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## Amidation of Carboxylic Acids with Amines by Nb<sub>2</sub>O<sub>5</sub> as Reusable Lewis Acid Catalyst

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**Abstract:** Among 28 types of heterogeneous and homogenous catalysts tested, Nb<sub>2</sub>O<sub>5</sub> shows the highest yield for direct amidation of *n*-dodecanoic acid with a less reactive amine (aniline). The catalytic amidation by Nb<sub>2</sub>O<sub>5</sub> is applicable to a wide range of carboxylic acids and amines with various functional groups, and the catalyst is reusable. Comparison of the results of the catalytic study and infrared (IR) study of the acetic acid adsorbed on the catalyst suggests that activation of carbonyl group of the carboxylic acid by Lewis acid sites on Nb<sub>2</sub>O<sub>5</sub> is responsible for the high activity of Nb<sub>2</sub>O<sub>5</sub>. Kinetic studies show that Lewis acid sites on Nb<sub>2</sub>O<sub>5</sub> is water-tolerant than conventional Lewis acidic oxides (Al<sub>2</sub>O<sub>3</sub>, TiO<sub>2</sub>). In comparison with the state-of-the-art homogeneous Lewis acid catalyst (ZrCl<sub>4</sub>) for amidation, Nb<sub>2</sub>O<sub>5</sub> undergoes less negative effect of basic additives in the solution, indicating that Nb<sub>2</sub>O<sub>5</sub> is a more base-tolerant Lewis acid catalyst than the homogeneous Lewis acid catalyst.

### Introduction

Amide bonds constitute the building blocks of pharmaceutically and biologically important compounds.<sup>[1-4]</sup> Conventionally, amides are prepared from carboxylic acids and amines via activated carboxylic acid derivatives such as carboxylic acid anhydrides or acyl chlorides or via activation with stoichiometric amount of a condensation agent for activation of carboxylic acid and water removal.<sup>[4]</sup> The conventional methods suffer from low atom efficiency and production of byproducts. It is generally accepted that the catalytic synthesis of amides from readily available starting materials is the priority area for the pharmaceutical industry.<sup>[1]</sup> As summarized in recent review articles,<sup>[5-9]</sup> the direct condensation of carboxylic acids and amines by boron-based<sup>[10-19]</sup> or metal-based<sup>[20-26]</sup> homogeneous catalysts and oxide-based heterogeneous catalysts,<sup>[27-40]</sup> plays a central role in the direct amidation. However, less reactive amines such as

anilines and less reactive carboxylic acids such as  $\alpha$ -hydroxycarboxylic acids and benzoic acids are not generally tolerated by previous catalysts. A rare example is a boronic acid catalyst developed by Ishihara,<sup>[13]</sup> who have shown that condensation of an equimolar mixture of  $\alpha$ -hydroxycarboxylic acids and primary or secondary amines proceeds with a boron-based catalyst under azeotropic reflux conditions in toluene. However, homogeneous catalytic methods have drawbacks of difficulties in catalyst/products separation and catalyst reuse. Moreover, Lewis acidic homogeneous catalysts have potential drawbacks such as suppression of activity by strong coordination of basic functional groups in a substrate (such as heterocyclic groups) and irreversible decomposition of the catalyst by water (as a byproduct). As for heterogeneous catalysts for the direct amidation, previous reports mainly studied N-formylation<sup>[4,32,35]</sup> or N-acetylation<sup>[4,39]</sup> of amines. Some of the previous heterogeneous systems for amidation suffer from drawbacks of limited scope and needs of excess amount of reagent or a special reaction method (microwave heating).<sup>[33,34]</sup>

In the course of our continuous studies on the amide bond forming reactions by heterogeneous Lewis acidic catalysts,<sup>[41-43]</sup> we have recently reported that Nb<sub>2</sub>O<sub>5</sub>, prepared by calcination of a commercial niobic acid, acts as base-tolerant Lewis acid catalyst for direct amidation of dicarboxylic acids with amines<sup>[43]</sup> and direct amidation of esters with amines.<sup>[42]</sup> We report herein that Nb<sub>2</sub>O<sub>5</sub> is an effective and reusable catalyst for direct condensation of less reactive carboxylic acids with less reactive amines. Catalytic results show wide applicability of the synthetic method, and IR spectroscopic and kinetic studies show that the high activity of Nb<sub>2</sub>O<sub>5</sub> is due to activation of carboxylic acids by Lewis acid sites of Nb<sub>2</sub>O<sub>5</sub> with base-tolerant nature.

## Experimental

**General.** Commercially available organic compounds (from Tokyo Chemical Industry or Aldrich) were used without further purification. GC (Shimadzu GC-2014) and GCMS (Shimadzu GCMS-QP2010) analyses were carried out with Ultra ALLOY<sup>+</sup>-1 capillary column (Frontier Laboratories Ltd.) using N<sub>2</sub> and He as the carrier. All reactions were carried out in oven-dried glassware under an inert atmosphere of nitrogen. Analytical TLC was performed on a Merck 60 F254 silica gel (0.25 mm thickness). Column chromatography was performed with silica gel 60 (spherical, 63-210  $\mu$ m, Kanto Chemical Co. Ltd.). Molecular sieves 4Å (MS4Å) was dehydrated at 100 °C.

