

Amidation of Carboxylic Acids with Amines by Nb₂O₅ as a Reusable Lewis Acid Catalyst

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Among 28 types of heterogeneous and homogenous catalysts tested, Nb_2O_5 shows the highest yield for direct amidation of *n*-dodecanoic acid with a less reactive amine (aniline). The catalytic amidation by Nb_2O_5 is applicable to a wide range of carboxylic acids and amines with various functional groups, and the catalyst is reusable. A comparison of the results of the catalytic study and an infrared study of the acetic acid adsorbed on the catalyst suggests that activation of the carbonyl group of the carboxylic acid by Lewis acid sites on Nb_2O_5 is responsi-

Introduction

Amide bonds constitute the building blocks of pharmaceutically and biologically important compounds.^[1-4] Conventionally, amides are prepared from carboxylic acids and amines via activated carboxylic acid derivatives such as carboxylic acid anhydrides or acyl chlorides or through activation with a stoichiometric amount of a condensation agent for activation of the carboxylic acid and water removal.^[4] The conventional methods suffer from low atom efficiency and the production of byproducts. It is generally accepted that the catalytic synthesis of amides from readily available starting materials is a priority area for the pharmaceutical industry.^[1] As summarized in recent review articles,^[5-9] the direct condensation of carboxylic acids and amines by boron-based^[10-19] or metal-based^[20-26] homogeneous catalysts and oxide-based heterogeneous catalysts^[27-40] plays a central role in direct amidation methods. However, less reactive amines such as anilines and less reactive carboxylic acids such as α -hydroxycarboxylic acids and benzoic acids are not generally tolerated by the previous catalysts. A rare example is a boronic acid catalyst developed by Ishihara and co-workers,^[13] who have shown that condensation of an equimolar mixture of α -hydroxycarboxylic acids and primary or secondary amines proceeds with a boron-based catalyst under azeotropic reflux conditions in toluene. However, homogene-

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ble for the high activity of the Nb₂O₅ catalyst. Kinetic studies show that Lewis acid sites on Nb₂O₅ are more water-tolerant than conventional Lewis acidic oxides (Al₂O₃, TiO₂). In comparison with the state-of-the-art homogeneous Lewis acid catalyst for amidation (ZrCl₄), Nb₂O₅ undergoes fewer negative effects from basic additives in the solution, which indicates that Nb₂O₅ is a more base-tolerant Lewis acid catalyst than the homogeneous Lewis acid catalyst.

ous catalytic methods have the drawback of difficulties in catalyst/product separation and catalyst reuse. Moreover, Lewis acidic homogenous catalysts have potential drawbacks such as the suppression of activity by strong coordination of basic functional groups in a substrate (such as heterocyclic groups) and the irreversible decomposition of the catalyst by water (as a byproduct). As for heterogeneous catalysts for direct amidation, previous reports mainly studied the N-formylation^[4,32,35] or N-acetylation^[4,39] of amines. Some of the previous heterogeneous systems for amidation suffer from the drawbacks of limited scope and the need for excess amounts of reagent or a special reaction method (microwave heating).^[33,34]

In the course of our continuous studies on amide-bondforming reactions by heterogeneous Lewis acidic catalysts,^[41-43] we have recently reported that Nb₂O₅, prepared by calcination of a commercial niobic acid, acts as a base-tolerant Lewis acid catalyst for the direct imidation of dicarboxylic acids with amines^[43] and the direct amidation of esters with amines.^[42] We report herein that Nb₂O₅ is an effective and reusable catalyst for the direct condensation of less reactive carboxylic acids with less reactive amines. The catalytic results show wide applicability of the synthetic method, and IR spectroscopic and kinetic studies show that the high activity of Nb₂O₅ is a result of activation of the carboxylic acids by the Lewis acid sites of Nb₂O₅ with a base-tolerant nature.

Experimental Section

General

Commercially available organic compounds (from Tokyo Chemical Industry or Aldrich) were used without further purification. GC (Shimadzu GC-2014) and GC–MS (Shimadzu GCMS-QP2010) analyses were performed with an Ultra ALLOY⁺-1 capillary column (Frontier Laboratories Ltd.) and with N_2 and He as the carrier. All reactions



were performed 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 μ m, Kanto Chemical Co. Ltd.). Molecular sieves (4 Å) was dehydrated at T = 100 °C.

