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Rh-Catalyzed [5+1] and [4+1] Cycloaddition Reactions of 1,4-Enyne Esters with CO: A Shortcut to Functionalized Resorcinols and Cyclopentenones

Takahide Fukuyama,*[a] Yuko Ohta,[a] Célia Brancour,[a] Kazusa Miyagawa,[a] Ilhyong Ryu,*[a] Anne-Lise Dhimane,[b] Louis Fensterbank,*[b] and Max Malacria*[b]

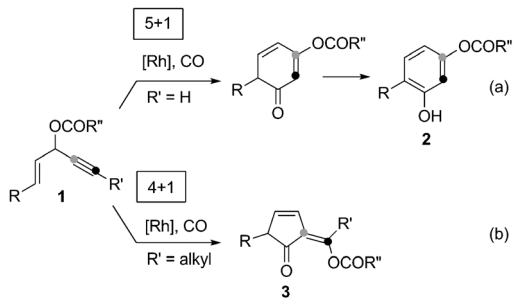
Abstract: We have developed novel Rh-catalyzed [n+1]-type cycloadditions of 1,4-enyne esters, which involve an acyloxy migration as a key step. The efficient preparation of functionalized resorcinols, including biaryl derivatives, from readily available 1,4-enyne esters and CO was achieved by Rh-catalyzed [5+1] cycloaddition accompanied by 1,2-acyloxy migration. When enyne esters had an internal alkyne moiety, the reaction proceeded by a [4+1]-type cycloaddition involving 1,3-acyloxy migration, leading to cyclopentenones.

Keywords: 1,4-enyne esters · acyloxy migration · carbonylation · cycloaddition · rhodium

Introduction

Connecting an alkene to an alkyne and submitting the corresponding 1,*n*-enyne to a catalytic amount of a transition metal has led to tremendous developments in organic synthesis, providing access to a wide variety of carbo- and heterocyclic systems.[1] While the most studied systems are 1,6-enynes, 1,5- and 1,4-enynes have also shown versatile reactivity patterns, particularly when flanked with an *O*-acyl group at the propargylic position and in the presence of electrophilic metal complexes.[2] For example, the well-known Rautenstrauch rearrangement,[3] which originally consists of the Pd^{II}- or the Pt^{II}-catalyzed rearrangement of 1-ethynyl-2-propenyl acetates **1** to give cyclopentadienyl acetates by 1,2-acyloxy migration, has recently lent itself to valuable variations—most notably that of gold catalysis.[4]

From a general perspective, the introduction of intermolecular reactions, such as carbonylations[5] and other incorporations,[6] in enyne cyclization processes greatly expands the scope and value of these reactions, as demonstrated by recent examples of metal-catalyzed multicomponent cycloadditions.[7] In this context, it appeared appealing to combine Rautenstrauch-type reactivity with a carbonylation event, aiming for a novel [5+1] cycloaddition[8] that could lead to resorcinols **2** (Scheme 1, pathway a). While the development of catalytic processes that lead to phenols and their congeners remains an important topic in organic synthesis,[9,10] resorcinols are particularly valuable compounds with important bioactivity,[11] demonstrating, for instance, efficient DNA cleavage properties under oxidative conditions, as well as antibacterial activities.[12] We confirmed the validity of this synthetic route by using enyne acetates **1** and rhodium(I) catalysis.[13] It is worth noting that Tang and coworkers recently devised versatile rhodium(I)-catalyzed sequences, relying on the trapping of Rautenstrauch-type intermediates with CO[14] and alkynes.[15]



Scheme 1. Two types of cyclocarbonylations of 1,4-enyne esters.

