



Accepted Article

Title: Esterification of Tertiary Amides by Alcohols Through C-N Bond Cleavage over CeO2

Authors: Ken-ichi Shimizu, Takashi Toyao, Md. Nurnobi Rashed, Yoshitsugu Morita, Takashi Kamachi, S. M. A. Hakim Siddiki, Md. A. Ali, A. S. Touchy, Kenichi Kon, Zen Maeno, and Kazunari Yoshizawa

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: ChemCatChem 10.1002/cctc.201801098

Link to VoR: http://dx.doi.org/10.1002/cctc.201801098



WILEY-VCH

www.chemcatchem.org

Esterification of Tertiary Amides by Alcohols Through C–N Bond Cleavage over CeO₂

Takashi Toyao,^[a,b] Md. Nurnobi Rashed,^[a] Yoshitsugu Morita,^[c,d] Takashi Kamachi,^[b,c,e] S. M. A. Hakim Siddiki,^{*[a]} Md. A. Ali,^[a] A. S. Touchy,^[a] Kenichi Kon,^[a] Zen Maeno,^[a] Kazunari Yoshizawa,^[b,c] Ken-ichi Shimizu^{*[a,b]}

Abstract: CeO₂ has been found to promote ester forming alcoholysis reactions of tertiary amides. The present catalytic system is operationally simple, recyclable, and it does not require additives. The esterification process displays a wide substrate scope (> 45 examples; up to 93% isolated yield). Results of a density functional theory (DFT) study combined with in situ FT-IR observations indicate that the process proceeds through rate limiting addition of a CeO₂ lattice oxygen to the carbonyl group of the adsorbed acetamide species with energy barrier of 17.0 kcal/mol. This value matches well with experimental value (17.9 kcal/mol) obtained from analysis of the Arrhenius plot. Further studies by in situ FT-IR and temperature programmed desorption using probe molecules demonstrate that both acidic and basic properties are important, and consequently, CeO₂ showed the best performance for the C-N bond cleavage reaction.

Introduction

Amides are important structural moieties in the preparation of a wide variety of pharmaceutical compounds and natural products.^[1] Moreover, amides are thermodynamically stable compounds owing to delocalization of the nitrogen lone pair into the carbonyl moiety. Whereas C–N bonds of amides are readily cleaved under mild conditions by enzymes such as proteases,^[2] similar non-enzymatic processes usually require strongly acidic or basic conditions.^[3] Although much effort has been devoted to developing C–N bond cleavage reactions,^[4] synthetic

- [b] Dr. T. Toyao, Dr. T. Kamachi, Prof. Dr. K. Yoshizawa, Prof. Dr. K. Shimizu Elements Strategy Initiative for Catalysis and Batteries. Kyoto.
- Elements Strategy Initiative for Catalysis and Batteries, Kyoto University, Katsura, Kyoto 615-8520 (Japan)
- [c] Dr. Y. Morita, Dr. T. Kamachi, Prof. Dr. K. Yoshizawa Institute for Materials Chemistry and Engineering and IRCCS, Kyushu University, Fukuoka 819-0395 (Japan)
- [d] Present address Dr. Y. Morita Department of Applied Chemistry, Faculty of Science and Engineering, Chuo University, 1-13-27 Kasuga, Bunkyo-ku (Japan)
 [e] Present address Dr. T. Kamachi
- Department of Life, Environment and Materials Science, Fukuoka Institute of Technology (FIT), 3-30-1 Wajiro-Higashi, Higashi-ku, Fukuoka 811-0295 (Japan)
 - Supporting information for this article is given via a link at the end of the document.

applications of amide chemistry are still limited by this reactivity issue. Among amide transformations, alcoholysis has received much attention because the resulting esters are more reactive and, as a result, undergo many useful transformations.^[5] Although various non-catalytic methods have been reported for amide alcoholysis,^[6] they generally suffer from the required use of excess amounts of promoters such as HCI and NaNO₂, the generation of inorganic or organic wastes, and limited substrate scope. It is noteworthy that twisted amides undergo alcoholysis under relatively mild neutral conditions.^[7] However, synthetic application of these substances are very limited.

From the viewpoint of sustainable chemistry, amide alcoholysis ideally should be carried out using catalytic processes. In this context, Mashima and co-workers developed a catalytic amide alcoholysis protocol that uses Zn(OTf)2, Sc(OTf)₃ or Mn(acac)₂ together with additives as promotors.^[8] Later, Atkinson and co-workers demonstrated that Sc(OTf)3 is an effective catalyst for this reaction.^[9] Subsequently, our group described an amide alcoholysis reaction, which uses CeO₂ as a heterogeneous catalyst and does not require additives.^[10] The CeO₂ catalyzed ester forming reaction occurs with 1-3 orders of magnitude higher rates than those promoted by other metal oxides. Moreover, the CeO₂ catalyzed reaction has a wide amide substrate scope and CeO₂ can be recycled. Furthermore, the results of density functional theory (DFT) calculations suggest that promotion of alcoholysis of primary amides by CeO₂ is a consequence of synergistic action of Lewis acid and base sites of the surface of the metal oxide.[11]

