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Ruthenium/Halide Catalytic System for C–C Bond Forming Reaction between Alkynes and Unsaturated Carbonyl Compounds

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Dedicated to Professor Jan E. Bäckvall on the occasion of his 60th birthday.

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Abstract: A ruthenium complex [triruthenium dodecacarbonyl, $Ru_3(CO)_{12}$] in the presence of bis(triphenylphosphine)iminium chloride ([PPN]Cl) catalyzes the conjugate addition of terminal alkynes to alkyl acrylates to give high yields of γ,δ-alkynyl esters. On the other hand, the linear codimerization reaction of terminal alkynes with alkyl acrylates proceeds in the presence of a catalytic amount of $Ru_3(CO)_{12}$ and lithium iodide to give the corresponding conjugate dienes. These two different types of catalytic carbon-carbon bond forming reactions are controlled only by the nature of halide ions, either a chloride or an iodide, with other conditions being kept almost the same.

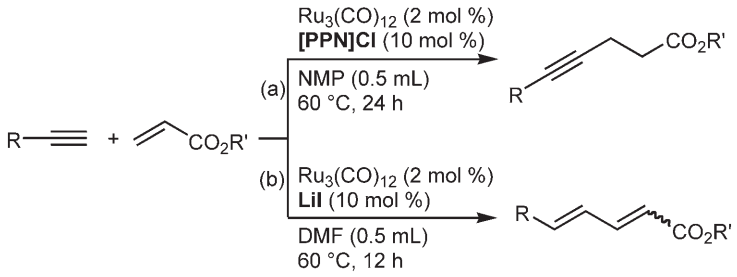
Keywords: alkynes; codimerization; conjugate addition; conjugate dienes; ruthenium

Introduction

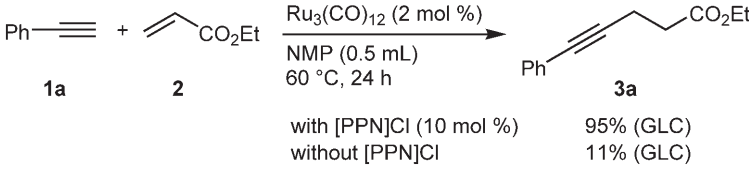
The conjugate addition of carbanions to α,β-unsaturated carbonyl compounds is one of the most attractive methods for constructing a new C–C bond.[1] Among a variety of carbon nucleophiles, terminal alkynes are of interest to create the internal alkynes bearing a carbonyl functionality. Classical methods for introducing an alkynyl moiety to organic acceptors by the conjugate addition reaction have used stoichiometric metal alkynylides.[2] The direct conjugate addition of terminal alkynes to acceptor alkenes or alkynes would be valuable because of the simple operation and its ability to minimize metallic wastes.[3] As for the catalytic direct conjugate addition reaction of terminal alkynes to acceptor alkenes, a few examples using palladium,[4] copper,[5] rhodium,[6] and ruthenium[7] catalysis have been reported. However, these reactions are mostly limited to reactive vinyl ketones and examples of the reaction with α,β-unsaturated esters are rare.

On the other hand, the catalytic codimerization reaction of alkynes with alkenes giving conjugate dienes is also of interest because of atom economy.[8] The leading studies on the codimerization reaction of alkynes with alkenes have been carried out by some research groups[9–11] They reported promising results, for example, for ruthenium-catalyzed codimerization of alkynes with acrylamides or alkyl acrylates (Mitsudo/Kondo)[9] and for the coupling reaction of unactivated alkenes with unactivated alkynes (Murakami/Ito, Yi, and Tsukuda),[10] and for the intramolecular cyclization of enynes to give 1,3-dienes (Trost[11a] and Mori[11b]). However, to the best of our knowledge, no efficient catalytic system for the codimerization of terminal alkynes with acrylates has been reported so far.

We have recently found that $Ru_3(CO)_{12}$ is an effective catalyst for the conjugate addition of phenylacetylene to ethyl acrylate in the presence of a chloride ion to give the corresponding γ,δ-alkynyl esters (Scheme 1 (a)).[12] During the course of further work, we also disclosed that the use of an iodide ion in place of the chloride resulted in the formation of the conjugate dienes from terminal alkynes and ethyl acrylate in the presence of the same ruthenium complex (Scheme 1 (b)). Here, we wish to report the ruthenium/halide catalytic system for two different types of



Scheme 1. Ruthenium-catalyzed reactions of terminal alkynes with alkyl acrylates.



