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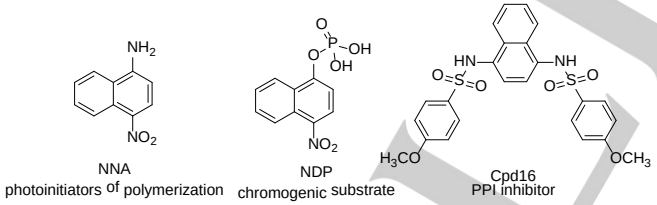
Copper-Catalyzed Regioselective Nitration and Azidation of 1-Naphthylamine Derivatives via remote C-H activation

Yandong Dou,[a,b] Biao Yin[b] Pengfei Zhang[c] and Qing Zhu*[a,b]

Abstract: A simple and facile protocols for copper-catalyzed regionselective C4 nitration and azidation of 1-naphthylamines via remote C-H activation that use of pyridyl amide fragment as the removable directing group have been firstly developed. These reactions proceed under mild conditions without any additives, tolerate a wide variety of functional groups, and afford a wide range of products in good to excellent yields. Control experiments suggest that those C−H activation reactions are likely to proceed through a single-electron-transfer (SET) process.

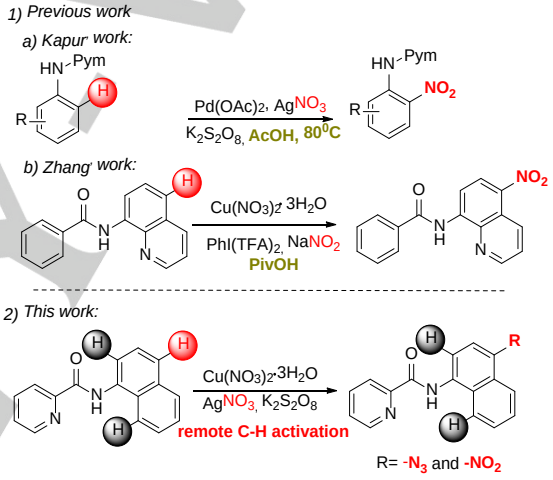
Introduction

Transition-metal-catalyzed C−H bond functionalization reactions of aromatics and heteroaromatics are an appealing and convenient tool for constructing C(sp2)−N bonds, including their use for aryl nitration and azidation reactions.[1] Nitroaryl and azidoaryl compounds are important building blocks in synthetic chemistry, with nitroarenes representing one of the most commonly targeted intermediates for the synthesis of agrochemicals, pesticides, pharmacology, dyes, and polymers.[2] The high synthetic utility of nitroaryl compounds is due to their ease of preparation and the number of synthetic transformation that are available to transform the nitro group into other functional groups (e.g. amino and diazo groups).[3] More specifically, nitro-naphthalenes represent an important class of synthetic intermediate that are extensively utilized for the production of pharmaceuticals, agrochemicals and dyes, whilst they are also widely used as photoinitiators for polymerization reactions (Scheme 1).[4]



Scheme 1. Applications of nitro-naphthalene compounds

A wide range of methodology is available for the nitration of aromatics and heteroaromatics, most notably the use of aromatic electrophilic nitration (EArS) reactions.[5] These EArS reactions are normally performed under relatively harsh conditions using conc. HNO_3–H_2SO_4, nitronium tetrafluoroborate, conc. HNO_3-mixed anhydrides, N-nitropyridinium salts, and $NaNO_3$–TFA as reagents for nitration. A number of drawbacks exist with those strongly acidic nitrating methodologies, however, with many reactions proceeding with poor regioselectivity, whilst poor functional group compatibility often leads to poor yields of nitrated products.[6] Moreover, stochiometric amounts of acidic waste as by-product will be generated in these reactions. To circumvent these problems, several alternative catalytic nitration methods have been developed, based on ipso-substitution and metal-catalyzed nitration reactions of aryl halides, pseudo-halides and organometallic compounds.[7] However, these promising transformations generally proceed with low atom economy and generate large amounts of waste, so the development of simple effective regioselective methods for the catalytic nitration of aromatics using this type of reaction is still required.



