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ARTICLE TYPE

Tandem Halogenation/Michael-initiated Ring-closing Reaction of α,β-Unsaturated Nitriles and Activated Methylene Compounds: One-pot Diastereoselective Synthesis of Functionalized Cyclopropanes †

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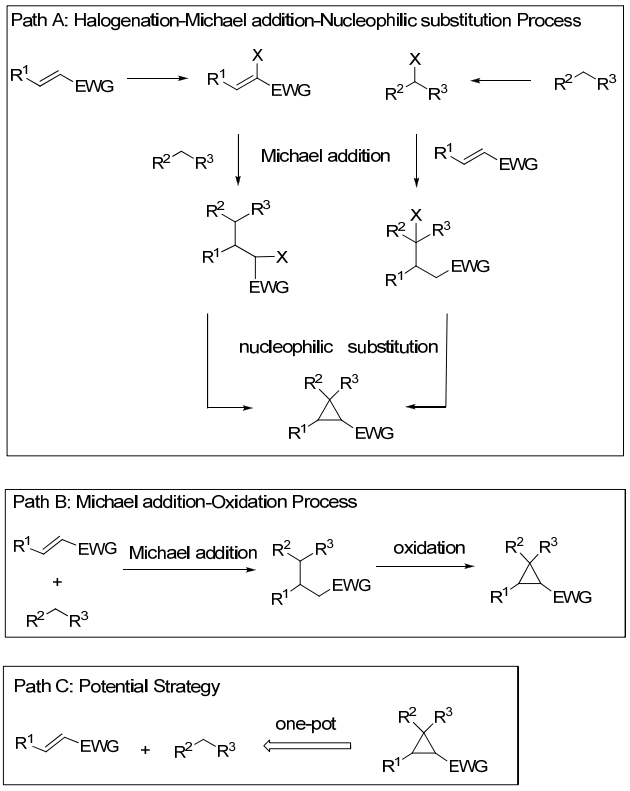
An efficient one-pot synthetic route to highly substituted cyclopropanes has been developed from readily available α,β-unsaturated nitriles and doubly activated methylene compounds under very mild conditions in highly diastereoselective manner, which involves halogenation, Michael addition and intramolecular ring-closing reaction sequences.

Introduction

Cyclopropanes have received considerable attention due to both their presence as a structural motif in a wide range of biologically active natural products and their ultilization as versatile intermediates in organic transformations.[1] The overwhelming importance of cyclopropane derivatives in organic synthesis has been recognized for their well-known 'unsaturated' character, which can lead to a variety of ring-opening reactants, such as electrophiles, nucleophiles and radicals.[2] So far, extensive work has generated many synthetic approaches for cyclopropanes, involving halomethylmetal-mediated cyclopropanation reaction (Simmons-Smith reaction),[3] base-prompted nucleophilic substitution of vicinal dihalides, [4] transition-metal-catalyzed decomposition of diazoalkanes [5] and Michael-initiated ring closing (MIRC) reaction.[6] Although there are exceptions, cyclopropanations *via* the MIRC reaction of acyclic olefins are usually non-stereospecific, and both (*E*)- and (*Z*)-olefins give the *trans*-cyclopropanes. It should be noted that the common MIRC reactions are a two-step strategy, in which the halogenations of activated methylene compounds or electron-deficient olefins proceeds in the first step, followed by Michael addition and base-mediated intramolecular nucleophilic substitution on the adduct (Scheme 1, path A).[7] Another MIRC strategy is oxidative cyclization of Michael adducts of electron-deficient olefins with activated methylene compounds (Scheme 1, path B).[8] To match the increasing scientific and practical demands, it is still of continued interest and great importance to explore new and straightforward methods to access to these highly strained cyclopropanes with more flexible substitution patterns along with high stereoselectivity.

During the course of our studies on heterocyclic chemistry based on 1,3-dicarbonyl compounds and their analogues,[9] we developed the synthesis of 2-pyridinones,[10] isoxazoles[11] and pyrazoles[11a] from a series of cyclopropanes, and achieved the synthesis of quinolin-2(1*H*)-ones[12] and 2-pyridinones[13] from α,β-unsaturated amides. In connection with our previous work, we are interested in exploring the possibility of synthesis of cyclopropanes directly from activated methylene compounds and electron-deficient alkenes (Scheme 1, path C). Herein, we wish to report our experimental results.



Scheme 1

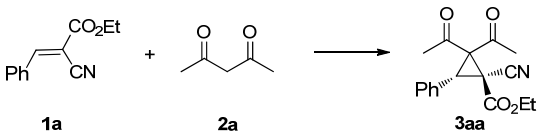
Results and discussion

The substrates, α,β-unsaturated nitriles **1a-q**, were prepared in good to excellent yields by the Knoevenagel condensation of nitriles with various aryl or hetero-aryl aldehydes under basic

conditions according to the reported procedure.[14] Thus, (*E*)-ethyl 2-cyano-3-phenylacrylate **1a** was selected from these substrates as a model compound and its reaction with acetylacetone **2a** was then attempted. Upon treatment of **1a** and **2a** (1.0 equiv) with *N*-bromosuccinimide (NBS, 1.0 equiv) in the presence of NaOH (2.0 equiv) in *N,N*-dimethylformamide (DMF) at room temperature for 24.0 h, a complex mixture was formed as indicated by TLC result and no product could be separated from the reaction system by silica gel column chromatography (Table 1, entry 1). Subjecting **1a** and **2a** to DMF in the presence of K_2CO_3 (2.0 equiv) at room temperature, the reaction could take place and furnished a colourless oil. The product was characterized as ethyl 2,2-diacetyl-1-cyano-3-phenylcyclo-propanecarboxylate **3aa** on the basis of its analytical data (Table 1, entry 2). It was worth noting that the reaction exhibited highly diastereoselectivity with a 95:5 ratio of *trans* and *cis* isomers determined by ^{1}H NMR.

