Ruthenium-Hydride and –Vinylidene Species as key Intermediates in Hydroamidation Reactions

Matthias Arndt, Mathieu Blanchot, Kifah S. M. Salih, Annette E. Buba, Lukas J. Gooßen*

Institut für Organische Chemie, TU Kaiserslautern, Erwin-Schrödinger-Straße-54, 67663 Kaiserslautern,
Tel.: (+49) 0631 205 2046, goossen@chemie.uni-kl.de

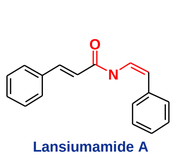
Abstract: The enamide moiety is an important motif often encountered in biologically active compounds and synthetic drugs. We have previously developed ruthenium-based complexes as effective catalysts for the *anti*-Markovnikov addition of amides, imides, and thioamides to terminal alkynes.[1] This method proved to be suitable for the synthesis of several natural products, namely botryllamides C and E, lansamide I, lansiumamides A and B. These new reaction pathways proceed in only one to three steps and yield the products in 57 to 98%, starting from cheap and easily available compounds.[2]

Comprehensive mechanistic studies were performed with the goal of getting a better understanding of the catalytic cycle. In this context the reaction mixture was investigated *in situ* by NMR (^{1}H, ^{1}H{P}, ^{2}H, ^{31}P, ^{31}P{H}, PP-COSY, HP-HMQC), ESI-MS/ -MS-MS and IR spectroscopy. Complemental deuterium labelling experiments and kinetic studies were carried out and lead to the conclusion that a redox neutral mechanism must be excluded for the hydroamidation. The new findings support a catalytic cycle starting from a ruthenium(0) species. Oxidative addition of the N-H nucleophile results in the formation of a ruthenium-amide-hydride species. The alkyne then inserts into the ruthenium-hydride bond generating a ruthenium-vinyl species, which in the rate-determining step rearranges to a ruthenium-vinylidene-hydride intermediate. This mechanism explains the *anti*-Markovnikov selectivity of such hydroamidation reactions and their restriction to terminal alkyne substrates.

The Enamide Functionality

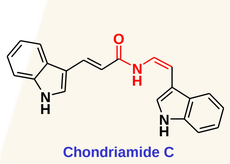
The enamide moiety is an important substructure often found in natural products and synthetic drugs.[3] Enamides and their derivatives are also versatile synthetic intermediates, *e. g.* for the preparation of heterocycles, chiral amines or amino acids.

