Tetrahedron 68 (2012) 3649–3653

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Facile and highly diastereoselective synthesis of 3-aminooxindoles via AgOAc-catalyzed vinylogous Mannich reaction

Yu-Hua Shi, Zheng Wang, Ying Shi, Wei-Ping Deng *

*School of Pharmacy and Shanghai Key Laboratory of New Drug Design, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, China*

ARTICLE INFO

*Article history:*
Received 24 November 2011
Received in revised form 14 February 2012
Accepted 21 February 2012
Available online 8 March 2012

ABSTRACT

A novel AgOAc-catalyzed vinylogous Mannich reaction between easily prepared imines **1** derived from isatins and trimethylsilyloxyfuran **2** (TMSOF) was developed. This method provided a facile synthetic route to get access to synthetically useful quaternary 3-aminooxindole in excellent yields (94–99%) and diastereoselectivities (>99:1).



## 1. Introduction

Oxindole, bearing a C3-quaternary center, is a common and important core structural motif found in many natural products and biologically active compounds.[1] Among them, 3-amino-3-substituted oxindoles have attracted much attention for their prominent biological activity in the field of medicinal chemistry,[2] including the potent gastrin/CCK-B receptor antagonist AG-041R[2a] and the vasopressin VIb receptor antagonist SSR-149415[2b,c] (Fig. 1). Although a great deal of effort has been dedicated to the synthesis of such important structure motif, including intramolecular α-arylation of amides,[3] alkylation of 3-aminooxindole,[4] Strecker reaction,[5] Mannich addition,[6] and direct α-amination of 3-substituted oxindoles,[7] developing a new synthetic method is of considerable importance and still remains a great challenge since the increasing demand for the varieties of quaternary 3-aminooxindoles in drug discovery.

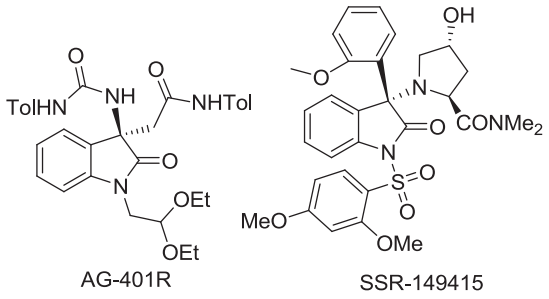
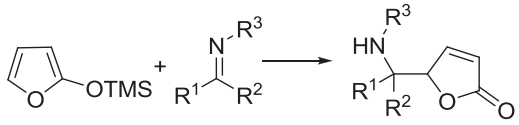



**Fig. 1.** Selected bioactive quaternary aminooxindoles and a related natural compound.

Vinylogous Mannich reaction,[8] emerged as a powerful tool for carbon–carbon bond formation in organic synthesis, and has gained increasing attention due to its facile access to complicated and highly functionalized δ-amino compounds. Vinylogous Mannich reaction of trimethylsilyloxyfuran (TMSOF) and ketoimine would constitute an efficient strategy (Scheme 1), affording two stereogenic centers, one with *N*-substituted quaternary carbon stereogenic center, appended to a γ-butenolide. Ketoimines derived from isatin, compared with aldimines, are often relatively unreactive, containing a sterically congested C=N bond. To the best of our knowledge, there are only two reported examples of such vinylogous Mannich reactions. In 2009, Dodd and his co-workers reported a vinylogous Mannich reaction between isoquinolines and TMSOF using acyl/sulfonyl chlorides as activating reagent.[9] In the same year, Snapper and Hoveyda reported the first asymmetric vinylogous Mannich reaction of TMSOF to α-ketoimine esters with high diastereo- and enantioselectivity.[10] However, a vinylogous Mannich reaction of isatin-based ketoimine and TMSOF for the synthesis of quaternary 3-aminooxindoles is still unknown. Herein, we would like to report a facile AgOAc-catalyzed vinylogous Mannich reaction of ketoimines derived from isatin and TMSOF, affording quaternary 3-substituted 3-aminooxindoles in high diastereoselectivity.



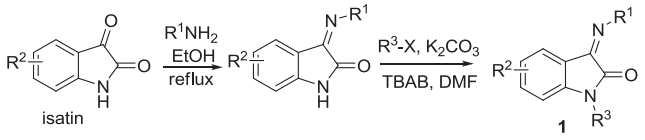

**Scheme 1.** Vinylogous Mannich reaction of ketoimine and TMSOF.

## 2. Results and discussion

The readily available ketoimines **1** were easily prepared by condensation of isatins with corresponding aniline, respectively, followed by *N* atom protection (Scheme 2).[11,12]

* Corresponding author. Tel./fax: +86 021 64252431; e-mail address: weiping_deng@ecust.edu.cn (W.-P. Deng).

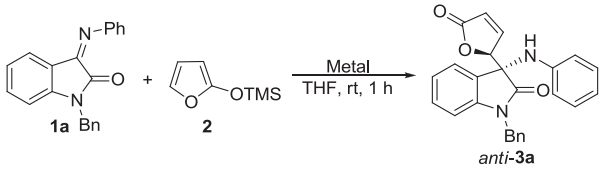
0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2012.02.046




**Scheme 2.** Synthesis of *N*-protected isatin-based imines **1**.

With the ketoimines **1** in hand, the model reaction of **1a** and **2** was chosen for the catalysts and reaction conditions screening (Table 1).