Scheme 2. Conjugate addition of terminal alkynes to ethyl acrylate.

carbon-carbon bond forming reaction controlled by the nature of the halide ion: one is the conjugate addition of terminal alkynes to ethyl acrylate and the other is the linear codimerization between terminal alkynes and ethyl acrylate.

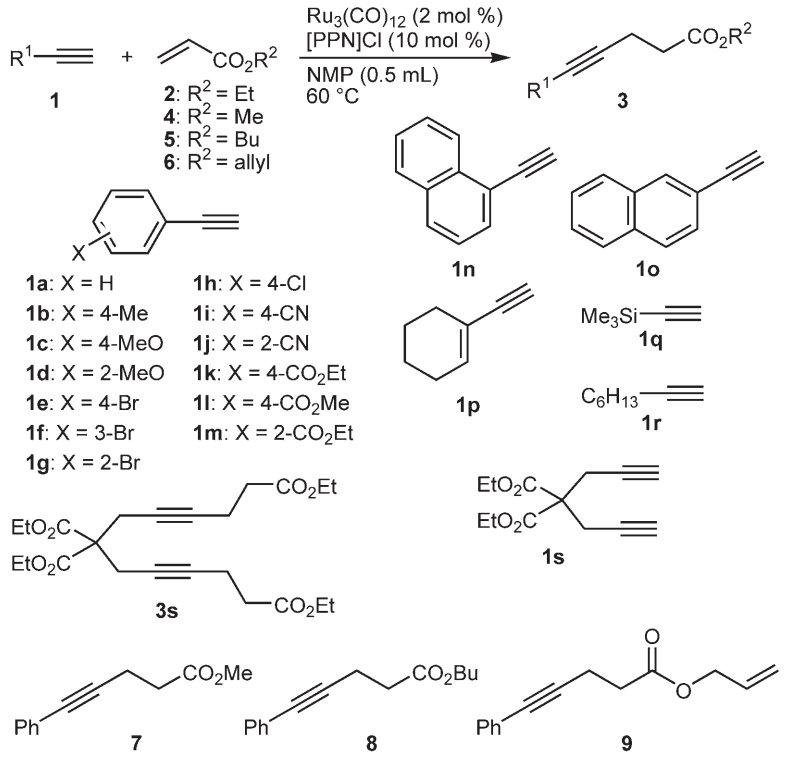
Results and Discussion

The conjugate addition of terminal alkynes to alkyl acrylates smoothly proceeded to give δ,γ-alkynyl esters under ruthenium/chloride catalysis. Thus, treatment of phenylacetylene (**1a**) with ethyl acrylate (**2**) in the presence of $Ru_3(CO)_{12}$ (2 mol%) and bis(triphenylphosphine)iminium chloride ([PPN]Cl, 10 mol%) in *N*-methylpyrrolidinone (NMP) at 60 °C for 24 h gave ethyl 5-phenylpent-4-ynoate (**3a**) in 95% yield (GLC) (Scheme 2).[13] Among several chloride sources ([PPN]Cl, Bu_4NCl, NaCl, KCl and LiCl) examined, [PPN]Cl, a highly dissociated salt, was revealed to be most effective.[12] In sharp contrast, the reaction without [PPN]Cl gave only 11% of **3a**. Other solvents, such as *N*,*N*-dimethylformamide (DMF) and tetrahydrofuran (THF) could also be employed without a significant decrease of the product yields.

