JOC The Journal of Organic Chemistry

ARTICLE

pubs.acs.org/joc

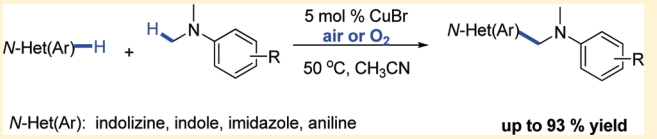
Copper-Catalyzed Oxidative Cross-Coupling of *N*,*N*-Dimethylanilines with Heteroarenes under Molecular Oxygen

Lehao Huang, Tianmin Niu, Jun Wu, and Yuhong Zhang*

Department of Chemistry, Zhejiang University, Hangzhou 310027, People's Republic of China

Supporting Information

ABSTRACT: Nitrogen-containing heterocyclic compounds are important motifs of pharmaceuticals and functional materials, and there has been a growing interest in new synthetic methods for their preparation. In this paper, we report a direct cross-coupling reaction of heteroarenes with *N*,*N*-dimethylanilines in the presence of copper catalyst. Oxygen and/or air are successfully used as the oxidant, which is of great importance to the industrialized economies. The reaction is compatible with a wide range of heterocycles, including indolizines, imidazoles, indoles, and aniline, to enable the formation of various alkylated heteroarenes under very mild reaction conditions.



INTRODUCTION

In the past years, great outcomes have been made in the discovery of novel methods for the construction of C−C bonds through the C−H activation.[1] Various conventional coupling reactions of two functionalized starting materials have been replaced by the improved cross-coupling reactions involving C−H activation/C−C bond forming processes that use one unfunctionalized material[2] or two unfunctionalized materials.[3,4] In particular, the functionalization of heteroarenes via the selective cross-dehydrogenative coupling (CDC) process has attracted much attention because it greatly increase the overall efficiency and improve atom economy (Scheme 1).[4e−4i,5a,5b] For instance, Li and co-workers reported an impressive example of copper-catalyzed indolation of tetrahydroisoquinolines, in which carbon−carbon bonds are constructed directly through the selective coupling of sp^2 C−H bonds and sp^3 C−H bonds.[4e] The crucial point for the success of this type of reactions is the employment of oxidants.[4e−4i,5] However, the need of hazardous or toxic oxidants such as TBHP and DDQ limits their further application. From an economical and environmental viewpoint, catalytic oxidation processes employing molecular oxygen or air as terminal oxidants are thus extremely valuable and will be more applicable to industrial catalysis. The development of CDC processes by the use of air/oxygen as oxidant has attached much attention in the past few years, and it remains the great challenge in this field.[4j−4m,6] To the best of our knowledge, only a few examples of catalyzed cross-dehydrogenative coupling reaction between sp^2 C−H and sp^3 C−H bonds were reported by the use of aerobic oxidations.[7] The development of practical catalytic methods by using O_2 as oxidant under mild conditions is highly desired (Scheme 1).

The oxidative transformations of tertiary amines with molecular oxygen under mild reaction conditions is a difficult and attractive research objective not only in bioinorganic chemistry but also in the diverse array of catalytic oxidation reactions for organic synthesis.[8] The mechanistic studies have indicated that the oxidative transformations involve a nucleophilic attack on iminium ion complex.[4j−4m,7a,7b,9] For instance, Klussmann et al. reported a copper-catalyzed aerobic oxidative coupling of tertiary amines with silyl enolates and ketene acetals.[9d] We also reported the applications of silyl enol ether in the reaction with various *N*,*N*-dimethylanilines for the synthesis of β-arylamino ketones in the presence of TBHP.[10] We envisioned that the electron-rich *N*-fused heteroarenes might be employed as nucleophiles to access to nucleophilic reaction with the iminium ion complex intermediate, which will result in the direct cross-coupling of sp^2 C−H bonds and sp^3 C−H bonds. Herein, we report the efficient aerobic copper-catalyzed oxidative cross-coupling of heterocyclic sp^2 C−H bonds with sp^3 C−H bonds of tertiary amine to efficiently give nitrogen-containing heterocyclic compounds under mild conditions.

RESULTS AND DISCUSSION

We initially selected 4-methyl-*N*,*N*-dimethylaniline (**1a**) and indolizine-1-carbonitrile (**2a**) as model substrates to probe the reaction conditions (Table 1). To our delight, the use of similar reaction conditions previously applied in the reaction of silyl enol ether[10] resulted in the desired direct sp^2 C−H and sp^3 C−H cross-coupling product in excellent yield (Table 1, entry 1). Although remarkable efficiency was obtained for the reaction, 1 equiv of hazardous TBHP was required as oxidant. Thus, we decided to investigate the aerobic catalysis for the coupling reaction. On the basis of previous reports,[4j−4m,7a,7b,9] we examined the reaction using iron, ruthenium, and copper salts as catalysts. The desired cross-coupling product **3a** was obtained in 11% yield when $FeCl_3$ was used as catalyst, while $RuCl_3$ was almost inactive (Table 1, entries 2 and 3). Significant aerobic cross-coupling occurred by the use of copper catalysts such as CuI, CuCl, Cu_2O, $CuBr_2$, and $Cu(OTf)_2$, and CuBr was found to be the most effective catalyst for this reaction (Table 1,

Received: December 3, 2010
Published: February 17, 2011

 © 2011 American Chemical Society dx.doi.org/10.1021/jo1023975 | *J. Org. Chem.* 2011, 76, 1759–1766

Scheme 1. The CDC Transformations with Various Oxidants

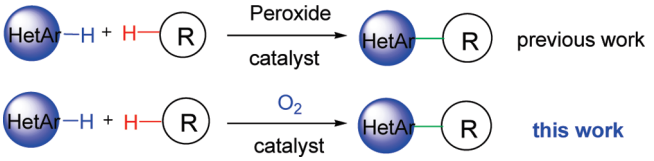
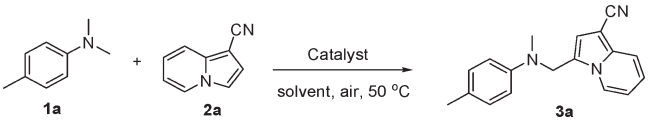


Table 1. Optimization of Reaction Conditions[a]



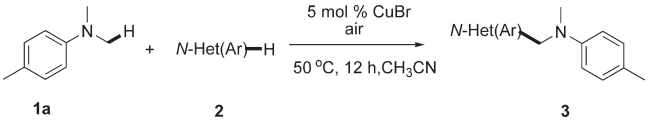
entry	catalyst	solvent	yield (%)
1[b]	CuBr	CH_3CN	92
2	$FeCl_3$	CH_3CN	11
3	$RuCl_3$	CH_3CN	trace
4	CuCl	CH_3CN	85
5	Cu_2O	CH_3CN	80
6	$CuBr_2$	CH_3CN	77
7	$Cu(OTf)_2$	CH_3CN	67
8	CuI	CH_3CN	35
9	CuBr	CH_3CN	90
10[c]	CuBr	CH_3CN	trace
11		CH_3CN	N.R
12	CuBr	CH_2Cl_2	trace
13	CuBr	toluene	14
14	CuBr	THF	72

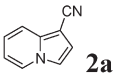
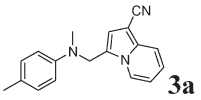
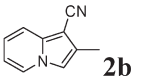
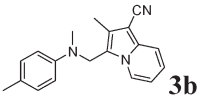
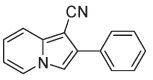
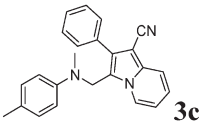
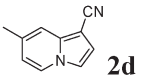
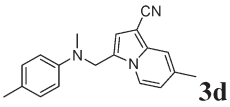
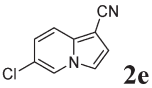
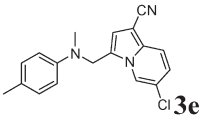
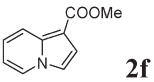
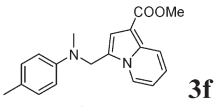
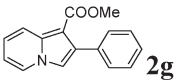
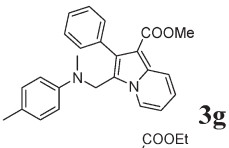
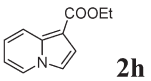
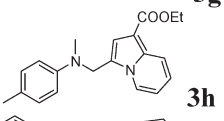
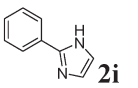
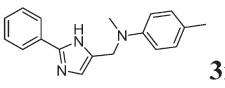
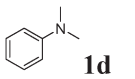
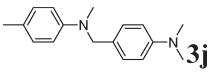
[a] Reaction conditions: indolizine-1-carbonitrile **2a** (71 mg, 0.5 mmol), 4-methyl-*N*,*N*-dimethylaniline **1a** (338 mg, 2.5 mmol), catalyst (0.025 mmol), solvent (5 mL), air, 50 °C, 12 h. [b] 0.10 mL of TBHP (5−6 M in decane) was added. [c] Reaction under nitrogen atmosphere.

entries 4−9). The reaction was sluggish under nitrogen atmosphere, and no product was detected in the absence of catalyst (Table 1, entries 10 and 11). Acetonitrile was superior to other solvents such as CH_2Cl_2, THF, and toluene (Table 1, entries 12−14). *Thus, a quite efficient sp^2 C−H and sp^3 C−H cross-coupling reaction was developed: treatment of two unfunctionalized substrates with 5 mol % of CuBr with stirring at 50 °C in air generated the cross-coupling product in 90% yield.*

