Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 6404

www.rsc.org/obc

PAPER

Copper-catalyzed domino coupling reaction: an efficient method to synthesize oxindoles†

Jen-Chieh Hsieh,* An-Yi Cheng, Jun-Hao Fu and Ting-Wei Kang

Received 30th April 2012, Accepted 11th June 2012
DOI: 10.1039/c2ob26110c

An efficient and novel procedure for a copper catalyzed domino coupling reaction has been developed, which afforded various oxindoles in good to excellent yields with tolerance of various substituents. In addition, this method could be applied to synthesize horsfiline and coerulescine in few steps with high total yields.

Introduction

Oxindole derivatives are very important compounds in organic synthesis because of their frequent discovery in the core structure of natural alkaloids[1] and bioactive compounds.[2] Although numerous strategies for the synthesis of oxindoles have been developed, they often involve palladium catalysis, for instance the Heck reaction,[3] Heck–cyanation,[4] cyanoamidation,[5] arylamidation[6] and α-arylation.[7] Recent research on the synthesis of oxindoles has been extended to the use of palladium catalytic C–H functionalization,[8] which has the advantages of atom economy and the easy preparation of substrates. While palladium catalysis is powerful, there are still some drawbacks such as high cost and air-sensitivity.

A copper-catalyzed coupling reaction is an alternative procedure with low cost and can be utilized under aerobic conditions.[9] Because of the advantages, it has received considerable attention. Many reports also revealed that copper-catalyzed coupling reactions can be involved in domino processes for the synthesis of complicated compounds and alkaloids;[10] however, only a few reports are related to the synthesis of oxindoles. In 2009, Kündig and Jia developed stoichiometric copper-mediated C–H functionalization to form oxindoles.[11] Later, Taylor realized the copper catalytic synthesis of oxindoles *via* C–H activation.[12] Typical intramolecular Ullmann type C–N coupling reactions were also utilized to synthesize oxindoles by Viswanathan and Katkevics.[13] However, the present literature involving copper-mediated coupling reactions always requires N-protected substrates to facilitate the synthesis of oxindoles. This limitation toughens the synthesis of natural alkaloids; thus, the development of the direct synthesis of oxindoles without N-substituents *via* copper catalysis is desirable. Our experience in transition-metal-catalyzed coupling reactions[14,15] encouraged us to explore the possibility for effecting this transformation *via* copper catalysis. To the best of our knowledge, this is the first example of the synthesis of oxindoles *via* copper-catalyzed multiple bond formation.

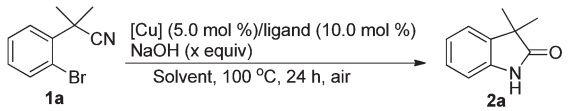
Results and discussion

In a preliminary reaction, treatment of 2-(2-bromophenyl)-2-methylpropanenitrile (**1a**) in the presence of 5 mol% CuI and 2.0 equiv NaOH in 5.0 mL DMF at 100 °C for 24 h afforded the corresponding 3,3-dimethylindolin-2-one (**2a**) in 21% yield (Table 1, entry 1). Most of the starting materials were unchanged even after a longer reaction time. Further investigation was focused on the effect of ligand, solvent, copper source and the amount of NaOH, and the results are summarized in Table 1. The effect of solvent is crucial; among the variously employed polar solvents, only *t*-BuOH significantly enhanced the reaction (entry 4). The employment of amino acids as ligands is very helpful (entries 5–10),[14] and *N*-acetylglycine showed the best ability, increasing the yield of **2a** to 69% (entry 9). Of the various copper sources (entries 11–13), CuI provided a better yield of **2a** than the others. It is noteworthy that the present catalytic reaction required NaOH to be the source of the oxygen atom; the desired product **2a** was not obtained without the presence of NaOH. In addition, the amount of NaOH (entries 14–16) is also influential, and 3 equivalents of NaOH was found to be optimal, improving the yield of **2a** to 87% (entry 15). The replacement of NaOH by LiOH or KOH slightly decreased the yield of **2a**. It was found that a small amount of KI could greatly improve the reaction and provide **2a** in excellent yield even for lower loadings of CuI (entries 17, 18);[16] however, the reaction could not provide any desired product **2a** unless CuI was present. In addition, this catalytic reaction proceeded well under both aerobic conditions and nitrogen atmosphere.

Department of Chemistry, Tamkang University, New Taipei City, 25137, Taiwan (R.O.C.). E-mail: jchsieh@mail.tku.edu.tw; Fax: +886-2-26209924; Tel: +886-2-26215656ext2545

