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N-Heterocyclic Carbene Iron(III) Porphyrin-Catalyzed Intramolecular C(sp^3)–H Amination of Alkyl Azides

Ka-Pan Shing, Yungen Liu, Bei Cao, Xiao-Yong Chang, Tingjie You, and Chi-Ming Che*

Abstract: *Metal-catalyzed intramolecular C-H amination of alkyl azides constitutes an appealing approach to alicyclic amines; challenges remain in broadening substrate scope, enhancing regioselectivity and applying to natural product synthesis. Herein we report an iron(III) porphyrin bearing axial N-heterocyclic carbene ligands which catalyzes intramolecular C(sp^3)-H amination of a wide variety of alkyl azides under microwave-assisted and thermal conditions, resulting in selective amination of tertiary, benzylic, allylic, secondary, and primary C-H bonds with up to 95% yield. 14 out of 17 substrates were cyclized selectively at C4 to give pyrrolidines. The regioselectivity at C4 or C5 could be tuned by modifying the C5-H reactivity. Mechanistic studies revealed a concerted or a fast re-bound mechanism for the amination reaction. The reaction has been applied to syntheses of tropane, nicotine, cis-octahydroindole and leelamine derivatives.*

Alicyclic amines are ubiquitous in naturally-found and pharmaceutically important molecules (Figure 1).[1] Development of metal-catalyzed intramolecular C-H amination for syntheses of alicyclic amines from alkyl azides (RN_3) via metal-alkylnitrene (M=NR) intermediates is appealing, as N_2 is the sole by-product and diverse types of RN_3 substrates are available.[2] Such catalytic systems,[3,4] first reported by Betley and co-workers using Fe-dipyrrinato catalysts (**A**, Figure 2) to produce pyrrolidines from amination of 2° or 3° C(sp^3)–H bonds of C(sp^3)-azides in good-to-excellent product yields,[3a,d] are complementary to other Fe-catalyzed C-H aminations of C(sp^2)-azides.[5] It remains a challenge to develop an efficient catalytic system that exhibits broader substrate scope (such as covering also 1° C-H bonds, pyridyl azides, cyclic secondary azides and/or tertiary azides), shows high regioselectivity (e.g. cyclization at C5 to give piperidines without a vinyl directing group), and is applicable to natural product synthesis. In this regard, we turned our attention to Fe porphyrin catalysts, owing to the analogy of C-H amination by heme Fe=NR species with C-H hydroxylation by Fe-oxo species of cytochrome P450 enzymes.[3a] We are particularly interested in developing Fe porphyrin catalysts bearing N-heterocyclic carbene (NHC) axial ligand, in view of elevation of catalytic efficiency of Ru(II) porphyrins by NHC axial ligand in carbene and aryl-nitrene C-H insertion reactions.[6] Also, the oxo ligand of heme Fe-oxo species bears oxyl radical character,[7] and for a Ru=O complex a strong oxyl radical character of the oxo ligand *trans* to NHC ligand was reported.[8] Previously we demonstrated microwave-accelerated iron porphyrin-catalyzed intermolecular phosphoryl-, sulfonyl- or aryl-nitrene transfer reactions.[9] Herein, we report the synthesis of an Fe-NHC porphyrin, [Fe^{III}(TDCPP)(IMe)$_2$]I (**B**, Figure 2), which can efficiently catalyze intramolecular amination of C-H bonds with a wide range of alkyl azides under thermal and microwave-assisted conditions. This strategy paves a way for facile conversion of alkyl azides to biologically and medicinally important alkaloids including tropane and nornicotine and also derivatives of *cis*-octahydroindole and leelamine.

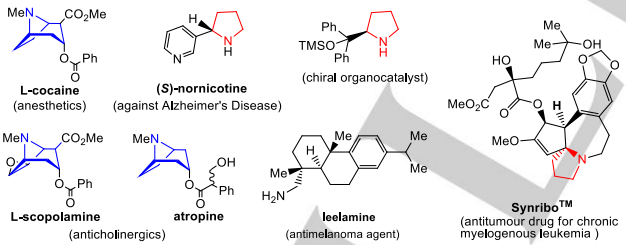

Figure 1. Examples of alkaloids/amines.

