Stereoselective Synthesis of 1-Aminocyclopropanecarboxylic Acid Derivatives via Ylide Cyclopropanation of Dehydroamino Acid Derivatives

Zhou, Rui[a](周锐) Deng, Xianming[b](邓贤明) Zheng, Juncheng*[,b](郑君成)
Shen, Qi*[,a](沈琪) Sun, Xiuli[b](孙秀丽) Tang, Yong[a,b](唐勇)

[a] *Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou, Jiangsu 215123, China*
[b] *State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, 345 Lingling Lu, Shanghai 200032, China*

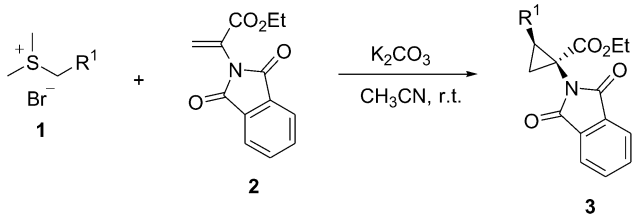
1-Aminocyclopropanecarboxylic acid derivatives are synthesized from readily available dehydroamino acid derivatives via sulfur ylide. A range of different ylides are employed and the corresponding aminocyclopropanes are afforded with reasonable diastereoselection in good yields.

Keywords amino acids, enantioselectivity, annulation, ylides, stereoselective synthesis

1-Aminocyclopropanecarboxylic acids (ACCs) have received considerable attention because of their biological activity, their potential applications in conformationally restricted peptides, as well as biosynthetic and mechanistic probes.[1,2] Although ylides proved to be efficient reagents for preparing enantioselective and diastereoselective construction of the cyclopropanes,[3,4] the synthesis of optical 1-aminocyclopropanecarboxylic acid derivatives via chiral ylide approach have not been studied systematically.[5] Of the synthetic methods developed for 1-aminocyclopropanecarboxylic acids,[5a,6] the reaction between ylide and dehydroamino acid derivatives proved to be a very competitive way, especially when considering stereoselection.[7] In this paper, we wish to report our efforts on the synthesis of 1-aminocyclopropanecarboxylic acid derivatives via sulfur ylides.

Our investigation was commenced with the cyclopropanation between stabilized sulfonium ylide and easily available dehydroamino acid derivatives. Fortunately, we found that amide-stabilized sulfonium salt **1a**, after deprotonation by K_2CO_3 in CH_3CN, could react with dehydroamino acid derivative **2** to afford cyclopropane amino acid ester **3a** with excellent diastereoselectivity (＞99/1) in 98% yield (Table 1, Entry 1). Under the same reaction conditions, a range of other stabilized sulfonium salt was then explored. As shown in Table 1, less steric amide did not deteriorate the cyclopropanation (Entries 2 and 3). In addition, ester stabilized ylide was found to be suitable to provide desired amino acid derivative in excellent yield and unique diastereoselection (Entries 4 and 5). Although a slight decrease of *d.r.* was observed when ketone stabilized sulfonium ylide was employed, product **3f** was obtained in 96% yield and 30/1 *d.r.*

Table 1 Cyclopropanation of stable sulfonium ylide with dehydroamino acid derivative **2**[a]



Entry	R^1	Yield[b]/%	d.r.[c]
1	CON^iPr_2 (**1a**)	98	＞99/1
2	$CONEt_2$ (**1b**)	96	＞99/1
3	$CONMe_2$ (**1c**)	95	＞99/1
4	$CO_2{}^tBu$ (**1d**)	95	＞99/1
5	CO_2Et (**1e**)	92	＞99/1
6	COPh (**1f**)	96	30/1

[a] To a stirred solution of salt **1** (0.3 mmol) and substrate **2** (49 mg, 0.2 mmol) in CH_3CN (2 mL) was added K_2CO_3 (62 mg, 0.3 mmol) in one portion at ambient temperature. [b] Isolated yield; [c] Determined by ^1H NMR.

* E-mail: tangy@sioc.ac.cn.; Fax: 0086-021-54925078.
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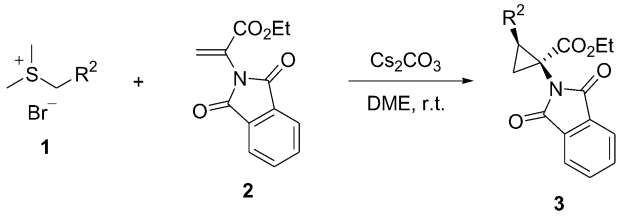
The cyclopropanation reaction was extended to aryl substituted semi-stabilized sulfonium ylide. A brief optimization revealed that the combination of Cs_2CO_3 and DME was the best, and representative results were summarized in Table 2. Aryl substituents of sulfonium salts with diverse electronic and steric properties were examined, and all worked well to afford products in yields ranging from 67% to 95% with good to excellent diastereoselection. For example, salt **1g** proceeded this reaction well to afford desired amino acid derivative in 95% yield and 9/1 *d.r.* Introducing strong electron-donating or electron-withdrawing group on aryl substituent led to decreased yield (Entries 1 vs. 5 and 6). Obvious steric effect could be easily identified in Table 2, and much better *d.r.* was delivered with increased hindrance on *orth*-position of aryl substituent (Entries 2, 3).

