DOI: 10.1002/ejoc.201101656

An Efficient Route to Quinolines and Other Compounds by Iron-Catalysed Cross-Dehydrogenative Coupling Reactions of Glycine Derivatives

Peng Liu,[a] Zhiming Wang,[a] Jue Lin,[a] and Xianming Hu*[a]

Keywords: Natural products / Amino acids / Nitrogen heterocycles / Iron / Cross-coupling / Oxidation

A simple method has been developed for functionalizing glycine derivatives by iron-catalysed cross-dehydrogenative coupling (CDC) reactions. In particular, *N*-arylglycine derivatives reacted with alkynes by oxidative C–H/C–H coupling reactions to provide a series of substituted quinolines starting from commercially inexpensive materials. Moreover, *N*-arylglycine esters can be oxidatively coupled to ketones by using $FeCl_3$ in the presence of DDQ.

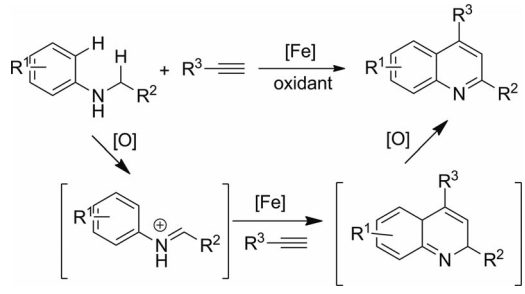
Introduction

There is considerable interest in methods for the functionalization of amino acids to provide molecules that are prevalent in bioactive natural products and therapeutic drug molecules.[1] Generally applicable and relatively cheap methods for the rapid modification of amino acids are highly sought after. Traditionally, the α-functionalization of amino acid derivatives has been accomplished by deprotonation with a strong base,[2] Claisen rearrangements[3] and UV photolysis.[4]

The direct cross-dehydrogenative coupling (CDC) of C–H bonds in C–C bond-forming reactions is more atom economic and environmentally friendly than these methods,[5] although selective oxidative functionalization of α-amino acid derivatives is still relatively rare.[6] As far as we know, the only two examples are those of Li and coworkers, who have developed CDC reactions of *N*-acetylglycine esters and *N*-arylglycine amides with malonates and alkynes in the presence of $Cu(OAc)_2$ (2.0 equiv.) catalysed by CuBr,[7] and Xie and Huang, who reported the coupling of *N*-arylglycine esters with ketones by cooperative catalysis by $Cu(OAc)_2$ and pyrrolidine in the presence of TBHP or DDQ as oxidant.[8]

Because of the low price, ready availability, non-toxicity and environmentally benign character, considerable effort has recently been directed towards developing these redox processes by using iron catalysts.[9] Herein, we report a method for functionalizing phenylglycine derivatives by direct CDC reactions using iron catalysis.

We have developed an efficient process in which oxidative coupling is carried out with an acetylene. The iron salts in a tandem process subsequently catalyse in situ the cyclization and dehydrogenation to form interesting quinoline derivatives. Two oxidative processes are involved, as shown in Scheme 1: i. the formation of an iminium ion intermediate, which will undergo the CDC reaction in the presence of an alkyne as nucleophile and ii. the final oxidative aromatization of the dihydroquinoline intermediate to form the quinoline unit. We note that quinolines and their derivatives occur in a large number of biologically active natural products, and they are also important starting materials for the chemical and pharmaceutical industry.[10] Although many approaches providing efficient access to quinolines have been developed,[11] this method provides an environmentally friendly and atom-economic synthesis of quinolines from glycine derivatives.



Scheme 1. Synthesis of quninolines in a one-pot reaction.

Results and Discussion

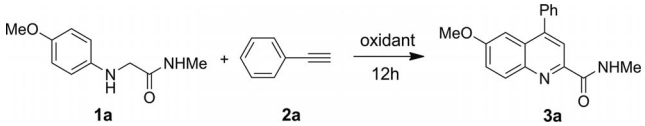
To initiate our study, we studied the reaction of phenylglycine derivative **1a** (1.0 equiv.) with phenylacetylene (**2a**, 1.2 equiv.) catalysed by various iron salts (10 mol-%) with di-*tert*-butyl peroxide (2.0 equiv.) as the oxidant in 1,2-dichloroethane (DCE) at 80 °C in a Schlenk tube. A Frie-

[a] State Key Laboratory of Virology, Ministry of Education Key Laboratory of Combinatorial Biosynthesis and Drug Discovery, Wuhan University, School of Pharmaceutical Sciences, Wuhan University,
Wuhan 430071, China
Fax: +86-27-6875-9850
E-mail: xmhu@whu.edu.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201101656.

del–Crafts reaction to provide the final product **3a** was assumed to occur after the coupling reaction. As seen in Table 1, $Fe(OTf)_3$ and $FeCl_3$ (entries 1 and 2, Table 1) were found to be the best catalysts with di-*tert*-butyl peroxide as oxidant. As seen from entries 3–5, $FeCl_2{\cdot}4H_2O$, $FeCl_3{\cdot}6H_2O$ and $Fe(ClO_4)_3$ are less effective as catalysts. Clearly a catalyst is necessary, as seen from entry 6. Iron complex $[Fe(dmf)_6(ClO_4)_3]$ was disappointing as catalyst (entry 7). The use of highly anhydrous $FeCl_3$ (entry 8) did not lead to significant improvement over laboratory-grade $FeCl_3$ (97% $FeCl_3$). We thus chose laboratory-grade $FeCl_3$ as the best catalyst owing to its cheapness and ready availability.