The reports describing both homogeneous and heterogeneous catalytic amide esterification processes represent important contributions to the field of synthetic chemistry. However, the fact that these catalytic reactions only apply to primary and secondary amides limits their preparative versatility. In general, C-N bond cleavage reactions of tertiary amides are more difficult owing to the higher degree of steric blocking of the carbonyl group and thermodynamic limitations associated with reverse reactions between ester and secondary amine products, which are more facile than those of NH₃ and primary amines produced from primary and secondary amides.^[12] In order to overcome this limitation, Garg and coworkers recently developed a method for conversion of various amides, including tertiary amides, to the corresponding esters that utilizes a Ni-based N-heterocyclic carbene (NHC) complex as a catalyst.^[12] In addition, this strategy was extended to develop a C-C bond forming reaction that produces ketones from tertiary amides.^[13] Several subsequent reports have described the use of similar catalysts (e.g., Pd-based NHC complexes) for C-N bond cleavage reactions of tertiary amides.^[14] Although enhancing the synthetic importance of C-N

[[]a] Dr. T. Toyao, Mr. Md. Nurboni Rashed, Dr. S. M. A. H. Siddiki, Dr. Md. A. Ali, Dr. A. S. Touchy, Dr. K. Kon, Dr. Z. Maeno, Prof. Dr. K. Shimizu, Institute for Catalysis and IRCCS, Hokkaido University, N-21, W-

^{10,} Sapporo 001-0021 (Japan) E-mail: hakim@cat.hokudai.ac.jp, kshimizu@cat.hokudai.ac.jp

bond cleavage reactions, the processes require additives and/or the use of elaborate ligand such as NHC, and difficulties are encountered with catalyst recycling. In order to be environmentally benign and adaptable to large-scales, catalyst employed for amide C–N bond cleavage reactions need to be readily available, heterogeneous and recyclable. To the best of our knowledge, such recyclable and additive-free heterogeneous systems have not yet been reported.

In the studies described below, we have described a heterogeneous catalytic system for esterification of tertiary amides by alcohols, which utilizes CeO_2 as the catalyst. The developed catalytic process is facile and it has a wide amide and alcohol substrate scope. The combined results arising from theoretical and experimental studies indicate that the reaction proceeds through the same mechanistic pathway followed in the alcoholysis reaction of primary amides. Importantly, cooperative effects of acid-base functions of CeO_2 would be a key for efficient promotion of the reaction. The results of this investigation have not only demonstrated the utility of a new C– N bond cleavage reaction of amides, they have also led to a better understanding of the behavior of CeO_2 , a catalyst that has attracted much attention recently.^[15]

Results and Discussion

The initial phase of this effort was designed to screen catalysts for the reaction between N,N-dimethylbenzamide and 1-octanol that forms octyl benzoate. Reactions were performed using the following conditions: amide (1 mmol), alcohol (4 mmol), CeO₂ (80 mg) and dodecane (0.2 mmol) as an internal standard in a Pyrex reaction tube (18 mL) under a N2 atmosphere at 175 °C for 36 h (see Supporting Information for detailed procedure of the reaction and a picture of the reaction apparatus). In reactions designed to remove the formed N,Ndimethylamine, HY zeolite (SiO₂/Al₂O₃ = 5.5) (0.1 g) enclosed in a filter paper was placed at the upper portion of the reaction vessel. The results (Table 1) showed that, among the metal oxides, solid acid and homogeneous catalysts tested, CeO2 (Daiichi Kigenso Kagaku Kogyo Co., Ltd (Type A), calcined at 600 °C for 3 h. see Figure 1 for TEM images) promoted the most efficient process giving the target ester in 97% GC yield. In addition, it was found that the CeO2 catalyzed reaction performed without utilizing HY zeolite generates the target ester in 94% yield. We checked the effect of the use of HY zeolite for the reaction several times and found that the reaction with the zeolite always gives better yield. In addition, the formed secondary amine (N.N-diethylamine) trapped by the HY zeolite was experimentally detected after the reaction between N,Ndiethylbenzamide and 1-octanol that forms octyl benzoate. Note that N.N-diethylbenzamide was used as a substrate for this purpose for ease of handling thanks to its higher boiling point than that of N,N-dimethylamine. The use of the HY zeolite could overcome the thermodynamic limitations associated with reverse reactions between the formed ester and secondary amine that is an well-known difficulty for the ester forming alcoholysis reactions of tertiary amides.[12,16]

Table	1.	Catalyst	screening	for	ester	formation	from	N,N-
dimethy	/lbenz	zamide an	d 1-octanol.	a				

ů.			U.
N ^{-Me}	+ 110	Catalyst	0 n-C ₇ H ₁₅
Me	HO <i>n</i> -C ₇ H ₁₅	175 °C, 36 h	
1 mmol	2 mmol		

Entry	Catalyst	Yield [%]⁵
1	CeO ₂	97
2 ^c	CeO ₂	94
3	Nb ₂ O ₅	43
4	CaO	38
5	ZrO ₂	28
6	MgO	24
7	TiO ₂	7
8	Al ₂ O ₃	6
9	Y ₂ O ₃	4
10	SiO ₂	6
11	ZnO	3
12	Fe-mont	20
13	Mont. K10	8
14	H-ZSM-5 (22)	7
15	H-Beta (75)	5
16	H-Y (5.5)	5
17	Amberlyst-15	38
18	Nafion-SiO ₂	12
19	Sulfated ZrO ₂	5
20 ^d	Sc(OTf) ₃	43
21 ^d	Ce(NO ₃) ₄	35
22 ^d	Ce ₃ (PO ₄) ₄	29
23 ^d	<i>p</i> -Toluenesulfonic acid (PTSA)	22
24 ^d	H2SO4	23

^aReaction conditions: 80 mg catalyst, 175 °C, 36 h, N₂ atmosphere, *N*,*N*-dimethylbenzamide (1 mmol), 1-octanol (2 mmol), HY zeolite (0.1 g) as a trapping agent, *n*-dodecane (0.2 mmol) as an internal standard. ^bYields were determined by using GC. ^cWithout HY zeolite. ^dThe same molar amount employed for CeO₂ was used.

