Iron-Catalyzed Intermolecular Amination of Benzylic C(sp³)–H Bonds

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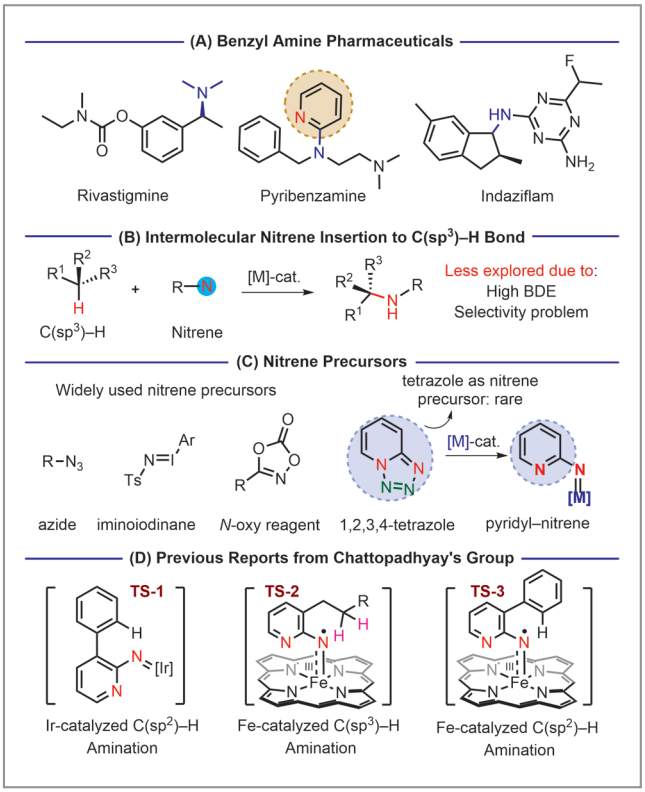
Benzyl amines are important motifs in organic chemistry owing to their extensive use in medicinal chemistry, drug discovery and materials science. Professor Buddhadeb Chattopadhyay at the Centre of Biomedical Research (CBMR), Lucknow (India) – whose research group has a strong interest in developing synthetic methods for accessing complex and functionalized benzyl amine frameworks – said: "Many top-selling marketed drugs such as Rivastigmine, Cinacalcet, Tripelennamine, and many more, contain benzyl amine functionalities (Scheme 1, A).[1] While various enzymatic and chemical synthetic methodologies are available for installing an amine functionality, development of a new catalytic process for direct installation of the amine group at a selected C–H bond of an organic molecule remains a vibrant area of research in medicinal and bio-organic chemistry." He added: "Importantly, while the process of C(sp²)–H bond amination is an established method that has been explored vastly, the amination of aliphatic C(sp³)–H bonds is much more challenging[2] because of the high bond dissociation energy of the C(sp³)–H bond, the absence of "active" HOMO or LUMO to interact with the transition metals, as well as problems towards controlling the selectivity (Scheme 1, B). In this context, whereas noble-metal catalysts have received remarkable attention for nitrene transfer reactions, base-metal complexes are relatively less explored for this purpose though they possibly have more efficiency than the noble-metal catalyst."[3]

Professor Chattopadhyay remarked that over the past few years, several efficient C–H amination processes have been developed by employing various nitrene sources, for example, azides,[4] *N*-oxy reagents,[5] and iminoiodinanes (Scheme 1, C).[6] However, the use of 1,2,3,4-tetrazole as nitrene source remained unexplored, although it could be potentially beneficial owing to its additional 2-pyridyl handle for finding new properties related to drug discovery and medicinal chemistry. "In early 1969, Huisgen and Fraunberg studied the reactivity of 1,2,3,4-tetrazole and found that it might be used as a nitrene source for the denitrogenative annulation with nitrile and aryl hydrocarbon amination.[7,8] Moving forward, in 1976 the Wentrup group reported denitrogenative thermal and photochemical nitrene–nitrene rearrangement reactions at very high temperature (>500 °C) under flash vacuum pyrolysis (FVP),"[9] said Professor Chattopadhyay, whose group was inspired by this pioneering work. They had the idea that if they could capture the productive pyridyl metal–nitrene intermediate, it would open numerous opportunities for the discovery of smart technologies that would be extremely welcome in the fields of medicinal chemistry, biochemistry, pharmaceutical chemistry and related areas. Notably, in recent years, Professor Chattopadhyay's group demonstrated that tetrazole can be employed as an effective nitrene precursor[10] for the intramolecular C(sp²)–H amination via iridium-catalyzed electrocyclization,[11] iron-catalyzed C(sp³)–H amination and C(sp²)–H amination via a radical mechanism (Scheme 1, D).[12,13] Professor Chattopadhyay remarked: "After that, we were keen to develop a method for intermolecular amination reaction using tetrazole as nitrene precursor to access 2-pyridyl-substituted benzylamine. In order to establish suitable reaction



