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Selective Mono- and Diamination of Ketones in a Combined Copper–Organocatalyst System

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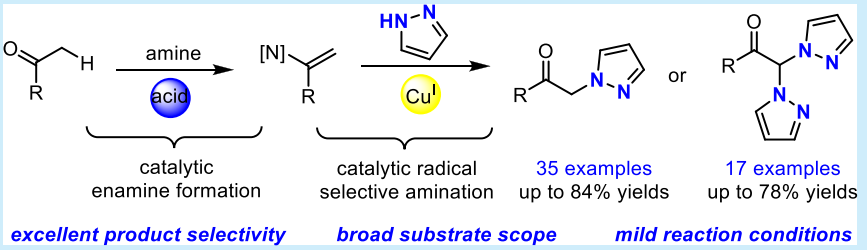
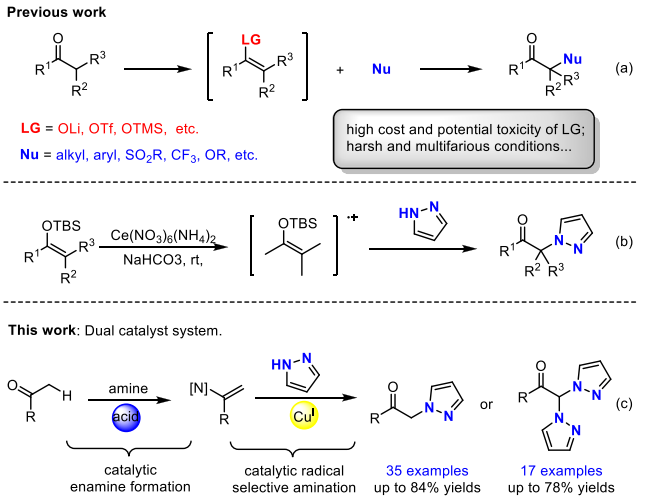


ABSTRACT: Herein, we report a simple and mild protocol for the chemoselective mono- and diamination of ketone using pyrazole as the amine source in a combined copper–organocatalyst system. Various substrates are compatible, providing the corresponding products in moderate to good yields. This strategy gives an efficient and convenient solution for the synthesis of α-pyrazole and α,α-dipyrazole ketone derivatives. The control experiment demonstrates that *in situ* generated hydrazone is a key intermediate in the transformation.

Over the past decade, remarkable advances have been made in the development of facile and practical strategies for the synthesis of α-functionalized ketones,[1] because such products are versatile intermediates in natural product synthesis, materials science, and pharmaceutical chemistry.[2] Methods for direct α-functionalization of ketones have been regarded as among the most promising approach to streamline organic synthesis as a result of the maximization of the step and atom economies. In this active field, various efficient catalytic methods have been developed, including the iodine-promoted transformation,[3] transition metal catalysis,[4] etc.[5] Among them, α-functionalization of ketones via prefunctionalized ketones with leaving groups has received growing attention (Scheme 1a). As early as in 2014, Dong's group described an amine and rhodium co-catalyzed α-alkylation of ketones with simple terminal olefins.[6] Recently, Nishikata and co-workers reported seminal work on α-alkylation of ketones via enamine-mediated dehalogenation to synthesize substituted 1,4-dicarbonyl compounds.[7] Maulide's group has a long-standing interest in the chemoselective triflic-anhydride-mediated activation of acetophenones via metal-free electrophilic activation.[8] In 2020, they demonstrated an efficient strategy to generate α-arylated acetophenones from vinyl triflates.[9] Jiang's group developed a copper-catalyzed coupling of oxime acetates with sodium sulfinates for the synthesis of β-ketosulfones.[10] Thomson's group[11] described another efficient strategy to generate α-pyrazole ketones in 2020, through a silyl enolether radical cation intermediate (Scheme 1b). Despite their utilities, most of these catalytic systems generally suffer from disadvantages, such as air and

Scheme 1. α-Functionalization of Ketones via Prefunctionalized Ketones: (a) α-Functionalization of Ketones, (b) α-Amination of Ketones, and (c) Selective Mono- and Diamination of Ketones



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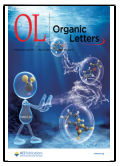

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moisture sensitivity and harsh reaction conditions. In fact, most of the methods can only be used for mono-C−H functionalization of ketones, and the C−H bifunctionalization of ketones was rarely reported. From the green and sustainable chemistry points of view, the development of more cost-effective, precision-controlled, and efficient strategies for the α-functionalization of ketones is highly requisite.

