Asymmetric Intermolecular Stetter Reactions of Aromatic Heterocyclic Aldehydes with Arylidenemalonates

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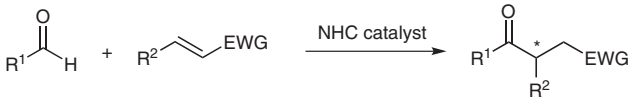
Abstract: The asymmetric Michael addition of aromatic heterocyclic aldehydes to arylidenemalonates catalyzed by N-heterocyclic carbenes is described. The ketomalonates are obtained in 84–98% yields and moderate to good enantioselectivities (30–78% ee). The enantiomeric excesses could be improved to excellent levels of up to 99% ee after a single recrystallization.

Key words: Stetter reaction, N-heterocyclic carbene, organocatalysis, nucleophilic acylation, umpolung

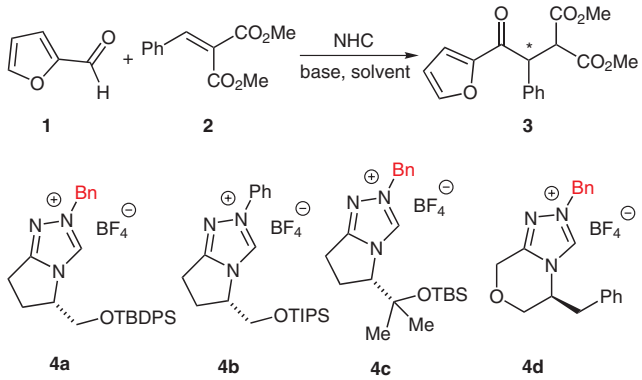
N-Heterocyclic carbene (NHC) organocatalysis is a rapidly growing field allowing a broad range of synthetic transformations.[1] Among the various catalytic carbon–carbon bond-forming processes, the Stetter reaction[2] plays an important role allowing conjugate nucleophilic acylations and thus the Umpolung of the classical carbonyl reactivity.[3] Although a number of efficient protocols for inter- and intramolecular Stetter reactions have been developed recently,[4] high asymmetric inductions in the classical intermolecular Stetter reaction (Scheme 1) remain a challenge. Especially, enantioselective nucleophilic acylations employing heterocyclic aldehydes as substrates in the intermolecular Stetter reaction[5] would open an entry to pharmaceutically interesting synthetic building blocks.

Based on our recent results in nucleophilic acylations of chalcones[6] we now wish to report on the application of the triazolium salt **4a** as a precatalyst in asymmetric intermolecular Stetter reactions of aromatic heterocyclic aldehydes with arylidenemalonates.

Our initial study began with the Stetter reaction of 2-furaldehyde (**1**) with dimethyl benzylidenemalonate (**2**) to form the keto diester **3** (Scheme 2). Several bicyclic triazolium type precatalysts **4a–d** were tested. Based on our previous studies with chalcone as Michael acceptor,[6] we were pleased to find that the precatalyst **4a** (10 mol%), easily prepared from the cheap enantiopure source pyroglutamic acid,[6,7] in the presence of DBU as base and THF as solvent at room temperature gave **3** in good yields (86%) and with an enantiomeric excess of 59% (Table 1, entry 1). The closely related precatalyst **4b** bearing an *N*-benzyl instead of an *N*-phenyl substituent afforded only furoin as the product of the corresponding benzoin condensation. This indicates that the *N*-benzyl substituent is



Scheme 1 The intermolecular Stetter reaction



Scheme 2 Asymmetric nucleophilic acylation of benzylidenemalonate catalyzed by different N-heterocyclic carbenes

crucial for the asymmetric Stetter reaction. Increasing the steric bulk of the catalyst side chain with a geminal dimethyl group as in **4c** did not give **3** and the sterically demanding Breslow intermediate[8] gave rise to furoin again. Even the novel and less bulky phenylalaninol-derived precatalyst **4d** bearing the crucial *N*-benzyl group did not result in the desired Stetter product.

