Selective *C3*-alkenylation of oxindole with aldehydes using heterogeneous CeO_2 catalyst

Md. Nurnobi Rashed,[a] Abeda Sultana Touchy,[a] Chandan Chaudhari,[b] Jeon Jaewan,[a] S. M. A. Hakim Siddiki,*[a] Takashi Toyao,[a,c] Ken-ichi Shimizu*[a,c]

[a]Institute for Catalysis, Hokkaido University, N-21, W-10, Sapporo 001-0021, Japan

[b]Department of Chemical Systems Engineering, Graduate school of Engineering, Nagoya University, Nagoya 464-8603, Japan

[c]Elements Strategy Initiative for Catalysts and Batteries, Kyoto University, Katsura, Kyoto 615-8520, Japan

*Corresponding authors

S. M. A. Hakim Siddiki, Ken-ichi Shimizu

Institute for Catalysis, Hokkaido University, N-21, W-10, Sapporo 001-0021, Japan

E-mail: hakim@cat.hokudai.ac.jp,kshimizu@cat.hokudai.ac.jp, Fax: +81-11-706-9163

Abstract: We report herein that a commercially available CeO_2 is an active and reusable catalyst for the *C3*-selective alkenylation of oxindole with aldehydes under solvent-free conditions. This catalytic method is generally applicable to different aromatic and aliphatic aldehydes, giving 3-alkyledene-oxindoles in high yields (87-99%) and high stereoselectivities (79-93% to *E*-isomers). This is the first example of the catalytic synthesis of 3-alkenyl-oxindoles from oxindole and various aliphatic aldehydes. The Lewis acid-base interaction between Lewis acid sites on CeO_2 and benzaldehyde was studied by in situ IR. The structure-activity relationship study using CeO_2 catalysts with different sizes suggests that defect-free CeO_2 surface is the active site for this reaction.

Keywords: Oxindole, aldehyde, aldol condensation, *C3*-alkenylation, CeO_2 catalysts

1. Introduction

Indoles, oxindoles, isatins and their derivaives are relevant nitrogen containing heterocycles widely distributed in natural products and pharmaceutical compounds [1]. Oxindole used as a neurodepressant tryptophan metabolite and physiologically present in mammalian brain/blood and influence brain functions [2]. 3-Alkyledene-oxindoles derivatives are medicinally important and exist in anticancer kinase inhibitor, anti-inflammatory drugs including Sunitinid, Tedinap respectively [3–5]. They are also well-known synthetic intermediates of natural products named TMC-95, Gelsemine and biologically appealing spirooxindoles [6–13]. Conventionally, secondary amine (piperidine/pyrrolidine) assisted Knoevenagel condensation reaction is applied to synthesize 3-alkyl/arylidene-oxindoles from oxindole and carbonyl compounds [14–17]. H. J. Lee et al. reported (*Z*)-selective synthesis of 3-arylidene-oxindoles employing stoichiometric amounts of $Ti(O^iPr)_4$/pyridine with unsymmetrical ketones [18]. D. Villemin et al. reported 3-alkenylation of oxindole with aromatic aldehydes promoted by excess amount (10 equiv.) of solid base (KF/Al_2O_3) under microwave radiation [19]. Brønsted acidic ionic liquid [20] were reported to promote 3-alkenylation reactions of oxindole with aromatic aldehydes, but this method used excess amount (>6.6 equiv.) of the Brønsted acids with respect to the substrates. Apart from these non-catalytic methods, Vankelecom and co-worker showed the catalytic synthesis of 3-benzylidene-oxindole by the reaction of oxindole with benzaldehyde using a Zr-incorporated UiO-66 MOF catalyst [21]. Recently, Chengjian and co-workers [22] reported that a homogeneous Re-complex catalyzed dehydrogenaive 3-alkenylation of *N*-substituted oxindoles with benzylic alcohols. However, these two catalytic methods are applicable to activated (aromatic and allylic) aldehydes and suffer from the difficulties in catalyst reuse. P. Gholamzadeha et al. demonstrated a reusable catalytic method using SO_3H-loaded silica catalyst, but the method is applicable only for activated aromatic aldehydes [23]. Hence, it is desirable to develop a reusable general heterogeneous catalyst for the 3-alkenylation of oxindoles with aldehydes including aliphatic (non-aromatic) aldehydes.

Organic synthesis employing heterogeneous CeO_2 catalysis fascinates much attention in the recent years [24–26]. Our group has studied a series of catalytic transformation of carboxylic acid derivatives using heterogeneous CeO_2 catalysts [27–36]. This access has advantages combined with the facility of catalyst preparation and exploitation of a recyclable heterogeneous catalyst. It is anticipated that this catalytic system would find applications to other challenging reactions that produce value-added chemicals in one-pot manner. Herein, we report a simple heterogenous

catalytic method using CeO_2 for the *C3*-alkenylation of oxindole with aldehydes including unactivated aliphatic aldehydes into the corresponding 3-alkenyl-oxindoles.

