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Ruthenium-catalyzed selective anti-Markovnikov *trans* addition of carboxylic acids and tail-to-tail dimerization of terminal alkynes

Karen Melis,[a] Pawel Samulkiewicz,[b] Jacek Rynkowski[b] and Francis Verpoort[a,*]

[a]*Department of Inorganic and Physical Chemistry, Ghent University, Krijgslaan 281 (S-3), 9000 Ghent, Belgium*
[b]*Institute of General Chemistry, Technical University of Lodz, 90-924 Lodz, ul. Zwirki 36, Poland*

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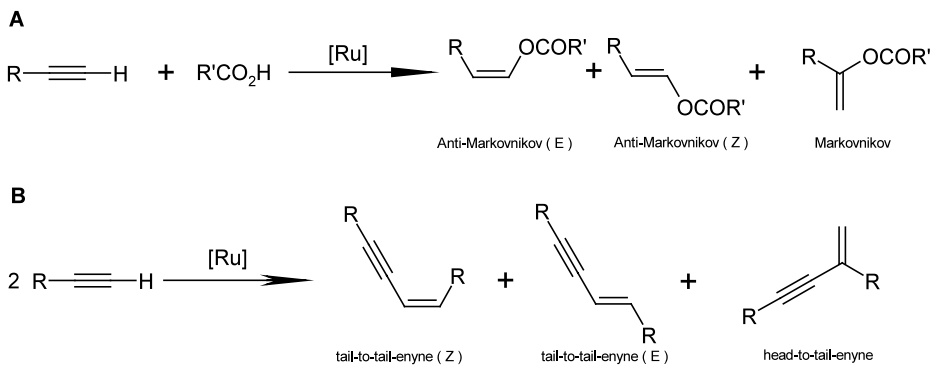
Abstract—Carboxylic acids react with terminal alkynes in the presence of a catalytic amount of $RuCl_x$(*p*-cymene)(triazol-5-ylidene) to selective generate *Z*-alk-1-en-1-yl esters. The anti-Markovnikov and *trans* addition on the terminal alkyne gives access to *Z*-alkene derivatives of phenylacetylene, *t*-butylacetylene, 1-octyne, 4-pentynoic acid and 1,7-octadiyne. The dimerization of terminal alkynes catalyzed with the same Ru-complex gives preferentially tail-to-tail coupling reactions.

Alkynes are highly reactive building blocks in organic synthesis, despite the fact that their positive enthalpy makes them metastable at room temperature, they react only at elevated temperatures and in the presence of suitable catalysts. Under these conditions, they are able to take part in a large number of reactions, which can be divided in reactions with retention or reactions with transformation of the triple bond.[1,2] An example of transformation of a terminal alkyne is the nucleophilic addition of carboxylic acids, which results in the formation of enol esters (Scheme 1A). Enol esters have specific industrial applications as monomers for the production of various polymers and copolymers. They are also useful reagents for carbon–carbon and carbon–heteroatom bond formation via the generation of enolates or acylation reactions.[3,4] Another type of reaction, which involves both retention and transformation of the triple bond, is the dimerization of two terminal alkynes to generate enyne derivatives (Scheme 1B). The sp-C–H bond of terminal alkynes undergoes oxidative addition to transition metal complexes to afford reactive alkynyl complexes. Capture of the intermediate with carbon electrophiles provides catalytic carbon–carbon bond formations. The motivation to synthesize enynes arises from their use as precursors for the synthesis of natural products as well as building blocks for further structural elaborations.[5–9]



Scheme 1.

* Corresponding author.

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Both reaction pathways proceed via an organometallic intermediate, i.e. a transition metal vinylidene species. The vinylidene species is spontaneously formed from terminal alkynes and coordinatively unsaturated metal species by a metal-promoted C–H insertion and a subsequent tautomerization.