**Table 1**
Catalysts screening[a]




| Entry | Metal | Yield (%) | dr (*anti*/*syn*)[d] |
|---|---|---|---|
| 1 | — | — | — |
| 2 | AgOAc | 98 | 99/1 |
| 3 | AgOTf | 31 | 99/1 |
| 4 | $AgBF_4$ | trace | — |
| 5 | $Cu(OAc)_2·H_2O$ | 36 | 99/1 |
| 6 | $Cu(OTf)_2$ | trace | — |
| 7 | $Cu(acac)_2$ | trace | — |
| 8 | $CuCl_2·2H_2O$ | trace | — |
| 9 | $Zn(OAc)_2·2H_2O$ | 36 | 99/1 |
| 10 | $Zn(OTf)_2$ | trace | — |
| 11 | $Ni(OAc)_2·4H_2O$ | trace | — |
| 12 | $Sc(OTf)_3$ | 92 | 99/1 |
| 13 | $Yb(OTf)_3$ | 48 | 99/1 |
| 14[b] | AgOAc | 92 | 99/1 |
| 15[c] | AgOAc | 73 | 99/1 |

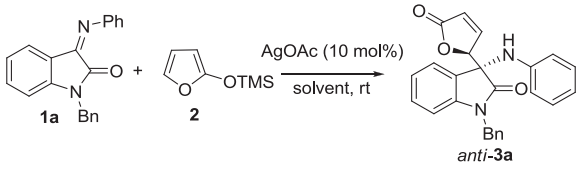
[a] The reaction was carried out in 0.1 mmol scale in the presence of 10 mol % of metal catalyst.
[b] AgOAc (5 mol %) was used, and 3 h was required.
[c] AgOAc (2 mol %) was used, and 6 h was required.
[d] The dr of isolated product were determined by $^1H$ NMR.

To our delight, AgOAc was the optimal catalyst to catalyze the reaction smoothly[10,13] and afforded 3-aminooxindole in nearly quantitative yield in THF at room temperature (Table 1, entry 2). It was worth noting that no desired product was detected in the absence of AgOAc catalyst under the same condition (entry 1), and other silver salts were found to be much less active for this reaction (entries 3, 4). A variety of metal salts, such as copper, zinc, nickel, and so on, were also tested in the model vinylogous Mannich reaction, and most of them were found not suitable to give corresponding product in low yields, except for $Sc(OTf)_3$ (Table 1, entry 12). Decreasing the AgOAc catalyst loading to 5 mol % gave the product in 92% yield, but a prolonged reaction time 3 h was required (entry 14). And moderate yield (73%) was obtained when 2 mol % AgOAc was used (entry 15).

Next, solvent effect was also investigated for this reaction (Table 2). THF was found optimal solvent and all other tried solvents gave inferior yields or no product for the reaction (entries 2–8).

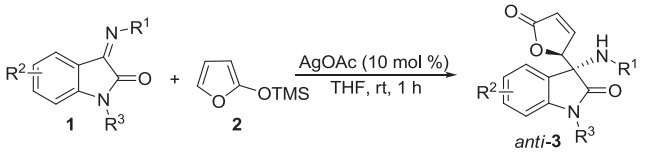
With the optimized conditions in hand, a variety of ketoimines were next explored to investigate the generality of this novel reaction, and the detailed results were presented in Table 3. The protection group on nitrogen atom was found to have no effect on the reactivity (Table 3, entries 1, 2). Gratifyingly, either electron-donating or withdrawing groups on phenyl group of $R^1$ showed similar reactivities to afford corresponding products **3c**–**f** in excellent yields (Table 3, entries 3–6). Furthermore, the yield of the reaction was not affected by the substituted group on oxindole, either the electron-withdrawing group or electron-donating one

**Table 2**
Solvent screening




| Entry | Solvent | Yield (%) | dr (*anti*/*syn*) |
|---|---|---|---|
| 1 | THF | 98 | 99/1 |
| 2 | $CHCl_3$ | 91 | 99/1 |
| 3 | $CH_2Cl_2$ | 89 | 99/1 |
| 4 | $CH_3CN$ | 64 | 99/1 |
| 5 | Toluene | 87 | 99/1 |
| 6 | $Et_2O$ | trace | — |
| 7 | EtOAc | trace | — |
| 8 | $CCl_4$ | trace | — |

**Table 3**
AgOAc-catalyzed vinylogous Mannich reaction of **1** and **2**




| Entry | $R^1$ | $R^2$ | $R^3$ | Yield (%) | dr (*anti*/*syn*) |
|---|---|---|---|---|---|
| 1(**1a**) | $C_6H_5$ | H | Bn | 98 | 99/1 |
| 2(**1b**) | $C_6H_5$ | H | allyl | 99 | 99/1 |
| 3(**1c**) | 4-Br–$C_6H_5$ | H | Bn | 98 | 99/1 |
| 4(**1d**) | 4-Cl–$C_6H_5$ | H | Bn | 98 | 99/1 |
| 5(**1e**) | 4-MeO–$C_6H_5$ | H | Bn | 97 | 99/1 |
| 6(**1f**) | 2-MeO–$C_6H_5$ | H | Bn | 94 | 99/1 |
| 7(**1g**) | $C_6H_5$ | 5-Br | Bn | 99 | 99/1 |
| 8(**1h**) | $C_6H_5$ | 5-Cl | Bn | 99 | 99/1 |
| 9(**1i**) | $C_6H_5$ | 5-Me | Bn | 99 | 99/1 |
| 10(**1j**) | 4-Cl–$C_6H_5$ | H | H | 90 | 99/1 |

(entries 7–9) gave corresponding product **3g**–**i** in quantitative yields. It is notable that the *N*-unprotected isatin imine **1j** was also reactive to TMSOF affording corresponding product **3j** in slightly lower yield (Table 3, entry 10, 90%).

The structure of corresponding products **3** was deduced by X-ray diffraction of a single crystal of **3c** as shown in Fig. 2, and the relative configuration were assigned as the *anti* isomer.

