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Copper-Catalyzed Oxidative Coupling–Annulation: One-Pot Synthesis of Indolizines from 2-Alkylazaarenes with Alkenes

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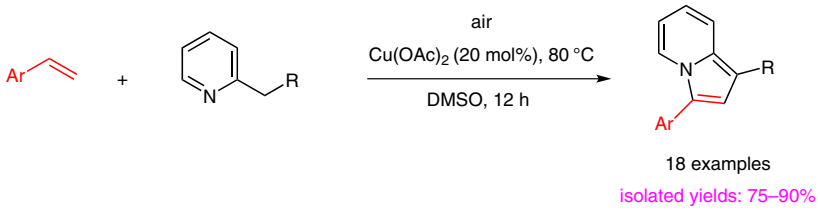

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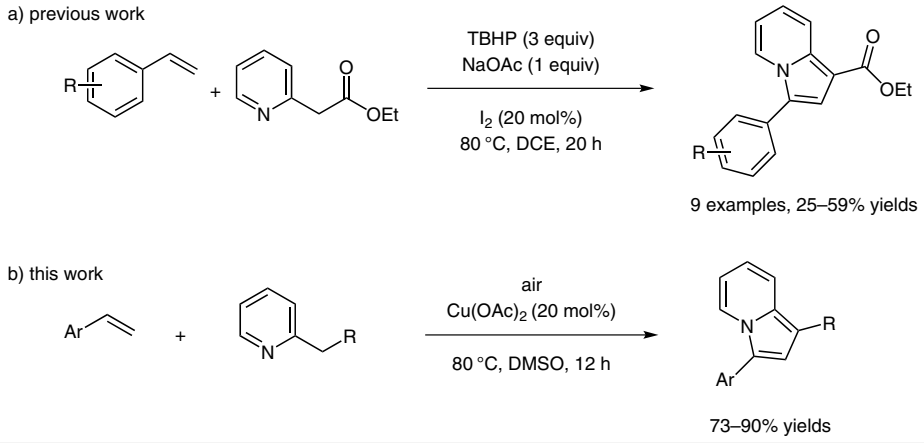
Abstract A novel copper-catalyzed highly selective oxidative coupling–annulation of 2-alkylazaarenes with terminal alkenes was achieved. This process provides a simple, efficient, and atom-economic way to construct indolizines in good yields.

Key words indolizines, alkenes, 2-alkylazaarenes, oxidative coupling, annulation

Indolizines are among the most important constituents in a wide range of natural products, pharmaceuticals, and materials.[1] Functionalized indolizines have shown many important biological activities including antibacterial,[2] antiviral,[3] anti-HIV,[4] anti-inflammatory,[5] 5-HT3 receptor antagonist,[6] muscular relaxant,[7] phosphatase inhibitive,[8] and antioxidizing.[9] In this regard, there are many reports for the synthesis of indolizines, such as Scholtz reaction,[10] Tschitschibabin reaction,[11] starting from N-substituted pyrrole ring,[12] Knoevenagel condensation–intramolecular aldol-type cyclization protocol,[13] multicomponent coupling reactions (MCR),[14] cycloaddition reactions of pyridines with alkenyldiazoacetates,[15] and C–H functionalization reaction.[16] However, some of these methods require tedious workup, harsh reaction conditions, or long reaction times. Others involve multistep synthetic operations or result in low yields. On the other hand, although numerous alternative successful examples have been reported in the literature for the preparation of indolizines, less attention has been paid to investigate cycloaddition reactions of 2-alkylazaarenes with alkenes. Lei et al. reported in 2015 that a direct oxidative coupling–annulation of 2-pyridinyl-β-esters with alkenes provides a way for the synthesis of indolizines in 25–59% yields; nevertheless, the reaction need three equivalents of TBHP and one equivalent of NaOAc (Scheme 1, a).[17] For these reasons, a straightforward, convenient, and highly regioselective route to synthesize indolizines from simple olefins has emerged as an attractive and challenging goal.

Recently, the use of copper-catalyzed reactions has emerged as a versatile tool for developing syntheses due to their numerous advantages, namely their relatively high efficiency, low cost, water compatibility, mild reaction conditions, operational simplicity, and eco-friendly catalytic reactions.[18] Herein, we describe a novel copper-catalyzed highly selective oxidative coupling–annulation of 2-alkylazaarenes with terminal alkenes for the formation of indolizines under mild conditions (Scheme 1, b).

