

## Selective Michael additions to alkylidenemalonates using thiourea-based bifunctional organocatalysts

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### Abstract

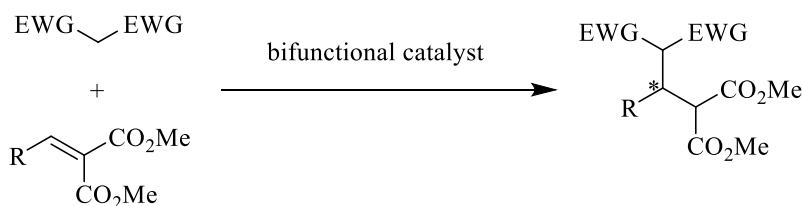
Bifunctional thiourea catalysts have been found to be excellent promoters of the challenging Michael addition to alkylidenemalonates giving high yields of up to 99%. Substrate structure was important for enantiodiscrimination, with aryl alkylidenemalonate acceptors furnishing products with *ee* values of up to 73%.

**Keywords:** Organocatalysis, alkylidenemalonates,  $\beta$ -diketones, nitromethane, Michael addition, bifunctional thiourea catalysts

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### Introduction

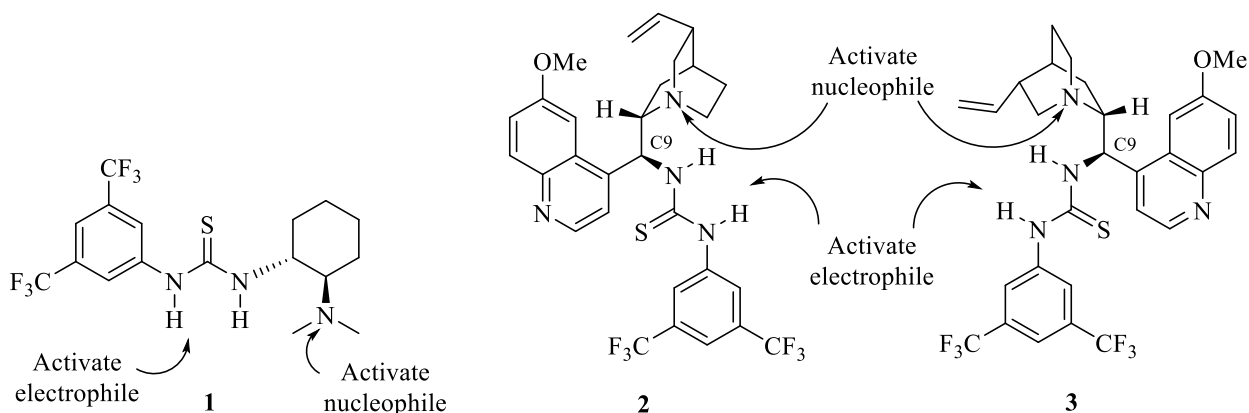
The development of simple and efficient asymmetric C-C bond forming reactions is a major challenge for the synthetic chemist.<sup>1,2</sup> In recent times, the organocatalysed Michael addition of carbon-centred nucleophiles to activated olefins has been established as a particularly effective method for the synthesis of enantiopure molecules.<sup>3-7</sup> Enamine and iminium ion generating organocatalysts have been successfully applied to the asymmetric Michael addition of aldehydes and ketones to a number of electron-deficient olefins, e.g. nitroolefins and  $\alpha,\beta$ -unsaturated sulfones,<sup>8</sup> vinyl phosphonates,<sup>9</sup> alkylidenemalonates<sup>10-13</sup> and  $\alpha,\beta$ -unsaturated aldehydes and ketones.<sup>14-17</sup> Bifunctional organocatalysts, such as those developed by Takemoto, Chen, Soós, Connon and Dixon, have also proven to be effective catalysts in asymmetric Michael additions but tend to be used with highly activated acceptors.<sup>18-22</sup> There have been considerably fewer publications reporting the use of bifunctional organocatalysts in the asymmetric Michael addition to the challenging alkylidenemalonates. Alkylidenemalonates are particularly difficult acceptors due to their reduced electrophilicity. Mayr's impressive and large study on the nucleophilicity and electrophilicity of many substrates details this reduced electrophilicity when compared with other common Michael acceptors.<sup>23-25</sup> Our interest in the Michael addition of pronucleophiles with a relatively acidic hydrogen to alkylidenemalonates is due to the potential synthetic utility of the functional group-rich chiral conjugate addition products (Scheme 1).