The optimization of the reaction conditions, including bases, the feed ratio of the base, reaction solvents, halogenated reagents and reaction temperature were then examined. In the case of organic base 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) was employed, low conversion was observed (Table 1, entry 3), whereas in the presence of triethylamine (Et_3N), the reaction of **1a** with **2a** afforded **3aa** in 85% yield (Table 1, entry 4). The result suggested that the added base has significant influence on the reaction. The reaction could also proceed in other solvents, such as acetonitrile, ethanol and tetrahydrofuran (Table 1, entries 5-7). Actually DMF was proved to be the most efficient medium for the cyclopropanation. Other halogenated reagents, such as *N*-chlorosuccinimide (NCS) and iodine, were employed but were less active than NBS (Table 1, entries 8 and 9). The experiments revealed that 2.0 equiv of Et_3N was effective for the reaction of **1a** with **2a** to form **3aa** (Table 1, entries 10 and 11). Meanwhile, high reaction temperature, for example 80 ^{o}C, resulted in a low yield (Table 1, entry 12).

Table 1. Reaction of **1a** with **2a** under Different Conditions. [a]

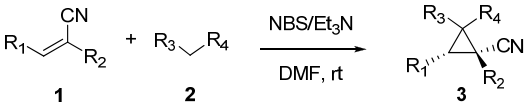


1a **2a** **3aa**

entry	base (equiv)	halogenated reagents	solvent	*T* (^{o}C)	time (h)	yield (%)[b]	*dr*[c]
1	NaOH (2.0)	NBS	DMF	rt	12.0	0	-
2	K_2CO_3 (2.0)	NBS	DMF	rt	1.0	67	>95:5
3	DBU (2.0)	NBS	DMF	rt	1.0	48	>95:5
4	**Et_3N (2.0)**	**NBS**	**DMF**	**rt**	**0.5**	**85**	**>95:5**
5	Et_3N (2.0)	NBS	CH_3CN	rt	0.5	79	>95:5
6	Et_3N (2.0)	NBS	EtOH	rt	1.0	62	>95:5
7	Et_3N (2.0)	NBS	THF	rt	12.0	54 (30)[d]	>95:5
8	Et_3N (2.0)	NCS	DMF	rt	1.0	trace	-
9	Et_3N (2.0)	I_2	DMF	rt	12.0	0	-
10	Et_3N (1.0)	NBS	DMF	rt	1.0	70 (18)[d]	>95:5
11	Et_3N (3.0)	NBS	DMF	rt	0.5	82	>95:5
12	Et_3N (2.0)	NBS	DMF	80	0.5	77	>95:5

[a] Reagents and conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), halogenated reagents (1.0 mmol), solvent (5.0 mL). [b] Isolated yields. [c] *trans*: *cis* determined by ^{1}H NMR. [d] Recovery of **1a** in parentheses.

Table 2. Synthesis of Cyclopropane **3** from α,β-Unsaturated Nitriles **1** and **2** at Room Temperature[a]



1 2 3

entry	1	R^1	R^2	2	R^3	R^4	3	yield (%)[b]	*dr*[c]
1	**1a**	Ph	CO_2Et	**2a**	Ac	Ac	**3aa**	85	>95:5
2	**1b**	4-ClC_6H_4	CO_2Et	**2a**	Ac	Ac	**3ba**	88	>95:5
3	**1c**	4-MeC_6H_4	CO_2Et	**2a**	Ac	Ac	**3ca**	82	>95:5
4	**1d**	4-$NO_2C_6H_4$	CO_2Et	**2a**	Ac	Ac	**3da**	90	>95:5
5	**1e**	3-MeC_6H_4	CO_2Et	**2a**	Ac	Ac	**3ea**	79	>95:5
6	**1f**	3-$NO_2C_6H_4$	CO_2Et	**2a**	Ac	Ac	**3fa**	86	>95:5
7	**1g**	2-ClC_6H_4	CO_2Et	**2a**	Ac	Ac	**3ga**	83	>95:5
8	**1h**	2-MeC_6H_4	CO_2Et	**2a**	Ac	Ac	**3ha**	82	>95:5
9	**1i**	2-$NO_2C_6H_4$	CO_2Et	**2a**	Ac	Ac	**3ia**	84	>95:5
10	**1j**	2-pyridyl	CO_2Et	**2a**	Ac	Ac	**3ja**	83	>95:5
11	**1k**	2-thienyl	CO_2Et	**2a**	Ac	Ac	**3ka**	86	>95:5
12	**1a**	Ph	CO_2Et	**2b**	CO_2Et	CO_2Et	**3ab**	80	>95:5
13	**1a**	Ph	CO_2Et	**2c**	CO_2Et	CO_2Et	**3ac**	82	>95:5
14	**1l**	Ph	C_6H_4NHCO	**2b**	CO_2Et	CO_2Et	**3lb**	83	>95:5
15	**1m**	4-ClC_6H_4	C_6H_4NHCO	**2b**	CO_2Et	CO_2Et	**3mb**	81	>95:5

[a] Reagents and conditions: **1** (1.0 mmol), **2** (1.0 mmol), NBS (1.0 mmol), Et_3N (2.0 mmol), solvent (5.0 mL). [b] Isolated yields.
[c] Determined by ^1H NMR..

To determine the scope and limitations of the cyclopropane synthesis, a series of reactions of α,β-unsaturated nitriles **1** with activated methylene compounds **2** were carried out under the identical conditions as for **3aa** in Table 1, entry 4. It was found that all the reactions of **1b-k** bearing aryl or hetero-aryl groups R^1 with **2a** proceeded smoothly to afford the corresponding multi-substituted cyclopropanes **3ba-ka** in good to high yields along with high diastereoselectivity (Table 2, entries 2-11). The *anti* relative stereochemistry of **3ba** was established by X-ray single crystal analysis (Figure 1) and its NMR spectral data. The efficiency of the cyclopropane synthesis proved to be suitable for dialkyl malonate **2b** or **2c** under the identical conditions (Table 2, entries 12 and 13). In the same fashion, 2-cyanoacrylamides **1l** and **1m** could react with **2b** to furnish the corresponding cyclopropanes **3lb** and **3mb** in good yields, respectively (Table 2, entries 14 and 15).

