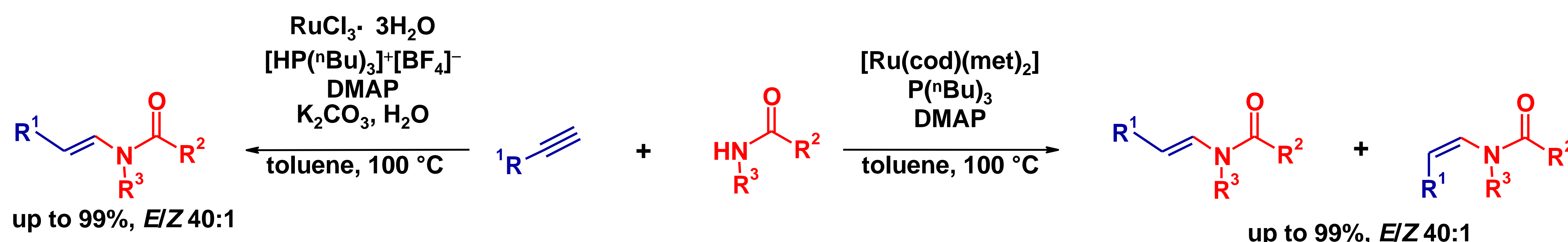


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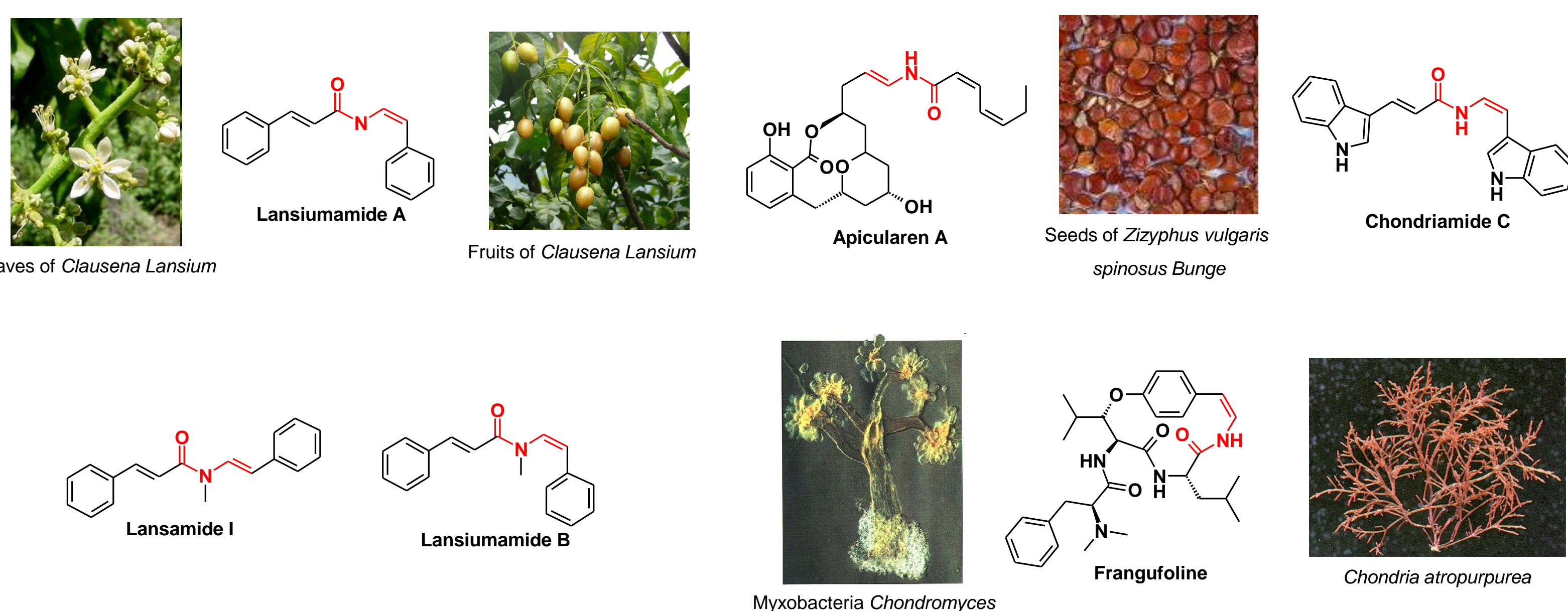


Abstract: The enamide moiety is an important motif often encountered in biologically active compounds and synthetic drugs. We have previously developed ruthenium-based complexes as effective catalysts for the *anti*-Markovnikov addition of amides, imides, and thioamides to terminal alkynes.¹ In an attempt to gain more insight about the mechanism we spectroscopically monitored *in situ* our catalytic system. The information thus obtained in combination with data provided by some complementary RuCp-complex catalyzed hydroamidation experiments allowed us to devise a new, second generation catalyst based on the inexpensive and easy-to-handle RuCl₃.² After diligent optimization, the new protocol matched or even surpassed the yields and selectivities obtained with the first-generation catalyst at a fraction of the original cost. The hydroamidation method proved to be an extremely valuable tool for the synthesis of natural products.