Recently, our main research interest focuses on the C−H functionalization of ketones.[12] In 2021, we developed an efficient olefination of ketones through a combination of heterogeneous catalysis and photocatalysis.[12a] Inspired from our previous studies, herein, we design and develop a controlled amination of ketones for the synthesis of α-pyrazole and α,α-dipyrazole ketones (Scheme 1c). In addition, α-pyrazole ketones are known for their outstanding biological activities,[13] such as anticonvulsant and antimicrobial as well as anticancer activities (Figure 1). It should be noted that this

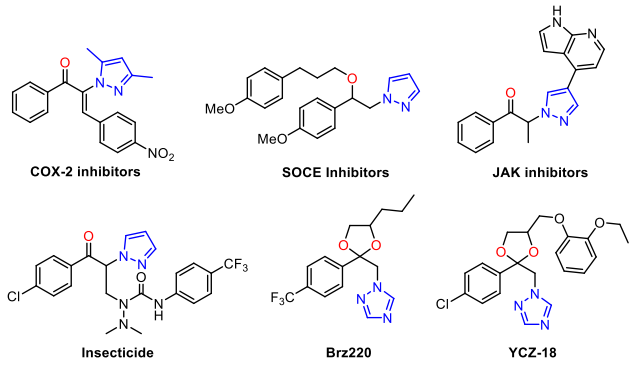


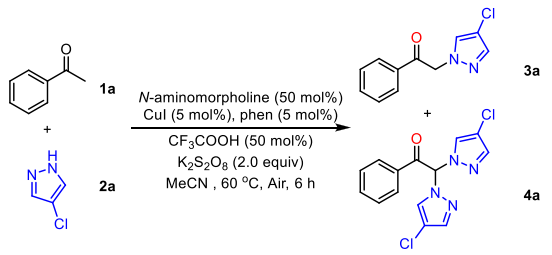
Figure 1. Representative bioactive α-pyrazole ketones.

catalytic system providing a novel and feasible approach for various α-pyrazole and α,α-dipyrazole ketones. As far as we know, this selective mono- and diamination has not yet been demonstrated.

Our initial investigation of this reaction focused on the screening of various auxiliary groups (Table S1 of the Supporting Information). The results showed that *N*-aminomorpholine gives the highest yield. Therefore, we selected *N*-aminomorpholine as the auxiliary group for further investigation. After evaluation of a variety of reaction parameters, such as metal catalysts, ligand, oxidants, and solvents (Table 1 and Tables S2−S5 of the Supporting Information), the monoaminated product (**3a**) was obtained in 64% yield under standard reaction conditions (entry 1 in Table 1). Next, the effect of acids was examined (entries 2−4 in Table 1). It was found that the monoaminated product could be obtained in 84% yield when AcOH was used as the acid. It should be noted that the diaminated product (**4a**) was obtained in a low yield, when we extended the reaction time to 12 h (entry 5 in Table 1). We further tried to optimize the reaction conditions to develop a diamination method. A 64% yield of compound **4a** was obtained when 3.0 equiv of pyrazole (**2a**) and $K_2S_2O_8$ was employed (entry 6 in Table 1). To our delight, a good yield of 78% was obtained when the amounts of pyrazole and $K_2S_2O_8$ were increased to 4.0 equiv (entry 7 in Table 1). Cu_2O, as the other Cu^I catalyst, was used in this transition, delivering the diaminated product in 32% yield (entry 8 in Table 1).

Then, the substrate scope of α-pyrazole acetophenone derivatives was explored (Scheme 2). Various kinds of azoles

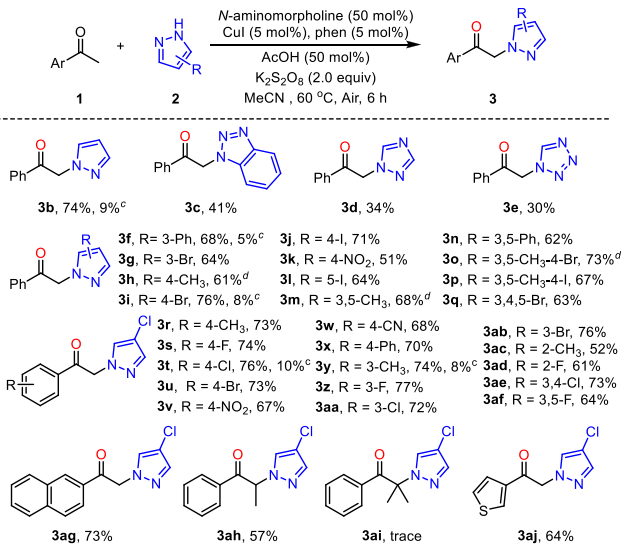
Table 1. Optimization of the Amination of Ketones[a]



entry	variation from the given conditions	yield[b] (%) 3a	4a
1	none	64	9
2	HCl instead of CF_3COOH	21	3
3	CH_3SO_3H instead of CF_3COOH	49	8
4	AcOH instead of CF_3COOH	84	10
5	extended reaction time (12 h)	53	26
6[c]	3.0 equiv of compound **2a** and $K_2S_2O_8$ was used	32	64
7[c]	4.0 equiv of compound **2a** and $K_2S_2O_8$ was used	14	78
8[c]	Cu_2O instead of CuI	32	3