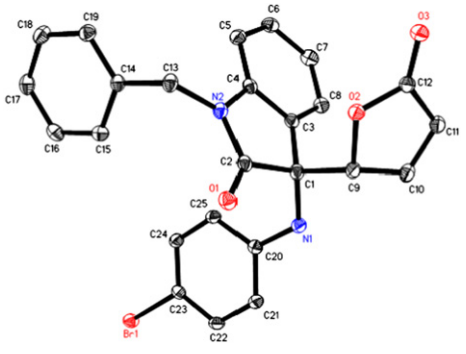


**Fig. 2.** ORTEP view and atom numbering scheme for **3c**.

Accordingly, the plausible mechanism was depicted in Fig. 3. According to well-known AgOAc bifunctional mechanism,[14] Ag(I) acts as the Lewis acid to coordinate 2 equiv of substrate **3a**, as well as the base after coordinating to TMSOF and releasing $OAc^-$, which is real base to capture the TMS group and consequently activate

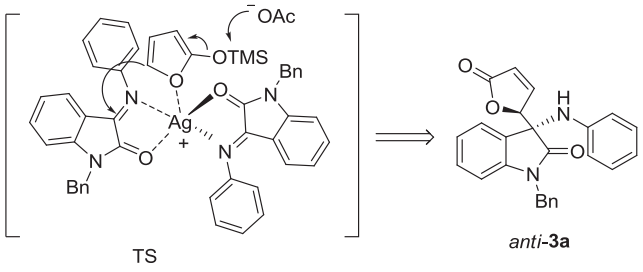



**Fig. 3.** Possible transition state for the formation of *anti*-**3a**.

TMSOF. The stereochemistry of resulting transition state (Fig. 3) was responsible for the exclusive *anti*-diastereoslectivity.

## 3. Conclusion

In conclusion, a facile vinylogous Mannich reaction of ketoimines derived from isatin and TMSOF was developed in the presence of AgOAc. The protocol provided a new and efficient synthesis of quaternary 3-amine-3-substituted oxindoles in excellent yields (94–99%) and diastereoselectivities (>99:1), which is the essential core structural motif in natural products and biologically active compounds. Further transformation of these products into a variety of oxindole-based alkaloid natural products and its asymmetric synthesis are presently in progress.

## 4. Experiment

### 4.1. General

All reagents and solvents were used as purchased if not otherwise stated. Melting points were obtained on a micro melting apparatus SGW X-4 and uncorrected. HRMS (EI) spectra were obtained on a Finigann MAT8401 instrument. $^1$H NMR spectra were recorded on a Bruker DPX 400 MHz spectrometer in chloroform-*d* or DMSO-$d_6$. $^{13}$C NMR spectra were recorded on a Bruker DPX 100 MHz spectrometer in chloroform-*d* or DMSO-$d_6$. Chemical shift values are reported in parts per million on the scale ($\delta_{TMS}$=0). Diastereomeric ratios were determined from $^1$H NMR. Infrared spectra were recorded on NICOLET 5SXC instrument as thin film; frequencies are given as wavenumbers (cm$^{-1}$).

### 4.2. General procedure for the synthesis of imines 1[11,12]

To a solution of isatin (14.7 g, 0.1 mol, 1.0 equiv) and aniline (0.15 mol, 1.5 equiv) in absolute ethanol was added 2–3 drops of acetic acid, and the reaction was heated to reflux for about 3 h. The residue was recrystallized to afford the imine as a yellowish solid.

The ketoimines (1.0 equiv) derived from isatin reacted with alkyl bromide (2.0 equiv) in the presence of $K_2CO_3$ (2.0 equiv) and tetrabutylammonium bromide (0.1 equiv) in DMF. After stirred overnight at room temperature, cold water was added to the mixture and the precipitate was filtrated, which was further purified by recrystallization from ethanol.

*4.2.1. (Z)-1-Benzyl-3-(phenylimino)indolin-2-one (**1a**).* Yellow solid; yield 86% (two steps); mp 139–140 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.48–7.29 (m, 7H), 7.26–7.17 (m, 2H), 7.04–7.00 (m, 2H), 6.78–6.68 (m, 2H), 6.63 (d, *J*=7.6 Hz, 1H), 5.01 (s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 163.4, 154.3, 150.3, 147.1, 135.1, 134.1, 129.5, 129.0, 128.0, 127.5, 126.2, 125.4, 122.8, 117.8, 115.8, 110.4, 44.0; IR (KBr) $\nu$ 3431, 2922, 1731, 1605, 1593, 1466, 1377, 1356, 1344, 1321, 1180, 1103, 1083, 852, 751, 701, 626, 535 cm$^{-1}$; HRMS (EI, *m*/*z*): calcd for $C_{21}H_{16}N_2O$: 312.1263, found: 312.1266.

*4.2.2. (Z)-1-Allyl-3-(phenylimino)indolin-2-one (**1b**).* Yellow solid; yield 80% (two steps); mp 102–103 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.43 (t, *J*=7.8 Hz, 2H), 7.37–7.29 (m, 1H), 7.26–7.21 (m, 1H), 7.01 (d, *J*=7.4 Hz, 2H), 6.86 (d, *J*=7.9 Hz, 1H), 6.75 (t, *J*=7.6 Hz, 1H), 6.63 (d, *J*=7.5 Hz, 1H), 5.99–5.77 (m, 1H), 5.45–5.20 (m, 2H), 4.45 (d, *J*=5.3 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 163.0, 154.3, 150.3, 147.2, 134.1, 130.8, 129.4, 126.2, 125.3, 122.7, 118.2, 117.7, 115.7, 110.2, 42.5; IR (KBr) $\nu$ 3433, 3205, 1728, 1657, 1605, 1468, 1401, 1374, 1355, 1197, 934, 754, 700 cm$^{-1}$; HRMS (EI, *m*/*z*): calcd for $C_{17}H_{14}N_2O$: 262.1106, found: 262.1109.

*4.2.3. (Z)-1-Benzyl-3-(4-bromophenylimino)indolin-2-one (**1c**).* Yellow solid; yield 89% (two steps); mp 183–185 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.56 (d, *J*=8.7 Hz, 2H), 7.41–7.26 (m, 6H), 6.93 (d, *J*=8.7 Hz, 2H), 6.80–6.67 (m, 3H), 5.01 (s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 163.2, 154.6, 149.1, 147.3, 135.0, 134.5, 132.6, 129.0, 128.0, 127.5, 126.2, 122.9, 119.8, 118.5, 115.6, 110.5, 44.1; IR (KBr) $\nu$ 3422, 3178, 1737, 1651, 1612, 1477, 1466, 1401, 1378, 1348, 843, 757, 645 cm$^{-1}$; HRMS (EI, *m*/*z*): calcd for $C_{21}H_{15}BrN_2O$: 390.0368, found: 390.0365.

