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Ru-Catalyzed Stereoselective Addition of Imides to Alkynes

Lukas J. Goossen,* Mathieu Blanchot, Claus Brinkmann, Käthe Goossen, Ralph Karch,† and Andreas Rivas-Nass†

Institut für Organische Chemie, Technische Universität Kaiserslautern, Erwin-Schrödinger-Strasse, Building 54, D-67663 Kaiserslautern, Germany, and UMICORE AG & CO. KG, Rodenbacher Chaussee 4, 63457 Hanau, Germany

goossen@chemie.uni-kl.de

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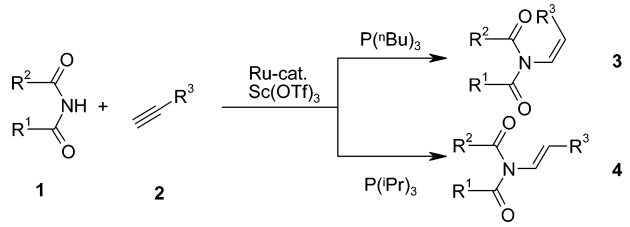

A catalyst system formed in situ from bis(2-methylallyl)-cycloocta-1,5-dieneruthenium(II) ((cod)Ru[met]$_2$), a phosphine, and scandium(III) trifluoromethanesulfonate (Sc(OTf)$_3$) was found to efficiently catalyze the *anti*-Markovnikov addition of imides to terminal alkynes, allowing mild and atom-economic synthesis of enimides. Depending on the phosphine employed, both the (*E*)- and the (*Z*)-isomer can be accessed stereoselectively.

Several fungicides,[1] metabolic drugs,[2] and functional materials[3] contain enimides as key structural elements (Figure 1). Currently, most approaches to the synthesis of this important substrate class rely on the multistep derivatization of simple enimides such as vinyl phthalimide.[4] These, in turn, are obtained by high-pressure vinylation reactions specific to these substrates.[5] Other synthetic approaches include the classical acid-catalyzed synthesis of enimides by condensation of imides and carbonyl compounds under rather drastic conditions,[6] the acylation of enamides or vinyl azides,[7] and the cross-coupling of imides with vinyl halides.[8]

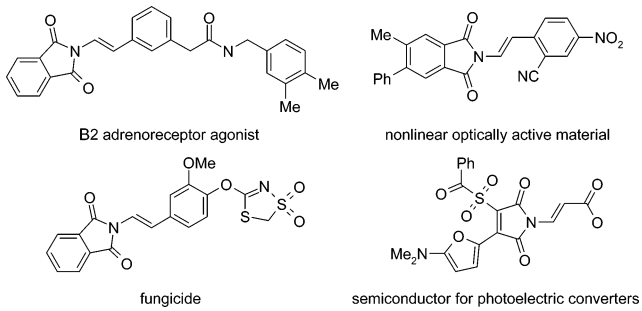

FIGURE 1. Enimides in bioactive or functional molecules

However, none of these allow a concise, environmentally benign, and generally applicable synthesis of enimides under mild conditions. In view of the synthetic importance of this structural motif, this remains a highly desirable goal.

The atom-economic addition of the N−H bond of readily available imides across the carbon−carbon triple bond of alkynes would arguably be a particularly elegant entry to enimides. In principle, such a reaction should be feasible in analogy to the related addition reactions of carboxylates,[9] amines,[10] and water[11] to alkynes. Recently, we were able to extend this reaction type even to the addition of comparably unreactive secondary amides,[12] with catalyst systems consisting of ruthenium, phosphines, and 4-dimethylaminopyridine (DMAP). Less nucleophilic derivatives such as primary amides and imides could not satisfactorily be converted with these catalysts.

We herein report on a new catalyst system consisting of ruthenium together with a Lewis acid cocatalyst that overcomes this key limitation, opening up an expedient new entry into the preparation of enimides from imides and alkynes.