Catalyst preparation

Niobic acid (Nb₂O₅·nH₂O, HY-340) was kindly supplied by CBMM. Nb_2O_5 (surface area = 54 m² g⁻¹) was prepared by calcination of niobic acid at $T = 500 \degree$ C for 3 h. MgO (JRC-MGO-3), TiO₂ (JRC-TIO-4), CeO₂ (JRC-CEO-3), H⁺-type Y zeolite (HY) with a SiO₂/Al₂O₃ ratio of 4.8 (JRC-Z-HY-4.8), H⁺-type BEA zeolite (HBEA) with a SiO₂/Al₂O₃ ratio of 25 (JRC-Z-HB25), and H⁺-type MFI zeolite (HMFI) with a SiO₂/Al₂O₃ ratio of 90 (JRC-Z5-90H) were supplied from the Catalysis Society of Japan. SiO₂ (Q-10, 300 m^2g^{-1}) was supplied from Fuji Silysia Chemical Ltd. ZrO₂·nH₂O was prepared by hydrolysis of zirconium oxynitrate 2-hydrate in water with aqueous NH₄OH solution, followed by filtration of the precipitate, washing with water three times, and drying at T = 200 °C. ZrO_2 , ZnO_1 , SnO_2 , MOO_3 , WO_3 , Ta_2O_5 , and CaO were prepared by calcination ($T = 500 \degree C$, t = 3 h) of the hydrous oxides ZrO₂·nH₂O, ZnO·nH₂O (Kishida Chemical), H₂SnO₃ (Kojundo Chemical Laboratory Co., Ltd.), H₂MoO₄ (Kanto Chemical), H₂WO₄ (Kanto Chemical), Ca(OH)₂ (Kanto Chemical), and Ta₂O₅·*n* H₂O (Mitsuwa Chemicals). γ -Al₂O₃ and θ -Al₂O₃ were prepared by calcination of γ -AlOOH (Catapal B Alumina purchased from Sasol) for 3 h at T = 900 and $1000 \,^{\circ}$ C, respectively. Montmorillonite K10 clay and sulfonic resins (Amberlyst-15 and Nafion-SiO₂ composite) were purchased from Aldrich. Fe³⁺-exchanged K10 clay (Fe³⁺-mont) was prepared by treating the clay with an aqueous solution of FeCl₃·6H₂O for 3 h at RT, followed by centrifugation, washing with deionized water four times, and drying in vacuo at RT. The Fe content in Fe³⁺-mont (0.46 wt %) was determined by inductively coupled plasma atomic emission spectroscopy (ICP-AES) analysis. Scandium(III) trifluoromethanesulfonate, Sc(OTf)₃, was purchased from Tokyo Chemical Industry. ZrCl₄ was purchased from WAKO. Cs_{2.5}H_{0.5}PW₁₂O₄₀ was prepared by titrating H₃PW₁₂O₄₀ (Nippon Inorganic Color and Chemicals Co.) with an aqueous solution of Cs₂CO₃ (0.10 mol dm⁻³) with vigorous stirring, followed by centrifuging and drying at $T = 200 \,^{\circ}$ C.

In situ IR

In situ IR spectra were recorded by a JASCO FT/IR-4200 spectrometer equipped with a mercury cadmium telluride detector. For the acetic acid adsorption IR study, a closed IR cell surrounded by a Dewar vessel was connected to an evacuation system. During the IR measurement, the IR cell was cooled by a freezing mixture of ethanol/liquid nitrogen in the Dewar vessel, and the thermocouple near the sample showed $T = (-75 \pm 5)^{\circ}$ C. The sample was pressed into a self-supporting wafer (40 mg, $\emptyset = 2$ cm) and mounted into the IR cell with CaF2 windows. Spectra were measured by accumulating 15 scans at a resolution of 4 cm⁻¹. After in situ pre-evacuation of the sample at $T = 500 \degree$ C for 0.5 h, a reference spectrum of the sample disc was measured at $T = (-75 \pm 5)^{\circ}$ C. The sample was then exposed to acetic acid (200 Pa) at $T = (-75 \pm 5)$ °C for 120 s, followed by evacuation for 500 s. A differential IR spectrum, with respect to the reference spectrum, was then recorded at $T = (-75 \pm 5)$ °C. The pyridine-adsorption IR study was performed at $T = 200 \,^{\circ}$ C with a flow-type IR cell connected to a flow reaction system. The IR disc of Nb₂O₅ in the IR cell was first dehydrated under an He flow at $T = 500 \,^{\circ}$ C, and then a background spectrum was taken under an He flow at $T = 200 \,^{\circ}$ C. H₂O (1.4 mmolg⁻¹) was then added to Nb₂O₅, followed by introduction of pyridine (0.3 mmol g⁻¹), purging with He for 600 s, and IR measurement of the adsorbed species at T = 200 °C.