We next explored the reactivity of various heteroarenes under the optimized reaction conditions as shown Table 2. In general, the substituted indolizines could be successfully used in this direct cross-coupling reaction to give the desired products in moderate to good yields (Table 2, entries 1−8). Notably, the electronic properties of the indolizine-1-carbonitrile substituent influenced the efficiency of the reaction. The electron-donating substituted indolizine-1-carbonitriles exhibited very good reactivity to afford the products in excellent yields (Table 2, entries 2−4), and in contrast, indolizine-1-carbonitrile with the electron-withdrawing substituted chloride group showed relatively lower reactivity (Table 2, entry 5). Moreover, substrates with substituents at the *C*-2 positions of indolizines could be smoothly transformed into the corresponding cross-coupling products,

Table 2. The Reaction of 4-Methyl-*N*,*N*-dimethylaniline 1a with *N*-Heteroarenes[a]



entry	het	product	yield %
1	 2a	 3a	90
2	 2b	 3b	92
3	 2c	 3c	93
4	 2d	 3d	83
5	 2e	 3e	44
6	 2f	 3f	72
7	 2g	 3g	68
8	 2h	 3h	72
9	 2i	 3i	25
10	 1d	 3j	32

[a] Reaction conditions: heteroarenes **2** (0.5 mmol), 4-methyl-*N*,*N*-dimethylaniline **1a** (338 mg, 2.5 mmol), CuBr (4 mg, 0.025 mmol), CH_3CN (5 mL), air, 50 °C, 12 h.

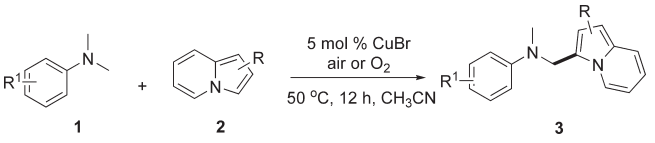
indicating the substantial tolerance of steric hindrance of the reaction (Table 2, entries 2, 3, and 7). Furthermore, 2-phenylimidazole and *N*,*N*-dimethylbenzenamine underwent the reaction as well to give the corresponding Mannich bases (Table 2, entries 9 and 10). This result supports the Friedel−Crafts-type reaction. The structure of this direct cross-coupling product was further confirmed by the X-ray crystallography of **3g** (see the SI).

Table 3 shows that a range of *N*,*N*-dimethylanilines participate in the direct cross-coupling reaction. The electron-rich *N*,*N*-dimethylanilines such as **1b** and **1c** worked well in air to give excellent yields (Table 3, entries 1-2). *N*,*N*-dimethylanilines **1d** and **1e** showed low reactivity in air, but worked well under an oxygen atmosphere to afford the corresponding cross-coupling

dx.doi.org/10.1021/jo1023975 |*J. Org. Chem.* 2011, 76, 1759–1766

products in moderate to good yields (Table 3, entries 3−6). 4-Chloro-*N*,*N*-dimethylbenzenamine gave the desired product in 86% yield under oxygen atmosphere (53% in air, Table 3, entry 7). The reaction of **1b** with indolizine ester **2f** provided the cross-coupling product in air in 73% yield (Table 3, entry 8). However, the use of **1d** and **1e** in this reaction with indolizine **2f** led to the generation of both the desired cross-coupling products (**3s** and **3t**) and the corresponding benzyl indolizines (**4s** and **4t**) (Table 3, entries 9 and 10).

Table 3. The Reaction of Anilines with Indolizines[a]



1 2 3

entry	aniline	indolizine	product	yield %
1	**1b**	**2a**	**3k**	92
2	**1c**	**2a**	**3l**	90
3	**1d**	**2a**	**3m**	64[b]
4	**1d**	**2b**	**3n**	64[b]
5	**1d**	**2d**	**3o**	76[b]
6	**1e**	**2a**	**3p**	70[b]
7	**1f**	**2a**	**3q**	53 (86[b])
8	**1b**	**2f**	**3r**	73
9	**1d**	**2f**	**3s** **4s**	70 (**3s**+**4s**=56+14)
10	**1e**	**2f**	**3t** **4t**	82 (**3t**+**4t**=70+12)

[a] Reaction conditions: indolizine **2** (0.5 mmol), *N*,*N*-dimethylanilines **1** (2.5 mmol), CuBr (4 mg, 0.025 mmol), CH_3CN (5 mL), air, 50 °C, 12 h. [b] Reaction under 1 atm oxygen atmosphere.

The production of **4s** and **4t** might take place through a retro-Mannich reaction of **3s** and **3t** by the second nucleophilic attack of anilline substrates on the direct cross-coupling products.[7a,7b,11] Thus, we attempted the reaction of indolizine coupling products (**3a**, **3f**) with *N*,*N*-dimethylbenzenamine (**1d**) in the presence of CuBr in air. Indeed, the benzylic product **4s** was obtained in 16% yield and the product **4a** was undetected. Since 3-benzylindolizines are the key structures of many bioactive molecules,[12] we are interested in the development of general processes to synthesis benzylic indolizine **4s** and **4a**. We found that the deamination reaction occurred smoothly in the presence of 10 mol % of anhydrous $FeCl_3$ to give the benzylic indolizines **4s** and **4a** in good yields (Scheme 2).

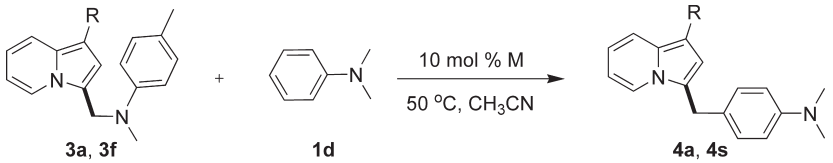
Indoles are important building blocks of natural products and pharmaceuticals.[13] Encouraged by the successful oxidative cross-coupling of *N*,*N*-dimethylanilines with the above heterocycles, we studied the cross-coupling reaction of indoles (Table 4). It was found that *N*-methyl indole was inactive. To our delight, the desired cross-coupling product **5a** was formed when *N*-free indole was used as the substrate under the optimal reaction conditions (Table 4, entry 1). Interestingly, we isolated the *N*-alkylated product **6a**, which might be formed by nucleophilic attack of **5a** on iminium cation complex of aniline. The electron-deficient indoles tolerated the reaction conditions well to give the products smoothly (Table 4, entries 2−4). However, the electron-rich indoles showed lower reactivity probably due to the instability of the products (Table 4, entry 5).[4h] Methyl 1*H*-indole-3-carboxylate participated in the reaction to give *N*-alkylated product **5f** in 42% yield (Table 4, entry 6). Ethyl indole-2-carboxylate **2p** carried out the reaction to give the product **5g** in lower yield, showing that the steric hindrance played a role in the reactivity (Table 4, entry 7).

On the basis of mechanism proposals in previous studies,[4j−4m,7a,7b,9,10] a plausible mechanism for the formation of coupling product is illustrated in Scheme 3. The oxidation of the α-C−H bond adjacent to nitrogen in aniline by the molecular oxygen under the assistance of copper catalyst leads to the formation of iminium cation intermediate **A**, which undergoes a Friedel−Crafts-type process with indolizines **2** to deliver the cross-coupling product **3** and regenerate the catalyst.

CONCLUSIONS

In summary, we have demonstrated an efficient copper-catalyzed direct cross-coupling of *N*-heterocyclic sp^2 C−H bonds with sp^3 C−H bonds of anilines. The reaction employs environmentally benign molecular oxygen or air as oxidant under very mild reaction conditions. A wide range of hererocycles, including indolizines, pyrolines, indoles, and aniline, participate in the reaction to afford the valuable alkylated nitrogen-containing

Scheme 2. The Synthesis of Benzylic Indolizines



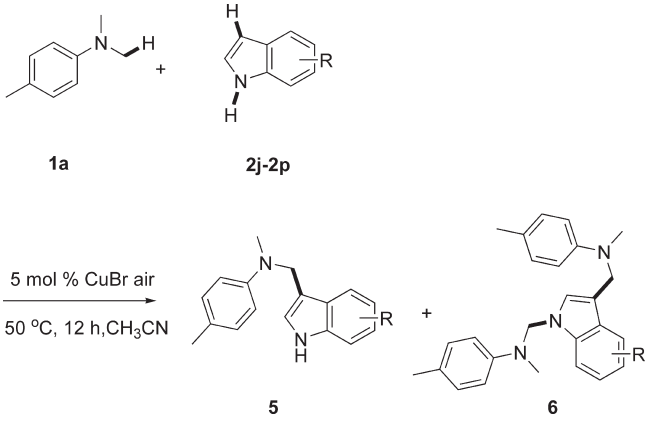
3a, **3f** **1d** **4a**, **4s**

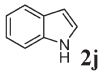
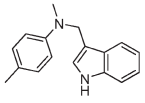
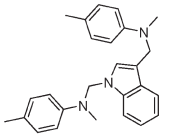
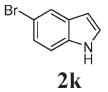
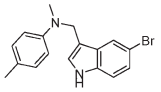
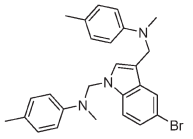
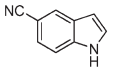
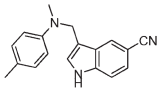
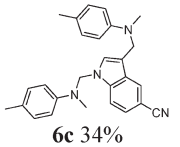
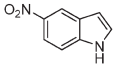
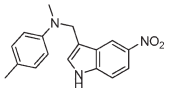
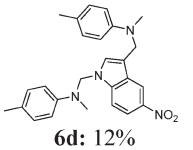
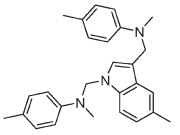
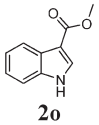
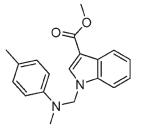
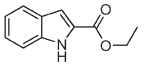
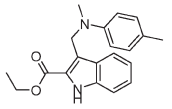
M=CuBr
R=CN, 12 h, N.R
R=COOMe, 12 h, 16 %

