

A. Nonheme Iron-Mediated Amination of C(sp³)-H Bonds.

Quinquepyridine-Supported Iron-Imide/Nitrene Intermediates by Experimental Studies and DFT Calculations

Chi-Ming Che* *et al. J. Am. Chem. Soc.* **2013**, *135*, 7194–7204.

B. Complex N-Heterocycle Synthesis via Iron-Catalyzed, Direct C-H Bond Amination

Theodore A. Betley* *et al. Science*, **2013**, *340*, 591–595.

1. Introduction

1-1. C(sp³)-H amination: Nitrene insertion into C(sp³)-H bond to make C-N bond

• Nitrene: N analogue of the carbene, too reactive and too unstable (**Figure 1**)

- Because of the ability of H atom abstraction/radical recombination to give C-N bond, nitrene has attracted much attention as a promising reagent for C-H amination.

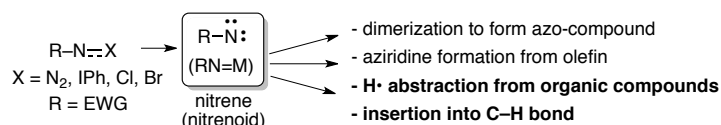


Figure 1. Generation and reactivity of nitrene species

=> Low efficiency and site-selectivity has been problem.

- Control of reactivity of nitrene has been achieved with the utilization of the transition metal catalysis (nitrenoid).
- Most general approach is rhodium catalysis (Initial report by Breslow (**1982**) => Du Bois C-H amination). Other metals such as Cu, Mn, Pd, Ru, Ag, have been also investigated (Müller, Che, Mansuy, Katsuki, Cenini, He,...).¹

1-2. Iron as an alternative catalyst

- Iron ... abundant, nontoxic => ideal metal as a catalyst

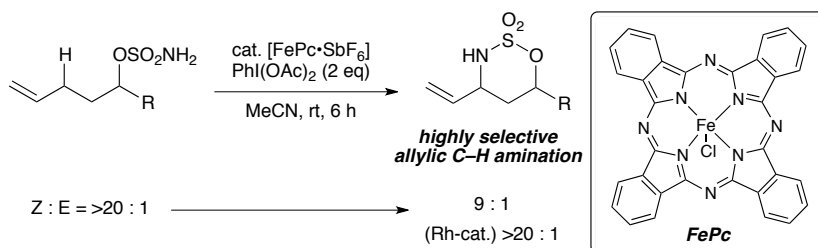
- Ligand framework is the key for achieving of C-H amination. Inspired by natural compounds “heme” (Fe=O supported by porphyrin-iron), many ligands have been developed to achieve C-H amination with iron-imide (Fe=N). However these ligands are not effective for achieving catalytic turnover.²

- Recently, the first general C(sp³)-H amination was achieved using a heme-like iron complex (**Scheme 1**).³

- This catalytic system shows unique selectivity, compared with Rh catalysis (e.g. isomerization).

=> Possibility of orthogonal reactivity of iron!

Scheme 1. Iron-catalyzed intramolecular allylic C-H amination and unique reactivity



Problems: Limited to allylic C-H bonds that have relatively low BDE (~89 kcal/mol) => **Limited scope**

No mechanistic study on the reason why FePc is good => **Further improvement of ligand design is difficult**

1-3. This work

- Two groups independently developed new ligand frameworks, which both enabled general iron-catalyzed C-H amination (**Figure 2**).

- These iron complexes are well defined and characterized by X-ray or ESI-MS, and putative intermediate was also proposed from results of mechanistic studies, supported by DFT calculations.

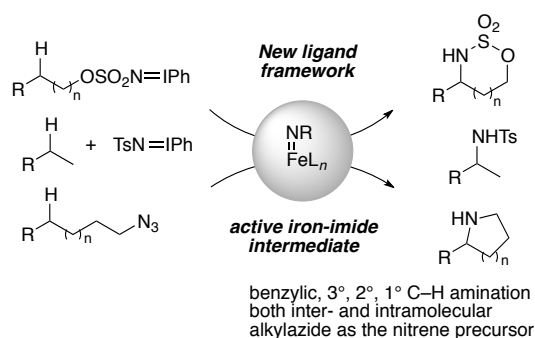


Figure 2. Ligand-controlled general C-H amination by iron catalysis

2. Results and Discussion

2-A. Quinquepyridine-iron complex (1) (Che *et al.*, Figure 3)

- Seven-coordinated iron complex (6 + 1) shows nitrene-transfer reactivity.^{2b}
 - This work: Five-coordination by the ligand + Two labile coordination site (5 + 2)
- Hypothesis: Iron-bis(imide/nitrene) complex shows high reactivity?

