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Versatile and sustainable alcoholysis of amides by reusable CeO_2 catalyst

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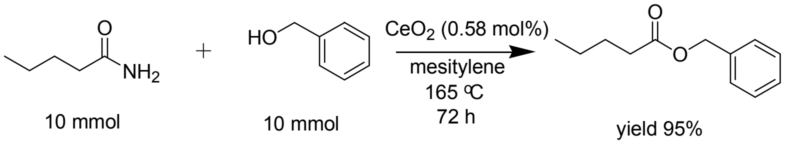
Abstract: CeO_2 catalyzed the esterification between equivalent molar ratio of primary amides and alcohols under neutral conditions, which provides the first versatile reusable catalytic system for direct alcoholysis of amides to esters with wider scope and 67 times higher turnover number (TON) than previous catalytic systems.

Amide bond is thermodynamically stable, and thus amide solvolysis usually requires heating under strongly acidic or basic conditions because of difficulty in cleavage of amide bond. Therefore, synthetic application of amide solvolysis is limited. Synthesis of ester by amide alcoholysis has attracted attention of organic chemists, but all of the reported methods are not effective in terms of generality and atom economy.[1-5] Although various non-catalytic methods of amide alcoholysis have been reported, they suffer from use of excess amount of promoter (such as HCl and $NaNO_2$), generation of inorganic or organic wastes, and limited substrate scope.[1-10] Twisted amides undergo alcoholysis under mild and neutral conditions,[11-13] but synthetic application of this reaction is quite limited. Mashima and co-workers demonstrated the first example of catalytic amide alcoholysis using $Zn(OTf)_2$,[14] though the method is only applicable to the reaction of β-hydroxyethylamides with *n*-BuOH, and stoichiometric amount of promoter was required. Very recently, Mashima et al.[15] developed combined catalytic system of $Sc(OTf)_3$ and boronic ester for alcoholysis of primary amide to the corresponding ester. However, the method is only applicable to the ethanol and 1-propanol and has drawbacks such as inability of catalyst reuse, low TON, necessity of excess amount of alcohol, and difficulty in catalyst/product separation. To the best of our knowledge, there are no reports on reusable catalysts for the alcoholysis of amide to the corresponding ester. As a part of our continuing interest in CeO_2-catalysed green organic syntheses,[16-20] we report herein a general catalytic system for esterification between equivalent molar ratios of amide and alcohol under additive-free neutral conditions using CeO_2 as reusable heterogeneous catalyst.

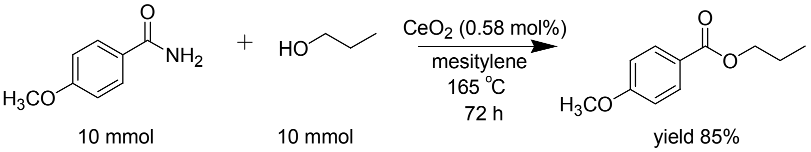
First, we performed catalyst screening adopting a model reaction of equimolar amount of *n*-valeramide and benzylalcohol in mesitylene under reflux conditions. Table 1 lists initial rate per gram of catalyst under the conditions in which conversions were below 25%. Among various metal oxides and solid acids tested (metal oxides: CeO_2, CaO, MgO, ZnO, Y_2O_3, TiO_2, ZrO_2, Nb_2O_5, Al_2O_3, SiO_2, solid acids: Amberlyst-15, HBEA, niobic acid, mont.K10, Nafion-SiO_2), CeO_2 showed

1-3 orders of magnitude higher rate of ester formation than the other metal oxides. Thermal reaction of *n*-valeramide and benzyl alcohol in the absence of any catalysts was found completely inactive for the ester formation.

Using the most effective catalyst, CeO$_2$, we studied general applicability of the present catalytic system. Table 2 shows the yields of the corresponding esters from the reaction of various primary amides with equimolar amount of benzylalcohol. Various aliphatic linear amides with short to long carbon chain (entries 1-5) were tolerated, giving 100% conversion of amide and high isolated yield (86-93%) of corresponding esters. Benzylamide, benzamides with electron-donating and electron-withdrawing groups (entries 6-11) and a heteroaromatic amide (entry 12) were converted to the corresponding esters in good to excellent isolated yield (75-95%) at 100% conversions of alcohols and amides. α-Disubstituted amide (entry 13) and aliphatic di-amide (entry 14) were also tolerated with good yield (86% and 75%). Gram-scale experiments with 10 mg of CeO$_2$ (0.58 mol% Ce) for the reaction of valeramide and benzylalcohol (eq. 1) and that of *p*-methoxybenzamide with 1-propanol (eq. 2) gave 95% and 85% yields, respectively. Based on the number of Ce cations on the surface of CeO$_2$ (1.067 mmol g-1),[21] turnover number (TON) for the latter reaction is 888, which is 67 times higher than the TON (13.2) of homogeneous catalytic system with Sc(OTf)$_3$ and boronic ester for the same reaction under excess amount of 1-propanol (6.7 equivalent).