The use of soluble Ce salts such as $Ce(NO_3)_4$ and $Ce_3(PO_4)_4$ as catalysts leads to lower yielding raections, Notably, the typical homogeneous Brønsted acids, *p*-toluenesulfonic acid (PTSA) and H₂SO₄, catalyze reactions that occur in only 22% and 23% respective yields.



Figure 1. TEM images of the CeO₂ catalyst.

Results from studies exploring the effect of alcohol concentration (see **Table S1** in the Supporting Information) showed that, even though a slight excess of 1-octanol was necessary to bring about complete reaction, 86% yield of *N*,*N*-dimethylbenzamide was obtained when 1.0 eq of the alcohol was employed. In addition, a gram-scale, CeO_2 promoted reaction of *N*,*N*-dimethylbenzamide using 2 eq. of 1-octanol (**Scheme 1**) proceeds efficiently to produce octyl benzoate in a yield reaching 86% after 72 h.



Scheme 1. Gram-scale reaction of *N*,*N*-dimethylbenzamide and 1-octanol. Conditions: 160 mg CeO₂, 175 °C, 72 h, N₂ atmosphere, *N*,*N*-dimethylbenzamide (10 mmol), 1-octanol (20 mmol), HY zeolite (1.0 g) as a trapping agent.

In order to examine the re-usability of the CeO₂ catalyst, a recycling test was performed (Figure 2). Following reaction of N,N-dimethylbenzamide and 1-octanol, CeO₂ was separated, washed with isopropanol, dried in air and used for an ensuing reaction. CeO₂ was found to be recyclable but the yield gradually decreased. It was also found that the catalytic performance can be recovered if the catalyst was subject to calcination at 600 °C for 3 h in the air. The results of a leaching test to demonstrate the heterogeneous nature of CeO₂ revealed that removal of the solid catalyst after a 6 h caused the alcoholysis reaction to cease (Figure 3). Inductively coupled plasma atomic emission spectroscopy (ICP-AES) was also utilized to confirm the heterogeneous nature of CeO₂. Specifically, the mixture after the reaction was subjected to filtration. Examination of the filtrate by using ICP-AES showed that less than 10 ppm of CeO₂ was present. In addition, x-ray diffraction (XRD) analysis showed that recovered CeO₂ is essentially the same as the original catalyst.



Figure 2. Recycling study for octyl benzoate formation process from N,N-dimethylbenzamide and 1-octanol over CeO₂.



Figure 3. Leaching test for octyl benzoate formation process from *N*,*N*-dimethylbenzamide and 1-octanol over CeO_2 . Reaction conditions: 80 mg catalyst, 175 °C, N₂ atmosphere, *N*,*N*-dimethylbenzamide (1 mmol), 1-octanol (2 mmol), HY zeolite (0.1 g) as a trapping agent, *n*-dodecane (0.2 mmol) as an internal standard.

In situ FT-IR was employed to gain information about interactions occuring between the amide and CeO₂ surface. For this purpose, 1 µL of N,N-dimethylacetamide preheated to 200 °C was injected into a self-supporting pellet of CeO₂ at 120 °C and surface species were analyzed (Figure 4(a) and S2). After introduction of N,N-dimethylacetamide, the spectrum of CeO₂ contains bands assigned to C=O stretching of adsorbed acetamide (1606 cm⁻¹) together with bands associated with a acetate ester (1554, 1430 cm⁻¹).^[11,17] The C=O stretching band of the acetamide adsorbed on CeO₂ (1606 cm⁻¹) appears at a lower wavenumber than that adsorbed on SiO₂ (1623 cm⁻¹) used for a reference (Fig. 4(a)), This finding indicates that a strong interaction exists between the CeO₂ surface and the carbonyl oxygen of the amide. Moreover, the intensity of the IR band due to adsorbed acetamide decreases with time, while the intensity of bands arising from an adsorbed acetate species increase with time.

Periodic DFT calculations were used to explore the mechanistic pathway proposed for the reaction of N.Ndimethylacetamide and benzylalcohol on the CeO₂(111) surface on the basis of the above findings by using in situ FT-IR. It was confirmed that CeO₂ gave the best performance for the reaction N.N-dimethylacetamide and benzylalcohol among the of catalysts tested in this study (Table S2) as well as the reaction of N.N-dimethlbenzamide and 1-octanol (Table 1). The CeO₂(111) surface was selected for this purpose because it is the most stable among those of CeO₂ commonly investigated.^[18] The proposed mechanistic sequence (Scheme 2 and Scheme S1 in the Supplementary Information) consists of (1) deprotonation of benzylalcohol (Fig. S3), (2) nucleophilic addition of a lattice oxygen of CeO₂ to the carbonyl carbon atom of N,N-dimethylacetamide (Fig. S4), (3) deamination (Fig. S6), and (4) ester formation (Fig. S7). The computed activation energy for each step in the catalytic cycle is given in Scheme 2. The key step in the overall process is nucleophilic addition of the lattice oxygen to the carbonyl carbon atom of N,Ndimethylacetamide on the CeO₂(111), as was proposed in earlier studies of alcoholysis reactions of primary amides.[11] This proposal is supported by the results of DFT calculations, which show that an alternative route involving OH addition to the carbonyl carbon of acetamide is less favorable (see Fig. S5).



