Quinolines

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Palladium-Catalyzed Sequential Formation of C–C Bonds: Efficient Assembly of 2-Substituted and 2,3-Disubstituted Quinolines**

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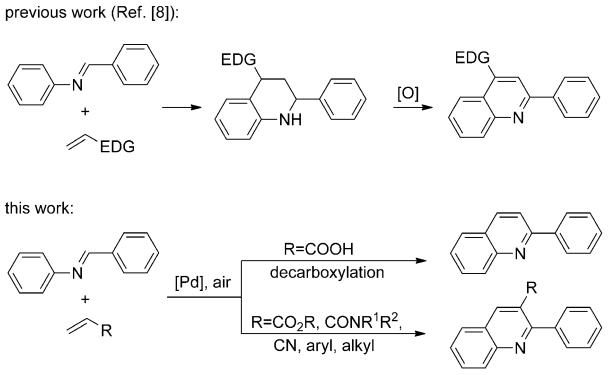
Transition-metal-catalyzed transformations are attractive methodologies for the synthesis of heterocyclic compounds, and enable the direct formation of complicated molecules from readily accessible starting materials under mild conditions.[1] The outstanding potential of palladium-catalyzed processes lies 1) in the diversity of available bond-forming processes, such as C–C, C–O, and C–N bond forming, 2) in the excellent chemo-, regio-, and stereoselectivity that is generally observed, and 3) in their great functional-group tolerance.[2] Besides, palladium-catalyzed processes constitute an efficient strategy to synthesize an increasingly wide range of polyfunctionalized compounds.[3]

Quinoline is one of the ubiquitous structural motifs that occur in natural products[4a] and pharmaceutically active substances.[4] 2-Arylquinoline scaffolds, for example, are associated with a wide range of biological properties, such as P-selectin antagonism, antimalarial, and antitumor activities.[5] Wide applications trigger continued interest in quinoline chemistry, and a variety of advanced methods for the synthesis of substituted quinolines have been developed over the years.[6] Because the substituents on the quinoline rings have a great influence on their properties, development of novel and expeditious approaches for the preparation of a diverse range of substituted quinolines, based on the idea of high efficiency and atom-economy, remains an active research area.

Because of the diverse pharmacological value of 2-arylquinolines, many synthetic protocols have been reported in recent years.[7] The most attractive strategy for the synthesis of these compounds is the acid-promoted imino-Diels–Alder (DA) reaction between N-aryl aldimines (electron-deficient azadienes) and electron-rich alkenes, such as vinyl enol ethers, enamines, etc., and subsequent oxidization, which has been a topic of continued interest for 40 years since the pioneering works of Povarov (Scheme 1).[8] However, electron-deficient olefins show much less reactivity in these reactions,[8f] and thus examples of imino-DA reactions between N-aryl aldimines and electron-deficient alkenes have not been reported for the synthesis of 2,3-disubstituted quinolines. Herein, we present a novel palladium-catalyzed reaction of easily available arylamines, aldehydes, and olefins in air[9] to synthesize 2-substituted and 2,3-disubstituted quinolines.[10] In this transformation, reactions of electron-deficient and electron-rich olefins proceed smoothly to give the corresponding products, and gratifyingly, when R is a carboxy group, decarboxylation[11] occurs to provide 2-substituted quinolines (Scheme 1).



Scheme 1. Synthesis of substituted quinolines. EDG = electron-donating group.

At the outset of this investigation, we explored the Pd-catalyzed reaction between benzaldehyde **1a**, aniline **2a**, and acrylic acid **3a**, followed by decarboxylation.[12] We found that the palladium catalyst was indispensable for the reaction, and that the addition of $LiBr{\cdot}H_2O$[13] could greatly improve the yield of the product. Furthermore, the reaction could efficiently proceed in air to give **3a** in excellent yield. After extensive screening of the reaction conditions (the palladium catalyst, additives, solvent, and pressure of oxygen), it was concluded that the optimized reaction conditions included the use of $PdCl_2$ as catalyst and $LiBr{\cdot}H_2O$ as additive in acetonitrile at 60 °C in air.

