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Dimerization of Terminal Arylalkynes in Aqueous Medium by Ruthenium and Acid Promoted (RAP) Catalysis: Acetate-Assisted (*sp*)C−(*sp*^{2})C Bond Formation

Alessandra Coniglio,[a] Mauro Bassetti,[a,*] Sergio E. García-Garrido,[b,*] and José Gimeno[b]

[a] Istituto CNR di Metodologie Chimiche, Sezione Meccanismi di Reazione, and Dipartimento di Chimica, Università "La Sapienza", P. le Aldo Moro 5, I-00185 Roma, Italy
Fax: (+39)-06-490-421; phone: (+39)-06-499-13769; e-mail: mauro.bassetti@uniroma1.it

[b] Departamento de Química Orgánica e Inorgánica, Instituto de Química Organometálica "Enrique Moles" (Unidad Asociada al C.S.I.C.), Universidad de Oviedo, C/Julían Clavería 8, E-33071 Oviedo, Principado de Asturias, Spain
Fax: (+34)-985-103-446; phone: (+34)-985-103-461; e-mail: garciagsergio@uniovi.es

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Dedicated to Dr. Christian Bruneau, on the occasion of his 60th birthday.

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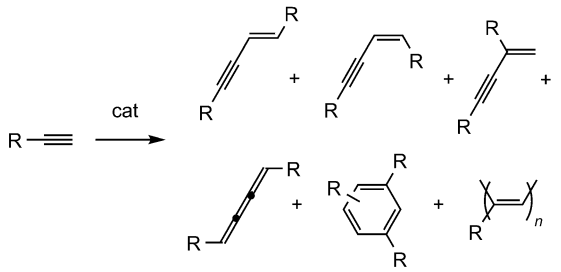
Abstract: The hexamethylbenzene ruthenium(II) dimer $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}C_6Me_6)\}]_2$ (5 mol%), tested among a series of ruthenium(II) and ruthenium(IV) complexes, represents an efficient precatalyst source for the dimerization of terminal arylalkynes ArC≡CH [Ar = C_6H_5, 3,4,5-$(OMe)_3C_6H_2$, 4-$MeOC_6H_4$, 2-$MeOC_6H_4$, 4-MeC_6H_4, 2,4,5-$Me_3C_6H_2$, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-HC(=O)C_6H_4, 4-CH_2=CHC_6H_4, 3-NCC_6H_4, 4-$O_2NC_6H_4$, 4-EtO_2C-$(CH_2)_3OC_6H_4$, 4-$HO(CH_2CH_2O)_3C_6H_4$, 3-$HO(CH_2CH_2O)_3$-C_6H_4] in acetic acid/water mixture (1:1, v/v). The reactions proceed for 24 h at room temperature under heterogeneous conditions and afford the dimeric enyne derivatives (*E*)-Ar−CH=CH−C≡C−Ar in high yields and stereoselectivity. The preformed acetato complex $[RuCl(\eta^6\text{-}C_6Me_6)(\kappa^2\text{-}OAc)]$ catalyzes the dimerization of phenylacetylene under analogous conditions, with rapid substrate conversion. The presence of cosolvents of acetic acid different from water reduces dramatically the efficiency and selectivity of the reaction. The aqueous medium facilitates the activation stage of the precatalyst by assisting the splitting of the ruthenium dimer. The addition or generation *in situ* of acetate salts results in shorter reactions times (0.5–3 h) and excellent yields, due to the rapid formation of active acetato complexes. Circumstantial evidence indicates that the π-bound alkyne molecule is activated by intramolecular proton abstraction. This is currently the most efficient, *E*-selective and wide-scope catalytic system for the alkyne dimerization reaction in protic aqueous media.

Keywords: bifunctional catalysis; conjugated enynes; dimerization; ruthenium carboxylate catalysts; terminal alkynes

Introduction

The development of organic transformations in aqueous media has become a major cornerstone in modern chemistry, in light of the expected environmental, safety and cost benefits.[1] In this context, the design and application of transition metal complexes for organic synthesis in water have rendered aqueous organometallic catalysis a rapidly emerging field.[2] In the past decade, we have been involved in the development and application of ruthenium complexes as catalysts for aqueous organic synthesis,[3] with special emphasis on the activation of alkynes.[4]

The catalytic dimerization of terminal alkynes is an atom economic process affording conjugated 1-en-3-yne moieties, which are key structural units found in natural and/or biologically active products[5] and in materials.[6] The reaction consisting in the formal self-addition of two alkyne molecules has gained increasing interest due to the advent of selective catalytic systems able to overcome the intrinsic limits of chemo-, regio- and stereo-selectivity,[7,8] which are



Scheme 1. Types of products of transition metal-catalyzed C–C couplings of terminal alkynes.

otherwise hindering any practical use of the reaction. In fact, several products can arise from the coupling process of alkynes, including dimeric *E*-, *Z*-, or *gem*-1-en-3-ynes, butatrienes, as well as cyclotrimers and linear oligomers (Scheme 1). Ideally, the catalytic system should be applicable to various substrates and provide one isomer in high yields. The implementation of the process in water-based media would represent a significant advancement in the field; in fact, some articles have started to appear in the literature based on catalysis by ruthenium or rhodium complexes in aqueous systems.[9]

We reported that (*E*)-1,4-diaryl-1-buten-3-ynes and hybrid metal organic systems can be obtained in the presence of the complex [{RuCl(μ-Cl)(η^6-*p*-cymene)}$_2$] (**I**) in AcOH.[10] The same catalytic system promotes the polyaddition of aromatic diynes and affords conjugated homo and co-polymers featuring the repeat unit (−Ar−C≡C−CH=CH−).[11] The active catalytic species, formed *in situ* by interaction with the terminal triple bond, is compatible with ring substituents of different nature and with the presence of water in the reaction mixture.[10a,12] In contrast with the majority of ruthenium catalysts which work in refluxing solvents,[13] the reactions promoted by **I**/AcOH proceed at room temperature and afford the enyne fragment with an *E*-configuration of the double bond. In light of the remarkable tolerance exhibited by this ruthenium-and-acid promoted (RAP) catalysis toward polar components in both substrate and medium, we have addressed in this work the development of the C–C coupling process in aqueous environment.