M=$FeCl_3$
R=CN, 4 h, 79 % ***4a***
R=COOMe, 2 h, 65 % ***4s***

dx.doi.org/10.1021/jo1023975 |*J. Org. Chem.* 2011, 76, 1759–1766

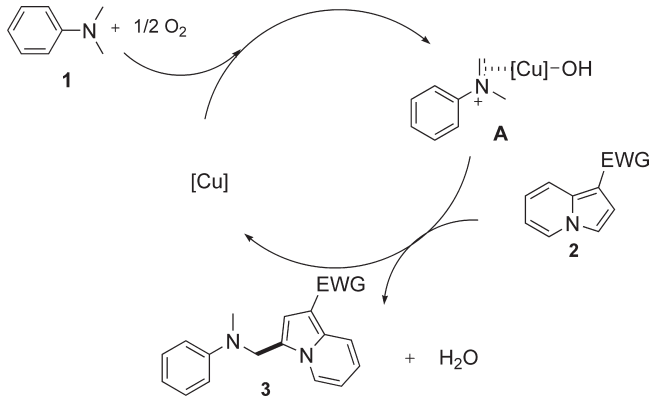
Table 4. The Reaction of 4-Methyl-*N*,*N*-dimethylaniline 1a with Indoles[a]



entry	indole	product and yield	
1	 **2j**	 **5a** 24 %	 **6a** 17 %
2	 **2k**	 **5b** 28%	 **6b** 24%
3	 **2l**	 **5c** 20%	 **6c** 34%
4	 **2m**	 **5d:** 49%	 **6d:** 12%
5	 **2n**	 **6e:** 12%	
6	 **2o**	 **5f:** 42%	
7	 **2p**	 **5g:** 30%	

[a] Reaction conditions: indoles **2** (0.5 mmol), 4-methyl-*N*,*N*-dimethylaniline **1a** (338 mg, 2.5 mmol), CuBr (4 mg, 0.025 mmol), CH_3CN (5 mL), air, 50 °C, 12 h.

Scheme 3. Plausible Mechanism



heterocycles. The extension of this method to oxygen-containing substrates is currently ongoing.

EXPERIMENTAL SECTION

General. Unless otherwise stated, all reactions were carried out in an oven-dried flask in air. CH_3CN were distilled over calcium hydride (CaH_2). ^1H NMR spectra were recorded at 400 or 500 MHz and the chemical shifts were reported in parts per million (δ) relative to internal standard TMS (0 ppm) for $CDCl_3$ or DMSO-d_6. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublet. The coupling constants, J, are reported in hertz (Hz). ^{13}C NMR spectra were recorded at 100 or 125 MHz and referenced to the internal solvent signals (center peak is 77.00 ppm in $CDCl_3$ or 39.90 ppm in DMSO-d_6). Mass spectroscopy data were collected on an HRMS-EI instrument. *N*,*N*-Dimethylaniline compounds **1b**, **1c**, and **1f**[10] were prepared by known methods. Indolizine compounds **2a**−**h**[3l,14] were synthesized following the reported procedures. Other materials were purchased from common commercial sources and used without additional purification.

The Preparation of *N*,*N*-Dimethylaniline Compounds 1b, 1c, and 1f[10]**.** To trimethyl phosphate (8.4 g, 60 mmol) was added aniline (40 mmol). The resulting mixture was stirred at 110 °C for 2 h and then cooled, then it was neutralized with 25 mL of NaOH (20%). After additional stirring at 110 °C for 12 h, the resulting solution was treated with water to dissolve Na_3PO_4. The organic layer was collected, and the aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic phase was dried over anhydrous magnesium sulfate. Removal of solvent under reduced pressure afforded the crude *N*,*N*-dimethylanilines, which was further purified on a silica gel column to afford the desired product.

4-Ethyl-*N*,*N*-dimethylbenzenamine (1b): red oil after purification by flash chromatography (eluent: ethyl acetate/petroleum ether = 1/80, v/v); ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 7.6 Hz, 2 H), 6.86 (d, J = 6.8 Hz, 2 H), 3.04 (s, 6 H), 2.73 (q, J = 7.1 Hz, 2 H), 1.37 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 132.4, 128.2, 113.0, 40.8, 27.7, 15.8.

4-*tert*-Butyl-*N*,*N*-dimethylbenzenamine (1c): red oil after purification by flash chromatography (eluent: ethyl acetate/petroleum ether = 1/80, v/v); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, J = 8.8, 2.4 Hz, 2 H), 6.80 (dd, J = 9.2, 2.8 Hz, 2 H), 2.99 (d, J = 2.8 Hz, 6 H), 1.38 (d, J = 2.4 Hz, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 139.2, 125.6, 112.5, 40.6, 33.5, 31.3.

4-Chloro-*N*,*N*-dimethylbenzenamine (1f): yellow solid after purification by flash chromatography (eluent: ethyl acetate/petroleum ether = 1/80, v/v); ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 9.6 Hz,

dx.doi.org/10.1021/jo1023975 |J. Org. Chem. 2011, 76, 1759–1766

2 H), 6.66 (d, J = 8.8 Hz, 2 H), 2.94 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 128.5, 121.1, 113.4, 40.3.

The Preparation of Indolizine Compounds 2a−h.[3l,14] **Step 1:** To a solution of pyridines (100 mmol) in EtOAc (60 mL) was added bromoacetic acid (100 mmol). After the mixture was stirred for 3 h at rt, the solid was filtered and dried in air to give *N*-(carboxymethyl)pyridinium bromides as a white solid.

Step 2: A suspension of *N*-(carboxymethyl)pyridinium bromides (10 mmol), alkene (50 mmol), Et_3N (1.5 mL), and MnO_2 (80 mmol) in toluene (80 mL) was stirred at 90 °C for 2 h (monitored by TLC). After the mixture was cooled to rt, the solid was filtered off and washed with acetone. The combined filtrates were evaporated to give a residue, which was further purified on a silica gel column to afford the corresponding indolizines **2a−h**.

Indolizine-1-carbonitrile (2a): pale solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1/6, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 6.4 Hz, 1 H), 7.56 (d, J = 8.8 Hz, 1 H), 7.23 (d, J = 2.4 Hz, 1 H), 7.03 (d, J = 6.8 Hz, 1 H), 6.98−7.00 (m, 1 H), 6.70−6.73 (m, 1 H).

2-Methylindolizine-1-carbonitrile (2b): pale solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1/6, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 6.4 Hz, 1 H), 7.43 (d, J = 8.4 Hz, 1 H), 7.00 (s, 1 H), 6.91−6.95 (m, 1 H), 6.60−6.63 (m, 1 H), 2.32 (s, 3 H).

2-Phenylindolizine-1-carbonitrile (2c): light yellow solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1/6, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 6.4 Hz, 1 H), 7.77 (d, J = 7.6 Hz, 2 H), 7.61 (d, J = 8.4 Hz, 1 H), 7.48−7.43 (m, 3 H), 7.37 (t, J = 7.2 Hz, 1 H), 7.06 (t, J = 7.2 Hz, 1 H), 6.75 (t, J = 7.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 132.3, 131.7, 129.0, 128.1, 127.3, 126.1, 122.6, 117.7, 117.2, 113.3, 111.2, 80.0.

7-Methylindolizine-1-carbonitrile (2d): light brown solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1/6, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 6.8 Hz, 1 H), 7.36 (s, 1 H), 7.14 (d, J = 2.4 Hz, 1 H), 6.93 (s, 1 H), 6.57 (d, J = 7.2 Hz, 1 H), 2.36 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 133.4, 125.8, 117.4, 116.5, 116.1, 115.6, 113.2, 79.8, 21.1.

6-Chloroindolizine-1-carbonitrile (2e): light yellow solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1/6, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1 H), 7.59 (d, J = 9.6 Hz, 1 H), 7.25 (d, J = 2.8 Hz, 1 H), 7.06−7.03 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 124.1, 123.7, 121.4, 118.3, 117.7, 116.2, 114.3, 83.2.

Methyl Indolizine-1-carboxylate (2f): black oil after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1/10, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.13 (d, J = 9.2 Hz, 1 H), 7.92 (d, J = 6.8 Hz, 1 H), 7.20 (d, J = 2.8 Hz, 1 H), 7.16 (d, J = 3.2 Hz, 1 H), 6.98 (dd, J = 8.4 Hz, 6.4 Hz, 1 H), 6.62 (t, J = 6.4 Hz, 1 H), 3.86 (s, 3 H).