Next, the substrate scope of the synthesis of substituted 2-arylquinolines was investigated under the optimized conditions (Scheme 2). The reaction worked well, regardless of the electron-donating or electron-withdrawing nature of the substituents on the benzaldehyde, and heteroaryl aldehydes, such as furan-2-carbaldehyde and thiophene-2-carbaldehyde, were also compatible with the reaction conditions, though thiophene-2-carbaldehyde furnished **4g** in relatively low yield. Both electron-deficient and electron-rich aniline components delivered the corresponding products in good to excellent yields. The reaction of 3,4-dimethylaniline gave two regioisomers, with almost exclusive formation of quinoline **4l**

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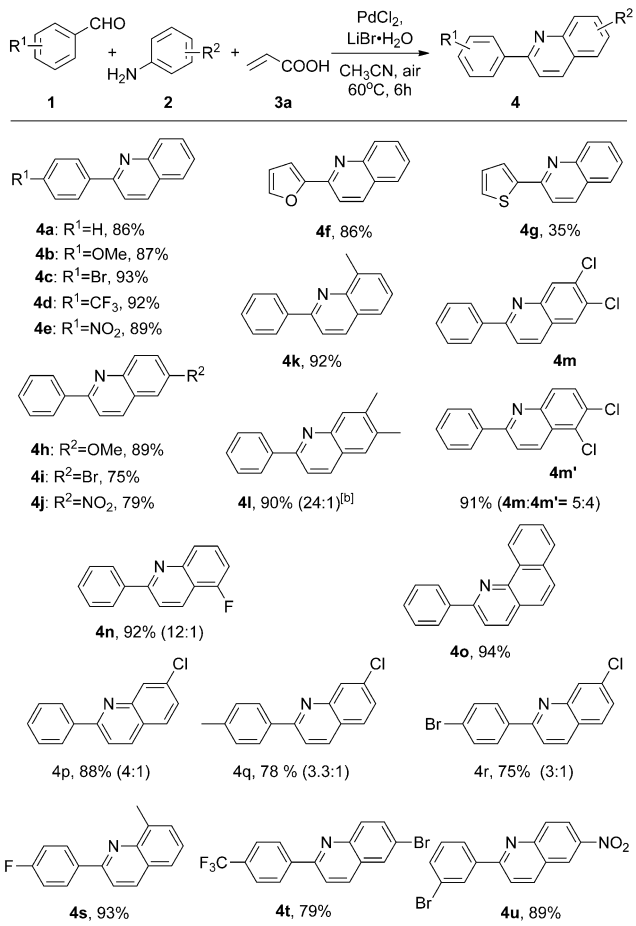
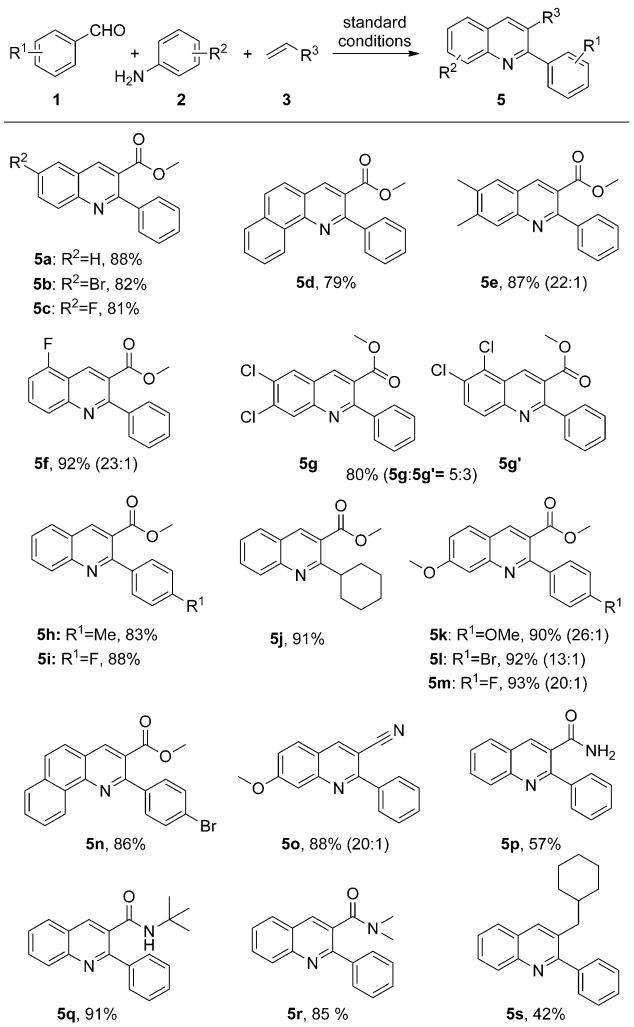


