Iron-Catalyzed Intramolecular C(sp^2)−H Amination

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In memory of Peter Hofmann

Abstract: *The nucleophilic iron complex Bu$_4$N[Fe(CO)$_3$-(NO)] (TBA[Fe]) catalyzes the direct intramolecular C−H amination of α-azidobiaryls and (azidoaryl)alkenes into the corresponding carbazoles and indoles, respectively, under mild conditions and with low catalyst loadings. These features and the broad functional-group tolerance render this method a particularly attractive alternative to established noble-metal-based procedures.*

Despite significant progress, direct C−H activation remains to be one of the most challenging transformations in the field of organometallic catalysis.[1] Apart from oxidative procedures, the activation of diazo compounds or azides represents an interesting alternative. Whereas the former processes commonly require significant amounts of a stoichiometric oxidant, N$_2$ is formed as the sole by-product in the latter. A variety of transition-metal-catalyzed processes for the activation of organic diazo compounds have been published;[2] however, the corresponding electrophilic azide activation as part of a C−H amination has mainly been limited to noble-metal catalysts.[3–5] Recently, the groups of Driver[4] and Betley[5] reported efficient and elegant processes based on (Rh^{II})$_2$ and Fe^I catalysts.
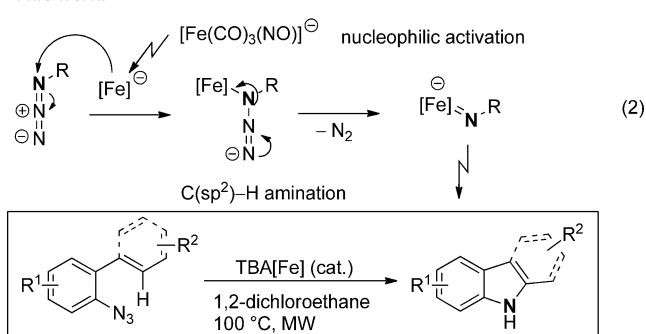
For a couple of years, our group has been interested in exploring the catalytic portfolio of the nucleophilic iron complex Bu$_4$N[Fe(CO)$_3$(NO)] (TBA[Fe]).[6] We were able to show that this electron-rich complex activates diazoesters for catalytic carbene transfer reactions [Eq. (1), Figure 1],[6k] a class of transformations that is commonly catalyzed by oxidized metal salts.[2] In this context, we initiated a research program aiming to develop C−H activations using nucleophilic Fe complexes. Considering the previously reported, but otherwise unprecedented, mode of diazoester activation, we wondered whether this mode of action could also enable the activation of azides. Herein, we present the successful realization of this concept of a metal-catalyzed nucleophilic azide activation and its application in catalytic intramolecular C(sp^2)−H amination to give a variety of substituted carbazoles and indoles [Eq. (2), Figure 1].

Following Driver's landmark reports on Rh-catalyzed carbazole[4c] and indole[4a,b] synthesis, we chose α-azidobiaryls as substrates in order to develop and, if successful, to

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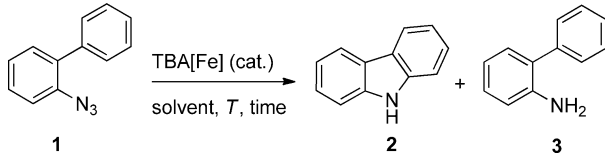
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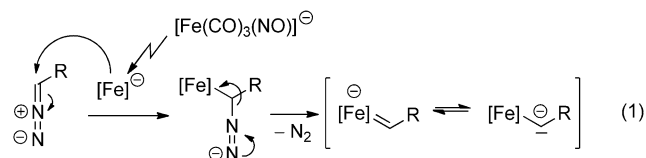
This work:

Figure 1. TBA[Fe]-catalyzed C(sp^2)−H amination.

benchmark our catalytic transformation. We used the conditions of the TBA[Fe]-catalyzed carbene transfer reaction[6k] as the starting point for the reaction of azide **1** (Table 1).

