Iron(III)-Catalyzed and Air-Mediated Tandem Reaction of Aldehydes, Alkynes and Amines: An Efficient Approach to Substituted Quinolines

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Quinolines and their derivatives occur in a large number of biologically active natural products, and they are also important starting materials for the chemical and pharmaceutical industry.^[1] Since Skraup reported the synthesis of quinoline in 1880 for the first time,^[2] there have been great achievements in this area, and many synthetic methods based on the use of transition-metal catalysts have been developed.^[3] However, the limited availability of starting materials is the main drawback of many of these methods. For example, the Friedländer reaction, one of the most useful methods for synthesizing quinolines, is based on the Aldol condensation of unstable 2-aminobenzaldehydes, which are generated in situ by reduction of 2-nitrobenzaldehyde derivatives, which themselves are not readily available.^[4] Considering their importance in pharmacology and functional material chemistry, the development of more facile and economic synthetic approaches is still desirable.

Recently, iron has emerged as a very promising catalyst for cross-coupling reactions, and therefore it has been attracting increasing research interest from chemists due to its low price, non-toxicity, and environmentally friendly character.^[5] In the course of our research on synthesizing propargylamines by the FeCl₃-catalyzed three-component coupling of aldehydes, alkynes, and amines [Eq. (1)],^[6] we found that when aniline was used to replace the secondary amine, 2, 4diphenyl-substituted quinoline [Eq. (2)] instead of the expected propargylamine product was formed in 56% yield with 70% conversion after 48 h under argon, and the structure was confirmed by the X-ray crystallographic analysis.^[7]

Inspired by this result, we next further investigated this reaction in detail. Gratifyingly, when we decreased the load-



ing of aniline from 1.3 equiv to 1.05 equiv and increased the concentration of catalyst from $0.025 \text{ mmol}\text{mL}^{-1}$ to 0.1 mmol mL⁻¹ in toluene at 110 °C under an air atmosphere, the desired quinoline was afforded in 70% yield. Following these general conditions, we then examined the scope of this reaction, and the results are summarized in Table 1.

Phenylacetylene and aniline were initially used as model substrates for exploring the aldehyde substrate scope. From Table 1 (see below), it can be seen that when the aromatic aldehyde carried an electron-donating group or an electron-withdrawing group, the reactions proceeded smoothly to give the corresponding quinolines in moderate to good yields (entries 2–5). However, when a bulky 1-naphthaldehyde was used, the desired quinoline was obtained in a lower yield of 56 % (entry 6). Additionally, a heteroaromatic aldehyde is also compatible with this transformation and the expected product was afforded in 83 % yield (entry 7). However, when an aliphatic aldehyde (cyclohexanecarboxaldehyde) was subjected to the reaction, the desired product was obtained only in 30 % yield.

Then, we elucidated the scope of amine substrates that were applicable for this reaction; both *p*-toluidine and *p*-methoxyaniline were good substrates for this transformation and the corressponding products were afforded in 95% and 65% yields (entries 8 and 9), respectively. The halogen-containing anilines were also subjected to the reaction conditions, and the desired quinolines were obtained in moderate to excellent yields (entries 10-12).

Subsequently, the scope of alkynes in this reaction was further investigated, and it was found that substituted phenylacetylenes, heteroaromatic alkynes, and aliphatic alkynes



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Table 1.	Synthesis	of quinoline	s by iron	(III)-catalyzed	three-component	cou-
pling/hy	droarylatio	on of aldehyd	es, alkyn	es, and amines	[a]	

