Homogeneous Catalysis

Ru-Catalyzed Anti-Markovnikov Addition of Amides to Alkynes: A Regio- and Stereoselective Synthesis of Enamides**

Lukas J. Gooßen, Jan E. Rauhaus, and Guojun Deng*

The enamide group is an important substructure that is often found in natural products[1] and synthetic drugs that have, amongst others, sedative,[2] cytotoxic,[3] or anti-inflammatory[4] properties. Moreover, they are versatile synthetic intermediates that can serve as substrates for polymerizations,[5] [4+2] cycloadditions,[6,7] cross-coupling reactions,[8] Heck olefinations,[9] halogenations,[8] enantioselective additions,[10] or asymmetric hydrogenations.[11] However, a regio- and stereoselective construction of enamide substructures is not at all trivial. Traditional syntheses—for example, from carbonyl compounds and amides[12] or from hydroxylamines and acetic anhydride[13]—require harsh conditions and yield mixtures of *E*/*Z* products. Metal-catalyzed coupling reactions of vinyl halides,[14] vinyl triflates,[15] or vinyl ethers[16] proceed under milder conditions but suffer from the limited availability of these substrates.

In our opinion, a catalytic addition of amides to alkynes would be an ideal synthetic entry to enamides, since it would use readily available starting materials and be inherently atom-economic (Scheme 1). Related addition reactions of carboxylates,[17] water,[18] and amines[19] are well-established.[20] However, to the best of our knowledge, there is only one reported protocol in the literature for a catalytic hydroamidation reaction of terminal alkynes:[21] Watanabe et al. found that in the presence of Ru_3CO_{12}/trialkylphosphane catalysts, a very limited range of formanilides and acetanilides can be added to 1-hexyne, albeit at extremely high temperatures (180 °C) and under pressure.[22] Clearly, much more effective catalyst systems are required to allow an application of this reaction in organic synthesis.

To identify a catalyst system for the desired hydroamidation reaction, we chose the reaction of 1-hexyne (**1a**) with 2-pyrrolidinone (**2a**) as a model system and investigated the catalytic activity of several ruthenium complexes under various conditions (Scheme 2, Table 1). As anticipated, no

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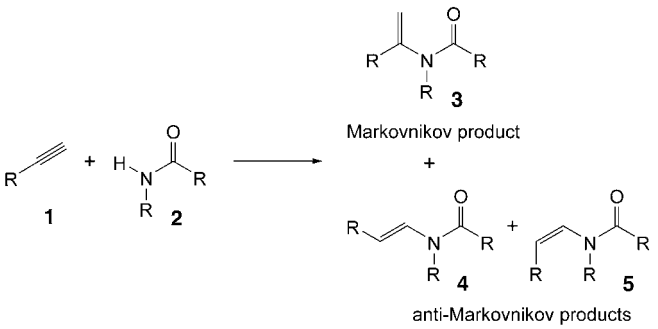
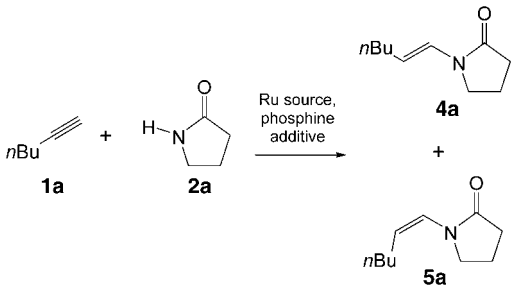


Scheme 1. Addition of amides to terminal alkynes.



Scheme 2. Addition of 2-pyrrolidinone to 1-hexyne.

enamide products were observed in the presence of the literature systems[21c,22] at ambient pressure and a temperature of only 100 °C (entries 1 and 2). In contrast, several other ruthenium sources, although inactive themselves (entries 2–5), displayed noticeable catalytic activity when combined with tri-*n*-butylphosphane (entries 6–10). In all cases, the anti-Markovnikov products **4a** and **5a** were formed regioselectively. However, a significant stereoselectivity ($E/Z > 10:1$) was observed only for 1,5-cyclooctadienebis(2-methallyl)ruthenium [Ru(methallyl)$_2$(cod)]; with all other ruthenium sources, **4a** and **5a** were formed in almost equal amounts. The reaction of [Ru(methallyl)$_2$(cod)] with monodentate phosphanes leads to the formation of isolable bis(2-methallyl)bis(phosphane)ruthenium(II) complexes, which show the same reactivity as the mixtures prepared in situ (entry 16).

Among all the ligands investigated, tri-*n*-butylphosphane gave the highest *E* selectivity in combination with [Ru(methallyl)$_2$(cod)] (entries 10–15). Triarylphosphanes were less effective, and use of the chelating phosphane bis(dicyclohexylphosphanyl)methane ($Cy_2PCH_2PCy_2$) even led to a reversal of the stereoselectivity in favor of the *Z* product (entry 12).

