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Amide-Oxazoline directed *Ortho*-C-H Nitration under Cu(II)-Mediated

Tian-Hong Gao,[a] Chun-Meng Wang,[a] Kai-Xiang Tang,[a] Yun-Gen Xu,[a] and Li-Ping Sun *[a]

Abstract: A Cu(II)-mediated *ortho*-C-H nitration using amide-oxazoline as the directing group has been developed. The reactions utilize sodium nitrite as the source of the nitro group under O_2 atmosphere and proceed smoothly. The desired products can be got in yields of 26-94%.

Introduction

Transition-metal-catalyzed C-H functionalization is becoming an attractive alternative, in recent years, for the formation of carbon-carbon and carbon-heteroatom bonds.[1] During the development of C-H functionalization, chelation-directed strategy that provides a powerful tool to enhance the efficiency and control the selectivity of C–H activation has caught more attention,[2] especially bidentate auxiliaries[3]. They can form an extremely stable bidentate metallocycle complex to improve the reactivity.[4] In this regard, 8-aminoquinoline, used as a bidentate auxiliary directing group, has been widely reported for the functionalization of C-H bonds[3,5] since the pioneering work of Daugulis and co-workers.[6] It can form a five-membered bis-dentate complex with a metal center.[6,7] In comparison, amide-oxazoline, prevalent organic motifs of relevance to functional molecules and medicinal chemistry (Figure 1),[8] can form a six-membered bis-dentate metallocycle complex[9] leading to its reactivity different from amide-quinoline DG. As a consequence, the further functionalization of substituted amide oxazolines has attracted tremendous interest. At this point, although some significant progress has been made, such as arylation[10a], trifluoromethylation[10b], hydroxylation[10c], amination[10d] *etc.*, *ortho* C-H nitration has not been reported and still represents a great challenge.

The incorporation of the nitro group into aromatics is of great significance to the chemical industry. Aromatic nitro compounds are very useful intermediates to construct various dyes, explosives, pharmaceuticals, plastics as well as natural products.[11] In term of its preparation, the classical method is to use a mixed acid system (HNO_3/H_2SO_4) and its derivatives as electrophilic nitrating reagents. Although these methods are useful to some extent, limitations still remain such as poor regioselectivity and terrible functional group tolerance due to the harsh reaction conditions.[12] To solve these problems, transition-metal-catalyzed or -mediated, chelation-assisted direct regioselective aromatic C-H nitrations under a mild condition have got much attention.[13] In addition, Guo and co-workers have accomplished the Ni-catalyzed remote C-H nitration of 2-aryl oxazolines, which undergoes a single electron transfer (SET) pathway.[14] Inspired by above content, we envisioned that if amide-oxazoline could be used as a bidentate auxiliary for the *ortho* nitration of arenes. Herein we report the first example of a Cu(II)-mediated, amide-oxazoline group-assisted *ortho* nitration of benzoic acid derivatives.

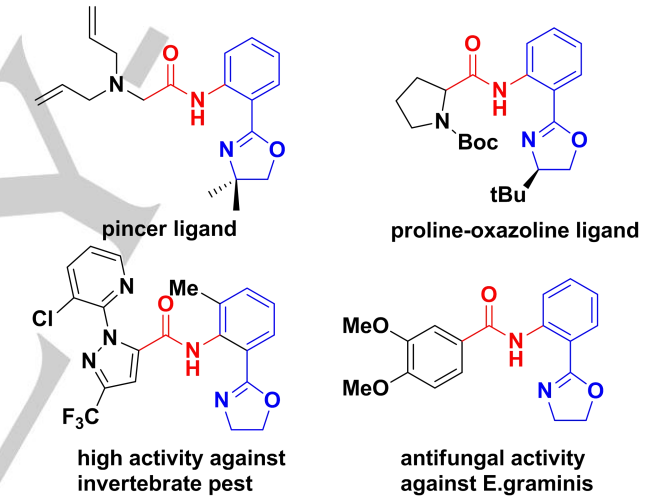

Figure 1. Representative application of molecules containing amide-oxazoline scaffolds.

Results and Discussion

We commenced our studies with amide **1a** as the model substrate to optimize reaction parameters (Table 1). Treating **1a** with 2 equivalents of $Cu(OAc)_2•H_2O$, 3 equivalents of $NaNO_2$, 2 equivalents of K_2HPO_4 in DMSO at 80 °C under air gave the desired nitration product **2a** in 57% yield (Table 1, entry 1). The use of other solvents such as DMF, DCE, CH_3CN didn't give good results (Table 1, entries 2-4). Then we considered the dosage of $NaNO_2$. But whether elevate or decrease amount gave unsatisfactory results (Table 1, entries 5 and 6). After a brief screening of bases, K_2HPO_4 remained the optimal choice (Table 1, entries 7 and 8). In a set of Cu salt type and amount screened, 2 equivalents of $Cu(OAc)_2•H_2O$ was