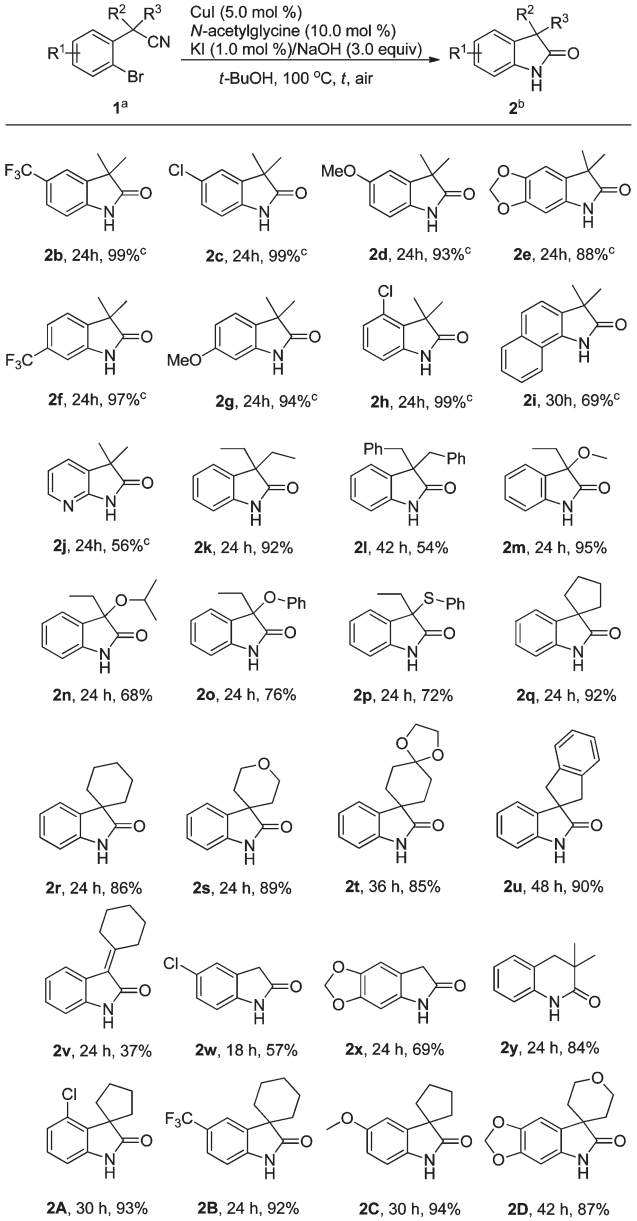
†Electronic supplementary information (ESI) available: Experimental procedure, characterization data, spectral data and copies of all compounds. See DOI: 10.1039/c2ob26110c

Table 1 Optimization of reaction conditions[a]



Entry	[Cu]	L	*x*	Solvent	Yield[b] (%)
1	CuI	None	2.0	DMF	21
2	CuI	None	2.0	DME	6
3	CuI	None	2.0	DMSO	17
4	CuI	None	2.0	*t*-BuOH	36
5	CuI	L1	2.0	*t*-BuOH	55
6	CuI	L2	2.0	*t*-BuOH	42
7	CuI	L3	2.0	*t*-BuOH	48
8	CuI	L4	2.0	*t*-BuOH	37
9	CuI	L5	2.0	*t*-BuOH	69
10	CuI	L6	2.0	*t*-BuOH	46
11	CuSCN	L5	2.0	*t*-BuOH	43
12	Cu_2O	L5	2.0	*t*-BuOH	38
13	$Cu(OTf)_2$	L5	2.0	*t*-BuOH	47
14	CuI	L5	1.5	*t*-BuOH	54
15	CuI	L5	3.0	*t*-BuOH	87
16	CuI	L5	4.0	*t*-BuOH	81
17[c]	CuI	L5	3.0	*t*-BuOH	99 (96)[d]
18[c,e]	CuI	L5	3.0	*t*-BuOH	97 (96)[d]

[a] 0.5 mmol scale. [b] ^{1}H NMR yield on the basis of internal standard mesitylene. [c] 1.0 mol% KI. [d] Isolated yield. [e] 3.0 mol% CuI with 6.0 mol% ligand.



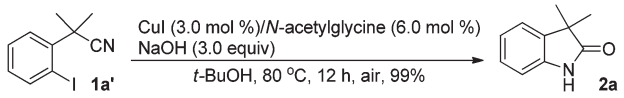
Scheme 1 Copper-catalyzed cyclization to form oxindole. [a]0.5 mmol scale. [b]All reported yields of **2** are isolated yields. [c]3.0 mol% CuI with 6.0 mol% ligand.

The copper-catalyzed reaction was successfully extended to various oxindoles; the results are listed in Scheme 1. The electronic effect of the arene moiety is slightly related to the yields (**2b–2h**). Thus, the EWG on the *para* position of bromide provided excellent yields of products **2b** and **2c**, but the EDG gave products **2d** and **2e** in slightly lower yields. Substituents on the *meta* position did not affect the reaction, the corresponding products **2f**, **2g** and **2h** were obtained in excellent yields. Naphthyl and pyridine moieties were also tolerated giving products **2i** and **2j** but they were obtained in moderate yields of 69% and 56%, respectively.

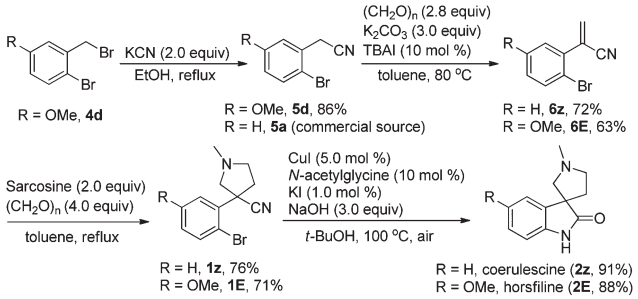
A wide variety of substituents and spiro rings on the 3,3 position of oxindole could be also well tolerated (**2k–2D**). It was observed that the size of the substituent on the 3,3 position of the oxindole dominated the yields of the reactions (**2k**, **2l**). Thus, the yield of the corresponding product was decreased along with the increase of the size of the substituent. Products with substituents on the 3 position containing oxygen and sulfur were afforded in moderate yields (**2m–2p**). The comparably lower yields were caused by the leaving of the RO- and RS-groups. A spiro ring on the 3,3 position of oxindoles were also obtained in good to excellent yields (**2q–2u**); it is interesting that the size of the substituents on the ring did not significantly affect the yields of the desired products. 3-Alkenyl oxindole (**2v**) could be prepared as well, which is related to large number of alkaloids and medicines.[1d] However, the low yield of **2v** was due to the nucleophilic addition of hydroxide to olefin. Not only the quaternary carbon on the 3 position, but also the products with secondary carbon on the 3,3-unsubstituted oxindoles (**2w**, **2x**) can be afforded in moderate yields. It was found that proton abstraction causing rearrangement and substitution for the secondary carbon occurs, but as a minor behavior. Cyclization for the six-membered ring was also possible; the corresponding product **2y** was obtained in good yield. Moreover, the combination of various substituents on the 3,3 position and on the arene moiety provided the corresponding products in excellent yields (**2A–2D**).