2. Experimental

2.1. General

Commercial compounds (Tokyo Chemical Industry, Sigma-Aldrich or Wako Pure Chemical Industries) were used without further purification. Substrates and products were analyzed by GC (Shimadzu GC-2014) and GCMS (Shimadzu GCMS-QP2010) with Ultra ALLOY$^+$-1 capillary column (Frontier Laboratories Ltd.) using N_2 and He as the carrier. Column chromatography was performed with silica gel 60 (spherical, 40-100 μm, Kanto Chemical Co. Ltd.).^{1}H and ^{13}C NMR spectra were recorded at ambient temperature on JEOL-ECX 600 (^{1}H: 600.17 MHz; ^{13}C: 150.92 MHz) spectrometer with tetramethylsilane as an internal standard.

2.2. Catalyst preparation

CeO_2 (JRC-CEO-1, 185.3 $m^2\ g^{-1}$, supplied by Santoku Co.), MgO (JRC-MGO-3, 19 $m^2\ g^{-1}$), and TiO_2 (JRC-TIO-4, 47 $m^2\ g^{-1}$) were supplied from Catalysis Society of Japan. SiO_2 (Q-10, 300 $m^2\ g^{-1}$) was supplied from Fuji Silysia Chemical Ltd. Different CeO_2 catalysts were prepared from CeO_2 (JRC-CEO-1) by calcinating at four different temperatures (500 ºC, 600 ºC, 800 ºC, and 1000 ºC) for 3 h. γ-Al_2O_3 (124 $m^2\ g^{-1}$) was prepared by calcination of γ-AlOOH (Catapal B Alumina purchased from Sasol) at 900 °C for 3 h. Niobic acid was supplied by CBMM, and Nb_2O_5 (54 $m^2\ g^{-1}$) was prepared by calcination of the niobic acid at 500 °C for 3 h. ZrO_2 (73 $m^2\ g^{-1}$) and SnO_2 (25 $m^2\ g^{-1}$) were prepared by calcination (500 °C, 3 h) of $ZrO_2{\cdot}nH_2O$ and H_2SnO_3 (Kojundo Chemical Laboratory Co., Ltd.). Hydroxides of Ca, Zn, Mg were commercially supplied. Hydroxides of La were prepared by hydrolysis of $La(NO_3)_3{\cdot}6H_2O$ by aqueous NH_4OH solution, followed by filtration, washing with distilled water, drying at 100 °C for 12 h, and by calcination at 500 °C for 3 h. Oxides of Ca (22 $m^2\ g^{-1}$), Zn(12 $m^2\ g^{-1}$) and La were prepared by calcination of these hydroxides at 500 °C for 3 h. Hβ-20 (HSZ-940HOA, 530 $m^2\ g^{-1}$) were purchased from Tosoh Co. A sulfonic resin (Amberlyst-15, 45 $m^2\ g^{-1}$) and montmorillonite K10 clay (mont. K10, 220 $m^2\ g^{-1}$) were purchased from Sigma-Aldrich. Scandium(III) trifluoromethanesulfonate $Sc(OTf)_3$, $Ce(NO_3)_4$ and $Ce_3(PO_4)_4$ were purchased from Tokyo Chemical Industry.

2.3. Catalytic tests

The solid catalysts, stored under ambient conditions, were used without any pretreatment. In a typical procedure, oxindole (1 mmol) and each of the aldehydes

(1.25 mmol) was subjected for condensation reaction in presence of 20 mg of catalysts. The reaction mixture was added to a reaction tube (Pyrex pressure tube, 13 mL), with a magnetic stirrer bar and placed in a heated reactor at 100 °C under N_2 with stirring at 400 rpm. After completion of the reaction, the reaction mixture was diluted by 2-propanol (3 mL) and *n*-dodecane (0.2 mmol) was added as an internal standard and the mixture was analyzed by GC-FID to determine the conversion and yield of the products. The GC-FID sensitivity of the product was determined using the isolated 3-alkeny-oxindole. After the reaction, the catalyst was separated through filtration and solvent was evaporated from the reaction mixture. The *E*/*Z* ratio of the isomers and total yield were determined by ^{1}H NMR analyses of crude reaction mixture using mesitylene as an internal. The *E* and *Z* isomers were assigned and confirmed in comparison with their reported ^{1}H NMR data [18]. The major product was isolated by column chromatography using silica gel 60 (spherical, 40-100 μm, Kanto Chemical Co. Ltd.) with hexane/ethyl acetate (95/5 to 80/20) as the eluting solvent. The isolated product was analyzed by ^{1}H NMR, ^{13}C NMR and GC-MS equipped with the same column as GC-FID.

2.4 Characterization

In situ IR spectra were recorded by a JASCO FT/IR-4200 spectrometer equipped with a mercury cadmium telluride detector. For the benzaldehyde adsorption IR study, a closed IR cell surrounded by a Dewar vessel was connected to an evacuation system. During the IR measurement, the IR cell was cooled by a freezing mixture of dry-ice/acetone in the Dewar vessel, and the thermocouple near the sample showed T = (-50 ±5) °C. The sample was pressed into a self-supporting wafer (40 mg) and mounted into the IR cell with CaF_2 windows. Spectra were measured by accumulating 15 scans at a resolution of 4 cm^{-1}. After in situ pre-evacuation of the sample at 500 °C for 0.5 h, a reference spectrum of the sample disc was measured at T = (-50±5) °C. The sample was then exposed to benzaldehyde (1 μL) under (650 Pa) at T = -50 °C for 600 s, followed by evacuation for 600 s. A differential IR spectrum, with respect to the reference spectrum, was then recorded at T = (-50±5) °C. XRD measurements were conducted using a Rigaku Miniflex with a Cu-Kα radiation source. N_2 adsorption measurements were carried out by using AUTOSORB 6AG (Yuasa Ionics Co.). The X-ray photoelectron spectroscopy (XPS) measurements were carried out using a JEOL JPS-9010MC with an Mg Kα anode operated at 10 mA and 10 kV. Binding energies were calibrated with respect to C1s at 284.2 eV.

