Heterocycles

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Copper-Catalyzed Aerobic Intramolecular Dehydrogenative Cyclization of N,N-Disubstituted Hydrazones through C_{sp^3}–H Functionalization**

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The development of methods for selective carbon–carbon (C-C) bond formation is of paramount importance in organic synthesis.[1] As major approaches, nucleophilic substitution and addition, Friedel–Crafts-type reactions, and cross-coupling reactions often require the use of prefunctionalized starting materials, which add additional costs and generate stoichiometric amounts of metal salts as waste. Therefore, the construction of C–C bonds through the direct use of unfunctionalized substrates through C–H bond functionalization has attracted considerable attention, and significant progress has been achieved in recent years.[2] Among these approaches, copper-catalyzed aerobic dehydrogenative coupling provides a powerful method for the direct functionalization at sp^3 carbon atoms α to amines or ethers.[3]

In 1993, Miura and co-workers reported the first example of this transformation by coupling *N*,*N*-dimethylanilines with alkynes in low to moderate yields.[4] Li and co-workers, as well as others have recently made significant progress in this area by expanding the substrate scope.[5] It is well accepted that an iminium ion intermediate is formed through amine oxidation by a copper source in the presence of an oxidant by a single-electron transfer (SET) process. The resulting iminium ion intermediate then acts as an electrophile for the subsequent nucleophilic addition.[6] The studies on the substrate scope showed that nitroalkanes, alkynes, cyanides, malonic esters, ketones, α,β-unsaturated carbonyl compounds, and electron-rich (hetero)arenes are all suitable nucleophiles. Furthermore, certain secondary amines, namely the *N*-aryl-substituted α-amino esters, ketones, and amides,[7] are also compatible under the oxidative conditions, and further improved product diversity. However, current progress is limited only to the intermolecular case, termed as the cross dehydrogenative coupling (CDC).[6a] In our continuing efforts toward the development of green chemistry for chemical syntheses, herein, we report the realization of the first example of this transformation in an intramolecular manner.

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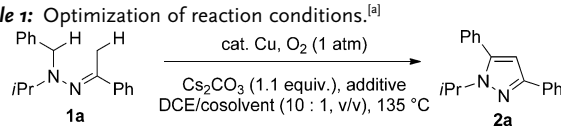
The requirement of an ideal internal nucleophile for the intramolecular cyclization led us to consider *N*,*N*-disubstituted hydrazones as potential substrates. Although the copper-catalyzed oxidative coupling reaction of hydrazones has not been explored, it was reported that hydrazines could be oxidized by rhodium(III) to form the corresponding iminium ion intermediates, which could then undergo cycloaddition with an electron-deficient alkene.[8] It is envisioned that if the selective oxidation of the nitrogen atom of a hydrazone is feasible by a copper source and an external oxidant, the in situ generated iminium ion intermediate could be trapped intramolecularly by nucleophilic addition of an enamine-type substructure, the tautomer of the imine moiety, to form a dihydropyrazole structure. Furthermore, the initial dihydropyrazole product could be aromatized to pyrazole under the oxidative conditions. On the basis of this design, copper-catalyzed aerobic intramolecular cyclization of *N*,*N*-disubstituted hydrazones by a double C_{sp^3}–H bond functionalization was developed and is reported here. This unprecedented transformation provides an efficient approach for the synthesis of pyrazoles, a privileged structure and prevalent motif in medicinal compounds and many biologically active natural products.[9] It is worth mentioning that current syntheses of 1,3,5-trisubstituted pyrazoles rely primarily on the cyclization of hydrazines with 1,3-dicarbonyl compounds, and in spite of providing a powerful approach, it often suffers from poor regioselectivity.

