

Cite this: *Green Chem.*, 2012, **14**, 717

www.rsc.org/greenchem

PAPER

Transamidation of amides with amines under solvent-free conditions using a CeO₂ catalyst†

Masazumi Tamura,^a Takuya Tonomura,^a Ken-ichi Shimizu^{*b} and Atsushi Satsuma^a

Received 21st October 2011, Accepted 25th November 2011

DOI: 10.1039/c2gc16316k

Among various metal oxides, cerium oxide (CeO₂) shows the highest catalytic activity for transamidation of picolinamide with *n*-octylamine. CeO₂ acts as a reusable and effective heterogeneous catalyst for transamidation under solvent-free conditions. Transamidation of a variety of amides and amines produced the corresponding *N*-alkyl amides in high yields. This method provides the first example of a heterogeneous catalyst for transamidation using aliphatic amines as substrates. Characterization of acid–base properties and kinetic studies suggest that the cooperation of the weak Lewis acid sites and adjacent strong base sites play important roles in the transamidation reaction.

Introduction

The amide bond is a fundamental component of biological and synthetic polymers (*i.e.*, proteins and nylons), and constitutes an important functional group in organic chemistry. It has been estimated that 25% of all synthetic pharmaceutical drugs contain an amide unit.¹ Consequently, the development of efficient amidation methods continues to be an important goal in synthetic chemistry. Traditional methods for the synthesis of amides are based on the coupling of activated carboxylic acid derivatives and amides, but there are limitations, such as the lability of the activated acid derivatives and tedious procedures.² Direct amide bond formation as a greener method has been investigated. Coupling of carboxylic acids with amines promoted by boric acids³ is one of the most successful examples of direct amide synthesis. In the view of green chemistry, recent efforts have been focused on heterogeneous catalysis for direct amidation of carboxylic acids with amines. However, most of them suffer from low activity, low selectivity or limited scope.⁴ Transamidation of amide with amines may provide an attractive alternative method of the direct amide bond formation. Examples of transamidation are scarce and the limited synthetic applications to date generally consist of intramolecular reactions.⁵ The difficulty of this reaction arises from the intrinsic strength of the amide C–N bond together with the presence of an acidic N–H bond in amides. Transamidation generally requires harsh conditions (>250 °C), long reaction times or stoichiometric reagents to cleave the chemically robust amide bond.⁶ An enzyme-mediated transformation is known, but it has limited scope and requires

highly evolved enzymes as well as a long reaction time.⁷ To overcome these disadvantages, new homogenous⁸ and heterogeneous catalysts⁹ are recently reported. Stahl *et al.* reported that Al(III), Sc(III), and group 4 metal complexes (Ti, Zr, Hf) catalyzed the transamidation under mild conditions.⁸ However, these homogenous catalysts suffer from the necessity of a solvent and difficulties in separation and recycling of the used catalyst. Generally, complex catalysts are not effective for highly polar compounds because of their strong coordination to the metal centers.^{8a} Heterogeneous catalysis for transamidation may overcome these problems. To the best of our knowledge, there is only one report using HfCl₄ supported on KSF-polyDMAP,⁹ which suffers from the need of a solvent and strong base, and has a limited scope; the reaction with aliphatic amines is unsuccessful.

CeO₂ has acid–base and redox properties and has been used as an effective catalyst for various organic reactions¹⁰ such as the dehydration of alcohols,¹¹ the alkylation of aromatic compounds,¹² dimerization of alcohols,¹³ aldehydes, esters^{13e} and carboxylic acids¹⁴ to ketones, cyclization of diols,¹⁵ and the reduction of benzoic acid.¹⁶ Most CeO₂-catalyzed reactions were carried out at high temperatures (typically 200–500 °C). In view of organic synthesis and green chemistry, it is important to study CeO₂-catalyzed organic reactions further at lower temperatures (<200 °C). As for CeO₂-catalyzed reactions at low temperatures (<200 °C), Tomishige *et al.* recently reported the carbonate synthesis from CO₂ and alcohols at 150 °C.¹⁷ Our research group found that CeO₂ acted as a highly active catalyst for the substrate-specific hydration of nitriles at low temperatures (30–100 °C).¹⁸

In this work we wish to report that commercial CeO₂, as a cheap and readily available solid, effectively catalyzes transamidation of various primary amides with various amines to yield corresponding *N*-alkyl amides in high yields at 160 °C under solvent-free conditions. For a wide range of metal oxides, characterizations of acid–base properties and catalytic tests were

^aDepartment of Molecular Design and Engineering, Graduate School of Engineering, Nagoya University, Nagoya, 464-8603, Japan

^bCatalysis Research Center, Hokkaido University, N-21W-10, Sapporo, 001-0021, Japan. E-mail: kshimizu@cat.hokudai.ac.jp; Fax: +81-11-706-9163; Tel: +81-11-706-9240

†Electronic supplementary information (ESI) available: See DOI: 10.1039/c2gc16316k

carried out to establish a catalyst design concept in terms of the acid–base properties of the metal oxide surface.

Experimental

General

The GC (Shimadzu GC-14B) and GCMS (Shimadzu GCMS-QP5000) analyses were carried out with a Rtx-65 capillary column (Shimadzu) or a DB-1 capillary column (Agilent J&W) using nitrogen as the carrier gas. All chemicals used for the organic reactions were of analytical grades and purchased commercially and were used without further purification.

Catalyst

CeO₂ (JRC-CEO3, surface area = 81 m² g⁻¹) was pre-calcined at 600 °C before being supplied by the Catalysis Society of Japan, and was used as the standard catalyst. CeO₂ (140 m² g⁻¹) was purchased from Rhodia Electronics Catalysis. Other metal oxides were commercially available or supplied from the Catalysis Society of Japan. The metal oxides except CeO₂ were calcined at 500 °C for 3 h before use in the reactions.