Scheme 2. Proposed mechanism for alcoholysis of amides on the CeO₂ surface. Computed activation energies (*E*a) are given in kcal/mol. Color code: beige: Ce; red: O; grey: C; blue: N; white; H.

The computional results also show that the rate determining step for the alcoholysis reaction involves addition of a lattice oxygen of CeO_2 to the carbonyl carbon atom of the amide. It should be noted that the calculated energy barrier for this rate determining step of 17.0 kcal/mol matches the experimentally determined value of 17.9 kcal/mol obtained from analysis of the Arrhenius plot displayed in **Figure 4b**.



Figure 4. (a) FT-IR spectra of adsorbed *N*,*N*-dimethylacetamide species on CeO₂ and SiO₂ at 120 °C (t = 200 s). At t = 0 s, 1 µL of acetamide was introduced on preheated catalysts at 200 °C to the FT-IR cell. (b) Arrhenius-type plot for the rates of ester formation reaction in the reaction of *N*,*N*-dimethylbenzamide and benzylalcohol. Temperature range = 135-180 °C.

Rationalizing the properties of catalysts and establishing theories for heterogeneous catalysis are challenging but inevitable tasks in order to understand the underlying phenomena and ultimately develop improved catalysts. As discussed above, the nucleophilic attack of the lattice oxygen atom to the carbonyl carbon atom of the tertially amide is a key step for this catalytic process. This fact suggests that strong basicity of lattice oxygen in metal oxides can lead to high reactivity and the basicity could be used as a descriptor to

explain the catalytic activity of the metal oxide catalysts for the alcoholysis of amides. It is known that O_{1s} binding energy of metal oxides determined by XPS analysis decreases with an increase in basicity of the metal oxides surface.[19] Note that the measurements were performed XPS without anv pretreatments.^[19b] Ester formation rate for the model reaction employing N,N-dimethylbenzamide and 1-octanol was plotted as a function of O_{1s} binding energy of metal oxide catalysts, as shown in Figure 5(A). Note that the ester formation rates were obtained for reactions with yields below 30%. Figure 5(A) indicates that there is a correlation between the catalytic performance and basicity of the metal oxides. This is most likely because that the activation energy for the nucleophilic attack (the rate-determining step) decreases with a decrease of the O_{1s} binding energy. In addition, the peak positions of the C-H stretching bands (v_{CH}) in the FT-IR spectra for adsorbed CHCI₃ on various metal oxides were also employed to rationalize the catalytic activities. It is known that the red shift of the bands indicate the presence of basic sites and the degree of the band shift is used as an indicator for basic strength.^[20] It should be noted that the spectrum of SiO₂ showed no peak, indicating that SiO₂ has no basic sites. It is clear that CeO₂ showed the highest bascity and initial reaction rate among the oxide catalysts explored. It was also observed that Nb₂O₅ and ZrO₂ showed relatively high initial reaction rate toward the reaction whereas they are not strongly basic from the results of FT-IR studies using CHCl₃. This fact suggests that Lewis acidic properties play role to promote the C-N bond cleavage reaction of amides as indicated by the DFT calculations. In order to examine the role of Lewis acidic nature of the catalysts more quantitatively, in situ FT-IR study was conducted by adsorbing N.Ndimethylacetamide on various metal oxide catalysts at 40 °C as given in Fig. S8. At this low temperature, N,Ndimethylacetamide is not converted to acetate ester species

even on the CeO₂ surface. The position of the C=O stretching bands (v_{CO}) of N,N-dimethylacetamide on Nb₂O₅ resonates at lower wavenumber (1651 cm⁻¹) than on other oxides (1656-1667 cm⁻¹), indicating that the Lewis-acidic sites on Nb₂O₅ interact with the carbonyl oxygen more strongly of N.Ndimethylacetamide than those on the other oxides.[21] The position of the v_{CO} on CeO₂ is seen at 1663 cm⁻¹, showing stronger Lewis acidic activation of C=O bond of N,Ndimethylacetamide than SiO₂, MgO and TiO₂. These results indicate that CeO₂ has both acid and base sites to activate N,Ndimethylacetamide, and therefore, CeO₂ serves as the best catalysts for the alcoholysis of amides. This fact is furthermore supported by temperature programmed desorption (TPD) measurements with CO_2 and NH_3 as probe molecules (Figure 7). These resullts demonstrate that both acidic and basic properties are important for the efficient progression of the alcoholysis reaction as indicated by DFT studies, and as a result, CeO₂ showed the best performance.

