Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 7108

www.rsc.org/obc

PAPER

Pd-Catalyzed C-3 functionalization of indolizines *via* C–H bond cleavage†

Baoli Zhao*

Received 30th March 2012, Accepted 17th July 2012
DOI: 10.1039/c2ob25643f

New transition metal-catalyzed methods for the arylation of indolizines by the direct cleavage of C–H bonds have been developed. A wide range of aryltrifluoroborate salts react with indolizines in the presence of $Pd(OAc)_2$ catalyst and AgOAc oxidant to give the arylated indolizines in high yields. Both electron-donating and electron-withdrawing groups perform smoothly while bromide and chlorine substituents are tolerated. In addition, the indolizines display similar reactivities in the Pd-catalyzed reaction with 3-phenylpropiolic acid to afford the corresponding C-3 alkynylated indolizines. These methods allow the direct functionalization of indolizines in one step.

Introduction

The functionalization of heteroaromatics, particularly arylation and alkynylation, *via* catalytic processes is of great importance in organic chemistry, and transition metal-catalyzed transformations such as the Suzuki coupling reaction[1] and Sonogashira coupling reaction[2] have emerged as powerful tools for accessing the arylation and alkynylation of heteroaromatics. Although these coupling reactions provide viable scaffolds for the functionalization of heteroaromatics, the preactivation of heteroaromatic carbon fragments with metal-containing functionalities and halides may involve several synthetic steps. Recently, the selective functionalization of C–H bonds has attracted substantial interest because such C–H activations often significantly shorten the number of steps of the synthesis and decrease byproduct waste.[3] The C–H functionalizations of heteroaromatics display even more advantages since some important types of heteroaromatic organometallic compounds have proven challenging to synthesize and may even be inadequately stable to participate in the cross-coupling process.[4]

Indolizines are important heterocycles and can be found in motifs of a wide variety of natural products with useful biological[5] and pharmaceutical properties.[6] Consequently, the functionalization of indolizines has attracted considerable interest in the past decades, and metal-catalyzed direct functionalization of indolizines was explored recently.[7] For instance, Gevorgyan and co-workers reported the palladium-catalyzed direct arylation of indolizines with aryl bromides.[8] In their reaction, the C–H bond of indolizines directly coupled with aryl bromides to selectively give the C-3 arylated indolizines in good yields. More recently, the copper-mediated direct halogenation of indolizines was developed by Xia and You,[9] in which 3-haloindolizines were selectively produced under mild reaction conditions and were conveniently further transformed to 3-arylated indolizines by Suzuki reaction. Subsequently, You and co-workers reported a palladium–copper bimetallic catalytic system with the assistance of CuCl and BQ to achieve the arylation of indolizine with aryl boronic acids in a yield of 63% in one step.[10] In this work, we investigate the C-3 arylation of indolizines with aryltrifluoroborate salts in the presence of a $Pd(OAc)_2$–AgOAc–KOAc catalytic system to form 3-arylated indolizines derivatives. Furthermore, we extend the indolizines' C-3 functionalization to alkynylation in DMSO–1,4-dioxane to form 3-alkynylindolizine derivatives under a N_2 atmosphere.

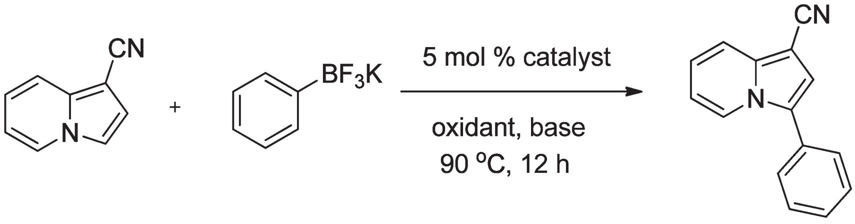
Results and discussion

C-3 Arylation of indolizines with aryltrifluoroborate salts

Organotrifluoroborates are considered as alternatives to organoboron coupling partners that can be simply prepared in large quantities and, unlike most organoboronic compounds, are completely air- and moisture-stable and stoichiometric determination can be highly reliable. To explore a high efficacy catalytic system for C-3 arylation, indolizine-1-carbonitrile and phenyltrifluoroborate salt were chosen as the benchmark substrates in the model reaction (Table 1). We obtained the desired product in a yield of 67% (Table 1, entry 1) in the presence of 5 mol% $Pd(OAc)_2$ in DMF at 90 °C for 12 h in air. The formation of the 3-phenylindolizine-1-carbonitrile was increased to 89% under pure nitrogen (Table 1, entry 2). Other palladium salts showed less activity, and several metals such as $RhCl(PPh_3)_3$, $RuCl_3$ and $Cu(OAc)_2$ were found to be incompatible with the reaction (Table 1, entries 3–10). Many silver(I) reagents such as Ag_2CO_3, Ag_2O, AgTFA and AgOTf were found to be effective and

Institute of Applied Chemistry and Department of Chemistry, University of Shaoxing, Shaoxing, Zhejiang Province 312000, People's Republic of China. E-mail: babygarfield@126.com; Fax: +86-575-88345682
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c2ob25643f

Table 1 The effect of metals, oxidants and bases on the reaction[a]



Entry	Catalyst	Oxidant	Base	Yield[b] %
1	$Pd(OAc)_2$	AgOAc	KOAc	67[c]
2	$Pd(OAc)_2$	AgOAc	KOAc	89
3	$RhCl(PPh_3)_3$	AgOAc	KOAc	Trace
4	$RuCl_3$	AgOAc	KOAc	Trace
5	$Cu(OAc)_2$	AgOAc	KOAc	Trace
6	$PdCl_2$	AgOAc	KOAc	75
7	$PdCl_2(PPh_3)_2$	AgOAc	KOAc	69
8	$Pd(PPh_3)_4$	AgOAc	KOAc	60
9	$Pd(dba)_2$	AgOAc	KOAc	66
10	$Pd_2(dba)_3$	AgOAc	KOAc	69
11	$Pd(OAc)_2$	Ag_2CO_3	KOAc	86
12	$Pd(OAc)_2$	Ag_2O	KOAc	80
13	$Pd(OAc)_2$	AgTFA	KOAc	74
14	$Pd(OAc)_2$	AgOTf	KOAc	81
15	$Pd(OAc)_2$	AgOAc	K_2CO_3	33
16	$Pd(OAc)_2$	AgOAc	Na_2CO_3	30
17	$Pd(OAc)_2$	AgOAc	K_3PO_4	19
18	$Pd(OAc)_2$	AgOAc	KOH	14
19	$Pd(OAc)_2$	AgOAc	KF	Trace
20	$Pd(OAc)_2$	AgOAc	NaOAc	85

[a] Reaction conditions: indolizines (0.3 mmol), potassium phenyltrifluoroborate salts (0.3 mmol), catalyst (0.015 mmol), oxidant (0.3 mmol), base (0.3 mmol), DMF (2 mL), 90 °C, 12 h, N_2. [b] Isolated yields of arylation. [c] The reaction was performed under air.

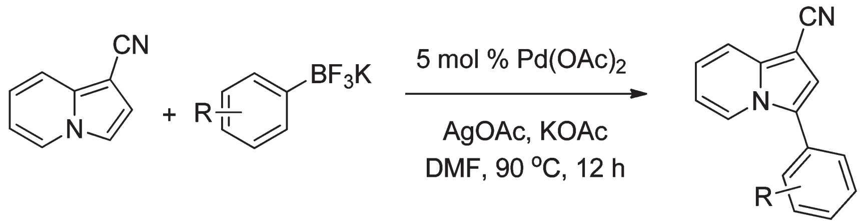
AgOAc performed the best (Table 1, entries 11–14). The screening of commonly used bases indicated that KOAc and NaOAc were suitable bases for this arylation (Table 1, entries 15–20). The reaction was sluggish in other solvents tested, including 1,4-dioxane, DMSO, CH_3CN, and toluene. No side products such as 3,3′-biindolizine-1,1′-dicarbonitrile were observed in the arylation of indolizine with phenyltrifluoroborate salts.

The scope of this reaction was then investigated under the optimized conditions. A wide range of aryltrifluoroborate salts were examined and the results are listed in Table 2. This system demonstrated a good functional group tolerance with both electrophilic and nucleophilic partners. Aryltrifluoroborate salts with electron-withdrawing groups like 4-trifluoromethyl and 3-fluoro afforded better yields (Table 2, entries 7 and 10) than aryltrifluoroborate salts with electron-donating group such as 4-methoxy, 4-*tert*-butyl, and 4-methyl (Table 2, entries 1, 3 and 4). Methyl, chloro, and trifluoromethyl phenyltrifluoroborate salts reacted similarly to provide the corresponding 3-arylindolizines, which shows that there is not much effect of *meta*- or *para*-substitution on the phenyltrifluoroborate salts (Table 2, entries 4, 5, 7, 8, 9 and 12). *ortho*-Substitution such as methyl and bromo decrease the yield of products noticeably (Table 2, entries 13 and 14). α-Naphthalene and β-naphthalene show diversity in their yields which reveals that steric effects exert action on the formation of the products (Table 2, entries 15 and 16). Notably, other functional groups like methylthio, trifluoromethoxy and formyl are tolerated in this catalyst system (Table 2, entries 2, 6 and 11). It is noteworthy to observe that when phenyltrifluoroborate salts are replaced by iodobenzene, C-3 arylation products can be accomplished in good yields in the same way (Table 2, entry 17). Nevertheless, it should be pointed out that carbon–halogen bonds tolerated the reaction conditions and the halogen-containing products were afforded smoothly without by-products being observed, which shows high functional group tolerance and selectivity.

