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$CaCl_2$, Bisoxazoline, and Malonate: A Protocol for an Asymmetric Michael Reaction

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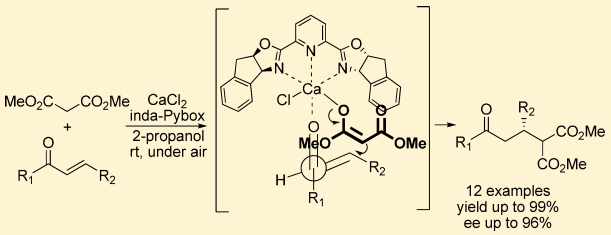
Supporting Information

ABSTRACT: A mild protocol for the asymmetric Michael addition of dimethyl malonate to various α,β-unsaturated carbonyl compounds was developed. The salient feature of this methodology is that a cheap and environmentally friendly Lewis acid, $CaCl_2$, was used as a catalyst. An aminoindanol- and pyridine-derived ligand provided in the presence of $CaCl_2$ Michael adducts in moderate to high enantioselectivities. The scope of the reaction was demonstrated.



INTRODUCTION

During the past two decades, the alkaline earth metals calcium, strontium, and barium have become attractive components for metal catalysts.[1−6] Their use in asymmetric reactions has been studied since the pioneering work of Shibasaki and Yamada in 1998.[7]

Nowadays, environmentally friendly reactions are of increasing interest. Of the alkaline earth metal catalysis, calcium catalysis is in particular highly sustainable, as it takes advantage of an inexpensive, nontoxic, and abundant metal as an alternative to transition metal catalysts, which often possess the opposite properties.[8] The complexation of chiral bisoxazoline-type ligands with metals can be effectively used in asymmetric catalysis.[9,10] Since most of them can be synthesized from readily available natural chiral amino acids, they are easily preparable and are cheap ligands for asymmetric catalysis.

An asymmetric 1,4-addition is one of the cornerstones of organic synthesis. A plethora of organocatalytic[11−13] and metal-catalyzed[14−16] methods have been used to carry out asymmetric Michael additions (only recent reviews have been cited). Among others, chiral Ca-complexes with bisoxazoline ligands have been used in this reaction by Kobayashi et al.[17−21] Various Ca-compounds, including isopropoxides, hexafluoroisopropoxides, triflates, triflic amides, and hexamethyldisilasanes have been used as sources of Ca. Recently, it was found that $CaCl_2$ can be used in Mannich reactions,[22,23] in [3 + 2] cycloaddition reactions,[24] in the synthesis of racemic dihydropyrimidinones,[25,26] in aldol reactions,[27] in Luche-type reduction of α,β-unsaturated ketones,[28] and in conjugated addition to nitrostryrenes.[29] It has also been shown that a BINOL complex derived from $CaCl_2$ can be used in the asymmetric Michael addition of malonates to enones in moderate enantioselectivity[30] and in the asymmetric epoxidation of one specific enone in the synthesis of Fenoprofen.[31]

In connection with our ongoing studies of asymmetric organocatalytic reactions of unsaturated 1,4-dicarbonyl compounds[32−34] we envisioned that a Ca-catalyzed reaction would be an environmentally benign alternative to existing methods. In this study, we demonstrated that the asymmetric addition of dimethyl malonate, which is a valuable reagent in organic synthesis,[35,36] to a variety of different unsaturated carbonyl compounds can be achieved with $CaCl_2$-bisoxazoline (Box) complexes in sustainable reaction conditions.

RESULTS AND DISCUSSION

Our initial studies on this matter began on the optimization of the reaction conditions for dimethyl malonate **1** and symmetric unsaturated 1,4-diketone **2** (Table 1). First, we tested four Box-ligands (Figure 1) in a complex with calcium(II) bis(trifluoromethanesulfonimide) ($Ca(NTf_2)_2$) (Table 1, entries 1−4). Although the reaction in 1,2-dichloroethane was quite slow, it was clear that of the four ligands the neutral coordinative ligand Inda-Pybox **L4** was superior to the others, giving product **3** with the highest enantiomeric excess of 82% and a yield of 60% (Table 1, entry 4). Then, several solvents were screened (Table 1, entries 5−12). All of them, with the exception of methanol, which resulted in low selectivity and yield (29% and 23%, respectively) (Table 1, entry 5), gave high yields and enantioselectivities. The reaction in toluene was unreasonably slow, affording 79% yield after 11 days (Table 1, entry 9). Both alcohol and ether solvents were comparable: the yields ranged from 70% to 99% and the enantioselectivities from 82% to 93%. The reaction at higher temperature (70 °C) in ethanol was completed in 2 h, but the enantioselectivity dropped from 82% ee (Table 1, entry 6) to 71% ee (Table 1, entry 7).

