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Copper(0)-induced aminocyclopropanation of olefins via deselenation of *N*,*N*-disubstituted aromatic selenoamides

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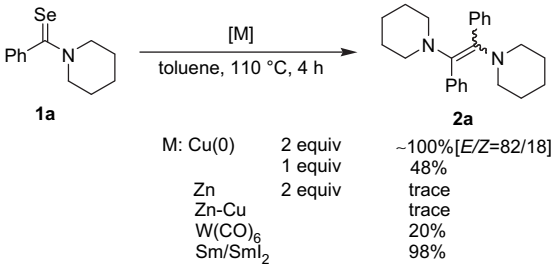
ABSTRACT

Upon heating of a mixture of *N*,*N*-disubstituted aromatic selenoamides and several electron-deficient olefins in the presence of copper(0) powder, a novel deselenative cyclopropanation takes place to afford the corresponding aminocyclopropanes in good yields. When acrylonitrile is employed as an electron-deficient olefin, the aminocyclopentanation occurs in preference to the aminocyclopropanation by prolonging the reaction time. The obtained aminocyclopropane derivatives can be converted to the corresponding 1,4-dicarbonyl compounds upon treatment with 2 N HCl.

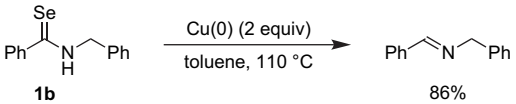
1. Introduction

N,*N*-Disubstituted selenoamides are among the most stable selenocarbonyl compounds and they can be prepared conveniently.[1] Therefore, the selenoamide is a useful candidate for investigation of the chemical properties of selenocarbonyl compounds bearing an adjacent heteroatom.[2] In 1991, we have reported the copper(0)-induced deselenative coupling reaction of selenoamides. For example, heating of *N*-(selenobenzoyl)piperidine (**1a**) in toluene at 110 °C in the presence of copper(0) afforded the corresponding 1,2-enediamine (**2a**) in good yield (Eq. 1).[3]

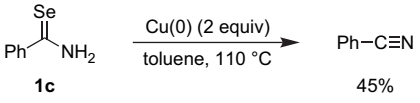


(1)

The driving forces of this deselenative coupling reaction are conceivably the higher affinity of selenium for soft metals such as copper and the high reactivity of carbon–selenium double bond.[4] Some other low-valent metal reagents such as Zn, Zn–Cu, and $W(CO)_6$ did not cause the deselenative coupling reaction satisfactorily, whereas the mixed system of Sm metal and SmI_2[5] as a powerful one-electron reducing reagent works well for this transformation.[6–8] When *N*-benzyl benzeneselenoamide (**1b**) and benzeneselenoamide (**1c**) were used as *N*-monosubstituted and *N*-unsubstituted selenoamides, the corresponding imine and nitrile were obtained as the deselenation products (Eqs. 2 and 3).



(2)



(3)

Although the precise mechanism for these deselenation reactions waits for the further detailed mechanistic investigations, a possible reaction pathway may involve the formation of α-aminocarbene species (or α-aminocarbenoids) as a key intermediate (**A**).[9]

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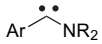
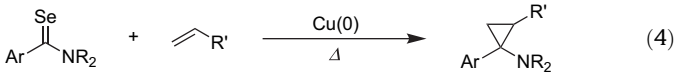


(**A**)

To capture the active intermediate (**A**) with olefins, we examined the copper(0)-induced reaction of *N*,*N*-disubstituted selenoamides in the presence of several olefins, and have found a novel aminocyclopropanation of olefins (Eq. 4).

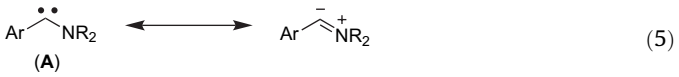


(4)

2. Results and discussions

We first examined the reaction of *N*-(selenobenzoyl)piperidine (**1a**) with several olefins in the presence of copper(0) powder (Table 1). In the cases of cyclohexene (**3a**) and *n*-butyl vinyl ether (**3b**), the copper(0)-induced thermal reaction of selenoamide (**1a**) afforded the deselenative coupling product (**2a**) in 56% and 25% (GLC) yields, respectively (entries 1 and 2). In sharp contrast, when *n*-butyl acrylate (**3c**) was employed for this reaction, a novel aminocyclopropanation of **3c** with **1a** took place successfully at 110 °C for 4 h, to give the corresponding aminocyclopropane (**4ac**)[10] in good yield (entries 3–5).