Scheme 2. C-H activation strategies for the synthesis of nitro-naphthylamines

Recently, a range of transition-metal-catalyzed C-H bond functionalizations have been developed for the direct nitration of aromatic C-H bonds.[8] Amongst these reactions, a number of directing group strategies have been developed, which employ a cyclometalation step to selectively direct the nitro group to the desired ring position.[9] The potential synthetic utility of these methods is greatly enhanced when removable directing groups are employed which can potentially be replaced by other functional groups. Nitrogen-containing heterocycles such as amino, tetrazole, etc. have proven to be the most efficient directing groups (DGs) in these C-H bond functionalization reations, but their synthetic utility remains low, because of the difficulty in removing or modifying their directing groups. [10] Therefore, in recent few years, a range of new methods have been developed to remove these type of thermodynamically stable aza-DGs, thus broadening the utitilty of these C-H activation reactions for organic synthesis.[11] Li and co-workers have previously employed pyridine as a directing group to achieve the selective ortho-nitration (azidation) of arenes using AcOH (TsOH) as an additive.[12] Kapur and co-workers have described a new palladium-catalyzed, heteroatom-directed strategy for C-H nitration of anilines using a pyrimidine fragment

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† Footnotes relating to the title and/or authors should appear here.

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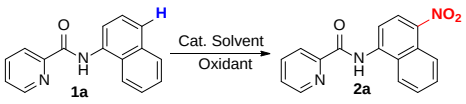
as a removable directing group and AcOH as an additive (Scheme 2-a).[11a] More recently, Zhang et al. developed a copper-catalyzed rapid C–H nitration reaction of 8-aminoquinolines using PivOH as an additive (Scheme 2-b).[8b] As can be seen from these reports, C-H nitration reactions utilizing pyridine as a directing group usually require an acid additive to proceed, which decreases the atom economy and increases the complexity of these protocols. Consequently, the development of a novel and simple method for C-H nitration using a removable directing group, without the need of acid as an additive, would enable these reactions to be applied to aryl substrates containing acid sensitive functional groups.

Herein, we report a copper-catalysted C-H nitration and azidation reactions of 1-naphthylamines that employ pyridyl amide groups as removable para- directing groups to control the remote regioselective C-H functionalization of naphthylamine substrates. To our best knowledge, this was the first example of C-H nitration and azidation at the C–4 point of 1‑naphthylamines via remote C-H activation.