Results of the reactions of several terminal alkynes (Scheme 3) bearing aromatic or vinylic substituents (**1b**–**1s**) with alkyl acrylates (**2**, **4**–**6**) are listed in Table 1. Aromatic alkynes having either an electron-donating or an electron-withdrawing group on the benzene ring gave the corresponding esters in moderate to high yields (entries 2–13). It is worth noting that bromo (**1e**–**1g**), chloro (**1h**), cyano (**1i** and **1j**) and alkoxycarbonyl (**1k**–**1m**) substituents were tolerated under the present reaction conditions to give the corresponding esters in moderate to good yields (entries 5–13). Naphthylacetylenes **1n** and **1o** also gave the corresponding ynoates **3n** and **3o** in good yields (entries 14 and 15). The reaction of an alkenylalkyne **1p** smoothly proceeded to give **3p** in 69% yield (entry 16). (Trimethylsilyl)acetylene (**1g**) and 1-octyne (**1r**) gave **3g** and **3r** in 45% and 41% yield, respectively (entries 17 and 18). The use of diyne **1s** afforded the corresponding double addition product **3s** in 65% yield (entry 19). Reactions of phenylacetylene (**1a**) with methyl acrylate (**4**), butyl acrylate (**5**), and allyl acrylate (**6**) gave the corresponding addition products **7**–**9** in 70–86% yield (entries 20–22). The addition of phenylacetylene to α- or β-substituted acrylates such as methyl crotonate and ethyl methacrylate and to a cyclic ester (5,6-dihydro-2*H*-pyran-2-one), unfortunately, resulted in the formation of a complex mixture of unidentified compounds, whereas an alkynoate **10** could also be used as an acceptor in place of alkyl acrylates to give the addition product enyne **11** in 63% yield (Scheme 4).

As expected from the so-far described results, this catalytic system could also be applied to the addition of terminal alkynes to vinyl ketones under very mild conditions (Scheme 5). Thus, the reaction of **1a** with methyl vinyl ketone (**12**), ethyl vinyl ketone (**13**), and phenyl vinyl ketone (**14**) gave the corresponding conjugate addition products **15**, **16**, and **17** in good to high yields. On the other hand, the addition to β-substituted enones such as 3-penten-2-one and 2-cyclohexen-1-one was sluggish to give only low yields of the desired products.

The γ,δ-alkynyl carbonyl compounds obtained here are known to be useful intermediates for biologically active compounds.[14] An example of the transformation of the γ,δ-alkynyl ester **9** is shown in Scheme 6. Heating of the solution of **9** in DMF in the presence of $Pd(PPh_3)_4$ (2.5 mol%) gave the lactone **18** in high yield (Scheme 6).[15]



Scheme 3. Scope of the reaction.

Table 1. Conjugate addition of terminal alkynes to acrylates.[a]

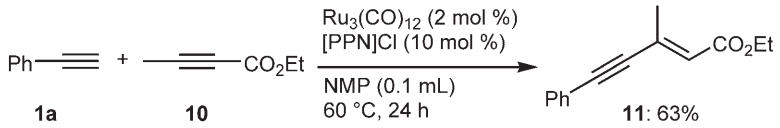
Entry	Alkyne	Acrylate	Time [h]	Product	Isolated yield [%]
1	**1a**	**2**	24	**3a**	89
2	**1b**	**2**	24	**3b**	86
3	**1c**	**2**	24	**3c**	88
4	**1d**	**2**	24	**3d**	65
5	**1e**	**2**	42	**3e**	77
6	**1f**	**2**	48	**3f**	76
7	**1g**	**2**	78	**3g**	77
8	**1h**	**2**	42	**3h**	76
9	**1i**	**2**	72	**3i**	48
10	**1j**	**2**	60	**3j**	60
11	**1k**	**2**	48	**3k**	71
12	**1l**	**2**	72	**3l**	65
13	**1m**	**2**	24	**3m**	80
14	**1n**	**2**	24	**3n**	77
15	**1o**	**2**	24	**3o**	77
16	**1p**	**2**	60	**3p**	69
17	**1q**	**2**	60	**3q**	45
18	**1r**	**2**	48	**3r**	41
19	**1s**	**2**	48	**3s**	65
20	**1a**	**4**	24	**7**	86
21	**1a**	**5**	24	**8**	75
22	**1a**	**6**	24	**9**	70

[a] *Reaction conditions:* alkyne **1** (1.0 mmol), acrylate (5.0 mmol), $Ru_3(CO)_{12}$ (2 mol% to **1**), [PPN]Cl (10 mol% to **1**), NMP (0.5 mL), at 60 °C.