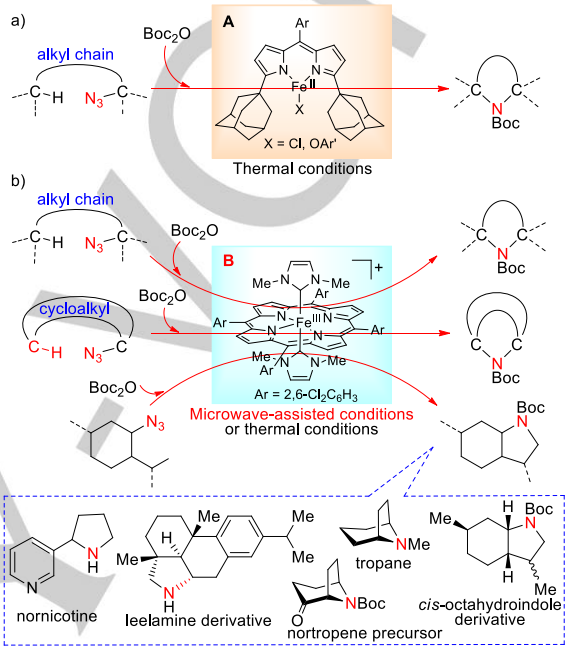

Figure 2. Examples of iron-catalyzed intramolecular C(sp^3)–H amination of alkyl azides. a) Developed by Betley and co-workers using Fe-dipyrrinato catalysts **A**. b) Described in this work using Fe-NHC porphyrin catalyst **B**.

Complex **B** was prepared by refluxing [Fe^{III}(TDCPP)]OTf with [HIMe]I in DMF and characterized by ESI-MS, UV/Vis, ^{1}H NMR (see Supporting Information), and X-ray crystal structure determination (Figure 3; ruffled conformation).[10] It is stable for up to several weeks towards air and moisture in solid state and solution. The Fe–C_{NHC} distances in **B** are 2.094(5) and 2.077(5) Å (C_{NHC}-Fe-C_{NHC} 179.7°), significantly longer than Fe–$C_{carbene}$ distances in [Fe(TPP)(CCl_2)(OH_2)] (1.83(3) Å)[11a] and [Fe(F_{20}-

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TPP)(CPh$_2$)(MeIm)] (1.827(5) Å).[11b] Complex **B** exhibits paramagnetic ^{1}H NMR signals (H_β: -0.99 ppm), and shows μ_{eff} of 1.63 μB (by Evans method) indicating a low-spin Fe(III) (*S* = 1/2) species.

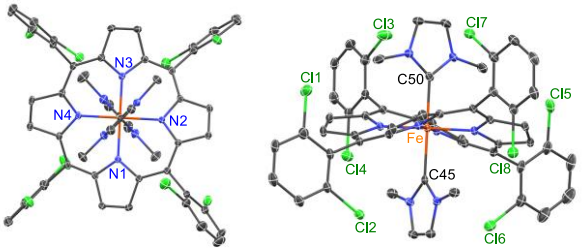
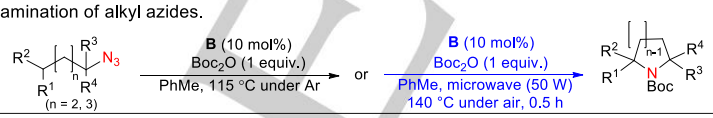


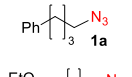
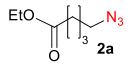
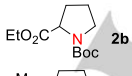
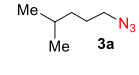
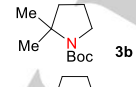
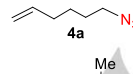
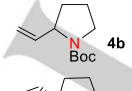
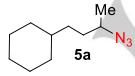
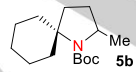
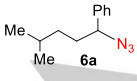
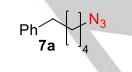
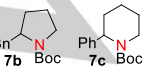
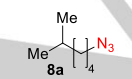
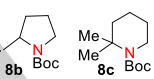
Figure 3. X-ray crystal structure of **B** (hydrogen atoms and counter-anion are omitted) at 30% probability thermal ellipsoids. a) Top view. b) Side view.