3. Results and Discussion

3.1. Optimization of the catalyst and reaction conditions

To find the optimal catalyst, we employed as a series of potential catalysts for the 3-alkenylation of oxindole (**1a**) with benzaldehyde (**2a**) into the corresponding 3-benzylidene-oxindole product (**3a**). A series of acidic or basic heterogeneous and homogeneous catalysts (20 mg) were tested for the 3-alkenylation of **1a** (1 mmol) and **2a** (1.2 mmol) under N_2 at 100 °C for 10 h. The conversion of **1a** and the yield of **3a** based on **1a** using different catalysts are summarized in Table 1. Without catalyst (entry 1), only 4% yield of **3a** was observed. Among the metal oxides (entries 2-11), CeO_2 (entry 2) showed the highest yield of **3a** (97%). Lewis acidic oxides including Nb_2O_5, TiO_2 and ZrO_2 gave **3a** in good yields (54-73%), SiO_2, SnO_2 and amphoteric oxides Al_2O_3, ZnO showed low yields of **3a** (19-32%). Basic oxides such as CaO, MgO and La_2O_3 (entries 10-12) provided **3a** in low yields (16-27%). Commercially available solid acids, including proton-exchanged zeolite Hβ-20 (entry 13), montmorillonite K10 clay (entry 14) and a sulfonic resin Amberlyst-15 (entry 15), gave **3a** in 15-40% yields. Homogeneous Lewis acid $Sc(OTf)_3$ (entry 16) afforded **3a** in 52% yield. We also screened Ce salts (entries 17-18), $Ce(NO_3)_4$ and $Ce_3(PO_4)_4$, which gave **3a** in 57% and 49% yield, respectively. Screening test in Table 1 exhibit that CeO_2 is the most effective catalyst for the 3-alkenylation of **1a** with **2a**.

Admitting CeO_2 as the best catalyst, we optimized the reaction conditions for the model 3-arenylation reaction as shown in Table 2. For the reaction at 80 ºC, the yield of **3a** depends on the molar amount of **2a**; the reaction with 1.25 equiv. of **2a** gave higher yield (78%) than that with 1 equiv. of **2a** (68%). The reactions of **1a** with 1.25 equiv. of **2a** at different temperatures (80-100 °C) under solvent-free conditions were tested (entries 2-4). The reaction at 100 °C gave the highest yield of **3a** (99%). The reactions of **1a** with 1.25 equiv. of **2a** at 100 °C in different solvent (entries 5-7) gave slightly lower yields (93-96%) than the solvent-free conditions. Under the optimized conditions (100 °C, 20 mg CeO_2, 1 mmol **1a**, and 1.25 mmol **2a**), the time course of the reaction (Fig. 1) shows that a reaction time of 10 h was sufficient to obtain the maximum yield of **3a** (99%).

3.2. Catalytic performance

We studied the reusability of CeO_2 for the alkenylation of **1a** with **2a** under the optimized conditions (Fig. 2). After completion of the reaction of each cycle 2-propanol (3 mL) was added to the reaction mixture and CeO_2 was separated by centrifugation, followed by consecutive washing with 2-propanol (3 mL) and acetone (3 mL), and

drying at 110 °C for 6 h. The recovered catalyst was then used for the next reaction cycle. The result shows that the catalyst was reusable for five cycles with slight gradual decrease in the **3a** yield (99-92%). Initial product formation rates were examined (at conversion less than 30%) for each cycle in addition to the final yields (**Fig. 2**). A significant loss of the initial rate was not observed but a slight decrease in the yield was observed. The yield was recovered after calcination of the CeO_2 catalyst at 400 ºC for 3 h. This indicates that the decrease in the final yield is not due to changes in the catalyst structure but due to carbonaceous compounds on the surface. The result in Fig. 2 shows that CeO_2 is a robust heterogeneous catalyst. XRD pattern of the catalyst after the fifth cycle is nearly consistent with that of fresh catalyst (Fig. S1), which suggests no change in the catalyst structure after the reaction.