*4.2.4. (Z)-1-Benzyl-3-(4-chlorophenylimino)indolin-2-one (**1d**).* Yellow solid; yield 84% (two steps); mp 199–200 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.44–7.27 (m, 8H), 6.99 (d, *J*=8.6 Hz, 2H), 6.80–6.70 (m, 3H), 5.01 (s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 163.2, 154.7, 148.6, 147.3, 135.0, 134.4, 130.8, 129.7, 129.0, 128.0, 127.5, 126.2, 122.8, 119.4, 115.6, 110.5, 44.1; IR (KBr) $\nu$ 3442, 3409, 1737, 1612, 1480, 1466, 1378, 1349, 1082, 844, 757, 705, 650, 634 cm$^{-1}$; HRMS (EI, *m*/*z*): calcd for $C_{21}H_{15}ClN_2O$: 346.0873, found: 346.0875.

*4.2.5. (Z)-1-Benzyl-3-(4-methoxyphenylimino)indolin-2-one (**1e**).* Yellow solid; yield 78% (two steps); mp 158–160 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.40–7.28 (m, 5H), 7.22 (dd, *J*=7.8, 1.0 Hz, 1H), 7.09–7.04 (m, 2H), 6.99–6.93 (m, 3H), 6.78–6.72 (m, 2H), 5.02 (s, 2H), 3.86 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 163.6, 157.8, 153.7, 147.0, 143.0, 135.2, 133.8, 128.9, 127.9, 127.5, 125.7, 122.6, 120.2, 116.0, 114.5, 110.3, 55.5, 44.0; IR (KBr) $\nu$ 3409, 2930, 1720, 1599, 1500, 1470, 1354, 1293, 1247, 1186, 1162, 1104, 1034, 762, 731 cm$^{-1}$; HRMS (EI, *m*/*z*): calcd for $C_{22}H_{18}N_2O_2$: 342.1368, found: 342.1371.

*4.2.6. (Z)-1-Benzyl-3-(2-methoxyphenylimino)indolin-2-one (**1f**).* Yellow solid; yield 75% (two steps); mp 134–136 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.41–7.29 (m, 5H), 7.25–7.18 (m, 2H), 7.02–6.99 (m, 3H), 6.76–6.70 (m, 3H), 5.01 (s, 2H), 3.76 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 163.3, 155.0, 148.3, 146.9, 139.1, 135.2, 133.9, 128.9, 127.9, 127.5, 126.5, 125.8, 122.8, 121.1, 119.3, 116.7, 111.8, 110.1, 55.7, 44.0; IR (KBr) $\nu$ 3445, 3021, 2906, 1730, 1610, 1591, 1490, 1471, 1454, 1378, 1354, 1251, 1182, 1114, 1018, 774, 759, 735, 695, 456 cm$^{-1}$; HRMS (EI, *m*/*z*): calcd for $C_{22}H_{18}N_2O_2$: 342.1368, found: 342.1370.

*4.2.7. (Z)-1-Benzyl-5-bromo-3-(phenylimino)indolin-2-one (**1g**).* Yellow solid; yield 87% (two steps); mp 154–155 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.48 (t, *J*=7.5 Hz, 2H), 7.40–7.29 (m, 7H), 7.04 (d, *J*=7.8 Hz, 2H), 6.75 (s, 1H), 6.65 (d, *J*=8.3 Hz, 1H), 5.02 (s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.8, 153.0, 149.7, 145.9, 136.5, 134.6, 129.6, 129.1, 128.9, 128.1, 127.4, 126.0, 119.4, 117.7, 115.3, 111.9, 44.1; IR (KBr) $\nu$ 3425, 3080, 1726, 1602, 1471, 1443, 1334, 1178, 826, 725, 693, 611 cm$^{-1}$; HRMS (EI, *m*/*z*): calcd for $C_{21}H_{15}BrN_2O$: 390.0368, found: 390.0366.

*4.2.8. (Z)-1-Benzyl-5-chloro-3-(phenylimino)indolin-2-one (**1h**).* Yellow solid; yield 84% (two steps); mp 157–158 °C; $^1$H NMR

(400 MHz, $CDCl_3$) $\delta$ 7.47 (t, $J$=7.4 Hz, 2H), 7.37–7.28 (m, 6H), 7.20 (d, $J$=8.4 Hz, 1H), 7.02 (d, $J$=7.7 Hz, 2H), 6.68 (d, $J$=8.3 Hz, 1H), 6.60 (s, 1H), 5.01 (s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.9, 153.2, 149.7, 145.5, 134.6, 133.6, 129.6, 129.0, 128.1, 127.4, 126.1, 126.0, 119.4, 117.7, 116.7, 111.4, 44.1; IR (KBr) $\nu$ 3449, 3076, 1725, 1656, 1602, 1470, 1442, 1402, 1369, 1352, 1333, 1178, 1126, 1081, 826, 811, 780, 725, 693, 624, 514 $cm^{-1}$; HRMS (EI, $m/z$): calcd for $C_{21}H_{15}ClN_2O$: 346.0873, found: 346.0876.

*4.2.9. (Z)-1-Benzyl-5-methyl-3-(phenylimino)indolin-2-one (**1i**).* Yellow solid; yield 80% (two steps); mp 137–138 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.51–7.27 (m, 8H), 7.04 (d, $J$=7.1 Hz, 3H), 6.64 (d, $J$=7.9 Hz, 1H), 6.42 (s, 1H), 5.01 (s, 2H), 2.03 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 163.5, 154.5, 150.4, 144.9, 135.2, 134.4, 132.2, 129.4, 128.9, 127.9, 127.5, 126.8, 125.3, 117.8, 115.8, 110.1, 44.0, 20.9; IR (KBr) $\nu$ 3056, 3028, 2925, 1728, 1658, 1608, 1591, 1480, 1454, 1433, 1355, 1342, 1185, 1123, 828, 759, 694, 634 $cm^{-1}$; HRMS (EI, $m/z$): calcd for $C_{22}H_{18}N_2O$: 326.1419, found: 326.1423.