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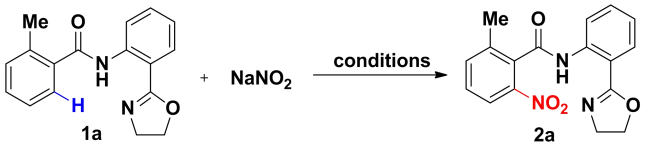
Table 1. Optimization of Reaction Conditions[a]



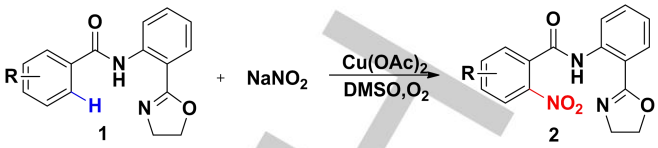
Entry	Cu salt	base	solvent	yield/%[b]
1	$Cu(OAc)_2•H_2O$	K_2HPO_4	DMSO	57
2	$Cu(OAc)_2•H_2O$	K_2HPO_4	DMF	40
3	$Cu(OAc)_2•H_2O$	K_2HPO_4	DCE	0
4	$Cu(OAc)_2•H_2O$	K_2HPO_4	CH_3CN	0
5[c]	$Cu(OAc)_2•H_2O$	K_2HPO_4	DMSO	20
6[d]	$Cu(OAc)_2•H_2O$	K_2HPO_4	DMSO	50
7	$Cu(OAc)_2•H_2O$	KOAc	DMSO	49
8	$Cu(OAc)_2•H_2O$	K_2CO_3	DMSO	47
9	$Cu(OAc)_2$	K_2HPO_4	DMSO	55
10	$Cu(OTf)_2$	K_2HPO_4	DMSO	0
11	$CuCl_2$	K_2HPO_4	DMSO	25
12[e]	$Cu(OAc)_2•H_2O$	K_2HPO_4	DMSO	50
13[f]	$Cu(OAc)_2•H_2O$	K_2HPO_4	DMSO	87
14[f]	$Cu(OAc)_2•H_2O$	/	DMSO	87
15[g]	$Cu(OAc)_2•H_2O$	/	DMSO	80
16[f]	$Cu(OAc)_2$	/	DMSO	80
17[g]	$Cu(OAc)_2$	/	DMSO	92

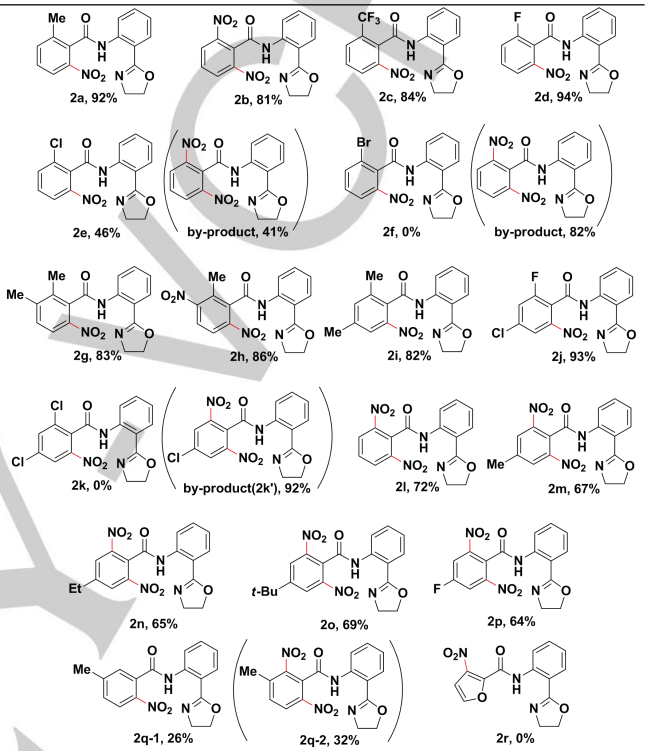
[a]Reaction Conditions: **1a** (0.1 mmol), Cu salt (0.2 mmol), $NaNO_2$ (0.3 mmol), base (0.2 mmol), solvent (1 mL), 12 h, 80 °C. [b]Isolated yield. [c]$NaNO_2$ (0.4 mmol). [d]$NaNO_2$ (0.15 mmol). [e]$Cu(OAc)_2•H_2O$ (0.1 mmol). [f]The reaction was carried out under O_2 at 70 °C. [g]The reaction was carried out under O_2 at 60 °C.

still the best choice (Table 1, entries 9-12). But beyond that, 2 equivalents of $Cu(OAc)_2$ demonstrated comparable efficiency (Table 1, entry 9). Subsequently, temperature and atmosphere were taken into consideration. To our delight, when we made the reaction at 70 °C under O_2 atmosphere, the yield of **2a** raised to 87% (Table 1, entry 13). Furthermore, the base K_2HPO_4 was not essential (Table 1, entry 14). Afterward, we kept lowering the temperature to 60 °C on the basis of entry 14, but we did not obtain the better yield (Table 1, entry 15). Given the comparable efficiency of $Cu(OAc)_2$ in our initial screen stages, we used $Cu(OAc)_2$ instead of $Cu(OAc)_2•H_2O$ and react at 70 °C and 60 °C under O_2 separately (Table 1, entries 16 and 17). To our surprise, the yield increased to 92% when 2 equivalents of $Cu(OAc)_2$ was employed at 60 °C under O_2. Finally, the optimum choice for the reaction was identified as follows: 2 equivalents of $Cu(OAc)_2$, 3 equivalents of $NaNO_2$ as nitro source and DMSO as the solvent under O_2 atmosphere at 60 °C.

