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Ligand-Controlled Regio- and Stereoselective Addition of Carboxylic Acids Onto Terminal Alkynes Catalyzed by Carbonylruthenium(0) Complexes

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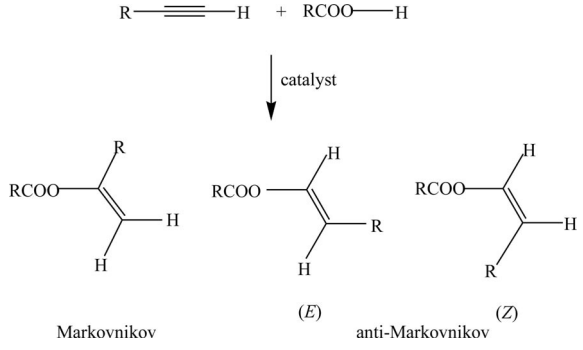
The addition of carboxylic acids onto terminal alkynes was catalyzed by mononuclear ruthenium(0) complexes to give enol esters in high yields. By using ligands with different electronic properties, product selectivity was achieved. *E*-enol esters were preferentially produced when tricarbonyl(η^4-diene)ruthenium complexes were used; while geminal enol esters were produced when tricarbonylbis(phosphane)-ruthenium complexes were used.

Introduction

Enol esters are useful starting materials for a wide variety of organic reactions.[1] Although there are many ways of obtaining enol esters, the transition-metal catalyzed direct addition of carboxylic acids onto alkynes is not only mercury-free, but is also the most economical synthesis method.[2,3] For example, Shvo et al. discovered carbonylruthenium complexes that have excellent catalytic activity towards hydrocarboxylation.[4] However, the selectivity issues associated with such systems are usually hard to ignore given that all three isomeric enol esters are formed (Scheme 1). As a result, many catalytic systems involving ruthenium,[5] or other transition metals,[6] have been studied to selectively produce one enol ester form



Scheme 1. The addition of carboxylic acids onto terminal alkynes catalyzed by transition metal complexes yields isomeric enol esters.

Many recently reported catalytic systems produce predominantly geminal (Markovnikov) or *Z*-enol esters (anti-Markovnikov).[5–7] For example, Dixneuf et al. managed to selectively produce the *Z*-enol ester by tuning the degree of steric hindrance around the catalyst metal centre.[8] Koley et al. illustrated the use of various bases to control the regioselectivity of their system to give geminal and *Z*-enol esters.[9] Systems for producing *E*-enol esters (anti-Markovnikov) remain not as well studied as those for the synthesis of *Z*-enols.[10]

In our work, we have used a variety of mononuclear ruthenium(0) catalysts for the hydrocarboxylation process. When using diene-ruthenium(0) complexes, the *E*-enol ester can be produced selectively. When phosphanes were used instead of dienes, the selectivity of the system was reversed to produce the geminal product predominantly. Since the ruthenium complexes are readily soluble in the substrates, the use of solvent was eliminated.[5d] It is noteworthy that for most cases a significant yield was obtained after a short reaction time under relatively mild conditions with low catalytic loading.

Results and Discussion

We find that the addition of carboxylic acids onto terminal alkynes can be catalyzed by a variety of ruthenium(0) complexes. The studied catalysts were classified into three groups: (i) trinuclear clusters: $Ru_3(CO)_{12}$ (**1**) and $Ru_3(CO)_9(PPh_3)_3$ (**2**); (ii) mononuclear diene complexes: $Ru(CO)_3$(1,3-cyclohexadiene) (**3**), $Ru(CO)_3$(α-terpinene) (**4**), $Ru(CO)_3$(2,5-norbornadiene) (**5**); and (iii) mononuclear phosphane complexes: $Ru(CO)_3[P(OEt_3)_3]_2$ (**6**), $Ru(CO)_4(PPh_3)$ (**7**), $Ru(CO)_3(PPh_3)_2$ (**8**) and $Ru(CO)_3(PCy_3)_2$ (**9**). The syntheses of **2**–**9** from commercially available **1** were straightforward. In addition, as infrared spectra recorded before each catalytic run did not indicate any sign of decomposition, these complexes are reasonably stable towards air and moisture. The organic products were characterized using ^{1}H NMR techniques, and their splitting patterns and chemical shifts were matched to those reported in literatures.[11]