Methyl 2-Phenylindolizine-1-carboxylate (2g): light green solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1/10, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 8.8 Hz, 1 H), 7.93 (d, J = 6.4 Hz, 1 H), 7.56 (d, J = 6.8 Hz, 2 H), 7.45−7.38 (m, 3 H), 7.23 (s, 1 H), 7.07 (t, J = 7.2 Hz, 1 H), 6.70 (t, J = 6.4 Hz, 1 H), 3.82 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 136.8, 134.9, 132.7, 129.9, 127.7, 127.1, 125.6, 122.6, 120.3, 113.9, 112.7, 101.1, 50.6.

Ethyl Indolizine-1-carboxylate (2h): black oil purification by column chromatography (eluent, ethyl acetate/petroleum ether = 1/10, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.8 Hz, 1 H), 7.98 (d, J = 6.8 Hz, 1 H), 7.25 (d, J = 2.8 Hz, 1 H), 7.21 (d, J = 3.2 Hz, 1 H), 7.00−7.05 (m, 1 H), 6.66−6.70 (m, 1 H), 4.38 (q, J = 6.8 Hz, 2 H), 1.41 (t, J = 7.2 Hz, 3 H).

Typical Procedure for Cross-Coupling Products 3a−t, 4t, 5a−g, and 6a−e. To a mixture of heteroarenes **2** or aniline **1d** (0.5 mmol), CuBr (4 mg, 0.025 mmol), and CH_3CN (5 mL) was added *N*,*N*-dimethylanilines **1** (2.5 mmol) at room temperature. The resulting mixture was stirred at 50 °C for 12 h under air or oxygen atmosphere. After the reaction, the mixture was filtered and the solvent was evaporated under vacuum. The residue was purified by column chromatography on silica gel to afford the desired product.

Typical Procedure for Benzylic Indolizines Products 4a and 4s. To a mixture of *N*-(indolizin-3-ylmethyl)-*N*,4-dimethylbenzenamine (**3a**, **3f**) (0.25 mmol), anhydrous $FeCl_3$ (4 mg, 0.025 mmol), and CH_3CN (2.5 mL) was added *N*,*N*-dimethylbenzenamine (151 mg, 1.25 mmol) at room temperature. The resulting mixture was stirred at 50 °C for 2−4 h under air. After the reaction, the mixture was filtered and the solvent was evaporated under vacuum. The residue was purified by column chromatography on silica gel to afford the desired product.

3-((Methyl(*p*-tolyl)amino)methyl)indolizine-1-carbonitrile (3a): 90% yield; white solid; ^{1}H NMR (400 MHz, CD_3SOCD_3) δ 8.24 (d, J = 6.8 Hz, 1 H), 7.65 (d, J = 8.4 Hz, 1 H), 7.20 (t, J = 7.8 Hz, 1 H), 7.00 (d, J = 8.0 Hz, 2 H), 6.97 (s, 1 H), 6.95 (t, J = 7.0 Hz, 1 H), 6.81 (d, J = 8.4 Hz, 2 H), 4.71 (s, 2 H), 2.80 (s, 3 H), 2.18 (s, 3 H); ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 147.8, 138.1, 129.9, 126.5, 125.8, 123.6, 123.2, 117.4, 117.2, 116.3, 114.4, 113.4, 79.6, 48.2, 38.6, 20.4; HRMS (EI) calcd for $C_{18}H_{17}N_3$ $[M]^+$ 275.1422, found 275.1426.

2-Methyl-3-((methyl(*p*-tolyl)amino)methyl)indolizine-1-carbonitrile (3b): 92% yield; white solid; ^{1}H NMR (400 MHz, CD_3SOCD_3) δ 8.07 (d, J = 6.8 Hz, 1 H), 7.57 (d, J = 8.8 Hz, 1 H), 7.15 (t, J = 7.6 Hz, 1 H), 7.02 (d, J = 7.6 Hz, 2 H), 6.91−6.85 (m, 3 H), 4.56 (s, 2 H), 2.51 (s, 3 H), 2.30 (s, 3 H), 2.18 (s, 3 H); ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 148.7, 137.0, 129.9, 127.4, 127.0, 125.5, 123.3, 119.8, 116.9, 116.7, 115.6, 113.2, 81.6, 46.1, 37.4, 20.4, 10.6; HRMS (EI) calcd for $C_{19}H_{19}N_3$ $[M]^+$ 289.1579, found 289.1590.

3-((Methyl(*p*-tolyl)amino)methyl)-2-phenylindolizine-1-carbonitrile (3c): 93% yield; white solid; ^{1}H NMR (400 MHz, CD_3SOCD_3) δ 8.24 (d, J = 6.8 Hz, 1 H), 7.20 (d, J = 8.4 Hz, 1 H), 7.53−7.46 (m, 5 H), 7.28 (t, J = 8.0 Hz, 1 H), 7.01−6.96 (m, 3 H), 6.78 (d, J = 8.0 Hz, 2 H), 4.63 (s, 2 H), 2.50 (s, 3 H), 2.17 (s, 3 H); ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 148.3, 137.8, 132.4, 131.8, 130.0, 129.8, 129.2, 128.6, 127.6, 126.1, 124.2, 119.8, 117.2, 116.9, 115.6, 114.0, 80.8, 46.4, 37.7, 20.4; HRMS (EI) calcd for $C_{24}H_{21}N_3$ $[M]^+$ 351.1735, found 351.1749.

7-Methyl-3-((methyl(*p*-tolyl)amino)methyl)indolizine-1-carbonitrile (3d): 83% yield; white solid; ^{1}H NMR (500 MHz, CD_3SOCD_3) δ 8.13 (d, J = 7.0 Hz, 1 H), 7.42 (s, 1 H), 7.00 (d, J = 8.5 Hz, 2 H), 6.89 (s, 1 H), 6.81 (d, J = 8.0 Hz, 2 H), 6.78 (d, J = 7.0 Hz, 1 H), 4.67 (s, 2 H), 2.77 (s, 3 H), 2.33 (s, 3 H), 2.18 (s, 3 H); ^{13}C NMR (125 MHz, CD_3SOCD_3) δ 147.9, 138.7, 134.1, 130.0, 126.6, 125.3, 122.8, 117.6, 116.1, 116.0, 115.7, 114.5, 78.1, 48.2, 38.5, 21.0, 20.4; HRMS (EI) calcd for $C_{19}H_{19}N_3$ $[M]^+$ 289.1579, found 289.1578.

6-Chloro-3-((methyl(*p*-tolyl)amino)methyl)indolizine-1-carbonitrile (3e): 44% yield; white solid; ^{1}H NMR (400 MHz, CD_3SOCD_3) δ 8.42 (s, 1 H), 7.67 (d, J = 9.2 Hz, 1 H), 7.19 (d, J = 9.6 Hz, 1 H), 6.98 (d, J = 7.6 Hz, 2 H), 6.93 (s, 1 H), 6.77 (d, J = 8.4 Hz, 2 H), 4.73 (s, 2 H), 2.81 (s, 3 H), 2.16 (s, 3 H); ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 147.7, 136.1, 129.9, 126.5, 124.8, 123.8, 123.6, 120.4, 118.4, 116.8, 116.6, 114.3, 81.4, 48.3, 38.7, 20.4; HRMS (EI) calcd for $C_{18}H_{16}N_3Cl$ $[M]^+$ 309.1033, found 309.1034.

Methyl 3-((methyl(*p*-tolyl)amino)methyl)indolizine-1-carboxylate (3f): 72% yield; white solid; ^{1}H NMR (400 MHz, CD_3SOCD_3) δ 8.18 (d, J = 6.8 Hz, 1 H), 8.08 (d, J = 8.8 Hz, 1 H), 7.18 (t, J = 7.6 Hz, 1 H), 7.00 (d, J = 8.4 Hz, 2 H), 6.92 (s, 1 H), 6.90 (t, J = 6.6 Hz, 1 H), 6.80 (d, J = 8.0 Hz, 2 H), 4.70 (s, 2 H), 3.75 (s, 3 H), 2.81 (s, 3 H), 2.18 (s, 3 H); ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 164.6, 147.9, 136.0, 130.0, 126.2, 125.3, 123.0, 122.7, 119.1, 115.4, 114.1, 112.9, 102.0, 51.0, 48.2, 38.5, 20.3; HRMS (EI) calcd for $C_{19}H_{20}N_2O_2$ $[M]^+$ 308.1525, found 308.1520.

Methyl 3-((methyl(*p*-tolyl)amino)methyl)-2-phenylindolizine-1- carboxylate (3g): 68% yield; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, J = 9.0 Hz, 1 H), 8.10 (d, J = 6.5 Hz, 1 H),

dx.doi.org/10.1021/jo1023975 |*J. Org. Chem.* 2011, 76, 1759–1766

7.44−7.34 (m, 5 H), 7.15 (t, J = 8.0 Hz, 1 H), 7.10 (d, J = 8.5 Hz, 2 H), 6.85 (d, J = 8.5 Hz, 2 H), 6.75 (t, J = 7.0 Hz, 1 H), 4.45 (s, 2 H), 3.73 (s, 3 H), 2.56 (s, 3 H), 2.29 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 148.7, 136.5, 135.0, 132.9, 130.6, 130.0, 128.3, 127.8, 127.3, 124.8, 123.0, 120.1, 119.8, 115.5, 113.0, 102.0, 50.8, 46.5, 37.0, 20.5; HRMS (EI) calcd for $C_{25}H_{24}N_2O_2$ $[M]^+$ 384.1838, found 384.1835.