Table 1. Optimization of the conditions for the CDC reaction of phenylglycine **1a** and acetylene **2a**.[a]



Entry	Catalyst	Solvent	*T* [°C]	Oxidant	Yield [%][b]
1	$Fe(OTf)_3$	DCE	80	$(tBuO)_2$	92
2	$FeCl_3$	DCE	80	$(tBuO)_2$	78
3	$FeCl_2{\cdot}4H_2O$	DCE	80	$(tBuO)_2$	23
4	$FeCl_3{\cdot}6H_2O$	DCE	80	$(tBuO)_2$	62
5	$Fe(ClO_4)_3$	DCE	80	$(tBuO)_2$	70
6	no cat.	DCE	80	$(tBuO)_2$	n.r.[c]
7	$[Fe(dmf)_6(ClO_4)_3]$	DCE	80	$(tBuO)_2$	23
8	$FeCl_3$ (>99.9%)	DCE	80	$(tBuO)_2$	81
9	$FeCl_3$	DCE	80	TBHP	59
10	$FeCl_3$	DCE	80	H_2O_2	<5
11	Cu_2O	DCE	80	$(tBuO)_2$	n.r.[c]
12	CF_3SO_3H	DCE	80	$(tBuO)_2$	39
13	$FeCl_3$	$CHCl_3$	60	$(tBuO)_2$	36
14	$FeCl_3$	CH_2Cl_2	40	$(tBuO)_2$	31
15	$FeCl_3$	CH_3CN	80	$(tBuO)_2$	59
16	$FeCl_3$	toluene	80	$(tBuO)_2$	23
17	$FeCl_3$	THF	60	$(tBuO)_2$	31
18	$FeCl_3$	MeOH	60	$(tBuO)_2$	6
19	$FeCl_3$	acetone	50	$(tBuO)_2$	18

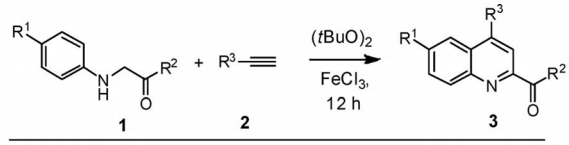
[a] Reagents and conditions: **1a**/**2a**/oxidant/cat. = 1:1.2:2:0.1, 12 h. [b] Isolated yield. [c] n.r.: no reaction (no quinoline product detected).

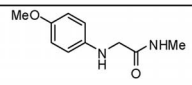
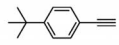
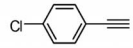
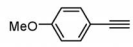
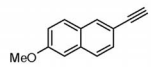
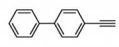
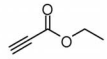
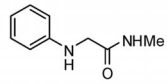
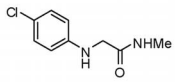
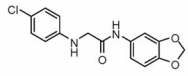
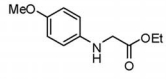
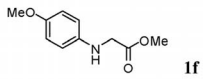
The effect of varying the oxidant was also examined. Both TBHP and H_2O_2 were found to lead to lower or no yields (entries 9 and 10). It has been reported that traces of metal impurities or contaminants can affect the catalytic activity (typically copper oxide in iron salts).[12] Note that when Cu_2O (10 mol-%) was employed as the catalyst, no quinoline product was detected (entry 11). This establishes that iron plays a crucial role in this reaction. Brønsted acid CF_3SO_3H was relatively ineffective as the catalyst (entry 12).

Different solvents were also screened and 1,2-dichloroethane (DCE) was found to be the best for this reaction (entries 13–19).

The scope of this method for the synthesis of quinoline derivatives was explored and the results are summarized in Table 2. Various phenylglycine derivatives and a range of substituted acetylenes were examined. Glycine derivative **1a**

Table 2. Functionalization of **1** by CDC reactions with alkynes **2**.[a]



Entry	1	Alkyne	3	Yield[b] (%)
1	 **1a**	 **2a**	**3a**	78
2	**1a**	 **2b**	**3b**	81
3	**1a**	 **2c**	**3c**	88
4	**1a**	 **2d**	**3d**	79
5	**1a**	 **2e**	**3e**	74
6	**1a**	 **2f**	**3f**	86
7	**1a**	 **2g**		n.r.[c]
8	 **1b**	**2a**	**3g**	62
9	 **1c**	**2a**	**3h**	81
10	**1c**	**2c**	**3i**	86
11	**1c**	**2d**	**3j**	68
12	 **1d**	**2a**	**3k**	79
13	**1d**	**2c**	**3l**	83
14[d]	 **1e**	**2a**	**3m**	76
15[d]	**1e**	**2c**	**3n**	79
16[d]	 **1f**	**2a**	**3o**	80
17[d]	**1f**	**2c**	**3p**	82

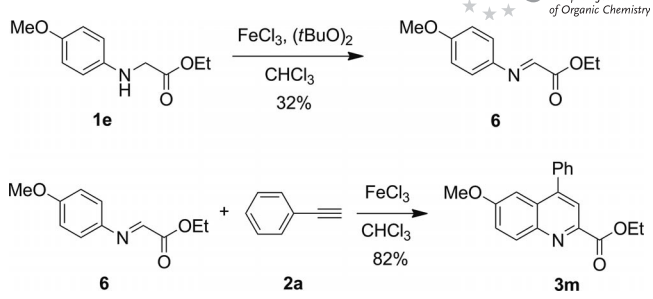
[a] Reagents and conditions: **1** (0.2 mmol), **2** (0.24 mmol), $(tBuO)_2$ (0.4 mmol), $FeCl_3$ (0.02 mmol), $ClCH_2CH_2Cl$, 80 °C, 12 h. [b] Isolated yield. [c] n.r.: no reaction (no quinoline product detected). [d] $CHCl_3$, 60 °C, 1 h.

readily reacted with various substituted alkynes, including **2b** with a bulky substituent at the phenyl 4-position, to give excellent yields (74–88%; entries 2–6). However, with electron-deficient alkyne **2g**, no quinoline product was detected (entry 7). Unsubstituted phenylglycine **1b** reacted with **2a** to give the desired product **3g** in 62% yield (entry 8), although the yield is somewhat lower than with the more reactive **1a**. Excellent product yields were also obtained with R^1 = Cl (entries 9–11). With R^2 an aromatic amine, the corresponding quinolines were obtained in 79 and 83% yields (entries 12 and 13).

When *N*-arylglycine esters **1e** and **1f** were used as substrates, no quinoline products were detected. However, when 1,2-dichloroethane was replaced with chloroform as solvent, quinoline products **3m**–**p** were obtained in good yields at 60 °C (entries 14–17). A detailed explanation of this unusual effect will require further investigation, which we hope will be carried out in the future.

To establish the practicality of the method, the reaction was scaled up to 0.1 mol. As an example, **1a** (19.4 g, 0.1 mol) readily reacted with **2a** (0.12 mol) under the conditions described and provided **3a** in 71% isolated yield.