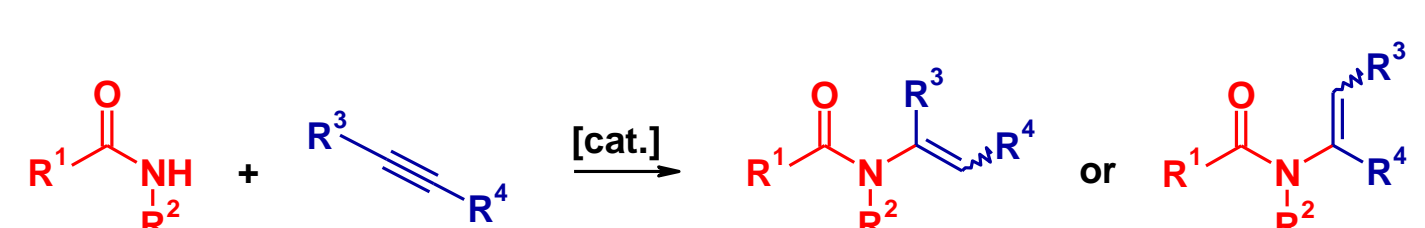
The Enamide Functionality

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 chiral amines or amino acids.



"Dream Reaction"

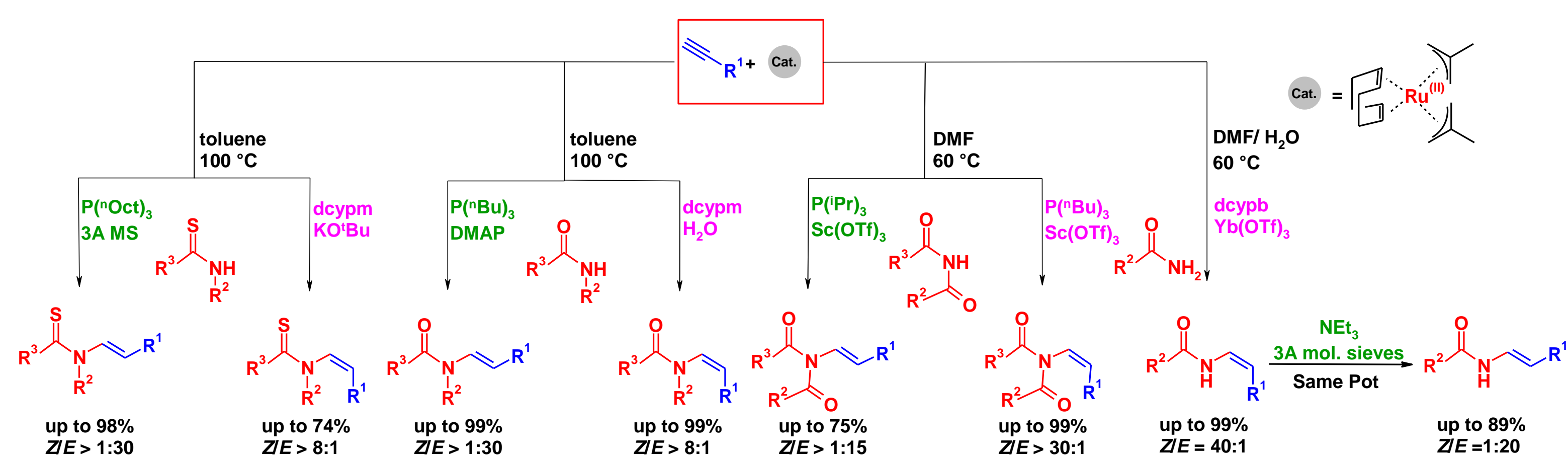
Traditional syntheses of enamides require harsh conditions, lead to the formation of mixtures of *E/Z* products or suffer from the limited availability of the starting materials. A much more attractive synthetic access route would be a catalytic addition of amides to alkynes.



