

Insertion of Ammonia into Alkenes To Build Aromatic N-Heterocycles

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Ammonia is one of the most-produced industrial chemicals, with a value of 144 million metric tons in 2020 (Figure 1). In addition to its use in fertilizers (~90% of the worldwide production), ammonia can also be utilized as a nitrogen source to build nitrogen-containing compounds.¹ “There is a series of advantages when using ammonia as a nitrogen source. It has an 82% mass-rate nitrogen incorporation and is reactive enough as a nucleophile. It is easy to store, transport, handle, and separate. On the other hand, there are several challenges in pursuing applications of ammonia in organic synthesis,” said Dr. Shuai Liu, from Nanjing University (P. R. of China), continuing: “First, the N–H bond in ammonia has a bond-dissociation energy of 107 kJ/mol, leading to a high barrier for direct cleavage by the catalyst. Second, ammonia is a strong ligand for diverse metal species, requiring demanding conditions for catalytic processes. Third, the resulting amine product could be more reactive than ammonia itself, posing additional difficulty in the control of chemoselectivity.” With this background, Dr. Shuai Liu and Professor Xu Cheng (also from Nanjing University, P. R. of China) recently reported their study on the direct insertion of ammonia into alkenes to build aromatic N-heterocycles with electricity as the driving force.

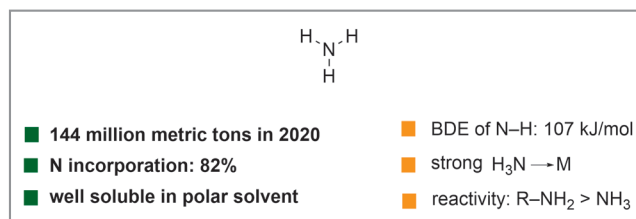
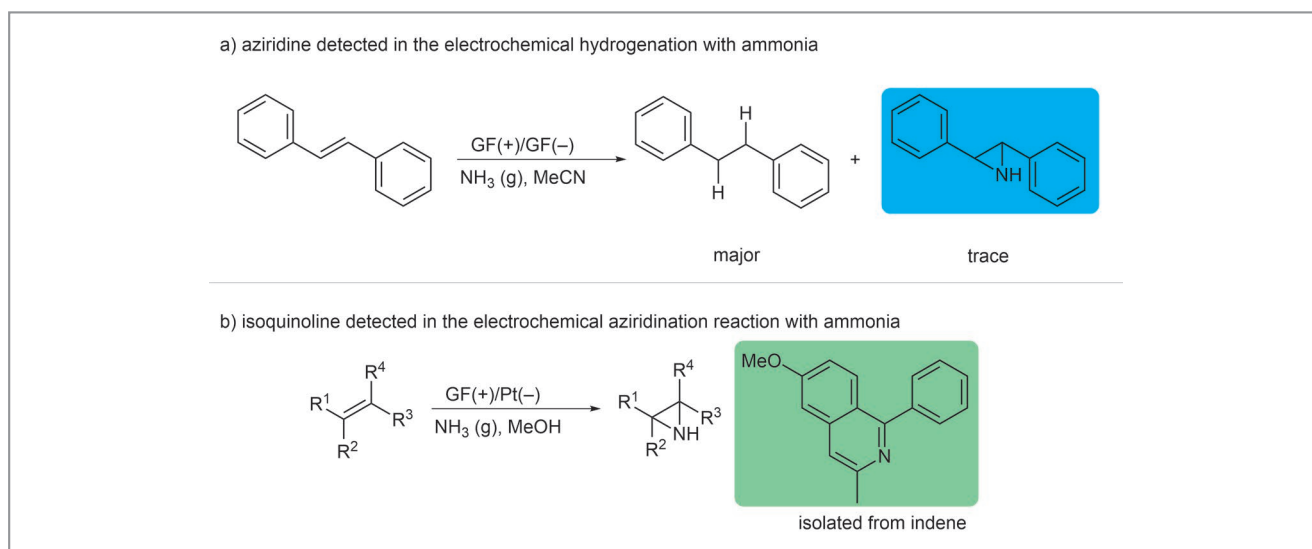


Figure 1 The factors of ammonia

This work is rooted in a previous research campaign where ammonia was employed as a hydrogen source: in 2019, Dr. Li and Professor Cheng reported the electrochemical hydrogenation of unsaturated functional groups with ammonia (Scheme 1a).² In that work, when stilbene was subjected to hydrogenation, a very small amount of aziridine product was detected. This finding led to a work on the aziridination of tetra-, tri-, and disubstituted alkenes using ammonia as a nitrogen source by Dr. Liu, Professor Cheng, and Professor Yong Liang (Scheme 1b).³ “It should be noted that during the preparation of that manuscript, Professor Timothy Noël and co-workers published their research on electrochemical