We recently reported the copper-catalyzed aerobic dehydrogenative cyclization of *N*-phenylhydrazones for the formation of cinnolines via α-imino aldehyde intermediates.[10] It was envisioned that replacement of the *N*-phenyl with an alkyl group could favor the selective oxidation of the amine moiety, and lead to subsequent cyclization. Thus, we began our investigation with the oxidative cyclization of 1-benzyl-1-isopropyl-2-(1-phenylethylidene)hydrazine (**1a**) with catalytic CuBr·DMS in the presence of 1.1 equivalents of Cs_2CO_3 as the base and 1 atm of O_2 as the oxidant at 135 °C (Table 1). After an extensive solvent screening, DCE was proven to be optimal, albeit with a low yield (entry 1). It was noticed that decomposition of starting material also occurred under the above reaction conditions. Therefore, screening of different additives to inhibit decomposition of **1a** was carried out, and it was found that DBU could alleviate the problem although the reaction yield was only slightly increased (entry 2). Further optimization showed that this reaction could be improved by the addition of a catalytic amount of KI, which presumably facilitates the cyclization (entry 3). To our delight, the addition of DMS as the cosolvent significantly

Table 1: Optimization of reaction conditions.[a]

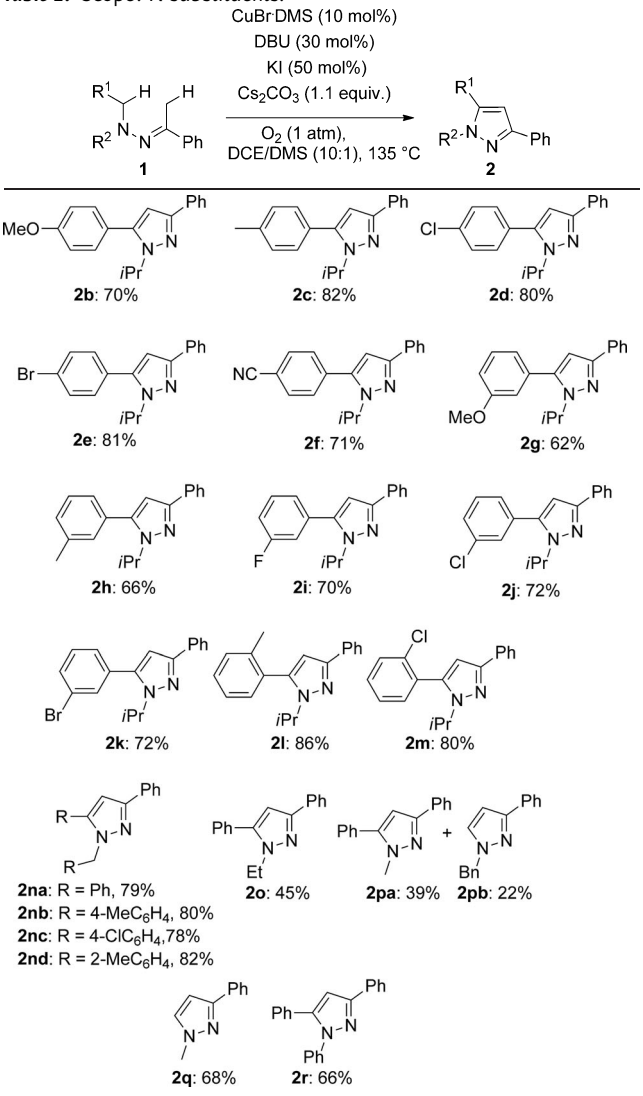


1a 2a

Entry	Cu source (mol%)	Additives (equiv)	Cosolvent	Yield [%][b]
1	CuBr·DMS (10)	–	–	15
2	CuBr·DMS (10)	DBU (0.3)	–	22
3	CuBr·DMS (10)	DBU (0.3)/KI (0.5)	–	33