Ethyl 3-((methyl(*p*-tolyl)amino)methyl)indolizine-1-carboxylate (3h): 72% yield; white solid; ^{1}H NMR (400 MHz, CD_3SOCD_3) δ 8.16 (d, J = 7.2 Hz, 1 H), 8.05 (d, J = 9.2 Hz, 1 H), 7.16 (t, J = 7.6 Hz, 1 H), 6.98 (d, J = 8.0 Hz, 2 H), 6.89−6.87 (m, 2 H), 6.80 (d, J = 7.6 Hz, 2 H), 4.69 (s, 2 H), 4.20 (q, J = 7.2 Hz, 2 H), 2.78 (s, 3 H), 2.16 (s, 3 H), 1.26 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 164.2, 147.9, 135.8, 130.0, 126.2, 125.3, 123.0, 122.7, 119.2, 115.5, 114.1, 112.9, 102.2, 59.3, 48.2, 38.4, 20.4, 14.9; HRMS (EI) calcd for $C_{20}H_{22}N_2O_2$ $[M]^+$ 322.1681, found 322.1677.

***N*,4-Dimethyl-*N*-((2-phenyl-1*H*-imidazol-5-yl)methyl)benzenamine (3i):** 25% yield; white solid; ^{1}H NMR (500 MHz, CD_3SOCD_3) δ 12.4 (s, 1 H), 7.93 (d, J = 8.0 Hz, 2 H), 7.45 (t, J = 8.0 Hz, 2 H), 7.34 (t, J = 7.5 Hz, 1 H), 6.99 (d, J = 7.5 Hz, 2 H), 6.92 (s, 1 H), 6.75 (d, J = 7.5 Hz, 2 H), 4.43 (s, 2 H), 2.97 (s, 3 H), 2.19 (s, 3 H); ^{13}C NMR (125 MHz, CD_3SOCD_3) δ 147.8, 145.6, 139.9, 131.3, 129.8, 129.2, 128.3, 125.2, 124.7, 115.4, 113.3, 50.7, 38.9, 20.4; HRMS (EI) calcd for $C_{18}H_{19}N_3$ $[M]^+$ 277.1579, found 277.1574.

***N*-(4-(Dimethylamino)benzyl)-*N*,4-dimethylbenzenamine (3j):**[15] 32% yield; light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, J = 8.0 Hz, 2 H), 7.08 (d, J = 8.4 Hz, 2 H), 6.76 (t, J = 8.0 Hz, 4 H), 4.44 (s, 2 H), 2.97 (s, 9 H), 2.30 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 148.1, 129.6, 128.0, 126.9, 125.6, 113.0, 112.8, 56.5, 40.8, 38.3, 20.3; HRMS (EI) calcd for $C_{17}H_{22}N_2$ $[M]^+$ 254.1783, found 254.1787.

3-(((4-Ethylphenyl)(methyl)amino)methyl)indolizine-1-carbonitrile (3k): 92% yield; white solid; ^{1}H NMR (500 MHz, CD_3SOCD_3) δ 8.24 (d, J = 7.0 Hz, 1 H), 7.65 (d, J = 9.5 Hz, 1 H), 7.19 (t, J = 7.8 Hz, 1 H), 7.03 (d, J = 8.5 Hz, 2 H), 6.99 (s, 1 H), 6.95 (t, J = 6.5 Hz, 1 H), 6.83 (d, J = 8.5 Hz, 2 H), 4.71 (s, 2 H), 2.80 (s, 3 H), 2.48 (q, J = 7.6 Hz, 2 H), 1.11 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 148.0, 138.1, 133.2, 128.7, 125.8, 123.6, 123.2, 117.4, 117.2, 116.3, 114.4, 113.4, 79.6, 48.2, 38.6, 27.6, 16.3; HRMS (EI) calcd for $C_{19}H_{19}N_3$ $[M]^+$ 289.1579, found 289.1576.

3-(((4-*tert*-Butylphenyl)(methyl)amino)methyl)indolizine-1-carbonitrile (3l): 90% yield; white solid; ^{1}H NMR (500 MHz, CD_3SOCD_3) δ 8.23 (d, J = 7.2 Hz, 1 H), 7.64 (d, J = 8.8 Hz, 1 H), 7.19−7.17 (m, 3 H), 7.00 (s, 1 H), 6.93 (t, J = 6.8 Hz, 1 H), 6.82 (d, J = 8.4 Hz, 2 H), 4.69 (s, 2 H), 2.79 (s, 3 H), 1.20 (s, 9 H); ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 147.7, 140.1, 138.1, 126.1, 125.8, 123.6, 123.3, 117.4, 117.2, 116.4, 114.0, 113.4, 79.6, 48.2, 38.5, 33.9, 31.8; HRMS (EI) calcd for $C_{21}H_{23}N_3$ $[M]^+$ 317.1892, found 317.1896.

3-((Methyl(phenyl)amino)methyl)indolizine-1-carbonitrile (3m): 64% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 6.8 Hz, 1 H), 7.66 (d, J = 8.8 Hz, 1 H), 7.30 (t, J = 8.0 Hz, 2 H), 7.09 (t, J = 7.8 Hz, 1 H), 6.95 (s, 1 H), 6.94 (d, J = 8.4 Hz, 2 H), 6.86 (t, J = 7.4 Hz, 1 H), 6.76 (t, J = 6.6 Hz, 1 H), 4.62 (s, 2 H), 2.79 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 138.7, 129.4, 124.4, 122.1, 121.8, 118.7, 117.9, 117.1, 116.9, 114.4, 113.0, 80.9, 48.6, 37.5; HRMS (EI) calcd for $C_{17}H_{15}N_3$ $[M]^+$ 261.1266, found 261.1271.

2-Methyl-3-((methyl(phenyl)amino)methyl)indolizine-1-carbonitrile (3n): 64% yield; white solid; ^{1}H NMR (500 MHz, CD_3SOCD_3) δ 8.07 (d, J = 7.0 Hz, 1 H), 7.60 (d, J = 9.0 Hz, 1 H), 7.24 (t, J = 8.0 Hz, 2 H), 7.17 (t, J = 7.5 Hz, 1 H), 7.01 (d, J = 8.0 Hz, 2 H), 6.89 (t, J = 6.5 Hz, 1 H), 6.77 (t, J = 7.5 Hz, 1 H), 4.65 (s, 2 H), 2.57 (s, 3 H), 2.34 (s, 3 H); ^{13}C NMR (125 MHz, CD_3SOCD_3) δ 150.7, 137.1, 129.6, 127.2, 125.4, 123.4, 119.7, 118.5, 116.9, 116.8, 115.0, 113.3, 81.8, 45.7, 36.9, 10.6; HRMS (EI) calcd for $C_{18}H_{17}N_3$ $[M]^+$ 275.1422, found 275.1428.

7-Methyl-3-((methyl(phenyl)amino)methyl)indolizine-1-carbonitrile (3o): 76% yield; white solid; ^{1}H NMR (500 MHz, CD_3SOCD_3) δ 8.13 (d, J = 7.0 Hz, 1 H), 7.43 (s, 1 H), 7.19 (t, J = 8.0 Hz, 2 H), 6.89 (s, 1 H), 6.88 (d, J = 9.0 Hz, 2 H), 6.79 (d, J = 7.5 Hz, 1 H), 6.70 (t, J = 7.0 Hz, 1 H), 4.74 (s, 2 H), 2.84 (s, 3 H), 2.34 (s, 3 H); ^{13}C NMR (125 MHz, CD_3SOCD_3) δ 149.9, 138.7, 134.1, 129.5, 125.2, 122.8, 117.7, 117.6, 116.0, 115.9, 115.7, 114.0, 78.1, 47.8, 38.2, 21.0; HRMS (EI) calcd for $C_{18}H_{17}N_3$ $[M]^+$ 275.1422, found 275.1430.

3-((Methyl(*m*-tolyl)amino)methyl)indolizine-1-carbonitrile (3p): 70% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 7.2 Hz, 1 H), 7.60 (d, J = 8.8 Hz, 1 H), 7.15 (t, J = 7.6 Hz, 1 H), 7.04 (t, J = 7.8 Hz, 1 H), 6.90 (s, 1 H), 6.73 (s, 1 H), 6.73−6.70 (m, 2 H), 6.65 (d, J = 7.6 Hz, 1 H), 4.56 (s, 2 H), 2.73 (s, 3 H), 2.31 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 139.2, 138.7, 129.2, 124.5, 122.1, 122.0, 119.6, 117.9, 117.0, 116.9, 115.2, 113.0, 111.5, 80.8, 48.6, 37.5, 21.9; HRMS (EI) calcd for $C_{18}H_{17}N_3$ $[M]^+$ 275.1422, found 275.1426.