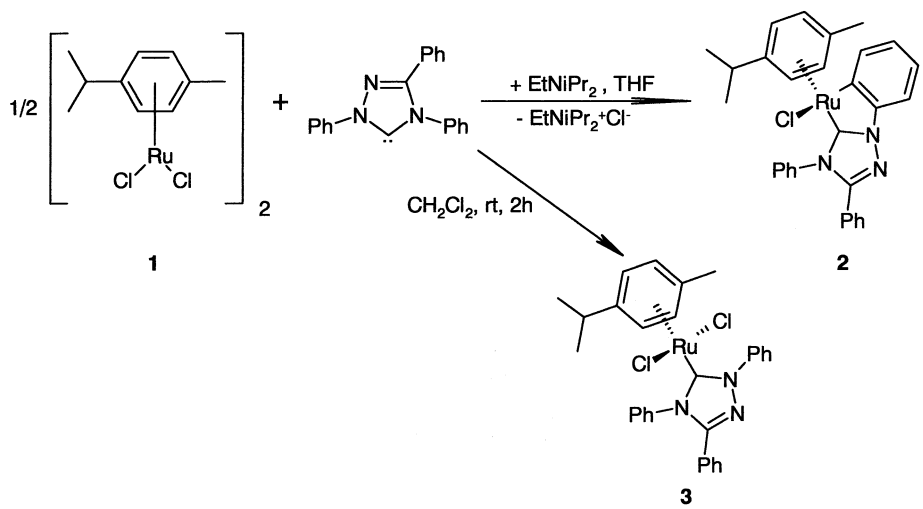
Low-valent ruthenium complexes have proven to be excellent catalysts for both organic reactions. The regioselectivity for Markovnikov addition has been significantly increased by the use of a variety of Ru-precursors such as $Ru_3(CO)_{12}$,[10,11] (arene)$RuCl_2(PR_3)$,[12–17] and bis-(η^5-cyclooctadienyl)ruthenium/PR_3 without and with addition of maleic anhydride.[18–21] The first anti-Markovnikov *trans*-addition in the presence of the $Ru(dppb)(\eta^3\text{-}CH_2CMe{=}CH_2)_2$ catalyst was reported by Dixneuf et al.[22] The diphosphine ligand bearing the longer chain such as dppb affords better chemoselectivity. Steric factors rather than electronic factors are responsible for the regioselective attack of carboxylic acids to the C_1 position of 1-alkynes. Ru-complexes containing a very bulky electron-donating ligand catalyze the dimerization of terminal alkynes into enynes very easily.[23]

These results tempted us to develop a system able to catalyze both enol ester formation and dimerization of terminal alkynes. Combining the features of $[RuCl_2(p\text{-cymene})]_2$ (**1**) to spontaneously form a Ru-vinylidene in the presence of a terminal alkyne and the strong electron-donating capacity of *N*-heterocyclic carbenes (NHC), complex **2** and complex **3** were synthesized (Scheme 2).[24–26]

Complex **2** was synthesized according to literature.[24] The addition of a base (EtN^iPr_2) is necessary to capture the released HCl molecule. It prevents the side reaction between the protic acid and the highly reactive free carbene and drives the reaction to its completion. The *ortho*-metallated *N*-phenylcarbene in complex **2** drastically reduces the free rotation about the carbon–metal bond (Ru–NCN) and creates a stereogenic center on the metal center.[27] The one-pot synthesis of the Ru-dimer and the triazol-5-ylidene ligand (complex **3**) was used without further purification.

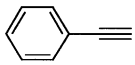
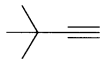
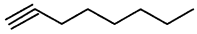
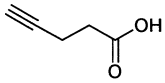
The activity of the two complexes (**2** and **3**) towards the enol ester formation of several terminal alkynes is shown in Tables 1 and 2. The overall yield is nearly quantitative for all reactions, except the addition of acetic acid to the aliphatic 1-octyne catalyzed by complex **3** only reaches 45% (entry 5b). The catalytic reactions by the pure Ru-complex **2** proceed at a lower rate, which is shown in the longer reaction times. From literature it is known that (arene)$RuCl_2(PR_3)$ complexes are very efficient catalysts for the regio-selective Markovnikov addition of carboxylates to the internal carbon of the triple bond of terminal alkynes and thus the production of alk-1-en-2-yl esters. Except for the addition of isovaleric acid to phenylacetylene catalyzed by complex **2** (entry 3a), the overall regio-selectivity is reversed compared to complex **1**, towards the anti-Markovnikov addition. This can be explained by the increased sterical hindrance of the triazol-5-ylidene ligand versus PR_3. The *ortho*-metallated NHC–Ru complex **2** possesses an additional stereo-selectivity for *Z*-alk-1-en-1-yl esters. This is attributed to the hindered rotation about the C–M bond. The aliphatic substrate, 1-octyne, shows no regioselectivity at all (entries 5a and 5b). This means that next to the steric influence of the NHC ligand, the bulkiness of the substrate plays an important role in the regioselectivity. The combination of the sterical hindrance of the NHC in complex **2** and of the isopropyl group on isovaleric acid results in a Markovnikov regioselectivity. The intramolecular addition proceeds smoothly and is highly selective for the formation of the 6-ring adducts (entries 6a and 6b). By this way, unsaturated lactones can be easily prepared in high yield. Intermolecular addition is excluded since no oligomerization or polymerization was observed during the experiment.

