ChemPubSoc Europe
DOI: 10.1002/chem.201404538
CHEMISTRY
A European Journal
Communication

Organic Synthesis

Versatile and Sustainable Synthesis of Cyclic Imides from Dicarboxylic Acids and Amines by Nb_2O_5 as a Base-Tolerant Heterogeneous Lewis Acid Catalyst

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Abstract: Catalytic condensation of dicarboxylics acid and amines without excess amount of activating reagents is the most atom-efficient but unprecedented synthetic method of cyclic imides. Here we present the first general catalytic method, proceeding selectively and efficiently in the presence of a commercial Nb_2O_5 as a reusable and base-tolerant heterogeneous Lewis acid catalyst. The method is effective for the direct synthesis of pharmaceutically or industrially important cyclic imides, such as phensuximide, *N*-hydroxyphthalimide (NHPI), and unsubstituted cyclic imides from dicarboxylic acid or anhydrides with amines, hydroxylamine, or ammonia.

Cyclic imides and their derivatives are an important class of compounds with numerous applications in biological, medicinal, synthetic, and polymer chemistry[1,2] and are used as intermediates in dyes and polymer industries.[1a,b,2] Despite their wide applicability, synthetic methods of cyclic imides from readily available starting materials are limited. The typical methods[1,3–5] are the dehydrative condensation of an anhydride with an amine at high temperatures or in the presence of an excess amount of promoter (Lewis acid, base, dehydrating agent, or ionic liquids)[3] and the cyclization of an amic acid with the help of acidic reagents,[4] which suffer from low atom efficiency and production of byproducts. Although new synthetic routes from nitriles,[6] halides,[7] alkyne,[8] pyridin-2-ylmethylamines,[9] aryl boronic acids,[10] aliphatic amides,[11,12a] cyclic amines,[12b] isocyanates,[13] and phthalimide[14] using transition-metal catalysis (carbonylation, oxidation, etc.)[6–13] or excess amounts of I(III) oxidant[14] have been developed, these homogeneous catalytic methods have drawbacks of narrow substrate scope, needs of various additives or toxic reagents (CO), no reusability of expensive catalysts, and difficulties in catalyst/products separation. Hong et al.[1a,15] reported the atom-efficient synthesis of cyclic imides by dehydrogenative coupling of diols and amines. However, the method has problems, such as limited substrate scope of diols and amines, no catalyst reusability and the need of 0.2 equivalents of NaH.

Potentially, condensation of dicarboxylic acids with amines can be a general synthetic route to cyclic imides. A few noncatalytic methods under harsh conditions ($T=250$-$380\,^{\circ}C$, $P=\sim 330$ bar) were reported.[5a,b] Only one example of the catalytic method using an organocatalyst is known, but the substrate scope is limited to only one example.[5c] The reaction might be also catalyzed by Lewis acids, but co-presence of basic molecules, amine and water (as byproduct), in the solution suppress Lewis acidity by hindering coordination or irreversibly decomposing the catalyst. Recent reports showed that some metal oxides, such as Nb_2O_5,[16a] act as water-tolerant Lewis acid catalysts.[16] If a metal oxide acts as a Lewis acid catalyst even in the presence of stronger base, such as amines, they can effectively catalyze the condensation of dicarboxylic acids with amines. In the course of our own studies into developing efficient amide bond-forming reactions by metal oxides or Lewis acidic catalysts,[17] we have found that Nb_2O_5 shows "base-tolerant" catalysis for this reaction. Herein, we report the first general catalytic method of direct cyclic imide synthesis from dicarboxylic acids with amines and ammonia under mild conditions using Nb_2O_5 catalyst prepared by calcination of a commercial niobic acid. The method is effective for the direct synthesis of some industrially important cyclic imides, including *N*-hydroxyphthalimide and unsubstituted cyclic imides.

First, the reaction between an equimolar amount of succinic acid and *n*-octylamine under reflux conditions in hexane was tested as a model reaction to optimize the different parameters (Table 1). Under the conditions in which the reaction hardly proceeded in the absence of catalyst (Table 1, entry 1), we screened 14 types of metal oxides (entries 2–14). In the oxide catalysts tested, Nb_2O_5 shows the highest yield (99 %) of the corresponding imide. Conventional solid Lewis acids (TiO_2 and γ-Al_2O_3)[18] show moderate yields (entries 4, 6). We also tested water-tolerant Brønsted acidic heterogeneous catalysts,[19] including HZSM5 zeolite with a SiO_2/Al_2O_3 ratio of 90 (entry 15), Cs-exchanged heteropoly acid (entry 16) and commercial acidic resins (entries 17, 18), as well as water-tolerant homogeneous Lewis acids,[20] $Sc(OTf)_3$, $Yb(OTf)_3$, and $HfCl_4$ (entries 19-21). These catalysts gave small amounts of the product

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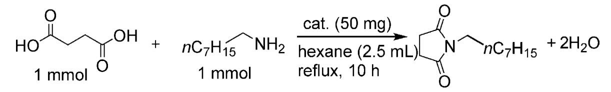
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201404538.