Results and Discussion

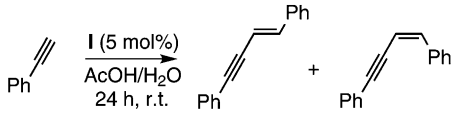
Our investigation developed along the following lines: (i) the choice of the most appropriate reaction conditions for the dimerization of phenylacetylene (**1**) catalyzed by the complex [{RuCl(μ-Cl)(η^6-*p*-cymene)Cl}$_2$] (**I**) in aqueous AcOH; (ii) the selection of the most active and selective ruthenium precursor; (iii) the application of the dimerization process to various aromatic terminal alkynes; (iv) the improvement of the reaction efficiency by using additives, in particular acetate salts as cocatalysts.

Acetic acid and water (1:1) were introduced into a Schlenk tube previously charged with complex **I** (5 mol%). The addition of phenylacetylene upon stirring caused the immediate formation of dark orange droplets which disappeared a few minutes later in the heterogeneous mixture. The unsoluble dimer 1,4-diphenyl-1-buten-3-yne was isolated from the reaction mixture in 38% yield (*E*:*Z* stereoisomeric ratio 99:1) by filtration followed by column chromatography. Other experiments were then performed using AcOH/H_2O in different volume ratios in order to find how the composition of the medium was affecting the reaction. As shown in Table 1, the two solvents in nearly equal volumes afforded the best combination of *E*-stereoselectivity and conversion into the 1,4-diphenylenyne (entry 1).

Catalyst Screening

The influence of the precatalyst on the reaction stereoselectivity was studied for a wide series of ruthenium complexes including analogous dimeric derivatives [{RuX(μ-X)(η^6-arene)}$_2$] (X = Cl, arene = mesityl, hexamethylbenzene; X = I, arene = *p*-cymene), mononuclear ruthenium(II) complexes [$RuCl_2$(η^6-*p*-cymene)(PMe_3)], [RuCl(η^5-indenyl)(PPh_3)$_2$], [$RuCl_2$(PPh_3)$_3$], and the dimeric ruthenium(IV) complex [{RuCl(μ-Cl)(η^3:η^3-$C_{10}H_6$)}$_2$] ($C_{10}H_{16}$ = 2,7-dimethylocta-2,6-diene-1,8-diyl), and their activity was compared

Table 1. Dimerization of phenylacetylene (**1**) catalyzed by complex [{RuCl(μ-Cl)(η^6-*p*-cymene)}$_2$] (**I**) in different acetic acid/water mixtures.[a]



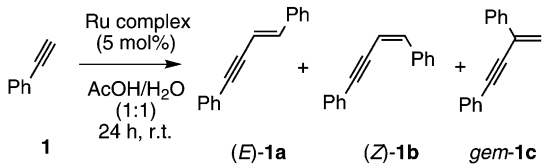
Entry	AcOH/H_2O	**1a**+**1b** [%][b,c]	*E*/*Z*[b]
1	1:1	75	96:4
2	4:6	71	97:3
3	3:7	69	97:3
4	2:8	29	74:16
5	1:9	21	77:23

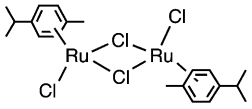
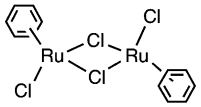
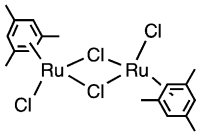
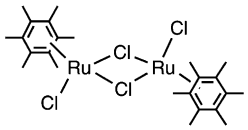
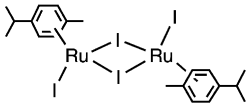
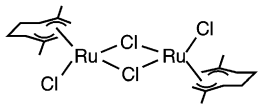
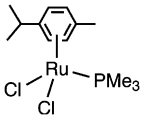
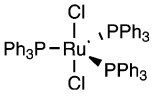
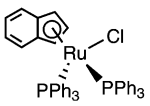
[a] *Reaction conditions:* **1** (100 μL, 0.91 mmol), **I** (28 mg, 0.044 mmol), AcOH/H_2O (10 mL), 24 h, room temperature.

[b] Determined on the basis of ^{1}H NMR analysis of the crude extracts, by integration of the enyne signals *vs.* the overall aromatic region.

[c] Other unidentified species were also formed; the *gem*-enyne isomer was observed only in traces (<1%).

Table 2. Dimerization of phenylacetylene (**1**) catalyzed by various ruthenium complexes in acetic acid/water (1:1 v/v).[a]



Entry	Ruthenium complex	Enynes [%][b,c]	*E*:*Z*:*gem*[b]
1		75	96:4:0
2		92	84:16:0
3		47	100:0:0
4		86	100:0:0
5		42	65:31:4
6		35	74:18:8
7		64	80:10:10
8		24	54:46:0
9		12	62:38:0

[a] *Reaction conditions:* **1** (100 μL, 0.91 mmol), ruthenium complex (5 mol%), AcOH/H_2O (10 mL, 1:1, v:v), 24 h, room temperature.

[b] Determined on the basis of ^{1}H NMR analysis of the crude extracts, by integration of the enyne signals *vs.* the overall aromatic protons.

[c] Other unidentified species were also formed.

to that of the *p*-cymene complex **I**. The reactions were performed using phenylacetylene as substrate and a 1:1 solvent mixture of AcOH/H_2O. The results are reported in Table 2.