Scheme 2. Synthesis of substituted 2-phenylquinolines. Reaction conditions: aldehyde **1** (0.5 mmol), arylamine **2** (0.5 mmol), acrylic acid **3a** (1 mmol), $PdCl_2$ (0.025 mol, 5 mol%), $LiBr{\cdot}H_2O$ (0.5 mmol, 1 equiv), in acetonitrile (2 mL) at 60°C in air for 8 h. Yields of isolated products are reported.



Scheme 3. Synthesis of a variety of substituted quinolines. Reaction conditions: aldehyde **1** (0.5 mmol), arylamine **2** (0.5 mmol), terminal olefin **3** (1 mmol), $PdCl_2$ (0.025 mol, 5 mol%), $LiBr{\cdot}H_2O$ (0.5 mmol, 1 equiv), in acetonitrile (2 mL) at 60°C in air for 8 h. Yields of isolated products are reported.

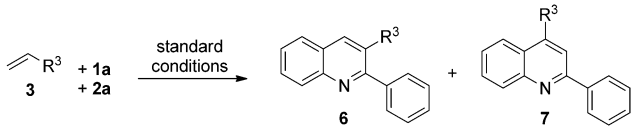
(24:1 d.r.). In the case of 3-fluoroaniline, two regioisomeric quinoline products were formed, and, intriguingly, 5-substituted regioisomer **4n** (12:1 d.r.) was obtained as the main product, that is, the more acidic hydrogen atom was preferentially activated in these reactions. Whereas good selectivity were observed with a fluoro-substituted aniline, 3-chlorophenylamine led to the formation of two quinoline regioisomers with decreased selectivity, and the 7-substituted regioisomer was the major product (**4p**–**4r**). Evidently, both the electronic character and steric demand of the substituents increase the selectivity in this transformation. The substrate 3,4-dichloroaniline led to poorly selective formation of two regioisomeric products **4m** and **4m′** (5:4 d.r.). Furthermore, many useful substituents, such as halogen atoms, a trifluoromethyl group, and heterocycles (furyl and thienyl groups), were successfully introduced into the product.

After the successful conversion of acrylic acid to substituted 2-phenylquinoline, we were interested in extending the method to other terminal olefins to prepare a variety of substituted quinolines (Scheme 3). To our delight, reactions of aldehydes, arylamines, and methyl acrylate proceeded smoothly to give 2,3-disubstituted quinolines in good to excellent yields; decarboxylation did not occur. In accordance with the results of reactions with acrylic acid, 3,4-dimethylaniline reacted well with benzaldehyde **1a** and methyl acrylate, and **5e** was formed as the major regioisomeric product (22:1 d.r.). When 3-fluoroaniline was used as the substrate, quinoline **5f** was obtained as the main regioisomer (23:1 d.r.), which was in good agreement with the result obtained when the corresponding reaction was performed with acrylic acid instead of methyl acrylate. 3,4-Dichloroaniline gave two regioisomeric products **5g** and **5g′** with poor selectivity (5:3 d.r.). It is noteworthy that the reaction of 3-methoxyaniline proceeded exclusively at the sterically less-hindered aromatic carbon atom of the aniline to afford the major products in good selectivity (**5k**–**5m** and **5o**). The reaction of cyclohexanecarbaldehyde also proceeded smoothly to afford product **5j** in excellent yield. Furthermore, other alkenes with electron-withdrawing groups, including acrylonitrile and acrylamide, gave the corresponding 2,3-disubstituted quinolines **5o**–**5r** in good to excellent yields. Remarkably, allylcy-

clohexane as aliphatic olefin was also converted successfully to the desired product **5s**, albeit in moderate yield. The structure of **5m** was further characterized by X-ray crystal diffraction measurement.[12]

