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Author(s)	Rashed, Md. Numobi; Siddiki, S. M. A. Hakim; Touchy, Abeda Sultana; Jamil, Md. A. R.; Poly, Sharmin Sultana; Toyao, Takashi; Maeno, Zen; Shimizu, Ken-ichi
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Direct Phenolysis Reactions of Unactivated Amides into Phenolic Esters Promoted by a Heterogeneous CeO2 Catalyst

Md. Nurnobi Rashed,[a] S.M.A. Hakim Siddiki,[a,*] Abeda S. Touchy,[a] Md. A. R. Jamil,[a] Sharmin Sultana Poly,[a] Takashi Toyao,[a,b] Zen Maeno,[a] Ken-ichi Shimizu[a,b*]

[a]   Mr. Md. Nurnobi Rashed, Dr. S. M. A. H. Siddiki, Dr. A. S. Touchy, Mr. Md. A. R. Jamil, Ms. S. S. Poly, Dr. T. Toyao, Dr. Z. Maeno, Prof. Dr. K. 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
[b]   Dr. T. Toyao, Prof. Dr. K. Shimizu
         Elements Strategy Initiative for Catalysis and Batteries, Kyoto University, Katsura, Kyoto 615-8520 (Japan)

Abstract: The direct catalytic esterification of amides that leads to the construction of C–O bonds through the cleavage of amide C–N bonds is a highly attractive strategy in organic synthesis. While aliphatic and aromatic alcohols can be readily used for the alcoholysis of activated and unactivated amides, the introduction of phenols is more challenging due to their lower nucleophilicity in the phenolysis of unactivated amides. Herein, we demonstrate that phenols can be used for the phenolysis of unactivated amides into the corresponding phenolic esters using a simple heterogenous catalytic system based on CeO_2 under additive-free reaction conditions. The method tolerates a broad variety of functional groups (>50 examples) in the substrates. Results of kinetic studies afforded mechanistic insights into the principles governing this reaction, suggesting that the cooperative effects of the acid-base functions of catalysts would be of paramount importance for the efficient progression of the C–N bond breaking process, and consequently, CeO_2 showed the best catalytic performance among the catalysts explored.

keywords: phenolysis • unactivated amides • phenolic esters • heterogeneous CeO_2 catalyst • acid-base cooperation

Introduction

Amides represent one of the most abundant functional moieties in natural and synthetic compounds.[1,2] They are an indispensable structural motif in proteins, peptides, resins, fibres, polymers, enzymes, drugs, and define most of the biological functionalities in plants.[3] The direct functionalization of amides is thus a highly attractive strategy in organic syntheses, where the major challenge lies in the cleavage of the amide C–N bond, which is due to the functional group interconversion arising from amidic resonance (Figure 1A)[4] that renders amides poor electrophiles and unreactive toward nucleophiles. Conventionally, enzyme- or strong-acid/base-mediated C–N bond cleavage reactions of amides with alcohols generate huge amounts of undesired byproducts.[5–8] Recently, catalytic C–N bond cleavage reactions, specifically the alcoholysis of amides into the corresponding esters, have received much attention and several examples have been reported.[9–15] In general, the structural diversity of esters is relatively wide and they have found numerous applications in the chemical and pharmaceutical industry.[16] It should also be noted here that the transformation and derivatization of esters is easier than that of amides due to the higher reactivity of the former relative to the latter.

The direct phenolysis of amides into the corresponding phenolic esters has not yet been studied extensively, mostly due to the stability of the amide group and the phenoxide ion, respectively (Figure 1B).[17] Phenolic esters are encountered in a wide range of biologically active compounds, agrochemicals, and natural products.[18] Additionally, the conversion of phenols into the corresponding esters is an environmentally beneficial process as phenol is considered a severe pollutant due to its harmful and toxic effects.[19] Generally, phenolic esters are synthesized via non-catalytic reactions between phenols and acyl halides, carboxylic acids, or anhydrides in the presence of stoichiometric amounts of strong acids or bases.[20] A series of alternative catalytic methods for the esterification of phenols has been reported, including the Cu-catalyzed synthesis of phenolic esters of aryl boronic acids,[21] the Pd-catalyzed alkoxycarbonylation of aryl hydrazines with phenols,[22] the Mo(CO)$_6$-mediated alkoxycarbonylation of arylhalides,[23] and the Pd/C-catalyzed synthesis of aromatic esters from aryl halides.[16] However, the synthesis of phenolic esters from amides has rarely been studied.

Szostak and co-workers have reported a non-catalytic method for the synthesis of phenyl esters from N-Boc- or tosyl-activated amides using a large excess of K$_3$PO$_4$.[4] Xiuling and co-workers have reported the phenolysis of amides into esters mediated by sub-stoichiometric amounts of iron salts as well as mineral and carboxylic acids.[24] The first catalytic example for the phenolysis of N-Boc-activated aromatic amides using a homogeneous cobalt catalyst was reported by Danoun and

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co-workers.[25] This method requires several additives including a bipyridine ligand, a large excess of an activated Mn reductant, trimethylsilylchloride as a manganese-activating agent, and a hazardous dimethylformamide/pyridine mixture as the solvent. However, the method suffers from limited scope (only two examples) and a low yield of the esters (35-39%). Recently, Bhanage and co-workers have reported a tandem electrochemical on-off catalytic method for the synthesis of phenolic esters of activated *N*-methoxyamides.[18] In this method, the electrocatalyst *t*-butylammonium iodide in a Pt-Cu electrode system forms dimers of the *N*-alkoxyamide, followed by an acylation of this dimer with phenol catalyzed by $Zn(OTf)_2$ in the presence of a large excess of solvent and base. However, this system produces undesirable byproducts and its sensitivity toward unactivated, hindered, and/or heterocyclic substrates is relatively low.

Thus, the direct catalytic conversion of amides into phenolic esters, which would potentially be conducted under mild reaction conditions, represents a synthetic challenge. Furthermore, the aforementioned homogeneous methods suffer from the use of stochiometric amounts of catalysts as well as inorganic and organic additives (acids/bases), and from difficulties associated with catalyst/product separation. Hence, a direct reusable catalytic method for the phenolysis of unactivated amides into the corresponding esters represents a highly desirable research target.

Herein, we report a simple, additive-free and reusable heterogenous catalytic system based on CeO_2 for the direct phenolysis of unactivated amides into the corresponding phenolic esters. A systematic mechanistic study revealed that the unique combination of acid/base and redox properties of CeO_2[26–30] promotes this esterification reaction. This catalytic system not only offers a facile means to cleave the amide C–N bond, but also significantly promotes the use of amides and phenols as important building blocks for the synthesis of valuable esters. Moreover, the obtained results also provide a better understanding of the catalytic behavior of CeO_2, which has been of significant interest recently.[31–41]
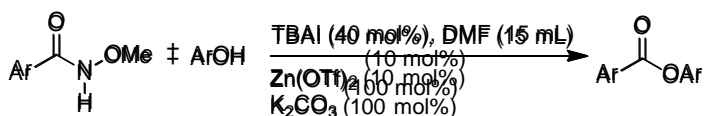
Previous methods based on homogeneous catalysis

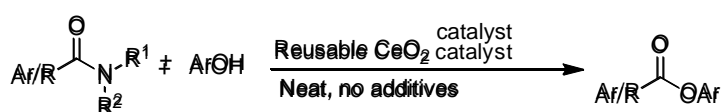**Co-catalyzed phenolysis of activated amides[25]**

CoBr₂ (5 mol%), bipy (10 mol%)
Mn (100 mol%), TMSCl (trace)
DMF/Pyridine (1:1) = 5 mL
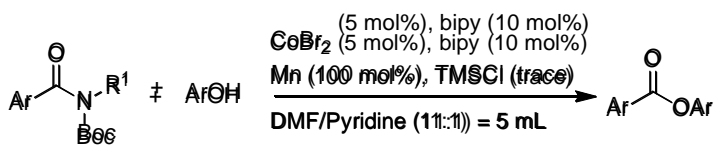
TMSCl ≡ Tetramethylsilyl chloride

Phenolysis of N-methoxy amides using Zn(OTf)₂ and TBAI[18]

TBAI (40 mol%), DMF (15 mL)
Zn(OTf)₂ (10 mol%)
K₂CO₃ (100 mol%)

TBAI ≡ Tetrabutylmmonium iodide

This work: A reusable heterogeneous catalyst with high TON

Reusable CeO₂ catalyst
Neat, no additives

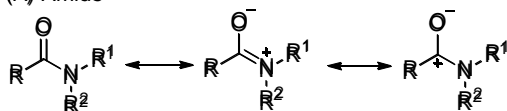*Unactivated amides*   *Wide substrate scope*
                                         high yield, high TON

Scheme 1. Comparison of different phenolysis methods for activated amides (homogeneous systems) and the present study, which uses a CeO₂ catalyst for unactivated amides.
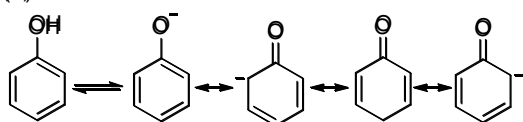
(A) Amide

Rotation barrier C–N bond = 15-20 kcal/mol
Resonance energy = 19-26 kcal/mol
Bond length C–N bond = 1.33 Å[4]

(B) Phenol

Acidity phenol (pKa = 9.95) 10^5 times > Acidity aliphatic alcohols
1/3 of acidity due to inductive effects and
*2/3 of acidity due to resonance stabilization[17]*

Figure 1. Comparative stability of amides (A) and phenols (B).