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R ¹⁻	сно + _{R²}	₩H ₂ + R ³ -=== -	FeCl ₃ (10%) toluene, 110 °C air, 24h	R^2 N	R^1
Entry	Aldehyde	Amine	Alkyne	Product	Yield [%] ^[b]
1	СНО 1а	✓NH₂ 2a	3a	1 aa	70
2		2a	3a	1bb	72
3	О-СНО	2a	3a	1cc	83
4		2a	3a	1 dd	65
5	СНО	2 a	3a	1ee	85
6	1f	2 a	3a	1 ff	56
7	S CHO 1g	2a	3a	1gg	83
8	1a		3a	2bb	92
9	1a		3a	2 cc	65
10	1a		3a	2 dd	90
11	1a		3a	2ee	95
12	1a	Br NH ₂	3a	2 ff	70
13	1a	2a	0-<	3bb	85
14	1a	2 a	F ₃ C	3cc	62
15	1a	2a	<u></u>	3 dd	92
16	1a	2 a	s	3ee	88

[a] Reaction conditions: aldehyde (1.0 mmol), amine (1.05 mmol), alkyne (1.5 mmol), FeCl₃ (0.1 mmol), toluene (1 mL), 110 °C, under an air atmosphere. [b] Isolated yield calculated on the basis of aldehyde.

were perfectly suitable substrates for this transformation, and the expected products were obtained in moderate to excellent yields (entries 13–16).

Based on the experimental results above and together with our previous work,^[6] a tentative mechanism was proposed (Scheme 1). Intermediate **A** was initially formed by coordination of imine, which was generated in situ, and alkyne to Fe^{III} ,^[8] and then addition of alkyne to imine forms



Scheme 1. Mechanism for iron-catalyzed tandem coupling/hydroarylation of aldehyde, alkyne, and amine.

the propargylamine intermediate **B**, which then undergoes an intramolecular hydroarylation^[9,10] of alkyne to give dihydroquinoline intermediate C.^[11] In this course, we deem that the forming of the propargylamine intermediate **B** and the subsequent hydroarylation reaction experience a cooperative process since we did not detect the propargylamine **B** in the reaction mixture. A final oxidation of **C** by O₂ in air affords the quinoline product.^[12] Comparing with the similar AuCl₃-mediated process, the stronger Lewis acidity of FeCl₃ than AuCl₃ appears to be the main reason for the higher efficiency of our catalytic system.^[11]

In summary, we have developed a facile and economic method for the construction of quinolines by the FeCl₃-catalyzed three-component coupling/hydroarylation/dehydrogenation of aldehydes, alkynes, and amines for the first time. A series of 2, 4-disubstituted quinolines have been synthesized from simple and readily available starting materials. Further studies on the reaction mechanism and the synthetic application are currently ongoing in our group.

Experimental Section

Typical procedure: To a 10 mL flask were sequentially added toluene (1 mL), FeCl₃ (16.2 mg, 0.1 mmol), benzaldehyde (0.104 mL, 1.0 mmol), aniline (0.096 mL, 1.05 mmol), and phenylacetylene (0.168 mL, 1.5 mmol) under an air atmosphere. The reaction mixture was then stirred at 110 °C until the substrate had been consumed completely (ca. 24 h), and then it was cooled to room temperature and filtered through a short silica gel column using CH₂Cl₂ as eluent. After evaporation of the solvent, the residue was purified by flash chromatography (petroleum ether/AcOEt = 20:1) to afford **1aa** (197 mg, 70 % yield).

