Synthetic Methods

DOI: 10.1002/anie.201204339

Copper-Catalyzed Aerobic Dehydrogenative Cyclization of N-Methyl-N-phenylhydrazones: Synthesis of Cinnolines**

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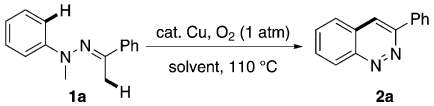
Selective carbon–carbon (C–C) bond formation is one of the most important processes in organic chemistry since it enables key steps in the synthesis of complex organic molecules from simple precursors. Traditionally, the construction of C–C bonds relies primarily on prefunctionalized substrates, which usually requires additional synthetic steps, and thus reduces the overall efficiency of this transformation.[1] For this reason, C–C bond formation reactions through transition-metal-catalyzed direct functionalization of relatively unreactive C–H bonds have emerged as a major topic of research in organic chemistry.[2] Among them, copper-catalyzed aerobic dehydrogenative coupling reactions from two carbon–hydrogen (C–H) bonds have received renewed interest in recent years with the following inherent advantages: maximizing atom economy by avoiding prefunctionalization of the coupling partners, and avoidance of toxic by-products with molecular oxygen as the sole oxidant.[3]

Since the discovery of the Glaser reaction or the oxidative dimerization of terminal alkynes[4] over 140 years ago, many efforts have been devoted to this field to construct new C–C bonds. A number of copper-catalyzed aerobic dehydrogenative coupling reactions through a C_{sp}–H or C_{sp^2}–H bond functionalization process have been developed, including oxidative dimerization of phenols,[5] naphthols,[6] and electron-deficient arenes,[7] cross-coupling of terminal alkynes with electron-deficient arenes,[8] and intramolecular dehydrogenative cylization of anilides.[9] In comparison, the development of copper-catalyzed aerobic dehydrogenative coupling at sp^3-carbon atoms is still in its infancy and the current advances suffer severely from restricted substrate scope, namely substrates with the sp^3-carbon atom adjacent to a heteroatom[10] or malonic amide derivative.[11] In our continued efforts toward the development of transition-metal-catalyzed coupling reactions on novel substrates,[12] herein we report N-methyl-N-phenylhydrazones as unprecedented substrates for copper-catalyzed aerobic intramolecular dehydrogenative cyclization for the formation of cinnolines,[13] a privileged structure in many medicinal compounds with a broad range of biological activities including antibacterial, anticancer, antifungal, antihypertensive, antiinflammatory, and antiulcer activities.[14]

Our investigation began with the oxidative cyclization of 1-methyl-1-phenyl-2-(1-phenylethylidene)hydrazine (**1a**) with catalytic $CuSO_4$ in the presence of O_2 (1 atm). To our delight, the cyclization reaction was successful with DMF, DMA, or DCE as the solvent, albeit in low yields (Table 1, entries 1–3). An extensive catalyst screening showed that although other Cu^{II} and Cu^{I} sources could catalyze the

Table 1: Optimization of reaction conditions.[a]