Under the optimized reaction conditions, we investigated the substrate scope for the *C3*-alkenylation of oxindole with various aromatic and aliphatic aldehydes by CeO_2. The yields of alkylidene-oxindoles are shown in Scheme 1. Note that the yields of the major products (*E* isomers) were estimated from the weight of the isolated *E* isomers, while the total yields of *E*, *Z* isomers and the *E*/*Z* ratios in parenthesis were determined by ^{1}H NMR. The benzaldehydes, including electron-donating (methyl, *t*-butyl, *N,N*-dimethyl, methoxy at the *para* positions; **2b**-**2e** and hydroxy at *ortho* position **2f**) and electron-withdrawing groups (chloride, nitro at the *para* positions; **2g**, **2h**) were successfully transformed into the corresponding 3-benzylidene-oxindoles (**3a**-**3h**) in high total yield (88-99%). Regardless of the electronic nature, substrates with substituents at the *para* position selectively afford *E* isomers. Sterically congested substrate **2f** with hydroxy group at the *ortho* position exceptionally formed *Z* isomer (84%, *E*/*Z* = 8:92; **3f**) as a major product. Benzaldehyde homologue i.e., 1-naphthaldehyde is also well tolerated in this *E*-selective 3-arenylation reaction and afford high yield of 3-nepthalen-1-ylmethylene-oxindole (87%, *E*/*Z* = 93:7; **3i**). Heteroaromatic aldehydes (e.g. isonicotinyl and furanyl groups) were successfully transformed into the corresponding 3-arylidene-oxindoles in high yield (90%, *E*/*Z* = 84:16; **3j** and 93%, *E*/*Z* = 85:15; **3k**). An allylic aldehyde also underwent alkenylation to give 3-phenylallylidene-oxindole **3l** in high yield and high *E* selectivity. Aliphatic aldehydes including linear and branched substituents at α-carbon atoms were successfully converted to the corresponding 3-alkelidene-oxindoles (**3m**-**3p**) in high yields and high *E* selectivity. To our knowledge, this is the first example of the catalytic C3-alkenylation of oxindole with aliphatic aldehydes.

We also demonstrated the gram scale reaction for this CeO_2 promoted 3-alkenyl-oxindole synthesis using different aldehydes (12.5 mmol) with 10 mmol of

1a and 20 mg of CeO_2 catalysts. The yields of the corresponding 3-alkenyl-oxindole products are shown in Scheme 2. The reaction of **1a** with benzaldehyde **2a**, *p*-methyl-benzaldehyde **2b**, *p*-chloro-benzaldehyde **2g**, isonicotinaldehyde **2j** and 1-octanal **2o** gave the corresponding 3-alkenyl-oxindoles in 82-93% yield.

3.3. Active sites and possible mechanism

We prepared CeO_2 catalysts calcined at four different temperatures (500 ºC, 600 ºC, 800 ºC, and 1000 ºC), and the structure and catalytic activity of these comparative catalysts were compared with the standard CeO_2 catalyst (as received JRC-CEO-1) which was originally calcined at 300 ºC. X-ray diffraction patterns of the CeO_2 catalysts (Fig. 3) show that the samples show the same crystal phase (fluorite structure). Average size of CeO_2 crystals, calculated from the half-width of the peak at 28.5º using the Scherrer equation, was plotted versus calcination temperature in Fig. 5(B). The crystal size increases with the calcination temperature. The BET surface area (Table S1) estimated using the N_2 adsorption isotherms (Fig. 4) are plotted in Fig. 5(B) as a function of calcination temperatures. The surface areas of the CeO_2 catalysts decreased with the calcination temperature. We carried out catalytic tests for the standard reaction of **1a** and **2a** using these CeO_2 catalysts to obtain the rates of **3a** formation per catalyst weight (Table S1). As shown in Fig. 5(A), the rate per catalyst weight decreases with increase in the calcination temperature. The rates per catalyst weight were divided by the BET surface areas to give the rate per surface area. As shown in Fig. 5(A), the rate per surface areas of the CeO_2 catalysts increases with the calcination temperature. Clearly, the intrinsic catalytic activity of CeO_2 increases with decrease in surface area of CeO_2. This suggests that defect-free CeO_2 surface, possibly the most stable (111) surface, is the active site for this alkenylation reaction.

To check the presence of surface Ce^{3+}, we studied X-ray photoelectron spectroscopy (XPS) analysis for CeO_2 catalysts (Fig. 6). A strong peak due to Ce^{4+} species (918 eV) [37-38] are observed in the Ce 3d XPS spectra for all the catalysts. A weak shoulder peak at 884 eV due to Ce^{3+} species [37-38] are observed for the catalyst calcined at 300-800 °C, but another characteristic peak for Ce^{3+} species at 904 eV is not clearly observed for these catalysts. These results suggest that Ce species in all the catalysts are basically in Ce^{4+} state and Ce^{3+} species are present at the surface as a minor Ce species.

The high activity of CeO_2 in the present reaction may be due to acid-base bifunctional property [27, 35, 36] of CeO_2 as shown in Scheme 3. First, we studied Lewis acid-base interaction between surface Ce cation and carbonyl oxygen of

benzaldehyde using in situ IR experiment of benzaldehyde adsorbed on CeO_2 (calcined at 300 ºC, 600 ºC and 800 ºC) at -50°C (Fig. 7). The benzaldehyde adsorbed on CeO_2 catalysts gave the C=O stretching band at lower wavenumber (1682-1685 cm^{-1}) than that on non-Lewis acidic oxide, SiO_2 (1690 cm^{-1}). The IR band intensity of the C=O stretching band slightly increases with calcination temperature is nearly same for these three CeO_2 catalysts. Considering that the surface areas of CeO_2 decreases with calcination temperature, the IR result suggests that the density of Lewis acid sites increases with calcined temperature. Hence, the steep increase in the catalytic activity from 600 to 800 ºC in Fig. 5A may be due to the higher density of the Lewis acid sites. This indicates that Lewis acid-base interaction between the carbonyl group (Lewis base) and the Ce^{4+} Lewis acid site increases nucleophilicity of the adsorbed aldehyde on CeO_2. We have previously shown that the basic sites of CeO_2 are effective for aldol condensation of ketones to form α,β-unsaturated ketone [39]. In the present condensation reaction, the basic sites of CeO_2 (i.e., surface oxygen atom) should abstract the proton of α-carbon to the carbonyl group in oxindole to give an enolate intermediate. Finally, nucleophilic attack of the enolate to the aldehyde activated over the Ce^{4+} site and subsequent dehydration results in the formation of the final product as illustrated in Scheme 3.

