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Rhodium-catalyzed rapid synthesis of substituted phenols from cyclobutenones and alkynes or alkenes via C–C bond cleavage

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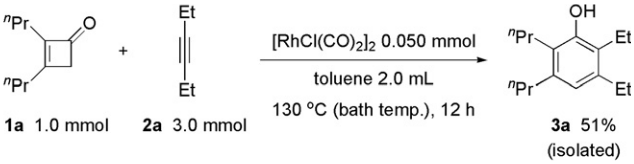
Abstract—A novel rhodium-catalyzed synthesis of substituted phenols by the ring-opening reaction of cyclobutenones with alkynes as well as electron-deficient alkenes has been developed. Both reactions involve C–C bond cleavage of cyclobutenones, and an (η^4-vinylketene)rhodium complex rather than a rhodacyclopentenone is considered to be a key intermediate.

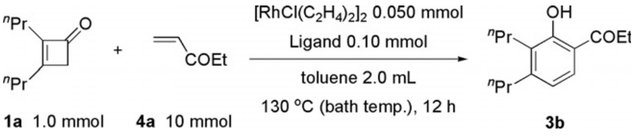
The reconstruction of new carbon skeletons after C–C bond cleavage, leading to the rapid and selective synthesis of novel organic molecules,[1] is an important goal of many recent studies in organic, organometallic, and industrial chemistry from an atom-economical perspective.[2] Recently, we developed the rhodium-catalyzed direct coupling of cyclobutenones with 2-norbornenes via C–C bond cleavage of cyclobutenones, to give cyclopentene (under an argon atmosphere) and cyclohexenone derivatives (under 30 atm of carbon monoxide pressure) in high yield, respectively.[3] This result prompted us to examine the reaction of cyclobutenones with alkynes and/or other alkenes to construct phenols. Although a pioneering study by Liebeskind and co-workers revealed that rhodacyclopentenones obtained by the stoichiometric reaction of $RhCl(PPh_3)_3$ with cyclobutenones are unreactive toward alkynes and in no case were any phenol products detected,[4] we found that an appropriate choice of the ligands enables the rhodium-catalyzed ring-opening reaction of cyclobutenones with alkynes to phenols. For example, the reaction of 2,3-dipropylcyclobutenone (**1a**) with 3-hexyne (**2a**) in the presence of a catalytic amount of $[RhCl(CO)_2]_2$ in toluene at 130 °C (bath temperature) for 12 h under an argon atmosphere gave the corresponding phenol, 2,3-diethyl-5,6-dipropylphenol (**3a**), in an isolated yield of 51%, Eq. 1.



(1)

Since a similar nickel-catalyzed synthesis of phenols from cyclobutenones and alkynes under mild reaction conditions has already been reported,[5] we next investigated the reaction of cyclobutenones with *alkenes*.[6] Fortunately, we succeeded in developing a direct method for the synthesis of 2-substituted phenols by the rhodium-catalyzed ring-opening reaction of cyclobutenones with electron-deficient *alkenes* via C–C bond cleavage, followed by dehydrogenation/isomerization.

First, the catalytic activity of several transition-metal complexes was examined in the synthesis of 2-propionyl-5,6-dipropylphenol (**3b**) by the ring-opening reaction of 2,3-dipropylcyclobutenone (**1a**) with ethyl vinyl ketone (**4a**), Eq. 2.



(2)

Keywords: Rhodium; Catalyst; Phenol; Cyclobutenone; C–C Bond cleavage.

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Among the catalysts examined, several rhodium complexes, such as $[RhCl(CO)_2]_2$ (**3b**, 47%), $[RhCl(C_2H_4)_2]_2$ (**3b**, 42%), and $[RhCl(1,5\text{-cyclooctadiene})]_2$ (**3b**, 41%), showed good catalytic activity. $[RhCl(cyclooctene)_2]_2$ (**3b**, 36%), $RhH(PPh_3)_4$ (**3b**, 32%), and $[Rh(OAc)_2]_2$ (**3b**, 15%) also showed moderate catalytic activity. Other rhodium complexes, such as $RhCl(PPh_3)_3$, $RhCl(CO)(PPh_3)_3$ and $RhH(CO)(PPh_3)_3$, and ruthenium complexes, such as $Ru(CO)_3(PPh_3)_2$, $RuCl_2(PPh_3)_3$ and $[RuCl_2(CO)_3]_2$, as well as $IrCl(CO)(PPh_3)_2$ and $Pd(PPh_3)_4$, were totally ineffective.