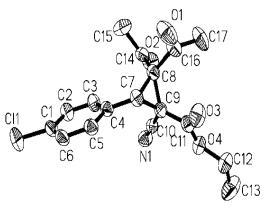
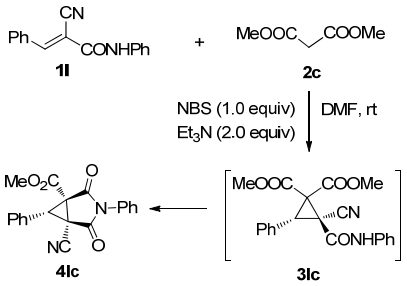


Figure 1. ORTEP drawing of **3ba**

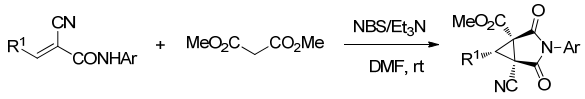
Next, we intended to expand the one-pot cyclopropanes synthesis to 2-cyanoacrylamides **1** and dimethyl malonate **2c** under the identical conditions described above. When **1l**, **2c** (1.0 equiv), Et_3N (2.0 equiv), and NBS (1.0 equiv) were subjected into DMF at room temperature, the reaction furnished a white solid after work-up and purification by column chromatography of the resulting reaction mixture. Interestingly, the product was characterized as methyl 5-cyano-2,4-dioxo-3,6-diphenyl-3-azabicyclo[3.1.0]hexane-1-carboxylate **4lc** on the basis of analytical data, instead of the corresponding cyclopropane of type **3**. The formation of **4lc** suggested that **3lc** could be generated in the reaction, but it quickly underwent an intramolecular imidation reaction as shown in Scheme 2. The NMR results of **4lc** revealed that this reaction proceeded in a high diastereoselective manner.

The 3-azabicyclo[3.1.0]hexane synthesis was proven to be suitable for 2-cyanoacrylamides **1m-q** with varied substituents and dimethyl malonate **2c** to afford the corresponding **4mc-4qc** in good to high yields (Table 3, entry 2-6). In very recent work on the oxidative cyclization of Michael adducts of electron-



Scheme 2. Reaction of α, β-Unsaturated Amide **1l** and Dimethyl Malonate **2c**

Table 3 Reactions of α,β-Unsaturated Amides **1** and Dimethyl malonate **2c** at Room Temperature [a]



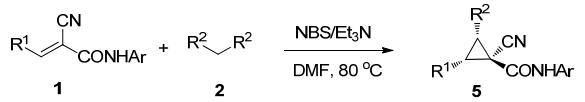
1 2c 4

entry	1	R^1	Ar	4	yield (%) [b]	*dr* [c]
1	**1l**	Ph	Ph	**4lc**	81	>95:5
2	**1m**	4-ClC_6H_4	Ph	**4mc**	83	>95:5
3	**1n**	4-MeC_6H_4	Ph	**4nc**	86	>95:5
4	**1o**	Ph	4-ClC_6H_4	**4oc**	84	>95:5
5	**1p**	Ph	4-MeC_6H_4	**4pc**	88	>95:5
6	**1q**	4-$MeOC_6H_4$	4-MeC_6H_4	**4qc**	77	>95:5

[a] Reagents and conditions: **1** (1.0 mmol), **2c** (1.0 mmol), NBS (1.0 mmol), Et_3N (2.0 mmol), DMF (5.0 mL), rt, 0.5-2.5 h. [b]Isolated yields. [c] Determined by ^1H NMR

deficient olefins with activated methylene compounds by Wang and coworkers, they also obtained the 3-azabicyclo[3.1.0] hexane but with very low yield.[8] Therefore, we provided a facile and efficient protocol for the synthesis of 3-azabicyclo[3.1.0] hexanes of type **4**.

Table 4. Reactions of α, β-Unsaturated Amides **1** and Dialkyl malonates **2** at 80 °C[a]



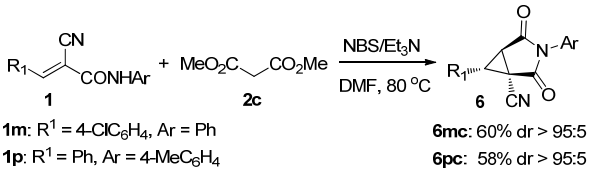
1 2 5

entry	1	R^1	Ar	R^2	5	yield (%) [b]	*dr* [c]
1	**1l**	Ph	Ph	CO_2Me	**5lc**	62	>95:5
2	**1n**	4-MeC_6H_4	Ph	CO_2Me	**5nc**	63	>95:5
3	**1o**	Ph	4-ClC_6H_4	CO_2Me	**5oc**	67	>95:5
4	**1l**	Ph	Ph	CO_2Et	**5lb** [d]	53	>95:5
5	**1m**	4-ClC_6H_4	Ph	CO_2Et	**5mb**	51	>95:5

[a] Reagents and conditions: **1** (1.0 mmol), **2c** (1.0 mmol), NBS (1.0 mmol), Et_3N (2.0 mmol), DMF (5.0 mL), 80 °C, 10.0-12.0 h. [b]Isolated yields. [c] Determined by ^1H NMR. [d] See ref. 8c.

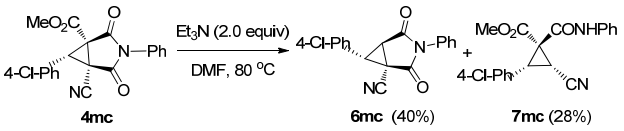
The above results encouraged us to examine the reaction of **1l**, **2c** (1.0 equiv) and NBS (1.0 equiv) performed with Et_3N (2.0 equiv) in DMF at 80 °C. It was not surprising that cyclopropane **5lc** was obtained as the predominant product (Table 4, entry 1). The NMR results of **5lc** revealed that this reaction proceeded in a high diastereoselective manner. Under the identical conditions, α, β-unsaturated amides **1n** and **1o** could react with NBS (1.0 equiv) and **2c** in the presence of Et_3N to afford cyclopropanes **5nc** and **5oc** in moderate yields, respectively (Table 4, entries 2 and 3). The synthetic efficiency was also evaluated by performing the reaction of α, β-unsaturated amides **1l** and **1m** with diethyl malonate **2b**, respectively (Table 4, entries 4 and 5). The *anti* relative stereochemistry **5lb** was established by ^1H NMR and confirmed by comparing with those reported data.[8c]

However, when 2-cyanoacrylamides **1m** or **1p** was treated with **2c** in the presence of NBS (1.0 equiv) and Et_3N (2.0 equiv) in DMF at 80 °C for 12.0 h, 2,4-dioxo-3-azabicyclo[3.1.0] hexane-1-carbonitriles **6mc** and **6pc** were obtained, respectively, as shown in Scheme 3. The results revealed that the substituents on the aryl groups R^1 and Ar of 2-cyanoacrylamides **1** had much influence on their reaction with dimethyl malonate **2c**. Possibly, compounds **6** could be generated from the tandem the ester hydrolysis, decarboxylation and intramolecular cyclization of **3** or the direct decarboxylation of **4**.



