Direct Synthesis of Amides and Imides by using Heterogeneous Lewis Acid Catalysts

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ABSTRACT

Amide bond formation avoiding poor atom economy reagents are strongly preferred and get the highest attention as a priority area in organic synthesis and pharmaceutical industry. 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 dehydrating agent. Lewis acid promoted amidation reaction is also developed. These methods have some limitations of low atom efficiency and production of byproducts. Lewis acid catalyzed amidation have additional drawbacks, such as limited substrate scope and high catalyst loading. These drawbacks may be caused by the suppression of Lewis acid by basic molecules (amines and water as byproduct), present in the reaction mixture. The author hypothesized that water and base tolerant Lewis acid catalyst may catalyze the amidation of carboxylic acid with amines more effectively. This thesis focuses on direct synthesis of amide bond by using base tolerant heterogeneous Lewis acid catalyst. Five types of Lewis acid catalytic systems are developed for synthesis of amide and imide with a wide substrate scope.

In chapter 2, various Lewis and Brønsted acid catalysts including water tolerant $Sc(OTf)_3$, Cs-exchanged heteropoly acid were investigated for the amidation of n-dodecanoic acid with aniline. Among them Nb_2O_5 showed the highest catalytic activity for the above reaction. This simple and atom-efficient method tolerates various functional groups and is applicable to challenging substrates such as anilines and α-hydroxycarboxylic acids. I investigated the reusability of catalyst and general applicability of the present catalytic system. Kinetics studies showed that the Lewis acid site of Nb_2O_5, as the active site for the amidation is more tolerant to the co-present basic molecules than other used catalyst.

In chapter 3, I examined various Lewis and Brønsted acid catalysts including some effective homogeneous catalysts ($La(OTf)_3$, NaOMe) for direct amidation of methyl benzoate with aniline. I found that Nb_2O_5 showed the highest catalytic activity for this reaction. I investigated the reusability of catalyst and general applicability of the present catalytic system. This Lewis acid catalyst is effective for various functionalities and is applicable to challenging substrates such as anilines and α-hydroxyesters. This result

demonstrate the first successful example of heterogeneous catalysis for direct amidation of esters with amines.

For chapter 4, I examined various Lewis and Brønsted acid catalysts, water tolerant homogneous and heterogeneous catalysts and commercial acidic resins for direct imidation of succinic acid with *n*-octylamine. Among those used catalyst Nb_2O_5 showed highest catalytic activity to the corresponding *n*-octylsuccinimide. The catalyst was reusable and easy separable from the mixture. Preliminary mechanistic studies suggested that Lewis acid site of Nb_2O_5 has higher tolerance to basic molecules (amines and water) than other used catalyst. This results demonstrate the first heterogeneous Lewis acid catalytic system for imidation of dicarboxylic acid with amines and ammonia.

In chapter 5, for condensation reaction of carboxylic anhydride and amine, I investigated several Lewis acid catalysts including some metal oxide and water tolerant homogeneous Lewis acid catalysts. Nb_2O_5 showed the best catalytic activity for the imidation of succinic anhydride with aniline than other screened catalyst. I investigated the reusability of catalyst and general applicability of the present catalytic system. These results demonstrate the first reusable Lewis acid catalysis to synthesize cyclic imide from carboxylic anhydrides with amines and ammonia.

In chapter 6, I examined different types of catalyst for transamidation of benzamide with *n*-octyl amine. Among them Fe-mont acts as an effective heterogeneous catalyst for the transamidation of benzamide with *n*-octyl amine. I investigated the reusability of catalyst and general applicability of the present catalytic system. Catalytic cycle showed that carbonyl oxygen is activated by Fe^{3+} Lewis acid. This results shows that Fe-mont is an efficient catalyst for the transamidation reaction.

Chapter 7 is the general conclusion. Chapters 2-6 show the precise examples of heterogeneous Lewis acid catalysis for the direct synthesis of amide and imide from various substrates. By using these simple methodology, I synthesized various important amides and imides from readily available starting materials. Mechanistic studies suggested that the Lewis acid site of Nb_2O_5 is tolerant to base present in the reaction mixture which makes it highly effective for amidation and imidation reaction. These heterogeneous Lewis acid catalysts can be applied to other reactions involving activation of carbonyl groups in the presence of amines.

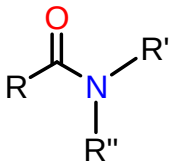
Contents

Chapter 1

General Introduction

1.1. Introduction to Amide:

Amides contain a functional group which consists of a C=O (carbonyl) directly bound to a nitrogen:



The amide functional group involves a nitrogen atom (and lone pair), but unlike an amine, the nitrogen center is not basic, due to the electron-withdrawing effect of the C=O group.

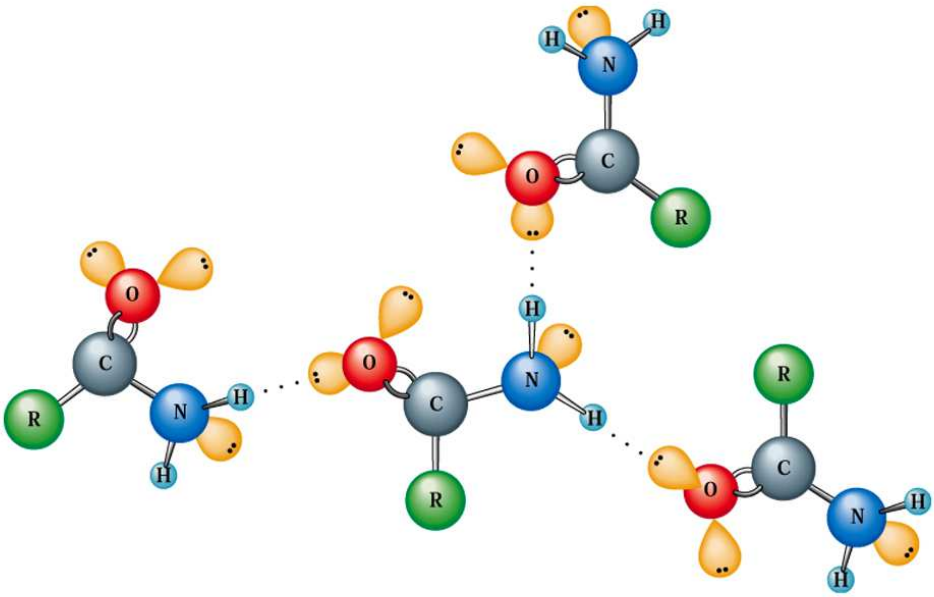
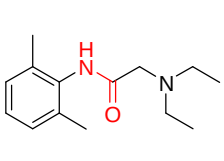


Figure 1.1. Amide bond

The amides are ubiquitous and important functional groups in natural and synthetic organic compounds. It is essential to sustain life and constitute the building blocks of pharmaceutical molecules, agrochemicals and natural products.[1-4] The structural aspects of amide bonds, specifically the partial delocalization of electrons over the N-C-O bond and their hydrogen bonding abilities, play vital roles in their properties as a functional group within a larger molecule. (Figure 1.2)



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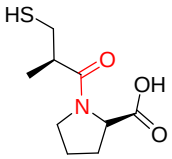

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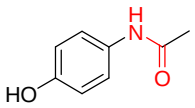

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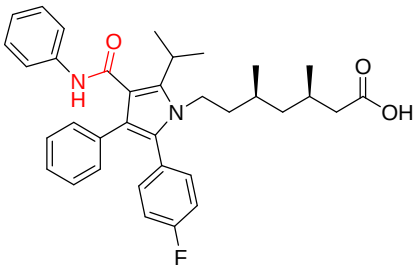
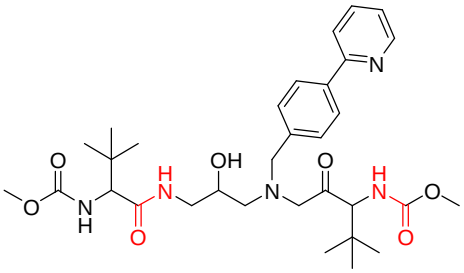
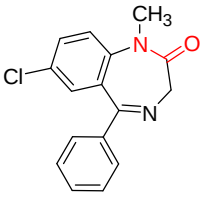


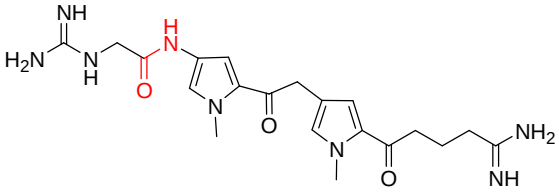
Atorvastatin 1.2.4



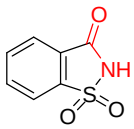
Atazanvir 1.2.5



Valium 1.2.6



congocidine 1.2.6

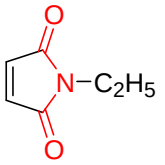


Saccharin 1.2.7

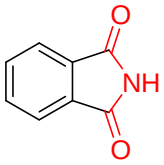
Figure 1.2. Amide bonds containing drug molecules (1.2.1-1.2.5), natural products (1.2.6), agrochemicals (1.2.7)

1.2. Cyclic Imide

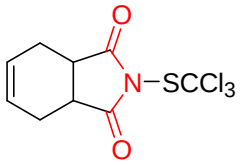
Cyclic imides and their derivatives are an important class of compounds with numerous applications in biological, medicinal, synthetic, and polymer chemistry[5, 6] and are used as intermediates in dyes and polymer industries.[5a, b, 6] Some important cyclic imide structures are given below (Figure 1.3).