4	CuBr·DMS (10)	DBU (0.3)/KI (0.5)	DMS	80 (77)[c]
5	CuBr·DMS (10)	–	DMS	46
6	CuBr·DMS (10)	DBU (0.3)	DMS	67
7	CuBr·DMS (10)	KI (0.5)	DMS	53
8	$(CuOTf)_2$·benzene (5)	DBU (0.3)/KI (0.5)	DMS	73
9	CuI (10)	DBU (0.3)/KI (0.5)	DMS	70
10	$Cu(OTf)_2$ (10)	DBU (0.3)/KI (0.5)	DMS	66
11	$Cu(OAc)_2$ (10)	DBU (0.3)/KI (0.5)	DMS	68
12	$CuBr_2$ (10)	DBU (0.3)/KI (0.5)	DMS	72
13	$CuCl_2$ (10)	DBU (0.3)/KI (0.5)	DMS	70
14	$CuSO_4$ (10)	DBU (0.3)/KI (0.5)	DMS	69
15	$Cu(TFA)_2$ (10)	DBU (0.3)/KI (0.5)	DMS	75

[a] Reaction conditions: **1a** (0.3 mmol), Cu source, Cs_2CO_3 (1.1 equiv), additive, O_2 (1 atm), 3 mL of solvent, 135 °C, 5 h. [b] Yields and conversions are based on **1a**, determined by ^1H NMR spectroscopy of the crude reaction mixture using dibromomethane as the internal standard. [c] Yield of the isolated product. DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, DMS = dimethylsulfide, TFA = trifluoroacetate.

Table 2: Scope: N substituents.[a,b]



[a] Reaction conditions: **1** (0.3 mmol), CuBr·DMS (10 mol%), Cs_2CO_3 (1.1 equiv), DBU (30 mol%), KI (50 mol%), O_2 (1 atm), 3 mL solvent (DCE/DMS = 10:1, v/v), 135 °C, 5 h. [b] Yield of the isolated product.

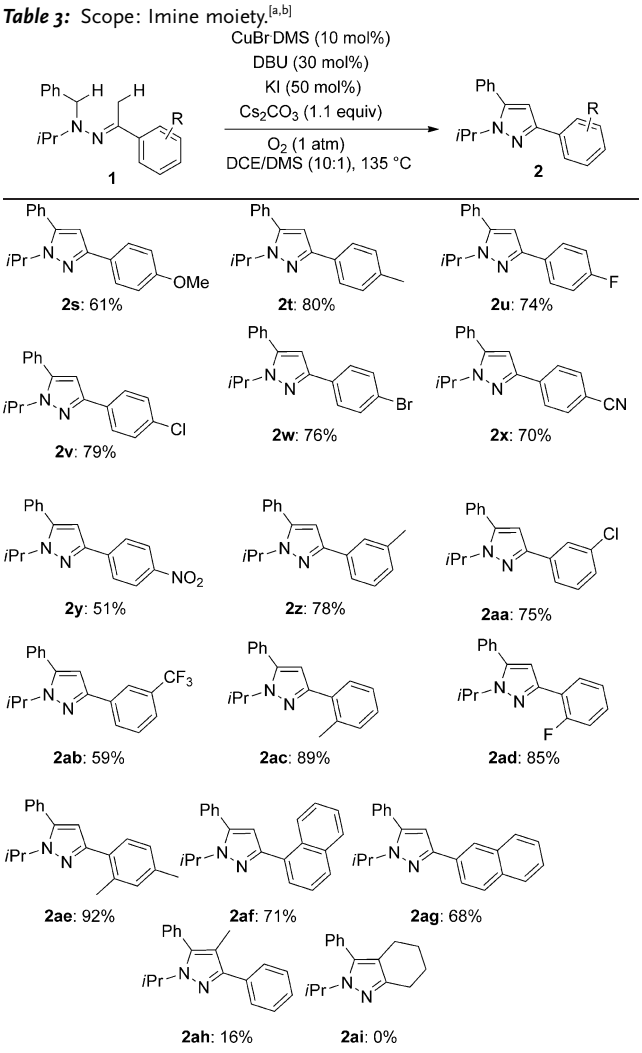
enhanced the tolerance of the substrate to the oxidative conditions and improved the efficiency of this transformation, thus providing the desired product **2a** in 80% yield (entry 4). In addition, other copper(I) or copper(II) sources could also effectively catalyze this reaction under the above modified reaction conditions (entries 9–15).