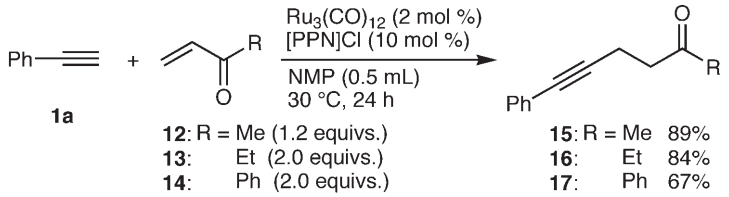
Plausible Reaction Pathway

Deuterium labeling experiments gave us some information about the reaction pathway. Thus, treatment of phenylacetylene-*d* (**1a**-*d*) with ethyl acrylate (**2**) in NMP at 60 °C for 6 h gave the α-deuteriated alkynyl ester **3a**-*d* in 40% yield, where 68% of deuterium was incorporated (Scheme 7). On the other hand, the reaction of **1a** with ethyl acrylate in the presence of D_2O under the same reaction conditions gave **3a**-*d* in 21% yield with >99% deuterium incorporation.[16] The high deuterium incorporation in the latter reaction clearly shows the presence of a protonolysis step of some intermediate enolates in the present catalytic reaction.

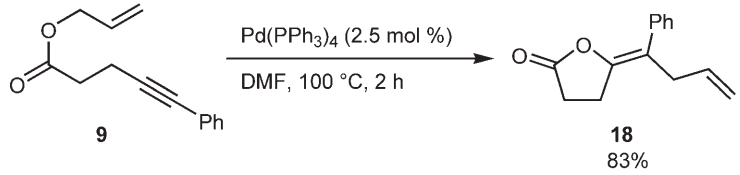
The reaction of $Ru_3(CO)_{12}$ with [PPN]Cl has been known to give several multinuclear ruthenium complexes, such as $[PPN][Ru_4(\mu\text{-}Cl)(CO)_{13}]$ (**A**), $[PPN][Ru_3(\mu\text{-}Cl)(CO)_{10}]$, $[PPN][Ru_3(\mu_3\text{-}Cl)(CO)_9]$, and $[PPN]_2[Ru_4(\mu\text{-}Cl)_2(CO)_{11}]$ in equilibrium in the presence of CO.[17] By taking account of these facts, we propose the catalytic cycle of the present ruthenium-catalyzed conjugate addition of phenylacetylene to ethyl acrylate as shown in Scheme 8. A tetranuclear species $[PPN][Ru_4(\mu\text{-}Cl)(CO)_{13}]$ (**A**) generated from $Ru_3(CO)_{12}$ and [PPN]Cl[17] reacts with phenylacetylene (**1a**) to give the complex **B**.[18] Subsequent attack of the complex **B** to ethyl acrylate (**2**) gives the intermediate enolate **C**, followed by the protonation with



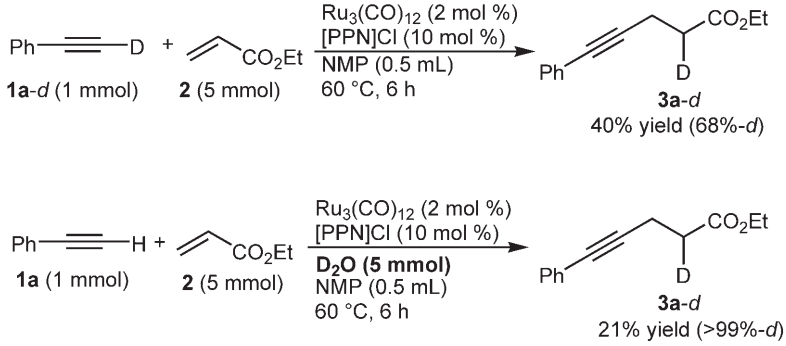
Scheme 4. Addition to ynoate **10**.



Scheme 5. Addition of **1a** to vinyl ketones.



Scheme 6. Cyclization of γ,δ-alkynyl esters **9**.

