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Regioselective Hydrogenolysis of Donor-Acceptor Cyclopropanes with Zn-AcOH Reductive System

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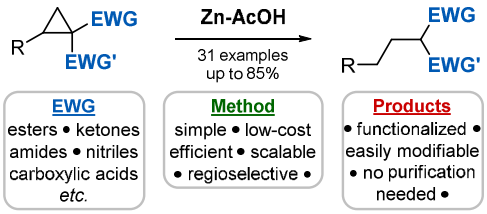
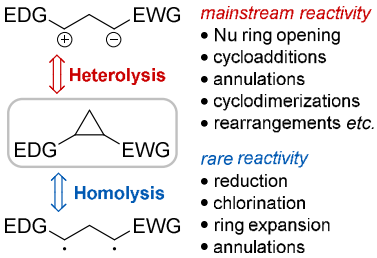


ABSTRACT: A convenient low-cost method for regioselective ring-opening of donor-acceptor cyclopropanes with the Zn-AcOH reductive system was developed. The general character of the method was displayed *via* efficient reduction of a representative series of 2-(het)arylcyclopropane-1,1-diesters as well as donor-acceptor cyclopropanes with other types of electron-withdrawing activating groups. This method opens a rapid access to γ-substituted propyl-1,1-diesters, ketoesters, cyanoesters, cyanoamides, dinitriles, *etc*., many of which are not readily accessible with alternative methods. The utility of the synthesized compounds was demonstrated by transforming them into valuable acyclic and cyclic compounds (including pharmacologically relevant carbazoles, δ-lactams and oxindole derivatives).

INTRODUCTION

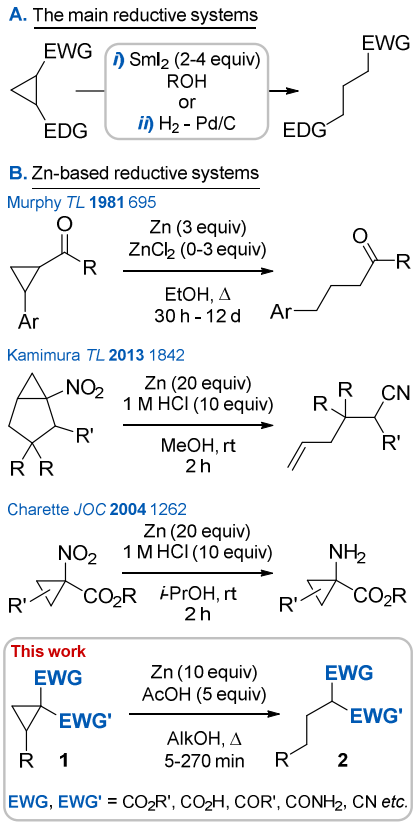
Donor-acceptor (DA) cyclopropanes are widely known as versatile easily modifiable building blocks for the construction of variously functionalized acyclic and cyclic compounds, mostly due to their tendency to undergo heterolytic cleavage of the selectively activated C-C bond between donor and acceptor substituents (Scheme 1).[1–13] This mode of reactivity defines the principal trends in the research of these compounds and, thus, has been and is being investigated systematically and thoroughly.

Scheme 1. Two Types of Activated C-C Bond Cleavage in DA Cyclopropanes



Meanwhile, homolytic small ring-opening is a much rarer reactivity of DA cyclopropanes, exemplified by ring-opening reduction[14–29] as well as several other isolated examples.[30–32] Two reductive systems are mainly used in relation to DA cyclopropanes: SmI_2-AlkOH[19–24] and H_2-Pd/C[25,26] (Scheme 2, **A**). However they are relatively expensive and may cause overreduction (SmI_2) or hydrogenation of multiple bonds (Pd). At the same time, the application of much cheaper and milder Zn-based reductive systems for DA cyclopropane reduction was limited to several specific cases (Scheme 2, **B**).[27–29]

Scheme 2. Reactions of DA Cyclopropanes with Various Reductive Systems



Two- and three-component Zn-EtOH or Zn-$ZnCl_2$-EtOH systems were used for the reduction of 2-aryl-substituted ketocyclopropanes while 2-alkyl-substituted analogs were found to be stable under those conditions.[27] Unusual ring-opening rearrangement was recently reported for annulated nitrocyclopropanes upon treatment with a Zn-HCl-MeOH reductive system,[29] although the application of similar conditions for 2-aryl and alkyl-substituted cyclopropane-1,1-nitroesters resulted in nitro-to-amino group reduction without small ring cleavage.[28] Therefore, currently there is no general method for ring-opening reduction of DA cyclopropanes with Zn-based reductive systems.

Here we report a practical and low-cost method for efficient regioselective hydrogenolysis of differently substituted DA cyclopropanes with the Zn-AcOH reductive system (Scheme 2). The method allows for rapid reduction of 2-(het)aryl-substituted cyclopropane-1,1-diesters, ketoesters, cyanoesters, cyanoamides, dinitriles **1** into the corresponding functionalized propane derivatives **2**. Commonly, these compounds are perceived as products of alkylation of active methylene compounds. Though this approach appears to be more convenient, many alkylating

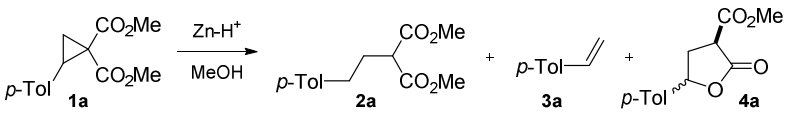
agents, especially those with electron-abundant (het)aryl substituents, are unstable or even inaccessible. Moreover, in order to avoid double alkylation, a significant excess of the methylene component has to be added. Therefore, our approach is a new advanced alternative affording **2**, including those variations of it with highly electron-abundant aryl and hetaryl substituents. The proposed procedure provides desired compounds with sufficient purity to obviate chromatography and can be easily scaled up with no loss in efficiency.

RESULTS AND DISCUSSION

Reduction of 2-(het)arylcyclopropane-1,1-diesters into 2-(het)arylethylmalonates

At the beginning of this study, we carried out a brief series of experiments using cyclopropane **1a** as a model substrate which was treated with different Zn-containing reductive systems (Table 1). We revealed that the traditional Zn-NH_4Cl reductive system provided complete conversion of **1a** within 45 min in MeOH under reflux leading to **2a** in 62% NMR yield along with styrene **3a** (11%) and lactone **4a** (5%) (entry 1). Introducing a strong Brønsted acid, aq HCl, at ambient temperature resulted in 92% conversion of **1a** in 15 min and increase in the percentage of lactone **4a**, while the yield of the desired product **2a** decreased (entry 2). For an identical reaction at 0 °C, only 20% conversion was achieved (entry 3). The best results were obtained when Zn-AcOH reductive systems were examined (entries 4-7). We have found that Zn-AcOH in a 20:10 ratio allowed for complete conversion of **1a** in just 5 min in MeOH as well as EtOH under reflux. In both cases, only trace amounts of **3a** and **4a** were detected while the yields of **2a** were comparable (entries 4, 5). Twofold decrease in the initial amount of Zn-AcOH afforded the best result: **2a** was isolated in a 77% yield (entry 6). Further decrease in Zn-AcOH loading led to noticeable deceleration (entry 7). It is noteworthy that even substoichiometric amounts of AcOH (0.5 equiv) were found to be sufficient, although complete **1a**-into-**2a** conversion was achieved in 200 min.

Table 1. Optimization of the reaction conditions



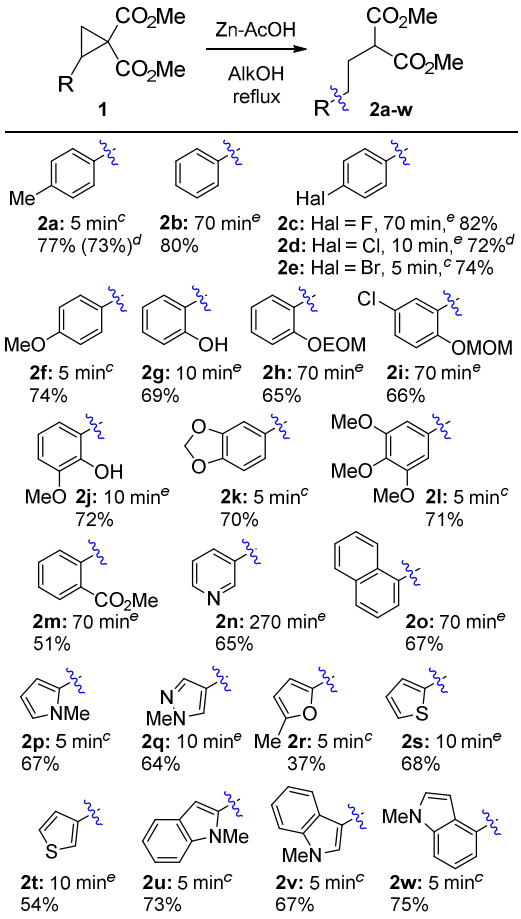
entry	Zn/H$^+$ (mol%)	T [°C]	t [min]	Yield [%][a]			
				1a	2a	3a	4a
1[c]	Zn (20)/NH_4Cl (20)	reflux	45	-	62	11	5
2	Zn (20)/HCl (15)	20	15	8	51	-	13
3	Zn (20)/HCl (15)	0	15	80	14	-	-
4	Zn (20)/AcOH (10)	reflux	5	-	72	-[b]	-[b]
5	Zn (20)/AcOH (10)	reflux[c]	5	-	68	-[b]	-[b]
6	**Zn (10)/AcOH (5)**	**reflux**	**5**	**-**	**77[d]**	**-[b]**	**-[b]**
7	Zn (5)/AcOH (3)	reflux	15	2	70	-[b]	-[b]

[a]NMR yield. [b]Only trace amounts were detected. [c]Ethanol was used as a solvent. [d]Isolated yield.

Afterwards, we studied the scope of DA cyclopropanes available for this process. Initially, a series of cyclopropane-1,1-diesters **1b-w**, containing various aryl and hetaryl substituents, was examined under optimized conditions (Table 2). In most cases, reductive ring opening proceeds efficiently under standard conditions in MeOH under reflux in 5 min, leading to corresponding ethylmalonates **2** in good yields. Slightly reduced reactivity was observed for phenylcyclopropane **1b** whose reaction was carried out in EtOH under reflux; furthermore, reaction time was extended up to 70 min. A slight discrepancy was revealed between the reactivities of 2-thienyl-cyclopropane **1s**, which was converted into **2s** in 15 min in MeOH under reflux, and 3-thienyl-derivative **1t** whose complete conversion into **2t** was achieved in *ca*. 1 h. However, this difference was completely negated in ethanol under reflux. The steric effect of *ortho*-substituents in the aromatic ring also reduces the reactivity of the starting compounds. The reduction of cyclopropanes **1g-j** with *ortho*-substituted electron-abundant aryls as well as *o*-methoxycarbonyl **1m** and naphthyl **1o** derivatives, generally takes more time to complete. Among them, 5-chloro-2-methoxymethoxy-cyclopropane **1i** was found to be the least reactive substrate, undergoing transformation into **2i** in 1 h. It is noteworthy that deprotection of MOM- or EOM-derivatives was not observed under the studied conditions. The reduction of cyclopropane **1n**, containing electron-deficient 3-pyridine substituent, was the slowest, with the conversion to **2n** completed in 270 min. The decrease in the yield of furyl derivative **1r** is caused

by partial furan ring opening into 1,4-diketone under studied conditions. However, the obtained products **2** were mostly pure.

Table 2. Variation of Electron-Donating Groups[a,b]



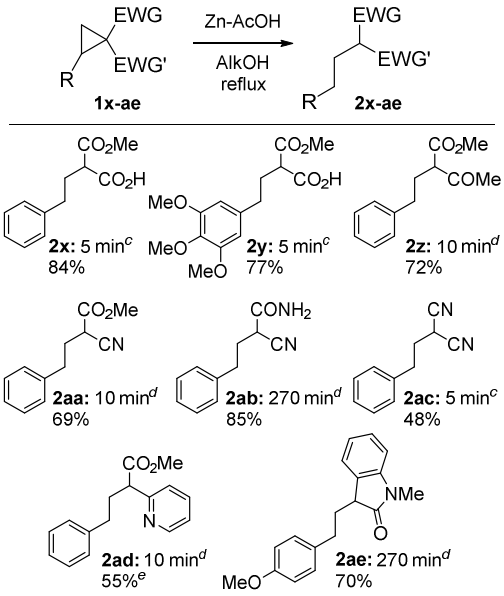
[a]Reaction conditions: 0.1 M solution of **1** (0.5 mmol), Zn (5 mmol), AcOH (2.5 mmol). [b]Isolated yield. [c]MeOH was used as a solvent. [d]Yield in 2.5 (for **1a**) and 5.2 (for **1d**) gram-scale synthesis. [e]EtOH was used as a solvent.

Reduction of DA cyclopropanes containing various electron-withdrawing activating groups

Next, DA cyclopropanes **1x-ae** with various electron-withdrawing substituents were studied in their reactions with Zn-AcOH (Table 3). We have found that hemimalonates **1x,y** (irrespective of the donating abilities of the aryl substituents) and dinitrile **1ac** exhibited high reactivity towards the Zn-AcOH reductive system, affording products **2x,y,ac** under standard conditions (MeOH, reflux, 5 min). Ketoester **1z** and cyanoester **1aa** were found to be more reactive *vs*. their

diester analog **1b**. Reduction of 2-pyridyl-derivative **1ad** under identical conditions led to the desired product **2ad** in a 55% yield only. Meanwhile, the fragmentation product, methyl 2-(pyridin-2-yl)acetate, was additionally isolated in a 30% yield (see below, Scheme 5). Within the studied series of DA cyclopropanes, amides **1ab,ae** were the least reactive substrates: their complete conversion into the corresponding products **2ab,ae** could only be achieved in 270 min.

Table 3. Varying Electron-Withdrawing Groups[a,b]



[a]Reaction conditions: 0.1 M solution of **1** (0.5 mmol), Zn (5 mmol), AcOH (2.5 mmol). [b]Isolated yield. [c]MeOH was usd as a solvent. [d]EtOH was used as a solvent. [e]Methyl 2-(pyridin-2-yl)acetate was additionally isolated in a 30% yield.

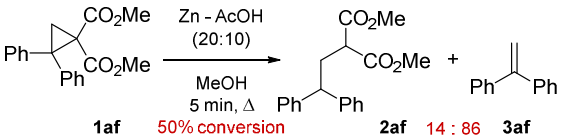
Reaction mechanism

In most of the studied reactions, trace amounts of the corresponding styrenes **3** were detected. Thus, relatively low-intensive characteristic resonances of $CH{=}CH_2$ tri-spine systems of **3** were observed in the ^{1}H NMR spectra of most reaction mixtures. For the reduction of cyclopropanes **1** with electron-abundant aryl substituents, molar percentages of styrenes **3** were higher than for the reactions of cyclopropanes containing the phenyl group or electron-withdrawing aryls. In the reduction of 2-pyridine-derivative **1ad**, the desired product **2ad** was

obtained along with the corresponding methylene compound, methyl 2-(pyridin-2-yl)acetate, in a 65:35 ratio.

The reduction of 2,2-diphenylcyclopropane-1,1-diester **1af** with Zn-AcOH (20:10 equiv) for 5 min in MeOH under reflux proceeded with 50% conversion according to the ^{1}H NMR spectrum of the reaction mixture. However, the molar percentage of the immediate reduction product **2af** was only 7%, whereas the major components of the reaction mixture were 1,1-diphenylethylene **3af** (43%) and dimethylmalonate, apparently pointing to fragmentation of **2af** (Scheme 3).