Herein, we give a full account of the [5+1] transformation that gives access to aromatic substrates **2** from acyclic precursors **1** with a monosubstituted alkyne moiety (R′=H). We also report the related [4+1] cycloaddition of disubstituted alkynes **1** (R′=alkyl), leading to cyclopentenones **3**, based on an initial 1,3-acyloxy migration (Scheme 1, pathway b).[16,17]

[a] Prof. T. Fukuyama, Y. Ohta, Dr. C. Brancour, K. Miyagawa, Prof. I. Ryu
Department of Chemistry, Graduate School of Science
Osaka Prefecture University, Sakai, Osaka 599-8531 (Japan)
Fax: (+81) 72-254-9695
E-mail: fukuyama@c.s.osakafu-u.ac.jp
ryu@c.s.osakafu-u.ac.jp

[b] Dr. A.-L. Dhimane, Prof. L. Fensterbank, Prof. M. Malacria
UPMC Univ. Paris 6
Institut Parisien de Chimie Moléculaire CNRS
UMR 7201, 4 Place Jussieu, C. 229, 75005 Paris (France)
E-mail: louis.fensterbank@upmc.fr
max.malacria@upmc.fr

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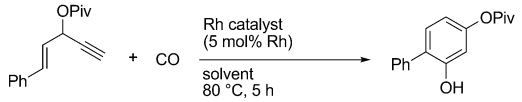
Results and Discussion

We started our study with **1a** as a model substrate to obtain 4-phenyl-substituted resorcinol derivative **2a**. Initial attempts with platinum and gold salts did not lead to the carbonylation adduct, but to 3-phenylcyclopentenone[18] in various yields. We then examined the reaction by using rhodium catalysts. When the reaction was carried out in the presence of $[RhCl(PPh_3)_3]$ under 50 atm of CO in CH_2Cl_2 at 80 °C for 5 h, no carbonylation product was obtained (Table 1, entry 1). The reaction with $[Rh_6(CO)_{16}]$ gave only a trace amount of the desired resorcinol **2a** through the [5+1] cycloaddition reaction. With $[Rh_2(OAc)_4]$, $[Rh_2(OCOCF_3)_4]$, and $[\{RhCl_2Cp^*\}_2]$ (Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl), the resorcinol **2a** was obtained in moderate yields, while the conversion was insufficient and 3-phenylcyclopentenone was formed as a by-product (entries 3–5). The yield of **2a** increased with the $[\{RhCl(CO)_2\}_2]$ catalyst (entry 6). When the reaction was carried out by using toluene and dichloroethane as solvent, the yield of **2a** slightly decreased (entries 8 and 9), whereas the reaction by using $CHCl_3$ gave a complex mixture (entry 10). While the reaction under 80 atm of CO gave **2a** in 76% yield (entry 12), the carbonylated product **2a** was obtained in moderate yield under 20 atm of CO, in which a significant amount of unidentified polymeric materials were formed as by-products (entry 11).

Table 1. Rh-catalyzed [5+1] cycloaddition of enyne ester **1a** with CO leading to resorcinol derivative **2a**.[a]



1a (0.5 M) **2a**

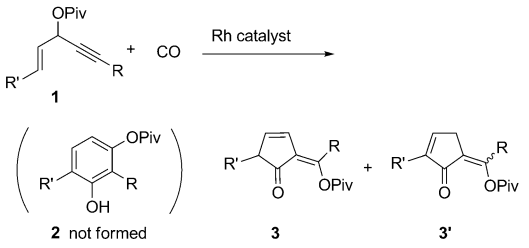
Entry	Catalyst	Solvent	CO [atm]	Yield [%][b]
1	$[RhCl(PPh_3)_3]$	CH_2Cl_2	50	n.r.
2	$[Rh_6(CO)_{16}]$	CH_2Cl_2	50	traces
3	$[Rh_2(OAc)_4]$	CH_2Cl_2	50	30
4	$[Rh_2(OCOCF_3)_4]$	CH_2Cl_2	50	28
5	$[\{RhCl_2Cp^*\}_2]$	CH_2Cl_2	50	40
6	$[\{RhCl(CO)_2\}_2]$	CH_2Cl_2	50	66
7	$[\{RhCl(cod)\}_2]$	CH_2Cl_2	50	51
8	$[\{RhCl(CO)_2\}_2]$	toluene	50	45
9	$[\{RhCl(CO)_2\}_2]$	$ClCH_2CH_2Cl$	50	50
10	$[\{RhCl(CO)_2\}_2]$	$CHCl_3$	50	complex mixture
11	$[\{RhCl(CO)_2\}_2]$	CH_2Cl_2	20	41
12	$[\{RhCl(CO)_2\}_2]$	CH_2Cl_2	80	76