In order to improve the enantioselectivity, we next screened various reaction conditions. As shown in Table 1, organic bases such as Et_3N resulted in poor conversion (8%) and a variety of inorganic bases (*t*-BuOK, K_2CO_3, and Cs_2CO_3) in THF led to an improvement (entries 6–8). To our delight, the precatalyst **4a** with Cs_2CO_3 in THF gave the desired product in high yield of 90% and 78% ee (entry 8). By switching to other solvents such as dichloromethane, toluene, or even a protic solvent such as EtOH, it turned out that THF is the best choice for both the selectivity and reactivity. It is worthy to note that the system of KHMDS combined with toluene afforded comparable results in 77% yield and 70% ee (entry 12). Increasing the temperature to 40 °C led to a small increase of the yield from 90 to 94%, but a significant decrease in enantioselectivity was observed (entry 13).

Next, with the optimum catalytic conditions identified, the scope of the reaction was explored. Employing the developed protocol, several aromatic heterocyclic aldehydes

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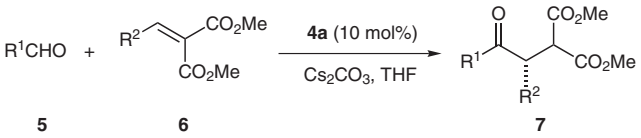
Table 1 Optimization of the Reaction Conditions for the Keto Diester **3**[a]

Entry	Precat.	Base	Solvent	Yield (%)[b]	ee (%)[c]
1	**4a**	DBU	THF	86	59
2	**4b**	DBU	THF	0	–
3	**4c**	DBU	THF	0	–
4	**4d**	DBU	THF	0	–
5	**4a**	Et_3N	THF	8	n.d.
6	**4a**	K_2CO_3	THF	66	65
7	**4a**	*t*-BuOK	THF	73	65
8	**4a**	Cs_2CO_3	THF	90	78 (>99)[d]
9	**4a**	Cs_2CO_3	CH_2Cl_2	5	n.d.
10	**4a**	Cs_2CO_3	toluene	3	n.d.
11	**4a**	Cs_2CO_3	EtOH	42	48
12	**4a**	KHMDS	toluene	77	70 (98)[d]
13	**4a**	Cs_2CO_3	THF	94	60[e]

[a] The reaction was performed at 23 °C for 6 h.
[b] Determined by GC.
[c] Determined by HPLC with a chiral stationary phase (Daicel Chiralpak AD).
[d] The value in brackets refers to the ee after recrystallization.
[e] The reaction was performed at 40 °C.



Scheme 3 Asymmetric intermolecular Stetter reactions with arylidenemalonates

5 and arylidenemalonates **6** could be smoothly transformed to the corresponding Stetter products **7** (Scheme 3). As summarized in Table 2, furfural reacted with various arylidenemalonates, easily prepared by Knoevenagel condensation,[9] bearing halogen or alkyl substituents in the *para* and *meta* position of the phenyl ring in excellent yields (84–92%) and enantioselectivities of 62–78% ee. With a single recrystallization the enantiomeric excesses of the Stetter products **7a–e** could be enhanced to practical levels of 90–99% ee. Interestingly, in two cases, **7b** and **7e**, the racemate crystallized first and the highly enantioenriched ketomalonates were isolated from the mother liquor. Besides furfural, 2-pyridinecarbaldehyde gave **7f** in an excellent yield of 94%; however, the asymmetric induction was low (ee = 30%). A pyridine moiety can also be present in the malonate Michael acceptor and an excellent yield of 98% could be achieved for **7g**, albeit with a modest ee of 40%. In contrast, no reaction was observed in the case of 2-pyrrolecarbaldehyde.

Table 2 Substrate Scope of the Asymmetric Intermolecular Stetter Reaction with Arylidenemalonates

7	R^1	R^2	Yield (%)[a]	ee (%)[b,c]
a	2-furyl	Ph	90 (53)	78 (99)
b	2-furyl	4-ClC_6H_4	92 (50)	62 (95)[d]
c	2-furyl	3-ClC_6H_4	85 (45)	68 (94)
d	2-furyl	4-BrC_6H_4	88 (42)	70 (99)
e	2-furyl	4-MeC_6H_4	84 (60)	72 (90)[d]
f	2-pyridyl	Ph	94	30[e]
g	2-furyl	2-pyridyl	98	40[e]

[a] Values in brackets are the yields after recrystallization.
[b] The enantiomeric excesses were determined by HPLC with a chiral stationary phase (Daicel Chiralpak AD).
[c] Values in brackets refer to the enantiomeric excesses after recrystallization.
[d] The racemate crystallized, and the enantioenriched products were obtained from the mother liquor.
[e] The products were obtained as thick oils.