As a starting point for catalyst development, we used the reaction of succinimide with 1-hexyne to investigate the catalytic activity of several ruthenium complexes under various conditions (Scheme 1, Table 1). Due to the insufficient solubility of succinimide in less polar organic solvents, we carried out the screening experiments in DMF. Combinations of several Ru precursors with phosphine ligands in DMF at 100 °C gave low conversions, at most (entries 1−3). As the presence of bases is decisive in Ru-catalyzed additions of carboxylic acids and amides to alkynes,[9c,12] we next studied their effect on the desired transformation. An improvement in yield was observed when adding DMAP to [(*p*-cymene)RuCl$_2$]$_2$/tri-2-furylphosphine and to (cod)Ru[met]$_2$/tri-*n*-butylphosphine (entries 4 and 5). However, screening a range of bases did not lead to an improvement of the reaction yield beyond a threshold of 20%, interestingly reached with magnesium carbonate (entry 6). Suspecting that the Lewis acidic magnesium ion might have a share in the beneficial effect of this additive, we extended our search to

† UMICORE AG & CO. KG.

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SCHEME 1. Model Reaction: Addition of Succinimide to Hexyne

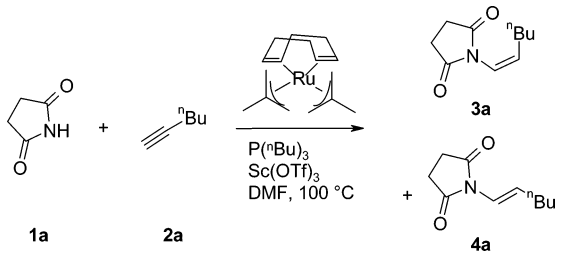


TABLE 1. Optimization of the Catalyst and Conditions[a]

entry	Ru precursor	ligand	additive	yield/% (ratio **3**:**4**)
1	$[(p\text{-cymene})RuCl_2]_2$	P(2-furyl)$_3$		0
2	(cod)Ru[met]$_2$	P(^{n}Bu)$_3$		8 (2:1)
3	$Ru_3(CO)_{12}$	P(^{n}Bu)$_3$		0
4	$[(p\text{-cymene})RuCl_2]_2$	P(2-furyl)$_3$	DMAP	16 (2:1)
5	(cod)Ru[met]$_2$	P(^{n}Bu)$_3$	DMAP	18 (2:1)
6	(cod)Ru[met]$_2$	P(^{n}Bu)$_3$	$MgCO_3$	20 (2:1)
7	(cod)Ru[met]$_2$	P(^{n}Bu)$_3$	Yb(OTf)$_3$	98 (7:1)
8	(cod)Ru[met]$_2$	P(^{n}Bu)$_3$	Sc(OTf)$_3$	90 (6:1)
9	(cod)Ru[met]$_2$	P(^{n}Bu)$_3$	Yb(NO_3)$_3$	80 (6:1)
10	(cod)Ru[met]$_2$	P(^{n}Bu)$_3$	KBr	12 (3:1)
11	(cod)Ru[met]$_2$	P(2-pyridyl)Ph$_2$	Yb(OTf)$_3$	19 (1:1)
12	(cod)Ru[met]$_2$	$PCy_2CH_2PCy_2$	Yb(OTf)$_3$	61 (8:1)
13	(cod)Ru[met]$_2$	P(2-furyl)$_3$	Yb(OTf)$_3$	4 (2:1)
14	(cod)Ru[met]$_2$	PPh_3	Yb(OTf)$_3$	53 (1:2)
15	(cod)Ru[met]$_2$	PPh(Et)$_2$	Yb(OTf)$_3$	33 (1:10)
16	(cod)Ru[met]$_2$	PCy_3	Yb(OTf)$_3$	24 (1:5)
17[b]	(cod)Ru[met]$_2$	P(^{n}Bu)$_3$	Yb(OTf)$_3$	0
18[c]	(cod)Ru[met]$_2$	P(^{n}Bu)$_3$	Yb(OTf)$_3$	16 (2:1)
19[d]	(cod)Ru[met]$_2$	P(^{n}Bu)$_3$	Yb(OTf)$_3$	98 (7:1)
20[e]	(cod)Ru[met]$_2$	P(^{n}Bu)$_3$	Yb(OTf)$_3$	45 (10:1)
21[d]	(cod)Ru[met]$_2$	P(^{i}Pr)$_3$	Sc(OTf)$_3$	48 (1:15)
22[d,f]	(cod)Ru[met]$_2$	P(^{i}Pr)$_3$	Sc(OTf)$_3$	78 (1:15)

[a] Conditions: 1.00 mmol of succinimide, 2.00 mmol of 1-hexyne, 0.02 mmol of Ru precursor, 0.06 mmol of ligand, 0.04 mmol of additive, DMF, 100 °C, 15 h; yields determined by GC using *n*-tetradecane as internal standard. [b] In acetonitrile. [c] In toluene. [d] At 60 °C. [e] At 25 °C. [f] 0.05 mmol of Ru precursor, 0.15 mmol of ligand, 0.04 mmol of additive.