To extend the applicability of our reaction, we next turned our attention to styrene derivatives as alkene substrates. Under the standard reaction conditions, the reactions of various styrene derivatives proceeded well with benzaldehyde **1a** and aniline **2a** to afford the desired 2,3-diphenylquinolines, along with some 2,4-diphenylquinolines as side products (Table 1).[14] In general, the selectivity toward 2,3-diphenyl-

Table 1: Reactions with styrene derivatives.[a]

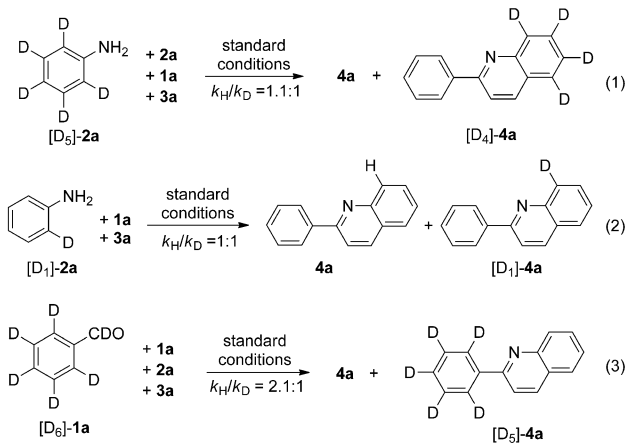


Entry	R^3	6	7	Yield [%][b] (6+7)	6:7
1	C_6H_5	**6a**	**7a**	83	3.5:1
2	4-FC_6H_4	**6b**	**7b**	79	1:1.3
3	4-ClC_6H_4	**6c**	**7c**	87	19:1
4	3-BrC_6H_4	**6d**	**7d**	73	15:1
5	4-CNC_6H_4	**6e**	**7e**	77	14:1
6	4-$OMeC_6H_4$	**6f**	**7f**	89	1:32
7	4-MeC_6H_4	**6g**	**7g**	82	1:1
8	4-$tBuC_6H_4$	**6h**	**7h**	81	1:3

[a] Reaction conditions: benzaldehyde **1a** (0.5 mmol), aniline **2a** (0.5 mmol), styrene derivative **3** (1 mmol), $PdCl_2$ (0.025 mmol, 5 mol%), $LiBr{\cdot}H_2O$ (0.5 mmol, 1 equiv), in acetonitrile (2 mL) at 60°C in air for 8 h. [b] Yields of isolated products.

quinolines from styrene substrates with electron-withdrawing substituents was better than that with electron-donating substituents. For example, while styrene gave regioisomers **6a** and **7a** in a ratio of 7:2, styrenes with electron-withdrawing substituents (4-chloro, 3-bromo, and 4-cyano) afforded the desired 2,3-diphenylquinolines (**6c–6e**) in good selectivity (>14:1). However, 4-fluoro and 4-methyl styrene gave two regioisomeric products in poor selectivity with a ratio of around 1:1. A mixture of two products, with 2,4-diphenylquinoline **7h** as the major one, was obtained with 4-*tert*-butyl styrene. 2,4-Diphenylquinoline **7f** was exclusively formed from 4-methoxy styrene.

