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Direct Synthesis of Cyclic Imides from Carboxylic Anhydrides and Amines by Nb_2O_5 as a Water-tolerant Lewis acid Catalyst

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Dedication ((optional))

Abstract: In the 20 types of heterogeneous and homogenous catalysts screened, Nb_2O_5 shows the highest activity for synthesis of *N*-phenylsuccinimide by dehydrative condensation of succinic anhydride and aniline. Nb_2O_5 is applicable to the direct imidation a wide range of carboxylic anhydrides with NH_3 or amines with various functional groups and is reusable. Kinetic studies show that Lewis acid catalysis of Nb_2O_5 is more water-tolerant than a Lewis acidic oxide (TiO_2) and a homogeneous Lewis acid ($ZrCl_4$), which results in higher yield of imides by Nb_2O_5.

Cyclic imides and their derivatives are an important class of substrates for biological and chemical applications[1,2] and used as intermediates in the industrial production of drugs, dyes and polymers.[1a,1b,2] However, sustainable synthetic methods of cyclic imides from readily available starting materials are limited. General methods for synthesis of cyclic imides are the dehydrative condensation of a dicarboxylic acid[3] or its anhydride[3f,4,5] with an amine under harsh conditions (250-380 °C, ~330 bar)[3a,b] or under microwave heating,[5] and the cyclization of an amic acid with the help of acidic reagents or in the presence of excess amount of promoter (Lewis acid, base, dehydrating agent). These methods suffer from some of the drawbacks of low atom-efficiency, limited substrate scope, production of stoichiometric amount of byproducts, and need of special procedure (microwave heating). New synthetic routs from nitriles,[7] halides,[8] alkynes,[9] aryl boronic acids,[10] aromatic amides,[11] aliphatic amides,[12] cyclic amines[13] have been developed, but these homogeneous catalytic methods have drawbacks of low atom-efficiency, narrow substrate scope, needs of toxic reagents or additives, and difficulties in catalyst/products separation and catalyst reuse. For example, a reusable heterogeneous catalytic system by Pd/C[8d] suffers from needs of halides and CO as less environmentally benign reagents. One of the most effective synthesis of cyclic imides via dehydrogenative coupling of diols and amines (or nitriles) catalyzed by a Ru complex[1a,14] still suffers from limited substrate scope of diols and amines.

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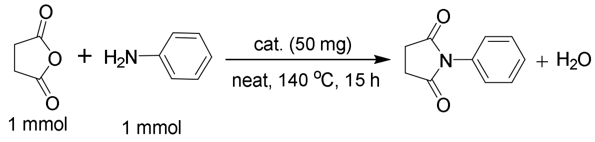
Catalytic synthesis of cyclic imides by condensation of cyclic anhydrides with amines is one of the most deriable route. A few catalytic methods using $TaCl_5/SiO_2$[15a,15b] or DABCO[15c] were reported to synthesize cyclic imides from cyclic anhydrides with amines. These methods[15] suffer from some of the drawbacks such as quite limited substrate scope, no results on the catalyst reuse, and needs of large catalyst loading and special method (microwave heating).[15a,15b] Potentially, the reaction is catalyzed by Lewis acid, but co-presence of water as byproduct can suppress Lewis acidity by hindering coordination. Inspired by recent reports that several metal oxides, such as Nb_2O_5,[16a] act as water-tolerant Lewis acid catalysts,[16] we have recently reported that Nb_2O_5 acts as water-tolerant Lewis acid catalyst for direct imidation of dicarboxylic acids with amines[17] and direct amidation of esters with amines.[18] We reported our preliminary results on cyclic imides synthesis from cyclic anhydride,[17] but detailed catalytic properties such as substrate scope and kinetic studies were not reported. Here, we report a general catalytic method of direct cyclic imides synthesis from cyclic anhydride with amines (or ammonia) under solvent-free conditions.

