An Effective [Fe^{III}(TF$_4$DMAP)Cl] Catalyst for C–H Bond Amination with Aryl and Alkyl Azides

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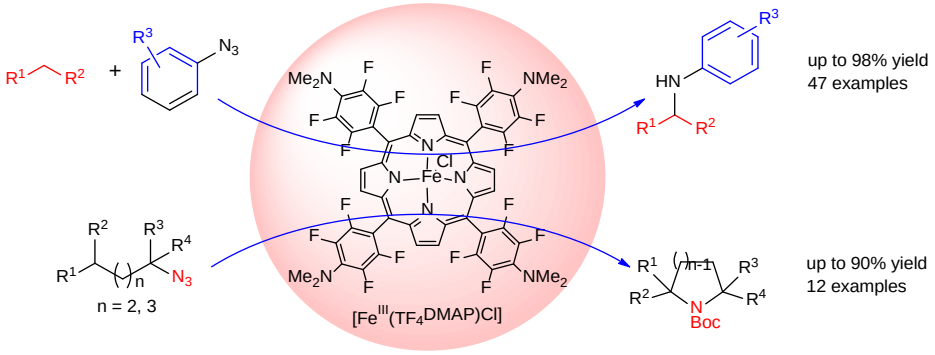


Abstract: [Fe^{III}(TF$_4$DMAP)Cl] can efficiently catalyze intermolecular sp^3 C–H amination using aryl azides and intramolecular sp^3 C–H amination of alkyl azides in moderate-to-high product yields. At catalyst loading down to 1 mol%, the reactions display high chemo- and regioselectivity with broad substrate scope and are effective for late-stage functionalization of complex natural/ bioactive molecules.

Catalytic C−H amination with nitrene sources represents one of general and efficient approaches to the formation of C−N bonds, which are ubiquitous in molecules of pharmaceutical and/or biological interests.[1] The ubiquity of chemically similar C−H bonds in complex molecules presents major challenges for site-selective C−H amination, including direct functionalization of C−H bonds, via nitrene insertion, for late-stage modification of natural products.[2] Among generally used nitrene sources (e.g., *N*-arylsulfonylimino phenyliodinanes,[3] bromamine-T,[4] chloramine-T,[5] and organic azides[6]), organic azides offer a broad nitrene scope and high atom efficiency. Transition metal catalysts are well documented to be effective for the decomposition of these nitrene sources to generate metal-nitrene intermediates.[7] Compared with other transition-metal catalysts, iron complexes are inexpensive and biocompatible, and often exhibit unique catalytic activity in nitrene insertion reactions of organic azides.[8,9,10,11b,d-k] For example, iron-dipyrrinato complex[9] and N-heterocyclic carbene iron(III) porphyrin[10] were found to be effective for C−H amination of alkyl azides, which remains a formidable challenge for the commonly used Rh and Cu catalysts. In view of the importance of iron catalysts in C−H amination via nitrene transfer,[8-11] the development of more efficient iron catalyst for C−H amination using organic azides as nitrene sources with high selectivity and broad substrate scope (covering complex molecules/natural products) is highly appealing. Our recent work revealed that [Fe^{III}(TF$_4$DMAP)Cl] [12] (Figure 1, TF$_4$DMAP = *meso*-tetrakis(*o*,*o*,*m*,*m*-tetrafluoro-*p*-(dimethylamino)phenyl)por-phyrinato dianion) is efficient in catalyzing anti-Markovnikov oxidation of terminal aryl alkenes to aldehydes with H_2O_2 as a terminal oxidant,[13] which involves a reactive iron-oxo porphyrin intermediate. This finding promoted us to examine the catalytic activity of this complex in isoelectronically related nitrene transfer/