[a] Reactions were performed on a 0.5 mmol scale with substrate **1a** (0.05 M) for 5 h at 80 °C. [b] Isolated yields after flash chromatography on SiO_2; cod = 1,5-cyclooctadiene; n.r. = not rationalized.

After determining the optimal reaction conditions, we set out to define the scope of the present [5+1]-type resorcinol synthesis (Table 2). The cyclization process was also successful when the ester group was changed from pivalate to acetate (entry 2), whereas alcohol (R^4 = H), silyl ether (R^4 = TBDMS), and benzyl ether ($R^4 = CH_2Ph$) failed to react with CO. The reaction was compatible with varying electronic effects of substituents on the aromatic ring; thus, functional groups, such as trifluoromethyl (entry 3) and methoxy groups (entry 4), could be implemented. Enynes **1e** and **f** with *ortho*-substituted phenyl groups also worked well to give the corresponding aryl substituted resorcinols **2e** and **f** in good yields (entries 5 and 6). 4-Methyl and 3-methyl-substituted enynes **1g** and **h** gave methyl-phenyl-substituted resorcinols **2g** and **h**, respectively (entries 7 and 8). In the case of **1h**, a mixture of *E/Z* isomers (1:0.22) was used. However, it turned out that the *Z* isomer was not reactive towards the carbonylative cyclization (see below for a rationalization).

Alkylated enyne esters were also investigated. The present catalytic system was tolerant and comparable in reactivity to 1-ethynyl-2-propenyl pivalates bearing alkyl chains. Me, *n*Bu, and *i*Pr substitution of the alkene terminus allowed the formation of the desired products in 58 to 74% yield (entries 9–11). Enyne **1l** with a cyclohexene moiety gave tetrahydronaphthalene derivative **2l** (entry 12). The reaction of enyne **1m** with no substituents on the alkene terminus gave the corresponding resorcinol **2m** in moderate yield, which can lead to the natural product olivetol[19] (entry 13). In this case, the formation of noncarbonylated cyclopentenone competed.

We next investigated an enyne ester with an alkyl substituent on the alkyne terminus. Interestingly, it was found that a [4+1] cycloaddition reaction,[20] involving a 1,3acyloxy migration, took place to give cyclopentenone **3** and isomerized product **3′**, in which resorcinol derivative **2** was not formed (Scheme 2).

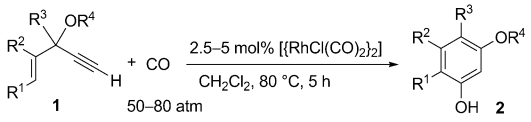


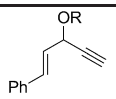
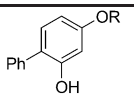
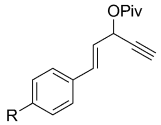
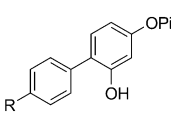
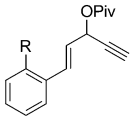
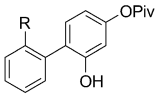
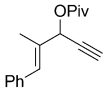
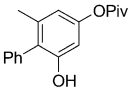
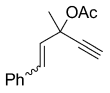
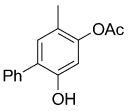
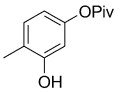
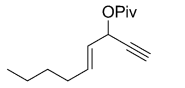
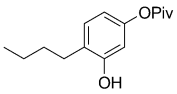
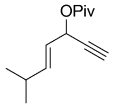
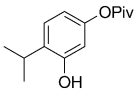
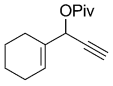
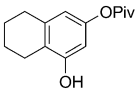
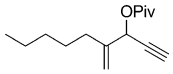
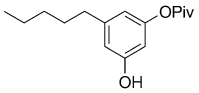
Scheme 2.

