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Coordination strategy induced selective C-H amination of 8-animoquinolines

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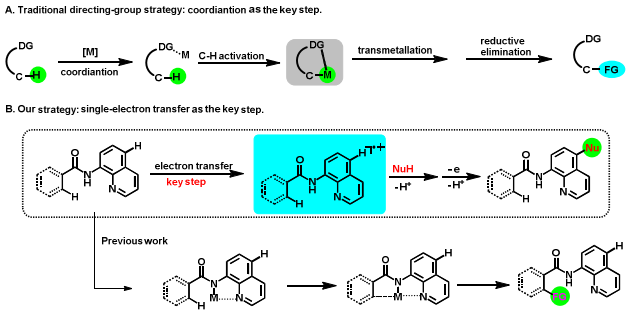
In this work, we broke through the directing function of the amide group. Instead, the coordination interaction between metal and "directing-group" played the role to enhance the reactivity of substrate. Using this strategy, we realized the selective amination of 8-aminoquinolins on the C5 position employing azoles as the source of amine. Various kinds of 8-aminoquinolines and different substituted azoles were compatible to afford the corresponding C-N coupling products.

The C-H activation strategy provides an ideal way to the construction of C-C/C-X (X=N, O, P etc.) bonds for the broad existence of C-H bonds in organic molecules. During the past several decades, transition metal catalyzed C-H activation reactions have made great progress in the field of organic synthesis methodology.[1] For selective C-H activation, directing-group strategy was employed widely to verify different C-H bonds in complex structures and have shown great application prospect for the synthesis of complicated structures.[2] Mechanistically, coordination, C-H activation and subsequently transmetallation and reductive elimination steps were usually involved (Scheme 1A). Coordination interaction was the key step for the selectivity and directing group was crucial in the C-H activation step. In addition, this directing-group strategy went through two-electron transfer process generally.

For its strong coordination capability, the nitrogen-containing group was usually employed as directing-group in transition metal catalyzed C-H activation reactions. In addition, C-H activation reactions directed by amide group have shown great application potential in the field of synthetic methodology. Different kinds of chemical transformations including C-C/C-N/C-P/C-S etc. bonds formation have been developed.[3] Especially, 8-animoquinoline was an excellent directing-group which has two coordination sites and has received extensive research in the past ten years. Employing Cu/Ni/Pd/Co etc. as the catalyst, amounts of transformations including functionalization of Csp^2-H and Csp^3-H have been realized.[4] In addition, the modification of the C5 position of 8-aminoquinoline also draws much research attention in the synthetic methodology.[5] Here, we developed a coordination interaction promoted selective C-H activation strategy, which underwent an entirely different pathway compared to traditional directing-group pattern (Scheme 1B). Firstly, the interaction between substrate and high-valent metal center produced the organometallic reagent and subsequent single-electron transfer step afforded the radical species which was crucial to selectivity for its electron distribution. The target product was finally obtained through a nucleophilic addtion/single-electron transfer/deprotonation process. Different from conventional strategy, in our model, the radical cation species which formed from single-electron transfer process was explainable for the selectivity.



Scheme 1. (**A**) Traditional fuctional-group strategy for selective C-H activation. (**B**) Coordination strategy induced selective C-H activation.

XAFS and DFT evidence for the single-electron transfer process. To check the feasibility of our strategy, XAFS was initially employed to demonstrate the electron transfer process. As shown in Figure 1A, the XANES spectrum of the $CuBr_2$ solution gave a pre-edge at 8995.0 eV (Figure 1A, red line). After the addition of 8-aminoquinoline **1a** at 80 °C, a new Cu species with the edge energy of 8982.6 eV was observed (Figure 1A, black line). This edge energy was close to reported Cu(I) standard sample.[6] The EXAFS result

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showed that no nitrogen atom coordinated to the Cu(I) center (Figure S1), which indicated that the 8-animoquinoline didn't coordinate with copper after the reaction. In addition, density functional theory (DFT) calculation was employed to probe the reactivity of radical cation species generated via the oxidation process. As shown in Figure 1B, the calculated Mulliken atomic spin densities (ASD) of radical cation **1a'** suggested that the spin density on C5 position was 0.43, which was much higher than that on other carbon positions or nitrogen positions. Frontier molecular orbital (FMO) analysis also revealed that the β-LUMO of **1a'** was mainly located on C5 position. Therefore, both ASD results and FMO analysis supported that the C5 position has higher reactivity and nucleophiles would preferentially react at C5 position in subsequent transformation.