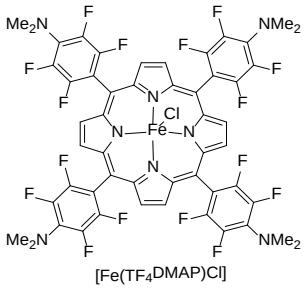
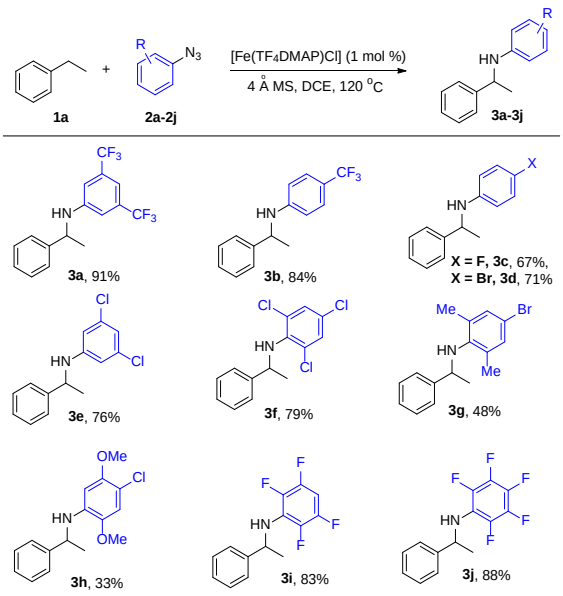


Figure 1. Structure of iron porphyrin [Fe(TF$_4$DMAP)Cl].

insertion reactions. Herein we report an efficient C−H amination with aryl and alkyl azides catalyzed by [Fe^{III}(TF$_4$DMAP)Cl] under thermal conditions and its application in derivatization of natural products.

At the outset, we evaluated the catalytic activity of [Fe^{III}(TF$_4$DMAP)Cl] in the C−H amination of ethylbenzene (**1a**) with 3,5-bistrifluoromethylphenyl azide (**2a**); the desired amine **3a** was obtained in 91% isolated yield when the reaction was performed in DCE at 120 ℃ for 12 h. Under the optimized reaction conditions, we investigated the scope of aryl azides as the nitrene source using **1a** as a model substrate (Scheme 1). High yields (67-84%) of C−H amination products were obtained for mono-*para*-substituted aryl azides (**3b-3d**). 3,5-Dichlorophenyl azide (**2e**) and 2,4,6-trichlorophenyl azide (**2f**) afforded the corresponding amines **3e** and **3f** in 76% and 79% yield, respectively. When aryl azides containing electron-donating substituent(s) (**2g** and **2h**) were used as the nitrene sources, the corresponding amines **3g** and **3h** were obtained in moderate yields. The beneficial effect of incorporating multi electron-withdrawing substituents was also demonstrated in the reactions of 2,3,5,6-tetrafluoro- and pentafluorophenyl azides (**2i**, **2j**) which afforded the corresponding amines in high yields (**3i**, 83%; **3j**, 88%).

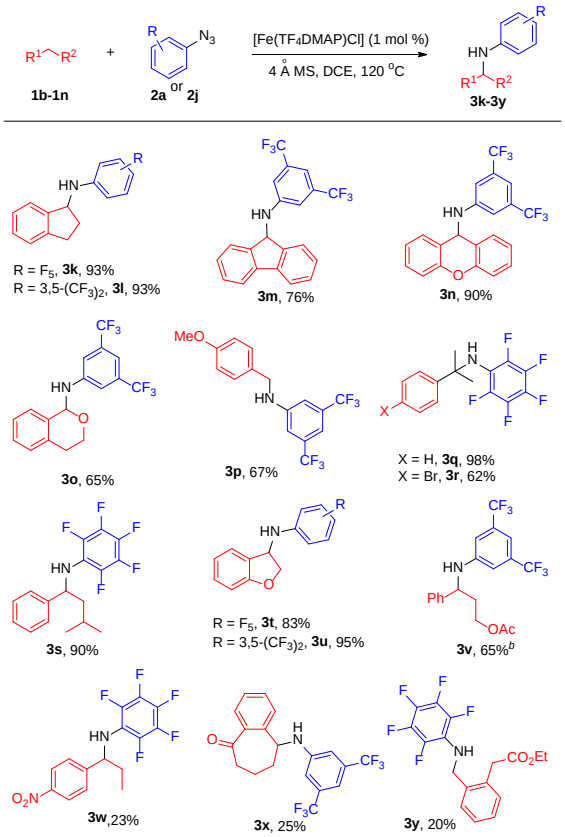
Scheme 1. Scope of Aryl Azides.[a]



