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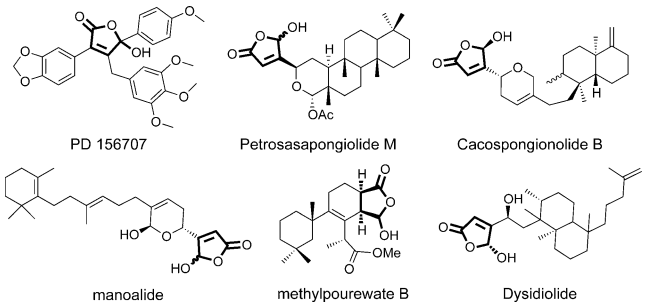
Intermolecular [2+2+1] Carbonylative Cycloaddition of Aldehydes with Alkynes, and Subsequent Oxidation to γ-Hydroxybutenolides by a Supported Ruthenium Catalyst

*Hiroki Miura, Kazuki Takeuchi, and Tetsuya Shishido**

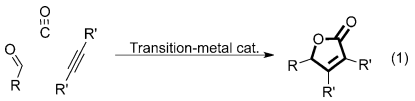
Abstract: *Intermolecular [2+2+1] carbonylative cycloaddition of aldehydes with alkynes and subsequent oxidation to γ-hydroxybutenolides is achieved using a supported ruthenium catalyst. A ceria-supported ruthenium catalyst promotes the reaction efficiently, even with an ambient pressure of CO or without external CO, thus giving the corresponding γ-hydroxybutenolide derivatives in good to high yields. Moreover this catalyst can be reused with no loss of activity.*

γ-Hydroxybutenolides are often found in a variety of natural products and artificial pharmaceutical materials (Scheme 1) which demonstrate an important class of bioactivities, such as anti-inflammatory, antitumor, anticancer, and antimicrobial activity.[1] In particular, PD 156707 has attracted much interest as a candidate motif for the endthelin A receptor antagonist.[2] Thus, considerable efforts have been devoted to the development of synthetic strategies which realize rapid and straightforward construction of highly functionalized γ-hydroxybutenolide moieties.



Scheme 1. Selected example of substituted γ-hydroxybutenolides which demonstrate bioactivities.

The key step in the syntheses of γ-hydroxybutenolides is the construction of the five-membered lactone scaffold. In this regard, [2+2+1] carbonylative cycloaddition of an aldehyde with alkyne functionalities, well-known as oxa-Pauson–Khand reactions [*oxa*-PKRs; Eq. (1)], are one of the most powerful tools leading to butenolide derivatives, thanks to their inherent 100% atom efficiency.[3] Such *oxa*-PKRs, however, have been limited to titanium-mediated or titanium-catalyzed,[4] molybdenum-mediated,[5] and ruthenium-catalyzed[6] intramolecular-type reactions which employ tethered ynals as substrates. Moreover, in many cases, the reactions have been conducted under pressurized CO conditions (>5 atm). Thus, the development of intermolecular [2+2+1] carbonylative cycloaddition of simple aldehyde and alkyne moieties with an ambient pressure of CO remains a challenging subject.



In contrast, the use of supported metal catalysts attract much attention from the perspective of green and sustainable chemistry because of their high recyclability and low contamination of metallic species into products after catalytic reactions.[7] We have reported that CeO_2-supported ruthenium catalysts were very effective for a series of organic transformations, including C–C bond-forming reactions.[8] These results encourage us to explore further application of Ru/CeO_2 catalysts for the construction of finely tuned carbon architectures.

Here, we demonstrate ruthenium-catalyzed intermolecular [2+2+1] carbonylative cycloaddition of aldehydes with alkynes, and subsequent oxidation which enables straightforward construction of γ-hydroxybutenolides. A ceria-supported ruthenium catalyst promotes the reaction efficiently, even with an ambient pressure of CO, or without external CO. Furthermore the CeO_2-supported ruthenium catalyst could be reused with no loss of activity.

The [2+2+1] carbonylative cycloaddition of *p*-anisaldehyde (**1a**) with diphenylacetylene (**2a**) in the presence of a catalytic amount of Ru/CeO_2 (2.5 mol% as Ru) together with Xantphos[9] under 1 atm of CO (balloon) took place to give the corresponding butenolide **3a** in 72% yield (GC; Scheme 2). Surprisingly, the prolonged stirring of the reaction mixture, including Ru/CeO_2 under air at room temperature, promoted oxidation of **3a**, which generated the γ-hydroxybutenolide **4a** as a stable product in 72% yield upon isolation.