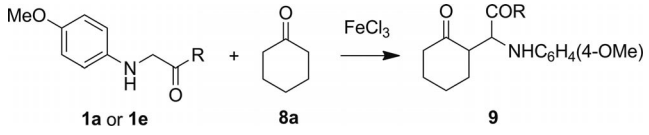
A radical mechanism for the oxidative dehydrogenation seems probable. This idea is supported by the observation that addition of a radical inhibitor, 2,6-di-*tert*-butyl-4-methylphenol (BHT, 1.0 equiv.), to the reaction of **1a** with **2a** led to a reduction in the yield of **3a** from 78 to 25%. To gain further mechanistic insights, the reaction of **1e** with $(t\text{BuO})_2$ in $CHCl_3$ was examined (reactions with **1a** failed to lead to identifiable products). Reaction for 1 h in the absence of alkyne led to the isolation of imine **6** in 32% yield. Imine **6** reacted with acetylene **2a** in the presence of a catalytic amount of $FeCl_3$ to give the desired product **3m** in 82% yield (Scheme 2). Based on these experimental results, the tentative mechanism shown in Scheme 3 has been proposed. A *tert*-butoxyl radical, generated by the iron-catalysed decomposition of $(t\text{BuO})_2$, abstracts a hydrogen atom from **1e** to form radical **4**. Single electron transfer (SET) from **4** leads to iminium ion **5**, which deprotonates to give imine **6**. Subsequent nucleophilic attack of the alkyne on **6** generates **7**, which then undergoes an intramolecular Friedel–Crafts reaction and oxidation catalysed by $FeCl_3$ to give the quinoline product **3m**. Excess $(t\text{BuO})_2$ ensures that Fe^{2+} is reoxidized to Fe^{3+}.



Scheme 2. Mechanistic probe for the CDC reaction of **1e** and alkyne with $(t\text{BuO})_2$.

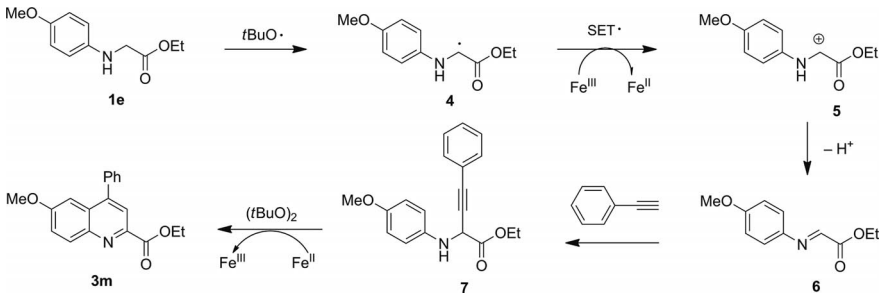
We also examined the CDC reactions of ketones with glycine derivatives. The results are shown in Table 3. When cyclohexanone (**8a**) was employed instead of an alkyne in the reaction with **1a** with the combination of $FeCl_3$ and di-*tert*-butyl peroxide or DDQ, no reaction was detected (entries 1 and 2). The reaction between *N*-(4-methoxyphenyl)glycine ester **1e** and **8a** (15.0 equiv.) catalysed by $FeCl_3$ (10 mol-%) with di-*tert*-butyl peroxide (2.0 equiv.) as oxidant in 1,2-dichloroethane also failed (entry 3). However, when di-*tert*-butyl peroxide was replaced with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as the oxidant, the coupling product **9a** was obtained in 10% yield

Table 3. Optimization of the conditions for the reaction of phenylglycine with ketone **8a**.[a]



Entry	R	Solvent	*T* [°C]	Oxidant	Yield [%][b]
1	NHMe	$ClCH_2CH_2Cl$	80	$(t\text{BuO})_2$	n.r.[c]
2	NHMe	$ClCH_2CH_2Cl$	80	DDQ	n.r.[c]
3	OEt	$ClCH_2CH_2Cl$	80	$(t\text{BuO})_2$	n.r.[c]
4	OEt	$ClCH_2CH_2Cl$	80	DDQ	10 (4:1)[d]
5	OEt	$CHCl_3$	60	DDQ	51 (6:1)[d]
6	OEt	CH_2Cl_2	40	DDQ	n.r.[c]

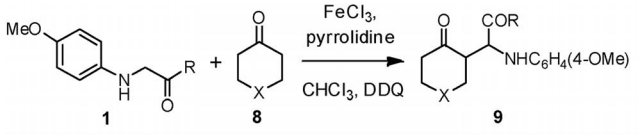
[a] Reagents and conditions: **1a** or **1e** (0.2 mmol), **8a** (15.0 equiv.), oxidant (0.24 mmol), $FeCl_3$ (0.02 mmol), solvent (1 mL), 12 h. [b] Isolated yield. [c] n.r.: no reaction (no product detected). [d] Diastereomeric ratio: *anti*/*syn*.



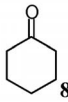
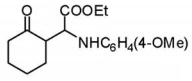
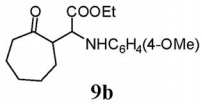
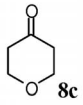
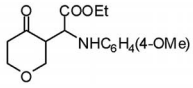
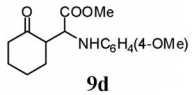
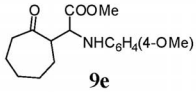
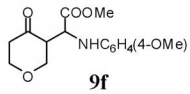
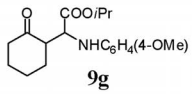
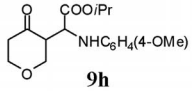
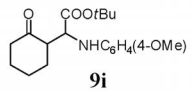
Scheme 3. Proposed mechanism for the CDC reaction of **1e** and alkyne with $(t\text{BuO})_2$ and $FeCl_3$.

(entry 4). Different solvents were screened and chloroform was found to be the best, giving a yield of 51% after 12 h reaction time and a diastereoselectivity of 6:1 (entry 5).