4. Conclusion

CeO_2 was found to be an efficient catalyst for synthesis of *E* selective 3-alkenyl-oxindoles from oxindole and aldehydes. The present method is the first general heterogeneous catalytic *C3*-selective alkenylation reaction of oxindole using both aromatic/aliphatic (unactivated) aldehydes. The study on the structure-activity relationship suggests that defect-free CeO_2 surface, possibly the most stable (111) surface, is the active site for this alkenylation reaction. The specific catalysis of CeO_2 in the present reaction can be due to its Lewis acid-base bifunctional property and where defect free CeO_2 surface is active site for this reaction.

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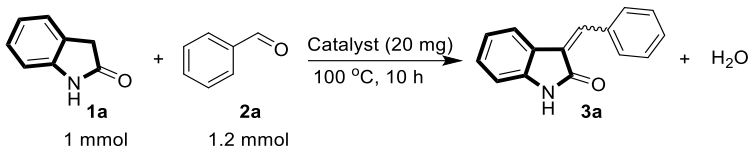
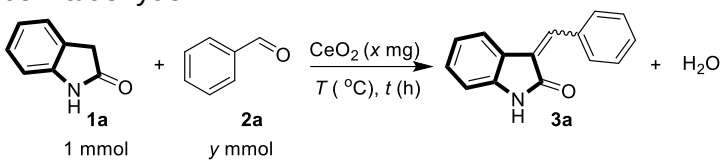
Table 1. *C3*-alkenylation of oxindole with benzaldehyde by various catalysts



Entry	Catalysts	**1a** conv. (%)	**3a** yield (%)[a]
1	blank	8	4
2	CeO_2	100	99
3	Nb_2O_5	76	73
4	TiO_2	58	54
5	ZrO_2	67	64
6	SiO_2	25	21
7	SnO_2	35	32
8	Al_2O_3	26	22
9	ZnO	22	19
10	CaO	20	16
11	MgO	29	25
12	La_2O_3	31	27
13	Hβ-20	23	20
14	mont. K10	18	15
15	Amberlyst-15	43	40
16	$Sc(OTf)_3$	55	52
17	$Ce(NO_3)_3$	61	57
18	$Ce_3(PO_4)_4$	53	49

