Hydroamidation

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Synthesis of Secondary Enamides by Ruthenium-Catalyzed Selective Addition of Amides to Terminal Alkynes**

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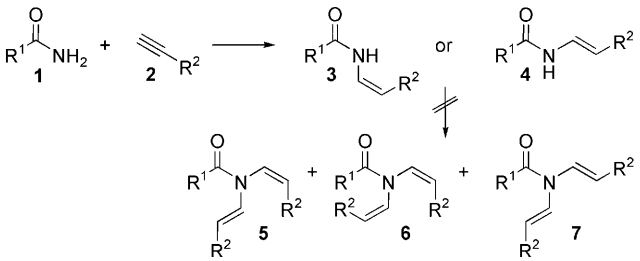
Secondary enamides are abundant in functional materials[1] and biologically active natural products, such as lansiumamide A,[2] TMC-95A-D,[3] crocacin,[4] alatamide,[5] aspergillamides A–B, chondriamide C, lobatamides A–F, and a range of marine metabolites.[6] Furthermore, they are versatile synthetic intermediates for the synthesis of heterocycles,[7] cross-couplings,[8] and Heck reactions.[9] Traditional syntheses, namely condensations of carbonyl derivatives with amides[10] or acylations of imines,[11] require harsh reaction conditions and are not stereoselective, leading to product mixtures with the *E* isomer as the major product. This thermodynamically favored isomer can also be synthesized by the isomerization of *N*-allyl amides,[12] oxidative amidation of alkenes,[13] or codimerization of *N*-vinyl amides with alkenes.[14] In contrast, the thermodynamically disfavored *Z*-enamides are much harder to obtain selectively. In stereospecific syntheses, such as the Curtius rearrangement of α,β-unsaturated acyl azides,[15] elimination of β-hydroxy-α-silylamides,[16] and catalytic cross-couplings of amides with vinyl halides, pseudohalides,[17] or alkenyltrifluoroborate salts,[18] the question of selectivity is transferred to the preparation of the starting materials.

As an alternative to these methods, we recently presented a ruthenium-catalyzed anti-Markovnikov hydroamidation of terminal alkynes.[19–22] In this atom-economic transformation, the stereochemistry of the products is controlled by the choice of ligands, so that both *E*- and *Z*-enamides can be synthesized selectively from easily available starting materials. Unfortunately, this procedure is strictly limited to secondary amides. For the primary amide substrates, which would give access to the more valuable secondary enamides, we have observed either no conversion at all, or mostly double vinylation products in traces and as mixtures of *E*/*Z* isomers and rotamers. The lower reactivity of primary compared to secondary amides is easily explained by their lower nucleophilicity, and underlines the magnitude of challenge presented by this class of substrates. A highly developed catalyst system is required that reaches new levels of activity and stereoselectivity for the anti-Markovnikov addition of primary amides to alkynes. However, this catalyst must be designed such that it does not allow further conversion of the more nucleophilic and sterically only slightly more demanding monovinylated products **3** or **4** (Scheme 1).



Scheme 1. Stereo- and chemoselectivity in hydroamidations.

To identify a catalyst system with such unique attributes, we selected the reaction of benzamide with 1-hexyne as the model system to examine the catalytic activity of various ruthenium sources in combination with a range of ligands, solvents, and additives (Table 1). As expected, a combination of bis(2-methallyl)(cycloocta-1,5-diene)ruthenium(II) [(cod)Ru(met)$_2$] with tri-*n*-butylphosphine and 4-(dimethylamino)pyridine (DMAP), the most effective system for the analogous reaction of secondary amides, led to only marginal conversion and displayed no selectivity for the monoaddition products (entry 1). Other ruthenium precursors were found to be even less effective (entries 2, 3). Solvent screening revealed that DMF was uniquely effective, resulting in an increase in yield (entries 4–6). Based on the reasoning that the coordination of a Lewis acid to the carbonyl oxygen would acidify the amide protons, and therefore serve the same purpose as an added base, we replaced DMAP by a Lewis acid (entries 9, 10). We had previously found that DMAP helps the deprotonation of the amide substrate and facilitates its coordination to the ruthenium center. The replacement of DMAP indeed led to a dramatic increase in catalyst activity, and a 59% yield was achieved with ytterbium triflate (Yb(OTf)$_3$; entry 10).