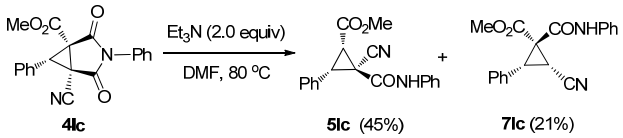
Scheme 3. Reactions of 2-Cyanoacrylamides **1** and Dimethyl malonate **2c** at 80 °C

Thus, the reaction of 2,4-dioxo-3-azabicyclo[3.1.0]hexane **4mc** with Et_3N (2.0 equiv) was performed in DMF at 80 °C for 5.0 h. Two products were obtained after work-up and purification by column chromatography of the resulting reaction mixture, which were characterized as 6-(4-chlorophenyl)-2,4-dioxo-3-phenyl-3-azabicyclo[3.1.0]hexane-1-carbonitrile **6mc** and methyl 2-(4-chlorophenyl)-3-cyano-1-(phenylcarbamoyl) cyclopropanecarboxylate **7mc**, respectively, on the basis of their analytical data (Scheme 4). The results suggested that **4mc** underwent a direct decarboxylation to give **6mc** and a tandem imide hydrolysis and decarboxylation to afford **7mc**.



Scheme 4. Ring-opening Reaction of 2,4-Dioxo-3-azabicyclo[3.1.0] hexane **4mc**

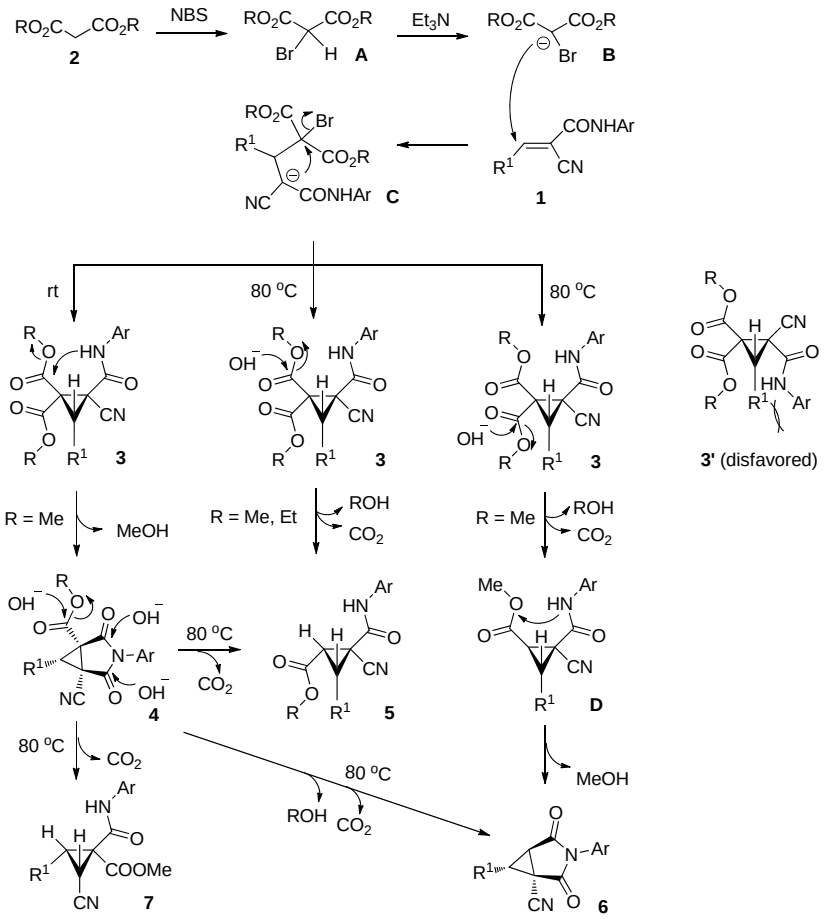
Under the identical conditions, the reaction of 2,4-dioxo-3-azabicyclo[3.1.0]hexane **4lc** was conducted. Two main products were obtained after work-up and purification by column chromatography of the resulting mixture, which were characterized as methyl 2-cyano-3-phenyl-2-(phenylcarbamoyl) cyclopropanecarboxylate **5lc** and methyl 2-cyano-3-phenyl-1-(phenylcarbamoyl)cyclopropanecarboxylate **7lc**, respectively (Scheme 5). These results revealed that **4lc** underwent regioselective imide hydrolysis and decarboxylation.



Scheme 4. Ring-opening Reaction of 2,4-Dioxo-3-azabicyclo[3.1.0] hexane **4lc**

On the basis of all the results obtained together with reported literature, a plausible mechanism for the diastereoselective synthesis of compounds **4-7** from the α,β-unsaturated amide **1** and the dialkyl malonate **2** is proposed. As shown in Scheme 6, the transformation commences from the halogenation of activated methylene compounds **2** to generate bromide **A**.[15] In

presence of Et_3N, the deprotonation of **A** leads to the formation of carbanion **B**, which can undergo intermolecular Michael addition to α,β-unsaturated amide **1** to give intermediate **C** followed by an intramolecular ring closure to afford cyclopropane **3**.[7,16] Due to the steric effect, the diastereomer **3'** of **3** is disfavored and not detected in the reaction system. At room temperature, the resulting cyclopropane **3** bearing methyl R undergoes further cyclization reaction to give azabicyclo [3.1.0]hexane **4**, which upon treatment at 80 °C can furnish **5**, **6** and **7** depended on its substituent groups R^1 and Ar. Also, cyclopropane **5** can be generated directly from the reaction of α,β-unsaturated amide **1** and activated methylene compound **2** at 80 °C through the hydrolysis of the ester group and subsequent decarboxylation of **3**.