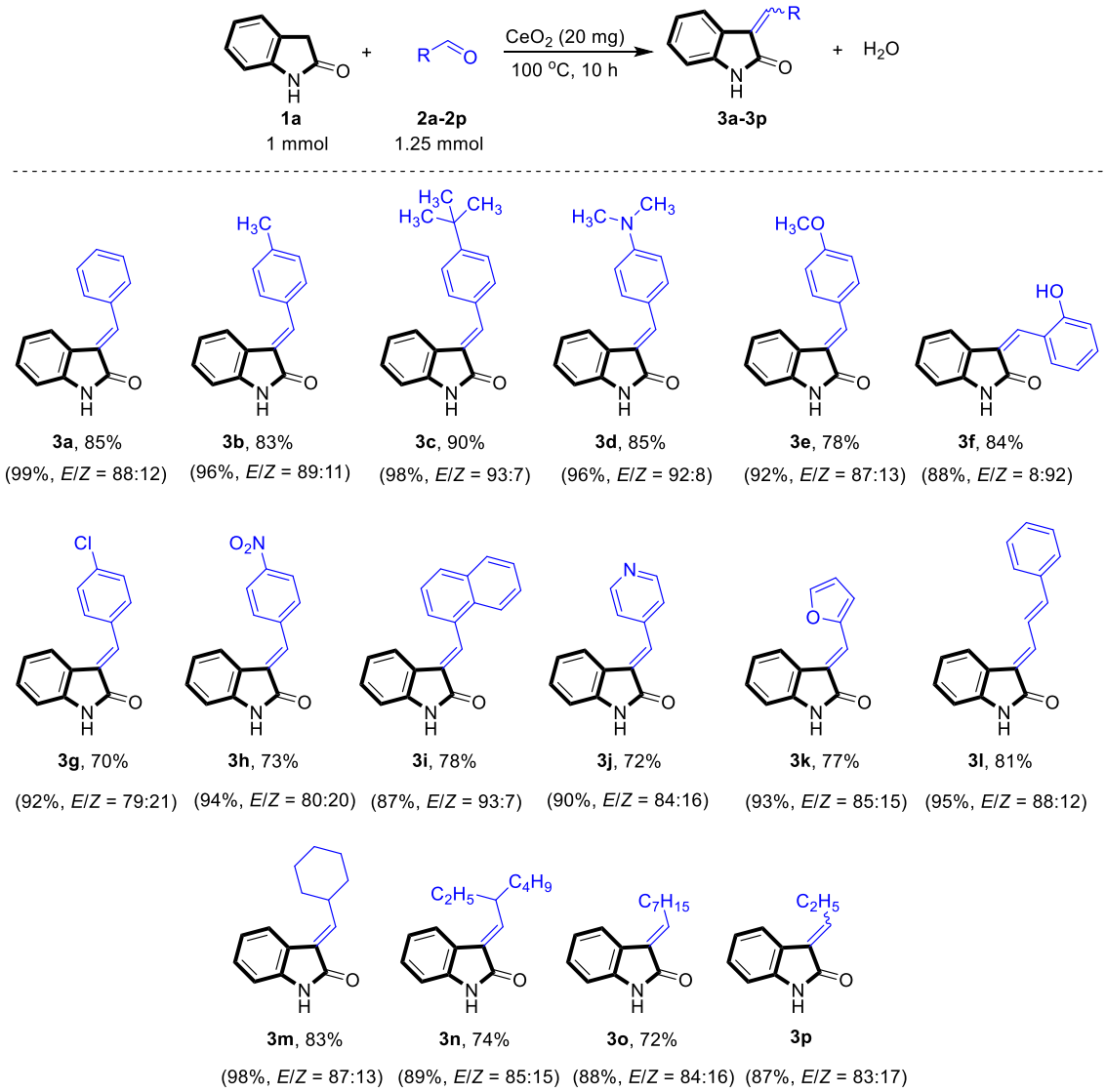
[a]GC yield

Table 2. Optimization of the conditions for *C3*-alkenylation of oxindole with benzaldehyde.

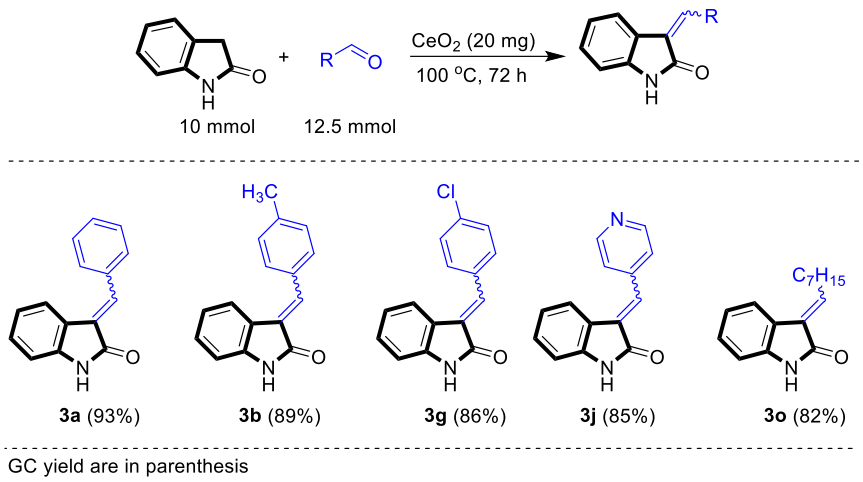


Entry	CeO_2 (*x* mg)	**2a** (*y* mmol)	Solvent	*T* (°C)	*t* (h)	**3a** yield (%)[a]
1	20	1	No	80	15	68
2	20	1.25	No	80	15	78
3	20	1.25	No	90	15	92
4	20	1.25	No	100	10	99
5	20	1.25	n-Decane	100	10	93
6	20	1.25	Toluene	100	10	96
7	20	1.25	1,4-Dioxane	100	10	94

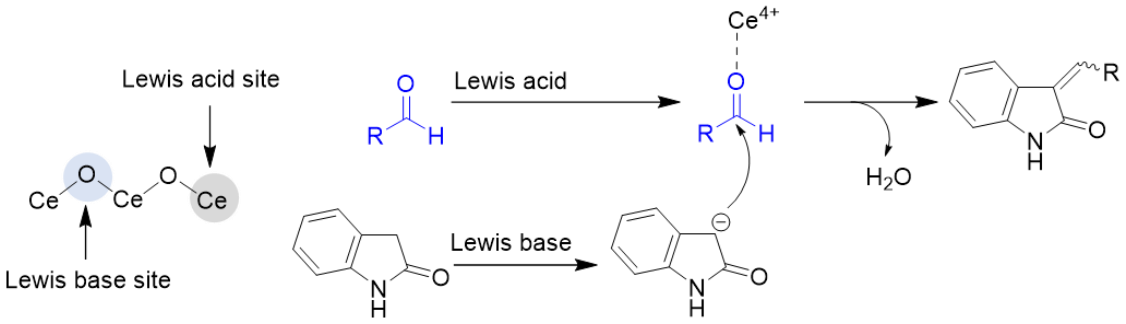
[a]GC yield.



Scheme 1. CeO_2 catalyzed C3-alkenylation of oxindole with aromatic and aliphatic aldehydes (2a-2p) to synthesize the corresponding 3-alkyledene-oxindoles (3a-3p).



Scheme 2. CeO_2 catalyzed gram scale alkenylation of oxindole to produce corresponding 3-alkylidene-oxindoles.



Scheme 3. Plausible reaction mechanism for the CeO_2-catalyzed 3-alkenyation of oxindole with aldehydes.