The dimeric chloride complexes [{RuCl(μ-Cl)(η^6-arene)}$_2$] exhibited the best stereoselectivity (entries 1–4), which increased with increasing electron-releasing properties (alkyl substitution) and steric hindrance of the arene ligand. Substitution of the chloride by iodide dramatically decreased both product stereoselectivity and conversion (entry 5 *vs.* 1).

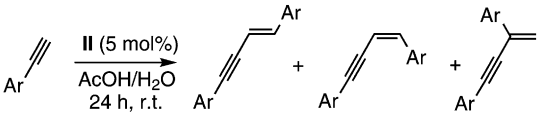
Phosphine-containing complexes behaved as poor catalysts (entries 7–9), and the same holds for the dimeric (allyl)ruthenium(IV) complex [{Ru(η^3:η^3-$C_{10}H_6$)(μ-Cl)Cl}]$_2$ (entry 6), which is otherwise an excellent catalyst for the cyclotrimerization of alkynes in water.[4d,g] Under the same reaction conditions, dimerization products were not observed in the presence of the mononuclear complexes [$RuCl_2$(η^3:η^2:η^3-$C_{12}H_{18}$)] ($C_{12}H_{18}$ = dodeca-2,6,10-triene-1,12-diyl),[14] [$RuCl_2$(DMSO)$_4$], and [{$RuCl_2$(η^4-COD)}$_n$] (COD = 1,5-cyclooctadiene), or of the water soluble salt [$RuCl_2$(η^6-*p*-cymene){PPh($OCH_2CH_2NMe_3$)$_2$}][SbF_6]$_2$. Therefore, the η^6-arene ruthenium(II) dichloride systems represent structurally well defined molecular fragments able to promote the selective dimerization of phenylacetylene, at room temperature in acidic aqueous medium.

Scope of the Reaction

On the basis of the highest conversion and selectivity exhibited by the hexamethylbenzene complex [{RuCl(μ-Cl)(η^6-C_6Me_6)}$_2$] (**II**) (Table 2, entry 4), this catalyst was used for studying the scope of the dimerization process under acidic aqueous conditions on a series of arylacetylenes with different ring substitution. The substrates, yields and stereoselectivity of the 1,4-diaryl-1-buten-3-yne products are reported in Table 3. Usually, the reactions proceeded under heterogeneous conditions due to the limited solubility of the ruthenium complex and the substrates employed. Nevertheless the isolated yields of the dimeric products, which in general precipitated from the reaction mixture (entries 1–14), were from good to satisfactory. Since loads of complex **II** lower than 5% resulted in decreasing yields of the enynes **3a** and **7a**, the reactions were run with 20:1 molar ratio of substrate to catalyst.

The diverse functional group compatibility, previously observed in RAP catalysis in neat acetic acid or under the one-pot desilylation-dimerization sequence,[10a,12] is maintained in the acetic acid/water mixture. In particular, arylacetylenes with either electron-donating (entries 2/3, 5/6) or -withdrawing substituents (entries 7–12) afforded enynes with *E*-stereoselectivity larger than 96% and similar yields, the compatible range of electronic effects varying from that of methoxy ($\sigma_p = -0.28$) to that of the nitro group ($\sigma_p = 0.81$). However, reduced yield and stereoselectivity were observed in the presence of the methoxy *ortho* substituent (entry 4). Potentially coordi-

Table 3. Dimerization of arylacetylenes (**1**–**16**) catalyzed by complex [{RuCl(μ-Cl)(η^6-C_6Me_6)}$_2$] (**II**), in acetic acid/water (1:1, v/v).[a]



Entry	Alkyne	Yield [%][b]	*E*:*Z*:*gem*[c]
1	**1**	64	100:0:0
2	**2**	93	98:2:0
3	**3**	95	100:0:0
4	**4**	37	90:8:2
5	**5**	65	99:1:0
6	**6**	70	100:0:0
7	**7**	74	100:0:0
8	**8**	62	100:0:0
9	**9**	72	99:1:0
10	**10**	85	98:2:0
11	**11**	38	100:0:0
12	**12**	68	96:4:0
13	**13**	60	100:0:0
14	**14**	69	98:2:0
15	**15**	42	87:13:0
16	**16**	30	98:2:0

[a] *Reaction conditions:* alkyne (0.9 mmol), **II** (30 mg, 0.045 mmol, 5 mol%), AcOH/H_2O (10 mL, 1:1, v:v), 24 h, room temperature.
[b] Isolated yields.
[c] Determined by ^{1}H NMR analysis.

nating moieties, such as −CHO, −CH=CH$_2$ or −C≡N, did not inhibit the dimerization process, although the yield of the cyano derivative appeared significantly lower (entries 10, 11, 13).[15] The efficiency of the catalytic system in the polar protic medium is maintained also in the presence of increased lipophilic character of the ring substituent, as for the ethyl-4-oxybutyrate chain in **14** (entry 14).

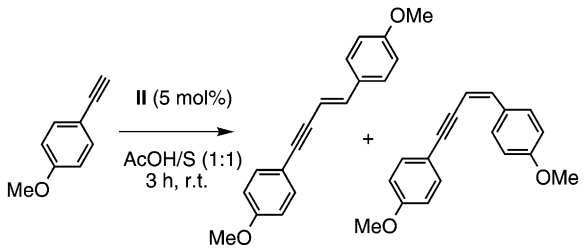
Unexpectedly, the substrates bearing the hydrophilic −(OCH$_2$CH$_2$)$_3$OH oxaethylene chain in either *meta* or *para* positions gave the corresponding *E*-enyne in appreciably lower yields (entries 15, 16). In these cases, the reactions proceeded under homogeneous conditions due to the increased solubility of both substrate and product in the reaction mixture. Although we have not explored further the reasons of this yield depression, it is possible that the enyne in solution acts as inhibitor of the catalytic system by competitive coordination of the enyne fragment to the ruthenium center.[16]