Results and Discussion

Table 1 Optimization of nitration conditions for nitration of naphthylamines

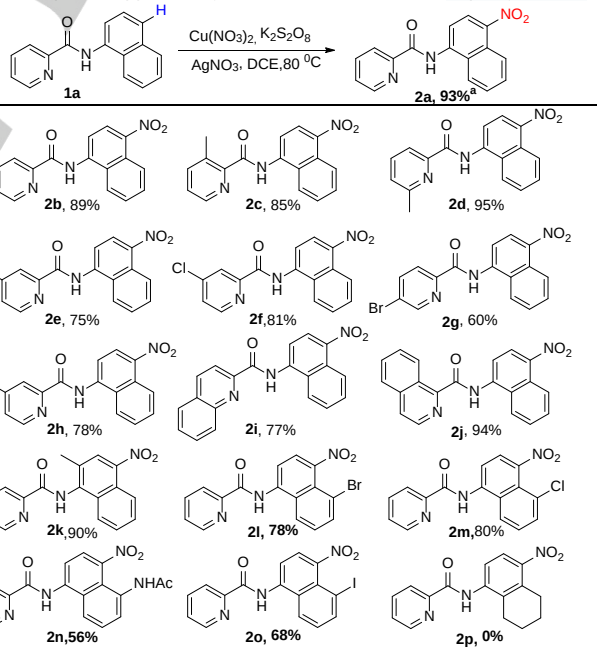


Entry	Cat.	Oxidant	Solv.	Source	additive	Yield%[a]
1	$Cu(OAc)_2$	$PhI(OAc)_2$	MeCN	$NaNO_2$	--	0
2	$Cu(NO_3)_2$	$PhI(OAc)_2$	MeCN	$NaNO_2$	--	55
3	$Cu(NO_3)_2$	$PhI(OAc)_2$	DMSO	$NaNO_2$	--	35
4	$Cu(NO_3)_2$	$PhI(OAc)_2$	DCE	$NaNO_2$	--	60
5	$Cu(NO_3)_2$	$K_2S_2O_8$	DCE	$NaNO_2$	--	58
6	$Cu(NO_3)_2$	$K_2S_2O_8$	DCE	$AgNO_3$	--	93
7	$Cu(NO_3)_2$	$K_2S_2O_8$	MeCN	$AgNO_3$	--	20
8	$Cu(OAc)_2$	$K_2S_2O_8$	DCE	$AgNO_3$	--	45
9	$Pd(OAc)_2$	$K_2S_2O_8$	DCE	$AgNO_3$	--	0
10	$PdCl_2$	$K_2S_2O_8$	DCE	$AgNO_3$	--	0
11	$NiCl_2$	$K_2S_2O_8$	DCE	$AgNO_3$	--	0
12	$CuCl_2$	$K_2S_2O_8$	DCE	$AgNO_3$	--	0
13	CuI	$K_2S_2O_8$	DCE	$AgNO_3$	--	Trace
14	$Cu(NO_3)_2$	MnO_2	DCE	$AgNO_3$	--	15
15	$Cu(NO_3)_2$	MnO_2	DCE	$AgNO_3$	--	5
16	$Cu(NO_3)_2$	$K_2S_2O_8$	DCE	$AgNO_3$	--	92[b]
17	$Cu(NO_3)_2$	$K_2S_2O_8$	DCE	KNO_3	--	0
18	$Pd(OAc)_2$	$K_2S_2O_8$	DCE	$AgNO_3$	AcOH	35
19	$Cu(NO_3)_2$	$PhI(OAc)_2$	MeCN	$NaNO_2$	PivOH	25
20	$Cu(NO_3)_2$	$K_2S_2O_8$	DCE	$Cu(NO_3)_2$	--	0[c]

$Cu(NO_3)_2$ used as $Cu(NO_3)_2$▪$3H_2O$. $Cu(NO_3)_2$ (0.2 equiv.) $K_2S_2O_8$ (2.0 equiv.), $AgNO_3$ (2.0 equiv.) at 80 ℃ for 12h. [a]: Isolated yields, [b]:under an atmosphere of N_2; c :$Cu(NO_3)_2$ (1 equiv.) $K_2S_2O_8$ (2.0 equiv.), at 80 ℃ for 12h.

Initial studies were carried out to optimise the nitration reaction of N-phenylpyrimidin-2-amine (**1a**) using $Cu(OAc)_2$ as catalyst and $NaNO_2$ as nitrating agent, which is the same as those reported previously in the literature for related C-H activation reactions (entry 1).[8] Unfortunately, these conditions afforded none of the desired nitrated, and so the reaction conditions were modified to employ $Cu(NO_3)_2$ as catalyst in the presence of $NaNO_2$ as nitrating agent and $PhI(OAc)_2$ as an oxidant in MeCN at 80 ℃. These conditions successfully gave the desired N-(4-nitronaphthalen-1-yl) picolinamide (**2a**) in 55% isolated yield. This nitration reaction condition was further explored using different nitrating sources, oxidants and solvents, with the yield of **2a** being increased to 93% using $Cu(NO_3)_2$▪$3H_2O$ (0.2 equiv.) as catalyst, $AgNO_3$ (2.0 equiv.) as nitrating agent, $K_2S_2O_8$ (2.0 equiv.) as oxidant and 1,2-dichloroethane (DCE) as solvent at 80 ℃. Reaction of **1a** in DCE under this condition gave N-(4-nitronaphthalen-1-yl) picolinamide **2a** in 60% yield after 12h. MeCN, DMSO, (Entries 2–3, Table 1) were also employed as solvents for this C-H functionalisation reaction with lower yields. Several other nitrating agents were then screened for nitrating activity, with the highest yield of **2a** being obtained using $AgNO_3$ as nitrating agent (entry 6) and no product being produced with KNO_3 (entry 17). Use of $Cu(OAc)_2$ (entry 8) as a catalyst gave **2a** in 45% yield, while the use of $PdCl_2$ (entry 10), $NiCl_2$ (entry 11), CuI (entry 13) and $Pd(OAc)_2$ (entry 9), gave none of the desired **2a**. MnO_2 and $PhI(OAc)_2$ proved to be less efficient oxidants than $K_2S_2O_8$ in these nitration reactions. However, under N_2 atmosphere, **2a** was isolated in 92% yield after 12 h. Increasing the temperature of these C-H functionalisation reactions from 30 to 100 ℃ did not improve the overall yield of **2a** (Entries 4–6, Table S1).