We examined a variety of structurally divergent indolizines to understand the scope and the generality of the C-3 arylation and the results are summarized in Table 3. Indolizine-1-carbonitrile, methyl indolizine-1-carboxylate, ethyl indolizine-1-carboxylate, and *n*-butylindolizine-1-carboxylate afforded the desired products in good yield (Table 3, entries 1–4). When 2-methylindolizine-1-carbonitrile was coupled with phenyltrifluoroborate salt, a 88% yield was obtained (Table 3, entry 5), which showed steric effects didn't restrain the formation of the desired product. 7-Methyl-indolizine-1-carbonitrile also proceeding smoothly under the model reaction system (Table 3, entry 6).

Indolizines are classified as electron-rich aromatic heterocycles, and their transformations catalyzed by palladium show strong electrophilic character with reactions occurring at the most electron-rich C3-position.[11] In our experiment concerning electrophiles, the electron-deficient aryltrifluoroborate salts are more reactive than the electron-rich aryltrifluoroborate salts, which is consistent with the electrophilic substitution mechanism. On the basis of the previous chemistry and our results,

Table 2 The reaction of indolizine with aryltrifluoroborate salts[a]



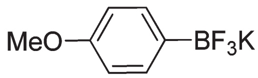
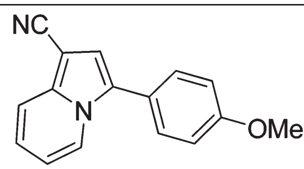
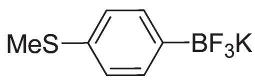
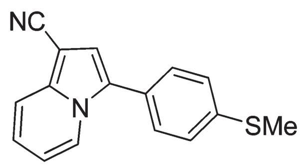
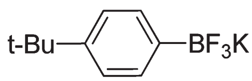
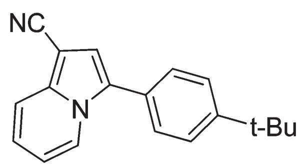
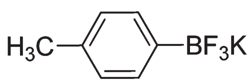
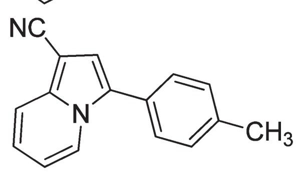
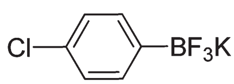
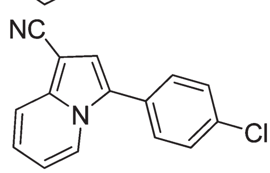
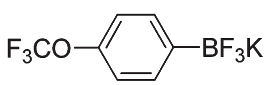
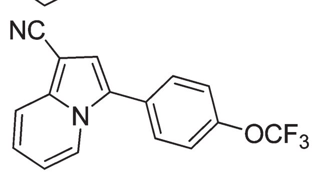
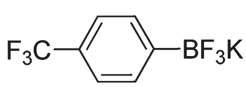
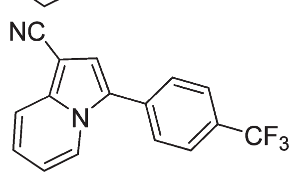
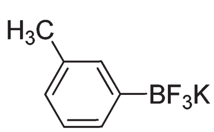
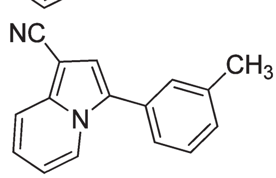
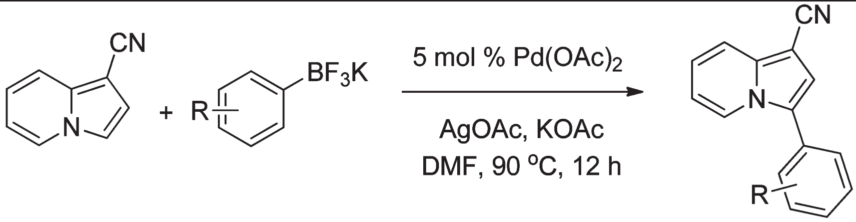
Entry	Aryltrifluoroborate salts	Product	Yield[b] (%)
1			80
2			78
3			81
4			86
5			77
6			66
7			91
8			75

Table 2 *(Contd.)*



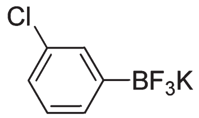
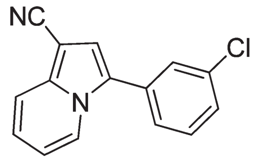
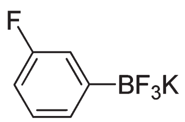
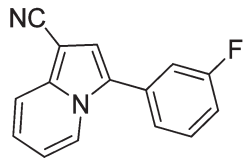
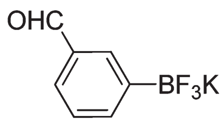
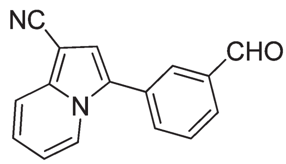
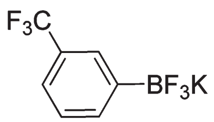
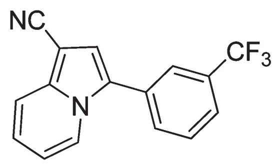
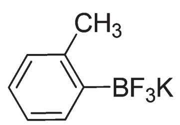
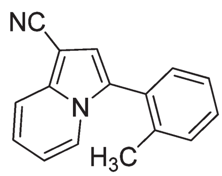
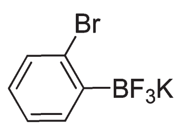
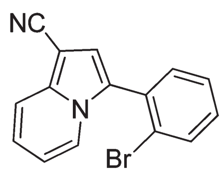
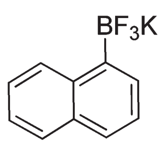
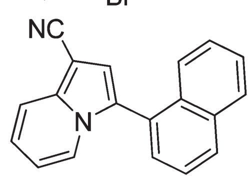
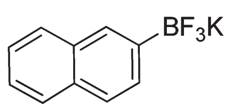
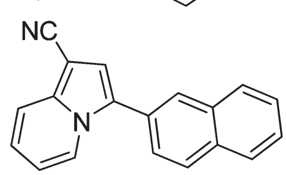
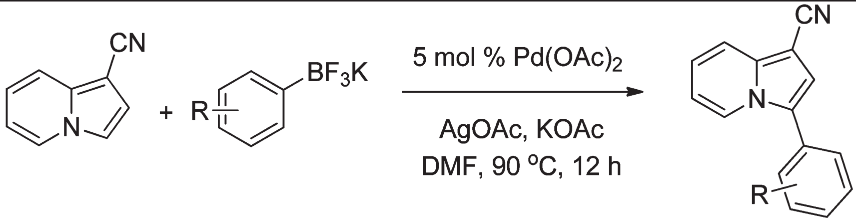
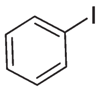
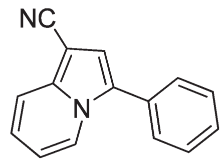
Entry	Aryltrifluoroborate salts	Product	Yield[b] (%)
9			79
10			92
11			81
12			93
13			44
14			40
15			46
16			86

Table 2 *(Contd.)*



Entry	Aryltrifluoroborate salts	Product	Yield[b] (%)
17			83[c]

[a] Reaction conditions: indolizine-1-carbonitrile (0.3 mmol), potassium aryltrifluoroborate salts (0.3 mmol), $Pd(OAc)_2$ (5 mol%), AgOAc (0.3 mmol), KOAc (0.3 mmol), DMF (2 mL), 90 °C, 12 h, N_2. [b] Isolated yields of arylation. [c] Iodobenzene in place of phenyltrifluoroborate salt.

we propose a plausible mechanism for this arylation reaction, as shown in Scheme 1. Arylpalladium intermediate A was generated by transmetalation between Pd(II) with aryltrifluoroborate salts in the first step. The electrophilic palladation first occurs preferentially at the C3-position of indolizine, and the subsequent deprotonation leads to the formation of intermediate B with the assistance of KOAc. Reductive elimination follows to produce the desired product, and Pd(0) species are generated, which are reoxidized to Pd(II) species by Ag(I) to complete the catalytic cycle.