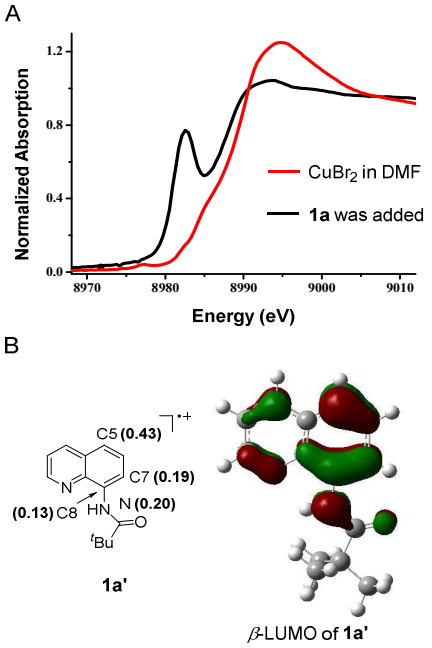
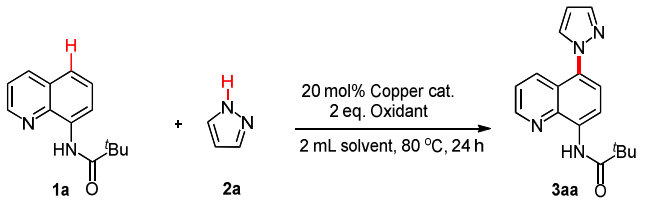


Figure 1. (A) XANES evidence for the single-electron transfer process between Cu(II) and **1a. (B)** Calculated Mulliken atomic spin densities (ASD) and lowest unoccupied molecular orbital (β-LUMO) of radical cation **1a'.**

Optimization of Reaction Conditions. Next, we turned our attention to the application of this oxidative induction strategy. From the aspect of synthetic chemistry, it is a very useful transformation to realize the construction of aryl C-N bonds through the direct cross-coupling of C-H/N-H.[7] Herein, we employed acyl-substituted 8-aminoquinoline **1a** and pyrazole **2a** as model substrates to construct the C-N bonds in selective manner and screened a series of reaction conditions. As our continuous interest in copper chemistry,[8] several available copper salts were employed as catalyst precursors (Table 1, entries 1-6). Different copper salts including Cu(I) and Cu(II) were able to afford the desired product, $CuCl_2$ and $Cu(OTf)_2$ could get the same result (Table 1, entries 1 and 5). Different kinds of oxidants which were usually employed in copper chemistry were screened and we found the $Na_2S_2O_8$ was the best partner (Table 1, entries 7-9). Screening of solvents showed that using DCE as solvent could afford the highest yield (Table 1, entries 10-12). Control experiments implied that oxidant was essential for the conversion (Table 1, entry 14) and copper catalyst played the role as a promoter (Table 1, entry 13). In addition, the reaction afforded trace amount of product only when operated at room temperature (Table 1, entry 15). In a word, we could get the best result using 20 mol% $CuCl_2$ or $Cu(OTf)_2$ as a catalyst, 2 equiv. $Na_2S_2O_8$ as the oxidant, and DCE as the solvent (Table 1, entries 1 and 5). The structure of the product **3aa** was also confirmed by X-Ray crystal.

Table 1. Optimization of Reaction Conditions[a]



Entry	Copperer	Oxidant	Solvent	Yield(%)[b]
1	$CuCl_2$	$Na_2S_2O_8$	DCE	72 (72)[c]
2	$CuBr_2$	$Na_2S_2O_8$	DCE	57
3	$Cu(OAc)_2$	$Na_2S_2O_8$	DCE	30
4	$Cu(acac)_2$	$Na_2S_2O_8$	DCE	16
5	$Cu(OTf)_2$	$Na_2S_2O_8$	DCE	72
6	CuBr	$Na_2S_2O_8$	DCE	37
7	$CuCl_2$	$PhI(OAc)_2$	DCE	n.d.
8	$CuCl_2$	Ag_2CO_3	DCE	trace
9	$CuCl_2$	DDQ	DCE	n.d.
10	$CuCl_2$	$Na_2S_2O_8$	MeCN	57
11	$CuCl_2$	$Na_2S_2O_8$	DMF	trace
12	$CuCl_2$	$Na_2S_2O_8$	DMSO	trace
13	-	$Na_2S_2O_8$	DCE	15
14	$CuCl_2$	-	DCE	n.d.
15[d]	$CuCl_2$	$Na_2S_2O_8$	DCE	trace

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (1.0 mmol), copper catalyst (0.05 mmol) and oxidant (0.5 mmol) was stirred in 2.0 mL solvent at 80 °C under N_2 atmosphere for 24 h. [b]The yield was determined by GC using biphenyl as an internal standard. [c]Isolated yield in parentheses. [d]Room temperature.