Having the optimal conditions in hand, we then explored the scope of benzamide substrates for this reaction (Table

Table 2. Scope of Nitration Reaction[a,b]





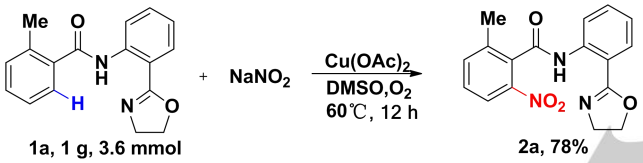
[a]Reaction Conditions: **1** (0.1 mmol), $Cu(OAc)_2$ (0.2 mmol), $NaNO_2$ (0.3 mmol), DMSO (1 mL) , 1.5~12 h, 50~70 °C. [b]Isolated yield.

2). Substrates containing both electron-donating and –withdrawing substituents at the *ortho* position afforded the desired products (**2a–2d**) in excellent yields except *o*-chloro and *o*-bromo substrates. They could be substituted by NO_2 especially *o*-bromo (**2e, 2f**). Bisubstituted substrates reacted without affecting the yields significantly (**2g–2j**, 82%-93% yields). 2,4-dichloro substituted substrate was also replaced by NO_2 at *ortho*-position, and then gained product **2k'**. For non- or *para*-substituted substrates, only double *ortho*-nitration products could be obtained (**2l–2p**). However, mono and double products could be got together, when a meta-substituent was borne on the benzene ring (**2q-1 and 2q-2**). Unfortunately, the reaction conditions could not be extended to the heterocyclic system (**2r**).

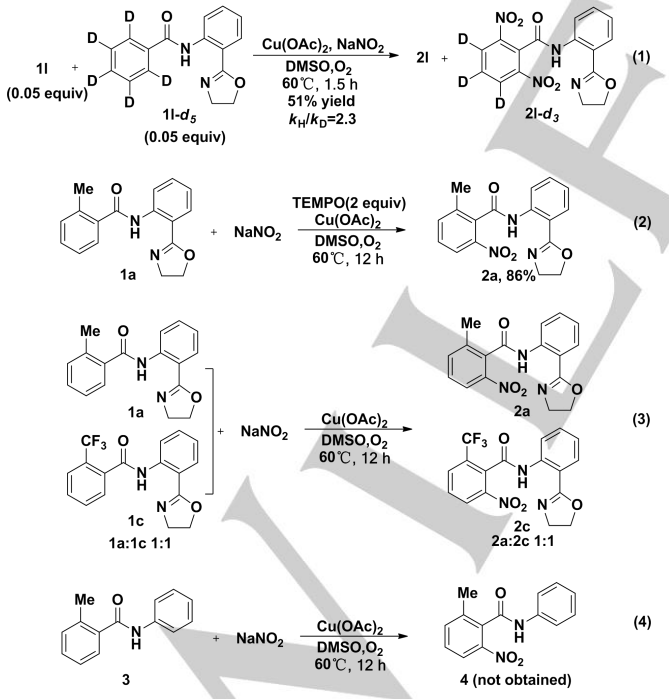
In order to explore more about the scalability of this methodology, we conducted a gram scale reaction with **1a** (Scheme 1). And the target product was gained in 78% yield.

To probe the reaction mechanism, we carried out several control experiments (Scheme 2). Firstly, **1l-*d*$_5$** was prepared and transformed under the optimized reaction

conditions to conduct the intermolecular competition experiment (Scheme 2, Eq.(1)). The intermolecular k_H/k_D of **1l** to **1l-*d*$_5$** was determined to be 2.3, indicating that the *ortho* C-H bond cleavage was involved in the rate-determining step. Then, we added radical scavenger 2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO, 2 equiv.) to the standard condition (Scheme 2, Eq.(2)). The yield was negligibly affected which suggested that a radical intermediate might not participate in the reaction. Next, when we used the equivalent of an electron-rich substrate (**1a**) and electron-deficient substrate (**1c**) to explore the electronic effect (Scheme 2, Eq.(3)), the products **2a** and **2c** were isolated in equal yields, showing that the electronic nature of substituents had minimal impact on the reactivity of the substrates. Finally, the effect of directing group was examined (Scheme 2, Eq.(4)). No product was generated when a monodentate directing group substrate **3** with structure similar to **1a** was attempted in the reaction, indicating that a bidentate coordinating group is indispensable for this nitrification.



