

Aliphatic C-H Activation: The Road Less Travelled to Amination

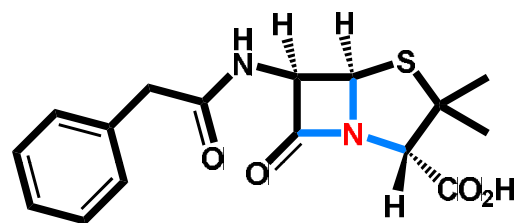
Reporter: Zhang-Pei Chen

Checker : Mu-Wang Chen

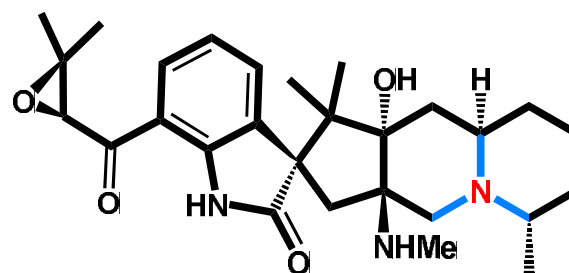
Date: 29/07/2014

Gaunt, M. J. *et al.*
Nature **2014**, *510*, 129.

Representative examples of some natural products

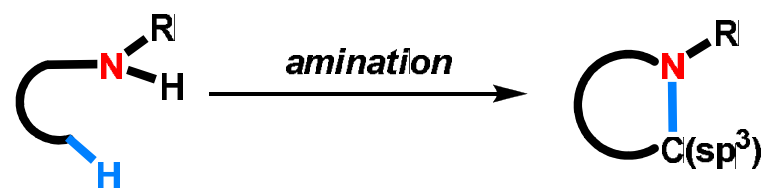


penicilin G

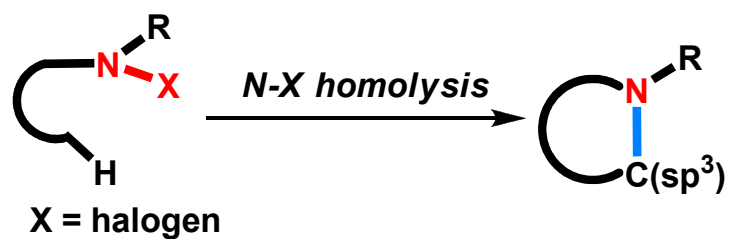


(+)-citrinadin B

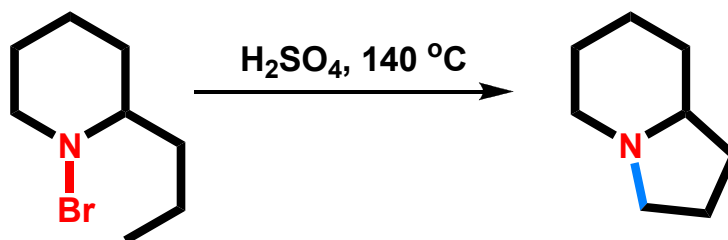
C(sp³)-H amination



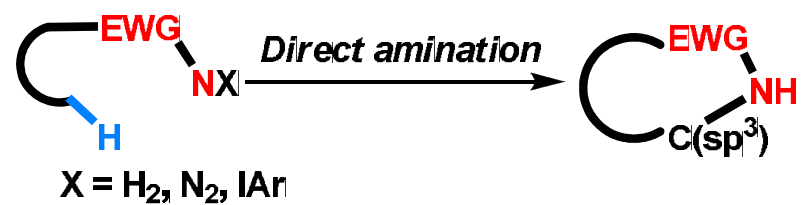
Hofmann-Löffler-Freytag reaction



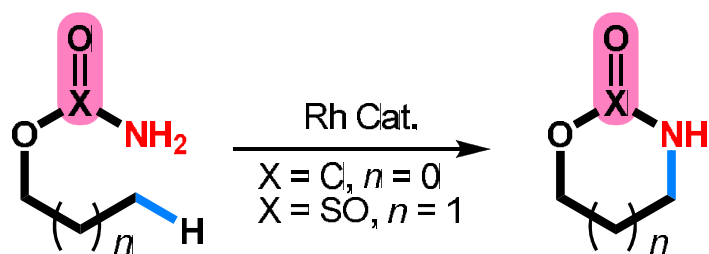
Hofmann (1880s)



