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Synthesis of Functionalized Hydroquinones via $[Cp^*RuCl_2]_2$-Catalyzed Cocyclization of Alkynes, α,β-Unsaturated Carbonyl Compounds, and Carbon Monoxide

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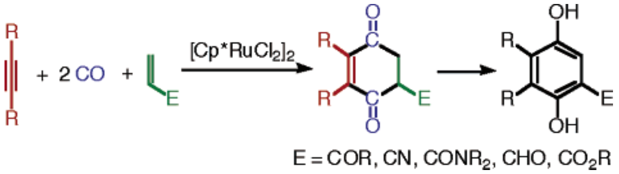
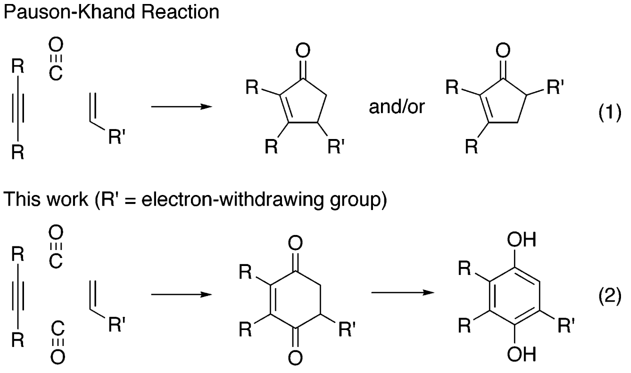
ABSTRACT



Catalytic [2 + 2 + 1 + 1] cocyclization reaction of an alkyne, an alkene, and two molecules of carbon monoxide, leading to functionalized hydroquinones, was studied. Using $[Cp^*RuCl_2]_2$ as a catalyst, we found that a variety of electron-deficient alkenes, such as α,β-unsaturated ketones, esters, amides, and nitriles, can be employed as an alkene coupling partner to give the corresponding hydroquinones.

The Pauson−Khand reaction, which represents transition-metal-catalyzed [2 + 2 + 1] cocyclization of an alkyne, an alkene, and carbon monoxide, has been widely studied and established as a useful method for the construction of cyclopentenones (Scheme 1, eq 1).[1] Having one more molecule of carbon monoxide, [2 + 2 + 1 + 1] cocyclization reactions of an alkyne, an alkene, and two molecules of

Scheme 1. Two Types of Cocyclization Reactions Using Alkyne, Alkene, and Carbon Monoxide



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[‡] Kyoto University.

(1) For reviews on the Pauson−Khand reaction, see: (a) Geis, O.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **1998**, *37*, 911. (b) Gibson, S. E.; Stevenazzi, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1800. (c) Blanco-Urgoiti, J.; Anorbe, L.; Pérez-Serrane, L.; Dominguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2004**, *33*, 32. (d) Boñaga, L. V. R.; Krafft, M. E. *Tetrahedron* **2004**, *60*, 9795. For Ru-catalyzed Pauson−Khand reaction, see: (e) Kondo, T.; Suzuki, N.; Okada, T.; Mitsudo, T. *J. Am. Chem. Soc.* **1997**, *119*, 6187. (f) Morimoto, T.; Chatani, N.; Fukumoto, Y.; Murai, S. *J. Org. Chem.* **1997**, *62*, 3762.

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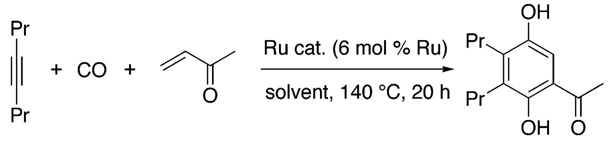
carbon monoxide would lead to substituted hydroquinones (Scheme 1, eq 2).[2] Hydroquinone framework is widely distributed in nature, and some hydroquinones are known to possess a broad spectrum of biological activities and unique reactivities.[3] Hydroquinones bearing polar functional groups are also used as a photographic developer as well as an intermediate in the synthesis of antioxidant and polymerization inhibitor.[3] We previously reported that strained alkenes, such as 2-norbornene, can participate in ruthenium-catalyzed [2 + 2 + 1 + 1] cocyclization, leading to the corresponding hydroquinone derivatives.[4] However, for the unique cocyclization reaction to be a general scheme, the restriction with regard to an alkene coupling partner should be overcome. Herein, we report that the [2 + 2 + 1 + 1] cocyclization reaction can be extended successfully to include a wide variety of electron-deficient alkenes as a coupling partner and $[Cp^*RuCl_2]_2$, a good catalyst for the unique cocyclization reaction.