Table 1. Catalyst screening for the synthesis of cyclic imide.



Entry	Catalyst	Yield [%][a]
1	no catalyst	<1
2	Nb_2O_5	99, 99,[b] 98,[c] 95,[d] 96,[e] 85[f]
3	niobic acid	67
4	TiO_2	61
5	ZnO	58
6	γ-Al_2O_3	52
7	CeO_2	51
8	ZrO_2	33
9	WO_3	20
10	SnO_2	12
11	Ta_2O_5	9
12	SiO_2	8
13	MoO_3	4
14	MgO	3
15	HZSM5 zeolite	3
16	$Cs_{2.5}H_{0.5}PW_{12}O_{40}$	3
17	Amberlyst-15	11
18	Nafion-SiO_2	4
19	$Sc(OTf)_3$	5
20	$Yb(OTf)_3$	4
21	$HfCl_4$	5

[a] GC yields. [b] Cycle 2. [c] Cycle 3. [d] Cycle 4. [e] Cycle 5. [f] Cycle 6.

Table 2. Summary of IR and kinetic results.

Catalyst	[LA][a] [mmol g^{-1}]	$\nu_{C=O}$[b] [cm^{-1}]	n_{acid}[c]	n_{amine}[d]	n_{H2O}[e]	TON[f]
Nb_2O_5	0.058	1686	0.3	-0.3	-0.8	341
TiO_2	0.083	1695	0.4	-1.2	-1.4	147
γ-Al_2O_3	0.148	1697	0.4	-1.6	-2.0	70
$Sc(OTf)_3$	2.0[g]	–	–	–	–	0.5

[a] The number of Lewis acid sites on the surface of oxides estimated by pyridine adsorption at 200 °C (from ref. [18]). [b] Position of $\nu_{C=O}$ IR band of adsorbed acetic acid (see Figure S1 in the Supporting Information). [c] Reaction order with respect to succinic acid (see Figure S2a in the Supporting Information). [d] Reaction order with respect to *n*-octylamine (Figure S2b in the Supporting Information). [e] Reaction order with respect to water (Figure S2c in the Supporting Information). [f] TON with respect to Lewis acid site. [g] Based on the molecular weight of $Sc(OTf)_3$.

(3–11 %). As listed in Table 2, the turnover number (TON) with respect to Lewis acid site of Nb_2O_5 (341) was 680 times higher than that of $Sc(OTf)_3$ (0.5).

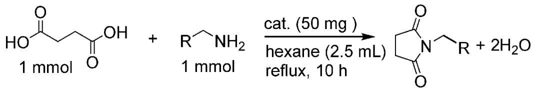
On the basis of the IR result of the CO adsorbed on the Nb^{5+} Lewis acid site on the prehydrated Nb_2O_5, Nakajima et al.[16a] showed that the Nb site acted as a Lewis acid site in the presence of water. To investigate the interaction of the Nb site with the carbonyl oxygen of a carboxylic group, we measured the in situ IR spectrum of acetic acid adsorbed on Nb_2O_5. The spectrum (see Figure S1 in the Supporting Information) shows the C=O stretching band of the adsorbed acetic acid ($\nu_{C=O}$) at a lower wavenumber ($\nu = 1686\ cm^{-1}$) than that on non-Lewis acidic oxide, SiO_2 ($\nu = 1703\ cm^{-1}$). This indicates the activation of the carbonyl group by a Nb^{5+} Lewis acid site.

