ACYL C-N BOND INSERTIONS OF AMIDES: NEW ELECTROPHILES FOR CROSS-COUPLING REACTIONS

Reported by Carter Cunningham February 13th, 2024

INTRODUCTION

The ubiquitous nature of amide bonds in pharmaceuticals and other small molecules has led to the widespread development of synthetic methods for acyl C-N bond formation. In fact, the acylation of amines is the most commonly used reaction in the synthesis of pharmaceuticals.[1] While many different manifolds exist for the formation of amide C-N bonds, the reverse process of amide C-N bond cleavage is significantly less explored. This is due to the well-studied phenomenon of the n → π* interaction from the nitrogen lone pair into the carbonyl antibonding orbital imparting significant resonance stabilization;[2] therefore, significantly harsh conditions or highly activated reagents are required to cleave this bond (**Figure 1**).[3] This intrinsic stability of amides imparts tolerance towards a myriad of reaction conditions, while their increased Lewis basicity provides synthetic utility as a directing group for both *ortho*-metallations and C-H functionalization reactions.[4] With these beneficial features in mind, amides have the potential to serve as valuable synthetic intermediates given the development of new methods that undergo mild and selective late-stage functionalization of amide C-N bonds.

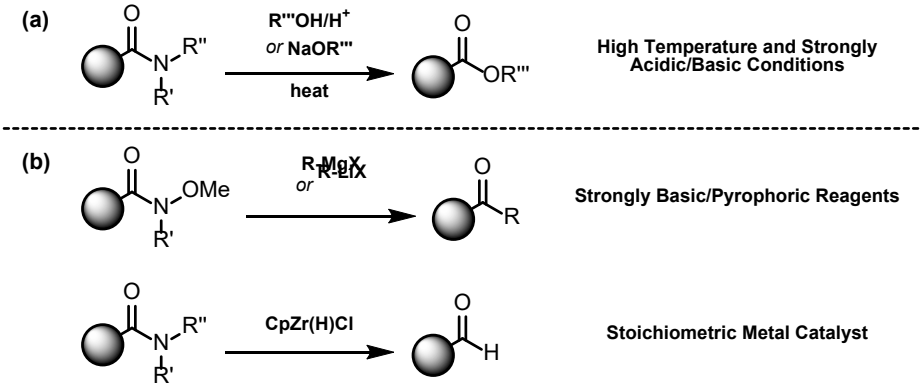

Figure 1. (a) Amide hydrolysis to yield the corresponding ester or carboxylic acid. (b) Amide reduction to yield the corresponding ketone or aldehyde

REACTION DEVELOPMENT AND SYNTHETIC APPLICATIONS

In a serendipitous occurrence in 2015, the groups of Garg[5a] and Szostak[5b] both reported examples of the transition-metal catalyzed insertion (and subsequent couplings) of amide C-N bonds utilizing slightly different strategies to activate the starting material by decreasing the contribution of orbital overlap from the n → π* interaction (**Figure 2**). Garg *et. al.* showed computationally that different benzamide *N*-substituents significantly lowered the barrier of oxidative addition by an electron-rich nickel (0) catalyst (**Figure 3**) and experimentally validated the results by performing the nickel-catalyzed esterification of multiple different benzamide electrophiles and alcohol nucleophiles.[5a] DFT

calculations were performed to understand the mechanism of this transformation, showcasing that oxidative addition to the amide C-N bond was likely the rate-limiting step with a 26.0 kcal mol^{-1} barrier.

More insight into the mechanism was expounded upon by Shi *et. al.* during their study of nickel-catalyzed decarbonylative borylation of amides, where a separate oxidative addition complex containing a nickel catalyst inserted into a naphthamide C-N bond was isolated during stoichiometric studies.[6] The ability to isolate this complex (and the corresponding decarbonylated species) was likely due to a change in the mechanism, where the subsequent decarbonylation or transmetallation with the bis(neopentyl glycolato)diboron species was now rate limiting; however, isolation of this complex gave credence to the ability of low-valent nickel catalysts to insert into amide C-N bonds.

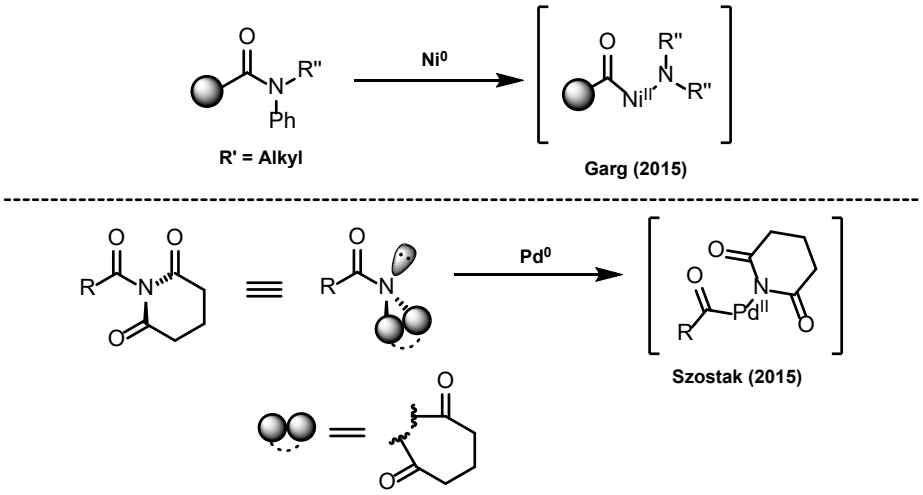

Figure 2. Different methods for decreasing the n → π* interaction of the C-N amide bond.

This initial foray into transition-metal catalyzed amide C-N bond insertion has rapidly prompted the exploration of many different amide electrophiles (e.g., benzamides, heteroaryl amides, aliphatic amides, etc.) and nucleophiles (e.g., alcohols, boronic acids, organozinc reagents, secondary amines, etc.) to undergo a wide variety of synthetically useful transformations.[7]

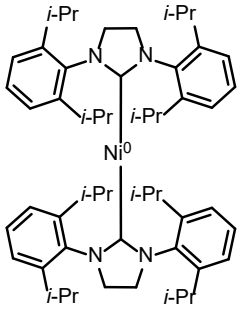

Figure 3. SIPr ligand bound to Ni^0 catalyst used for insertion into amide C-N bonds.

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