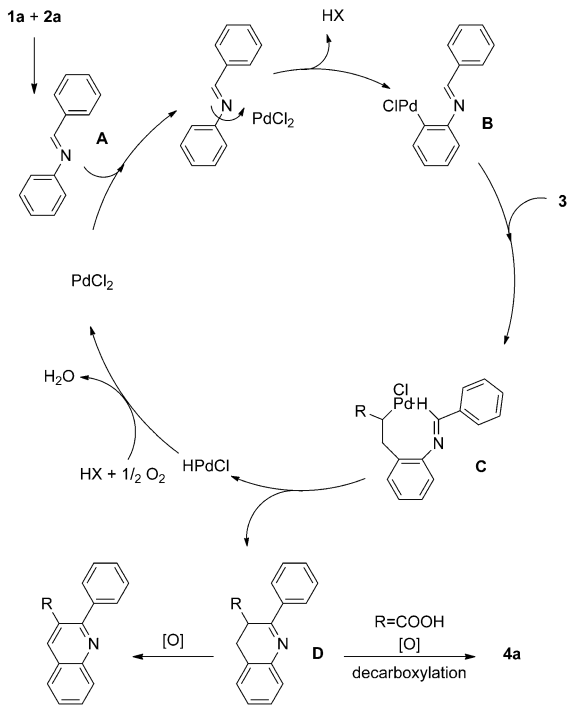
To probe the mechanism of the C–H bond cleavage, a mixture of substrates **2a** and [D_5]-**2a** (1:1) was subjected to the standard reaction conditions to determine the intermolecular isotope effect, and substrate [D_1]-**2a** was used to probe the intramolecular isotope effect (Scheme 4). Neither inter- nor intramolecular kinetic isotope effects were observed [$k_H/k_D \approx 1{:}1$, Eqs. (1) and (2) in Scheme 4], thus illustrating that the rate-limiting step does not involve the C–H cleavage of the aniline. Interestingly, when a mixture of substrates **1a** and [D_6]-**1a** (1:1) was used as the benzaldehyde reaction partner, the isotope effect (k_H/k_D) was determined to be 2.1:1 [Eq. (3) in Scheme 4]. These results indicate that the abstraction of the hydrogen atom from *N*-benzylideneaniline contributed to the rate-determining step during the process.



Scheme 4. Kinetic isotope effect (KIE) experiment.

Ultimately, when we subjected methyl 3-(2-benzylideneamino phenyl)acrylate to the standard reaction conditions, only a trace of the desired product **5a** was detected, thus indicating that intermediate **D** was not formed through 6π-electrocyclic rearrangement[15] of the intermediate derived by β-H elimination of **C**.[12] Actually, β-H elimination of **C** may be unfavored by the addition of excess halide ions in this reaction system.[13]

On the basis of the above-mentioned results, a possible catalytic cycle is shown in Scheme 5. The palladium catalyst reacts not only as a transition-metal catalyst, but also as a Lewis acid in the reaction. The reaction is initiated by *ortho* palladation of the palladium-catalyst-activated *N*-benzylideneaniline **A**, which is formed in situ from precursors **1a** and



Scheme 5. Possible mechanism for palladium-catalyzed cyclization reaction of aldehydes, amines, and alkenes.

2a, thus giving intermediate **B**.[16] Subsequent insertion of an alkene into the C–Pd bond is followed by abstraction of the hydrogen atom of *N*-benzylideneaniline, which is the rate-determining step of the reaction and leads to intermediate **C**. Subsequent reductive elimination generates **D** and releases Pd^0, which could be oxidized by O_2 to recover the Pd^{II} catalyst. Oxidation of **D** by both O_2 and *N*-benzylideneaniline **A**, which is reduced to the side product *N*-benzylaniline, afforded the product. Furthermore, when R is is a carboxy group, decarboxylation occurs under the reaction conditions to provide product **4a**.[11]

In conclusion, we have established a novel protocol based on the palladium-catalyzed sequential formation of two C–C bonds for the construction of a series of 2-substituted and 2,3-disubstituted quinolines from arylamines, aldehydes, and terminal olefins (electron-deficient and electron-rich olefins) under mild conditions. Gratifyingly, when acrylic acid is used in the transformation, decarboxylation occurs to provide 2-substituted quinolines. This methodology thus provides a tool for the synthesis of diversely substituted quinolines, apart from Povarov reactions. The products are expected to be useful intermediates for the preparation of pharmaceutically and biologically active compounds as well as functional materials. Moreover, the use of inexpensive starting materials and environmentally benign oxidants makes this atom-efficient method particularly attractive. Further investigations toward the scope of the reaction, a detailed mechanism, and applications in organic synthesis are ongoing in our laboratory.