The reaction of enyne **1n** with CO gave cyclopentenone **3a**, which was formed by a [4+1] cycloaddition, and isomerized **3a′** (*E*/*Z* = 19:81) in 67% total yield (**3a**/**3a′** = 54:46; Table 3, entry 1). While the reaction under a higher temperature gave similar results, the yields decreased under a lower temperature (entries 2 and 3). A similar result was obtained at 60 atm of CO (entry 4). The reaction was complete after 3 h to give 72% total yield of cyclopentenones (entry 5). The use of $[\{RhCl(cod)\}_2]$ resulted in slightly better yields of cyclopentenones **3a** and **3a′** (entry 6). In this reaction, conjugated enyne esters by 1,3-acyloxy shift onto an alkene moiety were also formed as by-products.

A variety of enynes with an alkyl substituent on the alkyne terminus were examined, and the results are summarized in Table 4. Benzoyl ester and acetate also worked

Table 2. $[RhCl(CO)_2]_2$-catalyzed synthesis of functionalized resorcinol derivatives by [5+1] cycloaddition.[a]



Entry	Enyne **1**		Resorcinol **2**		Yield [%][b]
1		**1a** R = Piv		**2a**	76
2		**1b** R = Ac		**2b**	67
3		**1c** R = CF_3		**2c**	56
4		**1d** R = OMe		**2d**	56
5[c]		**1e** R = Me		**2e**	67
6[c]		**1f** R = OMe		**2f**	61
7		**1g**		**2g**	53
8		**1h** *E*/*Z* (1:0.22)		**2h**	68[d]
9		**1i**		**2i**	58
10		**1j**		**2j**	64
11		**1k**		**2k**	74
12		**1l**		**2l**	58
13[e]		**1m**		**2m**	37

[a] Reactions were performed on a 0.5 mmol scale in dichloromethane (0.05–0.016 M) at 80 atm of CO, except for entry 8 (50 atm). [b] Isolated yields after flash chromatography on SiO_2. [c] $[\{RhCl(cod)\}_2]$ was used. [d] NMR yield of *E* isomer. [e] Reaction time: 15 h.

to give the corresponding cyclopentenones **3b** and **c** and their isomers (entries 2 and 3). Butyl-substituted enynes **1q** and **r** could be used for the present [4+1] cycloaddition reaction (entries 4 and 5). Enynes **1s** and **t** with an isopropyl substituent on the alkene moiety gave the corresponding cyclopentanones (entries 6 and 7). Unlike the [5+1] cycloaddition reaction, an enyne with no substituents on the alkene terminus worked in the [4+1] reaction (entries 8–10). Bicyclic ketones **3k** and **l** were obtained from enynes **1x** and **y**, respectively. Generally, enynes with longer alkyl chains gave higher yields of cyclopentenones compared to methyl-substituted enynes, because the Rautenstrauch rearrangement competed in the case of methyl-substituted enynes.

Possible mechanisms for the present [5+1] and [4+1] cycloaddition reactions are shown in Scheme 3. We postulate that the reaction is initiated by electrophilic activation of the alkyne moiety of **1** by the rhodium catalyst, leading to π-complex **A**.[21] For terminal alkynes, nucleophilic attack of an ester group occurs to generate a zwitterionic vinyl-rhodium species **B**, which undergoes 1,2-acyloxy migration[22] to give rhodium carbenoid **C**. The reaction with CO to give ketene **D** and subsequent 6π-electrocyclization[23] gives the transient intermediate **E**, which undergoes aromatization leading to **2**.[24] However, 1,3-acyloxy migration precedes this process in the case of internal alkynes,[22] in which the zwitterionic vinyl-rhodium species **F** is converted to rhodacyclopentadiene **F**. Successive carbonyl insertion and reductive elimination gives cyclopentenone **3**. An alternative path for cyclopentenone **3** includes the formation of vinyl allenes and subsequent oxidative cyclization that leads to **G.**[25]