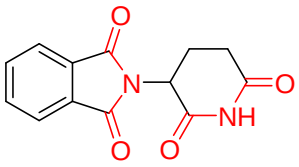
N-ethylmaleimide 1.3.1



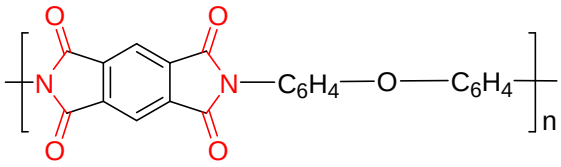
phthalimide 1.3.2



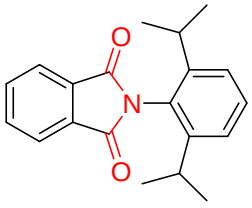
Captan 1.3.3



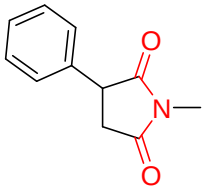
Thalidomide 1.3.4



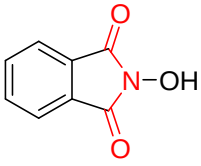
Kapton 1.3.5



PP-33. 1.3.6.



Phensuximide 1.3.7



Hydroxyphthalimide 1.3.8

Figure 1.3. Some important imide molecules. N-ethylmaleimide (1.3.1), a biochemical reagent; phthalimide (1.3.2), an industrial chemical intermediate; Captan (1.3.3), a controversial herbicide; thalidomide (1.3.4), a drug that once caused many birth defects; a subunit of Kapton (1.3.5), a high strength polymer used to make space suits; PP-33 (1.3.6) a α-TNF inhibitor named; phensuximide (1.3.7), an anticonvulsant drug; hydroxyphthalimide (1.3.8), a catalyst used for selective oxidation.

1.3. Importance of amide bond formation reaction

The importance of improving standard amide synthesis methods was highlighted in an article published in 2007[7] in which several leading pharmaceutical companies considered some influential reactions which are currently used but better reagents preferred, where amide bond formation avoiding poor atom economy reagents were placed in the required list. They preferred strongly to use alternative reagents for amide bond formation avoiding the use of poor atom economy reagents received nominations and possessed in top position from all of the pharmaceutical companies in the study and has been presented as a priority area shown in Table 1.1.

Table 1.1. Reactions companies would now use but would strongly prefer better reagents

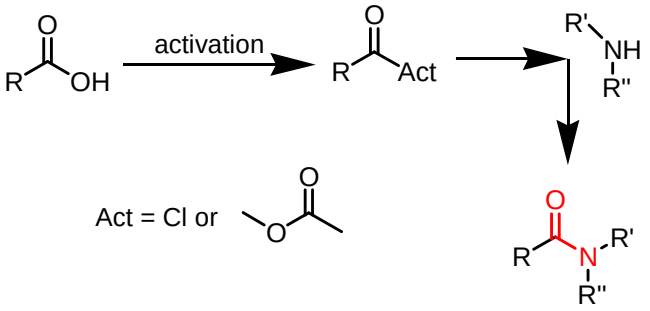
Research Area	**Number of Votes**
Amide formation avoiding poor atom economy reagents	**6**
OH activation for nucleophilic substition	5
Reduction of amides without hydride reagents	4
Safer and more environmentally friendly Mitsunobu reactions	3

1.4. Synthesis of amide

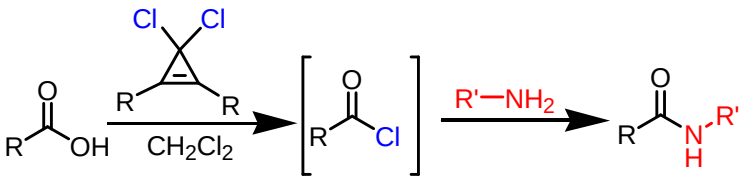
1.4.1. Conventional method

Via acylchloride formation

To activate carboxylic acids, conversion of -OH group of the caboxylic acid into good leaving group prior to the treatment with the amine, which act as stand-alone reagents for the production of new compounds such as acid chlorides, (mixed) anhydrides, carbonic anhydrides or active esters. For the presence of strong electrophilicity, acid chlorides may be readily converted to practically all other acyl derivatives and thus represent the most powerful means to achieve carboxylic acid functionalization. Recent report[8] by T. H. Lambert showed that the conversion of carboxylic acids to their corresponding acid chlorides, which occurs rapidly in the presence of amine base and 3,3-dichlorocyclopropenes via aromatic cation-activated nucleophilic acyl substitution. These methods of amide bond formation reaction, have some drawbacks to suffer from low atom efficiency, not eco-friendly and produce large amount unwanted byproducts.



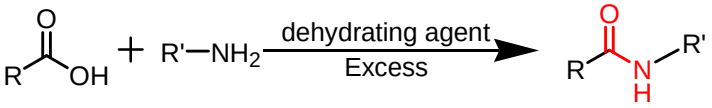
Scheme 1.1. Principle of the activation process for amide bond formation.



Scheme 1.2. Amide synthesis via acylchloride.[8]

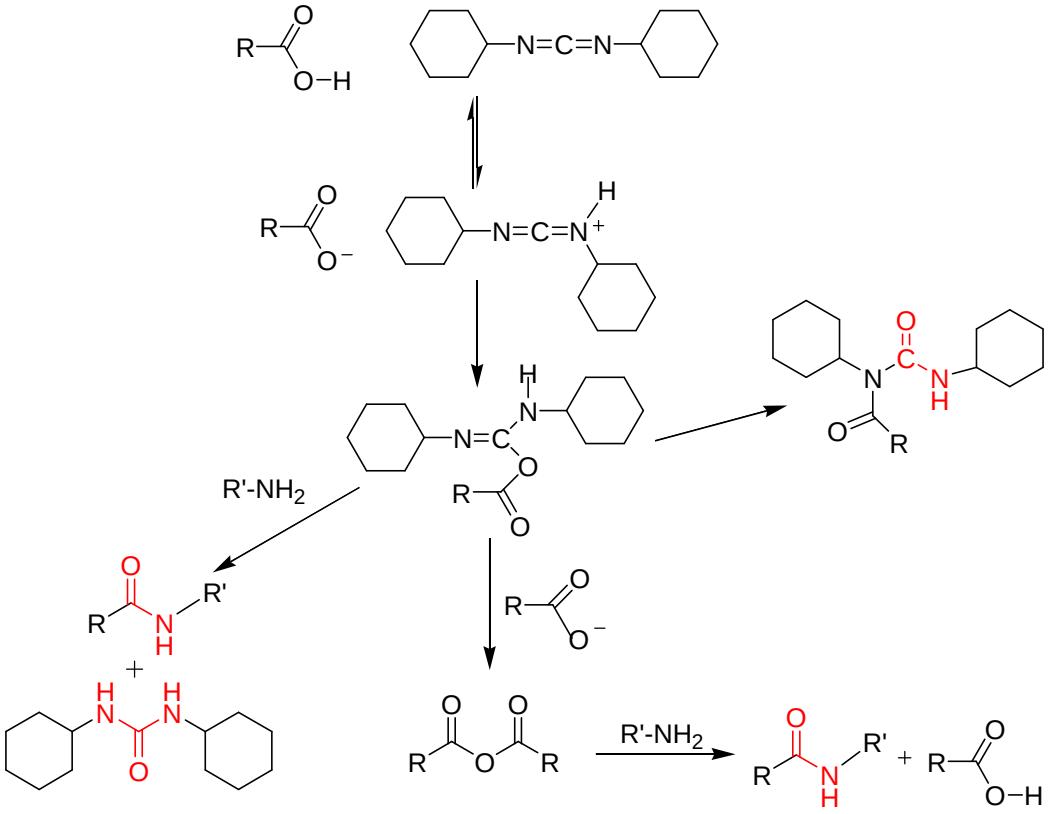
Using dehydrating reagent

Another conventional method to prepare amide from carboxylic acids and amines by using of stoichiometric amount of a dehydrating agent for activation of carboxylic acid by removing water.[9] This methods suffer from low atom efficiency and production of byproducts.