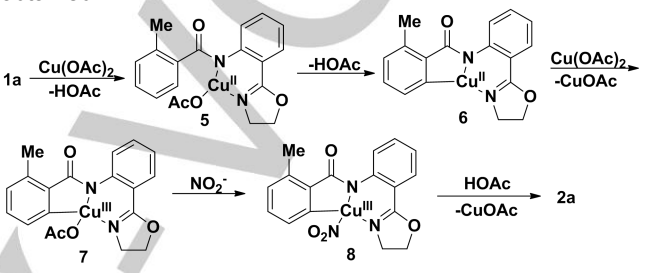
Scheme 1. Gram Scale Reaction



Scheme 2. Control Experiments

Although it is not distinct of the mechanism, a plausible reaction mechanism is proposed (Scheme 3) on the basis of our results and previous findings[9]. With the assistance of amide-oxazoline DG, a six-membered copper complex **5** is formed. Then copper complex undergoes C-H activation to form the aryl/Cu(II) intermediate **6**, followed by the oxidation of copper (II–III) complex **6**–**7**.[15] **7** next reacts with sodium nitrite to generate the copper complex **8**, which undergoes reductive elimination to afford the desired nitration product **2a**.

As for the formation of by-products, we speculate that during the process of C-H activation, the C-X (X=Cl, Br) bond is also activated and cleaves to form an organometallic intermediate, next undergoes nitration. So, the halogen is substituted by NO_2, and then by-products are obtained.



Scheme 3. Proposed Mechanism

Conclusions

In summary, we have developed the first copper(II)-mediated *ortho* C-H bond nitration using an amide-oxazoline directing group. The reaction process proceeds smoothly, uses easily accessible earth-abundant copper reagent, simple and readily available nitro source, and is free of base. This method enriches the construction of nitro compounds as well as proves more possibilities of amide-oxazoline directing group.

Experimental Section

General Information: Unless otherwise noted, all chemical reagents were commercially purchased and used without further purification. Analytical TLC was carried out by using pre-254 coated plates and visualized with UV light. Melting points (uncorrected) were determined on a RY-1 MP apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-300 spectrometer at 300 MHz and 75 MHz, respectively. Chemical shifts are reported in δ (ppm), relative to the internal standard of TMS. The signals observed are described as: s (singlet), d (doublet), t (triplet), q (quartet), m (multiple). Coupling constants are reported as *J* values in units of Hz. Mass spectrometry was obtained by using a Q-TOF high-resolution mass spectrometer. Flash column chromatography was performed over silica gel 200-300 m.

General Procedure for the Substrates 1a-1r: All the starting substrates (**1a-1r**) for nitration were prepared according to literature reported methods[9, 10d,14,16].

In a three-necked flask (500 mL), 2-aminobenzonitrile (29.5 g, 250 mmol) and $ZnCl_2$ (3.4 g, 25 mmol) were added, and then suspended in chlorobenzene (350 mL) under nitrogen. 2-aminoethanol(45 mL, 750 mmol) was added to the suspension via a syringe. The mixture was heated to reflux for 36 hours. After refluxing for 36 hours, the reaction mixture was cooled down to room temperature and the solvent was removed under reduced pressure. CH_2Cl_2 (250 mL) was added to the residue and washed with saturated $NaHCO_3$ (150 mL) and H_2O (150 mL). The aqueous fraction was extracted with CH_2Cl_2 (250 mL × 3). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether/ethyl acetate = 25/1) to give 2-(4,5-dihydrooxazol-2-yl)aniline.

2-(4,5-dihydrooxazol-2-yl)aniline (5 mmol) and acid chloride (5.5 mmol) were added to a 100 mL flask and then dissolved with THF (20 mL). Et_3N (7.5 mmol) was taken to the vigorously stirred solution via a syringe. The reaction was stirred at room temperature for 10 h and quenched with saturated $NaHCO_3$. And then the mixture was extracted with EtOAc. Combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether/ethyl acetate) to give the substrates.

General Procedure for Cu(II)-Mediated *ortho*-C−H Nitration of Arenes: An oven dried 25 mL two-necked flask, equipped with a stir bar, was charge with substrates **1a-1r** (0.1 mmol, 1 equiv), $Cu(OAc)_2$ (0.2 mmol, 2 equiv), $NaNO_2$ (0.3 mmol, 3 equiv) and DMSO (1 mL). Then reaction mixture was stirred at 50~70 °C under oxygen for 1.5~12 h. Upon completion, EtOAc was added to dilute the mixture and then washed with $NH_3•H_2O$ and H_2O. The organic fraction was dried over Na_2SO_4, evaporated and purified by flash column chromatography on silica gel with a gradient eluent of petroleum ether/ethyl acetate to give the nitration product **2a-2r**.