With the optimized reaction conditions in hand, we then carried out a study on the substrate scope with respect to the the amine moiety (Table 2). As expected, both electron-donating and electron-withdrawing groups on the phenyl ring are compatible under the current catalytic system (**2b–m**). In addition, halogens (F, Cl, and Br) are also tolerated, and thus allow additional transformation of the initial products. Furthermore, there is no apparent electronic or steric effect on this ring since good to high yields of the desired products were observed for substrates with either electron-donating or electron-withdrawing groups at the *para*, *meta*, and *ortho* positions. It is also noted that the isopropyl group can be replaced with another alkyl or phenyl group (**2n–r**), and thus allows the synthesis of pyrazoles having different substitution patterns.[11] Interestingly, with 1-benzyl-1-methyl-2-(1-phenylethylidene)hydrazine as the substrate, two products (**2pa** and **2pb**) were obtained, which were likely resulted from the competitive oxidation between the benzyl and methyl groups under the oxidative reaction conditions.

Next, the substrate scope with regard to the imine moiety was carried out. As shown in Table 3, a wide variety of aryl groups having either an electron-donating or electron-withdrawing substituent on the ring were tolerated under the current reaction conditions (**2s–ae**). Although there is no apparent electronic or steric effect on this ring, lower yields were observed with substrates having very strong electron-withdrawing groups (**2y** and **2ab**), presumably as a result of the instability of the starting materials under the oxidative reaction conditions. As expected, halogens (F, Cl, and Br) were also well tolerated. Furthermore, good yields of desired products were also obtained with the naphthalene substrates (**2af** and **2ag**). Unfortunately, α-substituted 1-benzyl-1-isopropyl-2-(1-phenylethylidene)hydrazines and aliphatic hydrazones were not well tolerated under the current catalyst system because of the competitive decomposition of starting materials (**2ah** and **2ai**).

On the basis of previous reports,[6a,b,12] a plausible reaction mechanism is proposed (Scheme 1). It is believed that the reaction is initiated by oxidation of the amine on **1** to form the iminium ion intermediate **B** via the intermediate **A** (route a).[3a,h] Alternatively, the intermediate **B** could also be generated through tautomerization of **1** to form the inter-

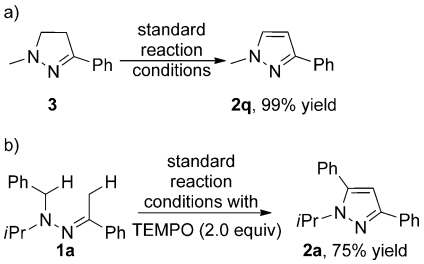
Table 3: Scope: Imine moiety.[a,b]



[a] Reaction conditions: same as in Table 2. [b] Yield of the isolated product.