Scheme 1.3. Amidation of carboxylic acid by dehydrating reagent.

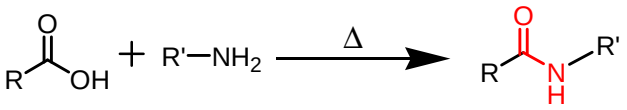
Compounds containing the carbodiimide functionality are dehydration agents and are often used to activate carboxylic acids towards amide formation. Selection of dehydrating reagent is however critical. A dehydrating reagent must be capable to handle with this whole portfolio of reactivity. Many reviews have been published,[10-15] on dehydrating reagents but these reviews sometimes not able to offer a critical view on the fact of making the choice of reagent difficult.



Scheme 1.4. Amidation by using dehydrating agent DCC (Dicyclohexyllcarbodiimide).[9]

Thermal amidation

Amides are also synthesized at high temperature and pressure from the combination of carboxylic acids and amines. At the ambient temperature, the reaction of these two functional groups does not occur spontaneously due to elimination of water, which takes place at high temperature (250-380 ˚C).[16] The condition is harsh and yield of the product is highly substrate dependent, as well as dependent on temperature, concentration of the substrate and other reaction parameters. (Scheme 1.5)

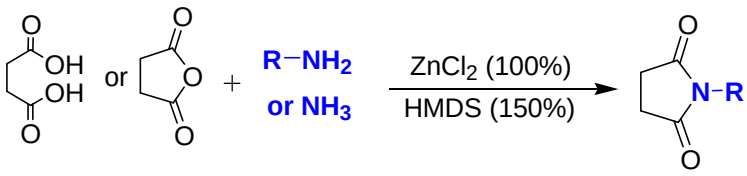


Scheme 1.5. Condition dependence in thermal amidation.

1.4.2. Lewis acid promoted amidation.

Imidation of dicarboxylic acid or carboxylic anhydridre by using stoichiometric amount of Lewis acid

Lewis acid promoted imidation of dicarboxylic acid or carboxylic anhydride with amines are developed. Imide derivatives are synthesized by the reaction of an carboxylic anhydride with an appropriately substituted amine and consecutive in situ cyclization of the produced amic acid in the presence of a stoichiometric amount of Lewis acid and HMDS. In order to demonstrate the concept, the N-benzylmaleamic acid was synthesized from maleic anhydride and benzylamine, under reflux condition of benzene with stoichiometric amount of Lewis acid (equimolar amounts of HMDS and $ZnCl_2$) to the corresponding maleimide derivative (Scheme 1).[17] This method suffers from drawbacks of low atom efficiency, limited substrate scope and production of stoichiometric amount of byproducts.

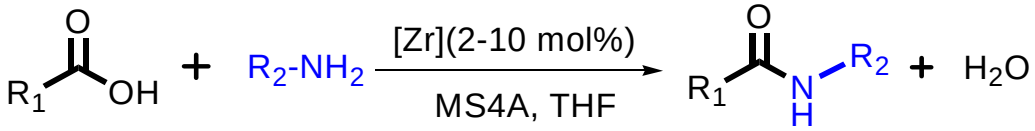


Scheme 1.6. Lewis acid promoted imidation.[17]

1.4.3. Lewis acid catalyzed amidation

Lewis acid catalyzed amidation of carboxylic acid.

The first Lewis acid catalytic intermolecular amidation protocol was published[18] by employing $Ti(OBu)_4$ as a catalyst for the amidation benzoic acid with aniline. By using 2 mol% catalyst loading under the reflux condition of *o*-xylene, the authors showed that the titanium butoxide complex was more effective catalyst than other Lewis acid catalyst such as $TiCl_4$, $SnCl_4$, Bu_2SnO, and $BF_3{\cdot}OEt_2$ in the amidation of benzoic acid and aniline. Recent report by H. Adolfsson[19] showed that by using 2-10 mol% of Lewis acid catalyst $ZrCl_4$ for the amidation of phenylacetic acid with benzylamine. However, these homogeneous catalytic methods have drawbacks of difficulties in catalyst/products separation, reusability of catalyst and limited substrate scope. Moreover, Lewis acidic homogenous 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).

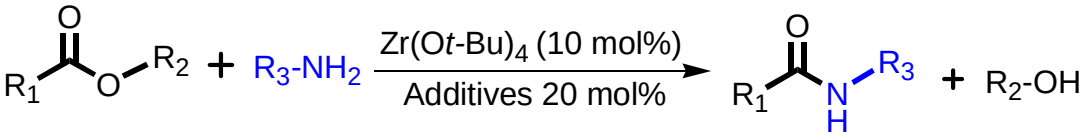


Scheme 1.7. Lewis acid catalyzed amidation of carboxylic acid.

Lewis acid catalyzed amidation of esters.

Lewis acid catalytic methods have also been developed for the amidation of esters with amines. For example, homogeneous Lewis acid catalytic methods by using $Zr(OtBu)_4$,[20a] and $La(OTf)_3$,[20b] and Lewis acids supported on ionic liquids[20c] have been reported as more effective catalysts for the amidation of esters but the reported methods suffer from drawbacks, including limited substrate scope, high catalyst loading (>10 mol% with respect to substrate), and the need for additives and difficulties in catalyst reuse. A few heterogeneous Lewis acid catalysts (montmorillonite clay[21a, b] and Al_2O_3 [21b]) catalyze

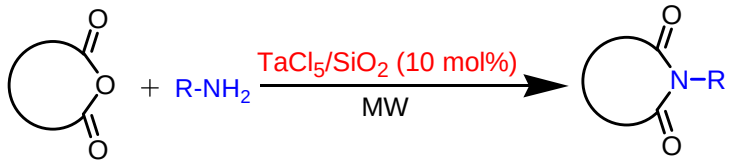
the reaction of methyl benzoate with NH_3 to give a mixture of benzamide and benzonitrile. However, the yields of the amide are low and the substrate scopes of various esters and amines are not reported.



Scheme 1.8. Lewis acid catalyzed amidation of ester.[20a]

Lewis acid catalyzed amidation of carboxylic anhydride.

Lewis acid catalyzed synthesis of cyclic imides by condensation of cyclic anhydrides with amines is one of the most desirable route. Chandrasekhar et al. reported the synthesis of cylcic imide from carboxylic anhydride with amines by using 10 mol% of the $TaCl_5/SiO_2$[22a,22b] as a Lewis acid catalyst under microwave heating. These methods[22] 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).



Scheme 1.9. Lewis acid catalyzed imidation of carboxylic anhydride.[22a]

1.4.4. Comparison of TON for different Lewis acid catalyzed amidation reaction.

Here is the comparison of turnover number and general applicability of some amidation reaction by using both homogeneous and heterogeneous Lewis acid catalysts.

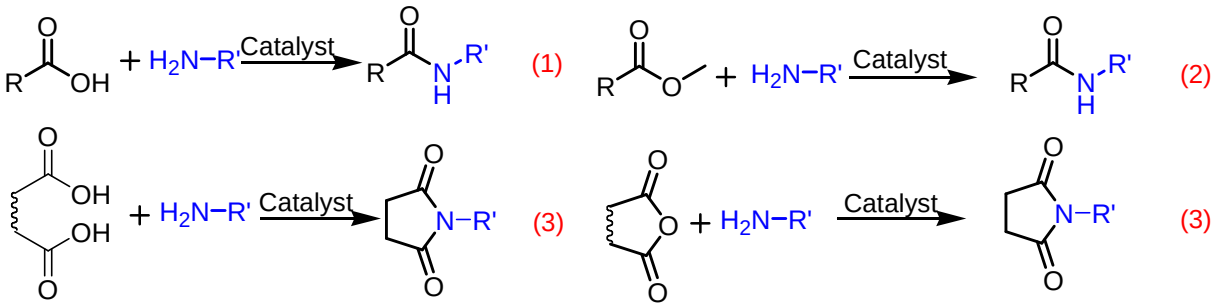


Table 1.2. Comparison of TON for present method with previous homogeneous and heterogneous Lewis acid catalytic methods.