Table 4. Functionalization of **1** by CDC reaction with cyclic ketones **8**.[a]



1 **8** **9**

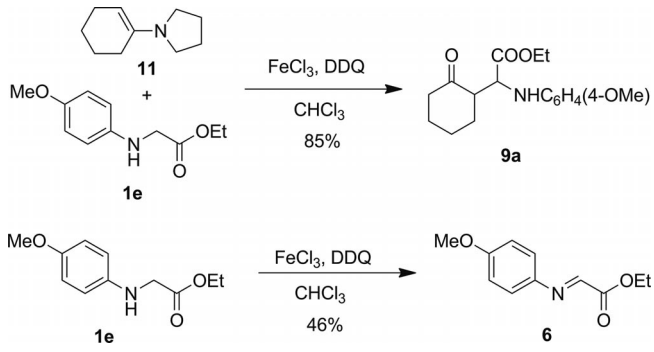
Entry	R	Ketone	Product	Yield[b] (%)	*dr*[c]
1	OEt **1e**	 **8a**	 **9a**	83	6:1
2[d]	**1e**	**8a**	**9a**	80	5:2
3	**1e**	 **8b**	 **9b**	69	2:3
4	**1e**	 **8c**	 **9c**	78	7:2
5	OMe **1f**	**8a**	 **9d**	76	7:1
6	**1f**	**8b**	 **9e**	63	2:3
7	**1f**	**8c**	 **9f**	72	2:1
8	O*i*Pr **1g**	**8a**	 **9g**	79	3:1
9	**1g**	**8b**	 **9h**	68	7:2
10	O*t*Bu **1h**	**8a**	 **9i**	70	5:1

[a] Reagents and conditions: **1** (0.2 mmol), **8** (15.0 equiv.), DDQ (0.24 mmol), pyrrolidine (0.06 mmol), $FeCl_3$ (0.02 mmol), $CHCl_3$, 60 °C, 12 h. [b] Isolated yield. [c] Diastereomeric ratio: *anti*/*syn*. [d] Room temperature.

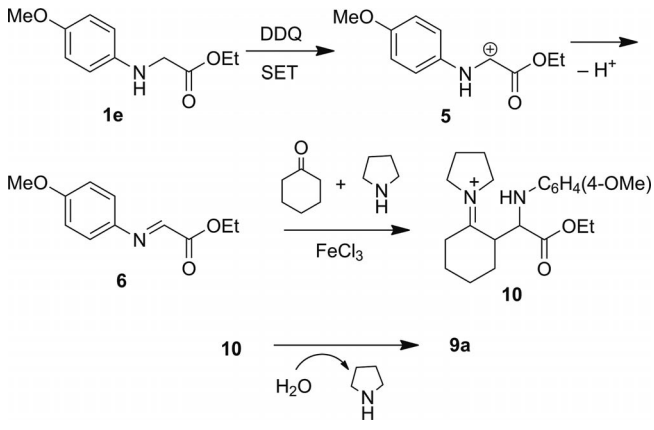
Co-catalysis using a secondary amine as organic catalyst and a metal has been reported; the intermediate enamines are more reactive than the ketones.[8] Pyrrolidine (30 mol-%) was added to increase the reactivity of cyclohexanone. Indeed, **9a** was obtained in increased yield (83%) at 60 °C (entry 1, Table 4). When the temperature was lowered to room temperature, **9a** was obtained in 80% yield, but the diastereoselectivity decreased to 5:2 (entry 2, Table 4).

The substrate scope of the iron-catalysed CDC reactions of ketones with the C–H bond of glycine derivatives was examined. In these experiments, **1e** readily underwent CDC reaction with different cyclic ketones to give the desired coupling products **9b** and **9c** in satisfactory yields (69 and 78%) and diastereoselectivities (2:3 and 7:2; entries 3 and 4). If the substituent on ester **1e** was changed from ethyl to methyl (**1f**), isopropyl (**1g**) or *tert*-butyl (**1h**), the reaction proceeded readily to give coupling products **9d**–**9i** in good yields (63–79%) with up to 7:1 diastereoselectivity (entries 5–10). Unfortunately, linear ketones such as acetone and acetophenone failed to react.

To gain an insight into the mechanism, the reaction of **1e** with enamine **11** derived from cyclohexanone and pyrrolidine was examined. The coupling product **9a** was obtained in 85% yield (Scheme 4). The imine intermediate **6** derived from **1e** was obtained in 46% yield under the catalytic conditions without cyclohexanone (Scheme 4). The radical inhibitor BHT was also added to the reaction system with cyclohexanone, pyrrolidine and DDQ. The yield



Scheme 4. Mechanistic probe for the CDC reactions with DDQ.



Scheme 5. Proposed mechanism for the reactions with DDQ.

of the coupling product **9a** then decreased from 83 to 19%. Based on the experimental results above, the reaction likely proceeds by a radical pathway analogous to that described in Scheme 3: iminium **5** deprotonates to give **6** as shown in Scheme 5. Nucleophilic attack by the enamine derived from cyclohexanone and pyrrolidine followed by hydrolysis leads to the final product **9a** and regenerates the pyrrolidine.

Conclusions

We have developed a facile and economic method for the functionalization of glycine derivatives. A series of substituted quinolines have been synthesized from commercially inexpensive starting materials by using an inexpensive, readily available catalyst. *N*-Arylglycine esters can also be functionalized with ketones by $FeCl_3$ in the presence of DDQ under mild conditions. This reaction could be applicable to other amino acids. The effectiveness of iron salts as catalysts makes these processes especially interesting. Further studies on the CDC reactions of secondary amines with other C–H bonds by iron catalysis and the synthetic applications are in progress.

Experimental Section

General: Reagents were obtained commercially and used without further purification unless indicated otherwise. Solvent was removed under reduced pressure and the residue obtained was purified by chromatography on a silica gel column (300–400 mesh) using a gradient solvent system (EtOAc/petroleum ether as eluent unless specified otherwise). ^1H and ^{13}C NMR spectra were measured with a Bruker DPX-400 spectrometer. Chemical shifts [ppm] were determined with tetramethylsilane (TMS) as internal reference. Mass spectra were determined with a Finnigan MAT 95 mass spectrometer.