Leaves of *Clausena Lansium*



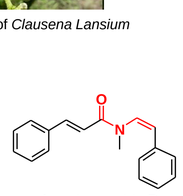
Lansiumamide A

Fruits of *Clausena Lansium*

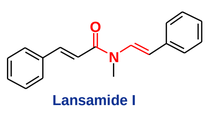


Chondriamide C

Marine ascidian *Botryllus Schlosseri*

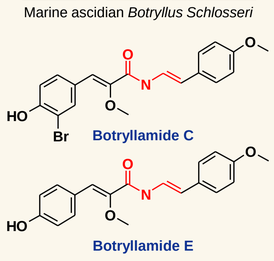


Lansiumamide B



Lansamide I

Chondria atropurpurea

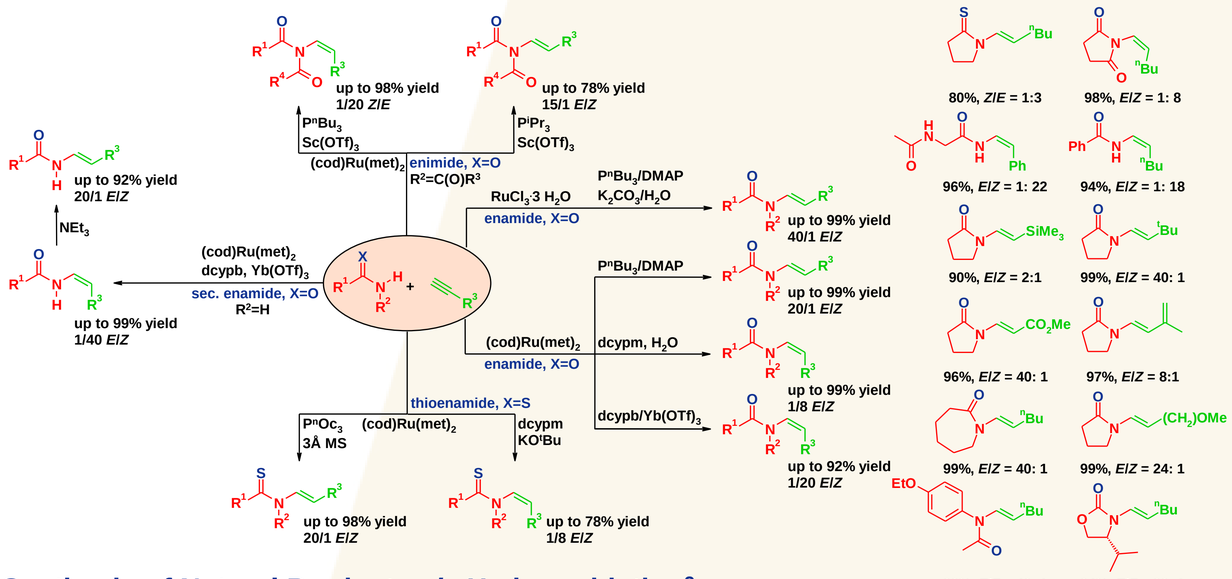


Botryllamide C

Botryllamide E

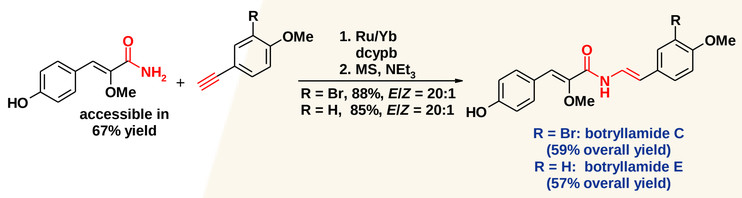
"Dream Reactions": Addition of Amides, Imides and Thioamides to Terminal Alkynes[1,4]

Traditional syntheses of enamides require harsh conditions, lead to the formation of mixtures of *E/Z* products or suffer from the limited availability of the starting materials.
A much more attractive synthetic access is the Ru-catalyzed addition of amides to alkynes:



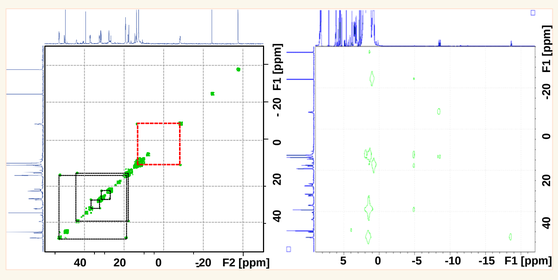
Synthesis of Natural Products *via* Hydroamidation[2]

Following the protocol for the addition of primary amides to terminal alkynes the natural products botryllamides C and E, lansiumamides A and B, and lansamide I could be synthesized in 1-3 steps and 57-98% overall yield.

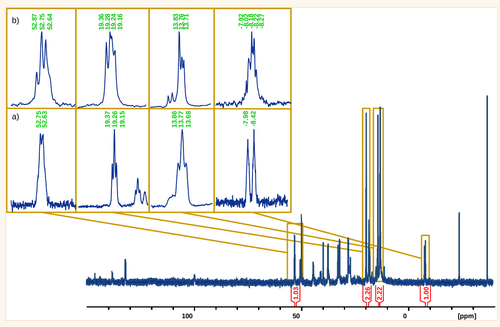


Mechanistic Investigations[5]

In situ NMR-Experiments



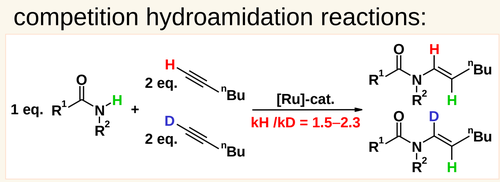
P,P-COSY and H,P-HMQC experiments with 2-pyrrolidinone; spectra measured at 298 K after 5 min at 100°C.