Scheme 3. Reduction of 2,2-Diphenylcyclopropane-1,1-Diester 1af

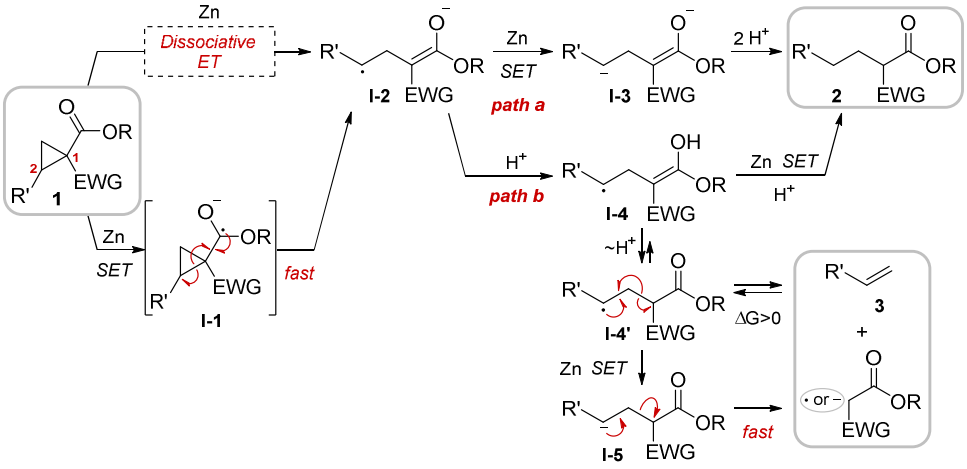


To identify the source of hydrogen in **2**, we carried out the reduction of **1a** in CH_3OD and obtained **2a**, mono-deuterated at the benzylic carbon. Therefore, the formation of **2** *via* radical hydrogen abstraction from the solvent is highly unlikely, whereas the protonation of the intermediate benzyl anion seems more probable. The KIE value of 4.3, measured with the mixture of CH_3OH-CD_3OD (1:4) acting as a medium, is consistent with proton transfer occurring during the reaction. These results, along with DFT calculations (B3LYP/ma-def-SVP/PCM) and well-known data related to the reduction of cyclopropanes with metal-based systems, allowed us to propose a mechanism for the studied process, visualized in Scheme 4.

Single electron transfer (SET) from Zn to **1** could lead to anion-radical **I-1**, which is known to rearrange to the acyclic anion-radical form **I-2**. The synergistic effect of an aryl group at C2 and strong anion-stabilizing groups at C1 ensures that this rearrangement is fast.[33–35] The calculation suggests that dissociative electron transfer (DET)[36,37] occurs upon the addition of an electron to the LUMO of **1**, directly affording **I-2**.[38] This key intermediate undergoes the second SET (path **a**) with the formation of dianion **I-3**,[21,22] yielding reduction product **2** *via* protonation.

Alternatively, protonation of **I-2** leads to radical **I-4**. Single electron reduction of **I-4** with subsequent protonation gives **2**. However, the more stable tautomeric form **I-4′** and especially the reduced form **I-5** are prone to *β*-scission. DFT calculations show that this process is characterized by a relatively high activation barrier ($\Delta G^{\neq}$ = 20.9 kcal/mol), being thermodynamically unfavorable (ΔG_{298} = 6.6 kcal/mol) toward **I-4′**. On the other hand, it is extremely fast and exergonic ($\Delta G^{\neq}$ = 0.6 kcal/mol, ΔG = -39.6 kcal/mol) for **I-5**.[39] This is especially significant for **1af** since the benzhydryl radical is known to accept electrons at a much lower rate than benzyl,[40] allowing for the tautomerization of **I-4** to **I-4′** and subsequent fragmentation to proceed more readily.

Scheme 4. Proposed Mechanism of DA Cyclopropane Reduction with Zn-AcOH System

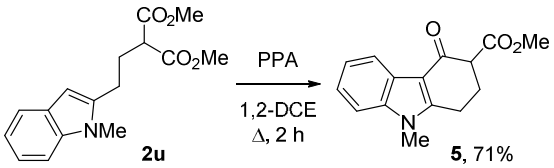


Transformations of the synthesized compounds

The presence of several functional groups in **2** furnishes various opportunities of their transformation and, thus, makes them valuable precursors of various acyclic and cyclic compounds.

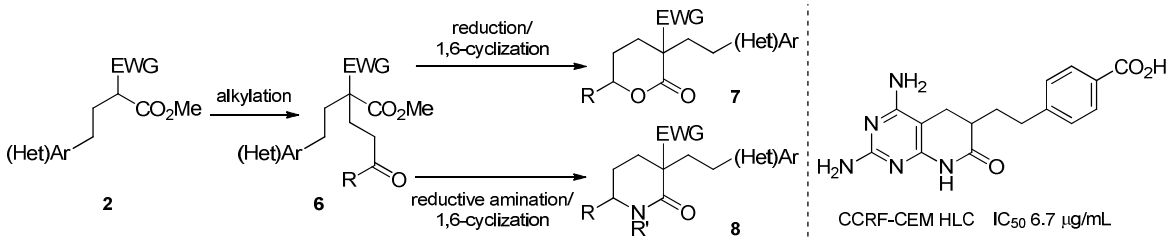
A rapid access to tetralins and their heterocyclic analogs can be provided *via* S_EAr in the cases when **2** contains an electron-abundant (het)aryl substituent.[41,42] Thus, carbazole derivative **5**[43] was obtained directly from indolylmalonate **2u** in a good yield (Scheme 5).

Scheme 5. Transformation of 2u into Carbazole 5



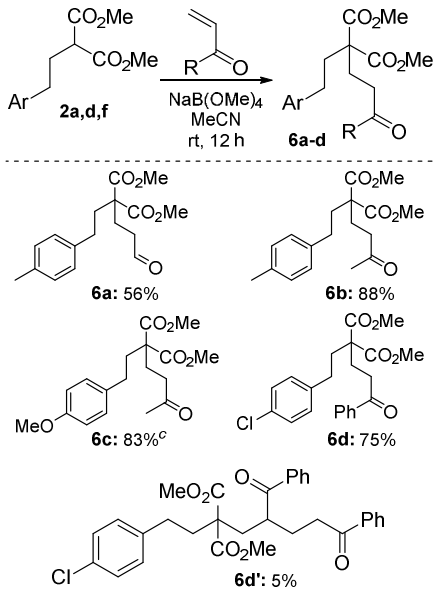
The presence of malonyl or similar CH-activated motifs in the molecules of compounds **2** opens up a plethora of opportunities for their transformations. The reactions of **2** with such C-electrophiles as alkyl and acyl halides, electrophilic alkenes (Michael acceptors), *etc*. allow for the prolongation and additional functionalization of the alkyl chain in **2**. Such preinstallation provides accesss to further easy assembly of the cyclic moiety in the target structures. In this context, we developed a divergent strategy for the synthesis of functionalized δ-lactones **7** and lactams **8** which are structural fragments of bioactive compounds[44,45] (Scheme 6).

Scheme 6. Divergent Strategy for the Synthesis of δ-Lactones 7 and δ-Lactams 8



In order to obtain alkylated products **6**, arylmalonates **2** were treated with acrolein, methyl- or phenylvinyl ketones in the presence of $NaB(OMe)_4$ as a catalyst[46] (Table 4). The efficiency of this method was demonstrated with a short series of compounds **2**, affording Michael adducts **6a-d** in good yields. While using acrolein or phenylvinyl ketone as Michael acceptors, yields of the corresponding products **6a** and **6d** were reduced due to repeated Michael addition acting as a side process and leading to tangible oligo- and polymerization. In particular, the product of double Michael addition **6d′** was isolated in a 5% yield from the reaction of **2d** with phenylvinyl ketone. Diethyl ester analog of **6c** was used in the synthesis of natural 4-(*p*-methoxyphenethyl)-cyclohex-2-en-1-one.[47]

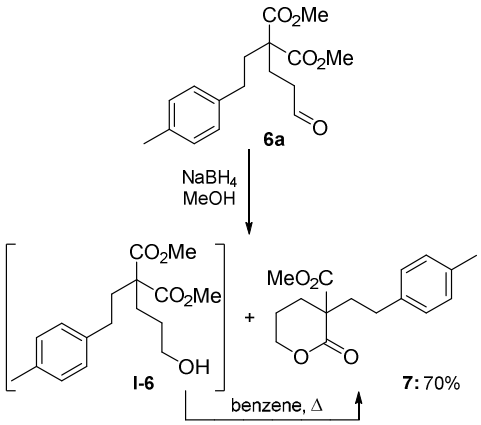
Table 4. Synthesis of Intermediate Products 6 *via* Alkylation of 2[a,b]



[a]Reaction conditions: 0.1 M solution of **2** (0.5 mmol) in MeCN, Michael acceptor (0.7-1.0 mmol), $NaB(OMe)_4$ (4 mg, 0.025 mmol). [b]Isolated yield. [c]Yield in 2.5 gram-scale synthesis.

Reduction of **6a** with $NaBH_4$ in methanol results in a mixture of the target lactone **7** and intermediate alcohol **I-6** which undergoes complete cyclization into **7** after heating in benzene under reflux (Scheme 7).

Scheme 7. Synthesis of δ-Lactone 7

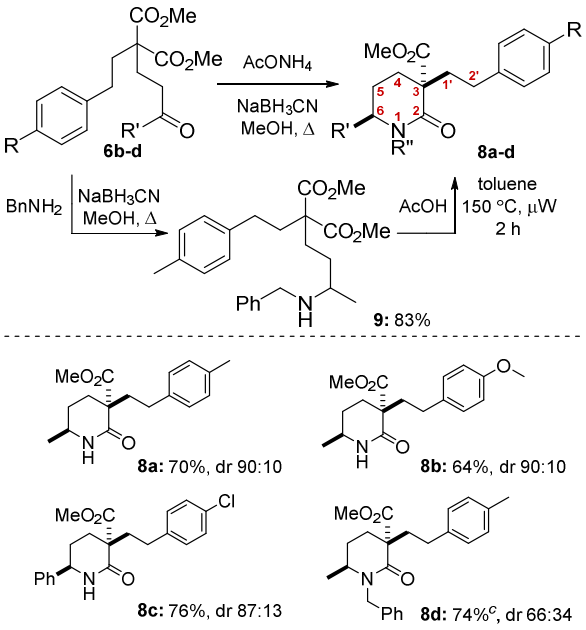


Lactams **8** were synthesized from ketones **6** under Borch reductive amination[48] conditions (Table 5). In the case of $AcONH_4$, reaction proceeded as a cascade of reductive amination and spontaneous 1,6-lactamization,[49] directly yielding lactams **8a-c**. This domino reaction proceeded with high diastereoselectivity, predominantly yielding diastereomers **8a-c** with a *cis*-relationship

between $ArCH_2CH_2$ and R′ substituents. The structure of the major isomer (3*RS*,6*RS*)-**8b** was unambiguously proved by single crystal X-ray analysis.[38,50]

Spontaneous lactamization did not proceed under the same conditions when benzylamine was employed. Therefore, lactam **8d** was obtained *via* initial synthesis of acyclic amine **9** followed by its lactamization under harsher conditions. In this case, significant decrease in diastereoselectivity was observed.

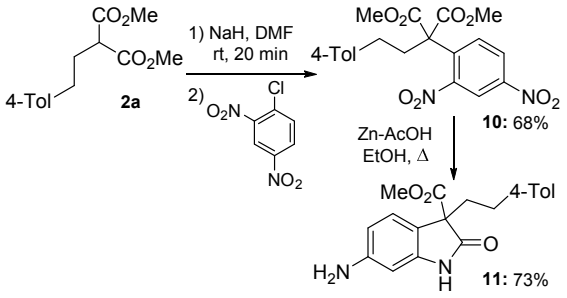
Table 5. Synthesis of δ-Lactams 8[a,b]



[a]Reaction conditions: 0.1 M solution of **6** (0.5 mmol) in MeOH, $NaBH_3CN$ (0.7 mmol), $AcONH_4$ (5 mmol) or $BnNH_2$ (1 mmol), heating under reflux for 3 h. [b]Isolated yield. [c]Two-step yield starting from **6b**.

The same concept related to preliminary arylation of **2** was used in the synthesis of oxindole derivative **11**. Intermediate acyclic product **10** was obtained by nucleophilic aromatic substitution in 1-chloro-2,4-dinitrobenzene (Scheme 8). Further reduction of NO_2 groups in the aryl fragment, followed by γ-lactamization, led to the assembly of the oxindole core in the final product **11**.

Scheme 8. Synthesis of Oxindole 11



CONCLUSION

In conclusion, we have developed a practical method for regioselective hydrogenolysis of DA cyclopropanes *via* reductive cleavage of the activated C-C bond between the donor and acceptor substituents with a Zn-AcOH reductive system. This system proved to be efficient for the conversion of 2-(het)aryl-substituted cyclopropanes, activated with ester, keto, cyano, amide groups *etc*. as acceptors, into the correspondingly functionalized propane derivatives.

The proposed mechanism for the studied process includes initial homolytic small-ring opening *via* electron transfer, followed by the transformation of the generated radical anion into the final propane derivative *via* proton and electron transfer. Fragmentation of acyclic intermediates yielding the corresponding styrene and an active methylene compound was revealed as the principal side process.

In order to show the potential utility of the synthesized products, selected representatives were transformed into derivatives of carbazole, δ-lactone and lactam as well as oxindole.

EXPERIMENTAL SECTION

General Information

NMR spectra were acquired at room temperature if not specified otherwise; the chemical shifts δ were measured in ppm with respect to solvent (^{1}H: $CDCl_3$, δ = 7.27 ppm; ^{13}C: $CDCl_3$, δ = 77.0 ppm). The structures of compounds were elucidated with the aid of 1D NMR (^{1}H, ^{13}C) and 2D NMR (^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC, ^{1}H–^{13}C HMBC, ^{1}H–^{1}H NOESY) spectroscopy. Low resolution mass spectra were recorded using MALDI technique with a TOF mass analyzer; anthracene was used as a matrix. High resolution mass spectra (HRMS) were performed using

ESI and Orbitrap mass analyzer. Elemental analyses were performed with elemental analyser instrument. Crystallographic data were collected at 150 K using graphite monochromatized Mo–Kα radiation (λ = 0.71073 A) using a ω-scan mode. Absorption corrections based on measurements of equivalent reflections were applied. The structures were solved by direct methods and refined by full matrix least squares on F^2 with anisotropic thermal parameters for all non-hydrogen atoms. Melting points (mp) were determined using capillary melting point apparatus. Microwave reactions were performed in a microwave synthesis reactor Monowave 300 (Anton Paar) in sealed reaction vessels; the temperature was monitored with external IR detector. Analytical thin layer chromatography (TLC) was carried out with silica gel plates (silica gel 60, F_{254}, supported on aluminium) visualized with UV lamp (254 nm). Column chromatography was performed on silica gel 60 (230-400 mesh).

DFT calculations were carried out with ORCA 4.0.0 suite of programs,[51] at the B3LYP[52,53] / ma-def-SVP[54,55] level of theory using RIJCOSX[56] approximation. Conductor-like PCM model[57,58] (MeOH as a solvent) was employed to account for solvation effects.

General Procedure for the Synthesis of Alkenes

The parent alkenes were synthesized *via* Knoevenagel condensation under piperidinium acetate catalysis. Solution of the corresponding benzaldehyde (1 equiv), methylene component (1 equiv), piperidine (0.05 equiv) and acetic acid (0.2 equiv) in benzene (3 M regarding benzaldehyde) was heated under reflux with 15-mL Dean-Stark trap for 2–6 h. After cooling to the ambient temperature, reaction mixture was diluted with ethyl acetate, washed twice with brine, dried with Na_2SO_4 and concentrated under reduced pressure. Residue was either purified by column chromatography on silica gel or used without purification.

Dimethyl 2-[2-(ethoxymethoxy)benzylidene]malonate (S1)

S1 was synthesized from 2-(ethoxymethoxy)benzaldehyde (14.38 g, 79 mmol) and dimethyl malonate (9.15 mL, 79 mmol). Yield 22.06 g (95%); yellowish oil; ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.22 (t, ^3J = 7.1 Hz, 3H, CH_3), 3.74 (q, ^3J = 7.1 Hz, 2H, CH_2O), 3.79 (s, 3H, CH_3O), 3.85 (s,

3H, CH_3O), 5.28 (s, 2H, OCH_2O), 6.95–6.98 (m, 1H, Ar), 7.18–7.20 (m, 1H, Ar), 7.34–7.36 (m, 2H, Ar), 8.13 (s, 1H, CH=); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 14.8 ($^1J_{CH}$ = 127 Hz, CH_3), 52.1 ($^1J_{CH}$ = 148 Hz, CH_3O), 52.2 ($^1J_{CH}$ = 148 Hz, CH_3O), 64.4 ($^1J_{CH}$ = 143 Hz, CH_2O), 93.2 ($^1J_{CH}$ = 165 Hz, OCH_2O), 114.5 (CH), 121.4 (CH), 122.7 (C), 125.3 (C), 128.5 (CH), 131.9 (CH), 138.6 (CH), 155.9 (C), 164.4 (CO_2Me), 166.9 (CO_2Me); MS (MALDI–TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{18}NaO_6^+$ 317; Found 317; Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.22; H, 6.16. Found: C, 61.17; H, 6.21.