The effect of phosphorus ligands was examined in the $[RhCl(C_2H_4)_2]_2$-catalyzed synthesis of **3b** from **1a** and **4a**. As shown in Table 1, the concomitant use of $P(cyclo\text{-}C_6H_{11})_3$ ligand completely suppressed the formation of the dimer of **1a**[3] and dramatically increased the catalytic activity of $[RhCl(C_2H_4)_2]_2$ to give **3b** in the best yield of 75% (entry 2). Catalyst systems combined with other phosphorus ligands, such as P^nBu_3, $P(^nC_8H_{17})_3$, P^iPr_3, P^tBu_2Me, P^tBu_3, and PPh_3, showed moderate catalytic activity (entries 3–8). Bidentate phosphines, such as 1,3-bis(diphenylphosphino)propane (dppp) and 1,2-bis(diphenylphosphino)ethane (dppe), decreased the catalytic activity of $[RhCl(C_2H_4)_2]_2$, leading to lower yields of **3b** (entries 9 and 10). Phosphites, such as $P(OPh)_3$, and $P(OBu)_3$, were also ineffective (entries 11 and 12).

Consequently, when the reaction of 2,3-dipropylcyclobutenone (**1a**, 1.0 mmol) with ethyl vinyl ketone (**4a**, 10 mmol) was carried out in the presence of a catalytic amount of $[RhCl(C_2H_4)_2]_2$ (0.050 mmol) and $P(cyclo\text{-}C_6H_{11})_3$ (0.10 mmol) in toluene (2.0 mL) at 130 °C (bath temperature) for 12 h under an argon atmosphere, the corresponding substituted phenol, 2-propionyl-5,6-dipropylphenol (**3b**), was obtained in 75% yield (isolated yield, 65%; entry 2). No regioisomeric byproduct was obtained at all.

The results obtained from the reaction of several cyclobutenones (**1a**–**c**) with ethyl vinyl ketone (**4a**) under optimized reaction conditions are summarized in Table 2. Cyclobutenones bearing an *n*-propyl substituent (**1a**) and ethyl substituent (**1b**) as well as bicyclic cyclobutenone (**1c**) reacted smoothly with ethyl vinyl ketone (**4a**) to give the corresponding substituted phenols (**3b**–**d**) in good yields (entries 1–3). Cyclobutenone **1a** also reacted with other electron-deficient alkenes, such as propyl vinyl ketone (**4b**) and methyl acrylate (**4c**), to give the corresponding substituted phenols (**3e** and **3f**) in moderate isolated yields (entries 4 and 5). However, no phenols were obtained from the reactions of **1a** with acrylonitrile (**4d**) and *N*,*N*-dimethylacrylamide (**4e**), probably due to their high coordination ability to an active rhodium species.

Table 1. The effect of phosphorus ligands on the $[RhCl(C_2H_4)_2]_2$-catalyzed synthesis of **3b** from **1a** and **4a**[a]

Entry	Ligand	Yield of **3a**[b] (%)
1	—	42
2	$P(cyclo\text{-}C_6H_{11})_3$	75 (65)
3	P^nBu_3	71
4	$P(^nC_8H_{17})_3$	57
5	P^iPr_3	30
6	P^tBu_2Me	44
7	P^tBu_3	32
8	PPh_3	22
9[c]	dppp	27
10[d]	dppe	12
11	$P(OPh)_3$	16
12	$P(O^nBu)_3$	14

[a] **1a** (1.0 mmol), **4a** (10 mmol), $[RhCl(C_2H_4)_2]_2$ (0.050 mmol), phosphorus ligand (0.10 mmol as a P atom), and toluene (2.0 mL) at 130 °C (bath temperature) for 12 h under an argon atmosphere.

