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From C–H to C–N Bonds: Three Challenges, Three Catalysts, Three Solutions

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§SCS-Metrohm Award for best oral presentation in Inorganic Chemistry

Abstract: N-heterocycles are key building blocks for many pharmaceutical products. An efficient and sustainable method for the synthesis of this class of compounds consists of the recently established intramolecular C–H amination reaction. Development of new iron-based catalysts for this transformation is of paramount importance. Herein, three major challenges in this field are addressed: the accessibility of the catalyst, the lack of mechanistic understanding, and the limited activity and robustness of the catalyst. These challenges are tackled by three different catalysts. The first catalyst is the commercially available FeI_2, that shows good activities, but is limited to substrates with activated C–H bonds. The $Fe(HMDS)_2$ catalyst is used to perfom in-depth mechanistic studies, revealing key intermediates of the C–H amination reaction. The third catalyst, featuring mesoionic carbene ligands, displays unprecedented activities and aminates various C–H bonds.

Keywords: Catalysis · C–H amination · Iron · Nitrenes

Wowa Stroek received his BSc (2017) and MSc (2019) at the University of Amsterdam. His Master thesis work was carried out in the group of Prof. Bas de Bruin. In 2019 he relocated to Switzerland to start his PhD in the group of Prof. Martin Albrecht at the University of Bern. For his thesis, which he successfully defended in 2023, he was awarded the Faculty prize of the University of Bern. Currently, he is a postdoctoral researcher in the same group. His research focuses on iron complexes for the intramolecular C–H amination reaction.

1. Introduction

N-heterocycles are a common motif in many biologically active compounds.[1] Especially in the pharmaceutical industry it is a key building block, as over 60% of the FDA approved drugs contain an N-heterocycle.[2,3] While many methods to synthesize this class of compounds are well established, they generally require prefunctionalization steps to facilitate the C–N bond formation and therefore suffer from poor atom economy.[4,5] A more efficient strategy to form C–N bonds is by C–H amination using *in situ* generated nitrenes.[6,7] Various nitrene precursors are known and vary greatly in their reactivity and side product formation.[8] Organic azides while less active, are an interesting class of nitrene precursors, as they produce N_2 as the only by-product.

In 2013, Betley pioneered the direct C–H amination of organic azides with a catalytic system based on iron to synthesize a variety of N-heterocycles (Fig. 1).[9] Although activities were limited to turnover numbers (TONs) of 5.7 and a stoichiometric amount of Boc_2O was required, this work set the foundation for next generation catalysts.[10–21] Especially with iron complexes major progress has been achieved by increasing the TONs to 620, making iron the metal of choice for this transformation (Fig. 1).[22] However, the addition of Boc_2O remained a necessity with iron catalysts, while systems based on nickel[15,16] and cobalt do not require this additive.[12] Further challenges that need to be addressed with iron catalysts include (Fig. 1): First, the sophisticated ligand systems, which makes the catalytic transformation less accessible for general use; Second, a thorough mechanistic understanding for a rational improvement of the catalytic performance; And third, higher activities are required to enhance the synthetic utility.

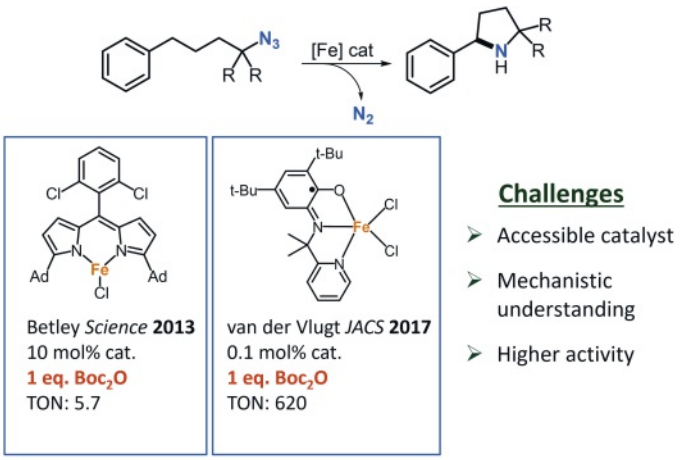

Fig. 1. Selected literature examples and challenges of the iron catalyzed intramolecular C–H amination using alkylazides.