Experimental Section

Typical procedure for the synthesis of 2-phenylquinoline **4**: A 25 mL Schlenk tube was charged with a solution of aldehyde **1** (0.5 mmol) and arylamine **2** (0.5 mmol) in MeCN (2 mL). $PdCl_2$ (0.025 mmol), $LiBr{\cdot}H_2O$ (0.5 mmol), and acrylic acid **3a** were added and, under magnetic stirring, the mixture was heated in air at 60 °C for 8 h. The solvent was removed under reduced pressure, and the products were isolated by column chromatography on silica gel (petroleum ether/ethyl acetate = 30:1→20:1) to give **4**, which was further recrystallized from ethyl acetate/petroleum ether (3–6 % ethyl acetate in petroleum ether). The structures of the known products were confirmed by comparison with reported spectroscopic data. Products **5**, **6**, and **7** were prepared using the same procedure as described for **4**.

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[1] a) G. Zeni, R. C. Larock, *Chem. Rev.* **2006**, *106*, 4644; b) I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127.

[2] a) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068; b) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318; c) G. Balme, E. Bossharth, N. Monteiro, *Eur. J. Org. Chem.* **2003**, 4101.

[3] a) J. Magano, J. R. Dunetz, *Chem. Rev.* **2011**, *111*, 2177; b) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2011**, *111*, PR215; c) R. Skoda-Földes, *Chem. Rev.* **2003**, *103*, 4095.

[4] a) J. P. Michael, *Nat. Prod. Rep.* **2008**, *25*, 166; b) B. D. Bax, P. F. Chan, D. S. Eggleston, A. Fosberry, D. R. Gentry, F. Gorrec, I. Giordano, M. M. Hann, A. Hennessy, M. Hibbs, J. Huang, E. Jones, J. Jones, K. K. Brown, C. J. Lewis, E. W. May, M. R. Saunders, O. Singh, C. E. Spitzfaden, C. Shen, A. Shillings, A. J. Theobald, A. Wohlkonig, N. D. Pearson, M. N. Gwynn, *Nature* **2010**, *466*, 935; c) M. Rouffet, C. A. F. de Oliveira, Y. Udi, A. Agrawal, I. Sagi, J. A. McCammon, S. M. Cohen, *J. Am. Chem. Soc.* **2010**, *132*, 8232; d) S. Andrews, S. J. Burgess, D. Skaalrud, J. Xu Kelly, D. H. Peyton, *J. Med. Chem.* **2010**, *53*, 916; e) A.-M. Lord, M. F. Mahon, M. D. Lloyd, M. D. Threadgill, *J. Med. Chem.* **2009**, *52*, 868; f) D. C. Behenna, J. L. Stockdill, B. M. Stoltz, *Angew. Chem.* **2008**, *120*, 2400; *Angew. Chem. Int. Ed.* **2008**, *47*, 2365; g) J. K. Natarajan, J. N. Alumasa, K. Yearick, K. A. Ekoue-Kovi, L. B. Casabianca, A. C. de Dios, C. Wolf, P. D. Roepe, *J. Med. Chem.* **2008**, *51*, 3466; h) K. Andries, P. Verhasselt, J. Guillemont, H. W. H. Göhlmann, J.-M. Neefs, H. Winkler, J. V. Gestel, P. Timmerman, M. Zhu, E. Lee, P. Williams, D. de Chaffoy, E. Huitric, S. Hoffner, E. Cambau, C. Truffot-Pernot, N. Lounis, V. Jarlier, *Science* **2005**, *307*, 223.

[5] a) N. Kaila, K. Janz, S. DeBernardo, P. W. Bedard, R. T. Camphausen, S. Tam, D. H. H. Tsao, J. C. Keith, Jr., C. Nickerson-Nutter, A. Shilling, R. Young-Sciame, Q. Wang, *J. Med. Chem.* **2007**, *50*, 21; b) M. Krishnamurthy, K. Simon, A. M. Orendt, P. A. Beal, *Angew. Chem.* **2007**, *119*, 7174; *Angew. Chem. Int. Ed.* **2007**, *46*, 7044; c) M. Krishnamurthy, B. D. Gooch, P. A. Beal, *Org. Lett.* **2004**, *6*, 63; d) J. B. Chaires, J. Ren, M. Henary, O. Zegrocka, G. R. Bishop, L. Strekowski, *J. Am. Chem. Soc.* **2003**, *125*, 7272; e) L. Strekowski, M. Say, M. Henary, P. Ruiz, L. Manzel, D. E. Macfarlane, A. J. Bojarski, *J. Med. Chem.* **2003**, *46*, 1242; f) L. Strekowski, Y. Gulevich, T. C. Baranowski, A. N. Parker, A. S. Kiselyov, S.-Y. Lin, F. A. Tanious, W. D. Wilson, *J. Med. Chem.* **1996**, *39*, 3980; g) G. J. Atwell, B. C. Baguley, W. A. Denny, *J. Med. Chem.* **1989**, *32*, 396; h) P. N. Craig, *J. Med. Chem.* **1972**, *15*, 144.