The results reported in Table 3 represent the largest data set of terminal alkynes amenable to catalytic dimerization in an aqueous medium. The compatibility of the procedure involves apolar, polar, or protic ring substituents, as well lipophilic or hydrophilic alkyl chains. Moreover, shorter reaction times and increased yields and stereoselectivity are exhibited in the presence of the hexamethylbenzene complex **II** in the aqueous environment with respect to the catalytic system based on [{RuCl(μ-Cl)(η^6-*p*-cymene)}$_2$] in neat acetic acid.[10a] For instance, the yields of (*E*)-RC$_6$H$_4$−CH=CH−C≡C−C$_6$H$_4$R changed from 43% (R = *p*-OMe, 48 h), 44% (R = *p*-Cl, 44 h) or 58% (R = *p*-NO$_2$, 48 h) with **I**/AcOH to 95, 62 or 68%, respectively, with **II**/AcOH-H_2O (24 h). This catalytic system exhibits a remarkable chemoselectivity, since products deriving from the hydration of the triple bond were not isolated or detected under the conditions of this work.

Medium and Additive Effects

Once established in our previous studies and in this work that acetic acid is an essential component in its dual role of cocatalyst and cosolvent,[17,18] some experiments were performed in order to test the influence of water in comparison with acetic acid and other solvents. The results obtained for the dimerization of 4-ethynylanisole (**3**) under different conditions are reported in Table 4. GC-MS analyses were performed after 3 h of reaction rather than at longer times, in order to appreciate differences in the extent of substrate conversions. Efficiency and stereoselectivity depended significantly on the nature of the cosolvent. It is remarkable that modest conversion and poor selectivity were observed from the reaction in neat acetic acid at room temperature (entry 1), thus highlighting the effect arising from the presence of water (entry 2). At this stage it can be suggested that the dissociation equilibrium of acetic acid in water

Table 4. Dimerization of 4-ethynylanysole (**3**) catalyzed by complex [{RuCl(μ-Cl)(η^6-C_6Me_6)}$_2$] (**II**) in acetic acid/cosolvent (S).[a]



3 **3a** **3b**

Entry	Solvent mixture	Residual **3** [%][b]	*E*-(**3a**) [%][b]	*Z*-(**3b**) [%][b]
1	AcOH	60	23	14
2	AcOH/H_2O	10	89	1
3	AcOH/D_2O	64	31	1
4	AcOH/MeOH	37	47	1
5	AcOH/Me_2CO	59	9	28
6	AcOH/CH_2Cl_2	26	41	28

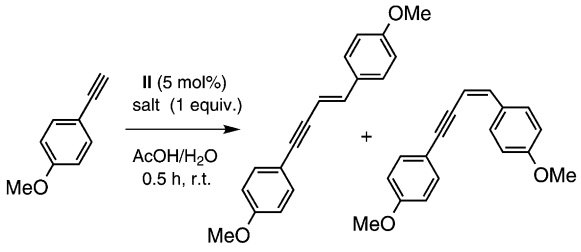
[a] *Reaction conditions:* **3** (0.9 mmol), **II** (30 mg, 0.045 mmol, 5 mol%), AcOH/cosolvent (10 mL, 1:1, v/v), room temperature.
[b] Relative GC percentages at 3 h reaction time.

generates acetate ions, which attack as nucleophilic species the ruthenium dimer and promote the formation of more soluble mononuclear species.[19] Water itself can act as oxygen donor for the splitting of the dimer **II**. Changing H_2O with D_2O, which implies the formation of AcOD as well as of 4-$MeOC_6H_4$–C≡CD, markedly reduced the efficiency of the dimerization (entry 3). In analogy with the low activity exhibited by the *p*-cymene complex **I** in AcOD in the dimerization of phenylacetylene,[10a] this indicates the existence of rate limiting proton transfer steps during the catalytic propagation stage.

With respect to the AcOH:H_2O mixture (entry 2), limited conversions were found with methanol, dichloromethane or acetone (entries 4–6), along with lack and even inversion of stereoselectivity in the latter case. This observation suggests that coordinative interactions of water molecules with metal intermediates take place in the course of the catalytic cycle.

The reaction of 4-ethynylanisole (**3**) catalyzed by **II** in AcOH/H_2O at room temperature was investigated upon addition of different salts and analyzed by GC-MS (Table 5). While the alkyne was still present in the absence of additives (27%, 30 min, entry 1), it was all consumed at the same reaction time in the presence of sodium acetate, equimolar with the substrate and in ten fold excess of ruthenium (entry 2). However, no increase of conversion was observed with only 0.5 equivalent of acetate. The addition of metal (K, Cs) carbonates or sodium sulfate also increased the conversion of **3**, which was otherwise depressed, with loss of stereoselectivity, in the presence of PF_6 salts (entries 6, 7). These experiments indicate that the catalytic system is sensitive to changes in the coordinative environment of the metal center and in particular that the presence of basic anions, most so of acetate, enhances the efficiency of the C–C coupling process.

Table 5. Dimerization of 4-ethynylanysole (**3**) catalyzed by complex **II** in AcOH/H_2O (1:1, v/v), in the presence of additives.[a]

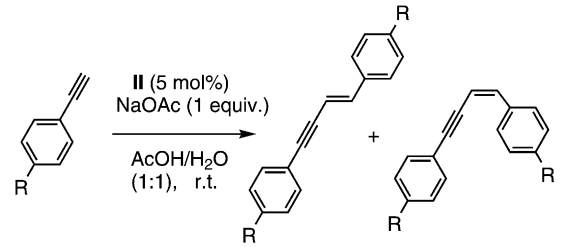


3 **3a** **3b**

Entry	Additive	Residual **3** [%][b]	*E*-(**3a**) [%][b]	*Z*-(**3b**) [%][b]
1	None	27	71	–
2	NaOAc	–	91	2
3	Na_2SO_4	15	65	16
4	K_2CO_3	17	78	2
5	Cs_2CO_3	11	81	2
6	$[NBu_4]PF_6$	55	26	15
7	$NaPF_6$	82	6	10

[a] *Reaction conditions:* **3** (0.9 mmol), additive (0.9 mmol), **II** (30 mg, 0.045 mmol, 5 mol%), AcOH/H_2O (10 mL, 1:1, v:v), room temperature.
[b] Relative GC percentages, determined by GC-MS analysis after 0.5 h reaction time.