[a]Reaction conditions: compound **1a** (0.2 mmol), compound **2a** (2.0 equiv), *N*-aminomorpholine (50 mol %), CuI (5 mol %), phen (5 mol %), CF_3COOH (50 mol %), $K_2S_2O_8$ (2.0 equiv), CH_3CN (1 mL), 60 °C, air, and 6 h. [b]Isolated yields. [c]AcOH (50 mol %) and 12 h.

Scheme 2. Selective Monoamination of Ketones[a,b]



[a]Reaction conditions: compound **1a** (0.2 mmol), compound **2a** (2.0 equiv), *N*-aminomorpholine (50 mol %), CuI (5 mol %), phen (5 mol %), AcOH (50 mol %), $K_2S_2O_8$ (2.0 equiv), CH_3CN (1 mL), 60 °C, air, and 6 h. [b]Isolated yields. [c]The yields of the diaminated product. [d]Reaction was performed on a 1 mmol scale.

were well-compatible under standard reaction conditions, affording the corresponding products (**3b**−**3e**) in 30−74% yield. We next investigated a wide range of pyrazole; functionalized pyrazoles containing either electron-donating or electron-withdrawing groups were well-compatible, giving the target products in moderate to good yields (**3f**−**3l**). Notably, multi-substituted pyrazoles were also tolerated under the standard conditions to give the target products (**3m**−**3q**) in 63−73% yield. Furthermore, various substituted acetophenones could couple with 4-chloropyrazole to form α-pyrazole acetophenone derivatives. The acetophenones, which bear

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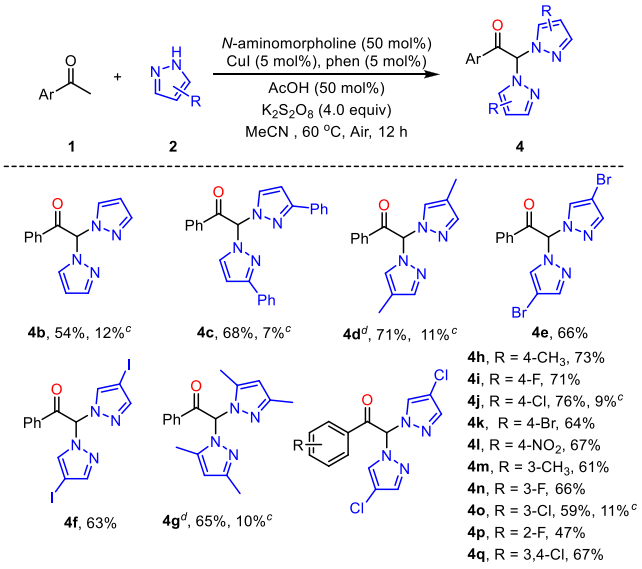
para-substituted groups, such as CH_3, F, Br, NO_2, CN, or Ph groups, could be converted into the corresponding products in moderate to good yields (**3r**−**3x**), and electron-withdrawing groups showed a negative effect on our reaction (**3v** and **3w**). When using the *ortho*- or *meta*-substituted acetophenones as the substrates, the corresponding products were formed in 52−77% yield (**3y**−**3af**). The substrates 2-acetonaphthone propiophenone and 3-acetylthiophene also gave good yields of *α*-pyrazole acetophenone derivatives (**3ag**, **3ah**, and **3aj**). Meanwhile, under the monoamination reaction conditions, the yields of diaminated products were about 5−10%. Unfortunately, isobutyrophenone was not suitable in our reaction.

