Stereoselective Synthesis of Cyclopropyl Indolyl Ketones with Indolylidene and Arsonium Ylide

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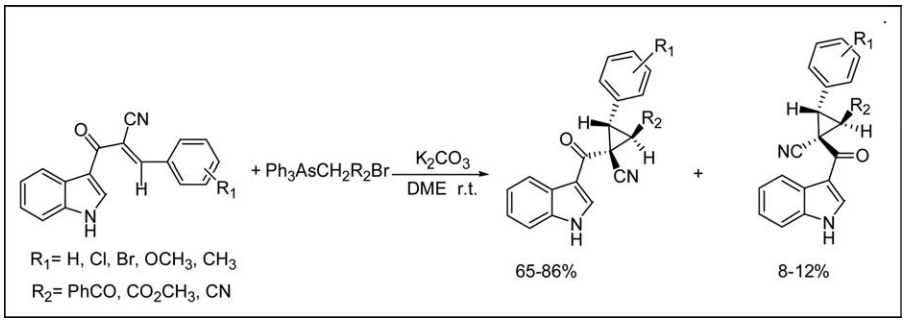

An efficient approach for stereoselective synthesis of cyclopropyl indolyl ketone from olefin and arsonium ylied was achieved. Its advantages are of mild condition, high yield, and good stereoselectivity. In addition, the one-pot cycloproparation of olefins with bromides and triphenylarsine was studied.

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INTRODUCTION

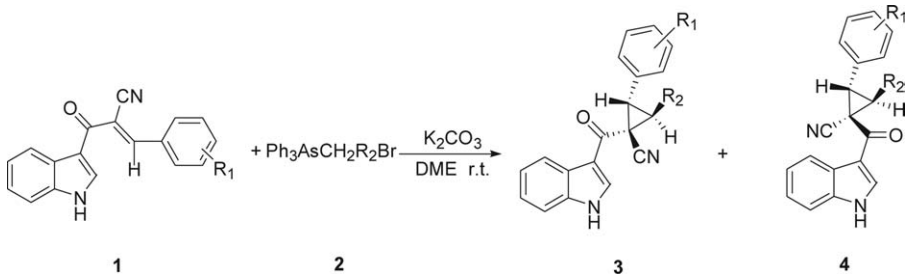
Cyclopropyl ketones occupy an important position in cyclopropane chemistry owing to their wide utility as potent synthetic blocks which have been extensively applied for the synthesis of complex molecules including heterocycles [1]. Therefore, the great efforts have been made to develop new method for synthesis of cyclopropyl ketones [2].

In recent years, the concept of privileged structures, which repeated occurrence in biologically active molecules, become important for the design and synthesis of drug candidates. The indole framework is a versatile and important structural motif frequently found in natural products, pharmaceuticals, and other synthetic compounds [3]. Thus, it is not surprising that a great deal of attention has been directed to development of efficient routes for the synthesis of these interesting compounds. Now, we become interested in the design and synthesis of the cyclopropyl indolyl ketones. Because of their unique ring strain and high reactivity, these novel cyclopropanes may serve as new and useful building blocks for construction of complex indoles. To the best of our knowledge, no approaches have been previously reported for synthesis of cyclopropyl indolyl ketones. Here, we report an effect procedure for preparation of cyclopropyl indolyl ketones *via* cyclopreparation of indolylidene with arsonium ylide (Scheme 1).

The needed indolylidenes were prepared according to the reported literature [4]. We tested some bases first. In the model experiment, a mixture of indolylidene **1a** (1 equiv), benzoylmethyltriphenylarsonium bromide **2a** (1.1 equiv) and base (3 equiv) in dimethoxyethane (DME) was stirred at room temperature to give compound **3a** and **4a**. The results showed that the K_2CO_3 as base provided the highest yield (entry 1, Table 1). And then, the screening for a suitable solvent was performed in the presence of K_2CO_3 at room temperature. It was found that DME was the best solvent for this reaction. The results were listed in Table 1. At the same time, the results in Table 1 also showed that bases, solvents, and temperature have no obvious influence on the ratio of product **3** and **4**.

To investigate the scope of this reaction, some indolyldienes and arsenium salts are examined with the optimized conditions and the results are shown in Table 2. It is worth noting that only compounds **3e–k** were obtained (entries 6–11, Table 2), when methoxycarbonylmethyltriphenylarsonium bromide and cyanomethyltriphenylarsonium bromide were used as arsonium salts instead of benzoylmethyltriphenylarsonium bromide.

Scheme 1



1 2 3 4

The structures of compounds **3a–k** and **4a–d** were characterized by ^{1}H NMR, ^{13}C NMR, MS, IR, elemental analysis, and X-ray diffraction (Fig. 1; Table 3). The relative configurations of product **3** and **4** are confirmed from NOE experiments of compounds **3b** (Fig. 2) and **4b** (Fig. 3). The cyclopropyl hydrogen with a trans configuration is deduced by the absence of NOE correlation between two protons situated at adjacent carbons in the cyclopropane ring of these compounds.

One-pot methodology has recently attracted increasing attention. Because it offers significant advantages such as a reduction in the number of synthetic steps, energy consumption and waste production, and high efficiency [5]. Thus, considerable efforts have been taken in developing new one-pot process. Our attention turned next to one-pot cyclopropanation reaction with triphenylarsine and bromide. (Scheme 2).