Table 6. Dimerization of 4-R-C_6H_4-C≡CH catalyzed by complex **II** in AcOH/H_2O (1:1, v/v), in the presence of NaOAc.[a]



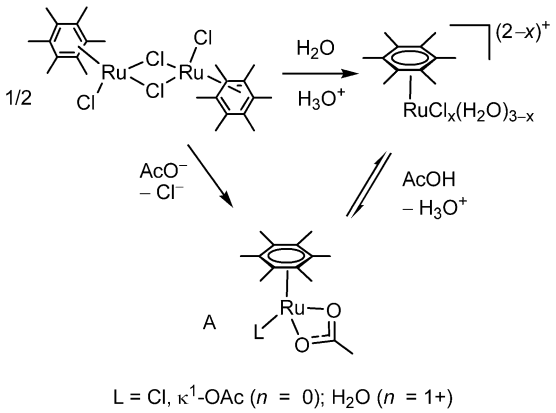
Entry	R	Time [h]	Yield [%][b]	*E*:*Z*[c]
1	CHO (**10**)	1	66	96:4
2	NO_2 (**12**)	3	88	94:6

[a] *Reaction conditions:* alkyne (1.0 mmol), **II** (30 mg, 0.045 mmol, 5 mol%), NaOAc (0.9 mmol), AcOH/H_2O (10 mL, 1:1, v:v), room temperature.
[b] Isolated yields.
[c] Determined by ^{1}H NMR analysis.

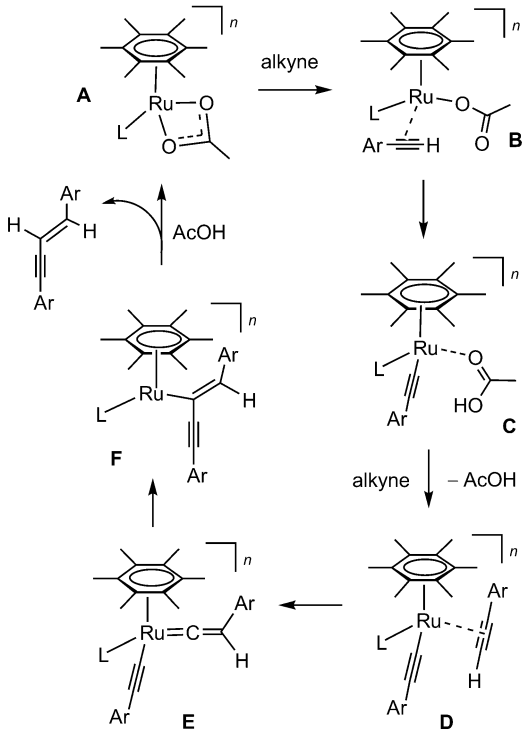
On the basis of these observations, the reactions of the *p*-formyl- and *p*-nitrophenylacetylenes were repeated in the presence of equimolar sodium acetate. The work-up was performed when TLC indicated the consumption of the starting material and the products were isolated by column chromatography (Table 6). The results indicate that the enyne products were obtained in considerably shorter reaction times than in the absence of the salt, and in similar yields and *E*-stereoselectivity (see Table 3 *vs.* Table 6).

The Catalytic Process

The reaction performed by complex **II** in AcOH/H_2O can be discussed in terms of activation stage and subsequent dimerization catalytic cycle, which we propose as represented in Scheme 2 and Scheme 3, respectively. Due to the dissociation equilibrium of acetic acid in water, it is likely that the splitting of the dimer **II** occurs by nucleophilic attack of the resulting acetate ions, with formation of mononuclear species.[20] In fact, carboxylate ruthenium(II) derivatives are known to form from dinuclear η^6-arene complexes upon heating with a mixture of carboxylic acid and acetic anydride or upon reaction at room temperature with metal carboxylates.[19,21] In particular, the complex [RuCl(κ^2-OAc)(η^6-*p*-cymene)] was structurally characterized.[21a,b] Under the conditions of this work, the presence of aqua complexes should also be taken into account, and we tentatively suggest the formation of species of type $[RuCl_x(\eta^6\text{-}C_6Me_6)(H_2O)_{3-x}]^{(2-x)+}$.



Scheme 2. Suggested pathways for initiation of **II** in AcOH/H_2O.



Scheme 3. Proposed catalytic cycle for the dimerization of arylalkynes in the presence of **II** in AcOH/H_2O (L = Cl or κ^1-AcO, *n* = 0; L = H_2O, *n* = 1+).

Indeed, mixed chloro aqua complexes are formed from dimeric arene ruthenium(II) precursors under acidic conditions in water.[22] It is also known that the substitution of chloride by water occurs rapidly in half-sandwich ruthenium(II) complexes,[23] a process especially fast for hexamethylbenzene derivatives,[23c] and that cationic species can form from neutral chloride precursors.[23b,d,24] The aqua complexes can equilibrate by ligand exchange with corresponding adducts of acetic acid,[25] then affording acetato complexes $[Ru(OAc)(\eta^6\text{-}C_6Me_6)L]^{n+}$ (**A**) upon release of HCl or

H_3O^+. The equilibration of the acetato ligand between bidentate and monodentate modes allows for a free coordination site in a κ^1-16e species and therefore for binding of the alkyne molecule. In agreement with these considerations, we found that phenylacetylene in AcOH:H_2O (1:1, v:v) was dimerized to the enyne **1a** (isolated yield: 73%, *E*:*Z*:*gem* = 100:0:0) in the presence of the mononuclear complex [RuCl(κ^2-OAc)(η^6-C_6Me_6)] (**III**) (10 mol%), which was prepared from complex **II** and sodium acetate in acetone. When the reaction was repeated with 5 mol% of **III** and followed by GC-MS, conversion of the substrate in about 90% was observed within 3 h, which indicates the high activity of this monoacetato chloride complex.