Scheme 1 Previous work, challenges and new opportunities

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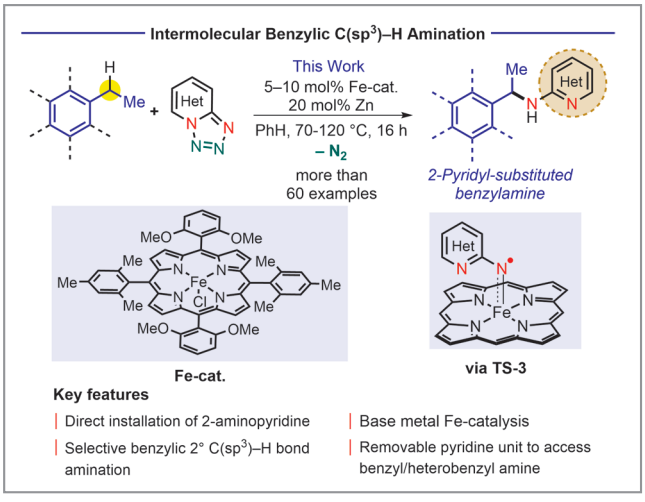
conditions for the C(sp³)–H amination, we commenced initial studies with simple feedstock ethyl benzene and 5-amide tetrazole, using previously developed conditions. Unfortunately, our previous catalyst systems[11,14] failed for the intermolecular C(sp³)–H amination, which may be explained by the challenges associated with the difficulty of the intermolecular C(sp³)–H bond amination."

After screening various catalytic systems, the group found that an iron porphyrin catalytic system containing both electron-donating mesityl and 2,6-dimethoxyphenyl units furnished the expected benzylic amination product in high yield (Scheme 2). Professor Chattopadhyay said: "There are many new findings stemming from this work, such as: i) Intermolecular amination at the more challenging secondary C–H bonds of gaseous hydrocarbons is reported in the literature by utilizing base-metal catalyst systems, such as cobalt or nickel, while intermolecular benzylic C(sp³)–H amination utilizing 1,2,3,4-tetrazole as a nitrene precursor via iron catalysis is still underdeveloped; in addition, this work differs from many other amination reactions where the nitrogen atom is usually substituted by a protecting group that needs to be removed to allow further elaboration of the products; ii) this method allows for selective amination of the secondary benzylic C(sp³)–H bond over the weaker tertiary, and sterically accessible primary benzylic C(sp³)–H bonds; iii) direct installation of 2-aminopyridine into the benzylic and heterobenzylic positions is highly important as this structural motif is found in many bioactive compounds; iv) The reaction conditions are simple and require just 5–10 mol% of the earth-abundant iron catalyst; and v) the scope of the reaction is broad with regards to benzylic substrates and tetrazole precursors."



Scheme 2 Concept of intermolecular C(sp³)–H amination

Various C(sp³)–H bonds were assessed for their reactivity (Scheme 3, A). The authors observed that several electronically distinct benzylic C(sp³)–H bonds underwent intermolecular amination, yielding the aminated products in high yields. Then, the group became interested in submitting pharmaceutically and medicinally important molecules to the C(sp³)–H amination. "We found that a substrate derived from naproxen (a nonsteroidal anti-inflammatory drug) and estrone (an important metabolite), featuring C–H bonds with different bond dissociation energies, afforded the aminated products with high selectivity and yield," remarked Professor Chattopadhyay. He continued: "Later, the group assessed the scope of various substituted and heterocyclic tetrazoles under the developed amination reaction conditions (Scheme 3, A) and found that the method exhibited excellent effectiveness, delivering the corresponding aminated products in good yields. We also performed several reactions to highlight the synthetic utility of the new intermolecular amination method: i) we synthesized primary amines (Scheme 3, B) from their standard pyridyl amine product; ii) we also synthesized a potential drug molecule Dapoxetine (which inhibits serotonin transport) in good yield from a simple starting material (Scheme 3, C); iii) we performed a large-scale synthesis (3.5 mmol, 62% yield; Scheme 3, D); and iv) we converted the diethyl amide group of the desired product into an important benzyl amine unit in good yield (Scheme 3, E)."