**Scheme 1.** Michael addition of pronucleophiles to alkylidenemalonates yielding highly functionalized chiral products.

The group of Barbas reported the conjugate addition of ketones to alkylidenemalonates *via* a pyrrolidine-derived catalyst in 2001.<sup>26</sup> In fact the majority of reports to date detailing organocatalytic Michael reactions involving alkylidenemalonate acceptors have employed covalent catalysts to promote the reaction.<sup>3,27</sup> To the best of our knowledge, Zhao and co-workers reported the first H-bonding bifunctional organocatalysed Michael addition to an alkylidenemalonate in 2008. Zhao's report outlines a tandem Michael-Knoevenagel reaction employing aromatic thiols as the pronucleophile in the synthesis of substituted thiochromanes.<sup>27</sup> There have been only two subsequent publications describing Michael type additions to alkylidenemalonates using H-bonding organocatalysts. In 2012 Yang *et al.* published an excellent paper discussing the use of novel guanidine derived organocatalysts in the addition of an  $\alpha,\beta$ -unsaturated  $\gamma$ -butyrolactam to alkylidenemalonates.<sup>28</sup> Yang generated an impressively high yielding and highly selective reaction. Recently, Quintavalla and co-workers reported the enantioselective conjugate addition of nitroalkanes to alkylidenemalonates using cinchona derived bifunctional organocatalysts.<sup>29</sup> It is this publication by Quintavalla that has prompted us to report our initial findings.

In this present study we have employed thiourea-based bifunctional organocatalysts in the enantioselective addition of  $\beta$ -diketones, malononitrile and nitromethane to alkyl and aryl alkylidenemalonates. Thiourea-based bifunctional organocatalysts have emerged as a viable catalytic design for many asymmetric transformations.<sup>30</sup> Typically, a thiourea-based bifunctional catalyst consists of a thiourea hydrogen bond donor moiety, for electrophile activation, and a basic amine functionality, for nucleophile activation, Figure 1.<sup>18,21</sup>



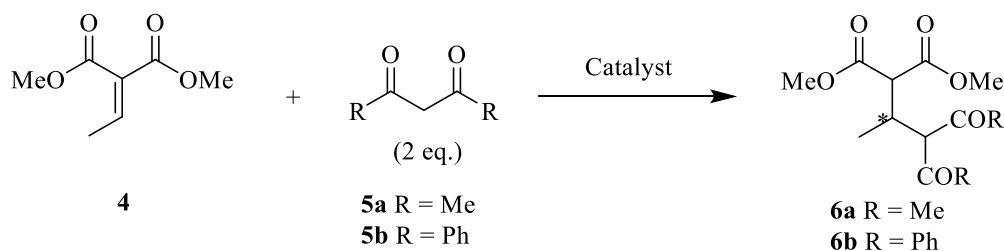
**Figure 1.** Bifunctional thiourea-based organocatalysts.

We expected that a thiourea-based amine organocatalyst, due to its dual modes of activation, would offer the best opportunity for the generation of selective Michael type addition to alkylidenemalonates. As a result, we focused our initial catalyst screen on the three thiourea-based organocatalysts depicted in Figure 1. Organocatalyst **1** has been a highly stereoselective promoter of Michael additions using activated olefins,<sup>18</sup> as have cinchona alkaloid-derived catalysts **2** and **3**.<sup>21</sup>

## Results and Discussion

The results from the catalyst screen are shown in Table 1. We employed the addition of 2,4-pentanedione to dimethyl ethylidenemalonate as our initial test reaction, entries 1-4, Table 1. In addition to our work on extended Michael acceptors,<sup>31</sup> our group is interested in conjugate additions to activated olefins and previous work indicated that the most selective addition of  $\beta$ -diketones to  $\beta$ -nitrostyrene using a thiourea-based organocatalyst occurred in toluene. As a result toluene was chosen as the solvent for this work.<sup>32</sup>

**Table 1.** Michael addition of  $\beta$ -diketones to dimethyl ethylidenemalonate

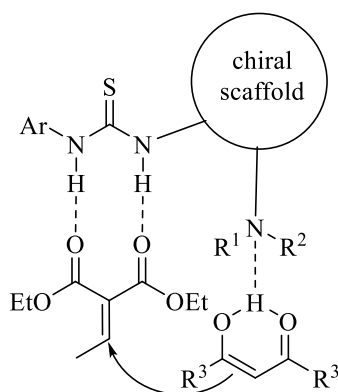


Entry	R	Catalyst	Loading (mol%)	Time (h)	Yield (%)	ee <sup>a</sup> (%)
1	Me	KO <sup>t</sup> Bu	5	5	97	-
2	Me	<b>2</b>	10	12	99	20