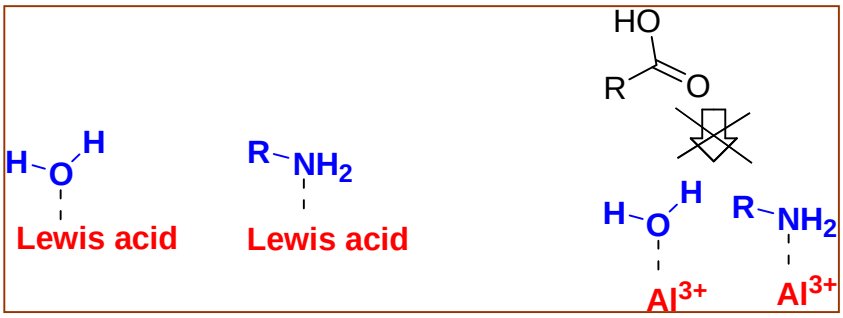
Reaction No.	**This Method**		**Homogeneous Method**		**Heterogeneous Method**	
	Catalyst	TON	Catalyst	TON	Catalyst	TON
1	Nb_2O_5	341	$ZrCl_4$[19]	8	Al_2O_3[26]	98
2	Nb_2O_5	303	$Zr(Ot\text{-}Bu)_4$[20a]	9	No example	-
3	Nb_2O_5	341	No example	-	No example	-
4	Nb_2O_5	310	No example	-	$TaCl_5$-SiO_2[22a]	9

The above comparison of TON for the different Lewis acid catalyzed amidation reaction showed that only Nb_2O_5 is useful catalyst for both amidation and imidation reaction as a heterogeneous Lewis acid catalyst. The TON for other homogeneous and heterogeneous catalyst is lower than Nb_2O_5. Among the above examples of previous Lewis acid catalyzed amidation and imidation reactions, some of the previous examples have very limited substrate scope.

1.4.5. Difficulties of Lewis acid catalyzed amidation

Presence of small amount of water can decompose a Lewis acid, such as $AlCl_3$[24], in the reaction mixture. For this reason Lewis-acid promoted/catalyzed organic reactions are usually done under complete anhydrous conditions. Lewis acid promoted amidation reactions have some limitations of low atom efficiency and production of byproducts. Lewis acid catalyzed amidation reaction have additional drawbacks, such as limited substrate scope, high catalyst loading and reusability of the catalyst. Previous comparison (table 1.2) showed that the turnover number for Lewis acid catalyzed amidation reaction is usually very low and there is no general application of Lewis acid catalyst for both amidation and imidation reaction with a wide substrate scope except Nb_2O_5.

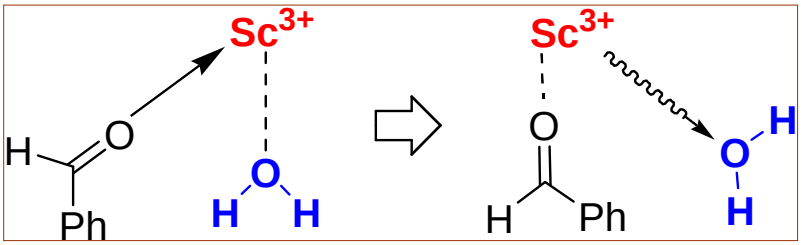
These drawbacks may be caused by the suppression of Lewis acid by basic molecules (amines and water as byproduct), hindering coordination with water and amine present in the reaction mixture. The author hypothesized that these drawbacks can be overcome if some Lewis acid catalyst is tolerant to basic molecules (amines and water as byproduct), present in the reaction mixture for the amidation of carboxylic acid, carboxylic anhydrides or esters with amines.



Scheme 1.10. Lewis acid catalyzed amidation, where Lewis acid coordinate with water and amines other than carboxylic acid.

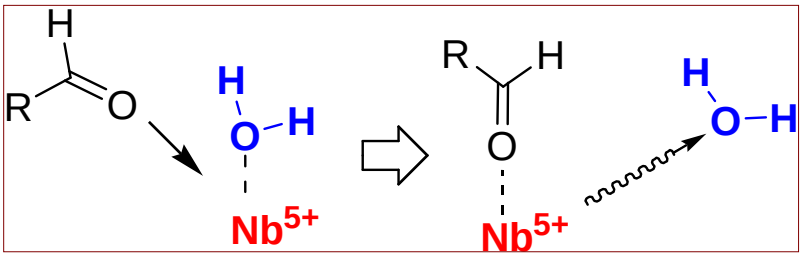
1.4.6. Water-tolerant Lewis acid catalyzed amidation.

The concept of water tolerant Lewis acid catalyst is developed. Kobayahi et.al[23] showed that $Sc(OTf)_3$, $Y(OTf)_3$, $Ln(OTf)_3$ and $Yb(OTf)_3$ can act as Lewis acid catalyst in water-containing solvents. They also showed that not only Sc(III), Y(III), Ln(III) but also Fe (II), Cu (II), Zn (II), Cd (II), and Pb (II) are also effective as Lewis acid catalyst in water containing solvents for the aldol reaction of benzaldehyde with silyl enol ether.



Scheme 1.11. Water-tolerant Lewis acid catalysis of $Sc(OTf)_3$

In literature,[24] Nb_2O_5 showed as a water-insoluble solid catalyst, for which the structure and chemical property have been described. Recent reports showed that some metal oxides, such as Nb_2O_5,[25a] acts as water-tolerant Lewis acid catalysts.[25]

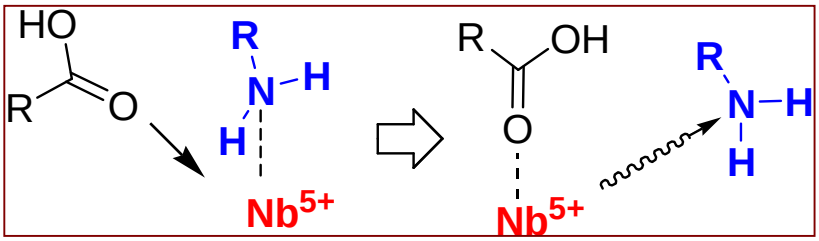


Scheme 1.12. Water-tolerant Lewis acid catalysis (Nakajima et. al).[25a]

1.4.7. Base-tolerant Lewis acid catalyzed amidation.

As we already know the water-tolerant properties of Nb_2O_5 in the literature,[24,25] so the author hypothesized that this catalyst may also be used as base-tolerant Lewis acid catalyst for amidation of carboxylic acid with amines. In that case, basic molecules

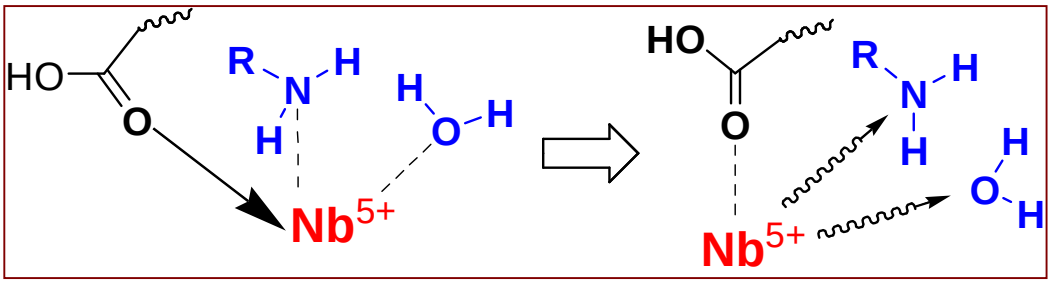
(amines) which are present in the reaction mixture can be replaced to water (as like scheme 1.12). So, water tolerant Nb_2O_5 Lewis acid acid catalyst can be used as effective base tolerant catalyst for amidation reaction.



Scheme 1.13. Concept of base-tolerant Lewis acid catalyzed amidation?

1.5. Concluding remarks

To avoid the limitations of the previous method for Lewis acid catalyzed amidation and imidation reaction, water tolerant as well as base-tolerant heterogeneous Lewis acid catalyst, Nb_2O_5 can be an effective base tolerant catalyst for the direct amidation of carboxylic acids and esters with amines and direct imidation of dicarboxylic acids and carboxylic anhydrides with amines.



Scheme 1.14. Water as well as base-tolerant Lewis acid catalyzed amidation?

1.6. Outlines of thesis

This thesis focuses on direct synthesis of amide bond by using base tolerant heterogeneous Lewis acid catalyst. Five types of Lewis acid catalytic systems are developed for synthesis of amide and imide with a wide substrate scope.

In chapter 2, various Lewis and Brønsted acid catalysts including water tolerant $Sc(OTf)_3$, Cs-exchanged heteropoly acid were investigated for the amidation of n-dodecanoic acid with aniline. Among them Nb_2O_5 showed the highest catalytic activity for the above reaction. This simple and atom-efficient method tolerates various functional groups and is applicable to challenging substrates such as anilines and α-hydroxycarboxylic acids. I investigated the reusability of catalyst and general applicability of the present catalytic system. Kinetics studies showed that the Lewis acid site of Nb_2O_5, as the active site for the amidation is more tolerant to the co-present basic molecules than other used catalyst.