It is worth noting that when the carbonylation of **1d** was carried out in the presence of MeOH (20 equiv), a low yield of methyl ester **4** was obtained together with resorcinol derivative **2d** (Scheme 4). Formation of **4** would originate from the nucleophilic trapping of ketene **D**.

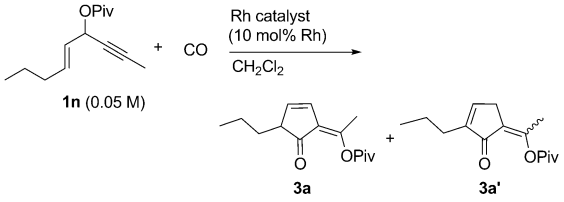
Conclusion

We have developed novel Rh-catalyzed [*n*+1]-type cycloadditions of 1,4-enyne esters, involving acyloxy migration as a key step. The efficient preparation of functionalized resorcinols, including biaryl derivatives, from readily available 1,4-enyne esters and CO was achieved by Rh-catalyzed [5+1] cycloaddition accompanied by 1,2-acyloxy migration. When enyne esters had an internal alkyne moiety, the reaction proceeded by [4+1]-type cycloaddition involving 1,3-acyloxy migration, leading to cyclopentenones. Further studies of this reaction toward target-oriented synthesis are underway in our laboratories.

Experimental Section

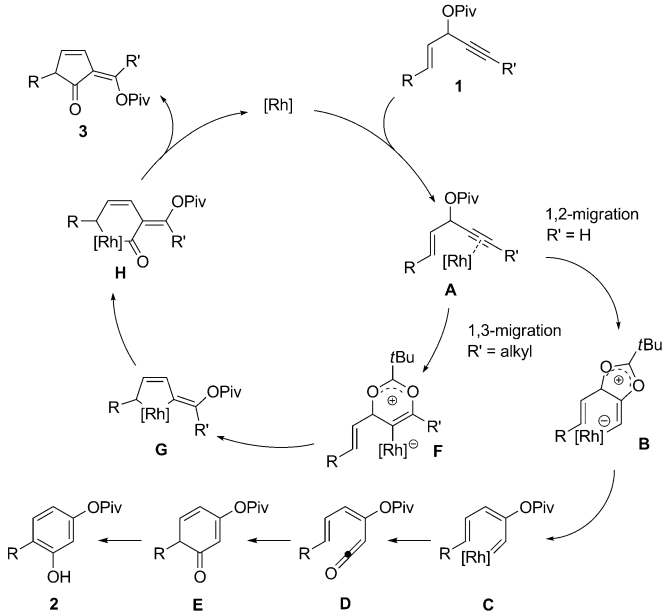
Typical procedure for the rhodium-catalyzed carbonylative cyclization of 1,4-enyne esters: A magnetic stir bar, (*E*)-1-phenyl-1-penten-4-yn-3-yl pivalate (**1a**, 128.5 mg, 0.53 mmol), $[RhCl(CO)_2]_2$ (4.9 mg, 0.013 mmol) and CH_2Cl_2 (10 mL) were placed in a 50 mL stainless steel autoclave. The autoclave was closed, purged three times with carbon monoxide, pressurized with carbon monoxide (80 atm), and then heated at 80 °C for 5 h. Excess of CO was discharged at room temperature. The autoclave was washed with ether and solvents were removed under reduced pres-

Table 3. Rh-catalyzed [4+1] cycloaddition of enyne ester **1n** with CO leading to cyclopentenones **3a** and **3a′**.[a]