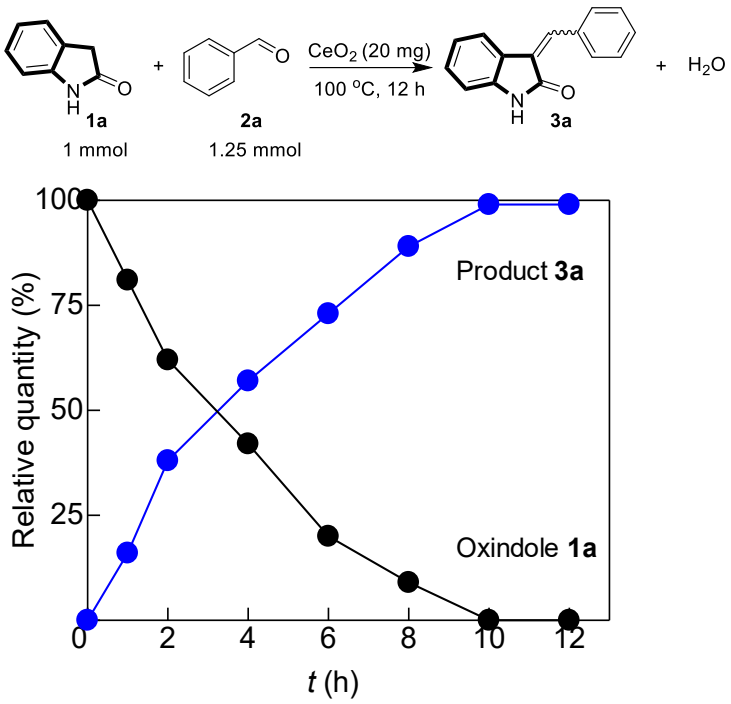


Fig. 1. Time course of the reaction of oxindole (1 mmol) with benzaldehyde (1.25 mmol) by CeO_2 (20 mg) at 100 °C.

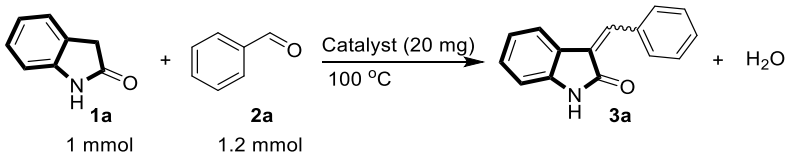


Fig. 2. Catalyst reuse for the synthesis of **3a** from **1a** and **2a**, promoted by CeO_2 catalysts under standard condition as shown in Table 1 (entry 2): (black bars) **3a** yields after 10 h and (green bars) initial rates of **3a** formation after 1 h.

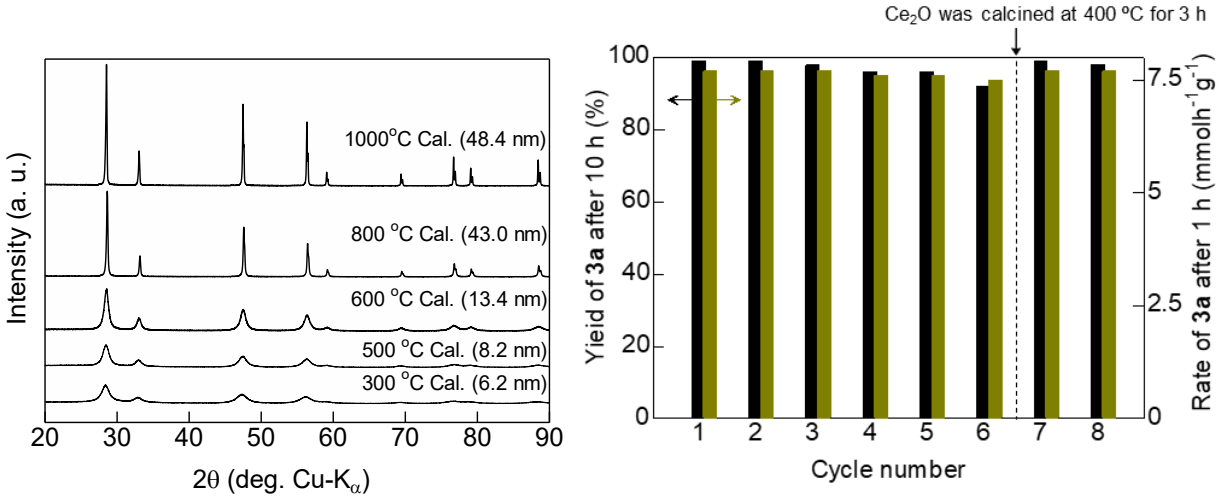


Fig. 3. XRD pattern of different CeO_2 catalysts calcined at different temperature, particle sizes are in parenthesis.

