyclohexanone and 10 mol% of catalyst in 0.25 mL solvent at room temperature for 4 days. [b]NMR yield. The number in parenthesis is isolated yield. [c]Determined by chiral HPLC or ^{1}H NMR, *syn* isomer is major. [d]5.0 equiv. of cyclohexanone and 15 mol% of catalyst were used. [e]1.0 equiv. of hexafluoroisopropanol (HFIP) was added.

We then investigated the substrates scope of the asymmetric Michael addition of ketones to alkylidene malonates under optimal conditions (Table 2). Cyclohexenone reacted with a variety of alkylidene malonates with aromatic substituents, leading to the formation of the Michael products **4** in good yields with high diastereoselectivities (up to >99:1) and excellent enantioselectivities (up to >99% *ee*) (entries 1–11). It should be mentioned that the attachment of an electron-donating group to the alkylidene malonates did not affect the activity and stereoselectivity of the reaction (entry 10 & 11); however, when a more sterically hindered substituent was attached, the reaction considerably slowed down, but the diastereoselectivity and enantioselectivity remained high (entries 4). Other six-membered cyclic ketones also reacted with dimethyl 2-(4-nitrobenzylidene)malonate to afford the Michael addition products with good yields and stereoselectivity (entries 17 & 18). Cyclopentanone reacted with alkylidene malonates bearing both electron-rich and electron-poor substituent in high yields (80–99%), offering excellent diastereoselectivity and enantioselectivity (96/4->99/1 *dr,* and 98%->99% *ee*) (entry 12-16). These results are significantly much higher than literature reported values for cyclopentanone (2/1-9/1 dr, 39–75% ee, 28-73% yields).[3b-c, 3e-f] For acyclic ketones, acetone gave the Michael addition product in high yield, but with moderate enantioselectivity (entry 19); the reaction of acetophenone resulted in low yield (entry 20).

Table 2. Asymmetric Michael Addition of Ketones to Alkylidene Malonates



2 **3** **4**

2a : R^1, R^2 = -$(CH_2)_3$- **2d** : R^1, R^2 = -(CH_2SCH_2)-
2b : R^1, R^2 = -$(CH_2)_2$- **2e** : R^1= R^2 = H
2c : R^1, R^2 = -(CH_2OCH_2)- **2f** : R^1 = H, R^2 = Ph

entry[a]	2	R^3/ R^4	3	4	yield[b] (%)	*syn*/*anti*[c]	*ee*[c] (%)
1[d]	**2a**	4-$NO_2C_6H_4$/Me	**3a**	**4a**	95	>99	>99
2	**2a**	4-$NO_2C_6H_4$/Et	**3b**	**4b**	88	98:2	>99
3[e]	**2a**	3-$NO_2C_6H_4$/Me	**3c**	**4c**	87	98:2	>99
4[f]	**2a**	2-$NO_2C_6H_4$/Me	**3d**	**4d**	65	>99	>99
5	**2a**	4-BrC_6H_4/Me	**3e**	**4e**	90	98:2	98
6	**2a**	4-ClC_6H_4/Me	**3f**	**4f**	99	99:1	>99
7	**2a**	4-CNC_6H_4/Me	**3g**	**4g**	85	99:1	99
8	**2a**	4-$CO_2MeC_6H_4$/Me	**3h**	**4h**	99	>99	>99
9	**2a**	C_6H_5/Me	**3i**	**4i**	80	99:1	98
10	**2a**	4-MeC_6H_4/Me	**3j**	**4j**	85	98:2	99
11[f]	**2a**	4-$MeOC_6H_4$/Me	**3k**	**4k**	95	99:1	>99
12	**2b**	4-$NO_2C_6H_4$/Me	**3a**	**4l**	99	96:4	98
13[e]	**2b**	4-$NO_2C_6H_4$/Et	**3b**	**4m**	80	99:1	>99
14[e]	**2b**	4-$MeOC_6H_4$/Me	**3k**	**4n**	80	99:1	>99
15[e]	**2b**	4-ClC_6H_4/Me	**3f**	**4o**	83	>99:1	>99
16[e]	**2b**	C_6H_5/Me	**3i**	**4p**	92	>99:1	>99
17[f]	**2c**	4-$NO_2C_6H_4$/Me	**3a**	**4q**	60	86:14	>99
18[f]	**2d**	4-$NO_2C_6H_4$/Me	**3a**	**4r**	70	99:1	>99
19[e]	**2e**	4-$NO_2C_6H_4$/Me	**3a**	**4s**	96	-	71
20[f]	**2f**	4-$NO_2C_6H_4$/Me	**3a**	**4t**	20	-	-

[a]Unless noted, reactions were carried out with 0.2 mmol of **3**, 1.0 mmol of **2**, 15 mol% of $Zn(SbF_6)_2$ and 30 mol% **1b** in 0.5 mL of THF at room temperature. [b]Isolated yield. [c]Determined by chiral HPLC or ^1H NMR. [d]The absolute configuration of the products is (*S*, *S*) and was determined by comparison with literature.[3d] [e]THF was replaced by CH_3CN. [f]1.0 equiv of hexafluoroisopropanol was added.