Typical procedures for the transamidation of amides

A typical procedure for transamidation of picolinamide with *n*-octylamine is as follows: CeO₂ (25 mg, 5.8 mol% Ce with respect to picolinamide) was added to the mixture of picolinamide (2.5 mmol), *n*-octylamine (5.0 mmol) in a reaction vessel equipped with a condenser under N₂. The resulting mixture was vigorously stirred at 160 °C. The reaction mixture was analyzed by GC. Conversion and yield of the products were determined based on picolinamide and *N*-octyl picolinamide using pentadecane as an internal standard. The products were identified by GCMS and confirmed by ¹H-NMR. After the reaction was complete, the CeO₂ catalyst was separated by centrifugation. In the catalyst recycling experiments, the separated catalyst was washed with acetone three times and calcined in air at 300 °C for 1 h. For measurement of the isolated yields, the reaction of amine (2.6 mmol) and primary amide (2.5 mmol) was carried out. After full conversion of the primary amide was confirmed by GC, the catalyst was separated by filtration. The crude product was purified by evaporating the filtrate at 70 °C to remove the unreacted amine. The resulting products were identified by GC, GCMS and ¹H-NMR.

In situ FTIR

In situ FTIR spectra were recorded at room temperature on a JASCO FT/IR-6100 equipped with a quartz IR cell connected to a conventional flow reaction system. The sample was pressed into a 30–80 mg self-supporting wafer and mounted into the quartz IR cell with CaF₂ windows. Spectra were measured, accumulating 15 or 35 scans at a resolution 4 cm⁻¹ in a flow of He. A reference spectrum of the catalyst wafer under He was subtracted from each spectrum. For the introduction of acetamide, *n*-butylamine and methanol to the IR disc, each liquid

compound was injected under a He flow preheated at 200, 150 and 100 °C, respectively, which was fed to the *in situ* IR cell. Then, the IR disk was purged with He, and the IR measurement was carried out.

XPS

The X-ray photoelectron spectroscopy (XPS) measurements were carried out using a JEOL JPS-900MC with an Al K α anode operated at 20 mA and 10 kV. The oxygen 1s core electron levels in the oxides were recorded. Binding energies were calibrated with respect to C_{1s} at 285.0 eV.

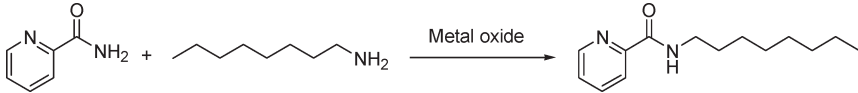
Results and discussion

Catalytic properties

First, the catalytic activity of the transamidation reaction between picolinamide and *n*-octylamine at 160 °C was examined with various metal oxides (Table 1). Transamidation hardly proceeded without a catalyst. For various metal oxides, the rate of *N*-octyl picolinamide formation per catalyst weight was measured under the condition in which conversions were below 30% (Table S1†). Using specific surface areas of metal oxides, the rate per catalyst surface area was calculated (Table 1). The results show that CeO₂ has the highest reaction rate (0.52 mmol h⁻¹ m⁻²) and highest yield of *N*-octyl picolinamide (91% after 8h), indicating that CeO₂ is the most effective catalyst for transamidation among the 11 metal oxides tested. It should be noted that the aliphatic amine, which was unsuccessful in the previous report⁹ with HfCl₄/KSF-polyDMAP, reacted to afford the corresponding amide in high yield.

Next, we investigated the substrate scope of the CeO₂-catalyzed transamidation. Transamidation of various amides with *n*-octylamine was examined by CeO₂ (Table 2). Benzamide derivatives (Table 2, entries 1–7), benzylamide (Table 2, entries 8 and 9), heteroaromatic amides (Table 2, entries 10–17) and linear fatty amides (Table 2, entries 18–21) reacted to afford the corresponding amides in high yield (72–99% yields). Transamidation of amides with one equivalent of *n*-octylamine was also successful, providing the corresponding amide in good isolated yields (Table 2, entries 2,4,6,9,11,13,19,21). Note that the transamidation of heteroaromatic amides, which is difficult to catalyze using homogenous catalysts, can be transformed to the corresponding amides in high yields. Owing to the pharmaceutical importance of heteroaromatic carboxamide structures,¹⁹ the present method is important from a practical viewpoint. Transamidation of hexanamide with various amines was examined using CeO₂ (Table 3). Aliphatic amines (Table 3, entries 1 and 2), benzyl amine (Table 3, entry 3) and benzyl amine derivatives having an electron-donating group (Table 3, entries 4 and 5) reacted to afford the corresponding amides in high yields (88–99% yields). The reaction of a branched amine (Table 3, entry 6) was successful, and the yield of the product was 78%. A secondary amine, morpholine (Table 3, entry 7), was also converted in high yield to the corresponding amide, which is a useful intermediate for organic synthesis.²⁰

A further advantage of this solid catalytic system is its reusability. We studied the reuse of CeO₂ for the transamidation of

Table 1 Transamidation by various metal oxides^a


Catalyst	S_{BET} ($\text{m}^2 \text{g}^{-1}$)	t (h)	Yield (%)	r^b ($\text{mmol h}^{-1} \text{m}^{-2}$)
CeO ₂	81	0.5	21.1	0.52
TiO ₂	47	1	14.3	0.30
Nb ₂ O ₅	54	1	15.3	0.28
ZrO ₂	73	1	12.9	0.18
Al ₂ O ₃	124	1	10.3	0.08
Sc ₂ O ₃	24	1	6.1	0.25
SiO ₂	300	2	10.1	0.02
Er ₂ O ₃	9	1	1.6	0.18
La ₂ O ₃	18	1.5	2.4	0.09
MgO	19	2	2.2	0.06
CaO	59	2	1.5	0.01
Blank	—	1	0.0	—

^a Reaction conditions: picolinamide (2.5 mmol), *n*-octylamine (5.0 mmol), metal oxide (25 mg), $T = 160$ °C. Yield of *N*-octyl picolinamide was determined by GC. ^b Initial formation rate of *N*-octyl picolinamide per catalyst surface area measured under the conditions in which the yield of *N*-octyl picolinamide was below 30%.

hexanamide with *n*-octylamine (Fig. 1). The catalyst can be easily retrieved from the reaction mixture by centrifugation or filtration. For each successive use, the catalyst was washed with acetone three times to remove the products, followed by calcination in air at 300 °C for 1 h. After this treatment, the recovered catalyst was reused at least three times without any marked loss of its high catalytic efficiency.