Lastly, to understand the C(sp³)–H amination reaction, Professor Chattopadhyay and his co-workers proposed a radical mechanism, which is supported by the following mechanistic studies: i) kinetic isotope effect (KIE) experiment (intermolecularly and intramolecularly); ii) radical trapping experiment using TEMPO; and iii) Hammett plot. Based on this body of experimental evidence, the authors proposed the radical mechanism illustrated in Scheme 4. From the KIE value of this amination reaction, Professor Chattopadhyay inferred that C–H bond cleavage might be the rate-limiting step for the intermolecular C(sp³)–H benzylic amination.

Professor Chattopadhyay summarized his group's work: "We have developed a catalytic system for the intermolecular benzylic C(sp³)–H amination reaction utilizing 1,2,3,4-tetrazole as nitrene precursors via Fe(II)-based catalysis. This work empowers direct installation of a 2-aminopyridine unit into benzylic and heterobenzylic positions. Moreover, in the literature, we observed that 2-aminopyridine is native to many heterocyclic compounds, but there is a lack of proper focus on it. Furthermore, the 2-aminopyridine alone also exhibits pharmacological activity: crizotinib and lorlatinib are examples of drugs developed by Pfizer to treat non-small cell lung cancer. Cyclometalated complexes with aminopyridines

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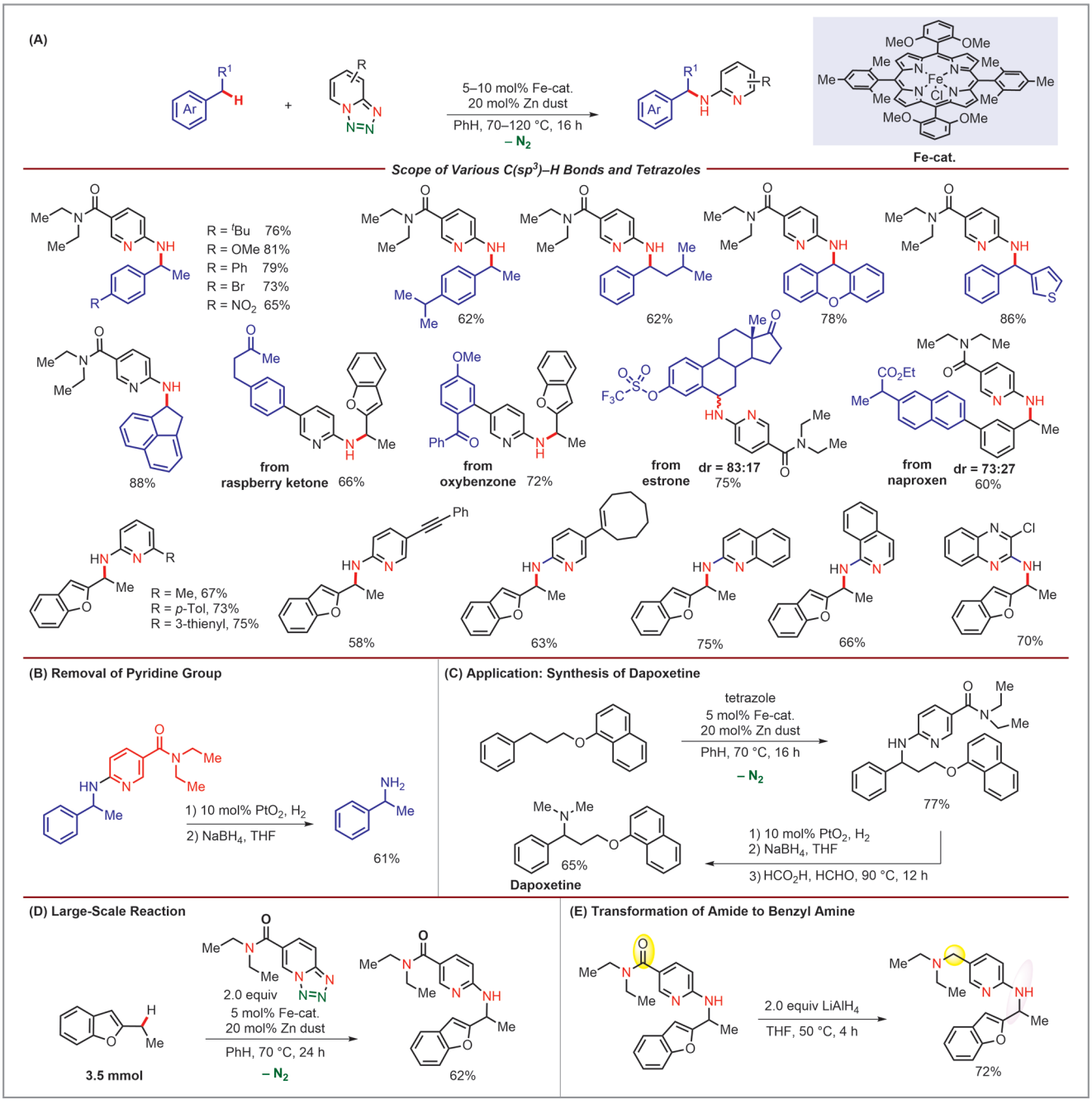

