

Photo-Induced Construction of *N*-Aryl Amides by Fe Catalysis

Yong-Kang Mei⁺,^[a, b] Xiang-Ting Min⁺,^[a] Shi-Yu Guo,^[a] Chang-Hui Liu,^[a, b] Xiang-Xin Zhang,^[a, b] Ding-Wei Ji,^{*[a]} Boshun Wan,^[a] and Qing-An Chen^{*[a, b]}

Amides have played a vital role in polymeric materials, natural products and pharmaceuticals. In recent years, transition metal catalyzed C–N bond formation reaction provides a reliable strategy for amides construction. Herein, we disclosed a photo-induced electrophilic amidation reaction with *N*-meth-

Introduction

Amide is a fundamental structural unit that is prevalently found in materials,^[1] natural products^[2] and pharmaceuticals.^[3] The construction of amide skeletons is usually present in the most process of drug R&D.^[4] Traditionally, amides are synthesized via the dehydrative condensation of activated carboxylic acids with amines promoted by amide coupling reagents in stoichiometric amounts.^[5] Alternatively, catalytic methods, such as Ullmann-Goldberg^[6] reaction, Buchwald-Hartwig reaction^[7] and oxidative Chan-Lam reaction,^[8] have witnessed considerable development. Nevertheless, stoichiometric bases, oxidants or raised temperature were required in these protocols. Thus, efficient C–N bond formation methods under concise and mild condition are still highly desirable.

During the past decade, the electrophilic amination of organometals has been becoming a robust tool in forging C–N bonds.^[9] In this regard, Liebeskind pioneered electrophilic amidation with *N*-methoxyamides using a stoichiometric Cu salt.^[10] Later, an elegant Cu(I)-catalyzed version was reported by Lei's group with the help of reactive *N*-chloroamides (Scheme 1A).^[11] Recently, Chida *et al.* demonstrated that the amidation of arylborons could be realized under the Cu(II) catalysis. However, alkylated amide precursors were crucial for reactivity guarantee (Scheme 1B).^[12] Besides, Miura and co-authors revealed a C–N coupling reaction between arylboronic

[a]	YK. Mei, ⁺ XT. Min, ⁺ SY. Guo, CH. Liu, XX. Zhang, Dr. DW. Ji,				
	Prof. Dr. B. Wan, Prof. Dr. QA. Chen				
	Dalian Institute of Chemical Physics				
	Chinese Academy of Sciences				
	457 Zhongshan Road, Dalian 116023, China				
	E-mail: dingweiji@dicp.ac.cn				
	qachen@dicp.ac.cn				
	http://www.lbcs.dicp.ac.cn				
[b]	YK. Mei, ⁺ CH. Liu, XX. Zhang, Prof. Dr. QA. Chen				
	University of Chinese Academy of Sciences,				
	Beijing 100049, China				

- [⁺] These authors contributed equally to this work.
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oxyamides and arylboronic acids at low temperature using a simple iron salt as the catalyst precursor. Initial mechanistic studies suggested that crucial amide radical species was involved.

A Cu(I)-catalyzed electrophilic amidation (Lei, 2006)



Scheme 1. Transition-metal catalyzed electrophilic amidation of organoboron.

acids and activated *O*-acylhydroxylamines under noble Rh catalysis.^[13] Nevertheless, the reaction was completely inhibited using bench-stable *N*-methoxybenzamides (Scheme 1C). It should also be noted that all these catalytic protocols still required the sacrifice of excess base or salt, thus diminishing their atom economy.

In addition to well-defined but expensive photocatalysts, the use of earth abundant iron complexes has brought new opportunities.^[14] Very recent, Bao group reported an ironcatalyzed nitrene transfer reactions under light irradiation.^[15] Inspired by our long-standing interests in photo-promoted organic transformation,^[16] we herein developed a photoinduced electrophilic amidation with stable *N*-methoxyamides and boronic acids under Fe catalysis. Different from the previous nitrene intermediate mechanism, this electrophilic amidation is enabled by *N*-radical through intramolecular



MLCT/SET process (Scheme 1D). During the preparation of this manuscript, a similar C–N coupling reaction was also disclosed by Qiu and co-workers under Fe(III) catalysis at $120 \,^{\circ}C.^{[17]}$ Distinguished from their thermally induced approach which mainly focused on aryl substituted substrates, broad functional groups such as alkenylated or alkynylated substrates could be tolerated under the current benign conditions.