Catalytic tests

We used the 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 toluene (2 mL) and Nb₂O₅ (50 mg) were added to a reaction vessel (pyrex cylinder) with a reflux condenser and a magnetic stirrer. The reaction mixture was heated to reflux under an N₂ atmosphere and stirred at 400 rpm. For azeotropic removal of water, a funnel containing 4 Å molecular sieves (0.2 g) on a cotton plug was placed in the top of the cylinder surmounted by a reflux condenser. After completion of the reaction, 2-propanol (4 mL) was added to the mixture, and the Nb₂O₅ catalyst was separated by centrifugation. For the catalytic tests in Table 1 and Figures 1, 4, 5, and 6, the reaction mixture was analyzed by GC and the yield of the products was determined by using *n*-dodecane as an internal standard. For the reactions in Tables 3–5, the product was then identified by using GC–MS and ¹H NMR and ¹³C NMR spectroscopy analyses.

Results and Discussion

Catalyst screening

We performed a model reaction between an equimolar amount of *n*-dodecanoic acid and aniline under azeotropic reflux conditions. Table 1 summarizes the yield of the corresponding amide with various catalysts including metal oxides and standard heterogeneous and homogeneous acid catalysts. Figure 1 shows the 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 nonpolar solvents under azeotropic reflux conditions.[21,43,44] For the model reaction reported in Table 1, we used aniline, as one of the least reactive amines in the literature, for the thermal amidation reaction.^[21,44] We confirmed that the thermal reaction in the absence of catalyst gave only 1% yield of the amide (Table 1, entry 1). We screened 17 types of simple metal oxides (Table 1, entries 2-19) including two of the hydrates (Table 1, entries 4 and 11). Among the oxides tested, Nb₂O₅ showed the highest yield (99%) of the amide. In the literature, TiO_{2} ZnO_{1} ZnO_{2} $AI_{2}O_{3}$ $ZrO_{2} nH_{2}O_{1}$ SiO_{2} $ZrO_{2} nH_{2}O_{1}$ SiO_{2} $P^{3+}-mont_{1}$ and the $HY^{[28]}$ and $HBEA^{[29]}$ zeolites were reported to be effective for the direct amidation. However, these catalysts showed lower yields than Nb₂O₅. For example, conventional solid Lewis acids^[45,46] such as TiO₂, alumina, and Fe³⁺-mont (Table 1, entries 5, 8, 9, and 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,^[47] such as a high-silica zeolite



Table 1. Catalyst screening for amidation of <i>n</i> -dodecanoic acid with aniline.						
$n-C_{11}H_{23} \longrightarrow OH + H_2N \longrightarrow 50 \text{ mg cat.} $ $1 \text{ mmol} \qquad 1 \text{ mmol} \qquad 2 \text{ mL toluene} $ $30 \text{ h} $	H + H ₂ O					
Entry Catalyst	Yield [%] ^[a]					
1 no catalyst	1					
2 Nb ₂ O ₅	99					
3 ^(b) Nb ₂ O ₅	96					
4 niobic acid	74					
5 TiO ₂	51					
6 ZnO	21					
7 WO ₃	16					
8 θ-Al ₂ O ₃	11					
9 γ-Al ₂ O ₃	9					
10 MoO ₃	9					
11 $ZrO_2 n H_2O$	9					
12 CeO ₂	7					
13 ZrO ₂	6					
14 Ta ₂ O ₅	6					
15 CaO	5					
16 SnO ₂	5					
17 MgO	1					
19 SiO ₂	13					
20 Fe ³⁺ -mont	66					
21 HY	7					
22 HBEA	27					
23 HMFI	26					
24 Cs _{2.5} H _{0.5} PW ₁₂ O ₄₀	7					
25 Amberlyst-15	4					
26 Nafion-SiO ₂	30					
27 Sc(OTf) ₃	2					
28 ZrCl ₄	71					
29 ^[c] H ₂ SO ₄	1					
30 PTSA ^[d]	19					

[a] Yields measured by GC analysis. [b] Under reflux conditions without azeotropic water removal for t=40 h. [c] Aqueous solution of H₂SO₄ (30 wt %). [d] PTSA: *p*-Toluenesulfonic acid.