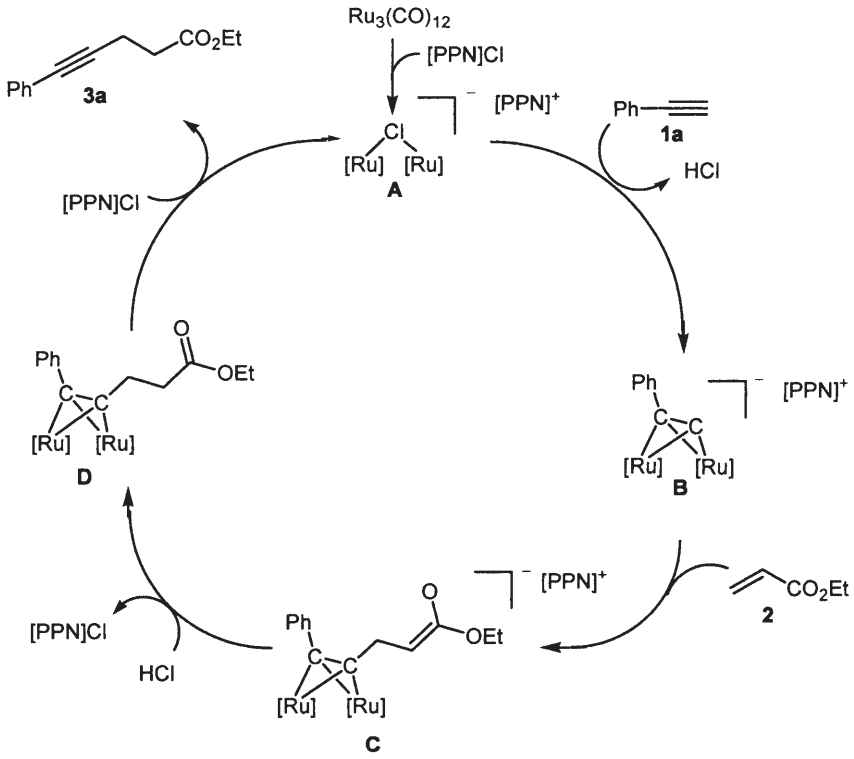


Scheme 7. Deuterium labeling experiments.

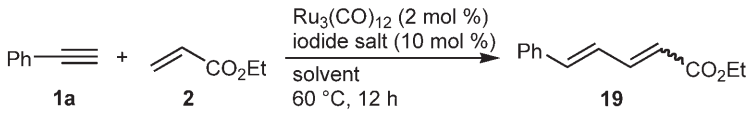
HCl and ligand exchange with [PPN]Cl to give the addition product **3a**, regenerating the species **A**.[19] Actually, we separately confirmed that the ruthenium complex **A** generated *in situ* can catalyze the present conjugate addition reaction.[20]

Linear Codimerization

As described above, we demonstrated that the ruthenium/chloride catalytic system is efficient for the direct conjugate addition of terminal alkynes to alkyl acrylates. During the continuation of this work, we disclosed that the use of an iodide ion in place of a chloride ion gave the conjugate dienes instead of the expected conjugate addition products, alkynyl esters (Scheme 9). Thus, treatment of phenylacetylene (**1a**) with ethyl acrylate (**2**) in the presence of 2 mol% of $Ru_3(CO)_{12}$ and 10 mol% of lithium iodide in DMF at 60°C for 12 h gave a linear codimerized compound, ethyl 5-phenylpenta-2,4-dienoate (**19**) in 64% yield (2*E*,4*Z*/2*E*,4*E* = 74/26) (Table 2, entry 1). Although a significant difference of the product yields was not observed by changing the kind of iodides (entries 1–4), the use of lithium iodide gave a slightly higher yield. In the present linear codimerization, the reaction was much dependent on the type of solvent, DMF and NMP being revealed to be effective



Scheme 8. Plausible reaction pathway.



Scheme 9. Codimerization of alkynes with ethyl acrylate.

Table 2. Codimerization of terminal alkynes with acrylates.[a]

Entry	Solvent	Additive	Isolated yield [%]
1	DMF	LiI	64
2	DMF	NaI	62
3	DMF	KI	59
4	DMF	[PPN]I	57
5	NMP	LiI	61
6	MeOH	LiI	17
7	1,2-dimethoxyethane	LiI	7
8	tetrahydrofuran	LiI	6

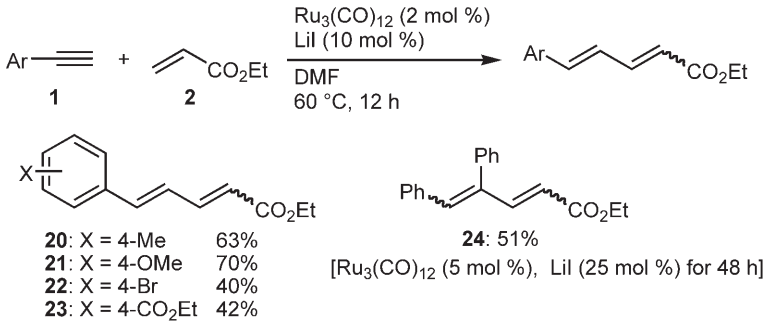
[a] *Reaction conditions:* alkyne **1a** (1.0 mmol), ethyl acrylate **2** (5.0 mmol), $Ru_3(CO)_{12}$ (2 mol% to **1a**), additive (10 mol% to **1a**), solvent (0.5 mL), at 60 °C for 12 h.

