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Copper-Catalyzed Diamination of Alkenes of Unsaturated Ketohydrazones with Amines

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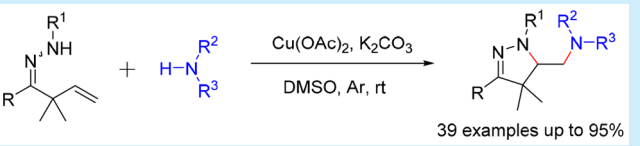
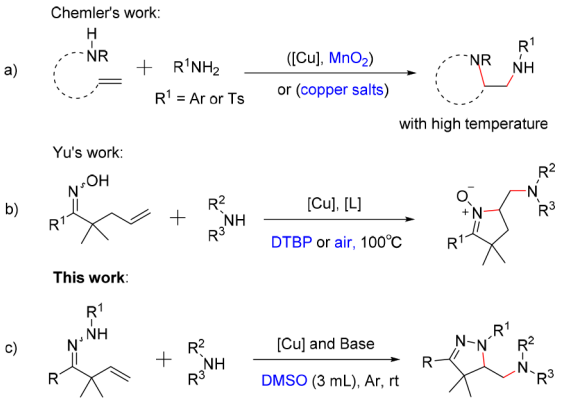
Supporting Information

ABSTRACT: A convenient copper-catalyzed intra-/intermolecular diamination of *β,γ*-unsaturated hydrazones has been developed with simple amines as external amine sources. The protocol enables efficient access to various nitrogen-containing pyrazolines under mild reaction conditions.



Vicinal diamines are widely represented in biologically active compounds, synthetic building blocks, materials, catalysts, and ligands.[1] The direct diamination of alkenes provides a straightforward route to the synthesis of such useful compounds and is therefore of great interest.[2] In particular, a number of elegant transition metal catalyzed alkene diamination methods have been reported.[3] [Pd]-, [Ni]-, [Au]-, or [Cu]-catalyzed alkene diaminations with *N,N′*-disubstituted ureas have been developed in the presence of an external oxidant.[4] A few reports also make use of diaziridines,[5] *N*-fluorobenzenesulfonimide,[6] or *O*-acylhydroxylamines[7] as both nitrogen sources and internal oxidants for framing these skeletons. Recently, the Chemler group employed copper salts or MnO_2 as an external oxidant, establishing the Cu-catalyzed and Cu-promoted intra-/intermolecular alkene diamination reactions with sulfonamides or anilines (Scheme 1a).[8] In 2016, the Yu group reported a copper-catalyzed intra-/intermolecular diamination of *γ,δ*-unsaturated ketoximes and simple amines by using di-*tert*-butyl peroxide (DTBP) or air as the external oxidant (Scheme 1b).[9] Although impressive achievements have been made, current diamination methods still have limitations, particularly that most of them need to be carried out at high temperature and required a stoichiometric amount of environmentally unfriendly oxidants. Therefore, it is of great value to develop more efficient and greener methodologies for the alkene diaminations under mild conditions.

Scheme 1. Copper-Catalyzed and Copper-Promoted Intra-/Intermolecular Alkene Diaminations



Pyrazoline derivatives are known to possess potent biological activities, including antiproliferative, antimalarial, and antibacterial activities and are also served as versatile intermediates in organic synthesis.[10] Consequently, these nitrogen heterocycles have attracted much interest from synthetic and pharmaceutical chemists. Traditionally, pyrazoline derivatives are synthesized via the thermal cycloaddition reactions.[11] In recent years, the method of hydrazonyl radical-mediated difunctionalization of *β,γ*-unsaturated hydrazones with a functional group has emerged as a new powerful tool to construct functionalized pyrazolines.[12] Inspired by these works and our continued interesting in constructing functionalized heterocycles,[13] we decided to test whether *β,γ*-unsaturated hydrazones with simple amines could carry out a direct diamination and afford the corresponding amine-substituted pyrazolines (Scheme 1, c).