Dimethyl 2-[5-chloro-2-(methoxymethoxy)benzylidene]malonate (S2)

S2 was synthesized from 5-chloro-2-(methoxymethoxy)benzaldehyde (6.13 g, 30.6 mmol) and dimethyl malonate (3.50 mL, 30.6 mmol). Yield 9.54 g (99%); yellowish oil; R_f = 0.29 (petroleum ether : diethyl ether, 2:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 3.45 (s, 3H, CH_3O), 3.80 (s, 3H, CH_3O), 3.83 (s, 3H, CH_3O), 5.18 (s, 2H, OCH_2O), 7.09 (d, ^3J = 8.7 Hz, 1H, Ar), 7.26 (dd, ^3J = 8.7, ^4J = 2.6 Hz, 1H, Ar), 7.28 (d, ^4J = 2.6 Hz, 1H, Ar), 7.99 (s, 1H, CH=); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 52.4 ($^1J_{CH}$ = 147 Hz, CH_3O), 52.6 ($^1J_{CH}$ = 147 Hz, CH_3O), 56.3 ($^1J_{CH}$ = 143 Hz, CH_3O), 94.8 ($^1J_{CH}$ = 167 Hz, OCH_2O), 116.0 (CH, Ar), 124.3 (C), 126.78 (C), 126.80 (C), 128.4 (CH, Ar), 131.4 (CH, Ar), 137.2 (CH=), 154.4 (C, Ar), 164.2 (CO_2Me), 166.4 (CO_2Me); MS (MALDI–TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{15}ClNaO_6^+$ 337; Found 337; Anal. Calcd for $C_{14}H_{15}ClO_6$: C, 53.43; H, 4.80. Found: C, 53.25; H, 4.84.

Dimethyl 2-[3-methoxy-2-(methoxymethoxy)benzylidene]malonate (S3)

S3 was synthesized from 3-methoxy-2-(methoxymethoxy)benzaldehyde (3.93 g, 20 mmol) and dimethyl malonate (2.29 mL, 20 mmol). Yield 5.59 g (90%); yellowish oil; R_f = 0.31 (petroleum ether : diethyl ether, 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.53 (s, 3H, CH_3O), 3.73 (s, 3H, CH_3O), 3.78 (s, 3H, CH_3O), 3.79 (s, 3H, CH_3O), 5.08 (s, 2H, OCH_2O), 6.91 (dd, ^3J = 7.6, ^4J = 1.5 Hz, 1H, Ar), 6.92 (dd, ^3J = 8.3, ^4J = 1.5 Hz, 1H, Ar), 6.99 (dd, ^3J = 8.3, ^3J = 7.6 Hz, 1H, Ar), 8.13 (s, 1H, CH=); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 52.2 (CH_3O), 52.3 (CH_3O), 55.6 (CH_3O), 57.5 (CH_3O), 98.9 (OCH_2O), 114.3 (CH, Ar), 119.9 (CH, Ar), 124.2 (CH, Ar), 126.1 (C), 127.9

(C), 139.2 (CH=), 145.0 (C, Ar), 152.1 (C, Ar), 164.3 (CO$_2$Me), 166.6 (CO$_2$Me); MS (MALDI–TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{18}NaO_7^+$ 333; Found 333; Anal. Calcd for $C_{15}H_{18}O_7$: C, 58.06; H, 5.85. Found: C, 57.66; H, 5.98.

Dimethyl 2-[2-(methoxycarbonyl)benzylidene]malonate (S4)

S4 was synthesized from methyl 2-formylbenzoate (4.58 g, 28 mmol) and dimethyl malonate (3.20 mL, 28 mmol). Yield 3.89 g (50%); colorless oil; R_f = 0.40 (petroleum ether : diethyl ether, 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 3.60 (s, 3H, CH_3O), 3.85 (s, 3H, CH_3O), 3.90 (s, 3H, CH_3O), 7.33 (br.d, ^3J = 7.7 Hz, 1H, Ar), 7.42–7.46 (m, 1H, Ar), 7.49–7.53 (m, 1H, Ar), 8.05 (dd, ^3J = 7.8, ^4J = 1.4 Hz, 1H, Ar), 8.42 (br.s, 1H, CH=); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 52.1 ($^1J_{CH}$ = 147 Hz, CH_3O), 52.3 ($^1J_{CH}$ = 147 Hz, CH_3O), 52.5 ($^1J_{CH}$ = 147 Hz, CH_3O), 126.8 (C), 128.7 (CH, Ar), 128.9 (C), 129.3 (CH, Ar), 130.8 (CH, Ar), 132.3 (CH, Ar), 135.9 (C), 145.2 (CH=), 164.2 (CO$_2$Me), 166.1 (CO$_2$Me), 166.4 (CO$_2$Me); MS (MALDI–TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{14}NaO_6^+$ 301; Found 301; Anal. Calcd for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07. Found: C, 60.43; H, 5.01.

General Procedure for the Synthesis of Cyclopropanes 1

Cyclopropanes **1a-y,aa,ad** were synthesized under Corey-Chaykovsky reaction conditions. To suspension of NaH (1.1 equiv, 60% suspension in mineral oil) in dry DMF (0.5 M) Me_3SOI (1.1 equiv) was added in one portion under inert atmosphere. After stirring for 20 min at ambient temperature, resulting mixture was cooled with ice-water bath, and alkene (1 equiv) was added portionwise under vigorous stirring. The mixture was stirred for additional 3–7 h, quenched with ice water (15 mL) and extracted with EtOAc (3×25 mL). Combined organic fractions were washed with water (5×15 mL), dried with Na_2SO_4 and concentrated under reduced pressure. Residue was purified by column chromatography on silica gel.

Dimethyl 2-[2-(ethoxymethoxy)phenyl]cyclopropane-1,1-dicarboxylate (1h)

1h was synthesized from alkene **S1** (5.88 g, 20 mmol). Yield 4.37 g (71%); yellowish oil; R_f = 0.37 (petroleum ether : diethyl ether, 2:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.24 (t, ^3J = 7.1 Hz,

3H, CH_3), 1.75 (dd, ^2J = 5.1, ^3J = 9.2 Hz, 1H, CH_2), 2.22 (dd, ^2J = 5.1, ^3J = 8.3 Hz, 1H, CH_2), 3.32 (s, 3H, CH_3O), 3.35 (dd, ^3J = 9.2, ^3J = 8.3 Hz, 1H, CH), 3.74 (dq, ^2J = 9.7, ^3J = 7.1 Hz, 1H, CH_2O), 3.79 (dq, ^2J = 9.7, ^3J = 7.1 Hz, 1H, CH_2O), 3.80 (s, 3H, CH_3O), 5.24 (s, 2H, OCH_2O), 6.90–6.92 (m, 1H, Ar), 6.98–7.00 (m, 1H, Ar), 7.08–7.10 (m, 1H, Ar), 7.19–7.22 (m, 1H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 15.0 ($^1J_{CH}$ = 127 Hz, CH_3), 18.5 ($^1J_{CH}$ = 165 Hz, CH_2), 28.5 ($^1J_{CH}$ = 167 Hz, CH), 36.3 (C), 51.9 ($^1J_{CH}$ = 147 Hz, CH_3O), 52.5 ($^1J_{CH}$ = 147 Hz, CH_3O), 64.1 ($^1J_{CH}$ = 142 Hz, CH_2O), 93.3 ($^1J_{CH}$ = 165 Hz, OCH_2O), 113.8 (CH, Ar), 120.9 (CH, Ar), 123.7 (C, Ar), 127.7 (CH, Ar), 128.6 (CH, Ar), 157.1 (C, Ar), 167.1 (CO_2Me), 170.3 (CO_2Me); MS (MALDI–TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{20}NaO_6^+$ 331; Found 331; Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. Found: C, 62.17; H, 6.61.

Dimethyl 2-[5-chloro-2-(methoxymethoxy)phenyl]cyclopropane-1,1-dicarboxylate (1i)

1i was synthesized from alkene **S2** (9.54 g, 30.3 mmol). Yield 6.26 g (63%); yellowish oil; R_f = 0.41 (petroleum ether : ethyl acetate, 3:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.72 (dd, ^2J = 5.2, ^3J = 9.2 Hz, 1H, CH_2), 2.14 (dd, ^2J = 5.2, ^3J = 8.4 Hz, 1H, CH_2), 3.26 (dd, ^3J = 9.2, ^3J = 8.4 Hz, 1H, CH), 3.36 (s, 3H, CH_3O), 3.46 (s, 3H, CH_3O), 3.77 (s, 3H, CH_3O), 5.13 (d, ^2J = 6.8 Hz, 1H, OCH_2O), 5.15 (d, ^2J = 6.8 Hz, 1H, OCH_2O), 6.95 (br.d, ^4J = 2.6 Hz, 1H, Ar), 6.98 (d, ^3J = 8.8 Hz, 1H, Ar), 7.12 (dd, ^3J = 8.8, ^4J = 2.6 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 18.5 ($^1J_{CH}$ = 166 Hz, CH_2), 28.0 ($^1J_{CH}$ = 169 Hz, CH), 36.2 (C), 52.1 ($^1J_{CH}$ = 147 Hz, CH_3O), 52.7 ($^1J_{CH}$ = 147 Hz, CH_3O), 55.9 ($^1J_{CH}$ = 143 Hz, CH_3O), 94.6 ($^1J_{CH}$ = 166 Hz, OCH_2O), 114.9 (CH, Ar), 125.7 (C, Ar), 126.0 (C, Ar), 127.9 (CH, Ar), 128.3 (CH, Ar), 155.4 (C, Ar), 166.8 (CO_2Me), 170.0 (CO_2Me); MS (MALDI–TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{17}ClNaO_6^+$ 351; Found 351; Anal. Calcd for $C_{15}H_{17}ClO_6$: C, 54.80; H, 5.21. Found: C, 54.49; H, 5.36.

Dimethyl 2-[3-methoxy-2-(methoxymethoxy)phenyl]cyclopropane-1,1-dicarboxylate (1j′)

1j′ was synthesized from alkene **S3** (5.50 g, 17.7 mmol). Yield 3.73 g (65%); yellowish oil; R_f = 0.25 (petroleum ether : diethyl ether, 2:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.75 (dd, ^2J = 5.2, ^3J = 9.3 Hz, 1H, CH_2), 2.18 (dd, ^2J = 5.2, ^3J = 8.3 Hz, 1H, CH_2), 3.37 (s, 3H, CH_3O), 3.47 (dd, ^3J =

9.3, ^{3}J = 8.3 Hz, 1H, CH), 3.57 (s, 3H, CH_3O), 3.76 (s, 3H, CH_3O), 3.81 (s, 3H, CH_3O), 5.06 (d, ^{2}J = 5.7 Hz, 1H, OCH_2O), 5.16 (d, ^{2}J = 5.7 Hz, 1H, OCH_2O), 6.53 (br.d, ^{3}J = 7.8 Hz, 1H, Ar), 6.81 (br.d, ^{3}J = 8.2 Hz, 1H, Ar), 6.94 (dd, ^{3}J = 8.2, ^{3}J = 7.8 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 18.8 ($^{1}J_{CH}$ = 165 Hz, CH_2), 28.0 ($^{1}J_{CH}$ = 168 Hz, CH), 37.3 (C), 52.1 ($^{1}J_{CH}$ = 147 Hz, CH_3O), 52.6 ($^{1}J_{CH}$ = 147 Hz, CH_3O), 55.7 ($^{1}J_{CH}$ = 144 Hz, CH_3O), 57.3 ($^{1}J_{CH}$ = 143 Hz, CH_3O), 98.9 ($^{1}J_{CH}$ = 167 Hz, OCH_2O), 111.7 (CH, Ar), 118.8 (CH, Ar), 123.5 (CH, Ar), 128.8 (C, Ar), 146.3 (C, Ar), 152.2 (C, Ar), 167.0 (CO_2Me), 170.1 (CO_2Me); MS (MALDI–TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{20}NaO_7^+$ 347; Found 347; Anal. Calcd for $C_{16}H_{20}O_7$: C, 59.25; H, 6.22. Found: C, 59.07; H, 6.37.

General Procedure for the Synthesis of Cyclopropanes 1g,j

Cyclopropanes **1g,j** were synthesized *via* acidic deprotection of **1h,j'**. To 0.25 M solution of the corresponding protected cyclopropane in methanol aq HCl (2 M for EOM, 1 M for MOM; 1 mL/mmol) was added dropwise under cooling (ice-water bath). Resulting mixture was stirred at ambient temperature for 24 h, quenched with water and extracted with ethyl acetate. Combined organic fractions were washed with brine, once with aq $NaHCO_3$, then dried with Na_2SO_4 and concentrated under reduced pressure. Residue was purified by column chromatography on silica gel.

Dimethyl 2-(2-hydroxyphenyl)cyclopropane-1,1-dicarboxylate (1g)[50]

1g was synthesized *via* deprotection of **1h** (3.11 g, 10.1 mmol). Yield 2.26 g (90%); white crystals; mp 89–90 °C; R_f = 0.22 (petroleum ether : diethyl ether, 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.81 (dd, ^{2}J = 5.1, ^{3}J = 9.2 Hz, 1H, CH_2), 2.21 (dd, ^{2}J = 5.1, ^{3}J = 8.2 Hz, 1H, CH_2), 3.15 (dd, ^{3}J = 9.2, ^{3}J = 8.2 Hz, 1H, CH), 3.41 (s, 3H, CH_3O), 3.83 (s, 3H, CH_3O), 5.54 (br.s, 1H, OH), 6.83–6.89 (m, 2H, Ar), 7.03 (br.d, ^{3}J = 7.5 Hz, 1H, Ar), 7.14–7.18 (m, 1H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 18.4 ($^{1}J_{CH}$ = 166 Hz, CH_2), 28.2 ($^{1}J_{CH}$ = 166 Hz, CH), 36.2 (C), 52.4 ($^{1}J_{CH}$ = 147 Hz, CH_3O), 52.9 ($^{1}J_{CH}$ = 147 Hz, CH_3O), 115.7 (CH, Ar), 120.2 (CH, Ar), 121.1 (C, Ar), 128.6 (CH, Ar), 128.9 (CH, Ar), 155.8 (C, Ar), 167.5 (CO_2Me), 170.3 (CO_2Me); MS

(MALDI–TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{14}O_5Na^+$ 273; Found 273; Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.72; H, 5.93.

Dimethyl 2-(2-hydroxy-3-methoxyphenyl)cyclopropane-1,1-dicarboxylate (1j)

1j was synthesized *via* deprotection of **1j'** (5.09 g, 15.7 mmol). Yield 3.88 g (88%); white solid; R_f = 0.27 (petroleum ether : diethyl ether, 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.76 (dd, ^2J = 5.0, ^3J = 9.3 Hz, 1H, CH_2), 2.21 (dd, ^2J = 5.0, ^3J = 8.3 Hz, 1H, CH_2), 3.33 (dd, ^3J = 9.3, ^3J = 8.3 Hz, 1H, CH), 3.39 (s, 3H, CH_3O), 3.79 (s, 3H, CH_3O), 3.86 (s, 3H, CH_3O), 5.82 (s, 1H, OH), 6.59 (dd, ^3J = 7.6, ^4J = 1.6 Hz, 1H, Ar), 6.74 (dd, ^3J = 8.1, ^3J = 7.6 Hz, 1H, Ar), 6.77 (dd, ^3J = 8.1, ^4J = 1.6 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 18.8 ($^1J_{CH}$ = 166 Hz, CH_2), 27.9 ($^1J_{CH}$ = 168 Hz, CH), 36.3 (C), 52.1 ($^1J_{CH}$ = 148 Hz, CH_3O), 52.6 ($^1J_{CH}$ = 148 Hz, CH_3O), 56.0 ($^1J_{CH}$ = 145 Hz, CH_3O), 109.9 (CH, Ar), 118.9 (CH, Ar), 120.1 (CH, Ar), 120.6 (C, Ar), 145.5 (C, Ar), 146.2 (C, Ar), 167.3 (CO_2Me), 170.3 (CO_2Me); MS (MALDI–TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{16}NaO_6^+$ 303; Found 303; Anal. Calcd for $C_{14}H_{16}O_6$: C, 59.99; H, 5.75. Found: C, 59.74; H, 5.73.

