

Preview

N-Containing Heterocycles on Demand by Merging Ni Catalysis and Photoredox PCET

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Nitrogen-containing heterocycles are among the most ubiquitous motifs in pharmaceuticals. Therefore, the design of mild, practical, and modular protocols for their synthesis is still in high demand. In this issue of *Chem*, Molander and co-workers report the merger of visible-light photoredox proton-coupled electron transfer (PCET) with nickel catalysis as a vehicle for rapidly accessing privileged five-membered heterocyclic cores from simple precursors.

The presence of nitrogen-containing heterocycles in more than half of the small-molecule drugs approved by the USFDA is so pervasive that the inclusion of these structures is often visualized as a necessary requisite in industrial endeavors.¹ Among these, particularly prevalent are five-membered nitrogen-containing heterocycles, such as pyrrolidones, oxazolidinones, or imidazolidinones, among many others.² Although significant progress has been made for preparing these rather appealing structures by a myriad of synthetic methods, it is a worthwhile endeavor to contemplate possible alternative ways to synthesize them with improved flexibility, generality, and practicality.

Driven by the favorable attributes of visible-light-mediated photoredox catalysis—an emerging new synthetic tool that enables challenging bond-forming reactions that are oftentimes not accessible under standard approaches³—chemists have been challenged to forge C(sp³)-N bonds via light-induced processes. Among various conceivable scenarios, the ability to harness the inherent reactivity of amidyl radicals might open a gateway to nitrogen-containing heterocycles. Any synthetic approach aimed at accessing well-defined amidyl radicals from

ubiquitous N-H bonds under mild conditions, however, might face notorious chemical constraints: (1) the N-H bond-dissociation free energy is exceptionally high (~100 kcal/mol), so homolytic cleavage is thermodynamically uphill; and (2) conventional methods for generating amidyl radicals via N-H scission typically require strong stoichiometric oxidants (DMP, IBX, or peroxides), whereas harsh conditions such as UV light irradiation and/or reducing agents are needed when pre-functionalized N-X motifs (X = Cl, SPh, OAr or SO₂Ar) are employed. This limits the synthetic utility of these protocols, particularly when these technologies are applied within the context of late-stage functionalization of advanced synthetic intermediates. Therefore, one could conclude that a milder method capable of accessing amidyl radicals in a practical and reliable manner might provide a new fertile ground for applications on industrial venues while offering new reactivity principles for the total synthesis of structurally complex natural products.

In 2015, Knowles and co-workers demonstrated that amidyl radicals could be generated under exceptionally mild conditions from unfunctionalized amides via concerted proton-coupled electron transfer (PCET) in

combination with photoredox catalysis,⁴ thus opening new chemical space for the synthesis of amides and related compounds via C-N bond-forming reactions.⁵ Although recent disclosures have shown that photochemically driven hydrogen-atom-transfer pathways can successfully be interfaced with nickel-catalyzed cross-coupling reactions,⁶⁻⁹ the ability to synergistically combine the modularity of PCET with the flexibility in synthetic design offered by transition-metal catalysts has still remained an unexplored cartography. In this issue of *Chem*, Molander and co-workers report the successful realization of this goal by taming the reactivity of amidyl radical intermediates as a gateway to enabling the visible-light-mediated photochemical difunctionalization of unactivated olefins en route to a variety of medically relevant five-membered nitrogen-containing heterocycles via sequential C(sp³)-N and C(sp²)-C(sp³) bond formations (Figure 1).¹⁰

Preliminary mechanistic experiments suggest the initial PCET-mediated formation of an amidyl radical that subsequently triggers a rapid 5-exo-trig cyclization with a pending olefin, leading to a transient alkyl radical intermediate. Although there exists a reasonable ambiguity on whether the alkyl radical is intercepted by either L_nNi(0) or aryl-Ni(II)L_n oxidative addition species, a final reductive elimination would ultimately deliver the targeted