Table 2 Cyclopropanation of aryl substituted sulfonium ylide with dehydroamino acid derivative **2**[a]



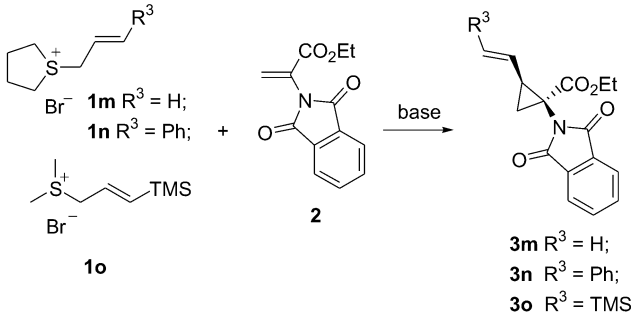
Entry	R^2	Yield[b]/%	*d.r.*[c]
1	C_6H_5 (**1g**)	95	9/1
2	*o*-$CH_3C_6H_4$ (**1h**)	95	>99/1
3	2,6-$Cl_2C_6H_3$ (**1i**)	86	>99/1
4	*m*-$TBSOC_6H_4$ (**1j**)	90	12/1
5	*p*-$CH_3OC_6H_4$ (**1k**)	67	9/1
6	*p*-$NO_2C_6H_4$ (**1l**)	71	>99/1

[a] To a stirred solution of salt **1** (0.3 mmol) and substrate **2** (49 mg, 0.2 mmol) in DME (2 mL) was added Cs_2CO_3 (98 mg, 0.3 mmol) in one portion at ambient conditions. [b] Isolated yield; [c] Determined by ^{1}H NMR.

Further studies showed that vinylcyclopropanyl amino acid derivatives could also be synthesized via this route. As listed in Table 3, the cyclopropanation of allylic sulfonium salt **1m** with substrate **2** proceeded well to give desired product in 86% yield and 3.9/1 diastereoselective ratio (Entry 1). Similar to the steric effect exhibited in aryl substituted sulfonium salts (Entries 1—3, Table 2), the introduction of bulky group on allyl group of sulfonium salts also led to an improved distereoselection.

Encouraged by above results, we decided to investigate the enantioselective synthesis of ACCs derivatives via chiral sulfonium ylide route. To the best of our knowledge, only two relevant examples have been documented so far. Aggarwal *et al*. reported the reaction of a chiral silylated allylic sulfur ylide which was generated from diazo compound *in situ* with *α*-aminoacrylate to afford the desired vinyl substituted cyclopropane amino acid with 71% *de* and 75% *ee*.[7] Guant *et al*. also documented the asymmetric cyclopropanation of dehydroamino acid derivatives using chiral ammonium ylide in good yield with 97% *ee*.[4g]

Table 3 Cyclopropanation of allylic semi-stabilized sulfonium salt with dehydroamino acid derivative **2**[a]



Entry	Salt	Condition	Yield[b]/%	*d.r.*[c]
1	**1m**	A	86	3.9/1
2	**1n**	B	72	3.5/1
3	**1o**	A	79	9.3/1

[a] Condition A: To a stirred solution of salt **1** (0.3 mmol) and substrate **2** (49 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) was added *t*-BuOK (34 mg, 0.3 mmol) in one portion at −20 ℃. Condition B : To a stirred solution of salt **1** (0.3 mmol) and substrate **2** (49 mg, 0.2 mmol) in DME (2 mL) was added Cs_2CO_3 (98 mg, 0.3 mmol) in one portion at ambient conditions. [b] Isolated yield; [c] Determined by ^{1}H NMR.

We initiated our study by testing reaction of camphor-derived sulfonium salts with dehydroamino acid derivatives. Under the optimal conditions, we found that amide substituted sulfonium salt **4a**, after deprotonation by *t*-BuOK, could react with **2** in CH_3CN at −40 ℃ to afford cyclopropane amino acid ester **3a** with excellent diastereoselectivity (>99/1) and good enantioselectivity (92% *ee*) in 95% overall yield (Table 4, Entry 1).

Further studies showed that the yield and enantioselectivity of the cyclopropanation process were significantly influenced by the substituents of chiral sulfonium salt. When the steric hindrance of the amide substituted sulfonium salts decreased, the *ee* of corresponding products dropped to moderate (Table 4, Entries 1—3). However, the ester substituted sulfonium salt showed contradicting behavior, where better *ee* was achieved with salt **4e** compared with bulky salt **4d** (Table 4, Entries 4, 5).

The reaction was useful in the synthesis of cyclopropane amino aicd derivatives.[8] As shown in Scheme 1, the phthaloyl group of **3g** could be easily removed at room temperature in the presence of hydrazine hydrate, furnishing **5-Z** in 78% yield; Subsequent treatment of **5-Z** with 4 mol•L^{-1} HCl under the reflux temperature for 24 h provide aminoacid **6-Z** in 58% yield.