Table 2 depicts the activity of both catalytic systems for the nucleophilic addition of acetic acid on a dialkyne,



Scheme 2.

Table 1. Enol ester formation catalyzed by complexes **2** and **3** (toluene, 110°C, alkyne/acid/catalyst = 94/112/1)

Entry [1]	Alkyne	Acid	Time (h)[2]	% Yield[3]	% M[3]	% Anti-M (E+Z)[3]	% Anti-M (E)[3]	% Anti-M (Z)[3]
1a		HCOOH	4	100	12	88	30	70
1b			3	68	0	100	76	24
2a		CH_3COOH	12	100	6	94	22	78
2b			5	97	11	89	88	22
3a		$(CH_3)_2CHCH_2COOH$	13	100	59	41	46	54
3b			5	93	6	94	32	68
4a		CH_3COOH	6	77	43	57	91	9
4b			24	96	7	93	8	92
5a		CH_3COOH	22	95	33	67	55	45
5b			4	45	48	52	81	19
6a			2.	100	3	97		
6b			2	98	7	93		

1) a: catalyst **2**, b : catalyst **3**; 2) Time presents the timeperiod at which the conversion reaches a plateau or is complete ; 3)Yield and selectivity as determined with ^{1}H-NMR and GC-MS.

Table 2. Addition of acetic acid to 1,7 octadiyne catalyzed by complexes **2** and **3** (toluene, 110°C, alkyne/acid/catalyst = 94/224/1)

Entry[a]	Time (h)	% Yield[b]	% Mono-substitution[b]	% M[b]	% Anti-M[b]	% Di-substitution[b]	% M[b]	% Anti-M[b]	%M-anti-M[b]
7a	4	91	15	16	84	85	18	37	45
7b	2.5	76	27	16	84	63	28	16	56

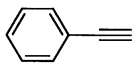
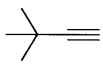
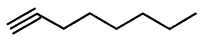
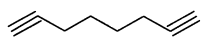
[a] (a) Catalyst **2**, (b) catalyst **3**.
[b] Yield and selectivity as determined with ^{1}H NMR and GC–MS.

1,7-octadiyne. The conversion of the dialkyne is 91 and 76%, respectively, for complexes **2** and **3**. The major product is the disubstitution with on one end a Markovnikov addition and on the other end an anti-Markovnikov addition (entries 7a and 7b—%M-anti-M). A small amount of dialkynes has only one triple bond converted into an anti-Markovnikov enol ester endgroup (15 and 27%, respectively).

Another typical Ru-catalyzed reaction is the dimerization of terminal alkynes. Contrary to other transition-metal catalysts such as Ti, Pd, and Rh where most reactions afford head-to-tail products, Ru complexes selectively catalyze tail-to-tail coupling reactions of terminal alkynes.[28] Complexes **2** and **3** also preferentially form tail-to-tail enynes (Table 3). The exception is the dimerization of 1-octyne catalyzed by **3**, where the regioselectivity is reversed (entry 10b). For 1,7-octadiyne 25 and 48% (for **2** and **3**, respectively) of the enyne product consists of a head-to-tail coupling on one end and tail-to-tail adduct on the other end. Besides the formation of the dimeric product, the production of trimeric and higher oligomeric products is present.

The synthesized Ru complexes, consisting of a labile *p*-cymene and a strong *N*-heterocyclic carbene donor, display a very high regioselectivity towards the anti-Markovnikov addition of carboxylic acids on terminal alkynes. The pure complex **2** exhibits an additional stereoselectivity to produce *Z*-alk-1-en-1-yl esters. The dimerization of alkynes shows a preference for tail-to-tail coupling reactions.

Table 3. Dimerization of terminal alkynes catalyzed by **2** and **3** (toluene, 110°C, alkyne/catalyst = 100/1)

Entry[1]	Alkyne	Time (h)[2]	% Yield[3]	head-to-tail enyne[3]	tail-to-tail enyne[3]
8a		8	53	42	58
8b		6	60	10	90
9a		6	78	34	66
9b		10	94	33	67
10a		24	30	13	87
10b		3	60	82	18
11a		22	57	41	25
11b		4	30	46	6

1) a: catalyst **2**, b: catalyst **3**; 2) Time presents the timeperiod at which the conversion reaches a plateau or is complete ; 3)Yield and selectivity as determined with ^{1}H-NMR and GC-MS.

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