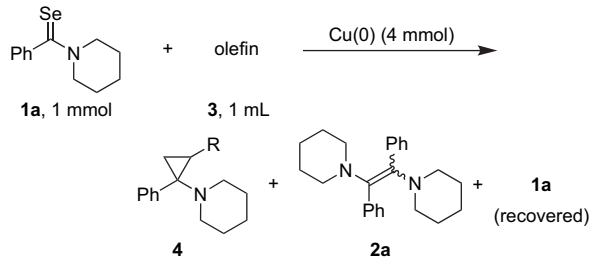
If the reaction involves the formation of α-aminocarbene species (**A**), they may have nucleophilic character through the conjugation shown in Eq. 5, and prefer the reaction with electron-poor olefins like **3c**.[11,12]



(5)

The representative results of the aminocyclopropanation of several olefins are summarized in Table 2. Methyl, ethyl, and *tert*-butyl acrylates (**3d**, **3e**, and **3f**) underwent aminocyclopropanation with *N*-(selenobenzoyl)piperidine (**1a**) to afford the corresponding aminocyclopropanes (**4ad**, **4ae**, and **4af**) in good yields, respectively (entries 2, 3, and 4). Similar conditions can be employed with methyl vinyl ketone (**3g**) and styrene (**3h**), **4ag** and **4ah** were obtained in moderate yields (entries 5 and 6). In the cases of allylbenzene and vinyl acetate, unfortunately, oligomerization of these olefins proceeded exclusively.

Table 1
Copper(0)-induced reaction of *N*-(selenobenzoyl)piperidine (**1a**) with several olefins (**3**)[a]



Entry	Olefin	Conditions	Yield[a] (%)		
			4	**2a**	**1a**
1	**3a**	(94 °C, 14 h)	—	56	44
2	**3b**	(83 °C, 7 h)	—	25	60
3	**3c**	(100 °C, 4 h)	**4ac**, 43	7	47
4		(110 °C, 4 h)	67 (66)	15	—
5		(130 °C, 4 h)	54	24	—

[a] GLC (isolated) yield.

Table 2
Copper(0)-induced aminocyclopropanation of olefins (**3**) with selenoamides (**1**)[a]

Entry	Selenoamide	Olefin	Product	Yield[b] (%)
1	**1a**	—$CO_2{}^nBu$ **3c**	**4ac**	66
2		—CO_2Me **3d**	**4ad**	68
3		—CO_2Et **3e**	**4ae**	70
4		—$CO_2{}^tBu$ **3f**	**4af**	75
5		—COMe **3g**	**4ag**	44
6		—Ph **3h**	**4ah**	46
7	**1d**	**3c**	**4dc**	34
8	**1e**	**3c**	**4ec**	68
9[c]	**1f**	**3c**	**4fc**	ND

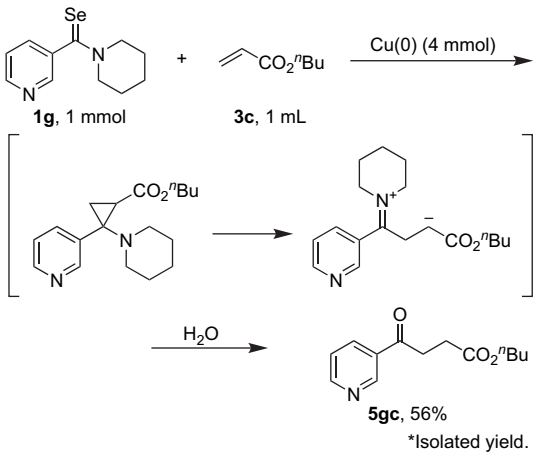
[a] Reaction conditions: selenoamide (**1a**, 1.0 mmol), olefins (**2**, 1 mL), Cu(0) (4.0 mmol), 110 °C, 4 h.
[b] Isolated yield.
[c] 1,2-Enediamine (**2f**) was obtained in 88% isolated yield (*E*/*Z*=84:16).

Next, we examined the reactions using several selenoamides. The thermal reaction of *N*,*N*-dimethyl benzeneselenoamide (**1d**) with *n*-butyl acrylate (**3c**) in the presence of copper(0) provided **4dc** in moderate yield (entry 7). Aromatic selenoamides such as *N*-(4-methyl-selenobenzoyl)piperidine (**1e**) also afforded the corresponding aminocyclopropane (**4ec**) in good yield (entry 8). On the other hand, *N*-(3-chloro-selenobenzoyl)piperidine (**1f**) did not provide the desired aminocyclopropane (**4fc**), but 1,2-enediamine (**2f**) was obtained in 88% (*E*/*Z*=84:16) yield (entry 9). Probably owing to the influence of Cl substituent on the reactivity of aminocarbene species, the aminocyclopropanation did not proceed.