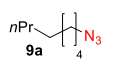
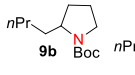
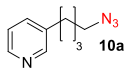
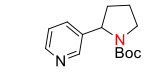
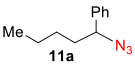
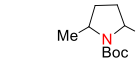
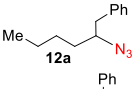
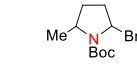
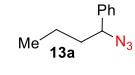
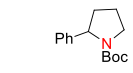
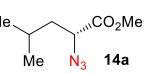
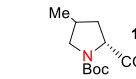
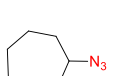
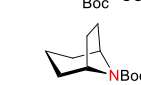
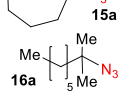
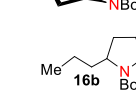
Treatment of Ph(CH$_2$)$_4$N$_3$ (**1a**), added via a syringe pump over 2 hours, with 20, 10, and 5 mol% of **B** at 115 °C in toluene containing 1 equiv. of Boc$_2$O, afforded pyrrolidine **1b** in 77%, 74%, and 50% isolated yield, respectively. Thus, 10 mol% of **B** was used in subsequent studies, which covered a wide variety of alkyl azides **1a**-**16a** (Table 1). The intramolecular C-H amination of primary alkyl azides **9a** and **10a** (with the latter bearing a pyridyl group), secondary alkyl azides **11a**–**14a**, cycloalkyl azide **15a**, and tertiary alkyl azide **16a** *have not been reported in previous works*.[3,4]

As shown in Table 1, **B** catalyzed intramolecular amination of **1a**–**16a** with product yields of up to 95%. The reactions of **1a**–**6a** gave pyrrolidines in 74-95% yields (entries 1, 3–6), except for **2a** (bearing electron-withdrawing ester group) which gave pyrrolidine **2b** in 50% yield (entry 2). For **7a**, a mixture of pyrrolidine **7b** and piperidine **7c**, corresponding to amination at C4-H and C5-H, respectively, was obtained in 50% combined yield with **7b**/**7c** ratio of 1:1 (entry 7), similar to the result obtained using 100 mol% of catalyst **A**.[3a] Using catalyst **B**, **8a** was converted to pyrrolidine **8b** and piperidine **8c** in 56% combined yield *with* ***8c*** *as the major product* (**8b**/**8c** = 1:5), opposite to the preferential formation of pyrrolidine **8b** (**8b**/**8c** = 1.5:1; combined yield of **8b,c**: 47%) observed for **A** used in 100 mol%,[3a] *indicating an unusual regioselectivity of catalyst* ***B***. For **9a**–**16a**, their intramolecular C–H amination catalyzed by **B** also showed good-to-excellent product yields and/or remarkable selectivity: (i) **9a** (devoid of allylic, benzylic, and 3° C–H bonds) resulted in a markedly higher C4-H (over C5-H) selectivity than **7a** and **8a**, affording pyrrolidine **9b** as the major product, together with minor amount of piperidine **9c** (**9b**/**9c** 5:1, entry 9). (ii) **10a** (bearing a pyridyl group) gave the pyridyl pyrrolidine **10b** in 65% yield (entry 10; using 10 mol% of [Fe^{III}(TDCPP)Cl] showed no substrate conversion). (iii) For **11a** with an α-Ph group, a 90% yield of **11b** (*syn*/*anti* 5:1) was obtained (entry 11). Changing the α-Ph group to a benzyl group lowered the catalytic activity and selectivity (cf. entries 11 and 12). (iv) **13a** with *1° C4-H* bonds and α-Ph group was cyclized to give pyrrolidine **1b** in 50% yield (entry 13). Remarkably, **14a** bearing α-ester group, an inexpensive chiral substrate prepared from *D*-leucine, underwent *1° C4-H amination* to give a proline-like product **14b** in 85% yield (*syn*/*anti* 2:1, entry 14), substantially higher than the 50% yield obtained for proline-like **2b** (entry 2). In literature, a 17% isolated yield of pyrrolidine product was reported for the intramolecular 1° C-H amination of CH$_3$(CH$_2$)$_2$C(CH$_3$)$_2$N$_3$ catalyzed by **A** (10 mol%).[3a] (v) **15a**, an azido-cycloalkane, was converted to a tropane product **15b** in 63% yield (entry 15); the latter bears a unique [3.2.1] bicyclic structure prevalent in a wide range of naturally-found compounds such as alkaloids. (vi) *Tertiary alkyl azide* **16a** containing both C4-H and C5-H gave pyrrolidine **16b** in 82% yield (conversion: 95%) *without piperidine product being observed* (entry 16), due possibly to enhancement of the five-membered ring selectivity by Thrope-Ingold effect. *These findings altogether contribute the first example of metal-catalyzed intramolecular C-H amination of a tertiary*