Scope of 8-aminoquinolines. With the optimized conditions in hand, we turned our attention to the exploration of substrate scope. As shown in Scheme 2, we firstly evaluated different substituted 8-aminoquinolines employing pyrazole **2a** as co-partner. Various kinds of alkylamides showed excellent reactivity, affording the corresponding amination product in high yields (**3aa-3fa**). In particular, cycloalkane amide was also a good reaction partner to produce the C-N structure in 68% yield (**3ea**). It is worth mentioning that halogen atom which could provide a further functionalization site was well tolerated under the reaction conditions (**3fa**). Amazingly, alkene which existed in many natural products showed good tolerance under our catalytic system, giving the selective amination product in 53% yield (**3ga**). Apart from alkylamides, arylamides were also good reaction partners (**3ha-3la**). Methyl-substituted aryl showed similar reactivity (**3ia-3ka**). Notably,

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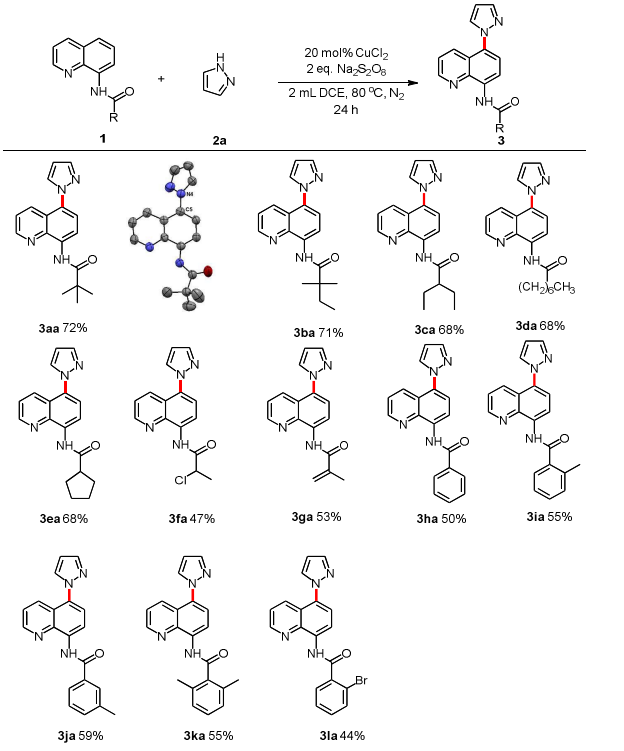
halogen substituted phenyl afforded 44% yield which could be further functionalized (**3la**).

Scheme 2. Substrate scope of 8-aminoquinolines.[a]

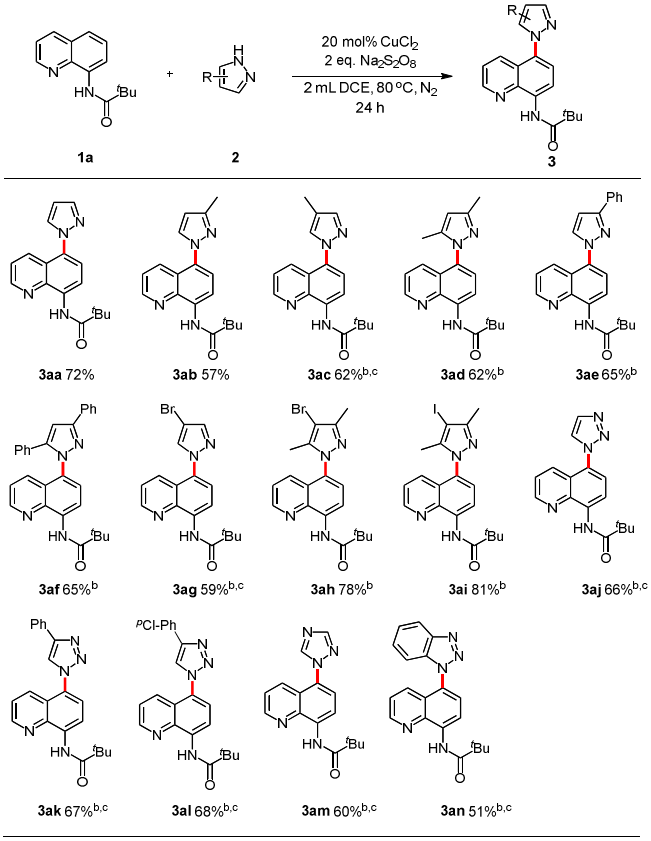


[a]Reaction conditions: **1** (0.25 mmol), **2a** (1.0 mmol), $CuCl_2$ (0.05 mmol) and $Na_2S_2O_8$ (0.5 mmol) was stirred in 2.0 mL DCE at 80°C under N_2 atmosphere for 24 hours.

