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

Lukas J. Goossen,*,† Mathieu Blanchot,† Kifah S. M. Salih,† Ralf Karch,‡ and Andreas Rivas-Nass‡

Fachbereich Chemie, TU Kaiserslautern, Erwin-Schrödinger-Strasse, Building 54, D-67663 Kaiserslautern, Germany, and UMICORE AG & CO. KG, Rodenbacher Chaussee 4, D-63457 Hanau, Germany

goossen@chemie.uni-kl.de

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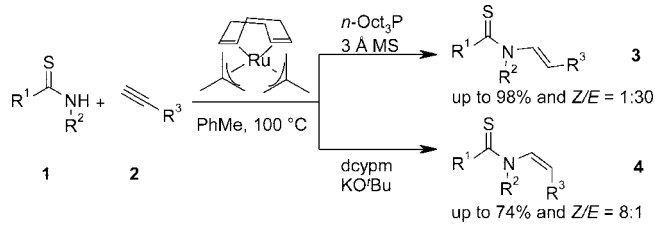
ABSTRACT



A catalyst system generated *in situ* from bis(2-methallyl)-cycloocta-1,5-diene-ruthenium(II) and a phosphine was found to efficiently catalyze the addition of thioamides to terminal alkynes with exclusive formation of the *anti*-Markovnikov thioenamide products. The stereoselectivity of the addition is usually high and controlled by the choice of the phosphine ligand, whereas the (*E*)-isomers are predominantly formed in the presence of tri(*n*-octyl)phosphine, the use of bis(dicyclohexylphosphino)methane preferentially leads to the formation of the (*Z*)-configured thioenamides.

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] The remarkable neglect of thioenamides in organic synthesis and drug discovery is easily explained by the lack of a concise and generally applicable synthetic entry to this substrate class: at present, thioenamides are only accessible by treating the analogous enamides, which themselves are not easily synthesized, with Lawesson's reagent[2,3] or other similarly aggressive sulfurizing agents.[4] This synthetic approach does not tolerate many sensitive functionalities, and the required workup and purification steps are rather complex and difficult. Thus, the development of an expedient synthetic entry to the thioenamides substrate class remains a highly desirable target.

The practical synthesis of thioenamides via regio- and stereoselective ruthenium-catalyzed *anti*-Markovnikov addition of thioamides to terminal alkynes disclosed herein (see equation in Abstract) promises to meet this long-standing synthetic challenge.[5]

† TU Kaiserslautern Chemie.
‡ UMICORE AG & CO. KG.

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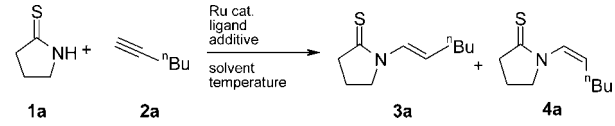
The analogous addition of nucleophiles such as carboxylates,[6] amines,[7] water,[8] amides,[9] and imides[10] to alkynes represents a particularly atom-economical entry to other synthetically valuable substrate classes, provided that the regio- and stereochemistry of the transformation can efficiently be controlled by the catalyst system. We have previously developed several Ru(II)-catalysts that allow the selective *anti*-Markovnikov addition of various nitrogen nucleophiles, including amides, urethanes, carbamates, imides, and ureas, to terminal alkynes.[9,10] However, none of these catalysts mediates the conversion of thioenamides. This may be attributed to the substantially higher acidity of thioamides compared to amides (pK_a of 2-pyrrolidone, 24.2; pyrrolidine-2-thione, 18.1),[11] along with the fact that sulfur-containing compounds are known catalyst poisons due to their strong interaction with late transition metals. As an added difficulty, thioamides are ambident nucleophiles and can react at the nitrogen or sulfur terminus depending on the electrophile used, following the HSAB concept. For example, the reaction of pyrrolidine-2-thione with ethyl bromoacetate affords the corresponding thioimino ester,[12] whereas with benzoyl chloride, the thioenamide is formed.[13] This additional chemoselectivity issue also had to be controlled in our planned transition metal-catalyzed reaction.