Having successfully applied the enamine-metal Lewis acid bifunctional catalysts to the asymmetric Michael addition of ketones to alkylidene malonates, we attempted the Michael addition to allylidene malonates. Asymmetric conjugate addition of ketones to allylidene malonates has never been reported in the literature, but will also be interesting as it adds more functional groups to a complex entity which is useful in natural product synthesis and pharmaceutical industry. Conjugate addition of cyclohexanone to allylidene malonates occurred to give exclusively 1,4-addition products (Table 3). After condition screening (for details see Supporting Information), the best results were obtained when $Zn(OTf)_2$ and ligand **1b** in DCM were used. Good yields and very good enantioselectivities were obtained with cyclohexanone and allylidene malonates with both aryl and alkyl substituents (entries 1-8). Other cyclic ketones including cyclopentanone, tetrahydropyran-4-one, and tetrahydrothiopyran-4-one also reacted with dimethyl 2-(3-phenylallylidene)malonates to afford the Michael adducts in modest yields and modest to very good stereoselectivity (entries 9-11).

Table 3. Asymmetric Michael Addition of Ketones to Allylidene Malonates

2 **5** **6**

2a : R^1, R^2 = -$(CH_2)_3$- **2c** : R^1, R^2 = -(CH_2OCH_2)-
2b : R^1, R^2 = -$(CH_2)_2$- **2d** : R^1, R^2 = -(CH_2SCH_2)-

Entry[a]	2	R^3\R^4	5	6	Yield[b] (%)	*dr*[c]	*ee*[c] (%)
1	**2a**	C_6H_5\Me	**5a**	**6a**	83	1.9:1	98/95
2[d]	**2a**	C_6H_5\Me	**5a**	**6a**	77	4:1	91/90
3	**2a**	C_6H_5\Et	**5b**	**6b**	99	1.6:1	95/95
4	**2a**	4-$NO_2C_6H_4$\Me	**5c**	**6c**	80	1.6:1	96/91
5	**2a**	4-ClC_6H_4\Me	**5d**	**6d**	78	1.7:1	92/96
6	**2a**	4-BrC_6H_4\Me	**5e**	**6e**	74	1.7:1	95/98
7	**2a**	4-$MeOC_6H_4$\Me	**5f**	**6f**	80	1.4:1	93/97
8	**2a**	*n*-Pr\Me	**5g**	**6g**	83	1.4:1	98/97
9	**2b**	C_6H_5\Me	**5a**	**6h**	50	4:1	80/74
10	**2c**	C_6H_5\Me	**5a**	**6i**	62	2.3:1	91/57
11	**2d**	C_6H_5\Me	**5a**	**6j**	64	3.5:1	57/69

[a]Unless noted, reactions were carried out with 0.2 mmol of **5**, 1 mmol of **2**, 10 mol% $Zn(OTf)_2$ and 20 mol% **1b** in 0.5 mL DCM at room temperature. [b]Isolated yield. [c]Determined by ^1H NMR or Chiral HPLC. [d]Reaction was catalyzed by 10 mol% of $Zn(SbF_6)_2$ and 20 mol% of **1a** in 0.5 mL THF at room temperature for 5 days.

In summary, enamine-metal Lewis acid bifunctional catalysts have been successfully applied to the asymmetric Michael addition of ketones for the first time. Excellent diastereoselectivities and enantioselectivies, the best results so far to our knowledge, were obtained with alkylidene malonates. These enamine-metal Lewis acid bifunctional catalysts worked especially well for the asymmetric Michael addition of cyclopentanone to alkylidene malonates offering significantly much higher stereoselectivity and yields than those obtained from organocatalysts. Allylidene malonates was introduced for the first time as the Michael acceptor to the addition of ketones. This reaction also displayed relatively larger substrate scope of ketones and alkylidene malonates. It is notable that only 5.0 equiv. of ketones was used in this reaction without significantly decreasing the reaction activity.

Experimental Section:

Dimethyl 2-((4-nitrophenyl)(2-oxocyclohexyl)methyl)malonate (4a). Reaction time 4d; Yield 69.0 mg, 95%; White solid; $[\alpha]_D^{25}$= -53.7 (*c* = 0.283, $CHCl_3$); HPLC analysis chiralpak AD-H, *i*-PrOH/hexanes = 10/90, 0.7 mL/min; 238 nm, t_r (minor) = 34.17, t_r (major) = 41.09 min. ^{1}H NMR spectrum of **4a** matches with the data reported in the literature.[3d-f]

Diethyl 2-((4-nitrophenyl)(2-oxocyclohexyl)methyl)malonate (4b). Reaction time 5d; Yield 68.9 mg, 88%; White solid; HPLC analysis chiralpak AD-H, *i*-PrOH/hexanes = 10/90, 0.7 mL/min; 238 nm, t_r (minor) = 36.75, t_r (major) = 64.81 min; ^{1}H NMR and ^{13}C NMR spectra of **4b** match with the data reported in literature.[3e-f]

Dimethyl 2-((3-nitrophenyl)(2-oxocyclohexyl)methyl)malonate (4c). Reaction time 6d, Yield 63.2 mg, 87%; White solid; HPLC analysis chiralpak AD-H, *i*-PrOH/hexanes = 10/90, 0.5 mL/min; 238 nm, t_r (minor) = 34.35, t_r (major) = 44.48 min; ^{1}H NMR and ^{13}C NMR spectra of **4c** match with the data reported in literature.[3e-f]

Dimethyl 2-((2-nitrophenyl)(2-oxocyclohexyl)methyl)malonate (4d). Reaction time 12d; Yield 47.3 mg, 65%; Yellow oil; HPLC analysis chiralpak AD-H, *i*-PrOH/hexanes = 10/90, 1.0 mL/min; 238 nm, t_r (minor) = 26.74, t_r (major) = 36.98 min; ^{1}H NMR spectrum of **4d** matches with the data reported in literature.[3f]

