Ruthenium-Catalyzed Stereoselective *anti*-Markovnikov Addition of Thioamides to Alkynes

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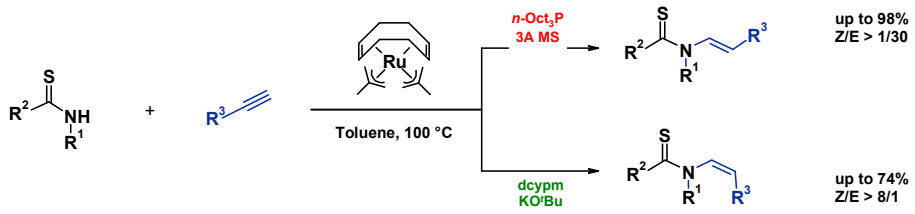
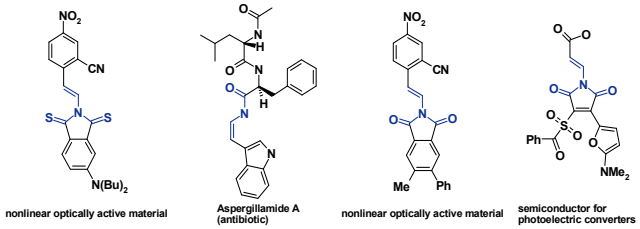
Abstract: Based on our previous work on the addition of secondary amides and imides to terminal alkynes, we have developed a broadly applicable protocol for the catalytic addition of others N-nucleophiles such as thioamides and thiocarbamates to terminal alkynes. Depending on the phosphine and the additives employed, both the (*E*)- and the (*Z*)-isomer can be accessed stereoselectively. The developed catalyst system allows the conversion of inactivated alkynes (such as 1-Hexine) as good as activated ones to the desired products.



The Enamide Functionality

Enamides are abundant substructures in natural products and bioactive molecules.[1] As this moiety has been reported to function as a pharmacophore, enamides are routinely included in compound libraries used for lead discovery. In sharp contrast, thioenamides, which should be of considerable interest as structural variants of such subunits with distinct electronic and steric properties, are only scarcely found in the chemical literature. Among the very few reactions investigated starting from this compound class are the photochemical preparation of isoquinolinethiones or thiazolines from aromatic thioenamides.[2]

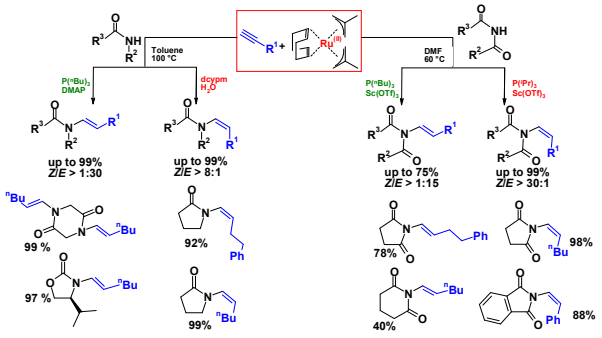


nonlinear optically active material | Aspergillamide A (antibiotic) | nonlinear optically active material | semiconductor for photoelectric converters

The remarkable neglect of thioenamides in organic synthesis and drug discovery is easily explained as no concise and generally applicable synthetic entry to this substrate class has yet been reported: At present, thioenamides are only accessible by treating the analogous enamides, which themselves are not easily synthesized, with Lawesson's reagent, or other aggressive sulfurizing agents.[2,3]

Catalyzed Addition of Amides and Imides to Terminal Alkynes[4]

Recently, we disclosed the first pattern of an efficient catalytic addition reaction of secondary amides to terminal alkynes,[4a] using a catalyst generated *in situ* from Ru(cod)[met]$_2$, phosphine and DMAP. After that, we discovered new catalyst systems based on the same Ru-sources able to perform the addition of imides[4b] to terminal alkynes in very good yields and selectivities. These systems proved to be generally applicable to a plethora of amides and imides.

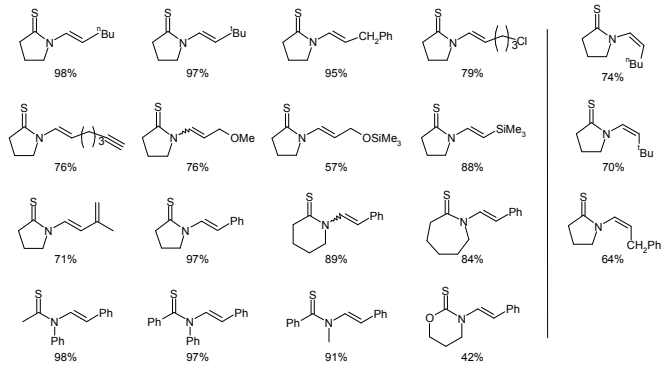


Addition of Thioamide to Alkynes[5]

However, none of previous catalysts mediates the conversion of thioenamides. This may be attributed to the substantially higher acidity of thioamides compared to amides (pKa of 2-pyrrolidone: 24.2, pyrrolidine-2-thione: 18.1),[6] along with the fact that sulfur-containing compounds are known catalyst poisons due to their strong interaction with late transition metals.

Quite recently, we revealed a new protocol including an effective catalyst generated *in situ* from Ru(cod)[met]2, tri-*n*-octylphosphine and molecular sieves to catalyze the addition of thioamides to terminal alkynes. Moderate to excellent yields were reached with good selectivities of (*E*)-products. On the other hand, when the bidentate phosphine, bis(dicyclohexylphosphino)methane, combined with the same Ru-source and potassium *t*-butoxide were necessary to convert the selectivity to the (*Z*)-product in reasonable yields.

Under the optimized conditions, *anti*-Markovnikov-products are observed exclusively, and products arising from reaction at the *S*- rather than the *N*-terminus of the thioamide could never be detected.



The practical synthesis of thioenamides *via* regio- and stereoselective ruthenium-catalyzed anti-Markovnikov promises to meet this long-standing synthetic challenge.

Future perspectives

We are presently pursuing the mechanistic steps of addition of various *N*-neucleophile to terminal alkynes using deuterium-labeled starting materials. An intermediacy of Ruthenium vinylidene complexes which including 1,2-H shifting would be clear to investigate using 1-[D]-alkynes or deuterated amides in the catalytic reaction.

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

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