As in our recently disclosed protocol for the anti-Markovnikov addition of carboxylic acids to alkynes,[17c] the addition of pyridine derivatives (2 equiv with respect to ruthenium) strongly enhanced the catalyst performance; other additives had no beneficial effects (entries 17–22). 4-(*N*,*N*-Dimethylamino)pyridine (DMAP), in particular, led to a significant increase in both the activity and the stereoselectivity of the [Ru(methallyl)$_2$(cod)]/P*n*Bu$_3$ catalyst system, and allowed the synthesis of **4a** in almost quantitative yield with an *E*/*Z* selectivity of 28:1 (entry 22). Gratifyingly,

Table 1: Optimization of reaction conditions for Scheme 2.[a]

Entry	Ru source	Ligand	Additive	Yield [%]	**4a**/**5a**[b]
1	$[Ru_3(CO)_{12}]$	P*n*Bu$_3$	–	0	nd
2	$RuCl_3 \cdot H_2O$	–	–	0	nd
3	[Ru(acac)$_3$]	–	–	0	nd
4	$[Ru_3(CO)_{12}]$	–	–	0	nd
5	$[\{RuCl_2(p\text{-cymene})\}_2]$	–	–	0	nd
6	$RuCl_3 \cdot H_2O$	P*n*Bu$_3$	–	79	1:1
7	[Ru(acac)$_3$]	P*n*Bu$_3$	–	0	nd
8	$[\{RuCl_2(p\text{-cymene})\}_2]$	P*n*Bu$_3$	–	95	1:1
9	$[RuCl_2(cod)]$	P*n*Bu$_3$	–	92	1:1
10	[Ru(methallyl)$_2$(cod)]	P*n*Bu$_3$	–	67	11:1
11	[Ru(methallyl)$_2$(cod)]	PCy_3	–	25	3:1
12	[Ru(methallyl)$_2$(cod)]	$Cy_2PCH_2PCy_2$	–	30	1:2
13	[Ru(methallyl)$_2$(cod)]	P(1-Np)$_3$	–	0	nd
14	[Ru(methallyl)$_2$(cod)]	P(*p*-FC$_6$H$_4$)$_3$	–	85	3:1
15	[Ru(methallyl)$_2$(cod)]	PPh_3	–	62	2:1
16	[Ru(methallyl)$_2$(PPh_3)$_2$]	–	–	66	2:1
17	[Ru(methallyl)$_2$(cod)]	P*n*Bu$_3$	$AgNO_3$	0	nd
18	[Ru(methallyl)$_2$(cod)]	P*n*Bu$_3$	NaO*t*Bu	52	9:1
19	[Ru(methallyl)$_2$(cod)]	P*n*Bu$_3$	NEt_3	61	5:2
20	[Ru(methallyl)$_2$(cod)]	P*n*Bu$_3$	DABCO	50	5:1
21	[Ru(methallyl)$_2$(cod)]	P*n*Bu$_3$	pyridine	95	19:1
22	[Ru(methallyl)$_2$(cod)]	P*n*Bu$_3$	DMAP	93	28:1
23	[Ru(methallyl)$_2$(cod)]	$Cy_2PCH_2PCy_2$	DMAP	<5	nd
24	[Ru(methallyl)$_2$(cod)]	P*n*Bu$_3$	DMAP/H_2O[c]	86	21:1
25[d]	[Ru(methallyl)$_2$(cod)]	P*n*Bu$_3$	DMAP	88	28:1
26[e]	[Ru(methallyl)$_2$(cod)]	P*n*Bu$_3$	DMAP	84	33:1
27	[Ru(methallyl)$_2$(cod)]	$Cy_2PCH_2PCy_2$	H_2O[c]	75	1:5
28	[Ru(methallyl)$_2$(cod)]	$Cy_2PCH_2PCy_2$	H_2O[f]	98	1:5

[a] Conditions: pyrrolidinone (1.0 mmol), 1-hexyne (2.0 mmol), ruthenium source (0.02 mmol), ligand (0.06 mmol; or 0.03 mmol for chelating ligands), additive (0.04 mmol), toluene (3 mL), 100 °C, 15 h. The yields and selectivities were determined by GC using *n*-tetradecane as the internal standard. Abbreviations: acac = acetylacetonate; Np = naphthyl; DABCO = 1,4-diazabicyclo[2.2.2]octane. [b] nd = not determined. [c] 0.5 mmol H_2O; [d] The reaction vessel was briefly purged with air. [e] 1.2 mmol 1-hexyne. [f] 8-mmol H_2O.

the presence of air and moisture had only a minor influence on the yields and selectivities of this optimized reaction protocol (entries 22, 24, and 25).