Scheme 6. Plausible Mechanism of the Reaction of α,β-Unsaturated Amides **1** and Dialkyl Malonates **2**

Conclusions

In summary, a facile and efficient one-pot synthesis of highly functionalized cyclopropanes has been developed from readily electron-deficient alkenes and activated methylene compounds in moderate to good yields with high diastereoselectivity under very mild conditions, which involves halogenation, intermolecular Michael addition and cyclopropanation. This protocol, combining construction and modification of the cyclopropane skeleton, increases the structural diversity of final products from readily available starting materials. Further work on the utilization and extension of the scope of the methodology is currently under investigation in our laboratory.

Experimental

General

All reagents were purchased from commercial sources and used without further treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel. ^1H NMR and ^{13}C NMR spectra were recorded at 300 MHz, 400 MHz and 100 MHz, respectively, with TMS as internal standard. IR spectra (KBr) were recorded on a FTIR spectrophotometer in the range of 400-4000 cm^{-1}. Petroleum ether (PE) used was the fraction boiling in the range 60-90 °C.

Typical procedure for the synthesis of cyclopropanes 3 and 3-azabicyclo[3.1.0] hexanes 4 (3a as an example):

To a well-stirred solution of **1a** (1.0 mmol, 201 mg) and **2a** (1.0 mmol, 100 mg) in DMF (5.0 mL) was added NBS (1.0 mmol, 178 mg) and Et_3N (2.0 mmol, 202 mg) in one portio n at room temperature. The reaction mixture was then stirred for 0.5 h. After **1a** was consumed (monitored by TLC), the resulting mixture was poured into saturated aqueous NaCl (50 mL), which

was extracted with dichloromethane (3×20 mL). The combined organic phase was washed with water, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by flash silica gel chromatography (petroleum ether: ethyl acetate = 6:1, v/v) to give **3aa** as a colourless oil; yield 254 mg (85 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.37 (t, J = 7.2 Hz, 3H), 2.14 (s, 3H), 2.33 (s, 3H), 3.76 (s, 1H), 4.28-4.37 (m, 2H), 7.33-7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.9, 28.7, 30.0, 30.8, 40.5, 62.0, 64.2, 113.3, 128.5, 128.8, 128.9, 129.5, 164.7, 195.7, 196.7; IR (KBr): ν = 2993, 2924, 2245, 1740, 1711, 1364, 1273, 1207, 700, 503 cm^{-1}; Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.00; H, 5.74; N, 4.69.

3ba: yield 293 mg (88%); white solid; mp 97-100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35-1.39 (m, 3H), 2.17 (s, 3H), 2.33 (s, 3H), 3.71 (s, 1H), 4.28-4.37 (m, 2H), 7.28 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 28.7, 30.0, 30.8, 39.7, 61.6, 64.3, 113.1, 128.0, 129.1, 129.9, 135.0, 164.4, 195.4, 196.5; Anal. Calcd for $C_{17}H_{16}ClNO_4$: C, 61.18; H, 4.83; N, 4.20. Found: C, 60.85, H, 4.84; N, 4.18.

Crystal data for **3ba**: $C_{17}H_{16}ClNO_4$, white crystal, M = 333.76, triclinic, P -1, a = 7.7069(10) Å, b = 10.4968(14) Å, c = 11.1874(15) Å, α = 93.206(2) °, β = 102.273(2) °, γ = 104.014(2) °, V = 852.5(2) Å^3, Z = 8, T = 293 (2), F000 = 348.0. CCDC deposition number: 970838. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

3ca: yield 257 mg (82%); colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34-1.39 (m, 3H), 2.15 (s, 3H), 2.33 (s, 3H), 2.34 (s, 3H), 3.73 (s, 1H), 4.30-4.34 (m, 2H), 7.19-7.21 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 21.1, 28.7, 30.0, 30.8, 40.6, 61.9, 64.2, 113.4, 126.4, 128.4, 129.7, 138.9, 164.8, 195.9, 196.8; IR (KBr): ν = 3032, 2993, 2926, 2908, 2243, 1742, 1709, 1362, 1271, 1204, 1047, 843, 582 cm^{-1}; Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.72; H, 6.13; N, 4.46.

3da: yield 310 mg (90%); white solid; mp 125-126 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (t, J = 7.2 Hz, 3H), 2.24 (s, 3H), 2.38 (s, 3H), 3.82 (s, 1H), 4.31-4.41 (m, 2H), 7.55 (d, J = 8.8 Hz, 2H), 8.24 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 28.7, 29.9, 31.0, 39.2, 61.2, 64.6, 112.6, 123.8, 129.7, 136.7, 147.8, 164.0, 194.6, 196.2; IR (KBr): ν = 3119, 3090, 2991, 2941, 2249, 1755, 1717, 1607, 1522, 1352, 1259, 1227, 1078, 854, 698 cm^{-1}; Anal. Calcd for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.14. Found: C, 59.14; H, 4.69; N, 8.17.

3ea: yield 247 mg (79%); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, J = 6.6 Hz, 3H), 2.12 (s, 3H), 2.32 (s, 3H), 2.33 (s, 3H) 3.72 (s, 1H), 4.28-4.32 (m, 2H), 7.08-7.24 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 21.2, 28.6, 29.9, 30.6, 40.5, 61.8, 64.1, 113.2, 125.1, 128.7, 129.3, 129.4, 129.5, 138.7, 164.7, 195.7, 196.7; IR (KBr): ν = 3001, 2982, 2924, 2245, 1736, 1717, 1607, 1360, 1271, 1215, 1049, 997, 702 cm^{-1}; Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.21; H, 6.08; N, 4.46.