Dimethyl 2-((4-bromophenyl)(2-oxocyclohexyl)methyl)malonate (4e). Reaction time 6d; Yield 71.5 mg, 90%; white solid; HPLC analysis chiralpak AD-H, *i*-PrOH/hexanes = 5/95, 0.5 mL/min; 238 nm, t_r (minor) = 37.65, t_r (major) = 39.84 min; ^{1}H NMR and ^{13}C NMR spectra of **4e** match with the data reported in literature.[3f]

Dimethyl 2-((4-chlorophenyl)(2-oxocyclohexyl)methyl)malonate (4f). Reaction time 7d; Yield 69.9 mg, 99%; White solid; HPLC analysis chiralpak AD-H, *i*-PrOH/hexanes = 10/90, 0.3 mL/min; 238 nm, t_r (minor) = 36.99, t_r (major) = 40.33 min; ^{1}H NMR and ^{13}C NMR spectra of **4f** match with the data reported in literature.[3f]

Dimethyl 2-((4-cyanophenyl)(2-oxocyclohexyl)methyl)malonate (4g). Reaction time 4d; Yield 58.4 mg, 85%; White solid; HPLC analysis chiralpak AD-H, *i*-PrOH/hexanes = 10/90, 1.0 mL/min; 238 nm, t_r (minor) = 25.11, t_r (major) = 29.79 min; ^{1}H NMR and ^{13}C NMR spectra of **4g** match with the data reported in literature.[3f]

Dimethyl 2-((4-(methoxycarbonyl)phenyl)(2-oxocyclohexyl)methyl)malonate (4h). Reaction time 4d, Yield 74.5 mg, 99%; Colorless oil; $[\alpha]_D^{25}$= -57.0 (*c* = -0.379, $CHCl_3$); HPLC analysis chiralpak AD-H, *i*-PrOH/hexanes = 10/90, 0.5 mL/min; 238 nm, t_r (major) = 17.02, t_r (minor) = 20.90 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 4.08-4.04 (m, 1H), 3.99 (d, *J* = 9.0 Hz, 1 H), 3.88 (s, 3H), 3.65 (s, 3H), 3.46 (s, 3H), 2.98-2.92 (m, 1H), 2.46-2.34 (m, 2H), 2.00-1.96 (m, 1H), 1.76-1.68 (m, 2H), 1.62-1.50 (m, 2H), 1.14-1.08 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.5, 168.7, 168.2, 166.8, 144.2, 129.4, 128.9, 55.3, 52.8, 52.5, 52.2, 52.0, 43.7, 42.1, 32.0, 27.9, 24.7; MS (ESI) 399.2 $(M+Na)^+$; HRMS (ESI) calculated for ($C_{20}H_{24}O_7$+Na) 399.1420, found 399.1413.

Dimethyl 2-((2-oxocyclohexyl)(phenyl)methyl)malonate (4i). Reaction time 8d; Yield 50.9 mg, 80%; White solid; HPLC analysis chiralpak AD-H, *i*-PrOH/hexanes = 5/95, 0.4 mL/min; 238 nm, t_r (minor) = 38.57, t_r (major) = 42.15 min; ^{1}H NMR and ^{13}C NMR spectra of **4i** match with the data reported in literature.[3f]

Dimethyl 2-((2-oxocyclohexyl)(p-tolyl)methyl)malonate (4j). Reaction time 6d; Yield 56.5 mg, 85%; White solid, mp 52-54 ^{o}C; $[\alpha]_D^{25}$= -46.9 (*c* = 0.507, $CHCl_3$); HPLC analysis chiralpak AD-H, *i*-PrOH/hexanes = 5/95, 0.4 mL/min; 224 nm, t_r (minor) = 38.03, t_r (major) = 44.90 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 3.96-3.90 (m, 2H), 3.65 (s, 3H), 3.47 (s, 3H), 2.92-2.88 (m, 1H), 2.48-2.42 (m, 1H), 2.38-2.32 (m, 1H), 2.28 (s, 3H), 1.98-1.92 (m, 1H), 1.76-1.52 (m, 4H), 1.18-1.12 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.4, 169.0, 168.5, 136.6, 135.7, 129.1, 128.9, 55.9, 53.3, 52.4, 52.1, 43.6, 42.1, 32.1, 28.0, 24.5, 21.0; MS (ESI) 355.2 $(M+Na)^+$; HRMS (ESI) calculated for ($C_{19}H_{24}O_5$+Na) 355.1521, found 355.1535.

Dimethyl 2-((4-methoxyphenyl)(2-oxocyclohexyl)methyl)malonate (4k). Reaction time 8d; Yield 66.2 mg, 95%; White solid; HPLC analysis chiralpak AD-H, *i*-PrOH/hexanes = 10/90, 0.5 mL/min; 238 nm, t_r (minor) = 31.01, t_r (major) = 32.51 min; ^{1}H NMR and ^{13}C NMR spectra of **4k** match with the data reported in literature.[3f]

Dimethyl 2-((4-nitrophenyl)(2-oxocyclopentyl)methyl)malonate (4l). Reaction time 3d; Yield 69.1 mg, 99%; White solid; HPLC analysis chiralcel OD-H, *i*-PrOH/hexanes = 5/95, 0.7 mL/min; 224 nm, t_r (minor) = 39.03, t_r (major) = 47.05 min; ^{1}H NMR and ^{13}C NMR spectra of **4l** match with the data reported in literature.[3e-f]