We were now able to address the problem of selectivity, and found that sterically demanding, electron-rich chelating phosphines resulted in a major enhancement of the *Z*/*E* ratio (entry 11–16). Using 1,4-bis-(dicyclohexylphosphino)butane, the selectivity for the *Z* product **3** was increased to a 4:1 ratio (entry 16). Moreover, owing to the high activity of the catalyst system, the reaction temperature could be reduced to 60 °C (entry 17). This led to substantially better yields of the monoaddition products, largely because their hydrolysis by

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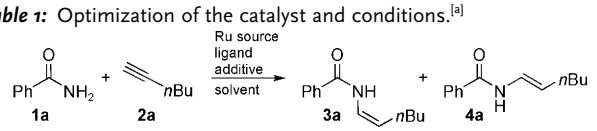
Table 1: Optimization of the catalyst and conditions.[a]



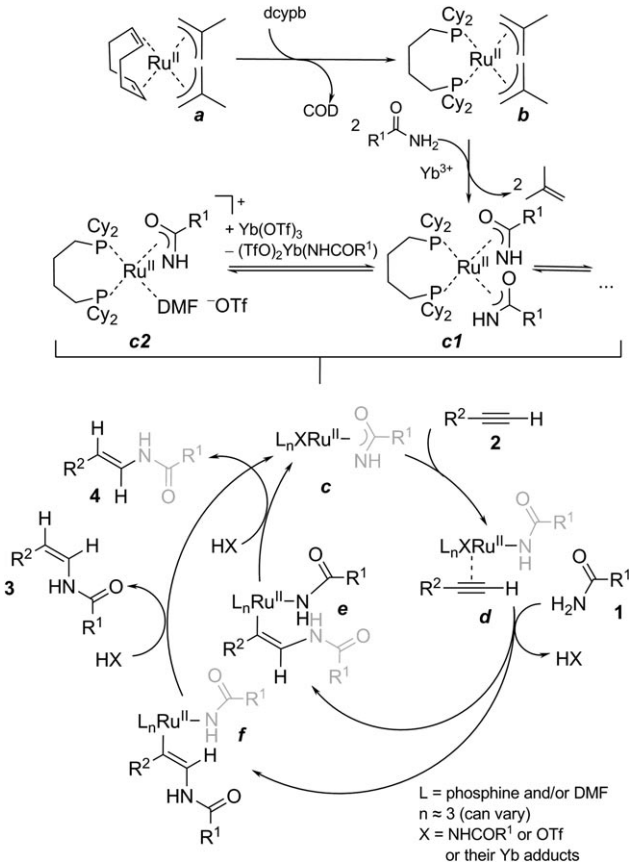
	Ru source	Solv.	Ligand	Additive	Yield [%]	3a:4a
1	$[(cod)Ru\{met\}]_2$	PhMe	nBu_3P	DMAP	2	nd
2	Ru_3CO_{12}	"	"	"	0	nd
3	$[\{(p\text{-cm})RuCl_2\}_2]$	"	"	"	2	nd
4	$[(cod)Ru(met)_2]$	THF	"	"	3	nd
5	"	MeCN	"	"	3	nd
6	"	DMF	"	"	17	1:2
7	"	"	"	Na_2CO_3	16	2:3
8	"	"	"	KI	17	1:1
9	"	"	"	$Mg(OTf)_2$	45	2:1
10	"	"	"	$Yb(OTf)_3$	59	3:2
11	"	"	$P(o\text{-Fur})_3$	"	0	nd
12	"	"	PPh_3	"	10	1:1
13	"	"	johnphos	"	0	nd
14	"	"	tBu_3P	"	2	nd
15	"	"	$P(iPr)Ph_2$	"	14	2:1
16	"	"	dcypb	"	55	4:1
17[b]	"	"	"		95	12:1
18[b]	"	DMF[c]	"		98	18:1
19[b]	"	DMF[c]	"		97[d]	18:1
20	"	DMF[e]	nBu_3P	"	98	2:5
21	"	DMF	dcypb	"	89[f]	1:4