### 4.3. Procedure for the synthesis of TMSOF 2[15]

A 1-L three-necked flask, equipped with a reflux condenser and a dropping funnel, was charged with furfural (48 g, 0.5 mol), $CH_2Cl_2$ (250 mL), formic acid (46 g, 1.0 mol), $Na_2SO_4$ (50 g), and $K_2CO_3$ (17.5 g). The mixture was vigorously stirred and 30% $H_2O_2$ (38 mL) was added in one portion. Vigorous stirring was continued for 30–45 min after which refluxed gently. Then 30% $H_2O_2$ (63 mL) was added dropwise with continued stirring. The mixture was stirred overnight after cooling to room temperature. The organic phase was separated, and the aqueous layer was extracted with 50 mL $CH_2Cl_2$. The combined organic phase was concentrated in vacuo. 100 mL toluene was added and formic acid was removed by azeotropic distillation. Another 100 mL toluene was added to the reisdue, followed by 1.3 mL triethylamine, and the mixture was allowed to stand for 1 h. After toluene was evaporated, the residual liquid was distilled in vacuo to afford furanone (19.7 g, 47%) as colorless liquid at 63–66 °C/5.9 mmHg.

To furanone (19.7 g, 0.142 mol) $Et_3N$ (36.0 mL, 0.26 mol) was added, followed by TMSCl (19.7 g, 0.235 mol) at 0 °C under $N_2$. The reaction mixture was filtrated through silica gel, and the cake was washed with dry $Et_2O$ to give a clear filtrate. Fractional distillation under reduced pressure of the mixture afforded **2** (13.0 g, 58%) as a yellowish liquid at 76–78 °C/27 mmHg (lit. 44–46 °C/17 mmHg).

$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.83–6.81 (m, 1H), 6.22–6.20 (m, 1H), 5.11 (d, $J$=3.1 Hz, 1H), 0.30 (s, 9H).

### 4.4. Typical procedure for vinylogous Mannich reaction

To a solution of imines **1** derived from isatin (0.1 mmol, 1.0 equiv) and anhydrous AgOAc (1.6 mg, 0.01 mol, 0.1 equiv) in 1 mL THF was added 2-(trimethylsilyloxy)furan (TMSOF) (34 μL, 0.2 mmol, 2.0 equiv), and then the reaction was stirred for 1 h. The solvent was removed in vacuo and the residue was purified by flash chromatography (petroleum ether/EtOAc=4/1 to 2/1) to afford the product as a gray-white or white solid.

*4.4.1. 1-Benzyl-3-(5-oxo-2,5-dihydrofuran-2-yl)-3-(phenylamino)indolin-2-one (**3a**).* Off-white solid; yield 98%; mp 204–206 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.45 (dd, $J$=5.8, 1.5 Hz, 1H), 7.30 (d, $J$=7.5 Hz, 1H), 7.20–7.11 (m, 4H), 7.08–6.97 (m, 3H), 6.89 (t, $J$=7.9 Hz, 2H), 6.72 (t, $J$=8.1 Hz, 2H), 6.37–6.26 (m, 2H), 6.20 (dd, $J$=5.8, 2.0 Hz, 1H), 5.26 (t, $J$=1.7 Hz, 1H), 4.98 (d, $J$=15.6 Hz, 1H), 4.66 (d, $J$=15.6 Hz, 1H), 4.44 (br s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ 175.4, 171.5, 154.7, 145.9, 143.4, 136.3, 130.4, 129.2, 129.0, 128.0, 127.9, 125.7, 124.1, 123.6, 122.5, 118.6, 114.8, 110.3, 84.2, 66.4, 43.7; IR (KBr) $\nu$ 3300, 3065, 2924, 1792, 1768, 1692, 1603, 1489, 1469, 1374, 1340, 1259, 1181, 1153, 1107, 1081, 1050, 889, 818, 755, 695, 513 $cm^{-1}$; HRMS (EI, $m/z$): calcd for $C_{25}H_{20}N_2O_3$: 396.1474, found: 396.1476.

*4.4.2. 1-Allyl-3-(5-oxo-2,5-dihydrofuran-2-yl)-3-(phenylamino)indolin-2-one (**3b**).* Off-white solid; yield 99%; mp 185–186 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.59 (dd, $J$=5.8, 1.4 Hz, 1H), 7.43–7.33 (m, 2H), 7.14–7.07 (m, 1H), 6.99 (t, $J$=7.9 Hz, 2H), 6.92 (d, $J$=7.8 Hz, 1H), 6.77 (t, $J$=7.4 Hz, 1H), 6.37 (d, $J$=7.7 Hz, 2H), 6.29 (dd, $J$=5.8, 1.9 Hz, 1H), 5.81–5.70 (m, 1H), 5.37–5.30 (m, 1H), 5.26–5.09 (m, 2H), 4.64 (br s, 1H), 4.43–4.31 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 173.9, 171.2, 151.2, 144.1, 142.7, 130.6, 130.4, 129.0, 125.6, 124.7, 124.5, 123.0, 121.0, 118.2, 117.6, 110.0, 84.7, 66.9, 42.7; IR (KBr) $\nu$ 3302, 3063, 1792, 1768, 1700, 1613, 1600, 1499, 1487, 1467, 1432, 1379, 1358, 1339, 1306, 1256, 1189, 1153, 1108, 1086, 1047, 924, 896, 816, 752, 692, 655, 508 $cm^{-1}$; HRMS(EI, $m/z$): calcd for $C_{21}H_{18}N_2O_3$: 346.1317, found: 346.1316.