Diethyl 2-((4-nitrophenyl)(2-oxocyclopentyl)methyl)malonate (4m). Reaction time 4d; Yield 60.4 mg, 80%;Yellow oil; HPLC analysis chiralpak AS-H, *i*-PrOH/hexanes = 10/90, 0.7 mL/min; 224 nm, t_r (minor) = 21.33, t_r (major) = 22.65 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 4.24-4.18 (m, 2H), 4.13-4.08 (m, 2H), 3.96-3.88 (m, 2H), 2.60-2.52 (m, 1H), 2.26-2.20 (m, 1H), 2.10-2.03 (m, 1H), 1.92-1.80 (m, 2H), 1.72-1.68 (m, 1H), 1.52-1.44 (m, 1H), 1.26 (t, *J* = 7.0 Hz,

3H), 1.00 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 217.4, 167.8, 167.2, 147.0, 146.1, 130.3, 123.3, 62.0, 61.5, 54.7, 51.6, 43.7, 38.4, 26.1, 20.4, 14.0, 13.7. MS (ESI) 400.2 $(M+Na)^+$; HRMS (ESI) calculated for ($C_{19}H_{23}NO_7$+Na) 400.1372, found 400.1375.

Dimethyl 2-((4-methoxyphenyl)(2-oxocyclopentyl)methyl)malonate (4n). Reaction time 7d; Yield 53.5 mg, 80%; Yellow oil; HPLC analysis chiralpak AS-H, *i*-PrOH/hexanes = 5/95, 0.5 mL/min; 224 nm, t_r (major) = 40.69, t_r (minor) = 45.41 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 4.07 (d, *J* = 11.0 Hz, 1H), 3.92 (dd, *J* = 11.0 Hz & 5.5 Hz, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.44 (s, 3H), 2.50-2.42 (m, 1H), 2.22-2.16 (m, 1H), 2.04-1.98 (m, 1H), 1.88-1.80 (m, 2H), 1.70-1.58 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 218.7, 168.8, 168.1, 158.5, 130.2, 130.1, 113.5, 55.1, 55.1, 52.7, 52.3, 51.9, 43.6, 38.7, 26.3, 20.4. MS (ESI) 357.2 $(M+Na)^+$; HRMS (ESI) calculated for ($C_{18}H_{22}O_6$+Na) 357.1314, found 357.1320.

Dimethyl 2-((4-chlorophenyl)(2-oxocyclopentyl)methyl)malonate (4o). Reaction time 7d; Yield 56.2 mg, 83%;White solid, mp 75-77 ^{o}C; HPLC analysis chiralpak AD-H, *i*-PrOH/hexanes = 5/95, 0.4 mL/min; 224 nm, t_r (minor) = 46.50, t_r (major) = 49.05 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.5 Hz, 2H), 7.13 (d, *J* = 8.5 Hz, 2H), 4.10 (d, *J* = 10.5 Hz, 1H), 3.95 (dd, *J* = 10.5 Hz & 5.5 Hz, 1H), 3.74 (s, 3H), 3.46 (s, 3H), 2.50-2.42 (m, 1H), 2.22-2.16 (m, 1H), 2.06-2.00 (m, 1H), 1.88-1.80 (m, 2H), 1.70-1.62 (m, 1H), 1.56-1.50 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 218.1, 168.6, 167.9, 136.8, 133.1, 130.5, 128.4, 54.7, 52.8, 52.4, 51.6, 43.7, 38.5, 26.3, 20.4. MS (ESI) 361.2 $(M+Na)^+$; HRMS (ESI) calculated for ($C_{17}H_{19}ClO_5$+Na) 361.0819, found 361.0816.

Dimethyl 2-((2-oxocyclopentyl)(phenyl)methyl)malonate (4p). Reaction time 7d; Yield 56.0 mg, 92%; Yellow oil; HPLC analysis chiralpak AD-H, *i*-PrOH/hexanes = 5/95,

0.4 mL/min; 224 nm, t_r (minor) = 39.15, t_r (major) = 41.09 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.18 (m, 5H), 4.15 (d, *J* = 11.0 Hz, 1H), 3.98 (dd, *J* = 11.0 Hz & 5.5 Hz, 1H), 3.76 (s, 3H), 3.43 (s, 3H), 2.56-2.50 (m, 1H), 2.22-2.16 (m, 1H), 2.07-2.00 (m, 1H), 1.89-1.80 (m, 2H), 1.72-1.58 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 218.6, 168.8, 168.1, 138.3, 129.1, 128.2, 127.1, 55.0, 52.7, 52.2, 51.8, 44.4, 38.6, 26.4, 20.4. MS (ESI) 327.2 $(M+Na)^+$; HRMS (ESI) calculated for ($C_{17}H_{20}O_5$+Na) 327.1208, found327.1192.