Next, the scope of calcium salts was explored, and reaction conditions were optimized. As the reaction with $Ca(NTf_2)_2$ in ethanol gave full conversion in 21 h (Table 1, entry 6), ethanol

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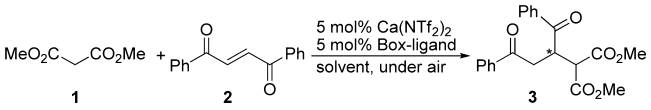
Table 1. Optimization of the Reaction Conditions[a]



entry	ligand	solvent	*T*	time	yield (%)[b]	ee (%)[c]
1	**L1**	DCE	70 °C	28 h	99	*rac*
2	**L2**	DCE	70 °C	7 d	45	64
3	**L3**	DCE	70 °C	7 d	49	−75
4	**L4**	DCE	70 °C	7 d	60	82
5	**L4**	MeOH	rt	70 h	23	29
6	**L4**	EtOH	rt	21 h	99	82
7	**L4**	EtOH	70 °C	2 h	99	71
8	**L4**	2-propanol	rt	46 h	79	88
9	**L4**	toluene	rt	11 d	72	90
10	**L4**	Et_2O	rt	48 h	74	90
11	**L4**	THF	rt	29 h	70	92
12	**L4**	MTBE	rt	48 h	79	93

[a]Typical reaction conditions: a mixture of **1** (0.13 mmol), **2** (0.13 mmol), $Ca(NTf_2)_2$ (0.006 mmol), and a Box-ligand (0.006 mmol) was stirred in a suitable undried solvent (1 mL) under air. [b]Isolated yield. [c]Determined by HPLC analysis.

was used as the initial solvent for the screening. Although both reactions with calcium 1,1,1,3,3,3-hexafluoroisopropoxide ($Ca(HFIP)_2$) and calcium bis(trimethylsilyl)amide ($Ca(HMDS)_2$) as the calcium salts were completed in 4 h with quantitative yields, the enantioselectivities were only 20% and 27%, respectively (Table 2, entries 1 and 2). With calcium halides, longer reaction times were needed, but considerably higher enantioselectivities were achieved (Table 2, entries 3 and 4). Calcium chloride is preferable to calcium iodide because of easier handling and lower cost. Screening of solvents for calcium chloride revealed that in ether solvents the reaction times were prolonged, while the enantioselectivities remained high (ee 85% in THF and 96% in MTBE; Table 2, entries 5 and 6). Water, as the most sustainable solvent, was also tested, but no reaction was observed within 1 day (Table 2, entry 7). The reaction in 2-propanol gave the best combination of yield and enantioselectivity (87% ee and 92% ee, respectively; Table 2, entry 8). Decreasing the catalyst loading from 5 mol % to 1 mol % resulted in a considerable decrease in reaction rate, affording 81% yield in 4 days and retaining a high enantiomeric excess of 90% (Table 2, entry 9). Since it has been shown that the addition of an amine in Lewis acid catalyzed reactions can enhance the reactivity and selectivity of the reaction,[37] we tested the effect of amines with different basicities in our reaction system. The obtained results showed that the reaction was remarkably faster in the presence of triethylamine, morpholine, and imidazole (pK_{aH}^+ 10.68, 8.45, and 6.95, respectively).[38,39] The reaction was completed in 4 h, but the added amines decreased the enantioselectivity of the reaction

Table 2. Additional Screening for the 1,4-Addition Reaction[a]

entry	Ca-salt	solvent	time	yield (%)[b]	ee (%)[c]
1	$Ca(HFIP)_2$	EtOH	4 h	99	20
2	$Ca(HMDS)_2$	EtOH	4 h	99	27
3	CaI_2	EtOH	48 h	96	82
4	$CaCl_2$	EtOH	24 h	96	81
5	$CaCl_2$	THF	5 d	55	85
6	$CaCl_2$	MTBE	5 d	13	96
7	$CaCl_2$	H_2O	24 h	nr[d]	
8	$CaCl_2$	2-propanol	24 h	87	92
9[e]	$CaCl_2$	2-propanol	4 d	81	90

[a]Typical reaction conditions: a mixture of **1** (0.13 mmol), **2** (0.13 mmol), Ca(II)-salt (0.006 mmol), and Inda-Pybox **L4** (0.006 mmol) was stirred in a suitable undried solvent (1 mL) at room temperature under air. [b]Isolated yield. [c]Determined by HPLC analysis. [d]No reaction. [e]1 mol % of $CaCl_2$ and Inda-Pybox **L4** were used.

