



Organometallic catalysis in aqueous–organic two-phase systems: Rhodium-catalyzed coupling reaction of but-3-enoic acid with allyl derivatives; influence of the reaction media

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ARTICLE INFO

Article history:

Received 20 March 2008
Received in revised form 15 April 2008
Accepted 17 April 2008
Available online 25 April 2008

Keywords:

Organometallic catalysis
Aqueous–organic two-phase systems
C–C coupling
Rhodium
Heptadienoic acids

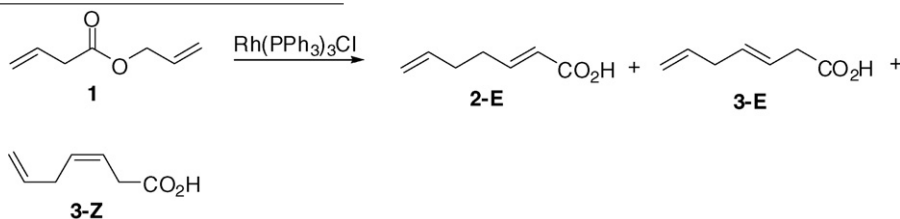
ABSTRACT

A simple and efficient procedure is described for the synthesis of 2,6- and 3,6-heptadienoic acids and allyl esters consisting of Rh-catalyzed coupling of but-3-enoic acid and allyl derivatives such as allyl bromide, allyl acetate, and allyl methyl carbonate in alkaline water or in alkaline water/organic two-phase systems. 2,6-Heptadienoate derivatives are the main products in water as acids and in biphasic systems as acids and allyl esters. The latter can be selectively obtained via one-pot cascade esterification reaction using allyl bromide in biphasic systems. The nature of organic solvent, the base concentration and the addition of triphenylphosphine (TPP) in biphasic media allow to tune the regioselectivity of the reaction towards 3,6- or 2,6-derivatives. Substituted but-3-enoic acids and allyl bromides, and pent-4-enoic acid led to moderate or poor results.

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1. Introduction

Organometallic catalysis in aqueous–organic two-phase systems appears as a useful and environmentally friendly technique for producing organic compounds meeting more and more urgent ecological requirements. A biphasic system of two mutually immiscible solvents can be an elegant way to maintain the advantages of homogeneous catalysis in combination with an easy recovery of the catalyst [1,2]. Studies have shown that the peculiar properties of water as a reaction medium can be exploited to improve reactions performance, or to explore new reactivity of organic compounds



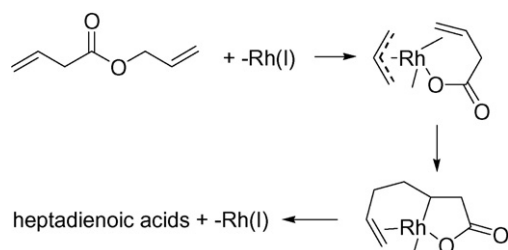
[3]. Over the last few years we addressed our interest to the technology connected with water or organic–aqueous two-phase

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homogeneous catalysis. In particular we investigated the rearrangement in aqueous media of allyl but-3-enoate to 2,6- and 3,6-heptadienoic acids [4], useful compounds for the synthesis of intermediates of biological and pharmaceutical interest [5]. This type of rearrangement was described for the first time several years ago by Chiusoli et al. [6]. The catalytic reaction (Eq. (1)) was carried out in aprotic solvents such as acetonitrile, chloroform and tetrahydrofuran in the presence of a phosphorous-containing Rh(I) complex $[\text{Rh}(\text{PPh}_3)_3\text{Cl}]$ under mild conditions yielding a mixture of 2,6- and 3,6-heptadienoic acids, the latter isomer being predominant.

(1)

This approach took advantage of the chelating effect for achieving the formation of a new C–C bond [7–9]. In fact, the formation of a chelate complex of rhodium with the butenoate group can assist the oxidative addition of allyl but-3-enoate to the metal center, which thus holds the double bond in the appropriate position for insertion into the allyl–rhodium bond (Scheme 1). A final β -hydrogen



Scheme 1.

elimination step then leads to heptadienoic acids with regeneration of the catalyst [7].

We recently experimented an efficient and environmentally compatible protocol for the preparation of heptadienoic acids and esters based on the rearrangement of allyl but-3-enoate in alkaline aqueous media in the presence of a catalytic amount of a Rh(I) complex containing olefinic ligands [4]. 2,6-Heptadienoic acid derivatives were the main isomers in water. With the aim of developing a more practical approach to the synthesis of heptadienoic acids or esters we have considered the accomplishment of the rhodium-catalyzed reaction in an alkaline water solution or in an alkaline aqueous–organic two-phase system starting directly from but-3-enoic acid and an allylic derivative thus avoiding the previous preparation of allyl but-3-enoate. Proofs about the chemoselectivity of the reaction with regard to heptadienoic acid or allyl ester formation have been pursued. Combinations of different allyl substrates with various solvents and the

presence of phosphine ligands have been examined with regard to the regioselectivity of the reaction. On the basis of the ligand coordinating ability for the rhodium species and the solvent properties, the formation of 2-6- or 3,6-heptadienoic acids and their respective allyl esters may be selectively influenced.

2. Results and discussion

2.1. Preliminary results

Three different allylic substrates have been used: allyl bromide, allyl acetate and allyl methyl carbonate. We first caused the three allyl derivatives to react with but-3-enoic acid in the presence of a catalytic amount of $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ in a K_2CO_3 /water–organic two-phase system or in a K_2CO_3 aqueous solution. Different solvents such as toluene, chlorobenzene (CIPh), butyronitrile ($\text{C}_3\text{H}_7\text{CN}$) and diethoxyethane (DEE) were considered when employing biphasic systems. The mixture was stirred at 75°C for 23 h. At the end of the reaction the allyl esters of but-3-enoic, 3,6-, 2,6-heptadienoic and 4-allyl-3,6-heptadienoic acids were recovered from the organic phase. The respective acids were recovered from the aqueous phase containing their potassium salts through acidification with HCl solution. Eq. (2) shows the products formed after HCl treatment. For simplicity, in the following part of this work, the above mentioned products will be referred to as “acids”; it must however always be kept in mind that in the reaction mixture they are always present as potassium salts, due to the alkaline water conditions, and are recovered as acids after reaction workup.