3	Me	<b>3</b>	10	24	87	(-)-14
4	Me	<b>1</b>	10	24	99	(-)-16
5	Ph	KO <sup>t</sup> Bu	5	5	88	-
6	Ph	<b>2</b>	10	24	96	28

Reaction conditions: 0.028 mL (0.2 mmol) diethyl ethylidenemalonate, 0.4 mmol pronucleophile, 10 mol% catalyst, 0.8 mL toluene. <sup>a</sup>Enantiomeric excess determined by chiral HPLC analysis (Chiralpak IC).

All catalysts generated a high yielding reaction, 87-99%, with modest enantioselectivity. Of the three reactions employing 2,4-pentanedione as the Michael donor, catalyst **2** gave the highest selectivity, furnishing the product in 20% *ee*. Our group have previously applied the same catalysts in a highly enantioselective addition of  $\beta$ -diketones to  $\beta$ -nitrostyrene.<sup>32</sup> The reduced selectivity with dimethyl ethylidenemalonate, when compared to nitrostyrene, may result from the inferior Lewis basicity of the carbonyl group, in comparison to a nitro group, and hence a weaker catalyst-acceptor interaction.<sup>3</sup> This weaker interaction with the Lewis acid catalyst may allow the competing and non-stereoselective background reaction to dominate. The Michael addition of 1,3-diphenylpropane-1,3-dione to dimethyl ethylidenemalonate also generated a high yielding reaction, 88-96%, but again only modest enantioselectivity was observed, entries 5-6, Table 1, although catalyst **2** gave a higher *ee* value (28%) with 1,3-diphenylpropane-1,3-dione. The presence of two carbonyl groups allows for convenient H-bonding with the thiourea moiety of the organocatalyst. Figure 2 shows the postulated transition state model, showing activation by the thiourea catalyst of the alkylidenemalonate acceptor and the 1,3-diketone pronucleophile.

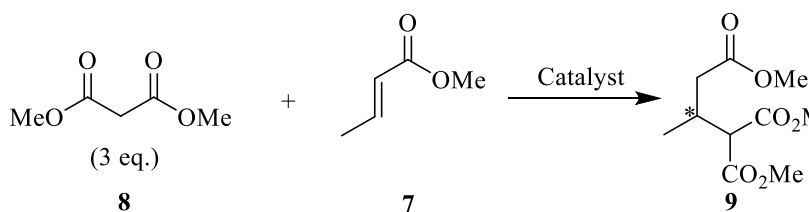


**Figure 2.** Simultaneous activation of the alkylidenemalonate electrophile and the 1,3-diketone Michael donor.

We also explored the reactivity of the simpler  $\alpha,\beta$ -unsaturated ester, methyl crotonate **7**, Table 2, reasoning that this substrate would yield useful product synthons in a more atom-efficient manner. For this reaction the initial pronucleophile chosen was dimethyl malonate, a

prominent Michael donor in conjugate addition reactions. Several base catalysts were screened in the addition of the 1,3-diester to methyl crotonate, Table 2. Triethylamine and DABCO were chosen as the first nitrogen-based achiral promoters of this reaction due to their low cost and ready availability. As no product was detected in these reactions we then tested quinuclidine (the basic unit in our organocatalysts) and the cinchona alkaloid quinine, reasoning that the presence of the H-bonding hydroxyl group in the latter catalyst would activate the Michael acceptor toward attack from the incipient carbanion. Although the amine bases are weak bases,  $pK_a \approx 9$ -10, we wondered if they would promote the conjugate addition *via* a general base catalyzed mechanism ( $pK_a$  of dimethyl malonate  $\approx 13$ ). However, only reactions employing the stronger inorganic bases generated the desired product. We therefore propose that the reduced electrophilicity of methyl crotonate prevents the amine catalysts from promoting a General Base Catalysed reaction and that the Michael addition can only occur under Specific Base Catalysis with the stronger inorganic bases.