Dimethyl 2-[2-(methoxycarbonyl)phenyl]cyclopropane-1,1-dicarboxylate (1m)

1m was synthesized from alkene **S4** (1.41 g, 5.1 mmol); reaction time 24h. Conversion 85%, yield 0.69 g (47%); colorless oil; R_f = 0.36 (petroleum ether : diethyl ether, 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.80 (dd, ^2J = 5.1, ^3J = 9.0 Hz, 1H, CH_2), 2.18 (dd, ^2J = 5.1, ^3J = 8.5 Hz, 1H, CH_2), 3.28 (s, 3H, CH_3O), 3.76 (dd, ^3J = 9.0, ^3J = 8.5 Hz, 1H, CH), 3.80 (s, 3H, CH_3O), 3.85 (s, 3H, CH_3O), 7.23 (br.d, ^3J = 7.8 Hz, 1H, Ar), 7.29–7.33 (m, 1H, Ar), 7.40–7.44 (m, 1H, Ar), 7.93 (dd, ^3J = 7.8, ^4J = 1.4 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 19.8 ($^1J_{CH}$ = 165 Hz, CH_2), 32.8 ($^1J_{CH}$ = 170 Hz, CH), 35.9 (C), 51.9 ($^1J_{CH}$ = 147 Hz, CH_3O), 52.0 ($^1J_{CH}$ = 147 Hz, CH_3O), 52.5 ($^1J_{CH}$ = 147 Hz, CH_3O), 127.5 (CH, Ar), 129.6 (CH, Ar), 130.7 (CH, Ar), 131.5 (C, Ar), 131.8 (CH, Ar), 135.8 (C, Ar), 167.1 (CO_2Me), 167.3 (CO_2Me), 170.1 (CO_2Me); MS (MALDI–TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{16}NaO_6^+$ 315; Found 315; Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52. Found: C, 61.30; H, 5.56.

1-(Methoxycarbonyl)-2-(3,4,5-trimethoxyphenyl)cyclopropanecarboxylic acid (1y)

Dimethyl 2-(3,4,5-trimethoxyphenyl)cyclopropane-1,1-dicarboxylate (**1l**) (1.78 g, 5.5 mmol) was dissolved in the mixture of MeOH (4 mL) and 1.7 M aq NaOH (1.25 equiv, 4 mL). The solution was stirred for 1.5 h, then was diluted with EtOAc and water to separate layers. The aqueous layer was acidified with 5% HCl (pH 1), then extracted three times with EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. Yield 1.4 g (82%); white crystals, mp 122–123 °C; R_f = 0.47 (petroleum ether : ethyl acetate, 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.24 (dd, ^2J = 4.8, ^3J = 9.4 Hz, 1H, CH_2), 2.35 (dd, ^2J = 4.8, ^3J = 8.6 Hz, 1H, CH_2), 3.35 (dd, ^3J = 9.4, ^3J = 8.5 Hz, 1H, CH), 3.37 (s, 3H, CH_3O), 3.82 (s, 3H, CH_3O), 3.84 (s, 6H, 2×CH_3O), 6.45 (s, 2H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 21.4 (CH_2), 34.0 (C), 40.2 (CH), 52.7 (CH_3O), 56.2 (2×CH_3O), 60.9 (CH_3O), 106.1 (2×CH, Ar), 129.7 (C, Ar), 137.7 (C, Ar), 153.0 (2×C, Ar), 170.9 (CO), 172.8 (CO); MS (MALDI–TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{18}NaO_7^+$ 333; Found 333; Anal. Calcd for $C_{15}H_{18}O_7$: C, 58.06; H, 5.85. Found: C, 57.62; H, 5.92.

Methyl (1*RS*,2*SR*)-2-phenyl-1-(pyridin-2-yl)cyclopropane-1-carboxylate (1ad)

1ad was synthesized from methyl 3-phenyl-2-(pyridin-2-yl)acrylate (510 mg, 2.13 mmol). Yield 426 mg (79%); colorless oil; R_f = 0.51 (petroleum ether : ethyl acetate, 3:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.82 (dd, ^2J = 4.9, ^3J = 9.1 Hz, 1H, CH_2), 2.42 (dd, ^2J = 4.9, ^3J = 7.8 Hz, 1H, CH_2), 3.35(s, 3H, CH_3), 3.41 (dd, ^3J = 9.1, ^3J = 7.8 Hz, 1H, CH), 7.17–7.19 (m, 1H, Py), 7.22–7.24 (m, 1H, Ph), 7.29–7.31 (m, 2H, Ph), 7.33–7.34 (m, 2H, Ph), 7.56–7.57 (m, 1H, Py), 7.65–7.68 (m, 1H, Py), 8.56-8.58 (m, 1H, Py); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 20.0 (CH_2), 33.7 (CH), 39.6 (C), 51.7 (CH_3), 121.7 (CH, Ar), 123.6 (CH, Ar), 126.8 (CH, Ar), 128.0 (2×CH, Ar), 128.9 (2×CH, Ar), 136.1 (CH, Ar), 136.4 (C, Ar), 149.0 (CH, Ar), 158.1 (C, Ar), 170.4 (*C*O_2Me); Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 76.25; H, 5.75; N, 5.57.

General Procedure for the Reductive Ring Opening of Cyclopropanes 1

To 0.1 M solution of cyclopropane **1** (0.5 mmol) in the corresponding alcohol zinc dust (325 mg, 5 mmol) and acetic acid (150 μL, 2.5 mmol) were sequentially added. The mixture was heated under reflux for specified time. After cooling to the ambient temperature, remaining zinc was filtered off and washed with ethyl acetate (5 mL). Filtrate was diluted with water (10 mL) and extracted with ethyl acetate (2×20 mL), combined organic fractions were dried with Na_2SO_4 and concentrated under reduced pressure. Product **2** was purified by column chromatography on silica gel.

Dimethyl [2-(4-methylphenyl)ethyl]malonate (2a)

MeOH, 5 min. Yield 96 mg (77%) (1.83 g, 73% for 10 mmol run); colorless oil; R_f = 0.20 (petroleum ether : diethyl ether, 3:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.20–2.26 (m, 2H, C(2)H_2), 2.33 (s, 3H, CH_3), 2.61–2.65 (m, 2H, C(3)H_2), 3.39 (t, ^3J = 7.6 Hz, 1H, CH), 3.75 (s, 6H, 2×CH_3O), 7.08 (d, ^3J = 7.9 Hz, 2H, Ar), 7.11 (d, ^3J = 7.9 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 20.9 ($^1J_{CH}$ = 126 Hz, CH_3), 30.4 ($^1J_{CH}$ = 132 Hz, C(2)H_2), 32.8 ($^1J_{CH}$ = 127 Hz, C(3)H_2), 50.8 ($^1J_{CH}$ = 132 Hz, CH), 52.4 ($^1J_{CH}$ = 148 Hz, 2×CH_3O), 128.3 (2×CH, Ar), 129.1 (2×CH, Ar), 135.6 (C, Ar), 137.3 (C, Ar), 169.7 (2×*C*O_2Me); MS (MALDI–TOF) m/z: $[M + K]^+$ Calcd for $C_{14}H_{18}KO_4^+$ 289; Found 289. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.26; H, 7.22.

Dimethyl (2-phenylethyl)malonate (2b)[26,59]

EtOH, 70 min. Yield 94 mg (80%); colorless oil; R_f = 0.54 (petroleum ether : diethyl ether, 2:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.23–2.28 (m, 2H, CH_2), 2.65–2.69 (m, 2H, CH_2), 3.40 (t, ^3J = 7.5 Hz, 1H, CH), 3.74 (s, 6H, 2×CH_3O), 7.18–7.23 (m, 3H, Ph), 7.28–7.32 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 30.2 ($^1J_{CH}$ = 132 Hz, CH_2), 33.2 ($^1J_{CH}$ = 127 Hz, CH_2), 50.7 ($^1J_{CH}$ = 130 Hz, CH), 52.3 ($^1J_{CH}$ = 148 Hz, 2×CH_3O), 126.1 (CH, Ph), 128.34 (2×CH, Ph), 128.37 (2×CH, Ph), 140.4 (C, Ar), 169.6 (2×*C*O_2Me); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{13}H_{17}O_4^+$ 237.1121; Found 237.1120.

Dimethyl [2-(4-fluorophenyl)ethyl]malonate (2c)

EtOH, 70 min. Yield 104 mg (82%); colorless oil; R_f = 0.33 (petroleum ether : diethyl ether, 2:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.17–2.22 (m, 2H, CH_2), 2.60–2.64 (m, 2H, CH_2), 3.36 (t, ^3J = 7.4 Hz, 1H, CH), 3.73 (s, 6H, 2×CH_3O), 6.96 (dd, $^3J_{HH}$ = 8.7, $^3J_{HF}$ = 8.8 Hz, 2H, Ar), 7.12 (dd, $^3J_{HH}$ = 8.7, $^4J_{HF}$ = 5.4 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 30.4 ($^1J_{CH}$ = 133 Hz, CH_2), 32.4 ($^1J_{CH}$ = 128 Hz, CH_2), 50.7 ($^1J_{CH}$ = 132 Hz, CH), 52.4 ($^1J_{CH}$ = 148 Hz, 2×CH_3O), 115.1 ($^2J_{CF}$ = 21 Hz, 2×CH, Ar), 129.8 ($^3J_{CF}$ = 8 Hz, 2×CH, Ar), 136.0 ($^4J_{CF}$ = 3 Hz, C, Ar), 161.4 ($^1J_{CF}$ = 243 Hz, C, Ar), 169.5 (2×CO_2Me); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{13}H_{16}FO_4^+$ 255.1027; Found 255.1032.

Dimethyl [2-(4-chlorophenyl)ethyl]malonate (2d)

EtOH, 10 min. Yield 3.74 g (72% for 19 mmol run); colorless oil; R_f = 0.53 (petroleum ether : diethyl ether, 2:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.18–2.23 (m, 2H, CH_2), 2.61–2.65 (m, 2H, CH_2), 3.36 (t, ^3J = 7.4 Hz, 1H, CH), 3.74 (s, 6H, 2×CH_3O), 7.11 (d, ^3J = 8.3 Hz, 2H, Ar), 7.26 (d, ^3J = 8.3 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 30.2 ($^1J_{CH}$ = 132 Hz, CH_2), 32.6 ($^1J_{CH}$ = 127 Hz, CH_2), 50.7 ($^1J_{CH}$ = 132 Hz, CH), 52.5 ($^1J_{CH}$ = 147 Hz, 2×CH_3O), 128.6 (2×CH, Ar), 129.8 (2×CH, Ar), 132.0 (C, Ar), 138.9 (C, Ar), 169.5 (2×CO_2Me); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{13}H_{16}ClO_4^+$ 271.0732; Found 271.0737.

Dimethyl [2-(4-bromophenyl)ethyl]malonate (2e)

MeOH, 5 min. Yield 117 mg (74%); colorless oil; R_f = 0.24 (petroleum ether : diethyl ether, 3:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.17–2.23 (m, 2H, CH_2), 2.58–2.63 (m, 2H, CH_2), 3.35 (t, ^3J = 7.4 Hz, 1H, CH), 3.73 (s, 6H, 2×CH_3O), 7.05 (d, ^3J = 8.4 Hz, 2H, Ar), 7.40 (d, ^3J = 8.4 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 30.1 ($^1J_{CH}$ = 132 Hz, CH_2), 32.6 ($^1J_{CH}$ = 128 Hz, CH_2), 50.7 ($^1J_{CH}$ = 132 Hz, CH), 52.5 ($^1J_{CH}$ = 147 Hz, 2×CH_3O), 120.0 (C, Ar), 130.2 (2×CH, Ar), 131.5 (2×CH, Ar), 139.4 (C, Ar), 169.5 (2×CO_2Me); Anal. Calcd for $C_{13}H_{15}BrO_4$: C, 49.54; H, 4.80. Found: C, 49.56; H, 4.91.

Dimethyl [2-(4-methoxyphenyl)ethyl]malonate (2f)

MeOH, 5 min. Yield 98 mg (74%); colorless oil; R_f = 0.28 (petroleum ether : diethyl ether, 3:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.18–2.23 (m, 2H, CH_2), 2.58–2.62 (m, 2H, CH_2), 3.38 (t, ^3J = 7.5 Hz, 1H, CH), 3.74 (s, 6H, 2×CH_3O), 3.79 (s, 3H, CH_3O), 6.83 (d, ^3J = 8.7 Hz, 2H, Ar), 7.10 (d, ^3J = 8.7 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 30.6 ($^1J_{CH}$ = 132 Hz, CH_2), 32.3 ($^1J_{CH}$ = 128 Hz, CH_2), 50.8 ($^1J_{CH}$ = 132 Hz, CH), 52.4 ($^1J_{CH}$ = 148 Hz, 2×CH_3O), 55.2 ($^1J_{CH}$ = 144 Hz, CH_3O), 113.8 (2×CH, Ar), 129.4 (2×CH, Ar), 132.4 (C, Ar), 158.0 (C, Ar), 169.7 (2×*C*O_2Me); Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 63.17; H, 6.90.

Dimethyl [2-(2-hydroxyphenyl)ethyl]malonate (2g)

EtOH, 10 min. Yield 87 mg (69%); colorless oil; R_f = 0.47 (petroleum ether : ethyl acetate, 2:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.17–2.21 (m, 2H, CH_2), 2.66–2.68 (m, 2H, CH_2), 3.40 (t, ^3J = 7.1 Hz, 1H, CH), 3.77 (s, 6H, 2×CH_3O), 6.19 (s, 1H, OH), 6.84 (d, ^3J = 7.8 Hz, 1H, Ar), 6.84–6.86 (m, 1H, Ar), 7.08 (dd, ^3J = 7.9, ^4J = 1.7 Hz, 1H, Ar), 7.12 (ddd, ^3J = 7.8, ^3J = 7.6, ^4J = 1.7 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 27.8 ($^1J_{CH}$ = 128 Hz, CH_2), 28.8 ($^1J_{CH}$ = 132 Hz, CH_2), 50.5 ($^1J_{CH}$ = 132 Hz, CH), 52.8 ($^1J_{CH}$ = 148 Hz, 2×CH_3O), 115.9 (CH, Ar), 120.4 (CH, Ar), 126.1 (C, Ar), 127.9 (CH, Ar), 130.2 (CH, Ar), 154.2 (C, Ar), 170.2 (2×*C*O_2Me); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{16}NaO_5^+$ 275.0890; Found 275.0891.

Dimethyl {2-[2-(ethoxymethoxy)phenyl]ethyl}malonate (2h)

EtOH, 70 min. Yield 101 mg (65%); colorless oil; R_f = 0.45 (petroleum ether : ethyl acetate, 3:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.24 (t, ^3J = 7.1 Hz, 3H, CH_3), 2.20–2.25 (m, 2H, CH_2), 2.66–2.70 (m, 2H, CH_2), 3.40 (t, ^3J = 7.4 Hz, 1H, CH), 3.73 (s, 6H, 2×CH_3O), 3.74 (q, ^3J = 7.1 Hz, 2H, CH_2O), 5.24 (s, 2H, OCH_2O), 6.93 (ddd, ^3J = 7.5, ^3J = 7.4, ^4J = 1.0 Hz, 1H, Ar), 7.10 (dd, ^3J = 8.2, ^4J = 1.0 Hz, 1H, Ar), 7.12 (dd, ^3J = 7.5, ^4J = 1.7 Hz, 1H, Ar), 7.17 (ddd, ^3J = 8.2, ^3J = 7.4, ^4J = 1.7 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 15.0 ($^1J_{CH}$ = 126 Hz, CH_3), 28.0 ($^1J_{CH}$ = 130 Hz, CH_2), 28.9 ($^1J_{CH}$ = 132 Hz, CH_2), 51.1 ($^1J_{CH}$ = 132 Hz, CH), 52.3 ($^1J_{CH}$ = 147 Hz, 2×CH_3O), 64.2 ($^1J_{CH}$ = 142 Hz, CH_2O), 93.0 ($^1J_{CH}$ = 165 Hz, OCH_2O), 113.8 (CH, Ar),

121.4 (CH, Ar), 127.5 (CH, Ar), 129.3 (C, Ar), 130.1 (CH, Ar), 155.3 (C, Ar), 169.8 (2×*C*O_2Me); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{22}NaO_6^+$ 333.1309; Found 333.1325.