To identify the suitable conditions for the process, great number of solvents and metal salts were initially screened using styrene (**1a**, 0.5 mmol) with ethyl 2-(pyridine-2-yl) acetate (**2a**, 0.5 mmol) as a model system (Table 1). Initially, the reaction of **1a** and **2a** failed to afford the desired product in the presence of $CuSO_4{\cdot}5H_2O$ in DMSO at 80 °C for 12 hours (Table 1, entry 1). But the reaction successfully gave **3aa**[20] in 80% yield when $CuSO_4{\cdot}5H_2O$ was replaced by $Cu(OAc)_2$ (Table 1, entry 2). According to our efforts, $CuCl_2$ and CuCl could also provide the indolizine product, albeit in a low yield (Table 1, entries 3 and 5), but other Cu(II) salts such as $Cu(OTf)_2$ were totally ineffective (Table 1, entry 4). Furthermore, with the $AuBr_3$ as the catalysts, the target product **3aa** was also not increased at all (Table 1, entry 6). In addition, in the presence of other catalysts such as $FeCl_3$, $BiCl_3$, or AgOAc, the process was totally ineffective (Table 1, entries 7–9). Further study suggested that solvents had a strong effect on this process. The reactions were merely in lower yields or totally restrained when they were performed in other solvents (Table 1, entries 10–16). It is noted that no desired product could be obtained when the reaction was conducted under argon atmosphere (Table 1, entry

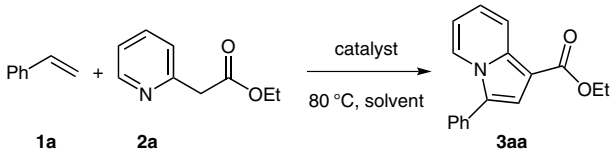


Scheme 1 Comparison of Lei's and our work.

17). Hence, the combination of 20 mol% $Cu(OAc)_2$ in DMSO at 80 °C for 12 hours was found to be the best reaction conditions for this copper-catalyzed crossing-coupling–cyclization–oxidation process.

With the optimized reaction conditions in hand, various terminal alkenes 1 were allowed to react with different 2-alkylazaarenes **2** to access the corresponding indolizine products **3** (Scheme 2). The reaction was readily extended to a variety of aryl-substituted terminal alkenes. Promoted by $Cu(OAc)_2$, almost all the aryl-substituted terminal alkenes are effective under the standard conditions. It is noteworthy that steric effects had little influence on this sequential reaction. Regardless of the substitution pattern of the aryl ring (*ortho* or *para*) of the aryl olefins used in the reaction, it gave the corresponding indolizine products in a same yield (Scheme 2, **3ba** and **3ca**). The terminal aryl alkene **1d** possessing an electron-donating group at the aryl ring (Ar = 4-$MeOC_6H_4$) reacted without a hitch and afforded the desired product **3da**[20] in 90% yield. Substrates **1e** and **1f** possessing an electron-withdrawing group (Ar = 4-FC_6H_4, 4-BrC_6H_4) at the benzene ring also reacted smoothly and afforded the desired products **3ea** and **3fa**[20] in 75% and 78% yields, respectively. Obviously, electron-rich terminal alkenes provided the desired products in higher yields than electron-poor terminal alkenes did. Unfortunately, the reaction of styrenes with strong electron-deficient substituents, such as CF_3 and COOMe, failed to afford the desired products. Additionally, terminal alkene containing a naphthalene moiety could also be employed to yield the indolizine scaffold without any difficulties (Scheme 2, entry **3ga**). What's more, heterocyclic substituted alkene devoted to promote the synthesis of indolizine ring (Scheme 2, entry **3ha**). However, the reactions of aliphatic alkenes (e.g., pent-1-ene) and internal alkenes (e.g. *trans*-stilbene) failed to afford the desired products.

