Synthesis of Aminoindolizine and Quinoline Derivatives via $Fe(acac)_3$/TBAOH-Catalyzed Sequential Cross-Coupling–Cycloisomerization Reactions

Sachin S. Patil, Sachin V. Patil, Vivek D. Bobade*

Department of Chemistry, HPT Arts and RYK Science College, Nasik 422005, India
Fax +91(253)2574682; E-mail: v_bobade31@rediffmail.com

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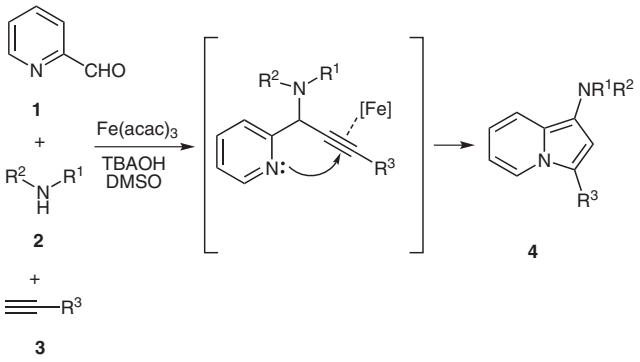
Abstract: $Fe(acac)_3$/TBAOH-catalyzed three-component coupling–cycloisomerization reaction of aldehydes, terminal alkynes, and amines provides a diverse range of heterocyclic compounds such as aminoindolizines and quinoline derivatives.

Key word: aminoindolizines, quinoline derivatives, tetrabutylammonium hydroxide (TBAOH), $Fe(acac)_3$ catalyst, cross-coupling, cycloisomerization

The ongoing interest for developing new versatile and efficient syntheses of heterocycles has always been a common thread in the synthetic community. In the past decade the concepts of multicomponent processes, domino reactions, and sequential transformations, where complex and highly diverse structures are created in a one-pot fashion, have considerably stimulated both academia and industry.[1,2] As diversity-oriented syntheses,[3] particularly multicomponent reactions (MCR), focus on synthetic efficiency and reaction design, mastering unusual combinations and sequences of elementary organic reactions under similar conditions is a major challenge in engineering novel types of MCR. In the past decade, transition-metal-catalyzed MCR involving cascade C–C and C–N bond formations have been widely used in the synthesis of heterocycles such as indolizines,[4] imidazo[1,2-pyridines],[5] quinolines,[6] benzo[*b*]furans,[7] aminoindolines, and aminoindoles.[8,9] However, these processes required expensive transition-metal catalysts such Au, Ag, Rh and high temperatures. Iron salts have been explored as effective, alternative, and promising transition-metal catalysts and have received attention in recent years because they are inexpensive, readily available, and are environmentally benign.

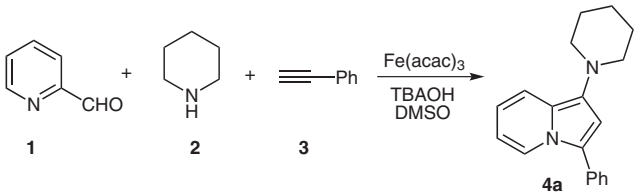
Recently, we reported the TBAOH-catalyzed synthesis of propargylpyridine.[10] During the course of reaction a byproduct (3-phenyl-1-piperidin-1-yl)indolizine was formed due to cycloisomerization of the propargylpyridine. Inspired by this result, we became interested in developing a direct route to indolizines from readily available precursors. Herein, we report the synthesis of 3-substituted indolizines involving $Fe(acac)_3$/TBAOH-catalyzed three-component coupling–cycloisomerization reaction of heteroaryl aldehydes, amines, and terminal alkynes in DMSO (Scheme 1).



Scheme 1

We first examined the coupling reaction of pyridine-2-carboxaldehyde, piperidine, and phenylacetylene, with TBAOH as base and $Fe(acac)_3$ as catalyst, to optimize reaction conditions, and representative results are summarized in Table 1.