The carbonylative coupling reaction of 4-octyne (**1a**) with methyl vinyl ketone (**2a**) was examined under a variety of conditions (Table 1). When the reaction of **1a** with **2a** was carried out using $Ru_3(CO)_{12}$ as a catalyst and toluene as a solvent under 20 atm of carbon monoxide, the desired

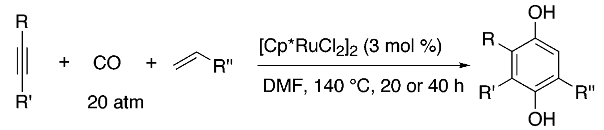
Table 1. Catalytic Activity of Several Ruthenium Complexes for Cocyclization of 4-Octyne (**1a**), Methyl Vinyl Ketone (**2a**), and Carbon Monoxide[a]



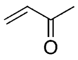
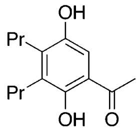
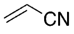
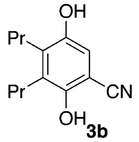
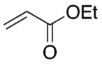
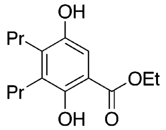
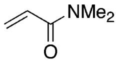
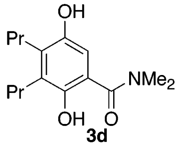
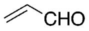
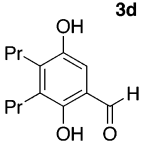
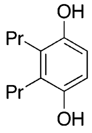
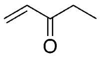
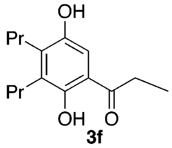
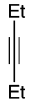
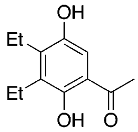
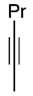
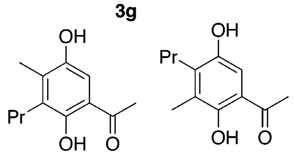
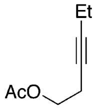
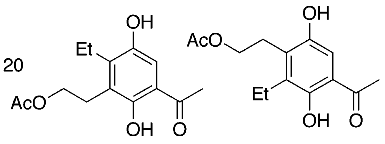
entry	catalyst	solvent	**3a** yield (%)[b]
1	$Ru_3(CO)_{12}$	toluene	53
2	$Ru_3(CO)_{12}$	DMF	65
3	$Ru_3(CO)_{12}$	CH_3CN	60
4	$Ru_3(CO)_{12}$	*N*-methylpiperidine	24
5[c]	$Ru_3(CO)_{12}$	DMF	51
6	$[RuCl_2(CO)_3]_2$	DMF	27
7	$[RuCl_2(\eta^6\text{-mesitylene})]_2$	DMF	39
8	$CpRuCl(PPh_3)_2$	DMF	26
9	$RuHCl(PPh_3)_3$	DMF	48
10	$[Cp^*RuCl_2]_2$	DMF	79

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), catalyst (0.03 mmol as Ru atom), solvent (2 mL), 140 °C, 20 h. [b] Isolated yields by flash chromatography on SiO_2. [c] CO (40 atm).

Table 2. $[Cp^*RuCl_2]_2$-Catalyzed Cocyclization of Alkynes, Electron-Deficient Alkenes, and Carbon Monoxide[a]



1 2 3

entry	alkyne	alkene	time (h)	product	yield (%)[b]
1	 **1a**	 **2a**	20	 **3a**	79%
2	**1a**	 **2b**	40	 **3b**	68%
3[c]	**1a**	 **2c**	40	 **3c**	75%
4	**1a**	 **2d**	40	 **3d**	46%
5[c]	**1a**	 **2e**	20	 **3e** 39%  **4** 3%	
6	**1a**	 **2f**	20	 **3f**	54%
7	 **1b**	**2a**	20	 **3g**	60%
8	 **1c**	**2a**	20	 **3h**, **3h'**	62% (57:43)[d]
9	 **1d**	**2a**	20	 **3i**, **3i'**	75% (60:40)[d]

[a] Reaction conditions: **1** (0.5 mmol), **2** (1.5 mmol), $[Cp^*RuCl_2]_2$ (3 mol %), CO (20 atm), DMF (2 mL), 140 °C. [b] Isolated yields by flash chromatography on SiO_2. [c] **2** (2.5 mmol). [d] Regioisomeric ratio was determined by ^1H NMR analysis of a crude reaction mixture. The absolute regiochemistry of the products was not determined.

