Ruthenium Catalyzed Activation and Amidation of Carboxylic Acids

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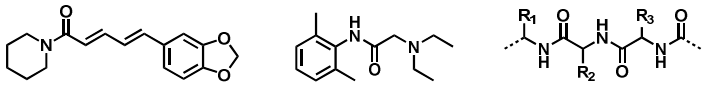
Abstract

Within the last decades the field of amide bond formation has gained more and more attention since a huge number of amides and peptides have shown interesting biological activity. As the direct coupling of carboxylic acids and amines is only possible at highly elevated temperatures with a resulting low tolerance towards functional groups,[1] a broad variety of coupling agents have been developed. However their use leads to high costs and the production of large amounts of waste, which is often hard to separate. As an alternative we have investigated the *in situ* activation of carboxylic acids with alkynes to form enol esters. A subsequent aminolysis step yields the corresponding amides along with an easily removable ketone as the only byproduct.

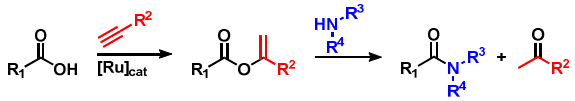
Introduction

Amide bond formations are of fundamental importance in modern chemistry. Since many biological active natural products and approximately 25% of all approved pharmaceuticals contain one or more amide bonds, it is desirable to develop efficient and sustainable methods for their synthesis.

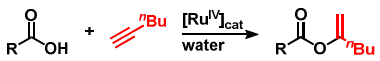


Piperin | Lidocain | Peptide Structure

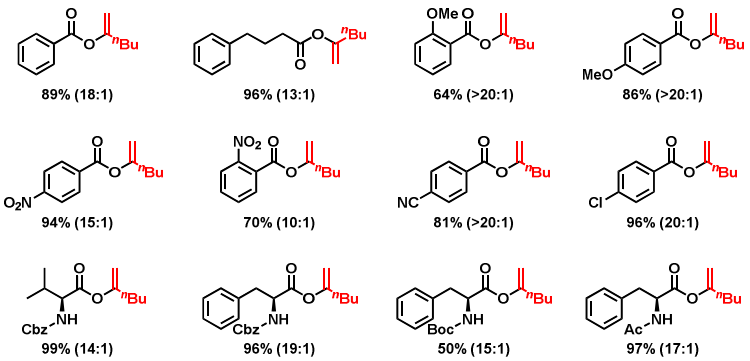
Hitherto many different methods for the coupling of carboxylic acids with amines have been described in literature, such as the use of activated acids (acyl halides/azides, anhydrides), coupling agents (such as DCC or EDC) or active esters. While each of these procedures has its fields of application, all of them bear disadvantages like high costs, toxic/carcinogenic reagents, low tolerance towards functional groups or large amounts of formed side products which are hard to separate.[2]
To overcome these disadvantages, the Ruthenium-catalyzed addition of alkynes to carboxylic acids has been employed to form enol esters as intermediates in the amide formation process. These esters are known to react readily with nucleophiles such as alcohols and amines, yielding an easy-removable, non-toxic ketone as the only byproduct.[3]



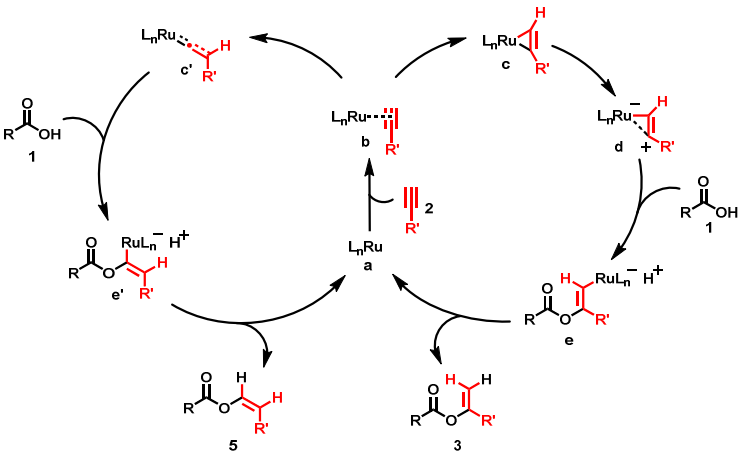
Enol Ester Formation



For the first reaction step, a highly active, air and water stable Ruthenium(IV)-based system was developed. Compared to the Ru(II)-species described in literature,[4] they are able to promote this reaction with water as a solvent. Unlike other described Ruthenium(IV)-systems,[5] this catalyst does not require any preformation prior to use. A broad variety of both carboxylic and amino acids could be coupled Markovnikov-selectively to 1-hexyne to give the corresponding enol esters in good to excellent yields.

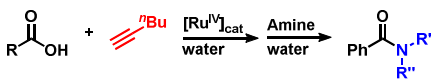


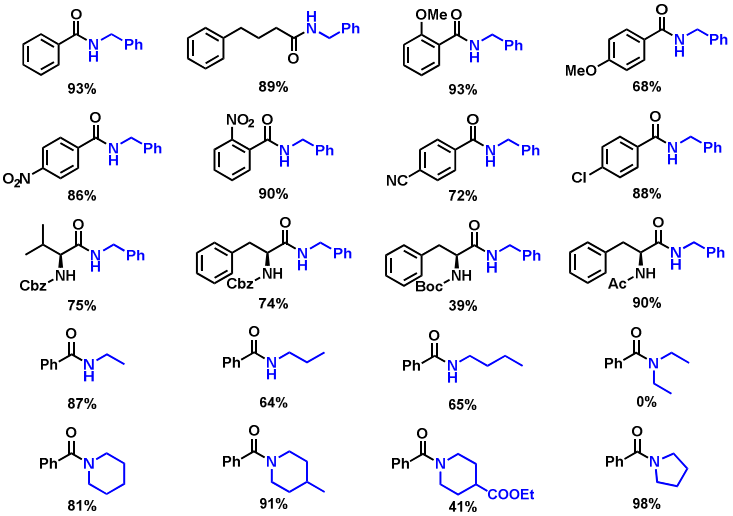
Proposed Mechanism for the Enol Ester Formation



Amide Bond Formation *via* Aminolysis of Enol Esters

Since the aminolysis of these intermediates is possible without any catalyst, our main goal was the development of a one-pot process in which the second reaction step is combinable to the first one. Due to the intrinsic reactivity of amines and carboxylic acids in water, an acid-base reaction took place and interfered with the desired reaction. By combining both steps in a sequentially performed one-pot-two-step process, this problem was eluded and the desired amides were isolated in good to excellent yields.





References and Further Information

[1] L. J. Gooßen, D. Ohlmann, P. Lange, *Synthesis* **2009**, *1*, 160–164.
[2] C. A. Montalbetti, V. Falque, *Tetrahedron* **2005**, *61*, 10827–10852.
[3] Z. Kabouche, C. Bruneau, P. Dixneuf, *Tett Lett.* **1991**, *39*, 5359–5362.
[4] L. J. Gooßen, J. Paetzold, D. Koley, *Chem. Commun.* **2003**, 706–707.
[5] J. Francos, J. Gimeno, V. Cadierno, *Organometallics* **2011**, *30*, 852–862.

Acknowledgement

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