[6] a) Y. Matsubara, S. Hirakawa, Y. Yamaguchi, Z.-i. Yoshida, *Angew. Chem.* **2011**, *123*, 7812; *Angew. Chem. Int. Ed.* **2011**, *50*, 7670; b) H. Richter, O. G. Mancheño, *Org. Lett.* **2011**, *13*, 6066; c) G. Shan, X. Sun, Q. Xia, Y. Rao, *Org. Lett.* **2011**, *13*, 5770; d) F. Yu, S. Yan, L. Hu, Y. Wang, J. Lin, *Org. Lett.* **2011**, *13*, 4782; e) G.-L. Gao, Y.-N. Niu, Z.-Y. Yan, H.-L. Wang, G.-W. Wang, A. Shaukat, Y.-M. Liang, *J. Org. Chem.* **2010**, *75*, 1305; f) B. Karataş, R. Aumann, *Organometallics* **2010**, *29*, 801; g) K. Cao, F.-M. Zhang, Y.-Q. Tu, X.-T. Zhuo, C.-A. Fan, *Chem. Eur. J.* **2009**, *15*, 6332; h) S. Tanaka, M. Yasuda, A. Baba, *J. Org. Chem.* **2006**, *71*, 800.

[7] a) S. Cai, J. Zeng, Y. Bai, X.-W. Liu, *J. Org. Chem.* **2012**, *77*, 801; b) X. Zhang, B. Liu, X. Shu, Y. Gao, H. Lv, J. Zhu, *J. Org. Chem.* **2012**, *77*, 501; c) S. Fan, J. Yang, X. Zhang, *Org. Lett.* **2011**, *13*, 4374; d) N. T. Patil, V. S. Raut, *J. Org. Chem.* **2010**, *75*, 6961; e) Z. Huo, I. D. Gridnev, Y. Yamamoto, *J. Org. Chem.* **2010**, *75*, 1266; f) M. Tobisu, I. Hyodo, N. Chatani, *J. Am. Chem. Soc.* **2009**, *131*, 12070; g) L.-C. Campeau, D. R. Stuart, J.-P. Leclerc, M. Bertrand-Laperle, E. Villemure, H.-Y. Sun, S. Lasserre, N. Guimond, M. Lecavallier, K. Fagnou, *J. Am. Chem. Soc.* **2009**, *131*, 3291; h) A. M. Berman, J. C. Lewis, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2008**, *130*, 14926; i) C. A. Fleckenstein, H. Plenio, *J. Org. Chem.* **2008**, *73*, 3236; j) M. Movassaghi, M. D. Hill, *J. Am. Chem. Soc.* **2006**, *128*, 4592.

[8] a) L. S. Povarov, *Russ. Chem. Rev.* **1967**, *36*, 656; b) G. Dagousset, J. Zhu, G. Masson, *J. Am. Chem. Soc.* **2011**, *133*, 14804; c) E. Vicente-García, F. Catti, R. Ramón, R. Lavilla, *Org. Lett.* **2010**, *12*, 860; d) H. Liu, G. Dagousset, G. Masson, P. Retailleau, J. Zhu, *J. Am. Chem. Soc.* **2009**, *131*, 4598; e) M.-G. Shen, C. Cai, W.-B. Yi, *J. Heterocycl. Chem.* **2009**, *46*, 796; f) N. Shindoh, H. Tokuyama, Y. Takemoto, K. Takasu, *J. Org. Chem.* **2008**, *73*,

7451; g) T. Demaude, L. Knerr, P. Pasau, *J. Comb. Chem.* **2004**, *6*, 768.