Scheme 3 Intermolecular C(sp³)–H amination and its applications

as ligands also exhibit anticancer activity. These types of moieties highlight the importance of 2-aminopyridine as a bioactive and pharmacological agent."

Professor Chattopadhyay added: "Mechanistic studies revealed that the C(sp³)–H amination proceeds via the formation of a benzylic radical intermediate. This study reports the discovery of a new method for 2-pyridine-substituted benzylamine synthesis using inexpensive, biocompatible base-metal catalysis that should have wide application in the context of medicinal chemistry and drug discovery. In addition, while the denitrogenative transformation of 1,2,3,4-tetrazoles was previously assumed to be not viable, our findings have en-

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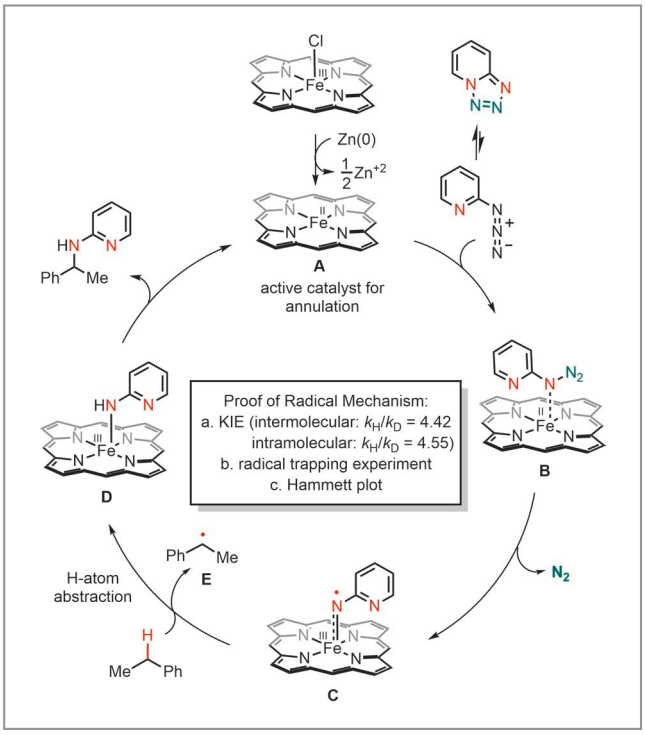

Scheme 4 Radical mechanism for intermolecular C(sp^3)–H amination

abled a new area for catalysis research with important implications in organic chemistry." He concluded: "Our future goal will be achieving asymmetric catalysis by developing new chiral catalysts for C–H amination reactions."

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