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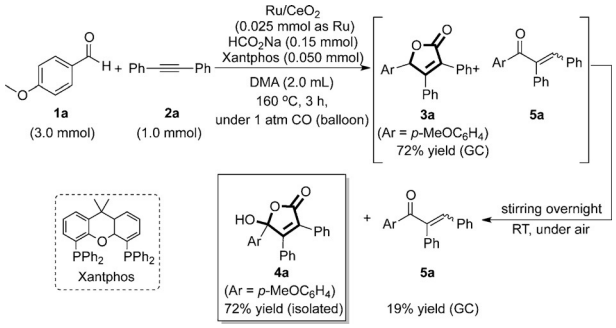


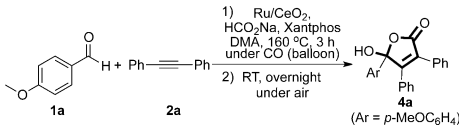
Scheme 2. Synthesis of the γ-hydroxybutenolide **4a** by the [2+2+1] carbonylative cycloaddition of an aldehyde and alkyne, with subsequent oxidation by Ru/CeO_2.

During the reaction, the hydroacylated product **5a** was also formed in 19% yield (GC) as a byproduct.[10]

Table 1 shows the results of the optimization of the reaction conditions.[11] Ru/CeO_2 gave a higher yield of **4a** than did $[Ru(acac)_3]$, $[\{RuCl_2(p\text{-cymene})\}_2]$, and $[Ru_3(CO)_{12}]$ (entries 1–4). This outcome is probably because of the macro-ligand nature of CeO_2, such as basic properties and steric effects, which enhance the selectivity and stability of active ruthenium species. When HCO_2Na is absent, the reaction with either Ru/CeO_2 or $[\{RuCl_2(p\text{-cymene})\}_2]$ resulted in no conversion of the substrates (entries 5 and 6). In contrast, a zero-valent ruthenium complex, namely $[Ru_3(CO)_{12}]$, showed moderate activity without HCO_2Na (entry 7), thus suggesting that the active species is a ruthenium(0) species, and that HCO_2Na works as a reductant to promote the transformation of high-valent ruthenium species into an active ruthenium(0) species, which is effective for the first step, the [2+2+1] cycloaddition.[8f,i,12] Ruthenium catalysts supported on SiO_2, Al_2O_3, TiO_2, and ZrO_2 showed no activities (entry 8).[13] Xantphos was also indispensable for the present reaction and the other phosphines listed in entries 9–12 were totally ineffective. No consumption of substrates was observed under pressurized CO conditions (entry 13). This observation implies that an excess of CO inhibits the coordination of the substrates to the active ruthenium center. The present Ru/CeO_2 catalytic system could be employed on a gram scale to furnish **4a** in a yield of 58% (2.08 g of **4a** was isolated; entry 14). Note that **3a**, formed through the [2+2+1] cycloaddition, was completely converted during overnight oxidation under air.

Under the optimized reaction conditions, a variety of γ-hydroxybutenolides was synthesized by the intermolecular [2+2+1] carbonylative cycloaddition of aldehydes with alkynes, and subsequent oxidation with the catalytic system of Ru/CeO_2, HCO_2Na, and Xantphos (Table 2). Note that byproducts were formed through hydrogenation and hydroacylation of alkynes in all the following cases (see below). The reaction of substituted aromatic aldehydes smoothly proceeded to give the corresponding γ-hydroxybutenolides (**4b**–**i**) in moderate to good yields. In contrast, the reaction of 2,4,6-trimethylaldehyde (**1p**) did not give the corresponding γ-hydroxybutenolide, while the hydroacylated product **5p** was obtained as a major product (Scheme 3).[8i] Symmetrical