3fa: yield 296 mg (86%); white solid; mp 103-106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36-1.40 (m, 3H), 2.28 (d, J = 2.0 Hz, 3H), 2.40 (d, J = 2.0 Hz, 3H), 3.84 (s, 1H), 4.33-4.37 (m, 2H), 7.56-7.68 (m, 2H), 8.20-8.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 29.0, 30.1, 31.2, 39.3, 61.0, 64.6, 112.7, 123.7, 124.5, 130.0, 131.8, 134.2, 148.3, 164.1, 194.8, 196.5; IR (KBr): ν = 3088, 3005, 2989, 2249, 1744, 1705, 1529, 1350, 1275, 1215, 1095, 741 cm^{-1}; Anal. Calcd for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.14. Found: C, 59.12; H, 4.69; N, 8.15.

3ga: yield 276 mg (83%); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, J = 6.9 Hz, 3H), 2.30 (s, 3H), 2.55 (s, 3H), 3.84 (s, 1H), 4.31-4.35 (m, 2H), 7.31-7.52 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 29.6, 30.1, 32.3, 39.1, 58.5, 64.3, 112.8, 127.2, 128.0, 129.8, 129.8, 130.1, 134.3, 164.7, 194.2, 199.4; IR (KBr): ν = 3082, 2991, 2932, 2245, 1744, 1705, 1572, 1367, 1259, 1231, 851, 754 cm^{-1}; Anal. Calcd for $C_{17}H_{16}ClNO_4$: C, 61.18; H, 4.83; N, 4.20. Found: C, 60.86; H, 4.84; N, 4.18.

3ha: yield 257 mg (82%); yellow solid; mp 86-88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36-1.41 (m, 3H), 2.18 (d, J = 2.4 Hz, 3H), 2.37 (d, J = 2.8 Hz, 3H), 2.40 (d, J = 2.8 Hz, 3H), 3.82 (s, 1H), 4.33-4.39 (m, 2H), 7.19-7.33 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 19.8, 29.2, 30.2, 31.1, 39.5, 60.6, 64.3, 113.7, 126.3, 127.6, 128.1, 128.8, 131.0, 138.0, 164.7, 196.4, 197.8; IR (KBr): ν = 3119, 3103, 3020, 2997, 2241, 1724, 1364, 1283, 1219, 1009, 856, 716 cm^{-1}; Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.73; H, 6.10; N, 4.48.

3ia: yield 289 mg (84%); white solid; mp 121-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, J = 7.2 Hz, 3H), 2.31 (s, 3H), 2.61 (s, 3H), 4.18 (s, 1H), 4.32-4.42 (m, 2H), 7.53-7.60 (m, 2H), 7.69 (t, J = 7.2 Hz, 1H), 8.13 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 29.5, 30.0, 33.4, 39.9, 58.4, 64.5, 112.9, 125.2, 125.9, 129.6, 132.1, 133.8, 148.9, 164.5, 195.5, 199.8; IR (KBr): ν = 3007, 2966, 2926, 2249, 1740, 1717, 1514, 1342, 1205, 1045, 858, 739 cm^{-1}; Anal. Calcd for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.14. Found: C, 59.45; H, 4.66; N, 8.11.

3ja: yield 249 mg (83%); yellow solid; mp 102-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32-1.36 (m, 3H), 2.27-2.28 (m, 6H), 3.76 (s, 1H), 4.25-4.34 (m, 2H), 7.21-7.24 (m, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.69-7.73 (m, 1H), 8.48 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 28.1, 29.7, 31.8, 41.5, 62.2, 64.0, 112.9, 123.3, 125.1, 136.9, 148.6, 149.9, 164.8, 194.7, 196.3; IR (KBr): ν = 3047, 2997, 2945, 2247, 1724, 1705, 1358, 1286, 1223, 1205, 1013, 754 cm^{-1}; Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.64; H, 5.38; N, 9.29.

3ka: yield 262 mg (86%); yellow solid; mp 76-78 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, J = 6.9 Hz, 3H), 2.18 (s, 3H), 2.30 (s, 3H), 3.88 (s, 1H), 4.29-4.33 (m, 2H), 7.01-7.02 (m, 1H), 7.08 (br, 1H), 7.31-7.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 28.5, 29.4, 31.6, 35.9, 62.2, 64.2, 112.9, 126.3, 126.9, 127.6, 130.9, 164.2, 194.8, 195.8; IR (KBr): ν = 3024, 2984, 2926, 2245, 1740, 1703, 1369, 1238, 1219, 1095, 744 cm^{-1}; Anal. Calcd for $C_{15}H_{15}NO_4S$: C, 59.00; H, 4.95; N, 4.59. Found: C, 58.76; H, 4.94; N, 4.58.

3ab: yield 287 mg (80%); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (t, J = 7.2 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.39 (t, J = 7.2 Hz, 3H), 3.93 (s, 1H), 4.10-4.41 (m, 6H), 7.34-7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 13.8, 13.9, 30.7, 39.2, 47.8, 62.8, 63.0, 64.1, 112.7, 128.6, 128.6, 128.7, 129.7, 162.5, 163.8, 164.3; IR (KBr): v = 3092, 3063, 2986, 2941, 2249, 1747, 1732, 1369, 1258, 1070, 858, 698 cm^{-1}; Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.22; H, 5.87; N, 3.91.

3ac: yield 272 mg (82%); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (t, J = 7.2 Hz, 3H), 3.68 (s, 3H), 3.81 (s 3H), 3.93 (s, 1H), 4.26-4.44 (m, 2H), 7.35 (s, 5H); ^{13}C NMR (100 MHz, DMSO) δ 13.8, 30.7, 39.3, 47.6, 53.4, 53.5, 64.2, 112.4, 128.4, 128.6, 128.7, 129.3, 162.7, 164.2, 164.3; Anal. Calcd for $C_{17}H_{17}NO_6$: C, 61.63; H, 5.17; N, 4.23. Found: C, 61.43; H, 5.14; N, 4.22.