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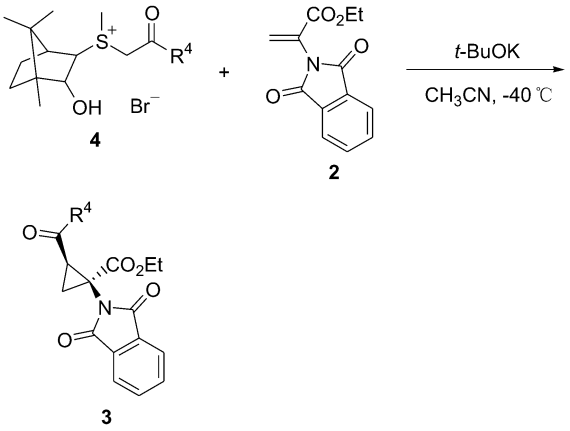
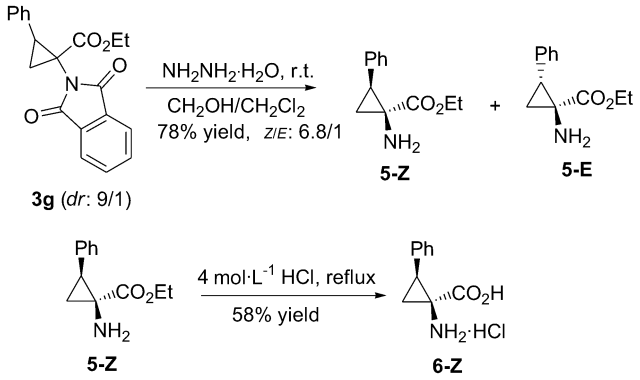
Table 4 Asymmetric reaction of sulfonium salt **4** with dehydroamino acid derivatives **2**[a]



Entry	R^4	Yield[b]/%	*d.r.*[c]	*ee*[d]/%
1	N^iPr_2 (**4a**)	95	>99/1	92
2	NEt_2 (**4b**)	88	>99/1	82
3	NMe_2 (**4c**)	75	>99/1	76
4	O^tBu (**4d**)	44	>99/1	10
5	OEt (**4e**)	65	>99/1	42

[a] To a stirred solution of salt **4** (0.25 mmol) in CH_3CN (3 mL) was added *t*-BuOK (28 mg, 0.25 mmol) at −40 ℃, substrate **2** (49 mg, 0.2mmol) was added after 45 min. [b] Isolated yield; [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC.

Scheme 1 Synthesis of 2-arylcyclopropane amino acid



Conclusions

In summary, the cyclopropanation reaction between sulfonium salts and dehydroamino acid derivatives was studied, and 1-aminocyclopropanecarboxylic acid derivatives were prepared in moderate to excellent ylieds. High diastereoselectivities and enantioselectivities could be obtained under convenient conditions with the use of optical camphor sulfonium salts. The synthetic procedure is simple, and all starting materials are easily available. Further studies on the applications of this reaction in organic synthesis are underway in our laboratory.

Experimental section

All reactions were carried out under N_2 unless otherwise noted. All solvents were purified according to standard methods prior to use. ^{1}H NMR and ^{13}C NMR spectra were recorded in chloroform-*d*3, *d*-DMSO or CD_3OD on a VARIAN Mercury 300 MHz or 400 MHz. All IR (Perkin-Elmer 983, BioRad FTS-185 or Bruker-Tensor 27), MSLR and MSHR (HP5989A and Premier CAB088) data were obtained by the analytical center of Shanghai Institute of Organic Chemistry.

General procedure for synthesis of racemic 1-aminocyclopropanecarboxylic acids (3a—3o)

To a stirred mixture of sulfonium salt **1** (0.3 mmol) and subsrate **2** (0.2 mmol) in solvent (2 mL) was added base (0.3 mmol) at desired temperature in one portion. The resulting mixture was continuing stirred at the same temperature until the substrate disappeared (monitored by TLC). The reaction mixture was passed through a short pad of silica gel, and eluted with ethyl acetate. The filtrate was concentrated and the residue was purified by flash column chromatography to afford cyclopropanes.

General procedure for synthesis of chiral 1-aminocyclopropanecarboxylic acids (3a—3e)

To a stirred solution of sulfonium salt **4** (0.25 mmol) in CH_3CN (2 mL) was added *t*-BuOK (0.25 mmol) at −40 ℃. The resulting mixture was stirred at −40 ℃ for 45 min, and then **2** (0.2 mmol) was added to the obtained solution. The resulting mixture was stirred at −40 ℃ until the substrate disappeared (monitored by TLC). The reaction mixture was passed through a short pad of silica gel, and eluted with ethyl acetate. The filtrate was concentrated and the residue was purified by flash column chromatography to afford cyclopropanes.

Characterization data of all new synthesized compounds

Dimethyl (diisopropylcarbamoylmethyl)sulfonium bromide (1a) White solid, 75% yield; ^{1}H NMR ($CDCl_3$/TMS, 400 MHz) δ: 5.61 (s, 2H), 4.01—3.92 (m, 1H), 3.52—3.43 (m, 1H), 3.37 (s, 6H), 1.36 (d, J=9.2 Hz, 6H), 1.29 (d, J = 8.4 Hz, 6H); ^{13}C NMR ($CDCl_3$/TMS, 100 MHz) δ: 161.66, 51.21, 50.72, 46.70, 25.17, 20.84, 20.18; IR (neat) ν: 1627 (s), 1043 (m), 788 (m) cm^{-1}; MS (ESI) *m*/*z*: 204.0; HRMS (ESI) calcd for $C_{10}H_{22}NOS^+$ 204.1417, found 204.1423.