Nitrene C(sp³)-H insertion

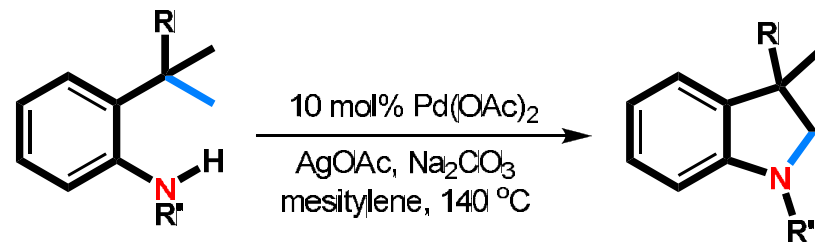


Du Bois



Directed C(sp³)-H activation

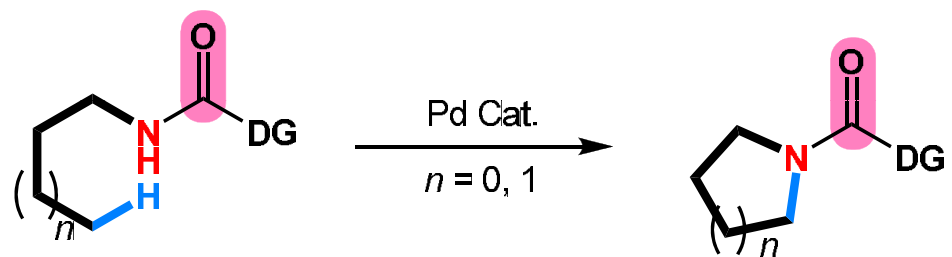
Glorius



R' = Carbonyl

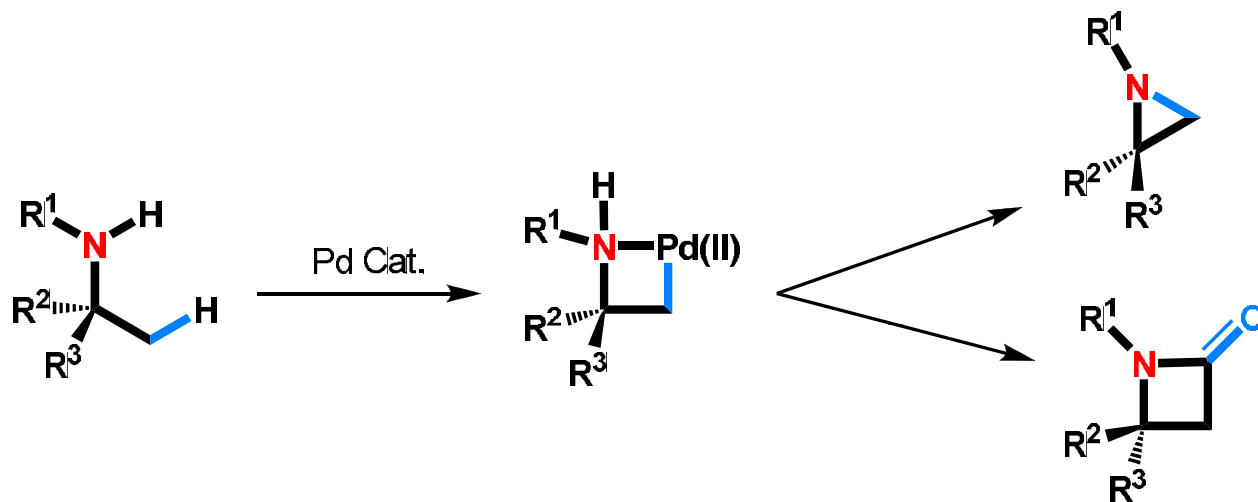
Directed C(sp³)-H activation

Daugulis & Chen

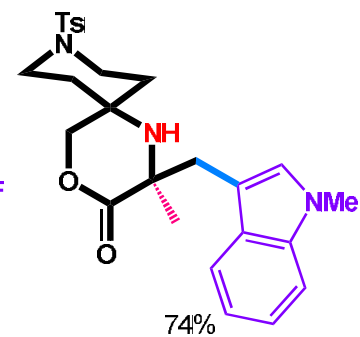
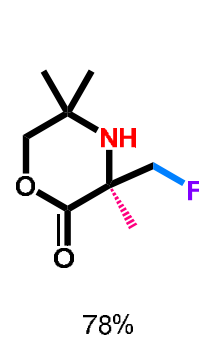
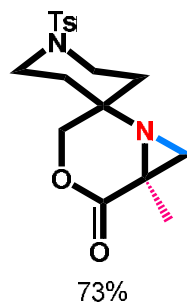