(Table 3, entries 2−5). Pyridine (pK_{aH}^+ 5.23)[40] was not basic enough to enhance the reactivity but still a slight drop in the

Table 3. Effect of Basic Additives[a]

entry	additive	time (h)	yield (%)[b]	ee (%)[c]
1		24	87	92
2	Et_3N (10 mol %)	4	99	66
3	Et_3N (5 mol %)	4	99	74
4	morpholine (5 mol %)	4	91	84
5	imidazole (5 mol %)	4	94	84
6	pyridine (5 mol %)	24	98	86

[a]Typical reaction conditions: a mixture of **1** (0.13 mmol), **2** (0.13 mmol), $CaCl_2$ (0.006 mmol), Inda-Pybox **L4** (0.006 mmol), and an additive was stirred in 2-propanol (1 mL) at room temperature under air. [b]Isolated yield. [c]Determined by HPLC analysis.

enantioselectivity was detected (Table 3, entry 6). To exclude the possibility of racemization of the formed product during the reaction with a basic additive, an additional experiment was carried out. After mixing compound **3** with triethylamine in 2-propanol for 18 h, enantioselectivity was determined by HPLC, which showed the same ee value as before. Then $CaCl_2$ and Inda-Pybox **L4** were also added to the aforementioned reaction mixture, and it was further stirred for 4 days. Again, HPLC analysis showed that there was no decrease in the ee value of compound **3**. In further studies, imidazole was used as the basic additive for slow reactions. It yielded the smallest drop in enantioselectivity while enhancing the reaction rate multifold.

With the suitable reaction conditions in hand, we examined the scope of the electrophiles used in a 1,4-addition reaction of dimethyl malonate **1**. The results are shown in Table 4. First, the addition to aryl-substituted *α,β*-unsaturated diketones **4a−d** (R^1 = Ar, R^2 = $COCH_3$) was investigated (Table 4, entries 1−

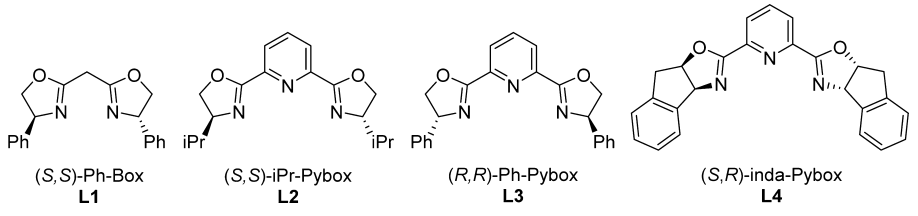


Figure 1. Bisoxazoline ligands used in the current study.

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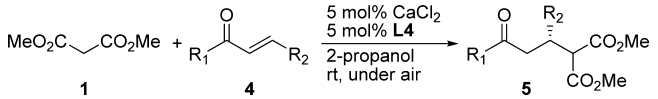
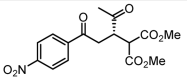
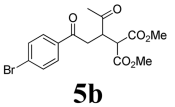
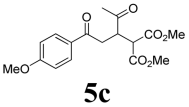
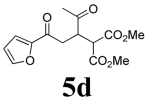
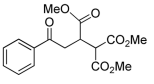
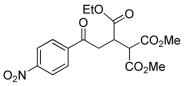
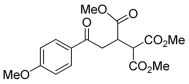
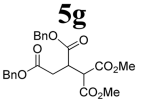
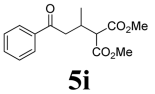
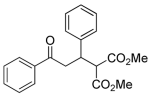
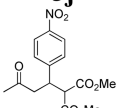
Table 4. α,β-Unsaturated Carbonyl Compounds in 1,4-Addition Reaction[a]



entry	starting compound **4**	product **5**	time	yield (%)[b]	ee (%)[c]
1[d]	**4a** R_1 = *p*-NO_2Ph, R_2 = $COCH_3$	 **5a**	3 d	82	88 (*S*)
2	**4b** R_1 = *p*-BrPh, R_2 = $COCH_3$	 **5b**	46 h	98	82
3	**4c** R_1 = *p*-MeOPh, R_2 = $COCH_3$	 **5c**	48 h	81	85
4	**4d** R_1 = 2-furanyl, R_2 = $COCH_3$	 **5d**	60 h	87	82
5	**4e** R_1 = Ph, R_2 = CO_2CH_3	 **5e**	48 h	86	84
6	**4f** R_1 = *p*-NO_2Ph, R_2 = $CO_2CH_2CH_3$	 **5f**	11 h	96	78
7	**4g** R_1 = *p*-MeOPh, R_2 = CO_2CH_3	 **5g**	48 h	64	84
8	**4h** R_1 = R_2 = CO_2Bn	 **5h**	10 d 7 d[f]	traces 45	n.d.[e] 29
9	**4i** R_1 = Ph, R_2 = CH_3	 **5i**	4 d 24 h[f]	53 72	76 77
10	**4j** R_1 = R_2 = Ph	 **5j**	4 d 3 d[f]	14 89	9 20
11	**4k** R_1 = CH_3, R_2 = *p*-NO_2Ph	 **5k**	7 d 3 d[f]	traces 44	7 26

[a]Typical reaction conditions: a mixture of **1** (0.13 mmol), **4** (0.13 mmol), $CaCl_2$ (0.006 mmol), and Inda-Pybox **L4** (0.006 mmol) was stirred in undried 2-propanol (1 mL) at room temperature under air. [b]Isolated yield. [c]Determined by HPLC analysis. [d]Reaction temperature: −20 °C. [e]Not determined. [f]5 mol % imidazole (0.006 mmol) was added.