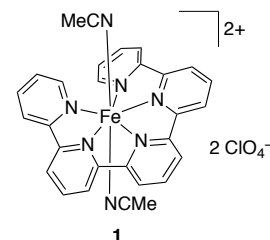
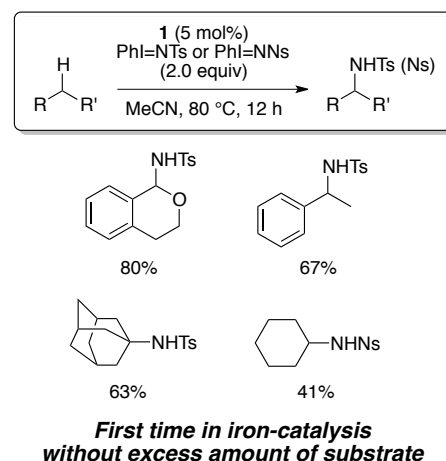
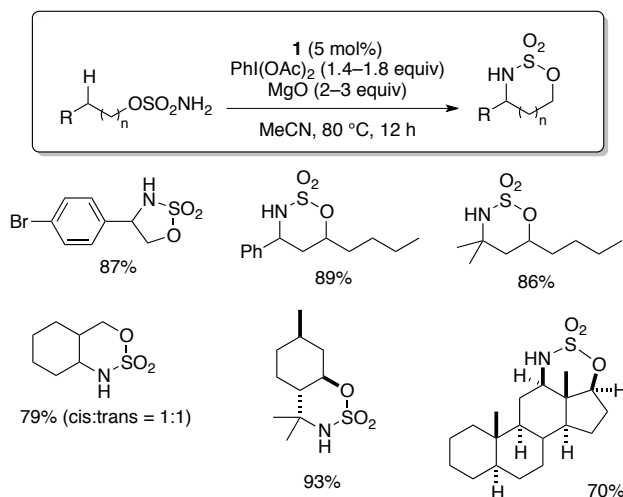


Figure 3. Quinquepyridine iron complex [Fe(qpy)(MeCN)₂](ClO₄)₂ (1)

Results (Scheme 2, Scheme 3)

Scheme 2. Intramolecular C(sp³)-H amination with tosylamine catalyzed by 1 **Scheme 3.** Intermolecular C(sp³)-H amination catalyzed by 1



- Direct amination of benzylic, 3°, and 2° C-H bonds has been achieved with catalytic amount of iron (5 mol%).
- Intermolecular C-H amination also proceeded.
- 4-coordinate, 3-coordinate ligands (Fe-monoimide) => no reaction

Mechanistic Investigations

a) KIE study, Hammett Plot

- Intermolecular KIE (cyclohexane): $k_H/k_D = 3.4$ (80 °C)
 - Hammett plot (**Figure 4**): reaction becomes faster when Y = EDG.
- => C-H abstraction is slow⁴

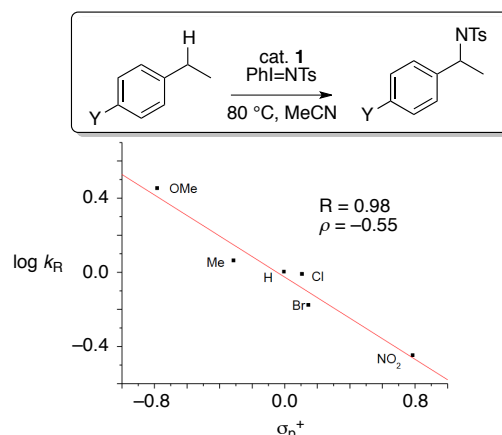


Figure 4. Plot of log k_R vs σ_{p^+} for amination of p -YC₆H₄Et

b) ESI-MS, equimolar experiments

- In ESI-MS analysis, several iron imide/nitrene complexes (C_X) were detected depending on the reaction conditions.

- complex 1 : PhI=NTs = 1:4 (**Figure 5**)

Peaks of bisimide (C_{NTs}), monoimide (C), [Fe(qpy)]²⁺ were observed. => C_{NTs} may involve in this reaction

- complex 1 : PhI=NTs = 1:1 (data not shown)

Prominent peak which can be assigned to [Fe(qpy)(NTs)(ClO₄)]⁺ (C_{ClO4}) was observed. No peak of C or C_{NTs} were detected.