When selenoamide (**1g**) was employed for this reaction, the corresponding aminocyclopropane was not obtained, but 1,4-dicarbonyl compound (**5gc**) was formed in 56% yield (Scheme 1). It was reported that aminocyclopropanes underwent hydrolysis to form the corresponding 1,4-dicarbonyl compounds.[13] Most probably due to the basic character of the pyridyl group, the generated aminocyclopropane might undergo hydrolysis to provide **5gc**.

The configuration of **4ec** was determined by DIFNOE-NMR experiments (Fig. 1). NOE was observed between H_a and both H_b and *o*-H of aryl group. Therefore, it is suggested that the piperidyl group holds a *Z*-position to the ester group.[14]

Next, we examined the reaction of selenoamide (**1a**) with acrylonitrile (**3i**) in the presence of copper(0) (Eq. 6). When the reaction was performed for 4 h, the corresponding aminocyclopropane carbonitrile (**4ai**) was obtained in 38% yield. Interestingly, the prolonged reaction time (14 h) resulted in the formation of aminocyclopentane dicarbonitrile (**6ai**), along with



Scheme 1. A plausible reaction pathway for the formation of 1,4-dicarbonyl compound (**5gc**).

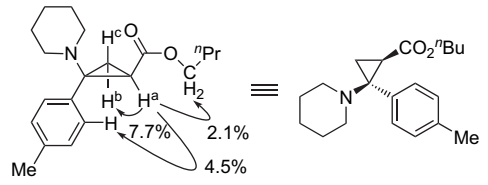
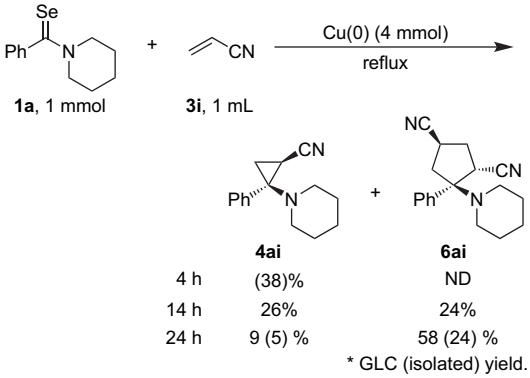


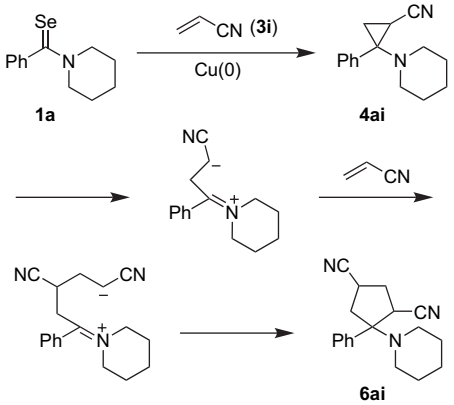
Figure 1. DIFNOE-NMR experiment and configuration of aminocyclopropane (**4ec**).

aminocyclopropane (**4ai**).[15] After the reaction was performed for 24 h, the reaction afforded **6ai** with good selectivity.[16]



(6)

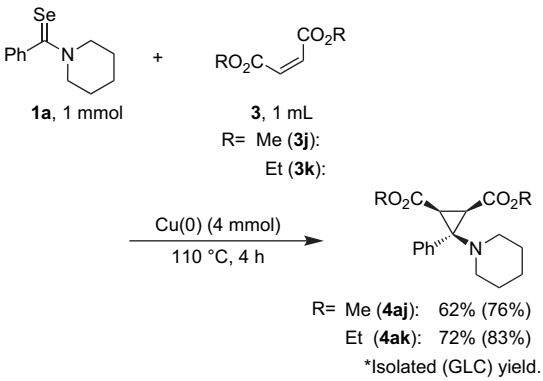
These results suggest that the cyclopentanation reaction may proceed via aminocyclopropane (**4ai**).[17] A plausible reaction pathway for this cyclopentanation reaction is indicated in Scheme 2:



Scheme 2. A plausible reaction pathway for the formation of aminocyclopentane (**6ai**).