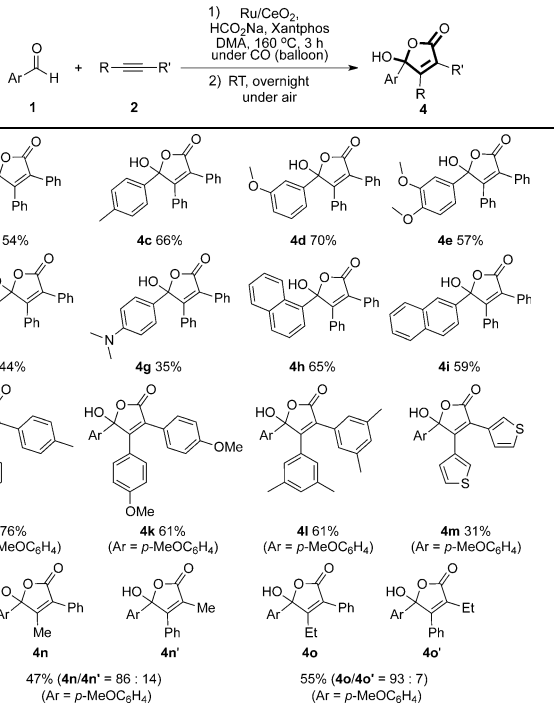
Table 1: Optimization of the reaction conditions.



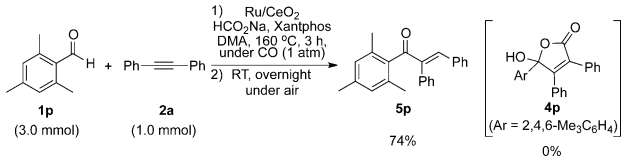
Entry	Variation from the standard reaction conditions[a]	Yield [%][b]
1	none	72
2	$[\{RuCl_2(p\text{-cymene})\}_2]$ in place of Ru/CeO_2	62
3	$[Ru(acac)_3]$ in place of Ru/CeO_2	50
4	$[Ru_3(CO)_{12}]$ in place of Ru/CeO_2	64
5	without HCO_2Na	0[c]
6	$[\{RuCl_2(p\text{-cymene})\}_2]$ in place of Ru/CeO_2, without HCO_2Na	0[c]
7	$[Ru_3(CO)_{12}]$ in place of Ru/CeO_2, without HCO_2Na	36
8	SiO_2-, Al_2O_3-, TiO_2-, or ZrO_2-supported Ru catalyst in place of Ru/CeO_2	0[c]
9	PPh_3 in place of Xantphos	0[c]
10	dppb in place of Xantphos	0[c]
11	dppf in place of Xantphos	0[c]
12	DPEphos in place of Xantphos	0[c]
13	CO (3 atm)[d]	0[c]
14	gram-scale reaction[e]	58

[a] Reaction conditions: 1) **1a** (3.0 mmol), **2a** (1.0 mmol), Ru/CeO_2 (125 mg, 2.5 mol% as Ru), HCO_2Na (0.15 mmol), Xantphos (0.10 mmol), DMA (2.0 mL), 160 °C, 3 h, CO (1 atm, balloon); 2) stirring overnight at RT under air. [b] Yield of the isolated product. [c] No conversion of **2a** was observed. [d] Reaction in a stainless steel autoclave. [e] Reaction run at 10 times the scale as that used in the standard reaction conditions.

Table 2: Scope with respect to the substrates.[a,b]



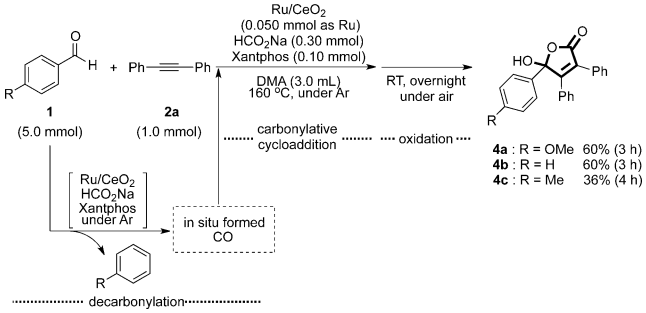
[a] Reaction conditions: 1) **1a** (3.0 mmol), **2a** (1.0 mmol), Ru/CeO_2 (125 mg, 2.5 mol% as Ru), HCO_2Na (0.15 mmol), Xantphos (0.10 mmol), DMA (2.0 mL), 160 °C, 3 h, CO (1 atm, balloon); 2) stirring overnight at RT under air. [b] Yield of the isolated product.