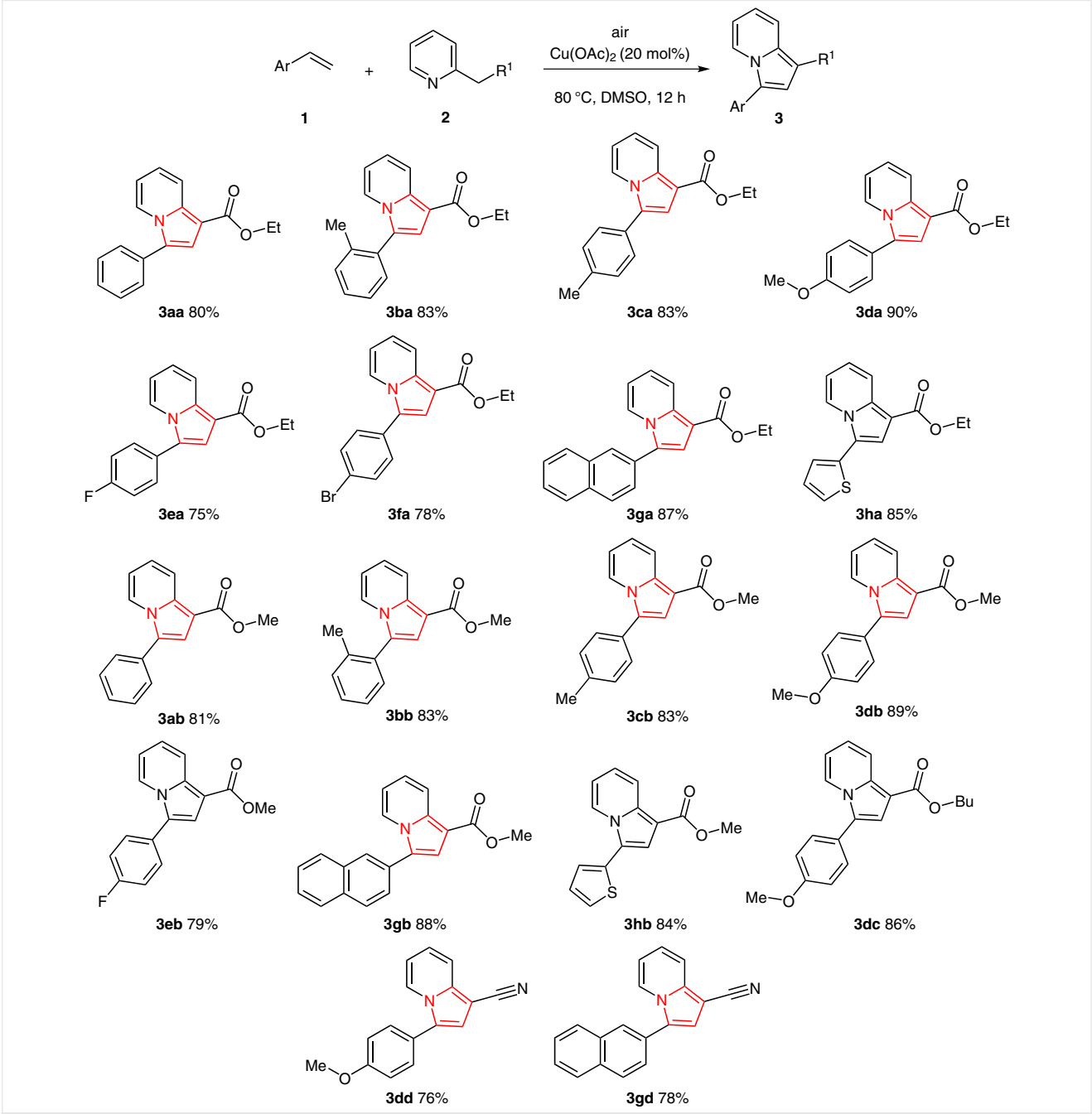
Table 1 Optimization of Reaction Conditions[a]