1a **2a**

Entry	Cu source (mol%)	Additives (equiv)	Solvent	Yield [%][b]
1	$CuSO_4$ (20)	–	DMF	37
2	$CuSO_4$ (20)	–	DMA	32
3	$CuSO_4$ (20)	–	DCE	30
4	$CuSO_4$ (20)	–	CH_3CN	< 5
5	$CuSO_4$ (20)	–	DMSO	trace
6	$CuSO_4$ (20)	–	NMP	trace
7	–	–	DMF	0
8	$Cu(OAc)_2$ (20)	–	DMF	22
9	$CuBr_2$ (20)	–	DMF	20
10	$CuCl_2$ (20)	–	DMF	19
11	CuF_2 (20)	–	DMF	17
12	$Cu(OH)_2CO_3$ (20)	–	DMF	16
13	$Cu(TFA)_2$ (20)	–	DMF	15
14	$Cu(OTf)_2$ (20)	–	DMF	12
15	CuI (20)	–	DMF	25
16	CuBr·DMS (20)	–	DMF	22
17	$CuSO_4$ (20)	Py (3.5)/CF_3SO_3H (1)	DMF	73
18	$CuSO_4$ (20)	Py (3.5)/TsOH (1)	DMF	55
19	$CuSO_4$ (20)	Py (3.5)/CF_3CO_2H (1)	DMF	47
20	$CuSO_4$ (20)	Py (3.5)/AcOH (1)	DMF	43
21	$CuSO_4$ (10)/CuI (10)	Py (3.5)/$PhCO_2H$ (1)	DMF	42
22	$CuSO_4$ (1.5)/CuI (7.5)	Py (3.5)/CF_3SO_3H (1)	DMF	83 (80)[c]
23	$CuSO_4$ (1.5)/CuI (5)	Py (3.5)/CF_3SO_3H (1)	DMF	70
24[d]	$CuSO_4$ (1.5)/CuI (7.5)	Py (3.5)/CF_3SO_3H (1)	DMF	20

[a] Reaction conditions: **1a** (0.3 mmol), Cu source, additive, O_2 (1 atm), 3 mL of solvent, 110 °C, 14 h unless otherwise noted. [b] Yields and conversions are based on **1a**, and determined by ^1H NMR analysis of the crude reaction mixture using dibromomethane as the internal standard. [c] Yield of isolated product. [d] Under air. DCE = 1,2-dichloroethane, DMF = *N*,*N*′-dimethylformamide, DMA = dimethylacetamide, DMS = dimethylsulfide, DMSO = dimethylsulfoxide, Py = pyridine, Tf = trifluoromethanesulfonyl, TFA = trifluoroacetic acid.

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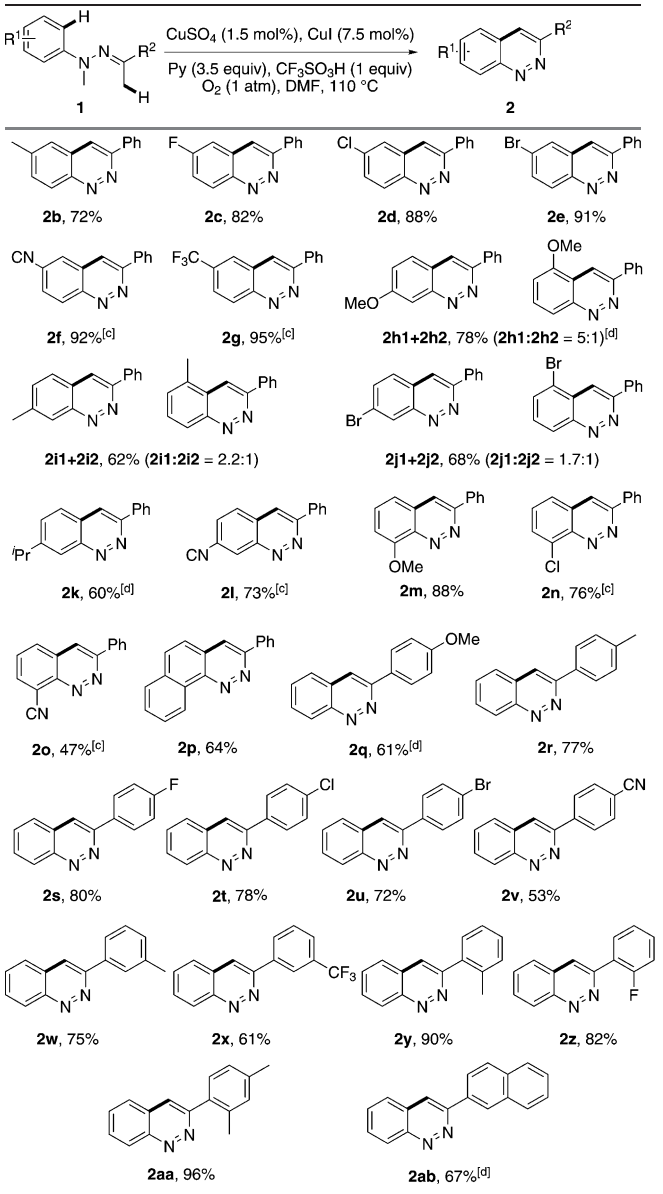
[**] We gratefully acknowledge Indiana University Purdue University Indianapolis for financial support. The Bruker 500 MHz NMR was purchased using funds from an NSF-MRI award (CHE-0619254).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201204339.