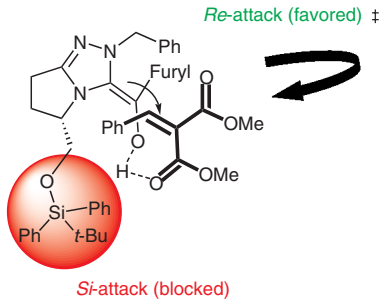


Figure 1 Proposed transition state

The *R*-configuration given for the keto diesters **7** is based on the relative topicity shown in the proposed transition state (Figure 1). The *Si*-face of the Breslow intermediate is blocked by the sterically demanding silyl group and the 1,4-addition occurs at the *Si*-face of the arylidenemalonate. This would be in accord with the recently reported stereochemical outcome of intermolecular Stetter reactions of aromatic aldehydes with chalcones.[6]

To illustrate the preparative utility of the enantioselective Stetter reaction, the addition of 2-furaldehyde to benzylidenemalonate was performed on a 10 mmol scale to give 2.58 g (82% yield) of **7a** in 80% ee, which opens a practical entry to gram-scale nucleophilic acylation products.

In summary, we have developed an asymmetric intermolecular Stetter reaction of aromatic heterocyclic aldehydes with arylidenemalonates, which afforded ketomalonates in good yields and excellent enantiomeric excesses after a single recrystallization. Efforts to extend the reaction scope and to optimize the catalyst structures are currently under way in our laboratories.

All solvents were dried by conventional methods. Toluene and THF were freshly distilled from Na/Pb alloy under argon. The aldehydes were freshly distilled or recrystallized, the arylidenemalonates were prepared according to standard literature procedures.[8] Other starting materials and reagents were purchased from commercial suppliers and used without further purification. Preparative column chromatography: Merck silica gel 60, particle size 0.040–0.063 mm (230–240 mesh, flash). Analytical TLC: silica gel 60, F254 plates from Merck, Darmstadt. Optical rotations were measured on a Perkin-Elmer P241 polarimeter. IR spectra were taken on a Perkin-Elmer FT/IR 1760 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Varian Gemini 300, Mercury 300 or Inova 400 spectrometers and all measurements were performed with TMS as internal standard. Mass spectra were acquired on a Finnigan SSQ 7000 spectrometer (CI 100 eV; EI 70 eV). Microanalyses were obtained with a Vario EL element analyzer. Melting points were determined with a Tottoli melting point apparatus and are uncorrected. Analytical HPLC was performed on Hewlett-Packard 1100 Series chromatographs using chiral stationary phases (Daicel OD, Daicel AD, Whelk).

Precatalysts 4c and 4d; General Procedure

A 100 mL round-bottomed flask was charged with the corresponding lactam[7,10] (5 mmol) and CH_2Cl_2 (50 mL). Trimethyloxonium tetrafluoroborate (0.8 g, 5.5 mmol) was added and the mixture stirred for 12 h at r.t. Benzylhydrazine (0.6 mL, 5.5 mmol) was added to the solution and stirred for another 12 h. The solvent was removed in vacuo and the product was used without further purification. Trimethyl orthoformate (30 mL) was added and the mixture was refluxed for 12 h. The excess of orthoformate was removed in vacuo to give the desired product. Compound **4c** was purified by chromatography on silica gel (eluent: EtOAc) to yield the product as a thick oil. Compound **4d** was purified by recrystallization from hot EtOAc to afford colorless crystals.

(*S*)-2-Benzyl-5-[2-(*tert*-butyldimethylsilyloxy)propan-2-yl]-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazol-2-ium Tetrafluoroborate (4c)

Yield: 1.35 g (60%); thick oil; $[\alpha]_D^{23}$ –12.6 (*c* 1.01, $CHCl_3$).