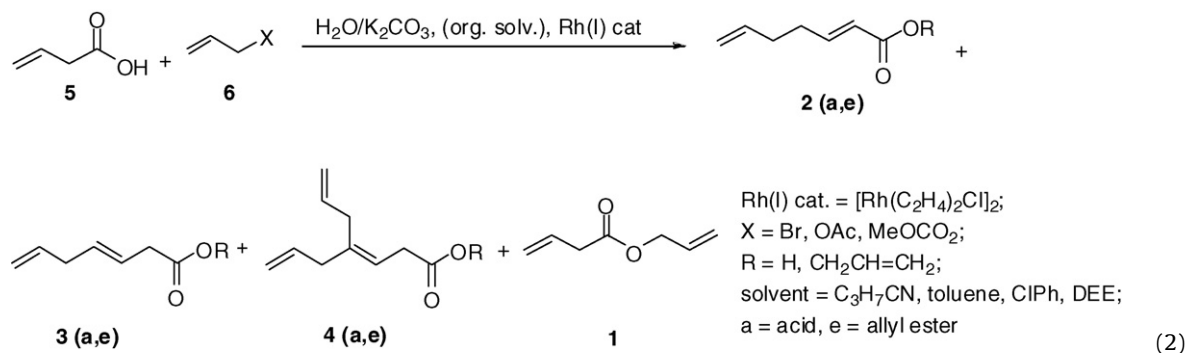
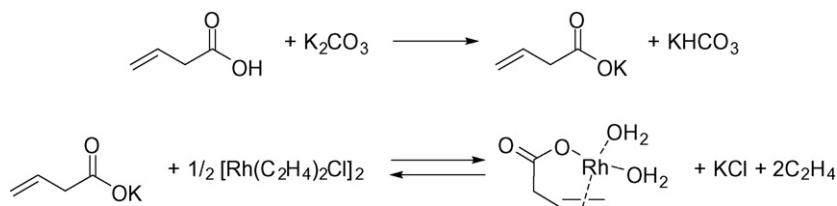


Table 1

Reactions of allyl derivatives $\text{XCH}_2\text{CH}=\text{CH}_2$ (8.5 mmol) with but-3-enoic acid (4.1 mmol) in the presence of $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ (0.021 mmol) in K_2CO_3 water solution (5 mL, K_2CO_3 concentration = 5 mmol/mL) or in alkaline water (1 mL, K_2CO_3 concentration = 5 mmol/mL)–organic solvent (4 mL) biphasic system

Entry	$\text{XCH}_2\text{CHCH}_2$	Solvent	Conversion (%)	Selectivity (%)							Total selectivity to 2,6-derivatives (%)	Selectivity ratio of 2,6-/3,6-derivatives	Total selectivity to acids (%)	
				5	3a	2a	4a	1	3e	2e				4e
1		H ₂ O	80	7	92						1	93	14.17	99
2		Toluene/H ₂ O	99	1	3		6	11	75	4	78	4.83	4	
3	X = Br	CIPh/H ₂ O	99	3	7	1	4	10	68	6	75	3.71	12	
4		DEE/H ₂ O	100	1	4	1	7	10	74	3	79	5.53	6	
5		C ₃ H ₇ CN/H ₂ O	93	9	4		2	22	61	2	65	1.94	13	
6		H ₂ O	83	8	90						90	10.71	99	
7		Toluene/H ₂ O	99	15	82				3	85	5.60	97		
8	X = MeOCO ₂	CIPh/H ₂ O	100	4	79	10			5	1	85	5.52	94	
9		DEE/H ₂ O	97	3	75	6	5	1	8	1	83	7.45	84	
10		C ₃ H ₇ CN/H ₂ O	100	5	81	8			6		87	6.61	94	
11		H ₂ O	93	12	88						88	7.45	100	
12		Toluene/H ₂ O	92	13	77	4		1	5		82	4.63	94	
13	X = AcO	CIPh/H ₂ O	93	13	85	1			1		86	6.20	99	
14		DEE/H ₂ O	91	12	85	1			1		86	6.26	99	
15		C ₃ H ₇ CN/H ₂ O	90	11	64		2	2	20		84	6.51	75	

Organic solvents: toluene, chlorobenzene (CIPh), 1,2-diethoxyethane (DEE), butyronitrile (C₃H₇CN). Reaction carried out for 23 h at 75°C under stirring (1000 rpm).



Conversions and selectivities are summarized in Table 1 along with the selectivity of 2,6-heptadienoic derivatives (acid+ester, **2a+2e**), selectivity ratios of 2,6-/3,6-derivatives (**2a+2e**)/(**3a+3e+4a+4e**) and the acid selectivities (**2a+3a+4a**).

Data reported in Table 1 provide significant results. In alkaline water solution conversions were slightly lower than the ones in biphasic systems, whichever allyl derivative was used (entries 1, 6 and 11). Four main products were observed: 2,6- and 3,6-heptadienoic acids, and their respective allyl esters; two by-products were also found in lower amounts: 4-allyl-3,6-heptadienoic acid, and its allyl ester.

The results (Table 1) show that in all cases the selectivity of 2,6-heptadienoate derivatives (acids and esters) was considerably higher than the one of 3,6-isomers independently of the allyl substrate. In alkaline water solution a significant increase of 2,6-heptadienoic acid was observed for all allyl derivatives under the used conditions (entries 1, 6 and 11). Allyl acetate and allyl methyl carbonate yielded acids as predominant products in all reaction media (entries 7–10 and 12–15), whereas the allyl esters were the main products with allyl bromide in all water–organic solvent media (entries 2–5).

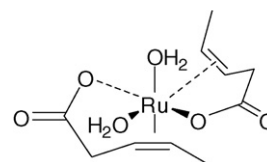
2.2. Regio- and chemoselectivities

The reaction conditions seemed to have a remarkable effect on regioselectivity (i.e. C=C double bond position) and chemoselectivity (i.e. production of acids or esters) of the reaction; we thus planned a series of experiments in order to ascertain the effects of different parameters on yields and selectivities of the different products.

Two alternative steps in the reaction course can account for the regioselectivity of the process. In our specific case, K_2CO_3 contained in the aqueous phase reacts with but-3-enoic acid forming a water-soluble potassium salt. In the same phase, a rhodium complex – free of water soluble ligands – $[Rh(C_2H_4)_2Cl]_2$, first is solvated by

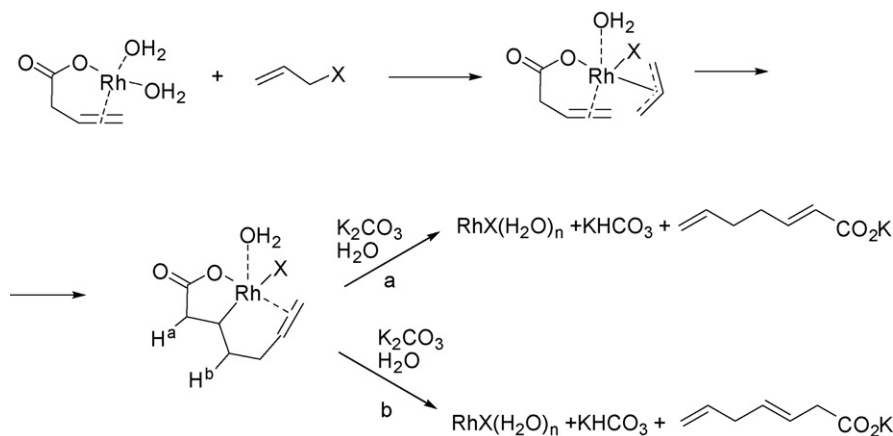
H_2O , then it interacts with the organic salt likely forming a Rh(I) complex according to Scheme 2. It is possible that the formation of the reaction intermediate occurs also directly from but-3-enoic acid without its previous transformation into potassium salt. However, some experiments carried out in defect or in absence of the base (Section 3.1) showed a slower initial dissolution of the rhodium complex $[Rh(C_2H_4)_2Cl]_2$, indicating that the active species is more easily formed by anion exchange rather than by interaction of but-3-enoic acid with Rh(I) complex.