**Catalyst preparation.** Niobic acid (Nb<sub>2</sub>O<sub>5</sub>·nH<sub>2</sub>O, HY-340) was kindly supplied by CBMM. Nb<sub>2</sub>O<sub>5</sub> (surface area = 54 m<sup>2</sup> g<sup>-1</sup>) was prepared by calcination of niobic acid at 500 °C for 3 h. MgO (JRC-MGO-3), TiO<sub>2</sub> (JRC-TIO-4), CeO<sub>2</sub> (JRC-CEO-3), H<sup>+</sup>-type Y zeolite (HY) with a SiO<sub>2</sub>/Al<sub>2</sub>O<sub>3</sub> ratio of 4.8 (JRC-Z-HY-4.8), H<sup>+</sup>-type BEA zeolite (HBEA) with a SiO<sub>2</sub>/Al<sub>2</sub>O<sub>3</sub> ratio

of 25 (JRC-Z-HB25) and H<sup>+</sup>-type MFI zeolite (HMFI) with a SiO<sub>2</sub>/Al<sub>2</sub>O<sub>3</sub> ratio of 90 (JRC-Z5-90H) were supplied from Catalysis Society of Japan. SiO<sub>2</sub> (Q-10, 300 m<sup>2</sup> g<sup>-1</sup>) was supplied from Fuji Silysia Chemical Ltd. ZrO<sub>2</sub>·nH<sub>2</sub>O was prepared by hydrolysis of zirconium oxynitrate 2-hydrate in water by aqueous NH<sub>4</sub>OH solution, followed by filtration of precipitate, washing with water three times, and drying at 200 °C. ZrO<sub>2</sub>, ZnO, SnO<sub>2</sub>, MoO<sub>3</sub>, WO<sub>3</sub>, Ta<sub>2</sub>O<sub>5</sub> and CaO were prepared by calcination (500 °C, 3 h) of the hydrous oxides: ZrO<sub>2</sub>·nH<sub>2</sub>O, ZnO·nH<sub>2</sub>O (Kishida Chemical), H<sub>2</sub>SnO<sub>3</sub> (Kojundo Chemical Laboratory Co., Ltd.), H<sub>2</sub>MoO<sub>4</sub> (Kanto Chemical), H<sub>2</sub>WO<sub>4</sub> (Kanto Chemical), Ca(OH)<sub>2</sub> (Kanto Chemical) and Ta<sub>2</sub>O<sub>5</sub>·nH<sub>2</sub>O (Mitsuwa Chemicals). γ-Al<sub>2</sub>O<sub>3</sub> and θ-Al<sub>2</sub>O<sub>3</sub> was prepared by calcination of γ-AlOOH (Catapal B Alumina purchased from Sasol) for 3 h at 900 °C and 1000 °C, respectively. Montmorillonite K10 clay and a sulfonic resins (Amberlyst-15® and nafion-SiO<sub>2</sub> composite) were purchased from Aldrich. Fe<sup>3+</sup>-exchanged K-10 (Fe<sup>3+</sup>-mont) was prepared by treating the clay with aqueous solution of FeCl<sub>3</sub>·6H<sub>2</sub>O for 3 h at room temperature, followed by centrifuging and washing with deionized water four times, and by drying in vacuo at room temperature. The Fe content in Fe<sup>3+</sup>-mont (0.46 wt%) was determined by ICP analysis. Scandium(III) trifluoromethanesulfonate, Sc(OTf)<sub>3</sub>, was purchased from Tokyo Chemical Industry. ZrCl<sub>4</sub> was purchased from WAKO. Cs<sub>2.5</sub>H<sub>0.5</sub>PW<sub>12</sub>O<sub>40</sub> was prepared by titrating H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub> (Nippon Inorganic Color and Chemicals Co.) by aqueous solution of Cs<sub>2</sub>CO<sub>3</sub> (0.10 mol dm<sup>-3</sup>) with vigorous stirring, followed by centrifuging and drying at 200 °C.

**In situ IR.** In situ IR spectra were recorded by a JASCO FT/IR-4200 spectrometer equipped with an MCT detector. For the acetic acid-adsorption IR study, a closed IR cell surrounded by the Dewar vessel was connected to an evacuation system. During the IR measurement, the IR cell was cooled by freezing mixture of ethanol/liquid nitrogen in the Dewar vessel, and the thermocouple near the sample showed -75 ± 5 °C. The sample was pressed into a 40 mg of self-supporting wafer ( $\phi = 2$  cm) and mounted into the IR cell with CaF<sub>2</sub> windows. Spectra were measured accumulating 15 scans at a resolution of 4 cm<sup>-1</sup>. After in situ pre-evacuation of the sample at 500 °C for 0.5 h, a reference spectrum of the sample disc was measured at -75 ± 5 °C. Then, the sample was exposed to 2 Pa of acetic acid at -75 ± 5 °C for 120 s, followed by evacuation for 500 s. Then a differential IR spectrum, with respect to the reference spectrum, was recorded at -75 ± 5 °C. The pyridine-adsorption IR study was carried out at 200 °C by a flow-type IR cell connected to a flow reaction system. The IR disc of Nb<sub>2</sub>O<sub>5</sub> in the IR cell was first dehydrated under He flow at 500 °C, and then a background spectrum was taken under He flow at 200 °C. Then, H<sub>2</sub>O (1.4 mmol/g) was introduced to Nb<sub>2</sub>O<sub>5</sub>, followed by introduction of pyridine (0.3 mmol/g), purging by He for 600 s, and by IR measurement of adsorbed species at 200 °C.

**Catalytic tests.** We used as-received solvent without dehydration. The heterogeneous

catalysts, stored under ambient conditions, were used for catalytic reactions without any pretreatment, and thus the catalyst surface was hydrated before the reaction.

Typically, carboxylic acid (1 mmol) and amine (1 mmol) in 2 mL toluene and 50 mg of Nb<sub>2</sub>O<sub>5</sub> were added to a reaction vessel (pyrex cylinder) with a reflux condenser and a magnetic starter. The reaction mixture was heated to reflux under N<sub>2</sub> atmosphere and stirred at 400 rpm. For azeotropic removal of water, a funnel containing 0.2 g of MS4Å on a cotton plug was placed in the upper side of the cylinder surmounted by a reflux condenser.