Reaction mechanism and the nature of the active species

To investigate the reaction mechanism of the CeO₂-catalysed transamidation, we studied the adsorption state of the amide and amine on the surface of CeO₂ by FTIR spectroscopy. First, the adsorption complexes formed from the introduction of acetamide to CeO₂ and SiO₂ at 30 °C were compared by *in situ* FTIR. The samples were first preheated in a He flow at 600 °C, followed by cooling to 30 °C. Then, acetamide (1 μL) was injected into the He flow preheated at 200 °C, which was fed to the samples. IR spectra were recorded at 30 °C, adsorbed species are shown in

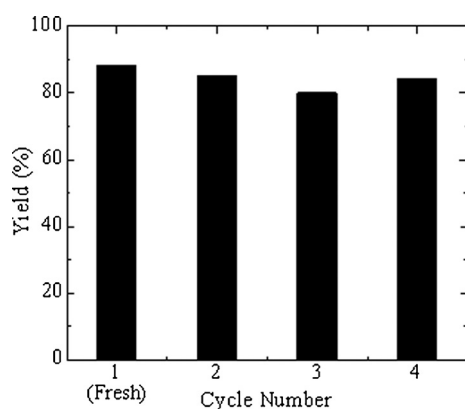


Fig. 1 Reusability of CeO₂ catalyst (5.8 mol%) for transamidation of hexanamide (2.5 mmol) with *n*-octylamine (5.0 mmol) at 160 °C ($t = 5$ h).

Fig. 2. The main bands at 1654 cm^{-1} (for CeO₂) and 1667 cm^{-1} (for SiO₂) are characteristic of the carbonyl stretching vibrations of the adsorbed acetamide species. The bands for CeO₂ is observed at lower wavenumbers than those of acetamide in the liquid phase (1660 cm^{-1}) and acetamide on SiO₂, indicating a weakened C=O bond strength in the acetamide species on CeO₂. This suggests that the carbonyl oxygen of the acetamide interacts with the acid sites on CeO₂.²¹ Taking into account our previous pyridine adsorption IR results, that CeO₂ has Lewis acid sites,²² it is shown that the carbonyl oxygen of acetamide interacts with the surface Lewis acid sites of CeO₂.

Next, the adsorption complexes formed from the introduction of *n*-butylamine (2 μL) to CeO₂ and SiO₂ at 30 °C were studied by *in situ* FTIR (Fig. 3). The spectra of CeO₂ shows bands at 1579 cm^{-1} (in the N–H bending region) and at 3348 and 3249 cm^{-1} (in the N–H stretching region) (Fig. 3a,b). According to a previous report,²³ the NH₃⁺ group produced by interaction of *n*-butylamine with the Brønsted acid site exhibits $\delta_s(\text{N–H})$ and $\delta_{\text{as}}(\text{N–H})$ in the region of 1504–1550 cm^{-1} and 1575–1600 cm^{-1} , respectively, while the coordinatively bonded *n*-butylamine on the Lewis acid sites show bands around

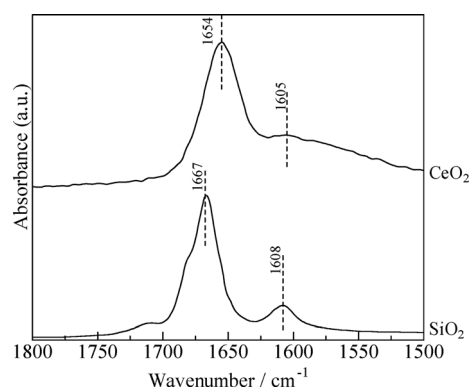
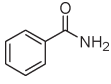
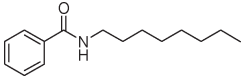
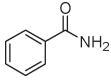
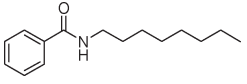
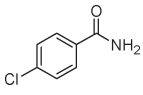
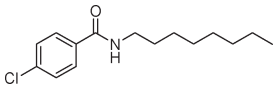
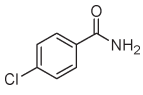
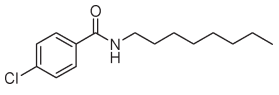
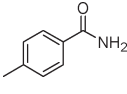
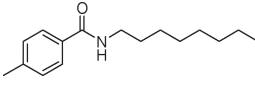
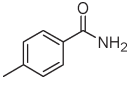
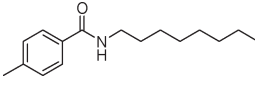
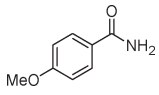
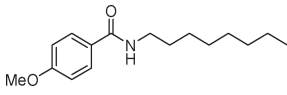
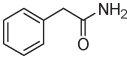
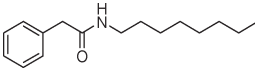
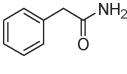
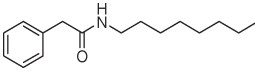
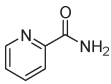
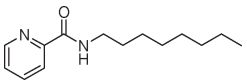
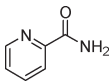
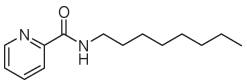
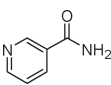
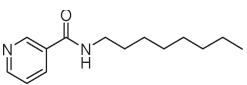
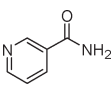
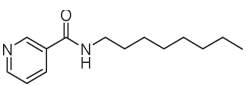
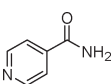
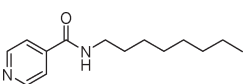
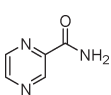
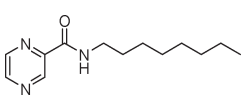
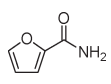
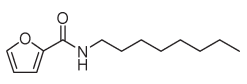
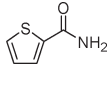
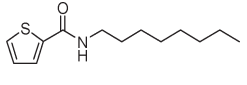