1a **2a** **3aa**

Entry	Catalyst	Solvent	Yield (%)[b]
1	$CuSO_4·5H_2O$	DMSO	0
2	$Cu(OAc)_2$	DMSO	80
3	$CuCl_2$	DMSO	20
4	$Cu(OTf)_2$	DMSO	0
5	CuCl	DMSO	10
6	$AuBr_3$	DMSO	20
7	$FeCl_3$	DMSO	0
8	$BiCl_3$	DMSO	0
9	AgOAc	DMSO	0
10	$Cu(OAc)_2$	1,4-dioxane	30
11	$Cu(OAc)_2$	AcOH	10
12	$Cu(OAc)_2$	DCE	10
13	$Cu(OAc)_2$	PhCl	0
14	$Cu(OAc)_2$	PhMe	0
15	$Cu(OAc)_2$	THF	0
16	$Cu(OAc)_2$	DMF	0
17[c]	$Cu(OAc)_2$	DMSO	0

[a] Reaction conditions: styrene (**1a**, 0.5 mmol), ethyl 2-(pyridine-2-yl)acetate (**2a**, 0.5 mmol), catalyst (20 mol% to **2a**), solvent (2.0 mL), 80 °C, 12 h.
[b] Isolated yield of pure product based on **2a**.
[c] The reaction was conducted under argon atmosphere.

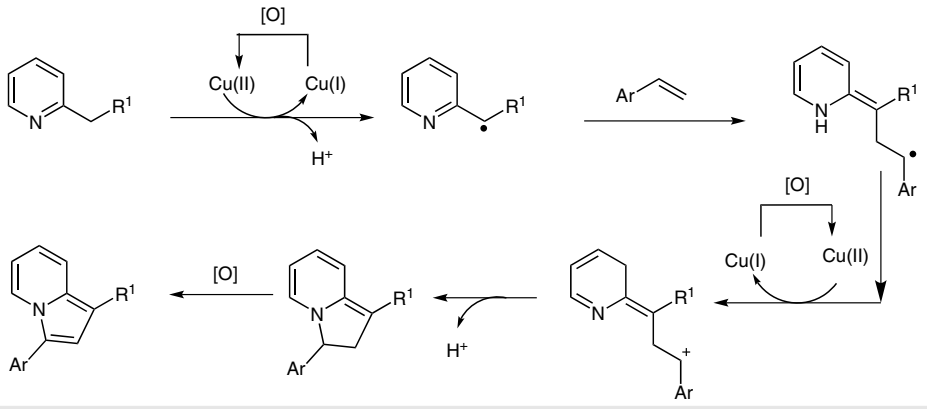


Scheme 2 Synthesis of indolizines catalyzed by $Cu(OAc)_2$. *Reagents and conditions*: terminal alkenes **1** (0.5 mmol), 2-alkylazaarenes **2** (0.5 mmol), $Cu(OAc)_2$ (20 mol% to **2**), solvent (4.0 mL), 80 °C, 12 h. Isolated yield of pure product based on **2** is given.

Various different 2-alkylazaarenes **2** were also found to be suitable reaction partners with terminal alkenes **1** in this reaction. The β-pyridine group of **2** could be ranged from ethyl to methyl or butyl esters, all of which reacted with terminal alkenes **1** to afford the corresponding indolizine products in good yields (Scheme 2, entries **3ab**–**dc**). Even 2-alkylazaarene bearing cyano groups were well tolerated in this transformation and offered the target products in good yields (Scheme 2, entries **3dd** and **3gd**).

When **1i** was used under the optimized conditions the reaction failed to produce the expected indolizine **3ia** but gave benzophenone (**4**) instead (Scheme 3).

Scheme 3 Copper-catalyzed oxidative coupling–annulation of **1i** and **2a**



Scheme 4 Possible reaction mechanism

It was observed that the addition of a radical scavenger (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO) suppressed the reaction completely. The results indicated that the radical mechanism was most likely in this reaction. On the basis of other previous works,[19] a proposed mechanism is illustrated in Scheme 4. The reaction generate a radical intermediate through loss of proton oxidized by copper(II), and subsequent single-electron insertion into styrene leads to C–C propagation, which is further oxidized by copper(II) to a carbocation, followed by subsequent intramolecular condensation of this β-pyridine intermediate and then oxidized by air to afford the final indolizine product.

In summary, we have developed an efficient approach to indolizine via a copper-catalyzed cross-coupling–cyclization–oxidation reaction of terminal alkenes and 2-alkylazaarenes under aerobic conditions in one step. Due to the easy availability of the starting materials and potential utilities of products, this method might be useful in organic synthesis and medicinal chemistry. From the synthetic point of view, this protocol represents an extremely simple, efficient, and atom-economic way to construct substituted indolizine in good yields with high selectivity, thus complementing the method for the rapid formation of multifunctional heterocycles.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378785.

