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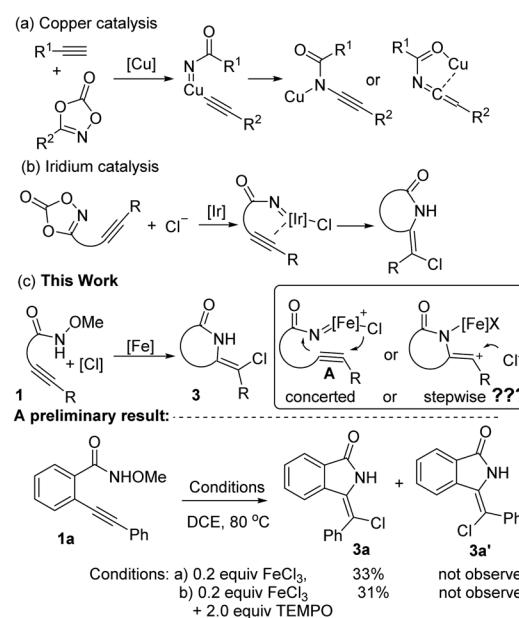
In this work, by using *N*-methoxybenzamides as efficient acyl nitrene precursors, an iron-catalyzed formal *cis*-haloamidation of alkyne is reported. Without assistance of additives, the reaction worked well in the presence of 50 mol% FeCl_3 or FeBr_3 , leading to a series of chloro/bromo-containing isoindolin-5-ones with high efficiency and wide reaction scope. In the reaction, the iron-facilitated haloamidation proceeds through a halo anion-participating concerted [3+2] cyclization to release the final products. The key intermediate ferric acyl nitrene A is generated *in situ* from a formal removal of MeOH .

Regarded as a highly reactive species, the nitrene intermediate has long attracted the attention of synthetic chemists.¹ This is most likely because, *via* a nitrene transfer reaction, nitrogen-containing building blocks can be incorporated into target products for the construction of structurally complex motifs. To date, a series of well-recognized nitrene precursors, which predominantly include azides, sulfonamides, and iminiodinanes, *etc.*, enable nitrene transfer reactions for C–N bond formation through typical C–H bond insertion and aziridination.

In addition to well-established C–H insertion and aziridinations,² nitrene/alkyne metalation has attracted significant attention. A rhodium-catalyzed nitrene/alkynes metalation was initially investigated by the Blakey, Panek, Xu, and Shi groups.³ The resulting rhodium nitrene could be trapped by an intramolecular/intermolecular allylic ester,^{3a,b} alkene/arene,^{3c,d} intramolecular cyclopropane,^{3e} and even by water.^{3f} It is noteworthy that this elegant methodology employs sulfonamides as precursors and the use of a stoichiometric amount of hypervalent iodide is thus required. Notably, enantioselective reactions have also been demonstrated.^{3g} Employing open-shell catalysis enabled by iminiodinanes,^{4a,c} Pérez and co-workers recently realized a Cu-catalyzed intermolecular radical

functionalization of the resulting copper nitrene with alkynes.^{4a} By adopting dioxazoles as acyl nitrene precursors, in 2019 De Bruin and co-workers found that ketenimine and ynamide species could be prepared *via* a copper-catalyzed acyl nitrene transfer into intramolecular C–C triple bonds (Scheme 1a).^{5a} In the reaction, the formation of ketenimines or ynamides was ascribed to the insertion of the resulting copper acyl nitrene into the copper acetylidy Cu–C bond. Distinctively, the dioxazole-derived nitrene transfer into intramolecular alkynes under iridium catalysis, developed by Chang and co-workers, proceeds through a chloro anion-participating concerted [3+2] cyclization mechanism (Scheme 1b).^{5b}

The use of amides or carbamates as acyl nitrene precursors is attracting the interest of chemists, and an array of publications



Scheme 1 Reaction design for iron-catalyzed acyl nitrene addition into alkynes.