Table 1. Intramolecular C-H amination of alkyl azides.



Entry	Substrate	Product	Conv. [%][a]	Yield [%][b]
1	 **1a**	 **1b**	>99 [>99]	74 [90]
2	 **2a**	 **2b**	>99 [>99]	50 [80]
3	 **3a**	 **3b**	>99	95
4	 **4a**	 **4b**	>99 [>99]	75 [88]
5	 **5a**	 **5b**	>99	84
6	 **6a**	 **6b**	>99	93
7	 **7a**	 **7b** **7c**	>99 [>99]	50 (**7b**/**7c** 1:1) [87] (**7b**/**7c** 1.3:1)
8	 **8a**	 **8b** **8c**	>99 [>99]	56 (**8b**/**8c** 1:5) [73] (**8b**/**8c** 1.3:1)

Entry	Substrate	Product	Conv. [%][a]	Yield [%][b]
9	 **9a**	 **9b** **9c**	>99 [>99]	65 (**9b**/**9c** 5:1) [65] (**9b**/**9c** >20:1)
10	 **10a**	 **10b**	>99 [>99]	65 [85]
11	 **11a**	 **11b**	>99	90 (*syn*/*anti* 5:1)
12	 **12a**	 **12b**	80	88 (*syn*/*anti* 1:1)
13	 **13a**	 **1b**	80 [>99]	50 [72]
14	 **14a**	 **14b**	77 [>99]	85 (*syn*/*anti* 2:1) [88] (*syn*/*anti* 1:1)
15	 **15a**	 **15b**	>99 [>99]	63 [86]
16	 **16a**	 **16b**	95	82

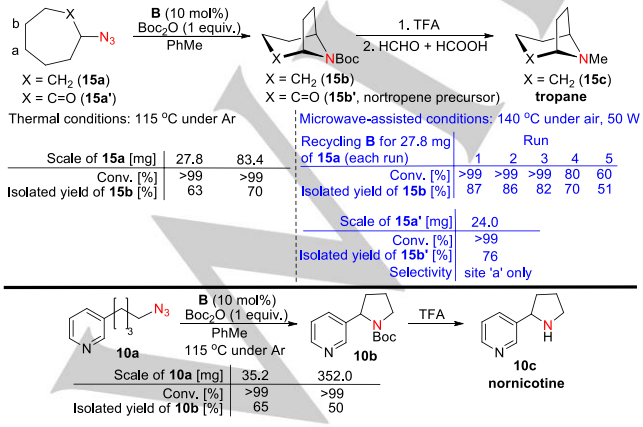
Thermal conditions: 10 mol% of **B**, alkyl azide (0.2 mmol, added via syringe pump within 5 h), Boc$_2$O (0.2 mmol) and 4 Å molecular sieves (100 mg) in toluene under argon overnight. Microwave-assisted conditions (results in square brackets): no molecular sieves, 140 °C under air (microwave power = 50 W) for 0.5 h, other conditions were the same except that azide was added in one-pot manner. [a] Based on the crude ^{1}H NMR spectrum with dimethyl fumarate as an internal standard. [b] isolated yield based on conversion for entries 1-6, 11-16 and ^{1}H NMR yield for entries 7-10.