Initial studies focused on screening the optimum reaction conditions, in the model experiments, a mixture of triphenylarsine **6** (0.1 equiv), methyl bromoacetate **5** (1.2 equiv), indolyidiene **1** (1.0 equiv), and bases (3.0 equiv) in solvent (5 mL) was stirred under reflux. The results are shown in Table 4. We found that the highest yield of cyclopropane **3f** was obtained in acetonitrile/K_2CO_3 system (entry 2, Table 4). Then, the amount of Ph_3As was tested under the similar condition. Through an effort to investigate the reaction condition, we chose 0.75 equiv of Ph_3As /acetonitrile/K_2CO_3 system as the optimum reaction condition. Because the amount of triphenylarsine changes from 0.75 equiv to 1 equiv, the differences in the yield and rate of cyclopropanation are not significant (entries 10 and 11, Table 4).

The scope of the one-pot of cyclopropanation with indolyidienes and bromides in the presence of trephenylarsine was further explored. The results are shown in Table 5.

A plausiblemechanism for the formation of product **3** and **4** is shown in Scheme 3. (1) The arsonium yilde **B** is generated from arsonium salt **A** with K_2CO_3 as base. (2) The ylide **B** nucleophilically attacks the olefin **C** to result in either transition state **D** or **E**. Apparently, the **E** should be favored over **D**, with the latter being higher energy given the steric repulsion between bulky X and Ar groups in the conformation of **D**. (3) The six-membered ring, locking conformation of intermediate **F**, is formed by nonbonding interactions between the negatively polarized oxygen in enolate ion and positively polarized X group, and the product **3** is given *via* cyclopropanation reaction. (4) When the X is benzoyl group, the intermediate **G** is formed due to the steric repulsion between bulky benzoyl and indolyl groups, and then the product **4** is yielded from **G**.

In conclusion, we have developed an efficient approach for stereoselective synthesis of cyclopropyl indolyl ketone from olefin and arsonium ylied. The advantages of this approach are of mild condition, high yield, and good stereoselectivity. In addition, the one-pot cycloproparation of olefins with bromides and triphenylarsine was also studied.

Table 1

Optimization of reaction condition of indolylidene with arsonium salt.

Entry	R_1	R_2	Base	Solvent	Temperature (°C)	Time (h)	Yield (%) **3**	Yield (%) **4**
1	4-Cl	COPh	K_2CO_3	DME	r.t.	2	68	12
2	4-Cl	COPh	$KF.2H_2O$	DME	r.t.	4	60	15
3	4-Cl	COPh	$NaHCO_3$	DME	r.t.	28	58	14
4	4-Cl	COPh	K_2CO_3	chloroform	r.t.	3.5	56	14
5	4-Cl	COPh	K_2CO_3	acetonitrile	r.t.	2.5	60	18
6	4-Cl	COPh	K_2CO_3	DME	0	4.5	67	15
7	4-Cl	COPh	K_2CO_3	DME	−15	6	68	15

DME, dimethoxyethane.

Table 2

Synthesis of cyclopropyl indolyl ketones with indolyldienes and arsenium salts.

Entry	Product	R1	R2	Reaction time (h)	Yield **3**(%)[a]	Yield **4**(%)[a]
1	**a**	H	COPh	2	71	10
2	**b**	4-Cl	COPh	2	68	12
3	**c**	3-Br	COPh	1.5	73	8
4	**d**	4-OCH_3	COPh	2	65	12
5	**e**	H	CO_2CH_3	3	76	0
6	**f**	4-Cl	CO_2CH_3	3	85	0
7	**g**	3-Br	CO_2CH_3	3.5	72	0
8	**h**	4-CH_3	CO_2CH_3	3	79	0
9	**i**	4-OCH_3	CO_2CH_3	4	70	0
10	**j**	H	CN	1	78	0
11	**k**	4-Cl	CN	1.5	85	0

[a]Isolated yield

EXPERIMENTAL

General Experimental Conditions. All reagents and solvents were obtained from commercial sources and used without purification. All melting points were uncorrected. Melting points were determined on WRS-1 digital melting point apparatus made by Shanghai physical instrument factory (SPOIF), China. IR spectra were measured in KBr on a PE-580B spectrometer. ^{1}H NMR spectra were recorded at a Bruker AM-500, using CD_3COCD_3 as solvent and TMS as internal reference. Mass spectra were taken with a HP5989A mass spectrometer at an ionizing voltage of 70 eV. Elemental analyses were measured on the elementar vario EL III. X-Ray crystal data were collected with Bruker Smart Apex2 CCD

General procedure for preparing 3a–k and 4a–d. A mixture of indolylidene 1 (1 mmol), arsonium bromide **2** (1.1 mmol) and K_2CO_3 (0.414 g, 3 mmol) in dimethoxyethane (DME) (5 mL) was stirred at room temperature. The completion of the reaction was determined by TLC. The DME was removed off under reduced pressure, and the residue was run on a silica-gel chromatographic column (eluant: petroleum ether–ethyl acetate (v: v = 6:1)). The desired products **3** and **4** can be obtained and triphenylarsine recovered, respectively.

General procedure of one-pot method for 3a–k and 4a–d. A mixture of indolyidiene 1 (1 mmol), bromide **5** (1.2 mmol), triphenylarsine 6 (0.225 g, 0.75 mmol), and K_2CO_3 (0.414 g, 3 mmol) was stirred in the refluxing CH_3CN (5 mL). The completion of the reaction was determined by TLC.The CH_3CN was removed off under reduced pressure, and the residue was run on a silica-gel chromatographic column (eluant: petroleum ether–ethyl acetate (v: v = 6:1)). The desired products **3** and **4** can be obtained and triphenylarsine recovered, respectively.