When phenylacetylene was used as a reagent in the hydrocarboxylation reaction (Table 1), it was observed that

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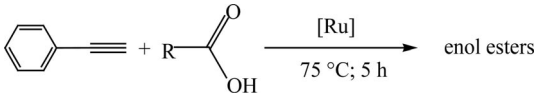
the substituent group (Ph, Me or *t*Bu) on the carboxylic acid reagent did not affect the enol ester yield significantly. However, it was found that when trinuclear complexes **1** and **2** were used the system gave a smaller enol ester yield (< 90%) compared to the mononuclear systems under the same reaction conditions. One possible reason is that the trinuclear complexes react with the substrates present and dissociate into monomeric ruthenium species. Only one, or some, of these species may exhibit catalytic behavior.[12,13] Hence the slightly lower yield can be attributed to the extra induction time required for conversion to occur, together with a lower catalytic loading due to formation of inactive species.

Table 1. Product details for the addition of carboxylic acids onto phenylacetylene catalyzed by complexes **1**–**9**.[a]

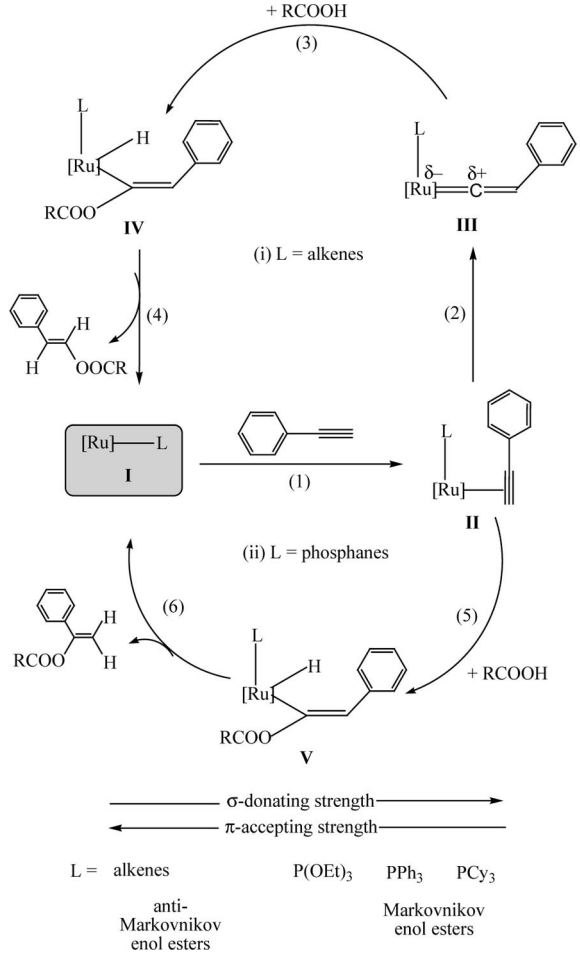


Entry	Complex	Acid	Yield[b]	Selectivity[c]	*E*/*Z*
1	**1**	PhCOOH	80 (73)	75	4.2
2		MeCOOH	75 (69)	89	3.1
3		*t*BuCOOH	75 (72)	90	2.8
4	**2**	PhCOOH	80 (75)	15	1.6
5		MeCOOH	82 (75)	20	3.3
6		*t*BuCOOH	80 (77)	20	1.2
7	**3**	PhCOOH	95 (90)	94	5.3
8		MeCOOH	96 (92)	97	4.4
9		*t*BuCOOH	93 (91)	95	4.2
10	**4**	PhCOOH	97 (95)	95	5.8
11		MeCOOH	94 (91)	95	5.0
12		*t*BuCOOH	95 (93)	98	4.4
13	**5**	PhCOOH	93 (89)	92	5.4
14		MeCOOH	99 (95)	98	4.6
15		*t*BuCOOH	92 (90)	97	4.2
16	**6**	PhCOOH	93 (87)	48	0.46
17		MeCOOH	93 (90)	39	0.74
18		*t*BuCOOH	90 (88)	41	0.71
19	**7**	PhCOOH	92 (87)	13	1.0
20		MeCOOH	92 (86)	13	1.2
21		*t*BuCOOH	91 (89)	12	1.2
22	**8**	PhCOOH	95 (89)	4.0	1.2
23		MeCOOH	97 (92)	3.9	1.5
24		*t*BuCOOH	92 (89)	4.2	1.1
25	**9**	PhCOOH	96 (91)	4.5	0.43
26		MeCOOH	94 (89)	4.9	0.52
27		*t*BuCOOH	93 (89)	4.8	0.50

[a] Reactions were carried out with 1% catalysis loading at 75 °C for 5 h. [b] Total enol ester yields were determined by ^{1}H NMR (isolated yields). [c] Ratio of anti-Markovnikov product yield to total enol ester yield (regioselectivity).

The regioselectivity of the system was not affected by the substituent on the acid, as inferred from the ratio of anti-Markovnikov to total enol ester yields (Table 1). Increasing the reaction temperature to 100 °C also has no effect on the overall selectivity of the system. On the other hand, there was a marked difference in regioselectivity when the comparatively poor σ-donating ligand (an alkene, in the form of η^2-diene) on the metal complex was replaced by strong σ-donating ligands (phosphanes).