However, while related addition reactions of carboxylates,⁴ water,⁵ and amines⁶ are well-established, to the best of our knowledge no efficient catalyst for a hydroamidation reaction has been reported.⁷

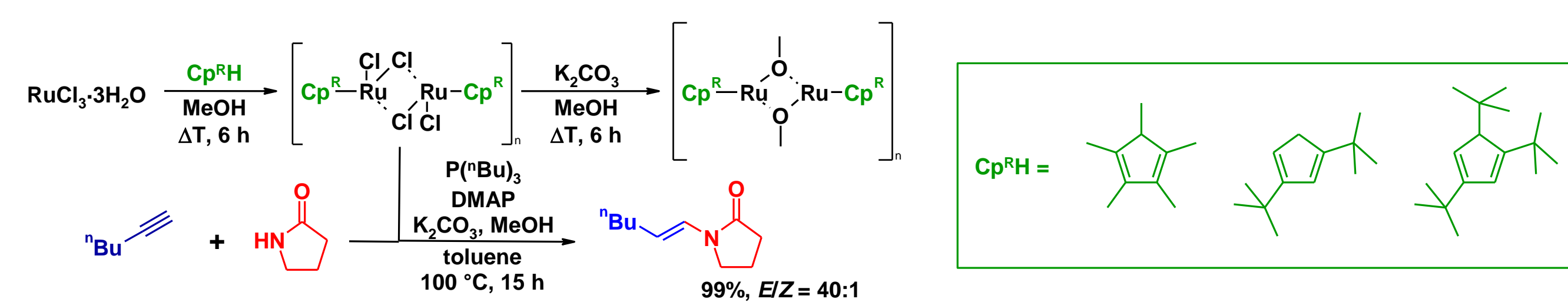
Catalyzed Addition of Amides, Imides and Thioamides to Terminal Alkynes¹

Recently, we developed new ruthenium-based catalyst systems for the *anti*-Markovnikov addition of secondary amides^{1a}, imides,^{1b} thioamides^{1c} or primary amides^{1d} to terminal alkynes. These systems proved to be generally applicable to a plethora of amides, imides and thioamides.



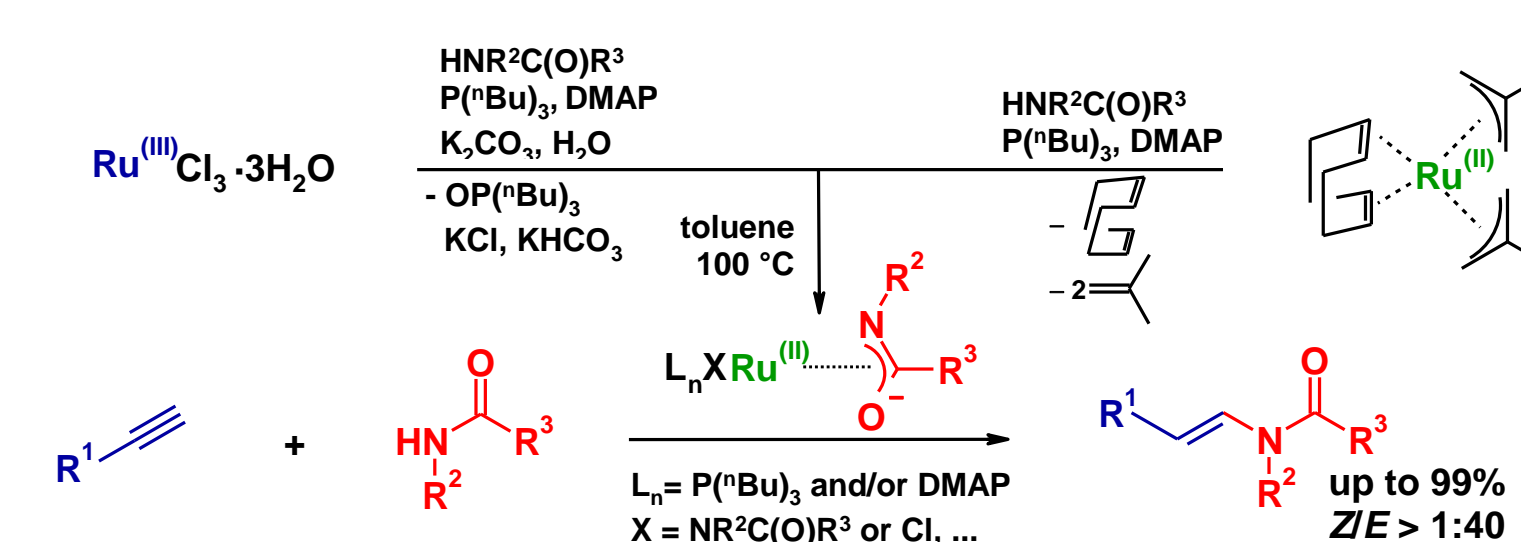
Development of a RuCl₃·3H₂O-based Protocol for the Catalytic Hydroamidation²

In an attempt to reverse the regioselectivity of the hydroamidation in favour of the Markovnikov product, we synthesized sterically demanding and electron-rich RuCp-complexes and utilized them in hydroamidation reactions.