General Procedure for the Synthesis of 3a–l: Compounds **1a**–**d** (0.20 mmol), $FeCl_3$ (0.02 mmol), phenylacetylene (0.24 mmol) and $(t\text{BuO})_2$ (0.40 mmol) were successively added to DCE (1 mL) in a Schlenk tube. The mixture was stirred for 12 h at 80 °C, filtered through a small pad of silica gel and concentrated in vacuo. Flash chromatography on silica gel using ethyl acetate/petroleum ether (1:3) furnished the final product. The spectroscopic data for **3d** are consistent with the literature.[11e]

3a: ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.23 (br. s, 1 H), 8.21 (s, 1 H), 8.04 (d, J = 9.2 Hz, 1 H), 7.54 (m, 4 H), 7.52 (m, 1 H), 7.41 (dd, J = 9.2, 2.8 Hz, 1 H), 7.24 (d, J = 2.8 Hz, 1 H), 3.81 (s, 3 H), 3.11 (d, J = 5.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 165.58, 159.08, 148.46, 147.35, 143.32, 138.22, 131.60, 129.51, 129.08, 128.85, 128.68, 122.82, 119.61, 103.68, 55.65, 26.36 ppm. MS (EI): m/z = 292 $[M]^+$. HRMS (EI): calcd. for $C_{18}H_{16}N_2O_2$ 292.1206; found 292.1205.

3b: ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.23 (br. s, 1 H), 8.21 (s, 1 H), 8.03 (d, J = 9.6 Hz, 1 H), 7.55 (d, J = 8.4 Hz, 2 H), 7.50 (d, J = 8.4 Hz, 2 H), 7.41 (dd, J = 9.6, 2.4 Hz, 1 H), 7.33 (d, J = 2.4 Hz, 1 H), 3.84 (s, 3 H), 3.11 (d, J = 6.0 Hz, 3 H), 1.41 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 165.63, 158.99, 151.78, 148.46, 147.36, 143.35, 135.23, 131.58, 129.24, 129.11, 125.79, 122.57, 119.63, 104.01, 55.74, 34.91, 31.50, 26.34 ppm. MS (EI): m/z = 348 $[M]^+$. HRMS (EI): calcd. for $C_{22}H_{24}N_2O_2$ 348.1832; found 348.1833.

3c: ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.21 (br. s, 1 H), 8.18 (s, 1 H), 8.04 (d, J = 8.8 Hz, 1 H), 7.52 (d, J = 8.6 Hz, 2 H), 7.48 (d, J = 8.6 Hz, 2 H), 7.42 (dd, J = 8.8, 2.4 Hz, 1 H), 7.16 (d, J = 2.4 Hz, 1 H), 3.82 (s, 3 H), 3.11 (d, J = 4.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 165.44, 159.28, 147.31, 147.11, 143.32, 136.64, 134.87, 131.73, 130.80, 129.15, 128.86, 122.98, 119.53, 103.32, 55.70, 26.36 ppm. MS (EI): m/z = 326 $[M]^+$. HRMS (EI): calcd. for $C_{18}H_{15}ClN_2O_2$ 326.0817; found 326.0821.

3e: ^1H NMR (400 MHz, $CDCl_3$): δ = 8.26 (s, 1 H), 8.24 (br. s, 1 H), 8.06 (d, J = 9.2 Hz, 1 H), 7.78 (d, J = 8.0 Hz, 2 H), 7.71 (d, J = 7.4 Hz, 2 H), 7.64 (d, J = 8.0 Hz, 2 H), 7.50 (t, J = 7.6 Hz, 2 H), 7.43 (m, 2 H), 7.32 (d, J = 2.4 Hz, 1 H), 3.84 (s, 3 H), 3.12 (d, J = 5.0 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.46, 159.01, 147.93, 147.24, 143.24, 141.37, 140.35, 137.00, 131.54, 129.87, 128.96, 128.91, 127.73, 127.41, 127.16, 122.73, 119.46, 103.56, 55.60, 26.25 ppm. MS (EI): m/z = 368 $[M]^+$. HRMS (EI): calcd. for $C_{24}H_{20}N_2O_2$ 368.1525; found 368.1601.

3f: ^1H NMR (400 MHz, $CDCl_3$): δ = 8.30 (s, 1 H), 8.25 (br. s, 1 H), 8.05 (d, J = 9.2 Hz, 1 H), 7.97 (s, 1 H), 7.89 (d, J = 8.4 Hz, 1 H), 7.82 (d, J = 9.6 Hz, 1 H), 7.63 (dd, J = 8.4, 1.7 Hz, 1 H), 7.42 (dd, J = 9.2, 2.8 Hz, 1 H), 7.31 (d, J = 2.7 Hz, 1 H), 7.26–7.21 (m, 2 H), 3.98 (s, 3 H), 3.77 (s, 3 H), 3.12 (d, J = 5.1 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.55, 158.96, 158.39, 148.39, 147.21, 143.26, 134.39, 133.27, 131.51, 129.82, 129.11, 128.87, 128.61, 127.58, 127.11, 122.72, 119.67, 119.60, 105.69, 103.60, 55.52, 55.43, 26.25 ppm. MS (EI): m/z = 372 $[M]^+$. HRMS (EI): calcd. for $C_{23}H_{20}N_2O_3$ 372.1474; found 372.1553.

3g: ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.31 (br. s, 1 H), 8.27 (s, 1 H), 8.15 (d, J = 9.2 Hz, 1 H), 7.99 (d, J = 8.8 Hz, 1 H), 7.77 (t, J = 8.6 Hz, 1 H), 7.57 (t, J = 8.8 Hz, 1 H), 7.54 (m, 5 H), 3.12 (d, J = 5.1 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 165.40, 150.21, 149.53, 147.29, 137.89, 130.17, 130.03, 129.76, 128.77, 128.76, 128.00, 127.91, 126.14, 119.19, 26.43 ppm. MS (EI): m/z = 262 $[M]^+$. HRMS (EI): calcd. for $C_{17}H_{14}N_2O$ 262.1101; found 262.1098.

3h: ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.28 (s, 1 H), 8.24 (br. s, 1 H), 8.07 (d, J = 9.6 Hz, 1 H), 7.94 (d, J = 2.0 Hz, 1 H), 7.69 (dd, J = 9.6, 2.0 Hz, 1 H), 7.53 (m, 5 H), 3.12 (d, J = 4.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 164.99, 149.71, 149.44, 145.63, 137.18, 134.12, 131.69, 131.04, 129.60, 129.06, 128.97, 128.53, 124.93, 119.97, 26.43 ppm. MS (EI): m/z = 296 $[M]^+$. HRMS (EI): calcd. for $C_{17}H_{13}ClN_2O$ 296.0711; found 296.0711.