The majority of enol esters catalyzed by complexes **3**, **4** and **5** were anti-Markovnikov while those catalyzed by complexes **6**, **7**, **8** and **9** were Markovnikov. The differences in electron density at the metal centre caused by the ligands, is responsible for this result. The initial reaction step is believed to be the dissociation of a ligand from the starting ruthenium complex **I**, so as to accommodate an incoming substrate molecule (Scheme 2). The metal centre of the resultant 16-electron alkyne-coordinated intermediate **II** would have varying degrees of electron density depending on the nature of the ligand **L** (alkene or phosphane).[14] The weak σ-donating and strong π-accepting nature of alkenes would reduce the electron density at the metal centre, favouring the formation of the vinylidene intermediate **III** (step 2), which is a well-accepted intermediate for anti-Mar-



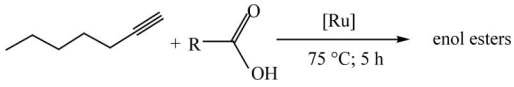
Scheme 2. Proposed reaction pathways for hydrocarboxlation reactions catalyzed by mononuclear Ru^0 complexes: (i) Alkenes (η^2-dienes) reduce the electron density at the metal centre and favours the formation of vinylidene intermediate (**III**). (ii) Phophines enhance the electron density at the metal centre and promote the addition of the acid to give intermediate (**V**).

kovnikov addition reactions.[15] Nucleophilic addition of acid onto the vinylidene (step 3) would give the Ru^{II} intermediate **IV**, which subsequently undergoes reductive elimination of the product (step 4) to complete the anti-Markovnikov addition cycle. On the other hand, the strong σ-donating and weak π-accepting nature of phosphanes would increase the electron density at the metal centre and disfavor the formation of the vinylidene intermediate **III**. From the phosphane-coordinated intermediate **II**, an oxidative addition process (step 5) would give intermediate **V**, which subsequently undergoes reductive elimination of the product (step 6) to complete the Markovnikov addition cycle. In line with our proposal, complex **6**, bearing the weaker σ-donating $P(OEt_3)_3$ ligands, is less selective compared to **8** and **9** that bear the stronger σ-donating PPh_3 and PCy_3 groups, respectively.