cyclization of **1a**, none of these catalysts improved the yield (entries 8–16). Upon realizing that the addition of a nucleophilic base could facilitate the demethylation, screening of different bases (pyridine, DMAP, DABCO, etc.) was carried out. Unfortunately, none of these bases improved the yield. However, the yield was increased by the addition of an acid along with excess pyridine, and the optimal results were obtained with 1 equivalent of CF_3SO_3H and 3.5 equivalent of pyridine (entry 22).

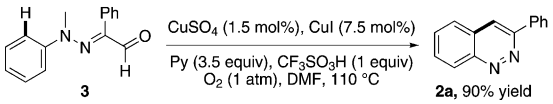
As shown in Table 2, this transformation is compatible with electron-rich and electron-deficient N-phenyl rings (**2b**–**o**). There is no apparent electronic or steric effect resulting from this ring, and good to high yields of product were obtained with both electron-donating or electron-withdrawing substituents (R^1) on either the *para*, *meta*, and *ortho* positions, with the exception of **2o**. The *meta*-OMe-, Me-, or Br-substituted substrates gave a mixture of *para* and *ortho*-substituted products (**2h**–**j**) with a preference for the *p*-substituted products, whereas substrates bearing the more hindered *i*Pr group and the electron-withdrawing CN group provided only the *p*-substituted products (**2k** and **2l**, respectively). As expected, halogens (F, Cl, and Br) were tolerated under the current reaction system, thus allowing further manipulation of the initial products. In contrast, there is an electronic effect resulting from substituents (R^2) on the other phenyl ring (**2q**–**z**). Generally, electron-donating groups on this ring provide higher yields than those with electron-withdrawing groups. It is noted that replacement of this phenyl group with an alkyl group gave only a trace amount of product as a result of the decomposition of the starting material under the oxidative conditions. It was also observed that this reaction failed with the introduction of an alkyl group on the carbon atom α to the imine moiety.

Table 2: Substrate scope.[a,b]



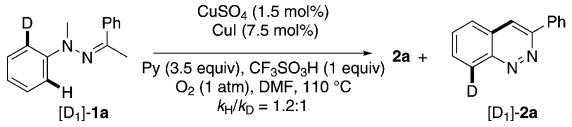
[a] Reaction conditions: **1** (0.3 mmol), $CuSO_4$ (1.5 mol%), CuI (7.5 mol%), Py (3.5 eq), CF_3SO_3H (1.0 eq), O_2 (1 atm), 3 mL of DMF, 110°C, 14 h unless otherwise noted. [b] Yield of isolated product. [c] The reaction was run at 150°C for 20 h. [d] The reaction was run at 95°C for 48 h.

It is noteworthy that under the current reaction conditions, a small amount of 2-(*N*-methyl-*N*-phenylhydrazono)-2-phenylacetaldehyde (**3**) was isolated along with the desired product **2a** from the reaction of **1a**. Furthermore, treatment of **3** under the cyclization reaction conditions provided **1a** in 90% yield (Scheme 1).