*4.4.3. 1-Benzyl-3-(4-bromophenylamino)-3-(5-oxo-2,5-dihydrofuran-2-yl)indolin-2-one (**3c**).* Off-white solid; yield 98%; mp 228–230 °C; $^1$H NMR (400 MHz, DMSO) $\delta$ 8.08 (dd, $J$=5.8, 1.3 Hz, 1H), 7.42–7.25 (m, 6H), 7.07–6.96 (m, 6H), 6.39 (dd, $J$=5.8, 1.8 Hz, 1H), 6.16 (d, $J$=8.9 Hz, 2H), 5.62 (t, $J$=1.5 Hz, 1H), 5.01 (s, 2H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ 175.0, 171.5, 154.5, 145.2, 143.4, 136.3, 131.8, 130.6, 129.0, 128.0, 125.7, 123.7, 123.6(7), 122.6(2), 116.9, 110.4, 109.8, 84.1, 66.4, 43.8; IR (KBr) $\nu$ 3342, 2963, 2923, 1751, 1716, 1613, 1593, 1530, 1488, 1467, 1369, 1349, 1330, 1315, 1261, 1180, 1106, 1074, 1023, 912, 801, 753, 698, 499 $cm^{-1}$; HRMS (EI, $m/z$): calcd for $C_{25}H_{19}BrN_2O_3$: 474.0579, found: 474.0582. Crystals of **3c** were monoclinic, space group $P2(1)/c$; empirical formula $C_{25}H_{19}BrN_2O_3$, formula weight, 475.33; $a$=14.0369(12) Å, $b$=13.8239(12) Å, $c$=11.0121(10) Å, $\alpha$=90°, $\beta$=95.6150(10)°, $\gamma$=90°, $V$=2126.3(3) $Å^3$; $T$=123(2) K; $\lambda$=0.71073 Å; $Z$=4, $D_{calcd}$=1.485 g $cm^{-3}$; $F(000)$=968, $\mu$=1.963 $mm^{-1}$; Crystal size=0.35×0.30×0.20 mm; reflections collected, 13,838; unique reflections ($R_{int}$=0.0154), 4151; $wR2$=0.0745(all data), $R1$=0.0249($I>2\sigma(I)$); Data in the $\theta$ range 1.46–26.00° were collected at 123(2) K on a Bruker Apex CCD diffractometer. The structure was solved by direct methods and refined by full-matrix least-squares using all $F^2$ data.

*4.4.4. 1-Benzyl-3-(4-chlorophenylamino)-3-(5-oxo-2,5-dihydrofuran-2-yl)indolin-2-one (**3d**).* Off-white solid; yield 98%; mp 247–249 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.48 (dd, $J$=5.8, 1.4 Hz, 1H), 7.38–7.34 (m, 1H), 7.32–7.27 (m, 4H), 7.11–7.04 (m, 3H), 6.95–6.86 (m, 2H), 6.80 (d, $J$=7.9 Hz, 1H), 6.33–6.22 (m, 3H), 5.34 (d, 1.6 Hz, 1H), 5.06 (d, $J$=15.5 Hz, 1H), 4.70 (d, $J$=15.5 Hz, 1H), 4.60 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 173.8, 171.0, 150.9, 142.6(3), 142.6(2), 134.8, 130.7, 129.0, 128.8, 128.0, 127.5, 126.5, 125.5, 124.7, 124.4, 123.3, 119.7, 110.2, 84.6, 67.1, 44.2; IR (KBr) $\nu$ 3344, 3323, 2925, 1789, 1762, 1747, 1705, 1611, 1598, 1528, 1489, 1466, 1374, 1347, 1314, 1256, 1179, 1152, 1105, 1084, 1047, 889, 816, 749, 698, 502 $cm^{-1}$; HRMS (EI, $m/z$): calcd for $C_{25}H_{19}ClN_2O_3$: 430.1084, found: 430.1088.

*4.4.5. 1-Benzyl-3-(4-methoxyphenylamino)-3-(5-oxo-2,5-dihydrofuran-2-yl)indolin-2-one (**3e**).* Off-white solid; yield 97%; mp 187–189 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.59 (dd, $J$=5.8, 1.2 Hz, 1H), 7.40 (d, $J$=7.4 Hz, 1H), 7.25–7.14 (m, 4H), 7.06 (t, $J$=7.5 Hz, 1H), 6.95–6.84 (m, 2H), 6.63 (d, $J$=7.8 Hz, 1H), 6.60–6.43 (m, 4H), 6.27 (dd, $J$=5.8, 1.9 Hz, 1H), 5.39 (t, $J$=1.5 Hz, 1H), 5.05 (d, $J$=15.8 Hz, 1H), 4.60 (d, $J$=15.8 Hz, 1H), 4.26 (br s, 1H), 3.68 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 174.6, 171.5, 155.8, 151.7, 143.3, 136.9, 135.0, 130.6, 128.8, 127.8, 127.3, 126.1, 124.7, 124.6, 123.4, 123.1, 114.4, 110.3, 84.9, 68.7, 55.5, 44.1; IR (KBr) $\nu$ 3313, 2898, 1791, 1768, 1692, 1609, 1513, 1485, 1466, 1435, 1374, 1289, 1247, 1180, 1158, 1107, 1079, 1028,

892, 816, 758, 732, 700, 638, 518 $cm^{-1}$; HRMS (EI, *m*/*z*): calcd for $C_{26}H_{22}N_2O_4$: 426.1580, found: 426.1579.

*4.4.6. 1-Benzyl-3-(2-methoxyphenylamino)-3-(5-oxo-2,5-dihydrofuran-2-yl)indolin-2-one (**3f**).* Off-white solid; yield 94%; mp 187–189 °C; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.63 (dd, *J*=5.8, 1.2 Hz, 1H), 7.34–7.24 (m, 7H), 7.02 (t, *J*=7.5 Hz, 1H), 6.84 (d, *J*=8.0 Hz, 1H), 6.75 (d, *J*=7.3 Hz, 1H), 6.70–6.64 (m, 1H), 6.41–6.35 (m, 1H), 6.27 (dd, *J*=5.8, 1.8 Hz, 1H), 5.73 (dd, *J*=7.9, 0.8 Hz, 1H), 5.35 (s, 1H), 5.21 (br s, 1H), 5.07 (d, *J*=15.5 Hz, 1H), 4.82 (d, *J*=15.5 Hz, 1H), 3.87 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 174.3, 171.1, 151.3, 148.1, 142.5, 135.2, 134.1, 130.3, 128.8, 127.9, 127.8, 125.6, 125.1, 124.4, 123.1, 120.8, 119.7, 113.5, 110.0(4), 109.9(7), 84.9, 66.2, 55.7, 44.4; IR (KBr) $\nu$ 3377, 2927, 1784, 1757, 1714, 1601, 1510, 1544, 1436, 1458, 1258, 1228, 1176, 1147, 1077, 1038, 1021, 889, 818, 734, 698, 580, 516 $cm^{-1}$; HRMS (EI, *m*/*z*): calcd for $C_{26}H_{22}N_2O_4$: 426.1580, found: 426.1582.