Scheme 3. Hydroacylation of the internal alkyne **2a** with **1p** by Ru/CeO_2. DMA = *N*,*N*-dimethylacetamide.

internal alkynes gave the corresponding products (**4j–l;** Table 2) in good isolated yields. The reaction of bis(thienyl)acetylene occurred to produce **4m** in 31% yield. Asymmetrical internal alkynes gave **4n**, **4n′** and **4o**, **4o′** as mixtures of regioisomers, with the ratio of 86:14 and 93:7, respectively. In both cases, the products where aryl substituents are located at the α-position to a carbonyl group were obtained as major isomers. Unfortunately, unsymmetrical internal alkynes with *tert*-butyl, trimethylsilyl, or alkoxycarbonyl groups could not participate in the present catalytic reaction.

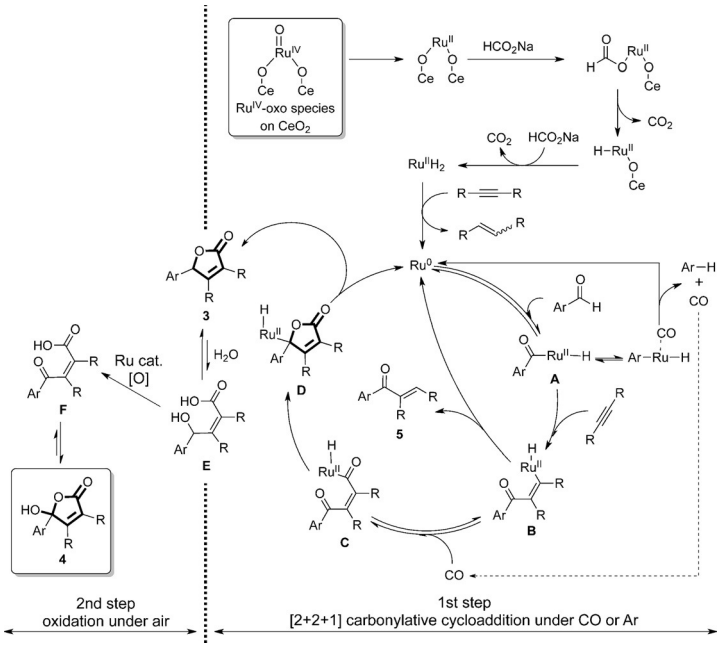
Molecular CO can be drawn from aldehydes by transition metal catalyzed decarbonylation.[14] The present active ruthenium species could also act as an effective decarbonylation catalyst to produce molecular CO, which can be utilized as an in situ formed C_1 source in the [2+2+1] carbonylative cycloaddition.[15] The desired products **4a–c** were obtained in moderate to good yields without external addition of gaseous CO by cascade decarbonylation, carbonylative cycloaddition, and oxidation (Scheme 4). Although it was previously reported that $[Ru_3(CO)_{12}]$-catalyzed carbonylative cycloadditions developed by Chatani and co-workers prefer CO pressurized conditions



Scheme 4. [2+2+1] carbonylative cycloaddition of aldehydes and alkynes without using external CO.

(> 5 atm),[3,6] the present reaction proceeded on Ru/CeO_2 even under a low concentration of CO. This outcome implies that the catalytic cycle in the present reaction is different from that proceeding via the formation of oxaruthenacycle intermediate.[3,6]

A possible reaction route to the formation of γ-hydroxybutenolides is shown in Scheme 5. Our previous study revealed the presence of isolated Ru^{IV}-oxo species on the surface of CeO_2, and it is transformed into a Ru^0 species upon treatment with HCO_2Na and alkyne in DMA.[8f,i,12] The [2+2+1] cycloaddition is initiated with the cleavage of the formyl C–H bond of the aldehyde by an in situ generated Ru^0 species to give the acyl-Ru^{II} intermediate **A**. Subsequently, insertion of the alkyne into the Ru–C bond of **A** leads to **B**. The hydroacylated product **5** can be formed through the reductive elimination from **B**. In contrast, when CO is present in the reaction system, insertion of CO into the Ru–C bond of **B** takes place to afford **C**, which undergoes intramolecular