Trans-2-benzoyl-1-(1H-indole-3-carbonyl)-3-phenyl-cyclopropanecarbonitrile (3a). This compound was obtained as white solid, mp 110–111°C (petroleum ether–ethyl acetate (v:v = 1:1)); ^{1}H NMR (500 MHz, hexadeuteroacetone): δ 4.03 (d, J = 8.0 Hz, 1H), 4.56 (d, J = 8.0 Hz 1H), 7.22-7.28 (m, 2H), 7.41–7.42 (m,1H), 7.44–7.57 (m, 5H), 7.64–7.69 (m, 3H), 8.19–8.21 (m, 3H), 8.44 (s, 1H), 11.21 (br s, 1H); ^{13}C NMR (125 MHz, hexadeuteroacetone): δ 36.0, 37.3, 38.0, 113.1, 115.7, 118.7, 122.7, 123.5, 124.6, 126.9, 129.1, 129.3, 129.4, 129.6, 134.4, 134.6, 135.3, 137.6, 137.8, 180.6, 192.3; IR

Table 3

Selected bond lengths and bond angels of compound **3f**.

Compound **3f**	Lengths (A)	Angels(deg)
C(4)-C(7)	1.482(4)	
C(7)-C(9)	1.510(4)	
C(7)-C(8)	1.509(4)	
C(8)-C(10)	1.475(4)	
C(8)-C(9)	1.527(4)	
C(9)-C(12)	1.450(4)	
C(9)-C(13)	1.535(4)	
C(9)-C(7)-C(8)		60.75(19)
C(7)-C(8)-C(9)		59.65(18)
C(7)-C(9)-C(8)		59.60(19)
C(5)-C(4)-C(7)		123.2(3)
C(3)-C(4)-C(7)		118.8(3)
C(4)-C(7)-C(9)		122.9(2)
C(4)-C(7)-C(8)		124.1(2)
C(10)-C(8)-C(7)		117.9(3)
C(10)-C(8)-C(9)		118.9(3)
C(12)-C(9)-C(7)		116.2(2)
C(12)-C(9)-C(8)		114.9(2)
C(7)-C(9)-C(13)		120.0(2)
C(12)-C(9)-C(13)		113.2(2)
C(8)-C(9)-C(13)		122.9(2)

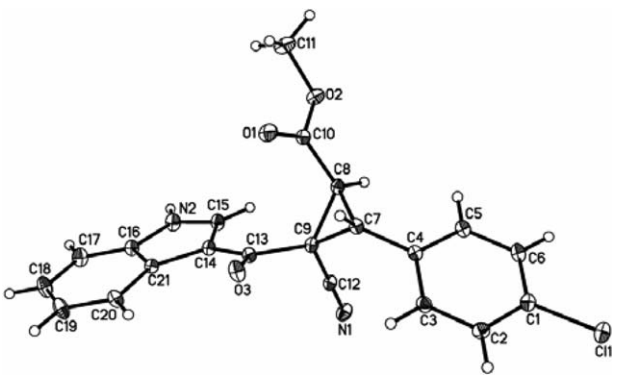


Figure 1. X-ray crystal structure of **3f**.

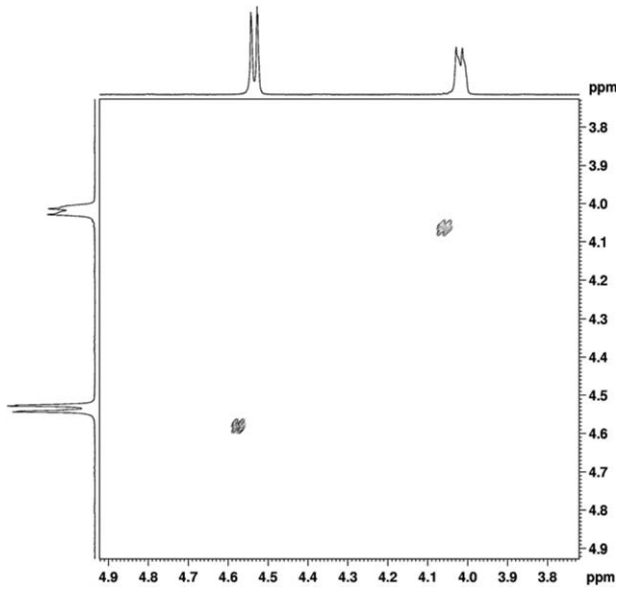


Figure 2. NOE spectrum of compound **3a**.

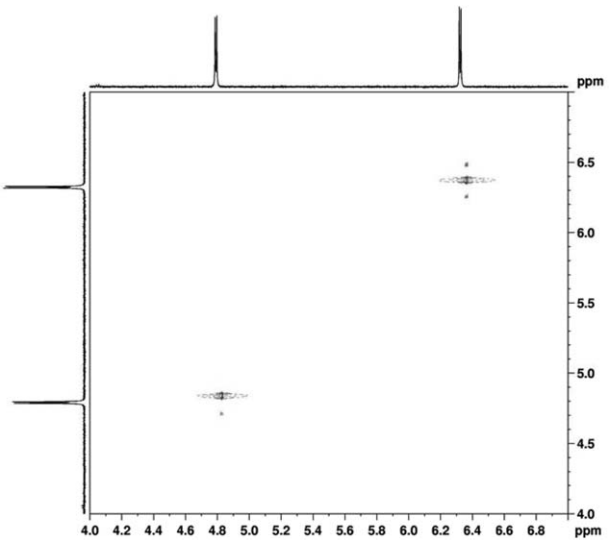


Figure 3. NOE spectrum of compound **3b**.

(potassium bromide): 3356, 2234 (CN), 1679 (CO), 1642 (CO), 1423, 750 cm^{-1}; ms (m/z) (%): 390 (M^+, 16), 388 (100); Anal. calcd. for $C_{26}H_{18}N_2O_2$: C, 79.98; H, 4.65; N, 7.17. Found: C, 80.15; H, 4.87; N, 6.96.

