Complex $N$-Heterocycle Synthesis via Iron-Catalyzed, Direct C–H Bond Amination

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Betley, T. A. et al.
Hemoproteins have diverse biological functions including the transportation of diatomic gases, chemical catalysis, and electron transfer.

A heme is a chemical compound of a type known as a prosthetic group consisting of an Fe$^{2+}$ (ferrous) ion contained in the centre of a large heterocyclic organic ring called a porphyrin, made up of four pyrrolic groups joined together by methine bridges.

The heme iron serves as a source or sink of electrons during electron transfer or redox chemistry. In peroxidase reactions, the porphyrin molecule also serves as an electron source. In the transportation or detection of diatomic gases, the gas binds to the heme iron.

From Wikipedia
Background >> Catalytic C–H Bond Functionalization by Metalloporphyrins

A. Hydroxylation: C–H oxene insertion

\[
\begin{align*}
R_1^1 & \quad + \\
\text{oxene source} & \quad \text{M(Por)} \\
R_2^2 & \quad \rightarrow \\
R_3^3 & \\
\quad & \quad R_1^1
\end{align*}
\]

B. Amination: C–H nitrene insertion

\[
\begin{align*}
R_1^1 & \quad + \\
\text{nitrene source} & \quad \text{M(Por)} \\
R_2^2 & \quad \rightarrow \\
R_3^3 & \\
\quad & \quad R_1^1
\end{align*}
\]

C. Alkylation: C–H carbene insertion

\[
\begin{align*}
R_1^1 & \quad + \\
\text{carbene source} & \quad \text{M(Por)} \\
R_2^2 & \quad \rightarrow \\
R_3^3 & \\
\quad & \quad R_1^1
\end{align*}
\]

Background >> **Types of Nonheme Iron–Imide/Nitrene Complexes**

The Synthesis of Metalloporphyrin Analogues

Catalyst Structure and C–H Bond Amination

Synthesis of Bimolecularly Coupled Fe$^{III}$ and Terminal Imido Complex

Proposed Catalytic Cycle for the Amination of C-H Bonds

**Radical recombination**

$$[\text{Fe}^III\text{Cl(OE}_2)]^S = 2$$

**Ligand exchange**

$$[\text{Fe}^III\text{Cl(L)}]$$

$$\text{N}_2$$

$$\text{L}$$

$$[\text{Fe}^III\text{Cl(N}_2\text{Ad)}]^S = 2$$

**H-atom transfer**

$$[\text{Fe}^III\text{Cl(Ad)}] + \text{H}$$

$$\text{S}_{\text{Fe}}(5/2) - \text{S}_{\text{Ar}}(1/2) = 2$$

**Imido formation**

$$[\text{Fe}^III\text{Cl(NAd)}] + \text{H}^+$$

$$\text{S}_{\text{Fe}}(5/2) - \text{S}_{\text{NR}}(1/2) = 2$$

Azide Cyclization and Iron-bound Pyrrolidine Products

\[
\text{Ar} = (1) \text{Mes} \\
(2) 2,6-\text{Cl}_2\text{C}_6\text{H}_3
\]

\[
\begin{align*}
R^1, R^2, R & = (5) \text{Ph, H, H} \\
(6) & \text{C}_2\text{H}_3, \text{H, H} \\
(7) & \text{Me, Me, H} \\
(8) & \text{Et, H, H} \\
(9) & \text{H, H, Me}
\end{align*}
\]

