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Regiocontrolled Ru-catalyzed addition of carboxylic acids to alkynes: practical protocols for the synthesis of vinyl esters†

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The catalytic activity of commercially available, air and water stable ruthenium complexes in the addition of carboxylic acids to terminal alkynes was found to be drastically enhanced by the addition of small quantities of base. Moreover, the regioselectivity of the reaction can be controlled by the choice of the base so that both the Markovnikov (Na_2CO_3) and the anti-Markovnikov products (DMAP) are now easily accessible in excellent selectivities.

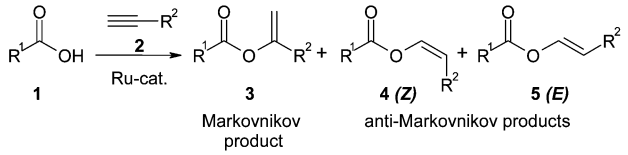
Vinyl esters such as vinyl acetates, acetoxystyrenes and vinyl haloacetates are important substrates for polymerization reactions.[1] Furthermore, they are utilized as mild acylating agents in the synthesis of various esters, amides[2] or α-halo ketones[3] and are important intermediates in enzyme-catalyzed kinetic resolutions of chiral alcohols.[4] Other applications include cyclopropanations,[5] [2 + 4]-, [2 + 2]-, and 1,3-dipolar cycloadditions,[6] asymmetric hydrogenation[7] and hydroformylation[8] reactions and the conversion to enamides.[9]

Common syntheses of vinyl esters are transesterifications with vinyl acetate or isopropenyl acetate,[10] or *O*-acylations of enolates.[11] A particularly efficient entry to these compounds is the ruthenium-catalyzed addition of carboxylic acids **1** to alkynes **2** (Scheme 1). This was first performed by Rotem *et al.* using $Ru_3(CO)_{12}$ as the catalyst under rather harsh conditions, giving rise mainly to the Markovnikov products.[12] In the groups of Mitsudo and Dixneuf, the reaction was further developed and more active catalysts were discovered, *e.g.* bis(cyclooctadienyl)Ru–phosphine–maleic anhydride or Ru(methallyl)$_2$–phosphine combinations.[13,14] It was also found that bidentate phosphines on the ruthenium reverse the selectivity of the addition, so that instead of alk-1-en-2-yl esters **3**, the (*Z*)-alk-1-en-1-yl esters **4** are predominantly formed.[14]

However, the practical value of this elegant transformation remained limited for organic chemists, since the catalytic activity of readily available ruthenium compounds is rather low,[15] and sufficiently active catalysts have to be especially synthesized from sensitive organometallic compounds (*i.e.* bis(cyclooctadienyl)Ru).[13]

We herein disclose a new catalyst system that is highly effective, yet consists solely of easy-to-handle, commercially available components and is thus particularly practical for applications in synthetic chemistry.‡

We chose the reaction of benzoic acid **1a** with 1-hexyne **2a** according to Scheme 1 (R^1 = phenyl, R^2 = *n*-butyl) as our model system and screened various ruthenium complexes in order to identify factors that influence their catalytic activity. Selected results are summarized in Table 1.



Scheme 1 Addition of carboxylic acids to terminal alkynes.

At a temperature of only 60 °C, commercially available ruthenium compounds display almost no catalytic activity for the desired transformation (Table 1, Entries 1–3). However, in the presence of a catalyst generated *in situ* from ((*p*-cumene)$RuCl_2)_2$ **6** and PPh_3, the addition proceeds with high selectivity for the Markovnikov product **3a**, though in modest yields (Entry 4). Better yields are obtained when using phosphines with strong π-acceptor ability such as tri-2-furyl phosphine (= $P(Fur)_3$) (Entries 5–7).

It was then investigated whether the addition of silver salts with non-coordinating counterions would generate more active cationic catalysts.[13] However, among the silver salts tested, solely $AgNO_3$ showed an accelerating effect (Entries 8–10).

Since the proposed catalytic cycle involves attack of the carboxylate onto the alkyne coordinated to the ruthenium,[2] we reasoned that the presence of catalytic amounts of base should increase the amount of carboxylate ions and might thus facilitate the reaction more effectively. Indeed, simply by adding a few mol% of sodium benzoate, the yields were drastically increased. The addition of inorganic bases to the reaction mixture had the same accelerating effect, best results being obtained with sodium carbonate (Entries 11–13). The reaction is insensitive to both air and water—a great advantage for preparative applications (Entry 14).

