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Transformylating amine with DMF to formamide

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We here report a new protocol for the formylation of various amines, primary or secondary, aromatic or alkyl, cyclic or linear, mono- or di-amine, with dimethylformamide (DMF) as the formylation reagent to obtain the corresponding formamides in good to excellent yields over CeO_2 catalyst. The reaction requires no homogeneous acidic or basic additives and is tolerant to water.

The formylation of amine is a crucial reaction in the synthesize of formamides, used as precursors, intermediates, and reagents in the chemical and pharmaceutical industries. Typical routes to prepare formamides employing formic acid and its derivatives, and organometallic carbonyl compounds as the formylation reagents require acids (such as AlCl₃ or SnCl₄) or bases (such as NaOH or NaOCH₃) as a catalyst or additive.^{1,2} Despite the success of DMF as a formylation reagent, mediation by homogeneous acids or bases increases the difficulty in separation.³ All of the above synthetic methodologies require either strong acids or bases, or radiation energy to activate amine or the formylation reagent, and thus to greatly enhance the transient energy to facilitate nucleophilic or electrophilic attack.⁴ For example, the formylation of chain aliphatic secondary amines needs a temperature of 200 °C in a microwaveassisted process to achieve better nucleophilicity of amines.⁵ However, undesirable side reactions simultaneously take place, limiting selectivity and requiring additional separation steps.

We consider a new method for formylation reaction by dual activation of amine and DMF substrates over relatively mild catalytic acidic and basic sites to generate formamide by virtue of surface metathesis to form new C–N bond on a solid catalyst. A similar idea has been proven to be remarkably efficient in aldol condensation over acid-base bifunctional mesoporous silica.⁶ Properly prepared metal oxides, such as ceria, have acid-base bifunctional properties.⁷ Recently Corma,⁸ Satsuma,⁹ and our group¹⁰ have shown that pristine

crystalline CeO₂ can catalyze organic syntheses, such as hydrolysis, Prins condensation, and CO₂ fixation reactions, under mild conditions. However, all these reactions were found to occur on either an acidic or basic single site. Few studies revealed the acid–base bifunctionality of ceria except one work by Satsuma *et al.*, who considered the acid–base function in catalysis but clarity in detail is still lacking.^{9a,11}

Acid–base bifunctionality should be only studied generally at temperatures less than 200 °C because higher temperatures will reform the catalyst surface, causing the redox functions of ceria to become dominant, such as in three-way catalysts or water-shift reactions.¹²

To evaluate the acid–base bifunctional property of CeO₂, we initiated investigations by examining the formylation of amine with DMF in the temperature range 100–180 °C. When a 2 mL DMF solution containing 1.5 mmol benzyl amine (BAn) and 100 mg CeO₂ powder (see ESI†) was stirred at 100 °C for 4 h in a sealed vessel, benzyl amide (BAd) was observed (>99%) with 80% conversion of BAn, as determined by GC-MS analysis (eqn (1)). Increasing the reaction temperature to 180 °C for 8 h increased the BAn conversion to 95% with selectivity of BAd >99%.

Transformylation with DMF was clearly confirmed. An isotopic labelling experiment with C_3D_7NO (Fig. S1, ESI[†]) was carried out under identical reaction conditions with C_3H_7NO (Fig. S2, ESI[†]). The molecular ion (M^+) peak of BAd at m/z 135 for the reaction in C_3H_7NO (eqn (1)) increased to m/z 136 for the reaction in C_3D_7NO (eqn (2)). The M^+ peak of DMA at m/z 45 (eqn (1)) increased to m/z 51 for the reaction in C_3D_7NO (eqn (2)). Thus both the H atom of the –CHO of BAd and the six H atoms of the two –CH₃ groups of DMA stem from DMF.



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Fig. 1 A rationale plot of acid-basicity of catalysts and catalytic results in the reaction of eqn (1). Acid-base data are from literature.¹³ No catalyst (1), NaY (2), H-MOR (3), HZSM-5 (4), HY (5), ZSM-22 (6), SAPO-11 (7), H- β (8), Eu₂O₃ (9), MgO (10), WO₃ (11), Y₂O₃ (12), Nb₂O₅ (13), V₂O₅ (14), α -MnO₂ (15), ZrO₂ (16), α -Al₂O₃ (17), TiO₂ (18), CeO₂ (19).