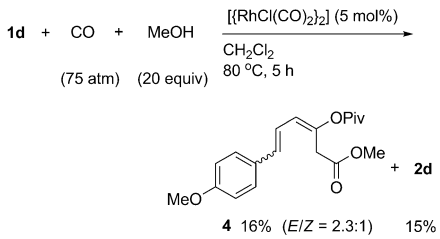


Entry	Rh catalyst	Temp. [°C]	CO [atm]	Time [h]	Total yield [%][b]	**3a**/**3a′** (*E*/*Z*)[c]
1	$[\{RhCl(CO)_2\}_2]$	80	80	5	67	54:46 (19:81)
2	$[\{RhCl(CO)_2\}_2]$	60	80	5	41	63:37 (20:80)
3	$[\{RhCl(CO)_2\}_2]$	100	80	5	65	58:42 (19:81)
4	$[\{RhCl(CO)_2\}_2]$	80	60	5	66	53:47 (19:81)
5	$[\{RhCl(CO)_2\}_2]$	80	60	3	72	49:51 (19:81)
6	$[\{RhCl(cod)\}_2]$	80	60	3	76	46:54 (21:79)

[a] Reactions were performed on a 0.5 mmol scale with substrate **1n** (0.05 M). [b] Isolated yields after flash chromatography on SiO_2. [c] Determined by ^1H NMR spectroscopy of a crude reaction mixture.

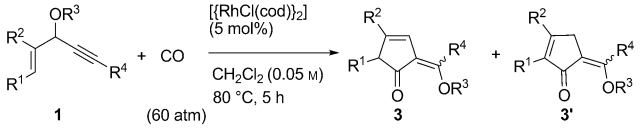


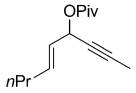
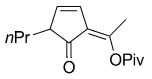
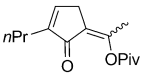
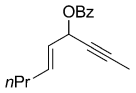
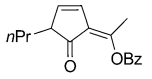
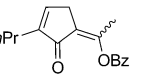
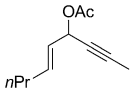
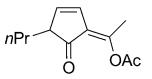
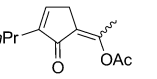
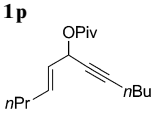
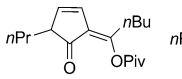
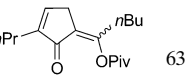
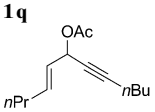
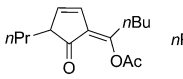
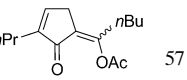
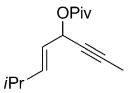
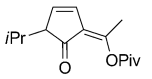
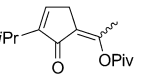
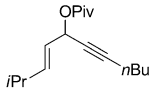
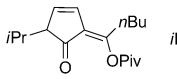
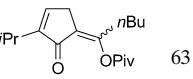
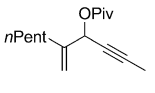
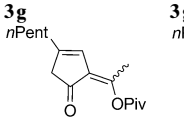
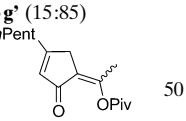
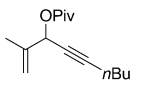
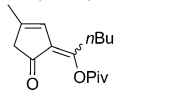
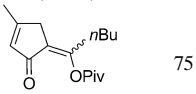
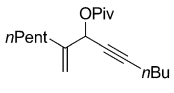
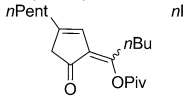
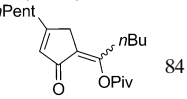
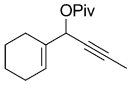
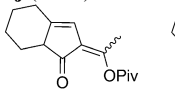
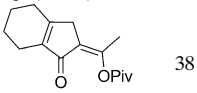
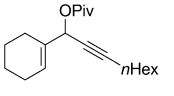
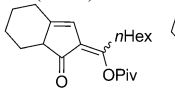
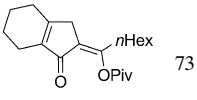
Scheme 3. Possible mechanisms for Rh-catalyzed [5+1] and [4+1] cycloaddition reactions.