**Table 2.** Michael addition of dimethyl malonate to methyl crotonate



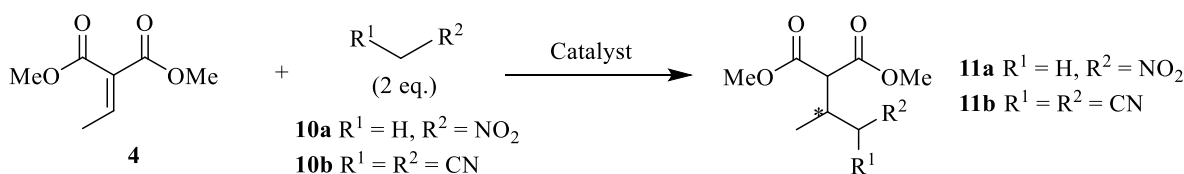
Entry	Catalyst	Loading (mol%)	Time (h)	Yield (%)
1	KO <sup>t</sup> Bu	5	96	94
2	K <sub>2</sub> CO <sub>3</sub>	10	96	35
3	K <sub>2</sub> CO <sub>3</sub>	100	96	88
4	NaOMe	100	96	65
5	Et <sub>3</sub> N	100	96	- <sup>a</sup>
6	DABCO	100	96	- <sup>a</sup>
7	Quinuclidine	100	96	- <sup>a</sup>
8	Quinine	100	96	- <sup>a</sup>

*Reaction conditions:* 0.015 mL (0.1 mmol) methyl crotonate, 0.34 mL (0.3 mmol) dimethyl malonate, catalyst, 2 mL diethyl ether. <sup>a</sup> No product detected.

Having established that a second activating ester group on the Michael acceptor is critical for reactivity we extended our substrate scope to non-carbonyl containing pronucleophiles. To do this we employed both nitromethane **10a** and malononitrile **10b** as pronucleophiles and report

their use in the organocatalytic Michael type addition to dimethyl ethylidenemalonate for the first time (Table 3). Mayr's reactivity scales indicate that both nitromethane and malononitrile are excellent nucleophiles, with nucleophilicity values (N) of 20.71 and 19.36, respectively (in DMSO).<sup>25</sup> We also found this to be the case, with nitromethane generating yields of up to 84%, entry 4, Table 3, and a much improved enantiomeric excess of 48%, entry 2, Table 3. Malononitrile also proved to be very reactive with yields of 75-89%. Unfortunately, the two product enantiomers could not be separated by chiral HPLC and hence the enantiomeric excess could not be determined.

**Table 3.** Michael addition of nitromethane and malononitrile to dimethyl ethylidenemalonate



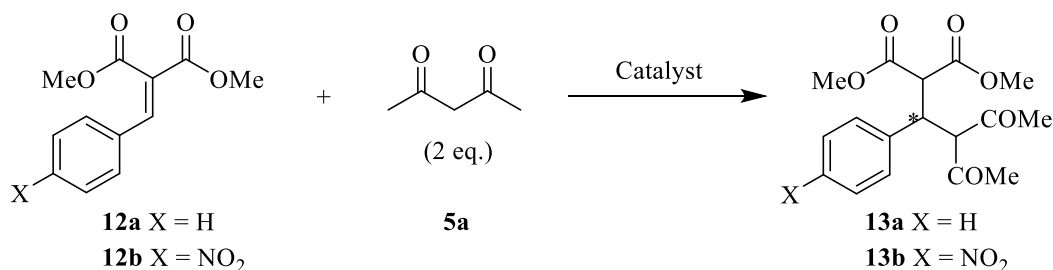
Entry	Catalyst	Product	Loading (mol%)	Time (h)	Yield (%)	ee <sup>a</sup> (%)
1	KO <sup>t</sup> Bu	<b>11a</b>	5	96	75	-
2	<b>2</b>	<b>11a</b>	10	96	73	48
3	<b>3</b>	<b>11a</b>	10	96	(-)-38	34
4	<b>1</b>	<b>11a</b>	10	96	(-)-84	44
5	KO <sup>t</sup> Bu	<b>11b</b>	5	12	75	n.d.
6	<b>2</b>	<b>11b</b>	10	4	82	n.d.
7	<b>3</b>	<b>11b</b>	10	6	79	n.d.
8	<b>1</b>	<b>11b</b>	10	2	88	n.d.

*Reaction conditions:* 0.028 mL (0.2 mmol) diethyl ethylidenemalonate, 0.4 mmol pronucleophile, 10 mol% catalyst, 0.8 mL toluene. <sup>a</sup> Enantiomeric excess determined by chiral HPLC analysis (Chiralpak IB, IC).