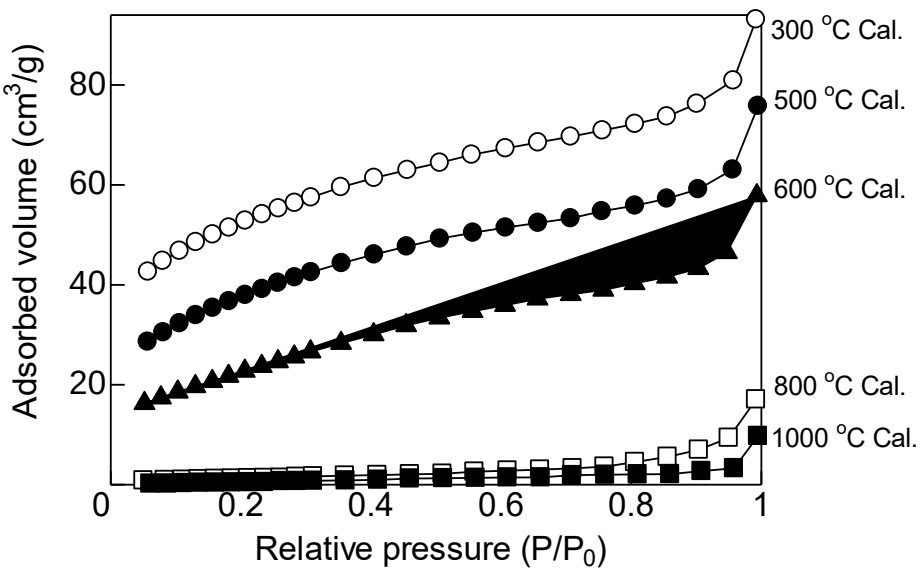


Fig. 4. N_2 adsorption isotherm for different CeO_2 catalysts calcined at different temperatures.

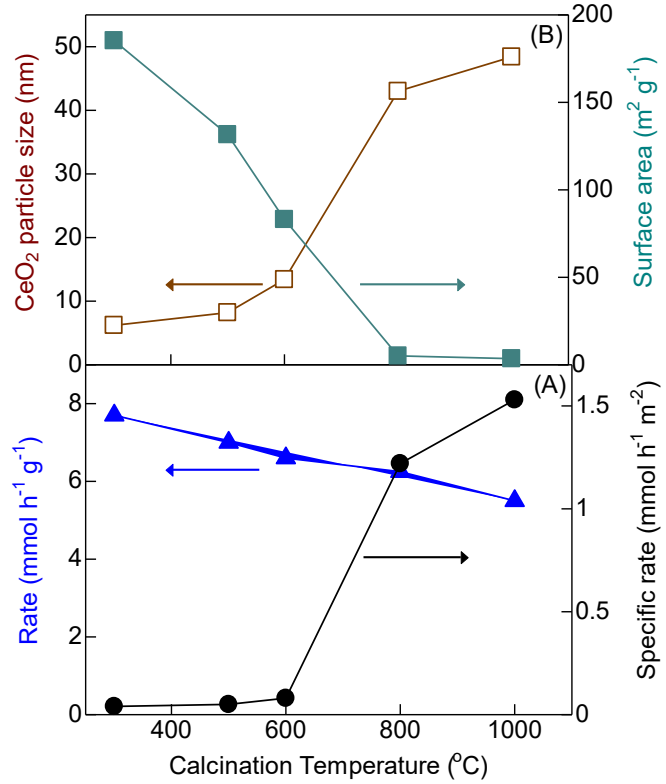


Fig. 5. Effect of calcination temperature of CeO_2 on (▲) the rates of **3a** formation per catalyst weight, (●) the rate of **3a** formation per the surface areas of CeO_2, (□) crystal size of CeO_2 and (■) BET surface areas of CeO_2. Reactions were performed under conditions where **1a** conversions were below 30%.

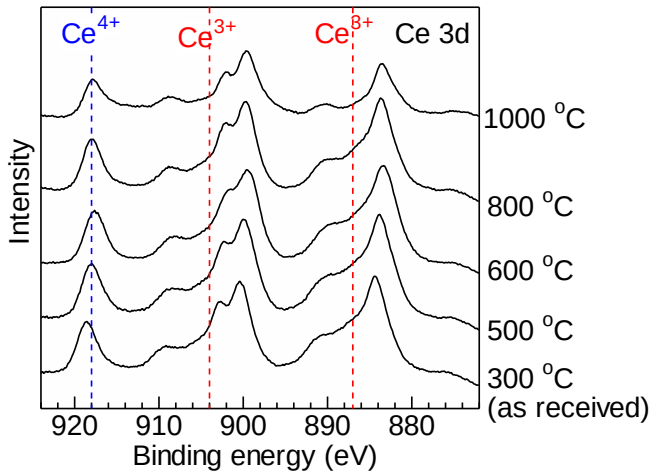


Fig. 6. XPS results of CeO_2 catalysts calcined at different temperatures.

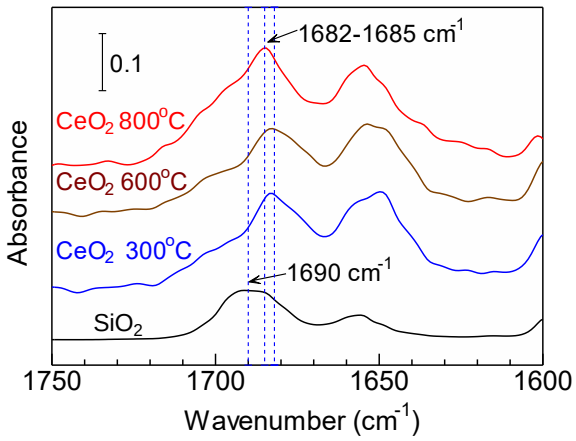


Fig. 7. IR spectra of benzaldehydes adsorbed on the SiO_2 and CeO_2 surface at -50 °C (t = 600 s).