The Rh complex has not yet been isolated, but an analogue ruthenium compound has been crystallized and characterized by X-ray diffraction analysis [10].



The Rh complex thus formed can distribute between the aqueous and organic phase, undergoing oxidative addition of the allylic derivative. Subsequent formation of a C–C bond and reductive β -hydrogen elimination provides 2,6- and 3,6-heptadienoic acids (Scheme 3, path a and b). Previously we proposed that the latter two steps are preferentially accomplished in organic solvents or in aqueous alkaline solution, respectively [4]. In organic solvents β -hydrogen elimination involves the less acidic hydrogen H^b as indicated in path b (Scheme 3) to afford 3,6-heptadienoates as the main reaction products. On the other hand, in alkaline water solution, β -hydrogen elimination preferentially occurs from the hydrogen H^a bonded to the α -carbon atom of the chain (path a in Scheme 3) through proton abstraction by the base, eventually leading to 2,6-heptadienoic acid as the main reaction product.

The allyl esters **2e** and **3e** of the two heptadienoic acids **2a** and **3a** are formed via consecutive one-pot base-catalyzed esterification with the excess of allyl bromide present in the reaction mixture.



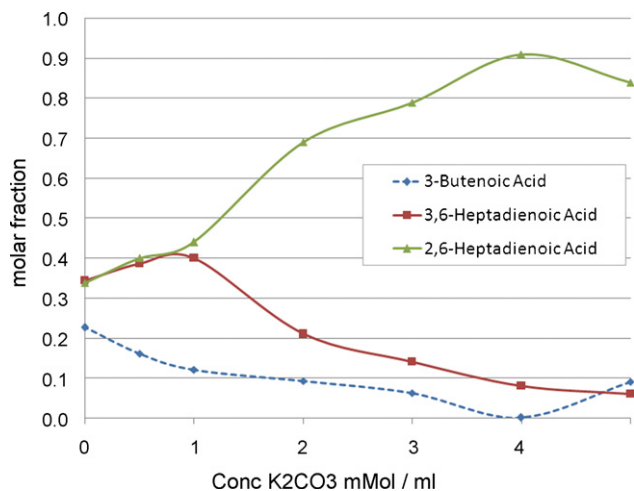


Diagram 1. Molar fractions in the mixture of the reaction of allyl bromide (8.5 mmol) and but-3-enoic acid (4.1 mmol) in water (5 mL) at variable K_2CO_3 concentrations after 23 h at 75 °C. Catalyst $[Rh(C_2H_4)_2Cl]_2$ (0.021 mmol). Compounds present in less than 3% amounts are omitted for clarity.

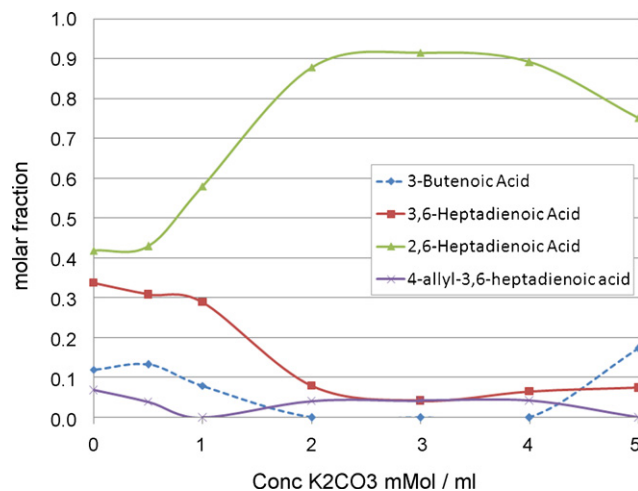


Diagram 3. Molar fractions in the mixture of the reaction of allyl methyl carbonate (8.5 mmol) and but-3-enoic acid (4.1 mmol) in water (5 mL) at variable K_2CO_3 concentrations after 23 h at 75 °C. Catalyst $[Rh(C_2H_4)_2Cl]_2$ (0.021 mmol). Compounds present in less than 3% amounts omitted for clarity.

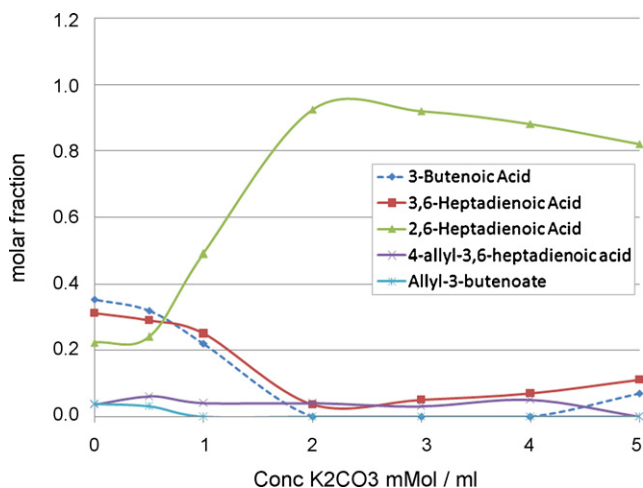


Diagram 2. Molar fractions in the mixture of the reaction of allyl acetate (8.5 mmol) and but-3-enoic acid (4.1 mmol) in water (5 mL) at variable K_2CO_3 concentrations after 23 h at 75 °C. Catalyst $[Rh(C_2H_4)_2Cl]_2$ (0.021 mmol). Compounds present in less than 3% amounts are omitted for clarity.

This was verified by monitoring the course of the reactions versus time, as described in Section 4.

3. Effect of the base concentration on the selectivity forwards 2,6- versus 3,6-derivatives

3.1. Aqueous systems

Experiments carried out at variable concentrations of base in water showed considerable effects on the regioselectivity of the reaction; 2,6-derivatives were favored at higher K_2CO_3 concentration. A set of reactions was carried out in water (5 mL) containing K_2CO_3 in a concentration ranging from 0 to 5.0 mmol/mL under the same conditions previously reported and with the same amounts of reagents and catalyst. The results are reported in Diagrams 1–3.

The conversions rise as the concentration of K_2CO_3 increases, likewise the yields and selectivities of 2,6-heptadienoic acid reach a maximum value that is kept up or decreases slowly with further increase of K_2CO_3 concentration owing to a drop of conversion.

Opposite is the course of 3,6-heptadienoic acid yields and selectivities.

