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Unusual Olefinic C–H Functionalization of Simple Chalcones Toward Aurones Enabled by the Rational Design of a Function-Integrated Heterogeneous Catalyst

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ABSTRACT

Flavonoids, which are ubiquitous plant secondary metabolites obtained from chalcones, mostly possess 6-membered C-ring derived from 6-endo-trig cyclization of chalcones. However, aurones, which are a class of flavonoids that rarely occur naturally, possess unusual 5-membered C-ring biosynthesized from chalcones by mainly performing B ring oxidation. Therefore, the chemical catalytic transformation from simple chalcones into aurones is attractive, because it overcomes the drawback of known limited enzyme catalysis. The catalytic transformation, however, has not yet been reported because of the preferential 6-membered ring formation as with the biosynthesis and the need for rare intramolecular olefinic C-H functionalization. Here, we developed the catalytic olefinic C-H functionalization of simple chalcones toward various aurones enabled by the rational design of a function-integrated heterogeneous catalyst—a Pd-on-Au bimetallic nanoparticle catalyst supported on CeO_2 —using O_2 in the air as the sole oxidant without any additives. In this system, the four conditions that were required for the challenging transformation toward aurones were achieved by the respective components of the catalyst—a) a supported Pd catalyst: a catalyst for the olefinic C-H functionalization of chalcones toward aurones, b) an Au promoter: an improvement in the catalytic activity by stabilizing Pd(0), c) a CeO₂ support: the inhibition of the 6-endo-trig cyclization utilizing the adsorption of chalcones, and d) a Pd-on-Au structure: the inhibition of Au-catalyzed flavone synthesis. This catalytic transformation will promote not only the pharmaceutical study of aurones but also the rational design of a heterogeneous catalyst for the development of organic reactions that are not yet realized by homogeneous catalysts or biocatalyst

KEYWORDS

C-H functionalization, heterogeneous catalyst, palladium, gold, bimetallic nanoparticle, ceria,

chalcone, aurone

Flavonoids—ubiquitous plant secondary metabolites possessing a $C_6-C_3-C_6$ skeleton, which originates from chalcones (2-benzylidene-2'-hydroxyacetophenone and its derivatives)—exhibit various biological activities such as anti-oxidant, anti-oncogenic, anti-inflammatory, cardiovascular action, and so on.¹ Almost all of the flavonoids possess 6-membered C-ring that was derived from flavanone through 6-*endo-trig* cyclization of the chalcones that were easily catalyzed by chalcone isomerase (CHI) (Figure 1, I).¹

However, aurones (2-benzylidene-coumaran-3-one and its derivatives), a class of minor flavonoids naturally that occur in limited plants such as *Antirrhinum majus* and *Cosmos*, possess an unusual 5-membered C-ring because of an exceptional mechanism (Figure 1, 1).^{1,2} Aurones are biosynthesized directly from chalcones *via* the oxidation of B-rings^{2a} mainly by polyphenol oxidases (PPO), such as aureusidin synthase (AmAS1)^{2b,c} and aurone synthase (AUS1)^{2d}, or by peroxidases (PRX), such as MtPRXs.^{2e,f} Therefore, the chemical catalytic transformation from simple chalcones into aurones that do not occur naturally is attractive, which overcomes the drawback of known limited enzyme catalysis. Further, the above-mentioned transformation is one of the most useful synthetic methods to produce aurones as compared with that of the other synthetic methods³⁻⁶ because chalcones are easily available through synthesis from simple aldehydes and ketones *via* the Claisen–Schmidt condensation or by extracting from the plants. Recently, various biological activities of aurones have also been revealed along with that of other flavonoids,^{2g-k} which have

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elevated the importance of the transformation into novel aurones in terms of their pharmaceutical application.