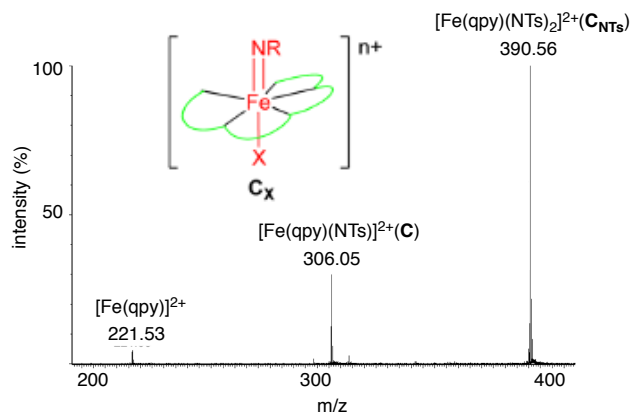


Figure 5. ESI-MS spectrum of the reaction of 1 with PhI=NTs (4 equiv) in MeCN.

- As shown in Table 1, excess amount of nitrene precursor is necessary to obtain aminated product (Compare entry 2 and 3 in **Table 1**)

=> Active species is C_{NTs} or C , not C_{ClO_4} .

c) DFT calculations

- Energy barriers of H-atom abstraction:

C_{NTs} : 15.3 kcal/mol C : 14.2 kcal/mol C_{ClO_4} : 17.6 kcal/mol

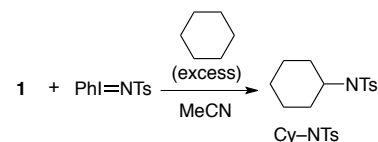
=> Corresponds to the experimental result.

- Both C_{NTs} and C , calculated Fe=N distance is markedly long (1.819, 1.884 Å

for C_{NTs} , 1.822 Å for C), suggesting Fe=N bond is so weak that imide ligand may have radical nitrene character and could be described as $[^{\cdot}NTs]^{-}$ => high reactivity for C-H abstraction

- Bis(imide)-iron complex may play pivotal role. Further experiment is required, but they failed to isolate C_{NTs} or C .

Table 1. Equimolar experiments



Entry	1 : PhI=NTs	Yield of Cy-NTs (equiv based on 1)
1	1 : 0.5	0
2	1 : 1	1
3	1 : 2	100
4	1 : 3	400

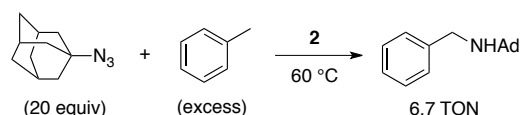
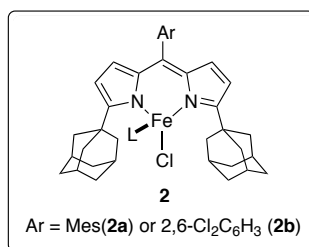
2-B. Dipyrinato-iron complex (Betley *et al.*, Scheme 4)

Ligand design for C-H amination:⁵

1) Strongly-donating substituents: nucleophilic metal complex that support Fe=N bond formation

2) Steric bulk: minimal coordination of Fe=N bond which may result in high reactivity of nitrene

Scheme 4. Dipyrinato iron complex **2** and their previous achievement



First intermolecular catalytic C-H amination with Fe

Notably, simple alkyl azide can be used as aminating reagent!

- Previously they achieved catalytic turnover of C-H amination, but reagents were excess and conversion is very low.

This work: Intramolecular reaction of alkyl azides to give N-heterocyclic compounds

Results (**Table 2**)

Table 2. Intramolecular C-H amination catalyzed by **2** for the synthesis of pyrrolidine derivatives

entry	azide	pyrrolidine	yield (%)	entry	azide	pyrrolidine	yield (%)
1			57	4			19
2			72	5			17
3			49				

- General synthesis of N-heterocycles via Fe-cat. C-H amination. EWG on the azide is not required.

- Notably, strong C-H bond such as, 2°, 1° C-H bond can be also aminated (entries 4 and 5).

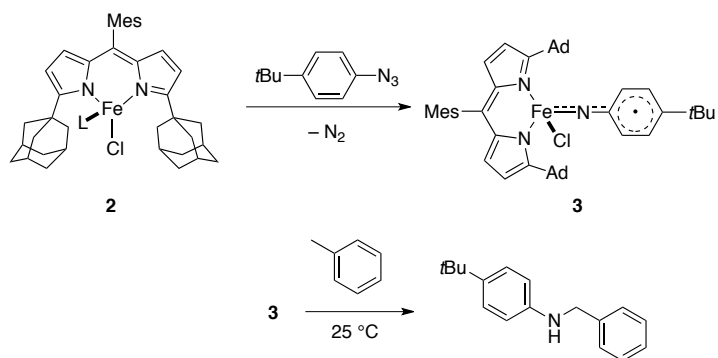
Property of complex **2**

In previous work,⁵ they isolated and fully characterized the iron imide complex (**3**) (**Scheme 5**).