After completion of the reaction, 2-propanol (4 mL) was added to the mixture, and the Nb<sub>2</sub>O<sub>5</sub> catalyst was separated by centrifugation. For the catalytic tests in Table 1 and Figures 1, 4, 5, 6 the reaction mixture was analyzed by GC, and yield of the products was determined using *n*-dodecane as an internal standard. For the reactions in Tables 3-5 the product was isolated by column chromatography. Then, the resulting product was identified using GCMS, <sup>1</sup>H-NMR and <sup>13</sup>C-NMR analyses.

## Results and discussion

**Catalyst screening.** We carried out as a model reaction between equimolar amount of *n*-dodecanoic acid and aniline under azeotropic reflux conditions. Table 1 summarizes the yield of the corresponding amide for various catalysts including metal oxides and standard heterogeneous and homogeneous acid catalysts. Figure 1 shows time-yield profiles for some representative catalysts. It is known that the direct formation of amides from reactive amines and carboxylic acids without catalyst occurs in non-polar solvents under azeotropic reflux conditions.<sup>[21,43,44]</sup> For the model reaction in Table 1, we used aniline as one of the least reactive amines in the literature for the thermal amidation reaction.<sup>[21,44]</sup> We confirmed that the thermal reaction in the absence of catalyst gave only 1% yield of the amide (entry 1). We screened 17 types of simple metal oxides (entries 2-19) including two of the hydrates (entries 4,11). Among the oxide tested, Nb<sub>2</sub>O<sub>5</sub> showed the highest yield (99%) of the amide. In the literature, TiO<sub>2</sub>,<sup>[33]</sup> ZnO,<sup>[32]</sup> Al<sub>2</sub>O<sub>3</sub>,<sup>[35,36]</sup> ZrO<sub>2</sub>.nH<sub>2</sub>O,<sup>[38]</sup> SiO<sub>2</sub>,<sup>[27]</sup> Fe<sup>3+</sup>-mont,<sup>[39,40]</sup> HY<sup>[28]</sup> and HBEA<sup>[29]</sup> zeolites were reported to be effective for the direct amidation. However, these catalysts showed lower yield than Nb<sub>2</sub>O<sub>5</sub>. For example, conventional solid Lewis acids<sup>[45,46]</sup> such as TiO<sub>2</sub> (entry 5), alumina (entries 8,9) and Fe<sup>3+</sup>-mont (entry 20) gave low to moderate yields (9-66%). Basic oxides (MgO, CaO) were ineffective. In the dehydrative amide condensation reaction, water produced during the reaction can suppress the catalytic activity by strong adsorption on acid sites of catalysts. Thus, water-tolerant acid catalysts may be effective for the reaction. We tested water-tolerant Brønsted acidic heterogeneous catalysts,<sup>[47]</sup> such as a high-silica zeolite (HMFI, entry 23), Cs-exchanged heteropoly acid (entry 24) and the acidic resin, Amberlyst-15 (entry 25) and Nafion-SiO<sub>2</sub> (entry 26), and a water-tolerant homogeneous Lewis acid,<sup>[48]</sup> such as Sc(OTf)<sub>3</sub>

(entry 27). However, these water-tolerant acid catalysts gave lower yield of the amide (2-30%) than Nb<sub>2</sub>O<sub>5</sub>. Homogenous Brønsted acids such as sulfuric acid (entry 29) and *p*-toluenesulfonic acid (PTSA, entry 30) also gave low yields. A hydrate of Nb<sub>2</sub>O<sub>5</sub> called niobic acid (entry 4), which has been studied as water-tolerant Lewis acid catalyst,<sup>[49]</sup> gave lower yield (74%) than Nb<sub>2</sub>O<sub>5</sub>.

**Lewis acidity of Nb<sub>2</sub>O<sub>5</sub>.** In our previous IR study of pyridine adsorption on Nb<sub>2</sub>O<sub>5</sub>, we showed that surface acid sites of dehydrated Nb<sub>2</sub>O<sub>5</sub> are mainly Lewis acidic sites (exposed Nb<sup>5+</sup> cations).<sup>[45]</sup> Figure 2 shows the IR spectrum of pyridine adsorbed on dehydrated and rehydrated Nb<sub>2</sub>O<sub>5</sub>. These spectra have basically the same features; the band at 1445 cm<sup>-1</sup> due to coordinated pyridine on Lewis acid site (exposed Nb<sup>5+</sup> cations) is dominant rather than the band at 1540 cm<sup>-1</sup> due to pyridinium ion due to Brønsted acid sites. The result shows that water does not essentially change the IR spectrum of adsorbed pyridine; Nb<sub>2</sub>O<sub>5</sub> is predominantly Lewis acidic even after re-hydration. To investigate the Lewis acid-base interaction between the Nb site and a carbonyl group of a model carboxylic acid, we measured in situ IR spectrum of acetic acid adsorbed on Nb<sub>2</sub>O<sub>5</sub>. The spectrum (Figure 3) showed a C=O stretching band of the adsorbed acetic acid ( $\nu_{\text{C=O}}$ ) at lower wavenumber (1686 cm<sup>-1</sup>) than non Lewis acidic oxide, SiO<sub>2</sub> (1703 cm<sup>-1</sup>) and conventional Lewis acidic oxides: TiO<sub>2</sub> (1695 cm<sup>-1</sup>) and Al<sub>2</sub>O<sub>3</sub> (1697 cm<sup>-1</sup>). This indicates that the surface of Nb<sub>2</sub>O<sub>5</sub> has the most effective Lewis acid sites for activation of the C=O bond of the carboxylic acid.