2-Methyl-benzyl-dimethylsulfonium bromide (1h) White solid, 60% yield; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ: 7.32—7.16 (m, 4H), 4.52 (s, 2H), 2.42 (s, 3H), 2.12 (s, 6H); ^{13}C NMR ($CDCl_3$/TMS, 100 MHz) δ: 138.26, 132.18, 131.26, 130.15, 126.69, 125.75, 44.65, 24.57, 19.92; IR (neat) ν: 1006 (m), 780 (s), 740 (m) cm^{-1}; MS (ESI) *m*/*z*: 167.1; HRMS (ESI) calcd for $C_{10}H_{15}S^+$ 167.0889, found 167.0887. Anal. calcd for $C_{10}H_{15}BrS$: C 48.59, H 6.12; found C 48.14, H 6.14.

2,6-Dichloro-benzyl-dimethylsulfonium bromide (1i) White solid, 65% yield; ^{1}H NMR (*d*-DMSO, 400

MHz) δ: 7.66—7.64 (m, 2H), 7.56—7.52 (m, 1H), 4.94 (s, 2H), 3.09 (s, 6H); ^{13}C NMR (CD_3OD, 100 MHz) δ: 137.94, 133.71, 130.60, 126.38, 44.26, 26.15; IR (neat) ν: 1430 (s), 782 (s), 766 (m) cm^{-1}; MS (ESI) *m*/*z*: 220.9; HRMS (ESI) calcd for $C_9H_{11}Cl_2S^+$ 220.9953, found 220.9959. Anal. calcd for $C_9H_{10}BrCl_2S$: C 35.79, H 3.67; found C 35.61, H 3.62.

3-((*tert*-Butyldimethylsilyl)oxy)-benzyl-dimethylsulfonium bromide (1j) White solid, 80% yield; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ: 7.31—7.27 (m, 1H), 7.19—7.16 (m, 1H), 6.97—6.90 (m, 2H), 5.21 (s, 2H), 3.22 (s, 6H), 0.98 (s, 9H), 0.218 (s, 3H), 0.217 (s, 3H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ: 155.99, 130.14, 128.06, 123.67, 121.97, 121.34, 45.50, 25.25, 24.10, 17.77, −4.68; IR (neat) ν: 1291 (w), 841 (s), 782 (m) cm^{-1}; MS (ESI) *m*/*z*: 283.1; HRMS (ESI) calcd for $C_{15}H_{27}OSiS^+$ 283.1546, found 283.1548. Anal. calcd for $C_{15}H_{27}BrOSSi$: C 49.57, H 7.49; found C 49.34, H 7.64.

Ethyl 2-(diisopropylcarbamoyl)-1-(1,3-dioxoisoindolin-2-yl)cyclopropanecarboxylate (3a) Colourless viscous liquid, 98% yield; $[\alpha]_D^{20}$ −43.3 (*c*=1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ: 7.87—7.69 (m, 4H), 4.43—4.30 (m, 1H), 4.19 (q, *J*=7.2 Hz, 2H), 3.62—3.52 (m, 1H), 3.03 (t, *J*=7.8 Hz, 1H), 2.51—2.47 (m, 1H), 2.02—1.97 (m, 1H), 1.44 (d, *J*=6.6 Hz, 3H), 1.31 (d, *J*=6.6 Hz, 3H), 1.25 (d, *J*=6.6 Hz, 3H), 1.19 (t, *J*=7.2 Hz, 3H), 1.10 (d, *J*=6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$/TMS, 100 MHz) δ: 169.18, 167.33, 167.03, 164.41, 133.68, 131.83, 130.92, 123.29, 122.44, 61.91, 48.37, 45.55, 37.05, 27.33, 21.27, 20.16, 19.89, 19.63, 19.37, 13.69; IR (thin film) ν: 2969 (m), 1783 (w), 1727 (s), 1634 (m), 722 (m) cm^{-1}; MS (EI) *m*/*z* (%): 386 (M^+, 13.07), 43 (100); HRMS (EI) calcd for $C_{21}H_{26}N_2O_5$ 386.1842, found 386.1848.

Ethyl 2-(diethylcarbamoyl)-1-(1,3-dioxoisoindolin-2-yl)cyclopropanecarboxylate (3b) Colorless viscous liquid, 96% yield; $[\alpha]_D^{20}$ − 63.7 (*c* = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$/TMS, 400 MHz) δ: 7.87—7.70 (m, 4H), 4.22—4.18 (m, 2H), 3.88—3.82 (m, 1H), 3.53—3.48 (m, 1H), 3.37—3.34 (m, 1H), 3.00—2.96 (m, 2H), 2.51—2.47 (m, 1H), 2.05—2.02 (m, 1H), 1.31 (t, *J*=7.6 Hz, 3H), 1.19 (t, *J*=7.2 Hz, 3H), 0.94 (t, *J*=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$/TMS, 100 MHz) δ: 169.21, 167.70, 167.18, 165.18, 133.98, 133.84, 132.00, 131.03, 123.48, 122.78, 62.14, 42.22, 40.85, 37.14, 26.40, 19.72, 14.30, 13.86, 11.98; IR (thin film) ν: 2978 (m), 1782 (w), 1726 (s), 1641 (m), 724 (m) cm^{-1}; MS (EI) *m*/*z* (%): 358 (M^+, 49.87), 211 (100); HRMS (EI) calcd for $C_{19}H_{22}N_2O_5$ 358.1529, found 358.1522.