References and Notes

(1) (a) Flitsch, W. *Comprehensive Heterocyclic Chemistry II*; Vol. 8; Pergamon Press: Oxford, **1984**, 237–248. (b) Yan, B.; Liu, Y. *Org. Lett.* **2007**, *9*, 4323. (c) Singh, G.-S.; Mmatli, E.-E. *Eur. J. Med. Chem.* **2011**, *46*, 5237. (d) Pourashraf, M.; Delair, P.; Rasmussen, M.-O.; Greene, A.-E. *J. Org. Chem.* **2000**, *65*, 6966. (e) Li, H.; Xia, Z.-Q.; Chen, S.-J.; Koya, K.; Ono, M.; Sun, L.-J. *Org. Process Res. Dev.* **2007**, *11*, 246.
(2) (a) Michael, J. P. *Alkaloids* **2001**, *55*, 91. (b) Michael, J. P. *Nat. Prod. Rep.* **2002**, *19*, 742.
(3) Liu, Y.-H.; Song, Z.-Q.; Yan, B. *Org. Lett.* **2007**, *9*, 409.
(4) (a) Facompre, M.; Tardy, C.; Bal-Mahieu, C.; Colson, P.; Perez, C.; Manzanares, I.; Cuevas, C.; Bailly, C. *Cancer Res.* **2003**, *63*, 7392. (b) Reddy, M.-V.; Rao, M.-R.; Rhodes, D.; Hansen, M.-S.; Rubins, K.; Bushman, F.-D.; Venkateswarlu, Y.; Faulkner, D.-J. *J. Med. Chem.* **1999**, *42*, 1901. (c) Østby, O.-B.; Dalhus, B.; Gundersen, L.-L.; Rise, F.; Bast, A.; Haenen, G.-R. M. M. *Eur. J. Org. Chem.* **2000**, 3763.