Trans-2-benzoyl-1-(1H-indole-3-carbonyl) -3-(4-chlorophenyl)-cyclopropanecarbonitrile (3b). This compound was obtained as white solid, mp 112–113°C (petroleum ether–ethyl acetate (v:v =1:1)); ^{1}H NMR (500 MHz, hexadeuteroacetone): δ 4.03 (d, J = 8.0 Hz, 1H), 4.56 (d, J = 8.0 Hz 1H), 7.21–7.24 (m, 2H), 7.51–7.57 (m, 5H), 7.64–7.67 (m, 1H), 7.71–7.72 (m, 2H), 8.16–8.20 (m, 3H), 8.43 (s, 1H), 11.22 (br s, 1H); ^{13}C NMR (125 MHz, hexadeuteroacetone): δ 35.2, 37.2, 38.1, 113.1, 115.6, 118.6, 122.7, 123.5, 124.7, 126.9, 129.4, 129.6, 129.7, 131.2, 133.6, 134.5, 134.6, 135.4, 137.6, 137.7, 180.4, 192.1; IR (potassium bromide): 3366, 2234 (CN), 1679 (CO), 1641 (CO), 1423, 751 cm-^{1}; ms (m/z) (%): 426 (M^+ +1, 1), 425 (M^+, 4), 319 (100); Anal. calcd. for $C_{26}H_{17}ClN_2O_2$: C, 73.50; H, 4.03; N, 6.59. Found: C, 73.32; H, 4.23; N, 6.81.

Trans-2-benzoyl-1-(1H-indole-3-carbonyl) -3-(3-bromo-phenyl)-cyclopropanecarbonitrile (3c). This compound was obtained as white solid, mp 214–215°C (petroleum ether–ethyl acetate (v:v = 1:1); ^{1}H NMR (500 MHz, hexadeuteroacetone): δ 4.05 (d, J = 8.0 Hz, 1H), 4.64 (d, J = 8.0 Hz 1H), 7.21–7.28 (m, 3H), 7.44–7.47 (m, 3H), 7,51–7.52 (m, 1H), 7.54–7.57 (m, 1H), 7.60–7.67 (m, 1H), 7.70–7.72 (m, 1H), 7.90–8.21 (m, 3H), 8.43 (s, 1H), 11.21 (br s 1H); ^{13}C NMR (125 MHz, hexadeuteroacetone): δ 35.1, 37.2, 38.0, 113.1, 115.6, 118.5, 122.7, 123.2, 123.5, 124.7, 126.9, 128.7, 129.4, 129.6, 131.5, 132.1, 132.2, 134.5, 135.4, 137.4, 137.6, 137.7, 180.3, 192.0. IR (potassium bromide): 3352, 2236 (CN), 1675 (CO), 1615 (CO), 1433, 746 cm^{-1}; ms (m/z) (%): 471 (M^+ +2, 1), 470 (M^+ +1, 4), 469 (M^+, 2), 105 (100). Anal. calcd. for $C_{26}H_{17}BrN_2O_2$: C, 66.54; H, 3.65; N, 5.97. Found: C, 66.20 ; H, 3.74; N, 5.87.

Trans-2-benzoyl-1-(1H-indole-3-carbonyl)-3-(4-methoxy-phenyl)-cyclopropanecarbonitrile (3d). This compound was obtained as white solid, mp 161°C (petroleum ether–ethyl acetate (v:v = 1:1)); ^{1}H NMR (500 MHz, hexadeuteroacetone): δ 3.85 (s, 3H), 3.94 (d, J = 8.0 Hz, 1H), 4.44 (d, J = 8.0 Hz 1H), 7.03–7.05 (m, 2H), 7.20–7.27 (m, 2H), 7.51–7.53 (m,1H), 7.54–7.64 (m, 2H), 7.66–7.67 (m, 3H), 8.15–8.19 (m, 3H), 8.43 (s, 1H), 11.20 (br s, 1H); ^{13}C NMR (125 MHz, hexadeuteroacetone): δ 35.8, 37.3, 38.3, 55.6, 113.1, 115.0, 115.8, 118.9, 122.7, 123.5, 124.6, 126.3, 126.9, 129.4, 129.6, 130.6, 134.4, 135.3, 137.6, 137.9, 160.7, 181.0, 192.4; IR (potassium bromide): 3220, 2233 (CN), 1677 (CO), 1637 (CO), 1425, 750 cm^{-1}; ms (m/z) (%): 420 (M^+, 7), 315 (100); Anal. calcd. for $C_{27}H_{20}N_2O_3$: C, 77.13; H, 4.79; N, 6.66. Found: C, 76.95; H, 4.98; N, 6.47.

Scheme 2

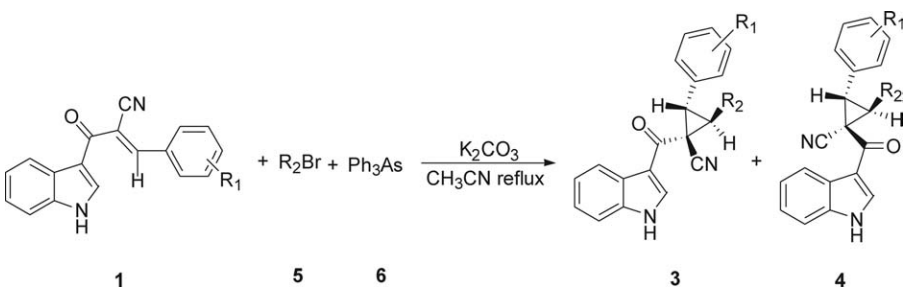


Table 4

Optimization of one-pot cyclopropanation reaction condition.