Table 1 Coupling Reaction of Pyridine-2-carboxaldehyde, Piperidine, and Phenylacetylene



Entry	Iron catalyst (mol%)[a]	TBAOH (mol%)	Solvent	Yield (%)
1	A (10)	10	DMSO	82
2	A (5)	10	DMSO	85
3	A (2)	10	DMSO	36
4	B (5)	10	DMSO	80
5	A (5)	5	DMSO	40
6	A (5)	–	DMSO	0
7	A (5)	10	DMF	25

[a] Pyridine-2-carboxaldehyde (1 mmol), piperidine (1.1 mmol), phenylacetylene (1.2 mmol) in DMSO until completion of reaction.
A = $Fe(acac)_3$, B = $Fe(ClO_4)_3$.

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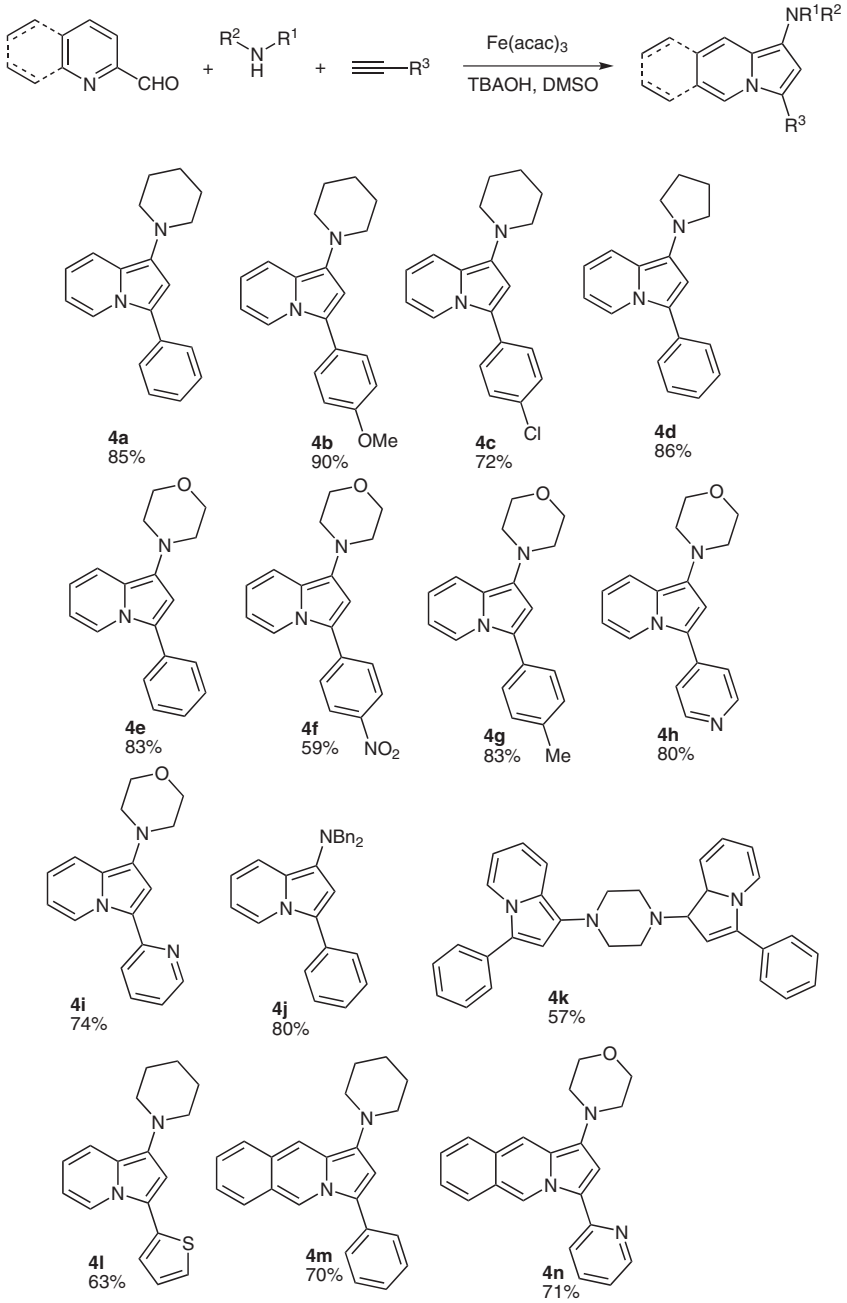
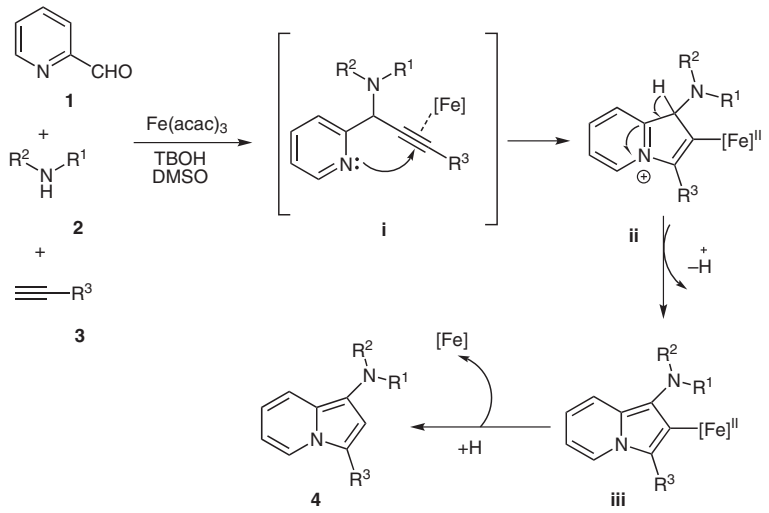
The three-component coupling–cycloisomerization reaction proceeded smoothly in DMSO to afford the desired product **4a** in up to 82% yield after 2.5 hours at room temperature (Table 1, entry 1). The loading of iron catalyst was optimized from a range of 2–10 mol% and 5 mol% was found to be most effective for this conversion (Table 1, entry 2). Lowering the catalyst to 2 mol% reduced the yield to 36% (Table 1, entry 3) In the absence of TBAOH no reaction was observed, (Table 1, entry 6), indicating that TBAOH plays a crucial role for this three-component coupling reaction. DMSO was found to be a better reaction solvent than DMF (Table 1, entry 7). With these optimized conditions, we examined the scope of this multicomponent reaction, and the results are summarized in Scheme 2.

