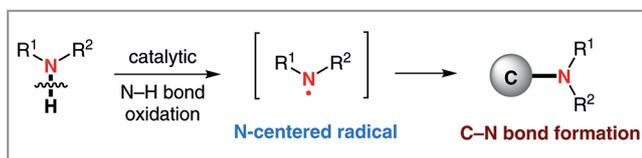


Catalytic N-Radical Cascade Reaction of Hydrazones by Oxidative Deprotonation Electron Transfer and TEMPO Mediation

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N-Centered radical reactions have been established as one of the most powerful and versatile methods for C–N bond formation towards the assembly of valuable and diversely functionalized N-containing compounds. Typically, the generation of reactive N-radical intermediates has relied mainly on reductive scission of the relatively weak N–O, N–N or N–X (X = Br, I) bonds by high-energy UV irradiation or radical initiators.¹ In contrast, the direct catalytic conversion of ubiquitous N–H bonds to N-centered radicals is an economic and attractive, but challenging, strategy for synthetic chemists (Scheme 1).²

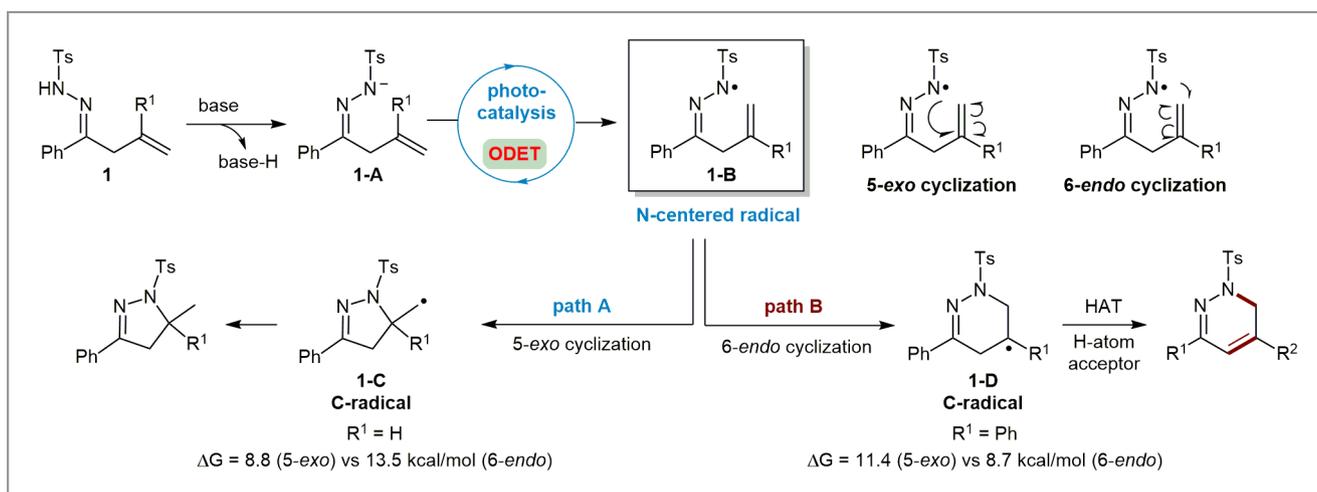


Scheme 1 The direct oxidative generation of N-centered radicals from N–H bonds

Recently, Professor Jia-Rong Chen's group at the Central China Normal University (Wuhan, P. R. of China) has been interested in visible-light photoredox-controlled reactions of N-radicals. Employing this strategy, they developed a no-

vel visible-light photocatalytic N-radical cascade reaction of β,γ -unsaturated hydrazones by combining oxidative deprotonation electron transfer (ODET) and hydrogen-atom transfer (HAT), which provided efficient access to various structurally diverse 1,6-dihydropyridazines (Scheme 2, Path B). "One of the most important outcomes of our current 6-*endo* radical cyclization is the mild generation of N-centered radicals directly from the recalcitrant N–H bonds via ODET under visible-light irradiation," said Professor Chen. The addition of a common base is essential to this process, which enables a facile SET oxidation of the resultant nitrogen anion intermediate **1-A** to form N-radical intermediate **1-B**. 2,2,6,6-Tetramethylpiperidine-*N*-oxyl (TEMPO) served as an H-atom acceptor to facilitate the subsequent formation of C–C double bonds by a HAT process.

In 2014, Professor Chen's group achieved a mild hydroamination of β,γ -unsaturated hydrazones for the first time via a visible-light-induced 5-*exo* cyclization of N-radical intermediate **1-B** (Scheme 2, Path A).³ "The remarkable feature of the current reaction is the exclusive 6-*endo* regioselectivity of the N-radical cyclization achieved by rational design of catalytic system and substrates," said Professor Chen. "Actually, the substitution patterns of the alkene moiety of hydrazones proved to be critical to the reaction's regioselectivity." Pro-



Scheme 2 Visible-light photocatalytic N-radical cascade reaction of unsaturated hydrazones