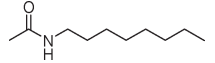

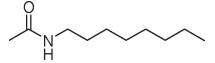
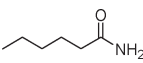
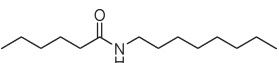
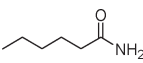
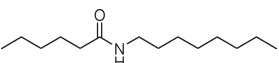
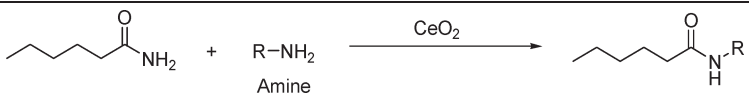


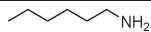
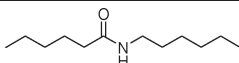
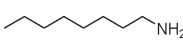
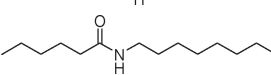
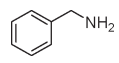
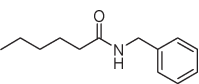
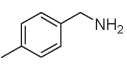
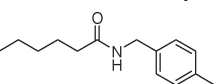
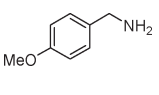
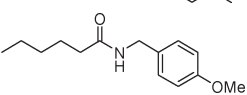
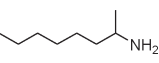
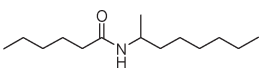

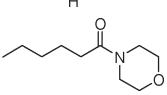
Fig. 2 IR spectra of acetamide adsorbed on CeO₂ and SiO₂ at 30 °C.

Table 2 Transamidation of various amides with *n*-octylamine^a

Entry	Amide	Product	<i>t</i> /h	Yield (%)
1			13	94
2 ^b			24	89 ^c
3			13	87
4 ^b			48	82 ^c
5			24	99
6 ^b			24	81 ^c
7			24	72
8			5	98
9 ^b			48	82 ^c
10			8	91
11 ^b			24	84 ^c
12			5	88
13 ^b			48	81 ^c
14			5	90
15			33	87
16			30	86
17			33	95
18			5	>99
19 ^b			24	85 ^c
20			5	88
21 ^b			24	84 ^c

^a Reaction conditions: amide (2.5 mmol), *n*-octylamine (5.0 mmol), CeO₂ (25 mg, 5.8 mol%), *T* = 160 °C. Yield of the product was determined by GC. ^b Amide/*n*-octylamine = 2.5 mmol/2.6 mmol. ^c Isolated yield.

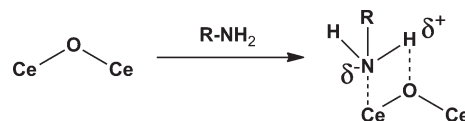
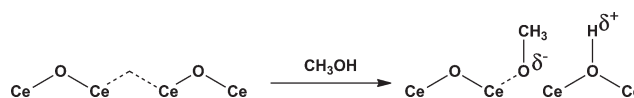
Table 3 Transamidation of hexanamide with various amines^a


Entry	Amine	Product	<i>t</i> (h)	Yield (%)
1			5	94
2			5	88
3			5	97
4			25	>99
5			5	92
6			24	78
7			24	97

^a Reaction conditions: hexanamide (2.5 mmol), amine (5.0 mmol), CeO₂ (25 mg), *T* = 160 °C. Yield of the product was determined by GC.

1600–1565 cm⁻¹. In the N–H bending region, the spectra exhibit no band at 1504–1550 cm⁻¹, indicating that CeO₂ has no Brønsted acid sites. The band for CeO₂ shifted to a lower wavenumber than for SiO₂. *n*-Butylamine did not desorb from CeO₂ even at 150 °C, while it desorbed from SiO₂ at 150 °C (not shown). This indicates that the band for CeO₂ is not assigned to the hydrogen-bonded *n*-butylamine, which is known to desorb at 150 °C.^{23b} From these results, it is concluded that *n*-butylamine is coordinatively adsorbed to the Lewis acid sites on the CeO₂ surface, while *n*-butylamine on SiO₂ is hydrogen-bonded. In the N–H stretching region for CeO₂, the bands at 3348 and 3249 cm⁻¹ due to $\nu_{\text{as}}(\text{NH})$ and $\nu_{\text{s}}(\text{NH})$ are observed at lower wavenumbers than those for *n*-butylamine in the gas phase (3410 and 3345 cm⁻¹)^{23a} and *n*-butylamine on SiO₂ (3375 and 3312 cm⁻¹). This indicates that N–H bonds of *n*-butylamine on CeO₂ are weakened by the surface Lewis acid site (Ce⁴⁺ cation) of CeO₂ (Scheme 1). In addition, the oxygen atom adjacent to the Ce⁴⁺ cation could assist in weakening the N–H bond, because it has a strong basicity (as shown below).

Using the results in Table 2 (entries 1–7), the relationship between $\log(k_{\text{X}}/k_{\text{H}})$ and the Brown–Okamoto parameter (σ^+) for transamidation of benzamides with various substituents is studied (Fig. 4). The order of reactivity for transamidation of benzamides was *p*-Cl > *p*-H > *p*-CH₃ > *p*-OCH₃. There is a fairly good linearity between $\log(k_{\text{X}}/k_{\text{H}})$ and σ^+ giving a positive slope ($\rho = 0.81$, $R^2 = 0.96$). The positive ρ value indicates that the reaction is favored by the presence of *para*-positioned electron-withdrawing groups and that a transition state in the rate-limiting step of transamidation involves a negative charge at the α -carbon atom adjacent to the benzene ring. Taking into account

**Scheme 1** Adsorption model of an amine on CeO₂.**Scheme 2** Adsorption model of methanol on CeO₂.²⁵

the FTIR results, the positive ρ value suggests that nucleophilic addition of $\text{RN}^{\delta-}\text{H}-\text{H}^{\delta+}$ adspecies on acid–base sites of CeO₂ to the activated amide carbon atom proceeds *via* a negatively charged transition state, and this step can be the rate-limiting step.