After exploring the scope of the reaction, we tested the reactivity of aryl iodide **1a′** and found that the reaction processed very smoothly and provided the corresponding product **2a** in excellent yield at a lower temperature and short reaction time (Scheme 2).

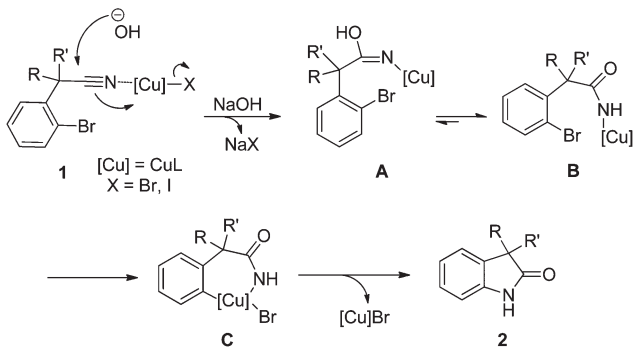
In order to extend the application of this developed method, the synthesis of alkaloids was attempted. Thus, we created a



Scheme 2 Reaction involving aryl iodide.



Scheme 3 Synthesis of (±)-coerulescine and (±)-horsfiline.



Scheme 4 Proposed mechanism.

novel synthetic route to form horsfiline[17,18] and coerulescine[19,20] by using this copper catalysis as the key step (Scheme 3). The synthesis began from the preparation of 2-(2-bromo-5-methoxyphenyl)acetonitrile **5d**. Olefination at the 2 position of compounds **5** provided **6** in moderate yields. The [3 + 2] cycloaddition of compounds **6** in the presence of sarcosine and formaldehyde gave **1z** and **1E** in 76% and 71% yields, respectively. Final cyclization by the copper catalytic domino reactions furnished (±)-coerulescine **2z** in 93% yield and (±)-horsfiline **2E** in 88% yield.

After examination of the reaction scope, we turned to studying the mechanism by doing a series of control experiments (see the ESI† for details), and a tentative pathway (Scheme 4) can be proposed according to these results. The copper complex in this reaction plays two different roles, one is acting as a Lewis acid and another is to couple the C–N bond. Thus, the reaction is likely to be initiated by the coordination of the nitrile to compound **1** to form a copper complex, which accelerates the following nucleophilic addition by hydroxide to form complex **A**. It should be noted that without copper complex, the direct hydrolysis from nitrile to amide in NaOH–*t*-BuOH needs almost twice the reaction time. Tautomerization of **A** provides complex **B**, which undergoes oxidative addition in an intramolecular manner to generate complex **C**. Reductive elimination of **C** affords compound **2** and regenerates copper complex.

Conclusions

In conclusion, we have developed a novel methodology for a copper-catalyzed domino coupling reaction. This is a very efficient synthetic route to provide various oxindole derivatives in moderate to excellent yields with tolerance of a wide variety of substrates. Moreover, we can also apply this method to synthesize (±)-coerulescine and (±)-horsfiline in a very efficient way with few steps and high total yields. Further studies to extend the application of this catalytic system are currently underway.

Experimental

General information

All reagents were purchased from Sigma-Aldrich, Fisher-Acros, TCI, or Alfa-Aesar, and were used without further purification unless otherwise noted. THF and Et_2O were distilled from sodium, and CH_3CN was distilled from CaH_2. All manipulations of oxygen- and moisture-sensitive materials were conducted with a standard Schlenk technique. Flash column chromatography was performed using silica gel (230–400 mesh). Analytical thin layer chromatography (TLC) was performed on 60 F_{254} (0.25 mm) plates and visualization was accomplished with UV light (254 and 354 nm) and/or an aqueous alkaline $KMnO_4$ solution followed by heating. Proton and carbon nuclear magnetic resonance spectra (^1H NMR and ^{13}C NMR) were recorded on Bruck 300 or Bruck 600 spectrometer with Me_4Si or solvent resonance as the internal standard (^1H NMR, Me_4Si at 0 ppm, $CHCl_3$ at 7.26 ppm; ^{13}C NMR, Me_4Si at 0 ppm, $CDCl_3$ at 77.0 ppm). ^1H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, br = broad, m = multiplet), coupling constants (Hz), and integration. IR spectral data were recorded on a Brucker TENSOR 37 spectrometer. Melting points (mp) were determined using a Fargo MP-1D. GC-MS data were obtained from the HP 5890 Series II GC/HP 5972 GC MASS Spectrometer System. High resolution mass spectral data were obtained from the MAT-95XL HRMS by using EI method.

General procedure for the copper-catalyzed domino reactions

To a screw-capped vial (10 mL) were added CuI (0.015 mmol, 2.9 mg, 3.0 mol%), KI (0.005 mmol, 0.9 mg, 1.0 mol%), *N*-acetylglycine (0.03 mmol, 3.5 mg, 6.0 mol%), NaOH (1.5 mmol, 60 mg, 3.0 equiv) and 2,2-disubstituted 2-(2-bromophenyl) acetonitrile (**1**, 0.5 mmol, 1.0 equiv) in *t*-BuOH (*tert*-butanol, 5.0 mL). The vial was sealed with a cap and allowed to stir at 100 °C for the specific reaction time. The crude reaction mixture was diluted with CH_2Cl_2, filtered through a thin Celite pad, and concentrated *in vacuo*. The residue was isolated using column chromatography by using hexane and ethyl acetate as eluent to give the pure product. Products **2** were obtained according to this procedure.