4). The electron-withdrawing *p*-nitrophenyl group activated a Michael acceptor, and the reaction was conducted at −20 °C in order to induce higher enantioselectivity, ending with adduct **5a** in 82% yield and 88% ee after 3 days (Table 4, entry 1). For diketone **4c**, with the electron-donating methoxy group in the phenyl ring, a higher temperature was needed, and the reaction was run at room temperature, affording product **5c** in high yield and ee (Table 4, entry 3). Both *p*-bromophenyl and furyl-substituted diketones reacted in similar ways (Table 4, entries 2 and 4). With ketoesters **4e−g** (R^1 = Ar, R^2 = COOEt or COOMe), again, the product with the electron-withdrawing group was obtained faster than the one with the electron-donating group, both giving high enantioselectivities; 78% for **5f** and 84% for **5g** were determined (Table 4, entries 6 and 7). In all cases, only one regioisomer was detected. Unfortunately, the unsaturated diester **4h** (R^1 = OBn, R^2 = COOBn) gave only traces of the desired product in 10 days. Therefore, imidazole was added to the reaction mixture, but still only 45% yield was

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obtained within 7 days with low enantioselectivity (Table 4, entry 8). Next, phenyl-substituted α,β-unsaturated ketones **4i** and **4j** (R^1 = Ph, R^2 = Me or Ph) were used as electrophiles (Table 4, entries 9 and 10). Product **5i** was isolated after 4 days with moderate yield and selectivity. Because of the low reactivity, imidazole was added, and the product was isolated after 24 h. No loss of enantioselectivity was observed, as the reactions yielded 76% ee and 77% ee, respectively (Table 4, entry 9). When chalcone **4j** was used as a starting material, the reaction without an additional base was extremely slow: only 14% of the product with low enantioselectivity was isolated. Although the addition of imidazole to the reaction mixture gave a high yield in 3 days, the enantiomeric excess of the product **5j** was only 20% (Table 4, entry 10). Phenyl-substituted unsaturated ketone **4k** (R^1 = Me, R^2 = Ar) afforded only traces of the product after 7 days. The reaction in the presence of imidazole gave **5k** with a 44% yield in 3 days in low enantioselectivity (ee 26%, Table 4, entry 11). It is clear that increased sterical hindrance at the reaction center decreases the enantioselectivity (Table 4, entries 10 and 11). Other Michael acceptors, such as 2-benzylidenemalonitrile, α-methyl-nitrostyrene, and *tert*-butyl 2-benzylidene-3-oxobutanoate, were less efficient substrates to Ca-catalyzed addition of malonate.

Absolute configuration (*S*) was unambiguously [Flack parameter x = 0.04(6)] determined by single crystal X-ray structure analysis of compound **5a** (Figure 2a and Supporting Information) and based on the reaction mechanism, it is presumed to be the same with all other substrates. According to the obtained results, we propose the chelation-controlled transition state model (Figure 2b). A nucleophilic enolate attacks a Michael acceptor from the *re*-face, affording the product with *S*-configuration. The *si*-face of the attack is more shielded by the indanol moiety of the ligand pointing forward. Because of the symmetry of the nucleophile, only one stereogenic center is formed, and the face of the attacking nucleophile is not important.

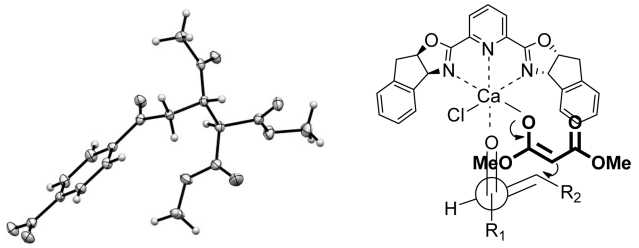

Figure 2. X-ray structure of **5a** (a) with thermal ellipsoids at the 50% probability level and the proposed chelation-controlled transition state model (b).

CONCLUSIONS

Since calcium is the fifth most abundant metal in the Earth's crust, its use in asymmetric catalysis is very attractive. We have shown that the catalytic system derived from calcium chloride and the easily preparable pyridine-bisoxazoline catalyzes a Michael addition to various α,β-unsaturated carbonyl compounds. The scope of the reaction was demonstrated. The most efficient substrates were aryl-substituted unsaturated 1,4-diketones and 1,4-ketoesters. The reactivity of less efficient substrates (e.g., unsaturated diesters and chalcones) can be increased by the addition of amines.