[a] Conditions: **1a** (5.0 mmol), **2** (0.5 mmol), [Fe(TF$_4$DMAP)Cl] (1 mol%), 4 Å MS (120 mg), DCE (2.0 mL), under argon, 120 °C; isolated yield.

We further investigated the scope of C−H amination under the optimized conditions. As depicted in Scheme 2, when benzylic C−H bonds were subjected to the reaction with aryl azide **2a** or **2j** as nitrene source, the corresponding C−H amination products (**3k-3y**) were obtained in 20–98% yields. It is noteworthy that for 4-methylanisole, containing primary benzylic C–H bond, the C–H amination proceeded smoothly in 67% yield (**3p**). The reaction protocol also worked well for tertiary benzylic C−H bonds as shown in the cases of **3q** (98% yield) and **3r** (62% yield). When the substrates have both benzylic C–H bonds and tertiary C−H bonds or C–H bonds adjacent to oxygen atom, benzylic C–H bonds were preferentially aminated in good-to-high yields (**3s-3v**). The electron-withdrawing substituent on phenyl ring was found to reduce the activity of benzylic C−H bonds, leading to low product yields (**3w-3y**). This is in agreement with the electrophilic nature of the reactive iron-imido/nitrene intermediate.

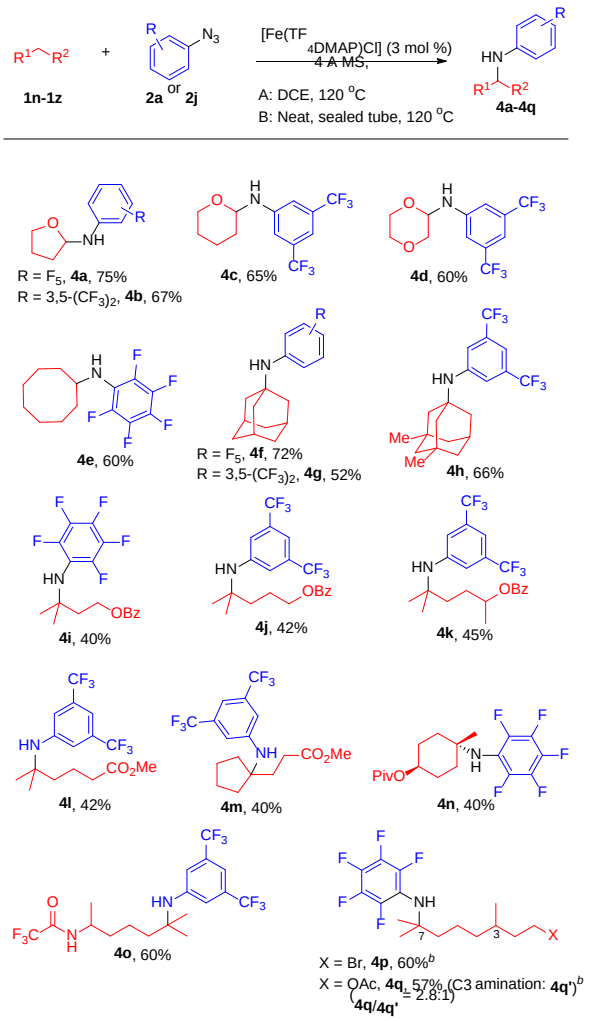
Scheme 2. Amination of Benzylic C–H Bonds with Aryl Azides.[a]



[a] Conditions: **1** (5.0 mmol), **2** (0.5 mmol), [Fe(TF$_4$DMAP)Cl] (1 mol%), 4 Å MS (120 mg), DCE (2.0 mL), under argon, 120 °C; isolated yield; [b] 2.5 mmol of substrate was used.