Dimethyl 2-((4-nitrophenyl)(4-oxotetrahydro-2H-pyran-3-yl)methyl)malonate (4q). Reaction time 12d; Yield 43.7 mg. 60%; Colorless oil; HPLC analysis chiralcel OJ-H, *i*-PrOH/hexanes = 20/80, 1.0 mL/min; 224 nm, t_r (minor) = 47.19 min, t_r (major) = 50.15 min; ^{1}H NMR and ^{13}C NMR spectra of **4q** match with the data reported in literature.[3f]

Dimethyl 2-((4-nitrophenyl)(4-oxotetrahydro-2H-thiopyran-3-yl)methyl)malonate (4r). Reaction time 12d; Yield 53.4 mg, 70%; white solid; HPLC analysis chiralpak AD-H, *i*-PrOH/hexanes = 10/90, 0.5 mL/min; 238 nm, t_r (minor) = 51.25, t_r (major) = 53.78 min; ^{1}H NMR and ^{13}C NMR spectra of **4r** match with the data reported in literature.[3f]

Dimethyl 2-(1-(4-nitrophenyl)-3-oxobutyl)malonate (4s). Reaction time 4d; Yield 62.0 mg, 96%; Colorless oil; $[\alpha]_D^{25}$= +8.6 (*c* = 0.633, $CHCl_3$); HPLC analysis chiralpak AD-H, *i*-PrOH/hexanes = 10/90, 1.0 mL/min; 238 nm, t_r (minor) = 24.55, t_r (major) = 36.27 min; ^{1}H NMR and ^{13}C NMR spectra of **4s** match with the data reported in literature.[3d-f]

Dimethyl 2-(1-(4-nitrophenyl)-3-oxo-3-phenylpropyl)malonate (4t): Reaction time 12d; Yield 15.4 mg, 20%; Yellow solid; ^{1}H NMR spectrum of **4t** matches with the data reported in literature.[3f]

(E)-dimethyl 2-(1-(2-oxocyclohexyl)-3-phenylallyl)malonate (6a). Reaction time 4d; Yield 57.1 mg, 83%; Yellow oil; $[\alpha]_D^{25}$= -63.4 (*c* = 0.172, $CHCl_3$); HPLC analysis

chiralpak AD-H, *i*-PrOH/hexanes = 10/90, 0.5 mL/min; 238 nm; **Major**: t_r (major) = 20.65 min, t_r (minor) = 23.55 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.20 (m, 5H), 6.49 (d, J=16.0 Hz, 1H), 6.24-6.18 (m, 1H), 3.98 (d, *J* = 6.0 Hz, 1H), 3.71 (s, 6H), 3.48-3.42 (m, 1H), 2.72-2.64 (m, 1H), 2.46-2.26 (m, 2H), 2.16-1.98 (m, 2H), 1.92-1.84 (m, 1H), 1.72-1.60 (m, 2H), 1.46-1.40 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.8, 168.9, 168.8, 136.9, 133.8, 128.5, 127.5, 126.8, 126.3, 54.0, 52.4, 52.2, 51.7, 42.4, 42.2, 32.1, 28.0, 24.8; **Minor**: t_r (minor) = 28.99 min, t_r (major) = 38.23 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.20 (m, 5H), 6.44-6.38 (m, 2H), 4.26 (d, *J* = 10.5 Hz, 1H), 3.74 (s, 3H), 3.63 (s, 3H), 3.00-2.94 (m, 1H), 2.76-2.72 (m, 1H), 2.46-2.26 (m, 2H), 2.16-1.98 (m, 2H), 1.92-1.84 (m, 1H), 1.72-1.60 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.5, 169.2, 168.9, 136.9, 134.1, 128.4, 127.5, 126.5, 126.4, 54.0, 52.4, 52.3, 50.1, 46.0, 42.8, 33.0, 27.3, 25.2; MS (ESI) 367.2 $(M+Na)^+$; HRMS (ESI) calculated for ($C_{20}H_{24}O_5$+Na) 367.1521, found 367.1509.

(E)-diethyl 2-(1-(2-oxocyclohexyl)-3-phenylallyl)malonate (6b). Reaction time 4d; Yield 73.7 mg, 99%; Yellow oil; $[\alpha]_D^{25}$= -37.5 (*c* = 0.419, $CHCl_3$); HPLC analysis chiralpak AD-H, *i*-PrOH/hexanes = 10/90, 0.5 mL/min; 238 nm; **Major**: t_r (minor) = 20.35 min, t_r (major) = 22.84 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.18 (m, 5H), 6.49 (d, *J* = 15.5 Hz, 1H), 6.26-6.18 (m, 1H), 4.20-4.06 (m, 4H), 3.92 (d, *J* = 7.0 Hz, 1H), 3.50-3.44 (m, 1H), 2.74-2.68 (m, 1H), 2.44-2.24 (m, 2H), 2.16-1.98 (m, 2H), 1.88-1.82 (m, 1H), 1.72-1.58 (m, 2H), 1.48-1.40 (m, 1H), 1.28-1.14 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.6, 168.5, 168.4, 136.9, 133.7, 128.4, 127.4, 126.8, 126.3, 61.3, 61.0, 54.1, 51.7, 42.4, 42.0, 31.8, 28.0, 24.8, 14.0; **Minor**: t_r (minor) = 24.81 min, t_r (major) = 39.85 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ7.38-7.18 (m, 5H), 6.42-6.38 (m, 2H), 4.20-4.06 (m,

5H), 2.98-2.92 (m, 1H), 2.82-2.74 (m, 1H), 2.44-2.24 (m, 2H), 2.16-1.98 (m, 2H), 1.88-1.82 (m, 1H), 1.72-1.58 (m, 3H), 1.28-1.14 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.4, 168.8, 168.5, 136.9, 134.0, 128.4, 127.4, 126.6, 126.3, 61.3, 61.1, 54.2, 50.9, 45.9, 42.8, 33.0, 27.4, 25.2, 14.0; MS (ESI) 395.3 $(M+Na)^+$; HRMS (ESI) calculated for ($C_{22}H_{28}O_5$+Na) 395.1834, found 395.1837.