Results and discussion

Optimization of the catalysts and the reaction conditions

To find the optimal catalyst and reaction conditions, we carried out an extensive survey of reaction parameters for the phenolysis of benzamide (**1a**) with phenol (**2a**) into the corresponding phenyl benzoate ester (**3a**). We screened a series of acidic or basic heterogeneous and homogeneous catalysts in the solvent-free model phenolysis reaction between **1a** (1 mmol) and **2a** (1.25 mmol) under an atmosphere of N_2 at 180 °C for 36 h. The conversion of **1a** and the yield of **3a** based on **1a** using different catalysts are summarized in Table 1. The phenolysis reaction in the absence of catalysts did not yield any **3a** (entry 1). Then, we tested a series of metal oxides (treated or untreated) in this benchmark reaction (entries 2-11). Among these, CeO_2 afforded the highest yield of **3a** (97%, entry 2). Acidic oxides such as Nb_2O_5, ZrO_2, TiO_2, and SiO_2 furnished **3a** in moderate to low yield (6-48%; entries 3-6). Amphoteric oxides such as Al_2O_3 and ZnO (entries 7 and 8) as well as basic oxides such as La_2O_3, Y_2O_3, and CaO (entries 9-11) provided **3a** in merely 2-27% yield. Commercially available solid acids, including montmorillonite K10 clay (entry 12) and Nafion/SiO_2 composite (entry 13), furnished lower yields of **3a** than CeO_2. The water-tolerant homogeneous Lewis acid $Sc(OTf)_3$ (entry 14) afforded **3a** in 50% yield. We also screened different Ce salts, including $Ce(NO_3)_4$, $Ce_3(PO_4)_4$, and $CeF_9O_9S_3$ (entries 15-17), which generated **3a** in 34%, 39%, and 52% yield respectively. Based on this screening study, it can be concluded that CeO_2 is the most effective catalyst for the phenolysis reaction between **1a** and **2a** to form **3a**.

Table 1. Catalyst screening for the phenolysis of benzamide (**1a**) with phenol (**2a**) to furnish phenyl benzoate (**3a**).
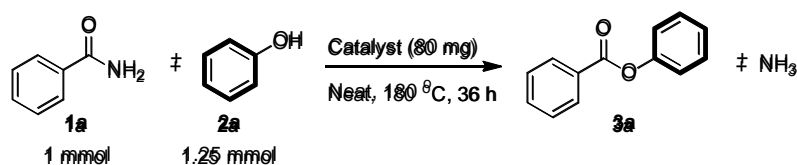
Entry	Catalyst	Conv. [%]	Yield [%][a]
1	none	0	0
2	CeO$_2$	100	97
3	Nb$_2$O$_5$	50	48
4	ZrO$_2$	47	44
5	TiO$_2$	40	36
6	SiO$_2$	8	6
7	Al$_2$O$_3$	27	25
8	ZnO	19	18
9	La$_2$O$_3$	32	27
10	Y$_2$O$_3$	9	7
11	CaO	5	2
12	Mont. K10	49	45
13	Nafion-SiO$_2$	41	38
14	Sc(OTf)$_3$	52	50
15	Ce(NO$_3$)$_4$	37	34
16	Ce$_3$(PO$_4$)$_4$	43	39
17	CeF$_9$O$_9$S$_3$	55	52

[a] GC yield.

Using CeO$_2$ as the most effective catalyst, we optimized the reaction conditions for the model phenolysis reaction as shown in Figure 2, which contains plots of the yield of **3a** and the conversion of **1a** as a function of (A) the amount of CeO$_2$ (20-100 mg), (B) the reaction temperature (150-190 °C), (C) the solvent, and (D) the reaction time (0-36 h). The optimal amount of **1a** (1 mmol) and **2a** (1.25 mmol) were identified as shown in Figure S1. The phenolysis yield of **3a** depends on the molar amount of **1a** and **2a** under otherwise optimized reaction conditions, i.e., 180 ºC, 36 h, 80 mg catalyst. The dependence of the yield of **3a** on the amount of catalyst (Figure 2A) under otherwise optimized conditions (180 °C, 36 h, 1 mmol **1a**, and 1.25 mmol **2a**) shows that 80 mg of CeO$_2$ affords the highest yield. Figure 2B shows the effect of the temperature on the yield of **3a** under otherwise optimized

conditions (36 h, 80 mg CeO$_2$, 1 mmol **1a**, and 1.25 mmol **2a**), and allows identifying 180 °C as the optimal temperature for this phenolysis reaction.

A comparison of the reactions in Figure 2C shows the dependence of the reaction in the presence and absence of solvent(s) under otherwise optimized conditions (180 °C, 36 h, 80 mg CeO$_2$, 1 mmol **1a**, and 1.25 mmol **2a**). These reactions demonstrate that a solvent-free reaction system affords the maximum yield of **3a**. The time course of the reaction under the optimized conditions (Figure 2D) shows the relative quantities of **1a** and **3a** as a function of time. The kinetic pattern revealed that a reaction time of 36 h was sufficient to obtain the maximum yield and selectivity of **3a** (97% yield).
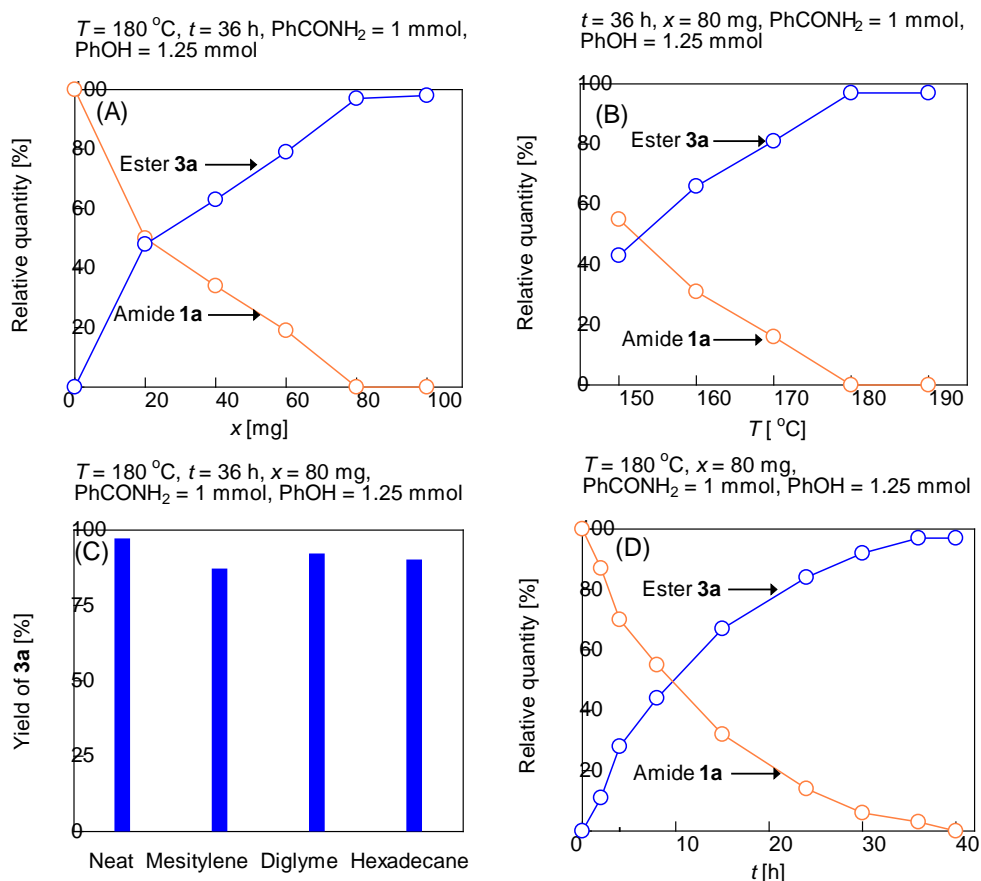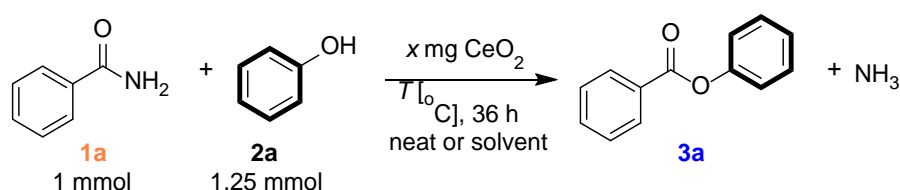

Figure 2. Optimization of the reaction conditions for the phenolysis of benzamide (**1a**) with phenol (**2a**) to produce phenyl benzoate (**3a**). The relative quantities of **1a** and **3a** are shown as a function of the (A) amount of CeO$_2$, (B) temperature, (C) solvent ($V_{solvent}$ = 0.5 mL), and (D) reaction time. The percentage yield of **3a** was analyzed by GC using n-dodecane as an internal standard.