3i: ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.26 (s, 1 H), 8.22 (br. s, 1 H), 8.15 (d, J = 9.2 Hz, 1 H), 7.88 (d, J = 2.0 Hz, 1 H), 7.71 (dd, J = 9.2, 2.0 Hz, 1 H), 7.54 (d, J = 8.8 Hz, 2 H), 7.45 (d, J = 8.8 Hz, 2 H), 3.12 (d, J = 4.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 164.85, 149.75, 148.12, 145.65, 135.57, 135.42, 134.43, 131.81, 131.23, 130.91, 129.31, 128.30, 124.60, 119.92, 26.45 ppm. MS (EI): m/z = 330 $[M]^+$. HRMS (EI): calcd. for $C_{17}H_{12}Cl_2N_2O$ 330.0321; found 330.0318.

3j: ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.26 (s, 1 H), 8.24 (br. s, 1 H), 8.07 (d, J = 8.8 Hz, 1 H), 7.99 (d, J = 2.4 Hz, 1 H), 7.68 (dd, J = 8.8, 2.4 Hz, 1 H), 7.46 (d, J = 8.6 Hz, 2 H), 7.08 (d, J = 8.6 Hz, 2 H), 3.92 (s, 3 H), 3.12 (d, J = 5.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 165.13, 160.40, 149.69, 149.23, 145.75, 133.98, 131.70, 130.96, 130.85, 129.47, 128.71, 125.04, 119.83, 114.55, 55.58, 26.43 ppm. MS (EI): m/z = 326 $[M]^+$. HRMS (EI): calcd. for $C_{18}H_{15}ClN_2O_2$ 326.0817; found 326.0817.

3k: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.09 (br. s, 1 H), 8.36 (s, 1 H), 8.18 (d, J = 9.2 Hz, 1 H), 7.98 (d, J = 2.2 Hz, 1 H), 7.74 (dd, J = 9.2, 2.2 Hz, 1 H), 7.56 (m, 6 H), 7.16 (dd, J = 8.4, 1.8 Hz, 1 H), 6.84 (d, J = 8.4 Hz, 1 H), 6.00 (s, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 161.77, 149.91, 149.58, 148.12, 145.49, 144.54, 137.14, 134.50, 132.28, 131.72, 131.34, 129.65, 129.22, 129.07, 128.71, 125.08, 119.97, 113.10, 108.42, 102.51, 101.49 ppm. MS (EI): m/z = 402 $[M]^+$. HRMS (EI): calcd. for $C_{23}H_{15}ClN_2O_3$ 402.0766; found 402.0763.

3l: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.05 (br. s, 1 H), 8.33 (s, 1 H), 8.18 (d, J = 9.6 Hz, 1 H), 7.90 (d, J = 1.6 Hz, 1 H), 7.75 (dd, J = 9.6, 2.4 Hz, 1 H), 7.57 (m, 3 H), 7.47 (d, J = 8.0 Hz, 2 H), 7.15 (dd, J = 8.4, 2.4 Hz, 1 H), 6.84 (d, J = 8.4 Hz, 1 H), 6.00 (s, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 161.62, 149.62, 148.57, 148.16, 145.49, 144.60, 135.58, 135.50, 134.79, 132.20, 131.85, 131.52, 130.94, 129.39, 128.48, 124.71, 119.92, 113.13, 108.41, 102.51, 101.52 ppm. MS (EI): m/z = 436 $[M]^+$. HRMS (EI): calcd. for $C_{23}H_{14}Cl_2N_2O_3$ 436.0376; found 436.0365.

General Procedure for the Synthesis of 3m–p: Compound **1e** or **1f** (0.20 mmol), $FeCl_3$ (0.02 mmol), phenylacetylene (0.24 mmol) and (tBuO)$_2$ (0.40 mmol) were successively added to $CHCl_3$ (1 mL) in a Schlenk tube. The mixture was stirred for 1 h at 60 °C, filtered through a small pad of silica gel and concentrated in vacuo. Flash chromatography on silica gel by using ethyl acetate/petroleum ether (1:3) furnished the final product. The spectroscopic data for **3m**,[11e] **3n**,[11e] **3o**[13] and **3p**[13] are consistent with the literature.

General Procedure for the Synthesis of 9a–i: Compounds **1e**–**h** (0.20 mmol), $FeCl_3$ (0.02 mmol), cyclohexanone (3.0 mmol, 15.0 equiv.), pyrrolidine (0.06 mmol, 30 mol-%) and DDQ (0.24 mmol) were successively added to $CHCl_3$ (1 mL) in a Schlenk tube. The mixture was stirred for 12 h at 60 °C, filtered through a small pad of silica gel and concentrated in vacuo. Flash chromatography on silica gel using ethyl acetate/petroleum ether (1:4) furnished the final product. The spectroscopic data for **9a**–**d**, **9g** and **9i** are consistent with the literature.[8]

9e: *dr* (*anti*/*syn*) = 2:3. Mixture of two diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.83–6.71 (m, 2 H), 6.67–6.65 (m, 2 H), 4.31–4.27 (m, 1 H), 3.74 (s, 3 H), 3.70 (s, 1.1 H), 3.68 (s, 1.8 H), 3.07 (m, 0.39 H), 2.94 (m, 0.59 H), 2.55–2.48 (m, 2 H), 2.06–1.82 (m, 4 H), 1.74–1.66 (m, 2 H), 1.63–1.52 (m, 2 H) ppm. MS (EI): m/z = 305 $[M]^+$. HRMS (EI): calcd. for $C_{17}H_{23}NO_4$ 305.1627; found 305.1702.

9f: *dr* (*anti*/*syn*) = 2:1. Mixture of two diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.81–6.74 (m, 2 H), 6.70 (d, J = 9.0 Hz, 0.65 H), 6.61 (d, J = 8.9 Hz, 1.27 H), 4.27–3.76 (m, 6 H), 3.73 (m, 3 H), 3.71 (s, 2 H), 3.69 (s, 1 H), 3.30–3.21 (m, 0.63 H), 2.95–2.91 (m, 0.34 H), 2.66–2.53 (m, 1.38 H), 2.46 (m, 0.66 H) ppm. MS (EI): m/z = 293 $[M]^+$. HRMS (EI): calcd. for $C_{15}H_{19}NO_5$ 293.1263; found 293.1279.