It was observed that the stereoselectivity (*E*/*Z* ratio, Table 1) of the system could be affected by the nature of the carboxylic acid. The exact cause for the difference in stereoselectivity remains unclear, as both steric and electronic factors could be involved. An attempt was made to alter the stereoselectivity of the products by attaching a bulky diene ligand (α-terpinene) with similar electronic properties to 1,3-cyclohexadiene on the ruthenium catalyst (complex **4**). The result shows that **4** enhanced the ratio of the *E*- to *Z*-enol esters by only 10% compared to **3**. It was also noticed that using conjugated or nonconjugated dienes as ligands has no significant effect on the performance of the catalyst.

The ruthenium complexes used in this study can also catalyze the addition of carboxylic acids onto aliphatic alkynes (Table 2). Although the product yield is acceptable, the aliphatic alkyne systems suffer from poor selectivity. In order to investigate the steric effect of the substituent group on the alkyne on the product selectivity, cyclohexylacetylene was used as substrate (Table 3). The results showed that the more bulky acetylene did not affect the reaction to a large extent. Hence we believe that the lack of selectivity was due to an electronic effect. In fact, when an aliphatic alkyne was present in intermediate **II** (Scheme 2) the electron density at the metal centre would increase, due to the more electron-rich C≡C bond, compared to when aromatic alkynes are bound to the metal centre. This increase in electron density at the metal centre would favour the oxidative addition of acids (step 5) to form intermediate **V** instead of the vinylidene intermediate **III** (step 2).

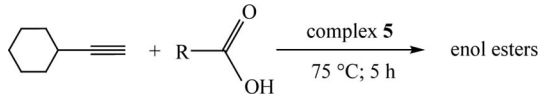
Table 2. Product details for the addition of carboxylic acids onto 1-heptyne catalyzed by complexes **1**–**5** and **8**.[a]



Entry	Complex	Acid	Yield[b]	Selectivity[c]	*E*/*Z*
1	**1**	PhCOOH	72 (64)	38	1.8
2		MeCOOH	74 (66)	43	2.1
3	**2**	PhCOOH	72 (67)	6.2	0.31
4		MeCOOH	75 (69)	7.3	0.35
5	**3**	PhCOOH	83 (77)	32	1.4
6		MeCOOH	85 (79)	50	2.8
7	**4**	PhCOOH	88 (82)	28	1.8
8		MeCOOH	85 (81)	50	2.2
9	**5**	PhCOOH	82 (76)	27	1.9
10		MeCOOH	85 (78)	56	1.9
11	**8**	PhCOOH	84 (80)	4.3	0.35
12		MeCOOH	82 (76)	4.5	0.39

[a] Reactions were carried out with 1% catalyst loading at 75 °C for 5 h. [b] Total enol ester yields were determined by ^{1}H NMR (isolated yields). [c] Ratio of anti-Markovnikov product yield to total enol ester yield (regioselectivity).

Table 3. Product details for the addition of carboxylic acids onto cyclohexylacetylene catalyzed by complex **5**.[a]



Entry	Acid	Yield[b]	Selectivity[c]	*E*/*Z*
1	PhCOOH	86 (82)	30	2.0
2	MeCOOH	81 (76)	76	1.8

[a] Reactions were carried out with 1% catalyst loading at 75 °C for 5 h. [b] Total enol ester yields were determined by ^{1}H NMR (isolated yields). [c] Ratio of anti-Markovnikov product yield to total enol ester yield (regioselectivity).

Conclusions

In summary, it was found that the addition of carboxylic acids onto alkynes can be catalyzed by mononuclear ruthenium(0) complexes. The nature of the acid did not affect the system greatly, while it was observed that ruthenium(0) complexes containing aromatic alkynes gave better product selectivity than those incorporating aliphatic alkynes. The regioselectivity of the product can be controlled by varying the electron density at the ruthenium centre. Alkenes (η^2-dienes) reduce the electron density at the metal centre, stabilizing the vinylidene intermediate allowing for anti-Markovnikov products to be formed preferentially. Phosphanes increase the electron density on the metal centre, prompting the occurrence of a direct oxidative addition processes to give the Markovnikov products. *E*-enol esters formed preferentially when $Ru(CO)_3(\eta^4$-diene) complexes were used.