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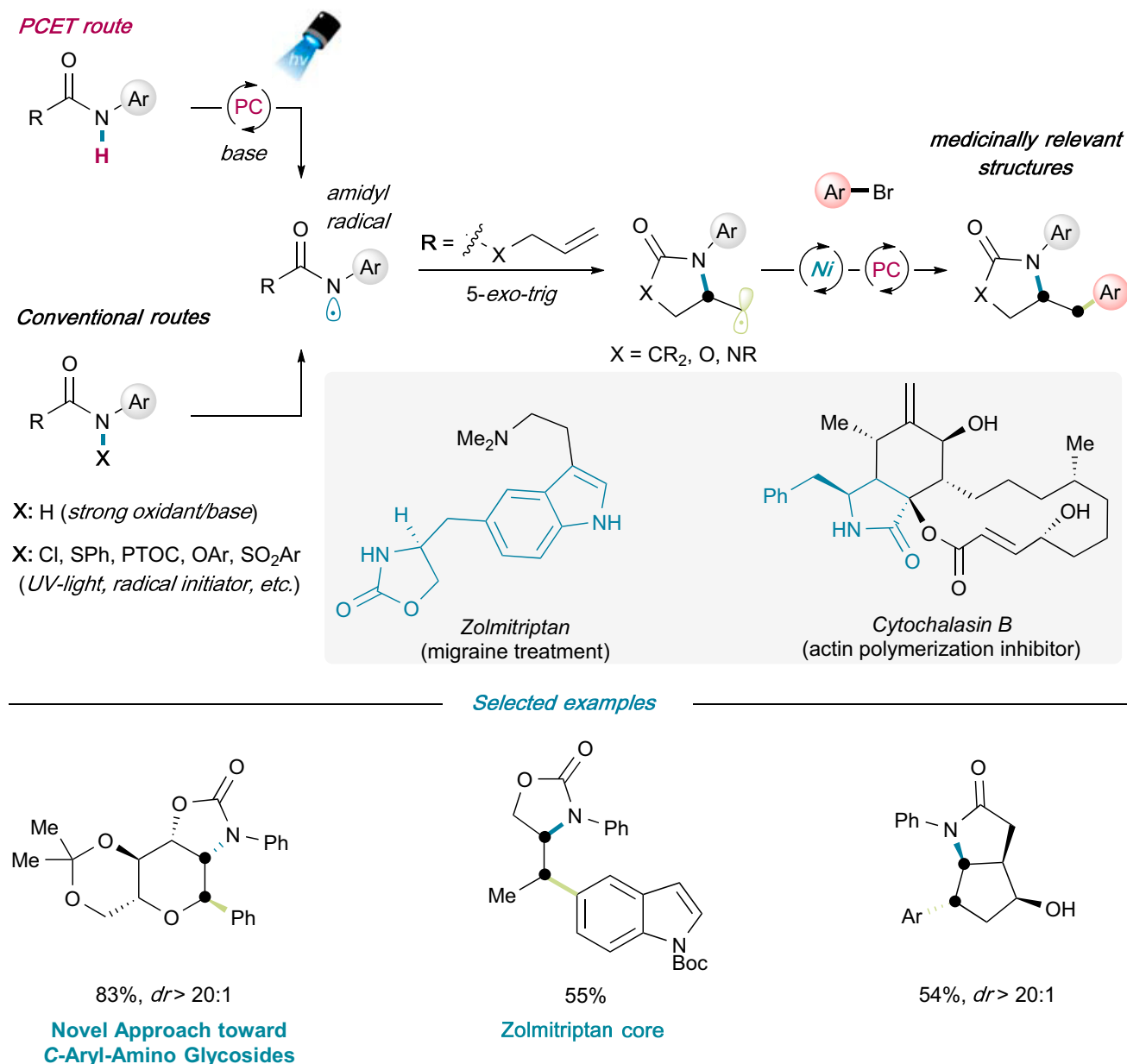


Figure 1. PCET/Ni-Catalyzed Synthesis of Pyrrolidones, Oxazolidinones, or Imidazolidinones

products. The resulting $L_nNi(II)$ is then interfaced with the photochemical regime by a final single-electron transfer event, thus recovering back the propagating catalytic species. The transformation is distinguished by a broad scope, including particularly challenging substrate combinations, and an excellent chemoselectivity profile, allowing access to a variety of five-membered nitrogen-containing

heterocycles in a cascade-type fashion from simple precursors. These virtues allow pyrrolidinone, oxazolidinone, and imidazolidinone formation to take place at late stages of syntheses, as illustrated by the successful preparation of aryl glycosides or zolmitriptan analogs, among others. In light of the data provided, it is fairly apparent that the approach reported by Molander and co-workers opens an orthogonal

gateway that complements existing methodologies for accessing N-heterocyclic products. In addition, this method provides a glimpse at the inherent potential that PCET and nickel catalysis offer for innovative heterocyclic chemistry. In view of the growing interest in nickel-catalyzed reactions and visible-light-mediated photoredox endeavors, it is inevitable to predict that this new technique will serve as the

blueprint to even more demanding targets, including the always-elusive densely functionalized heterocyclic cores possessing quaternary carbon centers, the means to switch the site-selectivity pattern for accessing a different set of nitrogen-containing heterocycles, and the development of enantioselective variants of this or related processes.

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Preview

Illuminating Fermi Resonances that Trigger Reaction in a Complex Molecule

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Transferring energy to specific molecular vibrations remains a challenge in the quest to control chemical reactions with light. In this issue of *Chem*, Rafiq et al. show that a quantum-mechanical Fermi resonance between a light-absorbing terpyridine-molybdenum complex and dinitrogen bridge directs energy to vibrations associated with bond activation.

One strategy for controlling chemical reactions with light aims to identify pathways by which energy from a photon absorbed by a molecule can be transferred to bond-activating vibrations. However, directing energy to such vibrations when they are spatially separated from a light absorber remains a daunting challenge. Molecular vibrations are in essence a quantum-mechanical system of coupled oscillators, in which Fermi resonances mediate energy flow.¹ A simple classical analog to energy transfer via Fermi resonance in a molecule is a child on a

swing. When the frequency of the child's kicking motion matches the frequency of the swing, energy is transferred from the child to the swing, and the child swings higher. Unlike the two degrees of freedom of the child and swing, there can be myriad combinations of coupled vibrations that allow energy to flow in a large molecule, greatly complicating selective energy transfer. However, under certain conditions and with proper tuning, Fermi resonances can direct energy from a chromophore to vibrations that activate a reaction before that energy is redis-

tributed to other degrees of freedom. In this issue of *Chem*, Rafiq et al.² report that Mo₂N₂, a terpyridine-molybdenum complex containing a dinitrogen bridge, exhibits a Fermi resonance switched on by the absorption of light, transferring energy to the spatially separated dinitrogen, which could facilitate reactions involving N₂.

To appreciate the significance of this development, it is helpful to first consider a generic quantum-mechanical system of many coupled oscillators, which can represent the vibrations of a large molecule. Random models for ensembles of molecules, each member a reasonable description of a molecule of interest, point both to the importance of Fermi resonances in energy flow through the vibrational state space (VSS) of a molecule and to the role of quantum-mechanical interference effects in energy transfer.^{1,3} Selection rules impose restrictions on the extent to which each state of the

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