Synthetic Methods

International Edition: DOI: 10.1002/anie.201508536
German Edition: DOI: 10.1002/ange.201508536

Strong Bonds Made Weak: Towards the General Utility of Amides as Synthetic Modules

*Stefan A. Ruider and Nuno Maulide**

amides · esters · homogenous catalysis · nickel · solvolysis

The amide bond is a ubiquitous functional group the structure of which decisively influences the biological and material properties of a vast number of compounds created by man and nature alike.[1] Whereas numerous methods for the formation of amide bonds have been developed,[2] it is noteworthy that amides find only limited use as synthetic modules. This comes as no surprise considering the typically high stability and rigidity of the amidic linkage.

It is textbook knowledge that the low reactivity of amides is a result of resonance stabilization (Figure 1),[1] resulting from the orbital overlap between the nitrogen lone pair and the anti-bonding orbital (π*) of the carbonyl group. This stabilization reduces the susceptibility of amides towards nucleophilic attack, and simultaneously grants the amidic carbonyl oxygen atom a pronounced Lewis basicity.

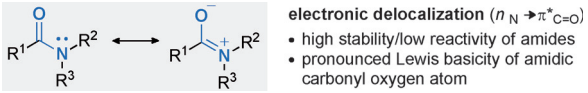

Figure 1. Resonance stabilization of amides (left) and resulting key physicochemical properties (right).

Considerable progress has been achieved for the conversion of amides into functional groups with lower oxidation states.[3] However, the potential for amides to also serve as intermediates in the preparation of carboxylic acid derivatives has remained untapped. Given that amides, as robust masked carboxylates, can be taken through conventional demanding sequences without much concern, the development of novel chemoselective and mild methods for their activation would open up new avenues in retrosynthetic planning. Very recently, Garg, Houk, and co-workers have presented a new concept for the selective activation and conversion of amides into esters in a one-step process (see below).[4]

Most of the previously reported, synthetically useful methods for the conversion of amides into esters and carboxylic acids involve the controlled generation of an electrophilic intermediate, such as an imidate or an iminium ether (Figure 2),[5] prior to hydrolysis or solvolysis. It is noteworthy that all of these methods harness the pronounced Lewis basicity of the amidic carbonyl oxygen atom. Pre-activation of the amide functional group usually proceeds readily at low temperatures (≤ room temperature) and with very appealing levels of chemoselectivity.

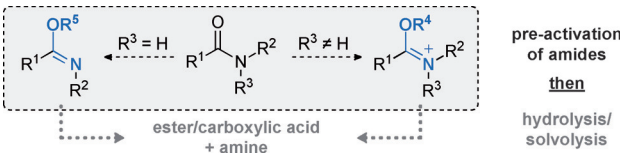

Figure 2. Traditional strategy for the conversion of amides into esters and carboxylic acids. $R^2 \neq H$.

Hanessian's report on the successful removal of the *N*-acetyl groups in acetamido deoxysugars using triethyloxonium tetrafluoroborate marked the first example of the above strategy (Figure 3 A).[6a] Despite its high functional-group tolerance (esters, acetals, and glycosidic linkages were unaffected) and the mild reaction conditions (1 equiv of $[Et_3O]BF_4$, CH_2Cl_2, RT), three decades passed before the general utility of this process was explored in more detail.[6b,c] The narrow product scope ($[Et_3O]BF_4 \rightarrow$ethyl ester, $[Me_3O]BF_4 \rightarrow$methyl ester), however, is a significant limitation to these methods.

An alternative process that relies on the same activation mode as described in Figure 2 was disclosed by Charette and

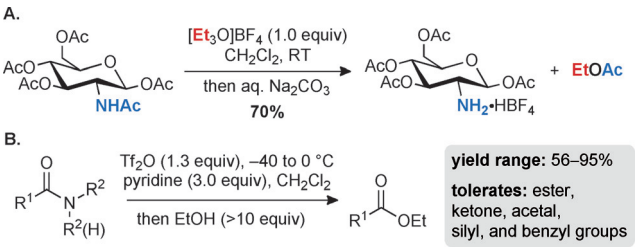

Figure 3. A) Seminal work on the two-step amide-to-ester conversion using a trialkyloxonium tetrafluoroborate salt as reported by Hanessian in 1967. B) Charette's two-step procedure for mild and chemoselective amide-to-ester conversions. R^1 = alkyl, vinyl, aryl; R^2 = alkyl, benzyl.

