Abstract: The enamine 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. This method proved to be suitable for the synthesis of several natural products, namely botryllamides C and E, lansamides 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.

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 (1H, 13C, 15N, 31P, 19F, 77Se), COSY, 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(II) 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-vinylidene 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 Enamine Functionality

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

"Dream Reactions": Addition of Amides, Imides and Thioamides to TerminalALKynes

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

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

In situ NMR Investigations

Mechanical Investigations

Mechanism for the Ru-catalyzed Hydroamidation

In situ ESI-MS Experiments

In situ NMR experiments

Kinetic Isotope Effects via NMR

Guided by high-field NMR spectroscopic investigation, the mechanism turned out to be a facile [2+2]-cycloaddition of the ruthenium enamide complex with the alkene which is followed by intramolecular C-H insertion.

In summary, the Ru-catalyzed hydroamidation is a versatile and efficient method for the synthesis of diversified enamides.

![Chemical structures and diagrams related to the text content.](image-url)