Direct alkynylation of indolizines with phenylpropiolic acid

Arylacetylenes are among the most fundamental and important π-conjugated systems in the various fields of organic chemistry. A powerful and reliable approach to these molecules is the Sonogashira coupling reaction. On the other hand, the metal-catalyzed direct alkynylation of arene C–H bonds with alkynyl halides has recently been receiving much attention as a complementary process to Sonogashira coupling. The pioneering work in this field was performed by Gevorgyan and co-workers[11] in 2007, who reported indolizines' alkynylation applying alkynyl halides as electrophiles.

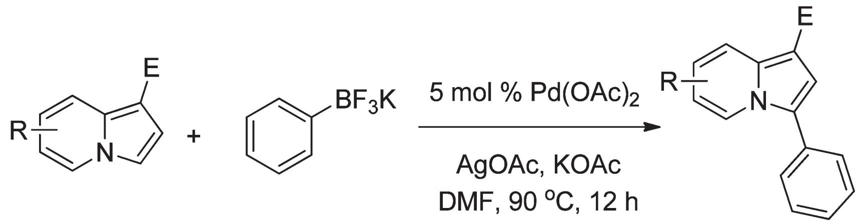
Carboxylic acids have been considered candidates for the coupling partner in transition metal catalyzed coupling reactions due to their environmental friendliness as leaving groups.[12] Several groups have employed alkynyl carboxylic acids as the coupling substrates in a variety of coupling reactions.[13] The direct alkynylation of heterocycles with phenylpropiolic acids would be an attractive approach in which the substrates can be easily prepared from the corresponding aldehydes. It offers a novel method to obtain alkynylation of heterocycles using aldehydes as precursors. Furthermore, phenylpropiolic acids are more accessible and cheaper than alkynyl bromides deriving from related alkynes. At the outset of our studies, there was little literature precedent for the direct C–H functionalization of (hetero)aromatics with phenylpropiolic acids. Here, we provide a new approach for straightforward and efficient access to diverse alkynyl heterocycles conceptually *via* decarboxylative couplings.

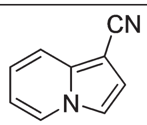
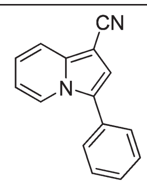
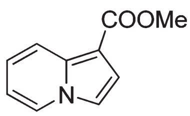
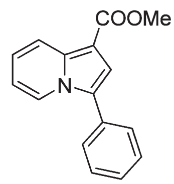
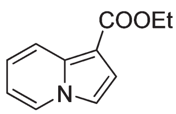
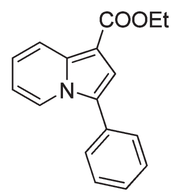
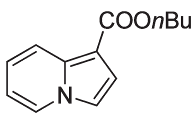
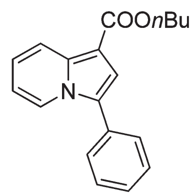
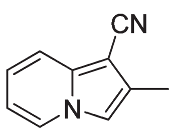
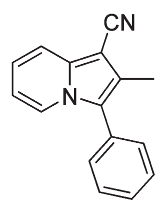
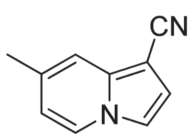
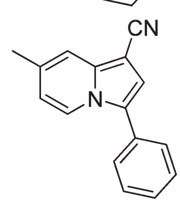
Initially, we optimized the reaction conditions using 3-phenylpropiolic acid and indolizine-1-carbonitrile as model substrates in DMSO with Ag_2CO_3 and $Pd(OAc)_2$ at 80 °C for 12 h under a N_2 atmosphere. Only 37% yield of desired product was isolated (Table 4, entry 1). When other solvents were introduced, mixed solvents gave increasing yields (Table 4, entries 2–5). The use of DMSO–1,4-dioxane, which performed the best, afforded the desired product in a yield of 83% (Table 4, entry 6). The oxidant also played an important role in the procedure; many silver salts such as AgOAc, Ag_2O and AgOTf also presented high activity (Table 4, entries 7–10). During the screening of catalysts, we found that the palladium sources had a dramatic effect on the reaction. Among the Pd species tested, $PdCl_2(PPh_3)_2$, $PdCl_2(CH_3CN)_2$, $Pd_2(dba)_3$ and $PdCl_2$ were not successful, and $Pd(TFA)_2$ was ineffective for this transformation (Table 4, entries 11–15).

We next tested a series of indolizines, which reacted with 3-arylpropiolic acid in moderate to good yields (Table 5). Methyl indolizine-1-carboxylate, ethyl indolizine-1-carboxylate, and *n*-butyl indolizine-1-carboxylate are compatible with the reaction conditions (Table 5, entries 2–4). 7-Methyl-indolizine-1-carbonitrile is a good substrate for the reaction to give desired products in 76% yield (Table 5, entry 5). The catalytic system could tolerate many functional groups, such as OMe and Cl. Electron-withdrawing or electron-donating groups on the aryl propiolic acids didn't show significant regularities (Table 5, entries 6–8).

The reaction mechanism is not clear currently. We propose that the transformation proceeds through direct Pd-catalyzed C–H alkynylation of electron-rich heterocycles operating *via* an electrophilic substitution pathway, analogous to the one previously postulated for the Pd(II)-catalyzed C-3 arylation of indolizines with aryltrifluoroborate salts.[11] The Ag(I)-catalyzed decarboxylation of phenylpropiolic acid forms alkynylsilver(0) intermediate A by releasing CO_2 (Scheme 2, cycle 1). These processes are initiated by transmetallation of alkynylsilver(0) intermediate A with Pd(II) species to form alkynylpalladium(II) intermediate B, followed by electrophilic attack of the generated Pd(II) species B to indolizine groups to form intermediate C.

Table 3 The reaction of phenyltrifluoroborate salt with various indolizines[a]



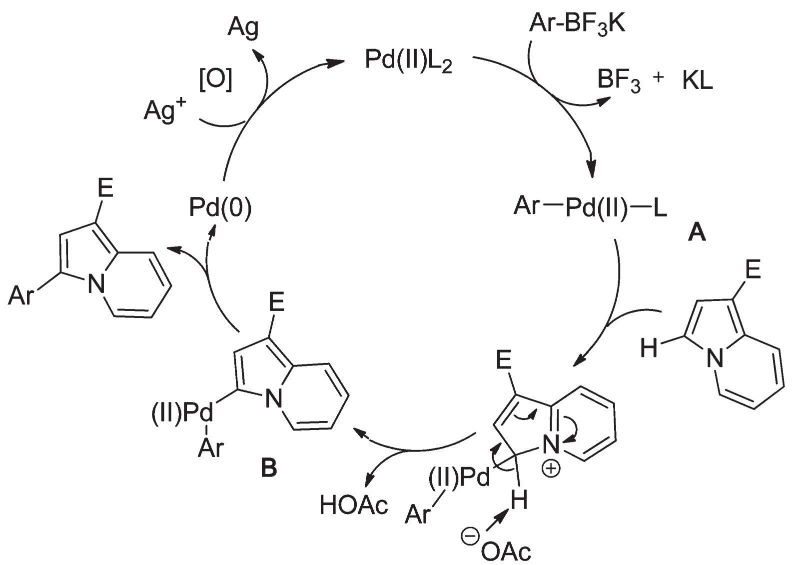
Entry	Indolizines	Products	Yield[b] %
1			93
2			85
3			86
4			84
5			88
6			73

[a] Reaction conditions: indolizines (0.3 mmol), potassium aryltrifluoroborate salts (0.3 mmol), $Pd(OAc)_2$ (0.015 mmol), AgOAc (0.3 mmol), KOAc (0.3 mmol), DMF (2 mL), 90 °C, 12 h, N_2. [b] Isolated yields of arylation.

Carbonate, which was derived from Ag_2CO_3, played the role of deprotonation in this stage. Reductive elimination of the latter furnishes alkynylpalladium intermediate C which releases desired product and Pd(0) species that are regenerated and oxidized to Pd(II) to complete the catalytic cycle (Scheme 2, cycle 2).

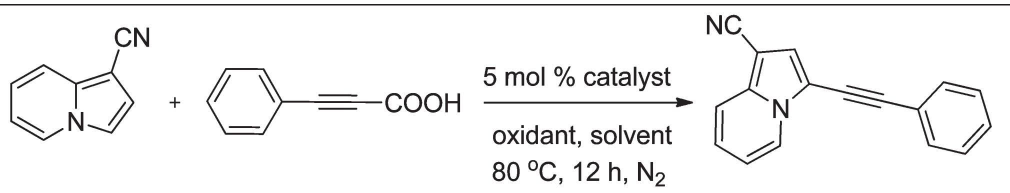
Conclusion

In conclusion, we report here our results concerning the systematic study of indolizines' C-3 functionalization involving C–H activation afford a diversity of C-3 substitution *via* arylation and



Scheme 1 The arylation mechanism proposed.

