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Cooperative Catalysis with Metal and Secondary Amine: Synthesis of 2-Substituted Quinolines via Addition/Cycloisomerization Cascade

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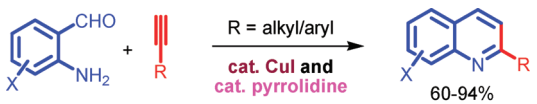

CuI and pyrrolidine catalysts co-operates with each other

A cooperative catalytic system, consisting of CuI and pyrrolidine, has been developed for an efficient synthesis of 2-substituted quinolines. A combination of both the catalysts is necessary; the use of either catalyst alone does not give the product.

In recent years, the concept of combining transition-metal catalysis with organocatalysis has emerged as a promising strategy for developing unique transformations.[1] In particular, a multicatalytic cascade involving an alkyne functionality, wherein soft transition-metal ions[2] are employed, would be considered a difficult task. Kirsch and co-workers developed a cooperative catalytic system consisting of a combination of a Au(I) complex and a secondary amine.[3] Dixon et al. found a mutually compatible combination of pyrrolidine and $Cu(OTf)_2-PPh_3$ for the synthesis of cyclopentenes.[4] Jørgensen et al. developed a route to cyclopentene carbaldehydes under cooperative catalysis by Cu(I)/Au(I) and a secondary amine.[5] A sequential procedure for the synthesis of substituted cyclic ether based on a secondary amine and Au(I) complexes has been reported by Krause and Alexakis.[6] Ding and Wu developed a binary catalytic system, consisting of AgOTf and a secondary amine, for the synthesis of 1,2-dihydroisoquinolines.[7]

Keeping in mind the above literature and our recent results on π-activation,[8] we considered a cooperative catalytic system, consisting of a metal and a secondary amine, as a potentially useful tool to access 2-substituted quinolines **3** from 2-aminobenzaldehydes **1** and terminal alkynes **2** (Scheme 1). Notably, 2-substituted quinolines are one of the most ubiquitous structural motifs found in numerous naturally occurring[9] and pharmacologically important compounds.[10]Herein, we report our findings on this study.[11]

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SCHEME 1. Concept of Cooperative Catalysis for the Synthesis of 2-Substituted Quinolines

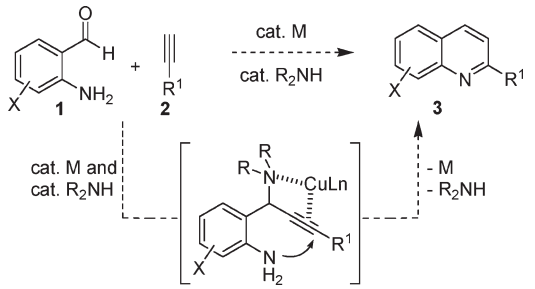
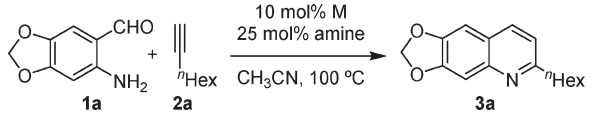


TABLE 1. Catalysts Screening Studies[a]

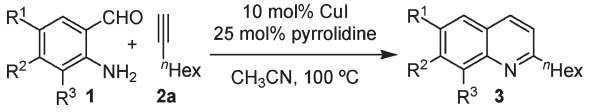


entry	M	amine	yield[b] (%)
1	CuCl	pyrrolidine	71
2	CuBr	pyrrolidine	56
3	**CuI**	**pyrrolidine**	**85**
4	$[Cu(CH_3CN)_4]PF_6$	pyrrolidine	82
5	$Cu(OTf)_2$	pyrrolidine	56
6	CuI	morpholine	82
7	CuI	piperidine	80
8	CuI	Et_2NH	50
9	CuI	$^iPr_2NH$	*c*
10	CuI	Cy_2NH	25
11	CuI	Bn_2NH	20
12	AgOTf	pyrrolidine	70
13	AuCl	pyrrolidine	50
14	PPh_3AuOTf	pyrrolidine	75
15	CuI		*c*
16		pyrrolidine	*c*

[a]A solution of the **1a** (0.30 mmol), 1-octyne **2a** (0.36 mmol), metal catalyst (10 mol %), and secondary amine (25 mol %) in CH_3CN (2 mL) was heated at 100 °C for 12 h. [b]Isolated yields. [c]Recovery of **1a** in 70−80% yield.