(5) Hagis, S.; Yamada, M.; Shirahase, K.; Okada, T.; Murakami, Y.; Ito, Y.; Matsuura, T.; Wada, M.; Kato, T.; Ueno, M.; Chikazawa, Y.; Yamada, K.; Ono, T.; Teshirogi, O. I. M. *J. Med. Chem.* **1996**, *39*, 3636.
(6) Bermudez, J.; Fake, C.-S.; Joiner, G.-F.; Joiner, K.-A.; King, F.-D.; Miner, W.-D.; Sanger, G.-J. *J. Med. Chem.* **1990**, *33*, 1919.
(7) (a) Gupta, S.-P.; Mathur, A.-N.; Nagappa, A.-N.; Kumar, D.; Kumaran, S. *Eur. J. Med. Chem.* **2003**, *38*, 867. (b) Hagishita, S.; Yamada, M.; Shirahase, K.; Okada, T.; Murakami, Y.; Ito, Y.; Matsuura, T.; Wada, M.; Kato, T.; Ueno, M.; Chikazawa, Y.; Yamada, K.; Ono, T.; Teshirogi, I.; Ohtani, M. *J. Med. Chem.* **1996**, *39*, 3636.
(8) Donnell, A. F.; Dollings, P. J.; Butera, J. A.; Dietrich, A. J.; Lipinski, K. K.; Ghavami, A.; Hirst, W. D. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2163.
(9) Østby, O.-B.; Dalhus, B.; Gundersen, L.-L.; Rise, F.; Bast, A.; Haenen, G. R. M. M. *Eur. J. Org. Chem.* **2000**, 3763.
(10) (a) Scholtz, M. *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 734. (b) Boekelheide, V.; Windgassen, R. J. *J. Am. Chem. Soc.* **1959**, *81*, 1456.
(11) (a) Tschitschibabin, A. E. *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 1607. (b) Hurst, J.; Melton, T.; Wibberley, D. G. *J. Chem. Soc.* **1965**, 2948. (c) Bora, U.; Saikia, A.; Boruah, R. C. *Org. Lett.* **2003**, *5*, 43.
(12) (a) Lee, J.-H.; Kim, I. *J. Org. Chem.* **2013**, *78*, 1283. (b) Nagaraj, M.; Boominathan, M.; Muthusubramanian, S.; Bhuvanesh, N. *Synlett* **2012**, *23*, 1353. (c) Zhu, H.; Stöckigt, J.; Yu, Y.; Zou, H. *Org. Lett.* **2011**, *13*, 2792. (d) Ge, Y.-Q.; Jia, J.; Yang, H.; Zhao, G.-L.; Zhan, F.-X.; Wang, J. *Heterocycles* **2009**, *78*, 725. (e) Kucukdisli, M.; Opatz, T. *J. Org. Chem.* **2013**, *78*, 6670. (f) Ohier, P.; Dach, A.; Decroix, B. *Tetrahedron* **1996**, *52*, 13547.
(13) (a) Kuznetsov, A.-G.; Bush, A.-A.; Rybakov, V.-B.; Babaev, E.-V. *Molecules* **2005**, *10*, 1074. (b) Toche, R.-B.; Bhavsar, D.-C.; Kazi, M.-A.; Bagul, S.-M.; Jachak, M.-N. *J. Heterocycl. Chem.* **2010**, *47*, 287. (c) Wang, K.; Herdtweck, E.; Dömling, A. *ACS Comb. Sci.* **2012**, *14*, 316. (d) Shen, Q.; Wang, L.; Yu, J.; Liu, M.; Qiu, J.; Fang, L.; Guo, F.; Tang, J. *Synthesis* **2012**, *44*, 389. (e) Siddiqui, Z.-N. *Tetrahedron Lett.* **2012**, *53*, 4974. (f) Kim, M.; Jung, Y.; Kim, I. *J. Org. Chem.* **2013**, *78*, 10395.
(14) (a) Bai, Y.-G.; Zeng, J.; Ma, J.-M.; Gorityala, B.-K.; Liu, X.-W. *J. Comb. Chem.* **2010**, *12*, 696. (b) Georgescu, E.; Georgescu, F.; Popa, M.-M.; Draghici, C.; Tarko, L.; Dumitrascu, F. *ACS Comb. Sci.* **2012**, *14*, 101. (c) Bora, U.; Saikia, A.; Boruah, R.-C. *Org. Lett.* **2003**, *5*, 435. (d) Zhu, H.-J.; Stöckigt, J.; Yu, Y.-P.; Zou, H.-B. *Org. Lett.* **2011**, *13*, 2792.
(15) Barluenga, J.; Lonzi, G.; Riesgo, L.; Lopez, L. A.; Tomas, M. *J. Am. Chem. Soc.* **2010**, *132*, 13200.
(16) (a) Yang, Y.; Xie, C.; Xie, Y.; Zhang, Y. *Org. Lett.* **2012**, *14*, 957. (b) Wang, X.; Li, S.-Y.; Pan, Y.-M.; Wang, H.; Liang, H.; Chen, Z.; Qin, X. *Org. Lett.* **2014**, *16*, 580. (c) Yang, Y.; Cheng, K.; Zhang, Y. *Org. Lett.* **2009**, *11*, 5606. (d) Xia, J.-B.; You, S.-L. *Org. Lett.* **2009**, *11*, 1187. (e) Wu, Q.; Zhao, D.; Qin, X.; Lan, J.; You, J. *Chem. Commun.* **2011**, *47*, 9188. (f) Xia, J.-B.; Wang, X.-Q.; You, S.-L. *J. Org. Chem.* **2009**, *74*, 456. (g) Tan, X.; Liang, Y.; Bao, F.; Wang, H.; Pan, Y. *Tetrahedron* **2014**, *70*, 6717. (h) Gao, M.; Tian, J.; Lei, A. *Chem. Asian J.* **2014**, *9*, 2068. (i) Tang, S.; Liu, K.; Long, Y.; Qi, X.; Lan, Y.; Lei, A. *Chem. Commun.* **2015**, *51*, 8769.
(17) Tang, S.; Liu, K.; Long, Y.; Gao, X.; Gao, M.; Lei, A. *Org. Lett.* **2015**, *17*, 2404.
(18) (a) Cai, X.; Xie, B. *Synthesis* **2015**, *47*, 737. (b) Dong, J.; Wu, Q.; You, J. *Tetrahedron Lett.* **2015**, *56*, 1591. (c) Liang, Y.; Liang, Y.-F.; Jiao, N. *Org. Chem. Front.* **2015**, *2*, 403. (d) Guo, X.-X.; Gu, D.-W.; Wu, Z.; Zhang, W. *Chem. Rev.* **2015**, *115*, 1622. (e) Zhang, D.-Y.; Hu, X.-P. *Tetrahedron Lett.* **2015**, *56*, 283. (f) Yang, F.; Li, J.; Xie, J.; Huang, Z.-Z. *Org. Lett.* **2010**, *12*, 5214. (g) Thapa, S.; Shrestha, B.; Gurung, S. K.; Giri, R. *Org. Biomol. Chem.* **2015**, *13*, 4816.
(19) (a) Liu, P.; Liu, J.-L.; Wang, H.-S.; Pan, Y.-M.; Liang, H.; Chen, Z.-F. *Chem. Commun.* **2014**, *50*, 4795. (b) Zhao, M.; Wang, F.; Li, X.-W. *Org. Lett.* **2012**, *14*, 1412.
(20) **Typical Experimental Procedure**