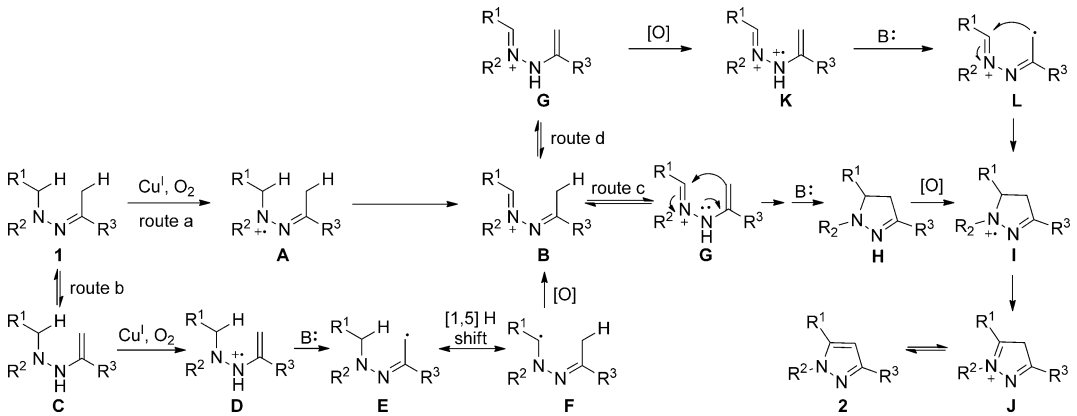
mediate **C**, followed by oxidation[3g] and subsequent 1,5-H shift[13] and oxidation (route b). Tautomerization of the imine moiety on **B** to the enamine-type structure **G** and subsequent intramolecular cyclization provides the dihydropyrazole intermediate **I**, presumably by a KI-assisted process. The intermediate **I** is then aromatized to form the pyrazole **2** under the oxidative conditions (route c). Alternatively, intermediate **I** could be formed by tautomerization of **B** to the enamine-type structure **G** followed by subsequent oxidation and radical cyclization (route d).[3g,14]

To further probe the reaction mechanism, a time-dependent study of copper-catalyzed oxidative cyclization of 1-benzyl-1-methyl-2-(1-phenylethylidene)hydrazine (**1q**) was carried out.[15] It was noticed that the intermediate **3** was rapidly formed during the reaction (within 10 min), and then completely consumed. Furthermore, treatment of this intermediate under standard reaction conditions gave **2q** in nearly quantitative yield (Scheme 2a). Furthermore, the addition of excess TEMPO has no apparent effect on this intramolecular cyclization reaction (Scheme 2b).[16] Based on the above observations, it is believed that the mechanism of this reaction proceeds by route a and then route c as shown in Scheme 1.[3a,5a,e]



Scheme 2. Control experiments. TEMPO = 2,2,6,6-tetramethylpiperidin-1-oxyl.

In summary, we have developed an efficient copper-catalyzed aerobic intramolecular dehydrogenative cyclization reaction of *N*,*N*-disubstituted hydrazones by C_{sp^3}–H oxidation, cyclization, and aromatization. This transformation is the first example of an intramolecular copper-catalyzed dehydrogenative coupling reaction via an iminium ion intermediate by a C_{sp^3}–H bond functionalization pathway. This novel method provides a complementary, environmen-



Scheme 1. Plausible reaction mechanism.

tally friendly, and atom-efficient approach to accessing pyrazole derivatives. Additional mechanistic investigation of this transformation is currently underway in our laboratory.

Experimental Section

A 50 mL Schlenk tube was charged with an N,N-disubstituted hydrazone (**1**, 0.3 mmol), CuBr·DMS (6.1 mg, 0.03 mmol), KI (24.9 mg, 0.15 mmol), DBU (13.3 μL, 0.09 mmol), Cs_2CO_3 (107 mg, 0.33 mmol), and the solvent mixture of DCE and DMS (10:1, v/v; 3.0 mL). The vial was then evacuated and filled with 1 atm O_2, and stirred rigorously at 135 °C for 5 h. After removal of the solvent, the residue was purified by flash chromatography on silica gel (gradient eluent of 2% EtOAc in hexanes, v/v) to give the desired product.

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[11] The relatively lower yields of **2o**–**q** compared with **2a** are due to the partial decomposition of the starting materials. The relatively lower yield of **2r** is presumably due to the decreased reduction potential of the amine nitrogen atom.
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[15] With 1-benzyl-1-isopropyl-2-(1-phenylethylidene) hydrazine (**1a**) as the substrate, a dehydrogenative intermediate (not isolable) was detected by GC/MS, and then was rapidly consumed.
[16] Under an argon atmosphere, this reaction gave less than 10% of the desired product **2a**.