The substrate scope of CeO2-catalyzed amide alcoholysis process under optimal reaction conditions was explored. The results displayed in Schemes 3 shows that the reaction is applicable to a wide range of amides and alcohols. In addition to the N,N-dimethylbenzamide (1a) used for the model reaction, benzamides containing N,N-diethyl (1b), N-methoxy-N-methyl (1d) were successfully transformed to the corresponding ester, octylbenzoate. N,N-Dimethyl amides of m-trifluoromethyl phenyl (1c), benzyl (1e) also gave the desired esters in excellent yields. Notably, alkyl amides (1f), (1g) of N,N-dimethyl and Nheterocyclic moieties (1h-1j) undergo esterification in high isolated yields. Secondary amides containing phenyl (1k and 1n), 4-chloro-phenyl (11), pyridyl (1m) and alkyl (1o and 1p) were also tolerated in alcoholysis reactions to give target esters. The alcohol scope of this CeO₂ catalyzed esterification reaction with N,N-dimethylbenzamide (1a) is given in Scheme 4. Various alcohols including aliphatic (3a-3e, 3g), olefinic (3f), methyltetrahydrofuryl (3h), benzylic alcohols (3i-3I) with electronelectron-withdrawing donating and substituents, heteroaromatic pyridyl (3m), methyl-thiophenyl (3n) and naphthyl (30) were successfully undergo alcoholysis reactions of 1a in high isolated yilds. In addition to the primary alcohols various secondary alcohols including aliphatic linear, branched, cyclic and aromatic (3p-3u) were also well tollerated in alcoholysis of N,N-dimethylbenzamide (1a) and dave corresponding esters. It was also demonstrated that N,Ndimethylacetamide (1g) efficiently reacted with various alcohols (at 155 °C to afford the corresponding esters (Scheme 5). At present, this CeO₂-catalyzed process requires high temperature (155-175 °C) for completing the reaction. However, the wide substrate scope obtained in this study is compatible with homogeneous catalytic systems.^[12,14] This wide substrate scope suggests that the present system can potentially be utilized for synthetic applicationos. Advantageously, CeO₂-catalyzed system does not require elaborate handling for performing the experiments or any additives which are usually needed for the homogeneous systems. Also, high recyclability of the catalyst is another important feature for this system.



Figure 5. Correlation between initial reaction rates of ester formation from *N*,*N*-dimethylbenzamide and 1-octanol and (A) XPS O_{1s} binding energies,^[19b] and (B) FT-IR band positions of C–H stretching mode of CHCl₃ adsorbed onto the supports.^[20]



Figure 6. Correlation between initial reaction rates of ester formation from N,N-dimethylbenzamide and 1-octanol and FT-IR band positions of C=O stretching mode of N,N-dimethylacetamide adsorbed onto the supports measured at 40 °C.



Figure 7. NH₃- and CO₂-TPD profiles for various oxides.

WILEY-VCH



Scheme 3. CeO₂-catalyzed ester formation from various amides and 1-octanol. Reaction conditions: 80 mg catalyst, 175 °C, 30-36 h, N₂ atmosphere, *amide* (1 mmol), 1-octanol (2 mmol), HY zeolite (0.1 g) as a trapping agent, Isolated yields are shown.



Scheme 4. CeO₂-catalyzed ester formation from *N*,*N*-dimethyl benzamide and various alsohols. Reaction conditions: 80 mg catalyst, 175 °C, 30-36 h, N₂ atmosphere, *N*,*N*-dimethyl benzamide (1 mmol), alcohol (2 mmol), HY zeolite (0.1 g) as a trapping agent, Isolated yields are shown.



Scheme 5. CeO₂-catalyzed ester formation from *N*,*N*-dimethylacetamide and various alsohols. Reaction conditions: 80 mg catalyst, 155 °C, 36 h, N₂ atmosphere, *N*,*N*-dimethylacetamide (1 mmol), alcohol (2 mmol, for **6a** and **6b**;10 mmol of MeOH and EtOH were used), HY zeolite (0.1 g) as a trapping agent, Isolated yields are shown.

Conclusions

In summary, we developed a heterogeneous catalytic system that promotes alcoholysis reactions of tertiary amides with alcohols. Unlike typical reactions utilizing homogeneous catalytic systems and requiring NHC complexes, the new process is operationally convenient and does not require additives. In addition, the catalyst is recyclable and the process has a wide substrate scope. A plausible mechanism, involving rate limiting nucleophilic addition of a CeO₂ lattice oxygen to the amide carbonyl, is proposed for the process based on the results from density functional theory (DFT) and in situ FT-IR studies. The presented catalysis of CeO2 was tried to be ratinalized with its acid and base properties by employing various methods such as XPS, FT-IR, and TPD. These results show that the catalysis required for promoting the C-N bond cleavage reaction is not simply understood by utilizing independent probe techniques. This is in agreement with the findings by DFT studies that acidbase cooperation is necessary for efficient progression of the reaction. As a result, CeO2, which has both acid and base properties, exhibits the best performance.

Experimental Section

Materials and Catalyst Preparation

Organic and inorganic compounds were purchased from common commercial suppliers (Tokyo Chemical Industry, Kanto Chemical, Wako Pure Chemical Industries, Nacalai Tesque, and SigmaAldrich) and used without further purification. CeO_2 was prepared by