[a] 1.00 mmol benzamide, 2.00 mmol 1-hexyne, 5 mol% Ru source, 15 mol% phosphine (6 mol% for bidentate), 4 mol% additive, 3 mL solvent, 100°C, 15 h. Yields determined by GC using *n*-tetradecane as internal standard, selectivities determined by HPLC. [b] 60°C. [c] Water as co-solvent (108 μL). [d] 6 h reaction time. [e] 500 mg 3 Å molecular sieves as additive. [f] After complete reaction, triethylamine (200 μL) and 3 Å molecular sieves (500 mg) were added, and the resulting mixture was stirred at 110°C for 24 h. Abbreviations: *p*-cm = *p*-cymol, johnphos = (2-biphenylyl)di-*tert*-butylphosphine, dcypb = 1,4-bis-(dicyclohexylphosphino)butane, Fur = furyl.

traces of water was slowed. At this moderate temperature, the presence of water was even found to enhance the selectivity (entry 18) so that finally, near complete conversion and an impressive 18:1 selectivity for the thermodynamically unfavorable and thus more interesting *Z*-enamide **3** was reached within 6 h reaction time (entry 19).

We next tried to invert the selectivity of the reaction in favor of the *E*-enamide **4** by modifying the catalyst system to further improve the synthetic utility of the hydroamidation process. The best result, obtained with nBu_3P as the ligand and 3 Å molecular sieves as additives, was a 2.5:1 ratio of *E*/*Z* isomer (entry 20), which was disappointing. A superior strategy, however, proved to be the in-situ isomerization of the double-bond isomers, after the reaction to form **3** is complete, by adding triethylamine and heating the reaction mixture to 110°C, and using molecular sieves to reduce the hydrolytic cleavage to a minimum (entry 21). In this way an *E*/*Z* ratio of 4:1 was achieved for the model system, and *E* selectivities of up to 20:1 were reached for other substrates (Table 2).

We believe that the catalytically active species in such hydroamidations are phosphine-stabilized ruthenium(II) amides, such as ***c*** (Scheme 2), generated from the catalyst

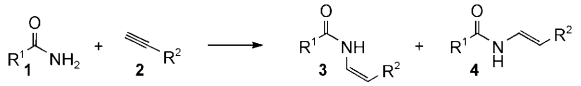


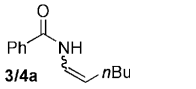
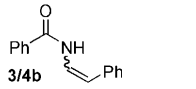
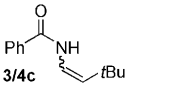
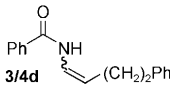
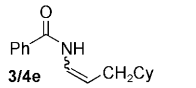
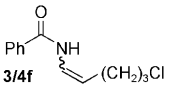
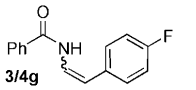
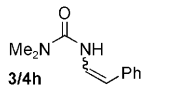
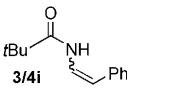
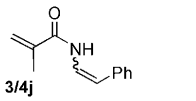
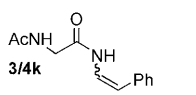
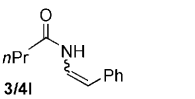
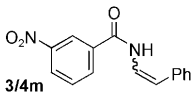
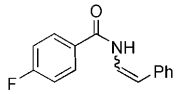
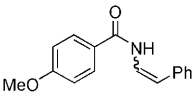
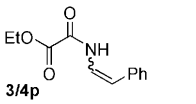
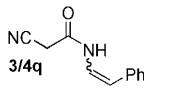
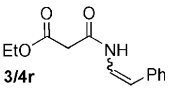
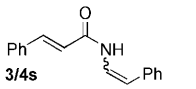
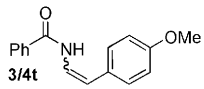
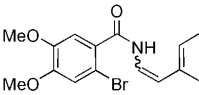
Scheme 2. Proposed reaction mechanism.