EXPERIMENTAL SECTION

General Remarks. All manipulations and reactions were conducted with no special precautions taken for the exclusion of moisture or air. Purchased chemicals and solvents were used as received. Ligands **L1** and **L2** were purchased and used as received. Ligands **L3** and **L4** were prepared according to the literature procedures.[41,42] Racemic standards were obtained by reacting electrophiles with dimethyl malonate in the presence of 1 equiv of K_2CO_3 in DCM at room temperature. ^{1}H and ^{13}C NMR spectra were measured on a 400 MHz instrument in $CDCl_3$. The TMS (δ = 0.00) peak was used as chemical shift reference. Mass spectra were recorded on a Q-TOF LC/MS spectrometer by using ESI ionization. Single crystal X-ray diffraction data for compound **5a** were collected on a diffractometer, using mirror-monochromatized Cu-Kα radiation (1.54178 Å). Chiral HPLC was performed by using a Chiralpak OD-H (250 × 4.6 mm) or Chiralpak AD-H (250 × 4.6 mm) column. Optical rotations were obtained at 25 °C in $CHCl_3$ and calibrated with pure solvent as a blank. Melting points were measured on a melting point apparatus and were uncorrected. For column chromatography, silica gel with a particle size of 0.063−0.2 mm was used.

General Procedure for the Asymmetric 1,4-Addition Reaction of Dimethyl Malonate with Electrophiles. To a solution of $CaCl_2$ (0.006 mmol) and Box-ligand **L4** (0.006 mmol) in 2-propanol (1 mL) were added dimethyl malonate **1** (0.13 mmol) and an electrophile **2** or **4** (0.13 mmol). If necessary, imidazole (0.006 mmol) was added to the reaction mixture. The reaction was stirred at room temperature under air. For the isolation of the product, the solvent was evaporated, and the residue was purified by flash chromatography on silica gel (heptane−EtOAc). The enantioselectivity was determined by HPLC analysis of the isolated product.

*Dimethyl 2-(1,4-Dioxo-1,4-diphenylbutan-2-yl)malonate (**3**).* Following the general procedure, the title compound **3** was obtained as a yellow oil (44 mg, 94% yield). The enantioselectivity was determined by chiral HPLC analysis (Chiralpak OD-H, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, 25 °C, λ = 254 nm), major isomer 12.49 min, 84% ee, $[\alpha]_D^{25}$ −19.01 (*c* 0.29, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12−8.00 (m, 2H), 8.00−7.87 (m, 2H), 7.63−7.52 (m, 2H), 7.52−7.39 (m, 4H), 5.00−4.87 (m, 1H), 3.96 (d, J = 8.7 Hz, 1H), 3.66 (s, 3H), 3.62 (s, 3H), 3.64−3.56 (m, 1H), 3.39 (dd, J = 18.2, 5.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.2, 196.6, 168.7, 168.5, 136.1, 135.6, 133.52, 133.45, 128.80, 128.77, 128.68, 128.2, 52.79, 52.78, 52.73, 40.7, 39.0; IR (KBr) 3061, 2954, 2849, 1752, 1736, 1682, 1597, 1449, 1436, 1329, 1290, 1260, 1226, 1195, 1159, 1024, 1002, 753, 690 cm^{-1}; HRMS (ESI, m/z) calcd for $[C_{21}H_{20}O_6]^+$ ([M + H]$^+$) 369.1333; found, 369.1335.

*Dimethyl 2-(1-(4-Nitrophenyl)-1,4-dioxopentan-3-yl)malonate (**5a**).* Following the general procedure, the reaction was stirred at −20 °C, obtaining the title compound **5a** as a yellow oil (37 mg, 82% yield). The enantioselectivity was determined by chiral HPLC analysis (Chiralpak OD-H, hexane/2-propanol = 70:30, flow rate = 1.0 mL/min, 25 °C, λ = 254 nm), major isomer 19.72 min, 88% ee. $[\alpha]_D^{25}$ −33.22 (*c* 0.04, $CHCl_3$) (determined for ee 71%, Table 1, entry 7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35−8.29 (m, 2H), 8.13−8.07 (m, 2H), 3.93 (td, J = 7.6, 4.3 Hz, 1H), 3.88 (d, J = 7.4 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 3.51 (dd, J = 18.4, 7.8 Hz, 1H), 3.36 (dd, J = 18.3, 4.3 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.6, 195.9, 168.35, 168.32, 150.6, 140.6, 129.2, 124.0, 53.03, 52.98, 52.2, 45.8, 38.8, 29.7; IR (KBr) 3112, 2957, 2919, 2850, 1749, 1735, 1718, 1696, 1604, 1528, 1436, 1347, 1319, 1263, 1213, 1161, 1011, 856, 745 cm^{-1}; HRMS (ESI, m/z) calcd for $[C_{16}H_{17}NO_8]^+$ ([M + Na]$^+$) 374.0846; found, 374.0855.