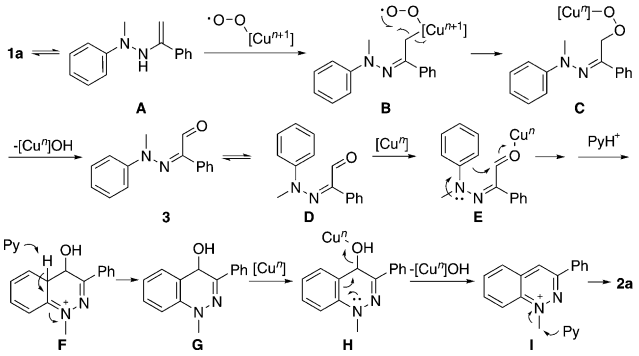
Scheme 1. Cyclization of 2-(*N*-methyl-*N*-phenylhydrazono)-2-phenylacetaldehyde (**3**).

To further probe the reaction mechanism, deuterium-labeling experiments were conducted (Scheme 2). No significant kinetic isotope effect was observed in the reaction of [D_1]-**1a**, thus suggesting that the arene C_{sp^2}–H bond cleavage might not be involved in the rate-determining step.[15]



Scheme 2. Deuterium-labeling experiments.

Based on the above observations, a reaction mechanism for the cyclization of **1a** is proposed (Scheme 3). It is believed that this transformation starts with the oxidation of **1a** into **3** through a copper-catalyzed process in the presence of oxygen.[16] Copper-assisted Friedel–Crafts-type cyclization of **3** generates the intermediate **G**.[17] Activation of **G** by a copper species, followed by loss of the hydroxy group, and a methyl group by nucleophilic substitution by pyridine, provides the desired product **2a**.



Scheme 3. Proposed reaction mechanism.

In summary, an efficient copper-catalyzed aerobic intramolecular dehydrogenative cyclization reaction of N-methyl-N-phenylhydrazones has been developed through sequential C_{sp^3}–H oxidation, cyclization, and aromatization processes. This transformation is the first example of copper-catalyzed coupling reactions of hydrazones through a C_{sp^3}–H bond functionalization pathway. This novel method provides an efficient access to cinnoline derivatives.

Experimental Section

A 50 mL Schlenk tube was charged with N-methyl-N-phenylhydrazones (**1**, 0.3 mmol), $CuSO_4$ (1.0 mg, 0.0045 mmol), CuI (4.2 mg, 0.0225 mmol), Py (84.4 μL, 1.05 mmol), and DMF (2.7 mL). Then a solution of CF_3SO_3H (26.5 μL, 0.3 mmol) in DMF (0.3 mL) was slowly added. The tube was evacuated and filled with 1 atm O_2, and stirred rigorously at 110 °C (unless otherwise noted) for 14–48 h. After removal of the solvent, the residue was purified by flash chromatography on silica gel (gradient eluent of 5 % EtOAc and 1 % Et_3N in hexanes, *v*/*v*) to yield the desired product as a colorless or pale-yellow solid.

Received: June 4, 2012
Published online: ■■ ■■, ■■■■

Keywords: C–C coupling · copper · heterocycles · oxygen · synthetic methods

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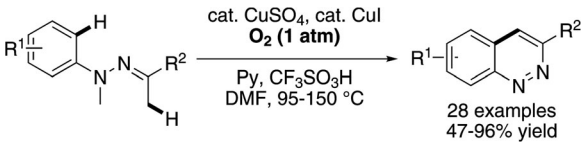
[17] In this process, a pyridinium salt is formed by the acid-base reaction of pyridine and trifluoromethanesulfonic acid, and presumably this salt acts as a proton donor to protonate a copper species formed from the Friedel–Crafts-type cyclization of **E**.

Communications

Synthetic Methods

G.-W. Zhang, J.-M. Miao, Y. Zhao, H.-B. Ge* ——— ■■■■–■■■■



Copper-Catalyzed Aerobic Dehydrogenative Cyclization of N-Methyl-N-phenylhydrazones: Synthesis of Cinnolines

O_2 leading the way: The title reaction proceeds through an oxidation/cyclization sequence, thus representing the first copper-catalyzed coupling reaction of hydrazones through a C_{sp^3}–H bond functionalization process (see scheme; DMF = *N*,*N*′-dimethylformamide, Py = pyridine). The method provides an environmentally friendly and atom-efficient approach to biologically active cinnoline derivatives.