2. Accessibility of the Catalyst

To explore if more accessible iron systems catalyze the intramolecular C–H amination, several commercially available iron salts were tested by reacting them with the model substrate (4-az-

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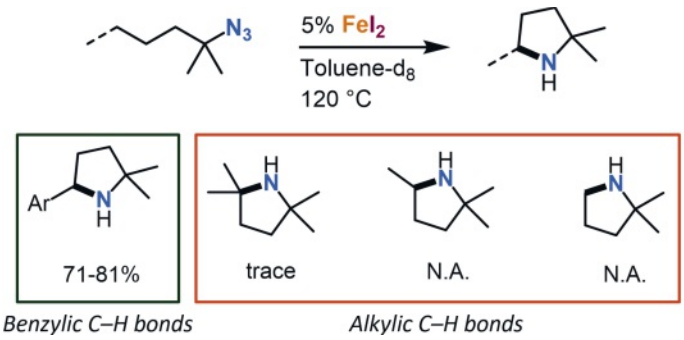
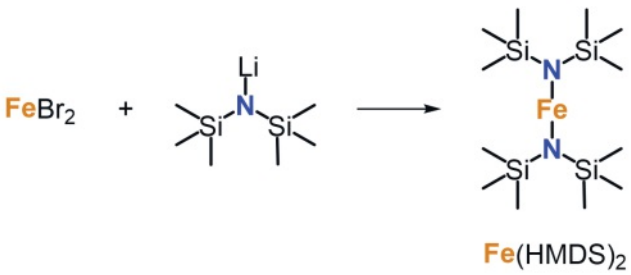
ido-4-methylpentyl)benzene at 120 °C (Scheme 1).[23] From the catalyst screening it appeared that $FeCl_2$, $FeBr_2$ and FeI_2 were catalytically active and yielded the pyrrolidine as the product. Noteworthy is that none of the iron salts required Boc_2O for catalytic activity. The highest yield was achieved with FeI_2 (83%), and a maximum TON of 370 was reached with 0.1 mol% catalyst loading. The accessibility of FeI_2 allows this method for pyrrolidine synthesis to be potentially implemented in organic synthesis and industrial applications. However, the C–H amination was limited to benzylic C–H bonds (Scheme 1). In-depth mechanistic studies to rationally improve the catalytic system were hindered by limited solubility of FeI_2, the ambiguous iron speciation in the presence of substrates and products, and the absence of any ancillary reporter group to probe catalytic intermediates or resting states.



Scheme 1. Selected substrate scope of the FeI_2 catalyzed intramolecular C–H amination using alkylazides (N.A. = not accessible).

3. Mechanistic Studies

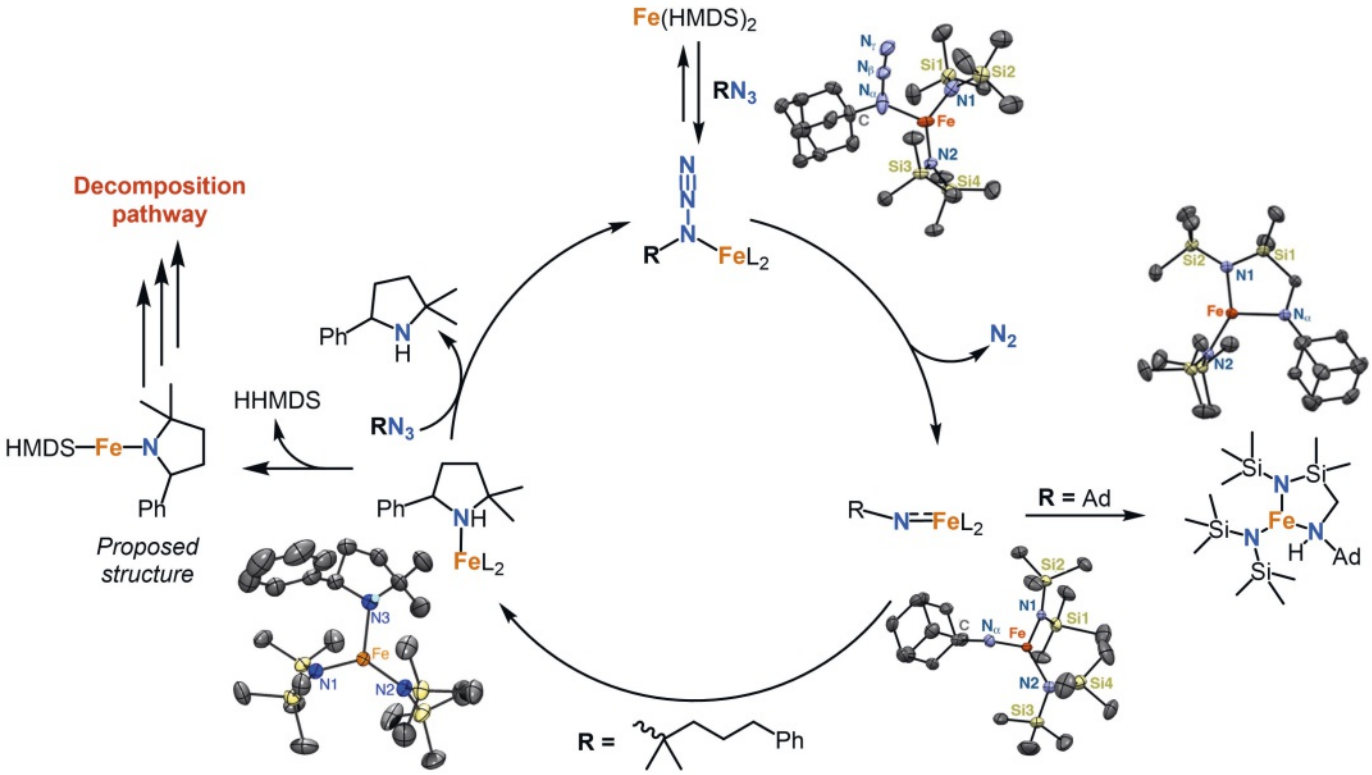
To address the limitations encountered with FeI_2 yet persevering the catalyst simplicity, $FeBr_2$ was reacted with two equivalents of commercially available LiHMDS (HMDS = hexamethyldisilazide), to obtain $Fe(HMDS)_2$ (Scheme 2).[24] This complex also