Entry	R_1	R_2	Base	Solvent	Triphenylarsine (equiv)	Temp (°C)	Time (h)	Yield **3f**(%)
1	4-Cl	CO_2CH_3	K_2CO_3	chloroform	0.1	reflux	48	47
2	4-Cl	CO_2CH_3	K_2CO_3	acetonitrile	0.1	reflux	3	55
3	4-Cl	CO_2CH_3	K_2CO_3	DME	0.1	reflux	2.5	45
4	4-Cl	CO_2CH_3	K_2CO_3	nitromethane	0.1	reflux		0
5	4-Cl	CO_2CH_3	$NaHCO_3$	acetonitrile	0.1	reflux	40	38
6	4-Cl	CO_2CH_3	$KF.2H_2O$	acetonitrile	0.1	reflux	48	?
7	4-Cl	CO_2CH_3	K_2CO_3	acetonitrile	0.05	reflux	7	40
8	4-Cl	CO_2CH_3	K_2CO_3	acetonitrile	0.25	reflux	2.5	63
9	4-Cl	CO_2CH_3	K_2CO_3	acetonitrile	0.5	reflux	2.5	66
10	4-Cl	CO_2CH_3	K_2CO_3	acetonitrile	0.75	reflux	2	72
11	4-Cl	CO_2CH_3	K_2CO_3	acetonitrile	1	reflux	2	75

Trans-1,3-dihydro-2-cyano-2-(1H-indole-3-carbonyl)-3-phenyl-cyclopropanecarboxylic acid methyl ester (3e). This compound was obtained as white solid, mp 165–166°C (petroleum ether–ethyl acetate (v:v = 1:1)); ^{1}H NMR (500 MHz, hexadeuteroacetone): δ 3.56 (d, J = 8.0 Hz, 1H), 3.57 (s, 3H), 3.78 (d, J = 8.0 Hz 1H), 7.28–7.33 (m, 2H), 7.40–7.43 (m, 1H), 7.46–7.49 (m, 2H), 7.55–7.60 (m, 3H), 8.26-8.28 (m, 1H), 8.46 (s, 1H), 11.33 (br s, 1H); ^{13}C NMR (125 MHz, hexadeuteroacetone): δ 34.5, 34.8, 34.9, 52.9, 113.2, 115.6, 118.3, 122.7, 123.6, 124.8, 126.9, 129.1, 129.2, 129.6, 134.0, 135.4, 137.8, 168.0, 180.4; IR (potassium bromide): 3400, 2241 (CN), 1730 (CO), 1660 (CO), 1425, 755 cm^{-1}; ms (m/z) (%): 345 (M^+ +1, 4), 344 (M^+, 24), 285 (100); Anal. calcd. for $C_{21}H_{16}N_2O_3$: C, 73.24; H, 4.68; N, 8.13. Found: C, 72.98; H, 4.89; N, 8.42.

Trans-1,3-dihydro-3-(4-chlorophenyl)-2-cyano-2-(1H-indole-3-carbonyl)-cyclopropanecarboxylic acid methyl ester (3f). This compound was obtained as white solid, mp 226–227°C (petroleum ether–ethyl acetate (v:v = 1:1)); ^{1}H NMR (500 MHz, hexadeuteroacetone): δ 3.59 (s, 3H), 3.60 (d, J = 8.0 Hz, 1H), 3.80 (d, J = 8.0 Hz 1H), 7.28–7.33 (m, 2H), 7.49–7.51 (m, 2H), 7.58–7.60 (m, 3H), 8.26–8.28 (m, 1H), 8.48 (s, 1H), 11.34 (br s, 1H); ^{13}C NMR (125 MHz, hexadeuteroacetone): δ 34.2, 34.7, 34.8, 52.9, 113.2, 115.5, 118.2, 122.6, 123.6, 124.8, 126.9, 129.7, 131.0, 133.1, 134.6, 135.5, 137.7, 167.8, 180.0; IR (potassium bromide): 3399, 2241 (CN), 1733 (CO), 1657 (CO), 1426, 753 cm^{-1}; ms (m/z) (%): 379 (M^+ +1, 10), 378 (M^+, 22), 319 (100); Anal. calcd. for $C_{21}H_{15}ClN_2O_3$: C, 66.58; H, 3.99; N, 7.40. Found: C, 66.49; H, 4.09; N, 7.53.

Trans-1,3-dihydro-3-(4-bromophenyl)-2-cyano-2-(1H-indole-3-carbonyl)-cyclopropanecarboxylic acid methyl ester (3g). This compound was obtained as white solid, mp 231–232°C (petroleum ether–ethyl acetate (v:v= 1:1)); ^{1}H NMR (500 MHz, hexadeuteroacetone): δ 3.59 (s, 3H), 3.67 (d, J = 8.0 Hz, 1H), 3.80 (d, J = 8.0 Hz 1H), 7.28–7.33 (m, 2H), 7.42–7.45 (m, 1H), 7.58–7.61 (m, 3H), 7.77–7.78 (m, 1H). 8.26–8.27 (m, 1H), 8.48 (s, 1H), 11.34 (br s, 1H); ^{13}C NMR (125 MHz, hexadeuteroacetone): δ 34.2, 34.6, 34.8, 52.9, 113.2, 115.5, 118.1, 122.6, 123.2, 123.6, 124.8, 126.9, 128.4, 131.6, 132.1, 132.2, 135.5, 136.8, 137.7, 167.7, 180.0; IR (potassium bromide): 3395, 2242 (CN), 1728 (CO), 1657 (CO), 1426, 753 cm^{-1}; ms (m/z) (%): 425 (M^+ +2, 4), 424 (M^+ +1, 18), 423 (M^+, 5), 365 (100), 363 (100); Anal. calcd. for $C_{21}H_{15}BrN_2O_3$: C, 59.59; H, 3.57; N, 6.62. Found: C, 59.75; H, 3.81; N, 6.40.