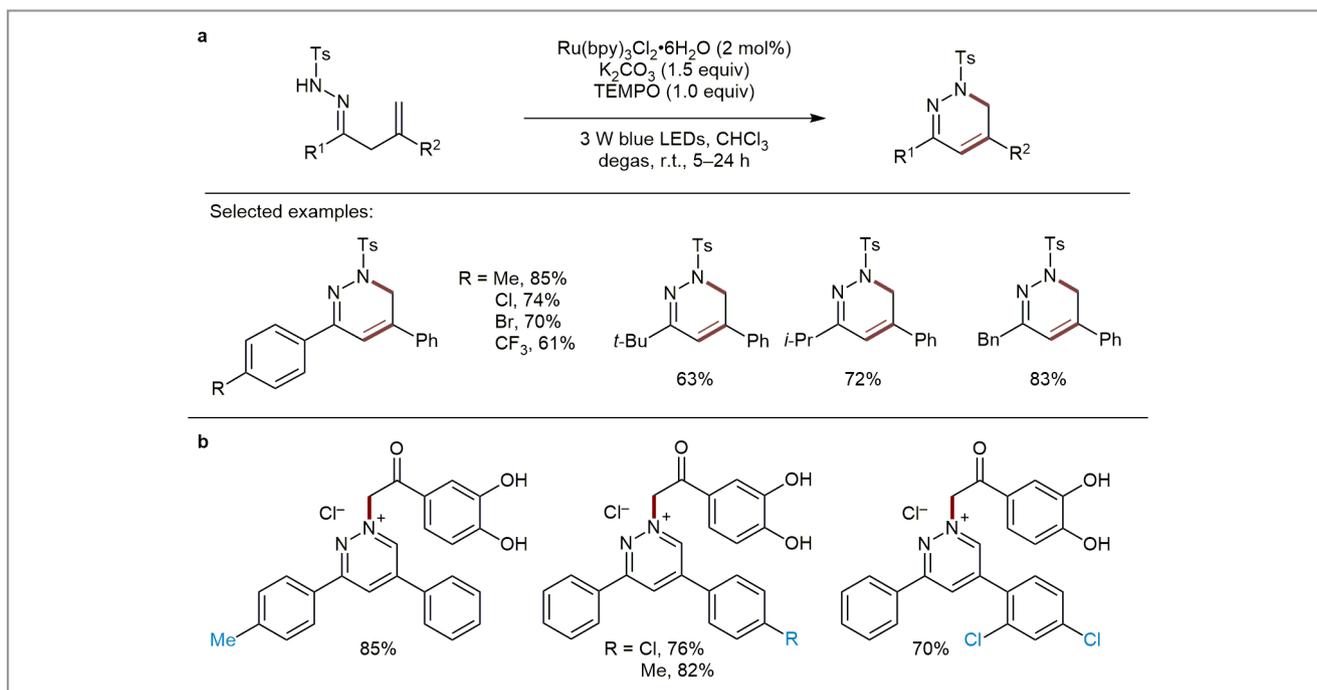
fessor Chen continued: “The 5-*exo* and 6-*endo* selectivity of N-radical cyclization is dependent on the activation free energy and the stability of the newly formed C-centered radical intermediates. For example, the 5-*exo* cyclization is much more favored than the 6-*endo* process when R¹ is an H-atom as shown by their activation free energy (8.8 vs 13.5 kcal/mol) (Scheme 2, Path A). In contrast, the 6-*endo* cyclization of the N-radical is more feasible than the 5-*exo* process when R¹ is a phenyl group, due to the stability of the newly generated benzyl radical **1-D**, which is consistent with the results of DFT calculations (11.4 vs 8.7 kcal/mol) (Scheme 2, Path B).”

“The reaction exhibits a remarkably wide substrate scope, and various aromatic and aliphatic unsaturated hydrazones can be well tolerated, affording the corresponding biologically important 1,6-dihydropyridazines in generally good yields (Scheme 3a),” said Professor Chen. He continued: “Moreover, 1,6-dihydropyridazines can be further applied to the synthesis of diazinium salts through two simple operations, and preliminary biological evaluation showed that these compounds display promising activities against four common clinical pathogenic fungi such as *Candida albicans*, *C. neoformans*, *C. glabrata* and *C. parapsilosis* (Scheme 3b).” To gain insight into the role of TEMPO and the reaction mechanisms, a series of control experiments, luminescence quenching experiments, ¹H NMR and electrochemical analysis were per-

formed. Based on these results, a visible-light-induced ODET process was established for the conversion of N–H bonds into N-radicals (**1** to **1-B**).

Professor Chen concluded: “We have developed an efficient photocatalytic N-radical cascade reaction of β,γ-unsaturated hydrazones via a visible-light-induced ODET/HAT strategy, enabling the efficient synthesis of various valuable 1,6-dihydropyridazines with good regioselectivities and yields.” He continued: “This straightforward and mild technique has great potential in the catalytic direct generation of other types of reactive N-radicals from N–H bonds, rendering it ideal for applications in the field of N-radical-based nitrogen installation.” Exploiting this strategy, the Chen group has also reported a general and selective oxidative radical oxyamination and dioxygenation of β,γ-unsaturated hydrazones and oximes.⁴

Matthew Fenske



Scheme 3 Selected substrate scope and synthetic application

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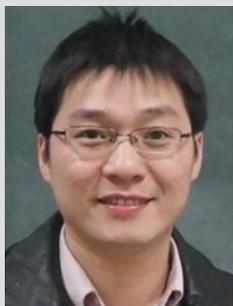
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