From the results of FTIR and kinetics measurements, the cooperation of acid and base sites is suggested to be important in the present catalytic system. CeO₂ is known to have acid–base pair sites. Lavalley *et al.* reported that methanol is dissociated on CeO₂, with coordinatively unsaturated Lewis acid–base pair sites to produce methoxy species on Lewis acid sites (exposed Ce⁴⁺) and H⁺ on Lewis base sites (exposed O²⁻) as shown in Scheme 2.^{24,25} Our FTIR spectra also showed that adsorption of methanol onto untreated CeO₂ resulted in the formation of methoxy species (Fig. S1†). To examine the correlation between the amount of Lewis acid–base pair sites and the reaction rate, we prepared various CeO₂ samples by calcining them at different

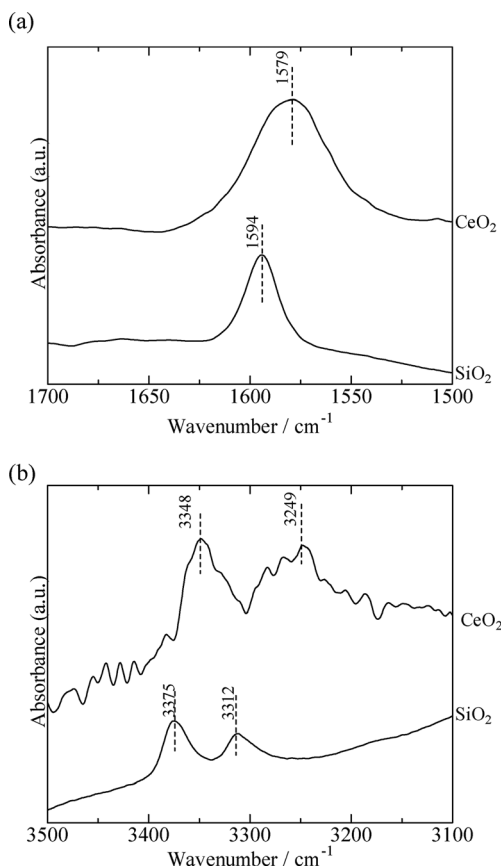


Fig. 3 IR spectra of *n*-butylamine adsorbed on CeO₂ and SiO₂ at 30 °C in the regions of (a) N–H bending (b) N–H stretching.

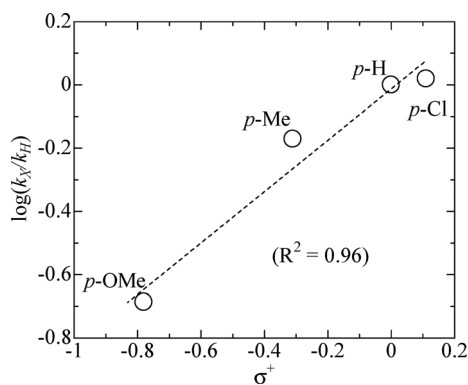


Fig. 4 Brown–Okamoto plot for the transamidation of *p*-substituted benzamide with *n*-octylamine by CeO₂. Conditions: amide (2.5 mmol), *n*-octylamine (5.0 mmol), CeO₂ (25 mg), *T* = 160 °C.

temperatures (500–1100 °C) and measured the initial rate for transamidation by these CeO₂ catalysts. These catalysts and the standard CeO₂ (JRC-CEO3) were also tested for the FTIR experiment of methanol adsorption (Fig. S1†). The number of Lewis acid–base pair sites was estimated from the $\nu(\text{OC})$ band area (970–1130 cm⁻¹) and the absorption coefficient of methoxy species (6.9 cm² μmol⁻¹) reported by Lavalley *et al.*^{25b} Fig. 5 shows a plot of the reaction rate *versus* the number of methoxy species, or in other words, the number of the coordinatively

unsaturated Lewis acid–base pair sites (Ce–O sites) on CeO₂. For a series of CeO₂ catalysts, there is a fairly good linearity between reaction rate and the amount of methoxy species ($R^2 = 0.98$), which indicates that Lewis acid–base pair sites on CeO₂ are active sites for the present transamidation reaction.

Next, correlations between the reaction rate and Lewis acid strength and base strength were examined separately (Fig. 6 and 7). Lewis acid strength was estimated by CD₃CN adsorption experiments using FTIR. There is a general tendency for CD₃CN species to coordinate to Lewis acid sites with higher acid strengths, giving a larger $\Delta\nu(\text{CN})$ value²⁶ (the band shift of adsorbed CD₃CN with respect to gas phase CD₃CN (2265 cm⁻¹)). Fig. 6 shows a plot of the reaction rate as a function of $\Delta\nu(\text{CN})$ on various metal oxides. Metal oxides with $\Delta\nu(\text{CN})$ values of nearly zero show significantly low activity, indicating that Lewis acid sites are required to catalyze the transamidation. Among a wide range of Lewis acidic metal oxides, the reaction rate increases with a decrease in $\Delta\nu(\text{CN})$, which suggests that lower Lewis acid strength is desirable for this system.

The base strengths of the metal oxides were estimated by their binding energy of the O_{1s} electron in the oxides using XPS

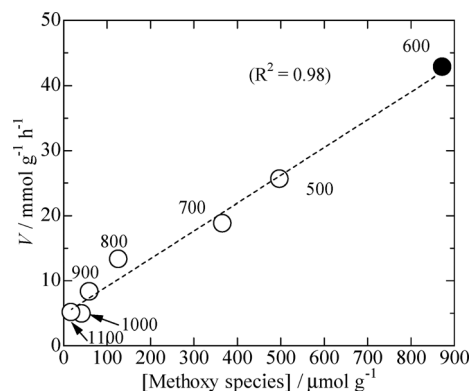


Fig. 5 The reaction rate of transamidation of picolinamide with *n*-octylamine as a function of the number of methoxy species on CeO₂ (●: JRC-CEO3, ○: Rhodia). The values in the graph are calcination temperatures (°C).