N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-2-methyl-6-nitrobenzamide (2a): Following the general procedure the title compound was synthesized at 60 °C for 12 h. Purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 8/1). Yellow solid (30 mg, 92%), mp: 163-164 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.51 (s, 1H), 8.83 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.89 (d, *J* = 7.9 Hz, 1H), 7.64–7.41 (m, 3H), 7.16 (t, *J* = 7.4 Hz, 1H), 4.33 (t, *J* = 9.5 Hz, 2H), 3.94 (t, *J* = 9.6 Hz, 2H), 2.52 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3, 164.1, 145.7, 138.9, 137.3, 135.7, 132.5, 132.2, 128.9, 128.7, 122.6, 121.6, 119.9, 113.2, 65.7, 54.0, 18.8. HRMS (ESI-QTOF) m/z Calcd for $C_{17}H_{15}N_3O_4$ $[M+H]^+$ 326.1141, found 326.1143.

N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-2,6-dinitrobenzamide (2b): Following the general procedure the title compound was synthesized at 60 °C for 1.5 h. Purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1). Yellow solid (28.8 mg, 81%), mp: 195-196 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.86 (s, 1H), 8.70 (d, *J* = 8.1 Hz, 1H), 8.43 (d, *J* = 8.2 Hz, 2H), 7.91 (d, *J* = 7.4 Hz, 1H), 7.82 (t, *J* = 8.2 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 4.36 (t, *J* = 9.4 Hz, 2H), 3.96 (t, *J* = 9.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 159.6, 147.5, 139.0, 132.8, 130.8, 129.5, 129.2, 128.3, 123.5, 120.6, 113.7, 66.3, 54.3. HRMS (ESI-QTOF) m/z Calcd for $C_{16}H_{12}N_4O_6$ $[M+H]^+$ 357.0835, found 357.0835.

N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-2-nitro-6-(trifluoromethyl)benzamide (2c): Following the general procedure the title compound was synthesized at 60 °C for 12 h. Purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 12/1). Yellow solid (32 mg, 84%), mp: 174-175 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.78 (s, 1H), 8.74 (d, *J* = 8.3 Hz, 1H), 8.34 (d, *J* = 8.3 Hz, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.74 (t, *J* = 8.1 Hz, 1H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 4.32 (t, *J* = 9.5 Hz, 2H), 3.91 (t, *J* = 9.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 160.7, 146.8, 142.0, 138.6, 132.2, 131.2 (q, J_{C-F} = 4.6 Hz), 129.8, 129.4 (d, J_{C-F} = 33.0 Hz), 128.6, 127.6, 122.9, 122.1 (d, J_{C-F} = 273.3 Hz), 119.9, 113.2, 65.8, 53.9. HRMS (ESI-QTOF) m/z Calcd for $C_{17}H_{12}F_3N_3O_4$ $[M+H]^+$ 380.0858, found 380.0856.

N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-2-fluoro-6-nitrobenzamide (2d): Following the general procedure the title compound was synthesized at 60 °C for 12 h. Purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 8/1). Yellow solid (31 mg, 94%), mp: 162-163 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.84 (s, 1H), 8.83 (d, *J* = 7.6 Hz, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.66–7.45 (m, 3H), 7.19 (t, *J* = 7.2 Hz, 1H), 4.36 (t, *J* = 9.1 Hz, 2H), 4.00 (t, *J* = 9.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 159.4, 159.3 (d, J_{C-F} = 251.6 Hz), 147.1, 139.2, 132.7, 130.9 (d, J_{C-F} = 8.6 Hz), 129.2, 123.3, 121.9 (d, J_{C-F} = 22.4 Hz), 120.4, 120.4, 120.3, 113.7, 66.3, 54.5. HRMS (ESI-QTOF) m/z Calcd for $C_{16}H_{12}FN_3O_4$ $[M+H]^+$ 330.0890, found 330.0888.

2-chloro-N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-6-nitrobenzamide (2e): Following the general procedure the title compound was synthesized at 60 °C for 5 h. Purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 8/1). Yellow solid (16 mg, 46%), mp: 179-180 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.71 (s, 1H), 8.80 (d, *J* = 8.2 Hz, 1H), 8.13 (d, *J* = 8.1 Hz, 1H), 7.89 (d, *J* = 7.9 Hz, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 2H), 7.18 (t, *J* = 7.5 Hz, 1H), 4.35 (t, *J* = 9.4 Hz, 2H), 3.97 (t, *J* = 9.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 161.2, 146.4, 138.6, 135.0, 133.1, 132.2, 132.1, 129.8, 128.7, 122.8, 122.6, 120.0, 113.3, 65.8, 54.0. HRMS (ESI-QTOF) m/z Calcd for $C_{16}H_{12}ClN_3O_4$ $[M+H]^+$ 346.0595, found 346.0592.

N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-2,3-dimethyl-6-nitrobenzamide (2g): Following the general procedure the title compound was synthesized at 70 °C for 12 h. Purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 8/1). Yellow solid (28 mg, 83%), mp: 185-186 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.46 (s, 1H), 8.86 (d, *J* = 8.4 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 7.9 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.17 (t, *J* = 7.7 Hz, 1H), 4.34 (t, *J* = 9.5 Hz, 2H), 3.95 (t, *J* = 9.5 Hz, 2H), 2.42 (d, *J* = 9.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 164.1, 144.6, 143.7, 138.9, 135.4, 132.7, 132.1, 130.1, 128.7, 122.5, 121.5, 119.9, 113.2, 65.7, 54.0, 20.3, 16.0. HRMS (ESI-QTOF) m/z Calcd for $C_{18}H_{17}N_3O_4$ $[M+H]^+$ 340.1297, found 340.1296.