3lb: yield 337 mg (83%); yellow solid; mp 78-83 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H), 4.14-4.29 (m, 5H), 7.18-7.23 (m, 1H) 7.35-7.39 (m, 7H), 7.54 (d, J = 8.1 Hz, 2H), 8.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 13.8, 32.1, 38.5, 47.9, 62.7, 63.0, 115.1, 120.4, 125.7, 128.5, 128.6, 128.8, 129.2, 130.0, 136.5, 159.5, 163.0, 163.8; IR (KBr): v = 3371, 3342, 3059, 2989, 2939, 2245, 1742, 1693, 1545, 1445, 1312, 1234, 1072, 752 cm^{-1}; Anal. Calcd for $C_{23}H_{22}N_2O_5$: C, 67.97; H, 5.46; N, 6.89. Found: C, 67.64; H, 5.47; N, 6.87.

3mb: yield 356 mg (81%); yellow solid; mp 96-100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16-1.26 (m, 6H), 4.11 (s, 1H), 4.16-4.28 (m, 4H), 7.18-7.23 (m, 1H), 7.35-7.39 (m, 6H), 7.53 (d, J = 8.1 Hz, 2H), 8.47 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 13.8, 32.2, 37.7, 47.8, 62.8, 63.2, 114.8, 120.5, 125.8, 128.6, 129.0, 129.2, 130.0, 134.7, 136.4, 159.2, 162.9, 163.6; IR (KBr): v = 3383, 3335, 2991, 2984, 2239, 1738, 1691, 1537, 1499, 1447, 1312, 1234, 1094, 758 cm^{-1}; Anal. Calcd for $C_{23}H_{21}ClN_2O_5$: C, 62.66; H, 4.80; N, 6.35. Found: C, 62.45; H, 4.81; N, 6.38.

4lc: yield 280 mg (81%); white solid; mp 239-242 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (s, 1H), 3.80 (s, 3H), 7.26-7.29 (m, 2H), 7.45-7.51 (m, 8H); ^{13}C NMR (100 MHz, DMSO) δ 31.4, 43.6, 45.9, 53.5, 112.1, 128.0, 128.8, 129.4, 130.1, 131.7, 161.5, 166.2, 166.7; Anal. Calcd for $C_{20}H_{14}N_2O_4$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.11; H, 4.06; N, 8.12.

4mc: yield 315 mg (83%); white solid; mp 230-232 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.72 (s, 3H), 4.73 (s, 1H), 7.35-7.57 (m, 9H); ^{13}C NMR (100 MHz, DMSO) δ 31.1, 43.0, 44.7, 53.2, 111.6, 127.5, 128.7, 129.0, 130.4, 131.2, 133.8, 161.1, 165.6, 166.1; Anal. Calcd for $C_{20}H_{13}ClN_2O_4$: C, 63.08; H, 3.44; N, 7.36. Found: C, 63.31; H, 3.43; N, 7.34.

4nc: yield 310 mg (86%); white solid; mp 218-220 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.64 (s, 1H), 3.81 (s, 3H), 7.22-7.34 (m, 6H), 7.42-7.52 (m, 3H); ^{13}C NMR (100 MHz, DMSO) δ 21.1, 31.4, 43.8, 45.9, 53.5, 112.2, 127.0, 128.0, 128.7, 129.4, 129.9, 131.7, 139.0, 161.5, 166.3, 166.8; Anal. Calcd for $C_{21}H_{16}N_2O_4$: C, 69.99; H, 4.48; N, 7.77. Found: C, 69.60; H, 4.50; N, 7.74.

4oc: yield 319 mg (84%); white solid; mp 232-234 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 1H), 3.80 (s, 3H), 7.24-7.26 (m, 2H), 7.45 (s, 5H), 7.48 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO) δ 31.4, 43.7, 45.8, 53.5, 112.0, 128.8, 129.4, 129.4, 129.5, 129.8, 130.0, 130.5, 134.1, 161.4, 166.0, 166.4; Anal. Calcd for $C_{20}H_{13}ClN_2O_4$: C, 63.08; H, 3.44; N, 7.36. Found: C, 63.21; H, 3.45; N, 7.40.

4pc: yield 317 mg (88%); white solid; mp 231-232 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.67 (s, 1H), 3.79 (s, 3H), 7.14 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.44 (br, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 29.3, 42.2, 45.0, 52.7, 109.1, 125.1, 126.6, 127.0, 127.6, 128.1, 128.8, 129.1, 138.7, 159.2, 164.5, 164.8; Anal. Calcd for $C_{21}H_{16}N_2O_4$: C, 69.99; H, 4.48; N, 7.77. Found: C, 69.65; H, 4.46; N, 7.80.

4qc: yield 300 mg (77%); white solid; mp 222-224 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.61 (s, 1H), 3.81 (s, 3H), 3.83 (s, 3H), 6.94 (d, J = 8.7 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO) δ 21.1, 31.4, 44.0, 45.7, 53.5, 55.6, 112.3, 114.8, 121.8, 127.8, 129.1, 129.8, 130.2, 139.1, 160.1, 161.5, 166.4, 166.8; Anal. Calcd for $C_{22}H_{18}N_2O_5$: C, 67.69; H, 4.65; N, 7.18. Found: C, 67.40; H, 4.66; N, 7.20.

Typical procedure for the synthesis of cyclopropanes 5 and 3-azabicyclo[3.1.0] hexanes 6 (5lc as an example):

To a well-stirred solution of **1l** (1.0 mmol, 248 mg) and **2c** (1.0 mmol, 132 mg) in DMF (5.0 mL) was added NBS (1.0 mmol, 178 mg) and Et_3N (2.0 mmol, 202 mg) in one portion at 80 °C. The reaction mixture was stirred for 10.0 h and then poured into saturated aqueous NaCl (50 mL), which was extracted with dichloromethane (3×20 mL). The combined organic phase was washed with water, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by flash silica gel chromatography (petroleum ether: ethyl acetate = 6:1, v/v) to give **5lc** as a white solid; yield 198 mg (62%); mp 106-108 °C; ^{1}H NMR (300 MHz, DMSO) δ 3.19 (d, J = 10.2 Hz, 1H), 3.57 (d, J = 10.2 Hz, 1H), 3.69 (s, 3H), 7.12-7.17 (m, 1H), 7.35-7.37 (m, 7H), 7.64 (d, J = 8.1 Hz, 2H), 10.53 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 28.2, 31.7, 34.6, 52.4, 115.0, 120.7, 124.6, 127.9, 128.4, 128.8, 129.3, 138.1, 161.5, 166.1; Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 70.86; H, 5.01; N, 8.70.