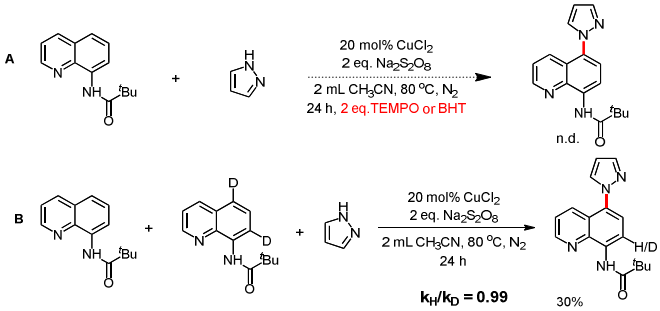
Scope of azoles. It is of great significance to develop efficient methods to the synthesis of functionalized azoles because they are important structural moieties in many kinds of pharmacologically active compounds and usually act as directing groups in transition-metal catalyzed reactions.[7b, 9] Therefore, we investigated a series of azoles using **1a** as co-partner. As shown in Scheme 3, methyl groups were tolerated well for pyrazoles to afford the corresponding molecules in approximately 60% yield (**3ab-3ad**). 3-Phenyl-1H-pyrazole and 3,5-diphenyl-1H-pyrazole were also good reaction partners (**3ae, 3af**). Notably, halogen atoms including bromine and iodine which could be further functionalized were compatible under our catalytic conditions (**3ag-3ai**). Apart from pyrazoles, various kinds of triazoles were good reaction partners under our system. 1,2,3-Triazole and 4-phenyl triazoles showed similar reactivity to afford the desired products in 66-68% yield (**3aj-3al**). In addition, 1,2,4-triazole was successfully employed in our system and produced the C-N structure in 60% yield. And benzotriazoles which were used as corrosion inhibitor of copper and its oxides were also compatible and afforded the target product in moderate yield under our conditions (**3an**).[10]

Mechanistic studies. To further confirm our coordination strategy, a series of control experiments were conducted. Firstly, when the substrate **4** or **5** was employed under our conditions, no C-N coupling product was detected which demonstrated the importance of the formed organometallic reagents. (Scheme S1). In addition, when the reaction was conducted under the addition of 2 equiv. TEMPO or BHT, the reaction was totally inhibited which suggested the radical pathway (Scheme 4A). Finally, an isotope labelling experiment employing equivalent **1a** and D_2-**1a** was conducted under standard conditions, and the result showed the cleavage step of C-H bond was not involved in the rate-determining step (Scheme 4B).

Scheme 3. Substrate scope of azoles.[a]



[a]Reaction conditions: **1a** (0.25 mmol), **2** (0.5 mmol), $CuCl_2$ (0.05 mmol) and $Na_2S_2O_8$ (0.5 mmol) were stirred in 2.0 mL solvent at 80°C under N_2 atmosphere for 24 hours. b, $Cu(OTf)_2$ instead of $CuCl_2$. c, MeCN instead of DCE.



Scheme 4. (**A**) Radical inhibition experiments. (**B**) Isotope labelling experiment.

Finally, on the basis of our experimental results, we proposed a mechanism for the selective C-H activation of 8-animoquinolines on the C5 position (Scheme 5). Initially, coordination of Cu(II) with **1** afforded the corresponding organometallic species **I** which subsequently went a single-electron transfer process, affording the radical cation **II**. The radical cation **II** was a crucial

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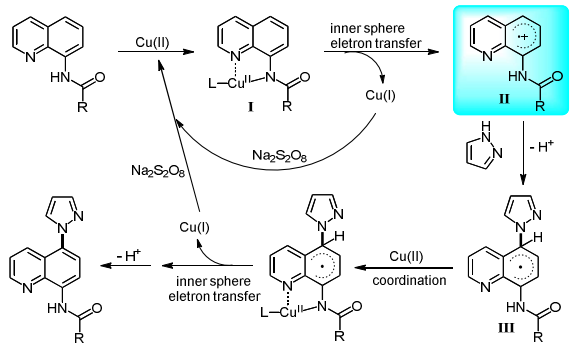
intermediate for the high selectivity as confirmed by theoretical calculation results. Then, nucleophilic addition and deprotonation produced the radical species **III**. The radical could react with Cu(II) and next single-electron transfer and deprotonation process afforded the target amination molecule. In this mechanism, the Cu(II) played the role as a medium of electron transfer process and $Na_2S_2O_8$ as the terminal oxidant.



Scheme 5. Proposed mechanism.

In conclusion, we have developed a coordination strategy induced C-H activation which realized the amination of 8-aminoquinolines on the C5 position selectively. A variety of substituents were well tolerated to afford the products in moderate to good yields. Spectroscopy methods provided evidence for the single-electron transfer process and control experiments showed the importance directed function of the pyridyl group. In addition, labelling experiments provided further information for the whole mechanism and theoretical calculation was employed to explain the high selectivity.

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Notes and references

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