Since *Z* enamides are of similar synthetic importance but particularly hard to synthesize,[23] we next set out to identify a complementary *Z*-selective hydroamidation catalyst. Starting with the [Ru(methallyl)$_2$(cod)]/$Cy_2PCH_2PCy_2$ system, which had already shown some *Z* selectivity (entry 12), we again studied the influence of additives. Interestingly, this catalyst was completely inhibited by the addition of DMAP (entry 23), while other bases and additives had only a minor influence on the reaction outcome. Only the addition of small quantities of water increased both its activity and *Z* selectivity, such that **5a** also became accessible in excellent yield (99 %, $Z/E = 5:1$; entries 27 and 28).

To make up for losses due to oligomerization and evaporation, the alkyne is best used in a slight excess of at least 1.2 equivalents (entries 22 and 26).

Currently, we can only speculate about the exact reaction mechanism; more in-depth investigations are underway. The *Z*-selective protocol is likely to follow the mechanism

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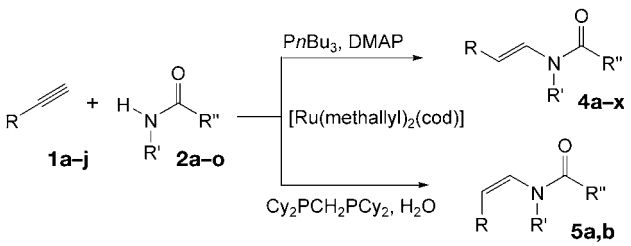
proposed for the addition of carboxylic acids to alkynes,[17] but it is difficult to pinpoint the origin of the reversal of selectivity when adding monodentate phosphanes and DMAP. A conceivable mechanism for the *E*-selective protocol might involve oxidative addition of the N–H bond to the ruthenium, followed by insertion of the alkyne into the resultant metal–nitrogen bond, and reductive elimination of the enamide product. On the other hand, the two mechanisms may mainly differ in concerted against stepwise addition of the nucleophile and the proton.[17a,b]

To investigate the scope of this new hydroamidation protocol, we applied it to the addition of a broad variety of nitrogen nucleophiles to several terminal alkynes (Scheme 3).

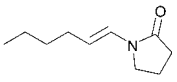
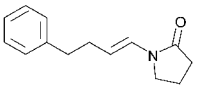
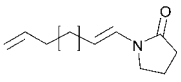
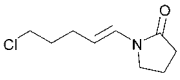
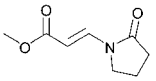
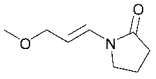
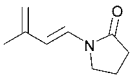
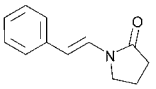
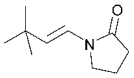
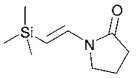
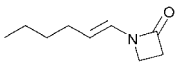
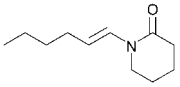
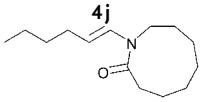
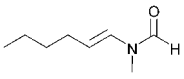
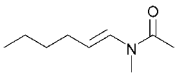
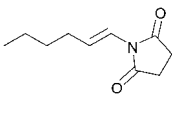
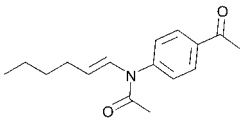
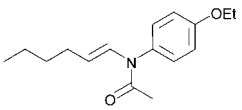
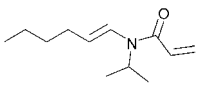
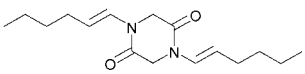
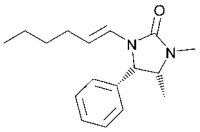
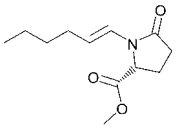
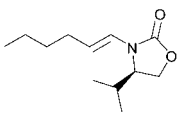
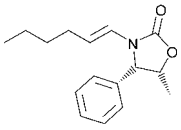


Scheme 3. Addition of N–H compounds to terminal alkynes.

Table 2 demonstrates the impressive scope of the *E*-selective reaction. Various alkynes were successfully converted into enamides, among them phenylacetylene, acetylenecarboxylic esters, trimethylsilylacetylene, and even conjugated enynes. The trimethylsilyl-enamides obtained should be attractive substrates for further coupling reactions, and the dienamides for hetero-Diels–Alder reactions.