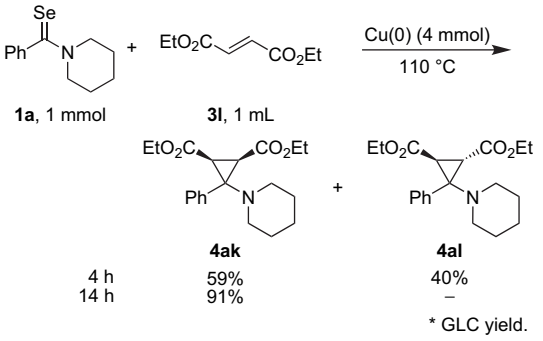
sequential insertion of **3i** into aminocyclopropane (**4ai**) may take place to give aminocyclopentane (**6ai**).

To clarify the stereoselectivity of the cyclopropanation, the copper(0)-induced reaction of a selenoamide with maleate or fumarate was attempted. In the cases of maleates (**3j** and **3k**), the deselenative cyclopropanation proceeded with excellent stereoselectivity, to afford the corresponding aminocyclopropanes (**4aj** and **4ak**), where two ester groups were located with *cis* relationship (Eq. 7).[18]



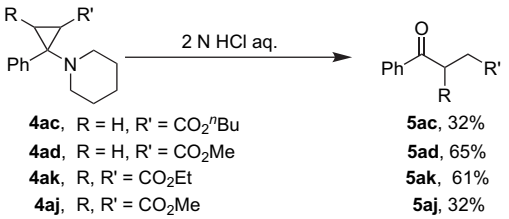
(7)

On the other hand, similar treatment of diethyl fumarate (**3l**) provided a mixture of *cis*- and *trans*-isomers (**4ak** and **4al**) (Eq. 8). Moreover, the prolonged reaction time led to the isomerization to give only the *cis*-isomer (**4ak**). This result suggests that the *trans*-isomer may be an initial product, which gradually converts to the corresponding *cis*-isomer.[19]



(8)

These aminocyclopropanation products are potentially useful synthetic intermediates.[20] For example, aminocyclopropanes can be easily converted into 1,4-dicarbonyl compounds by acidic hydrolysis.[13,21] 1,4-Dicarbonyl compounds are useful key intermediates for substituted cyclopentenones,[22] such as jasmones and prostaglandins, and for five-membered heterocyclic compounds,[23] such as furans, pyrroles, thiophenes, and pyridazines. Thus, we examined the hydrolysis of aminocyclopropanes to produce the corresponding 1,4-dicarbonyl compounds. Treatment of the aminocyclopropane bearing carbonyl group such as **4ac** with 2 N HCl led to deaminative ring-opening reaction to give the corresponding 1,4-dicarbonyl compound (**5ac**) in 32% yield (Eq. 9). Similar conditions could be employed with **4ad**, **4aj**, and **4ak**, and the corresponding 1,4-dicarbonyl products **5ad**, **5aj**, and **5ak** were obtained in good yields, respectively.



(9)

3. Conclusion

In summary, we have described the copper(0)-induced cyclopropanation of several electron-deficient olefins (**3**) via deselenation of selenoamides (**1**) to afford aminocyclopropanes (**4**). Aminocyclopropanes can be easily converted to 1,4-dicarbonyl compounds by treatment with 2 N HCl. Further studies on the precise mechanism of this cyclopropanation is now in progress.

4. Experimental section

4.1. Synthesis of selenoamides, e.g., *N*-(selenobenzoyl)-piperidine (1a)[1b]

A stirred mixture of benzonitrile (1.2 mL, 11.8 mmol), selenium (1.05 g, 13.1 mmol), H_2O (2.4 mL, 133 mmol), Et_3N (2.4 mL, 17.3 mmol), and THF (10 mL) in a 50 mL stainless steel autoclave was heated under the pressure of CO (1.5 MPa: initial pressure at 25 °C) at 110 °C for overnight. After the reaction, CO was purged in the well-ventilated hood, and to the reaction mixture was added piperidine (2.0 mL, 19.7 mmol), and then the resulting mixture was heated in an autoclave at 110 °C for 4 h. After the reaction, the reaction mixture was slightly acidified with aqueous 2 N HCl and extracted with Et_2O. The combined extracts were dried over $MgSO_4$, filtered, and evaporated. The crude material was purified by column chromatography on silica gel affording 1.28 g (43%) of *N*-(selenobenzoyl)piperidine (**1a**) as a yellow crystal (mp 89 °C).