(E)-dimethyl 2-(3-(4-nitrophenyl)-1-(2-oxocyclohexyl)allyl)malonate (6c). Reaction time 5d; Yield 62.3 mg, 80%; Yellow oil; $[\alpha]_D^{25}$= -49.2 (*c* = 0.567, $CHCl_3$); HPLC analysis chiralpak AD-H, *i*-PrOH/hexanes = 20/80, 1.0 mL/min; 238 nm; **Major**: t_r (major) = 18.52 min, t_r (minor) = 25.96 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 9.0 Hz, 2H), 7.45 (d, *J* = 9.0 Hz, 2H), 6.62-6.38 (m, 2H), 3.97 (d, *J* = 6.0 Hz, 1H), 3.68 (s, 6H), 3.48-3.42 (m, 1H), 2.72-2.64 (m, 1H), 2.44-2.24 (m, 2H), 2.16-2.00 (m, 2H), 1.92-1.84 (m, 1H), 1.72-1.56 (m, 2H), 1.42-1.36 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.2, 168.7, 146.8, 143.3, 132.1, 126.8, 123.9, 53.6, 52.5, 52.3, 51.4, 42.5, 42.1, 32.1, 28.0, 24.9; **Minor**: t_r (minor) = 27.23 min, t_r (major) = 40.84 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 9.0 Hz, 2H), 7.45 (d, *J* = 9.0 Hz, 2H), 6.62-6.38 (m, 2H), 4.18 (d, *J* = 10.5 Hz, 1H), 3.71 (s, 3H), 3.60 (s, 3H), 3.02-2.96 (m, 1H), 2.76-2.72 (m, 1H), 2.44-2.24 (m, 2H), 2.16-2.00 (m, 2H), 1.92-1.84 (m, 1H), 1.72-1.56 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.3, 168.8, 146.8, 143.2, 132.1, 132.0, 126.8, 123.9, 53.6, 52.5, 52.3, 50.9, 45.7, 42.8, 33.2, 27.4, 25.2; MS (ESI) 412.2 $(M+Na)^+$; HRMS (ESI) calculated for ($C_{20}H_{23}O_7N$+Na) 412.1372, found 412.1382.

(E)-dimethyl 2-(3-(4-chlorophenyl)-1-(2-oxocyclohexyl)allyl)malonate (6d). Reaction time 4d; Yield 59.1 mg, 78%; Yellow oil; $[\alpha]_D^{25}$= -69.8(*c* = 0.486, $CHCl_3$); HPLC analysis chiralpak AD-H, *i*-PrOH/hexanes = 10/90, 0.5 mL/min; 238 nm; **Major**: t_r

(major) = 24.31 min, t_r (minor) = 37.94 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.24 (m, 4H), 6.44 (d, *J* = 16.0 Hz, 1H), 6.22-6.16 (m, 1H), 3.96 (d, *J* = 6.5 Hz, 1H), 3.69 (s, 6H), 3.44-3.39 (m, 1H), 2.74-2.68 (m, 1H), 2.46-2.24 (m, 2H), 2.14-1.96 (m, 2H), 1.90-1.82 (m, 1H), 1.72-1.56 (m, 2H), 1.44-1.34 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.6, 168.8, 168.8, 135.4, 132.6, 128.6, 127.6, 127.5, 53.9, 52.4, 52.2, 51.5, 42.4, 42.1, 32.0, 28.00, 24.9; **Minor**: t_r (minor) = 42.77 min, t_r (major) = 58.13min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.24 (m, 4H), 6.38-6.34 (m, 2H), 4.22 (d, *J* = 10.5 Hz, 1H), 3.73(s, 3H), 3.62(s, 3H), 2.98-2.92 (m, 1H), 2.78-2.74 (m, 1H), 2.46-2.24 (m, 2H), 2.14-1.96 (m, 2H), 1.90-1.82 (m, 1H), 1.72-1.56 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.5, 169.0, 168.8, 135.3, 133.1, 132.8, 128.5, 127.5, 127.3, 53.9, 52.4, 52.3, 50.8, 45.8, 42.8, 33.1, 27.4, 25.1; MS (ESI) 401.2 $(M+Na)^+$; HRMS (ESI) calculated for ($C_{20}H_{23}O_5Cl$+Na) 401.1132, found 401.1120.

(E)-dimethyl 2-(3-(4-bromophenyl)-1-(2-oxocyclohexyl)allyl)malonate (6e). Reaction time 4d; Yield 62.6 mg, 74%;Yellow oil; $[\alpha]_D^{25}$= -50.3 (*c* = 0.499, $CHCl_3$); HPLC analysis chiralpak AD-H, *i*-PrOH/hexanes = 10/90, 0.5 mL/min; 238 nm; **Major**: t_r (major) = 26.43 min, t_r(minor) = 41.21 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.5Hz, 2H), 7.19 (d, *J* = 8.5Hz, 2H), 6.42-6.16 (m, 2H), 3.94 (d, *J* = 6.5 Hz, 1H), 3.67 (s, 6H), 3.42-3.36 (m, 1H), 2.70-2.64 (m, 1H), 2.40-2.20 (m, 2H), 2.10-1.92 (m, 2H), 1.98-1.90 (m, 1H), 1.70-1.54(m, 2H), 1.42-1.32 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.6, 168.8, 168.8, 135.8, 132.6, 131.5, 127.8, 127.7, 121.2, 53.8, 52.4, 52.2, 51.5, 42.4, 42.1, 32.1, 28.0, 24.9; **Minor**: t_r (minor) = 45.41 min, t_r (major) = 63.13 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.5Hz, 2H), 7.19 (d, *J* = 8.5Hz, 2H), 6.42-6.16 (m, 2H), 4.19 (d, *J* = 10.5 Hz, 1H), 3.70 (s, 3H), 3.59 (s, 3H), 2.94-2.89 (m, 1H), 2.74-2.70 (m,