3,3-Dimethylindolin-2-one (2a). White solid, mp: 182–184 °C; IR (KBr): 3450, 3096, 1717, 1676, 1410, 1226, 1172, 738, 618, 492 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.62 (br, 1H), 7.20 (t, J = 7.8 Hz, 2H), 7.04 (t, J = 7.8 Hz, 1H), 6.94

(d, J = 7.2 Hz, 1H), 1.41 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 183.9, 139.8, 136.3, 127.6, 122.6, 122.4, 109.8, 44.6, 24.3; HRMS: $C_{10}H_{11}NO$ calculated 161.0841, found 161.0838.

3,3-Dimethyl-5-(trifluoromethyl)indolin-2-one (2b). White solid, mp: 152–154 °C; IR (KBr): 3450, 2930, 2880, 1729, 1629, 1339, 1095, 897, 816, 779, 537 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.89 (br, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.43 (s, 1H), 7.02 (d, J = 7.8 Hz, 1H), 1.44 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 183.8, 142.9, 136.7, 125.5, 125.0 (q, J = 31.5 Hz), 124.4 (q, J = 270 Hz), 119.8, 109.7, 44.8, 24.2; HRMS: $C_{11}H_{10}F_3NO$ calculated 229.0714, found 229.0715.

5-Chloro-3,3-dimethylindolin-2-one (2c). White solid, mp: 162–164 °C; IR (KBr): 3468, 3167, 2874, 2926, 2853, 2304, 1731, 1670, 1481, 1204 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.14 (br, 1H), 7.18–7.16 (m, 2H), 6.88 (d, J = 8.4 Hz, 1H), 1.40 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 183.9, 138.4, 138.0, 127.9, 127.6, 123.2, 110.9, 45.1, 24.2; HRMS: $C_{10}H_{10}ClNO$ calculated 195.0451, found 195.0453.

5-Methoxy-3,3-dimethylindolin-2-one (2d). White solid, mp: 154–156 °C; IR (KBr): 3483, 2966, 1702, 1452, 1029, 596 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.14 (br, 1H), 6.83–6.79 (m, 2H), 6.73 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 3.79 (s, 3H), 1.39 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 183.5, 155.9, 137.7, 133.0, 111.9, 110.1, 110.0, 55.8, 45.1, 24.4; HRMS: $C_{11}H_{13}NO_2$ calculated 191.0946, found 191.0951.

7,7-Dimethyl-5*H*-[1,3]dioxolo[4,5-*f*]indol-6(7*H*)-one (2e). White solid, mp: 244–246 °C; IR (KBr): 3467, 2925, 2284, 1701, 1476, 1118, 1035, 680, 486 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.63 (br, 1H), 6.70 (s, 1H), 6.53 (s, 1H), 5.91 (s, 2H), 1.36 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 184.4, 146.8, 143.2, 133.5, 128.2, 104.1, 100.9, 93.6, 45.0, 24.5; HRMS: $C_{11}H_{11}NO_3$ calculated 205.0739, found 205.0740.

3,3-Dimethyl-6-(trifluoromethyl)indolin-2-one (2f). White solid, mp: 180–181 °C; IR (KBr): 3449, 2970, 2637, 1676, 1460, 1355, 1157, 1052, 640, 519 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.35 (br, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H), 7.21 (s, 1H), 1.44 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 184.0, 140.4, 140.0, 130.3 (q, J = 31.5 Hz), 124.0 (q, J = 270 Hz), 122.8, 119.6 (d, J = 3 Hz), 106.9 (d, J = 3 Hz), 44.9, 24.1; HRMS: $C_{11}H_{10}F_3NO$ calculated 229.0714, found 229.0712.

6-Methoxy-3,3-dimethylindolin-2-one (2g). White solid, mp: 167–169 °C; IR (KBr): 3856, 3449, 3192, 2969, 1712, 1672, 1384, 1351, 1157, 740, 572 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.42 (br, 1H), 7.07 (d, J = 7.8 Hz, 1H), 6.56 (dd, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 1H), 6.53 (d, J = 2.4 Hz, 1H), 3.80 (s, 3H), 1.38 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 184.4, 159.7, 140.7, 128.3, 123.2, 107.2, 97.2, 55.5, 44.2, 24.5; HRMS: $C_{11}H_{13}NO_2$ calculated 191.0946, found 191.0948.

4-Chloro-3,3-dimethylindolin-2-one (2h). White solid, mp: 136–138 °C; IR (KBr): 3469, 3152, 2826, 1723, 1676, 1619, 1247, 1188, 661 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.50 (br, 1H), 7.13 (t, J = 7.8 Hz, 1H), 6.97 (dd, J_1 = 7.8 Hz, J_2 = 0.6 Hz, 1H), 6.88 (dd, J_1 = 7.8 Hz, J_2 = 0.6 Hz, 1H), 1.55 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 183.8, 141.7, 132.0, 130.6, 128.9, 123.5, 108.6, 46.3, 21.3; HRMS: $C_{10}H_{10}ClNO$ calculated 195.0451, found 195.0454.

3,3-Dimethyl-1*H*-benzo[*g*]indol-2(3*H*)-one (2i). White solid, mp: 222–224 °C; IR (KBr): 3468, 2970, 1703, 1459, 1197, 812, 558 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.97 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.57 (t, J = 6.6 Hz, 1H), 7.49 (t, J = 6.6 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 2.17 (br, 1H), 1.53 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 185.7, 135.7, 133.3, 130.8, 128.6, 126.1, 125.8, 122.4, 121.6, 120.2, 119.8, 46.0, 24.2; HRMS: $C_{14}H_{13}NO$ calculated 211.0997, found 211.0994.