Initial results were rather poor: The reaction resulted in at least two different products, that is, the desired carbazole **2** and amine **3** (Table 1, entry 1). Further studies revealed that solvent and ligand significantly affected the product distribution. Whereas the addition of ligands led to a decrease in conversion, changing the solvent and adjusting the temperature shifted the product distribution towards the formation of the desired carbazole **2**. The best results were obtained with only 5 mol% of TBA[Fe] and 1,2-dichloroethane as the solvent at a temperature of 100°C for 68 h. Importantly, only little conversion was observed in the absence of the Fe complex under otherwise identical reaction conditions. At this point, we envisioned microwave irradiation to be a useful method to accelerate the reaction through more efficient energy transfer. Indeed, after only 1 h of microwave irradiation (200 W, 100°C) at a decreased catalyst loading of 2.5 mol% under otherwise identical conditions, **1** was fully converted, and carbazole **2** was isolated in 78% yield. Amine **3** and the diazo-coupling product that is formed by dimerization of the nitrene ligand were observed as minor side products. However, these products were only visible in the ^{1}H NMR spectrum of the crude reaction mixture. Impor-

Table 1: Optimization of the TBA[Fe]-catalyzed aryl C(sp²)−H amination.[a]

Entry	Cat. [mol%]	Solvent	t [h]	T [°C]	Conv. [%][b] (2/3)
1	10	CH₂Cl₂	16	80	5/5
2	10	CHCl₃	16	80	5/5
3	10	1,2-DCE	16	80	28/5
4	10	1,2-DCE	16	100	47/<5
5	5	1,2-DCE	16	100	52/<5
6	5	1,2-DCE	68	100	71/<5
7	5	1,2-DCE	1 (MW)	100	75/n.d.
8	2.5	1,2-DCE	1 (MW)	100	79/n.d.
9	1.25	1,2-DCE	1 (MW)	100	54/n.d.
10	0	1,2-DCE	1 (MW)	100	<5/n.d.

[a] All reactions were performed on a 0.35 mmol scale in anhydrous solvents (0.5 M). [b] Conversions determined by analytical HPLC using 1,3,5-trimethoxybenzene as the internal standard. 1,2-DCE = 1,2-dichloroethane.

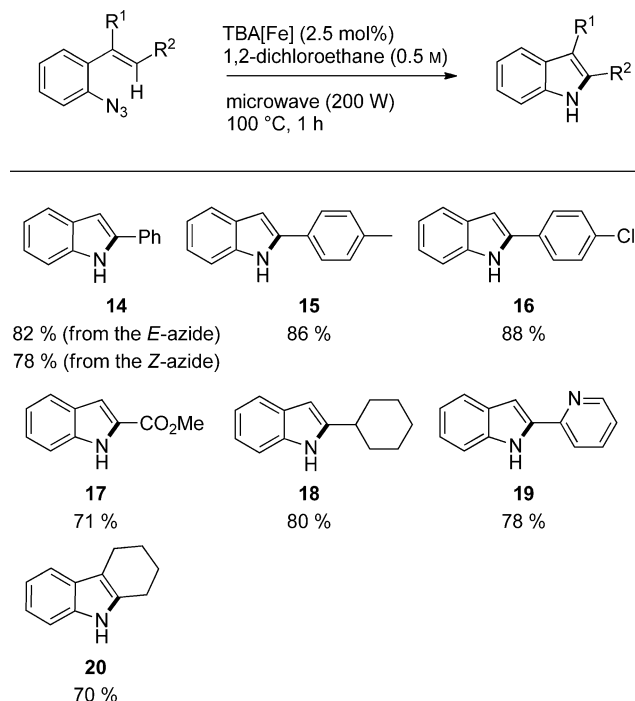tantly, only traces of product were obtained under these conditions in the absence of the Fe catalyst.

A subsequent evaluation of the scope and limitation of the TBA[Fe]-catalyzed nitrene insertion reaction proved the reaction to be broadly applicable (Scheme 1).