**Base-tolerant catalysis of Nb<sub>2</sub>O<sub>5</sub> for amidation.** Lewis acidic catalysts for the direct amidation should work even in the presence of water, because the reaction yields water as coproduct. We studied the effect of water removal and water addition on the time-yield profiles for some Lewis acidic metal oxide catalysts (Nb<sub>2</sub>O<sub>5</sub>, TiO<sub>2</sub> and Al<sub>2</sub>O<sub>3</sub>) for the model amidation of *n*-dodecanoic acid and aniline (Figure 1). For all the catalysts, the standard azeotropic reflux conditions gave higher activity than the reaction without azeotropic water removal, and the reaction without azeotropic water removal with 3 mmol H<sub>2</sub>O in the initial mixture gave the lowest activity. However, the negative impact of the water was lower for Nb<sub>2</sub>O<sub>5</sub> than TiO<sub>2</sub> and Al<sub>2</sub>O<sub>3</sub>. As shown in Figure 4, the initial rate of amide formation with Nb<sub>2</sub>O<sub>5</sub> and TiO<sub>2</sub> decreased with increase in the initial concentration of water. This indicates that water inhibits the activity of these catalysts. The slope was lower for Nb<sub>2</sub>O<sub>5</sub> than TiO<sub>2</sub>, and the reaction orders with respect to water were -0.3 and -1.8 for Nb<sub>2</sub>O<sub>5</sub> and TiO<sub>2</sub>, respectively. This indicates that water-tolerance of Nb<sub>2</sub>O<sub>5</sub> is higher than TiO<sub>2</sub>.

ZrCl<sub>4</sub> is a well established Lewis acidic homogenous catalyst for the direct amidation.<sup>[20-22]</sup> Generally, the activity of homogeneous Lewis acid can be reduced by water and organic bases. To compare base-tolerance of ZrCl<sub>4</sub> and Nb<sub>2</sub>O<sub>5</sub>, we measured the yield of the amide in the standard reaction for 30 h with ZrCl<sub>4</sub> or Nb<sub>2</sub>O<sub>5</sub> under the azeotropic reflux conditions in the

absence or presence of 0.5 equiv. of basic additives: H<sub>2</sub>O, 2,6-dimethylpyridine, pyridine, and triethylamine (Figure 4). Although we used the same molar amount of the catalyst (0.38 mmol), ZrCl<sub>4</sub> was dissolved in the reaction mixture while Nb<sub>2</sub>O<sub>5</sub> was insoluble. Clearly, the additive-free condition gave higher yield for both catalysts, but negative effects of the additives were lower for Nb<sub>2</sub>O<sub>5</sub> than ZrCl<sub>4</sub>. Note that 0.5 mmol of the basic molecules added to the mixture is 172 times larger than the number of surface Lewis acid sites on the Nb<sub>2</sub>O<sub>5</sub> catalyst used. This suggests that the active site (Nb<sup>5+</sup> Lewis acid site) interacts preferentially with the reactant (carboxylic acid) in the presence of excess amount of basic molecules. Summarizing the above results, we can conclude that Lewis acid site of Nb<sub>2</sub>O<sub>5</sub> has higher tolerance to basic molecules than conventional solid Lewis acids and a typical homogeneous Lewis acid. The water-tolerant character of the Nb<sup>5+</sup> Lewis acid sites of niobium oxide is consistent with the pioneering work by Nakajima et al.<sup>[49]</sup>

**Performance of Nb<sub>2</sub>O<sub>5</sub>-catalyzed amidation.** As listed in Table 2, the turnover number (TON) with respect to the Lewis acid site of Nb<sub>2</sub>O<sub>5</sub> (341) was more than 200 times higher than those of ZrCl<sub>4</sub> (a well established homogenous catalyst for the direct amidation<sup>[20-22]</sup>) and Sc(OTf)<sub>3</sub> (a well established “water-tolerant” Lewis acid<sup>[48]</sup>). TON of Nb<sub>2</sub>O<sub>5</sub> was 5 times larger than that of TiO<sub>2</sub>. As discussed in the above section, the higher catalytic efficiency of Nb<sub>2</sub>O<sub>5</sub> can be due to the higher water-tolerance and more effective Lewis acid activation of the C=O bond by Nb<sub>2</sub>O<sub>5</sub> than TiO<sub>2</sub>. It is important to note that the water-tolerance of Nb<sub>2</sub>O<sub>5</sub> enabled the amidation without azeotropic water removal; the reaction by Nb<sub>2</sub>O<sub>5</sub> under simple reflux condition for 40 h resulted in 96% yield of the amide (Table 1, entry 3).

We studied the reusability of Nb<sub>2</sub>O<sub>5</sub>. After the standard reaction (Table 1, entry 2), the catalyst was separated from the mixture by centrifugation, followed by washing with acetone, and by drying at 90 °C for 3 h. ICP-AES analysis of the solution confirmed that the content of Nb in the solution was below the detection limit. The recovered catalyst was reused five times without a marked loss of its catalytic activity (Figure 6). For the standard reaction, the reaction was completely terminated by removing the Nb<sub>2</sub>O<sub>5</sub> catalyst from the reaction mixture after 4 h (at 19% yield), and further heating of the filtrate for 26 h did not increase the yield. These results indicate that Nb<sub>2</sub>O<sub>5</sub> acts as a reusable heterogeneous catalyst.

Then, we explored the generality and scope of the Nb<sub>2</sub>O<sub>5</sub>-catalyzed direct amidation of carboxyl acids with different amines (Table 3-5). As listed in Table 3, anilines (entries 1-6) with electron-donating and electron-withdrawing functional groups, benzyl amines (entries 7-9) with electron-rich and electron-poor ring, heteroaromatic amine (entry 10), aliphatic primary amines (entries 11-13) with various functional groups (phenyl, -C=C and hydroxyl groups, reacted with equimolar amount of *n*-dodecanoic acid to give the corresponding amide in good to high isolated yields (80-98%). Due to the low nucleophilicity, the least reactive amines, -Br and -Cl

substituted anilines (entries 5,6) and allylamine (entry 12) required higher temperature (reflux in *o*-xylene). A secondary amine, morpholine (entry 14) was also tolerated to give the corresponding tertiary amide in high yield.