However, the literature contains no report about the catalytic transformation from simple chalcones into aurones.⁷ For one thing, the control of 5-exo/6-endo-trig cyclization of chalcones is quite difficult; only 6-endo-trig cyclization-i.e. intramolecular oxa-Michael addition-proceeds to produce flavanones⁸ that is similar to the biosynthesis of flavonoids in nature; to the best of our knowledge, the literature contains no reports about the 5-exo-trig cyclization. Thus, the direct oxidative cyclization of chalcones, 5-membered/6-membered oxidative cyclization, is also difficult to control; 6-membered oxidative cyclization dominantly proceeds to produce flavones via 6-endo-trig cyclization (Figure 1, II-a).9 Only when (super)stoichiometric amounts of metal oxidants, typically Hg(OAc)₂, are used, does the 5-membered oxidative cyclization into aurones proceed because of the intermediate formed by the coordination of a chalcone to a metal species to inhibit the 6-membered cyclization (Figure 1, II-a).⁶ For another thing, the catalytic transformation from chalcones into aurones is regarded as "intramolecular α -olefinic C-H functionalization" (including formal C-H functionalization; in this manuscript, an olefinic C-H bond closer to a directing group is defined as α -olefinic C–H), which has been rarely reported. To the best of our knowledge, a formal intramolecular α -olefinic C-H functionalization even via Pd-catalyzed Wacker-type cyclization has never been reported.¹⁰ Recently, a Rh-catalyzed pioneering formal intramolecular α-olefinic C-H functionalization of β -substituted-2'-hydroxyacrylophenone was reported by Glorius *et al*; however, the system could not be applied to the transformation of chalcones into aurones that was observed in

the literature (Figure 1, II-b).¹¹ As for intramolecular directed α -olefinic C–H functionalization, a recent report by Yu *et al.* to synthesize 4-imino- β -lactams was observed to be pioneering,¹² while numerous examples of β -olefinic C–H functionalization have been reported.¹³ Therefore, the development of innovative multifunctional catalysts to control difficult cyclization and rare C–H functionalization is indispensable to achieve this challenging catalytic transformation into aurones.

Novel difficult organic transformations have been mostly developed on the basis of homogeneous catalysts; however, in terms of the integration of multiple functions to achieve unusual reactions, heterogeneous catalysts also exhibit considerable potential. Indeed, as for comparatively typical organic syntheses, the literature contains several reports about tandem reactions and concerted catalysis *via* function-integrated heterogeneous catalysts.¹⁴ Heterogeneous catalysts are mainly composed of a) a main active species for the target reactions, b) a promoter for the catalysis, and c) a support to disperse and stabilize the active species.¹⁵ Furthermore, the design of d) the morphology of these three components enables control of catalytic activity, selectivity, and longevity, which can lead to a novel unique catalysis that differs from homogeneous catalysis.

Herein, through the rational design of a function-integrated heterogeneous catalyst based on the aforementioned components, four requirements for the catalytic transformation of chalcones into aurones were achieved—a) a supported Pd catalyst: a catalyst for α -olefinic C–H functionalization of chalcones, b) an Au promoter: an improvement of the catalytic activity by the stabilization of Pd(0), c) a CeO₂ support: the inhibition of the 6-*endo-trig* cyclization utilizing the adsorption of chalcones, and d) a Pd-on-Au structure: the inhibition of Au-catalyzed flavone

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synthesis (Figure 1, III). That is, we have successfully developed an unusual catalytic transformation from simple chalcones into aurones over Pd-on-Au bimetallic nanoparticles supported on CeO_2 (Pd/Au/CeO₂) using O₂ in air as the sole oxidant without any additives for the first time.



for transformation into aurones, b) improvement of catalytic activity, c) inhibition of 6-endo-trig cyclization, and d) inhibition of flavone synthesis.

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RESULTS AND DISCUSSION

Catalyst Preparation and Characterization. Hutchings et al. reported Au@Pd core-shell structures formed from Au and Pd species impregnated on metal oxides by calcination at approximately 200–400 °C.¹⁶ Referring to the report, in the present work, we prepared Pd/Au/CeO₂ through calcination at 300 °C for 2 h after Au and Pd species were supported on CeO₂ separately in this order via a deposition-precipitation method (see Experimental Section). Transmission electron microscopy (TEM) images of the Pd/Au/CeO₂ revealed that the metal species were dispersedly supported on CeO₂ as nanoparticles with a mean diameter of 2.2 nm (σ = 1.0 nm) (Figure 2a,b). The high-angle annular dark-field scanning transmission electron microscopy (HAADF-STEM) image in Figure 2c and STEM energy-dispersive X-ray spectroscopy (STEM-EDS) mapping images (Figure 2d–f) indicate that the nanoparticles consisted of both Au and Pd. Each particle observed by HAADF-STEM possessed almost the same structure, though clear direct observation of the Pd-on-Au structure was quite difficult because of the small nanoparticle size (Figure S1). In addition, X-ray photoelectron spectroscopy (XPS) spectra of the freshly prepared Pd/Au/CeO₂ catalyst indicate a Pd valence of II and an Au valence of 0 (Figure 2g,h). Given the aforementioned results, the proposed structure of Pd oxides covering the surface of Au nanoparticles is valid. According to the X-ray diffraction (XRD) (Figure S2) and Ce L_{III} -edge X-ray absorption near edge structure (XANES) analyses (Figure S3), the structure of the CeO₂ support was not affected by the preparation. Thus, the Pd-on-Au bimetallic nanoparticle catalyst supported on CeO₂ was successfully prepared.