*Dimethyl 2-(1-(4-Bromophenyl)-1,4-dioxopentan-3-yl)malonate (**5b**).* Following the general procedure, the title compound **5b** was obtained as a white solid (48 mg, 98% yield). The enantioselectivity was determined by chiral HPLC analysis (Chiralpak AD-H, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, 25 °C, λ = 254 nm), major isomer 42.22 min, 82% ee, $[\alpha]^{25}_D$ = −31.55 (*c* 0.21, $CHCl_3$). mp 83−86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83−7.78 (m, 2H), 7.64−7.59 (m, 2H), 3.92 (td, J = 7.7, 4.6 Hz, 1H), 3.85 (d, J = 7.9 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.41 (dd, J = 18.2, 7.6 Hz, 1H), 3.29 (dd, J =

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18.2, 4.6 Hz, 1H), 2.36 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.2, 196.1, 168.48, 168.44, 134.8, 132.0, 129.6, 128.8, 52.92, 52.86, 52.5, 45.6, 38.5, 29.8 ppm; IR (KBr) 3004, 2955, 2847, 1750, 1735, 1717, 1687, 1586, 1436, 1399, 1356, 1264, 1225, 1160, 1071, 1008, 819 cm^{-1}; HRMS (ESI, m/z) calcd for $[C_{16}H_{17}O_6Br]^+$ ($[M + Na]^+$) 407.0101; found, 407.0105.

*Dimethyl 2-(1-(4-Methoxyphenyl)-1,4-dioxopentan-3-yl)-malonate (**5c**).* Following the general procedure, the title compound **5c** was obtained as a yellow oil (35 mg, 81% yield). The enantioselectivity was determined by chiral HPLC analysis (Chiralpak AD-H, hexane/2-propanol = 80:20, flow rate = 1.0 mL/min, 25 °C, λ = 254 nm), major isomer 28.86 min, 85% ee, $[\alpha]^{25}_D$ = −50.58 (c 0.13, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95−7.88 (m, 2H), 6.97−6.90 (m, 2H), 3.96−3.89 (m, 1H), 3.87 (s, 3H), 3.86 (d, J = 8.6 Hz, 1H), 3.73 (s, 3H), 3.70 (s, 3H), 3.37 (dd, J = 18.0, 7.4 Hz, 1H), 3.28 (dd, J = 18.0, 4.8 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.7, 195.4, 168.64, 168.60, 163.9, 130.4, 129.2, 113.9, 55.5, 52.85, 52.79, 52.72, 45.8, 38.3, 29.9; IR (KBr) 2956, 2844, 1751, 1736, 1717, 1676, 1601, 1576, 1512, 1436, 1356, 1259, 1170, 1115, 1027, 838 cm^{-1}; HRMS (ESI, m/z) calcd for $[C_{17}H_{20}O_7]^+$ ($[M + H]^+$) 337.1282; found, 337.1285.

*Dimethyl 2-(1-(Furan-2-yl)-1,4-dioxopentan-3-yl)malonate (**5d**).* Following the general procedure, the title compound **5d** was obtained as a yellow oil (33 mg, 87% yield). The enantioselectivity was determined by chiral HPLC analysis (Chiralpak AD-H, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, 25 °C, λ = 254 nm), major isomer 27.86 min, 82% ee, $[\alpha]^{25}_D$ = −64.58 (c 0.08, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 1.1 Hz, 1H), 7.22 (d, J = 3.6 Hz, 1H), 6.55 (dd, J = 3.6, 1.6 Hz, 1H), 3.92−3.86 (m, 1H), 3.85 (d, J = 8.4 Hz, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 3.28 (dd, J = 18.0, 7.2 Hz, 1H), 3.17 (dd, J = 18.0, 4.6 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.3, 185.9, 168.50, 168.49, 152.0, 146.7, 117.6, 112.5, 52.90, 52.84, 52.7, 45.3, 38.2, 29.9; IR (KBr) 3136, 3006, 2956, 2849, 1750, 1735, 1718, 1676, 1571, 1469, 1436, 1397, 1355, 1274, 1235, 1161, 1034, 883, 771 cm^{-1}; HRMS (ESI, m/z) calcd for $[C_{14}H_{16}O_7]^+$ ($[M + Na]^+$) 319.0788; found, 319.0792.