We also undertook a series of experiments aimed at expanding the scope of this methodology to arylalkylidenemalonates, namely dimethyl benzylidenemalonate **12a** and dimethyl 2-(4-nitrobenzylidene)malonate **12b**. The Mayr reactivity scales predict that the addition of 2,4-pentanedione (nucleophilicity value, N, of 17.64 in DMSO)<sup>24</sup> to diethyl benzylidenemalonate (electrophilicity value, E, of -20.55) would be quite slow. The same reactivity scales suggest that adding an electron withdrawing *para*-nitro group on the aryl ring of the alkylidene malonate will improve electrophilicity, diethyl 2-(4-nitrobenzylidene)malonate has higher electrophilicity value

(E) of -17.67.<sup>23</sup> We observed this improved reactivity in our work as dimethyl benzylidenemalonate **12a** proved to be completely unreactive in our hands, entry 1, Table 4. The nitro-substituted dimethyl 2-(4-nitrobenzylidene)malonate **12b** showed an improved reactivity with significant enantioselectivity (Entries 2-5, Table 4). As the acceptor **12a** was too poor an electrophile to undergo the organocatalyzed Michael addition we did not explore even less electrophilic substrates containing electron-donating substitutions on the aryl moiety.

**Table 4.** Michael addition of 2,4-pentanedione to arylalkylidenemalonates



Entry	Catalyst	Product	Loading (mol%)	Time (h)	Yield (%)	ee <sup>a</sup> (%)
1	<b>2</b>	<b>13a</b>	10	96	- <sup>b</sup>	-
2	KO <sup>t</sup> Bu	<b>13b</b>	5	96	56	-
3	<b>2</b>	<b>13b</b>	10	96	28	73
4	<b>3</b>	<b>13b</b>	10	96	17	56
5	<b>1</b>	<b>13b</b>	10	96	10	(-)-68

*Reaction conditions:* 0.1 mmol Michael acceptor, 0.2 mL (0.2 mmol) acetylacetone, 10 mol% catalyst, 0.4 mL toluene. <sup>a</sup>Enantiomeric excess determined by chiral HPLC analysis (Chiralpak IC). <sup>b</sup>No product detected.

As can be seen from Table 4, all three catalysts exhibited a greater degree of stereocontrol with arylalkylidenemalonate substrates compared to the alkyl substituted acceptors. We postulate that the improved selectivity is a consequence of the lower reactivity of dimethyl (4-nitrobenzylidene)malonate compared to dimethyl ethylidenemalonate. In the case of the  $\beta$ -alkyl-substituted acceptor, the  $\beta$ -carbon is sufficiently electrophilic to allow the non-stereoselective background reaction to occur. It is possible that the aromatic acceptor is too unreactive to allow this background reaction to occur and that it requires an interaction with the thiourea moiety to sufficiently activate it toward nucleophilic attack. The autocatalytic background Michael reaction is unable to proceed due to the lack of reactivity of the uncoordinated (and thus unactivated) electrophile. Thus the presence of the catalyst is essential for reactivity and a more stereoselective reaction ensues.

## Conclusions

In conclusion, we have demonstrated that thiourea-based bifunctional organocatalysts are excellent promoters of conjugate additions to the challenging Michael acceptors, alkylidenemalonates. The structure of the Michael acceptor is very important for enantioselectivity, with the *para*-nitro-substituted aromatic substrate giving the highest selectivities (up to 73% *ee*). The  $\beta$ -alkyl-substituted acceptor, dimethyl ethylidenemalonate, furnished Michael products in high yields but lower enantiomeric excess. It is likely that this is due to the relatively weak interaction between the catalyst and the carbonyl group of the acceptor, which results in the autocatalytic racemic background reaction prevailing.

## Supporting information available

NMR spectra and HPLC chromatograms are available free of charge via the Internet at <http://www.arkat-usa.org>.