Figure 2. Characterization of Pd/Au/CeO₂: a), b) TEM images and nanoparticle size distributions of Pd/Au/CeO₂ (mean diameter: 2.2 nm, σ = 1.0 nm). The size distributions were determined using 200 particles; c) HAADF-STEM image and STEM-EDS mapping images of Pd/Au/CeO₂, showing the distributions of d) Pd (yellow), e) Au (magenta) and f) Au and Pd together; g), h) XPS spectra of Pd/Au/CeO₂ around the Pd 3d region and Au 4f region, respectively; peak positions were calibrated using the C 1s peak (284.2 eV).

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Catalyst Design and Optimization of Conditions for Aurone Synthesis. We attempted the transformation from 2'-hydroxychalcone (1a) into aurone (2a) using various catalysts in butyl acetate (BuOAc) at 100 °C under an open air atmosphere (Table 1). Although homogeneous Pd species catalytically produced 2a, the yield was not satisfactory (entry 1, Table 1); the production of 2a stopped in the middle with the formation of Pd black (Figure S4), and the formation of flavanone (4a) could not be suppressed. To stabilize Pd species and to inhibit the 6-endo-trig cyclization, we prepared supported Pd catalysts (represented as Pd/support). Pd/Al₂O₃ and Pd/TiO₂ effectively increased the 2a yield, although flavanone 4a was still formed to some extent (entries 3 and 4, Table 1). Pd/CeO₂ effectively inhibited 4a production; however, 2a was obtained in a low yield (entry 2 vs entry 11, Table 1). The inhibition of 4a was possibly due to the coordination of phenoxide species derived from 1a toward Ce species, analogous to the typical aurone synthesis using stoichiometric reagents such as Hg(OAc)₂.⁶ In fact, when **1a** and the CeO₂ support were mixed under the same conditions described in Table 1, the CeO_2 support was colored, as revealed by both its appearance and its DR UV-Vis spectrum, suggesting that the phenoxide species derived from 1a was adsorbed onto CeO₂ (Figure S5).¹⁷ When only the CeO₂ support was used, **2a** was not produced at all (entry 1, Table S1). Among the other metal catalysts (Au, Cu, Ru, Rh, and Ni) supported on CeO₂, only Au showed the catalytic activity toward the synthesis of 2a (entry 5, Table 1 and entries 2-5, Table S1); however, the selectivity toward 2a was remarkably low because of the dominant formation of flavone (3a) catalyzed by Au.^{9c} Bimetallic nanoparticles composed of Pd and the other metal species (i.e. Pt-Pd, Cu-Pd, Rh-Pd, Ni-Pd, Pb-Pd, and Zn-Pd) supported on CeO₂ did not

improve the **2a** yield (entries 6–12, Table S1). Exceptionally, Au–Pd bimetallic nanoparticles supported on CeO₂ (Au–Pd/CeO₂) boosted the production of **2a** concomitantly with considerable **3a** production by Au catalysis (entry 6, Table 1). The physical mixture of Au/CeO₂ and Pd/CeO₂ also promoted the production of **2a**; however, the yield was not comparable to that achieved using Au–Pd/CeO₂ and **3a** production was dominant because of the bare Au catalyst (entry 7, Table 1). Thus, the Pd-on-Au bimetallic nanoparticle catalyst supported on CeO₂ (Pd/Au/CeO₂) was designed to retain the Au promotion effect while inhibiting the Au catalysis toward **3a** production; this catalyst resulted in a high yield of and high selectivity toward **2a** (entry 8, Table 1).¹⁸ The inhibition effect of Pd/Au/CeO₂ on the production of **3a** was also observed when the reaction was carried out starting from **4a** instead of **2a** (Figure S6).