3,3-Dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-2(3*H*)-one (2j). White solid, mp: 182–184 °C; IR (KBr): 3450, 3114, 2966, 2874, 1731, 1613, 1466, 1200, 1153, 777 cm^{-1}; ^{1} H NMR (600 MHz, $CDCl_3$): δ 8.16 (dd, J_1 = 5.4 Hz, J_2 = 1.8 Hz, 1H), 7.44 (dd, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H), 6.96 (dd, J_1 = 7.2 Hz, J_2 = 5.4 Hz, 1H), 1.87 (br, 1H), 1.42 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 182.1, 155.6, 146.1, 130.5, 130.4, 118.1, 44.6, 23.8; HRMS: $C_9H_{10}N_2O$ calculated 162.0793, found 162.0794.

3,3-Diethylindolin-2-one (2k). White solid, mp: 166–168 °C; IR (KBr): 3873, 3449, 3136, 2969, 2876, 1667, 1344, 1204, 744 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.40 (br, 1H), 7.20 (td, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 7.12 (d, J = 6.6 Hz, 1H), 7.06 (td, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H), 1.96–1.90 (m, 2H), 1.83–1.78 (m, 2H), 0.64 (t, J = 7.8 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 182.5, 141.3, 132.4, 127.6, 123.1, 122.4, 109.5, 54.9, 30.6, 8.7; HRMS: $C_{12}H_{15}NO$ calculated 189.1154, found 189.1159.

3,3-Dibenzylindolin-2-one (2l). White solid, mp: 218–220 °C; IR (KBr): 3450, 3083, 2919, 2854, 1718, 1625, 1241, 754, 696, 556 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.18–7.17 (m, 2H), 7.09–7.00 (m, 8H), 6.93 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 4H), 6.45 (dd, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H), 3.31 (d, J = 13.2 Hz, 2H), 3.17 (d, J = 13.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 180.1, 140.5, 135.8, 130.6, 130.1, 127.8, 127.7, 126.5, 124.8, 121.7, 109.2, 56.4, 43.5; HRMS: $C_{22}H_{19}NO$ calculated 313.1467, found 313.1463.

3-Ethyl-3-methoxyindolin-2-one (2m). Yellow solid, mp: 160–161 °C; IR (KBr): 3463, 3274, 2984, 2828, 1729, 1621, 1470, 1210, 1139, 765, 706, 646 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.65 (br, 1H), 7.30–7.27 (m, 2H), 7.10 (td, J_1 = 7.2 Hz, J_2 = 0.6 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 3.10 (s, 3H), 2.00 (q, J = 7.2 Hz, 2H), 0.79 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 178.8, 141.3, 129.7, 127.4, 124.6, 123.0, 110.3, 84.0, 53.2, 30.7, 7.3; HRMS: $C_{11}H_{13}NO_2$ calculated 191.0946, found 191.0942.

3-Ethyl-3-isopropoxyindolin-2-one (2n). White solid, mp: 171–172 °C; IR (KBr): 3449, 2923, 1754, 1689, 1625, 1384, 1107, 747, 497 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.00 (br, 1H), 7.30–7.25 (m, 2H), 7.07 (t, J = 7.8 Hz, 1H), 6.94 (d, J = 7.8 Hz, 1H), 3.46–3.42 (m, 1H), 1.96 (q, J = 7.2 Hz, 2H), 1.12 (d, J = 6.0 Hz, 3H), 0.99 (d, J = 6.6 Hz, 3H), 0.73 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 180.1, 141.0, 129.4, 128.8, 124.8, 122.7, 110.3, 83.1, 69.2, 31.6, 24.2, 23.3, 7.1; HRMS: $C_{13}H_{17}NO_2$ calculated 219.1259, found 219.1261.

3-Ethyl-3-phenoxyindolin-2-one (2o). White solid, mp: 125–127 °C; IR (KBr): 3449, 2923, 1721, 1619, 1544, 1324, 1115, 691, 489 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.42 (br, 1H), 7.28 (d, J = 7.2 Hz, 1H), 7.24 (td, J_1 = 7.8 Hz, J_2 = 0.6 Hz, 1H), 7.07–7.02 (m, 3H), 6.88–6.84 (m, 2H), 6.72 (q, J = 8.4 Hz, 2H), 2.25–2.17 (m, 2H), 0.91 (d, J = 7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 177.6, 155.7, 140.2, 129.7, 129.1, 127.8, 124.8, 123.0, 122.7, 119.0, 110.5, 84.1, 32.2, 7.1; HRMS: $C_{16}H_{15}NO_2$ calculated 253.1103, found 253.1108.

3-Ethyl-3-(phenylthio)indolin-2-one (2p). Yellow solid, mp: 134–136 °C; IR (KBr): 3449, 2923, 2853, 1639, 1384, 1118, 742, 492 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.30 (br, 1H), 7.32 (d, J = 7.2 Hz, 1H), 7.24–7.20 (m, 3H), 7.14 (td, J_1 = 7.8 Hz, J_2 = 0.6 Hz, 1H), 7.10–7.06 (m, 3H), 6.67 (d, J = 7.8 Hz, 1H), 2.24–2.17 (m, 1H), 2.16–2.10 (m, 1H), 0.77 (d, J = 7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 178.6, 140.6, 136.4, 129.9, 129.5, 129.3, 128.6, 128.3, 124.6, 122.6, 109.7, 60.1, 28.6, 9.3; HRMS: $C_{16}H_{15}NOS$ calculated 269.0874, found 269.0873.