Table 2 Scope of copper catalysed nitration reactions of naphthylamines

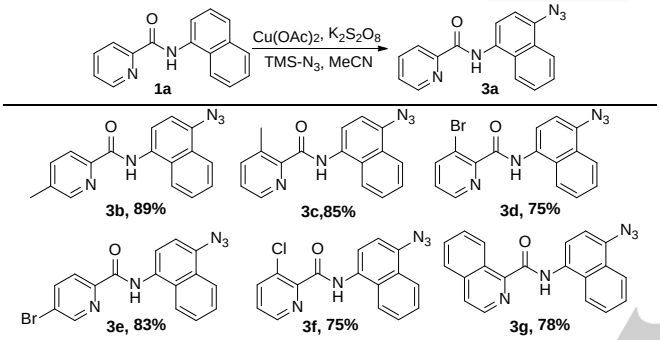


$Cu(NO_3)_2$ used as $Cu(NO_3)_2$▪$3H_2O$., $Cu(NO_3)_2$ (0.2 equiv.) , $K_2S_2O_8$ (2.0 equiv.), $AgNO_3$ (2.0 equiv.), at 80 ℃ for 12h, [a]: Isolated yields.

With the optimal conditions in hand, we then studied the scope and limiation of this C-H activation protocol for the nitration of a range of sixteen substituted naphthylamine pyridyl amides containing electron-donating (-Me, -OMe) and electron-withdrawing substituents (halogens), which gave their corresponding C-H nitration products in moderate to excellent yields (**2a-h**). These C-H functionalisation reactions showed

excellent regio- and chemoselectivity profiles, affording predominantly *para*-nitrated products (>75%) as major regioisomers, with the substituent pattern of the naphthylamine ring having little effect on the regioselectivity of nitration. Interestingly, the use of isoquinoline, and quinoline amides as directing groups were also well tolerated, affording their corresponding nitrated products **2i** and **2j** in good yields. A series of C-2 and C-5 subsituted naphthylamine derivatives containing electron-withdrawing groups (e.g. –Cl, -I, -Br) and weak electron-donating groups (e.g. -NHAc) in their naphthyl rings were also well tolerated under these conditions, affording their corresponding *para*-nitro-naphthylamines (**2l-o**) in good yield. By contrast, when N-(5, 6, 7, 8-tetrahydronaphthalen-1-yl)picolinamide(**2p**) chosen as the reagent, there was no directing product obtained.

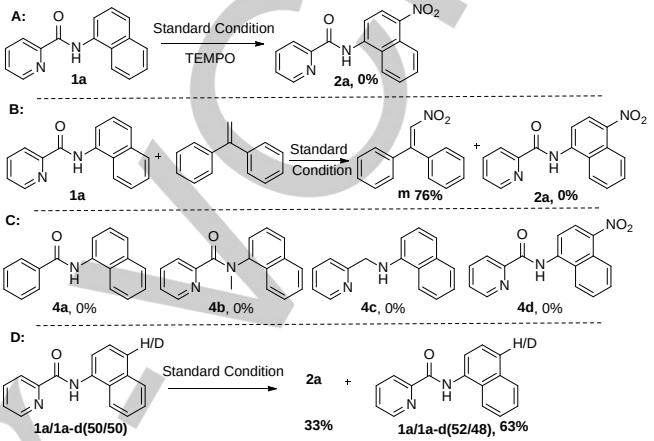
Table 3 Scope of copper catalysed azidation reaction of naphthylamines



$Cu(OAc)_2$ (0.2 equiv.) , $K_2S_2O_8$ (2.0 equiv.), TMS-N_3 (2.0 equiv.), r.t. for 12h, [a]: Isolated yields.