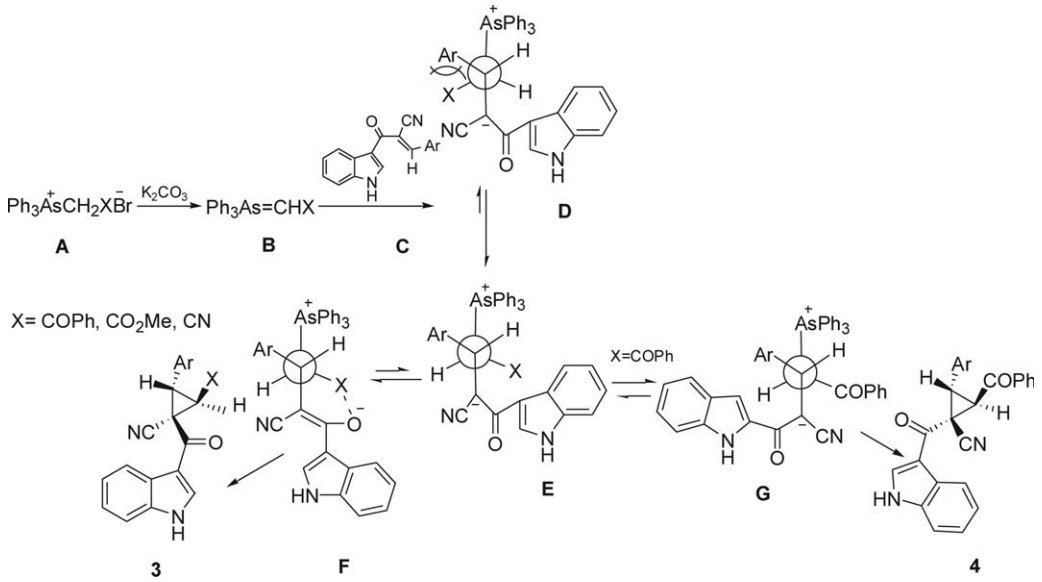
Trans-1,3-dihydro-2-cyano-2-(1H-indole-3-carbonyl)-3-(4-methylphenyl)-cyclopropanecarboxylic acid methyl ester (3h). This compound was obtained as white solid, mp 203–204°C (petroleum ether–ethyl acetate (v:v = 1:1)); ^{1}H NMR (500 MHz, hexadeuteroacetone): δ 2.36 (s, 3H), 3.51 (d, J = 7.5 Hz, 1H), 3.59 (s, 3H), 3.73 (d, J = 7.5 Hz 1H), 7.23–7.33 (m, 4H), 7.42–7.44 (m, 2H), 7.58–7.60 (m, 1H), 8.26–8.28 (m, 1H), 8.46 (s, 1H), 11.31 (br s, 1H); ^{13}C NMR (125 MHz, hexadeuteroacetone) δ 21.1, 34.5, 34.8, 34.9, 52.8, 113.2, 115.6, 118.4, 122.7, 123.6, 124.7, 126.9, 129.1, 130.3, 131.0, 135.4, 137.8, 138.9, 168.0, 180.5; IR (potassium bromide): 3398, 2240 (CN), 1732 (CO), 1658 (CO), 1426, 754 cm^{-1}; ms (m/z)

Table 5

Cyclopropanation of olefin with triphenylarsine and bromide *via* one-pot reaction.

Entry	Product	R1	R2	Reaction time (h)	Yield **3**(%)	Yield **4**(%)
1	**a**	H	COPh	2	48	5
2	**b**	4-Cl	COPh	2	58	7
3	**c**	3-Br	COPh	2.5	55	5
4	**d**	4-OCH_3	COPh	3	50	8
5	**e**	H	CO_2CH_3	3.5	65	0
6	**f**	4-Cl	CO_2CH_3	2	72	0
7	**g**	3-Br	CO_2CH_3	5	68	0
8	**h**	4-CH_3	CO_2CH_3	6	60	0
9	**i**	4-OCH_3	CO_2CH_3	4.5	66	0
10	**j**	H	CN	7	30	0
11	**k**	4-Cl	CN	15	35	0

Scheme 3



(%): 358 (M^+, 26), 299 (100); Anal. calcd. for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.92; H, 4.88; N, 7.57.

Trans-1,3-dihydro-2-cyano-2-(1H-indole-3-carbonyl)-3-(4-methoxyphenyl)-cyclopropanecarboxylic acid methyl ester (3i). This compound was obtained as white solid, mp 196–197°C (petroleum ether–ethyl acetate (v:v= 1:1)); ^{1}H NMR (500 MHz, hexadeuteroacetone): δ 3.49 (d, J = 8.0 Hz 1H), 3.60 (s, 3H), 3.72 (d, J = 8.0 Hz, 1H), 3.83 (s, 3H), 7.00–7.03 (m, 2H), 7.27–7.32 (m, 2H), 7.46–7.49 (m, 2H), 7.57–7.60 (m, 1H), 8.26–8.28 (m, 1H), 8.46 (s, 1H), 11.31 (br s, 1H); ^{13}C NMR (125 MHz, hexadeuteroacetone): δ 34.6, 34.7, 52.8, 55.6, 113.1, 113.2, 115.0, 115.6, 118.5, 122.6, 123.6, 124.7, 125.7, 126.9, 130.4, 135.4, 137.7, 160.7, 168.1, 180.6; IR (potassium bromide): 3340, 2239 (CN), 1731 (CO), 1658 (CO), 1427, 753 cm^{-1}; ms (m/z) (%): 374 (M^+, 48), 315 (100); Anal. calcd. for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.35; H, 5.02; N, 7.21.