At the outset of our studies, we chose *N*-phenyl-*β,γ*-unsaturated hydrazone **1a** and aniline **2a** as the substrates, 0.5 equiv $Cu(OAc)_2$ as the catalyst, 0.5 equiv of K_2CO_3 as the base, and DMF as solvent (Table 1, entry 1). The reaction was stirred at room temperature for 40 h under an argon atmosphere and gave the desired product **3a** in 74% yield, with **1a** recovered in 5% yield. Increasing the temperature to 45 °C gave a decreased yield of 56% (Table 1, entry 2). Subsequently, we investigated the influence of oxidants on the reaction. When the reaction was carried out under air, it produced the corresponding product **3a** in a lower yield (50%), while it failed to realize such a transformation when under an oxygen atmosphere (Table 1, entries 3−4). Then, DTBP,

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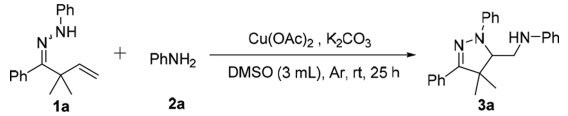
Table 1. Optimization of Reaction Conditions for Diamination of 1a with Aniline[a]



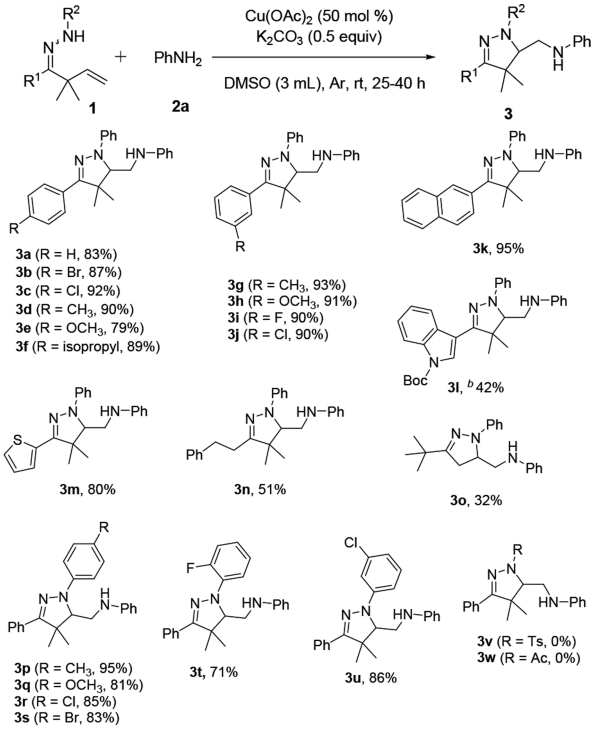
entry	[Cu]	solvent	base	t (h)	recovery of **1a**[b] (%)/ yield of **3a**[b] (%)
1	$Cu(OAc)_2$	DMF	K_2CO_3	40	5/74
2[c]	$Cu(OAc)_2$	DMF	K_2CO_3	15	−/56
3[d]	$Cu(OAc)_2$	DMF	K_2CO_3	40	9/50
4[e]	$Cu(OAc)_2$	DMF	K_2CO_3	40	9/trace
5[f]	$Cu(OAc)_2$	DMF	K_2CO_3	40	13/62
6	**$Cu(OAc)_2$**	**DMSO**	**K_2CO_3**	**25**	**−/83**
7	$Cu(OAc)_2$	CH_3CN	K_2CO_3	40	<2/32
8	$Cu(OAc)_2$	THF	K_2CO_3	40	53/7
9	CuOAc	DMSO	K_2CO_3	35	−/83
10	$Cu(OTf)_2$	DMSO	K_2CO_3	40	7/46
11	$Cu(OAc)_2$	DMSO	–	40	15/56
12	–	DMSO	K_2CO_3	25	92/N.R.

[a]All reactions were carried out by using **1a** (0.2 mmol), **2a** (2.0 equiv), copper salts (0.5 equiv), K_2CO_3 (0.5 equiv), oxidant (2.0 equiv), and DMSO (3 mL) under argon and stirred at room temperature, unless noted otherwise. [b]Isolated yield. [c]Reaction was carried out under 45 °C. [d]Reaction was carried out under air. [e]Reaction was carried out under oxygen. [f]1.0 equiv of $Cu(OAc)_2$ was used.

