

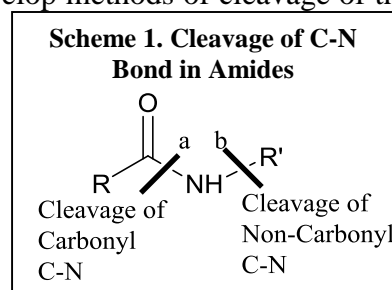
TRANSITION METAL CATALYZED CLEAVAGE OF THE C-N AMIDE BOND: APPLICATIONS IN ORGANIC SYNTHESIS

Reported by Subhanip Biswas

November 19th, 2015

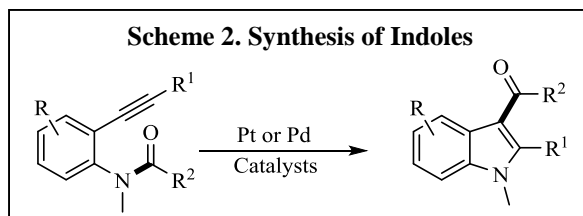
INTRODUCTION

Amides are one of the most ubiquitous functional groups occurring in nature; e.g. they are the key building blocks of proteins. Nature uses dedicated enzymes called proteases for the selective cleavage of the amide bonds.¹ Amides can be hydrolyzed to the corresponding carboxylic acid and the amine under drastic conditions using acids or bases. Synthetically useful transformations to afford the carbonyl derivatives or the amines involve the use of stoichiometric amounts of organometallic reagents.² Thus there is a need to develop methods of cleavage of the C-N bond which involve the use of catalysts. Transition metals, which are known to activate a wide variety of bonds occurring in organic compounds, serve as promising candidates for this purpose.¹ Two possible modes of C-N cleavage bond in amides are - the carbonyl C-N bond (Scheme 1a) or the non-carbonyl C-N bond (Scheme 1b).



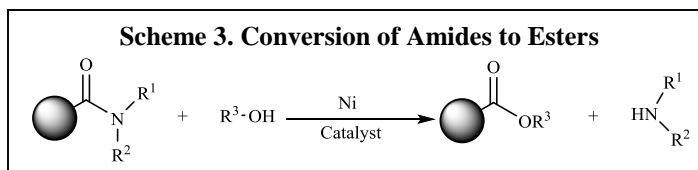
APPLICATIONS IN ORGANIC SYNTHESIS

The activation of C-N bonds in amides using transition metals is relatively a new field and has found applications in a variety of useful synthetic transformations; particularly in the synthesis of heterocycles like indoles and benzothiazoles; which are known to occur in drugs³ and natural products. In 2004, Yamamoto *et al.* developed a method for accessing indoles using a Pt catalyst for the intramolecular addition of an acyl group across an ortho alkynyl unit.^{4a} This method suffered from deacylation and was improved upon by the use of a Pd(II) catalyst (Scheme 2).^{4b} The C-N cleavage in these processes takes place via an acyl migration to an ammonium species.

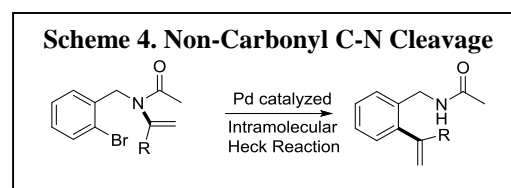


In 2015, Garg, Houk and coworkers demonstrated the direct C-N activation of amides using a Ni-NHC catalyst to convert amides to esters. The reaction has a very broad substrate scope such that aryl amides together with primary, secondary and tertiary alcohols participate in

the reaction. Sensitive functional groups (acetals, oxetanes, indoles and esters) are compatible and moderate to excellent yields of the corresponding benzoic esters are achieved (Scheme 3).¹



The cleavage of the non-carbonyl amide bond is also a viable synthetic strategy which has found applications in the field of cross-coupling reactions. In 2013, Itami *et al.* described the synthesis of heterobiaryls from 2-aminobenzothiazoles and arylboronic acids.⁵ Subsequently, Chatani and coworkers described a method for the reductive borylative cleavage of the aromatic C-N bond in N-aryl amides and carbamates.⁶ The method illustrates the use of amides as both a directing and removable activating group and accessing useful cross-coupling partners for the Suzuki-Miyaura reaction. Very recently, Loh *et al.* developed a method for the intramolecular Mizoroki-Heck reaction via a vinyl C-N cleavage to access 1,1'-disubstituted alkenes (Scheme 4).⁷ The new approach is complimentary to previous methods as it leads to a different substitution pattern than that normally formed in Heck reactions.



SUMMARY AND OUTLOOK

Transition metal catalyzed C-N cleavage of the amide bonds provides a platform for the easy construction of C-heteroatom or C-C bonds. It is anticipated that the substrate scope of the different reactions can be extended to fully utilize the potential of amides as versatile and valuable intermediates in organic synthesis.

REFERENCES

- Hie, L.; Fine Nathel, N. F.; Shah, T. K.; Baker, E. L.; Hong, X.; Yang, Y. F.; Liu, P.; Houk, K. N.; Garg, N. K. *Nature* **2015**, 524, 79.
- Pace, V.; Holzer, W.; Olofsson, B. *Adv. Synth. Catal.* **2014**, 356, 3697.
- Hroch, L.; Aitken, L.; Benek, O.; Dolezal, M.; Kuca, K.; Gunn-Moore, F.; Musilek, K. *Curr Med Chem.* **2015**, 22,730.
- (a) Shimada, T.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, 126, 10546. (b) Zhao, F.; Zhang, D.; Nian, Y.; Zhang, L.; Yang, W.; Liu, H. *Org. Lett.* **2014**, 16, 5124.
- Uehara, T. N.; Yamaguchi, J.; Itami, K. *Asian J. Org. Chem.* **2013**, 2, 938.
- Tobisu, M.; Nakamura, K.; Chatani, N. *J. Am. Chem. Soc.* **2014**, 136, 5587.
- Wang, M.; Zhang, X.; Zhuang, Y.-X.; Xu, Y.-H.; Loh, T.-P. *J. Am. Chem. Soc.* **2015**, 137, 1341.