Table 4 shows that the method is also effective for the amidation of various carboxylic acids with a less nucleophilic amine, aniline. Linear aliphatic carboxylic acids (entries 1-5) and a less reactive carboxylic acid, benzoic acid (entry 6) were converted to the corresponding amides in good to high isolated yield (81-98%). Amidation of a heteroaromatic carboxylic acid, pyridine-2-carboxylic acid (entry 7), with benzylamine was also succeeded to give 90% yield of the product.

Finally, we tested the amidation of more challenging carboxylic acids ( $\alpha$ -hydroxy,  $\beta$ -hydroxy and  $\beta$ -thio carboxylic acids) with various amines under azeotropic reflux in *o*-xylene (Table 5). It should be noted that only one report by Ishihara et al. have succeeded in the direct amidation of  $\alpha$ -hydroxy carboxylic acids with amines, but the previous method using  $\text{MeB(OH)}_2$  catalyst is not effective for less reactive amines such as aniline.<sup>[13]</sup> To our delight, our method was applicable to the synthesis of amides from aniline and  $\alpha$ -hydroxycarboxylic acids (entries 1,3) and a  $\beta$ -thiocarboxylic acid (entry 6). The  $\alpha$ -hydroxycarboxylic acids include an important biomass-derived chemical, lactic acid (entries 1,2), demonstrating that our method can contribute to production of fine chemicals from biomass feedstock. The method was also effective for the amidation of a  $\beta$ -hydroxycarboxylic acid, salicylic acid (entry 5), with benzylamine and gave the corresponding amide in 95% yield. We tentatively assume that the unprecedentedly efficient catalysis of  $\text{Nb}_2\text{O}_5$  for the amidation of challenging substrates is caused by the base-tolerant Lewis acid-activation of carboxylic acids, which is evidenced by IR (Figure 2,3) and kinetic studies (Figure 1,4,6).

## Conclusion

We have presented a versatile and sustainable method for direct amidation of carboxylic acids with various amines using  $\text{Nb}_2\text{O}_5$  as a reusable, inexpensive, and commercially available heterogeneous catalyst. This simple and atom-efficient method tolerates various functional groups and is applicable to challenging substrates such as anilines and  $\alpha$ -hydroxycarboxylic acids. The Lewis acid site of  $\text{Nb}_2\text{O}_5$ , as the active site for the amidation, has higher tolerance to the co-present basic molecules (water and tertiary and heteroaromatic amines) than the state-of-the-art homogeneous Lewis acid catalyst for the amidation ( $\text{ZrCl}_4$ ) and conventional Lewis acidic heterogeneous catalysts ( $\text{Al}_2\text{O}_3$ ,  $\text{TiO}_2$ ), which results in higher catalytic activity of  $\text{Nb}_2\text{O}_5$  than these catalysts.

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**Keywords:** amidation • carboxylic acids • amines • Lewis acid

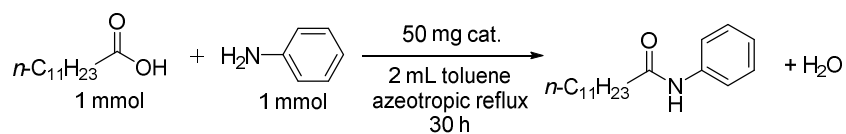
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**Table 1.** Catalyst screening for amidation of *n*-dodecanoic acid with aniline.

Entry	Catalyst	Yield [%] <sup>[a]</sup>
1	no catalyst	1
2	Nb <sub>2</sub> O <sub>5</sub>	99
3 <sup>[b]</sup>	Nb <sub>2</sub> O <sub>5</sub>	96
4	Niobic acid	74
5	TiO <sub>2</sub>	51
6	ZnO	21
7	WO <sub>3</sub>	16
8	θ-Al <sub>2</sub> O <sub>3</sub>	11
9	γ-Al <sub>2</sub> O <sub>3</sub>	9
10	MoO <sub>3</sub>	9
11	ZrO <sub>2</sub> · <i>n</i> H <sub>2</sub> O	9
12	CeO <sub>2</sub>	7
13	ZrO <sub>2</sub>	6
14	Ta <sub>2</sub> O <sub>5</sub>	6
15	CaO	5
16	SnO <sub>2</sub>	5
17	MgO	1
19	SiO <sub>2</sub>	13
20	Fe <sup>3+</sup> -mont	66
21	HY	7
22	HBEA	27
23	HMFI	26
24	CS <sub>2.5</sub> H <sub>0.5</sub> PW <sub>12</sub> O <sub>40</sub>	7
25	Amberlyst-15	4
26	Nafion-SiO <sub>2</sub>	30
27	Sc(OTf) <sub>3</sub>	2
28	ZrCl <sub>4</sub>	71
29 <sup>[c]</sup>	H <sub>2</sub> SO <sub>4</sub>	1
30	PTSA	19

<sup>[a]</sup> GC yields.<sup>[b]</sup> Under reflux conditions without azeotropic water removal for 40 h.<sup>[c]</sup> Aqueous solution of 30 wt% H<sub>2</sub>SO<sub>4</sub>.