Spiro[cyclopentane-1,3′-indolin]-2′-one (2q). White solid, mp: 122–124 °C; IR (KBr): 3449, 2956, 2928, 2281, 1703, 1619, 1384, 747, 492 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.55 (br, 1H), 7.18 (t, J = 7.8 Hz, 2H), 7.02 (td, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 6.90 (dd, J_1 = 7.8 Hz, J_2 = 0.6 Hz, 1H), 2.20–2.17 (m, 2H), 2.09–2.06 (m, 2H), 2.00–1.98 (m, 2H), 1.90–1.87 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 184.6, 140.0, 137.4, 127.3, 122.6, 122.5, 109.5, 54.4, 38.4, 26.7; HRMS: $C_{12}H_{13}NO$ calculated 187.0997, found 187.0993.

Spiro[cyclohexane-1,3′-indolin]-2′-one (2r). White solid, mp: 115–117 °C; IR (KBr): 3468, 2924, 2852, 1701, 1637, 1619, 1385, 1101, 746 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.68 (br, 1H), 7.45 (d, J = 7.2 Hz, 1H), 7.21 (td, J_1 = 7.8 Hz, J_2 = 0.6 Hz, 1H), 7.02 (td, J_1 = 7.2 Hz, J_2 = 0.6 Hz, 1H), 6.94 (d, J = 7.8 Hz, 1H), 1.97–1.92 (m, 2H), 1.90–1.85 (m, 2H), 1.80–1.73 (m, 3H), 1.66–1.60 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 183.3, 140.0, 135.8, 127.4, 124.2, 121.8, 109.7, 48.0, 32.9, 25.2, 21.1; HRMS: $C_{13}H_{15}NO$ calculated 201.1154, found 201.1156.

2′,3′,5′,6′-Tetrahydrospiro[indoline-3,4′-pyran]-2-one (2s). White solid, mp: 238–240 °C; IR (KBr): 3568, 3447, 2913, 1700, 1624, 1559, 1092 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.17 (br, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.23 (t, J = 6.6 Hz, 1H), 7.06 (t, J = 7.8 Hz, 1H), 6.92 (d, J = 7.8 Hz, 1H), 4.27–4.23 (m, 2H), 3.96–3.92 (m, 2H), 1.94–1.86 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 181.8, 139.8, 134.6, 128.0, 123.5, 122.5, 109.7, 62.9, 44.6, 32.9; HRMS: $C_{12}H_{13}NO_2$ calculated 203.0946, found 203.0944.

Dispiro[1,3-dioxolane-2,1′-cyclohexane-4′,3″-[3*H*]indol]-2″(1″-*H*)-one (2t). White solid, mp: 214–215 °C; IR (KBr): 3468, 2958, 2925, 2854, 1700, 1620, 1444, 1094, 750, 488 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 9.34 (br, 1H), 7.35 (d, J = 7.2 Hz, 1H), 7.20 (t, J = 7.8 Hz, 1H), 7.00 (t, J = 7.8 Hz, 1H), 6.96 (d, J = 7.8 Hz, 1H), 4.03 (s, 4H), 2.30–2.24 (m, 2H), 2.05–2.00 (m, 2H), 1.93–1.86 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 183.1, 140.2, 134.9, 127.7, 123.3, 122.0, 109.9, 108.1, 64.3, 46.5, 31.2, 30.1; HRMS: $C_{15}H_{17}NO_3$ calculated 259.1208, found 259.1202.

1,3-Dihydrospiro[indene-2,3′-indolin]-2′-one (2u). White solid, mp: 210–212 °C; IR (KBr): 3464, 3187, 1707, 1459, 1225, 1009, 749, 643 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.71 (br, 1H), 7.28–7.24 (m, 4H), 7.18 (t, J = 7.8 Hz, 1H), 6.93 (d, J = 7.8 Hz, 1H), 6.89 (t, J = 7.8 Hz, 1H), 6.83 (d, J = 7.8 Hz, 1H), 3.65 (d, J = 16.2 Hz, 2H), 3.13 (d, J = 15.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 182.6, 141.1, 139.6, 136.7, 128.0, 127.0, 124.5, 122.8, 121.9, 109.8, 54.5, 44.0; HRMS: $C_{16}H_{13}NO$ calculated 235.0997, found 235.1001.

3-Cyclohexylideneindolin-2-one (2v). White solid, mp: 204–206 °C; IR (KBr): 3449, 2926, 2854, 1690, 1618, 1467, 1217, 736 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.03 (br, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.16 (td, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 6.98 (td, J_1 = 7.8 Hz, J_2 = 0.6 Hz, 1H), 6.84 (d, J = 7.2 Hz, 1H), 3.35 (t, J = 6.6 Hz, 2H), 2.87 (t, J = 6.0 Hz, 2H), 1.86–1.82 (m, 2H), 1.80–1.76 (m, 2H), 1.72–1.68 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.9, 164.6, 139.3, 127.5, 124.3, 123.8, 121.5, 120.0, 109.3, 33.1, 30.0, 28.1, 27.8, 25.8; HRMS: $C_{14}H_{15}NO$ calculated 213.1154, found 213.1153.

5-Chloroindolin-2-one (2x). White solid, mp: 195–196 °C; IR (KBr): 3444, 2900, 1701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.50 (br, 1H), 7.21–7.18 (m, 2H), 7.01 (d, J = 7.8 Hz, 1H), 3.54 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.8, 140.9, 127.9, 127.7, 126.9, 125.1, 110.5, 36.1; HRMS: C_8H_6ClNO calculated 167.0138, found 167.0144.

5*H*-[1,3]Dioxolo[4,5-*f*]indol-6(7*H*)-one (2y). White solid, mp: 228–229 °C; IR (KBr): 742, 1295, 1475, 1720, 2915 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.91 (br, 1H), 6.74 (s, 1H), 6.47 (s, 1H), 5.92 (s, 2H), 3.46 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 177.6, 147.1, 143.1, 136.0, 116.7, 106.1, 100.1, 93.3, 36.4; HRMS: C_8H_7NO calculated 177.0426, found 177.0429.