(1)



(2)

Next we investigated the scope of alcohols. Table 3 shows the reaction of various alcohols with equimolar amount of benzamide. Linear and branched aliphatic alcohols (entries 1-12) and an allylalcohol were (entry 13) converted to the corresponding ester with 100% conversions and high isolated yields (80-90%). Benzyl alcohols with electron-donating or electron-withdrawing group (entries 14-19) reacted to afford the corresponding ester in good to high yields (75-89%). A heteroaromatic alcohol (entry 20) was also successfully converted to the ester with high yield (83%). The GC-MS analysis for all the reactions in Table 2 and Table 3 showed no formation of byproducts.

Finally, we studied reusability of the catalytic system. After the reaction of *n*-valeramide with benzylalcohol (entry 1 in Table 2), the catalyst was separated from the reaction mixture by centrifugation. The recovered catalyst was washed with acetone, followed by drying in air at 90 ^{o}C for 1 h. As shown in Figure 1, the recovered catalyst showed high yields (89-95%) in the successive 4 cycles. Although the yield was slightly decreased at 4th run, the activity was recovered in the 5th and 6th cycles simply by calcination (600 ^{o}C, 0.5 h, in air) of the catalyst after 4th run. The present system is truly heterogeneous catalytic system as evidenced by the following results. For the reaction of *n*-valeramide and benzylalcohol, we removed the catalyst from the reaction mixture at the initial stage of the reaction (28% yield after 1 h). Further continuation of the reaction under reflux conditions did not increase the product yield. ICP analysis of the filtrate confirmed that the content of Ce in the solution was below the detection limit. These results indicate that CeO$_2$ is a leaching-resistant and reusable heterogeneous catalyst for this reaction.

Conclusion

We found CeO_2-catalyzed esterification between equivalent molar ratios of amide and alcohol. This is the first additive-free and reusable heterogeneous catalytic system for direct alcoholysis of amides to esters with wider scope and 67 times higher TON than the previous homogeneous catalyst, and thus it provides a sustainable, general, and economic synthetic method of a wide range of esters.

Experimental Section

General: Commercially available organic and inorganic compounds (from Tokyo Chemical Industry, Wako Pure Chemical Industries, Kishida Chemical, or Mitsuwa Chemicals) were used without further purification. The GC (Shimadzu GC-14B) and GCMS (Shimadzu GCMS-QP2010) analyses were carried out with Ultra ALLOY capillary column UA^+-5 (Frontier Laboratories Ltd.) using nitrogen as the carrier gas.

Catalyst: CeO_2 (JRC-CEO3, surface area = 81 m^2 g^{-1}) pre-calcined at 600 ˚C before being supplied from the Catalysis Society of Japan was used as a standard catalyst. Other metal oxides (CeO_2, CaO, MgO, ZnO, Y_2O_3, TiO_2, ZrO_2, Nb_2O_5, Al_2O_3, SiO_2), comercially available or supplied from the Catalysis Society of Japan, where calcined at 500 ˚C for 3 h. These metal oxides were stored under air and used without any pretreatment. Solid acid HBEA was supplied from Catalysis Society of Japan, niobic acid (supplied by CBMM), Montmorillo-nite K10 clay (mont. K10), a sulfonic resin (Amberlyst-15) and Nafion-SiO_2 were purchased from Aldrich.

*Typical procedures of catalytic test: T*he mixture *n*-valeramide (1.0 mmol) and benzylalcohol (1.0 mmol) in mesitylene (1.5 g) was injected to the catalyst inside the reactor (cylindrical glass tube), followed by filling N_2. Then, the resulting mixture was magnetically stirred for 22 h under reflux condition; the bath temperature was 180 °C and reaction temperature was *ca* 165 °C. After cooling the mixture, followed by removal of the catalyst, the mixture was isolated by column chromatography using silica gel 60 (spherical, 63-210 μm, Kanto Chemical Co. Ltd.) and the eluting solvent of hexane/ethylacetate (19:1) and analyzed by ^1H NMR, ^{13}C NMR and GCMS. For the standard reaction of *n*-valeramide and benzyl alcohol for catalyst screening, catalyst recycle, conversion and yields of products were determined by GC using *n*-dodecane as an internal standard adopting the GC sensitivity estimated using the isolated product.