^{31}P-NMR experiments: with 2-pyrrolidinone after heating to 100°C for 5 min. a) ^{31}P-NMR (C_6D_6, 243 MHz, 298 K), b) ^{31}P{^{1}H}-NMR (C_6D_6, 243 MHz, 298 K).

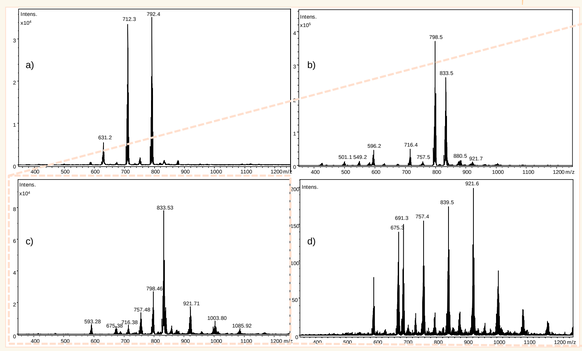
Kinetic Isotope Effects *via* NMR

competition hydroamidation reactions:

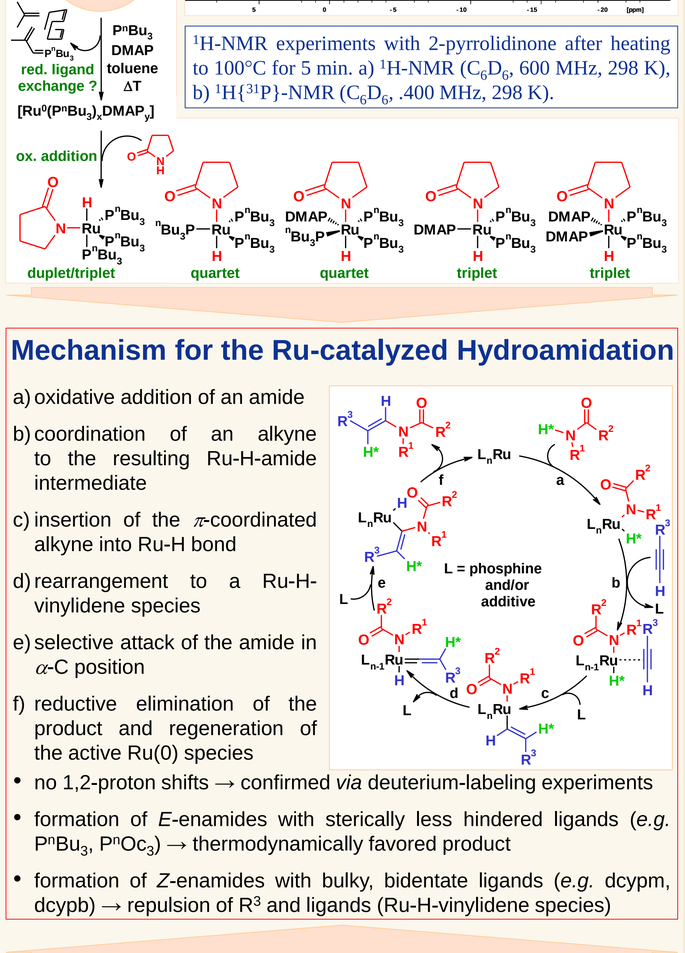


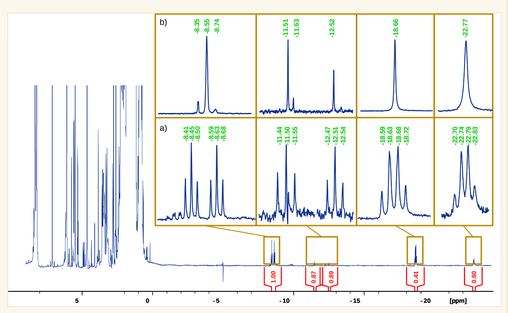
kH/kD= 1.5–2.3 → primary KIE → cleavage of the C(sp)-H bond of the alkyne in the rate-determining step → involvement of Ru-vinylidene species very likely → vinylidene formation see Wakatsuki[6] and Caulton[7]