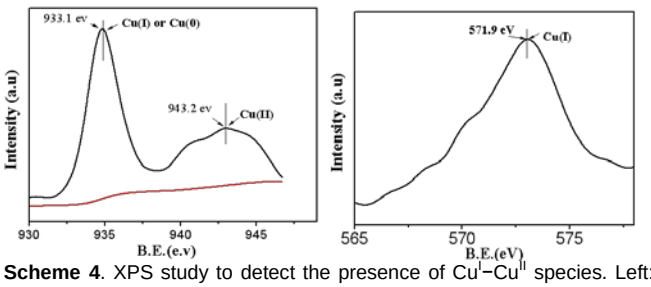
Having established effective conditions for the C-H nitration of naphthylamines, we next attempted to develop conditions that would enable *para*-C-H azidation of naphthylamines using TMS-N_3 as a convenient azido source. After carrying out a brief screen of reaction conditions for the azidation reaction of **1a**, it was found that a combination of $Cu(OAc)_2$, $K_2S_2O_8$ and TMS-N_3 gave *para* azido product **3a** in 89% yield (See Supplementary Table S2). The scope and limitation of this *para*-azidation reaction was then evaluated using a range of subsituted pyridyl, isoquinolinyl （**3g**）and pyridyl derivatives that contained a range of weak electron donating (**3b-c**), electron withdrawing (**3d-f**) in their aryl-acid ring systems, which gave their corresponding azido products in moderate to excellent yields (Table 3).

Several control experiments were then performed to try to understand the mechanism of these C-H activation reactions. Incorporation of 2.0 equiv. of 2, 2, 6, 6-(tetramethylpiperidin-1-yl)oxyl (TEMPO) as a radical scavenger into these reaction, no product **2a** being produced (Scheme 3-A), which suggests that this reaction indicated that the reaction system might involve a radical process. Furthermore, introduction of 1, 1-diphenylethylene as a radical acceptor (Scheme 3-B), the radical intercepted product **m** was detected, indicating that a nitro radical is involved in the nitration reactions of naphthylamines. We next employed a series of naphthylamides as control substrates that were predicted not to undergo this nitration reaction, because their structures would prevent formation of the copper (II) complexes required for the C-H activation process to occur (Scheme 3-C). As predicted, N-(Naphthalen-1-yl)benzamide **4a**, N-methyl-N-(naphthalen-1-yl)picolinamide **4b**, and N-(pyridin-2-ylmethyl)naphthalen-1-amine **4c** were not transformed under these C-H activation conditions, with no evidence of any para-nitrated products having been formed. Furthermore, use of a naphthylamine whose C-4 position was blocked with a nitro group (**4d**) resulted in no reaction, with no di-nitro products being formed. Furthermore, we carried out a kinetic isotope experiment (KIE) and observed a k_H/k_D value of 1.08 (Scheme 3D), which indicated that the cleavage of the aromatic C4−H bond is not the rate determining step and the substitution took place only at the para-position of **1a**.[13]