The effect of solvents was also very significant (Table S2). In low-polarity solvents such as toluene and diglyme, the production of 3a and 4a was substantially suppressed; however, the yields of 2a were low. In polar solvents such as alcohols, *N*,*N*-dimethylacetamide (DMA), and *N*,*N*-dimethylformamide (DMF), the yields of 2a were comparably high; however, considerable amounts of 3a and 4a were produced. BuOAc was the most suitable solvent for the efficient transformation into 2a with simultaneous suppression of 3a and 4a production. With optimization of the reaction temperature (Table S3), the ratio of Au and Pd (Figure S8), and the amount of catalysts, the yield of 2a reached 79% (entry 9, Table 1). Under an Ar atmosphere, 2a was hardly obtained, which revealed that O₂ in air functioned as the sole oxidant in this system (entry 10, Table 1).

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Table 1.	Effect	of	catalysts	on	the	transformation	from	2'-hydroxychalcone (1a) in	ito a	aurone
$(2a)^a$										

O OH 1a			O J Ja		0 0 4a
Fntry	Catalyst -	Conv. (%)	Y	ield (%	6)
Lintry	Catalyst	1a	2a	3a	4 a
1	Pd(TFA) ₂	38	12	2	16
2^b	Pd/CeO ₂	7	3	<1	4
3^b	Pd/TiO ₂	37	19	1	13
4^b	Pd/Al ₂ O ₃	47	16	3	25
5	Au/CeO ₂	>99	6	80	8
6	Au-Pd/CeO ₂	90	52	22	8
7	$Au/CeO_2 + Pd/CeO_2$	94	32	51	14
8	Pd/Au/CeO ₂	60	46	6	9
9 ^c	Pd/Au/CeO ₂	94	79	11	5
$10^{c,d}$	Pd/Au/CeO ₂	21	1	<1	13
11	None	16	<1	<1	16

^{*a*}Reaction conditions: **1a** (0.3 mmol), catalyst (Au and/or Pd: 2 mol%), BuOAc (2 mL), open air (1 atm), 100 °C, 24 h. Yields and conversions were determined by GC. ^{*b*}Supported Pd catalyst (50 mg, Pd: 1 mol%). ^{*c*}Catalyst (100 mg, Au: 5 mol%, Pd: 5 mol%). ^{*d*}Under Ar (1 atm). TFA = trifluoroacetate.

Heterogeneous Catalysis and Catalyst Reuse. To verify whether the observed catalytic reaction occurred on solid Pd/Au/CeO₂ or arose from leached metal species (Au and/or Pd) in the solution, Pd/Au/CeO₂ was removed by hot filtration during the reaction and the reaction was again carried out with the filtrate under the same conditions. The production of 2a completely stopped with the removal of Pd/Au/CeO₂ (Figure S8). In addition, Au and Pd species in the filtrate after the reaction were not detected by inductively coupled plasma atomic emission spectroscopy (ICP-AES) (Au: <0.003%, Pd: <0.02%). Therefore, the observed catalysis to perform the current transformation into aurones is truly heterogeneous. After the reaction under the optimized conditions, Pd/Au/CeO₂ could be readily retrieved from the reaction mixture by simple filtration. The retrieved Pd/Au/CeO₂ catalyst could be reused without a severe loss of its catalytic activity after it was calcined at 300 °C for 2 h, although the catalytic activity decreased when the calcination was not performed (Figure S9). TEM observations suggested that the size of the nanoparticles slightly increased during the reaction and was not affected by the calcination (Figure S10). Thus, the activity loss without calcination in the second reaction was not caused by an increase in nanoparticle size. XRD patterns and FT-IR spectra revealed no change of the basic structure of CeO₂ (Figures S11 and S12). However, in the FT-IR spectra collected after the reaction, peaks were observed at 1456 $\rm cm^{-1}$ and 1418 $\rm cm^{-1}$, which are possibly attributable to phenyl-ring stretching vibrations. These peaks disappeared after the catalyst was calcined at 300 °C. On the basis of these results, the adsorption of organic compounds onto the catalyst was likely the main reason for the loss of catalytic activity when the recovered catalyst was not calcined.