3,3-Dimethyl-3,4-dihydroquinolin-2(1*H*)-one (2y). Yellow solid, mp: 159–161 °C; IR (KBr): 3475, 3195, 3071, 2985, 2923, 1672, 1494, 1389, 762, 670 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.22 (br, 1H), 7.18 (t, J = 7.2 Hz, 1H), 7.14 (d, J = 7.2 Hz, 1H), 7.00 (t, J = 7.2 Hz, 1H), 6.78 (d, J = 7.8 Hz, 1H), 2.81 (s, 2H), 1.22 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 176.9, 136.6, 128.5, 127.4, 123.3, 123.2, 114.8, 40.2, 37.3, 24.3; HRMS: $C_{11}H_{13}NO$ calculated 175.0997, found 175.0993.

4′-Chlorospiro[cyclopentane-1,3′-indolin]-2′-one (2A). White solid, mp: 168–170 °C; IR (KBr): 3487, 3170, 3134, 2957, 2870, 1706, 1619, 1444, 1178, 661 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 9.25 (br, 1H), 7.11 (t, J = 7.8 Hz, 1H), 6.96 (d, J = 7.8 Hz, 1H), 6.83 (d, J = 7.8 Hz, 1H), 2.33–2.31 (m, 2H), 2.09–2.03 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): 185.4, 142.5, 131.9, 129.8, 128.6, 123.4, 108.2, 54.6, 35.0, 27.6; HRMS: $C_{12}H_{12}ClNO$ calculated 221.0607, found 221.0611.

5′-(Trifluoromethyl)spiro[cyclohexane-1,3′-indolin]-2′-one (2B). White solid, mp: 182–184 °C; IR (KBr): 3467, 2933, 1724, 1691, 1113, 825 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 9.11 (br, 1H), 7.64 (s, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 7.8 Hz, 1H), 2.00–1.97 (m, 2H), 1.91–1.86 (m, 2H), 1.77–1.64 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 183.3, 143.1, 136.3, 125.2, 124.5 (q, J = 270 Hz), 124.3 (q, J = 33 Hz), 121.0, 109.5, 48.0,

32.8, 25.0, 21.0; HRMS: $C_{14}H_{14}F_3NO$ calculated 269.1027, found 269.1025.

5′-Methoxyspiro[cyclopentane-1,3′-indolin]-2′-one (2C). White solid, mp: 180–182 °C; IR (KBr): 3460, 2956, 2862, 1682, 1652, 1635, 1491, 1209, 1029 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.86 (br, 1H), 6.82 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 6.79 (d, J = 3.0 Hz, 1H), 6.70 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 3.78 (s, 3H), 2.20–2.17 (m, 2H), 2.08–2.05 (m, 2H), 1.98–1.95 (m, 2H), 1.87–1.84 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 184.7, 155.9, 138.8, 133.6, 111.3, 110.2, 109.7, 55.8, 54.9, 38.4, 26.7; HRMS: $C_{13}H_{15}NO_2$ calculated 217.1103, found 217.1100.

2′,3′,5′,6′-Tetrahydrospiro[[1,3]dioxolo[4,5-*f*]indole-7,4′-pyran]-6(5*H*)-one (2D). White solid, mp: 276–277 °C; IR (KBr): 3461, 2923, 1721, 1631, 1474, 1267, 1176, 1111, 754, 409 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, bad solubility): δ 7.72 (br, 1H), 6.86 (s, 1H), 6.49 (s, 1H), 5.93 (s, 2H), 4.25–4.21 (m, 2H), 3.91–3.88 (m, 2H), 1.86–1.84 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 182.0, 147.0, 143.2, 133.6, 126.4, 104.9, 101.1, 93.2, 62.8, 44.8, 33.1; HRMS: $C_{13}H_{13}NO_4$ calculated 247.0845, found 247.0844.

(±)-Coerulescine (2z). Yellow solid, mp: 129–130 °C; IR (KBr): 3465, 3242, 2944, 2791, 1709, 1620, 1472, 1338, 1197, 753 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 9.04 (br, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.18 (t, J = 7.8 Hz, 1H), 7.03 (t, J = 7.8 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H), 3.02–2.98 (m, 1H), 2.90 (d, J = 9.6 Hz, 1H), 2.84–2.78 (m, 2H), 2.46 (s, 3H), 2.44–2.40 (m, 1H), 2.12–2.08 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 183.2, 140.2, 136.3, 127.7, 123.2, 122.7, 109.6, 66.4, 56.8, 53.7, 41.8, 37.9; HRMS: $C_{12}H_{14}N_2O$ calculated 202.1106, found 202.1104.

(±)-Horsfiline (2E). Yellow solid, mp: 159–160 °C; IR (KBr): 3449, 2922, 2851, 1702, 1492, 1208, 1032, 811, 669, 618 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.95 (br, 1H), 7.02 (d, J = 2.4 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 6.72 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 3.79 (s, 3H), 3.03–2.99 (m, 1H), 2.85 (s, 2H), 2.74 (q, J = 7.2 Hz, 1H), 2.45 (s, 3H), 2.43–2.39 (m, 1H), 2.11–2.06 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 182.4, 156.2, 137.7, 133.2, 112.4, 110.4, 109.6, 66.5, 56.7, 55.9, 54.1, 41.8, 38.1; HRMS: $C_{13}H_{16}N_2O_2$ calculated 232.1212, found 232.1211.

Acknowledgements

We thank the National Science Council of the Republic of China (NSC-99-2113-M-032-003-MY2) for the support of this research.