CeO₂-catalyzed phenolysis of amides with phenols into esters

We studied the heterogeneous catalytic properties of CeO_2 in the aforementioned phenolysis of amides under the previously established optimized reaction conditions. Moreover, we examined the reusability of this catalytic system in the model phenolysis reaction between **1a** and **2a** (Figure 3A). For that purpose, isopropanol (3 mL) was added to the reaction mixture after each reaction cycle, and CeO_2 was separated by centrifugation, followed by two consecutive washings with isopropanol (3 mL) and acetone (3 mL), and drying at 110 °C for 6 h. The thus recovered catalyst was then used for the next reaction cycle between **1a** and **2a**. The recovered catalyst was reusable for four cycles, albeit that a slight gradual decrease of the yield of **3a** (97-91%) was observed. The catalytic performance of the recovered catalyst after the fourth cycle (dotted line in Fig. 4A) could be increased to 96-97% by calcination (600 °C; 3 h; air). During this part of the recycling study, the initial rate of the formation of **3a**, where the conversion of the amide is below 30%, was also determined for each cycle (blue bars in Fig. 4A); the results show that the initial rate gradually decreases with increasing number of catalytic and recycling cycles. We also confirmed that the powder X-ray diffraction (XRD) pattern of the CeO_2 catalyst after the catalytic reaction was almost identical to that of the original sample (Figure S2), which indicates that the crystallinity of the catalyst remains almost unchanged during the catalysis.

To confirm the heterogeneous nature of the CeO_2 catalyst, leaching tests were carried out on the model reaction under standard conditions. For that purpose, the solid CeO_2 was separated by hot filtration after 4 h (28% yield of **3a**), which stopped the catalytic process (Figure 3B). Inductively coupled plasma atomic emission spectroscopy (ICP-AES) was used to confirm the heterogeneous nature of the CeO_2 catalyst. An ICP-AES analysis showed that the filtrate did hardly contain any leached Ce species ([Ce] below the detection limit of 10 ppb) in of the model reaction mixture under standard conditions after filtration. These results demonstrate that CeO_2 is a reusable heterogeneous catalyst for the phenolysis of amides into the corresponding esters.
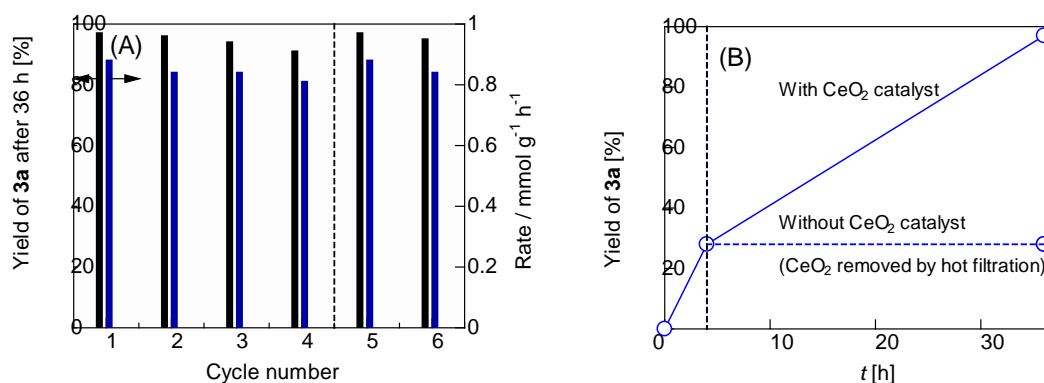

Figure 3. (A) Catalyst reusability for the CeO_2-catalyzed phenolysis of benzamide (**1a**) with phenol (**2a**) to afford phenyl benzoate (**3a**). Black bars: GC yield of **3a** after 36 h; blue bars: initial rate of the formation of **3a**, determined where the conversion of amide was below 30%. (B) Leaching study of

the CeO$_2$ catalyst in the reaction affording phenyl benzoate. Reaction conditions: catalyst (80 mg), benzamide (1 mmol), phenol (1.25 mmol), 180 °C, under N$_2$ atmosphere.

With the optimized reaction conditions in hand, we examined the substrate scope for the CeO$_2$-catalyzed phenolysis of amides. The results show that this system readily promotes the high-yield esterification of a wide range of amides with phenols (Schemes 2 and 3). Initially we tested aromatic, heterocyclic, allylic, sterically hindered α-carbon-containing, benzylic, and aliphatic primary amides in the reaction with **2a** (Scheme 2). A series of benzamides, including electron-donating (methyl at the *para* and *meta* positions, *tert*-butyl, methoxy at the *para* position, hydroxyl at the *ortho* and *para* positions, and an amine at the *para* position; **1b-1h**) and electron-withdrawing groups (fluoride at the *para* and *meta* positions, as well as chloride at the *para* position; **1i-1k**) were successfully transformed into the corresponding phenyl esters in good to high isolated yield (76-93%). Regardless of the electronic nature, substrates with substituents at the *para* position afford higher yields than those containing substituents at the *ortho* and *meta* positions, as evident from the methyl- (**1b**,**1c**), hydroxyl- (**1f**, **1g**) and fluoride-substituted amides (**1i, 1k**). Naphthyl-substituted amides (1- and 2-naphthamide) are well tolerated in this phenolysis and afford phenyl 1-naphthoate (84%; **3l**) and phenyl 2-naphthoate (85%; **3m**) in high yield. It should be noted that all these phenolic esters are formed in higher yield compared to those obtained from the catalytic phenolysis of *N*-methoxy-activated aromatic amides.[18] Heteroaromatic amides (e.g. nicotinyl, thiophenyl, and furanyl groups) can also be successfully transformed into the corresponding phenyl esters in good to high isolated yield (75-82% yields; **3n-3p**). In contrast, previously reported catalytic methods were only effective for the *N*-methoxy-activated furan-2-carboxamide. Allylic amides also underwent this phenolysis to give phenyl cinnamate ester **3q** in good yield. Aliphatic amides with sterically hindered quaternary (adamantyl- or pivaloyl-substituted) or tertiary (cyclohexyl-substituted) α-carbon atoms were also well tolerated in this reaction and the corresponding phenyl esters (**3r-3t**) were obtained in high isolated yield. It should also be noted that the quaternary-α-carbon-containing amides used in this reaction represent the first examples of such substrates in phenolysis reactions. Benzylic amides such as 2-(naphthalen-1-yl)-acetamide and 2-phenylacetamide were successfully transformed to the corresponding phenyl esters in good to high yield (**3u**: 78%; **3v**: 82%). Linear aliphatic amides of different chain length including C1, C4, C7, and C17 skeletons also underwent this phenolysis and furnished the corresponding phenyl alkanoate esters (**3w-3z**) in high yield (80-87%). It should also be noted that this is the first direct catalytic method for the phenolysis of unactivated primary amides to generate the corresponding phenyl esters.
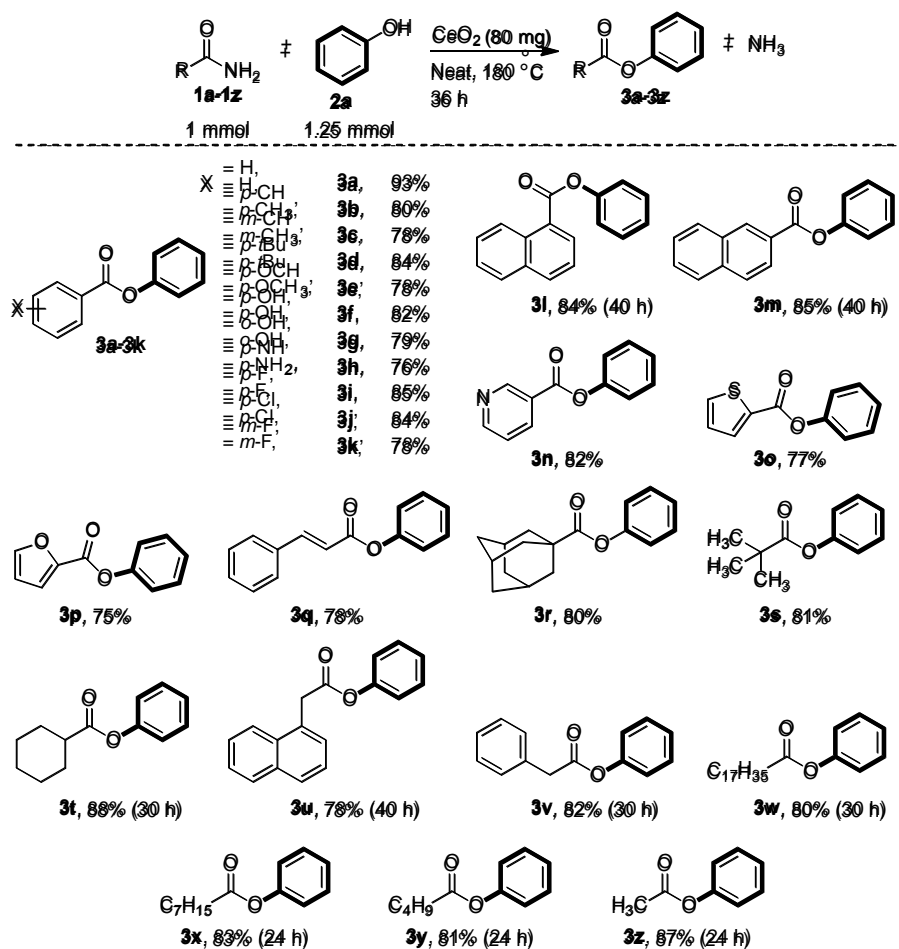
Scheme 2. Phenolysis of amides (**1a**-**1z**) with phenol (**2a**) into the corresponding esters (**3a**-**3z**); isolated yields are shown.