Given the good results of benzylic C–H bond amination, we then investigated the application of the amination for unactivated C−H bonds (Scheme 3). Tetrahydrofuran was reactive toward the C−H amination giving corresponding products in 67-75% yields (**4a**, **4b**). Tetrahydropyran and 1,4-dioxane also worked well with **2a** to give **4c**, **4d** in 65% and 60% yield respectively. Treatment of cyclooctane with **2j** in the presence of [Fe(TF$_4$DMAP)Cl] (1 mol%) gave C−H amination product **4e** in 60% yield. When 1°, 2°, 3° aliphatic C−H bonds and C−H bonds adjacent to oxygen atom are present in substrates, the Fe(III)-catalyzed C−H amination occurred at 3° C−H bond preferentially and in 40-72% yields (**4f-4o**). The site selectivity of the C−H amination for the substrates bearing multiple 3° C–H bonds was also examined by using two derivatives of dihydrocitronellol, each containing two 3° C−H sites. In both cases, the amination was favored at the site distal to the electron-withdrawing group (bromo or acetate, **4p**, **4q**). This regioselectivity could be attributed to the electron deactivation of C(3)−H bond by electron-withdrawing group.

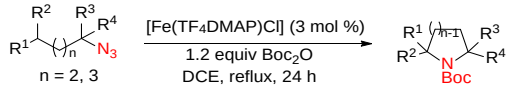
Scheme 3. Amination of Unactivated C–H Bonds with Aryl Azides.[a,b]

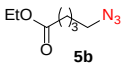
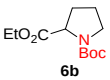
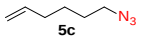
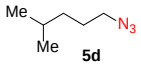
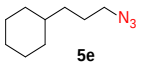
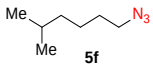
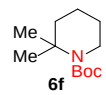
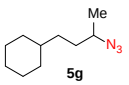
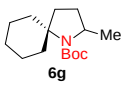
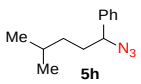
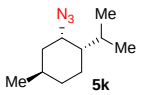
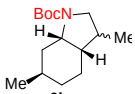


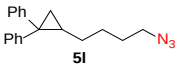
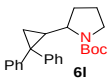
[a] Conditions A: **1** (1.0 mmol), **2** (0.2 mmol), [Fe(TF$_4$DMAP)Cl] (3 mol%), 4 Å MS (120 mg), DCE (1.0 mL), under argon, 120 °C; isolated yield; [b] Conditions B: the same as A except using neat **1** (1.0 mL) without DCE.

The intramolecular C–H amination of alkyl azides[9a,c,10,11g,i] is challenging because of facile 1,2-hydride shift of alkylnitrene intermediate. Our recent work[10] revealed that N-heterocyclic carbene iron(III) porphyrin [Fe^{III}(TDCPP)(IMe)$_2$]I (TDCPP = *meso*-tetrakis(2,6-dichlorophenyl)porphyrinato dianion) can efficiently catalyze intramolecular C–H amination of a broad array of alkyl azides. However, 10 mol% catalyst loading was required to guarantee high substrate conversion and product yields for the reaction. This promoted us to test the catalytic activity of [Fe(TF$_4$DMAP)Cl] for the intramolecular C–H amination of alkyl azides with lower catalyst loading. As depicted in Table 1, a variety of alkyl azides underwent intramolecular C–H amination in the presence of 3 mol% [Fe(TF$_4$DMAP)Cl] in 45-90% isolated yields. It is noteworthy that when alkyl azide **5f** was used, the six-membered piperidine product was selectively formed in 62% yield, showcasing the strong preference for amination at 3° C–H bond (entry 6, Table 1). For secondary alkyl azides **5g** and **5h**, the corresponding pyrrolidines were obtained in 78-90% yields (entries 7, 8, Table 1). Notably, when a cyclic secondary alkyl azide **5i** was subjected to the reaction, a tropane derivative with a bicyclic structure prevalent in a wide range of alkaloids, was isolated in 62% yield (entry 9, Table 1). Similarly, the α–azido ketone **5j** gave a tropane analogue in 86% yield, which is an important intermediate for the synthesis of Cocaine. Interestingly, a secondary alkyl azide **5k** derived from L-menthol underwent intramolecular amination exclusively at a 1° C–H bond to give the *cis*-octahydroindole in 45% yield with a *dr* ratio of 4.2:1 (entry 11, Table 1), revealing that primary unactivated aliphtic C–H bonds are also amenable for amination in this protocol when competing