To identify an efficient catalyst for the desired hydrothioamidation, we selected the reaction of pyrrolidine-2-thione (**1a**) with 1-hexyne (**2a**) as the model system and systematically examined the catalytic activity of various ruthenium sources in combination with different ligands, solvents, additives, and reaction conditions (Table 1). We initially employed a combination of bis(2-methallyl)-cycloocta-1,5-diene-ruthenium(II) [(cod)Ru(met)$_2$] with tri(*n*-butyl)phosphine and 4-(dimethylamino)pyridine (DMAP) in toluene, which was the most effective system for the analogous addition of amides to alkynes. Under these conditions, *N*-((*E*)-hex-1-enyl)pyrrolidine-2-thione (**3a**) was obtained in rather low yield and unsatisfactory stereoselectivity along with alkyne oligomerization products (entry 1). Substituting DMAP with inorganic bases led to higher yields but no improvements in selectivity (entry 2). Mild Lewis acids such as lithium chloride or 3 Å molecular sieves improved both yield and selectivity, with the added beneficial effect of the latter that it removed water from the reaction mixture, thus preserving the products from hydrolysis. As a result, **3a** was obtained in 93% yield and 11:1 stereoselectivity (entries 3, 4). Its identity was confirmed by comparison to a sample that was prepared via a literature procedure.[13] All alternative Ru-precursors tested were less effective than the (cod)Ru(met)$_2$ initially employed (entries 5−8). Furthermore, the use of tri(*n*-alkyl)phosphines was crucial for achieving high selectivities in favor of the (*E*)-products, best results having been obtained with tri(*n*-octyl)phosphine (entries 9−14). Nonpolar aromatic solvents such as toluene or mesitylene were most effective, but other solvents can also be used (entries 15−18). A temperature of 100 °C represents the best compromise between turnover rate and stereoselectivity (entries 19, 20).

Table 1. Optimization of the Catalyst and Conditions[a]



1a 2a 3a 4a

entry	Ru-precursor	ligand	additive	solvent	yield/% (**3a**:**4a**)[b]
1	(cod)Ru(met)$_2$	*n*-Bu$_3$P	DMAP	PhMe	40 (6:1)
2	"	"	K_2CO_3	"	84 (5:1)
3	"	"	LiCl	"	87 (9:1)
4	"	"	3 Å MS	"	93 (11:1)
5	[(*p*-cymene)RuCl$_2$]$_2$	"	"	"	72 (10:1)
6	(cod)RuCl$_2$	"	"	"	80 (9:1)
7	Ru$_3$(CO)$_{12}$	"	"	"	0 (nd)
8	RuCl$_3$	"	"	"	33 (8:1)
9	(cod)Ru(met)$_2$	PPh$_3$	"	"	43 (5:1)
10	"	PFur$_3$	"	"	66 (2:1)
11	"	*t*-Bu$_3$P	"	"	10 (nd)
12	"	*n*-Oct$_3$P	"	"	96 (16:1)
13	"	dppm	"	"	80 (4:1)
14	"	dcypm	"	"	15 (1:1)
15	"	*n*-Oct$_3$P	"	glyme	85 (12:1)
16	"	"	"	EtOH	55 (10:1)
17	"	"	"	DMF	98 (6:1)
18	"	"	"	mesit.	91 (13:1)
19[c]	"	"	"	"	82 (12:1)
20[d]	"	"	"	"	87 (16:1)
21	"	dcypm	K_2CO_3	PhMe	64 (1:1.5)
22	"	"	KO^{t}Bu	"	76 (1:2)
23[e]	"	*n*-Oct$_3$P	3 Å MS	"	84 (14:1)

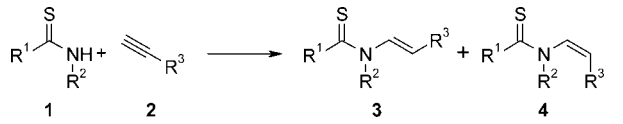
[a] Conditions: 0.50 mmol pyrrolidine-2-thione, 1.00 mmol 1-hexyne, 0.01 mmol Ru-precursor, 0.03 mmol ligand (0.015 mmol for chelating phosphines), 0.02 mmol additive or 250 mg 3 Å MS, solvent (1.5 mL), 100 °C, 15 h; dppm = bis(diphenylphosphino)methane, dcypm = bis(dicyclohexylphosphino)methane, mesit. = mesitylene. [b] Yields and selectivities determined by GC using *n*-tetradecane as internal standard. [c] Temperature of 80 °C. [d] Temperature of 120 °C. [e] Pyrrolidine-2-thione (0.5 mmol), 1-hexyne (0.5 mmol).

In an attempt to invert the stereoselectivity of the addition, we combined the ligand with the lowest (*E*)-selectivity, bis(dicyclohexylphosphino)methane (dcypm), with various additives, and found that the (*Z*)-isomer can indeed be obtained as the major product with 76% yield and 1:2 selectivity in the presence of potassium *tert*-butoxide (entries 21, 22). The alkyne is best used in excess to ensure complete conversion of the thioamide, as some alkyne is consumed by competing oligomerizations (entry 23).