[*] S. A. Ruider, Prof. Dr. N. Maulide
Universität Wien, Fakultät für Chemie
Institut für Organische Chemie
Währinger Strasse 38, 1090 Wien (Austria)
E-mail: nuno.maulide@univie.ac.at

co-workers in the late 1990s. Based on the electrophilic pre-activation of amides with trifluoromethanesulfonic anhydride (Tf_2O) and pyridine, a variety of secondary and tertiary amides could be readily converted into esters (Figure 3B).[7a,b] However, the large excess of alcohol nucleophile required limits its use to the synthesis of simple esters.[7c]

The pre-2015 state of the art of mild, direct amide-to-ester transformations is shown in Figure 4. In 2012, Booker-Milburn and Lloyd-Jones jointly reported the direct room-temperature substitution of tetramethylpiperidine (TMP) acetamides (Figure 4A).[8a] The ease with which these substitutions take place hinges on the ground-state destabiliza-

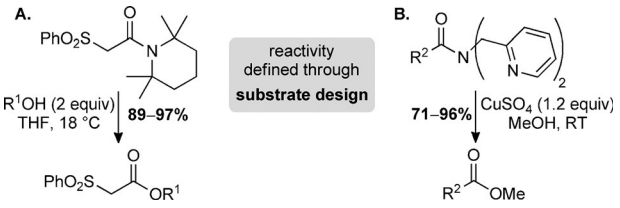

Figure 4. Recently described methods for direct and mild amide-to-ester conversion. A) Substitution of TMP acetamides at room temperature (Booker-Milburn and Lloyd-Jones). R^1 = H, alkyl, Ph. B) Copper-mediated solvolysis of bispicolylamine amides (Bannwarth). R^2 = alkyl, aryl, alkynyl.

tion of the amidic linkage (by increased allylic 1,3-strain) and the presence of a strongly electron-withdrawing group in the α-position of the amide moiety. A year earlier, Bannwarth had reported the copper-mediated room-temperature methanolysis of bispicolylamine-substituted amides (Figure 4B).[8b] Whereas both methods are based on intriguing new concepts, they entail the use of specifically designed substrates.

Figure 5A outlines the initial reaction design by Garg and Houk.[4] Aware of the ability of nickel(0) to activate strong carbon–heteroatom bonds,[9] the authors hypothesized that following oxidative addition of the amidic C–N bond (a previously unknown activation mode of Ni^0!), a reactive acyl nickel species would be formed, which could be harnessed to form new carbon–heteroatom or even new carbon–carbon bonds.

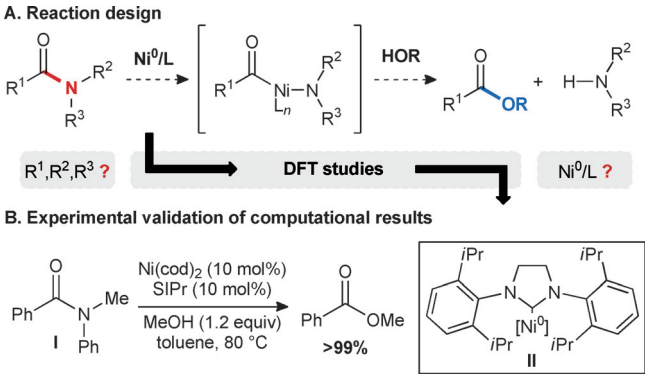

Figure 5. Development of the nickel-catalyzed direct amide-to-ester conversion. cod = 1,5-cyclooctadienyl.

Preliminary density-functional-theory (DFT) calculations on the nickel-catalyzed methanolysis of various amides indeed supported the outlined process. The computations indicated that the use of *N*-methyl-*N*-phenylbenzamide (**I**) and electron-rich N-heterocyclic carbene nickel complex **II** should render the overall process both thermodynamically and kinetically favorable (Figure 5A). In practice, heating a mixture of amide **I**, 10 mol% Ni catalyst **II** ($Ni(cod)_2$/SIPr), and 1.2 equiv MeOH in toluene for twelve hours at 80 °C afforded the corresponding methyl ester in quantitative yield (Figure 5B). The reaction can be applied to electron-rich and electron-poor aryl amides as well as heteroaryl amides. Primary, secondary, and even sterically hindered tertiary alcohols are tolerated. Furthermore, *N*-phenyl substitution is not a prerequisite to the success of the transformation. Tertiary benzamides featuring *N*-tosyl or even *N*-Boc substitution can be used as substrates with equal efficiency. Whereas secondary *N*-phenyl benzamides may also be used, their reactions require prolonged reaction times and higher temperatures. Aliphatic amides, however, fail to take part in the nickel-catalyzed process. Overall, the reaction produces the corresponding benzoic acid esters in moderate to excellent yields (49–99%), and a variety of sensitive functional groups (esters, acetals, oxetanes, indoles) are tolerated.