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(2) For [2 + 2 + 1 + 1] cocyclization using two molecules of alkynes and two molecules of CO, see: (a) Pino, P.; Braca, G. Carbon Monoxide Addition to Acetylenic Substrates. In *Organic Synthesis via Metal Carbonyls*; Wender, I., Pino, P., Eds.; Wiley: New York, 1977; Vol. 2, p 419. (b) Murayama, K.; Shio, T.; Yamamoto, Y. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1877. (c) Rameshkumar, C.; Periasamy, M. *Organometallics* **2000**, *19*, 2400. (d) Mathur, P.; Bhunia, A. K.; Mobin, S. M.; Singh, V. K.; Srinivasu, C. *Organometallics* **2004**, *23*, 3694.

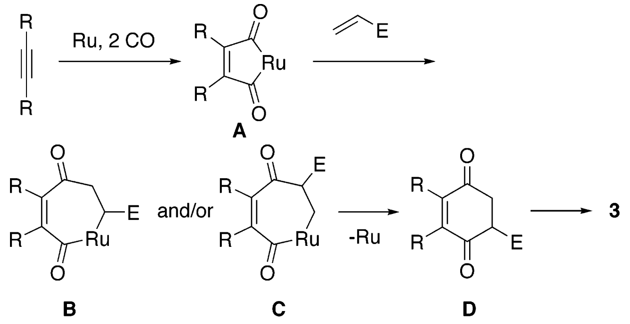
(3) (a) Thomson, R. H. *Naturally Occurring Quinones III*; Chapman and Hall: New York, 1987. (b) Weissermel, K.; Arpe, H.-J. *Industrial Organic Chemistry*, 4th ed.; Wiley-VCH: Weinheim, Germany, 2003; p 363.

hydroquinone, 5-acetyl-2,3-dipropyl-*p*-hydroquinone (**3a**), was obtained in 53% yield (entry 1). The use of DMF as a solvent resulted in the increase of the yield up to 65% (entry 2).[5] *N*-Methylpiperidine, which worked well for the reaction with 2-norbornenes as a solvent,[4] gave **3a** only in 24% yield with many undefined byproducts (entry 4). The reaction under higher CO pressure (40 atm) using DMF gave **3a** in somewhat lower yield (entry 5). Ruthenium complexes, such as [RuCl$_2$(CO)$_3$]$_2$, [RuCl$_2$(η^6-mesitylene)], CpRuCl(PPh$_3$)$_2$, and RuHCl(PPh$_3$)$_3$, also gave **3a**. However, the yields were low to modest (entries 6−9). Consequently, we found that [Cp*RuCl$_2$]$_2$ can effectively catalyze the reaction to give **3a** in 79% yield (entry 10).[6]

To explore the scope of the present reaction, several electron-deficient alkenes were subjected to the reaction conditions, in which [Cp*RuCl$_2$]$_2$ was used as the catalyst and DMF as the solvent. The results are summarized in Table 2. The reaction of **1a** with acrylonitrile (**2b**) and ethyl acrylate (**2c**) gave the corresponding hydroquinones, **3b** and **3c**, in good yield (entries 2 and 3). When acrylamide (**2d**) was used, the corresponding hydroquinone **3d** was obtained in 46% yield (entry 4). The reaction of acrolein (**2e**) gave 39% yield of 5-formylhydroquinone **3e** along with a small amount of decarbonylation product, 2,3-dipropyl-*p*-hydroquinone (**4**) (entry 5). We also examined unsymmetrically substituted alkynes, such as 2-hexyne (**1c**) and 1-acetoxy-3-hexyne (**1d**), which gave the corresponding hydroquinones as a mixture of regioisomers in 62 and 75% yield, respectively (entries 8 and 9). Methyl crotonate failed to react with **1a** and CO. Terminal alkynes, such as 1-hexyne, gave a complex mixture.[7]