*Trimethyl 4-Oxo-4-phenylbutane-1,1,2-tricarboxylate (**5e**).* Following the general procedure, the title compound **5e** was obtained as a colorless oil (35 mg, 86% yield). The enantioselectivity was determined by chiral HPLC analysis (Chiralpak OD-H, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, 25 °C, λ = 254 nm), major isomer 16.17 min, 84% ee, $[\alpha]^{25}_D$ = −8.60 (c 0.21, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00−7.93 (m, 2H), 7.61−7.54 (m, 1H), 7.51−7.43 (m, 2H), 4.04 (d, J = 6.6 Hz, 1H), 3.90−3.83 (m, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.70 (s, 3H), 3.63 (dd, J = 18.1, 6.8 Hz, 1H), 3.37 (dd, J = 18.1, 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.1, 172.6, 168.47, 168.41, 136.3, 133.4, 128.7, 128.1, 52.85, 52.79, 52.5, 52.0, 39.5, 37.5; IR (KBr) 3005, 2955, 2848, 1738, 1687, 1598, 1437, 1265, 1224, 1165, 1021, 1005, 756, 691 cm^{-1}; HRMS (ESI, m/z) calcd for $[C_{16}H_{18}O_7]^+$ ($[M + Na]^+$) 345.0945; found, 345.0950.

*2-Ethyl 1,1-Dimethyl 4-(4-nitrophenyl)-4-oxobutane-1,1,2-tricarboxylate (**5f**).* Following the general procedure, the title compound **5f** was obtained as a yellow oil (47 mg, 96% yield). The enantioselectivity was determined by chiral HPLC analysis (Chiralpak OD-H, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, 25 °C, λ = 254 nm), major isomer 59.07 min, 78% ee, $[\alpha]^{25}_D$ = −3.43 (c 0.19, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 8.8 Hz, 2H), 8.13 (d, J = 8.9 Hz, 2H), 4.23−4.12 (m, 2H), 4.07 (d, J = 5.9 Hz, 1H), 3.90−3.83 (m, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.70 (dd, J = 18.0, 7.5 Hz, 1H), 3.35 (dd, J = 18.0, 4.6 Hz, 1H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.0, 171.5, 168.3, 168.2, 150.4, 140.9, 129.1, 123.8, 61.6, 52.84, 52.77, 51.7, 39.6, 37.7, 13.9; IR (KBr) 3112, 2957, 1737, 1696, 1604, 1528, 1436, 1348, 1319, 1222, 1164, 1024, 854, 747 cm^{-1}; HRMS (ESI, m/z) calcd for $[C_{17}H_{19}NO_9]^+$ ($[M + Na]^+$) 404.0952; found, 404.0964.

*Trimethyl 4-(4-Methoxyphenyl)-4-oxobutane-1,1,2-tricarboxylate (**5g**).* Following the general procedure, the title compound **5g** was obtained as a yellow oil (29 mg, 64% yield). The enantioselectivity was determined by chiral HPLC analysis (Chiralpak AD-H, hexane/2-propanol = 80:20, flow rate = 1.0 mL/min, 25 °C, λ = 254 nm), major isomer 29.55 min, 84% ee, $[\alpha]^{25}_D$ = −10.18 (c 0.18, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97−7.91 (m, 2H), 6.98−6.90 (m, 2H), 4.03 (d, J = 6.7 Hz, 1H), 3.87 (s, 3H), 3.90−3.81 (m, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.69 (s, 3H), 3.56 (dd, J = 17.9, 6.7 Hz, 1H), 3.31 (dd, J = 17.9, 5.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.5, 172.8, 168.51, 168.46, 163.7, 130.4, 129.4, 113.8, 55.5, 52.82, 52.77, 52.5, 52.0, 39.6, 37.1; IR (KBr) 3005, 2955, 2844, 1738, 1677, 1601, 1576, 1512, 1436, 1309, 1261, 1170, 1025, 834 cm^{-1}; HRMS (ESI, m/z) calcd for $[C_{17}H_{20}O_8]^+$ ($[M + H]^+$) 353.1231; found, 353.1230.

*2,3-Dibenzyl 1,1-Dimethylpropane-1,1,2,3-tetracarboxylate (**5h**).* Following the general procedure, with the addition of imidazole, the title compound **5h** was obtained as a colorless oil (25 mg, 45% yield). The enantioselectivity was determined by chiral HPLC analysis (Chiralpak AD-H, hexane/2-propanol = 80:20, flow rate = 1.0 mL/min, 25 °C, λ = 210 nm), major isomer 14.45 min, 29% ee, $[\alpha]^{25}_D$ = −10.71 (c 0.20, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.27 (m, 10H), 5.10 (s, 2H), 5.07 (s, 2H), 3.96 (d, J = 6.9 Hz, 1H), 3.68 (s, 3H), 3.70−3.64 (m, 1H), 3.62 (s, 3H), 2.90 (dd, J = 17.1, 7.6 Hz, 1H), 2.77 (dd, J = 17.1, 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 171.0, 168.1, 168.0, 135.6, 135.3, 128.57, 128.53, 128.46, 128.39, 128.33, 128.32, 67.4, 66.7, 52.81, 52.75, 52.0, 40.5, 33.4; IR (KBr) 3066, 3034, 2955, 1739, 1587, 1499, 1456, 1436, 1387, 1164, 1003, 753, 699 cm^{-1}; HRMS (ESI, m/z) calcd for $[C_{23}H_{24}O_8]^+$ ($[M + H]^+$) 429.1544; found, 429.1544.