TBHP, TBPB, $K_2S_2O_8$, and DDQ were tested under argon, but no better results were observed (Supporting Information (SI) Table S1). When 1.0 equiv of $Cu(OAc)_2$ was used alone as the oxidant, the yield was decreased to 62% (Table 1, entry 5). Delightfully, when the solvent was changed to DMSO, the yield was improved to 83%, with a shortened reaction time (entry 6), while other solvents such as CH_3CN and THF were not suitable for this transformation (entries 7−8). These results indicated that DMSO as a solvent was crucial for this reaction. CuOAc produced the same yield after 35 h, while $Cu(OTf)_2$ only gave a yield of 46% (entries 9−10). Employment of other bases such as Na_2CO_3 and Et_3N provided inferior results. The loading of $Cu(OAc)_2$ and K_2CO_3 were evaluated as well, but there was no improvement in yield (Table S1). The subsequent control experiments revealed that both $Cu(OAc)_2$ and K_2CO_3 were crucial to this transformation (entries 11−12). (for details see SI Table S1).

With the optimized conditions in hand (Table 1, entry 6), we then examined the scope of this transformation. As shown in Scheme 2, various β,γ-unsaturated ketohydrazones were subjected to the standard conditions. First, a series of hydrazone substrates with a *para*-substituent on the phenyl ring including some with electronwithdrawing groups (Br, Cl) and some with electron-donating groups (Me, OMe, and isopropyl) underwent the diamination smoothly and provided the desired products in excellent yields (**3b−f**). Then, as shown in the synthesis of dihydropyrazoles **3g−j**, substrates with a 3-substituted phenyl ring were also proved to be suitable for the transformation. We continued to investigate the hydrazone substrates bearing aryls. **1k** and **1m** participated smoothly in the tandem reaction and gave rise to the corresponding pyrazolines in excellent yields, while **1l** only gave the desired product in 42% yield. Moreover, aliphatic β,γ-unsaturated hydrazones **1n** and **1o** could also give the desired products in 51% and 32% yields, respectively. We next examined the possible structural

Scheme 2. Substrate Scope of β,γ-Unsaturated Ketohydrazones[a]



[a]All reactions were carried out by using **1** (0.2 mmol), **2a** (2.0 equiv), $Cu(OAc)_2$ (0.5 equiv), K_2CO_3 (0.5 equiv), and DMSO (3 mL) under argon and stirred at room temperature for 25−40 h, unless noted otherwise. Isolation yields. [b]The reaction was carried out for 40 h, and **1l** was recovered in 34% yield.

variation of the *N*-Phenyl moiety. And substituted β,γ-unsaturated hydrazones with a range of electronic properties all proceeded well in the reaction to yield the desired pyrazolines in excellent yields (**3p−u**). However, *N*-tosyl and *N*-acetyl substituted ketohydrazones were inert in the reaction (**3v−w**).

To further demonstrate the synthetic potential of this method, a vast variety of simple amines were employed in this diamination reaction (Scheme 3). As expected, substituted anilines with a broad range of electronic properties worked well under the standard conditions and provided compounds **3ab−ah** in good to high yields. 2-Aminonaphthalene **2ai** and heterocyclic primary amine **2aj** were also suitable for this transformation. Use of primary aliphatic amine **2ak** could give the desired product **3ak** in 44% yield, while benzamide **2al** only gave a trace amount of the corresponding products under the stated conditions. Secondary aniline **2am** could be transformed into the desired product in 32% yield. Moreover, secondary aliphatic amines, such as dimethylamine, piperidine, morpholine, and pyrrolidine, are good aminating reagents as well. We can obtain the diamination products **3an−aq** in good yields with them.

To gain an insight into the mechanism of the chemical reaction, two control experiments were carried out as shown in Scheme 4. When the radical scavenger TEMPO (2, 2, 6, 6-tetramethylpiperidine-1-oxyl, 2 equiv) was added in the reaction under the standard reaction conditions, the desired compound **3a** could only be obtained in a trace amount and the pyrazoline **4**, which was obviously yielded from the trapping of