The relation between the yields and the concentrations of K_2CO_3 in H_2O as reported in Diagrams 1–3 can be explained on the base of the proposed assumptions. In the absence of a base conversions are lower. 2,6- and 3,6-Heptadienoic acids are formed in similar amounts regardless of the allyl derivative used. Addition of increasing amounts of K_2CO_3 leads to an improvement of conversion with all the allyl derivatives until complete disappearance of residual but-3-enoic acid is achieved. At the same time a rapid increase of the production of 2,6-heptadienoic acids is noticed in conjunction with a decrease of that of 3,6-acid. As anticipated, this is likely due to a more favored β -hydrogen elimination step of the acid proton H^a (Scheme 3, path a) when an excess of base is present. The maximum value is reached at a concentration of about 2 mmol/mL with allyl acetate and allyl methyl carbonate, while only at 4 mmol/mL with allyl bromide. This can be due to the higher stability of possible micellar structures formed by allyl bromide in basic water in comparison with those of acetate and methyl carbonate, more easily water-transferable through hydrogen bonds. At higher (>4 mmol/mL) K_2CO_3 concentrations both conversions and selectivities to 2,6-heptadienoic acid decrease again.

3.2. Biphasic systems

The investigation was extended to different biphasic media but limited to allyl bromide owing to its different behavior in comparison with the other two allyl substrates (Table 1). Thus, but-3-enoic acid and allyl bromide were caused to react in presence of different organic solvents and at variable concentrations of K_2CO_3 in water. Under these conditions the increase of K_2CO_3 concentration gives rise to a steady increase of 2,6-/3,6-derivative yield ratio with toluene, DEE and ClPh whereas it is approximately constant with butyronitrile (Diagram 4). An analogous trend, but with a more marked slope, obtained for the aqueous system under analogue conditions is shown for comparison. In aqueous systems, however, the products were almost exclusively acids while in biphasic systems mostly esters. No 2,6- to 3,6-isomerization occurred under these conditions. Thus, the 2,6-/3,6-yield ratio shown in Diagram 4 may be a measure of the relative reaction rate for the two competitive β -hydrogen elimination steps depicted in Scheme 3. The linear dependence (in the examined range of base concentrations) of the

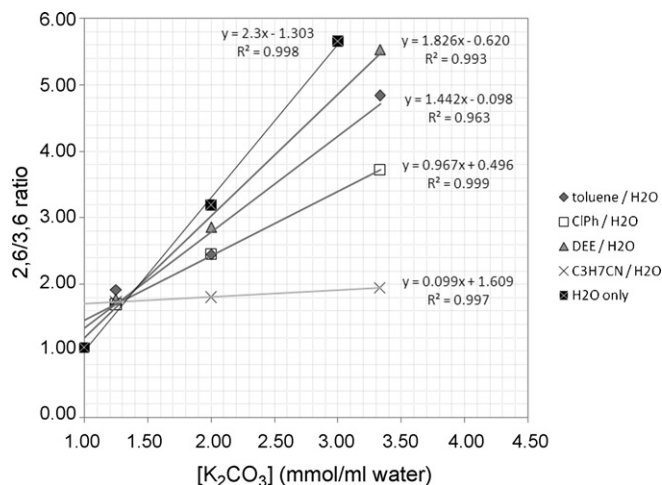


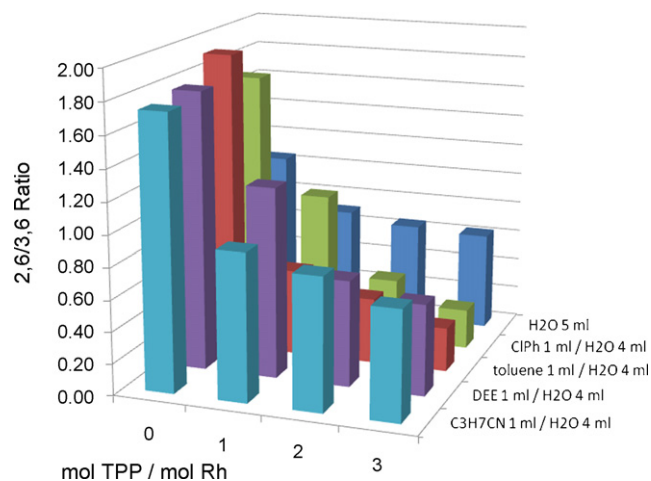
Diagram 4. Linear dependence of the 2,6-/3,6-derivative yield ratio vs. the base concentration for aqueous or biphasic system mixtures (total volume 5 mL). The same amount of K_2CO_3 was dissolved in decreasing volumes of water. Other conditions as reported in Diagrams 1–3.

relative rate of formation of 2,6-derivatives on the K_2CO_3 concentration can be taken as a proof that the base is directly involved in their formation.

The different behavior of butyronitrile may be ascribed to a competitive effect due to the coordinating ability of this solvent for rhodium complex. The presence of butyronitrile helps the rhodium transfer in organic solvent promoting the formation of 3,6-derivatives against the preferred formation of 2,6-derivatives in water, where K_2CO_3 concentration is growing.

4. Effect of triphenylphosphine as ligand on regioselectivity

The addition of a ligand such as TPP, able to bind to the metal and very soluble in the organic phase, can affect the distribution of the intermediate rhodium complex into the biphasic system producing consequences on the regioselectivity. Thus, the reaction of but-3-



Bar Chart 1. Comparison of the 2,6-/3,6-selectivity ratios for different solvent systems in presence of variable amounts of triphenylphosphine (TPP). Conditions as indicated in Table 2.

enoic acid and allyl bromide in the presence of $[Rh(C_2H_4)_2Cl]_2$ and different amounts of TPP were carried out under the conditions described in Table 2. Yields and selectivities are summarized in Table 2. The selectivity ratio of 2,6-/3,6-derivatives is reported in Bar Chart 1. A manifest decrease of the 2,6-/3,6-derivative selectivity ratio consistent with the rise of 3,6-derivatives owing to the addition of TPP equivalents is shown. The highest effect was obtained in toluene and ClPh biphasic system followed by DEE and C_3H_7CN , whereas in alkaline water the effect is negligible showing no appreciable variation of the ratio upon addition of TPP.