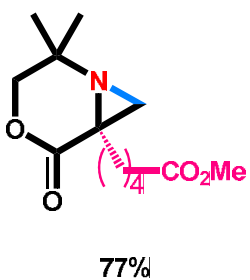
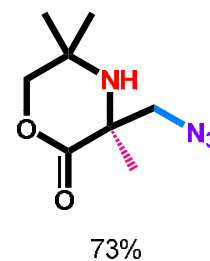
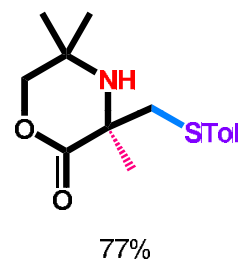
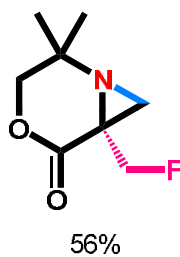
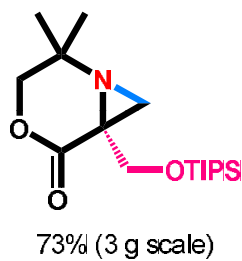
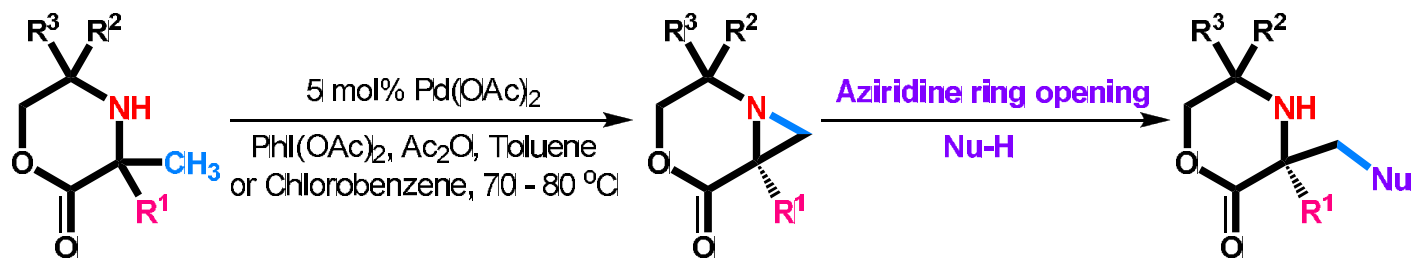


Daugulis, O. *et al.* *J. Am. Chem. Soc.* **2012**, *134*, 7.
Chen, G. *et al.* *J. Am. Chem. Soc.* **2012**, *134*, 3.