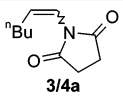
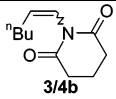
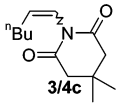
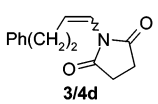
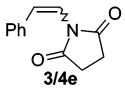
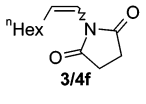
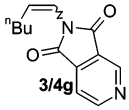
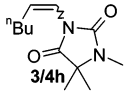
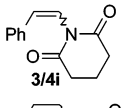
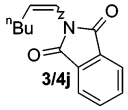
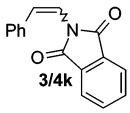
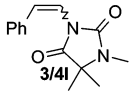
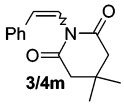
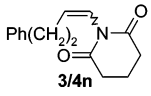
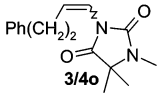
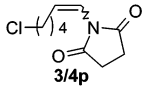
Lewis acids and were pleased to find that they caused a dramatic increase in catalyst productivity. Scandium and ytterbium triflate were particularly effective, leading to complete conversion of the starting imide and the formation of the desired product in good selectivities (entries 7 and 8).

Out of the phosphines evaluated, tri-*n*-butylphosphine remained the ligand of choice in terms of yield and selectivity, while sterically more demanding trialkylphosphines and less electron-rich triarylphosphines gave lower yields (entries 7, 11−16). Interestingly, the (*E*/*Z*) ratio was slightly higher for diethylphenylphosphine, though at unsatisfactory conversion (entry 15). Even when combined with the optimum set of ligand and additive, the activity of other ruthenium precursors remained by far inferior to that of (cod)Ru[met]$_2$.

In comparison to DMF, other solvents were less effective: low polarity solvents were unable to dissolve the polar reagents and catalyst sufficiently, and coordinating solvents, e.g., acetonitrile, appeared to slow down the reaction (entries 7, 17, 18). A reaction temperature of 60 °C turned out to be sufficient (entry 19), and a further decrease to 25 °C led to an increase in (*E*)-selectivity, though with a lower yield (entry 20).

As the choice of phosphine appeared to influence the stereochemical outcome of the reaction, we set out to identify one that would invert the stereochemistry of the transformation and indeed discovered that with triisopropylphosphine, the (*E*)-isomer became the major product (entry 21). The activity of this catalyst is somewhat lower, but after raising the catalyst loading to 5 mol %, the (*E*)-enimide **4a** was obtained in high yields and excellent selectivity (entry 22).

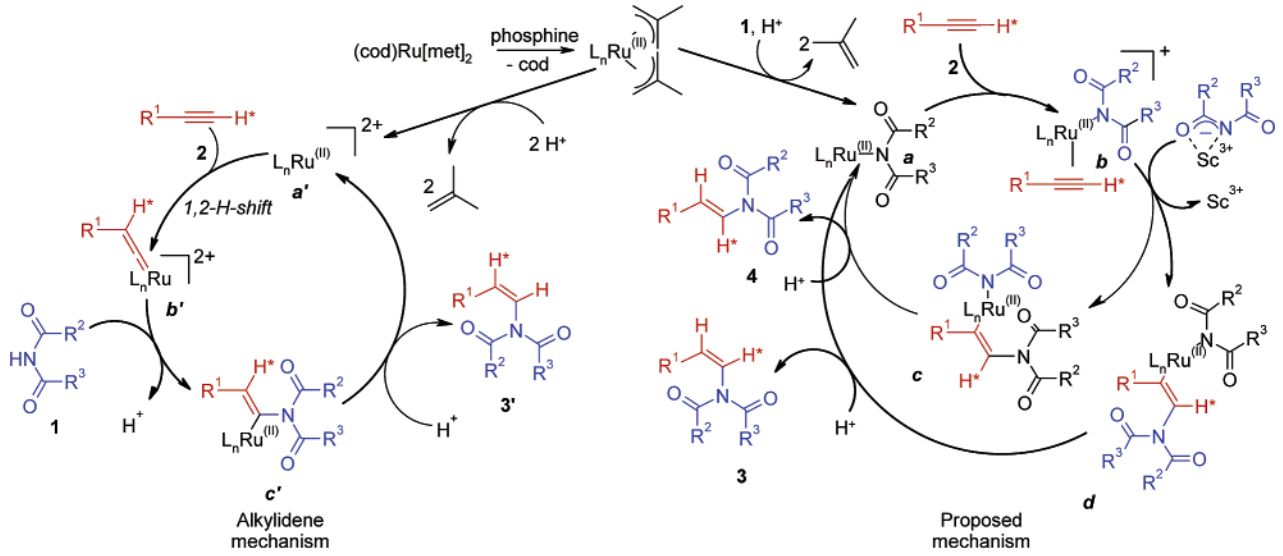
TABLE 2. Substrate Scope of the Enimide Synthesis[a]