5. Effect of rhodium distribution between the two phases on regioselectivity

In order to better demonstrate the correlation between the rhodium distribution between the two phases and the regioselectivity of the reaction, quantitative determinations of the rhodium

Table 2
Reactions of allyl bromide (8.5 mmol) with but-3-enoic acid (4.1 mmol) in the presence of $[Rh(C_2H_4)_2Cl]_2$ (0.021 mmol) and triphenylphosphine in water or biphasic systems

Entry	Solvent	TPP/Rh (mol/mol)	Conversion (%)	Selectivity (%)							Total selectivity to 2,6-derivatives (2a+2e)	Total selectivity to 3,6-derivatives (3a+3e+4a+4e)	Selectivity ratio of 2,6-/3,6-derivatives (2a+2e)/(3a+3e+4a+4e)
				5	3a	2a	4a	1	3e	2e			
16		0	88	45	50	1	–	1	1	1	51	48	1.05
17	H ₂ O	1	83	29	29	7	4	16	10	4	40	56	0.71
18	5 mL	2	86	25	27	12	2	19	11	3	38	59	0.65
19		3	84	29	23	–	6	26	13	4	36	58	0.63
20	Toluene	0	97	12	34	3	–	7	32	12	66	34	1.92
21	1 mL/H ₂ O	1	91	29	21	7	1	21	14	6	35	64	0.54
22	4 mL	2	98	22	19	23	–	14	10	10	29	70	0.42
23		3	96	41	19	18	–	13	3	7	22	78	0.28
24	ClPh	0	100	6	12	3	1	17	50	11	62	37	1.69
25	1 mL/H ₂ O	1	98	17	22	3	2	23	25	8	47	51	0.93
26	4 mL	2	100	15	11	1	3	38	17	15	28	69	0.40
27		3	100	15	7	7	6	35	12	18	19	75	0.25
28	DEE	0	98	10	19	4	9	14	39	5	58	33	1.77
29	1 mL/H ₂ O	1	91	22	29	–	2	12	24	10	53	44	1.21
30	4 mL	2	80	28	25	–	4	24	14	6	39	57	0.68
31		3	91	39	22	1	–	19	14	4	37	63	0.58
32	C ₃ H ₇ CN	0	99	6	14	4	1	21	48	5	63	36	1.74
33	1 mL/H ₂ O	1	91	36	40	4	–	8	9	3	48	52	0.94
34	4 mL	2	98	7	9	–	9	38	32	3	41	49	0.84
35		3	87	22	21	–	5	29	18	5	39	56	0.70

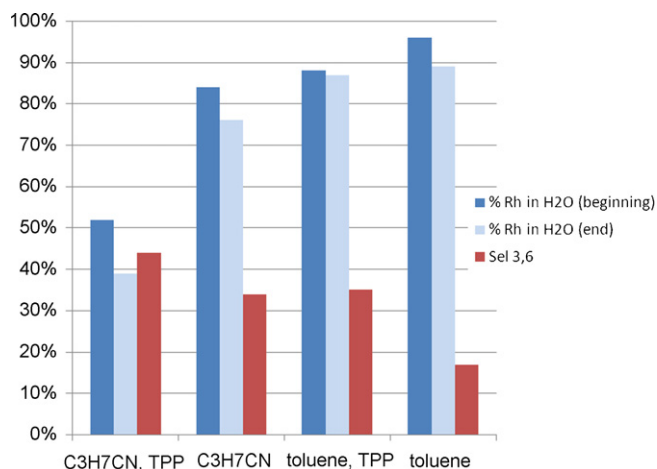
K_2CO_3 5 mmol. Solvent amounts as indicated. Reaction carried out for 23 h at 75 °C under stirring (1000 rpm).

Table 3

Relation between water phase Rh content and reaction selectivity to 3,6-derivatives for different water/organic solvent systems in the absence or the presence of one equivalent of TPP

	Rh in H ₂ O (beginning) (%)	Rh in H ₂ O (end) (%)	Selectivity to 3,6-isomers (%)
C ₃ H ₇ CN/H ₂ O, TPP (1 mmol/mmol Rh)	52	39	44
C ₃ H ₇ CN/H ₂ O	84	76	34
Toluene/H ₂ O, TPP (1 mmol/mmol Rh)	88	83	15
Toluene/H ₂ O	96	87	11

Rh amount determined by ICP analyses at the beginning and at the end of the reaction. Conditions: allyl bromide 8.5 mmol, but-3-enoic acid 4.1 mmol, [Rh(C₂H₄)₂Cl]₂ 0.021 mmol, K₂CO₃ 5 mmol, organic solvent 3 mL, H₂O 2 mL, reaction time 23 h, reaction temperature 75 °C.



Bar Chart 2. Relation between water phase Rh content and reaction selectivity to 3,6-derivatives for different water/organic solvent systems in the absence or the presence of one equivalent of TPP. Rh amount determined by ICP analyses at the beginning and at the end of the reaction. Conditions as indicated in Table 3.

dissolved in the organic phase and in the aqueous phase after reagent mixing as well as at the end of the reaction were carried out by ICP technique. Data of Rh ICP analyses and yields and selectivities of reactions carried out in water–toluene or water–butyronitrile systems are reported in Table 3 and in Bar Chart 2. The results show that the higher is the amount of rhodium dissolved in the aqueous phase, the higher is the selectivity to 2,6-derivatives. The addition of one equivalent of TPP causes a decrease of the amount of rhodium dissolved in water and simultaneously an increase of the 3,6-derivatives selectivity.

Since in all biphasic conditions a significant fraction of rhodium tends to be dissolved in water, as the results reported in Table 3 show, yielding mainly 2,6-heptadienoic acid derivatives, thus we investigated the possibility of carrying out the reactions in absence of water and base, in order to force the β -elimination step to take place according to path b as described in Scheme 3. Under these conditions, in the presence of [Rh(C₂H₄)₂Cl]₂, allyl bromide gave no reaction (likely because of catalyst deactivation due to the formation of HBr). The reactions of allyl acetate and allyl methyl carbonate with but-3-enoic acid in the presence of the same rhodium complex, provided low conversions (15–30%) except for allyl acetate in C₃H₇CN which, as expected, gave 3,6-derivatives as the main products (43% selectivity against 33% of 2,6-derivatives at 84% conversion). Allyl acetate and allyl methyl carbonate were also caused to react in absence of water K₂CO₃ solution in the four solvents utilizing Rh(PPh₃)₃Cl as a catalyst. In this case the best results were obtained in toluene with high yields and selectivity of 3,6-derivatives (74% yield of **3a** at 95% conversion for allyl methyl carbonate and 69% of **3a** at 93% conversion for allyl acetate.). Lower conversions (54–83%) and yields of **3a** (38–61%) were obtained in DEE, ClPh and C₃H₇CN.

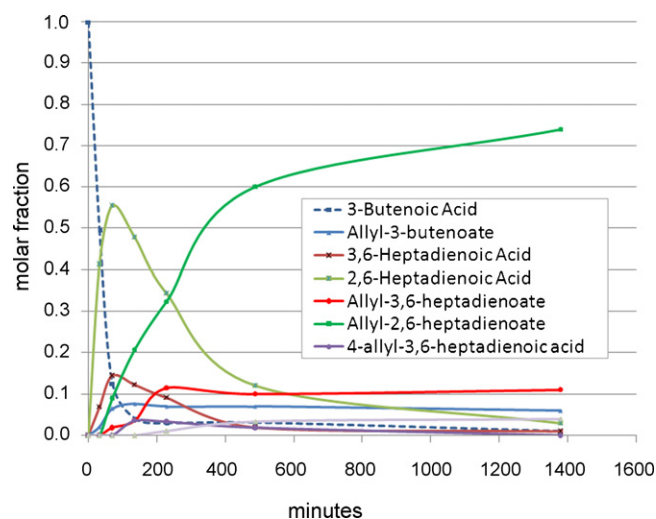


Diagram 5. Molar fractions in the mixture of the reaction of allyl bromide (8.5 mmol) and but-3-enoic acid (4.1 mmol) in toluene (4 mL)/water (1 mL) biphasic system at different times. K₂CO₃ 5 mmol, [Rh(C₂H₄)₂Cl]₂ 0.021 mmol, reaction temperature 75 °C. Compounds present in less than 3% amounts are omitted for clarity.