Trans-2,3-dihydro-1-(1H-indole-3-carbonyl)-3-phenyl-cyclopropane-1,2-dicarbonitrile (3j). This compound was obtained as white solid, mp 193–194°C (petroleum ether–ethyl acetate (v:v= 1:1)); ^{1}H NMR (500 MHz, hexadeuteroacetone): δ 3.59 (d, J = 9.0 Hz 1H), 3.64 (d, J = 9.0 Hz, 1H), 7.30–7.34 (m, 2H), 7.45–7.48 (m, 1H), 7.50–7.53 (m, 2H), 7.63–7.64 (m, 1H), 7.71–7.72 (m, 2H), 8.29–8.31 (m, 1H), 8.86 (s, 1H), 11.45 (br s, 1H); ^{13}C NMR (125 MHz, hexadeuteroacetone): δ 20.5, 32.3, 37.0, 113.3, 115.0, 115.8, 117.6, 122.9, 123.8, 124.9, 127.4, 129.7, 129.8, 130.4, 131.8, 135.7, 137.4, 180.0; IR (potassium bromide): 3278, 2245 (CN), 1615 (CO), 1425, 753 cm^{-1}; ms (m/z) (%): 311(M^+, 100); Anal. calcd. for $C_{20}H_{13}N_3O$: C, 77.16; H, 4.21; N, 13.50. Found: C, 77.39; H, 4.57; N, 13.30.

Trans-2,3-dihydro-3-(4-chlorophenyl)-1-(1H-indole-3-carbonyl)-cyclopropane-1,2-dicarbonitrile (3k). This compound was obtained as white solid, mp 201–202°C (petroleum ether–ethyl acetate (v:v = 1:1)); ^{1}H NMR (500 MHz, hexadeuteroacetone): δ 3.59 (d, J = 9.0 Hz 1H), 3.66 (d, J = 9.0 Hz, 1H), 7.29–7.35 (m, 2H), 7.55–7.57 (m, 2H), 7.62–7.64 (m, 1H), 7.74–7.76 (m, 2H), 8.28–8.30 (m, 1H), 8.60 (s, 1H), 11.46 (br s, 1H); ^{13}C NMR (125 MHz, hexadeuteroacetone): δ 20.8, 32.3, 36.2, 113.3, 115.1, 115.7, 117.5, 122.9, 123.9, 125.0, 127.4, 129.8, 130.8, 132.2, 135.3, 135.7, 137.4, 180.0; IR (potassium bromide): 3350, 2244 (CN), 1602 (CO), 1435, 751 cm^{-1}; ms (m/z) (%): 346 (M^+ +1, 33), 345 (M^+, 85), 144 (100); Anal. calcd. for $C_{20}H_{12}ClN_3O$: C, 59.59; H, 3.57; N, 6.62. Found: C, 59.81; H, 3.29; N, 6.49.

Cis-2-benzoyl-1-(1H-indole-3-carbonyl)-3-phenyl-cyclopropanecarbonitrile (4a). This compound was obtained as white solid, mp 220–221°C (petroleum ether–ethyl acetate (v:v = 1:1)); ^{1}H NMR (500 MHz, hexadeuteroacetone): δ 4.97 (d, J = 5.0 Hz, 1H), 6.32 (d, J = 5.0 Hz 1H), 7.12–7.15 (m, 2H), 7.23–7.26 (m, 3H), 7.37–7.40 (m, 1H), 7.44–7.47 (m, 3H), 7.56–7.62 (m, 2H), 7.72–7.75 (m, 1H), 8.01–8.07 (m, 2H), 8.29 (s, 1H), 11.15 (br s, 1 H); ^{13}C NMR (125 MHz, hexadeuteroacetone): δ 51.0, 79.8, 89.8, 104.4, 112.1, 117.3, 121.2, 121.6, 122.9, 125.2, 127.8, 128.0, 128.9, 129.0, 129.1, 129.2, 134.0, 134.2, 136.3, 140.9, 165.7, 193.3. IR (potassium bromide): 3292, 2196 (CN), 1706 (CO), 1610 (CO), 1163, 745 cm^{-1}; ms (m/z) (%): 390 (M^+, 20), 285 (100); Anal. calcd. for $C_{26}H_{18}N_2O_2$: C, 79.98; H, 4.65; N, 7.17. Found: C, 80.12; H, 4.80; N, 6.93.

Cis-2-benzoyl-1-(1H-indole-3-carbonyl)-3-(4-chlorophenyl)-cyclopropanecarbonitrile (4b). This compound was obtained as white solid, mp 212–213°C (petroleum ether–ethyl acetate (v:v = 1:1)); ^{1}H NMR (500 MHz, hexadeuteroacetone): δ 4.85 (d, J = 5.0 Hz, 1H), 6.34 (d, J = 5.0 Hz 1H), 7.12–7.15 (m, 1H), 7.22–7.26 (m, 1H), 7.50 (s, 4H), 7.56–7.58 (m, 1H), 7.60–7.63 9m, 2H), 7.72–7.76 (m, 1H), 7.99–7.80 (m, 1H), 8.00–8.09 (m, 2H), 8.29 (s, 1H), 11.17 (br s, 1 H); ^{13}C NMR (125 MHz, hexadeuteroacetone): δ 51.1, 80.3, 90.4, 105.2, 113.1, 118.0, 122.1, 122.5, 123.9, 126.0, 129.8, 130.0130.1, 130.2, 130.5, 134.2, 134.9, 135.0, 137.2, 140.7, 166.8, 194.0; IR (potassium bromide) 3265, 2202 (CN), 1703 (CO), 1611(CO), 1162, 747 cm^{-1}.; ms (m/z) (%):426 (M^+ +1, 5), 425 (M^+, 6), 105 (100); Anal. calcd. for $C_{26}H_{17}ClN_2O_2$: C, 73.50; H, 4.03; N, 6.59. Found: C, 73.29; H, 4.26; N, 6.79.