WILEY-VCH

calcination (T = 600 °C, t = 3 h, in air) of CeO₂ supplied from Daiichi Kigenso Kagaku Kogyo Co., Ltd (Type A). TiO2 (JRC-TIO-8), MgO (JRC-MGO-3), SiO₂-Al₂O₃ (JRC-SAL-2, $Al_2O_3 = 13.75$ wt%) and H-Beta zeolite (SiO₂/Al₂O₃ = 25±5, JRC-Z-HB25) were supplied by the Catalysis Society of Japan. y-Al2O3 was prepared by calcination of y-AlOOH (Catapal B Alumina, Sasol) at 900 °C for 3 h. SiO₂ (Q-10) was supplied by Fuji Silysia Chemical Ltd. SiO₂ (Q-10) was supplied by Fuji Silysia Chemical Ltd., while Nb₂O₅ was prepared by calcination (T = 500 °C, t = 3 h) of niobic acid (CBMM). ZnO was prepared by calcination (T = 500 °C, t = 3 h) of a hydroxide of Zn (Kishida Chemical). ZrO2 was prepared by calcining Zr hydroxide at 773 K for 3 h that was made via hydrolysis of ZrO(NO₃)₂·2H₂O with an aqueous NH₄OH solution. SnO₂ was prepared by calcination (T =500 °C, t = 3 h) of H₂SnO₃ (Kojundo Chemical Laboratory Co., Ltd.). CaO was prepared by calcination (T = 500 °C, t = 3 h) of Ca(OH)₂ (Kanto Chemical)). H-ZSM-5 (SiO₂/Al₂O₃ = 22) and HY (SiO₂/Al₂O₃ = 5.5) zeolites were obtained from TOSO Co., Ltd. Sulfated ZrO2 was kindly provided by Wako Pure Chemical Industries. Sulfonic resins (Amberlyst-15 and Nafion-SiO2 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 ($\phi = 2$ cm). The obtained pellet was placed in the quartz IR cell with CaF₂ windows connected to a conventional gas flow system. Prior to the measurement, the sample pellet was heated under He flow (20 cm³ min⁻¹) at 500 °C for 0.5 h. After cooling to 120 °C under the He flow, 1 µL of *N*,*N*-dimethylacetamide was injected to the sample through a line which was preheated at ca. 200 °C to vaporize *N*,*N*-dimethylacetamide. 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.

X-ray diffraction (XRD; Rigaku Miniflex) measurements were conducted using CuK α radiation. BET (Brunauer-Emmett-Teller) specific surface area of CeO₂ was determined to be 81 m² g⁻¹ from N₂ adsorption data measured by using BELCAT (MicrotracBEL). Transmission electron microscopy (TEM) was measured using a JEOL JEM-2100F TEM operated at 200 kV. Inductively coupled plasma-atomic emission spectroscopy (ICP-AES) analysis was carried out by using a SHIMADZU ICPE-9000 instrument.

CO₂- and NH₃-TPD measurements were carried out using BELCAT. Prior to each experiment, a catalyst (50 mg) was heated in a flow of He (20 mL min⁻¹) at 500 °C for 10 min, followed by cooling to ca. 40 °C under He flow. The catalyst was then exposed to a flow of CO₂ or NH₃ (20 mL min⁻¹) for 10 min. After purged in He for 30 min, the catalyst was heated linearly at 10 °C min⁻¹ until 600 °C in a flow of He, and outlet gas (CO₂, m/e = 44) were analyzed by the mass spectrometer (BEL Mass, BEL Japan, Inc.).

Catalytic Reactions

Typically, tertiary amide (1 mmol), alcohol (2 mmol) and CeO_2 (80 mg) were added to a Pyrex reaction vessel (16 mL). HY zeolite (5.5) (0.1 g) wrapped by a filter paper was also placed at the upper side of the reaction vessel for removal of formed amine as a by-product, as

given in Fig. 8. After sealing, the mixture was degassed and purged with N_2 . This was repeated for 5 times. The reaction vessel was placed on a heater equipped with a reflux condenser and a magnetic stirrer. The reaction mixture was heated at 175 °C and stirred at 400 rpm for 36 h under N₂ atmosphere. After completion of the reaction, 2-propanol (6 mL) was added to the mixture and the products were analyzed by GC (Shimadzu GC-14B with Ultra ALLOY capillary column UA+-1 of Frontier Laboratories Ltd., N2) and GCMS (SHIMADZU GCMS-QP2010 with Ultra ALLOY capillary column UA+-1 of Frontier Laboratories Ltd., N2). Product isolation was carried out by using column chromatography on silica gel 60 (spherical, 50-100 µm, Kanto Chemical Co. Ltd.) with hexane/ethylacetate (9/1) as the eluting solvent. The isolated products were then analyzed by using GC, and ¹H and ¹³C NMR. ¹H and ¹³C NMR spectra were recorded at ambient temperature on a JEOL-ECX 600 spectrometer (¹H: 600.17 MHz, ¹³C: 150.92 MHz), using tetramethylsilane as the internal standard. Isolated yields were determined relative to the starting amides.



Figure 8. Picture of the typical reaction apparatus for the esterification reaction of a tertiary amide by an alcohol.

For reusing the catalyst, after completion of the reaction, 2propanol (6 ml) was added to the reaction mixture and the catalyst was separated by centrifugation. The recovered catalyst was washed with 2-propanol for 3 times (3 mL for each time). After separating the catalyst by centrifugation, the recovered catalyst was dried at 100 °C in air for 12 h, and subsequently employed for the next run. A leaching test was performed in the same manner for the recycling test. After 6 h period of the reaction, the catalyst was separated by centrifugation. Subsequently, the separated solution was transferred to the reactor, followed by heating at 175 °C with magnetically stirring for another 29 h.

Computational Methods

Periodic DFT calculations were performed with the DMol3 program^[22] in Material Studio of Accelrys Inc. Perdew–Burke– Ernzerhof (PBE) generalized gradient functional was employed for the exchange-correlation energy. The wave functions were expanded in terms of numerical basis sets. We employed the DND basis set (double numerical basis set with the d-type polarization functions) for geometry optimization. Single-point energy calculations were performed with the larger DNP basis set (double numerical basis set with the d-type polarization functions for heavy atoms and the p-type polarization functions for hydrogen atoms). Brillouin zone integrations are performed on a Monkhorst–Pack^[23] k-point grid with a k-point spacing of 0.05 Å⁻¹ unless otherwise noted.