IR (KBr): 3139, 3036, 2951, 2856, 2812, 2361, 1833, 1648, 1586, 1532, 1459, 1379, 1258, 1047, 882, 835, 757, 522 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.00 and 1.10 (2 s, 6 H, $SiCH_3$), 0.67 [s, 9 H, $SiC(CH_3)_3$], 1.38 and 1.52 [2 s, 6 H,$C(CH_3)_2$], 2.77 (m, 1 H, NCHCH*H*), 2.97 (m, 1 H, NCHC*H*H), 3.07–3.16 [m, 2 H, $C(N)CH_2$], 4.76 (dd, *J* = 8.5, 3.6 Hz, 1 H, NCH), 5.53 (d, *J* = 5.8 Hz, 1 H, NC*H*HPh), 5.67 (d, *J* = 5.8 Hz, 1 H, NCH*H*Ph), 7.23–7.60 (m, 5 H, Ph-H), 9.73 (s, 1 H, NCHN).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –2.7, –2.5, 17.5, 21.6, 25.3, 26.2, 27.3, 28.6, 56.4, 70.0, 73.9, 108.5, 128.8, 129.0, 129.1, 129.2, 132.1, 138.9, 162.8.

MS (ESI): *m*/*z* = 372 (100, M^+), 240 (1), 87 (100, BF_4^-).

HRMS: *m*/*z* calcd for [$C_{21}H_{34}N_3OSi^+$ – 2 H]: 370.2315; found: 370.2309.

(*S*)-2,5-Dibenzyl-6,8-dihydro-5*H*-[1,2,4]triazolo[3,4-*c*][1,4]oxazin-2-ium Tetrafluoroborate (4d)

Yield: 1.7 g (85%); colorless crystals; mp 132 °C; $[\alpha]_D^{23}$ –46.5 (*c* 1.01, $CHCl_3$).

IR (KBr): 3437, 3176, 3063, 3030, 2959, 2854, 2361, 2340, 1357, 1545, 1496, 1453, 1402, 1370, 1305, 1190, 1160, 1062, 941, 903, 868, 830, 761, 709 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.13 (dd, *J* = 13.6, 9.4 Hz, 1 H, PhC*H*HCH), 3.37 (dd, *J* = 13.6, 6.4 Hz, 1 H, PhCH*H*CH), 3.95 (d, *J* = 1.4 Hz, 2 H, $CHCH_2O$), 4.79 (m, 1 H, NC*H*Bn), 4.80 [d, *J* = 16.1 Hz, 1 H, C(N)C*H*HO], 4.96 [d, *J* = 16.1 Hz, 1 H, C(N)CH*H*O], 5.40 (s, 2 H, NCH_2Ph), 7.13–7.22 (m, 5 H, Ph-H), 7.33–7.40 (m, 5 H, Ph-H), 9.37 (s, 1 H, NCHN).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.4, 56.2, 56.8, 61.9, 65.5, 127.6, 127.7, 129.1, 129.2, 129.3, 129.4, 129.5, 131.6, 134.5, 141.3, 149.4.

MS (ESI): *m*/*z* = 306 (100, M^+), 240 (1), 87 (100, BF_4^-).

Anal. Calcd for $C_{19}H_{20}N_3O^+BF_4^-$: C, 58.04; H, 5.13; N, 10.69. Found: C, 58.05; H, 5.66; N, 10.42.

Asymmetric Intermolecular Stetter Reaction; (*R*)-Dimethyl 2-[1-Phenyl-2-(furan-2-yl)-2-oxoethyl]malonate (7a); Typical Procedure

A dry, argon-flushed Schlenk tube was charged with precatalyst **4a** (27 mg, 0.05 mmol, 10 mol%), anhyd Cs_2CO_3 (16 mg, 0.05 mmol) and the dimethyl benzylidenemalonate (**6a**; 110 mg, 0.5 mmol). After the addition of absolute THF (1 mL) at r.t., 2-furaldehyde (58 mg, 0.6 mmol) was added and the mixture was stirred for 6 h. The solvent was evaporated and the residue was directly purified by flash chromatography on silica gel (eluent: pentane–Et_2O, 2:1) to give the Stetter product (127 mg, 90%) as a colorless solid. Crystallization from Et_2O afforded **7a** (75 mg, 53%) as a flocky colorless solid; mp 103 °C; $[\alpha]_D^{23}$ –194.5 (*c* 1.01, $CHCl_3$).

HPLC: t_R = 5.75 and 8.02 min (Daicel OD, 250 × 4.6 mm, *n*-heptane–*i*-PrOH, 8:2, 1.0 mL/min); t_R = 8.02 min; ee = 78%; ee after recrystallization, >99%.