[9] For recent developments on transition-metal-catalyzed reactions in air or under O_2 atmosphere, see: a) Z. Shi, C. Zhang, C. Tang, N. Jiao, *Chem. Soc. Rev.* **2012**, *41*, 3381; b) W. Wu, J. Xu, S. Huang, W. Su, *Chem. Commun.* **2011**, *47*, 9660; c) L. Huang, H. Jiang, C. Qi, X. Liu, *J. Am. Chem. Soc.* **2010**, *132*, 17652; d) H. Zhao, M. Wang, W. Su, M. Hong, *Adv. Synth. Catal.* **2010**, *352*, 1301; e) T. Punniyamurthy, S. Velusamy, J. Iqbal, *Chem. Rev.* **2005**, *105*, 2329.

[10] a) L. A. Mitscher, *Chem. Rev.* **2005**, *105*, 559; b) Y. Zhang, W. A. Guiguemde, M. Sigal, F. Zhu, M. C. Connelly, S. Nwaka, R. K. Guy, *Bioorg. Med. Chem.* **2010**, *18*, 2756; c) R. Ghodsi, A. Zarghi, B. Daraei, M. Hedayati, *Bioorg. Med. Chem.* **2010**, *18*, 1029; d) T.-H. Chuang, C.-H. Yang, P.-C. Kao, *Inorg. Chim. Acta* **2009**, *362*, 5017; e) P. Narender, U. Srinivas, M. Ravinder, B. A. Rao, C. Ramesh, K. Harakishore, B. Gangadasu, U. S. N. Murthy, V. J. Rao, *Bioorg. Med. Chem.* **2006**, *14*, 4600; f) D. V. Kravchenko, Y. A. Kuzovkova, V. M. Kysil, S. E. Tkachenko, S. Maliarchouk, I. M. Okun, K. V. Balakin, A. V. Ivachtchenko, *J. Med. Chem.* **2005**, *48*, 3680.

[11] For selected Pd^{II}-catalyzed decarboxylation reactions of arenas, see: a) P. Hu, M. Zhang, X. Jie, W. Su, *Angew. Chem.* **2012**, *124*, 231; *Angew. Chem. Int. Ed.* **2012**, *51*, 227; b) M. Zhang, J. Zhou, J. Kan, M. Wang, W. Su, M. Hong, *Chem. Commun.* **2010**, *46*, 5455; c) K. Xie, Z. Yang, X. Zhou, X. Li, S. Wang, Z. Tan, X. An, C.-C. Guo, *Org. Lett.* **2010**, *12*, 1564; d) P. Hu, J. Kan, W. Su, M. Hong, *Org. Lett.* **2009**, *11*, 2341; e) J. S. Dickstein, C. A. Mulrooney, E. M. O'Brien, B. J. Morgan, M. C. Kozlowski, *Org. Lett.* **2007**, *9*, 2441; f) D. Tanaka, S. P. Romeril, A. G. Myers, *J. Am. Chem. Soc.* **2005**, *127*, 10323.

[12] See the Supporting Information for details.

[13] The excess of halide ions from the additive can effectively inhibit the β-H elimination; see: a) Z. Wang, Z. Zhang, X. Lu, *Organometallics* **2000**, *19*, 775; b) Z. Zhang, X. Lu, Z. Xu, Q. Zhang, X. Han, *Organometallics* **2001**, *20*, 3724.

[14] It was reported previously that reactions of benzaldehyde, aniline, and styrene catalyzed by Lewis acids gave 2,4-disubstituted quinoline only; see Ref. [8e]. However, methods for the synthesis of 2,3-disubstituted quinoline simply from benzaldehyde, aniline, and styrene have not been reported before.

[15] L. G. Qiang, N. H. Baine, *J. Org. Chem.* **1988**, *53*, 4218.

[16] a) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315; b) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; c) M. Ye, G.-L. Gao, A. J. F. Edmunds, P. A. Worthington, J. A. Morris, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 19090; d) B. Xiao, T.-J. Gong, Z.-J. Liu, J.-H. Liu, D.-F. Luo, J. Xu, L. Liu, *J. Am. Chem. Soc.* **2011**, *133*, 9250; e) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; f) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173.