## Experimental Section

**General.** Reagents were used as purchased from suppliers, unless otherwise indicated. Solvents were distilled and dried before use. Toluene and anhydrous DMF were used as purchased. Reactions requiring inert conditions were performed in dried glassware under a positive pressure of argon. Reactions were monitored by thin layer chromatography using SiO<sub>2</sub> (silica gel 60 F254, Merck, coated aluminum plates), and visualizing by UV light or by aqueous KMnO<sub>4</sub> or phosphomolybdic acid solutions. Flash chromatography was carried out on SiO<sub>2</sub> (silica gel 60 F254, 230-400 mesh ASTM, Merck). <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded with a Bruker Avance 300 NMR spectrometer. Chemical shifts are reported in ppm relative to TMS internal standard ( $\delta$  = 0.00) in CDCl<sub>3</sub> for <sup>1</sup>H NMR spectra. For <sup>13</sup>C NMR spectra, solvent residual peaks ( $\delta$  = 77.0 ppm for CDCl<sub>3</sub>) were used as internal reference. Abbreviation of multiplicities is as follows: s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), br s (broad singlet). High-resolution mass spectrometric data was recorded with an Agilent Technologies 6410 Time of Flight LC/MS at NUI Maynooth. IR spectra were recorded with Perkin Elmer System 2000 FT-IR instrument. Optical rotations were obtained with a Perkin-Elmer 343 polarimeter ( $\lambda$  = 589 nm) using a 0.5 dm cell. Chiral HPLC analysis was performed with a Perkin Elmer Series 200 HPLC. The exact conditions are reported in connection with each analyzed substance. HPLC analyses were performed before crystallization steps to exclude possible additional enantioenrichment. Melting points were recorded with Stuart SMP11 melting point apparatus in open capillary tubes.

Organocatalysts **2** and **3** were prepared as per literature protocol.<sup>32</sup>

**Synthesis of trimethyl 2-methylpropane-1,1,3-tricarboxylate (9).**<sup>33</sup> To a stirred solution of dimethyl ethylidenemalonate (0.15 mL, 1 mmol) and dimethyl malonate (0.34 mL, 3 mmol) in diethyl ether (2 mL) was added base (5 mol% - 100 mol%). The reaction was monitored by TLC. Upon consumption of the starting material, the solvent was removed *in vacuo* and the crude residue was purified by flash chromatography (1:1 hexane : diethyl ether) to afford the conjugate addition product as a colourless oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  3.74 (s, 6H, OCH<sub>3</sub>), 3.68 (s, 3H, OCH<sub>3</sub>), 3.46 (d, *J* 7.2 Hz, 1H, CH(COOCH<sub>3</sub>)<sub>2</sub>), 2.82-2.68 (m, 1H, CH<sub>3</sub>CH), 2.55 (dd, *J* 15.8, 5.2 Hz, 1H, CH<sub>2</sub>(COOCH<sub>3</sub>)), 2.32 (dd, *J* 15.8, 6.9 Hz, 1H, CH<sub>2</sub>(COOCH<sub>3</sub>)), 1.07 (d, *J* 6.9 Hz, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  172.5 (C=O), 168.81 (C=O), 168.83 (C=O), 55.9 (CH(COOCH<sub>3</sub>)<sub>2</sub>), 52.4 (OCH<sub>3</sub>), 52.4 (OCH<sub>3</sub>), 51.6 (OCH<sub>3</sub>), 38.4 (CH<sub>2</sub>(COOCH<sub>3</sub>)), 30.2 (CHCH<sub>3</sub>), 17.6 (CH<sub>3</sub>).

**General procedure for the preparation of Michael adducts 6a, 6b, 11a, 11b, 13b.** To a stirred solution of the Michael acceptor (0.2 mmol) and pronucleophile (0.4 mmol) in toluene (0.8 mL) was added the chiral organocatalyst (0.02 mmol, 10 mol%). The reaction was monitored by TLC. Upon consumption of the  $\alpha,\beta$ -unsaturated compound (or after 96 h) the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography to afford the conjugate addition product.

**Dimethyl 2-(3-acetyl-4-oxopentan-2-yl)malonate (6a).** Flash column chromatography (1:1 hexane:diethyl ether) afforded **6a** as a colourless liquid. **6a** existed as an equilibrium mixture of keto and enol tautomers, with the keto form predominating. Ratio of keto: enol in CDCl<sub>3</sub> at 25 °C; 93: 7. b.p.: 96-98 °C @  $5 \times 10^{-2}$  torr.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): Keto:  $\delta$  3.97 (d, *J* 9.5 Hz, 1H, CH(COOCH<sub>3</sub>)<sub>2</sub>), 3.74 (s, 3H, COOCH<sub>3</sub>), 3.75 (s, 3H, COOCH<sub>3</sub>), 3.52 (d, *J* 5.3 Hz, 1H, CH(COCH<sub>3</sub>)<sub>2</sub>), 3.12-3.00 (m, 1H, CHCH<sub>3</sub>), 2.23 (s, 3H, COCH<sub>3</sub>), 2.19 (s, 3H, COCH<sub>3</sub>), 1.03 (d, *J* 7.1 Hz, 3H, CH<sub>3</sub>). Enol:  $\delta$  3.78 (s, 3H, COOCH<sub>3</sub>), 3.63 (s, 3H, COOCH<sub>3</sub>), 2.26 (s, 6H, COCH<sub>3</sub>), 1.27 (d, *J* 7.1 Hz, 3H, CH<sub>3</sub>)