6. Formation of allyl heptadienoates versus heptadienoic acids

Different allyl substrates gave different results with regard to chemoselectivity. Thus, we followed the reaction course versus time using a toluene–water mixture as reaction medium, employing all three reagents. The results are plotted in Diagrams 5–7.

The three allyl substrates showed a common initial behavior that is the formation of 2,6- and 3,6-heptadienoic acids, with a slower rate for the latter one. Allyl bromide only was found to react with the potassium salts of heptadienoic acids in alkaline biphasic medium leading to allyl ester formation; in addition the 3,6-heptadienoate anion reacted with allyl bromide to yield 4-allyl-3,6-heptadienoate derivative which subsequently was transformed into allyl ester. Esterification of potassium but-3-enoate with allyl bromide can take place efficiently as well, but, according to the data in Diagram 5, the initial rate of rhodium-catalyzed formation of 2,6- and 3,6-heptadienoate is faster than the esterification process. A control experiment of esterification in the absence of catalyst, of a mixture of but-3-enoic, 2,6- and 3,6-heptadienoic acids with allyl bromide in toluene–alkaline water biphasic system showed that the formation of allyl 2,6- and 3,6-heptadienoate is faster than the one of allyl but-3-enoate. Thus, it is allowed to infer that the C–C bond formation derives mainly from direct reaction of but-3-enoic acid and allyl bromide rather than from rearrangement of allyl but-3-enoate. Only in the case of unfavourable conditions for rhodium-catalyzed C–C coupling reaction, as for the processes shown in Eqs. (4) and (5), the formation of allyl esters of the starting acids is prevalent.

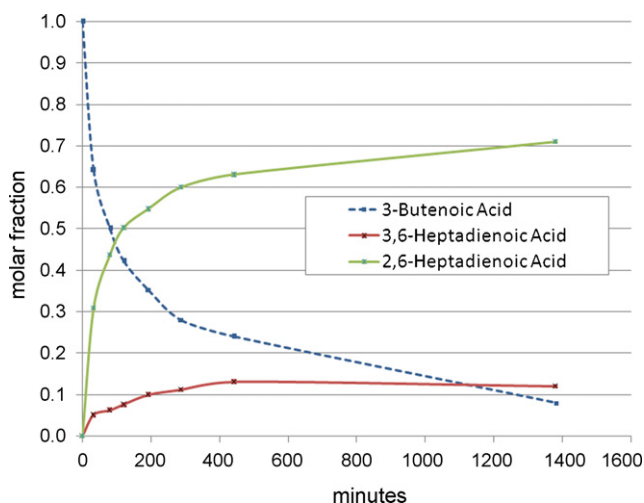


Diagram 6. Molar fractions in the mixture of the reaction of allyl acetate (8.5 mmol) and but-3-enoic acid (4.1 mmol) in toluene (4 mL)/water (1 mL) biphasic system at different times. K_2CO_3 5 mmol, $[Rh(C_2H_4)_2Cl]_2$ 0.021 mmol, reaction temperature 75 °C. Compounds present in less than 3% amounts are omitted for clarity.

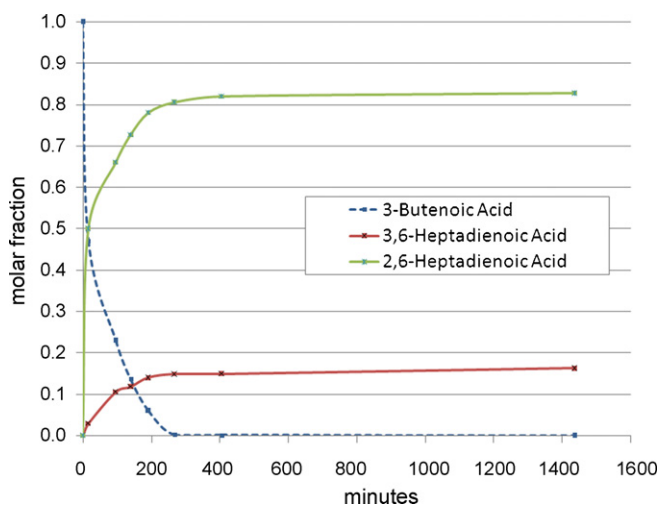


Diagram 7. Molar fractions in the mixture of the reaction of allyl methyl carbonate (8.5 mmol) and but-3-enoic acid (4.1 mmol) in toluene (4 mL)/water (1 mL) biphasic system at different times. K_2CO_3 5 mmol, $[Rh(C_2H_4)_2Cl]_2$ 0.021 mmol, reaction temperature 75 °C. Compounds present in less than 3% amounts are omitted for clarity.

At the end of the reaction the main product was allyl 2,6-heptadienoate along with lower amounts of allyl 3,6-heptadienoate, allyl 4-allyl-3,6-heptadienoate and, in very small amount, the respective acids (Diagram 5). By contrast, the reactions of allyl acetate and allyl methyl carbonate led to the formation of 2,6- and 3,6-heptadienoate potassium salts with negligible amounts of allyl esters (Diagrams 6 and 7).

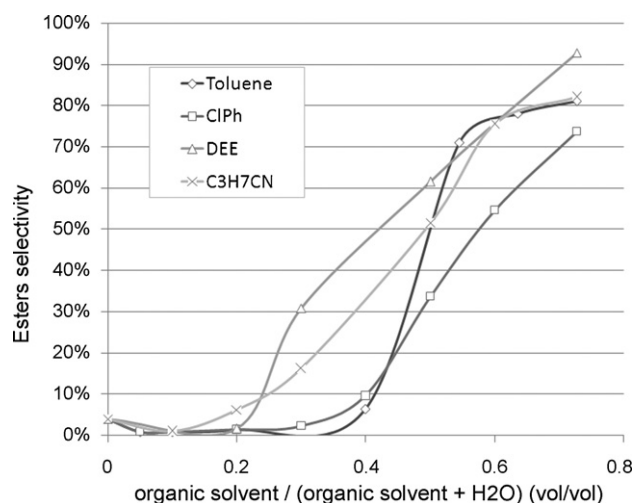


Diagram 8. Ester selectivity for different ratios of the system organic solvent/water in the reaction of allyl bromide (8.5 mmol) and but-3-enoic acid (4.1 mmol) after 23 h at 75 °C. Total volume of the mixture 5 mL. Constant concentration of K_2CO_3 (5 mmol/mL water). Catalyst $[Rh(C_2H_4)_2Cl]_2$ (0.021 mmol).