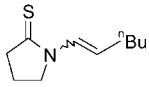
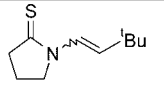
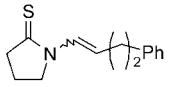
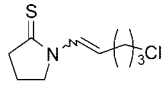
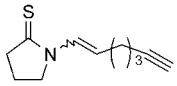
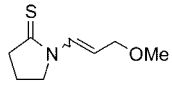
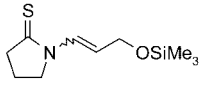
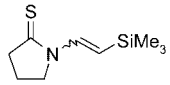
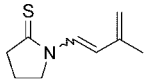
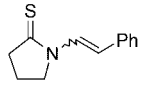
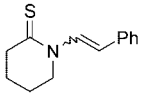
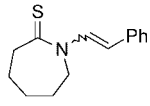
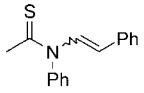
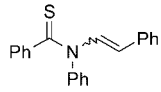
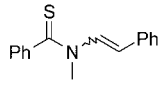
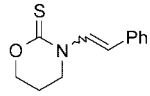
Under optimized conditions (entries 12, 22), *anti*-Markovnikov-products are observed exclusively, and products arising from reaction at the *S*- rather than the *N*-terminus of the thioamide could never be detected. We believe that the reaction follows a mechanism analogous to that proposed for the addition of imides to alkynes:[10] The alkyne first coordinates to an Ru(II)-thioamide species generated from the catalyst precursor, then a thioamide anion adds to the C−C triple bond giving rise to a η^1-Ru-vinyl complex.

(5) For a non-catalytic addition of thioamides to conjugated alkynes, see: Nakhmanovich, A. S.; Glotova, T. E.; Komarova, T. N.; Skvortsova, G. G.; Sigalov, M. B.; Modonov, V. B. *Zh. Org. Khim.* **1983**, *19*, 1428.

Table 2. Substrate Scope of the Thioenamide Synthesis[a]



1 2 3 4

product	yield/%[b] (ratio **3**/**4**)	product	yield/%[b] (ratio **3**/**4**)
 **3/4a**	98 (16:1) 74 (1:2)[c]	 **3/4b**	97 (13:1) 70 (1:8)[c]
 **3/4c**	95 (7:1) 64 (1:2)[c]	 **3/4d**	79 (15:1)[d]
 **3/4e**	76 (11:1)	 **3/4f**	76 (11:1)[d]
 **3/4g**	57 (19:1)	 **3/4h**	88 (1:1)[d]
 **3/4i**	71 (3:1)[d]	 **3/4j**	97 (6:1)
 **3/4k**	89 (5:1)[d,e]	 **3/4l**	84 (30:1)[d]
 **3/4m**	98 (30:1)[d]	 **3/4n**	97 (30:1)
 **3/4o**	91 (15:1)[d]	 **3/4p**	42 (2:1)[d]

[a] Conditions: 1.00 mmol thioamide, 2.00 mmol alkyne, 0.02 mmol (cod)Ru(met)$_2$, 0.06 mmol *n*-Oct$_3$P, 500 mg 3 Å MS, 3 mL toluene, 100 °C, 15 h. [b] Isolated yields, in brackets the stereoisomeric ratio as determined by GC. [c] (cod)Ru(met)$_2$ (0.05 mmol), 0.06 mmol dcypm, 0.04 mmol KO^{t}Bu. [d] (cod)Ru(met)$_2$ (0.05 mmol), 0.15 mmol *n*-Oct$_3$P. [e] Stereoisomeric ratio as determined by ^{1}H NMR.

Depending on whether the attack occurs from inside or outside the coordination sphere of the ruthenium, the metal will end up in (*E*)- or (*Z*)-position to the thioamide group. The product is liberated by protonolysis, regenerating the initial Ru(II)-species and completing the catalytic cycle.

To investigate the scope of the (*E*)-selective hydrothioamidation protocol, we applied it to the addition of a broad variety of thioamides to several terminal alkynes (Table 2). We were pleased to find that on one hand, pyrrolidine-2-thione added smoothly to various alkynes, among them alkyl- and aryl-substituted alkynes, trimethylsilylacetylene, and conjugated enynes. On the other hand, phenylacetylene reacted with a range of secondary thioamides bearing aromatic or aliphatic substitutents, as well as with an example for a thiocarbamate. In most cases, the products were obtained in good yields and high selectivities for the (*E*)-configured *anti*-Markovnikov-thioenamides. These representative examples illustrate that this protocol is likely to be generally applicable to the synthesis of functionalized (*E*)-thioenamides. Primary thioamides and internal alkynes were not converted.

The scope of the complementary (*Z*)-selective hydrothioamidation was also tested on a number of examples. The protocol and appears to be as high-yielding, but so far, the level of stereoselectivity never exceeded a moderate 1:8 ratio. Further work is aimed at extending the synthetic utility of this complementary protocol by improving the (*Z*)-selectivity with the help of customized ligands.

In summary, a Ru-based catalyst system has been developed that efficiently mediates the addition of thioamides to terminal alkynes, giving rise to (*E*)-configured *anti*-Markovnikov products. Various thioenamides can thus be obtained in high regio- and stereoselectivities, among them substrates attractive for further derivatization, for example, trimethylsilyl-thioenamides for cross-couplings, and thiodienamides for hetero-Diels−Alder reactions. A reversal of the stereoselectivity in favor of the (*Z*)-products was also achieved by modifying the phosphine ligand and base.

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Supporting Information Available: Complete experimental procedures including analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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