3-(((4-Chlorophenyl)(methyl)amino)methyl)indolizine-1-carbonitrile (3q): 86% yield; white solid; ^{1}H NMR (400 MHz, CD_3SOCD_3) δ 8.22 (d, J = 7.2 Hz, 1 H), 7.65 (d, J = 8.8 Hz, 1 H), 7.22−7.17 (m, 3 H), 6.96 (t, J = 7.2 Hz, 1 H), 6.94 (s, 1 H), 6.86 (d, J = 9.2 Hz, 2 H), 4.79 (s, 2 H), 2.88 (s, 3 H); ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 148.5, 138.2, 129.1, 125.7, 123.3, 123.1, 121.1, 117.4, 117.2, 116.0, 115.1, 113.5, 79.7, 47.8, 38.4; HRMS (EI) calcd for $C_{17}H_{14}N_3Cl$ $[M]^+$ 295.0876, found 295.0890.

Methyl 3-(((4-ethylphenyl)(methyl)amino)methyl)indolizine-1-carboxylate (3r): 73% yield; white solid; ^{1}H NMR (400 MHz, CD_3SOCD_3) δ 8.18 (d, J = 6.8 Hz, 1 H), 8.06 (d, J = 9.2 Hz, 1 H), 7.17 (t, J = 7.8 Hz, 1 H), 7.10 (d, J = 8.0 Hz, 2 H), 6.91 (s, 1 H), 6.90 (t, J = 6.4 Hz, 1 H), 6.80 (d, J = 7.6 Hz, 2 H), 4.70 (s, 2 H), 3.73 (s, 3 H), 2.80 (s, 3 H), 2.46 (q, J = 7.6 Hz, 2 H), 1.10 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 164.6, 148.0, 135.9, 132.9, 128.7, 125.3, 123.0, 122.7, 119.1, 115.5, 114.1, 113.0, 101.9, 51.0, 48.2, 38.5, 27.6, 16.3; HRMS (EI) calcd for $C_{20}H_{22}N_2O_2$ $[M]^+$ 322.1681, found 322.1682

Methyl 3-((methyl(phenyl)amino)methyl)indolizine-1-carboxylate (3s): 56% yield; white solid; ^{1}H NMR (400 MHz, CD_3SOCD_3) δ 8.19 (d, J = 7.2 Hz, 1 H), 8.07 (d, J = 9.2 Hz, 1 H), 7.21−7.16 (m, 3 H), 6.93−6.86 (m, 4 H), 6.68 (t, J = 7.2 Hz, 1 H), 4.78 (s, 2 H), 3.73 (s, 3 H), 2.88 (s, 3 H); ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 164.6, 149.8, 136.0, 129.5, 125.2, 123.0, 122.6, 119.1, 117.4, 115.3, 113.6, 113.0, 102.0, 51.0, 47.9, 38.2; HRMS (EI) calcd for $C_{18}H_{18}N_2O_2$ $[M]^+$ 294.1368, found 294.1345.

Methyl 3-(4-(dimethylamino)benzyl)indolizine-1-carboxylate (4s): 14% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 9.2 Hz, 1 H), 7.76 (d, J = 6.8 Hz, 1 H), 7.05−7.00 (m, 4 H), 6.69−6.63 (m, 3 H), 4.09 (s, 2 H), 3.89 (s, 3 H), 2.91 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 149.5, 136.5, 129.0, 124.6, 124.5, 123.2, 121.5, 119.8, 115.5, 113.0, 112.2, 102.4, 50.7, 40.7, 31.4; HRMS (EI) calcd for $C_{19}H_{20}N_2O_2$ $[M]^+$ 308.1525, found 308.1522.

Methyl 3-((methyl(*m*-tolyl)amino)methyl)indolizine-1-carboxylate (3t): 70% yield; white solid; ^{1}H NMR (400 MHz, CD_3SOCD_3) δ 8.19 (d, J = 7.2 Hz, 1 H), 8.08 (d, J = 8.8 Hz, 1 H), 7.20 (t, J = 7.8 Hz, 1 H), 7.07 (t, J = 7.6 Hz, 1 H), 6.92 (t, J = 6.4 Hz, 1 H), 6.90 (s, 1 H), 6.71−6.68 (m, 2 H), 6.52 (d, J = 7.2 Hz, 1 H), 4.77 (s, 2 H), 3.75 (s, 3 H), 2.86 (s, 3 H), 2.23 (s, 3 H); ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 164.6, 149.9, 138.5, 136.0, 129.3, 125.3, 123.0, 122.7, 119.1, 118.3, 115.2, 114.2, 113.0, 110.8, 102.0, 51.0, 47.9, 38.2, 21.9; HRMS (EI) calcd for $C_{19}H_{20}N_2O_2$ $[M]^+$ 308.1525, found 308.1533.

Methyl 3-(4-(dimethylamino)-2-methylbenzyl)indolizine-1-carboxylate (4t): 12% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 8.8 Hz, 1 H), 7.80 (d, J = 6.8 Hz, 1 H), 7.07 (t, J = 7.8 Hz, 1 H), 6.89 (s, 1 H), 6.81 (d, J = 8.4 Hz, 1 H), 6.73 (t, J = 6.4 Hz, 1 H), 6.65 (s, 1 H), 6.53 (d, J = 8.8 Hz, 1 H), 4.03 (s, 2 H), 3.88 (s, 3 H), 2.94 (s, 6 H), 2.31 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 149.7, 137.1, 136.1, 129.6, 124.3, 123.1, 123.0, 121.4, 119.8, 115.4, 115.0,

112.2, 110.7, 102.5, 50.7, 40.7, 29.2, 20.0; HRMS (EI) calcd for $C_{20}H_{22}N_2O_2$ $[M]^+$ 322.1681, found 322.1679.

***N*-((1*H*-indol-3-yl)methyl)-*N*,4-dimethylaniline (5a):**[4h] 24% yield; white solid; ^{1}H NMR (400 MHz, CD_3SOCD_3) δ 10.87 (s, 1 H), 7.50 (d, J = 8.0 Hz, 1 H), 7.33 (d, J = 8.0 Hz, 1 H), 7.14 (s, 1 H), 7.06 (t, J = 7.6 Hz, 1 H), 6.98−6.93 (m, 3 H), 6.76 (d, J = 8.5 Hz, 2 H), 4.57 (s, 2 H), 2.85 (s, 3 H), 2.17 (s, 3 H); ^{13}C NMR (125 MHz, CD_3SOCD_3) δ 148.2, 136.7, 129.7, 127.3, 124.9, 124.3, 121.4, 119.2, 118.9, 113.7, 111.9, 111.8, 48.2, 38.4, 20.4.

1,3-Bis((methyl(*p*-tolyl)amino)methyl)-1*H*-indole (6a): 17% yield; colorless liquid; ^{1}H NMR (400 MHz, CD_3SOCD_3) δ 7.46 (d, J = 7.6 Hz, 1 H), 7.40 (d, J = 8.4 Hz, 1 H), 7.06 (s, 1 H), 7.05 (t, J = 7.2 Hz, 1 H), 6.98 (d, J = 8.4 Hz, 2 H), 6.95 (t, J = 8.6 Hz, 3 H), 6.81 (d, J = 8.8 Hz, 2 H), 6.70 (d, J = 9.2 Hz, 2 H), 5.63 (s, 2 H), 4.48 (s, 2 H), 2.77 (s, 3 H), 2.75 (s, 3 H), 2.18 (s, 3 H), 2.16 (s, 3 H); ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 148.2, 146.5, 136.7, 129.9, 129.7, 127.8, 127.3, 127.2, 125.0, 121.7, 119.4, 119.3, 115.0, 113.7, 111.8, 110.8, 63.6, 48.2, 38.2, 37.5, 20.4, 20.3; HRMS (EI) calcd for $C_{26}H_{29}N_3$ $[M]^+$ 383.2361, found 383.2359.

***N*-((5-Bromo-1*H*-indol-3-yl)methyl)-*N*,4-dimethylaniline (5b):**[4h] 28% yield; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (s, 1 H), 7.74 (s, 1 H), 7.31 (dd, J = 8.5, 2.0 Hz, 1 H), 7.22 (d, J = 8.0 Hz, 1 H), 7.11 (d, J = 8.5 Hz, 2 H), 7.00 (s, 1 H), 6.84 (d, J = 8.5 Hz, 2 H), 4.51 (s, 2 H), 2.95 (s, 3 H), 2.32 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 135.2, 129.9, 128.9, 126.7, 125.2, 124.1, 122.0, 114.2, 113.3, 113.0, 112.8, 49.3, 38.6, 20.5.

1,3-Bis((methyl(*p*-tolyl)amino)methyl)-5-bromo-1*H*-indole (6b): 24% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s 1 H), 7.26 (dd, J = 8.2, 1.8 Hz, 1 H), 7.12 (d, J = 8.4 Hz, 2 H), 7.10 (t, J = 8.6 Hz, 3 H), 6.89 (s, 1 H), 6.80 (d, J = 8.4 Hz, 4 H), 5.45 (s, 2 H), 4.50 (s, 2 H), 2.86 (s, 3 H), 2.81 (s, 3 H), 2.33 (s, 3 H), 2.32 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 146.7, 135.5, 130.2, 130.0, 129.8, 129.4, 127.3, 126.8, 125.0, 122.3, 115.9, 114.4, 113.1, 112.5, 111.7, 65.5, 49.4, 38.5, 37.5, 20.7, 20.6; HRMS (EI) calcd for $C_{26}H_{28}BrN_3$ $[M]^+$ 461.1467, found 461.1455.