Table 4 Optimization of reaction conditions for alkynylation[a]



Entry	Catalyst	Oxidant	Solvent	Yield[b] %
1	$Pd(OAc)_2$	Ag_2CO_3	DMSO	37
2	$Pd(OAc)_2$	Ag_2CO_3	DMSO–*t*-BuOH	45
3	$Pd(OAc)_2$	Ag_2CO_3	DMSO–*i*-PivOH	57
4	$Pd(OAc)_2$	Ag_2CO_3	DMSO–DMF	33
5	$Pd(OAc)_2$	Ag_2CO_3	DMSO–THF	70
6	$Pd(OAc)_2$	Ag_2CO_3	DMSO–1,4-dioxane	83
7	$Pd(OAc)_2$	AgOAc	DMSO–1,4-dioxane	80
8	$Pd(OAc)_2$	Ag_2O	DMSO–1,4-dioxane	76
9	$Pd(OAc)_2$	AgTFA	DMSO–1,4-dioxane	56
10	$Pd(OAc)_2$	AgOTf	DMSO–1,4-dioxane	77
11	$PdCl_2(PPh_3)_2$	Ag_2CO_3	DMSO–1,4-dioxane	64
12	$PdCl_2(CH_3CN)_2$	Ag_2CO_3	DMSO–1,4-dioxane	66
13	$Pd(TFA)_2$	Ag_2CO_3	DMSO–1,4-dioxane	41
14	$PdCl_2$	Ag_2CO_3	DMSO–1,4-dioxane	79
15	$Pd_2(dba)_3$	Ag_2CO_3	DMSO–1,4-dioxane	70

[a] Reaction conditions: indolizine-1-carbonitrile (0.3 mmol), 3-phenylpropiolic acid (0.3 mmol), catalyst (0.015 mmol), oxidant (0.3 mmol), solvent (2 mL, v/v = 1 : 1), 80 °C, 12 h, N_2. [b] Isolated yields of alkynylation.

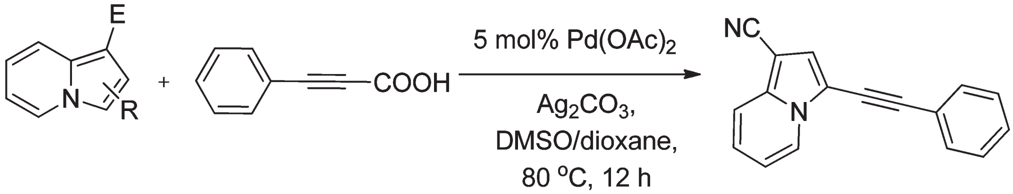
alkynylation. We discovered a well-precedented palladium-catalyzed regioselective direct C-3 arylation reaction with phenyltrifluoroborate salts. The mild reaction conditions enabled these transformations to tolerate different functional groups very well. Our studies also resulted in the direct alkynylation of indolizines with phenylpropiolic acid which can be used as a substitute for alkynyl halides *via* decarboxylative couplings. Undoubtedly, as part of the continuing exploration of new chemistry of the indolizine core, these reactions have great prospects for application in organic syntheses and industrial processes.

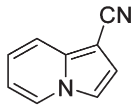
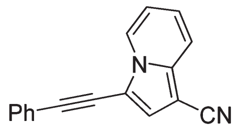
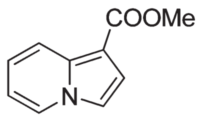
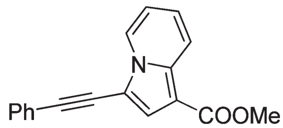
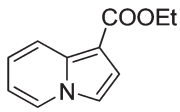
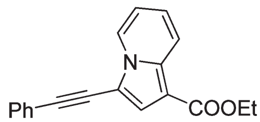
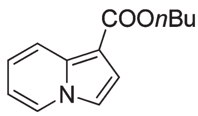
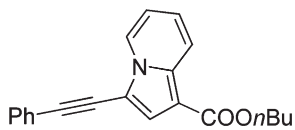
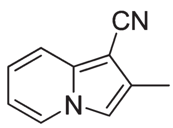
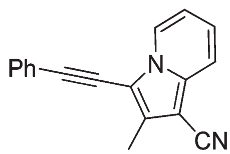
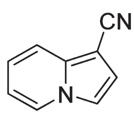
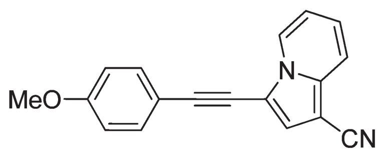
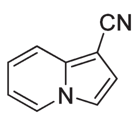
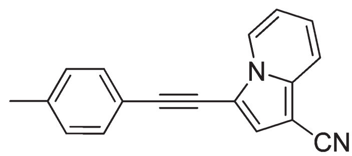
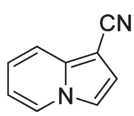
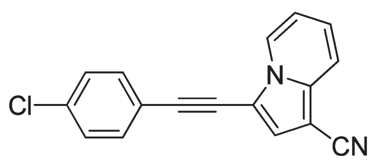
Experimental section

Preparation of C-3 arylation indolizines

A mixture of indolizines (0.3 mmol), potassium phenyltrifluoroborate salts (0.3 mmol), $Pd(OAc)_2$ (3 mg, 5 mol%), AgOAc (50 mg, 0.3 mmol), KOAc (59 mg, 0.6 mmol) in DMF (2 mL) was stirred at 90 °C under N_2 for 12 h. Afterward, the mixture was cooled to room temperature and filtered through a pad of celite. The crude product was

Table 5 The reaction of phenylpropiolic acid with various indolizines[a]

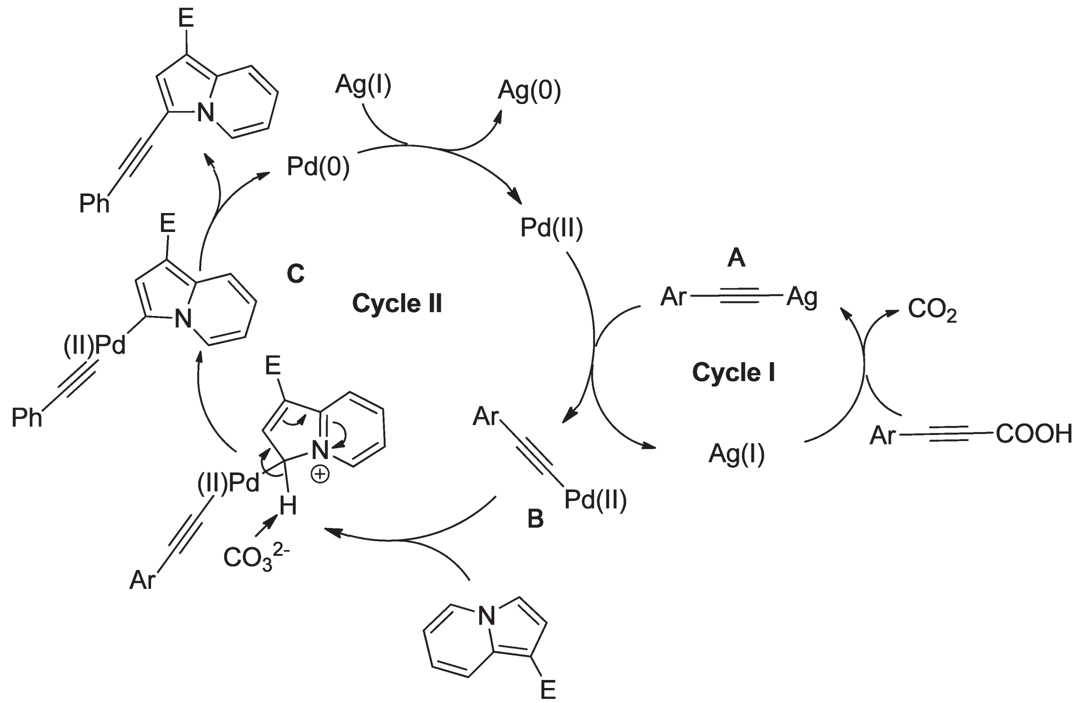


Entry	Indolizines	Products	Yield[b] %
1			81
2			79
3			75
4			78
5			76
6			81[c]
7			83[d]
8			77[e]

[a] Reaction conditions: indolizines (0.3 mmol), 3-phenylpropiolic acid (0.3 mmol), $Pd(OAc)_2$ (0.015 mmol), Ag_2CO_3 (0.3 mmol), DMSO–1,4-dioxane (1 : 1, 2 mL), 80 °C, 12 h, N_2. [b] Isolated yields of alkynylation. [c] Using 3-(4-methoxyphenyl)propiolic acid as alkynyl reagent. [d] Using 3-(*p*-tolyl)propiolic acid as alkynyl reagent. [e] Using 3-(4-chlorophenyl)propiolic acid as alkynyl reagent.

dissolved in Et_2O (20 mL), washed with water (2 × 10 mL) and brine (10 mL), then dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was subjected to flash column chromatography to obtain the desired product.