Results and Discussion

Initially, N-methoxybenzamide 1 a and phenylboronic acid 2 a were selected as model substrates to optimize the photoinduced reaction (Table 1 and Tables S1–S2 in Supplementary Information). To our delight, the desired amides product 3 aa was furnished in 27% yield using FeCl₂ as catalyst at 40°C under the irradiation of 450 nm blue LEDs (entry 1). A survey of solvents revealed that DCM was the optimal solvent than THF and PhCl (entries 1-3). No improvements on reactivity were achieved from the evaluation of iron catalysts (entries 4-6). Further screening of wavelengths revealed that 450-455 nm was the optimal wavelengths for this protocol (entries 3 and 7-9). Perhaps due to decreased light absorption efficiency, the increase of FeCl₂ led to a lower yield (entry 10). Only 70% yield was obtained without molecular sieve (entry 11). Additionally, the control experiments indicated that iron and light were both indispensable for the high yields (entries 12-13). The low yield observed in the dark probably resulted from the thermally induced pathway.^[17]

With the optimized conditions in hand, we evaluated the generality of *N*-methoxyamides substrates. As depicted in Scheme 2a, *N*-methoxyamides generally possessed satisfactory reactivities and were robust to afford products with decent yields. For instance, either electron-donating or electron-with-

Table 1. Optimization of the reaction conditions. ^[a]						
	1a	2a		3aa		
Entry	Cat. [10 mol %]	Wavelength	Solvent	3aa Yield [%] ^[a]		
1	FeCl ₂	450–455 nm	THF	27		
2	FeCl ₂	450–455 nm	PhCl	40		
3	FeCl ₂	450–455 nm	DCM	95		
4	FeCl ₃	450–455 nm	DCM	73		
5	$Fe(CF_3SO_3)_2$	450–455 nm	DCM	5 ^[d]		
6	Fe(OAc) ₂	450–455 nm	DCM	21 ^[d]		
7	FeCl₂	380–385 nm	DCM	76		
8	FeCl₂	430–435 nm	DCM	68		
9	FeCl ₂	480–485 nm	DCM	28		
10 ^[b]	FeCl ₂	450–455 nm	DCM	77		
11 ^[c]	FeCl₂	450–455 nm	DCM	70 ^[d]		
12	-	450–455 nm	DCM	2 ^[d]		
13	FeCl ₂	In dark	DCM	16 ^[d]		
[a] Reaction conditions: 1a (0.40 mmol), 2a (0.20 mmol), Cat. (10 mol%), MS ($4^{\frac{1}{2}}$ 2.4 mol DCM (0.5 ml) 40°C N 10 W blue LEDs 18 b isolated						

MS (4 Å, 2.4 mg), DCM (0.5 mL), 40 °C, $N_{\rm 2^\prime}$ 10 W blue LEDs, 18 h. Isolated yield was given. [b] FeCl_2 (50 mol%). [c] Without MS (4 Å). [d] Determined by GC-FID.

drawing substituents at the *para* or *meta-position* of phenyl ring were all well tolerated to deliver products in 37–95% yields (**3aa–3ja**). Besides, the C–N coupling reactions with N-methoxybenzamides bearing substituents at the *ortho*-position of benzenes proceeded smoothly as well, regarding of their steric hindrance (**3ka–3ma**). Probably due to the strong coordinated ability, the pyridylamide **1n** failed to furnish the corresponding product (**3na**). To our delight, the reaction showed good tolerance for *N*-methoxyamides bearing heterocyclic 2-thiophenyl and 2-furyl groups (**3oa–3pa**). Interestingly, alkenyl or alkynyl derived amides, which were usually daunting substrates under vigorous thermal conditions,^[17] were also suitable for this benign photo-induced catalysis to give **3pa–3ra** in acceptable yield.

Subsequently, we turned our attention to the scope of boronic acids. As shown in Scheme 2b, arylboronic acids with the phenyl group bearing electron-donating or electron-withdrawing substituents were all applicable, providing the amides 3 ab-3 ap in 21–95% yields. Notably, synthetically versatile groups, such as -Cl, -CN, -Br, -CHO and $-NO_2$ could be remained intact in these transforms, which highlights the capacities in molecular derivatization. In addition to phenylboronic acids, the reaction with 3-thienylboronic acid successfully generated corresponding product 3 aq in 41% yield. Satisfyingly, alkenylboronic acid was compatible as well, albeit in decreased yield (3 ar). While for some cases (3 ab, 3 ac, 3 ag, 3 ar), incomplete conversion of the starting materials resulted in poor yields.