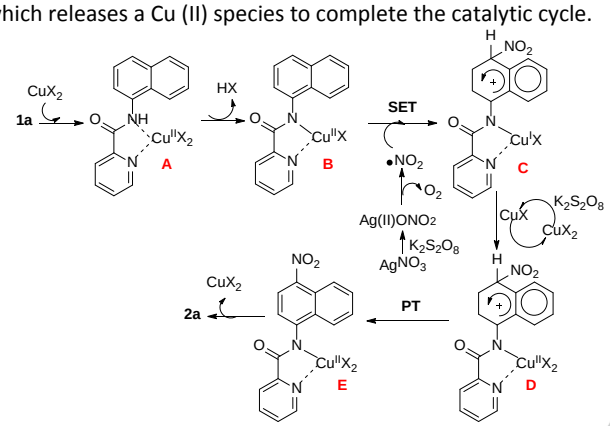
Scheme 3. Mechanistic studies on the nitration reaction of naphthylamines. Standard Condition: $Cu(NO_3)_2$ used as $Cu(NO_3)_2$•$3H_2O$., $Cu(NO_3)_2$ (0.2 equiv.) $K_2S_2O_8$ (2.0 equiv.), $AgNO_3$ (2.0 equiv.), 80 ℃, [a]: Isolated yields.

XPS (X-ray photoelectron spectroscopy) experiments were then employed to further explore the mechanism of these C-H functionalisation reactions, which revealed the presence of a binding energy (BE) peak at 943.2 eV that was assigned to the presence of Cu^{II} species, whilst a peak at 933.1 eV was assigned to either Cu^{I} or Cu(0) species whlie the pulverulence catalyst was tested with XPS.[14] Cu LM2 spectroscopy was then used to differentiate between the presence of Cu^{I} and Cu (0) species, with a peak at 570.9 eV indicating the presence of Cu^{I}. Therefore, these XPS results suggest that this C-H activation reaction proceeds via a catalytic species tha cycles between both Cu^{II} and Cu^{I} species. In addition, XPS experiments were also employed to further explore the cycle of Ag(I)/Ag(II), as we can see from Figure S4, a binding energy (BE) peak at 367.3 eV that was assigned to the presence of Ag^{II} species, whilst a peak at 367.8 eV was assigned to either Ag^{I} species. The BE and peak width values found in this study are in good agreement and show the same trends observed for Ag^{+} and Ag^{2+} as reported.[15]



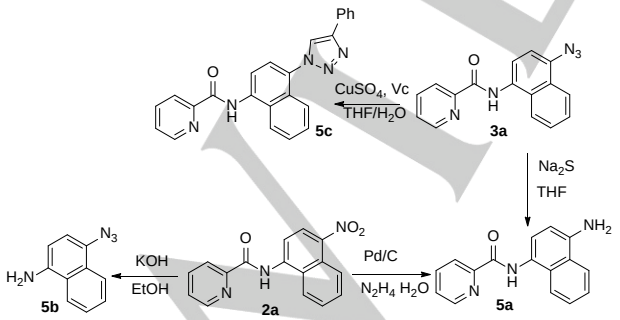
Scheme 4. XPS study to detect the presence of Cu^{I}–Cu^{II} species. Left: Cu 2p3/2 XPS, Right: Cu LM2 spectra.

Based on these observations and previous reports,[16] a plausible mechanism for our copper-catalyzed *para*-nitration reaction of *N*-(naphthalen-1-yl)picolinamide with picolinic acid is proposed in **Scheme 5.** The nitration reaction is initiated by complexation of the benzamide fragment of the naphthylamine **1a** to copper via its *N, N*-bidentate directing group to afford a Cu(II)-complex **A**. This Cu(II)-complex **A** then loses of HNO_3 to afford the Cu(II) intermediate **B**. A nitro radical species[17] (generated from reaction of $AgNO_3$ with $K_2S_2O_8$) then undergoes attack at the C-4 position of **B** to afford an aryl radical **C** species that is then oxidised to afford a cationic complex **D**. Proton transfer from **D** then occurs to afford a copper coomplexed nitroaryl intermediate **E**, with the desired product **2a** then being obtained catalyst dissociation, which releases a Cu (II) species to complete the catalytic cycle.