We were able to correlate the acid-base property with catalytic results. We referenced literature data and classified the zeolite and oxide catalysts into weak (W), medium (M), and strong (S), acidic (A) or basic (B) to correlate the acid-base property with catalytic results.¹³ No reaction occurred without a catalyst (Table S1, entry 1 (ESI[†]), and No. 1 in Fig. 1, and similarly hereafter). Reactions over protonic or Na⁺-exchanged zeolites were unselective towards BAd (No. 2-8), despite their medium to strong acidities. Reactions over either weak or strong acidic or basic oxides (No. 9-13), such as Eu₂O₃, MgO, WO₃, Y₂O₃ and Nb₂O₅, were sluggish, indicating either acidic or basic oxides have no distinctive activity for the reaction. Oxidative acidic oxides, such as V_2O_5 and MnO_2 (No. 14–15), obtained >80% conversion but the major product was N-benzylidene(phenyl)-methanamine, an amine self-coupling product.¹⁴ We further tested the oxides with medium to strong acidity, and weak to medium basicity, such as ZrO_2 , α -Al₂O₃, and anatase (No. 16-18). They exhibited better activity (>20%) and selectivity (52-96%) than the monofunctional oxides, but the results were far less attractive than over CeO₂.

The presence of water could deactivate the other catalysts, except for CeO₂, over which 5% water (vol/vol DMF) decreased the conversion to 67% at 100 °C, but had no effect on selectivity (Table S1, entry 21, ESI†). This can be explained by our previous study which revealed the Lewis acidic sites of CeO₂ were water-tolerant.¹⁰ Moreover, no clear dependence of catalytic activity on the specific surface area of zeolites and oxides was observed (Fig. S3, ESI†). Therefore the feature of CeO₂ with strong basicity and water-tolerant Lewis acidity might be the main reason for the better performance.

Monitoring the reaction showed BAn conversion rapidly increased to 68% in 2 h and 80% in 6 h at constant selectivity >99% for BAd (Fig. S4, ESI[†]). In a hot filtration test, the catalyst was filtered out after 0.5 h when the conversion reached 50%. The filtrate did not afford further conversion in the continuous reaction, suggesting that no catalytically active species were present in the liquid phase. In contrast, the conversion of BAn proceeded to 80% with catalyst in the closed reaction time. This result confirmed the observed catalysis was intrinsically heterogeneous.

Table 1 Morphologies, numbers of surface oxygen atoms, and benzyl amide yield over different types of nanosized CeO_2^a

Sample	C^b	S^{c}	T^d	V^e	Y
Rod	(110):(100) = 2:1	86	9.5	1.99-2.27	85(37)
Cube	(100)	21	2.9	2.27	7(13)
Octahedra	(111)	9	1.4	2.60	1(4)

^{*a*} Reaction conditions: catalyst 100 mg, BAn 1.5 mmol, DMF 2 mL, 100 °C, 4 h. ^{*b*} Crystalline facets and their ratio. ^{*c*} S_{BET} (m² g⁻¹). ^{*d*} Total number of surface oxygen atoms (×10¹⁹ atom per gram). ^{*e*} Vacancy formation energy (eV). ^{*f*} Yield of BAd (%). Data in parenthesis indicated the molar product per reaction time (h) per added surface area of CeO₂ (unit: μ mol m⁻² h⁻¹).

The CeO₂ catalyst was used more than five times with the conversion and selectivity remaining stable in the $\pm 5\%$ range error level for all tests (Fig. S5, ESI[†]).