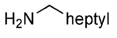
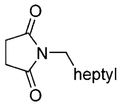
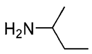
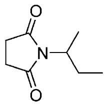
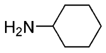
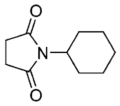
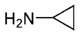
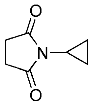
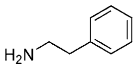
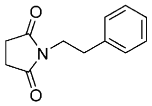
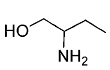
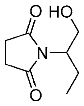
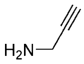
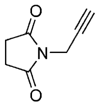
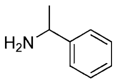
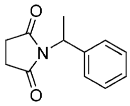
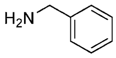
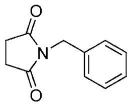
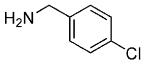
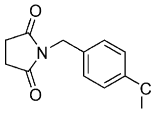
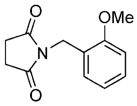
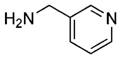
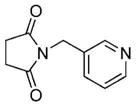
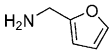
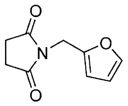
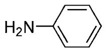
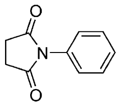
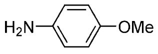
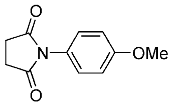
The Lewis acid–base interaction depends on the HOMO level of a nucleophile (base) and LUMO level of an electrophile (acid); the smaller HOMO–LUMO gap results in a more stable Lewis acid–base complex.[20c,21] Figure S3 (Supporting Information) shows distributions and energy levels of the HOMOs for succinic acid, *n*-octylamine, and water. As expected, the electrons in the HOMO of succinic acid are located on the oxygen atom of the carbonyl group, and those of *n*-octylamine are located on the nitrogen atom of the NH_2 group. The HOMO energy of succinic acid (−7.45 eV) is lower than that of *n*-octylamine (−6.23 eV). This indicates that a Lewis acid can interact with nitrogen atom of *n*-octylamine in preference to the carbonyl oxygen atom of succinic acid. This theoretical result was consistent with the kinetic results for the reaction of succinic acid and *n*-octylamine by Nb_2O_5 (Table 2). The reaction order with respect to succinic acid ($n_{acid} = 0.3$) was larger than that with respect to *n*-octylamine ($n_{amine} = -0.3$), which indicates that preferential adsorption of the amine over succinic acid on the surface active site inhibits the catalytic reaction. The n_{amine} value of Nb_2O_5 was larger than those of conventional solid Lewis acids, TiO_2 ($n_{amine} = -1.2$) and γ-Al_2O_3 ($n_{amine} = -1.6$). This suggests that the inhibition effect by the strong base (*n*-octylamine) on Nb_2O_5 is weaker than those on TiO_2 and γ-Al_2O_3. We also studied the kinetic study in the co-presence of water in the initial reaction mixture. The reaction order with respect to water (n_{H2O}) was negative for all the catalysts, which indicated that water inhibits the reaction. The inhibition effect by water for Nb_2O_5 ($n_{H2O} = -0.8$) was less significant than those for TiO_2 ($n_{H2O} = -1.4$) and γ-Al_2O_3 ($n_{H2O} = -2.0$). From these results, it is concluded that Lewis acid site of Nb_2O_5 has higher tolerance to basic molecules (amines and water) than conventional solid Lewis acids, which results in higher activity for cyclic imide synthesis from dicarboxylic acids with amines. As listed in Table 2, the $\nu_{C=O}$ IR band of the adsorbed acetic acid on Nb_2O_5 appeared at a lower wavenumber than those on TiO_2 ($\nu = 1695\ cm^{-1}$) and γ-Al_2O_3 ($\nu = 1697\ cm^{-1}$). This indicates that Lewis acid sites on Nb_2O_5 activate carboxyl groups more effectively than the conventional solid Lewis acids, which can cause effective activation of carboxylic acids.

We studied the reusability of Nb_2O_5. After the reaction, 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 five times without a marked loss of its catalytic activity (Table 1, entry 2). ICP-AES analysis of the solution confirmed that the content of Nb in the solution was below the detection limit. The results indicate that Nb_2O_5 acts as a reusable heterogeneous catalyst.[23]

Then, we studied condensation of succinic acid with different amines (Table 3). Under mild conditions (ca. 68 °C) with small amount of Nb_2O_5 (0.29 mol % based on the number of Lewis acid sites on Nb_2O_5[18]), a variety of aliphatic and aromatic amines with various functional groups reacted with equimolar amounts of succinic acid to give the N-substituted succinimde derivatives in good to high isolated yield. Linear-, branched-, and cyclo-alkyl amines (Table 3, entry 1–4), aliphatic amines with phenyl (entry 5), hydroxyl (entry 6), C≡C- (entry 7) groups, benzyl amines with electron-rich and -poor ring (en-

Table 3. Synthesis of succinimides from different amines by Nb_2O_5.