<sup>13</sup>C NMR (CDCl<sub>3</sub>): Keto:  $\delta$  203.5 ((CH<sub>3</sub>)C=O), 203.1 ((CH<sub>3</sub>)C=O), 168.7 ((H<sub>3</sub>CO)C=O), 168.5 ((H<sub>3</sub>CO)C=O), 71.3, (CH(COOCH<sub>3</sub>)<sub>2</sub>), 53.1 (CH(COCH<sub>3</sub>)<sub>2</sub>), 52.5 (OCH<sub>3</sub>), 53.3 (OCH<sub>3</sub>), 32.7 (CHCH<sub>3</sub>), 30.2 (COCH<sub>3</sub>), 29.4 (COCH<sub>3</sub>), 14.4 (CH<sub>3</sub>). Enol:  $\delta$  196.4 ((CH<sub>3</sub>)(C=O), 168.6 ((H<sub>3</sub>CO)C=O), 168.4 ((H<sub>3</sub>CO)C=O), 111.3 (C=C) 56.8 (CH(COOCH<sub>3</sub>)<sub>2</sub>), 53.4 (OCH<sub>3</sub>), 52.7 (OCH<sub>3</sub>), 32.0 (CHCH<sub>3</sub>), 24.5 (COCH<sub>3</sub>), 18.3 (CH<sub>3</sub>).

HRMS: *m/z* 281.0987 [C<sub>12</sub>H<sub>18</sub>O<sub>6</sub>Na (M + Na)<sup>+</sup> requires 281.0996]

HPLC (Chiralpak IC, 2% isopropyl alcohol in hexane, 1 mL/min, 238 m): *t*<sub>1</sub> = 16.4 min, *t*<sub>2</sub> = 18.1 min.

**Dimethyl 2-(3-benzoyl-4-oxo-phenylbutan-2-yl)malonate (6b):** Flash column chromatography (2:1 hexane:diethyl ether) afforded **6b** as a colourless liquid. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.06-7.99 (m, 4H, ArH), 7.55-7.39 (m, 6H, ArH), 5.96 (d, *J* 7.8 Hz, 1H, CH(CO<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 3.84 (d, *J* 6.2 Hz, 1H, CH(COPh)<sub>2</sub>), 3.68 (s, 6H, OCH<sub>3</sub>), 3.47-3.35 (m, 1H, CHCH<sub>3</sub>), 1.17 (d, *J* 7.3 Hz, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  195.4 ((Ph)C=O), 195.2 ((Ph)C=O), 169.2 ((H<sub>3</sub>CO)C=O), 169.0 ((H<sub>3</sub>CO)C=O), 136.9 (ArC), 136.0 (ArC), 133.8 (ArC), 133.6 (ArC), 128.9 (ArC), 128.7 (ArC), 128.5 (ArC), 57.5 (CH(COOCH<sub>3</sub>)<sub>2</sub>), 53.9 (CH(COPh)<sub>2</sub>), 52.4, 52.3 (OCH<sub>3</sub>), 34.2 (CHCH<sub>3</sub>), 14.3

(CH<sub>3</sub>). HRMS:  $m/z$  383.1498 [C<sub>22</sub>H<sub>23</sub>O<sub>6</sub> (M + H)<sup>+</sup> requires 383.1489]. HPLC (Chirlapak IB, 60% isopropyl alcohol in hexane, 1 mL/min, 238 m):  $t_1$  = 14.7 min,  $t_2$  = 20.5 min.

**Dimethyl 2-(1-nitropropan-2-yl)malonate (11a)**: Flash column chromatography (2:1 hexane : diethyl ether) afforded **11a** as a colourless liquid. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  4.65 (dd,  $J$  12.9, 5.1 Hz, 1H, NO<sub>2</sub>CH<sub>2</sub>), 4.47 (dd,  $J$  12.9, 7.7 Hz, 1H, NO<sub>2</sub>CH<sub>2</sub>), 3.78 (s, 6H, COOCH<sub>3</sub>), 3.55 (d,  $J$  6.9 Hz, 1H, CH(COOCH<sub>3</sub>)<sub>2</sub>), 3.11-2.98 (m, 1H, NO<sub>2</sub>CH<sub>2</sub>CH), 1.14 (d,  $J$  6.7 Hz, 1H, CH<sub>3</sub>).

<sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  168.1 (C=O), 168.1 (C=O), 78.4 (CH<sub>2</sub>NO<sub>2</sub>), 53.8 (CH(COOCH<sub>3</sub>)<sub>2</sub>), 52.81 (OCH<sub>3</sub>), 52.82 (OCH<sub>3</sub>), 32.0 (CHCH<sub>2</sub>NO<sub>2</sub>), 15.5 (CH<sub>3</sub>). HRMS:  $m/z$  220.0817 [C<sub>8</sub>H<sub>14</sub>NO<sub>6</sub> (M + H)<sup>+</sup> requires 220.0816]. HPLC (Chirlapak IC, 20% isopropyl alcohol in hexane, 1 mL/min, 238 m):  $t_1$  = 8.4 min,  $t_2$  = 9.6 min.

**Dimethyl 2-(1,1-dicyanopropan-2-yl)malonate (11b)**. Flash column chromatography (1:1 hexane : diethyl ether) afforded **11b** as a colourless liquid. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  4.53 (d,  $J$  5.0 Hz, 1H, CH(CN)<sub>2</sub>), 3.81 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 3.80 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 3.53 (d,  $J$  8.4 Hz, 1H, CH(CO<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 2.95-2.84 (m, 1H, CHCH<sub>2</sub>(CN)<sub>2</sub>), 1.36 (d,  $J$  6.9 Hz, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  167.5 (C=O), 167.2 (C=O), 111.2 (C $\equiv$ N), 110.9 (C $\equiv$ N), 53.4 (CH(CO<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 53.3 (OCH<sub>3</sub>), 53.2 (OCH<sub>3</sub>), 34.9 (CHCH<sub>2</sub>(CN)<sub>2</sub>), 26.8 (CH(CN)<sub>2</sub>), 15.0 (CH<sub>3</sub>). HRMS:  $m/z$  225.088 [C<sub>10</sub>H<sub>13</sub>N<sub>2</sub>O<sub>4</sub> (M + H)<sup>+</sup> requires 225.087]. HPLC (Chirlapak IB, 10% isopropyl alcohol in hexane, 1 mL/min, 238 m):  $t_1$  = 12.6 min,  $t_2$  = 13.6 min.

**Dimethyl 2-(2-acetyl-1-(4-nitrophenyl)-3-oxobutyl)malonate (13b)**. Flash column chromatography (1:1 hexane : diethyl ether) afforded **11b** as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.14 (d,  $J$  8.8 Hz, 2H, ArH), 7.50 (d,  $J$  8.8 Hz, 2H, ArH), 4.73 (d,  $J$  10.9 Hz, 1H, HC(CO<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 4.42 (dd,  $J$  10.9, 6.8 Hz, 1H, ArCH), 3.81 (d,  $J$  6.8 Hz, 1H, HC(COCH<sub>3</sub>)<sub>2</sub>), 3.66 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 3.60 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 2.29 (s, 3H, COCH<sub>3</sub>), 1.92 (s, 3H, COCH<sub>3</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  201.7 ((CH<sub>3</sub>)C=O), 201.4 ((CH<sub>3</sub>)C=O), 167.9 ((CH<sub>3</sub>O)C=O), 167.7 ((CH<sub>3</sub>O)C=O), 147.4 (ArC), 145.2 (ArC), 130.4 (ArC), 123.7 (ArC), 71.3 (HC(CO<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 54.6 (HC(COCH<sub>3</sub>)<sub>2</sub>), 52.9 (COOCH<sub>3</sub>), 52.7 (COOCH<sub>3</sub>), 43.4 (ArC), 30.4 (COCH<sub>3</sub>), 29.5 (COCH<sub>3</sub>). MS:  $m/z$  366.1183 [C<sub>17</sub>H<sub>20</sub>NO<sub>8</sub> (M + H)<sup>+</sup> requires 366.1183]

HPLC (Chirlapak IC, 30% isopropyl alcohol in hexane, 1 mL/min, 238 m):  $t_1$  = 13.3 min,  $t_2$  = 14.9 min.

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