N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-2-methyl-3,6-dinitrobenzamide (2h): Following the general procedure the title compound was synthesized at 70 °C for 12 h. Purified by flash column chromatography

on silica gel (petroleum ether/ethyl acetate = 15/1). Yellow solid (32 mg, 86%), mp: 184-185 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.79 (s, 1H), 8.78 (d, *J* = 8.2 Hz, 1H), 8.17 (d, *J* = 8.8 Hz, 1H), 7.95 (dd, *J* = 15.9, 8.5 Hz, 2H), 7.59 (t, *J* = 7.7 Hz, 1H), 7.22 (t, *J* = 7.4 Hz, 1H), 4.38 (t, *J* = 9.4 Hz, 2H), 3.99 (t, *J* = 9.4 Hz, 2H), 2.63 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 162.2, 153.4, 147.4, 138.8, 135.8, 132.8, 132.6, 129.3, 125.0, 123.7, 123.3, 120.4, 113.8, 66.4, 54.4, 16.1. HRMS (ESI-QTOF) m/z Calcd for $C_{17}H_{14}N_4O_6$ $[M+H]^+$ 371.0992, found 371.0986.

N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-2,4-dimethyl-6-nitrobenzamide (2i): Following the general procedure the title compound was synthesized at 70 °C for 12 h. Purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 12/1). Yellow solid (27.8 mg, 82%), mp: 197-198 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.47 (s, 1H), 8.84 (d, *J* = 8.3 Hz, 1H), 7.89 (d, *J* = 7.9 Hz, 1H), 7.83 (s, 1H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.39 (s, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 4.34 (t, *J* = 9.6 Hz, 2H), 3.96 (t, *J* = 9.5 Hz, 2H), 2.48 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 164.1, 145.7, 139.4, 139.0, 137.0, 136.3, 132.1, 129.9, 128.7, 122.4, 121.9, 119.8, 113.1, 65.7, 54.0, 20.5, 18.7. HRMS (ESI-QTOF) m/z Calcd for $C_{18}H_{17}N_3O_4$ $[M+H]^+$ 340.1297, found 340.1294.

4-chloro-N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-2-fluoro-6-nitrobenzamide (2j): Following the general procedure the title compound was synthesized at 50 °C for 4 h. Purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 18/1). Yellow solid (34 mg, 93%), mp: 166-167 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.89 (s, 1H), 8.79 (d, *J* = 7.8 Hz, 1H), 7.99 (s, 1H), 7.91 (d, *J* = 6.9 Hz, 1H), 7.58–7.53 (m, 2H), 7.19 (t, *J* = 7.6 Hz, 1H), 4.37 (t, *J* = 9.1 Hz, 2H), 4.02 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 159.2 (d, J_{C-F} = 254.9 Hz), 158.4, 139.0, 136.6 (d, J_{C-F} = 10.9 Hz), 132.7, 129.2, 123.5, 122.3 (d, J_{C-F} = 24.6 Hz), 121.1, 121.0 (d, J_{C-F} = 3.4 Hz), 120.8, 120.3, 113.7, 66.3, 54.5. HRMS (ESI-QTOF) m/z Calcd for $C_{16}H_{11}ClFN_3O_4$ $[M+H]^+$ 364.0500, found 364.0496.

4-chloro-N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-2,6-dinitrobenzamide (2k'): Following the general procedure the title compound was synthesized at 50 °C for 1.5 h. Purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1). Yellow solid (36 mg, 92%), mp: 220-221 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.88 (s, 1H), 8.64 (d, *J* = 8.1 Hz, 1H), 8.38 (s, 2H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.18 (t, *J* = 7.7 Hz, 1H), 4.34 (t, *J* = 9.3 Hz, 2H), 3.94 (t, *J* = 9.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 158.6, 148.0, 138.8, 136.8, 132.8, 129.6, 129.2, 126.6, 123.7, 120.6, 113.7, 66.4, 54.3. HRMS (ESI-QTOF) m/z Calcd for $C_{16}H_{11}ClN_4O_6$ $[M+H]^+$ 391.0445, found 391.0437.

N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-4-methyl-2,6-dinitrobenzamide (2m): Following the general procedure the title compound was synthesized at 60 °C for 1.5 h. Purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1). Yellow solid (24.8 mg, 67%), mp: 232-233 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.67 (s, 1H), 8.57 (d, *J* = 8.1 Hz, 1H), 8.09 (s, 2H), 7.76 (d, *J* = 7.9 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 4.22 (t, *J* = 9.5 Hz, 2H), 3.82 (t, *J* = 9.5 Hz, 2H), 2.51 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 159.8, 147.5, 142.3, 139.1, 132.7, 129.7, 129.1, 125.8, 123.4, 120.6, 113.7, 66.3, 54.3, 21.2. HRMS (ESI-QTOF) m/z Calcd for $C_{17}H_{14}N_4O_6$ $[M+H]^+$ 371.0992, found 371.0989.