1H), 2.40-2.20 (m, 2H), 2.10-1.92 (m, 2H), 1.98-1.90 (m, 1H), 1.70-1.54(m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.5, 169.0, 168.8, 135.8, 132.9, 131.5, 127.9, 127.4, 121.2, 53.9, 52.5, 52.3, 50.8, 45.8, 42.8, 33.1, 27.4, 25.2; MS (ESI) 445.4 $(M+Na)^+$; HRMS (ESI) calculated for ($C_{20}H_{23}O_5Br$+Na) 445.0627, found 445.0632.

(E)-dimethyl 2-(3-(4-methoxyphenyl)-1-(2-oxocyclohexyl)allyl)malonate (6f). Reaction time 5d; Yield 59.9 mg, 80%; Yellow oil; $[\alpha]_D^{25}$= -61.1(*c* = 0.280, $CHCl_3$); HPLC analysis chiralpak AD-H, *i*-PrOH/hexanes = 10/90, 0.5 mL/min; 238 nm; **Major**: t_r (major) = 31.67 min, t_r (minor) = 41.86 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.24 (m, 2H), 6.88-6.78 (m, 2H), 6.42 (d, *J* = 16.0 Hz, 1H), 6.08-6.00 (m, 1H), 3.95 (d, *J* = 6.5 Hz, 1H), 3.81 (s, 3H), 3.70 (s, 6H), 3.46-3.38 (m, 1H), 2.72-2.66 (m, 1H), 2.46-2.26 (m, 2H), 2.16-1.98 (m, 2H), 1.92-1.84 (m, 1H), 1.72-1.60 (m, 2H), 1.46-1.40 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.9, 169.0, 159.1, 133.2, 129.8, 129.7, 127.5, 124.5, 113.9, 55.3, 52.3, 52.2, 51.8, 46.0, 42.3, 32.0, 28.0, 24.8; **Minor**: t_r (minor) = 59.00 min, t_r (major) = 61.27 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.24 (m, 2H), 6.88-6.78 (m, 2H), 6.35 (d, *J* = 16.0 Hz, 1H), 6.26-6.18 (m, 1H), 4.24 (d, *J* = 10.5 Hz, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 3.62 (s, 3H), 2.96-2.90 (m, 1H), 2.78-2.72 (m, 1H), 2.46-2.26 (m, 2H), 2.16-1.98 (m, 2H), 1.92-1.84 (m, 1H), 1.72-1.60 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.6, 169.2, 168.9, 133.5, 129.8, 129.8, 127.5, 124.2, 113.8, 54.1, 52.4, 52.2, 50.9, 42.8, 42.4, 33.0, 27.3, 25.1; MS (ESI) 397.3 $(M+Na)^+$; HRMS (ESI) calculated for ($C_{21}H_{26}O_6$+Na) 397.1627, found 397.1624.

(E)-dimethyl 2-(1-(2-oxocyclohexyl)hex-2-en-1-yl)malonate (6g). Reaction time 6d; Yield 51.5 mg, 83%; Yellow oil; $[\alpha]_D^{25}$= -60.6(*c* = 0.358, $CHCl_3$); HPLC analysis chiralpak AD-H, *i*-PrOH/hexanes = 3/97, 0.5 mL/min; 210 nm; **Major**: t_r (major) = 20.56

min, t_r (minor) = 25.26 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.56-5.34 (m, 2H), 3.80 (d, *J* = 6.5 Hz, 1H), 3.60 (s, 6H), 3.22-3.16 (m, 1H), 2.58-2.50 (m, 1H), 2.40-2.16 (m, 5H), 1.68-1.52 (m, 2H), 1.38-1.26 (m, 3H), 0.88-0.80 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.1, 169.1, 168.9, 135.2, 126.6, 54.1, 52.2, 52.0, 51.5, 42.3, 41.9, 34.5, 31.8, 28.0, 24.7, 22.5, 13.5; **Minor**: t_r (minor) = 26.44 min, t_r (major) = 31.43 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.56-5.34 (m, 2H), 4.096 (d, *J* = 10.5 Hz, 1H), 3.67 (s, 3H), 3.64 (s, 3H), 2.74-2.68 (m, 1H), 2.62-2.58 (m, 1H), 2.40-2.16 (m, 5H), 1.68-1.52 (m, 3H), 1.38-1.26 (m, 2H), 0.88-0.80 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.5, 169.3, 169.0, 135.5, 126.4, 54.2, 52.3, 52.1, 50.7, 45.5, 42.7, 34.4, 32.7, 27.3, 25.1, 22.5, 13.5; MS (ESI) 333.2 $(M+Na)^+$; HRMS (ESI) calculated for ($C_{17}H_{26}O_5$+Na) 333.1678, found 333.1670.