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have suggested that N-protecting groups play a pivotal role in the formation of acyl nitrene intermediates; metal catalysts such as rhodium and iridium salts have been employed in these reactions.⁶ Very recently, our group developed an iron-catalyzed acyl nitrene/alkyne metalation of *N*-methoxyamides and β -dicarbonyl compounds for the synthesis of pyrrolo[2,1-*a*]isoindol-5-ones.⁷ In the reaction, using iron catalysis, *N*-methoxyamides serve as efficient acyl nitrene precursors through a formal removal of MeOH. Moreover, it is interesting that the resulting ferric acyl nitrene should be in a singlet state, which differs from the previous reports implying ferric imido radical species.^{6f,g,8} Considering the low cost of iron catalysts and their versatility,⁹ we herein report the further application of *N*-methoxylamides¹⁰ as acyl nitrene precursors in iron-catalyzed intramolecular acyl nitrene/alkyne metalation and chlorination (Scheme 1d). In addition to developing an alternative pathway for the preparation of various isoindolin-1-ones pre-products for structural elaboration, we have also provided further evidence for the formal ferric acyl nitrene-based chloroamidation (a concerted or stepwise pathway). With the projected idea in mind, a model reaction of *N*-methoxybenzamide **1a** in the presence of 0.2 equiv. of FeCl_3 was conducted in DCE at 80 °C. The preliminary result suggested that the above intramolecular acyl nitrene/alkyne metalation takes place, leading uniquely to a chloroamidative product (*Z*)-3-(chlorophenyl)methylene)isoindolin-1-one **3a** in 33% isolated yield. (*E*)-3-(chlorophenyl)methylene)isoindolin-1-one **3a'**, a well-known product derived from 5-*exo*-*dig* chlorocyclization,¹¹ was not observed. Furthermore, it was pleasing to find the undesired Curtius rearrangement byproduct was not observed.¹² The exact structure of product **3a** was identified by X-ray diffraction (CCDC†: 1992175). Additionally, a control experiment with 2.0 equiv. of TEMPO gave a similar yield (Scheme 1c), indicating the reaction probably proceeds through a non-radical pathway. Assuming that the chloroamidation is a stepwise process, it seems reasonable that the model reaction should produce a mixture of **3a** and **3a'**. The result that the reaction provides only (*Z*)-product **3a** provides some evidence of a concerted chloroamidation mechanism. It is believed that this ferric acyl nitrene-based chloroamidation may serve as an important supplement for the additive-free synthesis of chloro-containing heteroisoindolin-1-ones^{5b} and bromo-containing isoindolin-1-ones.¹³

The above positive result encouraged us to optimize the model reaction. To our delight, increasing the loading of FeCl_3 to 0.5 equiv. drastically improved the reaction efficiency, producing the target product **3a** in almost quantitative yield (entry 3, Table 1). Other N-nucleophilic or O-nucleophilic chlorocyclization byproducts were not detected.¹⁴ An increase or decrease in reaction temperature did not improve the reaction outcome, and inferior yields were obtained when the model reaction was carried out at 100 °C or 60 °C (entries 5 and 6, Table 1). No further improvement for reaction efficiency was observed when different solvents were employed (entries 8–10, Table 1). In order to reduce the FeCl_3 loading, reactions with various chloro sources were conducted (entries 11–13, Table 1). To our surprise, poorer results were obtained when KCl , NH_4Cl , and NaCl were used as replacements. These results suggest that the additional chloro source does not have a significant impact