In situ ESI-MS Experiments



ESI-MS spectra for the hydroamidation of 2-pyrolidinone and 1-hexyne. a) 100°C for 5 min without 1-hexyne; b) with 1-hexyne 5 min at 100°C; c) 40 min; d) 150 min.





^{1}H-NMR experiments with 2-pyrrolidinone after heating to 100°C for 5 min. a) ^{1}H-NMR (C_6D_6, 600 MHz, 298 K), b) ^{1}H{^{31}P}-NMR (C_6D_6, .400 MHz, 298 K).

Mechanism for the Ru-catalyzed Hydroamidation

a) oxidative addition of an amide

b) coordination of an alkyne to the resulting Ru-H-amide intermediate

c) insertion of the π-coordinated alkyne into Ru-H bond

d) rearrangement to a Ru-H-vinylidene species

e) selective attack of the amide in α-C position

f) reductive elimination of the product and regeneration of the active Ru(0) species

- no 1,2-proton shifts → confirmed *via* deuterium-labeling experiments
- formation of *E*-enamides with sterically less hindered ligands (*e.g.* P^{n}Bu$_3$, P^{n}Oc$_3$) → thermodynamically favored product
- formation of *Z*-enamides with bulky, bidentate ligands (*e.g.* dcypm, dcypb) → repulsion of R^3 and ligands (Ru-H-vinylidene species)

successful assignment of 7 different Ru intermediates and detection of [P^{n}Bu$_3$C$_4$H$_7^+$]-fragments (not displayed) → evidence for P^{n}Bu$_3$ mediated reductive ligand exchange

Literature and Further Reading (see also www.chemie.uni-kl.de/goossen)

(1) a) L. J. Gooßen, J. E. Rauhaus, D. Deng, *Angew. Chem. Int. Ed.* **2005**, *44*, 4042; b) L. J. Gooßen, K. S. M. Salih, M. Blanchot, *Angew. Chem. Int. Ed.* **2008**, *47*, 8492, c) L. J. Gooßen, M. Arndt, M. Blanchot, F. Rudolphi, F. Menges, G. Niedner-Schatteburg, *Adv. Synth. Cat.* **2008**, *350*, 2701.
(2) L. J. Gooßen, M. Blanchot, M. Arndt, K. S. M. Salih, *Synlett* **2010**, 1685.
(3) a) Yet, L. *Chem. Rev*. **2003**, *103*, 4283; b) Stefanuti, I.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2000**, *41*, 3735; c) Rao, M. R.; Faulkner, D. J. *J. Nat. Prod.* **2004**, *67*, 1064.
(4) a) L. J. Gooßen, M. Blanchot, C. Brinkmann, K. Gooßen, R. Karch, A. Rivas-Nass, *J. Org. Chem.* **2006**, *71*, 9506; b) L. J. Gooßen, M. Blanchot, K. S. M. Salih, K. Gooßen, *Synthesis* **2009**, 2283; c) L. J. Gooßen, M. Blanchot, K. S. M. Salih, R. Karch, A. Rivas-Nass, *Org. Lett.* **2008**, *10*, 4497; d) A. E. Buba, M. Arndt, L. J. Gooßen *J. Organomet. Chem.* **2010**, in press.
(5) Unpublished results.
(6) M. Tokunaga, T. Suzuki, N. Koga, T. Fukushima, A. Horiuchi, Y. Wakatsuki, *J. Am. Chem. Soc.* **2001**, *123*, 11917.
(7) M. Oliván, E. Clot, O. Eisenstein, K. G. Caulton, *Organometallics* **1998,** *17,* 3091.