Ethyl 2-(dimethylcarbamoyl)-1-(1,3-dioxoisoindolin-2-yl)cyclopropanecarboxylate (3c) Colorless viscous liquid, 95% yield; $[\alpha]_D^{20}$ − 47.6 (*c* = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$/TMS, 400 MHz) δ: 7.82—7.67 (m, 4H), 4.18—4.12 (m, 2H), 3.27 (s, 3H), 3.04 (dd, *J*=8.8, 7.6 Hz, 1H), 2.83 (s, 3H), 2.43 (dd, *J*=5.6, 7.6 Hz , 1H), 2.01 (dd, *J*=5.2, 9.2 Hz, 1H), 1.60 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$/TMS, 100 MHz) δ: 169.15, 167.89, 167.37, 166.34, 134.08, 133.93, 131.96, 131.05, 123.51, 123.13, 62.26, 37.62, 37.05, 35.89, 26.18, 19.64, 13.90; IR (thin film) ν: 2933 (m), 1783 (w), 1725 (s), 1649 (m), 718 (m) cm^{-1}; MS (EI) *m*/*z* (%): 330 (M^+, 19.80), 104 (100); HRMS (EI) calcd for $C_{17}H_{18}N_2O_5$ 330.1216, found 330.1218.

2-*tert*-Butyl-1-ethyl 1-(1,3-dioxoisoindolin-2-yl)-cyclopropane-1,2-dicarboxylate (3d) Colorless viscous liquid, 95% yield; $[\alpha]_D^{20}$ −7.5 (*c*=1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$/TMS, 400 MHz) δ: 7.85—7.69 (m, 4H), 4.12 (q, *J*=6.8 Hz, 2H), 2.80 (t, *J*=8.8 Hz, 1H), 2.12—2.08 (m, 2H), 1.31 (s, 9H), 1.16 (t, *J*=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$/TMS, 100 MHz) δ: 168.40, 167.81, 167.54, 167.42, 134.17, 134.10, 131.92, 131.20, 123.53, 123.11, 81.77, 62.34, 37.15, 28.45, 27.61, 20.24, 13.89; IR (thin film) ν: 2980 (m), 2934 (w), 1784 (m), 1728 (s), 721 (m) cm^{-1}; MS (ESI) *m*/*z* (%): 382.4 (M^+ +Na); HRMS (ESI) calcd for $C_{19}H_{21}NO_6Na$ (M+Na): 382.1267, found 382.1261.

Diethyl 1-(1,3-dioxoisoindolin-2-yl)cyclopropane-1,2-dicarboxylate (3e) Colorless viscous liquid, 92% yield; $[\alpha]_D^{20}$ − 28.5 (*c* = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ: 7.87—7.71 (m, 4H), 4.18—4.03 (m, 4H), 2.89 (t, *J*=8.7 Hz, 1H), 2.17 (d, *J*=8.7 Hz, 2H), 1.24—1.15 (m, 6H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ: 168.54, 168.12, 167.71, 167.38, 134.17, 134.08, 131.72, 131.00, 123.42, 123.29, 62.36, 61.29, 37.20, 27.20, 20.23, 13.80, 13.78.

Ethyl 2-benzoyl-1-(1,3-dioxoisoindolin-2-yl)cyclopropanecarboxylate (3f) Colorless viscous liquid, 96% yield; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ: 8.02—7.47 (m, 9H), 4.23 (q, *J*=6.9 Hz, 2H), 3.90 (t, *J*=7.8 Hz, 1H), 2.54 (dd, *J*=5.1, 7.5 Hz, 1H), 2.25 (dd, *J*=5.4, 9.3 Hz, 1H), 1.21 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ: 193.67, 168.58, 167.65, 167.45, 137.52, 134.15, 134.05, 133.06, 131.74, 130.93, 128.40, 128.31, 123.46, 123.36, 62.52, 39.92, 30.09, 21.04, 13.90; IR (thin film) ν: 2925 (m), 1781 (w), 1726 (s), 726 (w) cm^{-1}; MS (ESI) *m*/*z* (%): 364.5 (M^++H); HRMS (ESI) calcd for $C_{21}H_{18}NO_5$ (M+H) 364.1185, found 364.1180.

