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Cu-catalyzed direct C–H amination of 2-alkylazaarenes with azodicarboxylates via nucleophilic addition

Bo Qian, Lei Yang, Hanmin Huang *

State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, PR China

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ABSTRACT

An efficient Cu-catalyzed C–H amination of 2-alkylazaarenes with azodicarboxylates has been developed through nucleophilic addition of sp^3C–H bond to unsaturated nitrogen–nitrogen double bond. It provides an easy access to azaarene-containing hydrazines from simple and easily available starting materials.

Introduction

The elaboration of a new catalytic system for C–N bond construction from simple starting materials, leading to complex amines, remains one of the major challenges in organic synthesis.[1] Among many documented methods for C–N bond formation, the activation of inert C–H bond of hard nucleophiles and subsequently nucleophilic addition of C–H bond to unsaturated nitrogen-containing chemical bonds would be an attractive strategy for the synthesis of amines from simple starting materials.[2] For the success of such a catalytic process, the development of efficient catalytic method for conversion of a hard nucleophile to an active soft nucleophile via direct C–H activation and identifying a proper nitrogen-containing electrophile is a prerequisite.

Functionalized pyridines and related azaarenes, which are important heteroarenes, play increasingly important roles in natural compound synthesis and drug discovery.[3] Consequently, the development of mild, general, and efficient methods for direct C–H functionalization of pyridine and other azaarene cores has stimulated tremendous research efforts. In contrast, little progress has been made toward the functionalized sp^3C–H bond of the alkylazaarenes.[4] In this context, our group has developed an efficient methodology for activating benzylic C–H bond of 2-alkyl-substituted azaarenes and subsequently transforming related 2-alkylazaarenes into active nucleophiles under neutral conditions. This strategy has enabled the construction of various C–C bonds with great efficiency and selectivity via nucleophilic addition. In light of these initial findings, we decided to take one further step in developing new synthetic protocols for direct functionalization of 2-alkylazaarenes by this strategy. To this end, we turned our attention toward the construction of C–N bond via selective C–H cleavage and nucleophilic addition. Herein, we report an efficient copper-catalyzed nucleophilic addition of sp^3C–H bond to azodicarboxylates under mild neutral conditions.[5]

Azodicarboxylates are widely used as electrophiles for C–N bond formation reactions via nucleophilic addition.[6] Although many kinds of soft nucleophiles have been used as coupling partners for the corresponding nucleophilic addition reactions with azodicarboxylates under transition-metal-catalyzed or metal-free conditions, the direct incorporation of hard nucleophiles to this kind of nitrogen source is still limited. Hence, inspired by our previous results and other works,[7] we envisaged that the C–N bond formation reaction would be realized by the reaction of 2-alkylazaarenes with azodicarboxylates under proper reaction conditions, affording the corresponding hydrazine-containing functionalized heterocycles. As shown in Figure 1, the transformation might proceed via an active metal enamide species **C**, which would be dynamically formed when the acidity of the benzylic proton was enhanced by a suitable metal catalyst.

Results and discussion

At first, on the basis of our previous work, we examined the feasibility of the reaction between 2,6-lutidine **1a** and diisopropyl azodicarboxylate **2a** with Lewis acid as catalyst.[8] To our delight,

* Corresponding author. Tel.: +86 931 4968326; fax: +86 931 4968129.
E-mail address: hmhuang@licp.cas.cn (H. Huang).

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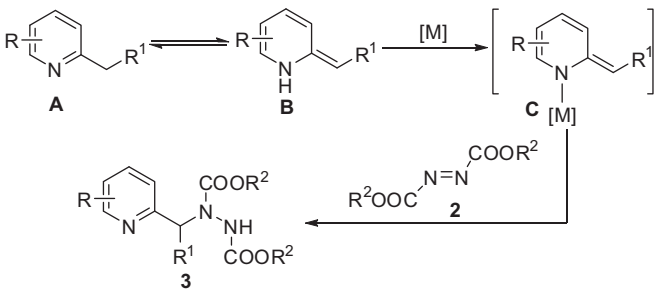
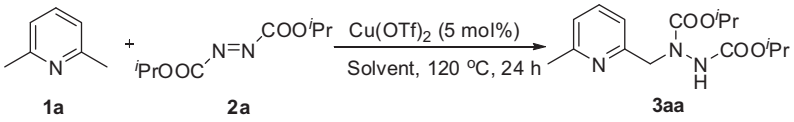


Figure 1. Reaction of 2-alkylazaarenes with azodicarboxylates.

the reaction could occur under the catalysis of $Cu(OTf)_2$, and 35% yield of the desired product **3aa** was obtained when the reaction was conducted using 5 mol % of $Cu(OTf)_2$ as catalyst and dioxane as solvent under argon atmosphere at 120 °C for 24 h (Table 1, entry 1). Encouraged by this result, we investigated the reaction conditions in detail, and the results were summarized in Table 1. An initial study of solvents with different polarity was conducted and the results showed that the reaction performed well in non-polar solvents. For example, 63% yield of **3aa** was obtained when xylene was used as solvent, which was much better than that obtained in other polar solvents. Thus, xylene was determined to be the most appropriate solvent for this transformation.