precursor $[(cod)Ru(met)_2]$ by substitution of the labile 1,5-cyclooctadiene ligand (COD) with phosphine ligands, and replacement of the basic methallyl by amide groups acidified with $Yb(OTf)_3$. ^1H NMR spectroscopic studies after catalyst preformation show that the coordinated COD is liberated, and 2-methylbutene is formed. In addition, 2,5-dimethylhexenes could not be detected by NMR spectroscopy or by GC-MS. These observations rule out the possibility of the ruthenium(0) species as the active catalyst because their formation using $[(cod)Ru(met)_2]$ ***a*** would most likely involve a reductive dimerization of the two methallyl ligands. In the presence of an ytterbium salt with non-coordinating triflate ligands, both ruthenium and ytterbium are likely to compete for the coordinating amide ligands, so that neutral ruthenium bisamide complexes ***c1*** will be in equilibrium with cationic solvent- and ligand-stabilized monoamide species ***c2***.

The actual catalytic cycle (Scheme 2) is likely to start with the coordination of an alkyne to a neutral or cationic ruthenium(II) amide complex ***c*** to give π-complex ***d***, followed by the addition of an amide nucleophile to the η^2-coordinated alkyne, yielding η^1-ruthenium vinyl complexes ***e*** or ***f***. The *E*- or the *Z*-configured amidoalkenyl ruthenium species will be formed depending on whether the amide comes from inside or outside the coordination sphere of ruthenium, respectively. An intermediacy of ruthenium vinylidene complexes, as has been proposed for the related catalytic addition of carboxylic acids to alkynes,[23] can be ruled out on the basis of deuteration studies. We have never observed the deuterium

Table 2: Scope of the hydroamidation protocols.[a]



Product		Yield [%]	(*Z*/*E*)	Product		Yield [%]	(*Z*/*E*)	Product		Yield [%]	(*Z*/*E*)
 **3/4a**	A	94	(18:1)	 **3/4b**	A	97	(18:1)	 **3/4c**	A	91	(>40:1)
	B	89	(1:4)		B	92	(1:18)		B	79	(1:20)
 **3/4d**	A	92	(17:1)	 **3/4e**	A	86	(23:1)	 **3/4f**	A	91	(31:1)
	B	85	(1:4)		B	85	(1:4)				
 **3/4g**	A	99	(20:1)	 **3/4h**	A	46	(30:1)	 **3/4i**	A	88	(10:1)
 **3/4j**	A	90	(19:1)	 **3/4k**	A	96	(22:1)	 **3/4l**	A	84	(14:1)
	B	83	(1:17)		B	77	(1:20)				
 **3/4m**	A	80	(20:1)	 **3/4n**	A	93	(19:1)	 **3/4o**	A	96	(18:1)
 **3/4p**	A	78	(35:1)[b]	 **3/4q**	A	31	(>40:1)	 **3/4r**	A	71	(19:1)[b]
	B	68	(1:14)								
 **3/4s**	A	98	(20:1)	 **3/4t**	A	83	(19:1)	 **3/4u**	A	60	(>40:1)
					B	79	(1:18)				

[a] Method A: 1.00 mmol benzamide, 2.00 mmol 1-hexyne, 5 mol% [(cod)Ru(met)$_2$], 6 mol% dcypb, 4 mol% Yb(OTf)$_3$, 3 mL DMF and 108 μL water as co-solvent, 60°C, 6 h. Yields reported are of isolated products, selectivities were determined by HPLC. Method B: After complete conversion following method A, 3 Å molecular sieves (500 mg) and triethylamine (200 μL) were added, and the mixture was heated to 110°C for 24 h. [b] The reaction was performed without water to avoid hydrolysis of the sensitive products.

shifting from the terminal to the 2-position in hydroamidations of 1-[D]-alkynes. By using an *N*,*N*-deuterated amide, the deuterium was exclusively found in the 2-position of the enamide products, which is in agreement with the mechanistic steps detailed below.