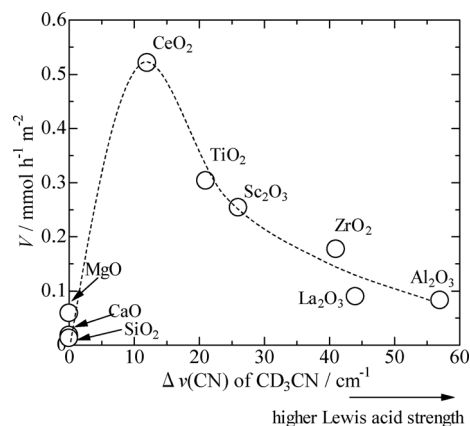


Fig. 6 Reaction rate of transamidation of 2-picolinamide with *n*-octylamine as a function of the IR band shift $\Delta\nu(\text{CN})$ of CD₃CN.

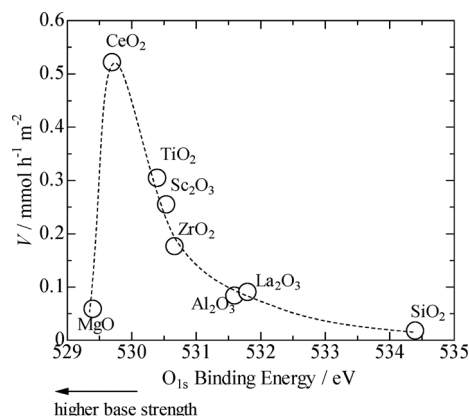


Fig. 7 Reaction rate of transamidation as a function of O_{1s} binding energy of metal oxides.

analysis. It is established that the O_{1s} binding energy of metal oxides decreases with an increase in the electron density of the oxygen in the metal oxide, or in other words, basicity of the metal oxide surface.²⁷ Fig. 7 shows the reaction rate as a function of the O_{1s} binding energy of metal oxides. Note that the position of the main peak was adopted when several peaks were observed. It is clear that the reaction rate decreases with an increase in the O_{1s} binding energy (lower base strength) except for MgO. As shown in Fig. 6, the low activity of MgO should originate from the absence of Lewis acidity. Therefore, it can be concluded that both weak Lewis acid sites and strong basic sites of metal oxides are indispensable for the transamidation reaction.

Based on the above discussions, a possible reaction mechanism of transamidation by CeO_2 is shown in Scheme 3. The catalytic cycle starts with the activation of the amide by Lewis acid sites and N–H activation of amine by acid–base pair sites (step 1). The adsorbed amide species undergoes an addition of

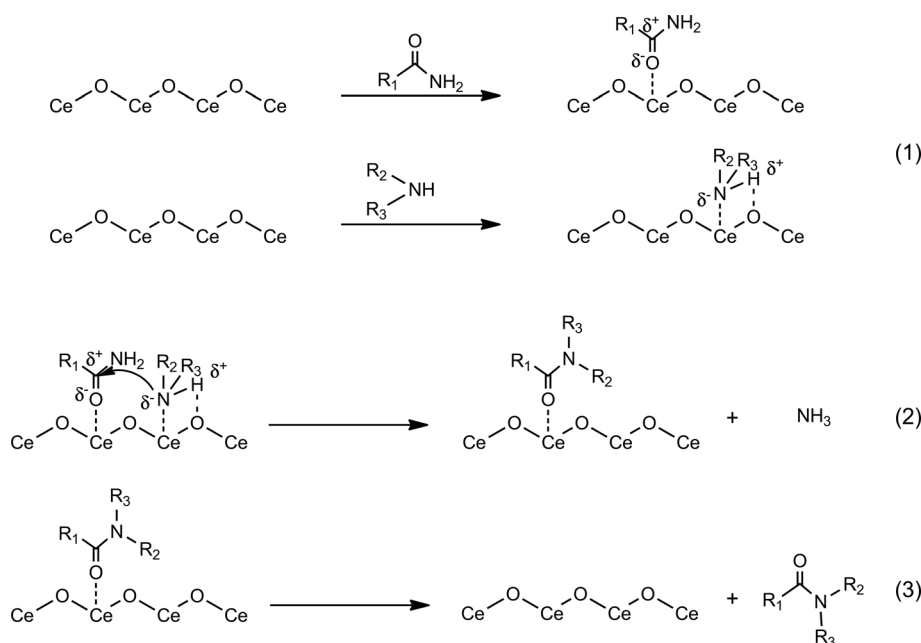
the activated amine to the primary amide carbon atom to give the N-alkyl amide *via* a negatively charged transition state (step 2). Finally, N-alkyl amide is desorbed to reproduce the acid–base site of CeO_2 (step 3). The coexistence of weak Lewis acid sites and adjacent strong basic sites is preferable to activate both a basic substrate and an acidic substrate. This bifunctional concept may be applicable to the design of new CeO_2 -catalyzed organic reactions.

Conclusion

We have demonstrated that CeO_2 acts as an effective heterogeneous catalyst for the transamidation reaction of amides with amines. This novel catalysis provides a clean, convenient and practical route for the direct N-alkyl amide synthesis in view of the following advantages: (1) The reaction proceeds smoothly and effectively under solventless conditions. (2) The catalyst is readily available, cheap, stable, reusable and a non-polluting solid that offers easy handling and ready work-up. (3) The present method is applicable in the synthesis of various N-alkyl amides, including useful aliphatic and heteroaromatic amides, in high yields. From spectroscopic and kinetic studies, it can be concluded that the cooperation of weak Lewis acid sites and adjacent strong base sites play important roles in the transamidation reaction. This bifunctional catalysis of CeO_2 may be applied to develop new catalytic systems for green organic synthesis.

References

- 1 A. K. Ghose, V. N. Viswanadhan and J. J. Wendoloski, *J. Comb. Chem.*, 1999, **1**, 55–68.
- 2 (a) C. A. G. N. Montalbetti and V. Falque, *Tetrahedron*, 2005, **61**, 10827–10852; (b) R. C. Larock, *Comprehensive Organic Transformations*, Wiley-VCH, Weinheim, 1999; (c) P. D. Bailey, I. D. Collier and K. M. Morgan, in *Comprehensive Organic Functional Group*



Scheme 3 Reaction mechanism of transamidation reaction.