3-(4-Methoxyphenyl)indolizine-1-carbonitrile (T 2-1). White solid. m.p. 241–242 °C. ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 8.19 (d, J = 6.8 Hz, 1 H), 7.67 (d, J = 8.4 Hz, 1 H), 7.41 (d, J = 8.4 Hz, 2 H), 7.02–7.08 (m, 3 H), 6.98 (s, 1 H), 6.72 (t, J = 7.2 Hz, 1 H), 3.88 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$)



Scheme 2 The alkynylation mechanism proposed.

δ 159.8, 138.2, 130.2, 126.8, 123.7, 122.4, 122.0, 118.1, 115.6, 114.7, 112.9, 81.8, 55.4. HRMS (EI) Calcd for $C_{16}H_{12}N_2O$ (M^+) 248.0950, Found 248.0957. Elem. Anal.: C, 77.40; H, 4.87; N, 11.29; O, 6.44.

3-(4-(Methylthio)phenyl)indolizine-1-carbonitrile (T 2-2). Yellow solid. m.p. 250–252 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) 8.25 (d, *J* = 7.2 Hz, 1 H), 7.71 (t, *J* = 9.6 Hz, 1 H), 7.38–7.45 (m, 4 H), 7.09 (t, *J* = 7.6 Hz, 1 H), 7.04 (s, 1 H), 6.76 (t, *J* = 6.8 Hz, 1 H), 2.56 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 139.6, 138.4, 129.0, 126.8, 126.6, 126.5, 123.7, 122.3, 118.2, 116.7, 116.1, 113.1, 82.2, 15.5. HRMS (EI) Calcd for $C_{16}H_{12}N_2S$ (M^+) 264.0721, Found 264.0725. Elem. Anal.: C, 72.70; H, 4.58; N, 10.60; S, 12.12.

3-(4-*tert*-Butylphenyl)indolizine-1-carbonitrile (T 2-3). White solid. m.p. 236–238 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) *δ* 8.29 (d, *J* = 7.6 Hz, 1 H), 7.68 (d, *J* = 8.8 Hz, 1 H), 7.54 (d, *J* = 8.0 Hz, 2 H), 7.44 (d, *J* = 8.0 Hz, 2 H), 7.06 (t, *J* = 7.6 Hz, 1 H), 7.02 (s, 1 H), 6.72 (t, *J* = 6.8 Hz, 1 H), 1.39 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 151.8, 138.3, 130.6, 129.1, 128.4, 127.2, 127.0, 126.2, 125.4, 123.9, 122.2, 118.1, 116.0, 113.0, 82.0, 34.8, 31.3. HRMS (ESI) Calcd for $C_{19}H_{18}N_2$ (M^+) 274.1470, Found 274.1479. Elem. Anal.: C, 83.18; H, 6.61; N, 10.21.

3-*p*-Tolylindolizine-1-carbonitrile (T 2-4). White solid. m.p. 232–233 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) *δ* 8.24 (d, *J* = 6.8 Hz, 1 H), 7.67 (d, *J* = 9.2 Hz, 1 H), 7.38 (d, *J* = 8.0 Hz, 2 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 7.06 (t, *J* = 8.0 Hz, 1 H), 7.00 (s, 1 H), 6.72 (t, *J* = 6.8 Hz, 1 H), 2.43 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 138.6, 138.3, 129.9, 128.6, 127.2, 127.0, 123.8, 122.1, 118.1, 117.0, 115.9, 113.0, 82.0, 21.3. HRMS (EI) Calcd for $C_{16}H_{12}N_2$ (M^+) 232.1000, Found 232.1001. Elem. Anal.: C, 82.73; H, 5.21; N, 12.06.

3-(4-Chlorophenyl)indolizine-1-carbonitrile (T 2-5). Light yellow solid. m.p. 244–246 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) *δ* 8.17 (d, *J* = 7.2 Hz, 1 H), 7.65 (d, *J* = 8.8 Hz, 1 H), 7.40–7.46 (m, 4 H), 7.06 (t, *J* = 8.0 Hz, 1 H), 7.00 (s, 1 H), 6.73 (t, *J* = 6.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 138.6, 138.3, 129.9, 128.6, 127.2, 127.0, 123.8, 122.1, 118.1, 117.0, 115.9, 113.0, 82.0. HRMS (EI) Calcd for $C_{15}H_9N_2Cl$ (M^+) 252.0454, Found 252.0452. Elem. Anal.: C, 71.29; H, 3.59; Cl, 14.03, N, 11.09.

3-(4-(Trifluoromethoxy)phenyl)indolizine-1-carbonitrile (T 2-6). White solid. m.p. 276–277 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) *δ* 8.26 (d, *J* = 6.8 Hz, 1 H), 7.69 (d, *J* = 9.6 Hz, 1 H), 7.55 (t, *J* = 8.4 Hz, 1 H), 7.46 (d, *J* = 7.6 Hz, 1 H), 7.37 (s, 1 H), 7.28 (t, *J* = 8.8 Hz, 1 H), 7.12 (t, *J* = 8.0 Hz, 1 H), 7.08 (s, 1 H), 7.80 (t, *J* = 6.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 149.81, 149.79, 138.7, 132.1, 131.8, 126.8, 125.2, 123.4, 122.8, 120.9, 120.8, 118.3, 116.9, 113.6, 82.7. HRMS (EI) Calcd for $C_{16}H_9N_2OF_3$ (M^+) 302.0667, Found 302.0664. Elem. Anal.: C, 63.58; H, 3.00; F, 18.86, N, 9.27, O, 5.29.

3-(4-(Trifluoromethyl)phenyl)indolizine-1-carbonitrile (T 2-7). White solid. m.p. 269–270 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) *δ* 8.29 (d, *J* = 6.8 Hz, 1 H), 7.77 (d, *J* = 8.4 Hz, 2 H), 7.68 (d, *J* = 8.8 Hz, 1 H), 7.65 (d, *J* = 8.4 Hz, 2 H), 7.13 (t, *J* = 6.4 Hz, 1 H), 7.10 (s, 1 H), 6.81 (t, *J* = 6.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 138.8, 133.8, 130.3 (q, *J* = 32 Hz), 128.6, 126.3 (q, *J* = 4.0 Hz), 125.3, 125.2, 123.5, 122.9, 122.5, 118.4, 117.1, 116.4, 113.7, 82.9. HRMS (EI) Calcd for $C_{16}H_9N_2F_3$ (M^+) 286.0718, Found 286.0713. Elem. Anal.: C, 67.13; H, 3.17; F, 19.91, N, 9.79.

3-*m*-Tolylindolizine-1-carbonitrile (T 2-8). White solid. m.p. 239–241 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) *δ* 8.34 (d, *J* =

7.2 Hz, 1 H), 7.74 (d, J = 9.2 Hz, 1 H), 7.46 (d, J = 7.6 Hz, 1 H), 7.31–7.38 (m, 3 H), 7.14 (t, J = 8.0 Hz, 1 H), 7.09 (s, 1 H), 6.80 (d, J = 6.8 Hz, 1 H), 2.50 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 138.3, 130.1, 129.4, 129.3, 129.1, 127.1, 125.6, 123.8, 118.1, 116.1, 113.0, 82.1, 21.4. HRMS (EI) Calcd for $C_{16}H_{12}N_2$ (M^+) 232.1000, Found 232.0998. Elem. Anal.: C, 82.73; H, 5.21; N, 12.06.

3-(3-Chlorophenyl)indolizine-1-carbonitrile (T 2-9). Yellow solid. m.p. 245–246 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.21 (d, J = 7.2 Hz, 1 H), 7.64 (d, J = 8.8 Hz, 1 H), 7.15 (s, 1 H), 7.06 (t, J = 8.0 Hz, 1 H), 7.01 (s, 1 H), 6.74 (t, J = 7.2 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 135.2, 131.9, 130.5, 128.6, 128.5, 126.6, 125.4, 123.5, 122.7, 118.3, 116.7, 113.5, 82.6. HRMS (EI) Calcd for $C_{15}H_9N_2Cl$ (M^+) 252.0454, Found 252.0448. Elem. Anal.: C, 71.29; H, 3.59; Cl, 14.03, N, 11.09.

3-(3-Fluorophenyl)indolizine-1-carbonitrile (T 2-10). White solid. m.p. 261–262 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.35 (d, J = 6.8 Hz, 1 H), 7.75 (d, J = 9.2 Hz, 1 H), 7.52–7.58 (m, 1 H), 7.37 (d, J = 7.6 Hz, 1 H), 7.28 (d, J = 9.6 Hz, 1 H), 7.15–7.22 (m, 2 H), 7.12 (s, 1 H), 6.85 (t, J = 6.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 161.9, 138.6, 132.2 (d, J = 7.7 Hz), 130.9 (d, J = 8.0 Hz), 125.6, 124.2 (d, J = 3.2 Hz), 123.6, 122.7, 118.3, 116.7, 115.6 (d, J = 8.9 Hz), 115.3 (d, J = 9.0 Hz), 113.4, 82.5. HRMS (EI) Calcd for $C_{15}H_9N_2F$ (M^+) 236.0750, Found 236.0745. Elem. Anal.: C, 76.26; H, 3.84; Cl, 8.04, N, 11.86.