Experimental Section

General Procedures: All reactions and manipulations were carried out under inert conditions. Triruthenium Dodecacarbonyl, $Ru_3(CO)_{12}$ (**1**) (Aldrich, 99%) was recrystallized from cyclohexane before use. Phenylacetylene, 1-heptyne, glacial acetic acid, pivalic acid, benzoic acid, 1,3-cyclohexadiene, 2,5-norbornadiene, α-terpinene, triphenylphosphane, tricyclohexylphosphane and triethylphosphite were obtained from Aldrich and used without further purification. Photolytic synthesis of the ruthenium precursors was done by placing the reaction flask 5–10 cm from a broadband lamp

(Philips, 11 W, 380–700 nm). IR spectra were collected with liquid samples in a cell with CaF_2 windows and 0.1 mm pathlength, with a Shimadzu IR Prestige-21 spectrometer. ^{1}H NMR spectra were recorded with a Bruker AMX 500 Fourier Transform Spectrometer at room temperature and the chemical shifts were referenced to tetramethylsilane. The organic product yields were calculated from the ^{1}H NMR spectra using reagent grade toluene or *tert*-butylbenzene as internal standard.

Complexes $Ru_3(CO)_9(PPh_3)_3$ (**2**),[16] $Ru(CO)_3(\eta^4$-diene) [diene = 1,3-cyclohexadiene (**3**), α-terpinene (**4**), 2,5-norbornadiene (**5**)],[17] $Ru(CO)_3[P(OEt)_3]_2$ (**6**)[18,19] and $Ru(CO)_4(PPh_3)$ (**7**)[20] were prepared according to their respective literature methods and characterized by standard spectroscopic techniques (see Tables 4 and 5).

Table 4. Peaks obeserved in the IR spectra of ruthenium complexes **1**–**9**.

Species	υCO /cm^{-1}	Medium	ref.
1	2060 (vs), 2030 (s), 2011 (m)	hexane	
2	1980 (s), 1969 (vs)	DCM	[16]
3	2061 (s), 1994 (s), 1988 (s)	hexane	[17]
4	2053 (s), 1985 (s), 1980 (s)	hexane	
5	2047 (s), 1980 (s, br.)	hexane	
6	1927 (s), 1916 (s)	hexane	[18]
7	2060 (s), 1987 (m), 1954 (vs)	hexane	[20]
8	1886 (s)	DCM	[20]
9	1871 (s), 1851 (s)	DCM	[21]

Table 5. Peaks obeserved in the ^{1}H NMR spectra of ruthenium complexes **4** and **5**.

Species	δ /ppm	Medium
4	5.27 (d, 1 H), 5.22 (d, 1 H), 1.88 (m, 4 H), 1.80 (m, 1 H), 1.67 (s, 3 H), 1.10 (d, 6 H)	$CDCl_3$
5	3.33 (d, 4 H), 1.43 (s, 2 H), 1.11 (t, 2 H)	$CDCl_3$

Synthesis of $Ru(CO)_3(PPh_3)_2$ (8) and $Ru(CO)_3(PCy_3)_2$ (9): The ruthenium complexes **8** and **9** were prepared using a procedure similar to one described in the literature.[19] Complex **1** (1 equiv.) and phosphane (10 equiv.) were dissolved in CH_3CN and the resultant solution was irradiated for 30 h. The pale yellow precipitate that formed was collected by filtration and washed with hexane.

Typical Procedure for Catalytic Reaction: Carboxylic acid (5 mmol, 1 equiv.), alkyne (1 equiv.), and the catalyst (0.01 equiv.) were stirred at 75 °C for 5 h. The reaction mixture was cooled and toluene was added as internal standard. The resulting mixture was then analyzed by ^{1}H NMR (Table 2). The product was purified by silica gel column chromatography, using a hexane/diethyl ether (10:1 v/v) solvent mixture as the eluent.

Supporting Information (see also the footnote on the first page of this article): Compound characterization and ^{1}H NMR spectra of catalytic runs.

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