Proof of principle studies were carried out using **1a** and 1-octyne **2a** as model substrates in acetonitrile. At first, we explored copper-based catalysts because they are highly tolerant toward basic amines and they are superior catalysts for alkynylation. To begin with, **1a** and **2a** were treated with 10 mol % of CuCl and 25 mol % of pyrrolidine in acetonitrile at 100 °C. Pleasingly, the reaction proceeded well, and the desired product **3a** was obtained in 71% yield (Table 1, entry 1). Next, various Cu(I) and Cu(II) catalysts were examined (entries 2−5); among them, CuI proved to be the best (entry 3). Using CuI as a catalyst, a variety of secondary amines were examined; however, the outcome turned out to be unsatisfactory (6−11) compared with the results described in entry 3. The other metal catalysts such as Ag(I) and Au(I) also gave products, albeit in moderate yields (entries 12−14). As can be judged from entries 15 and 16, the use of either of catalyst (CuI or pyrrolidine) alone does not give **3a**.

TABLE 2. Scope with 2-Aminobenzaldehydes[a]



entry	**1**	**3**	yield[b] (%)
1	**1b**, $R^1 = R^2 = R^3 = H$	**3b**	94
2	**1c**, R^1 = Me, $R^2 = R^3 = H$	**3c**	82
3	**1d**, $R^1 = R^3$ = Me, $R^2 = H$	**3d**	76
4	**1e**, R^1 = OMe, $R^2 = R^3 = H$	**3e**	78
5	**1f**, $R^1 = R^2$ = OMe, $R^3 = H$	**3f**	78
6	**1g**, $R^1 = R^3 = H$, R^2 = Cl	**3g**	80
7	**1h**, R^1 = Cl, $R^2 = H$, R^3 = Me	**3h**	90
8	**1i**, R^1 = Br, $R^2 = R^3 = H$	**3i**	72
9	**1j**, R^1 = COOMe, $R^2 = R^3 = H$	**3j**	62[c]
10	**1k**, $R^1 = R^3 = H$, R^2 = COOMe	**3k**	67[c]
11	**1l**, R^1 = CN, $R^2 = R_3 = H$	**3l**	72[d]
12	**1m**, $R^1 = NO_2$, $R^2 = R^3 = H$	**3m**	58[e]

[a]A solution of the **1** (0.30 mmol), 1-octyne **2a** (0.36 mmol), CuI (10 mol %), and pyrrolidine (25 mol %) in CH_3CN (2 mL) was heated at 100 °C for 12 h. [b]Isolated yields. [c]Reaction mixture was heated for 18 h. [d]Reaction mixture was heated for 36 h. [e]Reaction mixture was heated for 48 h.

With the optimized reaction conditions in hand, we then extended the reaction range to include 2-aminobenzaldehydes (Table 2). As illustrated in Table 2, 1-octyne was reacted with functionalized 2-aminobenzaldehydes bearing ortho, meta, and para substitutions on the aryl ring to give the corresponding products in moderate to good yields. Particularly noteworthy is the fact that halo substituents were well tolerated (entries 6−8); therefore, the products obtained have potential for further functionalization by conventional palladium-catalyzed cross-coupling reactions. Another advantage of this method is that even electron-withdrawing substituents, such as −COOMe, −CN, and $-NO_2$, in the 2-aminobenzaldehydes were tolerated, although longer reaction times were needed for the completion of the reaction (entries 9−12). It should be noted that the reaction is not applicable to the ketone, i.e., 2-aminoacetophenone or 2-aminobenzophenone.