(Table 2).[21] As shown in Scheme 10, under the same reaction conditions the use of aromatic alkynes bearing an electron-donating substituent (Me or MeO) on the benzene ring gave the corresponding dienes **20** and **21** in 63% and 70% yields, respectively. The use of aromatic alkynes with bromo and ethoxycarbonyl group gave the dienes **22** and **23** in moderate yields. This catalytic system could also be applied to the reaction of an internal alkyne, diphenylacetylene, to give the corresponding diene **24** in 51% yield.

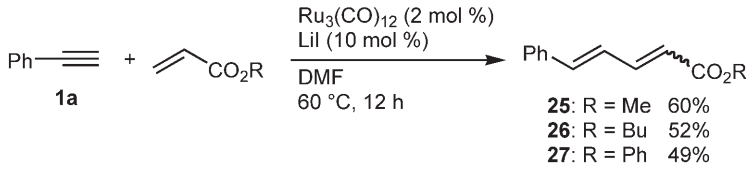
The codimerization of **1a** with other unsaturated esters such as methyl acrylate, butyl acrylate, and phenyl acrylate proceeded similarly to give the corresponding dienes (**25**–**27**) (Scheme 11). In contrast, the use of α- or β-substituted acrylates such as methyl crotonate and ethyl methacrylate gave a complex mixture of unidentified compounds.

Plausible Reaction Pathway

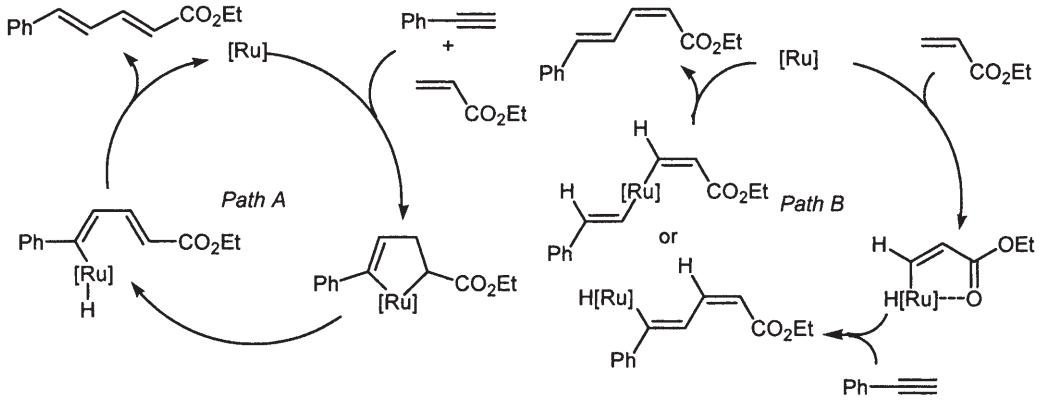
Two reaction pathways for the present codimerization may be proposed on the basis of the known ruthenium-catalyzed addition reaction of alkynes to alkenes (Scheme 12).[8a,9a,22] The first one involves the formation of ruthenacyclopentane intermediate from an alkyne, an acrylate and a ruthenium complex, followed by β-elimination and successive reductive elim-



Scheme 10. Scope of the codimerization of alkynes with ethyl acrylate.

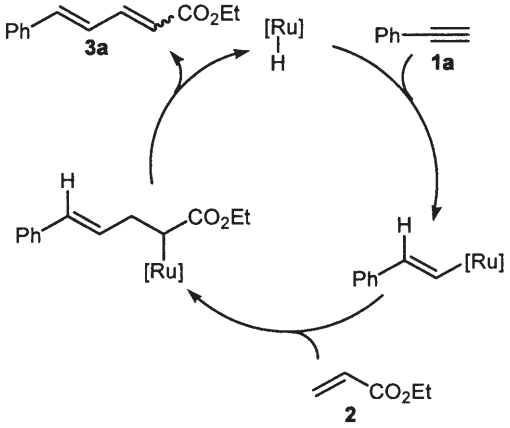


Scheme 11. Codimerization of phenylacetylene with acrylates.