To get insight into the mechanism of this reaction, preliminary mechanistic investigations have been conducted (Scheme 3). First, intermolecular competitive amidations of Nmethoxyamides/amides (1 a/4 a and 1 b/4 b) with phenylboronic acid 2a were conducted respectively to probe benzamide intermediates (Scheme 3a). In this text, N-aryl products from amides 4a or 4b were not obtained. These results indicated that amide species were not a feasible intermediate for C-N bond formation. Subjecting TEMPO (2,2,6,6-tetramethyl-piperidinooxy) as a radical inhibitor to the model reaction completely shut down the reaction (Scheme 3b, entry 1). BHT (butylated hydroxytoluene) also inhibited the reaction to some extent and N-radical adduct 5 was detected by LC-MS in this case (Scheme 3b, entry 2). While no phenyl radical adduct was detected when treated 2a with BHT alone under standard condition, 5 could be obtained in 10% vield from the reaction between 1a and BHT (Scheme 3b, entry 3). These results differed the mechanism from Bao's works in which phenyl radical involved.^[15] Instead, amide radical intermediate was supported in this catalysis.

Next, the UV-Vis absorption experiments were conducted (Scheme 3c). Firstly, substrate **1a** only showed weak lightabsorption in 350–400 nm wavelength. No visible-light response was observed for **2a** and FeCl₂, respectively. However, a strong absorption around 425–550 nm was observed when mixed FeCl₂ and **1a** together, indicating that the in-situ coordinated iron complex between FeCl₂ and **1a** could be easily excited by visible light irradiation. With regard to the importance of photonic input, the light on/off experiments





Conditions: 1 (2.0 eq.), 2 (0.20-0.40 mmol), FeCl₂ (10 mol%), 4 Å MS (~10 wt%), DCM (0.5 mL), 40 °C, N₂, 450-455 nm LEDs (10 W), 18 h. Isolated yield was given. ^a TBACI (tetrabutyl-ammonium chloride, 10 mol%) was added for solubility issue.

Scheme 2. Scope of *N*-methoxyamides and boronic acids.

confirmed that continuous irradiation of visible light was required for effective formation of **3 aa** (Scheme 3d).

Depending on the above results and literatures reports on photo-induced reactions,^[18] a plausible mechanism is presented in Scheme 4. Initially, the coordination of the amide 1 with FeCl₂ generates a visible-light-responsive intermediate **A**. Under the constant irradiation of blue light, complex **A** is stimulated and delivers Fe(III) species **B** through the metal-to-ligand charge-transfer (MLCT) path.^[19] Subsequently, a transmetalation step between **B** and phenylboronic acid **2** gives the radical intermediate **C**. After the intermolecular radical substitution with nitrogen radical, desired product **3** is formed and regenerates the Fe(II) catalyst via the SET process.

Conclusion

In conclusion, we have developed a practical electrophilic amination of boronic acids with *N*-methoxyamides under iron photocatalysis. Based on mechanistic studies, a photo-induced MLCT/SET process is proposed and allows the reaction steadily to proceed under mild conditions. Compared with noble metal catalysis or thermal-motivated condition, this protocol is also featured by its earth abundant catalyst, additive free and broad substrates tolerance. Further investigations on detailed mechanism, as well as the extension of this reaction pattern are now in progress in our laboratory.





Scheme 3. Mechanistic studies.



Scheme 4. Proposed mechanism.

Experimental Section

Typical procedure for photo-induced formation of N-aryl amides. To an oven-dried 20 mL quartz tube was added *N*-methoxyamide 1 (0.40 mmol), arylboronic acid **2** (0.20 mmol), FeCl₂ (0.02 mmol), MS (4 Å, 2.4 mg) and DCM (0.5 mL) in the glove box. Subsequently, the reaction mixture was stirred under the irradiation of a 10 W blue LEDs ($\lambda = 450-455$ nm) and the temperature of the heated reactor was set to 40 °C for 18 h. After the reaction completed, the crude product was purified by flash chromatography on silica gel to afford the corresponding product **3**.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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