9h: *dr* (*anti*/*syn*) = 7:2. Mixture of two diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.82–6.71 (m, 2 H), 6.64 (m, 2 H), 5.05 (m, 1 H), 4.64–4.51 (m, 1 H), 4.25–3.86 (m, 4 H), 3.73 (s, 3 H), 3.30–3.25 (m, 0.79 H), 3.12–3.08 (m, 0.23 H), 2.63–2.48 (m, 2 H), 1.26–1.21 (m, 6 H) ppm. MS (EI): m/z = 321 $[M]^+$. HRMS (EI): calcd. for $C_{17}H_{23}NO_5$ 321.1576; found 321.1608.

Synthesis of Imine 6 from 1e with (tBuO)$_2$: *N*-(4-Methoxyphenyl)-glycine ester (**1e**; 0.40 mmol), $FeCl_3$ (0.04 mmol) and (tBuO)$_2$ (0.48 mmol) were successively added to $CHCl_3$ (1 mL) in a Schlenk tube. The mixture was stirred for 1 h at 60 °C, filtered through a small pad of silica gel and concentrated in vacuo. Flash chromatography by using ethyl acetate/petroleum ether (1:5) furnished the final product **6** in 32% yield.

Synthesis of Quinoline 3m from 6: Imine **6** (0.20 mmol), $FeCl_3$ (0.02 mmol) and **2a** (0.24 mmol) were successively added to $CHCl_3$ (1 mL) in a Schlenk tube. The mixture was stirred for 5 h at 60 °C, filtered through a small pad of silica gel and concentrated in vacuo. Flash chromatography on silica gel using ethyl acetate/petroleum ether (1:4) furnished the final product **3m** in 82% yield.

Synthesis of Cyclohexanone 9a from 1e with 11: *N*-(4-Methoxyphenyl)glycine ester **1e** (0.20 mmol), $FeCl_3$ (0.02 mmol), **11** (0.22 mmol) and DDQ (0.24 mmol) were successively added to $CHCl_3$ (1 mL) in a Schlenk tube. The mixture was stirred for 12 h at 60 °C, filtered through a small pad of silica gel and concentrated in vacuo. Flash chromatography on silica gel using ethyl acetate/petroleum ether (1:4) furnished the final product **9a** in 85% yield.

Synthesis of Imine 6 from 1e with DDQ: *N*-(4-Methoxyphenyl)-glycine ester **1e** (0.20 mmol), $FeCl_3$ (0.02 mmol) and DDQ (0.24 mmol) were successively added to $CHCl_3$ (1 mL) in a Schlenk tube. The mixture was stirred for 1 h at 60 °C, filtered through a small pad of silica gel and concentrated in vacuo. Flash chromatography using ethyl acetate/petroleum ether (1:5) furnished the final product **6** in 46% yield.

General Procedure for the Reaction with Radical Inhibitor BHT: Compound **1a** (0.20 mmol), $FeCl_3$ (0.02 mmol), phenylacetylene (0.24 mmol), (tBuO)$_2$ (0.40 mmol) and BHT (0.20 mmol) were successively added to DCE (1 mL) in a Schlenk tube. The mixture was stirred for 12 h at 80 °C, filtered through a small pad of silica gel and concentrated in vacuo. Flash chromatography on silica gel by using ethyl acetate/petroleum ether (1:3) as eluent furnished the final product **3a** in 25% yield.

Compound **1e** (0.20 mmol), $FeCl_3$ (0.02 mmol), cyclohexanone (3.0 mmol, 15.0 equiv.), pyrrolidine (0.06 mmol, 30 mol-%), DDQ (0.24 mmol) and BHT (0.20 mmol) were successively added to $CHCl_3$ (1 mL) in a Schlenk tube. The mixture was stirred for 12 h at 60 °C, filtered through a small pad of silica gel and concentrated in vacuo. Flash chromatography on silica gel by using ethyl acetate/petroleum ether (1:4) as eluent furnished the final product **9a** in 19% yield.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra.

Acknowledgments

This investigation was supported by the Important National Science & Technology Specific Projects, China (grant number 2009ZX09301-14-1), the National Natural Science Foundation of China (NSFC) (grant number 21102107) and Chinese Postdoctoral Science Foundation (grant number 20110491199).

[1] a) O. Pillai, R. Panchagnula, *Drug Discovery Today* **2001**, *6*, 1056; b) R. W. Carrell, D. A. Lomas, *Lancet* **1997**, *350*, 134; c) A. G. Cochran, *Chem. Biol.* **2000**, *7*, R85; d) J. C. M. van Hest, D. A. Tirrell, *Chem. Commun.* **2001**, 1897.

[2] a) A. I. Meyers, *Aldrichim. Acta* **1985**, *18*, 59; b) P. Beak, W. J. Zajdel, D. B. Reitz, *Chem. Rev.* **1984**, *84*, 471.

[3] H. S. Knowles, K. Hunt, A. F. Parsons, *Tetrahedron Lett.* **2000**, *41*, 7121.

[4] a) B. Kibel, G. Hofle, W. Steglich, *Angew. Chem.* **1975**, *87*, 64; *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 58; b) K. Burger, K. Geith, K. Gaa, *Angew. Chem.* **1988**, *100*, 860; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 848; c) R. E. Ireland, R. H. Mueller,