Nb_2O_5 (surface area = 54 m^2 g^{-1}) was prepared by calcination of niobic acid (supplied by CBMM) at 500 °C for 3 h, and Lewis acidic characteristics of Nb_2O_5 were reported in our previous studies.[17-19]

As listed in Table 1, 20 types of the heterogeneous and homogeneous catalysts were screened for the model imidation of the equimolar amount of succinic anhydride and aniline under s conditions at 140 °C for 15 h (Table 1). Note that the reaction hardly proceeded in the catalyst-free conditions (entry 1). Thus, Table 1 shows the results of catalytic imidation. First, we screened 12 types of simple metal oxides (entries 2-13). Among the metal oxides tested, Nb_2O_5 showed the highest yield (90%) of the corresponding imide, *N*-phenyl succimide. Hydrate of Nb_2O_5 called niobic acid (entry 3) gave lower yield (22%) than Nb_2O_5. Two of the oxides having Lewis acidity (ZrO_2 and TiO_2)[19,20] show moderate yields of 59-65% (entries 4,5). The other oxides, such as SnO_2, γ-Al_2O_3, SiO_2 and CaO, showed low yields of 8-45%. Next, we tested conventional solid acids such as a Lewis acidic clay, Fe^{3+}-mont (entry 14), HBEA zeolite (entry 16), and water-tolerant Brønsted acid catalysts, including HZSM5 zeolite with SiO_2/Al_2O_3 ratio of 300 (entry 15) and commercial acidic resins (entries 17,18).[21] These solid acids gave low to moderate yields (31-60%) of *N*-phenyl succimide. Finally, we tested homogeneous Lewis acids[22] (entries 19-21) including a water-tolerant Lewis acids,[22c,22d] $Sc(OTf)_3$ (entry 21). These homogeneous catalysts gave low yields of the product (18-44%).

Table 1. Catalyst screening for synthesis of cyclic imide from anhydrides.



Entry	Catalyst	GC yield [%] [a]
1	blank	<1
2	Nb_2O_5	90
3	niobic acid	22
4	ZrO_2	65
5	TiO_2	59
6	SnO_2	45
7	Ta_2O_5	42
8	ZnO	38
9	γ-Al_2O_3	17
10	SiO_2	16
11	CeO_2	15
12	MgO	15
13	CaO	8
14	Fe^{3+}-mont	31
15	HZSM5	60
16	HBEA	40
17	Amberlyst-15	31
18	Nafion-SiO_2	46
19	$ZrCl_4$	44
20	$Sc(OTf)_3$	33
21	$HfCl_4$	18

With the most effective catalyst (Nb_2O_5), we tested the model reaction in the absence and the presence of different solvent (Table S1). We found that the solvent-free conditions showed the higher yield than those in the solvent such as toluene and *o*-xylene.

In order to discuss a possible reason why Nb_2O_5 showed the high catalytic activity for the model reaction of succinic anhydride with aniline, we studied the kinetic experiments. First, we measured initial rates of the imide formation in the absence and in the presence of H_2O (1, 3 and 5 mmol) using 50 mg of the catalysts. Two heterogeneous Lewis acid catalysts (Nb_2O_5 and TiO_2) and a homogeneous Lewis acid catalyst ($ZrCl_4$)[22a] were selected for a comparative purpose. Note that the rates were measured under the conditions where the conversions were below 40%. Figure 1A plots the reaction rates as a function of the initial concentration of water. For all the catalysts, the addition of water decreased the reaction rates, and the rate was lower at higher concentration of water. Figure 1B shows double logarithmic plots for the results in the presence of water in the initial mixture, in which the slope of the line corresponds to the reaction order with respect to water. The reaction orders are -0.11, -0.34, -0.50 for Nb_2O_5, TiO_2 and $ZrCl_4$, respectively, which clearly indicate that the negative impact of water increases in the order of Nb_2O_5 < TiO_2 < $ZrCl_4$. Figure 2 compares the time-yield profiles for the imidation in the absence of water. The initial slopes for Nb_2O_5, TiO_2 and $ZrCl_4$ do not markedly depend on the catalysts, but the final yield after 15 h depends strongly on the catalysts. The yield for Nb_2O_5 monotonically increased with time, while the yields for TiO_2 and $ZrCl_4$ leveled off. Considering that water is produced during the dehydrative condensation reaction, combined with the result that negative impact of water increases in the order of Nb_2O_5 < TiO_2 < $ZrCl_4$ (Figure 1), the result in Figure 2 indicates that the water molecules formed during the reaction inhibit the Lewis acid catalysis of TiO_2 and $ZrCl_4$, whereas the water molecules do not markedly inhibit the Lewis acid catalysis of Nb_2O_5. In other words, Nb_2O_5 is a more water-tolerance Lewis acid catalyst than TiO_2 and $ZrCl_4$.