In chapter 3, I examined various Lewis and Brønsted acid catalysts including some effective homogeneous catalysts ($La(OTf)_3$, NaOMe) for direct amidation of methyl benzoate with aniline. I found that Nb_2O_5 showed the highest catalytic activity for this reaction. I investigated the reusability of catalyst and general applicability of the present catalytic system. This Lewis acid catalyst is effective for various functionalities and is applicable to challenging substrates such as anilines and α-hydroxyesters. This result demonstrate the first successful example of heterogeneous catalysis for direct amidation of esters with amines.

For chapter 4, I examined various Lewis and Brønsted acid catalysts, water tolerant homogneous and heterogeneous catalysts and commercial acidic resins for direct imidation of succinic acid with *n*-octylamine. Among those used catalyst Nb_2O_5 showed highest catalytic activity to the corresponding *n*-octylsuccinimide. The catalyst was reusable and easy separable from the mixture. Preliminary mechanistic studies suggested that Lewis acid site of Nb_2O_5 has higher tolerance to basic molecules (amines and water) than other used catalysts. This results demonstrate the first heterogeneous Lewis acid catalytic system for imidation of dicarboxylic acid with amines and ammonia.

In chapter 5, for condensation reaction of carboxylic anhydride and amine, I investigated several Lewis acid catalyst including some metal oxide and water tolerant

homogeneous Lewis acid catalysts. Nb_2O_5 showed the best catalytic activity for the imidation of succinic anhydride with aniline than other screened catalysts. I investigated the reusability of catalyst and general applicability of the present catalytic system. These results demonstrate the first reusable Lewis acid catalysis to synthesize cyclic imide from carboxylic anhydrides with amines and ammonia.

In Chapter 6, I examined different types of catalyst for transamidation of benzamide with *n*-octyl amine. Among them Fe-mont acts as an effective heterogeneous catalyst for the transamidation of benzamide with *n*-octyl amine. I investigated the reusability of catalyst and general applicability of the present catalytic system. Catalytic cycle showed that carbonyl oxygen is activated by Fe^{3+} Lewis acid. This results shows that Fe-mont is an efficient catalyst for the transamidation reaction.

Chapter 7 is the general conclusion. Chapters 2-6 show the precise examples of heterogeneous Lewis acid catalysis for the direct synthesis of amide and imide from various substrates. By using these simple methodology, I synthesized various important amides and imides from readily available starting materials. Mechanistic studies suggested that the Lewis acid site of Nb_2O_5 is tolerant to base present in the reaction mixture which makes it highly effective for amidation and imidation reaction. These heterogeneous Lewis acid catalysts can be applied to other reactions involving activation of carbonyl groups in the presence of amines.

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Chapter 2

Amidation of Carboxylic Acids with Amines by Nb_2O_5 as Reusable Lewis Acid Catalyst

2.1. 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 via activation with stoichiometric amount of a condensation agent for activation of carboxylic acid and water removal.[4] 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.[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 the direct amidation. 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 previous catalysts. A rare example is a boronic acid catalyst developed by Ishihara,[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, homogeneous catalytic methods have drawbacks of difficulties in catalyst/products separation and catalyst reuse. Moreover, Lewis acidic homogenous 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[4,32,35] or *N*-acetylation[4,39] of amines. Some of the previous heterogeneous system for amidation suffer from drawbacks of limited scope and needs of excess amount of reagent or a special reaction method (microwave heating).[33,34]

In the course of our continuous studies on the amide bond forming reactions by heterogeneous Lewis acidic catalysts,[41-43] we have recently reported that Nb_2O_5, prepared by calcination of a commercial niobic acid, acts as base-tolerant Lewis acid catalyst for direct imidation of dicarboxylic acids with amines[43] and direct amidation of esters with amines.[42] We report herein that Nb_2O_5 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_2O_5 is due to activation of carboxylic acids by Lewis acid sites of Nb_2O_5 with base-tolerant nature.

2.2. 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$^+$-1 capillary column (Frontier Laboratories Ltd.) using N_2 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 μm, Kanto Chemical Co. Ltd.). Molecular sieves 4Å (MS4Å) was dehydrated at 100 °C.

Catalyst preparation.

Niobic acid ($Nb_2O_5{\cdot}nH_2O$, HY-340) was kindly supplied by CBMM. Nb_2O_5 (surface area = 54 m^2 g^{-1}) was prepared by calcination of niobic acid at 500 °C for 3 h. MgO (JRC-MGO-3), TiO_2 (JRC-TIO-4), CeO_2 (JRC-CEO-3), H^+-type Y zeolite (HY) with a SiO_2/Al_2O_3 ratio of 4.8 (JRC-Z-HY-4.8), H^+-type BEA zeolite (HBEA) with a SiO_2/Al_2O_3 ratio of 25 (JRC-Z-HB25) and H^+-type MFI zeolite (HMFI) with a SiO_2/Al_2O_3 ratio of 90 (JRC-Z5-90H) were supplied from Catalysis Society of Japan. SiO_2 (Q-10, 300 m^2 g^{-1}) was supplied from Fuji Silysia Chemical Ltd. $ZrO_2{\cdot}nH_2O$ was prepared by hydrolysis of zirconium oxynitrate 2-hydrate in water by aqueous NH_4OH solution, followed by filtration of precipitate, washing with water three times, and drying at 200 °C. ZrO_2, ZnO, SnO_2, MoO_3, WO_3, Ta_2O_5 and CaO were prepared by calcination (500 °C, 3 h) of the hydrous oxides: $ZrO_2{\cdot}nH_2O$, $ZnO{\cdot}nH_2O$ (Kishida Chemical), H_2SnO_3 (Kojundo Chemical Laboratory Co., Ltd.), H_2MoO_4 (Kanto Chemical), H_2WO_4 (Kanto Chemical), $Ca(OH)_2$ (Kanto Chemical) and $Ta_2O_5{\cdot}nH_2O$ (Mitsuwa Chemicals). γ-Al_2O_3 and θ-Al_2O_3 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_2 composite) were purchased from Aldrich.

Fe^{3+}-exchanged K-10 (Fe^{3+}-mont) was prepared by treating the clay with aqueous solution of $FeCl_3 \cdot 6H_2O$ 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^{3+}-mont (0.46 wt%) was determined by ICP analysis. Scandium(III) trifluoromethanesulfonate, $Sc(OTf)_3$, was purchased from Tokyo Chemical Industry. $ZrCl_4$ was purchased from WAKO. $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ was prepared by titrating $H_3PW_{12}O_{40}$ (Nippon Inorganic Color and Chemicals Co.) by aqueous solution of Cs_2CO_3 (0.10 mol dm^{-3}) 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 (ϕ = 2 cm) and mounted into the IR cell with CaF_2 windows. Spectra were measured accumulating 15 scans at a resolution of 4 cm^{-1}. 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_2O_5 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_2O (1.4 mmol/g) was introduced to Nb_2O_5, 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_2O_5 were added to a reaction vessel (pyrex cylinder) with a reflux condenser and a magnetic stirrer. The reaction mixture was heated to reflux under N_2 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_2O_5 catalyst was separated by centrifugation. For the catalytic tests in Table 2.1 and Figures 2.1, 2.4, 2.5 and 2.6 the reaction mixture was analyzed by GC, and yield of the products were determined using *n*-dodecane as an internal standard. For the reactions in Tables 2.3-2.5 the product was isolated by column chromatography. Then, the resulting product was identified using GCMS, ^{1}H-NMR, and ^{13}C-NMR analyses.

NMR and GC-MS analysis

^{1}H and ^{13}C NMR spectra were recorded using at ambient temperature by JEOL-ECX 600 operating at 600.17 and 150.92 MHz respectively with tetramethylsilane as an internal standard. All chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. All chemical shifts are reported relative to tetramethylsilane and *d*-solvent peaks (77.00 ppm, chloroform), respectively. Abbreviations used in the NMR experiments: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Structure of the reported cyclic imides was identified by spectral comparison with literature data or analogous to literature data.