- Transformations*, ed. A. R. Katritzky, O. Meth-Cohn and C. W. Rees, Pergamon, Cambridge, 1995, vol. 5, ch. 6.
- 3 (a) R. M. Al-Zoubi, O. Marion and D. G. Hall, *Angew. Chem., Int. Ed.*, 2008, **47**, 2876–2879; (b) T. Marcelli, *Angew. Chem., Int. Ed.*, 2010, **49**, 6840–6843; (c) H. Charville, D. Jackson, G. Hodge and A. Whiting, *Chem. Commun.*, 2010, **46**, 1813–1823; (d) K. Arnold, A. S. Batsanov, B. Davies and A. Whiting, *Green Chem.*, 2008, **10**, 124–134; (e) P. Starkov and T. D. Sheppard, *Org. Biomol. Chem.*, 2011, **9**, 1320–1323.
 - 4 (a) J. W. Comferford, J. H. Clark, D. J. Macquarrie and S. W. Breeden, *Chem. Commun.*, 2009, **14**, 2562–2564; (b) P. S. Chaudhari, S. D. Salim, R. V. Sawant and K. G. Akamachi, *Green Chem.*, 2010, **12**, 1707–1710; (c) K. Komura, Y. Nakano and M. Koketsu, *Green Chem.*, 2011, **13**, 828–831; (d) K. Ishihara, *Tetrahedron*, 2009, **65**, 1085–1109.
 - 5 (a) S. Calimsiz and M. A. Lipton, *J. Org. Chem.*, 2005, **70**, 6218–6221; (b) M. Alajarin, A. Vidal and F. Tovar, *Tetrahedron*, 2005, **61**, 1531–1537; (c) A. Klapars, S. Parris, K. W. Anderson and S. L. Buchwald, *J. Am. Chem. Soc.*, 2004, **126**, 3529–3533; (d) J. Lasri, M. E. González-Rosende and J. Sepúlveda-Arques, *Org. Lett.*, 2003, **5**, 3851–3853; (e) N. Langlois, *Tetrahedron Lett.*, 2002, **43**, 9531–9533; (f) E. Bon, D. C. H. Bigg and G. Bertrand, *J. Org. Chem.*, 1994, **59**, 4035–4036; (g) V. Gotor, R. Brieva, C. González and F. Rebollo, *Tetrahedron*, 1991, **47**, 9207–9214; (h) F. Zaragoza-Dörwald and G. Von Kiedrowski, *Synthesis*, 1988 (11), 917–918; (i) L. Crombie, R. C. F. Jones and D. Haigh, *Tetrahedron Lett.*, 1986, **27**, 5151–5154; (j) R. B. Martin, A. Parcell and R. I. Hendrick, *J. Am. Chem. Soc.*, 1964, **86**, 2406–2413.
 - 6 (a) L. F. Beste and R. C. Houtz, *J. Polym. Sci.*, 1952, **8**, 395–407; (b) N. Ogata, *Makromol. Chem.*, 1959, **30**, 212–224; (c) I. K. Miller, *J. Polym. Sci., Part A: Polym. Chem.*, 1976, **14**, 1403–1417; (d) R. J. McKinney, *U.S. Patent* 5302756, 1994; (e) R. J. McKinney, *U.S. Patent* 5,395,974, 1995.
 - 7 (a) M. V. Segreeva, V. V. Mozhaev, J. O. Rich and Y. L. Khmel'nitsky, *Biotechnol. Lett.*, 2000, **22**, 1419–1422; (b) P. G. Swann, R. A. Casanova, A. Desai, M. M. Frauenhoff, M. Urbancic, U. Slomczynska, A. J. Hopfinger, G. C. Le Breton and D. L. Venton, *Biopolymers*, 1996, **40**, 617–625.
 - 8 (a) N. A. Stephenson, J. Zhu, S. H. Gellman and S. S. Stahl, *J. Am. Chem. Soc.*, 2009, **131**, 10003–10008; (b) J. M. Hoerter, K. M. Otte, S. H. Gellman, Q. Cui and S. S. Stahl, *J. Am. Chem. Soc.*, 2008, **130**, 647–654; (c) J. M. Hoerter, K. M. Otte, S. H. Gellman and S. S. Stahl, *J. Am. Chem. Soc.*, 2006, **128**, 5177–5183; (d) D. K. Kissounko, J. M. Hoerter, I. A. Guzei, Q. Cui, S. H. Gellman and S. S. Stahl, *J. Am. Chem. Soc.*, 2007, **129**, 1776–1783; (e) S. E. Eldred, D. A. Stone, S. H. Gellman and S. S. Stahl, *J. Am. Chem. Soc.*, 2003, **125**, 3422–3423.
 - 9 M. Shi and S.-C. Cui, *Syn. Commun.*, 2005, **35**, 2847–2858.
 - 10 (a) A. Trovarelli, *Catalysis by Ceria and Related Materials*, Imperial College Press, London, 2002; (b) H. C. Yao and Y. F. Y. Yao, *J. Catal.*, 1984, **86**, 254–265; (c) L. Vivier and D. Duprez, *ChemSusChem*, 2010, **3**, 654–678.
 - 11 (a) S. Sato, R. Takahashi, T. Sodesawa, N. Honda and H. Shimizu, *Catal. Commun.*, 2003, **4**, 77–81; (b) S. Sato, R. Takahashi, T. Sodesawa and N. Honda, *J. Mol. Catal. A: Chem.*, 2004, **221**, 177–183; (c) N. Ichikawa, S. Sato, R. Takahashi and T. Sodesawa, *J. Mol. Catal. A: Chem.*, 2005, **231**, 181–189; (d) A. Igarashi, N. Ichikawa, S. Sato, R. Takahashi and T. Sodesawa, *Appl. Catal., A*, 2006, **300**, 50–57; (e) N. Ichikawa, S. Sato, R. Takahashi, T. Sodesawa, H. Fujita, T. Atoguchi and A. Shiga, *J. Catal.*, 2006, **239**, 13–22; (f) S. Sato, R. Takahashi, T. Sodesawa, A. Igarashi and H. Inoue, *Appl. Catal., A*, 2007, **328**, 109–116; (g) M. Kobune, S. Sato and R. Takahashi, *J. Mol. Catal. A: Chem.*, 2008, **279**, 10–19.