The transition state was determined by using the linear and quadratic synchronous transit (LST/QST) complete search method.^[24] As shown in **Fig. 9**, the CeO₂ catalyst was modeled by a supercell slab that consists of a 3×3 surface unit cell with nine atomic (111) surface layers (lattice constants a = b = 11.5 Å, 81 atoms) unless otherwise noted. The slab was separated by a vacuum space with a height of 20 Å. All atoms except the oxygen atoms in the bottom layer were fully relaxed.



Figure 9. Structure model of $CeO_2(111)$ used in this study. (a) Top view and (b) side view. Color code: beige: Ce; red: O.

Acknowledgements

This work was supported by the KAKENHI grants JP18K14051, JP17H01341, JP24109014, JP15K13710, JP17H03117, and JP15K05431 from the Japan Society for the Promotion of Science (JSPS), by the Japanese Ministry of Education, Culture, Sports, Science, and Technology (MEXT) within the projects "Integrated Research Consortium on Chemical Sciences (IRCCS)" and "Elements Strategy Initiative to Form Core Research Center", as well as by the JST-CREST project JPMJCR15P5, JPMJCR15P4, and JPMJCR17J3. The authors are indebted to the technical division of the Institute for Catalysis (Hokkaido University) for the manufacturing of experimental equipment.

Keywords: Amide alcoholysis \cdot C–N bond cleavage \cdot CeO₂ \cdot Acid and base cooperation

- a) A. Radzicka, R. Wolfenden, J. Am. Chem. Soc. 1996, 118, 6105–6109; b) R. M. Smith, D. E. J. Hansen, J. Am. Chem. Soc. 1998, 120, 8910–8913.
- a) B. W. Matthews, Acc. Chem. Res. 1988, 21, 333–340; b) D. W.
 Christianson, W. N. Lipscomb, Acc. Chem. Res. 1989, 22, 62–69.
- a) J. M. Bobbit, D. A. Scola, *J. Org. Chem.* **1960**, *25*, 560–564; b) T.
 Shiba, A. Koda, S. Kusumoto, T. Kaneko, *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2748–2753; c) D. J. Hamilton, M. J. Price, *J. Chem. Soc., Chem. Commun.* **1969**, *414*.
- [4] a) T. Takarada, M. Yashiro, M. Komiyama, *Chem.-Eur. J.* 2000, *6*, 3906–3913; b) M. Yashiro, Y. Sonobe, A. Yamamura, T. Takarada, M. Komiyama, Y. Fujii, *Org. Biomol. Chem.* 2003, *1*, 629–632; c) J. Hong, Y. Jiao, W. He, Z. Guo, Z. Yu, J. Zhang, L. Zhu, *Inorg. Chem.* 2010, *49*, 8148–8154; d) W. S. Chei, H. Ju, J. Suh, *Biol. Inorg. Chem.* 2011, *16*, 511–519; e) A. M. Protas, A. Bonna, E. Kopera, W. Bal, *Inorg. Biochem.* 2011, *105*, 10–16; f) K. Stroobants, E. Moelants, H. G. T. Ly, P. Proost, K. Bartik, T. N. Parac-Vogt, *Chem.-Eur. J.* 2013, *19*, 2848–2858; g) Y.

Seki, K. Tanabe, D. Sasaki, Y. Sohma, K. Oisaki, M. Kanai, *Angew. Chem. Int. Ed.* **2014**, *53*, 6501–6505.