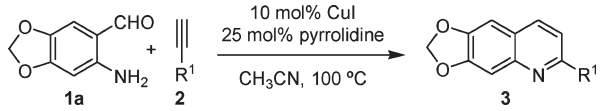
To further explore the generality and scope of this approach, a variety of terminal alkynes were investigated (Table 3). The aryl alkynes **2b** and **2c** on reaction with **1a** gave the expected product **3n** and **3o** in 61% and 67% yields, respectively (entries 1 and 2). Interestingly, enynes **2d** and **2e** also worked well to afford **3p** and **3q** in 85% and 60% yields, respectively (entries 3 and 4). Aliphatic terminal alkynes **2f**−**i** (entries 5−8) and cycloalkyl acetylenes **2j**−**k** (entries 9 and 10) were also found to be good substrates, giving the corresponding products **3r**−**w** in moderate to good yields. The reaction of heteroaromatic alkynes **2l** and **2m** with **1a** under the standard reaction conditions afforded **3x** and **3y** in 90% and 86% yields, respectively (entries 11 and 12).

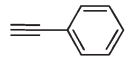
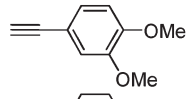
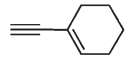
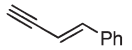
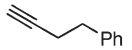
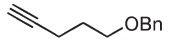
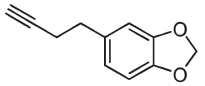
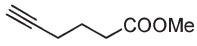
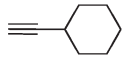
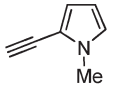
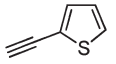
A mechanistic hypothesis based on the dual activation concept in which an organocatalyst is combined with π-acid, is proposed in Figure 1. At first, aldehyde **1** would condense in situ with the pyrrolidine to give an iminium ion **4**.[12] The iminium ion **4** on reaction with CuI and 1-octyne **2a** would

(11) A conceptually different process for the synthesis of quinolines has been reported. However, none of the processes is known to give 2-substituted (4-unsubstituted) quinolines; see: (a) Liu, X.-Y.; Ding, P.; Huang, J.-S.; Che, C.-M. *Org. Lett.* **2007**, *9*, 2645–2648. (b) Jiang, B.; Si, Y.-G. *J. Org. Chem.* **2002**, *67*, 9449–9451. (c) Tokunaga, M.; Eckert, M.; Wakatsuki, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 3222–3225.

(12) 2-Aminoacetophenone and 2-aminobenzophenone might have failed to undergo this reaction because of their reluctance to form iminium ion compared to corresponding aldehydes.

TABLE 3. Scope with Terminal Alkynes[a]



entry	2		3	yield[b]
1		**2b**	**3n**	61%
2		**2c**	**3o**	67%
3		**2d**	**3p**	85%
4		**2e**	**3q**	60%
5		**2f**	**3r**	88%
6		**2g**	**3s**	60%
7		**2h**	**3t**	87%
8		**2i**	**3u**	79%
9		**2j**	**3v**	81%[c]
10		**2k**	**3w**	64%
11		**2l**	**3x**	90%
12		**2m**	**3y**	86%

[a]A solution of the **1a** (0.30 mmol), terminal alkynes **2** (0.36 mmol), CuI (10 mol %), and pyrrolidine (25 mol %) in CH_3CN (2 mL) was heated at 100 °C for 12 h. [b]Isolated yields. [c]3 equiv of **2j** was used.

produce intermediate **5** with expulsion of water. A union of copper acetylide and iminium ion in **5** would then lead to the formation of copper-coordinated propargylamine derivative **6**.[13] The intermediate **6** would then undergo 6-*endo-dig* cyclization to form **7**. A protonation and aromatization would then occur to give **3a** with the liberation of CuI and pyrrolidine. To gain insight into the mechanism, an experiment was conducted using benzaldehyde as a substrate. Accordingly, a solution of benzaldehyde, 1-octyne, and pyrrolidine in acetonitrile was heated at 100 °C for 12 h in the presence of