Figure 1. Time-yield profiles for amidation of *n*-dodecanoic acid (1 mmol) with aniline (1 mmol) catalyzed by metal oxides (50 mg) under different conditions: \bigcirc : azeotropic reflux; \bigcirc : reflux (without azeotropic water removal); \bigtriangledown : reflux with 3 mmol of H₂O in the initial mixture.

(HMFI), Cs-exchanged heteropoly acid, and the acidic resins Amberlyst-15 and Nafion-SiO₂ (Table 1, entries 23–26, respectively), and also the water-tolerant homogeneous Lewis acid^[48] Sc(OTf)₃ (Table 1, entry 27). However, these water-tolerant acid catalysts gave lower yields of the amide (2—30%) than Nb₂O₅. Homogenous Brønsted acids such as sulfuric acid and *p*-toluenesulfonic acid (PTSA; Table 1, entries 29 and 30, respectively) also gave low yields. A hydrate of Nb₂O₅ called niobic

acid (Table 1, entry 4), which has been studied as a water-tolerant Lewis acid catalyst, $^{[49]}$ gave a lower yield (74%) than Nb₂O₅.

Lewis acidity of Nb₂O₅

In our previous IR study of pyridine adsorption on Nb_2O_5 , we showed that the surface acid sites of dehydrated Nb_2O_5 are mainly Lewis acidic sites (exposed Nb^{5+} cations).^[45] Figure 2



Figure 2. IR spectra of pyridine adsorbed on dehydrated Nb_2O_5 (dashed line) and rehydrated Nb_2O_5 (solid line) at T=200 °C.

shows the IR spectrum of pyridine adsorbed on dehydrated and rehydrated Nb₂O₅. These spectra have basically the same features; the band at $\tilde{\nu} = 1445 \text{ cm}^{-1}$ as a result of coordinated pyridine on Lewis acid sites (exposed Nb⁵⁺ cations) is dominant rather than the band at $\tilde{\nu} = 1540 \text{ cm}^{-1}$ as a result of pyridinium ions because of Brønsted acid sites. The result shows that water does not essentially change the IR spectrum of adsorbed pyridine; Nb₂O₅ is predominantly Lewis acidic even after rehydration. To investigate the Lewis acid–base interaction between the Nb site and a carbonyl group of a model carboxylic acid, we measured the in situ IR spectrum of acetic acid adsorbed on Nb₂O₅. The spectrum (Figure 3) showed a C=O stretching band of the adsorbed acetic acid ($\nu_{C=O}$) at



Figure 3. IR spectra of acetic acid adsorbed on Nb₂O₅, TiO₂, θ -Al₂O₃, and SiO₂ at T=-75 °C.

a lower wavenumber ($\tilde{\nu} = 1686 \text{ cm}^{-1}$) than the non Lewis acidic oxide SiO₂ ($\tilde{\nu} = 1703 \text{ cm}^{-1}$) and conventional Lewis acidic oxides (TiO₂: $\tilde{\nu} = 1695 \text{ cm}^{-1}$; Al₂O₃: $\tilde{\nu} = 1697 \text{ cm}^{-1}$). This indicates that the surface of Nb₂O₅ has the most effective Lewis acid sites for activation of the C=O bond of the carboxylic acid.

Base-tolerant catalysis by Nb₂O₅

Lewis acidic catalysts for direct amidation should work even in the presence of water, because the reaction yields water as a coproduct. We studied the effect of water removal and water addition on the time-yield profiles for some Lewis acidic metal oxide catalysts (Nb₂O₅, TiO₂, and Al₂O₃) for the model amidation of *n*-dodecanoic acid and aniline (Figure 1). For all of 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 of H₂O in the initial mixture gave the lowest activity. However, the negative impact of the water was lower for Nb₂O₅ than for TiO₂ and Al₂O₃. As shown in Figure 4, the initial



Figure 4. Initial rate for amidation of *n*-dodecanoic acid with aniline by Nb₂O₅ (\bigcirc) and TiO₂ (\bullet) as a function of the initial concentration of water ($C_{H_2O} = 1.1$ to 3.4 M).

rate of amide formation with Nb₂O₅ and TiO₂ decreased with an increase in the initial concentration of water. This indicates that water inhibits the activity of these catalysts. The slope was lower for Nb₂O₅ than TiO₂, and the reaction orders with respect to water were -0.3 and -1.8 for Nb₂O₅ and TiO₂, respectively. This indicates that the water tolerance of Nb₂O₅ is higher than that of TiO₂.