Subsequently, the substrate scope of diamination was investigated (Scheme 3). A variety of pyrazoles could react

Scheme 3. Selective Diamination of Ketones[a,b]



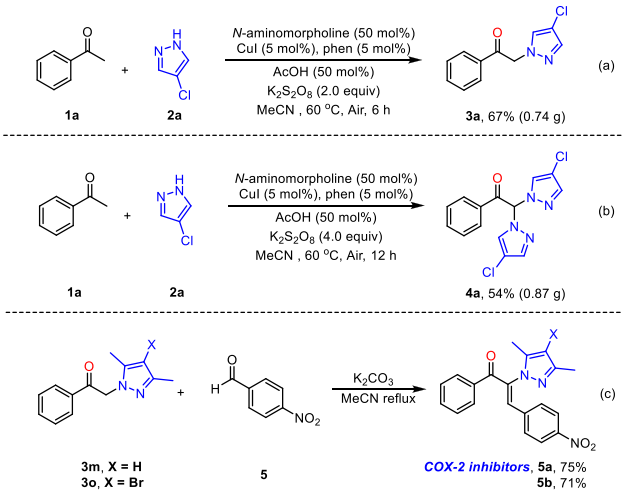
[a]Reaction conditions: compound **1a** (0.2 mmol), compound **2a** (4.0 equiv), *N*-aminomorpholine (50 mol %), CuI (5 mol %), phen (5 mol %), AcOH (50 mol %), $K_2S_2O_8$ (4.0 equiv), CH_3CN (1 mL), 60 °C, air, and 12 h. [b]Isolated yields. [c]The yields of the monoaminated product. [d]DCE instead of MeCN.

with acetophenones smoothly, delivering the diaminated products (**4b**−**4g**) in 54−71% yields. In addition, reactions between different substituted acetophenones and 4-chloropyrazole also proceed well, affording the diaminated products (**4h**−**4q**) in 59−76% yields. Steric hindrance of the substrate demonstrated a negative effect in our reaction, Similarly, under the diamination reaction condition, the yields of monoaminated products were about 7−12%.

The practical synthetic application of the procedure was also investigated. First, a gram-scale synthesis was performed. The monoaminated product (**3a**) was obtained in 67% yield (Scheme 4a), and the diaminated product (**4a**) was obtained in 54% yield (Scheme 4b). Then, potentially bioactive nonsteroidal anti-inflammatory drugs (NSAIDs) COX-2 inhibitors (**5a** and **5b**) could also be easily synthesized via further transformation.

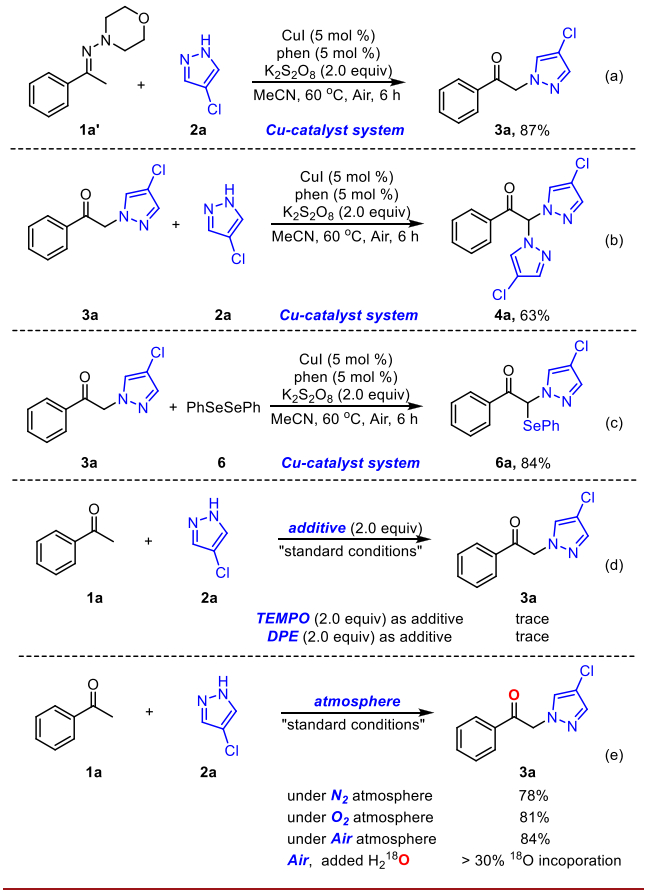
We conducted a preliminary mechanistic investigation to gain insight into the reaction mechanism. First, the monoaminated product (**3a**) could be obtained in good yield when acetophenone hydrazone was used as the substrate. This result demonstrated that the hydrazone structure plays a

Scheme 4. Further Chemistry



crucial role in this transformation (Scheme 5a). According to previous works,[14] hydrazone is important for this deprotona-