As can be seen from Scheme 2, this multicomponent process can be readily diversified through combinations of heteroaryl aldehydes, amines, and alkynes. Regarding aldehydes, pyridine-2-carboxaldehyde and 2-quinolinecarboxaldehyde undergo three-component coupling reaction to give products in good yields (products **4a**–**n**). With respect to the amine component, cyclic amines (e.g., piperidine, pyrrolidine, and morpholine) afforded products with moderate to excellent yields (products **4a**–**i** and **4k**,**l**). Dibenzylamine also gave product in excellent yield (product **4j**). The use of piperazine afforded a bridged indolizine in 57% yield (product **4k**). Aryl acetylenes with electron-donating groups at the *para* position (OMe and Me) afforded products in 90% and 83% yield, respectively (products **4b**,**g**) while the presence of an electron-with-



Scheme 2 Multicomponent reaction under optimized reaction conditions



Scheme 3

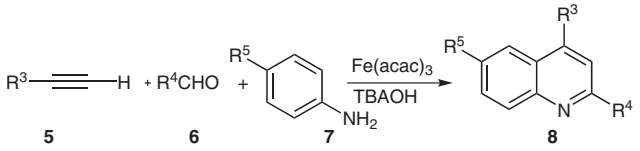
drawing substituent (NO_2) gave only 59% yield (product **4f**). Alkynes substituted with a six-membered heteroaromatic ring provided good yields of product (products **4h**,**i**) while a five-membered heterocyclic substituent on the alkyne gave lower yield of product (product **4l**). The reaction fails with aliphatic alkynes.

We propose the following mechanism for the formation of aminoindolizines, similar to the mechanism described in literature using gold-catalyzed reaction.[4a] First, a TBAOH-catalyzed three-component coupling of pyridine-2-carboxaldehyde, amine, and alkyne occurrs to afford NR^1R^2-substituted propargylic pyridine **4** via a Mannich reaction. Coordination of the alkyne **i** to the iron catalyst enhances the electrophilicity of the alkyne, and subsequent nucleophilic attack of the nitrogen lone pair would produce the cation **ii**, which undergoes deprotonation followed by demetalation of **iii** to afford indolizines **4** (Scheme 3).