**Table 2.** Summary of IR and kinetic results.

Catalyst	[LA] <sup>[a]</sup> /mmol g <sup>-1</sup>	$\nu_{\text{C=O}}$ <sup>[b]</sup> / cm <sup>-1</sup>	$n_{\text{H}_2\text{O}}$ <sup>[c]</sup>	TOF <sup>[d]</sup> / h <sup>-1</sup>	TON <sup>[d]</sup>
Nb <sub>2</sub> O <sub>5</sub>	0.058	1686	-0.4	11.4	341
TiO <sub>2</sub>	0.083	1695	-1.8	2.0	61
ZrCl <sub>4</sub>	4.3 <sup>[e]</sup>	-	-	0.006	1.7
Sc(OTf) <sub>3</sub>	2.0 <sup>[e]</sup>	-	-	0.003	0.1

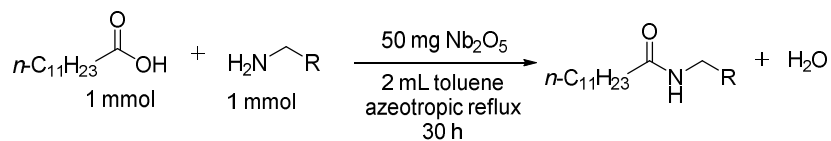
<sup>[a]</sup> The number of Lewis acid sites on the surface of oxides Nb<sub>2</sub>O<sub>5</sub> and TiO<sub>2</sub> estimated by pyridine adsorption at 200°C, which were reported in ref. 45.

<sup>[b]</sup> Position of  $\nu_{\text{C=O}}$  IR band of adsorbed acetic acid (Figure 4).

<sup>[c]</sup> Reaction order with respect to water (Figure 2).

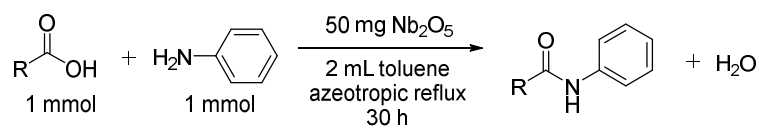
<sup>[d]</sup> Calculated with the number of Lewis acid site and the catalytic results in Table 1.

<sup>[e]</sup> Based on molecular weight of the salts.

**Table 3.** Nb<sub>2</sub>O<sub>5</sub>-catalyzed amidation of *n*-dodecanoic acid with various amines.

Entry	Amine	Product	Yield <sup>[a]</sup> [%]
1			98
2			98
3			97
4			98
5 <sup>[b]</sup>			80
6 <sup>[b]</sup>			97
7			88
8			80
9			94
10			95
11			83
12 <sup>[b]</sup>			98
13			96
14			81

<sup>[a]</sup> Isolated yields.<sup>[b]</sup> Under *o*-xylene reflux.

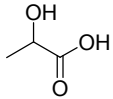
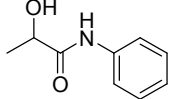
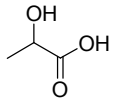
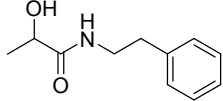
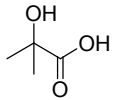
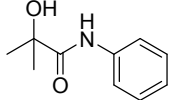
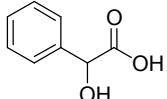
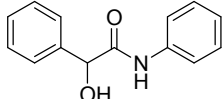
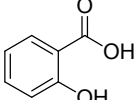
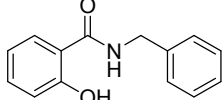
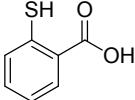
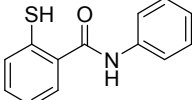
**Table 4.** Nb<sub>2</sub>O<sub>5</sub>-catalyzed amidation of various carboxylic acids with aniline or benzylamine.

Entry	Acid	Product	Yield <sup>[a]</sup> [%]
1			80
2			83
3			81
4 <sup>[b]</sup>			98
5			95
6 <sup>[b]</sup>			80
7 <sup>[b]</sup>			90

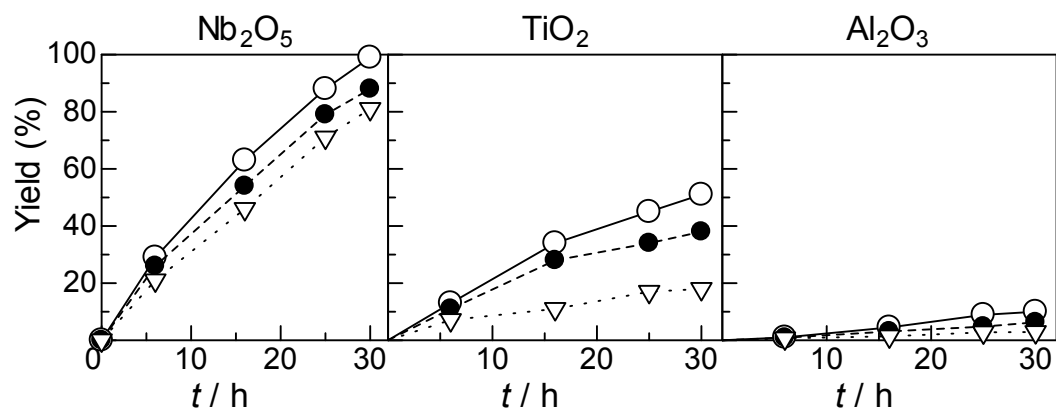
<sup>[a]</sup> Isolated yields.

<sup>[b]</sup> Under *o*-xylene reflux.