3-(3-Formylphenyl)indolizine-1-carbonitrile (T 2-11). White solid. m.p. 183–186 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 10.04 (s, 1 H), 8.01 (s, 1 H), 7.95 (d, J = 6.8 Hz, 1 H), 7.82–7.85 (m, 3 H), 7.26–7.29 (m, 2 H), 7.52–7.61 (m, 2 H), 7.18 (d, J = 6.8 Hz, 1 H), 6.93–6.99 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 140.6, 137.0, 132.9, 129.7, 129.4, 127.9, 126.4, 122.3, 117.8, 116.8, 113.9, 112.9, 82.8. HRMS (EI) Calcd for $C_{16}H_{10}N_2O$ (M^+) 246.0793, Found 246.0796. Elem. Anal.: C, 78.03; H, 4.09; N, 11.38; O, 6.50.

3-(3-(Trifluoromethyl)phenyl)indolizine-1-carbonitrile (T 2-12). White solid. m.p. 262–264 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.22 (d, J = 6.8 Hz, 1 H), 7.72 (s, 1 H), 7.63–7.72 (m, 4 H), 7.13 (t, J = 6.4 Hz, 1 H), 7.10 (s, 1 H), 6.80 (t, J = 6.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 131.8, 131.0, 129.9, 125.3 (q, J = 4.6 Hz), 123.3, 122.8, 118.4, 117.0, 116.5, 113.7, 82.8. HRMS (EI) Calcd for $C_{16}H_9N_2F_3$ (M^+) 286.0718, Found 286.0721. Elem. Anal.: C, 67.13; H, 3.17; F, 19.91, N, 9.79.

3-*o*-Tolylindolizine-1-carbonitrile (T 2-13). White solid. m.p. 209–210 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.77 (d, J = 9.2 Hz, 1 H), 7.70 (d, J = 6.8 Hz, 1 H), 7.37–7.50 (m, 4 H), 7.15 (t, J = 8.0 Hz, 1 H), 7.05 (s, 1 H), 6.78 (t, J = 6.8 Hz, 1 H), 2.17 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 137.4, 131.3, 130.7, 129.5, 129.2, 126.3, 125.9, 124.0, 122.0, 118.0, 116.5, 112.9, 81.4, 19.5. HRMS (EI) Calcd for $C_{16}H_{12}N_2$ (M^+) 232.1000, Found 232.0999. Elem. Anal.: C, 82.73; H, 5.21; N, 12.06.

3-(2-Bromophenyl)indolizine-1-carbonitrile (T 2-14). Yellow solid. m.p. 278–279 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.77 (d, J = 9.2 Hz, 1 H), 7.70 (d, J = 6.8 Hz, 1 H), 7.37–7.50 (m, 4 H), 7.15 (t, J = 8.0 Hz, 1 H), 7.05 (s, 1 H), 6.78 (t, J = 6.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 137.4, 131.3, 130.7, 129.5, 129.2, 126.3, 125.9, 124.0, 122.0, 118.0, 116.5, 112.9, 120.0, 81.4. HRMS (EI) Calcd for $C_{15}H_9N_2Br$ (M^+) 295.9949, Found 295.9944. Elem. Anal.: C, 60.63; H, 3.05; Br, 26.89; N, 9.43.

3-(Naphthalen-1-yl)indolizine-1-carbonitrile (T 2-15). White solid. m.p. 303–305 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.03–8.09 (m, 2 H), 7.83 (d, J = 8.8 Hz, 1 H), 7.60–7.69 (m, 4 H), 7.45–7.53 (m, 2 H), 7.24 (s, 1 H), 7.18 (t, J = 8.0 Hz, 1 H), 6.71 (t, J = 6.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 133.8, 132.1, 129.9, 129.5, 128.8, 127.3, 127.1, 126.5, 125.6, 125.0, 124.8, 124.5, 122.3, 118.0, 117.7, 112.8, 81.9. HRMS (ESI) Calcd for $C_{19}H_{12}N_2$ (M^+) 268.1000, Found 268.0992. Elem. Anal.: C, 85.05; H, 4.51; N, 10.44.

3-(Naphthalen-2-yl)indolizine-1-carbonitrile (T 2-16). White solid. m.p. 311–312 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.35 (d, J = 7.2 Hz, 1 H), 7.95–7.98 (m, 2 H), 7.86–7.91 (m, 2 H), 7.71 (d, J = 8.4 Hz, 1 H), 7.54–7.59 (m, 3 H), 7.12 (s, 1 H), 7.10 (t, J = 8.0 Hz, 1 H), 6.75 (t, J = 6.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 133.5, 133.0, 129.0, 128.0, 127.8, 127.7, 126.9, 126.8, 126.0, 123.7, 122.5, 118.2, 116.6, 113.2, 82.4. HRMS (ESI) Calcd for $C_{19}H_{12}N_2$ (M^+) 268.1000, Found 268.1002. Elem. Anal.: C, 85.05; H, 4.51; N, 10.44.

3-Phenylindolizine-1-carbonitrile (T 3-1). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.30 (d, J = 7.2 Hz, 1 H), 7.71 (d, J = 8.8 Hz, 1 H), 7.53–7.55 (m, 4 H), 7.46–7.49 (m, 1 H), 7.10 (t, J = 8.0 Hz, 1 H), 7.06 (s, 1 H), 6.77 (t, J = 6.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 137.7, 131.4, 130.7, 129.5, 129.2, 126.3, 125.9, 124.0, 122.0, 117.9, 116.5, 112.8, 81.4. HRMS (EI) Calcd for $C_{15}H_{10}N_2$ (M^+) 218.0844, Found 218.0839.

Methyl 3-phenylindolizine-1-carboxylate (T 3-2). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.27 (t, J = 8.8 Hz, 2 H), 7.50 (m, 4 H), 7.39 (t, J = 7.2 Hz, 1 H), 7.28 (s, 1 H), 7.06 (t, J = 8.0 Hz, 1 H), 6.69 (t, J = 7.6 Hz, 1 H), 3.91 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 136.4, 131.2, 129.1, 128.6, 128.0, 126.4, 123.3, 122.3, 120.7, 112.6, 103.9, 50.9. HRMS (EI) Calcd for $C_{16}H_{13}NO_2$ (M^+) 251.0946, Found 251.0951.

Ethyl 3-(1-*p*-tolylvinyl)indolizine-1-carboxylate (T 3-3). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.28 (t, J = 7.6 Hz, 2 H), 7.54 (d, J = 8.0 Hz, 2 H), 7.49 (t, J = 7.6 Hz, 2 H), 7.39 (t, J = 7.2 Hz, 1 H), 7.31 (s, 1 H), 7.06 (d, J = 7.6 Hz, 1 H), 6.69 (t, J = 6.8 Hz, 1 H), 4.40 (m, 2 H), 1.42 (t, J = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 136.3, 131.2, 129.0, 128.6, 128.0, 126.4, 123.3, 122.2, 120.1, 116.0, 112.5, 104.2, 59.5, 14.6. HRMS (EI) Calcd for $C_{17}H_{15}NO_2$ (M^+) 265.1103, Found 265.1104.

Butyl 3-phenylindolizine-1-carboxylate (T 3-4). Brown oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.28 (t, J = 7.2 Hz, 2 H), 7.55 (d, J = 8.0 Hz, 2 H), 7.50 (t, J = 7.6 Hz, 2 H), 7.40 (t, J = 7.2 Hz, 1 H), 7.32 (s, 1 H), 7.07 (m, 1 H), 6.70 (t, J = 7.6 Hz, 1 H), 4.36 (t, J = 6.8 Hz, 2 H), 1.80 (m, 2 H), 1.53 (m, 2 H), 1.01 (t, J = 7.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 136.3, 131.2, 129.1, 128.6, 128.0, 126.4, 123.3, 122.2, 120.1, 116.1, 114.9, 112.6, 104.3, 63.5, 31.1, 19.4, 13.8. HRMS (EI) Calcd for $C_{19}H_{19}NO_2$ (M^+) 293.1416, Found 293.1424. Elem. Anal.: C, 77.79; H, 6.53; N, 4.77, O, 10.91.