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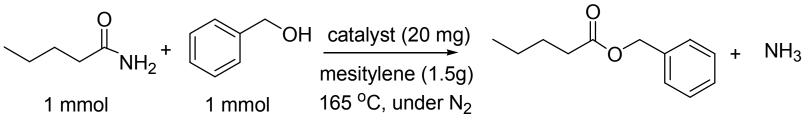
21 The number of Ce cations on the surface of CeO_2 was calculated with the density of the Ce atom on the (111) surface and the surface area of CeO_2.

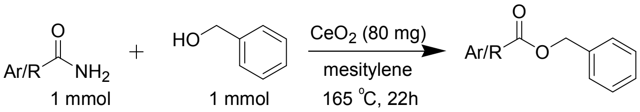
Table 1. Ester formation from amide and alcohols by metal oxide catalysts.

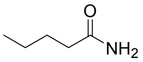
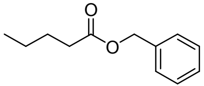
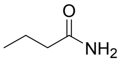
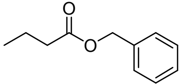
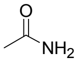
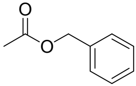
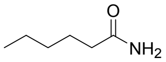
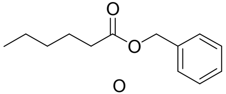
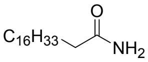
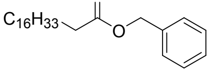
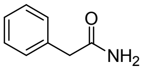
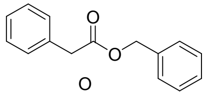
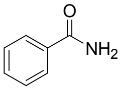
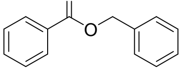
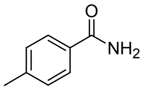
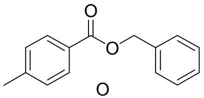
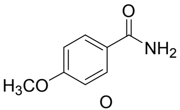
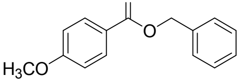
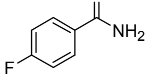
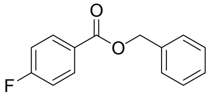
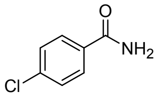
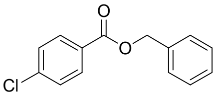
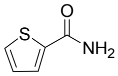
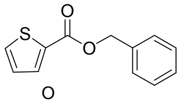
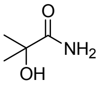
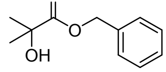
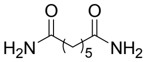
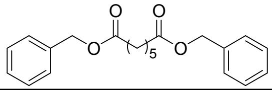


Catalyst	V^a/ mmol h^{-1} g^{-1}
CeO_2	41
CaO	2.7
MgO	0.22
ZnO	0.07
Y_2O_3	0.33
TiO_2	0.32
ZrO_2	0.37
Nb_2O_5	0.29
Al_2O_3	0.10
SiO_2	0.03
Amberlyst-15	2.17
HBEA	1.06
niobic acid	1.39
mont-K10	0.16
Nafion-SiO_2	0.72
blank	0

[a] Initial rate per gram of catalyst under the conditions in which conversions were below 25%.

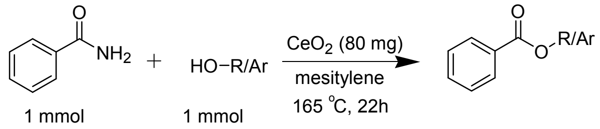
Table 2. CeO_2-catalyzed ester formation from various amide and benzylalcohol.