5nc: yield 211 mg (63%); white solid; mp 126-129 °C; ^{1}H NMR (400 MHz, DMSO) δ 2.31 (s, 3H), 3.16 (d, J = 10.4 Hz, 1H), 3.51 (d, J = 10.4 Hz, 1H), 3.68 (s, 3H), 7.13-7.16 (m, 1H), 7.20 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.34-7.38 (m, 2H), 7.63 (d, J = 8.0 Hz, 2H), 10.48 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 27.6, 34.1, 36.8, 52.7, 115.8, 120.5, 125.6, 127.4, 128.9, 129.2, 129.5, 136.5, 138.3, 161.5, 166.1; Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.66; H, 5.45; N, 8.33.

5oc: yield 237 mg (67%); white solid; mp 122-124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.17 (d, J = 10.2 Hz, 1H), 3.59 (d, J = 10.2 Hz, 1H), 3.74 (s, 3H), 7.36 (s, 7H), 7.49-7.51 (m, 2H), 8.43 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.5, 34.2, 36.9, 52.7, 115.6, 121.7, 128.5, 128.8, 129.0, 129.2, 130.3, 130.8, 135.1, 161.5, 165.9; Anal. Calcd for $C_{19}H_{15}ClN_2O_3$: C, 64.32; H, 4.26; N, 7.90. Found: C, 64.53; H, 4.27; N, 7.93.

5lb: yield 177 mg (53%); yellow solid; mp 113-116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, J = 7.2 Hz, 3H), 3.15 (d, J = 10.5 Hz, 1H), 3.59 (d, J = 10.5 Hz, 1H), 4.17-4.19 (m, 2H), 7.18-7.23 (m, 1H), 7.37-7.41 (m, 7H), 7.54-7.56 (m, 2H), 8.42 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 27.4, 34.2, 36.7, 61.9, 115.8, 120.5, 125.6, 128.4, 128.7, 129.1, 129.2, 130.6, 136.5, 161.5, 165.5; Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.44; H, 5.45; N, 8.35.

5mb: yield 188 mg (51%); yellow solid; mp 114-117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, J = 7.2 Hz, 3H), 3.14 (d, J = 10.5 Hz, 1H), 3.54 (d, J = 10.5 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 7.19-7.23 (m, 1H), 7.29-7.40 (m, 6H), 7.54 (d, J = 8.4 Hz, 2H), 8.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 27.4, 34.1, 35.9, 62.1, 115.5, 120.5, 125.7, 128.9, 129.2, 130.5, 134.5, 136.4, 161.2, 165.4; Anal. Calcd for $C_{20}H_{17}ClN_2O_3$: C, 65.13; H, 4.65; N, 7.60. Found: C, 64.93; H, 4.66; N, 7.62.

6mc: yield 193 mg (60%); white solid; mp 240-243 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.44 (d, J = 4.5 Hz, 1H), 3.64 (d, J = 4.5 Hz, 1H), 7.26-7.30 (m, 4H), 7.44-7.53 (m, 5H); ^{13}C NMR (100 MHz, DMSO) δ 29.5, 32.7, 42.3, 114.2, 128.4, 129.8, 129.9, 131.1, 131.7, 132.4, 134.7, 168.2, 170.9; Anal. Calcd for $C_{18}H_{11}ClN_2O_2$: C, 66.99; H, 3.44; N, 8.68. Found: C, 66.83; H, 3.43; N, 8.72.

6pc: yield 175 mg (58%); white solid; mp 242-245 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.46 (d, J = 4.5 Hz, 1H), 3.64 (d, J = 4.5 Hz, 1H), 7.15 (d, J = 8.4 Hz, 2H), 7.28-7.33 (m, 4H), 7.44-7.46 (m, 3H); ^{13}C NMR (100 MHz, DMSO) δ 21.7, 29.5, 32.7, 43.1, 114.3, 128.2, 129.2, 129.7, 129.8, 129.9, 130.3, 132.6, 139.4, 168.4, 171.2; Anal. Calcd for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27. Found: C, 75.17; H, 4.66; N, 9.25.

Typical procedure for the synthesis of cyclopropanes 7lc:

To a well-stirred solution of **4lc** (1.0 mmol, 346 mg) in DMF (5.0 mL) was added Et_3N (2.0 mmol, 202 mg) in one portion at 80 °C. The reaction mixture was then stirred for 5.0 h. After **4lc** was consumed (monitored by TLC), the resulting mixture was poured into saturated aqueous NaCl (50 mL), which was extracted with dichloromethane (3×20 mL). The combined organic phase was washed with water, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by flash silica gel chromatography (petroleum ether: ethyl acetate = 6:1, v/v) to give **7lc** as a white solid; yield 67 mg (21%); mp 165-167 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.41-3.43 (m, 4H), 3.50 (d, J = 9.6 Hz, 1H), 7.17 (d, J = 7.2 Hz, 1H), 7.35-7.40 (m, 7H), 7.60 (d, J = 7.8 Hz, 2H), 10.7 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 37.7, 38.4, 52.4, 115.5, 120.3, 125.0, 128.3, 128.5, 128.7, 129.1, 131.3, 137.2, 162.8, 168.8; Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 70.95; H, 5.04; N, 8.77.

7mc: yield 99 mg (28%); white solid; mp 186-188 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.40 (d, J = 10.0 Hz, 1H), 3.46 (d, J = 10.0 Hz, 1H), 3.49 (s, 3H), 7.18 (t, J = 7.6 Hz, 1H), 7.37-7.39 (m, 6H), 7.58 (d, J = 8.0 Hz, 2H), 10.61 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 16.3, 31.7, 41.5, 52.8, 115.7, 119.6, 123.9, 128.4, 128.7, 130.7, 131.0, 132.5, 138.7, 162.7, 165.2; Anal. Calcd for $C_{19}H_{15}ClN_2O_3$: C, 64.32; H, 4.26; N, 7.90. Found: C, 64.11; H, 4.27; N, 7.93.

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