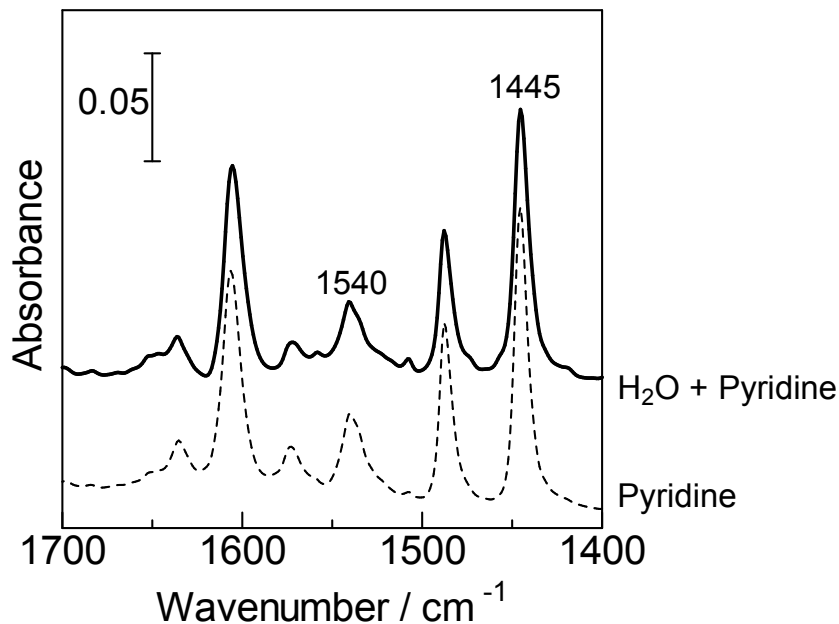
**Table 5.** Nb<sub>2</sub>O<sub>5</sub>-catalyzed amidation of  $\alpha$ -hydroxy and  $\beta$ -thio carboxylic acids with amines.<sup>[a]</sup>

Entry	Acid	Product	Yield [%]
1			69
2			80
3			71
4			65
5			95
6			87

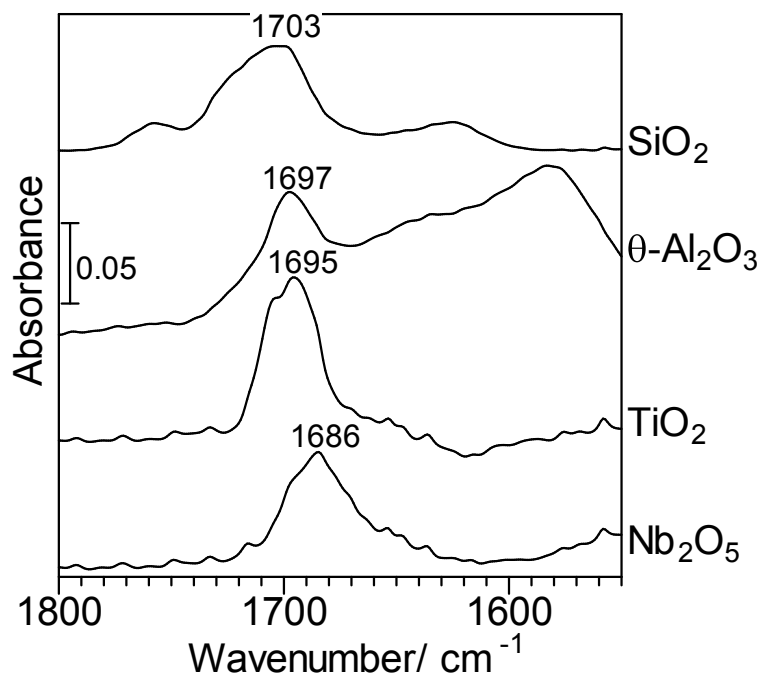
<sup>[a]</sup> Carboxylic acid (1 mmol), amine (1 mmol), *o*-xylene (2 mL), azeotropic reflux, 30 h. Yields are based on isolated yields.



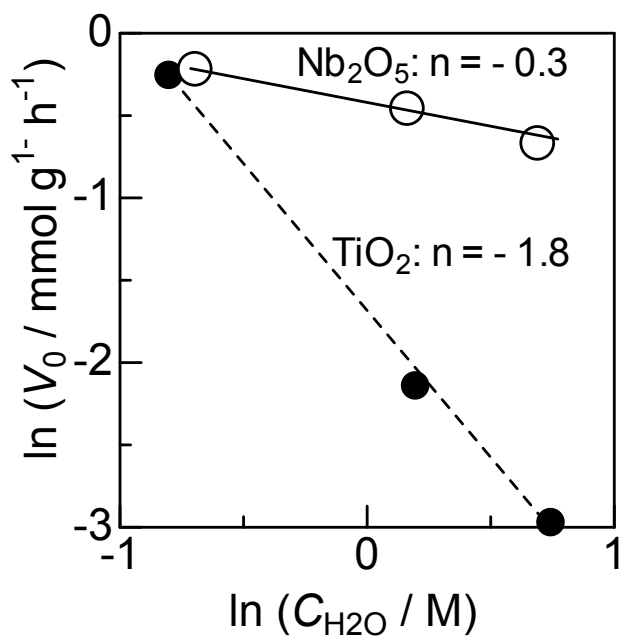
**Figure 1.** Time-yield profiles for amidation of *n*-dodecanoic acid (1 mmol) with aniline (1 mmol) catalyzed by metal oxides (50 mg) in different conditions: (○) azeotropic reflux; (●) reflux (without azeotropic water removal); (▽) reflux with 3 mmol of H<sub>2</sub>O in the initial mixture.