4.2. General procedure for copper(0)-induced cyclopropanation of selenoamide with electron-deficient olefins

A mixture of *N*-(selenobenzoyl)piperidine (**1a**, 253 mg, 1.0 mmol), diethyl maleate (**3k**, 1.0 mL, 7.0 mmol), and copper(0) powder (252 mg, 4.0 mmol) was stirred at 110 °C for 4 h under nitrogen atmosphere. The reaction mixture was cooled to room temperature and copper powder was filtered through a Celite pad, and excess olefin was removed from the filtrate under reduced pressure. Purification was performed by GPC, yielding 248 mg (72%) of (*Z*)-3-phenyl-3-piperidin-1-yl-cyclopropane-1,2-dicarboxylic acid diethyl ester (**4ak**). Then, **4ak** afforded 135 mg (61%) of 2-benzoyl-succinic acid diethyl ester (**5ak**) after work up with aqueous 2 N HCl.

*4.2.1. 2-Phenyl-2-piperidin-1-yl-cyclopropanecarboxylic acid n-butyl ester (**4ac**)*

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, J=7.3 Hz, 3H), 1.33–1.52 (m, 6H), 1.57–1.71 (m, 6H), 2.42–2.53 (m, 3H), 2.55 (dd, J=7.3, 7.8 Hz, 1H), 2.73 (dd, J=7.3, 7.8 Hz, 1H), 4.08 (t, J=6.4 Hz, 2H), 7.31–7.71 (m, 4H), 7.95–8.09 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 19.1, 24.0, 25.5, 30.6, 31.8, 53.9, 54.0, 64.3, 126.7, 128.4, 129.0, 129.9, 132.9, 136.5, 172.6; IR (NaCl) 2936, 2856, 1732, 1672, 1597, 1448, 1379, 1275, 1211, 1175, 1113, 1072, 1028, 1028, 1001, 644 cm^{-1}; MS (EI) m/z 301 (M^+, 5); HRMS (CI) calcd for $C_{19}H_{28}NO_2$ (M^++1): 302.2120, found 302.2126.

*4.2.2. 2-Phenyl-2-piperidin-1-yl-cyclopropanecarboxylic acid methyl ester (**4ad**)*

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26–1.36 (m, 2H), 1.41–1.78 (m, 6H), 2.43 (m, 3H), 2.53 (dd, J=6.8, 7.8 Hz, 1H), 2.68 (dd, J=6.8, 7.3 Hz, 1H), 3.68 (s, 3H), 7.29–7.70 (m, 3H), 7.92–8.09 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.2, 24.5, 25.8, 27.1, 31.9, 51.6, 54.1, 126.7, 128.3, 129.0, 130.0, 134.9, 136.4, 173.1; IR (NaCl) 2936, 2853, 2806, 1740, 1672, 1636, 1597, 1443, 1275, 1155, 1113, 1001, 854, 700, 644 cm^{-1}; MS (EI) m/z 259 (M^+, 0.3); HRMS (EI) calcd for $C_{16}H_{21}NO_2$ (M^+): 259.1572, found 259.1554.

*4.2.3. 2-Phenyl-2-piperidin-1-yl-cyclopropanecarboxylic acid ethyl ester (**4ae**)*

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J=7.4 Hz, 3H), 1.39–1.72 (m, 6H), 2.12–2.48 (m, 5H), 2.53 (dd, J=7.3, 7.8 Hz, 1H), 2.70 (dd, J=7.3, 7.8 Hz, 1H), 4.14 (t, J=7.3 Hz, 2H), 7.52 (t, J=7.8 Hz, 2H), 7.67 (t, J=7.3 Hz, 1H), 7.98 (d, J=10.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 24.0, 25.7 (2C), 32.1 (2C), 54.1 (2C), 60.2, 124.9, 127.9, 129.0, 129.9, 133.0, 134.8, 172.6; IR (NaCl) 2963, 2936, 2840, 1732, 1672, 1597, 1448, 1211, 1175, 1159, 1113, 1024, 719, 687, 644 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{23}NO_2$ (M^+): 273.1729, found 273.1723.