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Substrate Scope and Limitation. We examined the scope of the present Pd/Au/CeO₂-catalyzed transformation into aurones. Under the optimized reaction conditions, various aurones could be synthesized in a (Z)-selective fashion starting from simple chalcones (Table 2). The desired products were isolated by simple column chromatography on silica gel (see Experimental Section).¹⁹ The conversions of chalcones (1) and the yields of aurones (2), flavones (3), and flavanones (4) determined by gas chromatography (GC) are summarized in Table S4. When 2'-hydroxychalcones substituted with a methoxy group at their 2-, 3-, or 4-position were used as the substrates, the corresponding aurones (2b-2d) were synthesized. In the case of 2'-hydroxy-4-methylchalcone, 4'-methylaurone (2e) was obtained without benzylic oxidation of the methyl group. The chalcone with a 2-naphthyl group as the B ring was converted into the corresponding aurone (2f). The use of chalcones with various substituents at these Arings was also possible (2g-2j). In particular, 5'-fluoro-2'-hydroxychalcone was efficiently transformed into the corresponding aurone with a fluoro group (2g), which is an important group in the pharmaceutical field.²⁰ Thus, a novel aurone with potential medicinal applications, e.g. 5-fluoro-3'-methoxyaurone (2k), was also successfully synthesized. In addition, as a demonstration of using plant-derived substrates, we used flavokavain A (2'-hydroxy-4,4',6'-trimethoxychalcone), which is a flavonoid extracted from kava plants, as the substrate to obtain the corresponding aurone efficiently (21). However, this system was inapplicable to some substrates (2m-2o), possibly because their hydroxy groups could not easily access the Pd catalysts coordinated by the other groups.



^{*a*}Reaction conditions: **1** (0.3 mmol), Pd/Au/CeO₂ (100 mg, Au: 5 mol%, Pd: 5 mol%), BuOAc (2 mL), open air (1 atm), 100 °C, 24 h. Ratio of $\mathbf{2} = \mathbf{2} \times 100/(\mathbf{2} + \mathbf{3} + \mathbf{4})$ (%). The *E/Z* ratios were determined by GC analysis using biphenyl as an internal standard. The GC yields including the (*E*) isomer are shown. The values in parentheses are the isolated yields of the (*Z*) isomer. ^{*b*}48 h. ^{*c*}Pd/Au/CeO₂ (200 mg, Au: 9 mol%, Pd: 9 mol%). ^{*d*}50 h. ^{*e*}DMA (2 mL). ^{*f*}The isolated yield including the (*E*) isomer.

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Mechanistic Studies. The present transformation into aurones possibly proceeds through one of the following three paths (Scheme 1): directed α -olefinic C–H activation/reductive elimination (Path A), migratory insertion/ β -hydride elimination (Path B), or single electron transfer (SET)/radical cyclization/hydrogen-atom transfer (HAT) (Path C).²¹ The directed α -olefinic C–H activation included in Path A has rarely been reported;¹² however, the reductive elimination from the 6-membered palladacycle was the major reaction mechanism proposed in reported aurone syntheses from ynones.³ The reaction in Path B is well known as the Wacker-type cyclization;¹⁰ however, a formal intramolecular α -olefinic C–H functionalization *via* Pd-catalyzed Wacker-type cyclization has, to our knowledge, never been reported. Path C was declared in previous reports for aurone synthesis using a stoichiometric oxidant such as Pb(OAc)₄ or Mn(OAc)₃.^{6d,e}



Scheme 1. Possible paths of transformation from chalcones into aurones.

First, to verify whether a radical species is involved in this system, we carried out the reaction under the optimized conditions in the presence of an equimolecular amount of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) as a radical scavenger with respect to **1a** (Figure S13). The production rates of **2a** from **1a** did not decrease, indicating that radical species are irrelevant to this reaction; thus, Path C was excluded.

Next, to verify whether the reaction proceeds through Path A or Path B, we conducted the following control experiments (Figure 3): a) the reaction using $[\alpha$ -D]-2'-hydroxychalcone ($[\alpha$ -D]-1a) or $[\beta$ -D]-2'-hydroxychalcone ($[\beta$ -D]-1a) as the substrate to confirm a scrambling of deuterium atoms; b) isomerization of (*Z*)-aurone; c) oxidative cyclization of 2-allyl phenol and the reaction of 1a under the reported Wacker-type cyclization conditions;^{10a} and d) oxidative cyclization of 2-allyl phenol and the reaction of 1a under the present aurone synthesis conditions.