- a) N. V Kaminskaia, N. M. Kostic, *Inorg. Chem.* **1998**, *37*, 4302–4312;
 b) T. Deguchi, H. L. Xin, H. Morimoto, T. Ohshima, *ACS Catal.* **2017**, *7*, 3157–3161.
- [6] a) H. A. Taylor, T. W. Davis, J. Phys. Chem. 1928, 32,1467–1480; b) W. J. Greenlee, E. D. Thorsett, J. Org. Chem. 1981, 46, 5351–5353; c) L. E. Fisher, J. M. Caroon, S. R. Stabler, S. Lundberg, S. Zaidi, C. M. Sorensen, M. L. Sparacino, J. M. Muchowski, Can. J. Chem. 1994, 72, 142–145; d) E. H. White, J. Am. Chem. Soc. 1954, 76, 4497–4498; e) D. M. Shendage, R. Fröhlich, G. Haufe, Org. Lett. 2004, 6, 3675–3678; f) D. T. Glatzhofer, R. R. Roy, K. N. Cossey, Org. Lett. 2002, 4, 2349–2352; g) P. L. Anelli, M. Brocchetta, D. Palano, M. Visigalli, Tetrahedron Lett. 1997, 38, 2367–2368; h) L. C. Li, J. Ren, T. G. Liao, J. X. Jiang, H. J. Zhu, Eur. J. Org. Chem. 2007, 1026–1030; i) M. C. Bröhmer, S. Mundinger, S. Bräse, W. Bannwarth, Angew. Chem. Int. Ed. 2011, 50, 6175–6177.
- [7] a) J. Aubé, Angew. Chem. Int. Ed. 2012, 51, 3063–3065; b) S. Yamada, Angew. Chem. Int. Ed. 1993, 32, 1083–1085; c) M. Hutchby, C. E. Houlden, M. F. Haddow, S. N. G. Tyler, G. C. Lloyd-Jones, K. I. Booker-Milburn, Angew. Chem., Int. Ed. 2012, 51, 548–551.
- [8] a) Y. Kita, Y. Nishii, T. Higuchi, K. Mashima, *Angew. Chem. Int. Ed.* 2012, *51*, 5723–5726; b) Y. Kita, Y. Nishii, A. Onoue, K. Mashima, *Adv. Synth. Catal.* 2013, 355, 3391–3395; c) Y. Nishii, S. Akiyama, Y. Kita, K. Mashima, *Synlett* 2015, *26*, 1831–1834.
- [9] B. N. Atkinson, J. M. J. Williams, *Tetrahedron Lett.* **2014**, *55*, 6935–6938.
- S. M. A. H. Siddiki, A. S. Touchy, M. Tamura, K. Shimizu, *RSC Adv.* 2014, *4*, 35803-35807.
- [11] T. Kamachi, S. M. A. H. Siddiki, Y. Morita, M. N. Rashed, K. Kon, T. Toyao, K. Shimizu, K. Yoshizawa, *Catal. Today* 2018, 303, 256–262.
- [12] a) L. Hie, N. F. Fine Nathel, T. K. Shah, E. L. Baker, X. Hong, Y.-F. Yang, P. Liu, K. N. Houk, N. K. Garg, *Nature* **2015**, *524*, 79–83; b) J. E. Dander, N. K. Garg, *ACS Catal.* **2017**, *7*, 1413–1423.
- [13] a) B. J. Simmons, N. A. Weires, J. E. Dander, N. K. Garg, ACS Catal.
 2016, *6*, 3176–3179; b) N. A. Weires, E. L. Baker, N. K. Garg, Nat. Chem. **2016**, *8*, 75–79.
- P. Lei, G. Meng, M. Szostak, ACS Catal. 2017, 7, 1960–1965; b) G.
 Meng, P. Lei, M. Szostak, Org. Lett. 2017, 19, 2158–2161.
- [15] a) L. Vivier, D. Duprez, ChemSusChem 2010, 3, 654–678; b) M. Tamura, K. Shimizu, A. Satsuma, Chem. Lett. 2012, 41, 1397-1405; c) M. Tamura, A. Satsuma, K. Shimizu, Catal. Sci. Technol. 2013, 3, 1386-1393; d) T. Montini, M. Melchionna, M. Monai, P. Fornasiero, Chem. Rev. 2016, 116, 5987–6041; e) H. Duan, Y. Yamada, S. Sato, Chem. Lett. 2016, 45, 1036–1047; f) M. Tamura, R. Kishi, Y. Nakagawa, K. Tomishige, Nat. Commun. 2015, 6, 8580.
- [16] J. P. Guthrie, D. C. Pike, Y.-C. Lee, Can. J. Chem. 1992, 70, 1671– 1683.
- [17] A. Aboulayt, C. Binet, J.-C. Lavalley, J. Chem. Soc. Faraday Trans. 1995, 91, 2913-2920.
- [18] a) S. Agarwal, X. Zhu, E. J. M. Hensen, B. L. Mojet, L. Lefferts, *J. Phys. Chem. C* 2015, *119*, 12423–12433; b) Y. Q. Su, I. A. W. Filot, J. X. Liu, I. Tranca, E. J. M. Hensen, *Chem. Mater.* 2016, *28*, 5652–5658; c) A. Trovarelli, J. Llorca, *ACS Catal.* 2017, *7*, 4716–4735.
- a) Y. Nagai, T. Hirabayashi, K. Dohmae, N. Takagi, T. Minami, H. Shinjoh, S. Matsumoto, *J. Catal.* **2006**, *242*, 103–109; b) C. Chaudhari, S. M. A. H. Siddiki, M. Tamura, K. Shimizu, *RSC Adv.* **2014**, *4*, 53374–53379.
- [20] M. Tamura, K. Shimizu, A. Satsuma, Appl. Catal. A Gen. 2012, 433– 434, 135–145.
- [21] K. Shimizu, W. Onodera, A. S. Touchy, S. M. A. H. Siddiki, T. Toyao, K. Kon, *ChemistrySelect* 2016, 1, 736–740.
- [22] a) B. Delley, J. Chem. Phys. 1990, 92, 508–517; b) B. Delley, J. Chem. Phys. 2000, 113, 7756.
- [23] H. J. Monkhorst, J. D. Pack, *Phys. Rev. B* 1976, *13*, 5188–5192.



[24] N. Govind, M. Petersen, G. Fitzgerald, D. King-Smith, J. Andzelm, Comput. Mater. Sci., 2003, 28, 250–258.

10.1002/cctc.201801098

WILEY-VCH

Entry for the Table of Contents

FULL PAPER

Alcoholysis of tertiary amide, a C-N bond cleavage reaction, was achieved by a heterogeneous CeO₂ catalyst. The present catalytic system has advantages being facile and not requiring any additives. The catalyst is moreover recyclable and shows wide substrate scope toward the ester forming process. A possible catalytic mechanism is proposed on the basis of results from density functional theory (DFT) and in situ FT-IR studies.



Takashi Toyao, Md. Nurnobi Rashed, Yoshitsugu Morita, Takashi Kamachi,S. M. A. Hakim Siddiki,* Md. A. Ali, A. S. Touchy, K. Kon, Zen Maeno, Kazunari Yoshizawa, Kenichi Shimizu,*

Page No. – Page No.

Esterification of Tertiary Amides by Alcohols Through C–N Bond Cleavage over CeO₂