Various substituted carbazole derivatives were obtained in good to excellent yields. Alkoxy, alkyl, and nitro groups as well as halides were tolerated. Significant substitution effects were observed. In particular, the position of the substituent on the aryl moiety had a profound effect on the reactivity. Whereas the azide with a methoxy group *para* to the C−C bond gave the desired carbazole **5** in 70% yield, the isomeric *meta*-methoxy-substituted aryl azide was converted into carbazole **8** in 35% yield. The latter product was formed as a 7:1 mixture of regioisomers (*para/ortho*). These observations are in line with previous reports on similar rhodium-catalyzed processes.[4b,c]
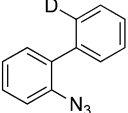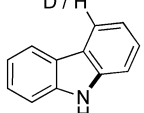
With these results in hand, we set out to expand the reaction scope towards an intramolecular activation of vinyl C(sp²)−H bonds, which would lead to substituted indole derivatives. We were pleased to find that this transformation can be performed under essentially identical reaction conditions (Scheme 2).

Various indole derivatives were obtained in a clean cyclization reaction. Both electron-rich and electron-poor (azidoaryl)alkenes were found to be reactive and transformed into the corresponding indoles in good to excellent yields. *E*- and *Z*-configured (azidoaryl)alkenes are equally reactive, and indole **14** was isolated in 82% or 78% yield starting from the corresponding *E*- or *Z*-configured (azidoaryl)alkene, respectively. Moreover, even trisubstituted olefins were reactive under these conditions.

The non-catalytic formal nitrene insertion into C−H bonds has been a matter of intense mechanistic investigations.[7] Most often, 2,6-(bisphenyl)arylazides were reacted,
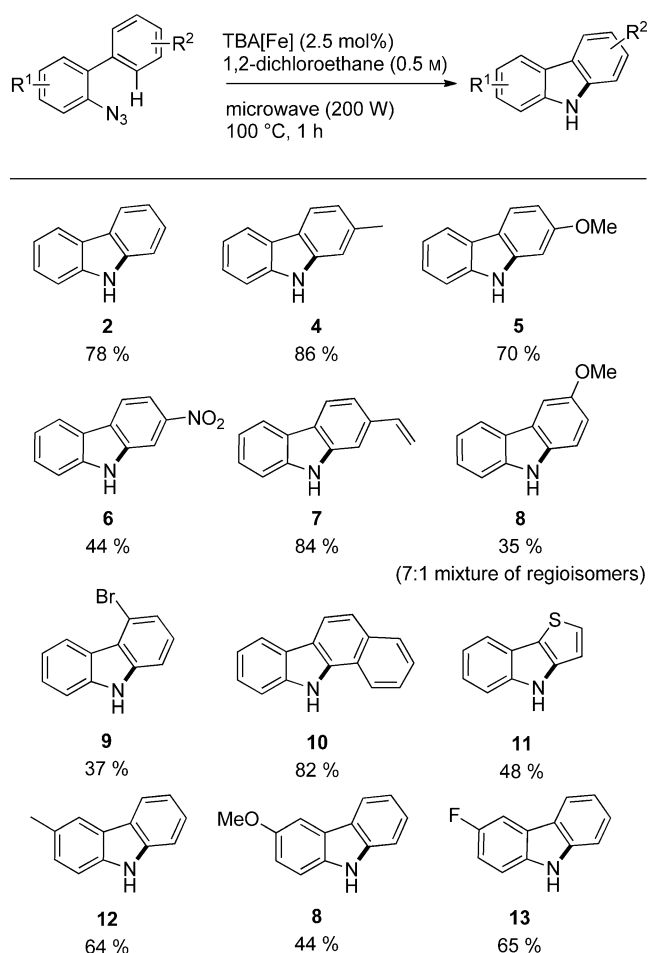
Scheme 1. TBA[Fe]-catalyzed intramolecular carbazole synthesis.

Scheme 2. TBA[Fe]-catalyzed intramolecular indole synthesis.