If the β -hydride elimination included in Path B occurs, the deuterium atoms would likely be scrambled between the aurones and Pd catalysts to produce partially D-labeled or non-labeled aurones when using [α -D]-1a or [β -D]-1a, respectively (Figure 3a). ¹H NMR analyses of the reaction solutions after the reactions indicated no scrambling of the deuterium atoms in this system (Figure S14)—hence, the existence of Path B cannot be confirmed. If reductive elimination included in Path A occurs, only (*Z*)-aurone should be produced. In the present system, the aurone was obtained in a (*Z*)-selective fashion, whereas small amounts of (*E*)-aurones were produced in the case of several substrates (E/Z = 1/99-7/93), which are derived from β -hydride elimination included in Path B or natural isomerization of (*Z*)-aurones.^{3d} The (*Z*)-isomer of **2a** was treated under the

optimized reaction conditions for 24 h, resulting in isomerization into the (*E*)-isomer whose ratio was approximately the same as that of the product synthesized from **1a** (Figure 3b). Thus, the small amounts of (*E*)-isomers are possibly produced by isomerization after the (*Z*)-selective aurone formation through Path A. As previously reported,^{10a} the oxidative cyclization of 2-allyl phenol efficiently proceeded reproducibly under the Wacker-type cyclization conditions using PdCl₂. The production of **2a** from **1a**, however, did not proceed at all under the Wacker-type cyclization conditions (Figure 3c). By contrast, under the aurone synthesis conditions using Pd/Au/CeO₂ in DMA, **2a** was produced from **1a**, whereas the Wacker-type cyclization of 2-allyl phenol hardly proceeded (Figure 3d).

On the basis of the aforementioned results, the present transformation from chalcones into aurones likely proceeds through Path A (Figure 3e). After the coordination of deprotonated 1 to the Pd center, intramolecular olefinic α -C–H activation directed by the phenoxide group occurs to produce a 6-membered palladacycle. Then, **2** is produced through reductive elimination from the palladacycle with concomitant formation of a reduced Pd species, *e.g.*, Pd(0), which is then re-oxidized by O₂ in air to complete the catalytic cycle. Under an O₂ atmosphere instead of an open air atmosphere, the production rate of **2a** increased (Figure S15). Moreover, as shown in Figure S13, TEMPO possibly worked as the re-oxidant of the reduced Pd species to promote the production rate of **2a**, although only TEMPO did not produce **2a** at all.^{9c,22} These results suggest that the re-oxidation of the Pd species is included in the turnover-limiting step of the present transformation into aurones under an open air atmosphere.

Finally, to demonstrate the effect of Au, we measured the reaction profiles for the transformation from **1a** into **2a** using Pd/CeO₂ or Pd/Au/CeO₂ under an open air atmosphere or an O₂ atmosphere (Figure S16). Compared with the catalyst with only Pd, that with coexisting Pd and Au exhibited improved catalytic activity and catalyst longevity. Moreover, in the absence of Au, the production rate of **2a** was independent of the O₂ partial pressure. XPS spectra revealed that Pd(II) species were stabilized in Pd/CeO₂ (Figure S17), which is consistent with previous reports²³ indicating that the reductive elimination step is difficult to induce. By contrast, when Pd/Au/CeO₂ was used, as previously mentioned, the re-oxidation of the reduced Pd species was included in the turnover-limiting step. Furthermore, Pd(0) species considerably formed in Pd/Au/CeO₂ after the reaction, whereas no Pd(0) species were present before the reaction (Figure S18). Therefore, Au species likely contributed to the stabilization of Pd(0)²⁴ during the reaction to promote the reductive elimination step.



Figure 3. Overview of the mechanistic studies on the transformation into aurones: a) Scrambling of deuterium using $[\alpha$ -D]-1a or $[\beta$ -D]-1a as a substrate under the optimized reaction conditions; b) Isomerization of (*Z*)-aurone under the optimized reaction conditions; c) Oxidative cyclization of 2-allyl phenol or 1a under the reported Wacker-type cyclization conditions as shown in the figure; d) Oxidative cyclization of 2-allyl phenol or 1a on the aurone synthesis conditions as shown in the figure; e) Proposed mechanism of transformation into aurones in this system.