alkyl azide with high product yield. Previously, the reaction of $EtO_2C(CH_2)_3C(CH_3)_2N_3$ catalyzed by **A** was reported to give the pyrrolidine product in 11% yield.[3a]

The aminations of 3° (**6a**), benzylic (**1a**), allylic (**4a**), 2° (**11a**), and 1° (**13a**) C4-H bonds afforded pyrrolidines in yields of 93%, 74%, 75%, 90%, and 50% (Table 1), respectively, indicating a reactivity order: 3° > 2°, benzylic, allylic >> 1° C-H bond. Of substrates **1a**-**16a**, **3a** gave C4-H amination product (**2b**) in the highest isolated yield of 95% (entry 3, Table 1), attributable to the high reactivity of 3° C4-H bond coupled with Thrope-Ingold effect. The preferential formation of piperidine **8c** from **8a** (entry 8, Table 1) reveals a reversal of regioselectivity by the presence of 3° C5-H bond, different from the vinyl-directed C5-H amination of CH_2=$CH(CH_2)_5N_3$ catalyzed by **A**.[3a]

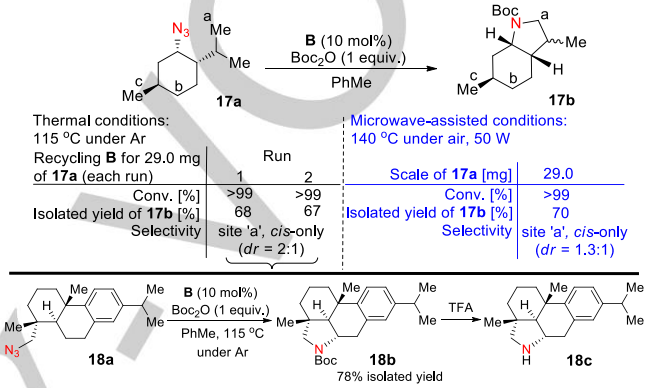
We also examined the **B**-catalyzed intramolecular C-H amination *under microwave-assisted conditions*; the results are depicted in Table 1 (see Supporting Information for optimization and control experiments). The microwave reactions showed *high tolerances with oxygen and moistures,* the reaction time was shortened (5 h → 0.5 h), and the product yields were improved (80-90% yields in 7 out of 10 entries) compared with the results obtained under thermal conditions. For the regioselectivity, the microwave-assisted conditions generally increased the proportion of C4-H amination, as exemplified by entry 9 with **9b**/**9c** ratio of >20:1. These unprecedented results render this iron porphyrin-NHC catalysis to be a simple, convenient and user-friendly method for selective construction of C-N bonds from alkylazides.

To show the application in natural product synthesis, we have developed a **B**-catalyzed C-H amination method, coupled with a facile *N*-methylation after Boc-deprotection, for the synthesis of tropane **15c** (which contains a fused piperidine-pyrrolidine structure) via **15b**, and scaling up the C-H amination reaction by 3-fold afforded **15b** in 70% yield (Scheme 1). In addition, the cyclization of **15a′** catalyzed by **B** led to the formation of a similar product **15b′** (76% isolated yield), which is an important intermediate to the synthesis of cocaines.[12] This method was further applied to the synthesis of a nicotine derivative, nornicotine (**10c**) via **10b**, with **10b** obtained in 50% yield upon scaling up the reaction by 10-fold, giving a quantitative amount of **10c** after treating **10b** with trifluoroacetic acid (Scheme 1). Under microwave-assisted conditions, catalyst **B** was recycled for 5 consecutive runs using **15a** as substrate (Scheme 1); the isolated yield of **15b** remained similar in the first three runs (87%, 86%, 82%) and was still good or moderate in the 4th run (70%) and 5th run (51%). Under the same conditions, catalyst [Fe^{III}(Por)Cl] (Por = F_{20}-TPP, TDCPP)] afforded <10% yield of **15b** even in the first run.