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and the regioselectivity of the C−N bond formation was analyzed. Moderate kinetic isotope effects of about 1.9:1 were reported.[7c] For the rhodium-catalyzed C−H amination, the same substrates were reacted, and a Hammett analysis was conducted to establish a profound mechanistic proposal.[4c] However, in our previous report on TBA[Fe]-catalyzed allylic amination,[6c] additional *ortho* substitution on the aniline derivative had been shown to inhibit the reaction, most likely for steric reasons. Therefore, we decided to analyze potential kinetic isotope effects by using monodeuterated aryl azide D-1 (Scheme 3).

conditions	isotope effect	yield	
TBA[Fe] (2.5 mol%) 1,2-dichloroethane (0.5 M) microwave (200 W) 100 °C, 1 h	$k_H/k_D = 1.63$	65 %	(1)
xylene (0.35 M) 150 °C, 16 h	$k_H/k_D = 1.63$	80 %	(2)
Rh$_2$(O$_2$CC$_3$F$_4$)$_4$ (5 mol%) toluene (0.5 M) 60 °C, 16 h	$k_H/k_D = 1.70$	62 %	(3)

Scheme 3. Kinetic isotope effects of the TBA[Fe]-catalyzed (1), non-catalyzed (2), and Rh-catalyzed (3) carbazole syntheses.

A moderate primary isotope effect of 1.63:1 was observed. Interestingly, the same effect was found for the non-catalytic thermal reaction, indicating the Fe-catalyzed process to have a similar rate-determining step, for example, the activation or migration of the H atom at the reactive aryl moiety. To compare these results with the Rh-catalyzed amination reaction developed by Driver and co-workers, we subjected D-1 to Driver's conditions and observed an isotope effect of 1.70:1. Based on the similarity of the results obtained for the non-catalyzed and Rh- and Fe-catalyzed amination reactions, we propose the following mechanism (Figure 2).

The [Fe(CO)$_3$(NO)] anion **I** reacts with aryl azide **II**, with release of N$_2$, to iron nitrene intermediate **III**, which—owing to the strong π-acceptor ligands on the metal center—generates a partial positive charge on the *ortho* (or homo-benzylic) carbon atom as visualized by the zwitterionic mesomeric structure **IV**. Metal-to-ligand charge transfer sets the stage for the C−N bond-forming process to give **V**, which is transformed into carbazole or indole **VI** through a 1,5-hydrogen shift.

In conclusion, we have described an operationally simple intramolecular C(sp^2)−H amination of aryl azides into functionalized carbazole or indole derivatives with Bu$_4$N[Fe-(CO)$_3$(NO)] as the catalyst. Broad functional-group tolerance and low catalyst loadings are characteristics of this catalytic procedure. The nucleophilic activation of the azide by the electron-rich Fe complex complements existing procedures,
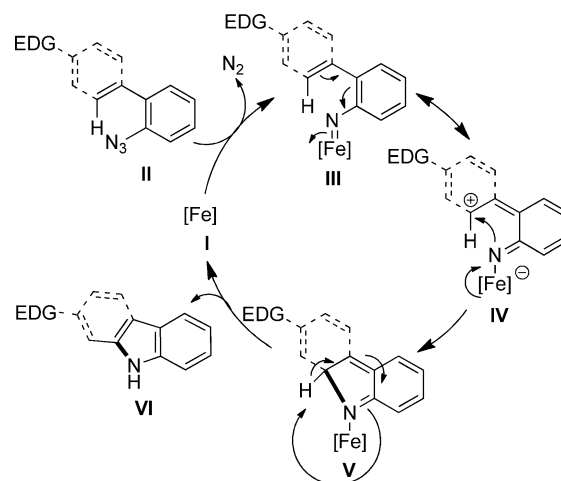

Figure 2. Mechanistic proposal.

which are mainly based on the use of oxidized transition-metal catalysts. Investigations towards the amination of C(sp^3)−H and C(sp^3)−N$_3$ bonds are currently underway in our laboratories.

Experimental Section

TBA[Fe] (0.009 mmol, 3.7 mg) and 1,2-dichloroethane (0.7 mL) were added to a 10 mL microwave tube with a magnetic stir bar under N$_2$ atmosphere. Subsequently, the azide (0.35 mmol) was added. The reaction mixture was stirred under microwave conditions (200 W) at 100 °C for 60 min. After cooling to ambient temperature and removal of the solvent, the product was purified by column chromatography on silica gel.

Acknowledgments

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