2.3. 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 2.1 summarizes the yield of the corresponding amide for various catalysts including metal oxides and standard heterogeneous and homogeneous acid catalysts. Figure 2.1 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.[21,43,44] For the model reaction in Table 2.1, 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 (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_2O_5 showed the highest yield (99%) of the amide. In the literature, TiO_2,[33] ZnO,[32] Al_2O_3,[35,36] $ZrO_2.nH_2O$,[38] SiO_2,[27] Fe^{3+}-mont,[39,40] HY[28] and HBEA[29] zeolites were reported to be effective for the direct amidation. However, these catalysts showed lower yield than Nb_2O_5. For example, conventional solid Lewis acids[45,46] such as TiO_2 (entry 5), alumina (entries 8,9) and Fe^{3+}-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,[47] 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_2 (entry 26), and a water-tolerant homogeneous Lewis acid,[48] such as $Sc(OTf)_3$ (entry 27). However, these water-tolerant acid catalysts gave lower yield of the amide (2-30%) than Nb_2O_5. Homogenous Brønsted acids such as sulfuric acid (entry 29) and *p*-toluenesulfonic acid (PTSA, entry 30) also gave low yields. A hydrate of Nb_2O_5 called niobic acid (entry 4), which has been studied as water-tolerant Lewis acid catalyst,[49] gave lower yield (74%) than Nb_2O_5.

Lewis acidity of Nb_2O_5. In our previous IR study of pyridine adsorption on Nb_2O_5, we showed that surface acid sites of dehydrated Nb_2O_5 are mainly Lewis acidic sites (exposed Nb^{5+} cations).[45] Figure 2.2 shows the IR spectrum of pyridine adsorbed on dehydrated and rehydrated Nb_2O_5. These spectra have basically the same features; the band at 1445 cm^{-1} due to coordinated pyridine on Lewis acid site (exposed Nb^{5+} cations) is dominant rather than the band at 1540 cm^{-1} 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_2O_5 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_2O_5. The spectrum (Figure 2.3) showed a C=O stretching band of the adsorbed acetic acid ($\nu_{C=O}$) at

lower wavenumber (1686 cm^{-1}) than non Lewis acidic oxide, SiO_2 (1703 cm^{-1}) and conventional Lewis acidic oxides: TiO_2 (1695 cm^{-1}) and Al_2O_3 (1697 cm^{-1}). This indicates that the surface of Nb_2O_5 has the most effective Lewis acid sites for activation of the C=O bond of the carboxylic acid.

Base-tolerant catalysis of Nb_2O_5 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_2O_5, TiO_2 and Al_2O_3) for the model amidation of *n*-dodecanoic acid and aniline (Figure 2.1). 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_2O in the initial mixture gave the lowest activity. However, the negative impact of the water was lower for Nb_2O_5 than TiO_2 and Al_2O_3. As shown in Figure 2.4, the initial rate of amide formation with Nb_2O_5 and TiO_2 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_2O_5 than TiO_2, and the reaction orders with respect to water were -0.3 and -1.8 for Nb_2O_5 and TiO_2, respectively. This indicates that water-tolerance of Nb_2O_5 is higher than TiO_2.

$ZrCl_4$ is a well established Lewis acidic homogenous catalyst for the direct amidation.[20-22] Generally, the activity of homogeneous Lewis acid can be reduced by water and organic bases. To compares base-tolerance of $ZrCl_4$ and Nb_2O_5, we measured the yield of the amide in the standard reaction for 30 h with $ZrCl_4$ or Nb_2O_5 under the azeotropic reflux conditions in the absence or presence of 0.5 equiv. of basic additives: H_2O, 2,6-dimethylpyridine, pyridine, and triethylamine (Figure 2.4). Although we used the same molar amount of the catalyst (0.38 mmol), $ZrCl_4$ was dissolved in the reaction mixture while Nb_2O_5 was insoluble. Clearly, the additive-free condition gave higher yield for both catalysts, but negative effects of the additives were lower for Nb_2O_5 than $ZrCl_4$. 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_2O_5 catalyst used. This suggests that the active site (Nb^{5+} 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_2O_5 has higher tolerance to basic molecules than conventional solid Lewis acids and a typical homogeneous Lewis acid. The water-tolerant character of the Nb^{5+} Lewis acid sites of niobium oxide is consistent with the pioneering work by Nakajima et al.[49]

Performance of Nb_2O_5-catalyzed amidation. As listed in Table 2.2, the turnover number (TON) with respect to the Lewis acid site of Nb_2O_5 (341) was more than 200 times higher than those of $ZrCl_4$ (a well established homogenous catalyst for the direct amidation[20-22]) and $Sc(OTf)_3$ (a well established "water-tolerant" Lewis acid[48]). TON of Nb_2O_5 was 5 times larger than that of TiO_2. As discussed in the above section, the higher catalytic efficiency of Nb_2O_5 can be due to the higher water-tolerance and more effective Lewis acid activation of the C=O bond by Nb_2O_5 than TiO_2. It is important to note that the water-tolerance of Nb_2O_5 enabled the amidation without azeotropic water removal; the reaction by Nb_2O_5 under simple reflux condition for 40 h resulted in 96% yield of the amide (Table 2.1, entry 3).

We studied the reusability of Nb_2O_5. After the standard reaction (Table 2.1, 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 2.6). For the standard reaction, the reaction was completely terminated by removing the Nb_2O_5 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_2O_5 acts as a reusable heterogeneous catalyst.

Then, we explored the generality and scope of the Nb_2O_5–catalyzed direct amidation of carboxyl acids with different amines (Table 2.3-2.5). As listed in Table 2.3, 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 tertially amide in high yield.

Table 2.4 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 (α-hydroxy, β-hydroxy and β-thio carboxylic acids) with various amines under azeotropic reflux in *o*-xylene (Table 2.5). It should be noted that only one report by Ishihara et al. have succeeded in the direct amidation of α-hydroxy carboxylic acids with amines, but the previous method using $MeB(OH)_2$ 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 (entries 1,3) and a β-thiocarboxylic acid (entry 6). The α-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 β-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 Nb_2O_5 for the amidation of challenging substrates is caused by the base-tolerant Lewis acid-activation of carboxylic acids, which is evidenced by IR (Figures 2.2 and 2.3) and kinetic studies (Figures 2.1, 2.4, and 2.6).

2.4. Conclusion

We have presented a versatile and sustainable method for direct amidation of carboxylic acids with various amines using Nb_2O_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 α-hydroxycarboxylic acids. The Lewis acid site of Nb_2O_5, as the active site for the amidation, has higher tolerance to the co-present basic molecules (water and tertially and heteroaromatic amines) than the state-of-the-art homogeneous Lewis acid catalyst for the amidation ($ZrCl_4$) and conventional Lewis acidic heterogeneous catalysts (Al_2O_3, TiO_2), which results in higher catalytic activity of Nb_2O_5 than these catalysts.

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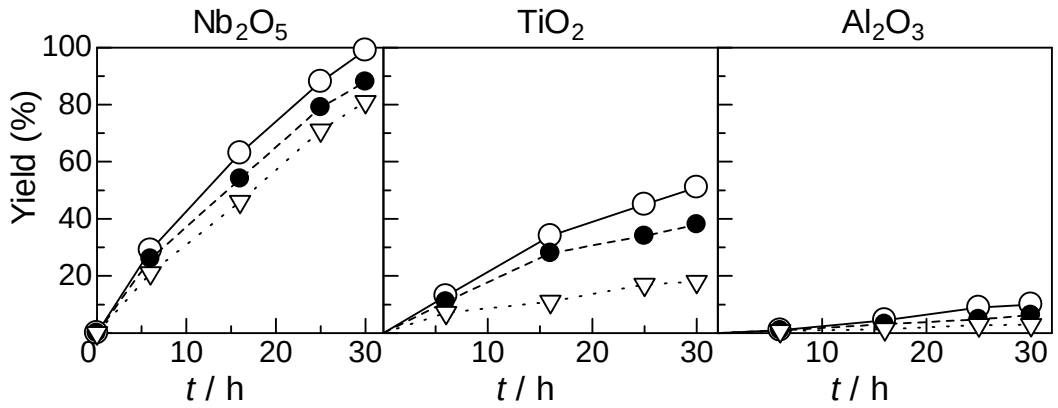


Figure 2.1. Time-yield profiles for amidation of *n*-dodecanoic acid (1 mmol) with aniline (1 mmol) catalyzed by metal oxides (50 mg) in different conditions: (○) azeotropic reflux; (●) reflux (without azeotropic water removal); (Δ) reflux with 3 mmol of H_2O in the initial mixture.