Scheme 2. Synthesis of the $Fe(HMDS)_2$ catalyst from $FeBr_2$ and LiHMDS (according to ref. 24).

produced pyrrolidine catalytically at 120 °C without Boc_2O when reacted with alkylazide substrates.[25] Despite the fast catalytic activity at early stages of the reaction, TONs were limited to 180 due to significantly decreased activity at later stages of the reaction.

The solubility of $Fe(HMDS)_2$ and its low activity at room temperature allowed for in-depth mechanistic studies. Monitoring of stoichiometric experiments with the catalyst and RN_3 by FTIR and ^1H NMR spectroscopy revealed a reversible binding of the azide on the iron center (Scheme 3). After 24 h the substrate fully reacted to afford coordinated pyrolidine on $Fe(HMDS)_2$ according to ^1H NMR spectroscopy and single crystal XRD analysis, without detection of any intermediate (Scheme 3). From previous reports it is proposed that the C–H amination occurs through a key nitrene intermediate formed by loss of N_2 by the organoazide complex. This intermediate either undergoes a stepwise hydrogen atom transfer (HAT) followed by a radical recombination, or a concerted C–H insertion to afford the C–N bond.[9,15,21,22] According to DFT calculations, the $Fe(HMDS)_2$ system goes through the postulated nitrene intermediate and forms the C–N bond by concerted C–H insertion. The energy barrier for this insertion step is calculated to be lower than for the formation of the nitrene (11.2 *vs* 22.6 kcal mol^{-1}), hence making the spectroscopic detection of the nitrene impossible.



Scheme 3. Proposed mechanism for the $Fe(HMDS)_2$ catalyzed intramolecular C–H amination using alkylazides.

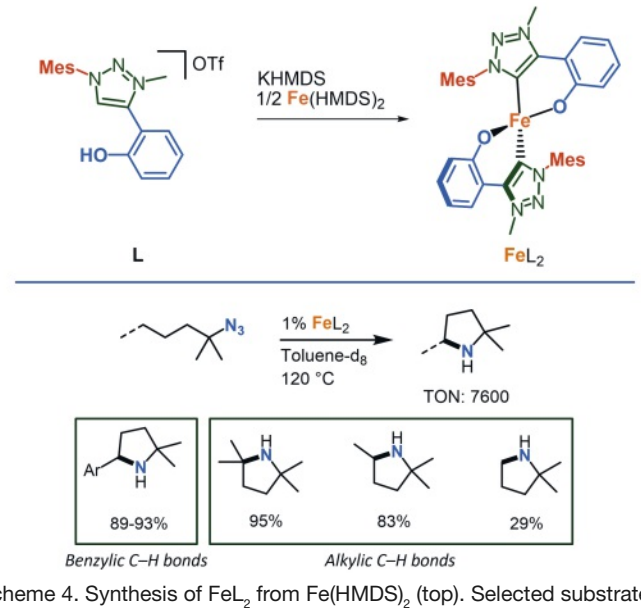
To prevent intramolecular C–H amination, AdN_3 was used as a substrate instead, which showed a comparable binding equilibrium and allowed for crystallization of the corresponding organoazide complex (Scheme 3),[26] similar results were obtained simultaneously by Werncke using $^tBuN_3$.[27] Upon irradiation of the AdN_3 complex crystal with UV light (λ = 365 nm) loss of N_2 was observed *in crystallo* allowing the key nitrene intermediate to be crystallographically characterized (Scheme 3). In solution the same nitrene was characterized by ^{57}Fe Mössbauer and ^{1}H NMR spectroscopy as a transient species. This highly reactive nitrene cannot undergo intermolecular C–H amination, and instead, it reacts in solution with the $N(SiMe_3)_2$ ligand *via* an inter-ligand C–H amination, forming a 5-membered metallacycle (Scheme 3). This product has been characterized by single crystal XRD analysis, ^{57}Fe Mössbauer and ^{1}H NMR spectroscopy.