A. K. Willard, *J. Am. Chem. Soc.* **1976**, *98*, 2868; d) U. Kazmaier, H. Mues, A. Krebs, *Chem. Eur. J.* **2002**, *8*, 1850.
[5] a) Z. Li, C.-J. Li, *Org. Lett.* **2004**, *6*, 4997; b) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2004**, *126*, 11810; c) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 3672; d) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 6968; e) S.-I. Murahashi, N. Komiya, H. Terai, *Angew. Chem.* **2005**, *117*, 7091; *Angew. Chem. Int. Ed.* **2005**, *44*, 6931; f) Z. Li, D. S. Bohle, C.-J. Li, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 8928; g) A. J. Catino, J. M. Nichols, B. J. Nettles, M. P. Doyle, *J. Am. Chem. Soc.* **2006**, *128*, 5648; h) M. Niu, Z. Yin, H. Fu, Y. Jiang, Y. Zhao, *J. Org. Chem.* **2008**, *73*, 3961; i) S.-I. Murahashi, D. Zhang, *Chem. Soc. Rev.* **2008**, *37*, 1490; j) L. Chu, X. Zhang, F.-L. Qing, *Org. Lett.* **2009**, *11*, 2197; k) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335.
[6] S.-I. Murahashi, N. Komiya, in: *Modern Oxidation Methods* (Ed.: J.-E. Bäckvall), Wiley-VCH, Weinheim, Germany, **2004**, pp. 165–191.
[7] a) L. Zhao, C.-J. Li, *Angew. Chem.* **2008**, *120*, 7183; *Angew. Chem. Int. Ed.* **2008**, *47*, 7075; b) L. Zhao, O. Basle, C.-J. Li, *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 4106.
[8] J. Xie, Z.-Z. Huang, *Angew. Chem. Int. Ed.* **2010**, *49*, 10181.
[9] a) C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217; b) B. Plietker, in: *Iron Catalysis in Organic Chemistry* (Ed.: B. Plietker), **2008** Wiley-VCH, Weinheim, Germany; c) S. Enthaler, K. Junge, M. Beller, *Angew. Chem.* **2008**, *120*, 3363; *Angew. Chem. Int. Ed.* **2008**, *47*, 3317; d) A. Correa, O. Garcia Mancheno, C. Bolm, *Chem. Soc. Rev.* **2008**, *37*, 1108; e) B. D. Sherry, A. Fürstner, *Acc. Chem. Res.* **2008**, *41*, 1500; f) W. M. Czaplik, M. Mayer, J. Cvengros, A. Jacobi von Wangelin, *ChemSusChem* **2009**, *2*, 396; g) W. M. Czaplik, M. Mayer, S. Grupe, A. Jacobi von Wangelin, *Pure Appl. Chem.* **2010**, *82*, 154; h) K. Junge, K. Schröder, M. Beller, *Chem. Commun.* **2011**, 4849; i) R. H. Morris, *Chem. Soc. Rev.* **2009**, *38*, 2282; j) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Rev.* **2011**, *111*, 1293; k) K. Itami, S. Higashi, M. Mineno, J. Yoshida, *Org. Lett.* **2005**, *7*, 1219; l) C. C. Kofink, B. Blank, S. Pagano, N. Gotz, P. Knochel, *Chem. Commun.* **2007**, 1954; m) A. Guerinot, S. Reymond, J. Cossy, *Angew. Chem.* **2007**, *119*, 6641; *Angew. Chem. Int. Ed.* **2007**, *46*, 6521; n) A. Fürstner, K. Majima, R. Martin, H. Krause, E. Kattnig, R. Goddard, C. W. Lehmann, *J. Am. Chem. Soc.* **2008**, *130*, 1992; o) S.-I. Murahashi, T. Nakae, H. Terai, N. Komiya, *J. Am. Chem. Soc.* **2008**, *130*, 11005; p) C. M. Rao Volla, P. Vogel, *Org. Lett.* **2009**, *11*, 1701; q) M. Ohta, M. P. Quick, J. Yamaguchi, B. Wünsch, K. Itami, *Chem. Asian J.* **2009**, *4*, 1416; r) P. Liu, C.-Y. Zhou, S. Xiang, C.-M. Che, *Chem. Commun.* **2010**, *46*, 2739; s) Y.-Z. Li, B.-J. Li, X.-Y. Lu, S. Lin, Z.-J. Shi, *Angew. Chem.* **2009**, *121*, 3875; *Angew. Chem. Int. Ed.* **2009**, *48*, 3817; t) H. Richter, O. G. Mancheño, *Eur. J. Org. Chem.* **2010**, 4460; u) M. Ghobrial, K. Harhammer, M. D. Mihovilovic, M. Schnürch, *Chem. Commun.* **2010**, *46*, 8836; v) E. Shirakawa, N. Uchiyama, T. Hayashi, *J. Org. Chem.* **2011**, *76*, 25.
[10] a) J. P. Michael, *Nat. Prod. Rep.* **1997**, *14*, 605; b) P. R. Kym, M. E. Kort, M. J. Coghlan, J. L. Moore, R. Tang, J. D. Ratajczyk, D. P. Larson, S. W. Elmore, J. K. Pratt, M. A. Stashko, H. D. Falls, C. W. Lin, M. Nakane, L. Miller, C. M. Tyree, J. N. Miner, P. B. Jacobson, D. M. Wilcox, P. Nguyen, B. C. Lane, *J. Med. Chem.* **2003**, *46*, 1016; c) L. Strekowski, M. Say, M. Henary, P. Ruiz, L. Manzel, D. E. Macfarlane, A. J. Bojarski, *J. Med. Chem.* **2003**, *46*, 1242; d) W. Sawada, H. Kayakiri, Y. Abe, K. Imai, A. Katayama, T. Oku, H. Tanaka, *J. Med. Chem.* **2004**, *47*, 1617.
[11] a) G. Jones, in: *Comprehensive Heterocyclic Chemistry II* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven, A. McKillop), Pergamon Press, Oxford, **1996**, vol. 5, p. 167; b) R. D. Larsen, in: *Science of Synthesis* (Ed.: D. S. Black), Thieme, Stuttgart, Germany, **2005**, vol. 15, pp. 389, 551; c) S. Madapa, Z. Tusi, S. Batra, *Curr. Org. Chem.* **2008**, *12*, 1116; d) J. Marco-Contelles, E. Pérez-Mayoral, A. Samadi, M. D. Carreiras, E. Soriano, *Chem. Rev.* **2009**, *109*, 2652; e) H. Huang, H. Jiang, K. Chen, H. Liu, *J. Org. Chem.* **2009**, *74*, 5476; f) K. Cao, F.-M. Zhang, Y.-Q. Tu, X.-T. Zhuo, C.-A. Fan, *Chem. Eur. J.* **2009**, *15*, 6332; g) A. Kulkarni, B. Török, *Green Chem.* **2010**, *12*, 875.
[12] S. L. Buchwald, C. Bolm, *Angew. Chem.* **2009**, *121*, 5694; *Angew. Chem. Int. Ed.* **2009**, *48*, 5586.
[13] Y.-C. Wu, L. Liu, H.-J. Li, D. Wang, Y.-J. Chen, *J. Org. Chem.* **2006**, *71*, 6592.

Received: November 17, 2011
Published Online: January 30, 2012