The reports highlighted herein provide a glimpse of the intriguing field of amide-to-ester transformations. Whereas several earlier methods are effective for chemoselective amide activation, each method features its individual drawbacks. Garg's recent work certainly marks a milestone in direct amide-to-ester conversions, although the current substrate limitations are likely to be the focus of future work. This report should nevertheless be recognized for its conceptual breakthrough in the nickel-catalyzed activation of amidic C–N bonds—a previously unknown mode of action of Ni^0. Further selective amide activations are now eagerly awaited towards broadening the use of amides as versatile and valuable synthetic intermediates in organic synthesis.

Acknowledgements

We are grateful to the University of Vienna and the European Research Council (ERC starting grant 278872) for generous financial support.

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 13856–13858
Angew. Chem. **2015**, *127*, 14062–14064

[1] *The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science* (Eds.: A. Greenberg, C. M. Breneman, J. F. Liebman), Wiley, New York, **2003**.
[2] For a recent critical review, see: V. R. Pattabiraman, J. W. Bode, *Nature* **2011**, *480*, 471–479.
[3] For an excellent recent review, see: V. Pace, W. Holzer, B. Olofsson, *Adv. Synth. Catal.* **2014**, *356*, 3697–3736.
[4] L. Hie, N. F. Fine Nathel, T. K. Shah, E. L. Baker, X. Hong, Y.-F. Yang, P. Liu, K. N. Houk, N. K. Garg, *Nature* **2015**, *524*, 79–83.
[5] For other amide hydrolysis/solvolysis strategies not discussed herein, see: a) T. A. Dineen, M. A. Zajac, A. G. Myers, *J. Am. Chem. Soc.* **2006**, *128*, 16406–16409; b) D. A. Evans, P. H. Carter,

C. J. Dinsmore, J. C. Barrow, J. L. Katz, D. W. Kung, *Tetrahedron Lett.* **1997**, *38*, 4535 – 4538; c) E. H. White, S. Paik, *Tetrahedron Lett.* **1994**, *35*, 7731 – 7734; d) E. H. White, *J. Am. Chem. Soc.* **1955**, *77*, 6011.

[6] a) S. Hanessian, *Tetrahedron Lett.* **1967**, *8*, 1549 – 1552; b) A. J. Kiessling, C. K. McClure, *Synth. Commun.* **1997**, *27*, 923 – 937; c) G. E. Keck, M. D. McLaws, T. T. Wager, *Tetrahedron* **2000**, *56*, 9875 – 9883.

[7] a) A. B. Charette, P. Chua, *Synlett* **1998**, 163 – 165; b) A. B. Charette, M. Grenon, *Can. J. Chem.* **2001**, *79*, 1694 – 1703; for a direct lactonization of alcohols and ethers onto amides; see: c) V. Valerio, D. Petkova, C. Madelaine, N. Maulide, *Chem. Eur. J.* **2013**, *19*, 2606 – 2610.

[8] a) M. Hutchby, C. E. Houlden, M. F. Haddow, S. N. G. Tyler, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Angew. Chem. Int. Ed.* **2012**, *51*, 548 – 551; *Angew. Chem.* **2012**, *124*, 563 – 566; b) M. C. Bröhmer, S. Mundinger, S. Bäse, W. Bannwarth, *Angew. Chem. Int. Ed.* **2011**, *50*, 6175 – 6177; *Angew. Chem.* **2011**, *123*, 6299 – 6301.

[9] For a recent review on homogenous nickel catalysis in synthesis, see: S. Z. Tasker, E. A. Standley, T. F. Jamison, *Nature* **2014**, *509*, 299 – 309.

Received: September 11, 2015
Published online: October 13, 2015