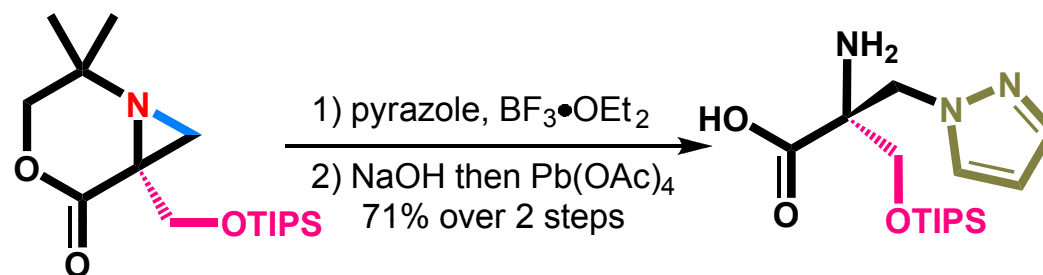
Directed C(sp³)-H activation



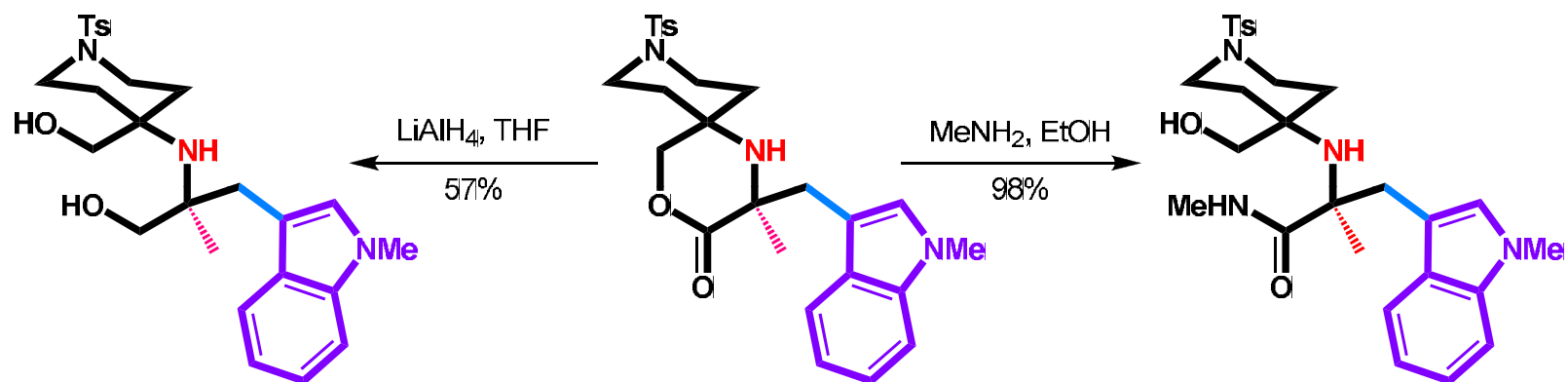
Directed C(sp³)-H activation