*4.2.4. 2-Phenyl-2-piperidin-1-yl-cyclopropanecarboxylic acid tert-butyl ester (**4af**)*

A pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.58 (br s, 13H), 1.57 (m, 3H), 2.23–2.52 (m, 5H), 2.63 (dd, J=7.3, 7.8 Hz, 1H), 7.40–7.70 (m, 3H), 7.89–8.11 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.2, 25.8, 28.0, 33.4, 52.8, 54.1, 54.3, 80.1, 127.8, 128.2, 128.8, 129.5, 130.8, 133.0, 172.0; IR (NaCl) 2934, 2853, 2777, 2739, 1730, 1638, 1443, 1367, 1354, 1302, 1273, 1252, 1150, 1113, 1072, 1032, 995, 849,756, 706 cm^{-1}; HRMS (CI) calcd for $C_{19}H_{28}NO_2$ (M^++1): 302.2120, found 302.2115.

*4.2.5. 1-(2-Phenyl-2-piperidin-1-yl-cyclopropyl)-ethanone (**4ag**)*

A pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (br s, 2H), 1.50–1.80 (m, 4H), 2.16 (s, 3H), 2.29–2.54 (m, 2H), 2.56–2.77 (m, 3H), 2.77 (dd, J=7.2, 8.0 Hz, 1H), 2.91 (dd, J=6.8, 7.6 Hz, 1H), 7.21–7.68 (m, 3H), 7.91–8.12 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 24.0, 25.7, 30.1, 38.2, 41.2, 53.3, 53.7, 54.4, 125.6, 126.5, 128.3, 129.9, 130.5, 142.8, 199.4; IR (NaCl) 2936, 2855, 2804, 1713, 1668, 1614, 1450, 1360, 1306, 1117, 1028, 976, 700, 667, 644 cm^{-1}; HRMS (CI) calcd for $C_{16}H_{22}NO$ (M^++1): 244.1701, found 244.1700.

*4.2.6. N-(1,2-Diphenyl-cyclopropyl)piperidine (**4ah**)*

A light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (m, 2H), 1.26 (m, 4H), 1.38 (dd, J=8.3, 1.0 Hz, 2H), 2.11 (m, 2H), 2.33 (t like, 3H), 7.14–7.32 (m, 8H), 7.45 (d, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 24.4, 26.1, 32.0, 50.8, 55.8, 125.4, 126.9, 127.1, 127.5, 128.3, 130.5, 138.8; IR (NaCl) 3056, 3023, 2932, 2801, 1601, 1497, 1443, 1319, 1247, 1118, 1032, 767, 748, 696 cm^{-1}; MS (FAB) m/z 278 (M^++1, 17).

*4.2.7. 2-(N,N-Dimethylamino)-2-phenyl-cyclopropanecarboxylic acid n-butyl ester (**4dc**)*

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J=7.2 Hz, 3H), 1.24 (m, 2H), 1.50 (m, 2H), 1.92–2.15 (m, 1H), 2.16–2.21 (m, 6H), 2.41–2.51 (m, 1H), 3.21–3.27 (m, 1H), 4.02 (m, 2H), 7.24–7.46 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 19.0, 27.3, 30.5, 40.1, 49.9, 52.5, 64.4, 64.5, 127.5, 127.7, 127.9, 128.3, 128.5, 133.2, 174.8; IR (NaCl) 2959, 2874, 2781, 1732, 1690, 1454, 1352, 1173, 1123, 1072, 1026, 758, 702 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{24}NO_2$ (M^++1): 262.1807, found: 262.1816.

*4.2.8. 2-Piperidin-1-yl-2-p-tolyl-cyclopropanecarboxylic acid n-butyl ester (**4ec**)*

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, J=7.2 Hz, 3H), 1.29–1.50 (m, 4H), 1.56–1.76 (m, 6H), 2.16–2.49 (m, 8H), 2.53 (dd, J=7.2, 7.6 Hz, 1H), 2.69 (dd, J=6.8, 7.6 Hz, 1H), 4.10 (t like, 2H), 7.15–7.35 (m, 2H), 7.85–7.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 19.0, 24.1, 25.6, 30.5, 32.0, 54.1, 64.1, 126.8, 128.8, 129.5, 129.8, 130.5, 139.2, 172.6; IR (NaCl) 2930, 2851, 2781, 1736, 1686, 1508, 1447, 1377, 1230, 1184, 1173, 1151, 1113, 1032, 1001, 908, 853, 820, 733 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{29}NO_2$ (M^+): 315.2198, found: 315.2205.