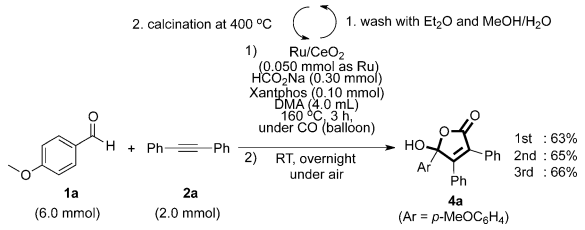


Scheme 5. Possible reaction route to γ-hydroxybutenolides.

cyclization leading to **D**. In the case of 2,4,6-trimethylbenzaldehyde (**1p**), the cyclization step must be suppressed by the steric repulsion of the methyl substituents at the *ortho*-position of aromatic aldehydes. The active Ru^0 species regenerates through reductive elimination of **D** together with the formation of the butenolide **3**. After changing the reaction atmosphere to open air, oxidation of γ-hydroxy acrylic acids (**E**), formed through hydrolysis of **3**, is promoted by the ruthenium catalyst with molecular oxygen to provide the γ-keto acrylic acids **F**. Finally tautomerization of **F** gives γ-hydroxybutenolides (**4**) as final products.[16] However, the oxidation route to **4** by the direct oxidation of the $C(sp^3)$–H bond of **3** has not been excluded.

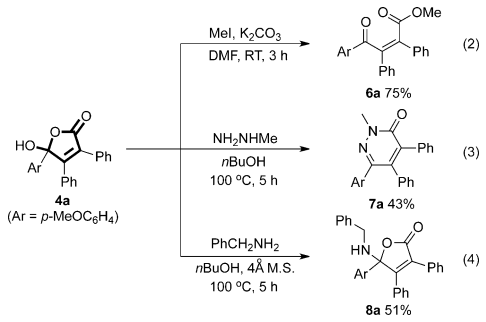
The most advantageous feature of supported catalysts is their high recyclability. The Ru/CeO_2 catalyst was successfully applied to the present reactions to produce **4a** without any decrease in the yields for at least three cycles (Scheme 6).

Although γ-hydroxybutenolides themselves are of great value in the field of biochemistry and pharmaceutical chemistry, further chemical transformation can convert them into various useful compounds. The treatment of **4a** with methyl iodide gave the α,β-unsaturated-γ-keto ester **6a** [Eq. (2); DMF = *N*,*N*-dimethylformamide].[17] The reaction with methylhydrazine produced the substituted pyridazinone derivative **7a** [Eq. (3)], which shows various important



Scheme 6. Recycling of Ru/CeO_2 catalyst.

pharmacological activities, such as fungicidal, antibacterial, anti-hypertensive, and anti-inflammatory properties.[18] Also, the γ-amino-butenolide **8a** was readily prepared by the treatment of **4a** with a simple primary amine [Eq. (4); M.S. = molecular sieves].



In summary, we have developed a novel synthetic route for γ-hydroxybutenolides by ruthenium-catalyzed intermolecular [2+2+1] carbonylative cycloaddition of aldehydes with alkynes, followed by oxidation. A ceria-supported ruthenium catalyst promotes the reaction, even with an ambient pressure of CO, or without external CO, thus giving the corresponding γ-hydroxybutenolides in good to high yields. It is noteworthy that the present catalytic system showed excellent environmental compatibility thanks to high recyclability of the Ru/CeO_2 catalyst. Further synthetic application of the Ru/CeO_2-catalyzed carbonylative reactions and mechanistic investigations are underway in our laboratory.

Acknowledgments

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Keywords: carbonylation · cycloaddition · heterocycles · ruthenium · supported catalyst

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[9] Abbreviations: Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; acac = acetylacetonate, dppb = 1,4-bis(diphenylphosphino)butane; dppf = 1,1′-bis-(diphenylphosphino)-ferrocene; DPEphos = 2,2′-bis(diphenylphosphino)diphenyl ether.

[10] Hydroacylation mainly occurred when an excess amount of alkyne was employed under an Ar atmosphere for the $RuCeO_2$/HCO_2Na/Xantphos system.[8i]

[11] More detailed results of the optimization of the reaction conditions are shown in the Supporting Information.

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