Dimethyl {2-[5-chloro-2-(methoxymethoxy)phenyl]ethyl}malonate (2i)

EtOH, 70 min. Yield 109 mg (66%); colorless oil; R_f = 0.56 (petroleum ether : ethyl acetate, 3:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.18–2.23 (m, 2H, CH_2), 2.62–2.66 (m, 2H, CH_2), 3.38 (t, ^3J = 7.4 Hz, 1H, CH), 3.46 (s, 3H, CH_3O), 3.73 (s, 6H, 2×CH_3O), 5.16 (s, 2H, OCH_2O), 7.00 (br.d, ^3J = 8.2 Hz, 1H, Ar), 7.10 (d, ^4J = 2.6 Hz, 1H, Ar), 7.11 (dd, ^3J = 8.2, ^4J = 2.6 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 27.9 ($^1J_{CH}$ = 129 Hz, CH_2), 28.6 ($^1J_{CH}$ = 132 Hz, CH_2), 51.0 ($^1J_{CH}$ = 132 Hz, CH), 52.4 ($^1J_{CH}$ = 147 Hz, 2×CH_3O), 56.0 ($^1J_{CH}$ = 142 Hz, CH_3O), 94.4 ($^1J_{CH}$ = 165 Hz, OCH_2O), 115.0 (CH, Ar), 126.4 (C, Ar), 127.2 (CH, Ar), 129.9 (CH, Ar), 131.3 (C, Ar), 153.7 (C, Ar), 169.6 (2×*C*O_2Me); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{20}ClO_6^+$ 331.0943; Found 331.0949.

Dimethyl [2-(2-hydroxy-3-methoxyphenyl)ethyl]malonate (2j)

EtOH, 10 min. Yield 102 mg (72%); colorless oil; R_f = 0.49 (petroleum ether : ethyl acetate, 2:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.22–2.28 (m, 2H, CH_2), 2.68–2.72 (m, 2H, CH_2), 3.42 (t, ^3J = 7.5 Hz, 1H, CH), 3.74 (s, 6H, 2×CH_3O), 3.87 (s, 3H, CH_3O), 5.76 (s, 1H, OH), 6.71–6.80 (m, 3H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 27.3 ($^1J_{CH}$ = 128 Hz, CH_2), 28.6 ($^1J_{CH}$ = 133 Hz, CH_2), 51.0 ($^1J_{CH}$ = 132 Hz, CH), 52.4 ($^1J_{CH}$ = 147 Hz, 2×CH_3O), 55.9 ($^1J_{CH}$ = 144 Hz, CH_3O), 108.8 (CH, Ar), 119.3 (CH, Ar), 122.4 (CH, Ar), 126.2 (C, Ar), 143.6 (C, Ar), 146.3 (C, Ar), 169.8 (2×*C*O_2Me); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{19}O_6^+$ 283.1176; Found 283.1185.

Dimethyl [2-(1,3-benzodioxol-5-yl)ethyl]malonate (2k)

MeOH, 5 min. Yield 98 mg (70%); colorless oil; R_f = 0.22 (petroleum ether : diethyl ether, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.14–2.20 (m, 2H, CH_2), 2.54–2.58 (m, 2H, CH_2), 3.36 (t, ^3J = 7.5 Hz, 1H, CH), 3.73 (s, 6H, 2×CH_3O), 5.91 (s, 2H, CH_2O), 6.61 (dd, ^3J = 7.9, ^4J = 1.6 Hz, 1H, Ar), 6.66 (d, ^4J = 1.6 Hz, 1H, Ar), 6.71 (d, ^3J = 7.9 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 30.5 (CH_2), 32.9 (CH_2), 50.6 (CH), 52.4 (2×CH_3O), 100.7 (CH_2O), 108.1 (CH, Ar), 108.8

(CH, Ar), 121.2 (CH, Ar), 134.1 (C, Ar), 145.8 (C, Ar), 147.6 (C, Ar), 169.6 (2×*C*O_2Me); MS (MALDI–TOF) m/z: $[M + K]^+$ Calcd for $C_{14}H_{16}KO_6^+$ 319; Found 319; Anal. Calcd for $C_{14}H_{16}O_6$: C, 59.99; H, 5.75. Found: C, 60.04; H, 5.77.

Dimethyl [2-(3,4,5-trimethoxyphenyl)ethyl]malonate (2l)

MeOH, 5 min. Yield 116 mg (71%); colorless oil; R_f = 0.40 (petroleum ether : ethyl acetate, 2:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.19–2.24 (m, 2H, CH_2), 2.57–2.61 (m, 2H, CH_2), 3.39 (t, ^3J = 7.4 Hz, 1H, CH), 3.74 (s, 6H, 2×CH_3O), 3.81 (s, 3H, CH_3O), 3.84 (s, 6H, 2×CH_3O), 6.39 (s, 2H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 30.4 ($^1J_{CH}$ = 133 Hz, CH_2), 33.7 ($^1J_{CH}$ = 128 Hz, CH_2), 50.8 ($^1J_{CH}$ = 132 Hz, CH), 52.4 ($^1J_{CH}$ = 148 Hz, 2×CH_3O), 56.0 ($^1J_{CH}$ = 144 Hz, 2×CH_3O), 60.7 ($^1J_{CH}$ = 144 Hz, CH_3O), 105.5 (2×CH, Ar), 136.1 (C, Ar), 136.5 (C, Ar), 153.2 (2×C, Ar), 169.6 (2×*C*O_2Me);

MS (MALDI–TOF) m/z: $[M + K]^+$ Calcd for $C_{16}H_{22}KO_7$ 365; Found 365; Anal. Calcd for $C_{16}H_{22}O_7$: C, 58.89; H, 6.80. Found: C, 58.90; H, 6.79.

Dimethyl {2-[2-(methoxycarbonyl)phenyl]ethyl}malonate (2m)

EtOH, 70 min. Yield 75 mg (51%); colorless oil; R_f = 0.40 (petroleum ether : ethyl acetate, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.17–2.25 (m, 2H, CH_2), 2.96–3.02 (m, 2H, CH_2), 3.43 (t, ^3J = 7.4 Hz, 1H, CH), 3.72 (s, 6H, 2×CH_3O), 3.87 (s, 3H, CH_3O), 7.22–7.28 (m, 2H, Ar), 7.38–7.44 (m, 1H, Ar), 7.88 (br.d, ^3J = 7.7 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 30.4 ($^1J_{CH}$ = 133 Hz, CH_2), 31.8 ($^1J_{CH}$ = 128 Hz, CH_2), 51.3 ($^1J_{CH}$ = 132 Hz, CH), 51.9 ($^1J_{CH}$ = 148 Hz, CH_3O), 52.4 ($^1J_{CH}$ = 144 Hz, 2×CH_3O), 126.3 (CH, Ar), 129.3 (C, Ar), 130.8 (CH, Ar), 131.1 (CH, Ar), 132.0 (CH, Ar), 142.5 (C, Ar), 167.6 (*C*O_2Me), 169.6 (2×*C*O_2Me); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{19}O_6^+$ 295.1176; Found 295.1182.

Dimethyl [2-(pyridin-3-yl)ethyl]malonate (2n)

EtOH, 270 min. Yield 77 mg (65%); colorless oil; R_f = 0.24 (petroleum ether : ethyl acetate, 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.18–2.24 (m, 2H, CH_2), 2.62–2.66 (m, 2H, CH_2), 3.36 (t, ^3J = 7.4 Hz, 1H, CH), 3.71 (s, 6H, 2×CH_3O), 7.20 (dd, ^3J = 7.8, ^3J = 4.8 Hz, 1H, Py), 7.50 (ddd,

^3J = 7.8, ^4J = 2.2, ^4J = 1.7 Hz, 1H, Py), 8.43 (d, ^4J = 2.2 Hz, 1H, Py), 8.44 (dd, ^3J = 4.8, ^4J = 1.7 Hz, 1H, Py); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 29.9 ($^1J_{CH}$ = 133 Hz, CH_2), 30.3 ($^1J_{CH}$ = 128 Hz, CH_2), 50.7 ($^1J_{CH}$ = 132 Hz, CH), 52.5 ($^1J_{CH}$ = 147 Hz, 2×CH_3O), 123.4 (CH, Py), 135.8 (C, Py), 135.9 (CH, Py), 147.7 (CH, Py), 149.8 (CH, Py), 169.3 (2×*C*O_2Me); Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.65; H, 6.33; N, 5.60.

Dimethyl [2-(naphthalen-1-yl)ethyl]malonate (2o)

EtOH, 70 min. Yield 96 mg (67%); colorless oil; R_f = 0.20 (petroleum ether : diethyl ether, 2:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.38–2.44 (m, 2H, CH_2), 3.14–3.19 (m, 2H, CH_2), 3.54 (t, ^3J = 7.4 Hz, 1H, CH), 3.79 (s, 6H, 2×CH_3O), 7.36 (dd, ^3J = 7.0, ^4J = 1.0 Hz, 1H, Ar), 7.43 (dd, ^3J = 8.2, ^3J = 7.0 Hz, 1H, Ar), 7.49–7.54 (m, 1H, Ar), 7.55–7.59 (m, 1H, Ar), 7.77 (br.d, ^3J = 8.2 Hz, 1H, Ar), 7.89 (br.d, ^3J = 8.0 Hz, 1H, Ar), 8.11 (br.d, ^3J = 8.5 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 29.7 ($^1J_{CH}$ = 132 Hz, CH_2), 30.6 ($^1J_{CH}$ = 128 Hz, CH_2), 51.2 ($^1J_{CH}$ = 132 Hz, CH), 52.4 ($^1J_{CH}$ = 148 Hz, 2×CH_3O), 123.6 (CH, Ar), 125.4 (CH, Ar), 125.5 (CH, Ar), 126.0 (CH, Ar), 126.3 (CH, Ar), 127.0 (CH, Ar), 128.7 (CH, Ar), 131.7 (C, Ar), 133.8 (C, Ar), 136.6 (C, Ar), 169.6 (2×*C*O_2Me); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{19}O_4^+$ 287.1278; Found 287.1283.

Dimethyl [2-(1-methyl-1*H*-pyrrol-2-yl)ethyl]malonate (2p)

MeOH, 5 min. Yield 81 mg (67%); colorless oil; R_f = 0.54 (petroleum ether : ethyl acetate, 2:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.22–2.27 (m, 2H, CH_2), 2.62–2.66 (m, 2H, CH_2), 3.50 (t, ^3J = 7.3 Hz, 1H, CH), 3.56 (s, 3H, CH_3N), 3.76 (s, 6H, 2×CH_3O), 5.92 (br.d, ^3J = 3.4 Hz, 1H, Ar), 6.06 (br.d, ^3J = 3.4 Hz, 1H, Ar), 6.57 (br. s, 1H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 23.8 ($^1J_{CH}$ = 127 Hz, CH_2), 27.9 ($^1J_{CH}$ = 133 Hz, CH_2), 33.3 ($^1J_{CH}$ = 138 Hz, CH_3N), 50.7 ($^1J_{CH}$ = 132 Hz, CH), 52.4 ($^1J_{CH}$ = 148 Hz, 2×CH_3O), 106.1 (CH, Ar), 106.5 (CH, Ar), 121.4 (CH, Ar), 130.9 (C, Ar), 169.5 (2×*C*O_2Me); MS (MALDI–TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{18}NO_4$ 240; Found 240; Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.02; H, 7.10; N, 5.89.

Dimethyl [2-(1-methyl-1*H*-pyrazol-4-yl)ethyl]malonate (2q)

EtOH, 10 min. Yield 77 mg (64%); colorless oil; R_f = 0.10 (petroleum ether : ethyl acetate, 2:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.07–2.12 (m, 2H, CH_2), 2.43–2.47 (m, 2H, CH_2), 3.35 (t, ^3J = 7.5 Hz, 1H, CH), 3.68 (s, 6H, 2×CH_3O), 3.80 (s, 3H, CH_3N), 7.13 (s, 1H, Ar), 7.25 (s, 1H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 21.6 ($^1J_{CH}$ = 128 Hz, CH_2), 29.9 ($^1J_{CH}$ = 132 Hz, CH_2), 38.6 ($^1J_{CH}$ = 141 Hz, CH_3N), 50.6 ($^1J_{CH}$ = 132 Hz, CH), 52.3 ($^1J_{CH}$ = 148 Hz, 2×CH_3O), 119.6 (C, Ar), 128.4 (CH, Ar), 138.5 (CH, Ar), 169.5 (2×*C*O_2Me); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{11}H_{17}N_2O_4^+$ 241.1183; Found 241.1183.

Dimethyl [2-(5-methylfuran-2-yl)ethyl]malonate (2r)

MeOH, 5 min. Yield 44 mg (37%); colorless oil; R_f = 0.67 (petroleum ether : ethyl acetate, 2:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.20–2.25 (m, 2H, CH_2), 2.24 (br. s, 3H, CH_3), 2.61–2.66 (m, 2H, CH_2), 3.42 (t, ^3J = 7.4 Hz, 1H, CH), 3.73 (s, 6H, 2×CH_3O), 5.83 (dq, ^3J = 2.9, ^4J = 1.0 Hz, 1H, Fu), 5.88 (d, ^3J = 2.9 Hz, 1H, Fu); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 13.4 ($^1J_{CH}$ = 128 Hz, CH_3), 25.6 ($^1J_{CH}$ = 128 Hz, CH_2), 27.3 ($^1J_{CH}$ = 133 Hz, CH_2), 50.7 ($^1J_{CH}$ = 132 Hz, CH), 52.4 ($^1J_{CH}$ = 147 Hz, 2×CH_3O), 105.8 (CH, Fu), 106.3 (CH, Fu), 150.7 (C, Fu), 152.1 (C, Fu), 169.5 (2×*C*O_2Me).

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{12}H_{17}O_5^+$ 241.1071; Found 241.1067.

Dimethyl [2-(thien-2-yl)ethyl]malonate (2s)

EtOH, 10 min. Yield 83 mg (68%); colorless oil; R_f = 0.77 (Al_2O_3, petroleum ether : ethyl acetate, 2:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.25–2.30 (m, 2H, CH_2), 2.86–2.91 (m, 2H, CH_2), 3.43 (t, ^3J = 7.5 Hz, 1H, CH), 3.73 (s, 6H, 2×CH_3O), 6.79–6.81 (m, 1H, Th), 6.91 (dd, ^3J = 5.1, ^3J = 3.4 Hz, 1H, Th), 7.14 (dd, ^3J = 5.1, ^4J = 1.2 Hz, 1H, Th); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 27.3 ($^1J_{CH}$ = 130 Hz, CH_2), 30.5 ($^1J_{CH}$ = 133 Hz, CH_2), 50.5 ($^1J_{CH}$ = 132 Hz, CH), 52.5 ($^1J_{CH}$ = 148 Hz, 2×CH_3O), 123.5 ($^1J_{CH}$ = 186 Hz, CH, Th), 124.8 ($^1J_{CH}$ = 166 Hz, CH, Th), 126.8 ($^1J_{CH}$ = 167 Hz, CH, Th), 142.9 (C, Th), 169.4 (2×*C*O_2Me); MS (MALDI–TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{15}O_4S$ 243; Found 243; Anal. Calcd for $C_{11}H_{14}O_4S$: C, 54.53; H, 5.82. Found: C, 54.47; H, 5.50.