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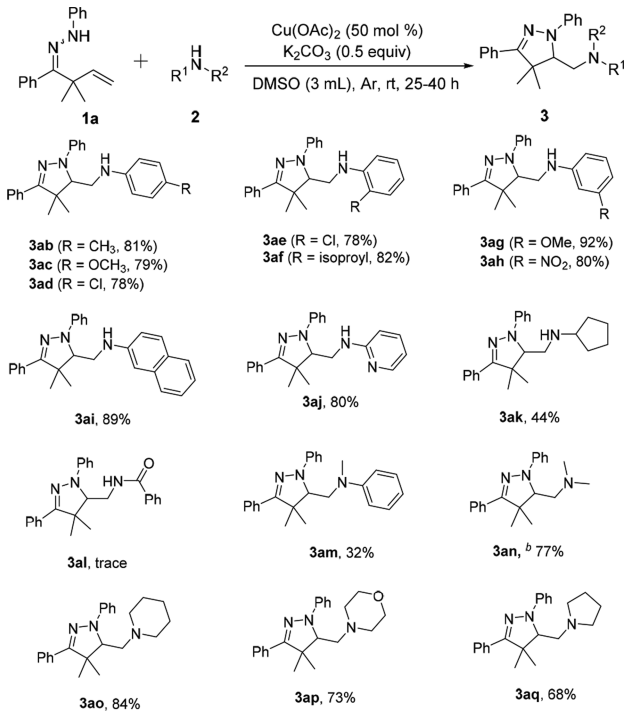
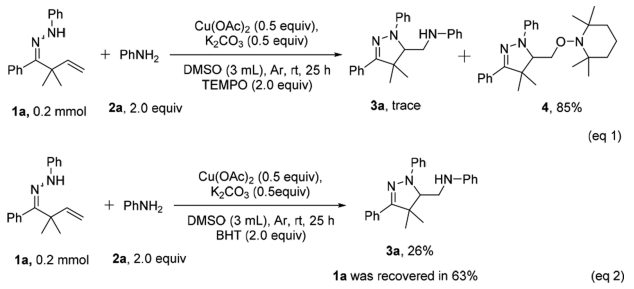
Scheme 3. Substrate Scope of Amines[a]



[a]All reactions were carried out by using **1a** (0.2 mmol), **2** (2.0 equiv), $Cu(OAc)_2$ (0.5 equiv), K_2CO_3 (0.5 equiv), and DMSO (3 mL) under argon and stirred at room temperature for 25−40 h, unless noted otherwise. Isolation yields. [b]Dimethylamine added as 2 M solution in THF.

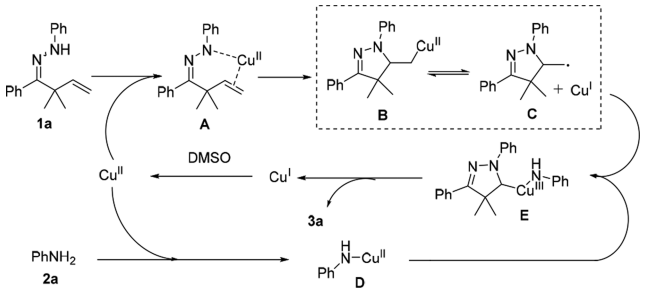
Scheme 4. Control Experiment



the C-centered radical derived from the 5-exo-trig cyclization of **1a** by TEMPO, was formed in 85% yield (eq 1). Furthermore, when BHT (butylated hydroxytoluene, 2 equiv) was added under the standard reaction conditions, the yield of the desired product **3a** was also sharply decreased to 26% and the substrate **1a** was recovered in 63% yield (eq 2). Together, these observations clearly suggest that a radical pathway was involved.

Although the reaction mechanism is not completely clear yet, on the basis of the above-mentioned results and literature reports,[5c,7,9] we propose a plausible mechanism for this transformation (Scheme 5). Initially, the intramolecular aminocupration of **1a** occurs upon alkene activation by a copper(II) catalyst via intermidate **A** to form alkyl-copper complex **B**. Intermidate **B** may undergo homocleavage to form the radical intermediate **C**. On the other hand, aniline **2a** reacts with the Cu(II) catalyst to form intermediate **D**. The obtained C-centered radical intermediate **C** couples with intermediate **D** to generate intermediate **E**, which was followed by a reductive elimination process to form the desired product **3a** and Cu(I).

Scheme 5. Proposed Mechanism



Finally, Cu(I) could be oxidized by DMSO to regenerate Cu(II).[14]

In summary, a highly efficient and practical copper-catalyzed intra-/intermolecular alkene diamination reaction between *β,γ*-unsaturated hydrazones and simple amines with DMSO as the oxidant has been developed. This transformation offers a useful method to access a variety of aminomethyl-functionalized pyrazolines, which are valuable building blocks in organic synthesis and medicine. Further studies on the mechanisms details of this reaction and more hydrazonyl radical promoted reactions are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03401.

Detailed experimental procedures and spectral data for all products (PDF)

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Notes

The authors declare no competing financial interest.

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