Using our optimized protocol, we also studied the coupling of aldehydes and primary amines with terminal alkynes to give 2,4-disubstituted quinoline derivatives in good yields (Table 2).

It was found that aldehydes bearing a wide range of substituents undergo coupling reaction to afford the desired products in good yield (Table 2, entries 1–10). The reac-

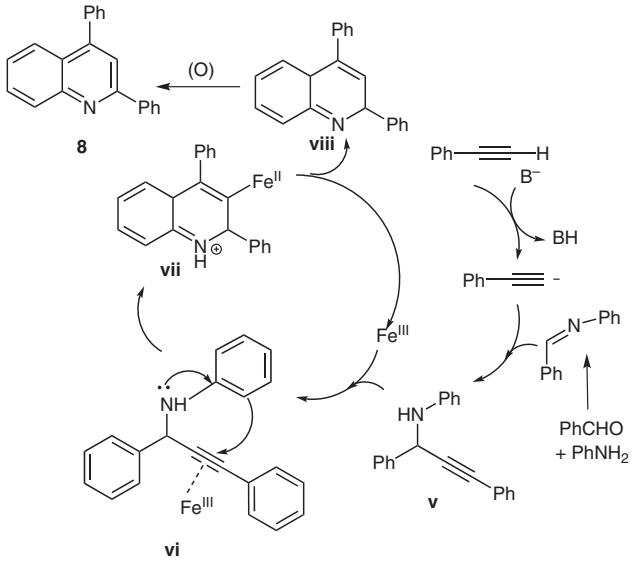
Table 2 Synthesis of 2,4-Disubstituted Quinoline Derivatives



Entry	Product	R^3	R^4	R^5	Yield (%)[a]	Mp (lit.)[b]
1	**8a**	Ph	4-FC_6H_4	H	73	67–69 (68–69)[11]
2	**8b**	Ph	4-CNC_6H_4	H	64	152–155 (154–156)[11]
3	**8c**	4-MeC_6H_4	Ph	Cl	81	87–88 (87–88)[11]
4	**8d**	4-MeC_6H_4	Naph	H	62	107–110 (108–109)[11]
5	**8e**[17]	4-$MeOC_6H_4$	Naph	H	61	265–269 (268–270)[11]
6	**8f**	Ph	Ph	H	78	99–101 (102)[12]
7	**8g**	Ph	4-$MeOC_6H_4$	H	84	oil[13]
8	**8h**	Ph	thienyl	H	86	89–92 (83–85)[14]
9	**8i**	Ph	*n*-Bu	H	56	oil[15]
10	**8j**	Ph	Cy	H	61	oil[11]

[a] Yield is based on aniline (**7**).
[b] Literature compounds have been previously reported; physical and spectral data were comparable.

tion of an aromatic aldehyde bearing electron-donating groups provided a higher yield (Table 2 entry 7), while an aldehyde with an electron-withdrawing substituent resulted in lower yield (Table 2 entry 2). The sterically hindered 1-naphthaldehyde also reacted under optimized conditions (Table 2, entries 4 and 5), and thiophene-2-carboxaldehyde aldehyde afforded a good yield of product **8h** (Table 2 entry 8), while aliphatic aldehydes gave lower yields (Table 2, entries 9 and 10).



Scheme 4 Postulated reaction mechanism

A plausible pathway involves $Fe(acac)_3$/TBAOH-catalyzed three-component reaction of aldehyde, amine, and alkyne to lead to formation of propargylamine **vi**.[10] The triple bond of propargylamine **vi** is activated by Lewis acidic Fe(III) to promote an intramolecular nucleophilic attack through the aniline aromatic-ring nitrogen. The resulting Fe(III) vinyl ate complex **vii** subsequently undergoes decomposition to give the dihydroquinoline intermediate **viii** and regenerates Fe(III) catalyst for further reactions (Scheme 4). In the presence of air, the generated dihydroquinoline could be further oxidized to afford quinoline **8**.

In summary, we have described effective $Fe(acac)_3$/TBAOH system for the three-component coupling–cycloisomerization reactions of aldehydes, terminal alkynes, and amines for synthesis of aminoindolizines and quinolines.