IR (KBr): 3854, 3744, 3432, 2361, 2340, 1742, 1668, 1560, 1464, 1313, 1194, 1150, 1088, 1015, 939, 784, 560 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.46 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 4.45 [d, *J* = 11.6 Hz, 1 H, $CH(CO_2Me)$], 5.12 (d, *J* = 11.6 Hz, 1 H, PhC*H*), 6.46 (m, 1 H, furyl-H), 7.21 (m, 1 H, furyl-H), 7.23–7.33 (m, 5 H, Ph-H), 7.53 (m, 1 H, furyl-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.4, 52.6, 53.0, 54.7, 112.4, 118.5, 128.0, 128.8, 128.9, 146.7, 168.2, 168.3, 185.5.

MS (EI, 70 eV): *m*/*z* (%) = 316 (20, M^+), 300 (20), 284 (24), 253 (11), 252 (35), 225 (10), 184 (15), 162 (6), 156 (3), 131 (18), 121 (37), 95 (100), 77 (6).

Anal. Calcd for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10. Found: C, 64.39; H, 5.03.

(*R*)-Dimethyl 2-[1-(4-Chlorophenyl)-2-(furan-2-yl)-2-oxoethyl]malonate (7b)

Yield: 161 mg (92%); colorless solid; mp 95 °C; $[\alpha]_D^{23}$ –222.2 (*c* 1.01, $CHCl_3$).

HPLC: t_R = 7.79 and 9.69 min (Daicel OD, 250 × 4 mm, *n*-heptane–*i*-PrOH, 9:1, 1.0 mL/min); t_R = 9.69 min; ee = 62%; ee after recrystallization, 97%.

IR (KBr): 3130, 2959, 1743, 1668, 1226, 1194, 1149, 1090, 1013, 940, 906, 784, 752, 716, 622, 562 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.42 (s, 3 H, OCH_3), 3.64 (s, 3 H, OCH_3), 4.35 [d, *J* = 11.6 Hz, 1 H, $CH(CO_2Me)_2$], 5.05 (d, *J* = 11.6 Hz, 1 H, PhC*H*), 6.52 (dd, *J* = 3.5, 2.5 Hz, 1 H, furyl-H), 7.15 (m, 1 H, furyl-H), 7.18–7.21 (m, 4 H, Ph-H), 7.64 (dd, *J* = 0.7, 1.8 Hz, 1 H, furyl-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.2, 52.6, 52.9, 54.5, 112.5, 118.7, 129.2, 130.2, 132.8, 134.2, 146.9, 151.4, 167.8, 168.2, 185.5.

MS (EI, 70 eV): *m*/*z* (%) = 350 (8, M^+), 317 (5), 285 (10), 258 (3), 195 (4), 164 (16), 154 (17), 136 (8), 114 (4), 102 (12), 101 (11), 95 (100), 75 (4), 59 (11).

Anal. Calcd for $C_{17}H_{15}ClO_6$: C, 58.21; H, 4.31. Found: C, 58.33; H, 4.66.

(*R*)-Dimethyl 2-[1-(3-Chlorophenyl)-2-(furan-2-yl)-2-oxoethyl]malonate (7c)

Yield: 148 mg (85%); colorless solid; mp 78 °C; $[\alpha]_D^{23}$ –240.0 (*c* 1.01, $CHCl_3$).

HPLC: t_R = 11.62 and 13.76 min (Whelk M, 250 × 4.6 mm, *n*-heptane–EtOH, 95:5, 1.0 mL/min); t_R = 11.62 min; ee = 68%; ee after recrystallization, 94%.

IR (KBr): 3418, 3127, 2956, 2363, 1739, 1656, 1564, 1463, 1394, 1310, 1255, 1225, 1194, 1086, 1023, 977, 615, 590, 540, 511cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.52 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 4.43 [d, *J* = 11.7 Hz, 1 H, C*H*(CO_2Me)$_2$], 5.12 (d, *J* = 11.7 Hz, 1 H, PhC*H*), 6.51 (dd, *J* = 1.7, 3.6 Hz, 1 H, furyl-H), 7.23–7.24 (m, 4 H, Ph-H), 7.26 (m, 1 H, furyl-H), 7.58 (dd, *J* = 1.0, 1.8 Hz, 1 H, furyl-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.4, 52.6, 53.1, 54.6, 112.6, 118.8, 127.1, 128.5, 128.9, 130.1, 147.1, 167.0, 168.0, 185.0.