Notes and references

1 (*a*) C. Marti and E. M. Carreira, *Eur. J. Org. Chem.*, 2003, 2209; (*b*) C. V. Galliford and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748; (*c*) B. M. Trost and M. K. Brennan, *Synthesis*, 2009, 3003; (*d*) A. Millemaggi and R. J. K. Taylor, *Eur. J. Org. Chem.*, 2010, 4527; (*e*) M. S. C. Pedras, E. E. Yaya and E. Glawischnig, *Nat. Prod. Rep.*, 2011, **28**, 1381.

2 For selected papers see: (*a*) L. L. Wang, J. J. Li, Z. B. Zheng, H. Y. Liu, G. J. Du and S. Li, *Eur. J. Pharmacol.*, 2004, **502**, 1; (*b*) G. C. Bignan, K. Battista, P. J. Connolly, M. J. Orsini, J. Liu, S. A. Middletona and A. B. Reitz, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 5022.

3 (*a*) A. B. Dounay, K. Hatanaka, J. J. Kodanko, M. Oestreich, L. E. Overman, L. A. Pfeifer and M. M. Weiss, *J. Am. Chem. Soc.*, 2003, **125**, 6261; (*b*) A. J. B. Lapierre, S. J. Geib and D. P. Curran, *J. Am. Chem. Soc.*, 2007, **129**, 494; (*c*) M. C. McDermott, G. R. Stephenson, D. L. Hughes and A. J. Walkington, *Org. Lett.*, 2006, **8**, 2917.

4 A. Pinto, Y. Jia, L. Neuville and J. Zhu, *Chem.–Eur. J.*, 2007, **13**, 961.

5 (*a*) Y. Kobayashi, H. Kamisaki, R. Yanada and Y. Takemoto, *Org. Lett.*, 2006, **8**, 2711; (*b*) Y. Yasui, H. Kamisaki and Y. Takemoto, *Org. Lett.*, 2008, **10**, 3303.

6 R. R. Poondra and N. J. Turner, *Org. Lett.*, 2005, **7**, 863.

7 (*a*) K. H. Shaughnessy, B. C. Hamann and J. F. Hartwig, *J. Org. Chem.*, 1998, **63**, 6546; (*b*) S. Lee and J. F. Hartwig, *J. Org. Chem.*, 2001, **66**, 3402; (*c*) J. A. Schiffner and M. Oestreich, *Eur. J. Org. Chem.*, 2011, 1148.

8 (*a*) E. J. Hennessy and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 12084; (*b*) A. Pinto, L. Neuville, P. Retailleau and J. Zhu, *Org. Lett.*, 2006, **8**, 4927; (*c*) A. Perry and R. J. K. Taylor, *Chem. Commun.*, 2009, 3249; (*d*) G. An, W. Zhou, G. Zhang, H. Sun, J. Han and Y. Pan, *Org. Lett.*, 2010, **12**, 4482.

9 (*a*) S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400; (*b*) G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.*, 2008, **108**, 3054.

10 Selected papers on Cu-catalyzed domino reactions: (*a*) A. Klapars, S. Parris, K. W. Anderson and S. L. Buchwald, *J. Am. Chem. Soc.*, 2004, **126**, 3529; (*b*) B. Zou, Q. Yuan and D. Ma, *Angew. Chem., Int. Ed.*, 2007, **46**, 2598; (*c*) J. Lu, X. Gong, H. Yang and H. Fu, *Chem. Commun.*, 2010, **46**, 4172.

11 Y.-X. Jia and E. P. Kündig, *Angew. Chem., Int. Ed.*, 2009, **48**, 1636.

12 (*a*) J. E. M. N. Klein, A. Perry, D. S. Pugh and R. J. K. Taylor, *Org. Lett.*, 2010, **12**, 3446; (*b*) C. L. Moody, V. Franckevičius, P. Drouhin, J. E. M. N. Klein and R. J. K. Taylor, *Tetrahedron Lett.*, 2012, **53**, 1897.

13 (*a*) V. A. Ignatenko, N. Deligonul and R. Viswanathan, *Org. Lett.*, 2010, **12**, 3594; (*b*) T. Kukosha, N. Trufilkina and M. Katkevics, *Synlett*, 2011, 2525.

14 A.-Y. Cheng and J.-C. Hsieh, *Tetrahedron Lett.*, 2012, **53**, 71.

15 J.-C. Hsieh, Y.-C. Chen, A.-Y. Cheng and H.-C. Tseng, *Org. Lett.*, 2012, **14**, 1282.

16 J. Zanon, A. Klapars and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 2890.

17 A. Jossang, P. Jossang, H. A. Hadi, T. Sevenet and B. Bodo, *J. Org. Chem.*, 1991, **56**, 6527.

18 Selected papers on the synthesis of horsfiline: (*a*) U. K. S. Kumar, H. Ila and H. Junjappa, *Org. Lett.*, 2001, **3**, 4193; (*b*) J. A. Murphy, R. Tripoli, T. A. Khan and U. W. Mali, *Org. Lett.*, 2005, **7**, 3287; (*c*) B. M. Trost and M. K. Brennan, *Org. Lett.*, 2006, **8**, 2027; (*d*) S. Jaegli, J.-P. Vors, L. Neuville and J. Zhu, *Synlett*, 2009, 2997.

19 N. Anderton, P. A. Cockrum, S. M. Colegate, J. A. Edgar, K. Flower, I. Vit and R. I. Willing, *Phytochemistry*, 1998, **48**, 437.

20 Selected papers on the synthesis of coerulescine: (*a*) N. Selvakumar, A. M. Azhagan, D. Srinivas and G. G. Krishna, *Tetrahedron Lett.*, 2002, **43**, 9175; (*b*) C. Li, C. Chan, A. C. Heimann and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, 2007, **46**, 1444; (*c*) J. D. White, Y. Li and D. C. Ihle, *J. Org. Chem.*, 2010, **75**, 3569.