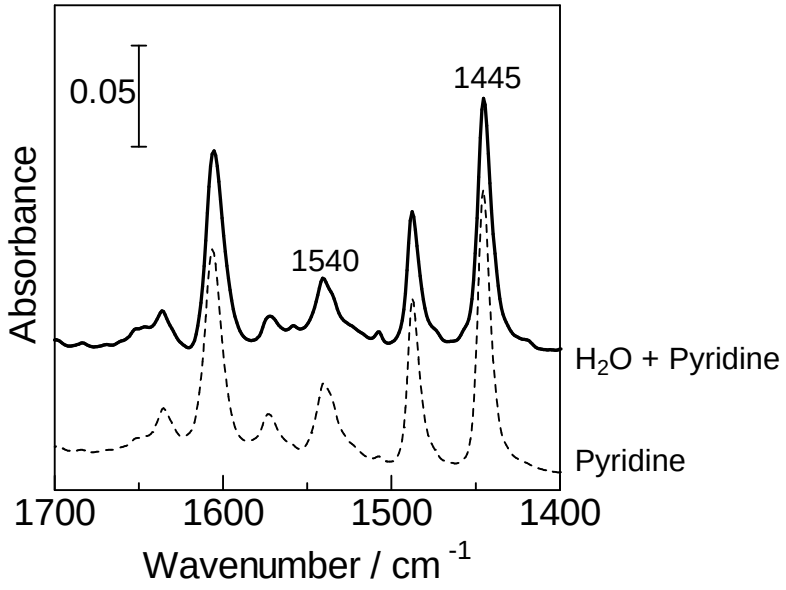


Figure 2.2. IR spectra of pyridine adsorbed on dehydrated Nb_2O_5 (dashed line) and rehydrated Nb_2O_5 (solid line) at 200 °C.

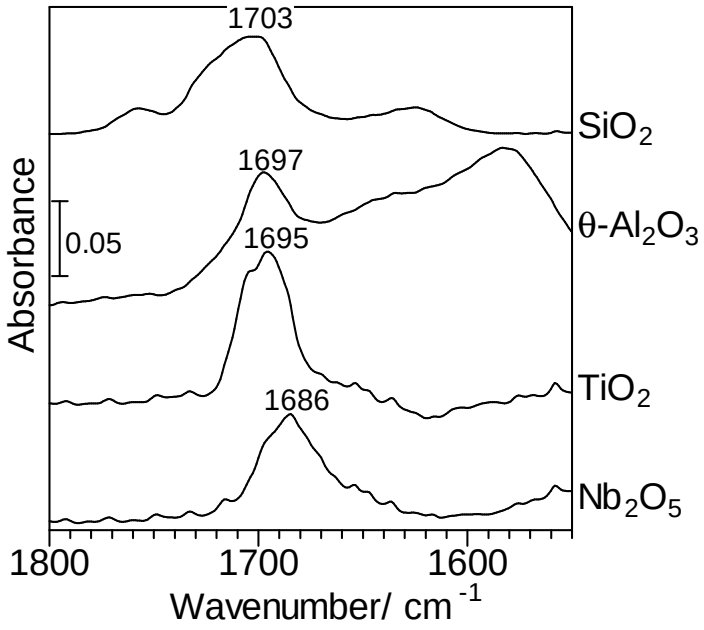


Figure 2.3. IR spectra of acetic acid adsorbed on Nb_2O_5, TiO_2, θ-Al_2O_3 and SiO_2 at - 75 ^oC.

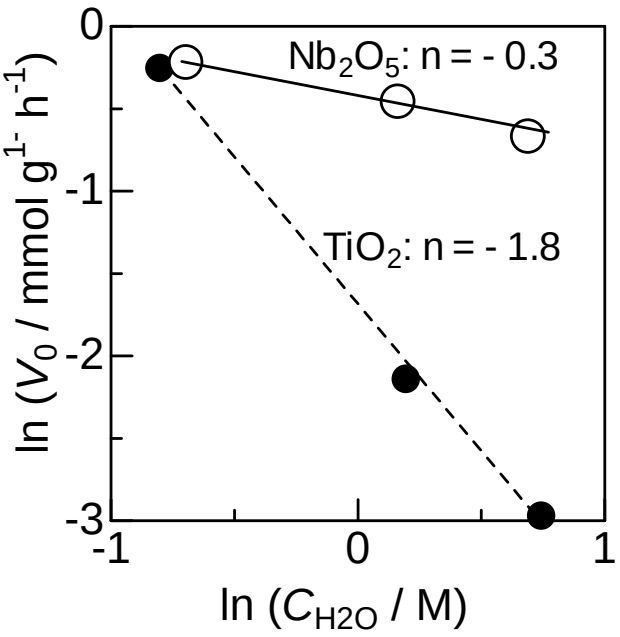


Figure 2.4. Initial rate for amidation of *n*-dodecanoic acid with aniline by (○) Nb_2O_5 and (●) TiO_2 as a function of the initial concentration of water (C_{H2O} = 1.1 to 3.4 M).

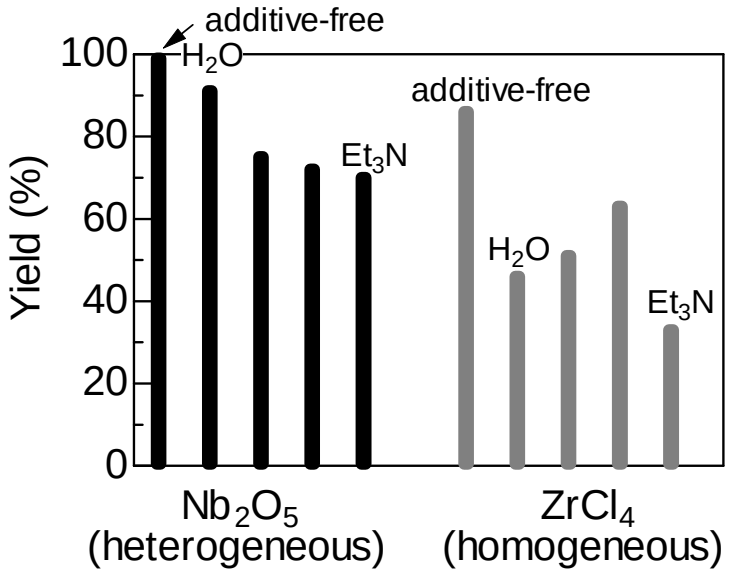


Figure 2.5. Yield of amide for the reaction of *n*-dodecanoic acid with aniline for 30 h by Nb_2O_5 (50 mg, 0.38 mmol) and $ZrCl_4$ (50 mg, 0.38 mmol) in the absence and presence of 0.5 mmol of basic additives: water, 2,6-dimethylpyridine, pyridine, triethylamine.

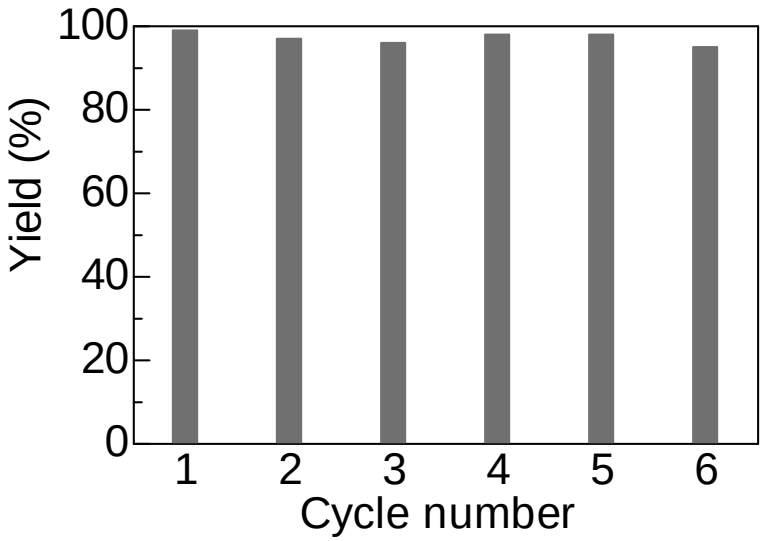
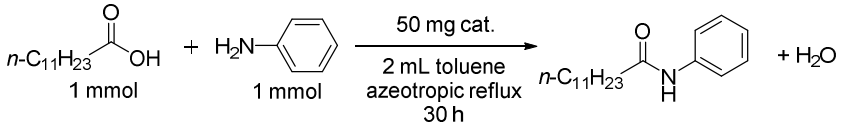


Figure 2.6. Reusability of Nb_2O_5 (50 mg) for amidation of *n*-dodecanoic acid (1 mmol) with aniline (1 mmol) in toluene reflux conditions for 30 h.

Table 2.1. Catalyst screening for amidation of *n*-dodecanoic acid with aniline.



Entry	Catalyst	Yield
1	no catalyst	1
2	Nb_2O_5	99
3[b]	Nb_2O_5	96
4	Niobic acid	74
5	TiO_2	51
6	ZnO	21
7	WO_3	16
8	θ-Al_2O_3	11
9	γ-Al_2O_3	9
10	MoO_3	9
11	$ZrO_2 \cdot nH_2O$	9
12	CeO_2	7
13	ZrO_2	6
14	Ta_2O_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_2SO_4	1
30	PTSA	19

[a] GC yields.