Subsequently, we examined the reaction scope with respect to the phenol component for the phenolysis of **1a** into the corresponding esters (Scheme 3). A series of phenols with electron-donating and -withdrawing substituents afforded the corresponding esters in good to high isolated yield (77-92%). Regardless of the position of the methyl group (*ortho*, *meta*, or *para*) in toluol, excellent yields of tolyl benzoate (**4a**-**4c**; 87-90%) were obtained. Moreover, phenols with *para*-methoxy, *para*-*n*-hexyl, *para*-*t*-butyl, *para*-phenyl, and *para*- or *meta*-amine substituents furnished the corresponding esters (**4d**-**4i**) in high yield. The *meta*- and *para*-amino-substituted phenols represent unprecedented examples for the catalytic phenolysis of *p*-aminophenyl benzoate (**4h**) and *m*-aminophenyl benzoate (**4i**), respectively. Phenols containing electron-withdrawing substituents such as the weakly electron-withdrawing *p*-fluoride-, *m*-chloride-, and *p*-bromide groups, or the moderately electron-withdrawing acyl group, as well as strongly electron-withdrawing trifluoromethyl and nitro groups generated the corresponding esters (**4j**-**4o**) in good to high yield. This phenolysis method is also applicable to phenol homologues including 1-naphthanol and 2-naphthanol for the synthesis of corresponding benzoate esters (**4p**: 80%; **4q**: 81%). Pyridin-4-ol, a hetero-homologue of phenol, is the first example that

engages in a phenolysis reaction with **1a** to form pyridin-4-yl benzoate ester (**4r**). Phenols that possess sterically hindered substituents including electron-donating and -withdrawing groups such as 3,5-dimethyl, 2,4,6-trimethyl, 2,4-6-trichloride, and 4-chloro-3,5-dimethyl substituents engaged in phenolysis reactions with **1a** to form the corresponding esters (**4t-4w**) in good to excellent yield (77-95%). This catalytic method is also applicable to the challenging hydroquinone substrate, which affords 1,4-phenylene dibenzoate ester (**4x**) in high yield (82%). The thus obtained esters (**4s-4x**) are the first examples to be obtained via the esterification of amides.
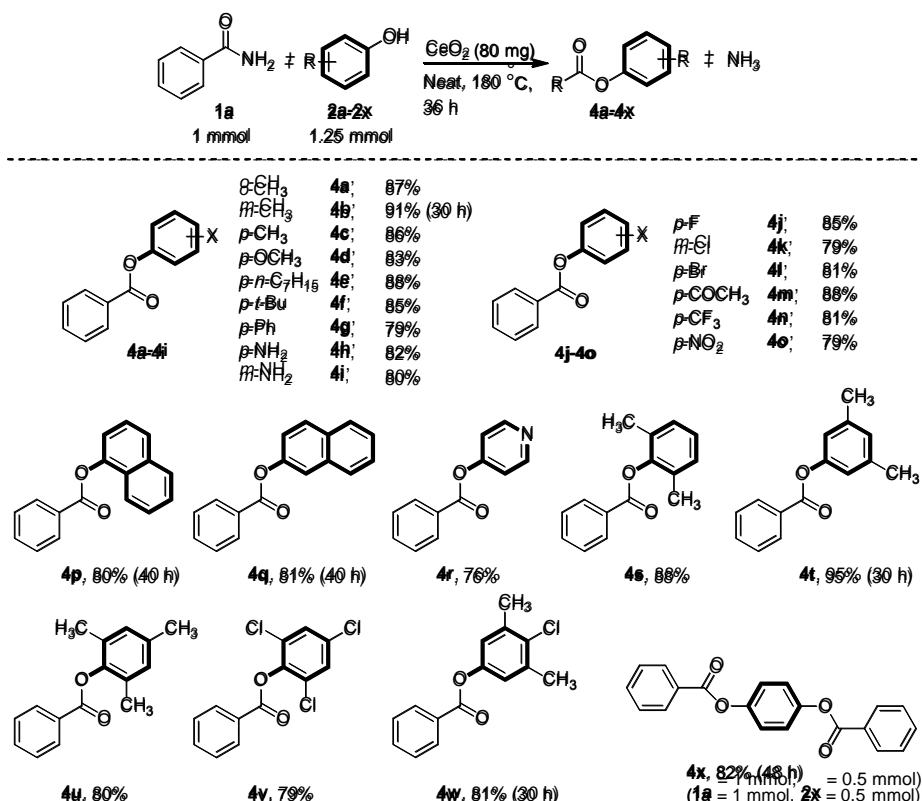
Scheme 3. Phenolysis of benzamide (**1a**) with various phenols (**2a-2x**) to afford the corresponding esters (**4a-4x**); isolated yields are shown.

We also examined this CeO$_2$-promoted phenolysis reaction (100 h) on the gram scale, using different amides (10 mmol) with phenols (12.5 mmol) and CeO$_2$ (80 mg); the observed results are summarized in Scheme 4. **1a**, acetamide, and *o*-hydroxy benzamide in combination with **2a** as well as **1a** in combination with different *p*-substituted phenols and phenol homologues were transformed into the corresponding esters in 80-93% yield. The TON values of these reactions were ~ 95-110 based on the number of Ce cations on the surface of CeO$_2$ (1.067 mmol g^{-1}).[43] It should be noted that product **3g** acts as an antiseptic and analgesic, while **4q** acts as an antiseptic.[18] Table 2 compares the catalytic activity of our method to that of the representative catalyst Zn(OTf)$_2$ in the phenolysis of amides. This homogeneous catalytic system is only effective for *N*-methoxy-activated