MS (EI, 70 eV): *m*/*z* (%) = 350 (10, M$^+$), 332 (8), 319 (10), 286 (10), 218 (10), 165 (10), 155 (8), 95 (100).

Anal. Calcd for $C_{17}H_{15}ClO_6$: C, 58.21; H, 4.31. Found: C, 58.64; H, 4.13.

(*R*)-Dimethyl 2-[1-(4-Bromophenyl)-2-(furan-2-yl)-2-oxoethyl]malonate (7d)

Yield: 173 mg (88%); colorless solid; mp 138 °C; $[\alpha]_D^{23}$ –168.6 (*c* 1.01, $CHCl_3$).

HPLC: t_R = 8.35 and 9.65 min (Daicel OD, 250 × 4.6 mm, *n*-heptane–*i*-PrOH, 8:2, 0.7 mL/min); t_R = 9.65; ee = 70%; ee after recrystallization, 99%.

IR (KBr): 3127, 2953, 2361, 2339, 1745, 1656, 1561, 1468, 1435, 1399, 1325, 1266, 1231, 1202, 1158, 1013, 939, 783, 748, 556 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.44 (s, 3 H, OCH_3), 3.65 (s, 3 H, OCH_3), 4.34 [d, *J* = 12.2 Hz, 1 H, C*H*(CO_2Me)$_2$], 5.04 (d, *J* = 12.2 Hz, 1 H, PhCH), 6.41 (dd, *J* = 1.7, 3.6 Hz, 1 H, furyl-H), 7.15 (m, 4 H, Ph-H), 7.33 (m, 2 H, furyl-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.3, 52.7, 52.8, 54.5, 112.5, 120.2, 122.3, 130.5, 132.2, 133.2. 146.5, 149.3, 167.7, 168.1, 185.3.

MS (EI, 70 eV): *m*/*z* (%) = 396 (13, M$^+$), 364 (10), 362 (10), 332 (21), 330 (22), 211 (7), 209 (11), 201 (12), 199 (15), 184 (3), 155 (2), 128 (4), 102 (11), 95 (100), 75 (2), 59 (7), 51 (2).

HRMS: *m*/*z* calcd for [$C_{17}H_{15}O_6Br$]: 394.0052; found: 394.0054.

(*R*)-Dimethyl 2-[1-*p*-Tolyl-2-(furan-2-yl)-2-oxoethyl]malonate (7e)

Yield: 138 mg (84%); colorless solid; mp 82 °C, $[\alpha]_D^{23}$ –180.8 (*c* 1.01, $CHCl_3$).

HPLC: t_R = 7.13 and 9.29 min (Daicel OD, 250 × 4.6 mm, *n*-heptane–*i*-PrOH, 9:1, 1.0 mL/min); t_R = 9.29; ee = 72%; ee after recrystallization, 90%.

IR (KBr): 3137, 2958, 2863, 2359, 2341, 1745, 1667, 1565, 1513, 1465, 1309, 1228, 1188, 149, 1039, 951, 776, 585 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.19 (s, 3 H, 4-CH_3Ph), 3.41 (s, 3 H, OCH_3), 3.49 (s, 3 H, OCH_3), 4.36 [d, *J* = 11.8 Hz, 1 H, C*H*(CO_2Me)$_2$], 5.01 (d, *J* = 11.8 Hz, 1 H, 4-CH_3PhC*H*), 6.38 (dd, *J* = 3.7, 1.8 Hz, 1 H, furyl-H), 7.01 (m, 2 H, Ph-H), 7.12 (m, 2 H, Ph-H), 7.13 (m, 1 H, furyl-H), 7.45 (dd, *J* = 0.7, 1.8 Hz, 1 H, furyl-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.9, 52.49, 52.60, 52.90, 54.70, 113.1, 118.5, 128.7, 129.6, 131.1, 137.9, 149.4, 151.6, 168.1, 168.5, 186.0.