Table 1. Intramolecular C–H Amination of Alkyl Azides.[a]



entry	substrate	product	conv. (%)	yield (%)
1	 **5a**	 **6a**	>99	66
2	 **5b**	 **6b**	>99	60
3	 **5c**	 **6c**	>99	82
4	 **5d**	 **6d**	>99	60
5	 **5e**	 **6e**	>99	76
6	 **5f**	 **6f**	>99	62
7	 **5g**	 **6g**	>99	78
8	 **5h**	 **6h**	>99	90
9	 **5i**	 **6i**	>99	62
10	 **5j**	 **6j**	>99	86
11	 **5k**	 **6k**	>99	45[b]

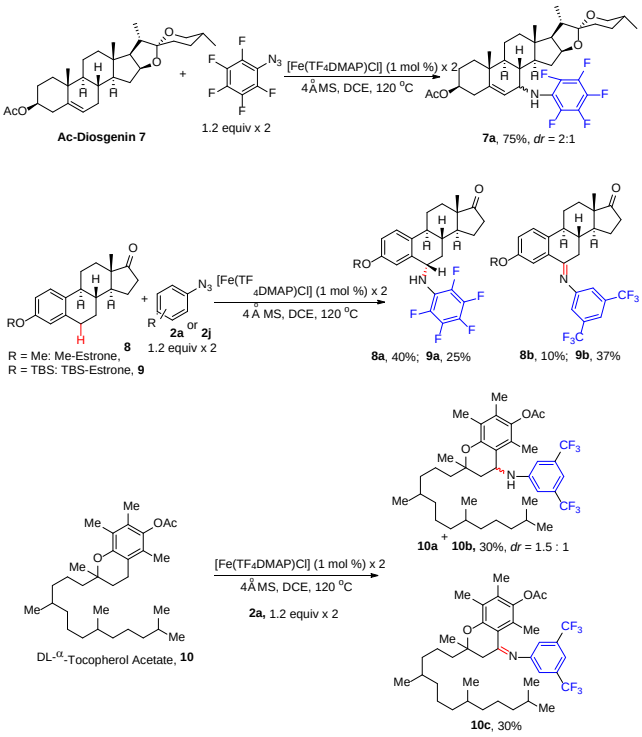
12	 **5l**	 **6l**	>99	78

[a] **2** (0.3 mmol), [Fe(TF$_4$DMAP)Cl] (3 mol%), Boc$_2$O (0.36 mmol), 4 Å MS (120 mg), DCE (2.0 mL), under argon, 120 °C; isolated yield. [b] *dr* = 4.2:1.

secondary or tertiary C−H bonds are inaccessible. For substrate **5l** bearing a cyclopropyl ring at C4, the iron-porphyrin-catalyzed reaction gave the pyrrolidine **6l** in 78% yield, with no cyclopropyl ring-opening product(s) observed in the crude ^{1}H NMR spectra. This is indicative of a concerted or very fast radical rebound mechanism for the C−H amination.