The catalytic cycle itself (Scheme 2) is here proposed on the basis of the large body of experimental information and accepted views for the dimerization of terminal alkynes promoted by ruthenium complexes, which in general start from or involve the formation of ruthenium acetylide and/or vinylidene species.[7,8,13b,26] We have adopted the available information to the present case, however by taking into specific account the nature of the precursor ruthenium complex, the presence of acetic acid and that of water, and the rate effects of the acetate, and so specific aspects related to this catalytic system.

The link between the activation stage and the catalytic cycle is the acetato complex **A** which forms adduct **B** with the alkyne. This same species accounts for the rapid reactions observed in the presence of the preformed chloride complex **III** or upon addition of acetate salts to dimer **II**, which increases its concentration (Scheme 2). Next, the acetylide intermediate **C** becomes easily accessible if intramolecular proton transfer occurs between the η^2-alkyne and the acetato ligand. Under the conditions of excess acetate salts, pathways involving intermolecular activation of the π-bound alkyne upon proton abstraction by solvated acetate ions cannot be excluded. The subsequent and more recognized steps involve the coordination of the second alkyne molecule and tautomerization to the vinylidene **E**,[27] alkynyl-vinylidene coupling with formation of a ruthenium enynyl intermediate **F**,[28] then release of the organic enyne by inter or intramolecular proton transfer from acid[18] or from the terminal alkyne itself.[29] In Scheme 2 and Scheme 3, the catalytic ruthenium species have been depicted with coordination of the arene ligand since removal of the C_6Me_6 fragment is unlikely under these mild reaction conditions. Moreover, the changes in the stereoselectivity observed from different arene precursors (Table 2) can be explained in terms of the steric effects imposed by the 6-membered ring in the course of the stereo-controlling step **E** to **F**. In fact, the regio- and stereochemistry of the enyne product are known to be markedly affected by the size of the ancillary ligands and of the alkyne substituents.[8n] Regarding the lower activity exhibited by the iodide dimeric complex *vs.* the chloride complex **II** (42 *vs.* 75% of conversion into **1a**+**1b**, Table 1), this may depend on the lower solubility of the former in the reaction medium, other than to specific effects operating along the catalytic cycle. Moreover, while the evident lack of stereoselectivity induced by the iodide complex may be a combination of steric, electronic and solvation effects difficult to disentagle, it points out to the influence imposed by a different X group in the precursor complex, thus implying that halide ions are affecting the catalytic process.

Due to the remarkable catalytic activity displayed in the presence of the acetate ion, we believe that step **B** to **C** represents the key innovative event in ruthenium-catalyzed alkyne dimerization. An analogous step has been proposed and described in the stoichiometric reaction of the bis-acetato complex [Ru(κ^2-OAc)$_2$(PPh_3)$_2$] with PhC≡CH affording the vinylidene containing species [Ru(κ^1-OAc)(κ^2-OAc)(=C=CHPh)(PPh_3)$_2$].[30] A detailed theorethical study has shown that the lowest energy pathway involves the intramolecular deprotonation of the π-alkyne complex by bound acetate to form a transient acetylide, which is then reprotonated to give the isolable vinylidene complex.[30a] Other cases of stoichiometric and catalytic reactions have been demonstrated in which the alkyne to vinylidene or acetylide transformations are assisted by intramolecular proton transfer to a basic ligand.[23d,31] Moreover, the (sp^2)-C–H functionalization of (hetero)arenes assisted by a coordinated base, in particular by carboxylates, has become largely recognized as a viable synthetic tool for C–C bond formation with organic halides.[32] In analogy to the present work, ruthenium(II) acetate or carbonate complexes generated *in situ* from the dimer **I** dramatically promote the C–C coupling of 2-pyridylbenzene with unactivated aryl chlorides,[32d] and display higher activity in water than in the organic NMP solvent.[33] When well defined ruthenium *p*-cymene carboxylate complexes are synthesized, these show a remarkable broad scope in the direct arylations of arenes.[21c,33] A kinetic study has shown recently that this C–H activation involves autocatalysis by the generated carboxylic acids and intermolecular deprotonation.[34]

Conclusions

The dimeric ruthenium complex [{RuCl(μ-Cl)(η^6-C_6Me_6)}$_2$] catalyzes at room temperature the dimerization of terminal arylalkynes in acetic acid/water mixture and affords linear 1,4-disubstituted *E*-enynes with satisfactory yields and wide functional group compatibility. In the aqueous medium, the hexamethylbenzene catalyst displays better efficiency and se-

lectivity than analogous arene complexes. The presence of water favours the solvolysis of the starting dimer complex and the formation of active acetato species. The efficiency of the reaction is enhanced dramatically in the presence of acetate, which assists the deprotonation of the alkyne. Thus, this dimerization process represents a new example of carboxylate ligands playing a key cooperative effect in bifunctional catalysts involved in H transfer reactions. The combination $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}C_6Me_6)\}_2]$/AcOH/$H_2O$/NaOAc represents the most efficient and *E*-selective catalytic system for dimerization of arylalkynes under mild conditions in protic media.