Subsequently, a variety of Lewis acid catalysts, which were effective for this type of reactions in other cases, were screened,[7b] and the results were shown in Table 2. Among the Lewis acid catalysts screened, the $Cu(OTf)_2$ demonstrated the best catalytic efficiency for giving the desired product **3aa** with 63% yield in the

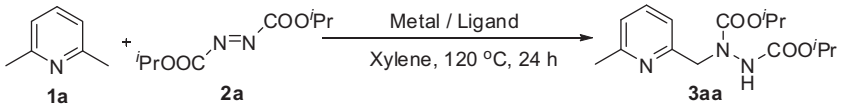
Table 1
Optimization of reaction conditions with solvent[a]



Entry	Catalyst	Solvent	Yield[b] (%)
1	$Cu(OTf)_2$	Dioxane	35
2	$Cu(OTf)_2$	CH_3CN	22
3	$Cu(OTf)_2$	DMF	23
4	$Cu(OTf)_2$	^{i}PrOH	NR
5	$Cu(OTf)_2$	MCPE	43
6	$Cu(OTf)_2$	THF	47
7	$Cu(OTf)_2$	CH_2Cl_2	35
8	$Cu(OTf)_2$	$PhCH_3$	53
9	$Cu(OTf)_2$	Xylene	63
10	$Cu(OTf)_2$	$PhCF_3$	57
11	$Cu(OTf)_2$	Mesitylene	44
12	$Cu(OTf)_2$	PhCl	54

[a] Reaction conditions: **1a** (0.75 mmol), **2a** (0.30 mmol), $Cu(OTf)_2$ (0.015 mmol), solvent (1.5 mL), 120 °C for 24 h.
[b] Isolated yield.

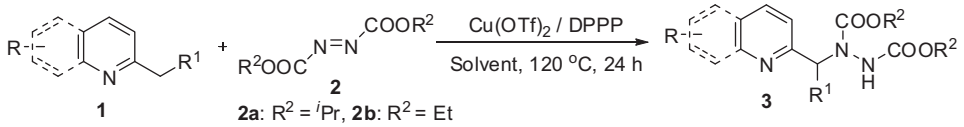
Table 2
Optimization of reaction conditions[a]