MS (EI, 70 eV): *m*/*z* (%) = 330 (34, M$^+$), 298 (19), 266 (49), 239 (7), 235 (10), 198 (4), 191 (10), 176 (5), 149 (3), 145 (21), 135 (100), 115 (14), 95 (39), 59 (6).

Anal. Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.27; H, 5.37.

(*R*)-Dimethyl 2-[1-Phenyl-2-(pyridin-2-yl)-2-oxoethyl]malonate (7f)

Yield: 154 mg (94%); colorless solid; mp 102 °C; $[\alpha]_D^{23}$ –123.1 (*c* 1.01, $CHCl_3$).

HPLC: t_R = 9.45 and 11.71 min (Daicel OD, 250 × 4.6 mm, *n*-heptane–*i*-PrOH, 8:2, 0.7 mL/min); t_R = 11.71 min; ee = 30%.

IR (KBr): 3049, 3007, 2954, 1750, 1728, 1696, 1581, 1493, 1439, 1295, 1258, 1191, 1158, 1093, 1027, 995, 965, 943, 918, 782, 761, 701, 603, 548 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.50 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 4.34 [d, *J* = 12.0 Hz, 1 H, C*H*(CO_2Me)$_2$], 5.04 (d, *J* = 12.0 Hz, 1 H, Ph-H), 7.15–7.28 (m, 3 H, Ph-H), 7.37–7.43 (m, 3 H, Ph-H and pyridyl-H), 7.66 (m, 1 H, pyridyl-H), 8.00 (m, 1 H, pyridyl-H), 8.70 (m, 1 H, pyridyl-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 50.3, 52.4, 52.8, 55.2, 122.8, 127.1, 127.7 128.6, 129.4, 134.3, 136.7, 149.0, 152.0, 168.2, 168.7, 168.3, 168.7, 198.2.

MS (EI, 70 eV): *m*/*z* (%) = 327 (85, M$^+$), 295 (85), 268 (100), 263 (70), 235 (75), 208 (70), 195 (75), 180 (50), 167 (60), 131 (85), 121 (80), 106 (75), 77 (80), 59 (45), 51 (46).

Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.32; N, 4.28. Found: C, 66.06; H, 5.24; N, 4.26.

(*R*)-Dimethyl 2-[2-(Furan-2-yl)-1-(pyridin-2-yl)-2-oxoethyl]malonate (7g)

Yield: 155 mg (98%); colorless oil; $[\alpha]_D^{23}$ –175.0 (*c* 1.01, $CHCl_3$).

HPLC: t_R = 9.07 and 11.35 min (Daicel OD, 250 × 4.6 mm, *n*-heptane–*i*-PrOH, 6:4, 0.7 mL/min); t_R = 11.35 min; ee = 40%.

IR (KBr): 2954, 2359, 2340, 1742, 1677, 1569, 1464, 1303, 1198, 1158, 1027, 758, 599 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.54 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 4.69 [d, *J* = 11.4 Hz, 1 H, C*H*(CO_2Me)$_2$], 5.38 (d, *J* = 11.4 Hz, 1 H, pyridyl-H), 6.50 (dd, *J* = 3.7, 1.7 Hz, 1 H, furyl-H), 7.15 (m, 1 H, pyridyl-H), 7.30 (dd, 1 H, *J* = 3.5, 1.0 Hz, pyridyl-H), 7.44 (m, 1 H, pyridyl-H), 7.56 (dd, *J* = 1.7, 0.7 Hz, 1 H, furyl-H), 7.63 (m, 1 H, pyridyl-H), 8.55 (m, 1 H, furyl-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.6, 52.9, 53.4, 55.3, 112.5, 119.0, 122.7, 124.1, 136.8, 146.8, 149.9, 151.7, 154.7, 168.2, 168.5, 184.5.

MS (EI, 70 eV): *m*/*z* (%) = 318 (44, M + 1$^+$), 317 (23, M$^+$), 289 (100), 263 (17), 258 (29), 254 (50), 231 (11), 230 (75), 226 (22), 204 (38), 198 (27), 190 (16), 186 (77), 170 (12), 158 (14), 132 (28), 104 (16), 95 (96), 78 (14), 78 (14), 51 (8).

HRMS: *m*/*z* calcd for [$C_{16}H_{15}NO_6$]: 318.0978; found: 318.0978.

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