The reaction mixture of terminal alkenes **1** (0.5 mmol), 2-alkylazaarenes **2** (0.5mmol), $Cu(OAc)_2$ (20 mol%), and DMSO (2 mL) in a 10 mL round-bottom flask was stirred at 80 °C for 12 h. Upon completion, the reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The solvent was removed under vacuum. The residue was purified by flash column chromatography to afford indolizines **3**.

Ethyl 3-Phenylindolizine-1-carboxylate (3aa)

Yellow solid (106 mg, 0.4 mmol, 80%); mp 61–62 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.18–8.23 (m, 2 H), 7.40–7.48 (m, 4 H), 7.34 (m, 1 H), 7.31–7.23 (s, 1 H), 6.98–7.01 (m, 1 H), 6.61–6.64 (m, 1 H), 4.31 (q, *J* = 7.1 Hz, 2 H), 1.35 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.1, 136.4, 131.3, 129.1, 128.6, 128.0, 126.4, 123.4, 122.3, 120.2, 116.1, 112.6, 104.2, 59.6, 14.7. ESI-HRMS: *m/z* calcd for $C_{17}H_{15}NO_2$: 265.11028; found: 265.10894.

Ethyl 3-(4-Bromophenyl)indolizine-1-carboxylate (3fa)

Yellow solid (134 mg, 0.39 mmol, 78%); mp 88–89 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.20–8.15 (m, 2 H), 7.55 (d, *J* = 8.4 Hz, 2 H), 7.34 (d, *J* = 8.4 Hz, 2 H), 7.22 (s, 1 H), 7.02–7.00 (m, 1 H), 6.65 (t, *J* = 6.8 Hz, 1 H), 4.31 (q, *J* = 7.1 Hz, 2 H), 1.34 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.9, 136.5, 132.3, 130.1, 130.0, 125.1, 123.1, 122.4, 121.9, 120.3, 116.4, 112.9, 104.5, 59.7, 14.7. ESI-HRMS: *m/z* calcd for $C_{17}H_{14}BrNO_2$: 343.02079 and 345.01874; found: 343.01908 and 345.01690.

Ethyl 3-(4-Methoxyphenyl)indolizine-1-carboxylate (3da)

Yellow solid (133 mg, 0.45 mmol, 90%); mp 112–113 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.18–8.15 (m, 1 H), 8.13–8.11 (m, 1 H), 7.38–7.35 (m, 2 H), 7.16 (s, 1 H), 6.98–6.93 (m, 3 H), 6.60 (dt, *J* = 6.8, 1.2 Hz, 1 H), 4.30 (q, *J* = 7.1 Hz, 2 H), 3.79 (s, 3 H), 1.34 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.1, 159.4, 136.0, 130.1, 126.2, 123.6, 123.3, 122.0, 120.1, 115.6, 114.5, 112.4, 103.9, 59.5, 55.4, 14.7. ESI-HRMS: *m/z* calcd for $C_{18}H_{17}NO_3$: 295.12084; found: 295.11933.