*4.4.7. 1-Benzyl-5-bromo-3-(5-oxo-2,5-dihydrofuran-2-yl)-3-(phenylamino)indolin-2-one (**3g**).* Off-white solid; yield 99%; mp 179–182 °C; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.58 (d, *J*=5.7 Hz, 1H), 7.47 (d, *J*=1.6 Hz, 1H), 7.39 (dd, *J*=8.3, 1.8 Hz, 1H), 7.29–7.26 (m, 3H), 7.15–7.06 (m, 2H), 6.99 (t, *J*=7.8 Hz, 2H), 6.83 (t, *J*=7.4 Hz, 1H), 6.66 (d, *J*=8.3 Hz, 1H), 6.38–6.28 (m, 3H), 5.37–5.25 (m, 1H), 5.07 (d, *J*=15.6 Hz, 1H), 4.71 (d, *J*=15.6 Hz, 1H), 4.51 (br s, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 173.7, 170.9, 150.8, 143.7, 141.6, 134.5, 133.4, 129.2, 128.9, 128.7, 128.0, 127.5, 126.9, 124.8, 121.5, 117.9, 116.0, 111.6, 84.4, 67.0, 44.4; IR (KBr) $\nu$ 3317, 2920, 2854, 1791, 1768, 1700, 1600, 1499, 1479, 1425, 1360, 1341, 1313, 1256, 1182, 1149, 1098, 1080, 1045, 892, 883, 820, 751, 699, 633, 536 $cm^{-1}$; HRMS (EI, *m*/*z*): calcd for $C_{25}H_{19}BrN_2O_3$: 474.0579, found:474.0585.

*4.4.8. 1-Benzyl-5-chloro-3-(5-oxo-2,5-dihydrofuran-2-yl)-3-(phenylamino)indolin-2-one (**3h**).* Off-white solid; yield 99%; mp 208–210 °C; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.61 (d, *J*=5.7 Hz, 1H), 7.35 (s, 1H), 7.27–7.22 (m, 4H), 7.15–7.10 (m, 2H), 7.01 (t, *J*=7.6 Hz, 2H), 6.84 (t, *J*=7.3 Hz, 1H), 6.73 (d, *J*=8.4 Hz, 1H), 6.44–6.29 (m, 3H), 5.33 (s, 1H), 5.10 (d, *J*=15.6 Hz, 1H), 4.73 (d, *J*=15.6 Hz, 1H), 4.52 (s, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 173.8, 170.9, 150.8, 143.7, 141.1, 134.5, 130.5, 129.3, 128.9, 128.8, 128.0, 127.5, 126.5, 126.0, 124.8, 121.5, 117.9, 111.1, 84.4, 67.0, 44.4; IR (KBr) $\nu$ 3325, 2917, 2852, 1790, 1768, 1700, 1601, 1499, 1484, 1433, 1329, 1314, 1254, 1181, 1148, 1100, 1082, 1047, 889, 824, 753, 698, 618, 547 $cm^{-1}$; HRMS (EI, *m*/*z*): calcd for $C_{25}H_{19}ClN_2O_3$: 430.1084, found: 430.1079.

*4.4.9. 1-Benzyl-5-methyl-3-(5-oxo-2,5-dihydrofuran-2-yl)-3-(phenylamino)indolin-2-one (**3i**).* Off-white solid; yield 99%; mp 203–206 °C; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.48 (d, *J*=5.4 Hz, 1H), 7.40–7.27 (m, 2H), 7.22–6.85 (m, 7H), 6.81–6.74 (d, *J*=7.3 Hz, 1H), 6.70 (d, *J*=7.9 Hz, 1H), 6.33 (d, *J*=7.8 Hz, 2H), 6.27 (d, *J*=5.5 Hz, 1H), 5.31 (s, 1H), 5.04 (d, *J*=15.5 Hz, 1H), 4.72 (d, *J*=15.5 Hz, 1H), 4.58 (s, 1H), 2.28 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 173.9, 171.3, 151.1, 144.2, 140.0, 135.1, 132.9, 130.8, 129.1, 128.8, 127.8, 127.7, 126.1, 124.9, 124.5, 120.9, 117.4, 109.9, 85.0, 66.8, 44.3, 21.1; IR (KBr) $\nu$ 3308, 2958, 2919, 2854, 1793, 1768, 1700, 1601, 1498, 1439, 1376, 1347, 1315, 1258, 1181, 1154, 1097, 1081, 1047, 892, 826, 809, 749, 737, 693, 626, 505 $cm^{-1}$; HRMS (EI, *m*/*z*): calcd for $C_{21}H_{18}N_2O_3$: 410.1630, found: 410.1633.