Besides lactams, various secondary amides, anilides, ureas, bislactams, carbamates, and even chiral auxiliaries for subsequent cycloaddition reactions[7] can be used as the N–H-

Table 2: Substrate scope of the hydroamidation reaction (Scheme 3).[a]

Product	Yield [%] (ratio **4**/**5**)	Product	Yield [%] (ratio **4**/**5**)	Product	Yield [%] (ratio **4**/**5**)
 **4a**	95 (28:1) 99 (1:5)[b]	 **4b**	97 (30:1) 92 (1:8)[b]	 **4c**	99 (30:1)
 **4d**	81 (30:1)	 **4e**	99 (30:1)	 **4f**	93 (8:1)
 **4g**	98 (24:1)	 **4h**	99 (30:1)	 **4i**	99 (30:1)
 **4j**	69 (3:1)	 **4k**	70 (2:1)	 **4l**	94 (30:1)
 **4m**	86 (30:1)	 **4n**	83 (30:1)	 **4o**	84 (3:1)
 **4p**	12 (1:2)	 **4q**	33 (30:1)	 **4r**	94 (30:1)
 **4s**	38 (30:1)	 **4t**	99 (30:1)	 **4u**	99 (23:1)
 **4v**	96 (6:1)	 **4w**	97 (30:1)	 **4x**	84 (24:1)

[a] Conditions: amide (1.0 mmol), alkyne (2.0 mmol), [Ru(methallyl)$_2$(cod)] (0.02 mmol), P*n*Bu$_3$ (0.06 mmol), DMAP (0.04 mmol), toluene (3 mL), 100 °C, 15 h; yields refer to isomeric mixtures of isolated products. [b] Complementary conditions: amide (1.0 mmol), alkyne (2.0 mmol), [Ru(methallyl)$_2$(cod)] (0.02 mmol), Cy$_2$PCH$_2$PCy$_2$ (0.03 mmol), water (8.0 mmol), toluene (3.0 mL), 100 °C, 15 h.

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coupling partner. The reaction proceeds smoothly even in the presence of sensitive functional groups such as esters, ethers, ketones, halides, or silanes. For most substrates, the *E* products were obtained in an isomeric ratio greater than 20:1, and only imides gave only moderate yields and selectivities; primary amides could not be converted.

The *Z*-selective protocol was also successfully applied to selected substrates (Table 2, first row). Although this protocol does not yet reach the selectivity of its *E*-selective counterpart, the examples **5a** and **5b** demonstrate that the stereoselectivity of the reaction can indeed be inverted by modifying the ligand system.

In summary, a ruthenium-catalyzed reaction has been developed that allows, for the first time, the anti-Markovnikov addition of secondary amides, anilides, lactams, ureas, bislactams, and carbamates to terminal alkynes. Two complementary protocols have been identified that provide stereoselective synthetic entries to either the *E* or the *Z* isomers. Due to the mild reaction conditions, the excellent availability of the starting materials, and the ideal atom economy, this new transformation is well-suited for applications in synthetic organic chemistry and drug discovery.

Experimental Section

4a: An oven-dried flask was charged with [Ru(methallyl)$_2$(cod)] (6.4 mg, 0.02 mmol) and DMAP (4.99 mg, 0.04 mmol), and flushed with argon. Subsequently, P*n*Bu$_3$ (15 μL, 0.06 mmol), 2-pyrrolidinone (**2a**; 85.1 mg, 1 mmol), 1-hexyne (**1a**; 229 μL, 2.0 mmol), and dry toluene (3.0 mL) were added with a syringe. The resulting green solution was stirred for 15 h at 100 °C, then poured into an aqueous $NaHCO_3$ solution (30 mL). The resulting mixture was extracted repeatedly with 20 mL portions of ethyl acetate, the combined organic layers were washed with water and brine, dried with $MgSO_4$, and filtered, and the volatiles were removed in vacuo. The residue was purified by column chromatography (SiO_2, ethyl acetate/hexanes 3:1) to yield **4a** (158.9 mg, 95 % yield, 97 % isomeric purity) as a colorless oil.

^{1}H NMR (300.1 MHz, $CDCl_3$): $\delta = 6.86$ (d, $^3J = 14.7$ Hz, 1H), 4.92 (dt, $^3J = 14.7$ Hz, 7.2 Hz, 1H), 3.48 (t, $^3J = 7.2$ Hz, 2H), 2.46 (t, $^3J = 8.1$ Hz, 2H), 2.01–2.14 (m, 4H), 1.24–1.39 (m, 4H), 0.88 ppm (t, $^3J = 7.2$ Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 172.2$, 123.6, 112.5, 45.3, 32.3, 31.3, 29.7, 22.1, 17.4, 13.9 ppm; MS (EI, 70 eV): *m*/*z* (%): 167 (20), 124 (100) $[M]^+$, 86 (23), 69 (12), 41 (21); HRMS (EI): calcd for $C_{10}H_{17}NO$: 167.131014; found: 167.130871.

The experiments in Table 2 were carried out analogously. All products were purified by column chromatography and characterized by NMR spectroscopy and standard/high-resolution mass spectrometry.

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