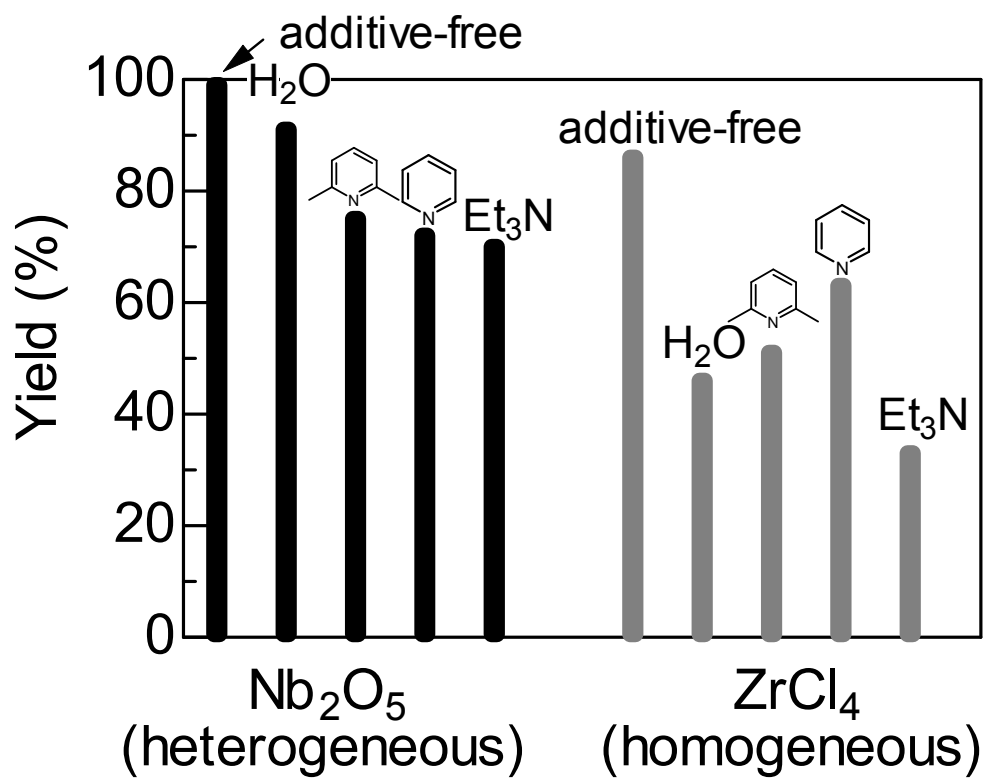
**Figure 2.** IR spectra of pyridine adsorbed on dehydrated Nb<sub>2</sub>O<sub>5</sub> (dashed line) and rehydrated Nb<sub>2</sub>O<sub>5</sub> (solid line) at 200 °C.



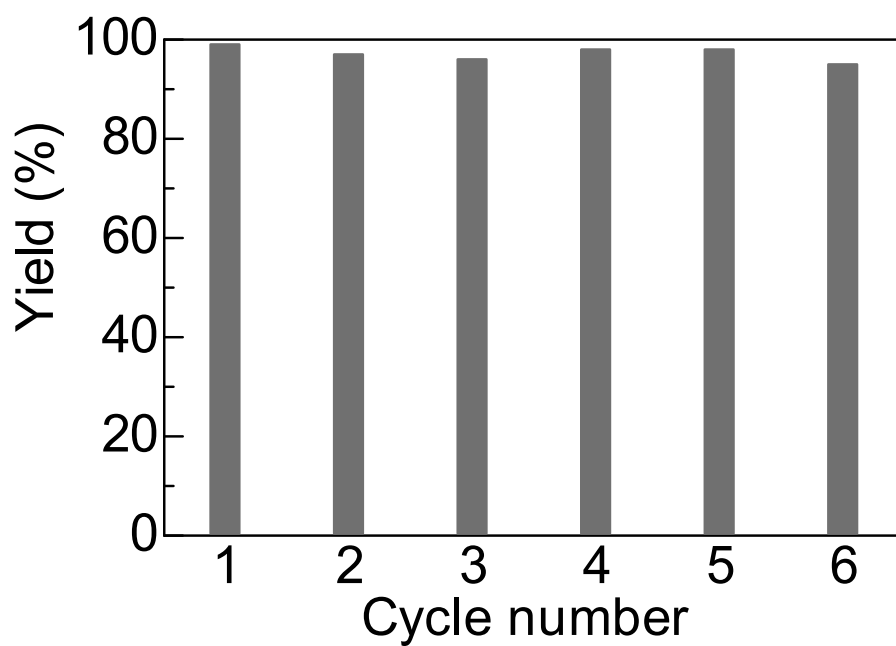
**Figure 3.** IR spectra of acetic acid adsorbed on Nb<sub>2</sub>O<sub>5</sub>, TiO<sub>2</sub>, θ-Al<sub>2</sub>O<sub>3</sub> and SiO<sub>2</sub> at - 75 °C.



**Figure 4.** Initial rate for amidation of *n*-dodecanoic acid with aniline by (○) Nb<sub>2</sub>O<sub>5</sub> and (●) TiO<sub>2</sub> as a function of the initial concentration of water ( $C_{\text{H}_2\text{O}} = 1.1$  to 3.4 M).



**Figure 5.** Yield of amide for the reaction of *n*-dodecanoic acid with aniline for 30 h by Nb<sub>2</sub>O<sub>5</sub> (50 mg, 0.38 mmol) and ZrCl<sub>4</sub> (50 mg, 0.38 mmol) in the absence and presence of 0.5 mmol of basic additives: water, 2,6-dimethylpyridine, pyridine, triethylamine.

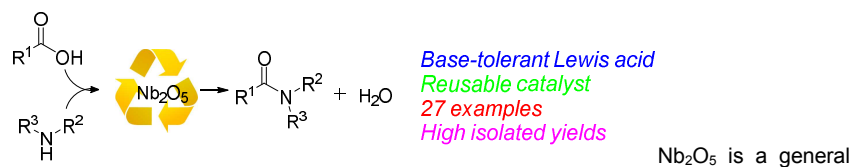


**Figure 6.** Reusability of Nb<sub>2</sub>O<sub>5</sub> (50 mg) for amidation of *n*-dodecanoic acid (1 mmol) with aniline (1 mmol) in toluene reflux conditions for 30 h.

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### Full Paper

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and reusable heterogeneous catalyst for direct amidation of carboxylic acids with amines due to base-tolerant Lewis acid catalysis of surface Nb<sup>5+</sup> sites.

Md. Ayub Ali, S. M. A. Hakim Siddiki,  
Wataru Onodera, Kenichi Kon, Ken-ichi  
Shimizu

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**Amidation of Carboxylic Acids with  
Amines by Nb<sub>2</sub>O<sub>5</sub> as Reusable Lewis  
Acid Catalyst**