Scheme 5. Proposed mechanism for the C-H functionalisation reactions of naphthylamines

A series of reduction and click reactions using were then performed on *N*-(4-nitronaphthalen-1-yl)picolinamide **2a** and *N*-(4-azidonaphthalen-1-yl)picolinamide **3a** to validate the synthetic potential of this methodology (**Scheme 6**, see Supporting Information for details). Therefore, treatment of **3a** with phenylacetylene in the presence of a catalytic amount of $CuSO_4$, Vc (Ascorbic Acid) gave its correspond triazole **5c** in 76% yield. Alternatively, treatment of **3a** with Na_2S resulted in reduction to afford amine **5a** in 85% yield, which could also be accessed via Pd/C mediated hydrogenation of **2a**. Removal of the pyridiyl directing group of **2a** was also demonstrated via hydrolysis with KOH in methanol at 85 ℃, which gave *para*-nitro-naphthylamine **5b** in 75% yield.[18]



Scheme 6. Typical transformations of **2a** and **3a**.

Conclusions

In summary, we developed a copper-catalyzed C-4 nitration and azidation of 1-naphthylamine derivative via remote C-H activation, and this process features the exclusive regioselective C-4 nitration and azidation of 1-naphthylamine and a broad substrate scope. The copper-catalyzed mononitration reaction involves a novel and efficient C−N bond forming reaction via direct C_{Ar}−H function without additive, and the directing group could remove after the reaction. To the best of our knowledge, this represents the first example of pyridine as a removable directing group for the direct para C-H nitration and azidation of naphthylamine via remote C-H activation. These two systems complement current C-H azidation and nitration reactions. The synthetic utility of the azidation products was demonstrated in subsequent functional-group transformations. Moreover, the convenient transformation of the azide functionality into an amine, triazole, imine, or aziridine group widens the application of this methodology.

Experimental Section

Typical procedure for the synthesis of products 2a： 25 mL Schlenk tube was equipped with a magnetic stir bar and charged with **1a** (0.2 mmol), $AgNO_3$(0.4 mmol, 2.0 equiv.), $K_2S_2O_8$ (0.4 mmol, 2 equiv.), $Cu(NO_3)_2$▪$_3H_2O$(0.04 mmol). 1, 2-dichloroethane(10 mL). The resulting mixture was heated at 80 ℃ for 12 h and then cooled to room temperature. The mixture was poured into water (10 mL), extracted with CH_2Cl_2 (3V), and washed with H_2O (3V). The combined organic layer was dried (anhydrous Mg_2SO_4) and filtered. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography (silicagel, 100@200 mesh; petroleum ether/EtOAc=10:1 v/v) to afford pure **2a** as a yellow solid.

Typical procedure for the synthesis of products 3a： 25 mL Schlenk tube was equipped with a magnetic stir bar and charged with **1a** (0.2 mmol), TMS-N_3(0.4 mmol, 2.0 equiv.), $K_2S_2O_8$ (0.4 mmol, 2 equiv.), $Cu(OAc)_2$ (0.04 mmol). MeCN(10 mL). The resulting mixture was heated at room temperature for 12 h. The mixture was poured into water (10 mL), extracted with CH_2Cl_2 (3V), and washed with H_2O (3V). The combined organic layer was dried (anhydrous Mg_2SO_4) and filtered. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography (silicagel, 100@200 mesh; petroleum ether/EtOAc=5:1 v/v) to afford pure **3a** as a yellow solid.

Acknowledgements

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Keywords: Nitration • Azidation • remote C-H activation • Copper-Catalyzed

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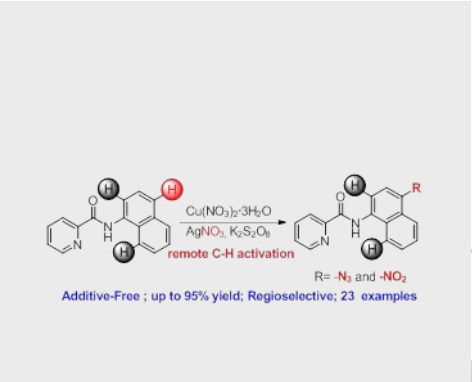

Key Topic*

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Copper-Catalyzed Regioselective Nitration and Azidation of 1-Naphthylamine Derivatives via remote C-H activation

C-H activation