The characterization of all these intermediates by various spectroscopic techniques provided strong support for the proposed mechanism of the $Fe(HMDS)_2$-catalyzed intramolecular C–H amination. Furthermore, monitoring of the catalytic reaction revealed that a decrease of catalytic activity was accompanied by the formation of $H–N(SiMe_3)_2$, observed by ^{1}H NMR spectroscopy. This indicates a catalyst decomposition pathway, where the HMDS ligand deprotonates the pyrolidine, followed by decoordination of $H–N(SiMe_3)_2$ (Scheme 3). This lability of the HMDS ligands is thus understood to be a weak point of the catalyst, prompting the incorporation of stronger coordinating ligands.

4. Increasing the Catalytic Activity

To this end, the HMDS ligands were substituted by C,O-bidentate ligands featuring a mesoionic carbene (MIC).[28] These MIC ligands have been used successfully to facilitate various catalytic transformations.[29–34] By reacting $Fe(HMDS)_2$ with KHMDS and two equivalents of L, a tetrahedral iron complex FeL_2 was obtained (Scheme 4). Due to the strongly coordinating ligands no signs of catalyst decomposition were observed, allowing the use of low catalyst loadings down to 0.01 mol%.

Under these conditions, complex FeL_2 achieved TONs up to 7600 after 1 week without the use of Boc_2O (Scheme 4). This TON is an order of magnitude higher than any other catalyst reported so far. Furthermore, contrary to FeI_2 the amination was not just limited to benzylic C–H bonds. Amination of tertiary and secondary alkylic C–H bonds also resulted in good yields (Scheme 4). Cyclization even occurred with primary C–H bonds, although in low yield.



Scheme 4. Synthesis of FeL_2 from $Fe(HMDS)_2$ (top). Selected substrate scope of the FeL_2 catalyzed intramolecular C–H amination using alkylazides (bottom).

5. Summary and Outlook

Iron-catalyzed intramolecular C–H amination using alkylazides offers an attractive methodology for the formation of pyrrolidines. While many catalysts are laborious to access, we have discovered that commercially available FeI_2 catalyzes the reaction with decent activities, reaching a TON of up to 370. The limited mechanistic understanding has been expanded substantially by using $Fe(HMDS)_2$ as catalyst, which demonstrated a slow azide activation and HAA (Hydrogen atom abstraction) at room temperature, allowing the isolation and crystallization of several key intermediates. These mechanistic studies are expected to facilitate the rational improvement of the catalyst. Finally, the rather limited activity and robustness of previous catalysts has been considerably improved by using a four-coordinate iron complex with robust mesoionic carbene ligands. This catalyst features unprecedented activities with up to 7600 TONs.

Further challenges remain, as the catalysts described herein are limited to tertiary azide substrates. High activity catalysts are highly desirable to also convert primary azides selectively without the need for stoichiometric amounts of Boc_2O. Such catalysts will significantly expand the applicability of the transformation. Also, current catalysts require high temperatures for good activities. Furthermore, to this date, only four catalytic systems are known to perform this transformation enantioselectively,[10,16,17,35] and only recently the first catalyst with iron has been reported using enzymes.[35] Since most natural products containing N-heterocycles only exist in one enantiomeric form, it is of paramount importance to develop more robust and selective catalysts to perform this C–H amination enantioselectively, especially with iron. The complex with the MIC ligands may serve as a good starting point, due to its easily tunable substituents. Introducing chiral groups may thus allow for induction of enantioselectivity.

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