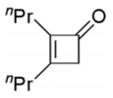
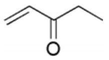
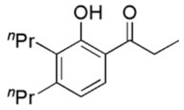
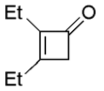
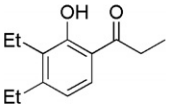
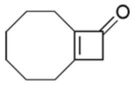
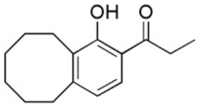
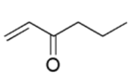
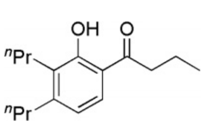
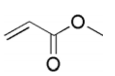
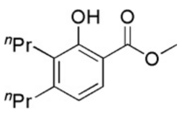
[b] GLC yield (isolated yield).

[c] 1,3-Bis(diphenylphosphino)propane.

[d] 1,2-Bis(diphenylphosphino)ethane.

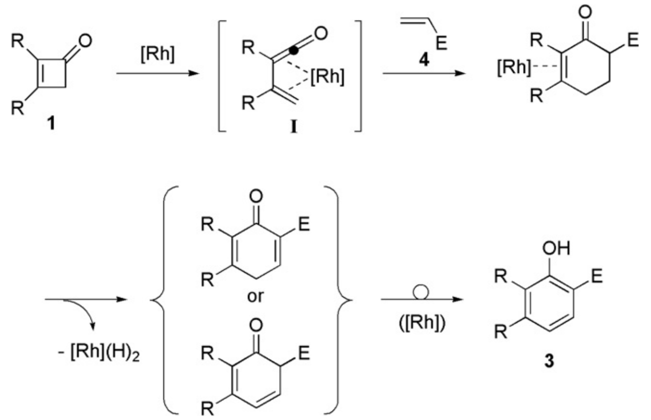
While the reaction mechanism is not yet clear, a possible mechanism is illustrated in Scheme 1. We believe that the oxidative addition of cyclobutenones (**1**) to an active rhodium center generated from $[RhCl(C_2H_4)_2]_2$ and $P(cyclo\text{-}C_6H_{11})_3$ would occur between a carbonyl and the α-carbon of cyclobutenone to give an (η^4-vinylketene)rhodium intermediate (**I**) rather than a rhoda-

Table 2. $[RhCl(C_2H_4)_2]_2$–$P(cyclo\text{-}C_6H_{11})_3$-Catalyzed synthesis of substituted phenols from cyclobutenones and electron-deficient alkenes[a]

Entry	Cyclobutenone (**1**)	Electron-deficient alkene (**4**)	Product of **3**[b] (%)
1	 **1a**	 **4a**	 **3b** 75 (65)
2	 **1b**	**4a**	 **3c** 73 (60)
3	 **1c**	**4a**	 **3d** (43)
4	**1a**	 **4b**	 **3e** 65 (41)
5	**1a**	 **4c**	 **3f** (40)

[a] Cyclobutenone **1** (1.0 mmol), electron-deficient alkene **4** (10.0 mmol), $[RhCl(C_2H_4)_2]_2$ (0.050 mmol), $P(cyclo\text{-}C_6H_{11})_3$ (0.10 mmol) and toulene (2.0 mL) at 130 °C (bath temperature) for 12 h under an argon atmosphere.

[b] Determined by GLC (figures in the parentheses are isolated yields).



Scheme 1. A possible mechanism for Rh-catalyzed synthesis of substituted phenols **3** from cyclobutenones **1** and electron-deficient alkenes **4**.

cyclopentenone intermediate (**II**) in the initial step.[4,7] The subsequent regioselective Diels–Alder-type reaction of an intermediate (**I**) with electron-deficient alkenes (**4**)[8] would give cyclohexenones, which are easily converted into the corresponding substituted phenols (**3**) by rapid dehydrogenation and isomerization.

In conclusion, we have developed the first rhodium-catalyzed direct and reconstructive synthesis of substituted phenols by the ring-opening reaction of cyclobutenones with alkynes and/or electron-deficient alkenes. The latter reaction is highly regioselective, and only 2-substituted phenols were obtained. In addition, since the alkenes used in this study are a readily available and inexpensive starting material relative to alkynes, the present method for the synthesis of phenols should be a highly useful and attractive process in organic, organometallic, and industrial chemistry. The isolation of key intermediates represented by an (η^4-vinylketene)-rhodium complex to elucidate the mechanism is currently under investigation.

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