Furthermore, we found that the amount of organic solvent present in the biphasic system affects the chemoselectivity of the reaction with allyl bromide. Thus, working at constant concentration of base, and leaving inalterate all the other reaction parameters, addition of increasing amounts of organic solvent promoted the cascade reaction of formation of the allyl esters from potassium heptadienoate as shown in Diagram 8. Thus, the selectivity to acids or esters can be controlled through the organic solvent/water (v/v) ratio and global selectivity to esters can rise to almost 95% in the case of diethoxyethane.

Once again, it is to be remarked that the allyl ester formation is a reaction unrelated to the rhodium presence, as demonstrated conducting the reaction of heptadienoate potassium salt and allyl bromide in absence of rhodium.

It is also to be remarked that, whereas different solvents behave similarly with respect to the formation of acids or esters, noticeable differences exist with respect to the composition (i.e. 2,6- or 3,6-isomers) of the acids or esters obtained, as already pointed out in the previous paragraphs.

7. Reactions of substituted butenoic acids and allyl derivatives

The work has been further extended by exploring the possibility of reacting substituted but-3-enoic acids and allyl bromides. The reactions of 4-substituted but-3-enoic acids take place according to Eq. (3), yielding 4-substituted 2,6- and 3,6-heptadienoic acids **8a** and **9a** and the respective allyl esters **8e** and **9e** along with some amounts of products **10** resulting from direct esterification of the starting acid **7**. The results of these experiments are reported in Table 4.

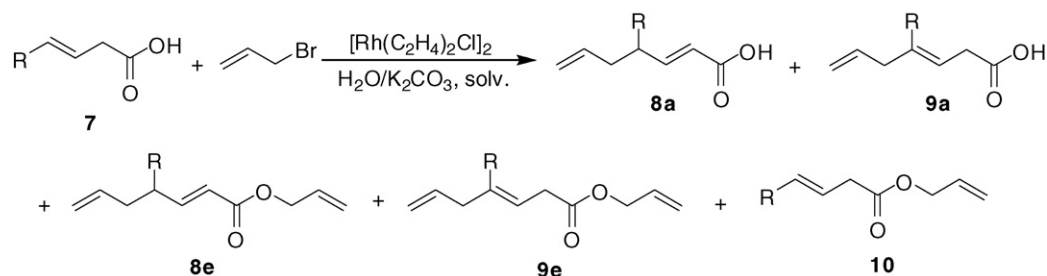


Table 4

Reactions of allyl bromide (8.5 mmol) with substituted but-3-enoic acids (4.1 mmol) in presence of $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ (0.021 mmol) in alkaline water (2 mL, $\text{K}_2\text{CO}_3 = 5$ mmol)–organic solvent (3 mL) biphasic system

Entry	R	T (°C)	Solvent	Conversion (%)	Yield (%)				
					7	8a	9a	8e	9e ^a
36	CH ₃ (<i>trans</i>)	75	C ₃ H ₇ CN	58	50	–	5	–	–
37	CH ₃ (<i>trans</i>)	75	Toluene	54	38	–	10	–	–
38	CH ₃ (<i>trans</i>)	100	C ₃ H ₇ CN	98	77	–	5	–	13
39	C ₂ H ₅ (<i>trans</i>)	100	Toluene	82	24	4	27	1	22
40	C ₂ H ₅ (<i>trans</i>)	100	C ₃ H ₇ CN	98	50	9	5	5	29
41	C ₂ H ₅ (<i>cis</i>)	100	Toluene	98	30	10	25	10	23
42	C ₂ H ₅ (<i>cis</i>)	100	C ₃ H ₇ CN	98	60	8	5	2	22

Reaction carried out for 23 h under stirring (1000 rpm).

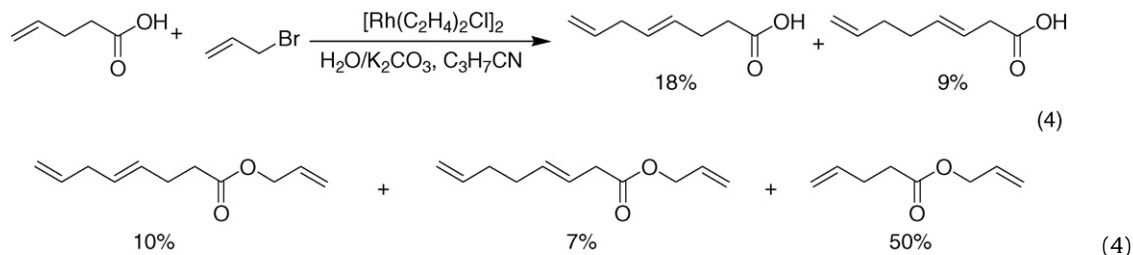
^a The geometry of the double bond of products **9a** and **9e** was not determined.

Table 5

Reactions of substituted allyl bromides **11** (8.5 mmol) with but-3-enoic acid (4.1 mmol) in presence of $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ (0.021 mmol) in alkaline water (2 mL, $\text{K}_2\text{CO}_3 = 5$ mmol)–organic solvent (3 mL) biphasic system

Entry	R ¹	R ²	R ³	Solvent	Conversion (%)	Yield (%)	
						5	12 13
43	CH ₃	H	H	C ₃ H ₇ CN	80	55	–
44	H	C ₆ H ₅	H	C ₃ H ₇ CN	52	18	–
45	H	H	–(CH ₂) ₃ –	C ₃ H ₇ CN	85	–	58

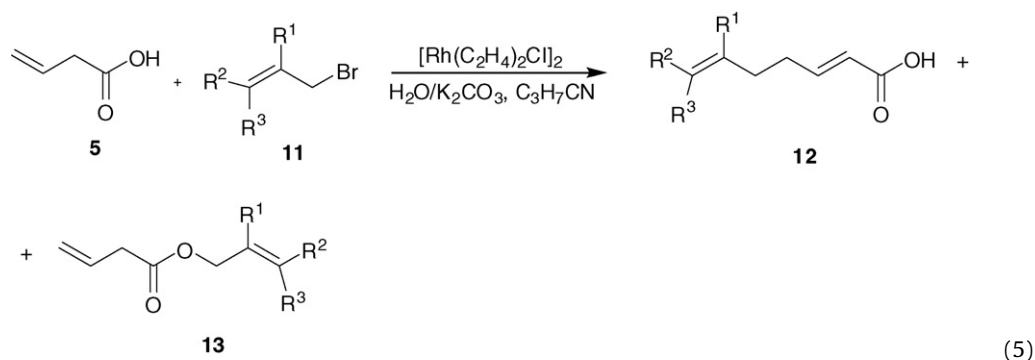
Reaction carried out for 23 h under stirring (1000 rpm).