*4.4.10. 3-(4-Chlorophenylamino)-3-(5-oxo-2,5-dihydrofuran -2-yl) indolin-2-one (**3j**).* Off-white solid; yield 90%; mp 218–220 °C; $^1H$ NMR (400 MHz, $CD_3CN$) $\delta$ 8.76 (br s, 1H), 7.68 (*J*=5.6 Hz, 1H), 7.31 (t, *J*=7.6 Hz, 1H), 7.70 (dd, *J*=5.6, 1.2 Hz, 1H), 7.00–6.92 (m, 4H), 6.29 (d, *J*=4.4 Hz, 2H), 6.20 (dd, *J*=5.8, 1.8 Hz, 1H), 5.36 (d, *J*=12.0 Hz, 1H); $^{13}C$ NMR (100 MHz, $CD_3CN$) $\delta$ 175.0, 170.9, 152.1, 143.9, 141.4, 130.1, 128.4, 125.1, 124.1, 123.5, 123.1, 121.9, 116.0, 110.4, 83.8, 66.2.; IR (KBr) $\nu$ 3285, 1802, 1759, 1707, 1622, 1492, 1471, 1326, 1252, 1204, 1164, 1089, 1043, 901, 823, 810, 754, 734, 711, 689, 662, 641 $cm^{-1}$; HRMS (EI, *m*/*z*): calcd for $C_{18}H_{13}ClN_2O_3$: 340.0615, found: 340.0620.

## Acknowledgements

This work was financially supported by the Natural Science Foundation of China (No. 20972047), the 'Shu Guang' project of Shanghai Municipal Education Commission, Shanghai Education Development Foundation (No. 09SG28), the Fundamental Research Funds for the Central Universities and the Shanghai Committee of Science and Technology (No. 11DZ2260600).

## Supplementary data

The copies of $^1H$ NMR and $^{13}C$ NMR of the compounds **3** are found in the Supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2012.02.046.

## References and notes

1. (a) Antonchick, A. P.; Gerding-Reimers, C.; Catarinella, M.; Schürmann, M.; Preut, H.; Ziegler, S.; Rauh, D.; Waldmann, H. *Nature Chem.* **2010**, *2*, 735; (b) Nicolaou, K. C.; Chen, D. Y.-K.; Huang, X.; Ling, T.; Bella, M.; Snyder, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 12888; (c) Netz, A.; Oost, T.; Geneste, H.; Braje, W. M.; Wernet, W.; Unger, L.; Hornberger, W.; Lubisch, W. PTC Int. Appl. WO2008080971, 2008; (d) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748.
2. (a) Ochi, M.; Kawasaki, K.; Kataoka, H.; Uchio, Y.; Nishi, H. *Biochem. Biophys. Res. Commun.* **2001**, *283*, 1118; (b) Bernard, K.; Bogliolo, S.; Ehrenfeld, J. *Br. J. Pharmacol.* **2005**, *144*, 1037; (c) Decaux, G.; Soupart, A.; Vassart, G. *Lancet* **2008**, *371*, 1624; (d) Claudine, S. G.; Sylvain, D.; Gilles, G.; Claudine, S. L. *Stress* **2003**, *6*, 199; (e) Takayama, H.; Mori, I.; Kitajima, M.; Aimi, N.; Lajis, N. H. *Org. Lett.* **2004**, *6*, 2945.
3. (a) Jia, Y.-X.; Hillgren, J. M.; Watson, M. L.; Marsden, S. P.; Kündig, E. P. *Chem. Commun.* **2008**, 4040; (b) Marsden, S. P.; Watson, M. L.; Raw, S. A. *Org. Lett.* **2008**, *10*, 2905.
4. (a) Emura, T.; Esaki, T.; Tachibana, K.; Shimizu, M. *J. Org. Chem.* **2006**, *71*, 8559; (b) Zhao, H.; Thurkauf, A.; Braun, J.; Brodbeck, R.; Kieltyka, A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2119.
5. Liu, Y.-L.; Zhou, F.; Cao, J.-J.; Ji, C.-B.; Ding, M.; Zhou, J. *Org. Biomol. Chem.* **2010**, *8*, 3847.
6. (a) Miyabe, H.; Yamaoka, Y.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 3324; (b) Lesma, G.; Landoni, N.; Pilati, T.; Sacchetti, A.; Silvani, A. *J. Org. Chem.* **2009**, *74*, 4537; (c) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Eur. J. Org. Chem.* **2010**, 2845; (d) Nishikawa, T.; Kajii, S.; Isobe, M. *Chem. Lett.* **2004**, *33*, 440.
7. (a) Cheng, L.; Liu, L.; Wang, D.; Chen, Y.-J. *Org. Lett.* **2009**, *11*, 3874; (b) Qian, Z.-Q.; Zhou, F.; Du, T.-P.; Wang, B.-L.; Ding, M.; Zhao, X.-L.; Zhou, J. *Chem. Commun.* **2009**, 6753; (c) Bui, T.; Hernández-Torres, G.; Milite, C.; Barbas, C. F., III. *Org. Lett.* **2010**, *12*, 5696; (d) Mouri, S.; Chen, Z.; Mitsunuma, H.; Furutachi, M.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 1255; (e) Yang, Z.; Wang, Z.; Bai, S.; Shen, K.; Chen, D.; Liu, X.; Lin, L.; Feng, X. *Chem.—Eur. J.* **2010**, *16*, 6632.
8. For typical reviews, see: (a) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895; (b) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221.
9. Hermange, P.; Dau, M. E. T. H.; Retailleau, P.; Dodd, R. H. *Org. Lett* **2009**, *11*, 4044.
10. Wieland, L. C.; Vieira, E. M.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 570.
11. Rajopadhye, M.; Dopp, F. D. *J. Heterocycl. Chem.* **1985**, *22*, 93.
12. Bouhfid, R.; Joly, N.; Massoui, M.; Cecchelli, R.; Lequart, V.; Martin, P.; Assassi, E. M. *Heterocycles* **2005**, *65*, 2949.
13. For selected literatures, see: (a) Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7230; (b) Mandai, H.; Mandai, K.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 17961; (c) González, A. S.; Arrayás, R. G.; Rivero, M. R.; Carretero, J. C. *Org. Lett.* **2008**, *10*, 4335; (d) Deng, H.-P.; Wei, Y.; Shi, M. *Adv. Synth. Catal.* **2009**, *351*, 2897.
14. (a) Zeng, W.; Zhou, Y. G. *Org. Lett.* **2005**, *7*, 5055; (b) Chen, Q.-A.; Wang, D.-S.; Zhou, Y.-G. *Chem. Commun.* **2010**, 4043.
15. Casiraghi, G.; Rassu, G. *Synthesis* **1995**, 607.