3-((Methyl(*p*-tolyl)amino)methyl)-1*H*-indole-5-carbonitrile (5c): 20% yield; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1 H), 7.94 (s, 1 H), 7.43 (t, J = 10.0 Hz, 2 H), 7.15 (s, 1 H), 7.10 (d, J = 8.5 Hz, 2 H), 6.83 (d, J = 8.0 Hz, 2 H), 4.62 (s, 2 H), 2.94 (s, 3 H), 2.30 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2, 138.4, 130.0, 127.1, 127.0, 125.3, 125.2, 125.0, 121.0, 114.6, 114.3, 112.3, 102.7, 49.4, 38.7, 20.5; HRMS (EI) calcd for $C_{18}H_{17}N_3$ $[M]^+$ 275.1422, found 275.1423.

1,3-Bis((methyl(*p*-tolyl)amino)methyl)-1*H*-indole-5-carbonitrile (6c): 34% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s 1 H), 7.39 (dd, J = 8.4, 1.6 Hz, 1 H), 7.30 (d, J = 8.8 Hz, 1 H), 7.12 (d, J = 8.4 Hz, 2 H), 7.08 (d, J = 8.4 Hz, 2 H), 7.01 (s, 1 H), 6.81 (d, J = 8.4 Hz, 2 H), 6.79 (d, J = 8.8 Hz, 2 H), 5.54 (s, 2 H), 4.54 (s, 2 H), 2.86 (s, 3 H), 2.84 (s, 3 H), 2.33 (s, 3 H), 2.31 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 146.4, 138.3, 130.3, 130.0, 129.8, 128.3, 127.9, 127.4, 125.3, 125.1, 120.9, 116.0, 114.7, 113.9, 111.0, 102.8, 65.7, 49.5, 38.7, 37.6, 20.7, 20.6; HRMS (EI) calcd for $C_{27}H_{28}N_4$ $[M]^+$ 408.2314, found 408.2311.

***N*,4-Dimethyl-*N*-((5-nitro-1*H*-indol-3-yl)methyl)aniline (5d):** 49% yield; light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1 H), 8.54 (d, J = 2.0 Hz, 1 H), 8.09 (dd, J = 9.2, 2.0 Hz, 1 H), 7.36 (d, J = 9.2 Hz, 1 H), 7.14 (s, 1 H), 7.07 (d, J = 8.4 Hz, 2 H), 6.81 (d, J = 8.8 Hz, 2 H), 4.64 (s, 2 H), 2.95 (s, 3 H), 2.27 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 141.6, 139.4, 129.7, 126.9, 126.3, 125.7, 117.8, 116.6, 116.0, 114.1, 111.1, 49.1, 38.7, 20.2; HRMS (EI) calcd for $C_{17}H_{17}N_3O_2$ $[M]^+$ 295.1321, found 295.1314.

1,3-Bis((methyl(*p*-tolyl)amino)methyl)-5-nitro-1*H*-indole (6d): 12% yield; light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, J = 2.0 Hz, 1 H), 8.04 (dd, J = 9.0, 2.0 Hz, 1 H), 7.23 (d, J = 9.2 Hz, 1 H), 7.08 (d, J = 8.4 Hz, 2 H), 7.05 (d, J = 8.8 Hz, 2 H), 6.98 (s, 1 H), 6.76 (t, J = 8.4 Hz, 4 H), 5.52 (s, 2 H), 4.56 (s, 2 H), 2.86 (s, 3 H), 2.82 (s, 3 H), 2.30 (s, 3 H), 2.27 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 146.4, 141.5, 139.4, 130.1, 129.7, 128.8, 127.2, 127.0, 117.6, 116.8, 115.9, 115.4, 115.2, 114.3, 110.0, 65.8, 49.2, 38.7, 37.5, 20.5, 20.4; HRMS (EI) calcd for $C_{26}H_{28}N_4O_2$ $[M]^+$ 428.2212, found 428.2206.

1,3-Bis((methyl(*p*-tolyl)amino)methyl)-5-methyl-1*H*-indole (6e): 12% yield; colorless liquid; ^{1}H NMR (400 MHz, CD_3SOCD_3) δ 7.26 (d, J = 8.4 Hz, 1 H), 7.21 (s, 1 H), 7.00 (s, 1 H), 6.97 (d, J = 8.4 Hz, 2 H), 6.93 (d, J = 8.4 Hz, 2 H), 6.86 (d, J = 8.2 Hz, 1 H), 6.79 (d, J = 9.2 Hz, 2 H), 6.69 (d, J = 8.8 Hz, 2 H), 5.59 (s, 2 H), 4.43 (s, 2 H), 2.74 (s, 3 H), 2.73 (s, 3 H), 2.29 (s, 3 H), 2.18 (s, 3 H), 2.16 (s, 3 H); ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 148.3, 146.5, 135.1, 129.8, 129.7, 128.0, 127.8, 127.3, 127.2, 125.1, 123.3, 119.0, 115.1, 113.8, 111.2, 110.6, 63.6, 48.3, 38.2, 37.5, 21.5, 20.4, 20.3; HRMS (EI) calcd for $C_{27}H_{31}N_3$ $[M]^+$ 397.2518, found 397.2507.

Methyl 1-((methyl(phenyl)amino)methyl)-1*H*-indole-3-carboxylate (5f): 42% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.0 Hz, 1 H), 7.82 (s, 1 H), 7.35−7.25 (m, 3 H), 7.12 (d, J = 8.4 Hz, 2 H), 6.81 (d, J = 8.4 Hz, 2 H), 5.58 (s, 2 H), 3.91 (s, 3 H), 2.99 (s, 3 H), 2.32 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 145.8, 136.1, 132.9, 130.0, 129.0, 127.0, 122.9, 122.1, 121.7, 114.7, 110.3, 107.5, 65.5, 50.9, 37.6, 20.4; HRMS (EI) calcd for $C_{19}H_{20}N_2O_2$ $[M]^+$ 308.1525, found 308.1522.

Ethyl 3-((methyl(*p*-tolyl)amino)methyl)-1*H*-indole-2-carboxylate (5g): 30% yield; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.04 (s, 1 H), 7.72 (d, J = 8.5 Hz, 1 H), 7.42 (d, J = 8.5 Hz, 1 H), 7.34 (t, J = 8.5 Hz, 1 H), 7.14 (d, J = 8.5 Hz, 2 H), 7.09 (t, J = 7.5 Hz, 1 H), 6.95 (d, J = 9.0 Hz, 2 H), 4.99 (s, 2 H), 4.49 (q, J = 7.0 Hz, 2 H), 2.87 (s, 3 H), 2.33 (s, 3 H), 1.46 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6, 149.1, 136.2, 129.9, 128.0, 126.7, 125.8, 124.3, 122.4, 121.5, 120.7, 114.4, 111.9, 61.3, 48.8, 37.8, 20.5, 14.7; HRMS (EI) calcd for $C_{20}H_{22}N_2O_2$ $[M]^+$ 322.1681, found 322.1684.

3-(4-(Dimethylamino)benzyl)indolizine-1-carbonitrile (4a): 79% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 7.2 Hz, 1 H), 7.62 (d, J = 8.8 Hz, 1 H), 7.03−6.99 (m, 3 H), 6.80 (s, 1 H), 6.70−6.67 (m, 3 H), 4.09 (s, 2 H), 2.92 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 138.2, 129.0, 125.2, 123.6, 121.4, 117.9, 117.3, 115.9, 113.0, 112.9, 112.6, 80.5, 40.6, 31.2; HRMS (EI) calcd for $C_{18}H_{17}N_3$ $[M]^+$ 275.1422, found 275.1431.

Methyl 3-(4-(dimethylamino)benzyl)indolizine-1-carboxylate (4s): 65% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 9.2 Hz, 1 H), 7.76 (d, J = 6.8 Hz, 1 H), 7.05−7.00 (m, 4 H), 6.69−6.63 (m, 3 H), 4.09 (s, 2 H), 3.89 (s, 3 H), 2.91 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 149.5, 136.5, 129.0, 124.6, 124.5, 123.2, 121.5, 119.8, 115.5, 113.0, 112.2, 102.4, 50.7, 40.7, 31.4; HRMS (EI) calcd for $C_{19}H_{20}N_2O_2$ $[M]^+$ 308.1525, found 308.1522.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedure, characterization of all compounds, and the crystallographic data of compound **3g**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: yhzhang@zju.edu.cn.

■ ACKNOWLEDGMENT

Funding from National Basic Research Program of China (No. 2011CB936003) and NSFC (No. 20872126, No. 2107216) is highly acknowledged.

■ REFERENCES

(1) For representative reviews, see: (a) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.*

2002, *102*, 1731. (c) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (e) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (f) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (g) Ackermann, L. *Chem. Commun.* **2010**, 4866. (h) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (i) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654. (j) Lu, H.; Zhang, X. P. *Chem. Soc. Rev.* DOI: 10.1039/c0cs00070a.