 - 12 (a) S. Sato, K. Koizumi and F. Nozaki, *Appl. Catal., A*, 1995, **133**, L7–10; (b) S. Sato, K. Koizumi and F. Nozaki, *J. Catal.*, 1998, **178**, 264–274; (c) S. Sato, R. Takahashi, T. Sodesawa, K. Matsumoto and Y. Kamimura, *J. Catal.*, 1999, **184**, 180–188.
 - 13 (a) H. Idriss, C. Diagne, J. P. Hindermann, A. Kiennemann and M. Barteau, *J. Catal.*, 1995, **155**, 219–237; (b) A. Yee, S. J. Morrison and H. Idriss, *J. Catal.*, 1999, **186**, 279–295; (c) N. Plint, D. Ghavalas, T. Vally, V. D. Sokolovski and N. J. Coville, *Catal. Today*, 1999, **49**, 71–77; (d) Y. Kamimura, S. Sato, R. Takahashi, T. Sodesawa and M. Fukui, *Chem. Lett.*, 2000, 232–233; (e) Y. Kamimura, S. Sato, R. Takahashi, T. Sodesawa and T. Akashi, *Appl. Catal., A*, 2003, **252**, 399–410.
 - 14 (a) M. Glinski, J. Kijenski and A. Jakubowski, *Appl. Catal., A*, 1995, **128**, 209–217; (b) T. S. Hendren and K. M. Dooley, *Catal. Today*, 2003, **85**, 333–351.
 - 15 T. Akashi, S. Sato, R. Takahashi, T. Sodesawa and K. Inui, *Catal. Commun.*, 2003, **4**, 411–447.
 - 16 Y. Sakata and V. Ponec, *Appl. Catal., A*, 1998, **166**, 173–184.
 - 17 (a) K. Tomishige, H. Yasuda, Y. Yoshida, M. Nurunnabi, B. Li and K. Kunimori, *Green Chem.*, 2004, **6**, 206–214; (b) M. Honda, A. Suzuki, B. Noorjahan, K. Fujimoto, K. Suzuki and K. Tomishige, *Chem. Commun.*, 2009, 4596–4598; (c) M. Honda, S. Kuno, N. Begum, K. Fujimoto, K. Suzuki, Y. Nakagawa and K. Tomishige, *Appl. Catal., A*, 2010, **384**, 165–170; (d) M. Honda, S. Kuno, S. Sonehara, K. Fujimoto, K. Suzuki, Y. Nakagawa and K. Tomishige, *ChemCatChem*, 2011, **3**, 365–370.
 - 18 M. Tamura, H. Wakasugi, K. Shimizu and A. Satsuma, *Chem. Eur. J.*, 2011, **17**, 11428–11431.
 - 19 (a) M. Scalone and P. Vogt, *U.S. Patent* 5534635, 1996; (b) P. M. Focati, R. Brescello, A. K. Powles, L. Cotarca, G. Sariato, R. Giovanetti, J. Foletto and F. Massaccesi, *WO 2008010796*, 2008; (c) V. Petter and S. Michelangelo, *J.P. Patent* 2268161, 1990; (d) R. Imhof and E. Kyburz, *U.S. Patent* 4764522, 1988; (e) N. I. Carruthers, C. R. Shah and D. M. Swanson, *U.S. Patent* 0222151, 2005.
 - 20 (a) R. Martin, P. Romea, F. U. Tey and J. Vilarrasa, *Synlett*, 1997, 1414; (b) C. Douat, A. Heitz, J. Martinez and J. A. Fehrentz, *Tetrahedron Lett.*, 2003, **41**, 37–40; (c) C. T. Clark, B. C. Milgram and K. A. Scheidt, *Org. Lett.*, 2004, **6**, 3977–3980.
 - 21 L.-F. Liao, C.-F. Lien, D.-L. Shieh, F.-C. Chen and J.-L. Lin, *Phys. Chem. Chem. Phys.*, 2002, **4**, 4584–4589.
 - 22 Pyridine adsorption FTIR experiment was carried out at 150 °C under a flow of He. Adsorption bands appear at 1440, 1485 and 1593 cm⁻¹ due to coordinatively bound pyridine on the Lewis acid (surface Ce cation). No bands due to a pyridinium ion formed by the adsorption of pyridine on a Brønsted acid were observed.
 - 23 (a) G. Ramis and G. Busca, *J. Mol. Struct.*, 1989, **193**, 93–100; (b) T. Morimoto, J. Imai and M. Nagao, *J. Phys. Chem.*, 1974, **78**, 704–708.
 - 24 J. C. Lavalley, *Catal. Today*, 1996, **27**, 377–401.
 - 25 (a) J. Lamotte, V. Morávek, M. Bensitel and J. C. Lavalley, *React. Kinet. Catal. Lett.*, 1988, **36**, 113–118; (b) A. Badri, C. Binet and J. C. Lavalley, *J. Chem. Soc., Faraday Trans.*, 1997, **93**, 1159–1168.
 - 26 (a) K. Shimizu, T. Higuchi, E. Takasugi, T. Hatamachi, T. Kodama and A. Satsuma, *J. Mol. Catal. A: Chem.*, 2008, **284**, 89–96; (b) D. Haffad, A. Chambellan and J. C. Lavalley, *Catal. Lett.*, 1998, **54**, 227–233.
 - 27 (a) A. Y. Stakheev, Y. Zhang, A. V. Ivanov, G. N. Baeva, D. E. Ramaker and D. C. Koningsberger, *J. Phys. Chem. C*, 2007, **111**, 3938–3948; (b) Y. Nagai, S. Hirabayashi, K. Dohmae, N. Takagi, T. Minami, H. Shinjoh and S. Matsumoto, *J. Catal.*, 2006, **242**, 103–109.