N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-4-ethyl-2,6-dinitrobenzamide (2n): Following the general procedure the title compound was synthesized at 60 °C for 2 h. Purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 8/1). Yellow solid (25 mg, 65%), mp: 207-208 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.76 (s, 1H), 8.67 (d, *J* = 8.4 Hz, 1H), 8.21 (s, 2H), 7.86 (d, *J* = 7.9 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.16 (t, *J* = 7.1 Hz, 1H), 4.33 (t, *J* = 9.4 Hz, 2H), 3.93 (t, *J* = 9.6 Hz, 2H), 2.90 (q, *J* = 7.6 Hz, 2H), 1.38 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 159.9, 148.3, 147.6, 139.1, 132.7, 129.1, 128.6, 125.9, 123.4, 120.6, 113.7, 66.3, 54.3, 28.4, 14.4. HRMS (ESI-QTOF) m/z Calcd for $C_{18}H_{16}N_4O_6$ $[M+H]^+$ 385.1148, found 385.1145.

4-(tert-butyl)-N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-2,6-dinitrobenzamide (2o): Following the general procedure the title compound was synthesized at 60 °C for 2 h. Purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 15/1). Yellow solid (28.6 mg, 69%), mp: 214-215 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.65 (s, 1H), 8.56 (d, *J* = 8.3 Hz, 1H), 8.26 (s, 2H), 7.76 (d, *J* = 7.9 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 4.23 (t, *J* = 9.5 Hz, 2H), 3.84 (t, *J* = 9.5 Hz, 2H), 1.34 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 159.9, 155.8, 147.6, 139.1, 132.7, 129.1, 126.4, 125.7, 123.4, 120.7, 113.8, 66.3, 54.3, 35.8, 30.7. HRMS (ESI-QTOF) m/z Calcd for $C_{20}H_{20}N_4O_6$ $[M+H]^+$ 413.1461, found 413.1458.

N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-4-fluoro-2,6-dinitrobenzamide (2p): Following the general procedure the title compound was synthesized at 50 °C for 1.5 h. Purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 12/1). Yellow solid (24 mg, 64%), mp: 205-206 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.85 (s, 1H), 8.64 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 7.1 Hz, 2H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 4.33 (t, *J* = 9.5 Hz, 2H), 3.92 (t, *J* = 9.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 161.2 (d, J_{C-F} = 257.8 Hz), 158.6, 148.5 (d, J_{C-F} = 8.1 Hz), 138.9, 132.8, 129.2, 124.8, 123.6, 120.5, 117.6 (d, J_{C-F} = 25.9 Hz), 113.7, 66.4, 54.3. HRMS (ESI-QTOF) m/z Calcd for $C_{16}H_{11}FN_4O_6$ $[M+H]^+$ 375.0741, found 375.0735.

N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-5-methyl-2-nitrobenzamide (2q-1): Following the general procedure the title compound was synthesized at 60 °C for 3 h. Purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 8/1). Yellow solid (8.5 mg, 26%), mp: 178-179 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.69 (s, 1H), 8.81 (d, *J* = 8.3 Hz, 1H), 7.97 (d, *J* = 8.3 Hz, 1H), 7.87 (d, *J* = 6.5 Hz, 1H), 7.61–7.43 (m, 2H), 7.38 (d, *J* = 8.5 Hz, 1H), 7.14 (t, *J* = 7.3 Hz, 1H), 4.35 (t, *J* = 9.4 Hz, 2H), 3.99 (t, *J* = 9.5 Hz, 2H), 2.49 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 145.0, 144.8, 139.5, 133.4, 132.7, 131.0, 129.6, 129.2, 124.7, 123.0, 120.1, 113.6, 66.3, 54.4, 21.5. HRMS (ESI-QTOF) m/z Calcd for $C_{17}H_{15}N_3O_4$ $[M+H]^+$ 326.1141, found 326.1138.

N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-3-methyl-2,6-dinitrobenzamide (2q-2): Following the general procedure the title compound was synthesized at 60 °C for 3 h. Purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1). Yellow solid (11.7 mg, 32%), mp: 196-197 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.94 (s, 1H), 8.65 (d, *J* = 8.4 Hz, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 7.4 Hz, 1H), 7.62–7.43 (m, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 4.35 (t, *J* = 9.5 Hz, 2H), 3.97 (t, *J* = 9.5 Hz, 2H), 2.51 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 159.4, 149.4, 145.0, 138.9, 137.6, 133.1, 132.7, 129.1, 127.3, 126.4,

123.6, 120.4, 113.8, 66.4, 54.3, 18.5. HRMS (ESI-QTOF) m/z Calcd for $C_{17}H_{14}N_4O_6$ $[M+H]^+$ 371.0992, found 371.0989.