(2) For representative references, see: (a) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. (b) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404. (c) Maleczka, R. E., Jr. *Science* **2009**, *323*, 1572. (d) Zhou, H.; Xu, Y.-H.; Chung, W.-J.; Loh, T.-P. *Angew. Chem., Int. Ed.* **2009**, *48*, 5355. (e) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882. (f) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2005**, *7*, 2229. (g) Baslé, O.; Li, C.-J. *Org. Lett.* **2008**, *10*, 3661. (h) Chaumontet, M.; Piccardi, R.; Audic, N.; Hitce, J.; Peglion, J.-L.; Clot, E.; Baudoin, O. *J. Am. Chem. Soc.* **2008**, *130*, 15157. (i) Nakao, Y.; Kashihara, N.; Kanyiva, K. S.; Hiyama, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 4451. (j) Kumaraswamy, G.; Murthy, A. N.; Pitchaiah, A. *J. Org. Chem.* **2010**, *75*, 3916. (k) Ye, X.; Xie, C.; Pan, Y.; Han, L.; Xie, T. *Org. Lett.* **2010**, *12*, 4240. (l) Zhang, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2007**, *9*, 3813.

(3) For representative reviews, see: (a) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (b) Ashenhurst, J. A. *Chem. Soc. Rev.* **2010**, *39*, 540. (c) Klussmann, M.; Sureshkumar, D. *Synthesis* **2010**. DOI: 10.1055/s-0030-1258303. (d) Scheuermann, C. J. *Chem. Asian J.* **2010**, *5*, 436. For representative references, see:(e) Yin, W.; He, C.; Chen, M.; Zhang, H.; Lei, A. *Org. Lett.* **2009**, *11*, 709. (f) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (g) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (h) Dohi, T.; Ito, M.; Morimoto, K.; Iwata, M.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 1301. (i) Zhao, X.; Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 5837. (j) Xi, P.; Yang, F.; Qin, S.; Zhao, D.; Lan, J.; Gao, G.; Hu, C.; You, J. *J. Am. Chem. Soc.* **2010**, *132*, 1822. (k) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125. (l) Yang, Y.; Cheng, K.; Zhang, Y. *Org. Lett.* **2009**, *11*, 5606. (m) Li, Z.; Yu, R.; Li, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7497. (n) Haro, T.; Nevado, C. *J. Am. Chem. Soc.* **2010**, *132*, 1512. (o) Richter, H.; Mancheño, O. G. *Eur. J. Org. Chem.* **2010**, 4460.

(4) For representative references of CDC transformations with tertiary amines, see: (a) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810. (b) Sud, A.; Sureshkumar, D.; Klussmann, M. *Chem. Commun.* **2009**, 3169. (c) Jovel, I.; Prateeptongkum, S.; Jackstell, R.; Vogl, N.; Weckbeckerb, C.; Beller, M. *Chem. Commun.* **2010**, 1956. (d) Han, W.; Ofial, A. R. *Chem. Commun.* **2009**, 6023. (e) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968. (f) Ohta, M.; Quick, M. P.; Yamaguchi, J.; Wünsch, B.; Itami, K. *Chem. Asian J.* **2009**, *4*, 1416. (g) Liu, P.; Zhou, C.-Y.; Xiang, S.; Che, C.-M. *Chem. Commun.* **2010**, 2739. (h) Yang, F.; Li, J.; Xie, J.; Huang, Z.-Z. *Org. Lett.* **2010**, *12*, 5214. (i) Shirakawa, E.; Uchiyama, N.; Hayashi, T. *J. Org. Chem.* **2011**, *76*, 25. (j) Shen, Y.; Li, M.; Wang, S.; Zhan, T.; Tan, Z.; Guo, C.-C. *Chem. Commun.* **2009**, 953. (k) Baslé, O.; Li, C.-J. *Chem. Commun.* **2009**, 4124. (l) Baslé, O.; Li, C.-J. *Green Chem.* **2007**, *9*, 1047. (m) Murata, S.; Teramoto, K.; Miura, M.; Nomura, M. *J. Chem. Res, Synop.* **1993**, 434. (n) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672. (o) Baslé, O.; Borduas, N.; Dubois, P.; Chapuzet, J. M.; Chan, T.-H.; Lessard, J.; Li, C.-J. *Chem.—Eur. J.* **2010**, *16*, 8162. (p) Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7075. (q) Rao Volla, C. M.; Vogel, P. *Org. Lett.* **2009**, *11*, 1701.

(5) (a) Deng, G.; Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6278. (b) Deng, G.; Li, C.-J. *Org. Lett.* **2009**, *11*, 1171. (c) Li, Y.-Z.; Li, B.-J.; Lu, X.-Y.; Lin, S.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3817. (d) Rong, Y.; Li, R.; Lu, W. *Organometallics* **2007**, *26*, 4376.

(6) (a) Yokota, T.; Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2003**, *125*, 1476. (b) Hatamoto, Y.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* **2004**, *6*, 4623. (c) Brasche, G.; García-Fortanet, J. S.; Buchwald, L. *Org. Lett.* **2008**, *10*, 2207. (d) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115. (e) Yoo, W.-J.; Correia, C. A.; Zhang, Y.; Li, C.-J. *Synlett* **2009**, 138. (f) King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 12068. (g) Pintér, Á.; Sud, A.; Sureshkumar, D.; Klussmann, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 5004. (h) Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422. (i) Hay, A. S. *J. Org. Chem.* **1962**, *27*, 3320. (j) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632. (k) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833. (l) Uemura, T.; Imoto, S.; Chatani, N. *Chem. Lett.* **2006**, *35*, 842. (m) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607. (n) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (o) Gao, Y. X.; Wang, G.; Chen, L.; Xu, P. X.; Zhao, Y. F.; Zhou, Y. B.; Han, L. B. *J. Am. Chem. Soc.* **2009**, *131*, 7956. (p) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2009**, *131*, 17052. (q) Wie, Y.; Zhao, H.; Kann, J.; Su, W.; Hong, M. *J. Am. Chem. Soc.* **2010**, *132*, 2522. (r) Niu, T.; Zhang, Y. *Tetrahedron Lett.* **2010**, *51*, 6847. (s) Kitahara, M.; Hirano, K.; Tsurugi, H.; Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 1772. (t) Yang, L.; Zhao, L.; Li, C.-J. *Chem. Commun.* **2010**, 4184.

(7) (a) Murata, S.; Miura, M.; Nomura, M. *J. Chem. Soc., Chem. Commun.* **1989**, 116. (b) Murata, S.; Miura, M.; Nomura, M. *J. Org. Chem.* **1989**, *54*, 4700. (c) Liégault, B.; Fagnou, K. *Organometallics* **2008**, *27*, 4841. (d) Andrews, P. C.; Junk, P. C.; Kemppinen, K. P.; Konstas, K.; Tuck, K. L. *Lett. Org. Chem.* **2009**, *6*, 229. (e) Klein, J. E. M. N.; Perry, A.; Pugh, D. S.; Taylor, R. J. K. *Org. Lett.* **2010**, *12*, 3446.

(8) (a) *Cytochrome P-450, Structure, Mechanism, and Biochemistry*, 2nd ed.; Ortiz de Montellano, P. R., Ed.; Plenum Press: New York, 1995. (b) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981; pp 387−397. (c) Murahashi, S.-I.; Zhang, D. *Chem. Soc. Rev.* **2008**, *37*, 1490. (d) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069.

(9) (a) Chiavarino, B.; Cipollini, R.; Crestoni, M. E.; Fornarini, S.; Lanucara, F.; Lapi, A. *J. Am. Chem. Soc.* **2008**, *130*, 3208. (b) Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312. (c) Murahashi, S.-I.; Naota, T.; Yonemura, K. *J. Am. Chem. Soc.* **1988**, *110*, 8256. (d) Sureshkumar, D.; Sud, A.; Klussmann, M. *Synlett* **2009**, 1558.

(10) Huang, L.; Zhang, X.; Zhang, Y. *Org. Lett.* **2009**, *11*, 3730.

(11) (a) Howe, E. E.; Zambito, A. J.; Snyder, H. R.; Tishler, M. *J. Am. Chem. Soc.* **1945**, *67*, 38. (b) Albright, J. D.; Snyder, H. R. *J. Am. Chem. Soc.* **1959**, *81*, 2239. (c) Iwao, M.; Motoi, O. *Tetrahedron Lett.* **1995**, *36*, 5929. (d) Chauder, B.; Larkin, A.; Snieckus, V. *Org. Lett.* **2002**, *4*, 815. (e) Herrán, G.; Segura, A.; Csákÿ, A. G. *Org. Lett.* **2007**, *9*, 961. (f) Li, H.; He, Z.; Guo, X.; Li, W.; Zhao, X.; Li, Z. *Org. Lett.* **2009**, *11*, 4176.

(12) (a) Li, H.; Xia, Z.; Chen, S.; Koya, K.; Ono, M.; Sun, L. *Org. Process Res. Dev.* **2007**, *11*, 246. (b) Zhou, H.; Danger, D. P.; Dock, S. T.; Hawley, L.; Roller, S. G.; Smith, C. D.; Handlon, A. L. *ACS Med. Chem. Lett.* **2010**, *1*, 19.

(13) For representative reviews, see: (a) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2005**, *22*, 73. (b) Kochanowska-Karamyan, A.-J.; Hamann, M.-T. *Chem. Rev.* **2010**, *110*, 4489.

(14) Zhang, L.; Liang, F.; Sun, L.; Hu, Y.; Hu, H. *Synthesis* **2000**, 1733.

(15) Pollak, I. E.; Grillot, G. F. *J. Org. Chem.* **1967**, *32*, 2892.