(E)-dimethyl 2-(1-(2-oxocyclopentyl)-3-phenylallyl)malonate (6h). Reaction time 12d; Yield 33.0 mg, 50%; Yellow oil; $[\alpha]_D^{25}$= -97.8 (c = 0.135, $CHCl_3$); HPLC analysis chiralpak AD-H, *i*-PrOH/hexanes = 10/90, 0.5 mL/min; 238 nm; **Major**: t_r (minor) = 20.03 min, t_r (major) = 26.41 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.20 (m, 5H), 6.47 (d, *J* = 16.0 Hz, 1H), 6.14-6.08 (m, 1H), 3.96 (d, *J* = 6.0 Hz, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 3.52-3.44 (m, 1H), 2.48-2.42 (m, 1H), 2.30-2.22 (m, 1H), 2.16-1.94 (m, 2H), 1.78-1.68 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 218.7, 168.7, 168.5, 136.8, 134.0, 128.5, 127.6, 126.4, 125.9, 54.4, 52.5, 52.4, 50.4, 42.8, 38.6, 26.4, 20.5; **Minor**: t_r (minor) = 30.51 min, t_r (major) = 35.29 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.20 (m, 5H), 6.52 (d, *J* = 16.0 Hz, 1H), 5.96-5.90 (m, 1H), 4.43 (d, *J* = 11.0 Hz, 1H), 3.74(s, 3H), 3.59 (s, 3H), 3.18-3.14 (m, 1H), 2.54-2.48 (m, 1H), 2.30-2.22 (m, 1H), 2.16-1.94 (m, 2H), 1.78-1.68 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 220.1, 168.2, 168.0, 136.5, 134.84, 128.5,

127.8, 126.6, 125.4, 53.7, 52.5, 52.3, 49.5, 44.1, 39.7, 28.0, 20.7; MS (ESI) 353.2 $(M+Na)^+$; HRMS (ESI) calculated for ($C_{19}H_{22}O_5$+Na) 353.1365, found m/z 353.1368.

(E)-dimethyl 2-(1-(4-oxotetrahydro-2H-pyran-3-yl)-3-phenylallyl)malonate (6i). Reaction time 8d; Yield 42.9 mg, 62%; Yellow oil; $[\alpha]_D^{25}$= -67.6 (*c* = 0.170, $CHCl_3$); HPLC analysis chiralpak AD-H, *i*-PrOH/hexanes = 10/90, 0.5 mL/min; 238 nm; **Major**: t_r (major) = 28.99 min, t_r (minor) = 49.75 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.22 (m, 5H), 6.53 (d, *J* = 16.0 Hz, 1H), 6.22-6.16 (m, 1H), 4.12-4.06 (m, 2H), 3.89 (d, *J* = 6.5 Hz, 1H), 3.86-3.80 (m, 1 H), 3.73 (s, 3H), 3.71 (s, 3H), 3.50-3.44 (m, 1H), 2.92-2.86 (m, 1H), 2.66-2.52 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.6, 168.6, 168.4, 136.5, 134.7, 128.5, 126.4, 125.3, 71.1, 68.6, 54.0, 52.6, 52.5, 52.4, 42.6, 40.6; **Minor**: t_r (minor) = 51.91 min, t_r (major) = 65.73 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.22 (m, 5H), 6.42 (d, *J* = 15.5 Hz, 1H), 6.34-6.26 (m, 1H), 4.28 (d, *J* = 10.5 Hz, 1H), 4.22-4.1 (m, 2H), 3.76 (s, 3H), 3.64 (s, 3H), 3.66-3.56 (m, 2H), 3.04-3.98 (m, 2H), 2.66-2.52 (m, 2H), 2.38-2.32 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.00, 168.7, 168.5, 136.5, 134.4, 127.3, 126.4, 125.5, 71.6, 68.0, 54.0, 52.6, 52.4, 51.3, 43.1, 42.4; MS (ESI) 369.2 $(M+Na)^+$; HRMS (ESI) calculated for ($C_{19}H_{22}O_6$+Na) 369.1314, found 369.1316.

(E)-dimethyl 2-(1-(4-oxotetrahydro-2H-thiopyran-3-yl)-3-phenylallyl)malonate (6j). Reaction time 10d; Yield 46.4 mg, 64%; Yellow oil; $[\alpha]_D^{25}$= -49.4 (*c* = 0.168, $CHCl_3$); HPLC analysis chiralpak AD-H, *i*-PrOH/hexanes = 10/90, 0.8 mL/min; 238 nm; **Major**: t_r (major) = 15.42 min, t_r (minor) = 22.02 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.22 (m, 5H), 6.56 (d, *J* = 16.0 Hz, 1H), 6.24-6.18 (m, 1H), 3.79 (d, *J* = 6.0 Hz, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 3.66-3.58 (m, 1H), 3.12-2.90 (m, 4H), 2.86-2.68 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.6, 168.6, 168.4, 136.5, 135.0, 128.5, 127.8, 126.4, 125.5, 54.0,

53.9, 52.5, 52.4, 44.2, 42.4, 34.6, 31.0; **Minor**: t_r (minor) = 35.25 min, t_r (major) = 53.23 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.22 (m, 5H), 6.46 (d, *J* = 15.5Hz, 1H), 6.38-6.30 (m, 1H), 4.16 (d, *J* = 10.0 Hz, 1H), 3.76 (s, 3H), 3.66 (s, 3H), 3.20-3.12 (m, 1H), 3.12-2.90 (m, 3H), 2.86-2.68 (m, 4H); MS (ESI) 385.2 $(M+Na)^+$; HRMS (ESI) calculated for ($C_{19}H_{22}O_5S$+Na) 385.1086, found 385.1090.

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Supporting Information Available: Full optimization detail, ^{1}H and ^{13}C NMR spectra and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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