Table 1 Ru-catalyzed addition of benzoic acid (**1a**) to hexyne (**2a**)

Entry	Ru-Precursor	Ligand	Additive	Conv. (%)	Sel. **3** (%)	Sel. **4** (%)
1	$RuCl_3$	—	—	< 1	—	—
2	$RuCl_3(PPh_3)_3$	—	—	< 1	—	—
3	**6**	—	—	< 1	—	—
4	**6**	PPh_3	—	10	97	2
5	**6**	$P(Cy)_3$	—	10	80	15
6	**6**	$P(p\text{-}Cl\text{-}C_6H_4)_3$	—	10	97	2
7	**6**	$P(Fur)_3$	—	15	97	2
8	**6**	$P(Fur)_3$	$AgNO_3$	85	95	4
9	**6**	$P(Fur)_3$	$AgClO_4$	5	90	n.d.
10	**6**	$P(Fur)_3$	$AgSbF_6$	< 1	—	—
11	**6**	$P(Fur)_3$	NaF	50	97	2
12	**6**	$P(Fur)_3$	PhCOONa	95	97	2
13	**6**	$P(Fur)_3$	Na_2CO_3	95	97	2
14[a]	**6**	$P(Fur)_3$	Na_2CO_3	95	97	2
15	**6**	$P(Fur)_3$	2,6-lutidine	< 1	—	—
16	**6**	$P(Fur)_3$	pyridine	20	< 1	98
17	**6**	$P(Fur)_3$	DMAP	20	< 1	98
18	**6**	PPh_3	DMAP	45	< 1	99
19	**6**	$P(p\text{-}Cl\text{-}C_6H_4)_3$	DMAP	65	< 1	99
20[b]	**6**	$P(p\text{-}Cl\text{-}C_6H_4)_3$	DMAP	90	< 1	99
21[c]	**6**	$P(Fur)_3$	Na_2CO_3	95	97	2
22[d]	**6**	$P(Fur)_3$	Na_2CO_3	< 1	—	—
23[e]	**6**	$P(Fur)_3$	Na_2CO_3	95	97	2

Conditions: 1.00 mmol benzoic acid, 1.30 mmol 1-hexyne, 0.01 mmol Ru-precursor, 0.02 mmol ligand, 0.04 mmol additive, toluene, 60 °C, 16 h.[a] 10 mmol water, no argon, 25 °C, 72 h. [b] 0.03 mmol ligand. [c] 1,2-Dichloroethane. [d] NMP. [e] Nonanoic acid, no solvent.

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In the presence of inorganic bases, the reactions showed high selectivities for the Markovnikov product **3a**. To our surprise, this selectivity was reversed when organic bases, *e.g.* pyridines, were added (Entries 15–17). In the presence of (4-dimethylamino)pyridine (DMAP), the selectivity for the (*Z*)-anti-Markovnikov product **4a** was 98 to 99%. Only trace quantities of **3a** and the *E*-isomer **5a** were observed. This effect may be rationalized by assuming that DMAP coordinates to the ruthenium, giving rise to a complex with similar selectivities to ruthenium compounds with chelating ligands.[14,16] For the anti-Markovnikov reaction variant, P(*p*-Cl-C_6H_4)$_3$ was slightly more effective than P(Fur)$_3$ (Entries 17–20).

Toluene, chloroform and 1,2-dichloroethane are suitable solvents for both reaction variants, while more strongly coordinating solvents lower the turnover rates (Entries 13, 21 and 22). When using liquid carboxylic acids, the reaction can also be carried out successfully without solvent (Entry 23).

After having identified highly active catalyst systems for both Markovnikov and anti-Markovnikov additions of carboxylic acids to 1-alkynes, we investigated the scope of our protocols using various carboxylic acids in combination with several alkynes. Selected results are summarized in Table 2. Electron-rich and electron-poor alkyl, aryl, and heteroaryl carboxylic acids give excellent yields with both catalyst systems. Even sterically hindered carboxylic acids are converted and a variety of functionalities including esters, ethers, aldehydes, carbamates, and even hydroxyl groups are tolerated.

While the Markovnikov addition of *N*-protected α- and β-amino acids proceeds smoothly, the α-amino acids give no conversion in the anti-Markovnikov reaction variant. Further experiments suggested that this may be due to the high C–H acidity of α-amino acids.