*Dimethyl 2-(4-Oxo-4-phenylbutan-2-yl)malonate (**5i**).* Following the general procedure, with the addition of imidazole, the title compound **5i** was obtained as a colorless oil (26 mg, 72% yield). The enantioselectivity was determined by chiral HPLC analysis (Chiralpak AD-H, hexane/2-propanol = 80:20, flow rate = 1.0 mL/min, 25 °C, λ = 254 nm), major isomer 6.92 min, 77% ee, $[\alpha]^{25}_D$ = −15.86 (c 0.07, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02−7.95 (m, 2H), 7.60−7.53 (m, 1H), 7.50−7.43 (m, 2H), 3.75 (s, 3H), 3.74 (s, 3H), 3.54 (d, J = 6.4 Hz, 1H), 3.27 (dd, J = 16.0, 4.0 Hz, 1H), 3.03−2.93 (m, 1H), 2.93 (dd, J = 16.1, 8.4 Hz, 1H), 1.09 (d, J = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.7, 169.14, 169.05, 136.9, 133.2, 128.6, 128.2, 56.1, 52.42, 52.40, 42.6, 29.6, 17.8; IR (KBr) 2955, 1750, 1734, 1685, 1598, 1581, 1449, 1436, 1219, 1160, 1023, 753, 691 cm^{-1}; HRMS (ESI, m/z) calcd for $[C_{15}H_{18}O_5]^+$ ($[M + H]^+$) 279.1227; found, 279.1228.

*Dimethyl 2-(3-Oxo-1,3-diphenylpropyl)malonate (**5j**).* Following the general procedure, with the addition of imidazole, the title compound **5j** was obtained as a white solid (39 mg, 89% yield). The enantioselectivity was determined by chiral HPLC analysis (Chiralpak AD-H, hexane/2-propanol = 80:20, flow rate = 1.0 mL/min, 25 °C, λ = 254 nm), major isomer 24.11 min, 20% ee, $[\alpha]^{25}_D$ = 5.83 (c 0.35, $CHCl_3$). mp 100−103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92−7.87 (m, 2H), 7.56−7.50 (m, 1H), 7.46−7.39 (m, 2H), 7.29−7.22 (m, 4H), 7.21−7.15 (m, 1H), 4.19 (td, J = 9.0, 5.0 Hz, 1H), 3.86 (d, J = 9.4 Hz, 1H), 3.73 (s, 3H), 3.55 (dd, J = 16.9, 5.0 Hz, 1H), 3.51 (s, 3H), 3.48 (dd, J = 16.9, 8.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.5, 168.7, 168.2, 140.4, 136.8, 133.1, 128.56, 128.49, 128.09, 128.07, 127.2, 57.3, 52.7, 52.4, 42.3, 40.8; IR (KBr) 3030, 2953, 2845, 1752, 1736, 1686, 1598, 1581, 1496, 1449, 1435, 1317, 1286, 1258, 1232, 1197, 1156, 1021, 750, 701 cm^{-1}; HRMS (ESI, m/z) calcd for $[C_{20}H_{20}O_5]^+$ ($[M + H]^+$) 341.1384; found, 341.1385.

*Dimethyl 2-(1-(4-Nitrophenyl)-3-oxobutyl)malonate (**5k**).* Following the general procedure, with the addition of imidazole, the title compound **5k** was obtained as a yellow oil (18 mg, 44% yield). The enantioselectivity was determined by chiral HPLC analysis (Chiralpak AD-H, hexane/2-propanol = 80:20, flow rate = 1.0 mL/min, 25 °C, λ = 254 nm), major isomer 23.64 min, 26% ee, $[\alpha]^{25}_D$ = 7.07 (c 0.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18−8.12 (m, 2H), 7.48−7.41 (m, 2H), 4.10 (td, J = 9.0, 4.9 Hz, 1H), 3.77 (d, J = 9.3 Hz, 1H), 3.74 (s, 3H), 3.55 (s, 3H), 3.06 (dd, J = 17.8, 4.9 Hz, 1H), 2.97 (dd, J = 17.8, 8.7 Hz, 1H), 2.07 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.0, 168.1, 167.6, 148.3, 147.1, 129.2, 123.7, 56.2, 52.9, 52.7, 46.5, 39.8, 30.3; IR (KBr) 2957, 1753, 1737, 1604, 1521, 1436, 1349, 1257, 1199, 1157, 1015, 857, 748, 700 cm^{-1}; HRMS (ESI, m/z) calcd for $[C_{15}H_{17}NO_7]^+$ ($[M + H]^+$) 324.1078; found, 324.1085.

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■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra, HPLC data, and X-ray crystal data of compound **5a** (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00769.

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Notes

The authors declare no competing financial interest.

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