Experimental Section

General Methods

^1H and ^{13}C NMR spectra were recorded on Bruker AvanceII 300 and DPX-300 spectrometers. Chemical shifts are reported in δ values relative to tetramethylsilane, with reference to internal solvent (^1H NMR: $CHCl_3$, 7.27 ppm; ^{13}C NMR: $CDCl_3$, 77.0 ppm), and coupling constants (*J*) are given in Hz. Infrared spectra were recorded on a Perkin–Elmer 1720-XFT spectrometer. GC-MS analyses were obtained on a Agilent Technologies 6890N Network GC System equipped with a 5973 Network Mass Selective Detector. High resolution ESI-TOF mass spectra were obtained on a Waters Micromass instrument. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated glass or aluminum plates, and preparative flash chromatography was performed using silica gel 60 (0.040–0.063 mm). The reactions were performed under an atmosphere of argon using vacuum-line and standard Schlenk techniques. The alkynes 3,4,5-trimethoxyphenylethyne (**2**),[35] 4-ethynylstyrene (**13**),[36] 1-(ethyl-4-oxy-butyrate)-4-ethynylbenzene (**14**),[37] 2-{2-[2-(4-ethynylphenoxy)ethoxy]ethoxy}-ethanol (**15**),[38] and 2-{2-[2-(3-ethynyl phenoxy)ethoxy]ethoxy}ethanol (**16**)[38] were obtained as described in the literature. The ruthenium complexes used as catalysts were commercially available with the exception of compounds $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}C_6Me_6)\}_2]$ (**II**),[39] $[RuCl_2(\eta^6\text{-}p\text{-cymene})(PMe_3)]$,[40] $[RuCl_2(\eta^3\text{:}\eta^2\text{:}\eta^3\text{-}C_{12}H_{18})]$,[41] $[\{RuCl_2(COD)\}_n]$,[42] $[RuCl_2(\eta^6\text{-}p\text{-cymene})\{PPh(OCH_2CH_2NMe_3)_2\}][SbF_6]_2$,[3c] and $[RuCl(\kappa^2\text{-}OAc)(\eta^6\text{-}C_6Me_6)]$,[19] which were prepared by following the methods reported in the literature. Glacial acetic acid (Carlo Erba, reagent grade) and all other reagents are commercially available and were used as received.

General Procedure for the Catalytic Dimerization of Terminal Arylalkynes

The ruthenium complex **II** (5 mol%) in a 100-mL Schlenk tube was degassed with two argon/vacuum cycles and then dissolved in acetic acid/water (10 mL, 1:1, v:v). After addition of the alkyne (0.9–2.5 mmol), and of the additive when appropriate, the tube was sealed with a rubber septum and the mixture allowed to react under stirring at room temperature (1–24 h). After addition of water, the mixture was extracted with dichloromethane (3×25 mL). The organic phase was washed with aqueous $NaHCO_3$, with water, then dried over $MgSO_4$. After removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel using different mixtures of hexane/dichloromethane as eluent.

1,1′-(*E*)-1-Buten-3-yne-1,4-diylbis(3,4,5-trimethoxybenzene) (2a): From 3,4,5-trimethoxyphenylethyne (**2**, 173 mg, 0.9 mmol) and complex **II** (30 mg, 0.045 mmol, 5 mol%) as a white solid; yield: 161 mg (93%). ^1H NMR (300 MHz, $CDCl_3$): δ=6.95 (d, *J*=16.3 Hz, 1H), 6.70 (s, 2H), 6.63 (s, 2H), 6.27 (d, *J*=16.0 Hz, 1H), 3.87 and 3.86 (two s, OMe, 18H); ^{13}C NMR (300 MHz, $CDCl_3$): δ=153.3, 153.0, 141.0 (Ar-*C*=C-), 138.8, 131.9, 118.3, 108.6, 107.3 (-*C*=C-Ar), 103.4, 91.8 and 87.9 (-C≡C-), 60.9, 56.0; IR (KBr): ν=2924, 1730, 1575, 1505, 1463, 1417, 1331, 1130, 994, 807, 627 cm^{-1}; HR-MS (ESI): *m/z*=385.1646, calcd. for $C_{22}H_{25}O_6$ $[M+H]^+$: 385.1573.

1,1′-(*E*)-1-Buten-3-yne-1,4-diylbis(2,4,5-trimethylbenzene) (5a): From 2,4,5-trimethylphenylethyne (**5**, 130 mg, 0.9 mmol) and complex **II** (30 mg, 0.045 mmol, 5 mol%) as a pale yellow solid; yield: 84 mg (65%). ^1H NMR (300 MHz, $CDCl_3$): δ=7.31 (s, 1H), 7.25 (s, 1H), 7.22 (d, *J*=16.3 Hz, 1H), 7.00 (s, 1H), 6.96 (s, 1H), 6.32 (d, *J*=16.1 Hz, 1H), 2.43, 2.35, 2.26, 2.25, 2.23 (s, Me, 18H); ^{13}C NMR (300 MHz, $CDCl_3$): δ=138.1, 137.3, 137.0, 136.9, 134.2, 133.7, 133.1, 132.82, 132.77, 131.9, 130.8, 126.0, 120.4, 108.2 (-*C*=C-Ar), 92.3 and 90.3 (-C≡C-Ar), 20.1, 19.7, 19.4, 19.3, 19.1, 19.0; IR (KBr): ν=2965, 2179, 1448, 1262, 1096, 951, 880, 801 cm^{-1}; HR-MS (ESI): *m/z*=289.1951, calcd. for $C_{22}H_{25}$ $[M+H]^+$: 289.1878.