Synthesis of Pyrrolidine Products with High-Spin Iron Imido Complexes

![Chemical structure and reaction scheme]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Azide</th>
<th>Pyrrolidine</th>
<th>Yield (%)*</th>
<th>Entry</th>
<th>Azide</th>
<th>Pyrrolidine</th>
<th>Yield (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph-H-H-N₃</td>
<td>Ph-PG-N₃</td>
<td>98† (PG = Fmoc)</td>
<td>98† (PG = Boc)</td>
<td>93†</td>
<td>57‡ §</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>=CH₂-H-H-N₃</td>
<td>=CH₂-PG-N₃</td>
<td>72‡ §</td>
<td>72‡ §</td>
<td>75†</td>
<td>93% ee</td>
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<tr>
<td>3</td>
<td>X-H-H-H-N₃</td>
<td>X-Boc-N₃</td>
<td>47</td>
<td>47</td>
<td>84</td>
<td>1.1:1.0 dr</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Ph-O-H-H-N₃</td>
<td>Ph-Boc-N₃</td>
<td>68†</td>
<td>68†</td>
<td>67</td>
<td></td>
<td></td>
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<tr>
<td>5</td>
<td>=CH₂-H-H-OTMS</td>
<td>=CH₂-OTMS</td>
<td>73</td>
<td>73</td>
<td>78†</td>
<td></td>
<td></td>
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<tr>
<td>6</td>
<td>Ph-H-H-N₃</td>
<td>Ph-PG-N₃</td>
<td>60</td>
<td>60</td>
<td>78†</td>
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<td></td>
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<td>11</td>
<td>9</td>
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<td>Ph-Boc-N₃</td>
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<td>84</td>
<td>1.1:1.0 dr</td>
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<td></td>
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<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td>11</td>
<td>84</td>
<td>1.1:1.0 dr</td>
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<td>Ph-H-H-H-H-N₃</td>
<td>Ph-Boc-N₃</td>
<td></td>
<td>84</td>
<td>1.1:1.0 dr</td>
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<td></td>
</tr>
</tbody>
</table>

*¹H NMR yield using ferrocene or trimethoxybenzene as an internal standard unless otherwise noted. † Stoichiometric reactions with one equivalent of catalyst 2. ‡ Isolated yield. § 10 mol% catalyst 2.
### Product Distribution for Azetidine, Pyrrolidine, and Piperidine

**Equation:**

\[
\begin{align*}
\text{R}^1 & \quad \text{H} \quad \text{R}^2 \\
\text{N}_3 & \quad \text{n} = 1, 2, 3 \\
\text{Boc}_2\text{O} (1 \text{ eq.}) & \quad \text{Benzene, } 23 \, ^\circ\text{C}, 12 \text{ h}
\end{align*}
\]

**Table:**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Azide</th>
<th>Product(s)</th>
<th>Conv. (%)</th>
<th>Ratio(s)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>N_3</td>
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<td></td>
</tr>
<tr>
<td>2</td>
<td>N_3</td>
<td></td>
<td>82</td>
<td></td>
</tr>
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<td>3</td>
<td>Ph_N_3</td>
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<tr>
<td>4</td>
<td>N_3</td>
<td></td>
<td>47</td>
<td>1.0:1.5</td>
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<tr>
<td>5</td>
<td>N_3</td>
<td></td>
<td>47</td>
<td>1.0:1.5</td>
</tr>
</tbody>
</table>

* Yields determined by \(^1\text{H} \text{NMR}^\) using ferrocene or trimethoxybenzene as internal standards.

† Ratios determined by integration of GC/MS peaks.
Mechanistic Studies

2 (20 mol%) Boc₂O (1 eq.)

K_H/K_D = 5.3 (23 °C)
5.1 (60 °C)

concerted

Stepwise

Fe^{III} radical imido

No 1,2 hydride shift

[Ad₂Fe]
Saturated, cyclic amines (N-heterocycles) are important building blocks for the synthesis of biologically active natural products, pharmaceutical agents, and materials. Current strategies for constructing saturated N-heterocycles are heavily dependent on functional group exchange, leading to inefficient synthetic protocols with poor atom economy and waste generation. A streamlined synthetic approach to this product class would rely on a catalyst capable of the direct amination of aliphatic C–H bonds. An advantage of this method is its potential to harness saturated hydrocarbon feedstocks. Unfortunately, current C–H bond functionalization protocols often require substrate preoxidation, directing groups, or strong chemical oxidants, which contribute to a lack of generality for this bond construction. Herein, we report an iron catalyst capable of functionalizing a broad range of aliphatic C–H bonds to form saturated, cyclic amine products.
The foregoing results have demonstrated the oxidative potency of the transiently formed, high-spin iron imido radical for the functionalization of both activated and unactivated aliphatic C–H bond substrates. This iron-mediated cyclization of linear azides provides facile entry into complex \( N \)-heterocyclic products from readily available substrates that cannot be achieved by azide photolysis or via classic Hoffmann-Löffler-Freytag methodologies. We anticipate the methodology described herein can be extended to produce a wide variety of saturated, cyclic structures.