A possible mechanism for the Ru-catalyzed [2 + 2 + 1 + 1] cocyclization reaction is summarized in Scheme 2. A maleoylruthenium complex **A** would be formed by the reaction of ruthenium with an alkyne and two molecules of carbon monoxide,[8] which would then react with an electron-deficient alkene to give seven-membered ruthenacycles **B** and/or **C**.[9] Reductive elimination to give **D**, followed by the enolization, would give the substituted hydroquinones **3**.

Scheme 2. Possible Mechanism of Cocyclization



In summary, we have developed a [2 + 2 + 1 + 1]-type cocyclization method for the synthesis of functionalized hydroquinones by [Cp*RuCl$_2$]$_2$-catalyzed cocyclization of alkynes, electron-deficient alkenes, and two molecules of carbon monoxide, in which [Cp*RuCl$_2$]$_2$ was used as an effective catalyst. Detailed mechanistic studies as well as further extension of the present cocyclization reaction are now ongoing in these laboratories.

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Supporting Information Available: General experimental procedure and spectral data for all products. This material is available free of charge via Internet at http://pubs.acs.org.

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(4) Suzuki, N.; Kondo, T.; Mitsudo, T. *Organometallics* **1998**, *17*, 766.

(5) It should be noted that the present conditions are not suitable for the reaction of 2-norbornene (35% yield).

(6) Typical procedure of [Cp*RuCl$_2$]$_2$-catalyzed cocyclization reactions leading to functionalized hydroquinones. A magnetic stirring bar, 4-octyne (**1a**, 58.3 mg, 0.53 mmol), methyl vinyl ketone (**2a**, 110 mg, 1.6 mmol), [Cp*RuCl$_2$]$_2$ (10.5 mg, 0.017 mmol), and DMF (2 mL) were placed in a 30 mL stainless steel autoclave. The autoclave was closed, purged three times with carbon monoxide, pressurized with CO (20 atm), and then heated at 140 °C for 20 h. After the reaction mixture was cooled to room temperature, gaseous materials were discharged. The reaction mixture was diluted with ether (50 mL) and washed with water. The aqueous layer was extracted with ether (2 × 30 mL). The combined organic layer was washed with water and dried over MgSO$_4$. After filtration, the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 5/1) to give the corresponding hydroquinone (**3a**, 99.3 mg, 79%) as a white solid.

(7) We also examined phenyl-substituted alkynes, such as diphenylacetylene and 1-phenyl-1-octyne. The former only gave a small amount of reduced product *cis*-stilbene, whereas the latter gave a complex mixture of the carbonylation products, which requires optimization of the reaction conditions.

(8) For recent examples of maleoylmetal complexes formed from an alkyne, two molecules of carbon monoxide, and a transition metal complex, see: (a) Cheng, M.-H.; Lee, G.-H.; Peng, S.-M.; Liu, R.-S. *Organometallics* **1991**, *10*, 3600. (b) Cheng, M.-H.; Syu, H.-G.; Lee, G.-H, Peng, S.-M.; Liu, R.-S. *Organometallics* **1993**, *12*, 108. (c) Mao, T.; Zhang, Z.; Washington, J.; Takats, J.; Jordan, R. B. *Organometallics* **1999**, *18*, 2331. (d) Barrow, M.; Cromhout, N. L.; Cunningham, D.; Manning, A. R.; McArdle, P. *J. Organomet. Chem.* **2000**, *612*, 61. (e) Barrow, M.; Cromhout, N. L.; Manning, A. R.; Gallagher, J. F. *J. Chem. Soc., Dalton Trans.* **2001**, 1352. (f) Elarraoui, A.; Ros. J.; Yáñez, R.; Solans, X.; Font-Bardia, M. *J. Organomet. Chem.* **2002**, *642*, 107.

(9) Reaction of maleoylmetal complexes with alkynes to form quinones has been extensively studied. Liebeskind, L. S.; Baysdon, S. L.; South, M. S.; Iyer, S.; Leeds, J. *Tetrahedron* **1985**, *41*, 5839 and references therein.