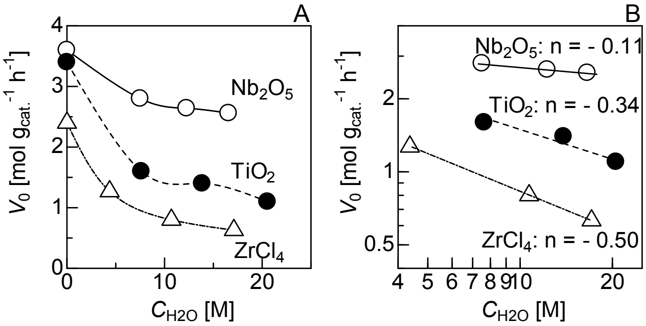


Figure 1. Initial rate for imidation of succinic anhydride (1 mmol) with aniline (1 mmol) in the presence of H_2O (0, 1, 3 and 5 mmol) catalyzed by 50 mg of Nb_2O_5, TiO_2 or $ZrCl_4$ as a function of the initial concentration of water.

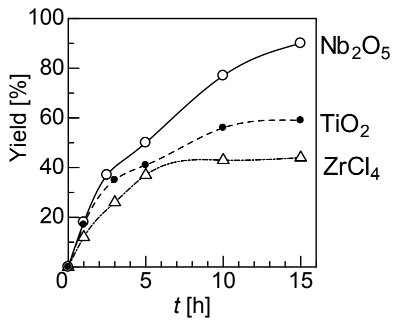


Figure 2. Time-yield profiles for imidation of succinic anhydride (1 mmol) with aniline (1 mmol) catalyzed by 50 mg of Nb_2O_5, TiO_2 or $ZrCl_4$.

Next, we studied effectiveness of the Nb_2O_5-catalyzed imidation of carboxylic anhydrides with amines. The result of gram scale reaction is shown in eqn (1). The reaction of 10 mmol of succinic anhydride with 10 mmol of *n*-octylamine with 50 mg of Nb_2O_5 for 67 h gave 79% yield of the corresponding imide. Previously, we reported the number of surface Lewis acid sites on the Nb_2O_5 catalyst by pyridine adsorption IR experiment at 200°C.[17,19] The turnover number (TON) with respect to Lewis acid site of Nb_2O_5 (0.056 mmol g^{-1}) was calculated to be 2820.

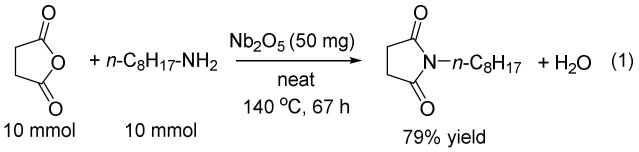


Figure 3 shows the reusability of Nb_2O_5 for the imidation of succinic anhydride (1 mmol) with *n*-octylamine (1 mmol) for 15 h. After the reaction, 4 mL of 2-propanol was added to the mixture, and the catalyst was separated from the mixture by centrifugation, followed by washing with acetone, and by drying at 90 °C for 3 h. The recovered catalyst was reused for four times without a marked decrease in the yield. ICP-AES analysis of the solution confirmed that the content of Nb in the solution was below the detection limit. From the results, we can conclude that Nb_2O_5 is as a reusable heterogeneous catalyst for the title reaction.