Various other terminal alkynes were converted in good yields and mostly in good selectivities. It is especially worth mentioning that gaseous propyne smoothly reacts at ambient pressure, so that no high-pressure equipment is required for the preparation of the synthetically particularly useful isopropenyl esters.[4]

Table 2 Scope of the Markovnikov and the anti-Markovnikov addition

R^1	R^2	Method	Prod.	Yield (%)	Sel[a] **3**:**4**
Phenyl	*n*-C_4H_9	A	**3a**	93	30:1
		B	**4a**	89	1:50
o-Tolyl	*n*-C_4H_9	A	**3b**	86	35:1
		B	**4b**	93	1:50
p-MeO-C_6H_4	*n*-C_4H_9	A	**3c**	88	15:1
		B	**4c**	90	1:50
p-H(CO)-C_6H_4	*n*-C_4H_9	A[b]	**3d**	87	10:1
		B[c]	**4d**	80	1:50
2-Thienyl	*n*-C_4H_9	A	**3e**	94	30:1
		B	**4e**	87	1:50
1-Me-pyrrol-2-yl	*n*-C_4H_9	A	**3f**	95	24:1
		B	**4f**	94	1:50
HO-*n*-$C_{11}H_{22}$	*n*-C_4H_9	A[b]	**3g**	61	15:1
		B	**4g**	72	1:50
m-AcO-C_6H_4	*n*-C_4H_9	A	**3i**	86	50:1
		B	**4i**	86	1:50
C_6H_5-C_2H_4	*n*-C_4H_9	A	**3j**	83	22:1
		B	**4j**	74	1:50
p-CF_3-C_6H_4	*n*-C_4H_9	A	**3k**	95	30:1
		B[c]	**4k**	78	1:50
Cbz-$NHCH_2CH_2$	*n*-C_4H_9	A[b]	**3l**	70	14:1
		B	**4l**	46	1:50
Cbz-$NHCH_2$	*n*-C_4H_9	A[b]	**3m**	82	14:1
		B	**4m**	< 5	n.d.
Phenyl	Phenyl	A[d]	**3n**	88	3:2
		B	**4n**	99	1:50
Phenyl	CH_3	A	**3o**	99	22:1
		B	**4o**	76	1:50
Phenyl	*t*-Butyl	A	**3p**	88	10:1
		B[c]	**4p**	68	1:50

Conditions: A: 5.00 mmol acid, 6.50 mmol alkyne, 0.02 mmol **6**, 0.04 mmol P(Fur)$_3$, 0.08 mmol Na_2CO_3, toluene, 50 °C, 16 h; *B*: 5.00 mmol acid, 6.50 mmol alkyne, 0.05 mmol ((*p*-cumene)$RuCl_2$)$_2$**6**, 0.15 mmol P(*p*-Cl-C_6H_4)$_3$, 0.20 mmol DMAP, toluene, 60 °C, 16 h.[a] Isomer **5** < 1 %. [b] In $CHCl_3$. [c] In 1,2-dichloroethane, 80 °C. [d] 70 °C.

Overall, we have developed highly efficient catalyst systems for both the Markovnikov and the anti-Markovnikov addition of carboxylic acids to terminal alkynes. The catalysts are generated *in situ* from air- and water-stable compounds that are commercially available at low cost. Thus, important drawbacks of this elegant transformation have been overcome.

Notes and references

‡ *Method A*: Benzoic acid (588 mg, 5.00 mmol) and Na_2CO_3 (9.40 mg, 0.08 mmol) were suspended in toluene (16 ml). Subsequently, a solution of ((*p*-cumene)$RuCl_2$)$_2$ (12.2 mg, 0.02 mmol) and tri(2-furyl)phosphine (9.20 mg, 0.04 mmol) in toluene (4 ml), and 1-hexyne (710 μl, 6.50 mmol) were added. The reaction mixture was heated to 50 °C. After complete conversion (GC), usually 16 h, the mixture was cooled and filtered over a small plug of silica gel. The solvent was removed and the crude mixture was purified by Kugelrohr distillation at 120 °C/0.1 mbar, yielding product **3a** (950 mg, 93%, isomeric purity > 96%) as a colorless liquid.

Method B: A solution of ((*p*-cumene)$RuCl_2$)$_2$ (30.6 mg, 0.05 mmol), tri(*p*-Cl-C_6H_4)phosphine (54.8 mg, 0.15 mmol) and DMAP (24.4 mg, 0.20 mmol) in dry toluene (4 ml) was added to a solution of benzoic acid (588 mg, 5.00 mmol) and 1-hexyne (710 μl, 6.50 mmol) in dry toluene (16 ml). The mixture was stirred for 16 h at 60 °C and worked up as above, yielding **4a** (908 mg, 89%, isomeric purity > 98 %).

All spectroscopic data (^{1}H-, ^{13}C-NMR, HRMS) was identical to that reported in the literature for the (*Z*)-isomer.

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