amides, whereas our system is effective for unactivated and *N*-methoxy-activated amides. In the phenolysis of **1a** by *p*-nitrophenol, the TON of the CeO$_2$ catalyst (95) is by two orders of magnitude higher than that of Zn(OTf)$_2$ for the same *N*-methoxy-activated amide.
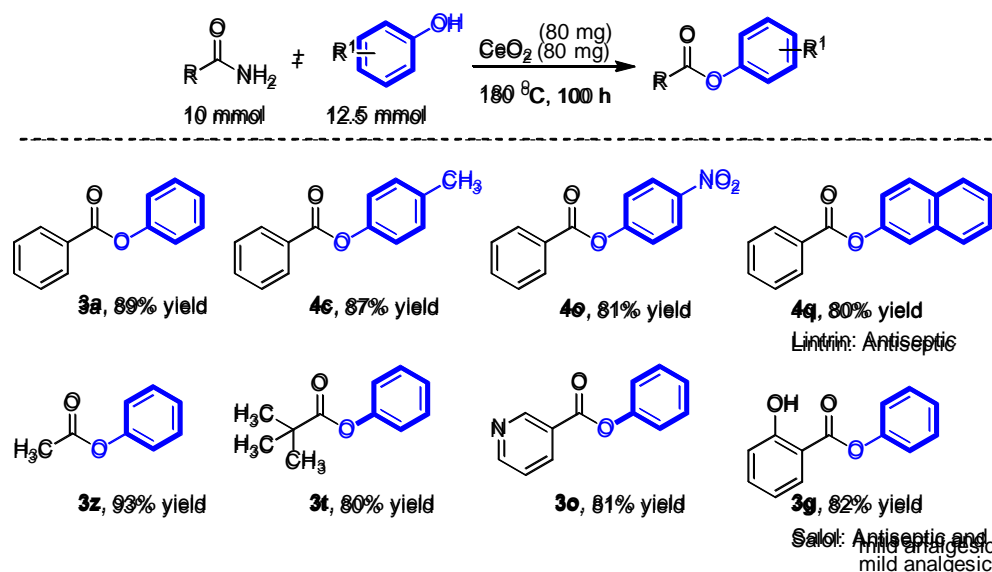
Scheme 4. Gram-scale phenolysis of amides to afford esters including the pharmaceutical agents Lintrin (**4q**) and Salol (**3g**); GC yields are shown.

Table 2. Phenolysis of benzamide (**1a**) with *p*-nitrophenol

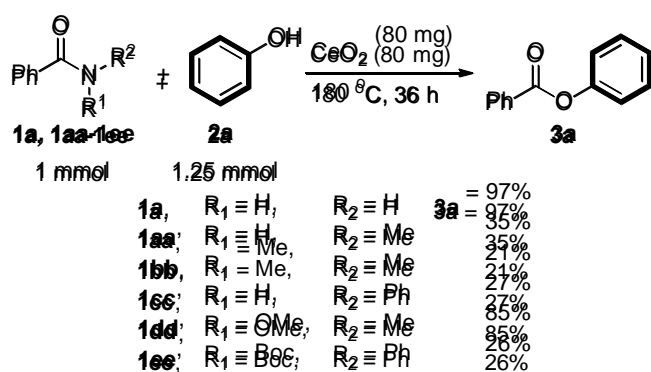| Catalyst	Additive	TON[a]	Catalyst reuse	Ref.
Zn(OTf)$_2$	0.4 equiv of TBAI 1.0 equiv of K$_2$CO$_3$ 15 mL of DMF	1.9	no	18
CeO$_2$	none	95	4 runs	this work

[a] TON per Ce cation on the CeO$_2$ surface.

Scheme 5 shows the results of the applicability and a comparative reactivity study of the phenolysis of unactivated and activated primary, secondary, and tertiary aromatic (benzamides), as well as aliphatic (acetamides) amides with phenols under the previously established optimized reaction conditions. A series of unactivated benzamides (**1a**, *N*-methylbenzamide, *N,N*-dimethylbenzamide, and *N*-phenylbenzamide) were subjected to this phenolysis and the results regarding the formation of the corresponding phenyl benzoate esters reveal a significant reactivity trend, i.e., the reactivity decreases in the order: **1a**>**1aa**>**1cc**>**1bb** based on the yield of representative ester **3a** (97-27%). This trend was attributed to the steric hindrance generated by the methyl and phenyl substituents. A similar reactivity trend was observed for the reactions of unactivated acetamides (acetamides, *N*-methylacetamide, *N,N*-dimethylacetamide, *N*-phenylacetamide) with **2a** in the formation of the corresponding acetate ester **3z** (98-33%), i.e., the reactivity decreases in the
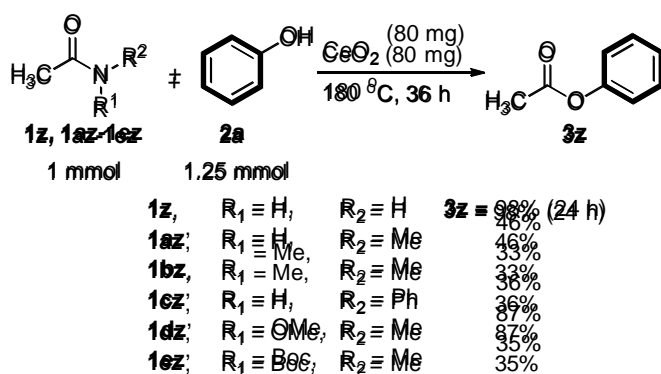
order: **1z>1az>1cz>1bz**. We also determined an experimental activation energy through an Arrhenius plot for the esterification of acetamide with different alcohols including *n*-octanol, benzyl alcohol, and phenol (Figure 4). The results show that a higher activation energy is required for the phenolysis of acetamide compared to that for the alcoholysis using *n*-octanol or benzyl alcohol.[14] This could potentially be rationalized in terms of the poor nucleophilicity and the generation of a weaker conjugate base of the phenoxide species relative to that of the alkoxide species, which retards the phenolysis toward the carboxylate species.

It is also important to consider the reactivity of the amides for this phenolysis by installation of amide-activating groups on the N atom under the concept of the amide-bond-destabilization platform.[4] In this context, we have examined activated benzamides (*N*-methoxy-*N*-methylbenzamide **1dd** and *tert*-butyl benzoyl(phenyl)carbamate **1ee**) and acetamides (*N*-methoxy-*N*-methylacetamide **1dz** and *tert*-butyl acetyl(methyl) carbamate **1ez**). The results show that amides activated by a methoxy group engage in the phenolysis and generate the corresponding benzoate ester (**3a**: 85%) and acetate ester (**3z**: 87%) in high yield. *Tert*-butoxycarbonyl-(Boc)-activated benzamide **1ee** and acetamide **1dz** were also tested and furnished the corresponding esters in low yield. This was attributed to a scissoring of the Boc group, which would lead to the unactivated *N*-phenylbenzamide (**1cc**) and *N*-methylacetamide (**1az**).

(A) Different *N*-substituted benzamides

	R_1	R_2		
1a,	$R_1 \equiv H$,	$R_2 \equiv H$	**3a** =	97%
1aa,	$R_1 \equiv Me$,	$R_2 \equiv Me$		35%
1bb,	$R_1 = Me$,	$R_2 \equiv Me$		21%
1cc,	$R_1 \equiv H$,	$R_2 \equiv Ph$		27%
1dd,	$R_1 \equiv OMe$,	$R_2 \equiv Me$		85%
1ee,	$R_1 \equiv Boc$,	$R_2 \equiv Ph$		26%

(B) Different *N*-substituted acetamides

	R_1	R_2		
1z,	$R_1 \equiv H$,	$R_2 \equiv H$	**3z** =	98% (24 h)
1az,	$R_1 \equiv Me$,	$R_2 \equiv Me$		46%
1bz,	$R_1 = Me$,	$R_2 \equiv Me$		33%
1cz,	$R_1 \equiv H$,	$R_2 \equiv Ph$		36%
1dz,	$R_1 \equiv OMe$,	$R_2 \equiv Me$		87%
1ez,	$R_1 \equiv Boc$,	$R_2 \equiv Me$		35%

Scheme 5. Phenolysis of (A) activated and unactivated *N*-substituted benzamides (**1a**, **1aa-1ee**) into phenyl benzoate (**3a**), and (B) activated and unactivated acetamides (**1j**, **1jj-1nn**) into phenyl acetate (**3z**); reaction conditions: CeO_2 (80 mg), 180 °C, 24-36 h, under N_2, amide (1 mmol), **2a** (1.25 mmol); GC yields are shown.
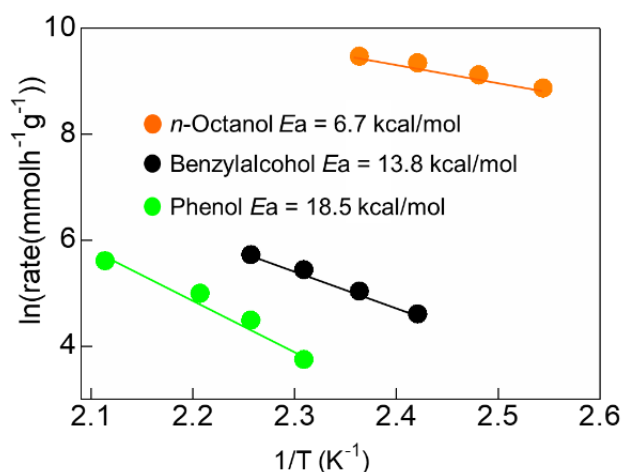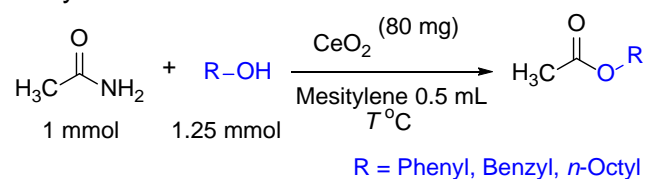

R = Phenyl, Benzyl, *n*-Octyl

Figure 4. Arrhenius plots for the esterification of acetamide by *n*-octanol (120-150 °C, 1 h), benzyl alcohol (135-175 °C, 2 h), and **2a** (160-200 °C, 4 h).