Dimethyl [2-(thien-3-yl)ethyl]malonate (2t)

EtOH, 10 min. Yield 65 mg (54%); colorless oil; R_f = 0.59 (petroleum ether : ethyl acetate, 4:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.22–2.27 (m, 2H, CH_2), 2.67–2.72 (m, 2H, CH_2), 3.39 (t, ^3J = 7.4 Hz, 1H, CH), 3.74 (s, 6H, 2×CH_3O), 6.94 (dd, ^3J = 5.0, ^4J = 1.3 Hz, 1H, Th), 6.96–6.98 (m, 1H, Th), 7.26 (dd, ^3J = 5.0 Hz, ^3J = 3.0 Hz, 1H, Th); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 27.7 ($^1J_{CH}$ = 128 Hz, CH_2), 29.5 ($^1J_{CH}$ = 132 Hz, CH_2), 50.9 ($^1J_{CH}$ = 133 Hz, CH), 52.4 ($^1J_{CH}$ = 147 Hz, 2×CH_3O), 120.8 (CH, Th), 125.6 (CH, Th), 128.0 (CH, Th), 140.7 (C, Th), 169.6 (2×*C*O_2Me); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{11}H_{15}O_4S^+$ 243.0686; Found 243.0687.

Dimethyl [2-(1-methyl-1*H*-indol-2-yl)ethyl]malonate (2u)

MeOH, 5 min. Yield 106 mg (73%), yellow crystals; mp 72–73 °C; R_f = 0.31 (petroleum ether : diethyl ether, 2:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.33–2.38 (m, 2H, CH_2), 2.84 (t, ^3J = 7.9 Hz, 2H, CH), 3.56 (t, ^3J = 7.3 Hz, 1H, CH_2), 3.69 (s, 3H, CH_3N), 3.77 (s, 6H, 2×CH_3O), 6.31 (br.s, 1H, Ind), 7.11 (dd, ^3J = 7.9 Hz, ^3J = 7.8 Hz, 1H, Ind), 7.20 (dd, ^3J = 8.1 Hz, ^3J = 7.9 Hz, 1H, Ind), 7.30 (d, ^3J = 8.1 Hz, 1H, Ind), 7.57 (d, ^3J = 7.8 Hz, 1H, Ind); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 24.3 (CH_2), 27.7 (CH_2), 29.3 (CH), 50.6 (CH_3), 52.5 (2×CH_3O), 99.5 (CH, Ind), 108.8 (CH, Ind), 119.3 (CH, Ind), 119.8 (CH, Ind), 120.8 (CH, Ind), 127.6 (C, Ind), 137.4 (C, Ind), 138.8 (C, Ind), 169.5 (2×*C*O_2Me); MS (MALDI–TOF) m/z: $[M]^+$ Calcd for $C_{16}H_{19}NO_4$ 289; Found 289; Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.52; H, 6.47; N, 4.85.

Dimethyl [2-(1-methyl-1*H*-indol-3-yl)ethyl]malonate (2v)

MeOH, 5 min. Yield 97 mg (67%); colorless oil; R_f = 0.66 (petroleum ether : ethyl acetate, 2:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.32–2.37 (m, 2H, CH_2), 2.81–2.86 (m, 2H, CH_2), 3.50 (t, ^3J = 7.5 Hz, 1H, CH_2), 3.758 (s, 6H, 2×CH_3O), 3.763 (s, 3H, CH_3N), 6.88 (s, 1H, Ind), 7.12–7.16 (m, 1H, Ind), 7.23–7.27 (m, 1H, Ind), 7.31 (br.d, ^3J = 8.1 Hz, 1H, Ind), 7.62 (br.d, ^3J = 7.9 Hz, 1H, Ind); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 22.6 (CH_2), 29.4 (CH_2), 32.5 (CH), 51.0 (CH_3), 52.4 (2×CH_3O), 109.1 (CH, Ind), 113.0 (C, Ind), 118.7 (CH, Ind), 118.9 (CH, Ind), 121.5 (CH, Ind), 126.5 (CH, Ind), 127.6 (C, Ind), 137.0 (C, Ind), 169.9 (2×*C*O_2Me); MS (MALDI–TOF) m/z:

$[M]^+$ Calcd for $C_{16}H_{19}NO_4$ 289; Found 289; Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.59; H, 6.40; N, 4.85.

Dimethyl [2-(1-methyl-1*H*-indol-4-yl)ethyl]malonate (2w)

MeOH, 5 min. Yield 109 mg (75%); colorless oil; R_f = 0.49 (petroleum ether : ethyl acetate, 2:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.38–2.43 (m, 2H, CH_2), 2.97–3.01 (m, 2H, CH_2), 3.49 (t, ^3J = 7.4 Hz, 1H, CH_2), 3.77 (s, 6H, 2×CH_3O), 3.80 (s, 3H, CH_3N), 6.57 (dd, ^3J = 3.1, ^4J = 0.9 Hz, 1H, Ind), 6.94–6.97 (m, 1H, Ind), 7.07 (d, ^3J = 3.1 Hz, 1H, Ind), 7.19 (dd, ^3J = 8.2, ^3J = 6.9 Hz, 1H, Ind), 7.23 (br.d, ^3J = 8.2 Hz, 1H, Ind); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 29.5 ($^1J_{CH}$ = 132 Hz, CH_2), 30.9 ($^1J_{CH}$ = 127 Hz, CH_2), 32.8 ($^1J_{CH}$ = 138 Hz, CH_3), 51.1 ($^1J_{CH}$ = 132 Hz, CH), 52.3 ($^1J_{CH}$ = 147 Hz, 2×CH_3O), 99.1 (CH, Ind), 107.5 (CH, Ind), 118.9 (CH, Ind), 121.6 (CH, Ind), 127.7 (C, Ind), 128.4 (CH, Ind), 132.7 (C, Ind), 136.7 (C, Ind), 169.8 (2×*C*O_2Me); MS (MALDI–TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{19}NNaO_4$ 312; Found 312; Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.51; H, 6.63; N, 4.87.

2-(Methoxycarbonyl)-4-phenylbutanoic acid (2x)

MeOH, 5 min. Yield 93 mg (84%); colorless oil; R_f = 0.34 (petroleum ether : ethyl acetate, 2:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.25–2.35 (m, 2H, CH_2), 2.71–2.75 (m, 2H, CH_2), 3.48 (t, ^3J = 7.4 Hz, 1H, CH), 3.78 (s, 3H, CH_3O), 7.21–7.26 (m, 3H, Ph), 7.31–7.35 (m, 2H, Ph), 11.48 (br.s, 1H, CO_2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 30.2 ($^1J_{CH}$ = 132 Hz, CH_2), 33.1 ($^1J_{CH}$ = 127 Hz, CH_2), 50.8 ($^1J_{CH}$ = 132 Hz, CH), 52.5 ($^1J_{CH}$ = 147 Hz, CH_3O), 126.2 (CH, Ph), 128.4 (4×CH, Ph), 140.2 (C, Ph), 169.5 (*C*O_2Me), 175.1 (CO_2H); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{12}H_{15}O_4^+$ 223.0965; Found 223.0964.

2-(Methoxycarbonyl)-4-(3,4,5-trimethoxyphenyl)butanoic acid (2y)

MeOH, 5 min. Yield 121 mg (77%); colorless oil; R_f = 0.11 (petroleum ether : ethyl acetate, 2:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.19–2.29 (m, 2H, CH_2), 2.61–2.66 (m, 2H, CH_2), 3.44 (t, ^3J = 7.4 Hz, 1H, CH), 3.77 (s, 3H, CH_3O), 3.82 (s, 3H, CH_3O), 3.84 (s, 6H, 2×CH_3O), 6.40 (s, 2H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 30.4 (CH_2), 33.6 (CH_2), 50.7 (CH), 52.6 (CH_3), 56.0

(2×CH_3O), 60.8 (CH_3O), 105.5 (2×CH, Ar), 136.0 (C, Ar), 136.4 (C, Ar), 153.2 (2×C, Ar), 169.5 (CO_2Me), 174.4 (CO_2H); MS (MALDI-TOF) m/z: $[M]^+$ Calcd for $C_{15}H_{20}O_7^+$ 312; Found 312; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{21}O_7^+$ 313.1282; Found 313.1284.

Methyl 3-oxo-2-(2-phenylethyl)butanoate (2z)[42]

EtOH, 10 min. Yield 79 mg (72%); colorless oil; R_f = 0.37 (petroleum ether : diethyl ether, 2:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.13–2.25 (m, 2H, CH_2), 2.20 (s, 3H, CH_3), 2.57–2.69 (m, 2H, CH_2), 3.43–3.48 (m, 1H, CH), 3.73 (s, 3H, CH_3O), 7.16–7.23 (m, 3H, Ph), 7.27–7.31 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 28.8 ($^1J_{CH}$ = 128 Hz, CH_3), 29.5 ($^1J_{CH}$ = 132 Hz, CH_2), 33.2 ($^1J_{CH}$ = 127 Hz, CH_2), 52.2 ($^1J_{CH}$ = 147 Hz, CH_3O), 58.5 ($^1J_{CH}$ = 131 Hz, CH), 126.1 (CH, Ph), 128.33 (2×CH, Ph), 128.36 (2×CH, Ph), 140.5 (C, Ph), 170.0 (CO_2Me), 202.6 (COMe).

Methyl 2-cyano-4-phenylbutanoate (2aa)[41]

EtOH, 10 min. Yield 70 mg (69%); colorless oil; R_f = 0.25 (petroleum ether : diethyl ether, 2:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.28 (dddd, ^2J = 13.7, ^3J = 8.4, ^3J = 8.2, ^3J = 6.3 Hz, 1H, CH_2), 2.31 (dddd, ^2J = 13.7, ^3J = 8.1, ^3J = 7.8, ^3J = 6.1 Hz, 1H, CH_2), 2.82 (ddd, ^2J = 14.0, ^3J = 8.2, ^3J = 7.8 Hz, 1H, CH_2), 2.91 (ddd, ^2J = 14.0, ^3J = 8.1, ^3J = 6.3 Hz, 1H, CH_2), 3.49 (dd, ^3J = 8.4, ^3J = 6.1 Hz, 1H, CH), 3.80 (s, 3H, CH_3O), 7.22–7.28 (m, 3H, Ph), 7.32–7.36 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 31.1 ($^1J_{CH}$ = 134 Hz, CH_2), 32.5 ($^1J_{CH}$ = 128 Hz, CH_2), 36.4 ($^1J_{CH}$ = 136 Hz, CH), 53.3 ($^1J_{CH}$ = 148 Hz, CH_3O), 116.1 (CN), 126.6 (CH, Ph), 128.4 (2×CH, Ph), 128.6 (2×CH, Ph), 138.8 (C, Ph), 166.3 (CO_2Me).

2-Cyano-4-phenylbutanamide (2ab)

EtOH, 270 min. Yield 80 mg (85%); yellowish solid; mp 148–149 °C. ^{1}H NMR (DMSO-d_6, 600 MHz) δ = 2.03–2.14 (m, 2H, CH_2), 2.64 (ddd, ^2J = 13.8, ^3J = 9.9, ^3J = 6.6 Hz, 1H, CH_2), 2.71 (ddd, ^2J = 13.8, ^3J = 9.8, ^3J = 5.9 Hz, 1H, CH_2), 3.63 (dd, ^3J = 8.1, ^3J = 6.6 Hz, 1H, CH), 7.20–7.23 (m, 3H, Ph), 7.30–7.32 (m, 2H, Ph), 7.47 (br.s, 1H, NH_2), 7.78 (br.s, 1H, NH_2); ^{13}C NMR (DMSO-d_6, 150 MHz) δ = 31.1 ($^1J_{CH}$ = 133 Hz, CH_2), 32.4 ($^1J_{CH}$ = 128 Hz, CH_2), 37.2 ($^1J_{CH}$ =

137 Hz, CH), 118.6 (CN), 126.3 (CH), 128.3 (2×CH, Ph), 128.5 (2×CH, Ph), 140.1 (C, Ph), 166.6 ($CONH_2$); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{11}H_{13}N_2O^+$ 189.1022; Found 189.1015.

(2-Phenylethyl)propanedinitrile (2ac)[39]

MeOH, 5 min. Yield 41 mg (48%); colorless oil; R_f = 0.38 (petroleum ether : diethyl ether, 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.34–2.40 (m, 2H, CH_2), 2.93–2.98 (m, 2H, CH_2), 3.59 (t, ^3J = 7.3 Hz, 1H, CH), 7.23 (br.d, ^3J = 7.4 Hz, 2H, Ph), 7.28–7.33 (m, 1H, Ph), 7.35–7.40 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 21.5 ($^1J_{CH}$ = 142 Hz, CH), 32.1 ($^1J_{CH}$ = 128 Hz, CH_2), 32.4 ($^1J_{CH}$ = 136 Hz, CH_2), 112.4 (2×CN), 127.3 (CH, Ph), 128.4 (2×CH, Ph), 129.1 (2×CH, Ph), 137.2 (C, Ph).

Methyl 4-phenyl-2-(pyridin-2-yl)butanoate (2ad)

EtOH, 10 min. Yield 71 mg (55%); colorless oil; R_f = 0.64 (diethyl ether). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.28 (dddd, ^2J = 13.6, ^3J = 9.2, ^3J = 7.4, ^3J = 6.3 Hz, 1H, CH_2), 2.47 (dddd, ^2J = 13.6, ^3J = 8.8, ^3J = 7.8, ^3J = 6.8 Hz, 1H, CH_2), 2.59 (ddd, ^2J = 13.8, ^3J = 8.8, ^3J = 6.3 Hz, 1H, CH_2), 2.62 (ddd, ^2J = 13.8, ^3J = 9.2, ^3J = 6.8 Hz, 1H, CH_2), 3.66 (s, 3H, CH_3O), 3.86 (dd, ^3J = 7.8, ^3J = 7.4 Hz, 1H, CH), 7.13–7.19 (m, 4H, Ph + Py), 7.23–7.29 (m, 3H, Ph + Py), 7.62 (ddd, ^3J = 7.7, ^3J = 7.7, ^4J = 1.9 Hz, 1H, Py), 8.57 (ddd, ^3J = 4.8, ^4J = 1.8, ^5J = 0.9 Hz, 1H, Py); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 33.4 ($^1J_{CH}$ = 126 Hz, CH_2), 33.6 ($^1J_{CH}$ = 130 Hz, CH_2), 51.8 ($^1J_{CH}$ = 147 Hz, CH_3O), 53.0 ($^1J_{CH}$ = 130 Hz, CH), 122.0 (CH, Py), 122.5 (CH, Py), 125.8 (CH, Ph), 128.2 (2×CH, Ph), 128.3 (2×CH, Ph), 136.5 (CH, Py), 141.1 (C, Ph), 149.3 (CH, Py), 158.3 (C, Py), 173.0 (CO_2Me); Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.19; H, 6.76; N, 5.31.

3-[2-(4-Methoxyphenyl)ethyl]-1-methyl-1,3-dihydro-2*H*-indol-2-one (2ae)

EtOH, 270 min. Yield 99 mg (70%); yellowish oil; R_f = 0.53 (petroleum ether : ethyl acetate, 2:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.21–2.26 (m, 2H, CH_2), 2.61 (ddd, ^2J = 13.7, ^3J = 8.5, ^3J = 7.1 Hz, 1H, CH_2), 2.70 (ddd, ^2J = 13.7, ^3J = 8.6, ^3J = 8.2 Hz, 1H, CH_2), 3.20 (s, 3H, CH_3N), 3.48 (t, ^3J = 6.1 Hz, 1H, CH), 3.78 (s, 3H, CH_3O), 6.82 (d, ^3J = 8.7 Hz, 2H, PMP), 6.84 (br.d, ^3J

= 7.8 Hz, 1H, Ind), 7.07–7.10 (m, 1H, Ind), 7.11 (d, ^3J = 8.7 Hz, 2H, PMP), 7.27–7.32 (m, 2H, Ind); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 26.1 ($^1J_{CH}$ = 139 Hz, CH_3N), 31.0 ($^1J_{CH}$ = 127 Hz, CH_2), 32.5 ($^1J_{CH}$ = 130 Hz, CH_2), 44.8 ($^1J_{CH}$ = 132 Hz, CH), 55.2 ($^1J_{CH}$ = 143 Hz, CH_3O), 107.9 (CH, Ind), 113.7 (2×CH, PMP), 122.3 (CH, Ind), 123.7 (CH, Ind), 127.8 (CH, Ind), 128.9 (C, Ind), 129.4 (2×CH, PMP), 133.2 (C, PMP), 144.3 (C, Ind), 157.8 (C, PMP), 177.6 (CO); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{20}NO_2^+$ 282.1489; Found 282.1490.