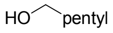
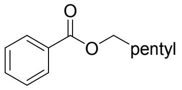
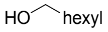
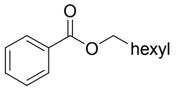
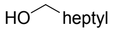
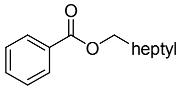
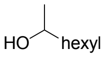
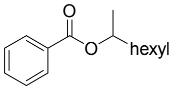
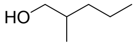
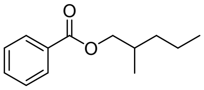
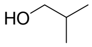
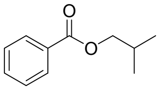
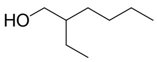
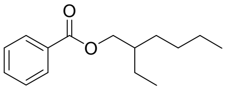
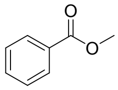
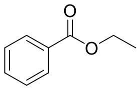
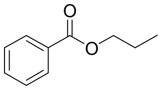
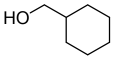
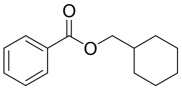
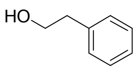
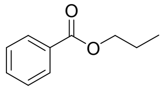
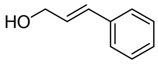
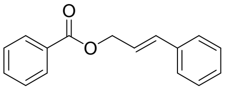
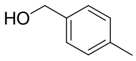
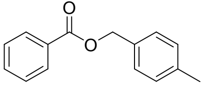


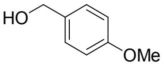
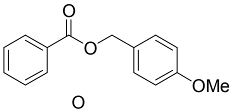
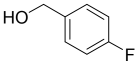
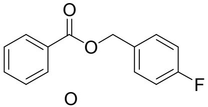
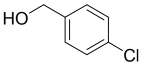
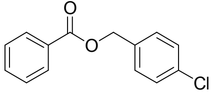
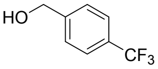
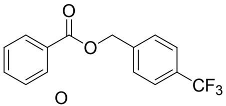
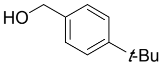
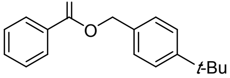
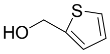
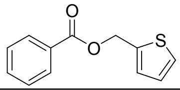
Entry	Amides	Products	Isolated yield(%)
1			93 (95)[a]
2			95
3			90
4			91
5			86
6			86
7			89
8			75
9			88
10			85
11			81
12			93
13			86
14[b]			75

[a] GC yield, [b] 2 mmol alcohol

Table 3. CeO_2-catalyzed ester formation from benzamide and various alcohols.



Entry	Alcohols	Products	Isolated yield(%)
1			88
2			90
3			88
4			85
5			80
6			82
7			75
8[a]	CH_3OH		90
9[a]	CH_3CH_2OH		93
10[a]	$CH_3CH_2CH_2OH$		85
11			78
12			88
13			86
14			83

15			80
16			85
17			83
18			75
19			81
20			83

[a] reaction in sealed tube, alcohol 3.0 mmol, [b] GC yield

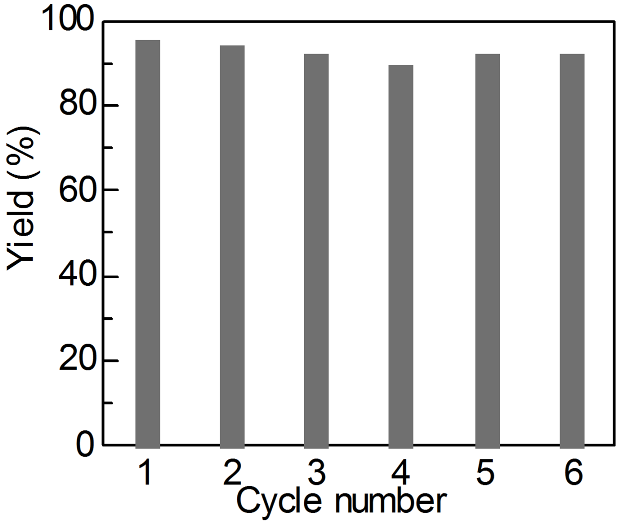


Fig. 1 Catalyst reuse for the reaction of *n*-valeramide with benzylalcohol at 165 °C (22 h).

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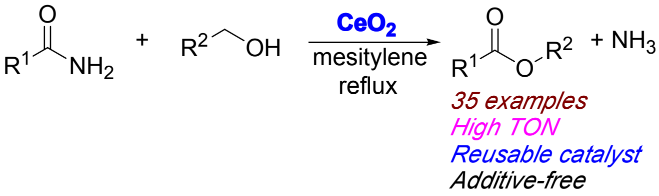

CeO_2 was found to be a versatile and reusable heterogeneous catalyst for direct alcoholysis of primary amides to esters under neutral conditions, providing a sustainable, general, and economic synthetic method of esters.