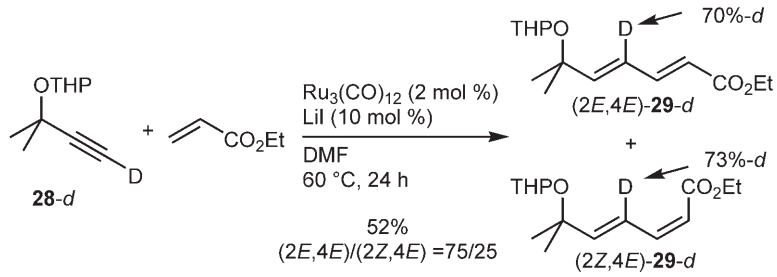


Scheme 12. Two plausible reaction pathways for the formation of (2*E*,4*E*) and (2*Z*,4*E*) isomers.

ination to give the conjugate diene, regenerating the active ruthenium species (path A). The second one consists of the reaction *via* the activation of the C–H bond of the acrylate, followed by the insertion of the alkyne to a produced ruthenium-hydride or ruthenium-carbon bond, and then by reductive elimination (path B). One more plausible pathway is to start from a ruthenium hydride as an active species, which adds first to **1a**, as shown in Scheme 13.[23] Among these three possibilities, the last one (Scheme 13) may explain the formation of both geometrical isomers in the present catalytic reaction. Thus, the insertion of an alkyne to a ruthenium-hydride bond gives a vinyl ruthenium species, followed by carboruthenation to ethyl acrylate, and then β-hydrogen elimination gives the isomeric products. On the other hand, the reaction of deuteriated alkyne (**28**-*d*) with ethyl acrylate



Scheme 13. A plausible reaction pathway starting from a ruthenium hydride species.



Scheme 14. Deuterium labeling experiments.

gave dienes **29**-*d*, which consisted of (2*E*,4*E*) and (2*Z*,4*E*) isomers (Scheme 14). Both isomers were deuteriated at the γ-position in *ca.* 70%. These results suggest that the pathway *via* a ruthenium vinylidene complex[10] is at least excluded, because this pathway should involve the deuterium migration of a terminal alkyne to the δ-position of the diene.

It has been reported that the reaction of $Ru_3(CO)_{12}$ with [PPN]I in THF at elevated temperature gives $[Ru_3(\mu_3\text{-}I)(CO)_9]$, which gives some ruthenium hydride complexes by the interaction with water.[17c] At present, however, the active species in this codimerization is not yet clear, and the possibility of the contribution of a monomeric ruthenium species cannot also be excluded.

Conclusions

The effective conjugate addition reaction of terminal alkynes to α,β-unsaturated carbonyl compounds proceeded under the catalysis of a commercially available ruthenium complex $[Ru_3(CO)_{12}]$ in the presence of [PPN]Cl. This catalytic system can be carried out under neutral and mild conditions to give γ,δ-alkynyl esters or ketones in good to high yields. On the other hand, the combination of $Ru_3(CO)_{12}$ and LiI catalyzed the linear codimerization of alkynes with acrylates to give conjugate dienes in moderate to good yields.

Experimental Section

General Methods

All anaerobic and moisture-sensitive manipulations were carried out with standard Schlenk techniques under predried N_2. NMR spectra were recorded on JEOL EX-400 (^{1}H NMR, 400 MHz; ^{13}C NMR, 100 MHz), JNM AL-300 (^{1}H NMR, 300 MHz; ^{13}C NMR, 75.5 MHz), and JEOL EX-270 (^{1}H NMR, 270 MHz, ^{13}C NMR, 67.7 MHz) instruments for solutions in $CDCl_3$ with Me_4Si as an internal standard. GLC analyses were performed on a Shimadzu GC-14A instrument (25 m × 0.33 mm, 50 mm film thickness, Shimadzu fused silica capillary column HiCapCBP-10-S-25–050) with a flame ionization detector and helium as carrier gas. Analytical thin-layer chromatography (TLC) was performed with silica gel 60 Merck F-254 plates. Column chromatography was performed with Merck silica gel 60. FT-IR spectra (thin film for liquids, KBr disk for solids) were recorded on a Nicolet Impact 400 spectrometer.