Methyl 9-methyl-4-oxo-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxylate (5)[43]

Polyphosphoric acid (PPA) (500 mg) was added to the solution of diester **2u** (144 mg, 0.5 mmol) in 1,2-dichloroethane (5 mL) and the resulting mixture was heated under reflux for 2 h. Then the mixture was diluted with water and the organic layer was separated. The aqueous layer was extracted with ethyl acetate. Combined organic fractions were washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. The product **5** was purified by column chromatography on silica gel. Yield 91 mg (71%); colorless oil; R_f = 0.32 (petroleum ether : ethyl acetate, 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.36–2.41 (m, 1H, CH_2), 2.55–2.61 (m, 1H, CH_2), 2.84 (ddd, ^2J = 17.0, ^3J = 7.7, ^3J = 5.3 Hz, 1H, CH_2), 2.84 (ddd, ^2J = 17.0, ^3J = 6.7, ^3J = 5.3 Hz, 1H, CH_2), 3.53 (dd, ^3J = 8.5, ^3J = 4.7 Hz, 1H, CH), 3.63 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 7.25–7.26 (m, 3H, Ind), 8.19–8.21 (m, 1H, Ind); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 20.4 ($^1J_{CH}$ = 129 Hz, CH_2), 26.1 ($^1J_{CH}$ = 134 Hz, CH_2), 29.8 ($^1J_{CH}$ = 140 Hz, CH_3N), 52.1 ($^1J_{CH}$ = 148 Hz, CH_3O), 53.0 ($^1J_{CH}$ = 132 Hz, CH), 109.2 ($^1J_{CH}$ = 162 Hz, CH, Ind), 111.6 (C, Ind), 121.5 ($^1J_{CH}$ = 165 Hz, CH, Ind), 122.7 ($^1J_{CH}$ = 160 Hz, CH, Ind), 123.2 ($^1J_{CH}$ = 160 Hz, CH, Ind), 124.8 (C, Ind), 137.5 (C, Ind), 151.3 (C, Ind), 171.1 (C=O), 187.3 (C=O).

General Procedure for the Synthesis of Malonates 6 *via* Michael Addition[46]

To a 0.1 M solution of malonate **2** (0.5 mmol) and Michael acceptor (0.7–1.0 mmol) in acetonitrile $NaB(OMe)_4$ (4 mg, 0.025 mmol) was added under argon atmosphere. The resulting mixture was stirred at room temperature for 12 h and concentrated under reduced pressure. Product **6** was purified by column chromatography on silica gel.

Dimethyl [2-(4-methylphenyl)ethyl](3-oxopropyl)malonate (6a)

6a was synthesized from **2a** and acrolein. Yield 86 mg (56%); colorless oil; R_f = 0.21 (petroleum ether : diethyl ether, 2:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.15–2.20 (m, 2H, CH_2), 2.27–2.32 (m, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.47–2.53 (m, 4H, CH_2), 3.74 (s, 6H, 2×CH_3O), 7.06 (d, ^3J = 7.9 Hz, 2H, Ar), 7.10 (d, ^3J = 7.9 Hz, 2H, Ar), 9.75 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 20.9 ($^1J_{CH}$ = 126 Hz, CH_3), 25.3 ($^1J_{CH}$ = 132 Hz, CH_2), 30.1 ($^1J_{CH}$ = 127 Hz, CH_2), 35.6 ($^1J_{CH}$ = 131 Hz, CH_2), 39.2 ($^1J_{CH}$ = 126 Hz, CH_2), 52.5 ($^1J_{CH}$ = 148 Hz, 2×CH_3O), 56.8 (C), 128.1 (2×CH, Ar), 129.1 (2×CH, Ar), 135.6 (C, Ar), 137.8 (C, Ar), 171.4 (2×*C*O_2Me), 200.6 (CHO); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{23}O_5^+$ 307.1540; Found 307.1545.

Dimethyl [2-(4-methylphenyl)ethyl](3-oxobutyl)malonate (6b)

6b was synthesized from **2a** and methyl vinyl ketone. Yield 141 mg (88%); colorless crystals, mp 63–64 °C; R_f = 0.25 (petroleum ether : diethyl ether, 2:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.13 (s, 3H, CH_3), 2.14–2.18 (m, 2H, CH_2), 2.22–2.26 (m, 2H, CH_2), 2.31 (s, 3H, CH_3), 2.45–2.51 (m, 4H, CH_2), 3.72 (s, 6H, 2×CH_3O), 7.06 (d, ^3J = 8.1 Hz, 2H, Ar), 7.09 (d, ^3J = 8.1 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 20.8 ($^1J_{CH}$ = 127 Hz, CH_3), 26.7 ($^1J_{CH}$ = 133 Hz, CH_2), 29.8 ($^1J_{CH}$ = 127 Hz, CH_3), 30.1 ($^1J_{CH}$ = 127 Hz, CH_2), 35.6 ($^1J_{CH}$ = 132 Hz, CH_2), 38.6 ($^1J_{CH}$ = 125 Hz, CH_2), 52.3 ($^1J_{CH}$ = 148 Hz, 2×CH_3O), 56.7 (C), 128.1 (2×CH, Ar), 129.0 (2×CH, Ar), 135.4 (C, Ar), 137.9 (C, Ar), 171.5 (2×*C*O_2Me), 207.0 (*C*OMe); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{25}O_5^+$ 321.1697; Found 321.1702.

Dimethyl [2-(4-methoxyphenyl)ethyl](3-oxobutyl)malonate (6c)

6c was synthesized from 9.4 mmol **2f** and methyl vinyl ketone. Yield 2.61 g (83%); colorless crystals, mp 51–52 °C; R_f = 0.30 (petroleum ether : diethyl ether, 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.12–2.16 (m, 2H, CH_2), 2.13 (s, 3H, CH_3), 2.21–2.26 (m, 2H, CH_2), 2.44–2.49 (m, 4H, CH_2), 3.72 (s, 6H, 2×CH_3O), 3.77 (s, 3H, CH_3O), 6.82 (d, ^3J = 8.4 Hz, 2H, PMP), 7.08 (d, ^3J = 8.4 Hz, 2H, PMP); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 26.8 ($^1J_{CH}$ = 133 Hz, CH_2), 29.7 ($^1J_{CH}$ = 126 Hz, CH_2), 29.9 ($^1J_{CH}$ = 127 Hz, CH_3), 35.8 ($^1J_{CH}$ = 132 Hz, CH_2), 38.7 ($^1J_{CH}$ = 125 Hz, CH_2),

52.4 ($^1J_{CH}$ = 148 Hz, 2×CH_3O), 55.2 ($^1J_{CH}$ = 144 Hz, CH_3O), 56.8 (C), 113.8 (2×CH, PMP), 129.2 (2×CH, PMP), 133.0 (C, PMP), 157.9 (C, PMP), 171.6 (2×*C*O_2Me), 207.1 (*C*OMe); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{25}O_6^+$ 337.1646; Found 337.1636.

Dimethyl [2-(4-chlorophenyl)ethyl](3-oxo-3-phenylpropyl)malonate (6d)

6d was synthesized from 0.61 mmol **2d** and phenyl vinyl ketone (which generated separately by treatment of the trimethyl 3-oxo-3-phenyl-1-propyl ammonium iodide[60] with aq $NaHCO_3$ at 40 °C). Yield 182 mg (75%); colorless oil; R_f = 0.52 (petroleum ether : ethyl acetate, 3:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.19–2.24 (m, 2H, CH_2), 2.40–2.44 (m, 2H, CH_2), 2.53–2.58 (m, 2H, CH_2), 3.00–3.05 (m, 2H, CH_2), 3.74 (s, 6H, 2×CH_3O), 7.11 (d, ^3J = 8.4 Hz, 2H, Ar), 7.23 (d, ^3J = 8.4 Hz, 2H, Ar), 7.43–7.47 (m, 2H, Ph), 7.54–7.57 (m, 1H, Ph), 7.93–7.97 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 27.5 ($^1J_{CH}$ = 133 Hz, CH_2), 30.1 ($^1J_{CH}$ = 127 Hz, CH_2), 33.7 ($^1J_{CH}$ = 126 Hz, CH_2), 35.7 ($^1J_{CH}$ = 132 Hz, CH_2), 52.5 ($^1J_{CH}$ = 148 Hz, 2×CH_3O), 56.9 (C), 127.9 (2×CH, Ar), 128.4 (2×CH, Ar), 128.5 (2×CH, Ar), 129.6 (2×CH, Ar), 131.8 (C, Ar), 133.1 (CH, Ph), 136.5 (C, Ph), 139.5 (C, Ar), 171.5 (2×*C*O_2Me), 198.6 (*C*OPh); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{24}ClO_5^+$ 403.1307; Found 403.1314.

Dimethyl 2-(2-benzoyl-5-oxo-5-phenylpentyl)-2-(4-chlorophenethyl)malonate (6d′)

The product of double Michael addition **6d′** was isolated in 5% yield (16 mg) from the reaction of **2d** with phenyl vinyl ketone. Colorless oil; R_f = 0.46 (petroleum ether : ethyl acetate, 3:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.85 (ddd, ^2J = 21.6, ^3J = 7.6, ^3J = 5.9 Hz, 1H, C(3′)H_2), 1.94 (ddd, ^2J = 14.1, ^3J = 12.3, ^3J = 5.0 Hz, 1H, C(1″)H_2), 2.13–2.21 (m, 3H, C(1″)H_2+C(1′)H_2+C(3′)H_2), 2.39 (ddd, ^2J = 13.6, ^3J = 12.3, ^3J = 4.8 Hz, 1H, C(2″)H_2), 2.54 (ddd, ^2J = 13.6, ^3J = 12.2, ^3J = 5.0 Hz, 1H, C(2″)H_2), 2.85 (dd, ^2J = 14.6, ^3J = 9.5 Hz, 1H, C(1′)H_2), 3.00 (ddd, ^2J = 17.9, ^3J = 7.4, ^3J = 5.9 Hz, 1H, C(4′)H_2), 3.13 (ddd, ^2J = 17.9, ^3J = 7.6, ^3J = 7.2 Hz, 1H, C(4′)H), 3.45 (s, 3H, CH_3O), 3.65 (s, 3H, CH_3O), 3.75–3.81 (m, 1H, C(2′)H), 7.02 (d, ^3J = 8.5 Hz, 2H, Ar), 7.19 (d, ^3J = 8.5 Hz, 2H, Ar), 7.42–7.49 (m, 4H, Ph+Ph), 7.53–7.58 (m, 2H, Ph+Ph), 7.89–7.92 (m, 2H, Ph), 8.04–8.07 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 28.2 (C(3′)H_2), 30.0

(C(2″)H_2), 33.3 (C(1′)H_2), 34.8 (C(4′)H_2), 36.0 (C(1″)H_2), 40.7 (C(2′)H), 52.3 (CH_3O), 52.5 (CH_3O), 57.2 (C(2)), 127.9 (2×CH, Ar), 128.4 (2×CH, Ar), 128.5 (2×CH, Ar), 128.6 (2×CH, Ar), 128.8 (2×CH, Ar), 129.7 (2×CH, Ar), 131.7 (C, Ar), 133.1 (CH, Ph), 133.3 (CH, Ph), 136.2 (C, Ph), 136.7 (C, Ph), 139.5 (C, Ar), 171.4 (*C*O_2Me), 171.6 (*C*O_2Me), 199.1 (*C*OPh), 202.1 (*C*OPh); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{31}H_{32}ClO_6^+$ 535.1882; Found 535.1890.

Methyl 3-[2-(4-methylphenyl)ethyl]-2-oxotetrahydro-2H-pyran-3-carboxylate (7)

To solution of **6a** (100 mg, 0.33 mmol) in MeOH (3 mL) $NaBH_4$ (25 mg, 0.66 mmol) was added in one portion. Resulting mixture was stirred at ambient temperature for 3 h, yielding desired lactone **7** and half-product **I-6** in 10:90 ratio. To achieve complete conversion into **7**, reaction mixture was concentrated under reduced pressure, redissolved in benzene (5 mL) and heated under reflux for additional 3 h. Resulting mixture was concentrated under reduced pressure. Product **7** was purified by column chromatography on silica gel. Yield 64 mg (70%); colorless oil; R_f = 0.25 (petroleum ether : diethyl ether, 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.87–2.04 (m, 3H, CH_2), 2.16–2.25 (m, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.47–2.52 (m, 1H, CH_2), 2.54–2.60 (m, 1H, CH_2), 2.68–2.75 (m, 1H, CH_2), 3.78 (s, 3H, CH_3O), 4.29–4.37 (m, 2H, CH_2O), 7.10 (br.s, 4H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 20.6 ($^1J_{CH}$ = 132 Hz, CH_2), 20.9 ($^1J_{CH}$ = 126 Hz, CH_3), 28.5 ($^1J_{CH}$ = 133 Hz, CH_2), 30.5 ($^1J_{CH}$ = 127 Hz, CH_2), 38.5 ($^1J_{CH}$ = 132 Hz, CH_2), 53.0 ($^1J_{CH}$ = 148 Hz, CH_3O), 54.1 (C), 68.8 ($^1J_{CH}$ = 150 Hz, CH_2O), 128.3 (2×CH, Ar), 129.1 (2×CH, Ar), 135.6 (C, Ar), 138.0 (C, Ar), 169.9 (CO), 171.8 (*C*O_2Me); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{21}O_4^+$ 277.1434; Found 277.1437.

General Procedure for the Synthesis of γ-Lactams 8 and Amine 9

To a solution of **6** (0.5 mmol) in MeOH (5mL) $AcONH_4$ (385 mg, 5 mmol) or $BnNH_2$ (110 μL, 1 mmol) was added. Resulting mixture was stirred at ambient temperature for 10 min and then heated under reflux for 3 h. The mixture was cooled, diluted with water and extracted with ethyl acetate. Combined organic fractions were washed with brine, dried with Na_2SO_4 and evaporated

under reduced pressure. Products **8** and **9** were isolated after column chromatography on silica gel; dr's were determined from ^{1}H NMR spectra of the reaction mixtures.

Methyl 6-methyl-3-[2-(4-methylphenyl)ethyl]-2-oxopiperidine-3-carboxylate (8a)

dr 90:10. (3*RS*,6*RS*)-**8a** (major isomer): yield 91 mg (63%); yellowish crystals, mp 94–95 °C; R_f = 0.24 (petroleum ether : ethyl acetate, 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.22 (d, ^3J = 6.4 Hz, 3H, CH_3), 1.49–1.57 (m, 1H, C(5)H_2), 1.92–1.98 (m, 1H, C(5)H_2), 1.99–2.04 (m, 1H, C(4)H_2), 2.14–2.20 (m, 1H, C(1')H_2), 2.21–2.27 (m, 2H, C(4)H_2+C(1')H_2), 2.31 (s, 3H, ArCH_3), 2.59–2.65 (m, 1H, C(2')H_2), 2.66–2.73 (m, 1H, C(2')H_2), 3.59–3.66 (m, 1H, C(6)H), 3.76 (s, 3H, CH_3O), 6.39 (s, 1H, NH), 7.09 (d, ^3J = 7.9 Hz, 2H, Ar), 7.12 (d, ^3J = 7.9 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 20.9 ($^1J_{CH}$ = 126 Hz, Ar*C*H_3), 22.5 ($^1J_{CH}$ = 127 Hz, CH_3), 26.7 ($^1J_{CH}$ = 131 Hz, C(5)H_2), 27.6 ($^1J_{CH}$ = 133 Hz, C(4)H_2), 30.7 ($^1J_{CH}$ = 128 Hz, C(2')H_2), 37.4 ($^1J_{CH}$ = 132 Hz, C(1')H_2), 48.1 ($^1J_{CH}$ = 140 Hz, C(6)H), 52.5 ($^1J_{CH}$ = 147 Hz, CH_3O), 53.3 (C(3)), 128.2 (2×CH, Ar), 129.0 (2×CH, Ar), 135.3 (C, Ar), 138.7 (C, Ar), 170.9 (C(2)), 173.0 (*C*O_2Me); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{24}NO_3^+$ 290.1751; Found 290.1758.