Scheme 4.

Table 4. Rh-catalyzed [4+1] cycloaddition of enyne esters with CO leading to cyclopentenones.[a]



Entry	Enyne **1**	**3** (*E*/*Z*)	**3′** (*E*/*Z*)	Total yield [%][b] (**3**/**3′**)
1[c]				76 % (46:54)
	1n	**3a**	**3a′** (21:79)	
2				51 % (41:59)
	1o	**3b**	**3b′** (17:83)	
3				49 % (43:57)
	1p	**3c**	**3c′** (8:92)	
4[c,d]				63 % (46:54)
	1q	**3d**	**3d′** (18:82)	
5				57 % (38:62)
	1r	**3e**	**3e′** (6:94)	
6				49 % (43:57)
	1s	**3f**	**3f′** (18:82)	
7				63 % (68:32)
	1t	**3g**	**3g′** (15:85)	
8				50 % (84:16)
	1u	**3h** (35:65)	**3h′** (18:82)	
9				75 % (79:21)
	1v	**3i** (56:44)	**3i′** (12:88)	
10				84 % (93:7)
	1w	**3j** (42:58)	**3j′** (14:86)	
11[d]				38 % (68:32)
	1x	**3k** (65:35)	**3k′**	
12				73 % (75:25)
	1y	**3l** (44:56)	**3l′**	

[a] Reactions were performed on a 0.5 mmol scale in dichloromethane (0.05 M) at 60 atm of CO. [b] Isolated yields. [c] Reaction time: 3 h. [d] $[\{RhCl(CO)_2\}_2]$ was used.

sure to give the crude reaction mixture (135 mg) as a brown oil. The residue was then purified by short flash chromatography on SiO_2 (Et_2O/hexane 3:7) to give **3a** as an orange solid (108.7 mg, 76%).

Acknowledgements

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[21] In the case of (*Z*)-**1h**, a π-coordinated intermediate might be difficult to be formed, because the phenyl group blocks the rhodium catalyst to approach to the alkyne moiety. Probably for this reason, the *Z*-isomer of **1h** would not be reactive towards the present carbonylative cyclization. Such observation with a *Z*-olefin has also been made by Toste, see ref. [4].

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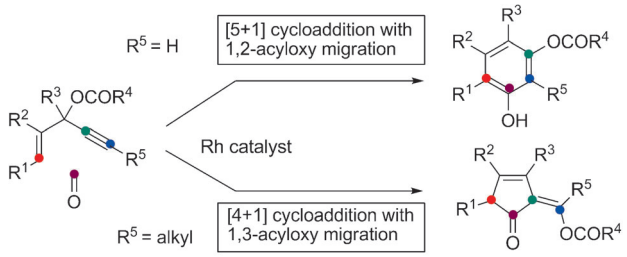
Cycloaddition Reactions

T. Fukuyama, Y. Ohta, C. Brancour, K. Miyagawa, I. Ryu,* A.-L. Dhimane, L. Fensterbank,* M. Malacria** ..... ▮▮▮▮–▮▮▮▮

Rh-Catalyzed [5+1] and [4+1] Cycloaddition Reactions of 1,4-Enyne Esters with CO: A Shortcut to Functionalized Resorcinols and Cyclopentenones



Rhodium-catalyzed carbonylation: New carbonylative cycloaddition reactions of enyne esters have been developed by using a Rh complex as the catalyst. The reaction of terminal alkynes with CO gave functionalized resorcinols by [5+1] cycloaddition acompanied by 1,2-acyloxy migration, whereas internal alkynes gave cyclopentenones by [4+1] cycloaddition involving 1,3-acyloxy migration (see scheme).