Scheme 1. Synthesis of tropane **15c** and nornicotine **10c**.

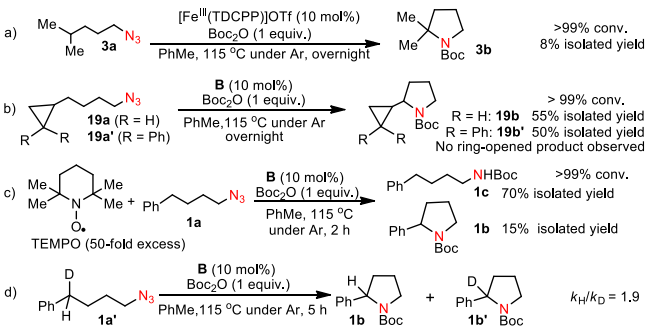
cis-Octahydroindole core is prevalent in natural products such as dysinosin A, a potent inhibitor of the blood coagulation cascade factor VIIa.[13] We synthesized a substituted azidocycloalkane **17a** (from a common starting material (L)-menthol), which underwent **B**-catalyzed intramolecular *1° C-H* amination to give *cis*-octahydroindole **17b** in 68% yield (>99% conversion, *dr* = 2:1) with excellent regioselectivity: only the 1° C4-H bond at site 'a' was aminated whereas the 2° and 1° C4-H bonds at sites 'b' and 'c', respectively, remain unreacted (Scheme 2). Recycling catalyst **B** for this reaction led to nearly no drop in its activity (Scheme 2). Under microwave-assisted conditions, the reaction showed the same regioselectivity giving **17b** in 70% yield (Scheme 2).



Scheme 2. Synthesis of *cis*-octahydroindole **17b** and leelamine derivatives **18b** and **18c**.

The **B**-catalyzed C–H amination method has also been applied to modification of leelamine (Figure 1), a potent anti-melanoma agent.[14] Upon treatment with imidazole-1-sulfonyl azide, leelamine was converted to azide **18a**, which underwent **B**-catalyzed cyclization to afford **18b** in 78% isolated yield, followed by reaction with TFA to give **18c** (Scheme 2).

To gain insight into the reaction mechanism, the effects of axial ligand and radical clock/trap and also kinetic isotope effects (KIE) were examined. [Fe^{III}(TDCPP)]OTf catalyzed the reaction of **3a** to give **3b** in only 8% yield (Scheme 3a), in contrast to the 95% yield obtained for catalyst **B**, revealing a vital role of the NHC axial ligand of **B** in the C-H amination. DFT-calculations showed that without NHC ligand, coordination of Fe^{3+} with alkyl azide seemingly requires breaking the heme co-planarity with Fe^{3+} being out of the porphyrin plane (Figure 4b, 0.37 Å displacement), which is significantly endogonic (Figure S2, ΔG = +10.73 kcal mol^{-1}). However, the heme co-planarity of the Iron(III) porphyrin is broken by the ruffled conformation engendered by ligation with NHC, resulting in less significant displacement of Fe^{3+} upon adduct formation with alkyl azide (Figure 4a, 0.15 Å). Such minimized displacement accounts for the slight exergonicity in the formation of



Scheme 3. a) Effect of axial ligand in catalyst. b) Effect of radical clocks. c) Effect of TEMPO. d) Kinetic isotope effect (KIE).

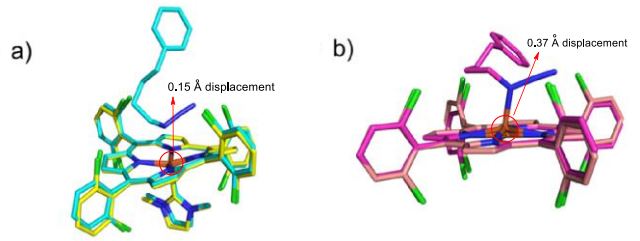


Figure 4. DFT-calculated geometric changes of a) $[Fe^{III}(TDCPP)(NHC)]^+$ and b) $[Fe^{III}(TDCPP)]^+$ upon binding azide **1a** (structures overlaid; Fe: orange, N: blue, Cl: green).