(13) Cu(I)-catalyzed three-component coupling reactions of aldehydes, terminal alkynes, and amines is a well-known process; for selected examples, see: (a) Nakamura, S.; Ohara, M.; Nakamura, Y.; Shibata, N.; Toru, T. *Chem.—Eur. J.* **2010**, *16*, 2360–2362. (b) Gommermann, N.; Knochel, P. *Chem.—Eur. J.* **2006**, *12*, 4380–4392. (c) Bisai, A.; Singh, V. K. *Org. Lett.* **2006**, *8*, 2405–2408. (d) Wei, C.; Mague, J. T.; Li, C. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5749–5754. (e) Shi, L.; Tu, Y. Q.; Wang, M.; Zhang, F. M.; Fan, C. A. *Org. Lett.* **2004**, *6*, 1001–1003. (f) Knöpfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971–5973. (g) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763–5766. (h) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638–5639. (i) Brannock, K. C.; Burpitt, R. D.; Thweatt, J. G. *J. Org. Chem.* **1963**, *28*, 1462–1464.

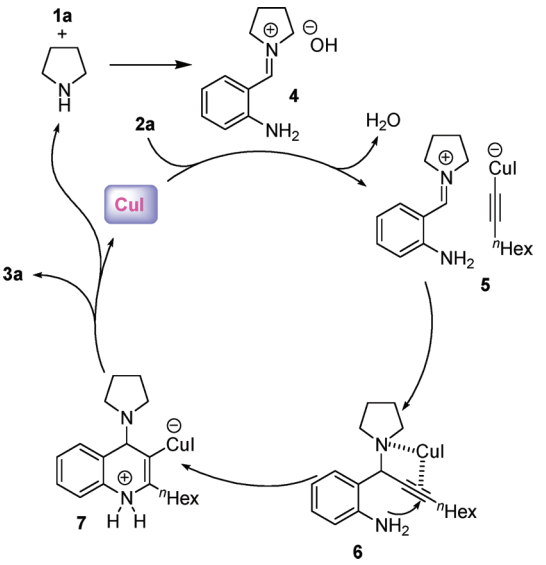


FIGURE 1. Proposed mechanism for cooperative catalysis.

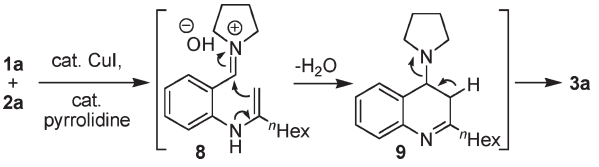


FIGURE 2. Alternative mechanism.

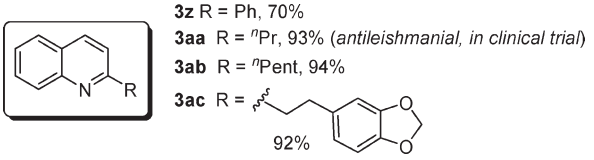


FIGURE 3. Application to the synthesis of biologically active compounds/natural products.

10 mol % of CuI. The reaction afforded the corresponding three-component coupling product in 90% yield.[14]

Another possible mechanism involving hydroamination between **1a** and **2a**, which triggers cycloisomerization (cf. **8** and **9**) to form **3a** (Figure 2), can be completely ruled out. None of the reactions produced C-2- and C-3-disubstituted regioisomeric quinolines, not even in trace amounts.[11a] In addition, the reaction between aniline and 1-octyne under the standard conditions did not afford the corresponding hydroamination product.