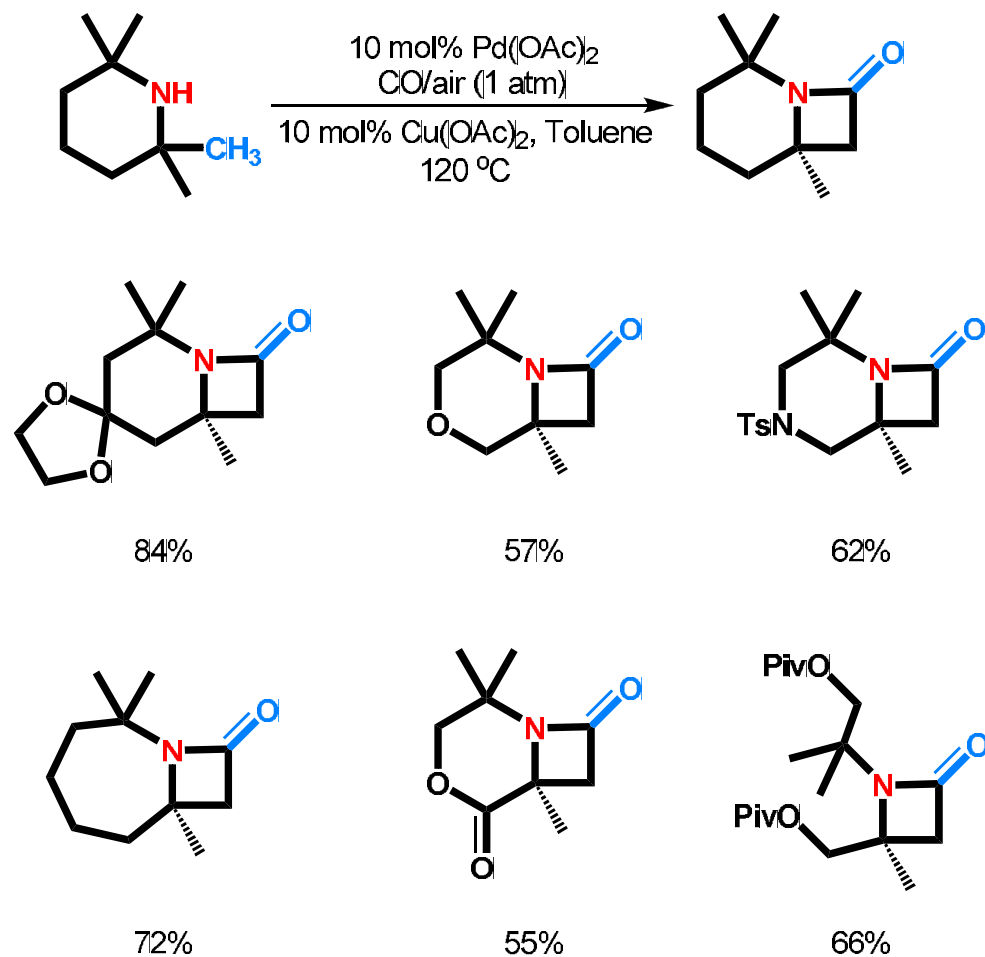
Directed C(sp³)-H activation



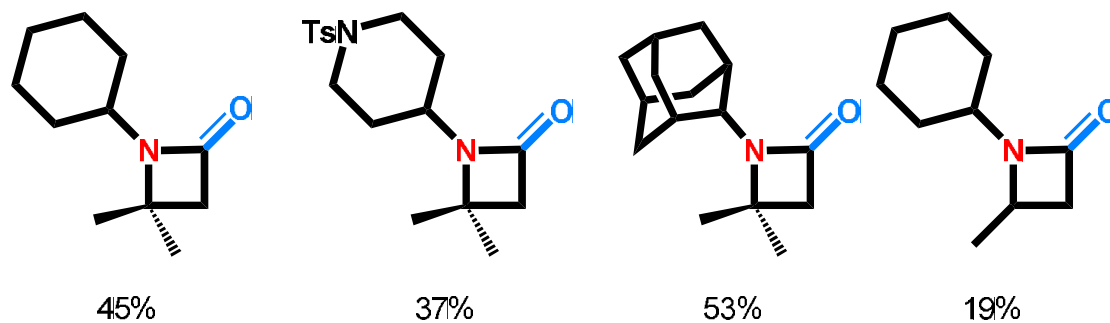
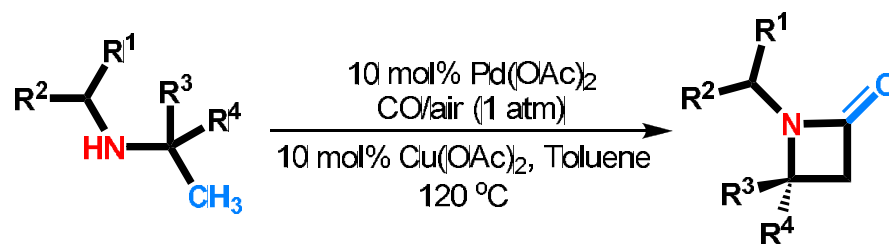
Directed C(sp³)-H activation