In the *E* selective pathway, a coordination site made vacant at the ruthenium center is filled as necessary by another amide, which also provides the proton required for protonolytic release of the enamide product and regeneration of the initial ruthenium(II) species ***c***. In the competing *Z* selective pathway, the proton is also formally provided by the amide, but the protons are expected to move easily and relatively fast between the free and the coordinated amide or the triflate species. This proton activity is enhanced by the Lewis acid ytterbium(III), which has a tendency to coordinate to the amides, thereby weakening their affinity to both ruthenium and the protons. As a result, the protonolysis and ligand exchange steps are facilitated. Thus, at any stage of the catalytic cycles, salt metathesis of the ruthenium(II) and ytterbium(III) species can occur, bridging the neutral and the cationic pathways.

Table 2 illustrates the wide scope and synthetic utility of the *Z* selective anti-Markovnikov hydroamidation. Benzamide was reacted with various alkynes, such as aliphatic, alicyclic, haloalkyl, and aromatic derivatives, yielding enamides **3a–g,t** in high yields and good to excellent *Z*/*E* selectivities. On the other hand, a range of primary amides, among them sensitive, highly functionalized derivatives, were added to phenylacetylene (**3h–s**). Common functional groups, such as ester, ether, alkene, nitrile, nitro, and halide groups are tolerated, and even fragile acrylic, oxalic, malonic or α-cyanoacetic amides were efficiently converted. Arguably, the unprecedented outcome was the synthesis of the enamide **3k**, in which a primary amide functionality was selectively vinylated in the presence of a secondary amide group.

The one-pot addition/isomerization sequence (Table 2, method B) was successfully applied to the synthesis of a representative selection of *E* enamides (**4a–e,j,k,p,t**). This sequence proved to be highly efficient and extremely general in its application. The *E* selectivities were usually high and functional groups were well-tolerated. As a result, terminal alkynes and amides can now also be successfully utilized as starting materials for the synthesis of *E*-enamides.

Enamides thus accessible in only one step from easily available materials include the natural products lansiumamide A (**3s**)[2] and alatamide (**4t**),[5] the previously published syntheses of which involved three to four steps and lower product yields. This also applies to compound **3u**, which is a key intermediate in Castedo's total synthesis of aristolactam.[7]

In summary, a new catalyst system has been developed that allows the chemo-, regio-, and stereoselective synthesis of secondary *Z*-enamides from easily available primary amides and terminal alkynes. In combination with an optional in-situ isomerization to the *E*-enamides, this catalyst system gives access to a fast synthetic route to the structural motif that is present in many natural products and is hard to access by other synthetic means.

Experimental Section

3a: An oven-dried flask was charged with bis(2-methallyl)(cycloocta-1,5-diene)ruthenium(II) (16.0 mg, 0.05 mmol), benzamide (**1a**, 121.1 mg, 1.00 mmol), 1,4-bis(dicyclohexylphosphino)butane (27.0 mg, 0.06 mmol), and ytterbium triflate (24.8 mg, 0.04 mmol) and flushed with nitrogen. Dry DMF (3.0 mL), 1-hexyne (**2a**, 229 μL, 2.00 mmol) and water (108 μL, 6.00 mmol) were then added with a syringe. The resulting solution was stirred for 6 h at 60 °C, then poured into an aqueous sodium bicarbonate solution (30 mL) and extracted repeatedly with 20 mL portions of ethyl acetate. The combined organic layers were washed with water and brine, dried over magnesium sulfate, filtered, and the volatiles were removed in vacuo. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 1:9) to obtain **3a** as a pale-yellow oil (191.1 mg, 94 %).

For explicit experimental data, including spectroscopic data, see the Supporting Information.

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