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- a) J. P. Michael, Nat. Prod. Rep. 1997, 14, 605; b) P. R. Kym, M. E. Kort, M. J. Coghlan, J. L. Moore, R. Tang, J. D. Ratajczyk, D. P. Larson, S. W. Elmore, J. K. Pratt, M. A. Stashko, H. D. Falls, C. W. Lin, M. Nakane, L. Miller, C. M. Tyree, J. N. Miner, P. B. Jacobson, D. M. Wilcox, P. Nguyen, B. C. Lane, J. Med. Chem. 2003, 46, 1016; c) L. Strekowski, M. Say, M. Henary, P. Ruiz, L. Manzel, D. E. Macfarlane, A. J. Bojarski, J. Med. Chem. 2003, 46, 1242; d) W. Sawada, H. Kayakiri, Y. Abe, K. Imai, A. Katayama, T. Oku, H. Tanaka, J. Med. Chem. 2004, 47, 1617.
- [2] Z. H. Skraup, Ber. Dtsch. Chem. Ges. 1880, 13, 2086.
- [3] For selected examples, see: a) P. Friedländer, *Ber. Dtsch. Chem. Ges.* 1882, 15, 2572; b) M. Beller, O. R. Thiel, H. Trauthwein, C. G. Hartung, *Chem. Eur. J.* 2000, 6, 2513; c) H. Amii, Y. Kishikawa, K. Uneyama, *Org. Lett.* 2001, 3, 1109; d) B. Jiang, Y.-G. Si, *J. Org. Chem.* 2002, 67, 9449; e) X. Zhang, M. A. Campo, T. Yao, R. C. Larock, *Org. Lett.* 2005, 7, 763; f) R. P. Korivi, C.-H. Cheng, *J. Org. Chem.* 2006, 71, 7079; g) M. Movassaghi, M. D. Hill, *J. Am. Chem. Soc.* 2006, 128, 4592; h) X.-Y. Liu, P. Ding, J.-S. Huang, C.-M. Che, *Org. Lett.* 2007, 9, 2645; i) K. C. Lekhok, D. Prajapati, R. C. Boruah, *Synlett* 2008, 655.
- [4] a) Y. Hsiao, N. R. Rivera, N. Yasuda, D. L. Hughes, P. J. Reider, Org. Lett. 2001, 3, 1101; b) Y.-Z. Hu, G. Zhang, R. P. Thummel, Org. Lett. 2003, 5, 2251; c) P. G. Dormer, K. K. Eng, R. N. Farr, G. R. Humphrey, J. C. McWilliams, P. J. Reider, J. W. Sager, R. P. Volante, J. Org. Chem. 2003, 68, 467; d) B. R. McNaughton, B. L. Miller, Org. Lett. 2003, 5, 4257.
- [5] For reviews, see: a) C. Bolm, J. Legros, J. L. Paih, L. Zani, *Chem. Rev.* 2004, 104, 6217; b) D. D. Díaz, P. O. Miranda, J. I. Padrón, V. S. Martín, *Curr. Org. Chem.* 2006, 10, 457; c) A. Correa, O. G. Manche-ño, C. Bolm, *Chem. Soc. Rev.* 2008, 37, 1108; d) S. Enthaler, K.

Junge, M. Beller, Angew. Chem. 2008, 120, 3363; Angew. Chem. Int. Ed. 2008, 47, 3317; e) B. D. Sherry, A. Fürstner, Acc. Chem. Res. 2008, 41, 1500.

- [6] During the preparation of our manuscript, Wang and co-workers reported a similar reaction, see: P. Li, Y. Zhang, L. Wang, *Chem. Eur. J. 2009*, *15*, 2045.
- [7] CCDC-722236 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ data_request/cif.
- [8] a) P. O. Miranda, D. D. Diaz, J. I. Padrón, M. A. Ramírez, V. S. Martín, J. Org. Chem. 2005, 70, 57; b) K. Kohno, K. Nakagawa, T. Yahagi, J.-C. Choi, H. Yasuda, T. Sakakura, J. Am. Chem. Soc. 2009, 131, 2784.
- [9] For an overview of hydroarylation reactions, see: V. Mamane, P. Hannen, A. Fürstner, *Chem. Eur. J.* 2004, 10, 4556.
- [10] A supporting experiment was performed by using the propargylamine 4 under current standard conditions, and the desired 2,4-diphenyl-substituted quinoline 1aa was obtained in 60% yield after 72 h.



- [11] For similar transformations catalyzed by AuCl₃, see: F. Xiao, Y. Chen, Y. Liu, J. Wang, *Tetrahedron* 2008, 64, 2755.
- [12] a) J. A. Damavandi, M. A. Zolfigol, B. Karami, *Synth. Commun.* 2001, *31*, 3183; b) T. P. Forrest, G. A. Douphinee, S. A. Deraniyagala, *Can. J. Chem.* 1985, *63*, 412.

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