Ethyl 1-(1,3-dioxoisoindolin-2-yl)-2-phenylcyclopropanecarboxylate (3g) Colorless viscous liquid, 95% yield; ^{1}H NMR ($CDCl_3$/TMS, 400 MHz) δ: 7.93—7.61 (m, 4.37H), 7.37—7.33 (m, 0.28H), 7.17—7.11 (m, 4.37H), 4.27—4.13 (m, 1.80H), 3.82—3.77 (m, 0.21H), 3.38 (t, *J*=9.2 Hz, 0.88H), 3.18 (t, *J*=9.6 Hz, 0.12H), 2.53—2.49 (m, 0.12H), 2.45—2.41 (m, 0.88H), 2.27 (dd, *J*=10, 6.8 Hz, 0.88H), 1.90 (dd, *J*=10, 6.4 Hz, 0.12H), 1.21 (t, *J*=7.2 Hz, 2.68H), 0.76 (t, *J*=7.2 Hz, 0.32H); ^{13}C NMR ($CDCl_3$/TMS, 100 MHz) δ: 169.71, 168.50, 166.76, 134.24, 133.97, 131.76, 130.71, 127.87, 127.80, 127.03, 123.23, 61.94, 39.05, 31.52, 18.99, 13.99; IR (thin film) ν: 2929 (m), 1782 (w), 1724 (s), 723 (w) cm^{-1}; MS (ESI) *m*/*z*: 358.3 (M+H$^+$); HRMS (ESI) calcd for $C_{20}H_{17}NO_4$ (M + Na) 358.1055, found 358.1050.

Ethyl 1-(1,3-dioxoisoindolin-2-yl)-2-*o*-tolylcyclo-

propanecarboxylate (3h) Colourless viscous liquid, 95% yield; ^{1}H NMR ($CDCl_3$/TMS, 400 MHz) δ: 7.83—7.64 (m, 4H), 7.15 (d, J=6.8 Hz, 1H), 7.01 (dt, J=7.6 Hz, 1.2 Hz, 1H), 6.84 (t, J=7.6 Hz, 1H), 6.62 (d, J=7.6 Hz 1H), 4.25—4.19 (m, 2H), 3.46—3.42 (m, 1H), 2.60—2.56 (m, 4H), 2.21 (dd, J=12.5, 6.8 Hz 1H), 1.21 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ: 169.85, 168.42, 166.68, 139.60, 133.86, 131.86, 131.64, 130.58, 129.89, 126.89, 124.93, 123.74, 123.06, 61.80, 38.93, 28.87, 19.80, 17.97, 13.96; IR (thin film) v: 2917 (m), 1717 (s), 717 (w) cm^{-1}; MS (ESI) m/z: 372.1 (M+Na$^+$); HRMS (ESI) calcd for $C_{21}H_{19}NO_4$ (M+Na$^+$) 372.1212, found 372.1206.

Ethyl 2-(2,6-dichlorophenyl)-1-(1,3-dioxoisoindolin-2-yl)cyclopropanecarboxylate (3i) Colourless viscous liquid, 86% yield; ^{1}H NMR ($CDCl_3$/TMS, 400 MHz) δ: 7.73—7.67 (m, 4H), 7.16 (d, J=7.6 Hz, 2H), 7.02—6.97 (m, 2H), 4.24—4.18 (m, 2H), 3.82—3.74 (m, 2H), 2.32—2.39 (m, 1H), 1.20 (t, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$/TMS, 100 MHz) δ: 169.7, 167.5, 134.1, 131.4, 129.1, 129.0, 128.3, 123.3, 62.1, 37.7, 31.0, 21.2, 14.1; IR (thin film) v: 1720 (s), 712 (m) cm^{-1}; MS (ESI) m/z: 426.0 (M+Na$^+$); HRMS (ESI) calcd for $C_{20}H_{15}Cl_2NO_4$ (M+Na$^+$) 426.0276, found 426.0270.

Ethyl 2-(3-((tert-butyldimethylsilyl)oxy)phenyl)-1-(1,3-dioxoisoindolin-2-yl)cyclopropane carboxylate (3j) Colourless viscous liquid, 90% yield; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ: 7.92—7.61 (m, 4.05H), 7.18—7.13 (m, 0.26H), 7.00 (t, J=7.8 Hz, 0.94H), 6.77 (d, J=7.8 Hz, 1.01H), 6.58 (d, J=7.8 Hz, 0.89H), 6.51 (s, 0.90H), 4.261—4.10 (m, 1.92H), 3.84—3.77 (m, 0.18H), 3.34—3.28 (m, 0.92H), 3.15—3.09 (m, 0.08H), 2.47—2.35 (m, 1.07H), 2.22 (dd, J=9.6, 6.6 Hz, 0.94H), 1.84 (dd, J=9.9, 6.0 Hz, 0.09H), 1.19 (t, J=7.2 Hz, 2.75H), 0.99 (s, 0.83H), 0.84 (s, 8.07H), 0.23 (s, 0.21H), 0.22 (s, 0.23H), −0.00 (s, 2.39H), −0.069 (s, 2.33); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ: 169.8, 155.2, 135.8, 134.0, 134.0, 133.9, 128.9, 123.4, 121.7, 119.3, 118.9, 62.0, 39.1, 31.4, 25.5, 19.1, 18.0, 14.1, −4.63, −4.81; IR (thin film) v: 1722 (s), 1281 (m), 717 (m) cm^{-1}; MS (ESI) m/z: 466.3 (M+H$^+$); HRMS (ESI) calcd for $C_{26}H_{31}NO_5$ (M+Na$^+$) 488.1869, found 488.1864.