*4.2.9. 4-Oxo-4-pyridin-3-yl-butyric acid n-butyl ester (**5gc**)*

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, J=7.2 Hz, 3H), 1.36 (m, 2H), 1.62 (m, 2H), 2.80 (t, J=6.4 Hz, 2H), 3.33 (t, J=6.4 Hz,

2H), 4.11 (t, *J*=6.6 Hz, 2H), 7.43 (m, 1H), 8.26 (d, *J*=8.0 Hz, 1H), 8.80 (d, *J*=3.2 Hz, 1H), 9.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 19.0, 27.9, 30.5, 33.5, 64.7, 123.6, 131.7, 135.2, 149.6, 153.6, 172.7, 197.1; IR (NaCl) 2961, 2934, 2874, 1732, 1693, 1585, 1420, 1315, 1171, 1069, 1026, 945, 704 cm^{-1}; HRMS (CI) calcd for $C_{13}H_{18}NO_3$ (M^++1): 236.1286, found: 236.1290.

4.2.10. 2-Phenyl-2-piperidin-1-yl-cyclopropane carbonitrile (**4ai**)

A pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.54 (m, 2H), 1.58–1.81 (m, 6H), 2.39–2.45 (m, 3H), 2.51 (dd, *J*=7.2, 7.2 Hz, 1H), 2.68 (dd, *J*=7.2, 7.6 Hz, 1H), 7.52 (dd, *J*=7.2, 8.0 Hz, 2H), 7.67 (dd, *J*=6.4, 7.2 Hz, 1H), 7.98 (d, *J*=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.6, 24.0, 25.7, 31.2, 34.2, 54.0, 54.1, 110.9, 129.0, 129.9, 134.9, 139.4; IR (NaCl) 2936, 2853, 2808, 2775, 2739, 2249, 1470, 1448, 1354, 1277, 1211, 1157, 1117, 1043, 991, 862, 754, 669 cm^{-1}; MS (EI) *m*/*z* 226 (M^+, 20); HRMS (EI) calcd for $C_{15}H_{18}N_2$ (M^+): 226.1470, found 226.1467.

4.2.11. 4-Phenyl-4-piperidin-1-yl-cyclopentane-1,3-dicarbonitrile (**6ai**)

A pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13–1.73 (m, 6H), 2.00–2.77 (m, 4H), 3.01 (dd, *J*=3.6, 18.2 Hz, 1H), 3.16 (dd, *J*=5.8, 17.4 Hz, 1H), 3.33 (dd, *J*=9.6, 18.2 Hz, 1H), 3.47–3.66 (m, 1H), 3.80 (d, *J*=9.6 Hz, 1H), 4.00–4.17 (m, 1H), 7.13–8.19 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0, 24.4, 25.7, 26.0, 26.2, 28.8, 39.2, 60.5, 61.5, 71.1, 111.3, 126.4, 128.2, 128.4, 128.6, 128.7, 134.7; IR (NaCl) 3059, 2936, 2855, 2808, 2741, 2245, 1628, 1578, 1447, 1493, 1375, 1352, 1275, 1259, 1238, 1157, 1115, 1028, 1003, 854, 787, 754, 706, 642 cm^{-1}; MS (EI) *m*/*z* 279 (M^+, 10); HRMS (EI) calcd for $C_{18}H_{21}N_3$–C_3H_3N (M^+−53.0277): 226.1459, found 226.1467.

4.2.12. 3-Phenyl-3-piperidin-1-yl-cyclopropane-1,2-dicarboxylic acid dimethyl ester (**4aj**)

A light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41–1.82 (m, 6H), 2.98 (s, 2H), 3.00–3.14 (m, 4H), 3.61 (s, 3H), 3.72 (s, 3H), 7.03–7.43 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9, 26.8, 36.1, 36.9, 50.7, 51.4, 52.0, 94.8, 127.8, 128.4, 129.0, 129.3, 129.7, 137.9, 163.5, 167.5; IR (NaCl) 3057, 2937, 2854, 1738, 1682, 1556, 1489, 1435, 1367, 1265, 1169, 1105, 1072, 1005, 953, 922, 770, 733, 667, 648 cm^{-1}; MS (EI) *m*/*z* 317 (M^+, 21); HRMS (FAB) calcd for $C_{18}H_{24}NO_4$ (M^++1): 318.1705, found: 318.1700.