Entry	Amine	Product	Yield [%][a]
1			98
2			80
3[b]			95
4			74
5			97
6[b]			75
7[b,c]			98
8[b,c]			81
9[d]			95
10[b]			85
11[b]			92
12			90
13[b,d]			82
14			90
15			88

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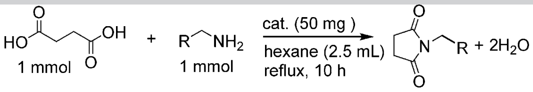
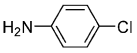
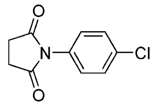
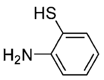
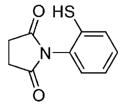


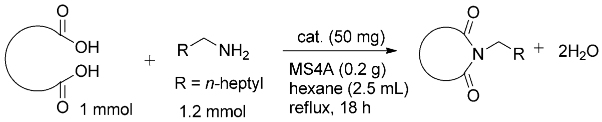
Entry	Amine	Product	Yield [%][a]
16			78
17			91

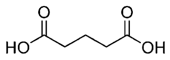
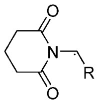
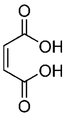
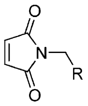
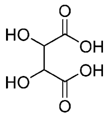
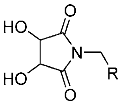
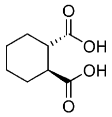
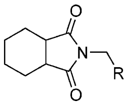
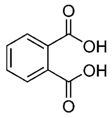
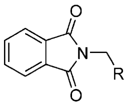
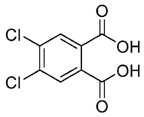
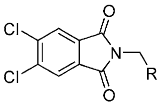
[a] Isolated yields. [b] 18 h, reflux in *n*-octane. [c] 30 h. [d] 40 h.

tries 9–11), heteroaromatic amines (entries 12,13), and anilines with different substituents (CH_3O–, Cl–, SH–) were tolerant, resulting in a good to high isolated yield of the *N*-aryl imides (74–98 %).

Next, we tested reactions of *n*-octylamine with various dicarboxylic acids, including less reactive ones (Table 4). Although the reaction with glutaric acid under the standard conditions gave 69 % yield of the corresponding imide, the uses of

Table 4. Cyclic imidation of dicarboxylic acids with *n*-octylamine by Nb_2O_5.



Entry	Acid	Product	Yield [%][a]
1[b]			84
2			68
3[c]			77
4[c]			91
5			98
6[b]			88

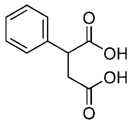
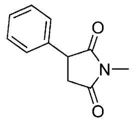
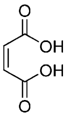
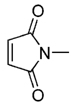
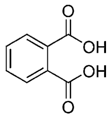
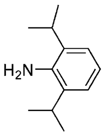
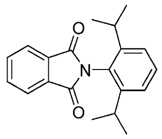
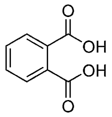
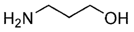
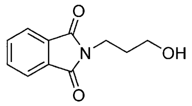
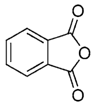
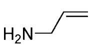
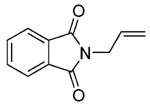
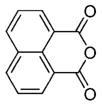
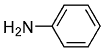
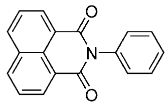
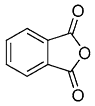
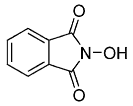
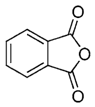
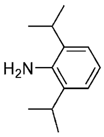
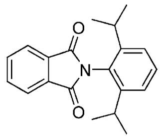
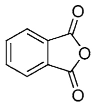
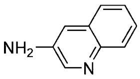
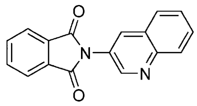
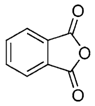
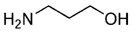
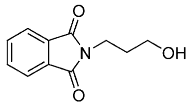
[a] Isolated yields. [b] 1 mmol amine. [c] 45 h.

1.2 equivalents of amine and 0.2 g of 4 Å molecular sieves (MS4A) pellets, placed at the upper side of the reaction vessel, resulted in an 84 % yield (Table 4, entry 1). Mareic acid (entry 2), DL-tartaric acid (entry 3), *trans*-1,2-cyclohexanedicarboxylic acid (entry 4), phthalic acid (entry 5), and 4,5-dichlorophthalic acid (entry 6) were selectively transformed to the corresponding cyclic imides in moderate to high yields (68–98 %).