ZrCl₄ is a well-established Lewis acidic homogenous catalyst for direct amidation.^[20–22] Generally, the activity of homogeneous Lewis acids can be reduced by water and organic bases. To compare the base tolerances of ZrCl₄ and Nb₂O₅, we measured the yield of the amide in the standard reaction for t=30 h with ZrCl₄ or Nb₂O₅ under the azeotropic reflux conditions in the absence or presence of basic additives (0.5 equiv.): H₂O, 2,6-dimethylpyridine, pyridine, and triethylamine (Figure 5). Although we used the same molar amount of the catalyst (0.38 mmol), ZrCl₄ was dissolved in the reaction mixture, whereas Nb₂O₅ was insoluble. Clearly, the additive-free condi-



Figure 5. Yield of amide for the reaction of *n*-dodecanoic acid with aniline for 30 h with Nb₂O₅ (50 mg, 0.38 mmol) and ZrCl₄ (50 mg, 0.38 mmol) in the absence and presence of the basic additives (0.5 mmol): water, 2,6-dimethyl-pyridine, pyridine, and triethylamine.

tions gave higher yields for both catalysts, but the negative effects of the additives were lower for Nb₂O₅ than for ZrCl₄. Notably, the 0.5 mmol of basic molecules added to the mixture is 172 times larger than the number of surface Lewis acid sites on the Nb₂O₅ catalyst used. This suggests that the active site (the Nb⁵⁺ Lewis acid site) interacts preferentially with the reactant (carboxylic acid) in the presence of an excess amount of basic molecules. To summarize the above results, we can conclude that the Lewis acid site of Nb₂O₅ has higher tolerance to basic molecules than conventional solid Lewis acids and a typical homogeneous Lewis acid. The water-tolerant character of the Nb⁵⁺ Lewis acid sites of Nb₂O₅ is consistent with the pioneering work by Nakajima et al.^[49]

Performance of Nb₂O₅-catalyzed amidation

As listed in Table 2, the turnover number (TON) with respect to the Lewis acid site of Nb₂O₅ (341) was more than 200 times higher than those of ZrCl₄ (a well-established homogenous catalyst for direct amidation^[20-22]) and Sc(OTf)₃ (a well-established "water-tolerant" Lewis acid^[48]). The TON of Nb₂O₅ was five times larger than that of TiO₂. As discussed in the above section, the higher catalytic efficiency of Nb₂O₅ can be attributed

Table 2. Summary of IR and kinetic results.							
Catalyst	LA ^[a] [mmol g ⁻¹]	$ u_{C=0}^{[b]} $ [cm ⁻¹]	n _{H20} [c]	$TOF^{[d]}$ $[h^{-1}]$	TON ^[d]		
Nb_2O_5 TiO_2 ZrCl ₄ Sc(OTf) ₃	0.058 0.083 4.3 2.0	1686 1695 –	-0.4 -1.8 - -	11.4 2.0 0.006 0.003	341 61 1.7 0.1		

[a] The number of Lewis acid sites on the surface of oxides Nb₂O₅ and TiO₂ was estimated by pyridine adsorption at T=200 °C, as reported in ref. [45]. The values for ZrCl₄ and Sc(OTf)₃ are based on the molecular weights of the salts. [b] Position of the $v_{C=0}$ IR band of adsorbed acetic acid (Figure 4). [c] Reaction order with respect to water (Figure 2). [d] TOF: Turnover frequency; TON: turnover number. Calculated from the number of Lewis acid sites and the catalytic results in Table 1.



to the higher water tolerance and more effective Lewis acid activation of the C=O bond by Nb₂O₅ than TiO₂. Notably, the water-tolerance of Nb₂O₅ enabled the amidation without azeotropic water removal; the reaction with Nb₂O₅ under simple reflux conditions for 40 h resulted in a 96% yield of the amide (Table 1, entry 3).