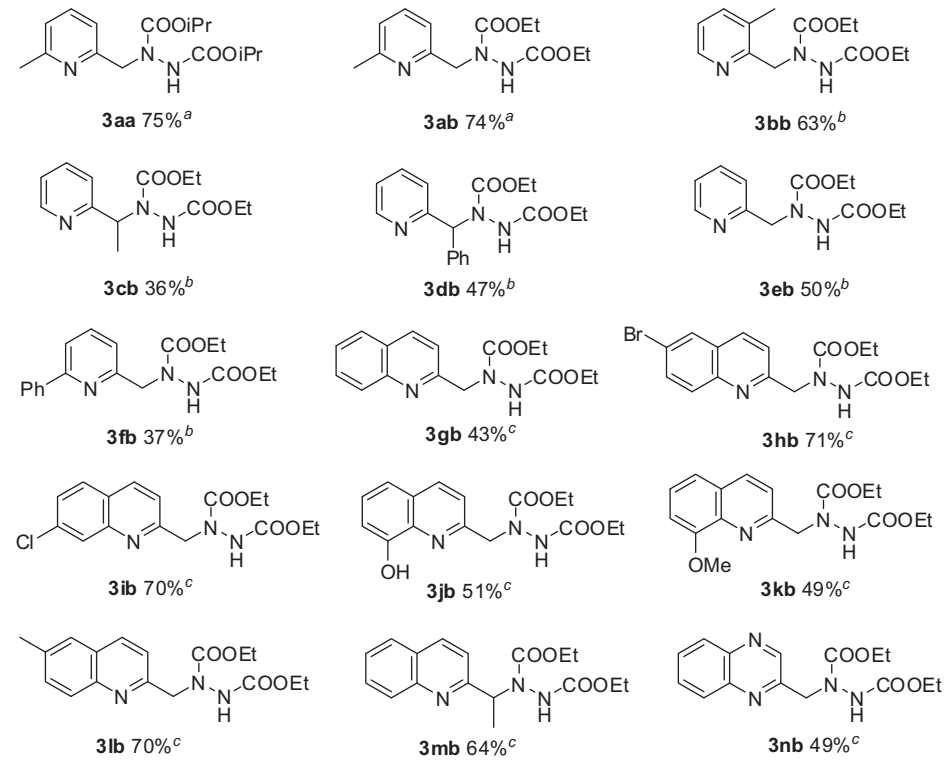


Entry	Catalyst	Ligand	Yield[b] (%)
1	$Zn(OTf)_2$	—	6
2	$AlCl_3$	—	40
3	$Sc(OTf)_3$	—	Trace
4	$Cu(OTf)_2$	—	63
5	$Cu(SbF_6)_2$	—	14
6	$Cu(BF_4)_2$	—	23
7	$Cu(OTs)_2$	—	42
8	$Cu(OAc)_2$	—	21
9	$Cu(ClO_4)_2$	—	24
10	$Cu(OTf)_2$	DPPE	55
11	$Cu(OTf)_2$	DPPP	75
12	$Cu(OTf)_2$	DPPPen	69
13	$Cu(OTf)_2$	DPPHex	45
14	—	—	NR

[a] Reaction conditions: **1a** (0.75 mmol), **2a** (0.30 mmol), metal catalyst (0.015 mmol), ligand (0.018 mmol), xylene (1.5 mL), 120 °C for 24 h.
[b] Isolated yield.

Table 3
Substrate scope of the reaction[a]





[a] Reaction conditions: **1** (0.75 mmol), **2** (0.3 mmol), $Cu(OTf)_2$ (0.015 mmol), DPPP (0.018 mmol), xylene (1.5 mL), 120 °C, 24 h.
[b] $Cu(OTf)_2$ (0.03 mmol), DPPP (0.036 mmol) in the mixture of toluene (1.0 mL) and THF (0.5 mL).
[c] $Cu(OTf)_2$ (0.003 mmol), DPPP (0.0036 mmol), in the mixture of toluene (1.0 mL) and THF (0.5 mL).

absence of ligand (Table 2, entry 4). Further experiments conducted for searching more active catalysts by changing the counteranion of the copper salts were proved to be unsuccessful. However, the efficiency of this reaction could be improved when DPPP was used as a ligand.[9] As a result, with $Cu(OTf)_2$/DPPP as catalyst, the yield of the desired product could be increased to 75% (Table 2, entry 11). Finally, control reactions demonstrated that the desired product was not observed at all in the absence of catalyst (Table 2, entry 14).

With the optimized reaction conditions in hand, we next explored the scope of the present reaction and a variety of azaarene-containing hydrazines **3** were prepared (Table 3). First, diethyl azodicarboxylate **2b** also demonstrated good reactivity in this transformation to give the corresponding product **3ab** in 74% yield under the optimized conditions.[10] A range of 2-methylpyridines (**1b**, **1e**, and **1f**), 2-ethylpyridine (**1c**), and 2-benzylpyridine (**1d**) were subjected to the reaction with diethyl azodicarboxylate **2b** as an electrophile and the corresponding products (**3bb**–**3fb**) were obtained in good yields. Besides the substituted 2-alkylpyridines, the substituted 2-alkylquinolines could also react with diethyl azodicarboxylate **2b** even in the absence of metal catalyst affording the desired addition products in lower yields. But higher activity was always observed in the presence of catalyst. Thus, in order to get higher yields, the corresponding reactions were conducted in the presence of 1 mol % of $Cu(OTf)_2$/DPPP under the modified conditions. Under the modified conditions, the hydrazine group could be successfully incorporated into the substituted quinaldines. The chloro and bromo group can survive the reaction conditions to give the corresponding functionalized hydrazines such as **3hb** and **3ib** in good yield. The ability to tolerate the incorporation of additional halogen substituents is useful for further functionalization with transition metal catalysis. Inclusion of additional free OH-substituent in the substrates was also possible, leading to a hydroxyl-substituted product (**3jb**), which was advantageous to further transformation too. Under the same reaction conditions, 2-ethylquinoline and 2-methylquinoxaline were also competent in this transformation to give the desired products **3mb** and **3nb** in good yields.

Conclusions

In summary, we have successfully developed a new protocol of copper-catalyzed selective C–H cleavage and subsequently nucleophilic addition of 2-alkylazaarenes to azodicarboxylates affording azaarene-containing hydrazines. The reactions proceed with good yield and give an easy access to azaarene-containing hydrazines from simple and easily available starting materials.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and full characterization of all products including ^{1}H, ^{13}C NMR and HRMS spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.055.

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