Unfortunately no beneficial influence of the Cp-Ligand could be observed. Furthermore, the results matched those of the [Ru(cod)(met)₂]-based protocol.⁸

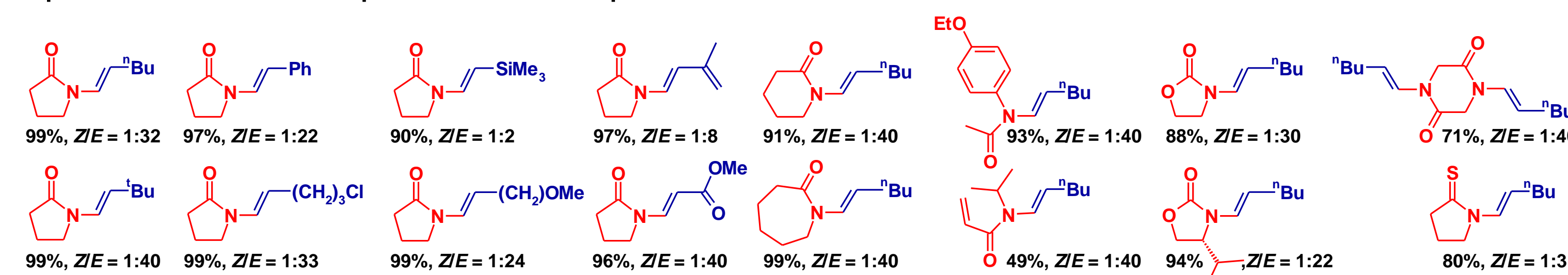
The information thus obtained in combination with spectroscopic investigations led us to the discovery of a new RuCl₃-based protocol. The key step is the selective reduction of Ru^{III} to Ru^{II} during the catalyst preformation, which is mediated by the employed phosphine, a process assisted by water.



Main features

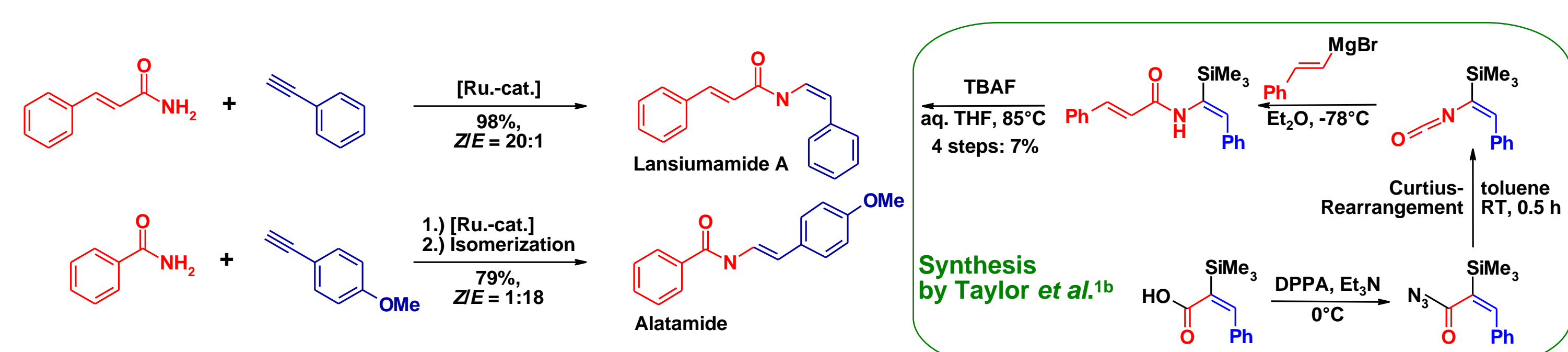
- 90% reduction of the catalyst cost
- replacement of air-sensitive, liquid P(ⁿBu)₃ by its tetrafluoroborate salt
- better fit for large-scale applications
- dramatic improvement of the synthetic applicability

Representative examples of the scope are illustrated below.



Synthesis of Natural Products via Hydroamidation^{1d}

Following the protocol for the addition of primary amides to terminal alkynes the natural products Lansiumamide A and Alatomide could be synthesized in high yields and stereoselectivities.



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

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- (8) Unpublished results.