We studied the reusability of Nb₂O₅. After the standard reaction (Table 1, entry 2), the catalyst was separated from the mixture by centrifugation, washed with acetone, and dried at T= 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 stan-



Figure 6. Reusability of Nb_2O_5 (50 mg) for amidation of *n*-dodecanoic acid (1 mmol) with aniline (1 mmol) in toluene heated to reflux for 30 h.

dard reaction, the reaction was completely terminated by removing the Nb₂O₅ 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 Nb₂O₅ acts as a reusable heterogeneous catalyst.

We then explored the generality and scope of the Nb₂O₅-catalyzed direct amidation of carboxylic acids with different amines (Tables 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 rings, heteroaromatic amines (entry 10), and aliphatic primary amines (entries 11-13) with various functional groups (phenyl, C=C, and hydroxy groups) all reacted with an equimolar amount of *n*-dodecanoic acid to give the corresponding amide in good to high yields (80-98%) after isolation. As a result of the low nucleophilicity, the least reactive amines, Brand Cl-substituted anilines (Table 3, entries 5 and 6) and allylamine (Table 3, entry 12) required higher temperature (heating to reflux in o-xylene). A secondary amine, morpholine (Table 3, 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 the less nucleophilic amine aniline. Linear aliphatic carboxylic acids (Table 4, entries 1–5) and the less reactive benzoic acid (Table 4, entry 6) were converted into the corresponding amides in good to high yields (81–98%) after isolation. The amidation of a heteroaromatic carboxylic acid, pyridine-2-carboxylic acid (Table 4,



entry 7), with benzylamine was also successful to give 90% yield of the product.

Finally, we tested the amidation of more challenging carboxylic acids (α -hydroxy-, β -hydroxy-, and β -thiocarboxylic acids) with various amines under azeotropic reflux in *o*-xylene (Table 5). Notably, there is only one report by Ishihara and coworkers for the successful direct amidation of α -hydroxycar-





Table 5. Nb ₂ O ₅ -catalyzed amidation of α -hydroxy-, β -hydroxy-, and β -thiocarboxylic acids with various amines. ^[a]								
Entry	Acid	Product	Yield ^[b] [%]					
1	ОН ————————————————————————————————————	OH HZ O	69					
2	он — он о	OH H O	80					
3	ОН ОН ОН		71					
4	ОН	OH NH	65					
5	ОН	O H OH	95					
6	SH О ОН	SH O H H	87					
[a] Reaction conditions: Carboxylic acid (1 mmol), amine (1 mmol), <i>o</i> -xylene (2 mL), azeotropic reflux, $t = 30$ h. [b] Yields of isolated products.								

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boxylic acids with amines, but the previous method with MeB(OH)₂ as the catalyst is not effective for less reactive amines such as aniline.^[13] To our delight, our method was applicable to the synthesis of amides from aniline and α -hydroxycarboxylic acids (Table 5, entries 1 and 3) and a β -thiocarboxylic acid (Table 5, entry 6). The α -hydroxycarboxylic acids include an important biomass-derived chemical, lactic acid (Table 5, entries 1 and 2), which demonstrates that our method can contribute to production of fine chemicals from biomass feedstock. The method was also effective for the amidation of a β hydroxycarboxylic acid, salicylic acid (Table 5, entry 5), with benzylamine and gave the corresponding amide in 95% yield. We tentatively assume that the unprecedentedly efficient catalysis of Nb₂O₅ for the amidation of challenging substrates is caused by the base-tolerant Lewis acid activation of carboxylic acids, which is evidenced by IR spectroscopy (Figures 2 and 3) and kinetic studies (Figures 1, 4, and 6).

Conclusions

We have presented a versatile and sustainable method for the direct amidation of carboxylic acids with various amines by using Nb₂O₅ 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 α -hydroxycarboxylic acids. The Lewis acid site of Nb₂O₅, as the active site for the amidation, has higher tolerance to the copresent basic molecules (water and tertiary and heteroaromatic amines) than the state-of-the-art homogeneous Lewis acidic heterogeneous catalysts (Al₂O₃ and TiO₂), which results in higher catalytic activity of Nb₂O₅ than of these catalysts.

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