Ethyl 2-(4-methoxyphenyl)-1-(1,3-dioxoisoindolin-2-yl)cyclopropanecarboxylate (3k) Colourless viscous liquid, 67% yield; ^{1}H NMR ($CDCl_3$/TMS, 400 MHz) δ: 8.03—7.61 (m, 4.32H), 7.51 (d, J=8.8 Hz, 0.21H), 7.43—7.39 (m, 0.09H), 7.18—7.14 (m, 0.10H), 7.03 (d, J=8.8 Hz, 1.77H), 6.86 (d, J=8.0 Hz, 0.27H), 6.67 (d, J=8.4 Hz, 1.75H), 4.24—4.10 (m, 1.87H), 3.82—3.77 (m, 0.59H), 3.67 (s, 2.58H), 3.31 (t, J=8.8 Hz, 0.90H), 3.10 (t, J=9.2 Hz, 0.10H), 2.46—2.43 (m, 0.12H), 2.38—2.34 (m, 0.88H), 2.24—2.20 (m, 0.91H), 1.87—1.83 (m, 0.10H), 1.18 (t, J=7.2 Hz, 2.82H), 0.81 (t, J=8.8 Hz, 0.32H); ^{13}C NMR ($CDCl_3$/TMS, 100 MHz) δ: 169.9, 158.6, 134.2, 134.0, 130.7, 129.0, 126.2, 123.5, 123.3, 113.4, 61.9, 55.0, 38.9, 31.1, 19.0, 14.0; IR (thin film) v: 1716 (s), 1284 (m), 717 (m) cm^{-1}; MS (ESI) m/z: 388.1 (M+Na$^+$); HRMS (ESI) calcd for $C_{21}H_{19}NO_5$ (M+Na$^+$) 388.1161, found 388.1155.

Ethyl 2-(4-nitrophenyl)-1-(1,3-dioxoisoindolin-2-yl)cyclopropanecarboxylate (3l) Colourless viscous liquid, 71% yield; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ: 8.04 (d, J=8.7 Hz, 2H), 7.87—7.63 (m, 4H), 7.30 (d, J=8.4 Hz, 2H), 4.24—4.17 (m, 2H), 3.45 (t, J=12 Hz, 1H), 2.48 (t, J=11.2 Hz, 1H), 2.41—2.35 (m, 1H), 1.21 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ: 169.04, 168.31, 166.87, 146.87, 142.39, 134.41, 131.57, 130.47, 128.90, 128.62, 128.34, 123.54, 123.11, 62.39, 39.66, 30.73, 19.54, 13.97; IR (thin film) v: 1715 (s), 1522 (w), 709 (m) cm^{-1}; MS (ESI) m/z: 403.1 (M+Na$^+$); HRMS (ESI) calcd for $C_{20}H_{16}N_2O_6$ (M+Na$^+$) 403.0906, found 403.0901.

Ethyl 1-(1,3-dioxoisoindolin-2-yl)-2-vinylcyclopropanecarboxylate (3m) Colorless viscous liquid, 86% yield; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ: 7.87—7.85 (m, 2.01H), 7.76—7.73 (m, 2.10H), 6.00—5.88 (m, 0.20H), 5.65—5.47 (m, 1.04H), 5.27 (d, J=10.2 Hz, 0.22H), 5.15 (d, J=17.1 Hz, 0.88H), 5.03 (d, J=9.9 Hz, 1H), 4.21—4.05 (m, 2.17H), 2.78 (q, J=8.4 Hz, 0.80H), 2.51—2.42 (m, 0.20H), 2.09—2.04 (m, 1.09H), 1.86—1.81 (m, 0.87H), 1.76—1.71 (m, 0.24H), 1.19—1.12 (m, 3.09H); ^{13}C NMR ($CDCl_3$/TMS, 100 MHz) δ: 169.8, 134.2, 132.7, 123.5, 119.1, 117.9, 61.9, 37.7, 29.9 19.6, 14.0; IR (thin film) v: 1717 (s), 717 (s) cm^{-1}; MS (ESI) m/z: 286.1 (M+H$^+$); HRMS (ESI) calcd for $C_{16}H_{15}NO_4$ (M+Na$^+$) 308.0899, found 308.0893.

Ethyl 1-(1,3-dioxoisoindolin-2-yl)-2-styrylcyclopropanecarboxylate (3n) Colorless viscous liquid, 72% yield; ^{1}H NMR ($CDCl_3$/TMS, 400 MHz) δ: 7.90—7.69 (m, 4.39H), 7.41—7.29 (m, 1.58H), 7.23—7.13 (m, 3.84H), 6.67 (d, J=16.0 Hz, 0.30H), 6.50 (d, J=16.0 Hz, 0.69H), 6.37 (dd, J=16.0, 8.4 Hz, 0.32H), 5.96 (dd, J=16.0, 7.2 Hz, 0.69H), 4.20—4.07 (m, 2.17H), 2.97—2.91 (m, 0.69H), 2.64 (q, J=9.2 Hz, 0.34H), 2.23—2.17 (m, 1.05H), 1.97—1.93 (m, 0.74H), 1.84 (dd, J=9.6, 6.0 Hz, 0.33H); ^{13}C NMR ($CDCl_3$/TMS, 100 MHz) δ: 169.8, 136.7, 134.2, 131.7, 132.7, 128.4, 127.4, 126.2, 124.4, 123.5, 62.0, 38.0, 29.9, 20.2, 14.0; IR (thin film) v: 1724 (s), 722 (m) cm^{-1}; MS (ESI) m/z: 384.3 (M+Na$^+$); HRMS (ESI) calcd for $C_{22}H_{19}NO_4$ (M+H$^+$) 362.1392, found 362.1387.