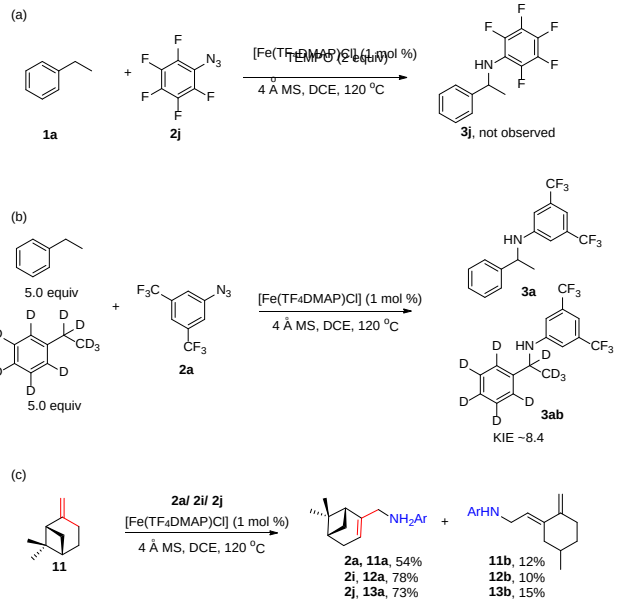
The high efficiency of the [Fe^{III}(TF$_4$DMAP)Cl] catalyst was further demonstrated by its applicability to the late-stage functionalization of complex natural product derivatives, which possess various C−H bonds and functional groups (Scheme 4). With **2j** as nitrene source, Ac-Diosgenin (**7**) underwent amination exclusively at the allylic C−H bond remote from the -OAc group, resulting in 75% isolated yield with a *dr* ratio of 2:1; Me-Estrone (**8**) reacted exclusively at the benzylic C−H bond with azide **2j**, giving the desired amine **8a** and its imine analogue **8b** in 40% and 10% yield, respectively, while amination of TBS-Estrone with azide **2a** gave amine **9a** and the corresponding imine **9b** in 25% and 37% yield, respectively. For the reaction of racemic DL-α-Tocopherol Acetate (**10**), the desired benzylic C−H amination products **10a** (*cis*) and **10b** (*trans*) were isolated in a combined 30% yield with a *dr* ratio of 1.5:1, along with 30% of imine product **10c**.

Scheme 4. Late-Stage C−H Functionalization of Natural Product Derivatives



Several experiments were performed to shed light on the mechanism of the catalytic C–H amination process. First, addition of TEMPO to a standard reaction mixture of **1a** and **2j** completely shut down the reaction, with no amination product **3j** observed (Scheme 5a). Second, the amination of a mixture of ethylbenzene and ethylbenzene-d_{10} with **2a** gave a kinetic isotope effect (KIE, k_H/k_D) of ~8.4 (Scheme 5b), suggesting that C–H bond cleavage is the rate-determining step. The KIE value is in the range of k_H/k_D ~5-13 reported for the H-atom abstraction by metal-nitrene/imido complexes.[14,15] Third, when (-)-β−pinene **11** was subjected to the reactions with three different azides **2a, 2i, 2j** separately, two types of allylic C–H aminated products were observed in each case (Scheme 5c), with the major ones presumably arising from a radical rearrangement or an alkene aziridination and subsequent ring opening process.[11b]

Scheme 5. Reaction mechanism study.



In summary, we have demonstrated that [Fe^{III}(TF$_4$DMAP)Cl] can efficiently catalyze C−H amination of aryl azides and alkyl azides with broad substrate scope and with high chemo- and regioselectivity. The catalytic system is highly effective for amination of a variety of sp^3 C–H bonds including unactivated aliphatic C−H bond, benzylic C−H bond, allylic C−H bond and 1°-3° C−H bonds. This catalytic protocol is also applicable to late-stage amination of complex natural product derivatives.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Detailed experimental procedures, characterization of new compounds, copies of NMR spectra.

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Notes

The authors declare no competing financial interest.

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