Product	Yield / %[b] (ratio 3/4)	Product	Yield / %[b] (ratio 3/4)
 **3/4a**	98 (8:1) 75 (1:15)[c]	 **3/4b**	58 (14:1) 40 (1:7)[c]
 **3/4c**	62 (9:1) 28 (1:7)[c]	 **3/4d**	99 (10:1) 78 (1:10)[c]
 **3/4e**	57 (20:1) 49 (1:15)[c]	 **3/4f**	74 (9:1)
 **3/4g**	14 (3:1)	 **3/4h**	90 (7:1)
 **3/4i**	60 (34:1)	 **3/4j**	88 (4:1)
 **3/4k**	53 (41:1)	 **3/4l**	33 (18:1)
 **3/4m**	50 (26:1)	 **3/4n**	88 (31:1)
 **3/4o**	94 (35:1)	 **3/4p**	57 (4:1)

[a] Conditions: 1.00 mmol of imide, 2.00 mmol of alkyne, 0.02 mmol of (cod)Ru[met]$_2$, 0.06 mmol of P(^{n}Bu)$_3$, 0.04 mmol of Sc(OTf)$_3$, 60 °C, 15 h. [b] Isolated yields, ratio of diastereoisomers determined by GC. [c] 0.05 mmol of (cod)Ru[met]$_2$, 0.15 mmol of P(^{i}Pr)$_3$, 0.04 mmol of Sc(OTf)$_3$, 60 °C, 15 h.

After optimizing the catalyst systems, we tested the generality of the two complementary reaction protocols with regard to both coupling partners (Table 2). An excess of the alkyne was used to make up for losses due to evaporation or oligomerization reactions. In our choice of substrates, we focused on cyclic derivatives since the products are not easily accessible by acylation of enamides and on the thermodynamically less stable (*Z*)-enimides. Gratifyingly, the (*Z*)-selective protocol proved to be suitable for a wide array of imides such as phthalimide, glutarimide, and dihydrouracil derivatives, leading to good yields and high selectivities for the *anti*-Markovnikov products (**3a**−**p**). Both alkyl- and aryl-substituted alkynes were smoothly converted. Particularly high stereoselectivities were observed for phenylacetylene (**3i**−**m**), which is interesting as this substrate gave the lowest selectivities in our enamide synthesis.[12] The scope of the (*E*)-selective protocol was investigated using a more limited number of substrates and always gave similarly high yields and selectivities (**4a**−**d**).

SCHEME 2. Possible Catalytic Cycles with and without Alkylidene Intermediates[a]



[a] L = phosphine, alkyne, solvent, or imide.

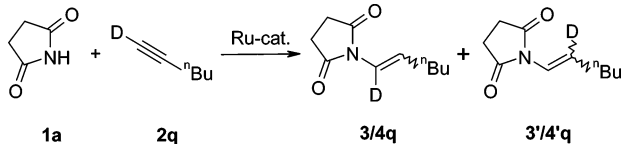
Based on the experimental observations detailed below, we believe that for this particular class of nucleophiles, the transformation proceeds via a different mechanism than the seemingly related the Ru-catalyzed addition of carboxylic acids to alkynes, which involves alkylidene intermediates (Scheme 2).[10]

In our proposed mechanism, the Ru(II) precursor is activated by protonation of the two methallyl groups, giving rise to a Ru(II) species (***a***) with at least one coordinated imide. This would explain why other ruthenium precursors with more strongly coordinating ligands, e.g., halides, were less effective.