As a further demonstration of the utility of a cooperative catalytic system, we thought of synthesizing some biologically active compounds/natural products.[9d,e] Accordingly, when 2-aminobenzaldehyde **1b** was treated with **2b**, 1-pentyne, 1-heptyne, and **2h** independently, under standard conditions, quinolines **3z**, **3aa**, **3ab**, and **3ac** were obtained in 70%, 93%, 94%, and 92% yields, respectively (Figure 3). Remarkably, 2-propylquinoline **3aa** is currently undergoing clinical trials.[10a]

In conclusion, we have developed a practical strategy to access 2-substituted quinolines from 2-aminobenzaldehyde

(14) See the Supporting Information for details.

and terminal alkynes through a tandem addition/cycloisomerization cascade catalyzed by a pyrrolidine and copper(I) iodide co-operative catalyst system. The developed method has been found to be applicable for the synthesis of naturally occurring and pharmaceutically important compounds. Since the enantioselective transfer hydrogenation of 2-substituted quinolines is known in the literature,[15] the present protocol may find use in the preparation of appropriately substituted quinolines, which can further be transformed into enantiopure tetrahydroquinoline natural products and their analogues.[16] As far as regioselectivitive synthesis of 2-substituted quinolines is concerned, the present protocol constitutes an advanced complement to Friedländer synthesis of quinolines.[17]

Experimental Section

General Procedure. To a screw-cap vial containing a stir bar were added 2-aminobenzaldehydes (0.3 mmol), terminal alkynes (0.36 mmol, 1.2 equiv), CuI (10 mol %), dry CH_3CN (2 mL), and pyrrolidine (25 mol %). The reaction vial was fitted with a cap, evacuated, and filled with nitrogen and heated at 100 °C for 12 h. The reaction mixture was allowed to warm to ambient temperature. The reaction mixture was diluted with ethyl acetate and filtered through a plug of silica gel. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by column chromatography (silica gel, hexane/EtOAc) to give the desired products **3**.

6-Hexyl[1,3]dioxolo[4,5-*g*]quinoline (3a): 85% yield; mp = 105−107 °C; pale yellow solid; R_f 0.50 (hexane/EtOAc = 80/20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 8.3 Hz, 1H), 7.29 (s, 1H), 7.08 (d, J = 8.3 Hz, 1H), 6.96 (s, 1H), 6.06 (s, 2H), 2.85 (t, J = 7.5 Hz, 2H), 1.77 (pent, J = 7.5 Hz, 2H), 1.45−1.25 (m, 6H), 0.89 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8,150.4, 147.0, 146.0, 135.0, 123.2, 119.4, 105.5, 102.6, 101.4, 39.0, 31.7, 30.1, 29.2, 22.5, 14.0; IR (KBr): ν_{max} 3041, 2920, 1618, 1503, 1462, 1240 cm^{-1}; MS (ESI) m/z 258 (M^+ + H); HRMS calcd for $C_{16}H_{19}NO_2$ (M^+ + H) 258.1494, found 258.1506.

2-Hexylquinoline (3b): 94% yield; pale yellow oil; R_f 0.64 (hexane/EtOAc = 80/20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 8.3 Hz, 2H), 7.72 (dd, J = 8.3, 1.5 Hz, 1H), 7.64 (td, J = 8.3, 1.5 Hz, 1H), 7.43 (td, J = 8.3, 1.5 Hz, 1H), 7.24 (d, J = 8.3 Hz, 1H), 2.94 (t, J = 7.5 Hz, 2H), 1.81 (pent, J = 7.5 Hz, 2H), 1.46 − 1.23 (m, 6H), 0.89 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9, 147.8, 136.0, 129.1, 128.7, 127.3, 126.6, 125.4, 121.2, 39.3, 31.6, 29.9, 29.1, 22.4, 13.9; IR (film) ν_{max} 3053, 2926, 2857, 1601, 1502 cm^{-1}; MS (ESI) m/z 214 (M^+ + H); HRMS calcd for $C_{15}H_{19}N$ (M^+ + H) 214.1595, found 214.1589.

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Supporting Information Available: All experimental procedures, analytical data, and copies of ^{1}H and ^{13}C NMR spectra of newly synthesized products. This material is available free of charge via the Internet at http://pubs.acs.org.

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