The results show that different organic solvents cause slight differences in the reaction course, as already pointed out in the first part of this work. Lower conversions of pent-3-enoic acid (**7**, R=CH₃) were obtained in comparison to 3-butenoic acid at the same temperature, indicating that steric hindrance on γ -carbon

The reaction of 4-pentenoic acid was carried out under the conditions reported in Table 4 according to Eq. (4). This substrate presents a different position of the C=C double bond (in γ to the carbonyl moiety instead of β). In this case, the chelation effect is less favored due to the formation of a 6-terms metallacycle instead of a 5-terms one. Moreover, in this case the β -elimination should take place *via* hydride abstraction even in alkaline water solution. This fact reflects on the yields, that were significantly lower than those obtained with 3-butenoic or 3-pentenoic acid. The main product obtained was allyl 4-pentenoate that derives from direct esterification of the substrate without catalyst intervention.

Various substituted allyl bromides were also tested according to Eq. (5). The results of this set of experiments are reported in Table 5. In this case the potential products are 6- and 7-substituted heptadienoic acids **12**.



decreases the reactivity of the substrate (entries 36 and 37); however, this problem was mitigated by rising the reaction temperature to 100 °C (entry 38). Electronic and statistical factors might be involved in the lower selectivity to 3,6-derivatives.

In most cases the predominant products were acids, but significant amounts of the corresponding allyl esters were formed (entries 38–42). It can thus be predicted that, in presence of a higher excess of allyl bromide, the main products would be esters **8e** and **9e**.

The conversions obtained are significantly lower than those obtained with the parent allyl bromide, meaning that the oxidative addition of the allyl derivative and the C–C coupling stage are significantly influenced by the presence of sterically hindered substituents. Only 2-methylallyl bromide (entry 43) gave satisfactory yields of 6-methylhepta-(2,6)dienoic acid. 3-Bromocyclohexene gave only the direct esterification product, while other bromides afforded no conversion at all.

8. Conclusions

In conclusion this work reports an effective procedure for the synthesis of 2,6- and 3,6-heptadienoic acids and allyl esters consisting of Rh-catalyzed coupling reaction of but-3-enoic acid and allyl derivatives such as allyl bromide, allyl acetate and allyl methyl carbonate in alkaline water or in alkaline water/organic solvent two-phase systems. 2,6-Heptadienoate derivatives are always prevalent in water as acids and in biphasic systems as acids or allyl esters. It is possible to selectively obtain allyl esters via one-pot cascade esterification reaction using allyl bromide in biphasic systems with high amounts of organic solvent. The presence and the concentration of K_2CO_3 , the nature of organic solvent or addition of TPP in biphasic media allow tuning the regioselectivity of the reaction towards 3,6-derivatives or 2,6-derivatives. Experimental evidences have been brought to explain the stages controlling the regio- and chemoselectivity of the reaction. Substituted but-3-enoic acids, substituted allyl substrates and pent-4-enoic acid lead to moderate or poor results under similar reaction conditions.

9. Experimental

9.1. General

Elemental analyses were carried out with a Carlo Erba Elemental Analyzer Mod. 1106. 1H and ^{13}C NMR spectra were taken on a Bruker AC300 (300 MHz) spectrometer. IR spectra were taken on a NICOLET 5700 FT-IR spectrometer. Mass spectra were obtained using a GC system HP6890 Series coupled with a HP 5973 Mass Selective Detector at 70 eV ionization voltage. All reactions were analyzed by TLC on silica gel 60 F_{254} or by GC using a HRGC Mega 2 series Fisons Instruments equipped with a polymethylsilicone + 5% phenylsilicone as a stationary phase (HP-5) capillary column. Column chromatography was performed on silica gel 60 (Merck, 70-230 mesh).

9.2. Materials

All the reagents and rhodium complexes were obtained from commercial suppliers and used without further purification. Triphenylphosphine was recrystallized from *n*-hexane and used immediately. The solvents were freshly purified by distillation and the products were purified by column chromatography using suitable eluents.

9.3. General procedure for the reaction of but-3-enoic acid 5 and allyl derivatives 6

An example of experimental procedure is reported here. Reagent amounts, solvent volumes and other parameters may vary as specified in the tables. $[Rh_2(C_2H_4)_2Cl]_2$ (0.021 mmol) or $Rh(PPh_3)_3Cl$ (0.041 mmol) and, if required, PPh_3 (1, 2 or 3 mmol per mmol of Rh atom) were loaded into a Schlenk apparatus and a solution of K_2CO_3 (amount specified in the tables), but-3-enoic acid (4.1 mmol) and water (volume specified in tables, mL) was added. Subsequently, the allyl derivative (8.5 mmol) and organic solvent (volumes specified in the tables, mL) were added.

The flask was placed in a pre-heated at the desired temperature oil bath for 23 h under stirring at 1000 rpm. The reaction mixture was recovered from the flask using 3×5 mL of K_2CO_3 -saturated water and 3×5 mL of dichloromethane. The mixture was then placed in a separatory funnel and the two phases were separated. The organic phase was analyzed via GC using the internal standard method for the quantitative determination. Alternatively

the solvent was removed under vacuum. Flash chromatography (silica gel) of the residue using a mixture of hexane/EtOAc (10/1) as eluent afforded ester products. The aqueous phase was acidified to pH 1 with 2M HCl and extracted with dichloromethane (3×10 mL). GC analyses, using the internal standard method, were performed on the organic extract. Alternatively, after removal of the solvent under vacuum, flash chromatography (silica gel) of the residue using a mixture of hexane/EtOAc (1/1) as eluent afforded acid products.

All yields were determined by GC according to the internal standard method. To obtain improved chromatographic peaks, organic acids were transformed in their respective methyl esters by treating with a CH_2N_2 solution in diethyl ether.

Analogous procedures were followed with but-3-enoic acids **5** and substituted allyl bromides **11**, substituted but-3-enoic acids **7**, pent-4-enoic and allyl bromide.

9.4. ICP analyses of rhodium

Quantitative determinations of rhodium by ICP technique were carried out at Chimica Generale ed Inorganica, Chimica Fisica, Chimica Analitica Department of Parma University. The samples were prepared according to a procedure reported in the literature [11].

9.5. Characterization of the products

All products were characterized by IR, 1H NMR and ^{13}C spectroscopies, MS spectrometry, elemental analysis. 1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions at 300 and 75 MHz, respectively, with Me_4Si as internal standard. Chemical shifts and coupling constants (*J*) are given in ppm (δ) and in Hz, respectively (Supplementary data).

Acknowledgements

Financial support from The Ministero dell'Università e della Ricerca Scientifica e Tecnologica (Progetto d'Interesse Nazionale PRIN 2006031888) is acknowledged. The facilities of Centro Interfacoltà di Misure (Università di Parma) were used for recording NMR spectra.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molcata.2008.04.015.

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