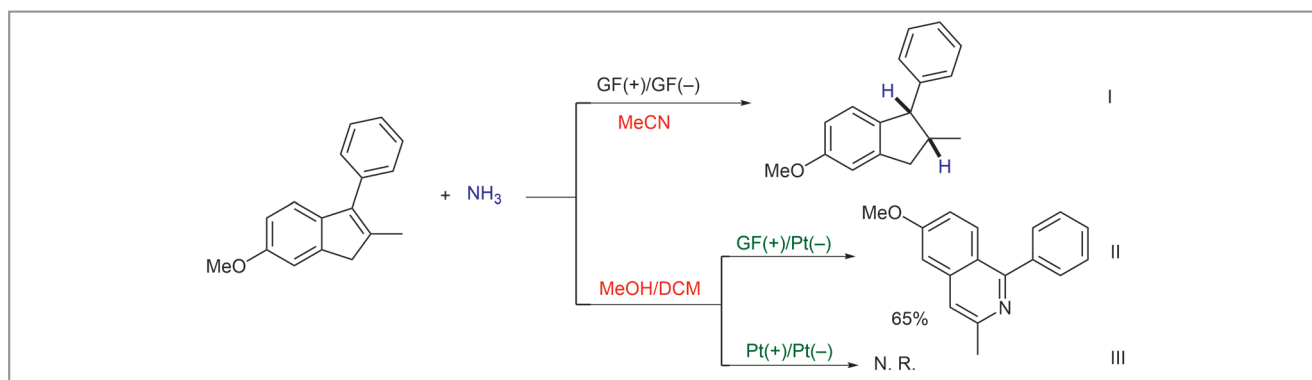
Scheme 1 The initial findings leading to the synthesis of isoquinoline with ammonia

aziridination using primary amines and ammonia,⁴ acknowledged Professor Cheng. “In our work, an unexpected product was found with a substrate having an indene substituent. After extensive characterization of this new compound, we confirmed that an isoquinoline was generated,” he added.

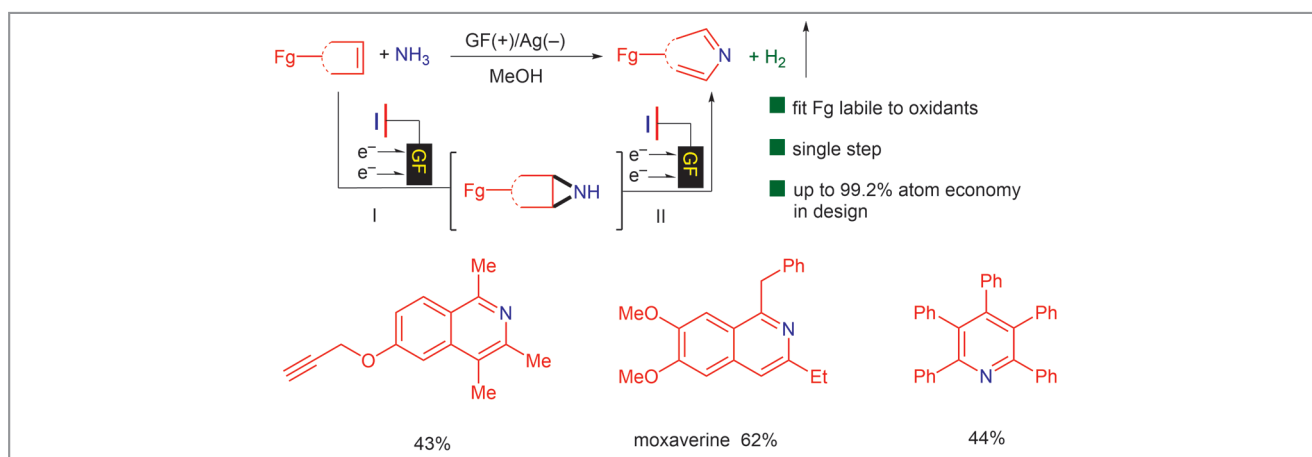
This result inspired the authors to study the potential of ammonia in the electrochemical reaction to build aromatic N-heterocycles. “We reasoned that this would be the most economical and convenient way to make aromatic N-heterocycles, since hydrogen would be the only by-product,” Prof. Cheng said, continuing: “Reported protocols for the preparation of aromatic N-heterocycles adopt the condensation of a nitrogen source with a pre-oxidized substrate.” Dr. Liu carried out an extensive screening of conditions and found that a graphite felt (GF) anode and MeOH are essential for this conversion. “When other solvents were applied, we always observed that the hydrogenation of the substrate was the predominant reaction (Scheme 2, I),” said Dr. Liu. He continued: “Instead, MeOH

was able to inhibit the hydrogenation pathway (Scheme 2, II). If a Pt anode was used rather than graphite felt, the decomposition of MeOH readily took place (Scheme 2, III). This was the common reaction in fuel cell.”