- Distance of Fe=N: 1.768 Å (longest so far)
- High spin ground state ($S = 2$, supported by Mössbauer measurements and DFT calculations)

=> Radical nitrene character [\cdot NTs] which shows high reactivity (same conclusions with the case 2-A)

Scheme 5. Synthesis and isolation of iron imide/nitrene intermediate (**3**)



Mechanistic investigations

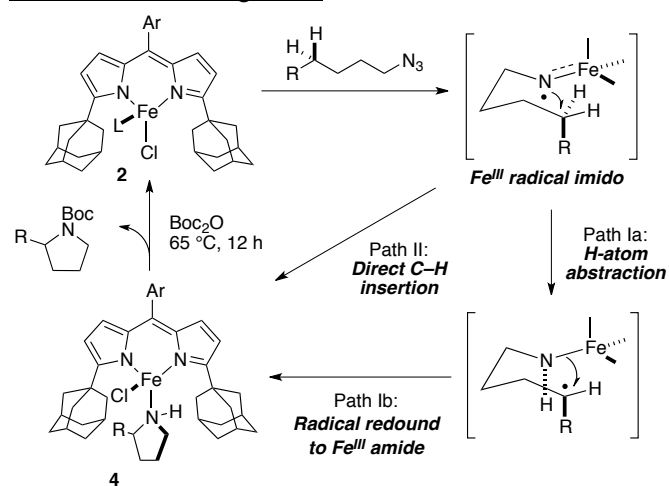
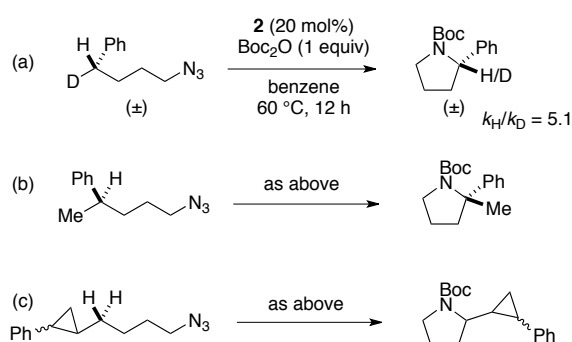


Figure 6. Proposed mechanism

Scheme 6. Mechanistic studies



They proposed two pathways, path I and II (**Figure 6**).

- Intermediate **4** is quantitatively obtained in the absence of Boc_2O .
- Intramolecular KIE (5.1) is similar to previous case, in which path I is proposed (**Scheme 6**, eq. (a)).
- Retention of the stereochemistry and radical clock experiment showed radical intermediate is less plausible (eq. (b) and (c)).

=> Finally they could not conclude which path is more plausible, although previous studies suggest path I.

If path I is operative, radical recombination should be very fast ($> 10^{11}/\text{s}$).

3. Conclusions

- Two general C–H amination methods have been developed, with different working hypotheses and ligand designs.
- C–H bond that have strong BDE, such as 2° , 1° C–H bonds can also be successfully aminated.
- Design of the ligand strongly affects distance of Fe=N bond, which leads to high reactivity of nitrene (supported by experimental results, spectroscopic analysis and theoretical studies)

¹ Zalatan, D. N.; Du Bois, J. *Top. Curr. Chem.* **2010**, *292*, 347–378.

² For example, (a) Jensen, M. P.; Mehn, M. P.; Que, L. *Angew. Chem. Int. Ed.* **2003**, *42*, 4357–4360. (b) Soo, H. S.; Sougrati, M. T.; Grandjean, F.; Long, G. L.; Chang, C. J. *Inorg. Chim. Acta* **2011**, *369*, 82–96.

³ Paradine, S. M.; White, M. C. *J. Am. Chem. Soc.* **2012**, *134*, 2036–2039.

⁴ Simmons, E. M.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2012**, *51*, 3066–3072.

⁵ (a) King, E. R.; Betley, T. A. *Inorg. Chem.* **2009**, *48*, 2361–2363. (b) King, E. R.; Hennessy, E. T.; Betley, T. A. *J. Am. Chem. Soc.* **2011**, *133*, 4917–4923.