Gram-Scale reaction: To a 250 mL two-necked flask was added substrates **1a** (1.0 g, 3.6 mmol), $Cu(OAc)_2$ (1308 mg, 7.2 mmol), $NaNO_2$ (745 mg, 10.8 mmol) and DMSO (36 mL). Then reaction flask was placed into a pre-heated oil bath and stirred at 60 °C under oxygen for 12 h. Upon completion, EtOAc was added to dilute the mixture and then washed with $NH_3•H_2O$ and H_2O. The organic fraction was dried over Na_2SO_4, evaporated and purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 8/1) to afford the product with 78% yield (905 mg).

Controlled Experiments

Intermolecular Competition Reaction Experiment: To a 25 mL two-necked flask were added substrates **1l** (0.05 mmol, 1 equiv), **1l-*d*$_5$** (0.05 mmol, 1 equiv), $Cu(OAc)_2$ (0.2 mmol, 2 equiv), $NaNO_2$ (0.3 mmol, 3 equiv), DMSO (1 mL). Then reaction mixture was stirred at 60 °C under oxygen for 1.5 h. Upon completion, EtOAc was added to dilute the mixture and then washed with $NH_3·H_2O$ and H_2O. The organic fraction was dried over Na_2SO_4, evaporated and a mixture of product **2l** and **2l-*d*$_3$** was purified by flash column chromatography on silica gel with a gradient eluent of petroleum ether and ethyl acetate. The intermolecular kinetic isotope effect was calculated to be k_H/k_D = 2.3 based on ^{1}H NMR spectral analyses.

Reaction in the Presence of Radical Quencher TEMPO: An oven dried 25 mL two-necked flask, equipped with a stir bar, was charge with substrates **1a** (0.1 mmol, 1 equiv), $Cu(OAc)_2$ (0.2 mmol, 2 equiv), $NaNO_2$ (0.3 mmol, 3 equiv), TEMPO (0.2 mmol, 2 equiv) and DMSO (1 mL). Then reaction mixture was stirred at 60 °C under oxygen for 12 h. Upon completion, EtOAc was added to dilute the mixture and then washed with $NH_3·H_2O$ and H_2O. The organic fraction was dried over Na_2SO_4, evaporated and purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 8/1) to afford the product with 86% yield (28 mg).

Electronic Effect Experiment between 1a and 1c: An oven dried 25 mL two-necked flask, equipped with a stir bar, was charge with substrates **1a** (0.05 mmol), **1c** (0.05 mmol), $Cu(OAc)_2$ (0.2 mmol, 2 equiv), $NaNO_2$ (0.3 mmol, 3 equiv) and DMSO (1 mL). Then reaction mixture was stirred at 60 °C under oxygen for 12 h. Upon completion, EtOAc was added to dilute the mixture and then washed with $NH_3·H_2O$ and H_2O. The organic fraction was dried over Na_2SO_4, evaporated and purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1) afford the mixed products 2a (13 mg, 80% yield) and 2c (15.5 mg, 82% yield). The ratio was close to 1:1.

Preparation of 2-methyl-N-phenylbenzamide 3: [17] aniline (465.7 mg, 5 mmol) and 2-Methylbenzoyl chloride (850.3 mg, 5.5 mmol) were added to a 100 mL flask and then dissolved with CH_2Cl_2 (20 mL). Et_3N (758.9 mg, 7.5 mmol) was taken to the vigorously stirred solution via a syringe. The reaction was stirred at room temperature for 10 h and quenched with saturated $NaHCO_3$. And then the mixture was extracted with EtOAc. Combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether/ethyl acetate = 25/1) to give product **3.**

Nitration of compound 3: An oven dried 25 mL two-necked flask, equipped with a stir bar, was charge with substrates **3** (0.1 mmol, 1 equiv), $Cu(OAc)_2$ (0.2 mmol, 2 equiv), $NaNO_2$ (0.3 mmol, 3 equiv) and DMSO (1 mL). Then reaction mixture was stirred at 60 °C under oxygen for 12 h. And there was no reaction proceeding.

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Keywords: Copper • C-H activation • Nitro compounds • Nitration • directing group

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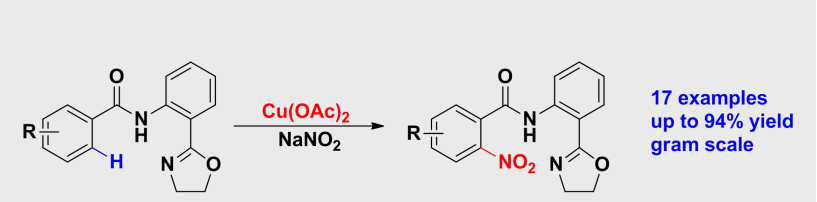

The first *ortho*-C-H nitration using amide-oxazoline as the directing group has been reported. The reactions utilize simple and readily available nitro source and proceed under Cu(II)-Mediated.

C-H Activation

Key Topic*

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Amide-Oxazoline directed *Ortho*-C-H Nitration under Cu(II)-Mediated