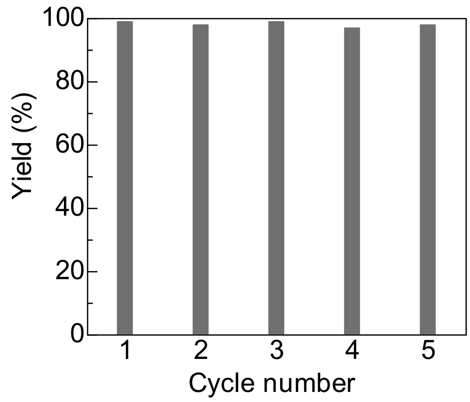
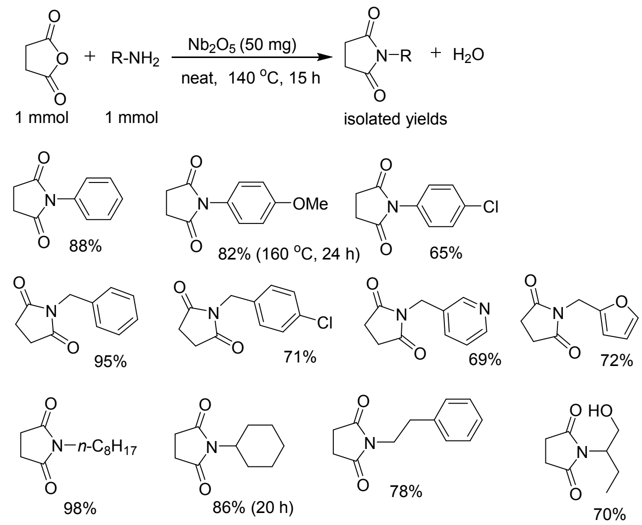
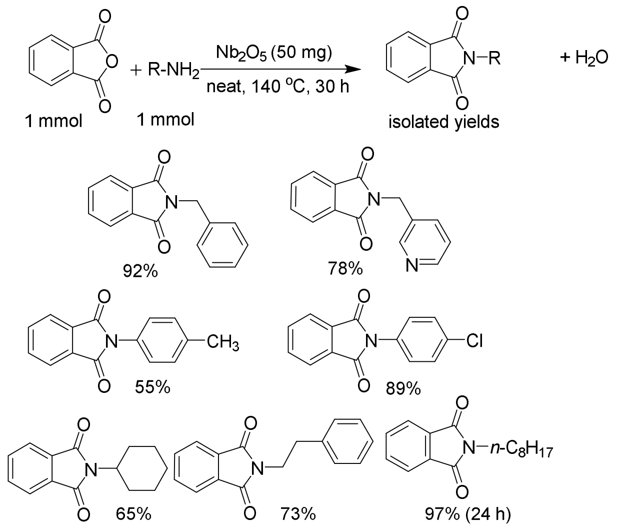


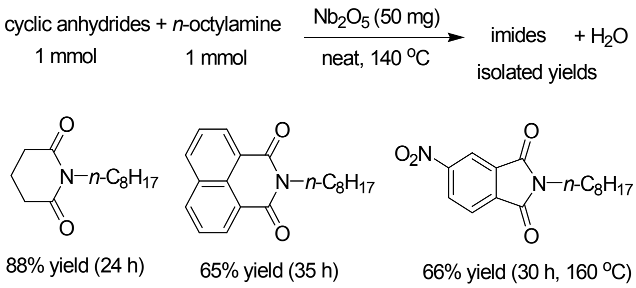
Figure 3. Reuse of Nb_2O_5 for imidation of succinic anhydride with *n*-octylamine under the conditions in Scheme 1.