To compare and ascertain the selectivity trends of this phenolysis reaction for different amides, we examined a series of competitive reactions (Scheme 6). In this comparison, aliphatic and aromatic amides (Scheme 6(1)) were compared, i.e., the competitive reaction of **1a** and **1z** with **2a**. The results show that acetamide reacts predominantly with **2a** in the presence of **1a** to give ester **3z** (81% yield). Secondly, we compared the reactions of amides that contain tertiary (**1t**) or quaternary α-carbon atoms (**1s**) with **2a** (Scheme 6(2)) to get further insight into how the steric and electronic effects of the amide substrates affect the phenolysis. In the presence of the sterically more hindered amide (**1s**) **2a** preferentially reacts with **1t** to afford the corresponding ester (**3t**) in 77% yield. The competitive reaction of **1a** and nicotinamide **1n** with **2a** was also examined, which revealed that **2a** preferentially reacts with **1a** (Scheme 6(3)). Finally, we compared the competitive reactions of aliphatic and aromatic alcohols with **1z**. The results show that the aromatic alcohol **2a** is completely inert in the presence of benzyl alcohol **2y** and *n*-octanol **2z**, which generate the corresponding esters (**4y** and **4z**) in 31% and 68% yield respectively. These results could potentially be used as guidelines for the selective synthesis of esters from a mixture of amides or alcohols.

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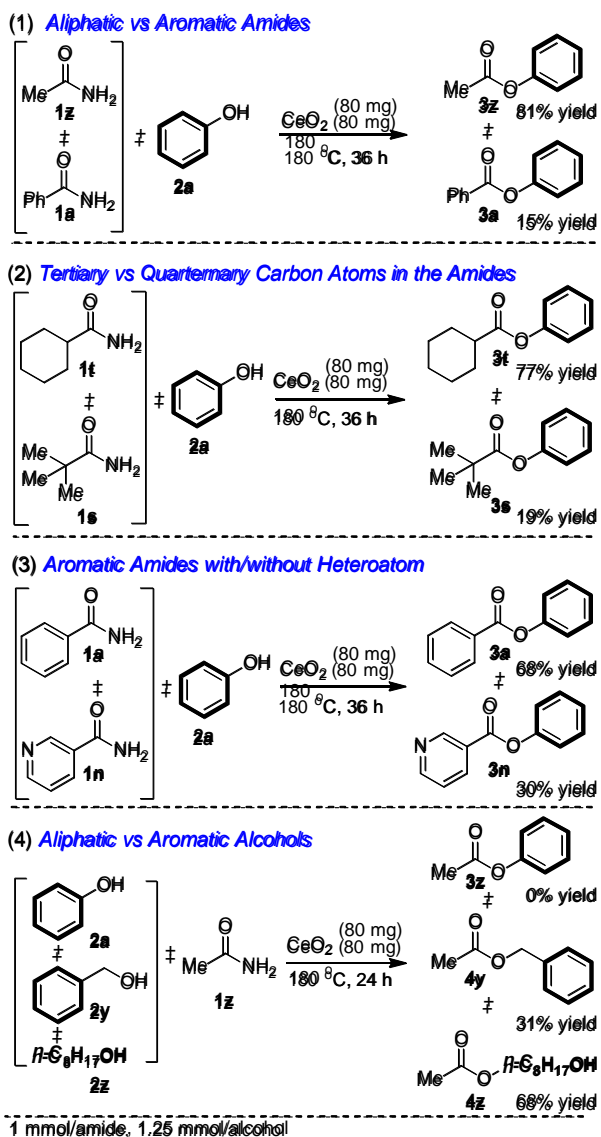
Scheme 6. Competitive phenolysis reactions using (1) aromatic and aliphatic amides, (2) amides containing tertiary or quaternary α carbon atoms, (3) aromatic and heteroaromatic amides, and (4) acetamide with a mixture of phenol, benzyl alcohol and *n*-octanol. GC yields are shown.

Mechanistic Study

The structure of the CeO_2 catalyst was characterized by XRD analysis (Figure S3), N_2 adsorption measurements, and high-angle annular dark-field scanning transmission electron microscopy (HAADF-STEM) images (Figure S4). The transmission electron microscopy (TEM) images of this sample have already been reported in our previous study.[14] Summarizing these results, our standard CeO_2 catalyst is composed of nanometer-sized CeO_2 particles with a fluorite-type structure and a BET specific surface area (S_{BET}) of 81 m^2 g^{-1}. The results of the temperature-programmed desorption (TPD) of NH_3 and CO_2 in our previous study[14] indicate the presence of acid and base sites on the standard CeO_2 catalyst. Figure 5 shows the IR spectrum of adsorbed phenol species on the CeO_2 surface at 120 °C. The observed peaks were assigned to phenoxide species coordinated to a cationic site.[45] This result indicates that the Lewis-acid site (Ce cation) is close to a base site (proton-abstraction site).
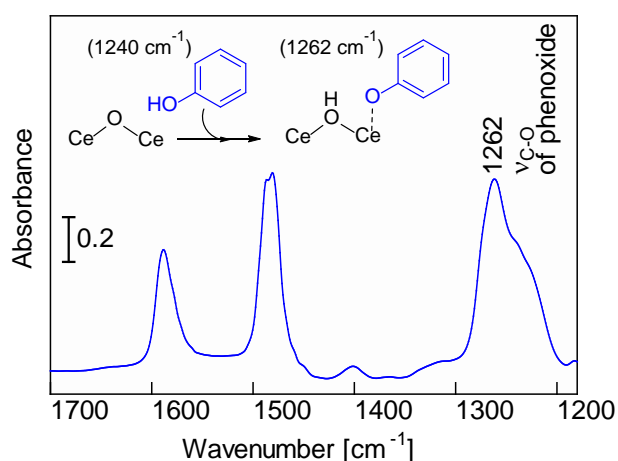

Figure 5. IR spectrum of phenoxide species on the CeO_2 surface at 120 °C (t = 700 s). Phenol (1 µL) was introduced to CeO_2, followed by purging with He (700 s).

We calcined CeO_2 catalysts at three different temperatures (600 °C, 800 °C, and 1000 °C). It should be noted that our standard CeO_2 catalyst was calcined at 600 °C. The XRD results (Figure S3) show that these catalysts share the same fluorite-type structure. Using these catalysts, we measured the rate of the formation of phenyl benzoate under conditions where conversions were < 30%. The rate per catalyst weight gradually decreased with increasing calcination temperature (Figure 6). The BET surface areas of the CeO_2 catalysts significantly decreased with increasing calcination temperature. The specific rate per surface areas of the CeO_2 catalysts increased with increasing calcination temperature. Taking into account a general trend that the number of surface oxygen vacancies and Ce^{3+} species on CeO_2 surfaces decreases upon calcination of CeO_2 at high

temperatures, these results suggest that the formation of a highly crystalline CeO_2 surface with less Ce^{3+} and oxygen vacancies plays an important role in this catalytic system.
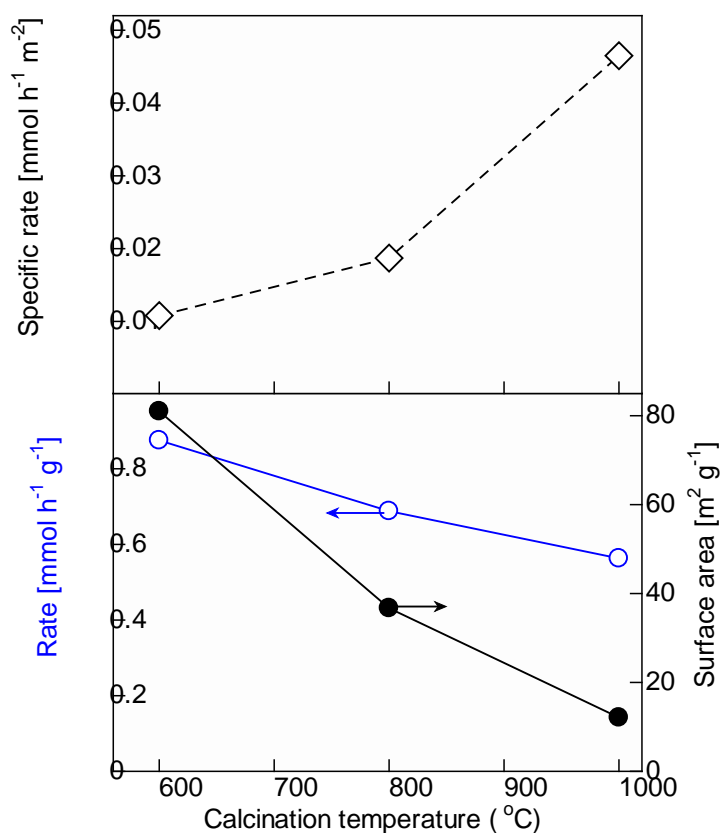

Figure 6. Effect of the calcination temperature of CeO_2 on the rates per catalyst weight (blue line) and surface areas (black line). (A) The initial reaction rate of the formation of phenyl benzoate per catalyst weight as a function of the calcination temperature. (B) The initial reaction rate normalized by the surface areas of the CeO_2 catalysts as a function of the calcination temperature. The reaction was carried out for 4 h under optimized conditions.