2-Methyl-3-phenylindolizine-1-carbonitrile (T 3-5). White solid. m.p. 253–254 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.03 (d, J = 7.2 Hz, 1 H), 7.62 (d, J = 9.2 Hz, 1 H), 7.56 (t, J = 7.6 Hz, 2 H), 7.48 (t, J = 8.0 Hz, 1 H), 7.43 (d, J = 8.0 Hz, 2 H), 7.05 (t, J = 8.0 Hz, 1 H), 6.67 (t, J = 6.8 Hz, 1 H), 2.39 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 130.1, 129.5, 129.2, 128.6, 126.1, 123.8, 122.1, 117.3, 116.8, 112.5, 83.4, 10.9. HRMS (EI) Calcd for $C_{16}H_{12}N_2$ (M^+) 232.1000, Found 232.0998. Elem. Anal.: C, 82.73; H, 5.21; N, 12.06.

7-Methyl-3-phenylindolizine-1-carbonitrile (T 3-6). White solid. m.p. 237–238 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.17 (d, J = 7.2 Hz, 1 H), 7.85 (d, J = 7.2 Hz, 1 H), 7.22 (d, J = 8.0 Hz, 2 H), 7.47–7.52 (m, 4 H), 7.41–7.45 (m, 2 H), 6.97 (s, 1 H), 6.57 (d, J = 7.2 Hz, 1 H), 2.39 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 133.4, 130.4, 129.2, 128.5, 128.3, 127.1, 126.2, 123.2, 116.5, 115.9, 115.7, 80.5, 21.1. HRMS (EI) Calcd for $C_{16}H_{12}N_2$ (M^+) 232.1000, Found 232.0996. Elem. Anal.: C, 82.73; H, 5.21; N, 12.06.

Preparation of C-3 alkynylation indolizines

A mixture of indolizines (0.3 mmol), 3-phenylpropiolic acid (0.3 mmol), $Pd(OAc)_2$ (3 mg, 5 mol%) and Ag_2CO_3 (83 mg, 0.3 mmol) in DMSO–1,4-dioxane (1 : 1, 2 mL) was stirred at 80 °C under N_2 for 12 h. Afterward, the mixture was cooled to room temperature and filtered through a pad of celite. The crude product was dissolved in Et_2O (10 mL), washed with water (2 × 10 mL) and brine (10 mL), then dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was subjected to flash column chromatography to obtain the desired product.

3-(Phenylethynyl)indolizine-1-carbonitrile (T 5-1). White solid. m.p. 276–278 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.37 (d, J = 6.8 Hz, 1 H), 7.67 (d, J = 8.8 Hz, 1 H), 7.56–7.58 (m, 2 H), 7.38–7.39 (m, 3 H), 7.28 (s, 1 H), 7.19 (t, J = 7.6 Hz, 1 H), 6.92 (t, J = 6.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 131.4, 128.9, 128.5, 125.7, 124.0, 122.1, 121.4, 117.9, 113.8, 97.2, 82.3. HRMS (EI) Calcd for $C_{17}H_{10}N_2$ (M^+) 242.0844, Found 242.0851. Elem. Anal.: C, 84.28; H, 4.16; N, 11.56.

Methyl 3-(phenylethynyl)indolizine-1-carboxylate (T 5-2). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.36 (d, J = 6.8 Hz, 1 H), 8.23 (d, J = 9.2 Hz, 1 H), 7.56–7.58 (m, 2 H), 7.52 (s, 1 H), 7.37–7.39 (m, 3 H), 7.17 (t, J = 8.0 Hz, 1 H), 6.88 (t, J = 6.8 Hz, 1 H), 3.91 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 136.3, 131.2, 128.5, 125.4, 123.8, 122.7, 121.1, 119.8, 117.9, 113.3, 108.2, 104.0, 97.0, 78.9, 51.1. HRMS (EI) Calcd for $C_{18}H_{13}NO_2$ (M^+) 275.0946, Found 275.0941.

Ethyl 3-(phenylethynyl)indolizine-1-carboxylate (T 5-3). White solid. m.p. 247–248 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.37 (d, J = 6.8 Hz, 1 H), 8.24 (d, J = 8.8 Hz, 1 H), 7.56–7.58 (m, 2 H), 7.55 (s, 1 H), 7.36–7.39 (m, 3 H), 7.17 (t, J = 8.0 Hz, 1 H), 6.88 (t, J = 7.2 Hz, 1 H), 4.36–4.41 (m, 2 H), 1.42 (t, J = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 136.2, 131.2, 128.5, 128.4, 125.3, 123.8, 122.7, 121.2, 119.8, 113.3, 108.1, 104.4, 97.0, 79.0, 59.7, 14.6. HRMS (EI) Calcd for $C_{19}H_{15}NO_2$ (M^+) 289.1103, Found 289.1106. Elem. Anal.: C, 78.87; H, 5.23; N, 4.84; O, 11.06.

Butyl 3-(phenylethynyl)indolizine-1-carboxylate (T 5-4). Brown solid. m.p. 260–262 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.36 (d, J = 6.8 Hz, 1 H), 8.23 (d, J = 9.6 Hz, 1 H), 7.55–7.58 (m, 2 H), 7.54 (s, 1 H), 7.36–7.38 (m, 3 H), 7.14–7.18 (m, 1 H), 6.87 (t, J = 7.6 Hz, 1 H), 4.33 (t, J = 6.4 Hz, 2 H), 1.74–1.79 (m, 2 H), 1.48–1.54 (m, 2 H), 1.00 (t, J = 7.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 136.2, 131.2, 128.5, 128.4, 125.3, 123.7, 122.7, 121.2, 119.8, 113.2, 108.1, 104.4, 97.0, 78.9, 63.6, 31.0, 19.4, 13.8. HRMS (EI) Calcd for $C_{21}H_{19}NO_2$ (M^+) 317.1416, Found 317.1422. Elem. Anal.: C, 79.47; H, 6.03; N, 4.41; O, 10.08.

2-Methyl-3-(phenylethynyl)indolizine-1-carbonitrile (T 5-5). White solid. m.p. 293–294 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.27 (d, J = 7.2 Hz, 1 H), 7.54–7.58 (m, 3 H), 7.39–7.40 (m, 3 H), 7.13 (t, J = 7.6 Hz, 1 H), 6.86 (t, J = 7.6 Hz, 1 H), 2.52 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 133.5, 131.2, 128.7, 128.5, 125.5, 123.8, 122.4, 117.1, 116.0, 113.3, 107.7, 99.6, 83.4, 77.3, 11.4. HRMS (EI) Calcd for $C_{18}H_{12}N_2$ (M^+) 256.1000, Found 256.1001. Elem. Anal.: C, 84.35; H, 4.72; N, 10.93.

3-((4-Methoxyphenyl)ethynyl)indolizine-1-carbonitrile (T 5-6). White solid. m.p. 296–297 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.18 (d, J = 6.8 Hz, 1 H), 7.67 (d, J = 8.4 Hz, 1 H), 7.42 (d, J = 8.8 Hz, 2 H), 7.02–7.07 (m, 3 H), 6.98 (s, 1 H), 6.71 (t, J = 7.2 Hz, 1 H), 3.87 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 138.2, 130.2, 126.8, 123.7, 122.4, 122.0, 118.1, 115.8, 114.6, 112.9, 104.0, 97.0, 81.8, 55.4. HRMS (EI) Calcd for $C_{18}H_{12}N_2O$ (M^+) 272.0950, Found 272.0952. Elem. Anal.: C, 79.39; H, 4.44; N, 10.29; O, 5.88.

3-(*p*-Tolylethynyl)indolizine-1-carbonitrile (T 5-7). White solid. m.p. 279–280 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.24 (d, J = 6.8 Hz, 1 H), 7.67 (d, J = 8.8 Hz, 1 H), 7.39 (d, J = 8.0 Hz, 2 H), 7.31 (d, J = 8.4 Hz, 2 H), 7.07 (t, J = 7.6 Hz, 1 H), 7.00 (s, 1 H), 6.73 (t, J = 6.8 Hz, 1 H), 2.43 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 138.2, 129.9, 128.6, 127.2, 127.0, 123.7, 122.2, 118.1, 117.0, 115.9, 112.9, 104.0, 96.9, 82.0, 21.3. HRMS (EI) Calcd for $C_{18}H_{12}N_2$ (M^+) 256.1000, Found 256.0999. Elem. Anal.: C, 84.35; H, 4.72; N, 10.93.

3-((4-Chlorophenyl)ethynyl)indolizine-1-carbonitrile (T 5-8). Yellow solid. m.p. 317–318 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.36 (d, J = 7.2 Hz, 1 H), 7.69 (d, J = 8.8 Hz, 1 H), 7.49 (d, J = 8.0 Hz, 2 H), 7.36 (d, J = 8.4 Hz, 2 H), 7.28 (s, 1 H), 7.21 (t, J = 8.0 Hz, 1 H), 6.95 (t, J = 6.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 134.9, 132.5, 128.9, 125.7, 124.1, 121.7, 120.6, 117.9, 115.9, 113.9, 108.5, 96.2, 82.5, 78.7. HRMS (EI) Calcd for $C_{17}H_9ClN_2$ (M^+) 276.0454, Found 276.0457. Elem. Anal.: C, 73.79; H, 3.28; Cl, 12.81, N, 10.12.