4,4′-(*E*)-1-Buten-3-yne-1,4-diylbis-styrene (13a): From 4-ethynylstyrene (**13**, 230 mg, 1.8 mmol) and complex **II** (60 mg, 0.09 mmol, 5 mol%) as a yellow solid; yield: 135 mg (60%). ^1H NMR (300 MHz, $CDCl_3$): δ=7.39 (m, 8H), 7.00 (d, *J*=16.2 Hz, 1H), 6.67 (dd, *J*=10.9 Hz, *J*=6.6 Hz, 2H), 6.36 (d, *J*=16.2 Hz, 1H), 5.74 (d, *J*=17.5 Hz, 2H), 5.25 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): δ=140.8, 137.9, 137.4, 136.3, 136.2, 135.8, 131.7, 126.6, 126.5, 126.2, 122.7, 114.7, 114.3, 107.9 (-*C*=C-Ar), 92.1 and 89.8 (-C≡C-Ar); IR (KBr): ν=3083, 3002, 2185, 1918, 1825, 1700, 1624, 1594, 1504, 1402, 1285, 1114, 992, 957, 908, 844, 668, 522 cm^{-1}; HR-MS (IQ): *m/z*=257.1334, calcd. for $C_{20}H_{17}$ $[M+H]^+$: 257.1252.

4-(4-{4-[4-(3-Ethoxycarbonylpropoxy)phenyl]-(*E*)-but-1-en-3-ynyl}phenoxy)butyric acid ethyl ester (14a): From 1-(ethyl-4-oxy-butyrate)-4-ethynylbenzene (**14**, 67 mg, 0.3 mmol), complex **II** (10 mg, 0.015 mmol, 5 mol%) as an orange solid; yield: 46 mg (69%). ^1H NMR (300 MHz, $CDCl_3$): δ=7.42–7.32 (m, 4H), 6.95 (d, *J*=16.2 Hz, 1H), 6.88–6.80 (m, 4H), 6.23 (d, *J*=16.2 Hz, 1H), 5.78 (d, *J*=11.8 Hz, 0.02H, *Z*-isomer), 4.15 (q, *J*=7.1 Hz, 4H), 4.02 (t, *J*=6.1 Hz, 4H), 2.52 (t, *J*=7.2 Hz, 4H), 2.12 (quint, *J*=6.9, 4H), 1.26 (t, *J*=7.2 Hz, 6H); ^{13}C NMR (300 MHz, $CDCl_3$): δ=173.1, 159.2, 158.7, 140.0, 134.0, 133.1, 132.8, 129.3, 127.7, 127.5, 125.6, 119.9, 115.7, 114.63, 114.59, 105.9 (-*C*=C-Ar), 91.0 and 87.9 (-C≡C-Ar), 66.73, 66.71, 60.4, 30.7, 24.5, 14.2; IR (KBr): ν=3434, 2973, 2185, 1727, 1600, 1507, 1467, 1244, 1172, 1036, 945, 808 cm^{-1}; HR-MS (ESI): *m/z*=465.2272, calcd. for $C_{28}H_{33}O_6$ $[M+H]^+$: 465.2199.

1,1′-(*E*)-1-Buten-3-yne-1,4-diylbis(4-{2-[2-(2-hydroxyethoxy)ethoxy]ethoxy}benzene) (15a): From 4-{2-[2-(2-hydroxyethoxy)ethoxy]ethoxy}phenylacetylene (**15**, 300 mg, 1.2 mmol) and complex **II** (40 mg, 0.0 6 mmol, 5 mol%) as a

white solid; yield: 126 mg (42%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.42$–7.33 (m, 4H), 6.97–6.86 (m, 5H), 6.60 (d, $J = 12$ Hz, 0.15H, *Z*-isomer), 6.23 (d, $J = 16.2$ Hz, 1H), 5.79 (d, $J = 12$ Hz, 0.15H, *Z*-isomer), 4.16 (m, 4H), 3.88 (m), 3.8–3.7 (m), 3.63 (m), 2.3 (br s, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 140.0$, 132.9, 127.5, 114.8, 114.6, 106.1, 72.4, 70.8, 70.4, 69.6, 67.4, 61.8; IR (KBr): $\nu = 3274$, 2877, 2189, 1669, 1601, 1507, 1448, 1359, 1247, 1179, 1105, 1062, 1030, 951, 924, 838, 693, 541 cm^{-1}; HR-MS (ESI): $m/z = 501.2483$, calcd. for $C_{28}H_{37}O_8$ $[M+H]^+$: 501.2410.

1,1′-(*E*)-1-Buten-3-yne-1,4-diylbis(3-{2-[2-(2-hydroxyethoxy)ethoxy]ethoxy}benzene) (16a): From 3-{2-[2-(2-hydroxyethoxy)ethoxy]ethoxy}phenyl acetylene (**16**, 220 mg, 0.9 mmol) and complex **II** (30 mg, 0.045 mmol, 5 mol%) as a dark yellow oil; yield: 65 mg (30%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.3$–7.2 (m, 2H), 7.10–6.95 (m, 5H), 6.92–6.82 (m, 2H), 6.35 (d, $J = 16.2$ Hz, 1H), 4.2–4.1 (m, 4H), 3.90–3.82 (m, 4H), 3.8–3.6 (m, 16H); ^{13}C NMR (300 MHz, $CDCl_3$): δ = 159.3, 158.7, 141.6 (Ar-*C*H=CH-), 138.0, 130.0, 129.8, 124.7, 119.6, 117.2, 115.9, 115.2, 112.6, 108.7 (Ar-CH=*C*H-), 92.1 and 89.0 (-C≡C-Ar), 72.8, 71.1, 70.6, 70.0, 67.7, 62.0; HR-MS(ESI): $m/z = 501.2496$, calcd for $C_{28}H_{37}O_8$ $[M+H]^+$: 501.2410.

Supporting Information

Characterization data of the (*E*)-enyne products, figures of the ^{1}H and ^{13}C NMR spectra of enynes **2a**, **5a**, **13a**, **14a**, **15a**, **16a**, synthetic procedures for the preparation of the alkynes **2**, **14**, **15** and **16** are available in the Supporting Information.

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