To elucidate the reaction mechanism of the CeO_2-catalyzed phenolysis reaction, control reactions and kinetic studies were carried out. In our previous studies on the esterification of amides by alcohols via cleavage of the C–N bond over CeO_2,[14,44] we have demonstrated that the reaction proceeds via the transformation of the amide substrate into a lattice-oxygen-coordinated carboxylate initiated by the nucleophilic attack of the lattice-bound oxygen atom of CeO_2 onto the carbonyl carbon atom of the amide, followed by a reaction with the alkoxide (formed by the deprotonation of an alcohol) to give the ester. Both the experimental and computational investigations demonstrated that the cooperative effects of the acid-base functions of CeO_2 are important for an efficient progression of the alcoholysis of amides via the cleavage of the C–N bond, and consequently, CeO_2 exhibited the best catalytic performance. Based on this finding, we speculated that the CeO_2-coordinated carboxylate is the crucial intermediate, rather than a free acid and/or an aldehyde, which undergo reactions with the

phenoxide to form phenolic esters under the present catalytic reaction conditions. Representative control reactions (Scheme 7) between phenol and benzoic acid and benzaldehyde under standard reaction conditions were thus tested. The observed low yield of the phenyl benzoate (3-4%) supports our hypothesis and confirms that free acids or aldehydes do not act as reaction intermediates.

Control reactions

Benzoic acid with phenol
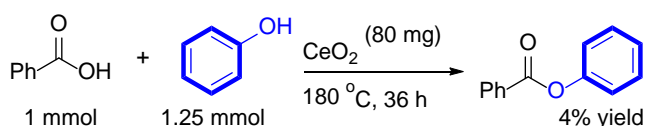
Benzaldehyde with phenol
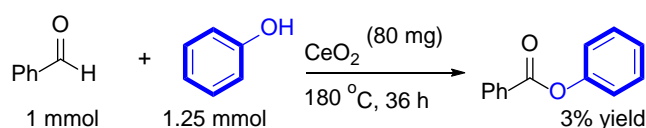
Scheme 7. Control reactions between phenol and benzoic acid or benzaldehyde under standard reaction conditions.

The influence of the concentration of acetamide and phenol on the initial rate of formation of phenyl acetate ester was also explored (Figure 7). We discovered a linear relationship on double logarithmic plots and the slopes of the lines correspond to the order (n) of the reaction. The ester formation rate increased with the concentration of phenol, which followed first-order reaction kinetics ($n = +1.02$, $R^2 = 0.99$) (Figure 7A). Conversely, a negative slope ($n = -0.19$) was observed upon increasing the concentration of acetamide (Figure 7B), which suggests that phenol is involved in the kinetically important steps.

The influence of different substituents (electron-donating and -withdrawing) on the phenol ring toward the reactivity divergence of the phenolysis reaction was examined using a Hammett study. During the phenolysis of benzamide (Figure 8A), the logarithm of the reaction rates was correlated directly to the substituent constant (σ), indicating that a linear free-energy relationship exists, wherein the slopes of the reaction rates are $0 < \rho < 1$. This in turn implies that the reaction is not very sensitive to the nature of the substituents on phenol and that a negative charge is generated (or a positive charge is lost) in the transition state of a kinetically important step.

The phenolysis of *para*-substituted benzamides with phenol revealed a good relationship between $\log(k_X/k_H)$ and the Brown-Okamoto parameter (σ^+).[27] Specifically, we observed good linearity with a positive slope ($\rho = +0.26$) (Figure 8B), which indicates that a transition state in the rate-limiting step of the phenolysis contains a negative charge at the α-carbon atom adjacent to the

benzene ring. Accordingly, it can be concluded that the nucleophilic addition of the phenoxide species to the activated carbonyl carbon atom of the amide proceeds via a negatively charged transition state, and that this could be the rate-limiting step of this reaction.[27]

Based on aforementioned experimental results and our previous computational studies on esterification of amides by alcohols via C–N bond cleavage over CeO_2,[14,44] a plausible reaction mechanism for the CeO_2-catalyzed phenolysis of acetamide to form phenyl acetate ester is proposed in Figure 9. The catalytic cycle should start with the deprotonation of the phenol to phenolate on one of the acid-base pair sites of CeO_2. Then, the adsorbed acetamide is activated by a nucleophilic attack of a lattice-bound oxygen of CeO_2 to produce the acetate. After the deamination step, a negatively charged transition state is produced via the addition of the phenolate to the acetate and this step would probably be rate-determining. Finally, the acetate ester would be desorbed to regenerate the free acid-base sites of the CeO_2 catalyst.

Thermodynamically, the reactions seem to proceed uphill, as amides are usually more stable than esters. A possible thermodynamic driving force that would explain the high yields of esters could be the release of NH_3 from the liquid phase, which would decrease the concentration of the product (NH_3) in the liquid phase, where the amide, phenol, ester, and catalyst are present.
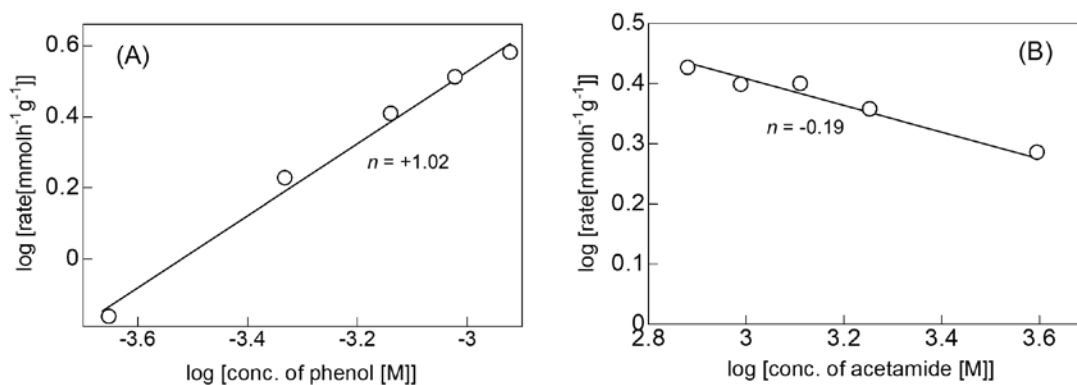