Table 1 Optimization of the reaction conditions^a

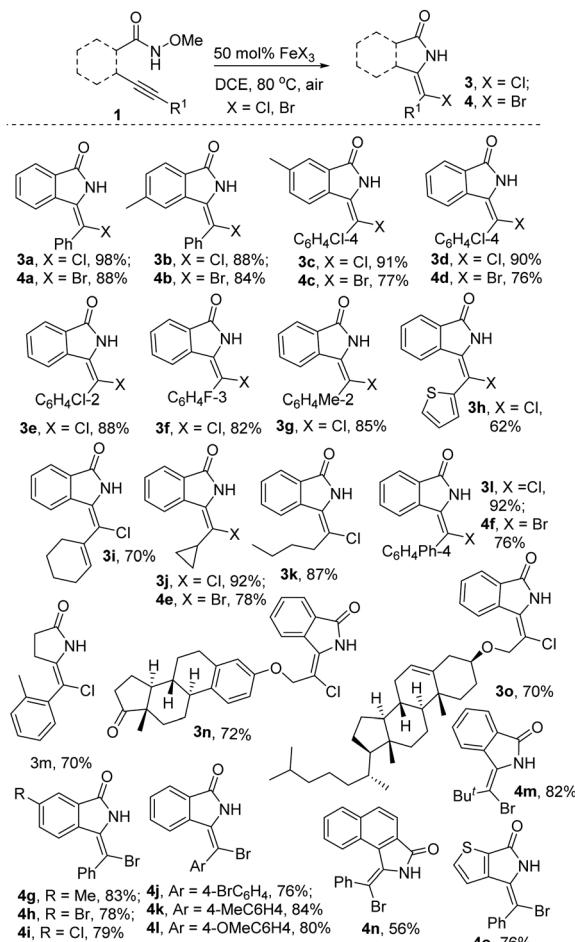
Entry	[Fe] (equiv.)	Sol.	Temp. (°C)	Yield of 3a ^b (%)
1	FeCl_3 (0.2)	DCE	80	33
2	FeCl_3 (0.4)	DCE	80	71
3	FeCl_3 (0.5)	DCE	80	98
4	FeCl_3 (1.0)	DCE	80	91
5	FeCl_3 (0.5)	DCE	60	81
6	FeCl_3 (0.5)	DCE	100	74
7	FeCl_3 (0.5)	DCE	80	79
8	FeCl_3 (0.5)	Toluene	80	80
9	FeCl_3 (0.5)	DMF	80	65
10	FeCl_3 (0.5)	THF	80	74
11	FeCl_3 (0.2) + KCl (1.5)	DCE	80	39
12	FeCl_3 (0.2) + NH_4Cl (1.5)	DCE	80	41
13	FeCl_3 (0.2) + NaCl (1.5)	DCE	80	43
14 ^c	FeCl_3 (0.5)	DCE	80	95

^a Conditions: the reaction of **1a** (0.2 mmol) was carried out under air atmosphere. ^b Isolated yield based on **1a**. ^c 2.0 equiv. of TEMPO was added.

on reaction efficiency, thus resulting in the need for a relatively high loading of iron salt. Addition of radical scavengers did not have a significant impact on the reaction yield (entry 14, Table 1), suggesting that the reaction does not involve the generation of a ferric imido radical species.⁸