Ethyl 2-((*E*)-2-(trimethylsilyl)vinyl)-1-(1,3-dioxoisoindolin-2-yl)cyclopropanecarboxylate (3o) Colorless viscous liquid, 79% yield; ^{1}H NMR ($CDCl_3$/TMS, 400 MHz) δ: 7.87—7.84 (m, 2.06H), 7.75—7.72 (m, 2.11H), 6.21—6.06 (m, 0.17H), 5.90 (dd, J=18.8, 6.0 Hz, 0.92H), 5.60 (d, J=18.8 Hz, 1H), 4.21—4.08 (m, 2.10H), 2.83 (q, J=8.4 Hz, 0.92H), 2.54—2.47 (m, 0.08H), 2.13—2.03 (m, 1.03H), 2.00—1.96 (m, 0.94H), 1.76—1.72 (m, 0.11H), 1.82 (t, J=7.2 Hz, 3.15H), 0.09 (s, 0.78H), −0.2 (s, 8.31H); ^{13}C NMR ($CDCl_3$/TMS, 100 MHz) δ: 169.58, 168.18, 167.56, 139.33, 134.07, 132.03, 131.69, 131.19, 123.29, 123.06, 61.74, 38.10, 31.48, 18.81, 13.95; IR (thin film) v: 1720

(s), 717 (s) cm^{-1}; MS (ESI) *m*/*z*: 358.3 ($M+H^+$); HRMS (ESI) calcd for $C_{19}H_{23}NO_4Si$ ($M + Na^+$) 380.1294, found 380.1288.

(*R*)-[2-(Diisopropylamino)-2-oxoethyl][(2*R*,3*S*,4*R*)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]methylsulfonium bromide (4a) White solide; $[\alpha]_D^{20}$ +92.3 (*c*=1.00, $CHCl_3$); ^1H NMR ($CDCl_3$/TMS, 300 MHz) δ: 5.71 (d, *J*=6.9 Hz, 1H), 5.50 (d, *J*=15.3 Hz, 1H), 5.17 (d, *J*=15.6 Hz, 1H), 4.39 (d, *J*=7.2 Hz, 1H), 4.16 (t, *J*=7.2 Hz, 1H), 4.09—4.03 (m, 1H), 3.46—3.37 (m, 1H), 3.11 (s, 3H), 2.01 (d, *J*=4.8 Hz, 1H), 1.89—1.81 (m, 1H), 1.54—1.46 (m, 1H), 1.33 (dd, *J*=6.3, 2.1 Hz, 6H), 1.24 (t, *J*=6.3 Hz, 6H), 1.15 (s, 3H), 0.92 (s, 3H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 161.4, 76.1, 62.0, 51.0, 50.1, 49.9, 47.2, 47.1, 46.2, 31.6, 27.5, 22.6, 20.8, 20.7, 20.5, 20.3, 20.0, 19.7, 11.1; IR (neat) ν: 3185 (w), 2963 (w), 2920 (w), 1738 (w), 1630 (s), 1448 (w), 1124 (s), 800 (m) cm^{-1}; MS (ESI) *m*/*z*: 342.3 $(M-Br)^+$. Anal. calcd for $C_{19}H_{36}BrNO_2$: C 54.02, H 8.59, N 3.32; found C 53.8, H 8.64, N 2.96.

(*R*)-[2-(*tert*-Butoxy)-2-oxoethyl][(2*R*,3*S*,4*R*)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]methylsulfonium bromide (4d) White solide; $[\alpha]_D^{20}$ +48.2 (*c*=1.00, $CHCl_3$); ^1H NMR ($CDCl_3$/TMS, 300 MHz) δ: 5.74 (d, *J*=6.9 Hz, 1H), 5.28—5.10 (m, 3H), 4.23 (t, *J*=7.2 Hz, 1H), 3.18 (s, 3H), 2.03 (d, *J*=4.8 Hz, 1H), 1.96—1.84 (m, 1H), 1.58—1.51 (m, 11H), 1.25—1.22 (m, 4H), 1.01 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (*d*-DMSO/TMS, 100 MHz) δ: 163.1, 84.6, 76.7, 63.7, 49.9, 47.1, 46.3, 45.8, 31.5, 27.5, 27.4, 22.3, 20.9, 20.1, 11.2; IR (film) ν: 3186 (w), 2982 (w), 2881 (w), 1719 (m), 1147 (s), 844 (m) cm^{-1}; MS (ESI) *m*/*z*: 315.3 $(M-Br)^+$. Anal. calcd for $C_{17}H_{31}BrO_3S$: C 51.35, H 8.10.

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