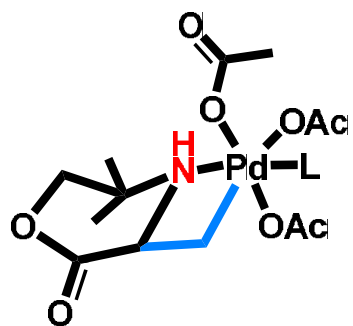
Directed C(sp³)-H activation



Directed C(sp³)-H activation

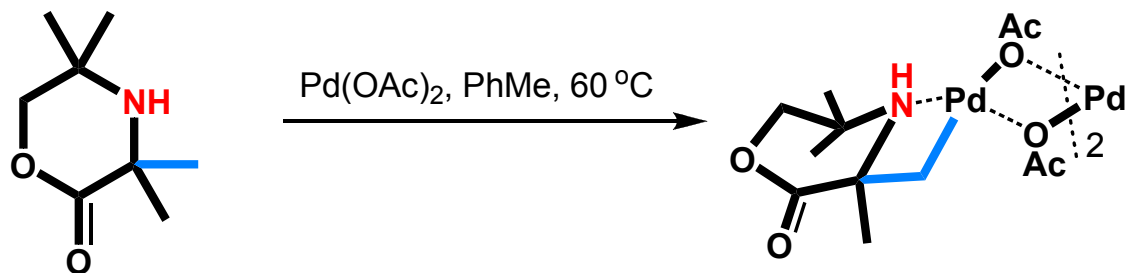


Directed C(sp³)-H activation

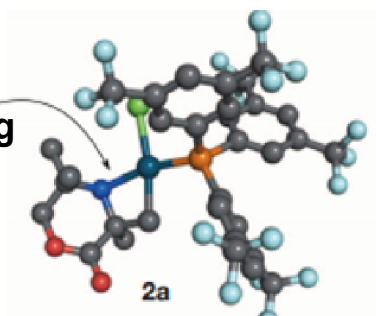


Putative Pd(IV) intermediate

Directed C(sp³)-H activation



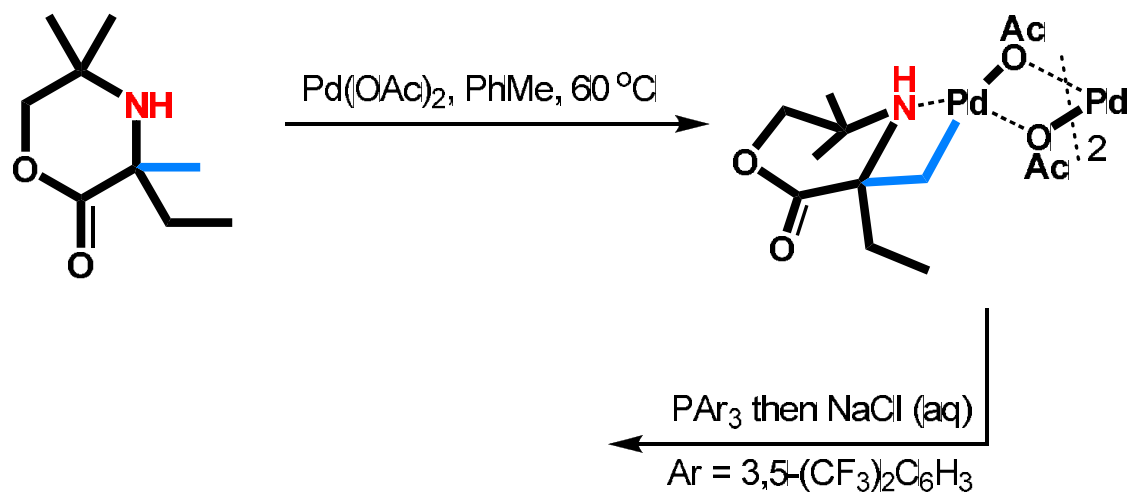
Four-membered-ring



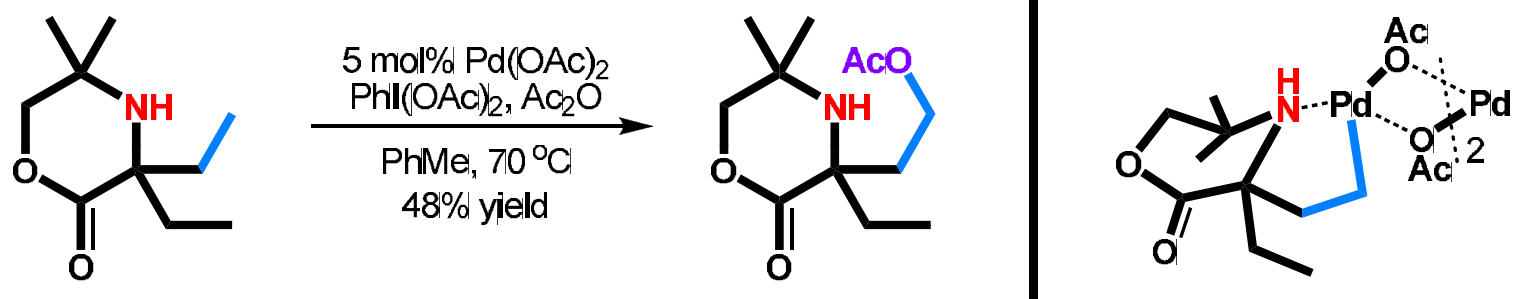
PAr_3 then NaCl (aq)