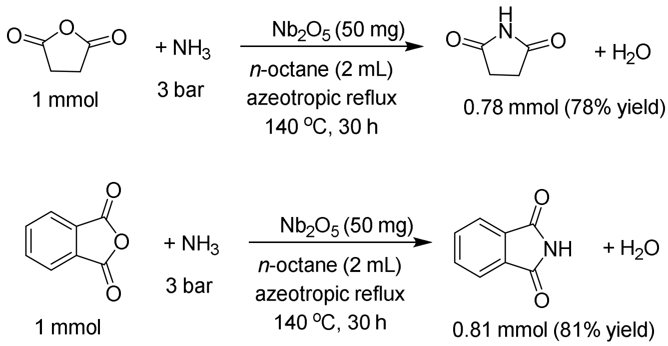
Scheme 1. Substrate scope for imidation of succinic anhydride with different amines.



Scheme 2. Synthesis of phthalimides from phthalic anhydride and various primary amines.



Scheme 3 Synthesis of *N*-substituted cyclic imide from cyclic anhydrides with *n*-octylamine.



Scheme 4 Imidation of cyclic anhydride and ammonia.

Finally, we studied substrate scope for the present catalytic system. Scheme 1 shows the results of imidation of succinic anhydride (1 mmol) with different amines (1 mmol). Under the standard solvent-free conditions using a small amount of Nb_2O_5 (0.29 mol% based on the number of Lewis acid sites on Nb_2O_5[17,19]), the mixture was heated at 140 °C for 15 h.

Anilines with different functional groups (H-, MeO-, Cl-) at *para*-position, benzylamines, heteroaromatic amines with pyridyl and furanyl groups, linear and cyclic aliphatic amines and amines with phenyl and hydroxyl groups were converted to the corresponding *N*-aryl imides with good to high isolated yields (65-98%).

The method was also effective for direct synthesis of phthalimides from readily available phthalic anhydride and equimolar amount of amines (Scheme 2). Benzyl amine, heteroaromatic amine, anilines with electron rich and electron poor groups, cyclohexylamine, phenylehtylamine, and *n*-octylamine were converted to the corresponding *N*-substituted phthalimides in modarate to high isolated yields (55-92%).

Scheme 3 shows the reactions of *n*-octylamine with various cyclic anhydrides. Gluteric anhydride, 1,8-naphthalic anhydride and 4-nitrophthalic anhydride were transformed to the corresponding *N*-substituted cyclic imides in moderate to high isolated yields (65-88%).

It is important to note that unsubstituted cyclic imides are also synthesized from cyclic anhydrides and ammonia under azeotropic reflux conditions in *n*-octane (Scheme 4). The reactions of succinic anhydride and phthalic anhydride in the closed stainless reactor under 3 bar NH_3 at 140 °C resulted in 78% yield succinimide and 81% yield of phthalimide, respectively.

Summarizing the above results, we can conclude that the present catalytic method with Nb_2O_5 is widely applicable to the direct imidation of various carboxylic anhydrides with ammonia or amines with various functional groups. To our knowledge, this is the first general catalytic method of imides synthesis from carboxylic anhydrides and amines using a reusable catalyst.

In conclusion, we have found that cyclic imides can be synthesized directly from various cyclic anhydrides with various amines or ammonia using Nb_2O_5 as reusable heterogeneous catalyst. This is a simple and general catalytic system for the synthesis of cyclic imides from readily available cyclic anhydrides and amines. Kinetic studies indicate that Lewis acid site of Nb_2O_5 has high tolerance to water, which results in high catalytic activity for imidation even in the presence of water formed during the reaction.

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Keywords: amination • ketones • primary amines • Lewis acid

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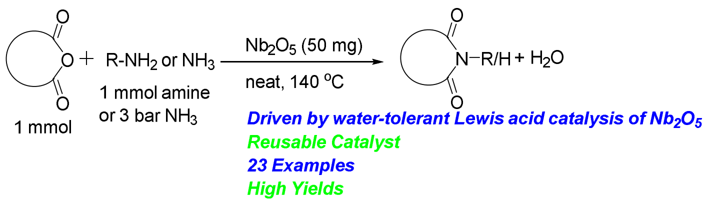

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