We prepared crystalline nano-octahedral, nano-cubic and nanorod CeO₂ according to the literature methods.¹⁵ The purpose was to confirm the active facet of CeO2, which is closely related to the surface acid-base property. Transmission electron microscopy (TEM) characterization indicated that these samples mainly exposed rod (110) and (100), cube (100) and octahedra (111) facets (Fig. S6, ESI[†]), respectively (Table 1). For a perfect sample, the surface oxygen of rod CeO₂ (110) and (100) is 9.5×10^{19} atom per gram, which is 3-fold and 7-fold of cube and octahedra, respectively. Theoretical studies have shown that the formation energy of anion vacancies for different CeO₂ surfaces follows the order of (110) < (100) < (111)which means that the ease of oxygen vacancy formation is (110) >(100) > (111). Using the specific surface area of CeO₂, the generation rate of BAd per added surface area per time (Y) was calculated, which followed the same sequence as the reaction rate in the BAn formylation. We concluded that the (110) facet is the most active crystalline facet for the BAn formylation reaction. This is understandable because the rod (110) facet is oxygen-terminated and thus has stronger basicity than the cube and octahedra.⁷ Accordingly oxygen defect sites on rod (110) are more acidic than the others because of the tendency to obtain a coordinatively saturated surface.

Calcination of CeO_2 at high temperature could decrease oxygen vacancy sites, and accordingly Lewis acidity. Fig. 2 shows the



Fig. 2 The transformylation reaction over CeO₂ calcined at different temperatures in air [500 mg (30 mL min⁻¹ gas)⁻¹]. Reaction conditions: catalyst 100 mg, BAn 1.5 mmol, DMF 2 mL, 100 °C, 4 h.

Table 2 Acidity and basicity of CeO₂

Property	Fresh	HCl-treated	TEA-treated
	CeO ₂	CeO ₂	CeO ₂
Acidity (mmoL g^{-1}) ^{<i>a</i>}	0.24	0.17	0.09
Basicity (mmoL g^{-1}) ^{<i>b</i>}	0.25	0.07	0.06
BAd yield (%)	80	0	16

 a As measured by NH₃ adsorption. This value includes total acidity and thus is larger than the pyridine adsorption result. b As measured by CO₂ adsorption.

catalytic results (right *Y*-axis) and Lewis acidity (left *Y*-axis) against calcination temperature. The concentration of Lewis acidic sites, measured by pyridine-adsorption, almost linearly decreased with increase in calcination temperature from 400 °C (0.07 mmol g⁻¹) to 700 °C (0.015 mmol g⁻¹) and levelled off at 800 °C, indicating the saturating tendency of surface cation sites. The BAd yield evolved in a similar trend, indicating that Lewis acidic sites of CeO₂ are indispensable for the reaction.

Acid- or alkali-treatment was expected to have a remarkable effect on the cooperative catalysis arising from the acidic and basic sites. Treating CeO₂ in an HCl solution (pH = 2–3) decreased the basicity from 0.25 mmoL g⁻¹ to 0.07 mmoL g⁻¹ (Table 2, Fig. S7, ESI†). Although the acidity was also slightly decreased, the HCl-treated catalyst had no activity for the reaction. Similarly, treating CeO₂ with triethylamine (TEA) decreased acidity from 0.24 mmoL g⁻¹ to 0.09 mmoL g⁻¹. Only 16% yield of BAn was obtained in the TEAtreated CeO₂. The treated CeO₂ offered far less yield than the untreated CeO₂ (80%). The results reinforce the postulation of cooperative action of Lewis acidic and basic sites of CeO₂ in amine transformylation.