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CONCLUSION

We have achieved the first catalytic transformation from simple chalcones into various aurones over Pd-on-Au bimetallic nanoparticles supported on CeO₂ through the rational design of a function-integrated heterogeneous catalyst; the designed system included the following four roles indispensable for the catalytic transformation—a) a supported Pd species: a novel catalyst for aurone synthesis via rare directed α -olefinic C-H functionalization, b) an Au promoter: an improvement of catalytic activity as a result of stabilization of Pd(0), c) a CeO₂ support: the inhibition of the 6-endo-trig cyclization on the surface, and d) a Pd-on-Au structure: the inhibition of Au-catalyzed flavone synthesis. This catalysis was confirmed to be heterogeneous, and the catalysts could be reused. In addition, O₂ served as the sole oxidant and no additives were needed, making this system truly environmentally friendly. This system was also significantly useful as an aurone synthesizing method; various aurones were synthesized starting from simple chalcones, including a natural compound extracted from plants, which will promote the pharmaceutical study of aurones. This study demonstrates the considerable potential of a heterogeneous catalyst design for novel difficult organic syntheses that have not yet been achieved using homogeneous catalysts or biocatalysts.

EXPERIMENTAL SECTION

Preparation of Pd/Au/CeO₂

The Pd-on-Au bimetallic nanoparticle catalyst supported on CeO₂ (Pd/Au/CeO₂) was prepared as follows. CeO₂ (2 g) was added to an aqueous solution of HAuCl₄ (3 mM, 100 mL), and the slurry was stirred for 2 min, followed by the addition of 10% aqueous NH₃ (360 μ L). After stirring for 14 h, the resulting mixture was filtered, washed with deionized water (1 L), and dried in vacuo, affording a supported Au precursor. This Au precursor was then dispersed in an aqueous solution of K_2PdCl_4 (3 mM), which was generated in situ from a mixture of PdCl₂ (0.3 mmol) and KCl (1.2 mmol) in 100 mL water, and stirred for 10 min. The pH of the solution was adjusted to 12.3 using an aqueous solution of NaOH (2 M). After the reaction mixture was stirred for 14 h, the precursor was filtered, washed, and dried in the aforementioned manner to give a supported Au-Pd precursor. After calcination of the Au-Pd precursor at 300 °C for 2 h, the desired Pd/Au/CeO₂ (Pd: 1.5 wt%, Au: 2.7 wt%) was obtained as a black powder. The catalysts for which the Pd/Au ratio is 1/3 (Pd: 0.7 wt%, Au: 4.0 wt%) or 3/1 (Pd: 2.2 wt%, Au: 1.2 wt%) were prepared using a similar procedure after adjusting the initial concentrations of metal sources to obtain the desired ratios. Similarly, Au/Pd/CeO₂ was prepared, by simply reversing the aforementioned order of the supporting metal species.

Catalytic reaction

The catalytic reaction was typically carried out according to the following procedure. Into a Pyrex glass reactor (volume: ca. 20 mL) were successively added Pd/Au/CeO₂ (100 mg, Au: 5 mol%, Pd: 5 mol%), biphenyl (0.1 mmol, internal standard), 2'-hydroxychalcone (**1a**, 0.3 mmol), BuOAc (2 mL), and a Teflon-coated magnetic stir bar; the mixture was then stirred at 100 °C under an open air atmosphere. The yields of products were determined by GC analysis using biphenyl as an internal standard. With respect to the isolation of products, after the reaction, the catalyst was removed by simple filtration and the filtrate was then concentrated by evaporation of BuOAc or DMA. The crude product was subjected to column chromatography on silica gel (typically using hexane/EtOAc = 8/2 as an eluent), giving the pure aurones.

ASSOCIATED CONTENT

The supporting information is available free of charge on the ACS Publication website.

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Notes

The authors declare no competing financial interests.

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Supporting Information. Brief statement in non-sentence format listing the contents of the material supplied as Supporting Information.

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TOC graphic

Unusual cyclization not yet realized by homogeneous catalysts or biocatalysts O₂ (in Air) Au-Pd R¹ ЮН -H₂O Aurone ²R² Chalcone Backbone of Flavonoids Rare Flavonoid with 5-membered C ring × CeO2 PdO_x PdO_x Pd-on-Au AU Au CeO, Function-Integrated Flavanone Flavone Catalyst Design

Preferential Cyclization: Route to Other Flavonoids