Figure 7. Formation rate of phenylacetate as a function of the concentration of (A) phenol (0.22 M to 1.19 M) and (B) acetamide (0.25 M to 1.32 M); reaction conditions: CeO_2 (80 mg), T = 180 ºC, t = 4 h.
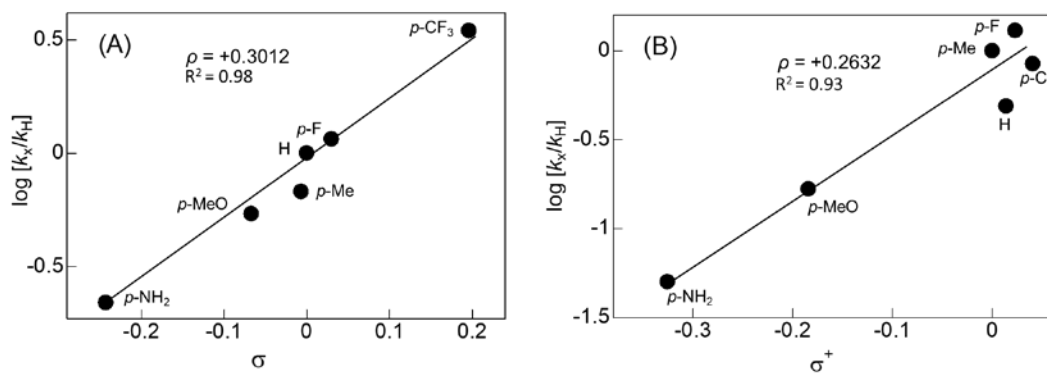
Figure 8. (A) Hammett study for sterically comparable *p*-substituted phenols with benzamide; (B) Brown-Okamoto plot for the phenolysis of *p*-substituted benzamide with phenol; reaction conditions: benzamide (1 mmol), phenol (1.25 mmol), CeO_2 (80 mg), $T = 180$ °C, $t = 4$ h.
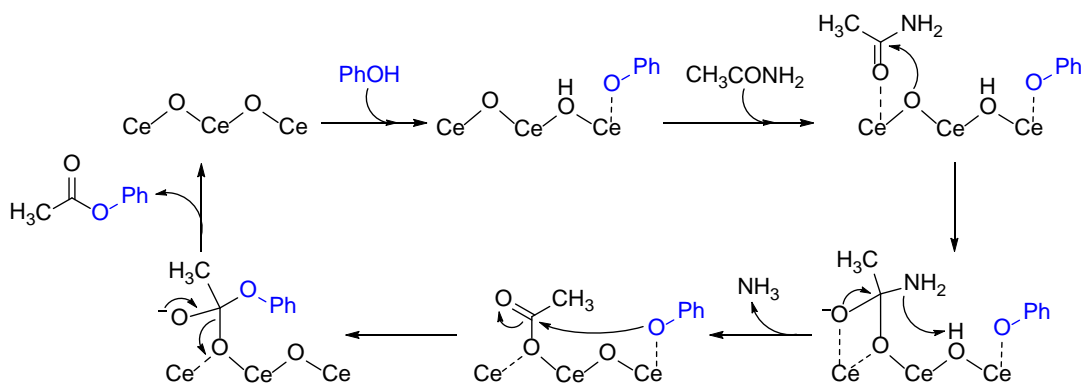

Figure 9. Plausible reaction mechanism for the CeO_2-catalyzed phenolysis of acetamide with phenol.

Conclusion

In summary, we have developed a reusable catalytic method for the phenolysis of unactivated amides into the corresponding phenolic esters using CeO_2 as a catalyst. This catalytic system overcomes the typical stability issue of amides and phenols and thus offers a straightforward route to phenolic esters. This method is compatible with a wide range of substrates including various functionalized amides and phenols. A plausible mechanistic study suggests that the rate-determining step of the reaction proceeds via a negatively charged transition state, in which the phenoxide engages in a nucleophilic addition to the carboxylate species, followed by the transformation into the ester. Compared to previously reported catalytic methods for the phenolysis of activated amides, our method offers the following advantages: 1) catalyst reusability and easy catalyst/product separation, 2) a wide substrate scope including aryl, heteroaryl, ally, and alkyl amides as well as different homologues of phenols, and 3) a higher TON compared to those of the corresponding activated amides.

Experimental section

General

We used commercially available organic and inorganic compounds that were purchased from Sigma Aldrich, Tokyo Chemical Industry, Wako Pure Chemical Industries, Kishida Chemical, or Mitsuwa Chemicals. The reagents were used as received. *N*-Boc-*N*-methyl acetamide and *N*-Boc-*N*-methyl benzamide were synthesized according to literature procedures.[25,46] Substrates and products were analyzed by GC (Shimadzu GC-2014) and GC-MS (Shimadzu GCMS-QP2010) with an Ultra ALLOY capillary column UA+-1 (Frontier Laboratories Ltd.) using N_2 and He as the carrier gas. ^{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) or JEOL-ECX ([1]H: 400 395.88; [13]C: 99.54 MHz) spectrometer with tetramethylsilane as an internal standard.

Catalysts preparation

CeO_2 (Type A) was supplied from Daiichi Kigenso Kagaku Kogyo Co., Ltd. and calcined (600 °C, 3 h) prior to use. TiO_2 (JRC-TIO-8) was supplied by the Catalysis Society of Japan. γ-Al_2O_3 was prepared by calcination (900 °C, 3 h) of γ-AlOOH (Catapal B Alumina, Sasol). SiO_2 (Q-10) was supplied by Fuji Silysia Chemical Ltd., while Nb_2O_5 was prepared by calcination (500 °C, 3 h) of niobic acid (CBMM). ZnO was prepared by calcination (500 °C, 3 h) of a hydroxide of Zn (Kishida Chemical). Y_2O_3 and ZrO_2 were prepared by calcination (500 °C, 3 h) of the corresponding hydroxides, which were prepared via hydrolysis of $Y(NO_3)_3.6H_2O$ and $ZrO(NO_3)_2 \cdot 2H_2O$ with an aqueous NH_4OH solution. CaO

was prepared by calcination (500 °C, 3 h) of $Ca(OH)_2$ (Kanto Chemical). La_2O_3 and $Ce(NO_3)_4$ were supplied by Wako Pure Chemical Industries, Japan. $Sc(OTf)_3$ (>98%) and $C_3CeF_9O_9S_3$ were obtained from TCI Co. Ltd., while $Ce_3(PO_4)_4$ (min. 99%) was supplied by Alfa Aesar, Ward Hill, China. Montmorillo-nite K10 clay (mont. K10) and Nafion-SiO_2 composite were purchased from Sigma-Aldrich.

Catalyst characterization

In situ FT-IR spectra were recorded at 120 °C by using a JASCO FT/IR-4200 with an MCT (Mercury-Cadmium-Telluride) detector. A sample (40 mg) was pressed to obtain a self-supporting pellet (ϕ = 2 cm). The obtained pellet was placed in the quartz IR cell with CaF_2 windows connected to a conventional gas flow system. Prior to the measurement, the sample pellet was heated under He flow (20 cm^3 min^{-1}) at 500 °C for 0.5 h. After cooling to 120 °C under the He flow, 1 µL of phenol was injected to the sample individually through a line which was preheated at ca. 200 °C to vaporize them. Spectra were measured accumulating 15 scans at a resolution of 4 cm^{-1}. A reference spectrum taken at 120 °C under He flow was subtracted from each spectrum. XRD measurements were conducted using a Rigaku Miniflex with a Cu-Kα radiation source. The ICP-AES analysis was performed using a SHIMADZU ICPE-9000. HAADF-STEM images were recorded on a JEM-ARM200F microscope (JEOL) at an acceleration voltage of 200 kV. The Cs-corrector CESCOR (CEOS) was used in the STEM mode.

Typical procedure for the phenolysis of amides

A Pyrex tube (20.0 mL) was charged with the amide (1.0 mmol), phenol (1.25 mmol), CeO_2 (80.0 mg), and dodecane (0.2 mmol) as an internal standard. The reaction mixture was heated to 180 °C and stirred for 36 h under an N_2 atmosphere. After completion of the reaction, isopropanol (3 mL) was added and the products were analyzed by the GC and GC-MS. The isolation of the products was accomplished by column chromatography on silica gel 60 (spherical, 50-100 µm, Kanto Chemical Co. Ltd.) with hexane/ethylacetate (75/25) as the eluent. The isolated products were then analyzed by GC and GC-MS as well as ^{1}H and ^{13}C NMR spectroscopy. Isolated yields were determined relative to the starting amides.

on Chemical Sciences (IRCCS)" and "Elements Strategy Initiative to Form Core Research Center". The authors are indebted to the technical division of the Institute for Catalysis (Hokkaido University) for manufacturing experimental equipment and thank technical staffs of the Open Facility of Hokkaido University for their help with STEM analyses.

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Entry for the Table of Contents

FULL PAPER

The heterogenous catalyst CeO_2 promotes the phenolysis of unactivated amides under solvent- and additive-free conditions. The developed catalytic method tolerates a broad variety of functional groups (>50 examples) in this challenging transformation and affords the corresponding phenolic esters.

Direct Phenolysis of Unactivated Amides to Phenolic Esters

$$Ar/R \overset{O}{\underset{R_2}{\overset{|}{\underset{}{N}}}} R_1 + ArOH \xrightarrow[\text{Neat, no additives}]{\text{Reusable } CeO_2 \text{ catalyst}} Ar/R \overset{O}{\underset{}{\overset{|}{\underset{}{}}}} OAr$$

Md. Nurnobi Rashed, S.M.A. Hakim Siddiki,* Abeda S. Touchy, Md. A. R. Jamil, Sharmin S. Poly, Takashi Toyao, Zen Maeno, Ken-ichi Shimizu,*

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Direct Phenolysis Reactions of Unactivated Amides into Phenolic Esters Promoted by a Heterogeneous CeO₂ Catalyst