Materials

$Ru_3(CO)_{12}$ and bis(triphenylphosphine)iminium chloride ([PPN]Cl) were commercially available and used without further purification. Bis(triphenylphosphine)iminium iodide ([PPN]I) was prepared from [PPN]Cl and lithium iodide by the literature method.[24] Terminal alkynes **1a–c**, and **1p–r** were purchased and used as received. Terminal acetylenes **1d–o** and **1s**[25] were synthesized by the literature methods. α, β-Unsaturated carbonyl compounds were commercially available except for allyl acrylate, which was prepared according to the known procedure from acryloyl chloride and allyl alcohol.[26] Enyne **11**[3a] and γ-ketoacetylenes **15**[7], **16**[2h] and **17**[27] are known compounds

Typical Procedure for the Conjugate Addition of Phenylacetylene (1a) to Ethyl Acrylate (2)

A mixture of $Ru_3(CO)_{12}$ (12.8 mg, 0.020 mmol), [PPN]Cl (57.4 mg, 0.10 mmol) and NMP (0.5 mL) in a 20 mL Schlenk tube was stirred at 60 °C under N_2. After 15 min, **2** (500.6 mg, 5.0 mmol) and **1a** (102.1 mg, 1.0 mmol) were added and the mixture was stirred at 60 °C for 24 h. The mixture was cooled to room temperature and filtered through a pad of Florisil. The filtrate was concentrated under vacuum to give an oil, which was subjected to column chromatography on SiO_2 with EtOAc-hexane (2/98) as eluent furnishing ethyl 5-phenyl-4-pentynoate (**3a**); colorless oil; IR (neat): $\nu = 1735$ (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.27$ (t, $J = 7.2$ Hz, 3H), 2.58–2.77 (m, 4H), 4.18 (q, $J = 7.2$ Hz, 2H), 7.20–7.50 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 14.2$, 15.4, 33.7, 60.6, 81.1, 88.0, 123.5, 127.7, 128.2, 131.6, 171.9; anal. calcd. for $C_{13}H_{14}O_2$: C 77.20, H 6.98; found: C 77.45, H 6.94.

When vinyl ketone was used as an acceptor, it was added at 30 °C after heating the mixture of $Ru_3(CO)_{12}$ and [PPN]Cl in DMF at 60 °C for 15 min.

Typical Procedure for the Codimerization of Phenylacetylene (1a) with Ethyl Acrylate (2)

A mixture of $Ru_3(CO)_{12}$ (12.8 mg, 0.020 mmol), LiI (13.4 mg, 0.10 mmol) and DMF (0.5 mL) in a 20 mL Schlenk

tube was stirred at 60 °C under N_2. After 15 min, **2** (500.6 mg, 5.0 mmol) and **1a** (102.1 mg, 1.0 mmol) were added and the mixture was stirred at 60 °C for 24 h. The mixture was filtered through a pad of Florisil. The filtrate was concentrated under vacuum to give an oil, which was subjected to column chromatography on SiO_2 with EtOAc-hexane (2/98) as eluent to give the product mixture composed of (2*E*,4*E*)-**19** and (2*Z*,4*E*)-**19** (yield: 64.7 mg, 0.32 mmol, 64%). The ratio of geometrical isomers was determined by ^{1}H NMR.

Ethyl 5-phenylpenta-2,4-dienoate [**19**, (2*E*,4*E*)/(2*Z*,4*E*) = 74/26]:[28] ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.29 (t), 4.22 (q), 5.72 [d, J = 11.2 Hz, 1H, (2*Z*,4*E*)-isomer], 5.99 [d, J = 15.3 Hz, 1H, (2*E*,4*E*)-isomer], 6.72–6.82 [m, 2H, (2*Z*,4*E*)-isomer], 6.85–6.92 [m, 2H, (2*E*,4*E*)-isomer], 7.25–7.55 (m), 8.16 [dd, J = 15.6, 11.4 Hz, 1H, (2*Z*,4*E*)-isomer].

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