Methyl 3-[2-(4-methoxyphenyl)ethyl]-6-methyl-2-oxopiperidine-3-carboxylate (8b)[50]

dr 90:10. (3*RS*,6*RS*)-**8b** (major isomer): yield 88 mg (58%); colorless crystals, mp 112–113 °C; R_f = 0.53 (ethyl acetate). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.21 (d, ^3J = 6.4 Hz, 3H, CH_3), 1.49–1.55 (m, 1H, CH_2), 1.92–1.97 (m, 1H, CH_2), 1.98–2.02 (m, 1H, CH_2), 2.15 (ddd, ^2J = 13.8, ^3J = 12.1, ^3J = 5.0 Hz, 1H, CH_2), 2.19–2.26 (m, 2H, CH_2), 2.57–2.62 (m, 1H, CH_2), 2.64–2.69 (m, 1H, CH_2), 3.59–3.64 (m, 1H, CH), 3.75 (s, 3H, CH_3O), 3.78 (s, 3H, CH_3O), 6.34 (s, 1H, NH), 6.82 (d, ^3J = 8.6 Hz, 2H, Ar), 7.14 (d, ^3J = 8.6 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 22.5 ($^1J_{CH}$ = 126 Hz, CH_3), 26.8 ($^1J_{CH}$ = 130 Hz, CH_2), 27.6 ($^1J_{CH}$ = 130 Hz, CH_2), 30.2 ($^1J_{CH}$ = 127 Hz, CH_2), 37.5 ($^1J_{CH}$ = 131 Hz, CH_2), 48.1 ($^1J_{CH}$ = 139 Hz, CH), 52.5 ($^1J_{CH}$ = 147 Hz, CH_3O), 53.3 (C), 55.2 ($^1J_{CH}$ = 143 Hz, CH_3O), 113.7 (2×CH, Ar), 129.3 (2×CH, Ar), 133.9 (C, Ar), 157.8 (C, Ar), 170.9 (CONH), 173.1 (*C*O_2Me); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{24}NO_4^+$ 306.1700; Found 306.1692.

Methyl 3-[2-(4-chlorophenyl)ethyl]-2-oxo-6-phenylpiperidine-3-carboxylate (8c)

dr 87:13.

(3*RS*,6*SR*)-**8c** (major isomer): yield 126 mg (68%); colorless crystals, mp 99–100 °C; R_f = 0.31 (petroleum ether : ethyl acetate, 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.84–1.90 (m, 1H, C(5)H_2), 1.92–1.98 (m, 1H, C(4)H_2), 2.18–2.28 (m, 4H, C(5)H_2+C(4)H_2+C(1')H_2), 2.62–2.75 (m, 2H, C(2')H_2), 3.78 (s, 3H, CH_3O), 4.69–4.73 (m, 1H, C(6)H), 6.42 (br.s, 1H, NH), 7.12 (br.d, ^3J = 8.5 Hz, 2H, Ar), 7.23 (br.d, ^3J = 8.5 Hz, 2H, Ar), 7.26–7.31 (m, 3H, Ph), 7.35–7.39 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 26.9 ($^1J_{CH}$ = 131 Hz, C(4)H_2), 28.2 ($^1J_{CH}$ = 131 Hz, C(5)H_2), 30.6 ($^1J_{CH}$ = 128 Hz, C(2')H_2), 37.5 ($^1J_{CH}$ = 132 Hz, C(1')H_2), 52.6 ($^1J_{CH}$ = 148 Hz, CH_3O), 53.6 (C(3)), 56.5 ($^1J_{CH}$ = 141 Hz, C(6)H), 125.9 (2×CH, Ar), 127.9 (CH, Ar), 128.4 (2×CH, Ar), 128.8 (2×CH, Ar), 129.8 (2×CH, Ar), 131.6 (C, Ar), 140.1 (C, Ar), 142.1 (C, Ar), 170.9 (C(2)), 172.8 (*C*O_2Me); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{21}H_{23}ClNO_3^+$ 372.1361; Found 372.1367.

(3*RS*,6*RS*)-**8c** (minor isomer): yield 15 mg (8%); colorless crystals, mp 156–157 °C; R_f = 0.50 (petroleum ether : ethyl acetate, 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.82–1.90 (m, 1H, C(5)H_2), 1.99–2.05 (m, 1H, C(4)H_2), 2.07–2.14 (m, 1H, C(5)H_2), 2.15–2.21 (m, 1H, C(1')H_2), 2.27–2.35 (m, 2H, C(4)H_2+C(1')H_2), 2.60–2.66 (m, 1H, C(2')H_2), 2.76–2.82 (m, 1H, C(2')H_2), 3.81 (s, 3H, CH_3O), 4.55 (dd, ^3J = 10.6, ^3J = 4.8 Hz, 1H, C(6)H), 5.97 (br.s, 1H, NH), 7.17 (br.d, ^3J = 8.3 Hz, 2H, Ar), 7.25 (br.d, ^3J = 8.3 Hz, 2H, Ar), 7.31–7.36 (m, 3H, Ph), 7.37–7.41 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 29.7 (C(5or4)H_2), 29.8 (C(4or5)H_2), 30.6 (C(2')H_2), 37.6 (C(1')H_2), 52.7 (CH_3O), 53.6 (C(3)), 58.4 (C(6)H), 126.1 (2×CH, Ar), 128.3 (CH, Ar), 128.5 (2×CH, Ar), 129.0 (2×CH, Ar), 129.8 (2×CH, Ar), 131.7 (C, Ar), 140.1 (C, Ar), 142.0 (C, Ar), 170.3 (C(2)), 173.1 (*C*O_2Me).

Dimethyl [2-(4-methylphenyl)ethyl][3-(benzylamino)butyl]malonate (9)

Yield 171 mg (83%); colorless oil; R_f = 0.18 (petroleum ether : ethyl acetate, 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.12 (d, ^3J = 6.4 Hz, 3H, CH_3), 1.25–1.32 (m, 1H, CH_2), 1.38–1.44 (m,

1H, CH_2), 1.53 (br.s, 1H, NH), 2.00–2.05 (m, 2H, CH_2), 2.18–2.21 (m, 2H, CH_2), 2.33 (s, 3H, CH_3), 2.47–2.50 (m, 2H, CH_2), 2.69–2.74 (m, 1H, CH), 3.73 (s, 3H, CH_3O), 3.74 (s, 3H, CH_3O), 3.75 (d, ^2J = 13.0 Hz, 1H, CH_2), 3.82 (d, ^2J = 13.0 Hz, 1H, CH_2), 7.08 (d, ^3J = 8.0 Hz, 2H, Ar), 7.11 (d, ^3J = 8.0 Hz, 2H, Ar), 7.24–7.27 (m, 1H, Ar), 7.32-7.36 (m, 4H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 20.2 ($^1J_{CH}$ = 125 Hz, CH_3), 20.9 ($^1J_{CH}$ = 127 Hz, CH_3), 29.0 ($^1J_{CH}$ = 129 Hz, CH_2), 30.2 ($^1J_{CH}$ = 127 Hz, CH_2), 30.9 ($^1J_{CH}$ = 123 Hz, CH_2), 34.6 ($^1J_{CH}$ = 131 Hz, CH_2), 51.2 ($^1J_{CH}$ = 132 Hz, CH_2), 52.3 ($^1J_{CH}$ = 148 Hz, 2×CH_3O), 52.4 ($^1J_{CH}$ = 132 Hz, CH), 57.5 (C), 126.7 (CH), 128.1 (2×CH, Ar), 128.2 (2×CH, Ar), 128.4 (2×CH, Ar), 129.1 (2×CH, Ar), 135.5 (C, Ar), 138.1 (C, Ar), 140.5 (C, Ar), 172.0 (2×CO_2Me); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{25}H_{34}NO_4^+$ 412.2482; Found 412.2478.

Methyl 1-benzyl-3-[2-(4-methylphenyl)ethyl]-6-methyl-2-oxopiperidine-3-carboxylate (8d)

Solution of amine **9** (171 mg, 0.4 mmol) and AcOH (24 μL, 0.4 mmol) in toluene (5 mL) was heated in microwave reactor at 150 °C for 2 h. Then, reaction mixture was concentrated under reduced pressure to give **8d** as a sample of adequate purity. dr 66:34. Yield 135 mg (89%); yellowish oil; R_f = 0.75 (petroleum ether : ethyl acetate, 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.26 (d, ^3J = 6.4 Hz, 3H **B**, CH_3), 1.28 (d, ^3J = 6.5 Hz, 3H **B**, CH_3), 1.59–1.66 (m, 1H **A**, 1H **B**, CH_2), 1.89–1.94 (m, 1H **B**, CH_2), 1.95–2.01 (m, 1H **B**, CH_2), 2.06–2.12 (m, 2H **A**, 1H **B**, CH_2), 2.16–2.26 (m, 3H **A**, CH_2), 2.29–2.34 (m, 1H **B**, CH_2), 2.34 (s, 3H **A**, 3H **B**, CH_3), 2.36–2.41 (m, 1H **A**, 1H **B**, CH_2), 2.57–2.66 (m, 1H **A**, 1H **B**, CH_2), 2.72–2.78 (m, 1H **A**, 1H **B**, CH_2), 2.48–2.57 (m, 1H **A**, 1H **B**, CH), 3.77 (s, 3H **A**, CH_3O), 3.80 (s, 3H **B**, CH_3O), 3.95 (d, ^3J = 15.1 Hz, 1H **A**, NCH_2), 4.22 (d, ^3J = 15.2 Hz, 1H **B**, NCH_2), 5.26 (d, ^3J = 15.2 Hz, 1H **B**, NCH_2), 5.51 (d, ^3J = 15.1 Hz, 1H **A**, NCH_2), 7.11–7.12 (m, 2H **A**, 2H **B**, Ar), 7.14–7.17 (m, 2H **A**, 2H **B**, Ar), 7.26–7.37 (m, 5H **A**, 5H **B**, Ar); (3*RS*,6*RS*)-**8d** (major isomer): ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 19.3 ($^1J_{CH}$ = 128 Hz, CH_3), 20.9 ($^1J_{CH}$ = 124 Hz, CH_3), 25.9 ($^1J_{CH}$ = 129 Hz, CH_2), 26.2 ($^1J_{CH}$ = 127 Hz, CH_2), 30.7 ($^1J_{CH}$ = 127 Hz, CH_2), 38.0 ($^1J_{CH}$ = 132 Hz, CH_2), 47.8 ($^1J_{CH}$ = 139 Hz, CH_2), 50.7 ($^1J_{CH}$ = 141 Hz, CH), 52.4 ($^1J_{CH}$ = 147 Hz, CH_3O), 54.1 (C), 127.12 (CH), 127.7 (2×CH,

Ar), 128.30 (2×CH, Ar), 128.4 (2×CH, Ar), 129.0 (2×CH, Ar), 135.2 (C, Ar), 137.6 (C, Ar), 138.7 (C, Ar), 168.8 (CONH), 173.8 (CO_2Me); (3*RS*,6*SR*)-**8d** (minor isomer): ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 20.3 ($^1J_{CH}$ = 124 Hz, CH_3), 20.9 ($^1J_{CH}$ = 124 Hz, CH_3), 27.3 ($^1J_{CH}$ = 129 Hz, CH_2), 27.5 ($^1J_{CH}$ = 129 Hz, CH_2), 31.0 ($^1J_{CH}$ = 127 Hz, CH_2), 38.5 ($^1J_{CH}$ = 131 Hz, CH_2), 47.5 ($^1J_{CH}$ = 140 Hz, CH_2), 51.9 ($^1J_{CH}$ = 142 Hz, CH), 52.4 ($^1J_{CH}$ = 147 Hz, CH_3O), 54.3 (C), 127.05 (CH), 127.6 (2×CH, Ar), 128.33 (2×CH, Ar), 128.5 (2×CH, Ar), 129.0 (2×CH, Ar), 135.2 (C, Ar), 137.8 (C, Ar), 138.9 (C, Ar), 169.1 (CONH), 173.6 (CO_2Me); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{24}H_{30}NO_3^+$ 380.2220; Found 380.2226.

Dimethyl (2,4-dinitrophenyl)[2-(4-methylphenyl)ethyl]malonate (10)

Sodium hydride (30 mg, 0.72 mmol) was added to a stirred solution of malonate **2a** (150 mg, 0.6 mmol) in DMF (1.5 mL) under argon atmosphere. Mixture was stirred for 20 min; then 1-chloro-2,4-dinitrobenzene (122 mg, 0.6 mmol) was added in one portion. The reaction mixture was stirred at ambient temperature for 30 min, quenched with water (15 mL) and extracted with ethyl acetate (3×15 mL). The combined organic fractions were washed with brine (4×10 mL), dried with Na_2SO_4 and concentrated under reduced pressure. Product **10** was purified by column chromatography on silica gel. Yield 170 mg (68%); white crystals, mp 127–128 °C; R_f = 0.14 (petroleum ether : diethyl ether, 2:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.33 (s, 3H, CH_3), 2.50–2.56 (m, 2H, CH_2), 2.79–2.85 (m, 2H, CH_2), 3.77 (s, 6H, 2×CH_3O), 7.06 (d, ^3J = 8.0 Hz, 2H, Ar), 7.11 (d, ^3J = 8.0 Hz, 2H, Ar), 7.70 (d, ^3J = 8.8 Hz, 1H, Ar), 8.49 (dd, ^3J = 8.8, ^4J = 2.5 Hz, 1H, Ar), 8.89 (d, ^4J = 2.5 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 21.0 (CH_3), 31.3 (CH_2), 37.5 (CH_2), 53.4 (2×CH_3O), 62.8 (C), 121.2 (CH, Ar), 126.7 (CH, Ar), 128.1 (2×CH, Ar), 129.3 (2×CH, Ar), 131.8 (CH, Ar), 136.1 (C, Ar), 137.0 (C, Ar), 138.7 (C, Ar), 147.1 (C, Ar), 149.9 (C, Ar), 168.5 (2×CO_2Me); MS (MALDI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{20}N_2NaO_8$) 439; Found 439. Anal. Calcd for $C_{20}H_{20}N_2O_8$: C, 57.69; H, 4.84; N, 6.73. Found: C, 57.71; H, 4.78; N, 6.75.

Methyl 6-amino-3-[2-(4-methylphenyl)ethyl]-2-oxo-2,3-dihydro-1*H*-indole-3-carboxylate (11)

To a stirred solution of **10** (145 mg, 0.35 mmol) in EtOH (4 mL) Zn (455 mg, 7 mmol) and acetic acid (200 μL, 3.5 mmol) were sequentially added. The resulting suspension was heated under reflux for 3 h. The reaction mixture was cooled to room temperature. Unreacted zinc was filtered off and washed with ethyl acetate. The combined organic fractions were concentrated under reduced pressure; to the residue aq HCl (0.5 M) was slowly added. The resulting solution was washed with CH_2Cl_2 (5 mL). Then saturated aq $NaHCO_3$ was added portionwise until CO_2 evolution was ceased. The resulting mixture (pH 8) was extracted with ethyl acetate. The combined organic fractions were washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. Pure product **11** was obtained in 73% yield (82 mg) as viscous yellow oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.28 (s, 3H, CH_3), 2.31–2.47 (m, 3H, CH_2), 2.49–2.56 (m, 1H, CH_2), 3.68 (s, 3H, CH_3O), 3.97 (br.s, 2H, NH_2), 6.35 (br.d, ^4J = 1.9 Hz, 1H, Ind), 6.38 (dd, ^3J = 8.0, ^4J = 1.9 Hz, 1H, Ind), 7.00 (d, ^3J = 7.9 Hz, 2H, Ar), 7.04 (d, ^3J = 7.9 Hz, 2H, Ar), 7.05 (d, ^3J = 8.0 Hz, 1H, Ind); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 20.9 (CH_3), 29.5 (CH_2), 36.0 (CH_2), 52.9 (CH_3O), 59.3 (C), 97.8 (CH, Ar), 109.2 (CH, Ar), 117.8 (C, Ar), 124.5 (CH, Ar), 128.2 (2×CH, Ar), 129.0 (2×CH, Ar), 135.4 (C, Ar), 138.0 (C, Ar), 142.5 (C, Ar), 147.5 (C, Ar), 170.2 (*C*O_2Me), 177.2 (CONH); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{21}N_2O_3^+$ 325.1547; Found 325.1555.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Crystallographic data for **1g** and (3*RS*,6*RS*)-**8b** (CIF)

Details of quantum chemical calculations

Copies of ^{1}H and ^{13}C NMR spectra (PDF)

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