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References and Notes

(1) (a) Zhu, J.; Bienayme, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, **2005**. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (c) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168.

(2) (a) Tietze, L. F.; Brasche, G.; Gericke, G. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, **2006**. (b) Tietze, L. F.; Beifuss, U. *Angew. Chem. Int. Ed.* **1993**, *32*, 131. (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

(3) (a) Arya, A.; Chou, D. T. H.; Baek, M. G. *Angew. Chem. Int. Ed.* **2001**, *40*, 339. (b) Burke, M. D.; Berger, E. M.; Schreiber, S. L. *Science* **2003**, *302*, 613. (c) Cox, B.; Denyer, J. C.; Binnie, A.; Donnelly, M. C.; Evans, B.; Green, D. V. S.; Lewis, J. A.; Mander, T. H.; Merritt, A. T.; Valler, M. J.; Watson, S. P. *Prog. Med. Chem.* **2000**, *37*, 83. (d) Schreiber, S. L. *Science* **2000**, *287*, 1964. (e) Schreiber, S. L.; Burke, M. D. *Angew. Chem. Int. Ed.* **2004**, *43*, 46.

(4) (a) Yan, B.; Liu, Y. *Org. Lett.* **2007**, *9*, 4323. (b) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074. (c) Kim, J. T.; Gevorgyan, V. *Org. Lett.* **2002**, *4*, 4697. (d) Kim, J. T.; Butt, J.; Gevorgyan, V. *J. Org. Chem.* **2004**, *69*, 5638. (e) Kim, J. T.; Gevorgyan, V. *J. Org. Chem.* **2005**, *70*, 2054. (f) Seregin, I. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 12050. (g) Smith, C. R.; Bunnelle, E. M.; Rhodes, A. J.; Sarpong, R. *Org. Lett.* **2007**, *9*, 1169. (h) Liu, Y. H.; Song, Z. Q.; Yan, B. *Org. Lett.* **2007**, *9*, 409. (i) Bai, Y.; Zeng, J.; Ma, J.; Gorityala, B. K.; Liu, X. W. *J. Comb. Chem.* **2010**, *12*, 696.

(5) Chernyak, N.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2010**, *49*, 2743.

(6) (a) Xiao, F.; Chen, Y.; Liu, Y.; Wang, J. *Tetrahedron* **2008**, *64*, 2755. (b) Zhang, Y.; Li, P.; Wang, L. *J. Heterocycl. Chem.* **2011**, *48*, 153. (c) Sakai, N.; Uchida, N.; Konakahar, T. *Synlett* **2008**, 1515.

(7) Li, H.; Liu, J.; Yan, B.; Li, Y. *Tetrahedron Lett.* **2009**, *50*, 2353.

(8) (a) Martin, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 3955. (b) Sapountzis, I.; Lin, W.; Kofink, C. C.; Despotopoulou, C.; Knochel, P. *Angew. Chem. Int. Ed.* **2005**, *44*, 1654. (c) Komeyama, K.; Morimoto, T.; Takaki, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 2938. (d) Plierker, B. *Angew. Chem. Int. Ed.* **2006**, *45*, 6053. (e) Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2007**, *129*, 8940. (f) Cahiez, G.; Moyeux, A.; Buendia, J.; Duplais, C. *J. Am. Chem. Soc.* **2007**, *129*, 13788. (g) Hatakeyama, T.; Nakamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 9844. (h) Gurinot, A.; Reymond, S.; Cossy, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 6521. (i) Li, Z.; Cao, L.; Li, C. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 6505. (j) Li, Z.; Yu, R.; Li, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 7497. (k) Volla, C. M. R.; Vogel, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 1305. (l) Carril, M.; Correa, A.; Bolm, C. *Angew. Chem. Int. Ed.* **2008**, *47*, 4862. (m) Egami, H.; Matsumoto, K.; Oguma, T.; Kunisu, T.; Katsuki, T. *J. Am. Chem. Soc.* **2010**, *132*, 13633.

(9) Chernyak, D.; Chernyak, N.; Gevorgyan, V. *Adv. Synth. Catal.* **2010**, *352*, 961.

