

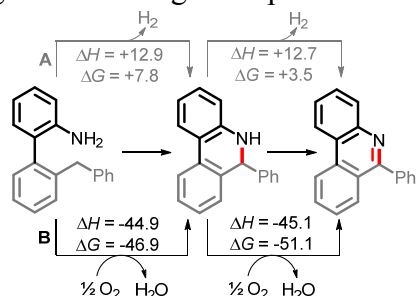
Reaction Cascades Initiated by Catalytic Oxidative C-H Activation via Hole Injection

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The ACS-PRF funding helped to start a new research direction in my lab aimed at the development of new mild C-H amination processes.

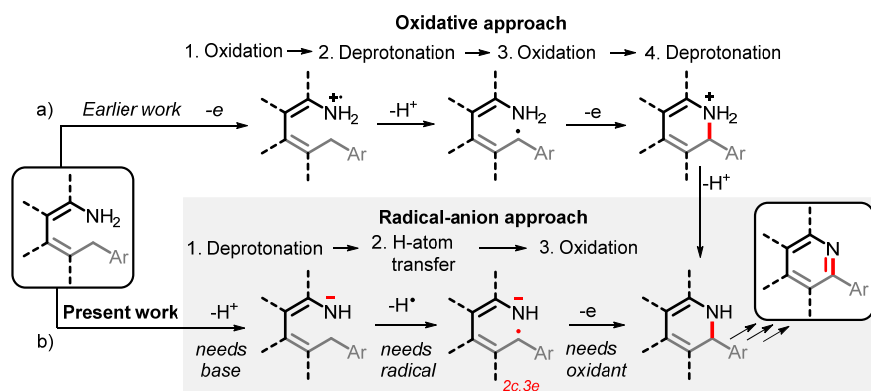
Direct construction of a C-N bond from a C(sp³)-H bond and an N-H bond is a challenging transformation, especially, when an unprotected primary amine is used as a partner for the notoriously unreactive C-H bonds. Even with the large amount of work conducted in this area, only a few literature methods for C(sp³)-H amination do not rely on transition metals (TMs). This is not surprising because a typical $\text{RNH}_2 + \text{R}_2\text{CH}_2 \rightarrow \text{RN}=\text{CR}_2$ conversion of unprotected amines to an imine with the loss of two H₂ molecules is thermodynamically unfavorable ($\Delta G = +11$ kcal/mol, Scheme 1, path A). The first N-C bond formation in this sequence is uphill by 8 kcal/mol (Scheme 1, top left). Even though C-H/N-H coupling becomes thermodynamically favorable when coupled with oxidation ($\Delta G = -47$ kcal/mol, Scheme 1, path B), significant kinetic barriers provide challenges in the design of a practical version of this reaction.



Scheme 1. Thermodynamics of A: dehydrogenative and B: oxidative C-N bond formations from C-H/N-H partners

We have initially disclosed on a FeCl₃-mediated oxidative approach to C-H amination with anilines based on a sequence of electron and proton transfers (Evoniuk, C. J.; Hill, S. P.; Hanson, K.; Alabugin, I. V. *Chem. Commun.* **2016**, 52, 7138). Although this approach is conceptually appealing, we reasoned that if SET is coupled to anionic conditions, milder oxidants can be used. Presently, we have developed a conceptually distinct approach that can couple N-H and C-H activation via a sequence of N-H deprotonation and H-abstraction, followed by an oxidation of the intermediate radical anion. The final step converts a 2c,3e “half-bond” formed in the first steps into a “normal” 2c,2e N-C bond. After the covalent C-N bond is formed, the above sequence of steps can be repeated to yield the product of a double N-H/C-H activation (Scheme 2). Although conceptual simplicity of this approach is appealing, finding the right combination of oxidant, radical and base that can work together was a daunting task, especially for unprotected amine

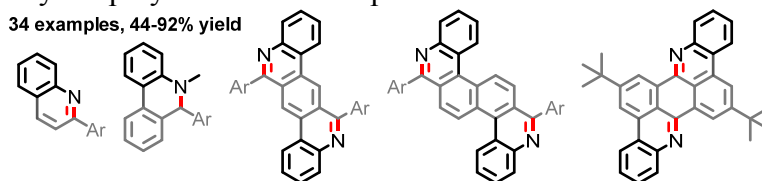
reagents susceptible to oxidation. Gratifyingly, we found the successful C(sp³)-H amination/iminination cascades with unprotected amines (Scheme 2) based on the combination of potassium *tert*-butoxide (*t*-BuOK), molecular oxygen and DMF.



Scheme 2. Comparison of the two approaches to making C=N moiety from the double activation of CH₂/NH₂ moieties. a) Earlier reported oxidative approach. b) The new radical-anionic approach.

Comprehensive computational analysis revealed the unusual mechanistic features of this tightly choreographed sequence of transformations. Each reaction component plays a separate role in the synergistic effort which involves a coordinated sequence of deprotonation, H-atom transfer and electron transfer for each C-N bond formation. *t*-Butoxide base plays two roles: a) it deprotonates nitrogen and b) provides sufficient concentration of deprotonated DMF that can be converted into a DMF radical. The role of DMF radical is in selective activation of the C-H bond partner in C-N bond formation via HAT that forms a C-centered radical. The C-N bond is formed initially as a 2c,3e interaction between the N-anion and C-radical, a process that is assisted by state crossing “ejecting” the extra electron into an orthogonal π -system and forging a “normal” 2c,2e C-N bond. This process of 2c,3e bond formation becomes much faster and more favorable thermodynamically when aniline is deprotonated, indicating that both the TS and the product of the “neutral” version of this process are considerably more acidic than the starting benzylic radical. Oxidation of the cyclic radical-anion intermediate by molecular oxygen finishes the sequence of deprotonation, HAT and oxidation that are necessary for the success of this deceptively simple transformation.

Furthermore, we were able to use the synthetic power of this method for the preparation of new families of N-heterocyclic polyaromatic π -acceptors.



The results of this work were published in a JACS paper: C. J. Evoniuk, G. d. P. Gomes, S. P. Hill, F. Satoshi, K. Hanson, I. V. Alabugin, J. Amer. Chem. Soc., 2017, 139, 16210–16221. <http://pubs.acs.org/doi/abs/10.1021/jacs.7b07519>

The first author of this manuscript, Mr. Chris Evoniuk, defended his PhD thesis and started his job at Intel. The joint 1st coauthor, Mr. Gabriel dos Passos Gomes received numerous awards, including, most recently the CAS SciFinder Future Leaders Award.