The first step of the actual catalytic cycle is then likely to be a coordination of the alkyne to the Ru(II) species, followed by an attack of an imide anion to the coordinated alkyne (***b***). This should be facilitated by coordination of the Lewis acid to the imide carbonyl groups, resulting in activation of the N−H bond. Depending on whether a coordinated imide attacks the alkyne and is replaced by an external imide anion or whether the latter directly attacks the coordinated alkyne, the (*Z*)-configured (***d***) or (*E*)-configured (***e***) ruthenium enimide complex forms. Protonolysis of the intermediate would probably proceed with preservation of the stereochemistry, regenerating the initial Ru(II) species (***a***) and completing the catalytic cycle. While related mechanisms are conceivable with a different order of steps, it is essential that the imide nitrogen atoms attack the alkyne moiety either from inside the coordination sphere of the ruthenium to cause selectivity for the (*E*)-enimide product or from outside to cause the (*Z*)-enimide product. The experimental findings can be rationalized by the higher steric demand of the tri-isopropylphosphine, which might favor the formation of Ru complexes with fewer phosphine ligands, thus leaving more room for the coordination of imides.

The intermediacy of Ru−alkylidene complexes (***b′***) also had to be considered as an alternative, as these are known to play a key role in numerous catalytic transformations involving ruthenium (Scheme 2, left-hand side).[13] As this mechanism would require a 1,2-shift of the alkyne proton, we decided to perform an experiment using 1-deuterated 1-hexyne (**2q**) that would allow us to distinguish between the two possible catalytic cycles (Scheme 3): Formation of the 2-deuterated enimides would be indicative of an alkylidene mechanism (**3′/4′q**), while 1-deuterated enimides (**3/4q**) as the products would be in agreement with our proposed catalytic cycles. As we solely detected the formation of products with the deuterium remaining in the 1-position for both reaction protocols, reaction pathways via Ru(II)-alkylidene complexes have to be excluded for this particular reaction.

SCHEME 3. Deuteration Experiment



In summary, two complementary catalyst systems have been developed that efficiently mediate the addition of imides to terminal alkynes, giving rise to either the (*E*)- or the (*Z*)-*anti*-Markovnikov products. The mechanism is apparently different from that proposed for the addition of carboxylic acids to alkynes, as it does not involve alkylidene intermediates. Various enimides can thus be obtained in high regio- and stereoselectivities.

Experimental Section

(*Z*)-Selective Protocol: Synthesis of *N*-((*Z*)-Hex-1-enyl)succinimide (3a). An oven-dried flask was charged with (cod)Ru[met]$_2$ (6.4 mg, 0.02 mmol), scandium triflate (19.7 mg, 0.04 mmol), and succinimide (**1a**; 99.1 mg, 1 mmol) and flushed with argon. Subsequently, tri-*n*-butylphosphine (15 μL, 0.06 mmol), 1-hexyne (**2a**; 229 μL, 2.0 mmol), and dry DMF (3.0 mL) were added via syringe. The resulting colorless solution was stirred for 15 h at 60 °C and then poured into an aqueous sodium bicarbonate 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 magnesium sulfate, and filtered, and the volatiles were removed in vacuo. The residue was

(13) Bruneau, C.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 2176.

purified by column chromatography. (silica gel, ethyl acetate/hexanes 3:1) to yield **3a** (177.6 mg, 98% yield, 92% isomeric purity) as a yellowish oil.

(*E*)-Selective Protocol: Synthesis of *N*-((*E*)-Hex-1-enyl)-succinimide (4a). Compound **4a** was prepared from the same starting materials in analogy to **3a**, using (cod)Ru[met]$_2$ (16 mg, 0.05 mmol), triisopropylphosphine (29 μL, 0.15 mmol), and scandium triflate (19.7 mg, 0.04 mmol) as the catalyst system yielding **4a** (135.5 mg, 75% yield, >95% isomeric purity) as a yellowish oil.

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for funding.

Supporting Information Available: Complete experimental procedures for the synthesis and characterization data (^{1}H NMR/^{13}C NMR, MS, elemental analyses) of compounds **2q**, **3a**−**n**,**q**, **4a**−**e**,**q**. This material is available free of charge via the Internet at http://pubs.acs.org.

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