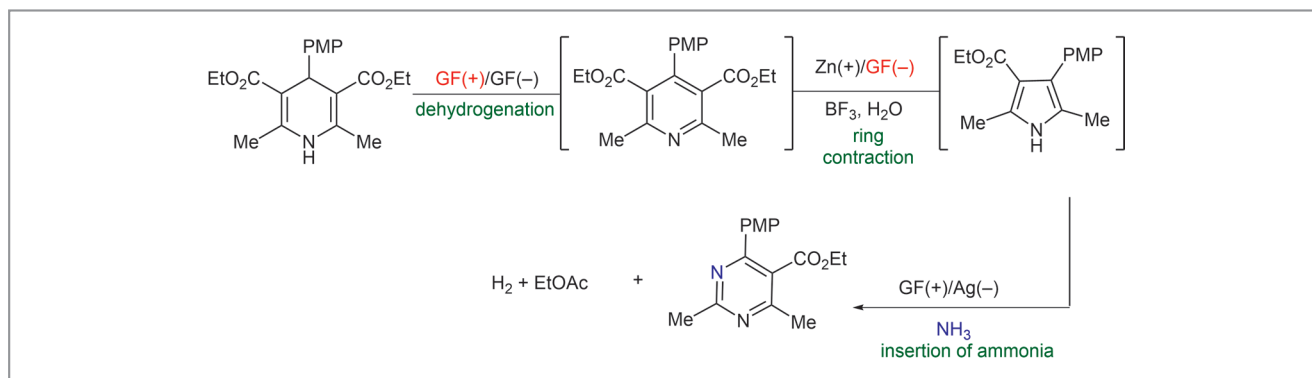
Subsequently, Dr. Liu started to explore the substrate scope of this transformation. A series of substituted indenenes were prepared and subjected to the electrochemical insertion of ammonia, affording the corresponding isoquinolines and pyridines (Scheme 3). “The reaction works well with indene-bearing substituents – like phenyl and alkyl – at specific position,” said Dr. Liu, “especially for the substituents able to stabilize the positive charge.” Dr. Liu further explained: “The activation of alkene at the anode would be one key stage of the overall transformation, which would give the cationic radical.” Therefore, careful analysis of the reaction mixture showed that an aziridine was the intermediate. Dr. Liu remarked: “This aziridine is quite unstable, as it would decompose even in the –20 °C freezer upon standing for a couple of



Scheme 2 Key factors regulating the chemoselectivity



Scheme 3 Reaction pathway and typical products



Scheme 4 Electrochemical approach to “edit” N-heterocycles

days, but without producing an isoquinoline.” Professor Cheng and Dr. Liu drafted a plausible reaction pathway in which the cyclic alkene is activated by anode oxidation and converts into an aziridine intermediate by trapping with ammonia (Scheme 3, I). “The next round of oxidation at the anode is the other key step of the process, driving the rearrangement of aziridine to isoquinoline (Scheme 3, II); cathode of Pt, Ag, and graphite felt could evolve hydrogen to balance the charge,” said Dr. Liu.

Next, an idea evolved into a plan (Scheme 4). “We reckoned we could now edit the heterocycles by using electricity, utilizing the Hantzsch ester as a starting material,” explained Professor Cheng and Dr. Liu. With this plan, Dr. Liu prepared the substituted Hantzsch ester and started exploring the electrochemical tandem reaction. “At first, the Hantzsch ester was converted into pyridine via a two-electron oxidation, then switching the electrode resulted in a rearrangement of pyridine to pyrrole,⁵ and finally insertion of ammonia into the pyrrole gave a pyrimidine with an unexplored substitution pattern,” said Dr. Liu, adding: “There is no need to isolate the intermediate.”

Professor Cheng concluded, “This article showed the potential of an electrochemical protocol capable of facilitating the introduction of ammonia into molecules, while giving an important clue on future reaction design.”

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About the authors

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Chemical Engineering at Xuzhou University of Technology (P. R. of China) as a lecturer. His studies focus on electrochemical heterocyclic synthesis.

Shuai Liu was born in 1993 in Jiangsu Province (P. R. of China). He received his Bachelor's degree from Jiangsu Normal University (P. R. of China) in 2015, and his Master's degree from the same university in 2018 under the supervision of Prof. Shu-Jiang Tu and Prof. Bo Jiang. He obtained his doctoral degree from Nanjing University (P. R. of China) in 2021 under the supervision of Prof. Xu Cheng. Currently, he is at the School of Materials and

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Xu Cheng was born in Tianjin (P. R. of China) and received his B.S. degree from Nankai University (P. R. of China) in 2000. In 2005, he received his Ph.D. from Nankai University in the group of Prof. Qin-Lin Zhou. Then he moved to the Max-Planck-Institut für Kohlenforschung, Mülheim an der Ruhr (Germany) and joined Prof. Benjamin List's group as a postdoc studying enantioselective organocatalysis. In 2009, he moved to the University of Texas at