The method was also effective for direct synthesis of pharmaceutically or industrially important cyclic imides from readily available dicarboxylic acid or anhydrides (Table 5). Using an aqueous solution of methylamine, phensuximide (an anticonvulsant) and *N*-methylmaleimide were prepared in high yield (Table 5, entries 1, 2). A α-TNF inhibitor named PP-33 (entries 3,8), *N*-(3-hydroxypropyl-pthalimide) (entries 4,10), *N*-allylphthalimide (entry 5), 1,8-naphthalimide (entry 6), and 2-quinolinephthalimide (entry 9) were synthesized in good to high yields (78–95 %). NHPI is a well-established promoter for the aerobic oxidation of organic substrates.[22] We gave the first example of the catalytic synthesis of NHPI from hydroxylamine and phthalic acid (entry 7).

Table 5. Synthesis of cyclic imide derivatives by Nb_2O_5.

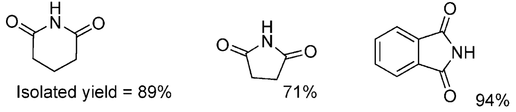
$$\underset{(1\ \text{mmol})}{\text{dicarboxylic acid or anhydrate}} + \underset{(1\ \text{mmol})}{\text{amine}} \xrightarrow[\text{hexane (2.5 mL), reflux, 30 h}]{\text{cat. (50 mg)}} \text{imides} + H_2O$$

Entry	Acid/anhydride	amine	Product	Yield [%][a]
1[b]		12 M CH_3NH_2 in H_2O		92
2[b]		12 M CH_3NH_2 in H_2O		81
3				78
4				92
5[c]				95
6[c]				95
7[c]		$NH_2OH{\cdot}HCl$		85
8				80
9[c]				93
10				90

[a] Isolated yields. [b] 4 mmol CH_3NH_2, 0.3 g MS4A. [c] No solvent, 36 h, 150 °C.

Unsubstituted cyclic imides were also synthesized from dicarboxlic acids in n-octane under 3 bar NH_3 at 140 °C [Eq. (1)]. Succinic acid, glutaric acid, and phthalic acid reacted with NH_3 to give succinimide, glutarimide, and phthalimide in good to excellent isolated yield (71–94 %).

$$\underset{1\ \text{mmol}}{\text{dicarboxylic acids}} + \underset{3\ \text{bar}}{NH_3} \xrightarrow[\text{MS4A (0.2 g), octane (2.5 mL), 140 °C, 30 h}]{\text{cat. (50 mg)}} \text{imides} + 2H_2O \quad (1)$$



In conclusion, we have reported that cyclic imides can be synthesized directly from various dicarboxylic acid or anhydrides with various amines, hydroxylamine, or ammonia by using Nb_2O_5 as reusable heterogeneous catalyst. This atom economical and simple method will provide a practical and convenient route to cyclic imides from readily available or biomass-derived starting materials. Preliminary mechanistic studies suggest that the Lewis acid site of Nb_2O_5 has a higher tolerance to basic molecules (amines and water) than conventional solid Lewis acids, which results in higher catalytic activity. Lewis acid catalysis of Nb_2O_5 even in the presence of strong base may be applicable to other acid-catalyzed reactions involving carbonyl compounds.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Nano Informatics" (25106010) from JSPS and a MEXT program “Elements Strategy Initiative to Form Core Research Center”.

Keywords: dicarboxylic acids · heterogeneous catalysis · imides · Lewis acids · niobium oxides

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[23] After 3 h of the standard reaction (Table 1, entry 2), the catalyst was removed from the reaction mixture. Further heating of the filtrate in reflux conditions did not increase the yield, which eliminated a homogeneous catalysis of soluble Nb species leached out of Nb_2O_5.

Received: July 23, 2014

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Organic Synthesis

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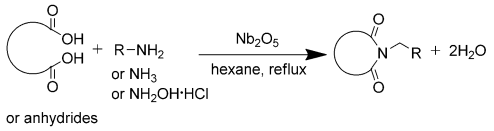
Versatile and Sustainable Synthesis of Cyclic Imides from Dicarboxylic Acids and Amines by Nb_2O_5 as a Base-Tolerant Heterogeneous Lewis Acid Catalyst



Neutral conditions
Reusable catalyst
36 examples
High isolated yields

A general catalytic method for the direct cyclic imide synthesis from dicarboxylic acids with amines or NH_3 under mild conditions using a reusable Nb_2O_5 catalyst is reported (see scheme). The method is effective for the synthesis of some pharmaceutically or industrially important cyclic imides, including *N*-hydroxyphthalimide and unsubstituted cyclic imides.