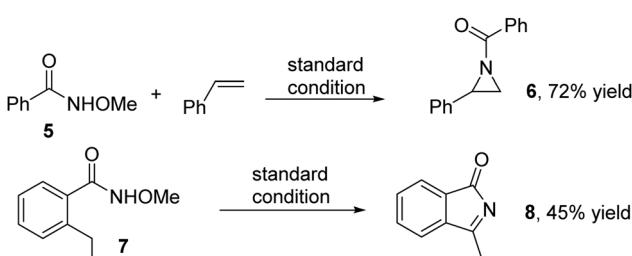
With the optimized conditions in hand, we investigated the scope of this reaction. The results are presented in Scheme 2. As shown in Scheme 2, the reaction is amenable to an array of functional groups, and a series of halo-containing isoindolin-1-ones **3a–3o** and **4a–4o** were obtained in good to excellent yields. For example, the reaction of *N*-methoxy-4-methyl-2-(phenylethynyl)benzamide **1b** under the standard conditions provided the desired products **3b** and **4b** in 88% and 84% yields, respectively. The reaction of 2-(cyclopropylethynyl)-*N*-methoxybenzamide proceeded smoothly, leading to the corresponding products **3j** in 92% yield and **4e** in 78% yield. From investigations of the substituent effect on the alkyne, it was found that the substituents such as aryl, alkyl, and heteroaryl groups were all tolerated. Some sensitive functional groups, including cyclohexyl, cyclopropyl and thiophene functionalities, were tolerated under the reaction conditions, with the formation of the desired products **3h**, **3i**, **3j**, **4e**, and **4o**. It is worth noting that the substrates with complex alkynes were efficient reaction partners. For instance, the corresponding products **3n** and **3o** were synthesized efficiently when estrone- and cholesterol-derived substrates were used. In particular, the reaction of *N*-methoxy-5-(*o*-tolyl)pent-4-ynamide **1m** also worked well, providing the desired product **3m** in 70% yield when FeCl_3 was used.

As mentioned above, it is envisioned that the reaction proceeds through a ferric acyl nitrenoid-based [3+2] cyclization

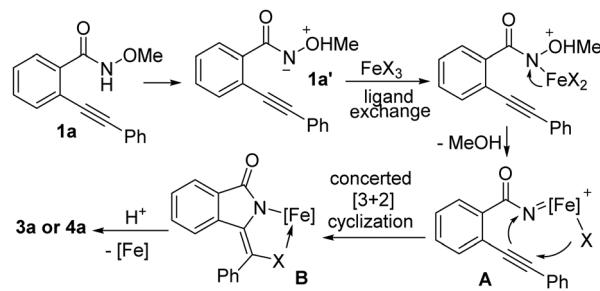
Scheme 2 Reaction scopes^{a,b}.

pathway. It is well known that nitrenes readily react with styrene and C–H bonds, and undergo aziridination and C–H insertion. To support our assumption, aziridination of *N*-methoxybenzamide 5 was carried out under the standard conditions. To our delight, the aziridinated product 6 was afforded in 72% yield. Furthermore, treatment of 2-ethyl-*N*-methoxybenzamide 7 with 50 mol% FeCl_3 under the standard conditions gave rise to a C–H insertion and sequential oxidation reaction, leading to isoindolin-1-one 8 in moderate yield (Scheme 3).

In light of the aforementioned results and the previous findings,^{7,15} a plausible mechanism has been proposed



Scheme 3 Iron-mediated acyl nitrene-based other reactions.



Scheme 4 A halo anion-participating [3+2] cyclization mechanism (other ligand in iron center is omitted).

(Scheme 4). In the reaction, a ferric acyl nitrene species **A** is generated *via* a formal removal of MeOH under iron catalysis. We reasoned the removal of MeOH involves 1,2-*H* migration^{15b} and ligand exchange with FeX_3 . Subsequently, the ferric acyl nitrene intermediate **A** undergoes a halo anion-participating concerted [3+2] cyclization, forming an isoindolin-1-one-containing ferric metallacycle intermediate **B**. Finally, protonation of the stable metallacycle intermediate **B** takes place to regenerate the iron catalyst and deliver the desired products 3 and 4.^{5b}

In conclusion, *N*-methoxybenzamides have been developed as efficient acyl nitrene precursors, and an iron-catalyzed formal *cis*-chloroamidation for the synthesis of isoindolin-1-ones has been reported. The reaction proceeds smoothly with broad functional group tolerance. Mechanistic studies suggest that the formal chloroamidation occurs *via* an iron-catalyzed acyl nitrene-based chloro anion-participating concerted [3+2] cyclization. Further transformations involving iron-catalyzed acyl nitrene/alkyne metalations with *N*-methoxybenzamides are being investigated in our laboratory, and the results will be reported in due course.

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Conflicts of interest

There are no conflicts to declare.

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