Iron(III)-alkylazide adduct (Figure S2, ΔG = -1.83 kcal mol^{-1}), which is beneficial to subsequent decomposition and cyclization.

We suggest that the catalytic cycle might be initiated by thermally driven dissociation of one NHC ligand from **B** to give $[Fe(TDCPP)(NHC)]^+$ (observable by ESI-MS analysis), which binds an alkyl azide to give $[Fe(TDCPP)(NHC)(N_3R)]^+$, with subsequent azide decomposition and cyclization to afford cyclic amine (Figure S3). For radical clock substrates **19a** and **19a′** bearing cyclopropyl rings at C4, the **B**-catalyzed reaction gave **19b** and **19b′** in 55% and 50% yields, respectively (Scheme 3b); no cyclopropyl ring-opened alkene product(s) was observed in the crude ^{1}H NMR spectra. This is indicative of a concerted or very fast re-bound mechanism for the step of C-H amination at C4. In the presence of TEMPO, the **B**-catalyzed reaction of **1a** gave **1b** in 15% yield, with amine byproduct **1c** formed in 70% yield (Scheme 3c); no radical-trapped species was observed. Possibly, intramolecular radical re-bound between carbon and nitrogen is faster than the intermolecular radical coupling with TEMPO. For the reaction of $PhC(D)H(CH_2)_3N_3$ (**1a′**) catalyzed by **B** at 115 °C, the KIE value based on **1b′/1b** ratio is 1.9 (Scheme 3d), markedly smaller than the KIE of 5.1 at 60 °C reported for catalyst **A**.[3a] These results could also be ascribed to C-H amination by a hydrogen abstraction mechanism with fast radical re-bound or a concerted-like mechanism.

In conclusion, a bis-NHC Fe(III)-porphyrin **B** has been synthesized, which catalyzes intramolecular C-H amination of alkyl azides at 1°, 2°, 3°, benzylic and allylic C-H bonds with high selectivity and up to 95% product yield under microwave-assisted/thermal conditions. The reactions selectively gave pyrrolidines (amination at C4-H), except for the presence of more reactive benzylic or 3° C5-H in which cases piperidines were also formed. The **B**-catalyzed reaction has been applied to the synthesis of nornicotine and *cis*-octahydroindole and leelamine derivatives and serves as an appealing method of constructing structurally complex and synthetic challenging tropanes (directly from an azidocycloalkane).

Acknowledgements

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Keywords: alkyl azides • C-H amination • iron • homogeneous catalysis • porphyrinoids

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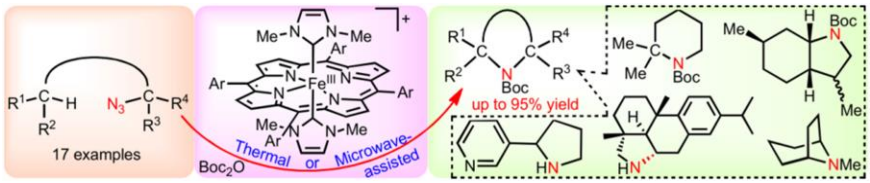

*Ka-Pan Shing, Yungen Liu, Bei Cao, Xiao-Yong Chang, Tingjie You, and Chi-Ming Che**

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N-Heterocyclic Carbene Iron(III) Porphyrin-Catalyzed Intramolecular C(sp^3)–H Amination of Alkyl Azides

An iron(III) porphyrin N-heterocyclic carbene complex catalyzed intramolecular C(sp^3)-H amination of a wide variety of primary, secondary and tertiary alkyl azides under microwave-assisted and thermal conditions resulting in selective amination of tertiary, benzylic, allylic, secondary, and primary C-H bonds with up to 95% yield. The reaction has been applied to syntheses of tropane, nicotine, *cis*-octahydroindole and leelamine derivatives.