Further investigations into the identity of active sites are currently underway, and preliminary analyses combining the catalytic data, acid-base treating tests and isotopic labelling results may suggest a tentative dual activation mechanism involving the cooperative catalysis of Lewis acidic and basic sites in the transformylation reaction (Fig. S8, ESI⁺). Amine is adsorbed on basic site via the Ce-O···H-N interaction and on Lewis acidic site by the N···Ce interaction. This is illustrated by in situ adsorption of *n*-butylamine as a model of amine molecule on CeO₂ (Fig. S9, ESI[†]). In the N–H stretching region, compared with *n*-butylamine in the gas phase (3415 cm^{-1} and 3350 cm^{-1}),^{9a} the bands at 3340 cm⁻¹ and 3268 cm⁻¹ are due to $v_{as}(NH)$ and $v_{s}(NH)$ redshifted, which was ascribed to the weak interaction of N-H bond with the basic site of CeO₂ via N-H···O-Ce. In the N-H bending region, the spectrum exhibited a band at 1560 cm⁻¹ attributed to the coordinatively adsorbed n-butylamine on Lewis acidic site via H-N...Ce interaction. The C=O bond of DMF is adsorbed on Lewis acidic site, which increases the positive charge on carbonyl carbon, and facilitates the nucleophilic attack from N of the adsorbed amine in the approximate distance. This is proved in DMF adsorption (Fig. S10, ESI⁺), the characteristic C=O adsorption band at 1655 cm⁻¹ (DMF film) red-shifted to 1646 cm⁻¹ (adsorbed DMF). Increase in the vacuum-treating temperature to 150 °C and then 200 °C could remove the adsorbed DMF, showing DMF was weakly bonded by the C=O interaction with Lewis acidic sites, probably via C=O···Ce adsorption. The breakage of the C-N bond of DMF and N-H bond of amine lead to a surface

Table 3 Transformylation of amines to amides^a



^{*a*} Reaction conditions: **3a–3q**: CeO₂ 100 mg, amines 1.5 mmol, DMF 2 mL, 150 $^{\circ}$ C, 24 h; **3r** and **3s**: CeO₂ 100 mg, amide 2 mL, BAn 1.5 mmol, 150 $^{\circ}$ C, 24 h.

metathesis process, simultaneously forming two new bonds and generating formamide and DMA.

This methodology has broad suitability. Various amines were transformylated with DMF to the corresponding formamides in good to excellent yields (Table 3). The GC chromatograms of the reaction mixture, and the mass spectra of major product and byproducts are given in the ESI.† Minor byproducts were detected, which were generated *via* the self-coupling of amines. Primary alkyl monoamine or diamine (**3a–3c**) gave >90% conversion and >90% selectivity for alkyl formamides. The secondary alkyl amines, dipropylamine (**3d**), *N*-methyl(phenyl)-methanamine (**3e**) and piperidine (**3g**), were converted with good formamide yields (\geq 84%).

In the case of the substrate dibenzylamine (**3f**), the product *N*,*N*-dibenzylformamide was obtained with low conversion (40%), probably due to two bulky benzyl groups which restrain the adsorption of substrates on ceria surface. The formylation of alkyl aromatic amine (**3h** and **3i**) gave a yield >74%.

In the formylation of benzylamine and its derivatives, the electronic effect of substituents had no significant effect. Electron-donating (**3j** and **3l**) group-substituted as well as the electron-withdrawing group-substituted benzylamines (**3k**) afforded comparably high conversion (>98%) and selectivity (~90%) for the corresponding formamides. It is understandable from the reaction mechanism that electronic perturbation does not occur in N–H and C–N bond activation steps.

It should be noted that O– or S-containing heterocyclic or aromatic amines also realized high activity and selectivity (**3m**, **3n** and **3o**). Transformylation of aniline (**3p**) and its derivatives (**3q**) produced the formamides in moderate conversion but excellent selectivity (>98%). Besides DMF, formamide and *N*,*N*-diethylformamide (DEF) were employed as the formylation reagents in the transformylation of BAn with high yields of formamides (**3r** and **3s**).

In conclusion we have developed a novel protocol for synthesizing up to twenty formamides by the transformylation of corresponding amine substrates, primary or secondary, aromatic or alkyl, cyclic or linear, mono- or di-amine, in good to excellent yields requiring no homogeneous acidic or basic additives and which tolerate water. The excellence of the CeO2 catalyst can be attributed to strong basicity and medium water-tolerant acidity, marking its difference from other catalysts. Although prior reports demonstrated the formylation of amines to amides, our system is the only reported heterogeneous catalyst to accomplish this reaction in good yields, with broad substrates suitability and without any additives. Further work is ongoing to elucidate the mechanism of the formylation route, investigate the nature of catalytically active sites, and examine its utility in other fine chemical synthesis, including the possibility of aldol condensations,¹⁷ where an acidbase bifunctional site is necessary.

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