4.2.13. 3-Phenyl-3-piperidin-1-yl-cyclopropane-1,2-dicarboxylic acid diethyl ester (**4ak**)

A light yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) [*Z*-isomer] δ 1.11–1.34 (m, 6H), 1.49–1.68 (m, 6H), 2.96 (s, 2H), 3.02 (t, *J*=5.1 Hz, 4H), 4.08 (q, *J*=7.3 Hz, 2H), 4.18 (q, *J*=7.3 Hz, 2H), 7.28–7.40 (m, 5H); [*E*-isomer] δ 1.00 (t, *J*=7.3 Hz, 3H), 1.29 (t, *J*=7.3 Hz, 3H), 1.36–1.55 (m, 6H), 2.25–2.55 (m, 4H), 2.83 (q, *J*=9.2 Hz, 2H), 3.88 (q, *J*=7.3 Hz, 2H), 4.10–4.30 (m, 2H), 7.15–7.50 (m, 5H); ^{13}C NMR (68 MHz, $CDCl_3$) [*Z*-isomer] δ 14.2, 14.5, 24.0, 26.8, 26.9, 37.3, 52.1, 59.2, 60.0, 127.8, 128.4, 128.9, 129.6, 129.9, 138.1, 163.2, 167.1; [*E*-isomer] δ 13.8, 14.3, 24.1, 26.1, 34.0, 35.7, 50.9, 60.4, 60.8, 127.6, 127.8, 129.4, 129.7, 129.9, 132.7, 167.9, 168.9; IR (NaCl) 2979, 2934, 2854, 1736, 1682, 1555, 1445, 1421, 1366, 1301, 1263, 1175, 1101, 1033, 1009, 919, 881, 768, 731, 704 cm^{-1}; MS (EI) *m*/*z* 345 (M^+, 18); HRMS (EI) calcd for $C_{20}H_{27}NO_4$ (M^+) 345.1940, found 345.1934.

4.2.14. n-Butyl 3-benzoylpropionate (**5ac**)

Yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.92 (t, *J*=7.6 Hz, 3H), 1.37 (m, 2H), 1.62 (m, 2H), 2.77 (t, *J*=6.6 Hz, 2H), 3.31 (t, *J*=6.61 Hz, 2H), 4.10 (t, *J*=6.9 Hz, 2H), 7.44–7.57 (m, 3H), 7.97–8.00 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.7, 19.1, 28.2, 30.6, 33.4, 64.5, 128.0, 128.6, 133.1, 136.6, 172.9, 198.1; IR (NaCl) 2977, 2934, 2854, 1736, 1682, 1555, 1445, 1421, 1366, 1301, 1236, 1175, 1101, 1033, 1009, 919, 881, 768, 731, 704 cm^{-1}; MS (EI) *m*/*z* 234 (M^+, 5); HRMS (CI) calcd for $C_{14}H_{19}O_3$ (M^++1) 235.1334, found 235.1338.

4.2.15. Methyl 3-benzoylpropionate (**5ad**)

A light yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.77 (t, *J*=6.6 Hz, 2H), 3.33 (t, *J*=6.6 Hz, 2H), 3.71 (s, 3H), 7.39–8.01 (m, 5H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 28.0, 33.4, 51.8, 126.7, 128.0, 128.6, 133.2, 173.3, 198.0; IR (NaCl) 2998, 2951, 2854, 1740, 1687, 1597, 1581, 1449, 1438, 1357, 1221, 1168, 1002, 750, 692 cm^{-1}; MS (EI) *m*/*z* 192 (M^+, 5).

4.2.16. 2-Benzoyl-succinic acid diethyl ester (**5ak**)

A pale yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.12–1.25 (m, 6H), 2.96–3.15 (m, 2H), 4.08–4.17 (m, 4H), 4.87 (t, *J*=7.2 Hz, 1H), 7.45–7.62 (m, 3H), 8.02–8.65 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.7, 13.9, 33.1, 49.4, 60.8, 61.6, 128.5, 128.7, 133.5, 135.8, 168.5, 171.0, 194.0; IR (NaCl) 2983, 1736, 1686, 1597, 1581, 1448, 1370, 1330, 1271, 1177, 1096, 1029, 951, 858, 741, 690 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{18}O_5$ (M^+) 278.1154, found 278.1157.

4.2.17. 2-Benzoyl-succinic acid dimethyl ester (**5aj**)

Yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.00 (t, *J*=6.4 Hz, 2H), 3.60 (s, 6H), 4.82 (t, *J*=7.3 Hz, 1H), 7.39–7.55 (m, 3H), 7.95–7.98 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 33.0, 49.2, 52.0, 52.7, 128.7, 128.8, 133.7, 135.7, 169.1, 171.6, 193.9; IR (NaCl) 2933, 2873, 1736, 1682, 1555, 1445, 1421, 1366, 1301, 1263, 1175, 1101, 1033, 1009, 919, 881, 768, 731, 704 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{15}O_5$ (M^++1) 251.0919, found 251.0924.

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