Scheme 5. Control Experiments



tion at the *α* position of acetophenone derivatives. The monoaminated product (**3a**) could be easily changed into the diaminated product (**4a**) under the Cu catalyst system (Scheme 5b). Furthermore, we selected diphenyl diselenide (PhSeSePh) to replace pyrazole. Similarly, the *α*,*α*-disubstituted product (**6a**) could be obtained in 84% yield (Scheme 5c). The transformation was completely inhibited in the presence of a radical scavenger under standard conditions. This

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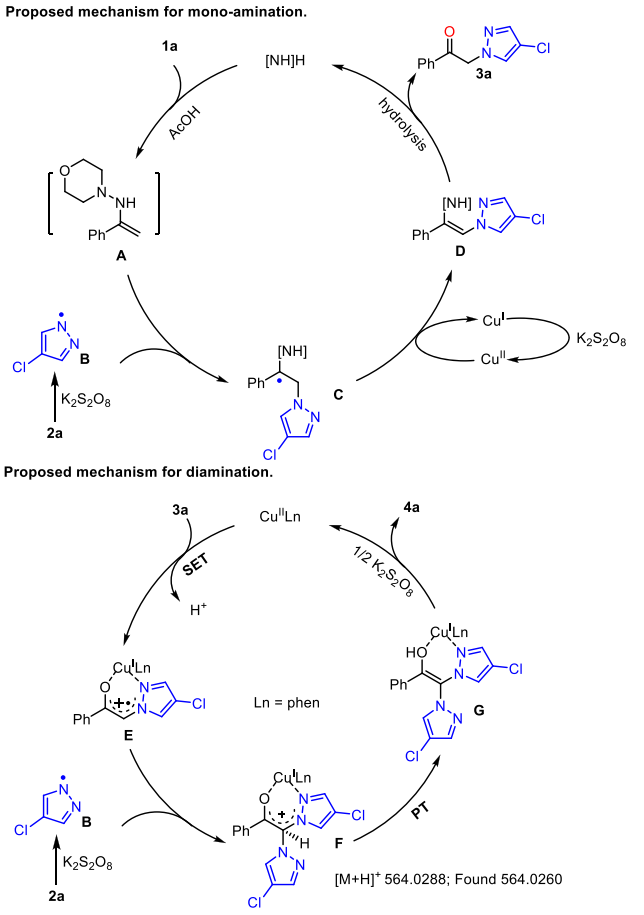
result supported that a radical pathway was involved (Scheme 5d). Subsequently, the reaction atmosphere of the transformation between compounds **1a** and **2a** was conducted (Scheme 5e). It was shown that the reaction proceeded smoothly under different atmospheres, affording the desired product **3a** in similar yields. In addition, the ^{18}O-labeling experiments were performed by adding $H_2{}^{18}O$ to the standard conditions, and the significant ^{18}O incorporation of compound **3a** was obtained. This result indicated that the O atom in carbonyl group of α-pyrazole acetophenone derivative **3a** came from moisture instead of O_2.

On the basis of the above results and previous reports,[15,16] we proposed a possible reaction mechanism (Scheme 6).

Scheme 6. Proposed Mechanism



Initially, enamine **A** is formed by the *N*-aminomorpholine ([NH]H) and AcOH catalysts. Afterward, pyrazole radical **B**, which is generated through the oxidation of $K_2S_2O_8$, attacks the enamine **A** to produce intermediate **C**. Subsequently, the generation of intermediate **D** was proposed via a single electron transfer process. The monoaminated product **3a** can be obtained by hydrolysis[6,7] with concomitant formation of *N*-aminomorpholine to complete the catalytic cycle through hydrolysis of intermediate **D**. For oxidative diamination of acetophenones,[17] a Cu(II) species existing in this catalytic system combines with substrate **3a** to generate the metal complex **E** through a single-electron transfer (SET) process. Then, activated pyrazole radical **B** reacts with complex **E** to generate intermediate **F**, which was detected by high-resolution mass spectrometry (HRMS). Finally, the diaminated product is obtained via the proton transfer (PT) process. Through the oxidation of $K_2S_2O_8$, Cu(I) species change to Cu(II) species and are then involved in the next catalytic cycle.

In summary, we have disclosed a dual catalyst system for the facile and controlled amination of acetophenones with azoles. A variety of acetophenones and azoles undergo the reaction smoothly, giving the corresponding aminated products in moderate-to-good yields. This method gives an efficient and convenient solution for the synthesis of α-pyrazole and α,α-dipyrazole ketone derivatives, which could be employed as useful synthetic building blocks for the construction of value-added fine chemicals.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c01140.

Experimental procedures and characterization data for all of the compounds (PDF)

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Notes

The authors declare no competing financial interest.

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