Cis-2-benzoyl-1-(1H-indole-3-carbonyl)-3-(3-bromophenyl)-cyclopropanecarbonitrile (4c). This compound was obtained as white solid, mp 194–195°C (petroleum ether–ethyl acetate (v:v= 1:1)); ^{1}H NMR (500 MHz, hexadeuteroacetone): δ 4.88 (d, J = 5.0 Hz, 1H), 6.39 (d, J = 5.0 Hz 1H), 7.11–7.14 (m, 1H), 7.22–7.25 (m, 1H), 7.41–7.44 (m, 1H), 7.55–7.57 (m, 2H), 7.60–7.63 (m, 3H), 7.66 (s, 1H), 7.73–7.76 (m,1H), 7.97–7.99 (m, 1H), 8.09–8.11 (m, 2H), 8.30 (s, 1H), 11.21 (br s, 1H); ^{13}C nmr (125 MHz, hexadeuteroacetone): δ 51.1, 80.1, 90.3, 105.2, 113.1, 118.0, 122.1, 122.5, 123.9, 126.0, 127.8, 129.8, 130.1, 130.2, 131.6, 131.9, 132.0, 134.9, 135.1, 137.2, 144.4, 166.8, 193.9; IR (potassium bromide) 3264, 2203 (CN), 1705 (CO), 1611 (CO), 1165, 747 cm^{-1}; ms (m/z) (%): 471 (M^+ +2, 2), 470 (M^+ +1, 11), 469 (M^+, 12), 105 (100); Anal. calcd. for $C_{26}H_{17}BrN_2O_2$: C, 66.54; H, 3.65; N, 5.97. Found: C, 66.39; H, 3.71; N, 5.82.

Cis-2-benzoyl-1-(1H-indole-3-carbonyl)-3-(4-methoxyphenyl)-cyclopropanecarbonitrile (4d). This compound was obtained as white solid, mp 211–212°C (petroleum ether–ethyl acetate (v:v = 1:1)); ^{1}H NMR (500 MHz, hexadeuteroacetone): δ 3.83 (s, 3H), 4.71 (d, J = 5.0 Hz, 1H), 6.27 (d, J = 5.0 Hz 1H), 6.99–7.00 (m, 1H), 7.01–7.02 (m, 1H), 7.12–7.15 (m, 2H), 7.22–7.26 (m, 1H), 7.35–7.38 (m, 2H), 7.56–7.61 (m, 1H), 7.71–7.75 (m, 2H), 8.02–8.05 (m, 3H), 8.06 (s, 1H), 11.15 (br s, 1 H); ^{13}C NMR (125 MHz, hexadeuteroacetone): δ 51.5, 55.6, 81.0, 90.8, 105.4, 113.0, 115.4, 118.2, 122.0, 122.6, 123.8, 126.1, 129.7, 129.8, 130.0, 133.5, 134.9, 135.0, 137.2, 160.5, 166.3, 194.2; IR ((potassium bromide) 3274, 2199 (CN), 1703 (CO), 1611 (CO), 1164, 743 cm^{-1}; ms (m/z) (%): 420 (M^+, 13), 315 (100); Anal. calcd. for $C_{27}H_{20}N_2O_3$: C, 77.13; H, 4.79; N, 6.66. Found: C, 76.89; H, 4.88; N, 6.52.

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REFERENCES AND NOTES

[1] (a) Han, Z.; Uehira, S.; Tsuritani, T.; Shinokubo, H.; Oshima, K. Tetrahedron 2001, 57, 987; (b) Bertozzi, F.; Gustalsson, M.; Olsson, R. Org lett 2002, 4, 3147; (c) Wurz, R. P.; Charette, A. B. Org lett 2005, 7, 2313; (d) Liu. L.; Montgomery, J. J Am Chem Soc 2006, 128, 5348; (e) Yang, Y.-H.; Shi, M. Org lett 2006, 8, 1709; (f) Yadav, J. S.; Subba Reddy, B. V.; Chandrakanth, D.; Satheesh, G. Tetrahedron lett 2007, 48, 8040; (g) Rashid, M. A.; Iqbal, I.; Rasool, N.; Imran, M.; Langer, P. Tetrahedron lett 2008, 49, 4266.

[2] (a) Wurz, R. P.; Charette, A. B. Org lett 2003, 5, 2327; (b) Concellón, J. M.; Rodriguez-Solla, H.; Méjica, C.; Blanco, E. G. Org lett 2007, 9, 2981.

[3] (a) Joule, J. A.; Mills, K. Heterocyclic Chemistry, 4 th ed.; Blackwell Science: Oxford, 2000; (b) Sundberg, R. J. Indoles; Academic Press: London, 1996; (c) Agarwal, S.; Caemmerer, S.; Filali, S.; Froehner, W.; Knoell, J.; Krahl, M. P.; Reddy, K. R.; Knolker, H.-J. Curr Org Chem 2005, 9, 1601; (d) O'Connor, S. E.; Maresh, J. J Nat Prod Rep 2006, 23, 532.

[4] Slätt, J.; Romero, I.; Bergman, J. Synthesis 2004, 2760.

[5] (a) Motokura, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. Tetrahedron Lett 2004, 45, 6029; (b) Rajapakse, H. A.; Zhu, H.; Young, M. B.; Mott, B. T. Tetrahedron Lett 2006, 47, 4827; (c) Yin, W.; Ma, Y.; Xu, J.; Zhao, Y. J Org Chem 2006, 71, 4312; (d) Savitha, V.; Niveditha, S. K.; Muralidharan, D.Perumal, P. T. Tetrahedron Lett 2007, 48, 2943; (e) Parenty, A. D. C.; Song, Y.-F.; Richmond, C. J.; Cronin, L. Org Lett 2007, 9, 2253.