(10) Patil, S. S.; Patil, S. V.; Bobade, V. D. *Synlett* **2011**, 1157.

(11) Kulkarni, A.; Török, B. *Green Chem.* **2010**, *12*, 875.

(12) Martínez, R.; Ramón, D. J.; Yus, M. *J. Org. Chem.* **2008**, *73*, 9778.

(13) Abbiati, G.; Arcadi, A.; Marinelli, F.; Rossi, E.; Verdecchia, M. *Synlett* **2006**, 3218.

(14) Leardini, R.; Nanni, D.; Tundo, A.; Zanardi, G.; Ruggieri, F. *J. Org. Chem.* **1992**, *57*, 1842.

(15) Kobayashi, K.; Yoneda, K.; Miyamoto, K.; Morikawa, O.; Konishi, H. *Tetrahedron* **2004**, *60*, 11639.

(16) **General Procedure for the Synthesis of Aminoindolizine Derivatives**

To a solution of TBAOH (0.1 mmol) in DMSO (5 mL), pyridine-2-carboxaldehyde (1.0 mmol), phenyl acetylene (1.2 mmol), morpholine (1.2 mmol), and $Fe(acac)_3$ (0.05 mmol) were added successively. The resulting mixture was stirred at r.t. until the reaction was complete as indicated by TLC. The mixture was then diluted with EtOAc (5 mL), washed with H_2O (2 × 5 mL), and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with sat. aq NaCl, dried over anhyd Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on Al_2O_3 to afford the target product as a yellow oil.

4-(Methoxyphenyl)-1-(piperidin-1-yl) indolizine[4a] (Table 2, Product 4b)

Pale yellow liquid. ^{1}H NMR (300 MHz, C_6D_6): δ = 1.40–1.48 (m, 2 H), 1.66–1.74 (m, 4 H), 3.01 (dd, *J* = 5.4 Hz, 4 H), 3.33 (s, 3 H), 6.04–6.09 (m, 1 H), 6.35 (dd, *J* = 9.0, 6.3 Hz, 1 H), 6.76 (s, 1 H), 6.78–6.83 (m, 2 H), 7.27–7.32 (m, 2 H), 7.58 (d, *J* = 9.3 Hz, 1 H), 7.91 (d, *J* = 7.5 Hz, 1 H). ^{13}C NMR (75 MHz, C_6D_6): δ = 24.8, 27.0, 54.8, 55.7, 106.0, 110.8, 114.0, 114.6, 118.4, 121.6, 122.5, 125.3, 125.6, 129.6, 131.7, 159.0. IR (neat): 2933, 1522, 1245, 1034, 835, 738 cm^{-1}.

(17) **General Procedure for the Preparation of Quinoline Derivatives**

A mixture of aldehyde (1 mmol) and aniline (1.4 mmol) was dissolved in DMSO (10 mL) and heated at 60 °C for 2 h. It was cooled to r.t., TBAOH (10 mol%), phenylacetylene (1.2 mmol), and $Fe(acac)_3$ were added, and the mixture stirred at r.t. overnight. The reaction mixture was poured into H_2O, and extracted with EtOAc (or CH_2Cl_2). The organic layer was washed with H_2O and dried over anhyd Na_2SO_4. The solvent was removed in vacuo. The product was purified by column chromatography on silica gel eluting with EtOAc–hexane (10:90).

4-(4-Methoxyphenyl)-2-(naphthalen-2-yl)quinoline (Table 3, Entry 5)

Pale yellow solid, mp 265–269 °C (lit.[11] 268–270 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.93 (s, 3 H), 7.10 (d, *J* = 8.4 Hz, 2 H), 7.26 (s, 1 H), 7.54 (m, 5 H), 7.75 (t, *J* = 8.1 Hz, 1 H), 7.96 (m, 4 H), 8.28 (d, *J* = 8.1 Hz, 1 H), 8.41 (d, *J* = 9 Hz, 1 H), 8.64 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.4. 114.0, 119.4, 125.0, 125.7, 126.6, 127.1, 127.7, 128.5, 128.8, 129.5, 130.0, 130.8, 131.3, 133.4, 136.2, 147.6, 149.8, 156.6, 164.2.