Acknowledgements

This study was supported by the Science Technology Department of Zhejiang Province (Grant # 2012R10014-15).

Notes and references

1 (*a*) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457–2483; (*b*) S. Kotha, K. Lahiri and D. Kashinath, *Tetrahedron*, 2002, **58**, 9633–9695; (*c*) K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem., Int. Ed.*, 2005, **44**, 4442–4489; (*d*) A. Zapf and M. Beller, *Chem. Commun.*, 2005, 431–440; (*e*) N. Miyaura, *Bull. Chem. Soc. Jpn.*, 2008, **81**, 1535–1553; (*f*) R. Martin and S. L. Buchwald, *Acc. Chem. Res.*, 2008, **41**, 1461–1473.

2 (*a*) B. M. Trost, *Science*, 1991, **254**, 1471–1477; (*b*) B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 259–281; (*c*) B. M. Trost, *Acc. Chem. Res.*, 2002, **35**, 695–705; (*d*) M. Eissen, R. Mazur, H. G. Quebbemann and K. H. Pennemann, *Helv. Chim. Acta*, 2004, **87**, 524–535.

3 For reviews, see: (*a*) A. E. Shilov and G. B. Shul'pin, *Chem. Rev.*, 1997, **97**, 2879–2932; (*b*) G. Dyker, *Angew. Chem., Int. Ed.*, 1999, **38**, 1699–1712; (*c*) Y. Guari, S. Sabo-Etienne and B. Chaudret, *Eur. J. Inorg. Chem.*, 1999, 1047–1055; (*d*) C. Jia, T. Kitamura and Y. Fujiwara, *Acc. Chem. Res.*, 2001, **34**, 633–639; (*e*) V. Ritleng, C. Sirlin and M. Pfeffer, *Chem. Rev.*, 2002, **102**, 1731–1769; (*f*) F. Kakiuchi and N. Chatani, *Adv. Synth. Catal.*, 2003, **345**, 1077–1101; (*g*) A. R. Dick and M. S. Sanford, *Tetrahedron*, 2006, **62**, 2439–2463; (*h*) C. I. Herrerías, X. Yao, Z. Li and C. J. Li, *Chem. Rev.*, 2007, **107**, 2546–2562; (*i*) L. C. Campeau, D. R. Stuart and K. Fagnou, *Aldrichimica Acta*, 2007, **40**, 35–41; (*j*) F. Kakiuchi, *Top. Organmet. Chem.*, 2008, **24**, 1–33; (*k*) B. J. Li, S. D. Yang and Z. J. Shi, *Synlett*, 2008, 949–957; (*l*) A. Mori and A. Sugie, *Bull. Chem. Soc. Jpn.*, 2008, **81**, 548–561; (*m*) J. Wencel-Delord, T. Dröge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740–4761.

4 Recent reviews: (*a*) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174–238; (*b*) T. Satoh and M. Miura, *Chem. Lett.*, 2007, **36**, 200–205; (*c*) G. P. McGlacken and L. M. Bateman, *Chem. Soc. Rev.*, 2009, **38**, 2447–2464; (*d*) I. V. Seregin and V. Gevorgyan, *Chem. Soc. Rev.*, 2007, **36**, 1173–1193; (*e*) Y. J. Park, J.-W. Park and C.-H. Jun, *Acc. Chem. Res.*, 2008, **41**, 222–234; (*f*) L. C. Lewis, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*, 2008, **41**, 1013–1025; (*g*) F. Kakiuchi and T. Kochi, *Synthesis*, 2008, 3013–3039; (*h*) O. Daugulis, H.-Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074–1086; (*i*) A. A. Kulkarni and O. Daugulis, *Synthesis*, 2009, 4087–4109; (*j*) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792–9826; (*k*) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Commun.*, 2010, **46**, 677–685; (*l*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147–1169.

5 (*a*) F. T. Swinbourne, J. Hunt and K. Klinkert, *Adv. Heterocycl. Chem.*, 1978, **23**, 103–170; (*b*) W. Flitsch, in *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katrizky and C. W. Rees, Pergamon, Oxford, 1984, vol. 4, p. 476; (*c*) J. P. Michael, *Nat. Prod. Rep.*, 1995, **12**, 535–552; (*d*) J. Mahon, L. K. Mehta, R. W. Middleton, J. Parrick and H. K. Rami, *J. Chem. Res.*, 1992, **5**(S), 362–363; (*e*) J. P. Michael, *Nat. Prod. Rep.*, 2002, **19**, 742–760.

6 (*a*) J. Bermudez, C. S. Fake, G. F. Joiner, K. A. Joiner, F. D. King, W. D. Miner and G. J. Sanger, *J. Med. Chem.*, 1990, **33**, 1924–1929; (*b*) S. Okada, K. Sawada, A. Kozo, S. Watarabe and H. Tanaka, *Brit. UK Pat. Appl.*, GB 2287706, 1995; S. Okada, K. Sawada, A. Kozo, S. Watarabe and H. Tanaka, *Chem. Abstr.*, 1995, **124**, 175847; (*c*) S. Hagishita, M. Yamada, K. Shirahase, T. Okada, Y. Murakami, Y. Ito, T. Matsuura, M. Wada, T. Kato, M. Ueno, Y. Chikazawa, K. Yamada, T. Ono, I. Teshirogi and M. Ohtani, *J. Med. Chem.*, 1996, **39**, 3636–3658; (*d*) O. B. Ostby, B. Dalhus, L.-L. Gundersen, F. Rise, A. Bast and G. R. M. M. Haenen, *Eur. J. Org. Chem.*, 2000, 3763–3770; (*e*) L. Halab, J. A. J. Becker, Z. Darula, D. Tourwe, B. L. Kieffer, F. Simonin and W. D. Lubell, *J. Med. Chem.*, 2002, **45**, 5353–5357; (*f*) W. H. Pearson and E. J. Hembre, *J. Org. Chem.*, 1996, **61**, 5546–5556.

7 (*a*) B. Liu, X. Qin, K. Li, X. Li, Q. Guo, J. Lan and J. You, *Chem.–Eur. J.*, 2010, **16**, 11836–11839; (*b*) D. Lapointe, T. Markiewicz, C. J. Whipp, A. Toderian and K. Fagnou, *J. Org. Chem.*, 2011, **76**, 749–759; (*c*) T. P. Pathak and M. S. Sigman, *Org. Lett.*, 2011, **13**, 2774–2777; (*d*) L. Huang, T. Niu, J. Wu and Y. Zhang, *J. Org. Chem.*, 2011, **76**, 1759–1766; (*e*) Y. Yang, L. Chen, Z. Zhang and Y. Zhang, *Org. Lett.*, 2011, **13**, 1342–1345; (*f*) Y. Yang, K. Cheng and Y. Zhang, *Org. Lett.*, 2009, **11**, 5606–5609.

8 C.-H. Park, V. Ryabova, I. V. Seregin, A. W. Sromek and V. Gevorgyan, *Org. Lett.*, 2004, **6**, 1159–1162.

9 J.-B. Xia and S.-L. You, *Org. Lett.*, 2009, **11**, 1187–1190.

10 P. Xi, F. Yang, S. Qin, D. Zhao, J. Lan, G. Gao, C. Hu and J. You, *J. Am. Chem. Soc.*, 2010, **132**, 1822–1824.

11 I. V. Seregin, V. Ryabova and V. Gevorgyan, *J. Am. Chem. Soc.*, 2007, **129**, 7742–7743.

12 N. Rodríguez and L. J. Goossen, *Chem. Soc. Rev.*, 2011, **40**, 5030–5048.

13 (*a*) J. Park, E. Park, A. Kim, S.-A. Park, Y. Lee, K.-W. Chi, Y. H. Jung and I. S. Kim, *J. Org. Chem.*, 2011, **76**, 2214–2219; (*b*) A. Park, K. Park, Y. Kim and S. Lee, *Org. Lett.*, 2011, **13**, 944–947; (*c*) H. Zhao, Y. Wei, J. Xu, J. Kan, W. Su and M. Hong, *J. Org. Chem.*, 2011, **76**, 882–893; (*d*) C. Feng and T.-P. Loh, *Chem. Commun.*, 2010, **46**, 4779–4781; (*e*) W.-W. Zhang, X.-G. Zhang and J.-H. Li, *J. Org. Chem.*, 2010, **75**, 5259–5264; (*f*) H. Kim and P. H. Lee, *Adv. Synth. Catal.*, 2009, **351**, 2827–2832; (*g*) J. Moon, M. Jang and S. Lee, *J. Org. Chem.*, 2009, **74**, 1403–1406; (*h*) D. K. Rayabarapu and J. A. Tunge, *J. Am. Chem. Soc.*, 2005, **127**, 13510–13511.