$\text{Ar} = 3,5\text{-(CF}_3)_2\text{C}_6\text{H}_3$

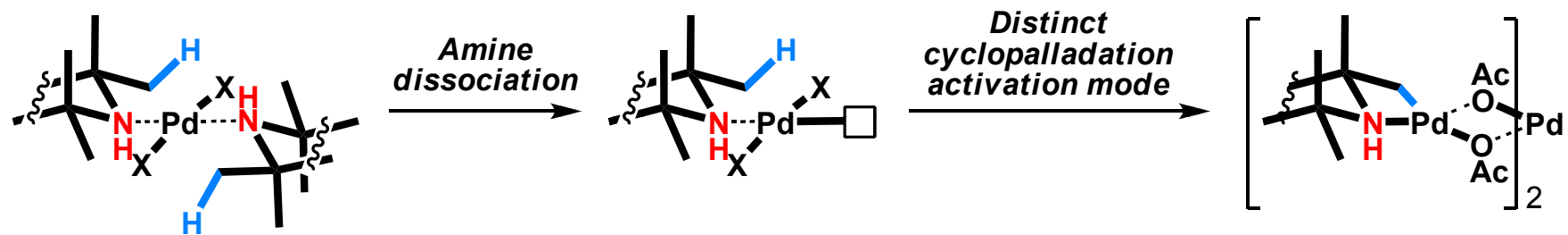
Directed C(sp³)-H activation



Directed C(sp³)-H amination

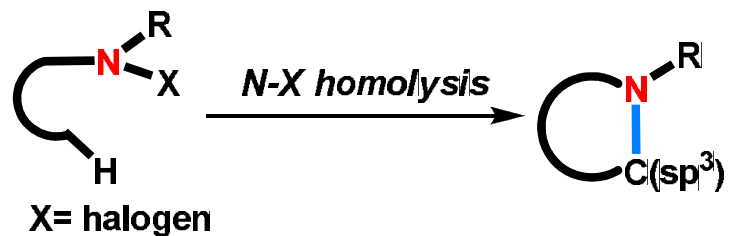


Directed C(sp³)-H activation

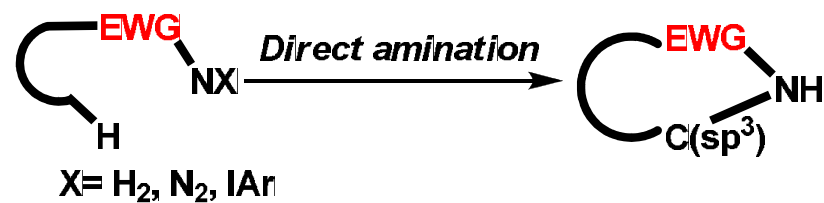


Summary

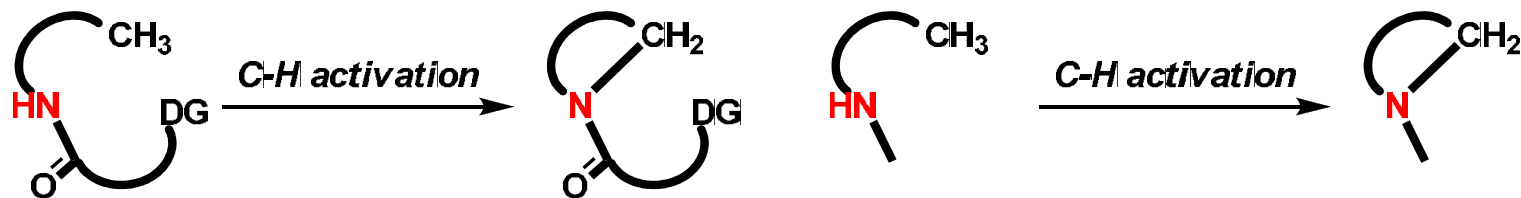
a) Hofmann-Löffler-Freytag reaction



b) Metal nitrene formation



c) Directed C-H activation



d) Oxidation coupling



The development of new chemical transformations based on catalytic functionalization of unactivated C-H bonds has the potential to simplify the synthesis of complex molecules dramatically. Transition metal catalysis has emerged as a powerful tool with which to convert these unreactive bonds into carbon-carbon and carbon-heteroatom bonds, but the selective transformation of aliphatic C-H bonds is still a challenge. The most successful approaches involve a 'directing group', which positions the metal catalyst near a particular C-H bond, so that the C-H functionalization step occurs via cyclometallation. Most directed aliphatic C-H activation processes proceed through a five-membered-ring cyclometallated intermediate. Considering the number of new reactions that have arisen from such intermediates, it seems likely that identification of distinct cyclometallation pathways would lead to the development of other useful chemical transformations. Here we report a palladium-catalysed C-H bond activation mode that proceeds through a four-membered-ring cyclopalladation pathway. The chemistry described here leads to the selective transformation of a methyl group that is adjacent to an unprotected secondary amine into a synthetically versatile nitrogen heterocycle. The scope of this previously unknown bond disconnection is highlighted through the development of C-H amination and carbonylation processes, leading to the synthesis of aziridines and β -lactams (respectively), and is suggestive of a generic C-H functionalization platform that could simplify the synthesis of aliphatic secondary amines, a class of small molecules that are particularly important features of many pharmaceutical agents.

Taken together, the present results represent an important initial advance that could substantially broaden this directed C–H activation methodology to further classes of secondary amine, and further reinforces the potential of a new strategic bond disconnection which converts simple methyl groups into a range of versatile strained nitrogen heterocycles. **As the physical and biological properties of aliphatic amines are central to the function of many important pharmaceuticals, chemical reagents and polymeric materials, we expect that such an approach to amine synthesis will be broadly useful in the synthesis of complex functional amines.**