[b] Under reflux conditions without azeotropic water removal for 40 h.

[c] Aqueous solution of 30 wt% H_2SO_4.

Table 2.2. Summary of IR and kinetic results.

Catalyst	[LA] [a] /mmol g^{-1}	$\upsilon_{C=O}$ [b] / cm^{-1}	n_{H2O} [c]	TOF [d]/ h^{-1}	TON [d]
Nb_2O_5	0.058	1686	-0.4	11.4	341
TiO_2	0.083	1695	-1.8	2.0	61
$ZrCl_4$	4.3[e]	-	-	0.006	1.7
$Sc(OTf)_3$	2.0[e]	-	-	0.003	0.1

[a] The number of Lewis acid sites on the surface of oxides Nb_2O_5 and TiO_2 estimated by pyridine adsorption at 200°C, which were reported in ref. 45.

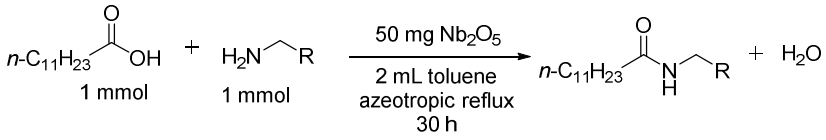
[b] Position of $\upsilon_{C=O}$ IR band of adsorbed acetic acid (Figure 2.4).

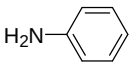
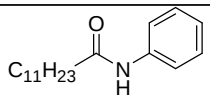
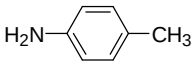
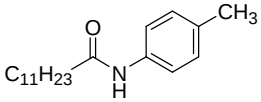
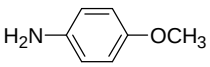
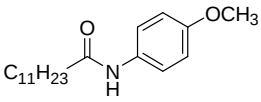
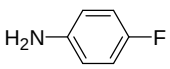
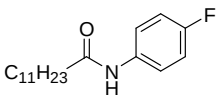
[c] Reaction order with respect to water (Figure 2.2).

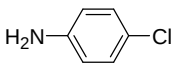
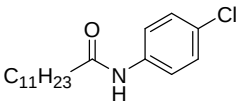
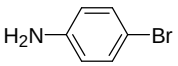
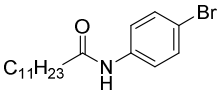
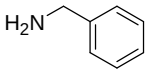
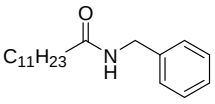
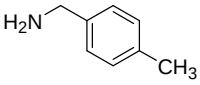
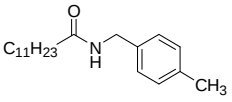
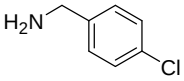
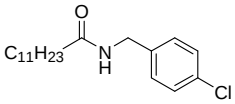
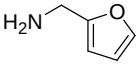
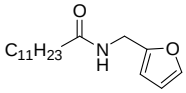
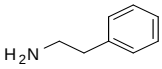
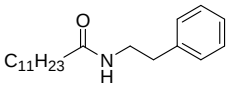
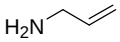
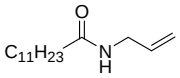
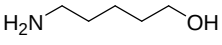
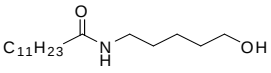
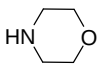
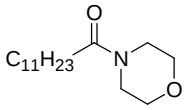
[d] Calculated with the number of Lewis acid site and the catalytic results in Table 2.1.

[e] Based on molecular weight of the salts.

Table 2.3. Nb_2O_5–catalyzed amidation of *n*-dodecanoic acid with various amines.



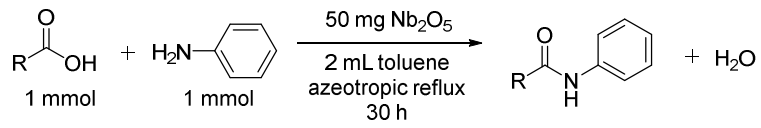
Entry	Amine	Product	Yield [a] [%]
1			98
2			98
3			97
4			98

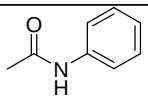
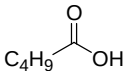
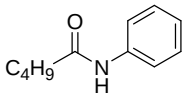
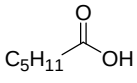
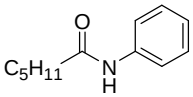
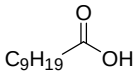
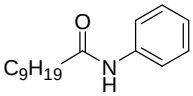
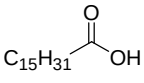
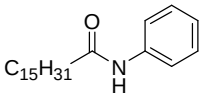
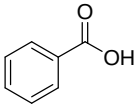
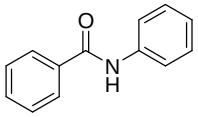
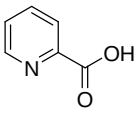
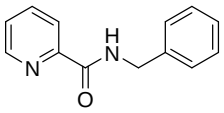
5[b]			80
6[b]			97
7			88
8			80
9			94
10			95
11			83
12[b]			98
13			96
14			81

[a] Isolated yields.

[b] Under *o*-xylene reflux.

Table 2.4. Nb_2O_5–catalyzed amidation of various carboxylic acids with aniline or benzylamine.

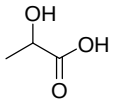
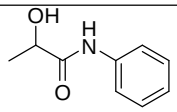
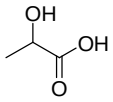
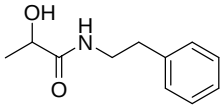
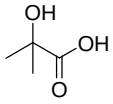
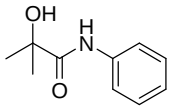
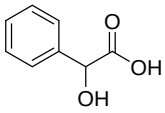
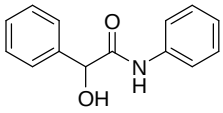
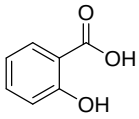
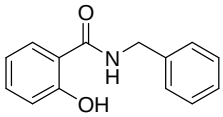
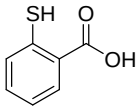
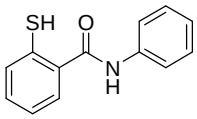


Entry	Acid	Product	Yield [a] [%]
1			80
2			83
3			81
4[b]			98
5			95
6[b]			80
7[b]			90

[a] Isolated yields.

[b] Under *o*-xylene reflux.

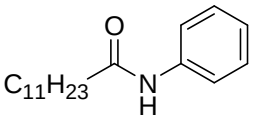
Table 2.5. Nb_2O_5–catalyzed amidation of α-hydroxy and β-thio carboxylic acids with amines.[a]

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

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

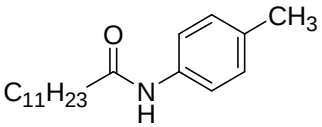
NMR and GC-MS analysis:

Dodecanoic acid phenylamide:[1]



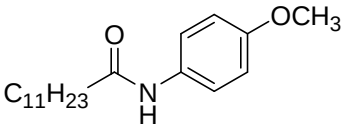
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.51 (d, *J* = 7.56 Hz, 2H), 7.41 (br s, 1H, -NH), 7.29 (t, *J*= 7.56 Hz, 2H), 7.08 (t, *J*= 7.56 Hz, 1H), 2.33 (t, *J*= 7.56 Hz, 2H), 1.73-1.68 (m, 2H), 1.36-1.25 (m, 16H), 0.87 (t, *J* = 7.56 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 171.54, 137.98, 128.90 (C×2), 124.10, 119.80 (C×2), 37.79, 31.87, 29.58(C×2), 29.46, 29.36, 29.30, 29.25, 25.63, 22.64, 14.07; GC-MS m/e 275.225.

Dodecanoic acid p-tolylamide:[2]



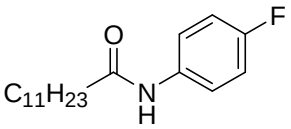
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.38 (d, *J* = 7.89 Hz, 2H), 7.24 (br s, 1H, -NH), 7.10 (d, *J*= 7.89 Hz, 2H), 2.35-2.31 (m, 2H), 2.30 (s, 3H), 1.73-1.68 (m, 2H), 1.36-1.25 (m, 16H), 0.87 (t, *J* = 6.90 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 171.39, 135.36, 133.72, 129.40 (C×2), 119.87 (C×2), 37.76, 31.87, 29.58 (C×2), 29.46, 29.36, 29.30, 29.26, 25.66, 22.66, 20.81, 14.07; GC-MS m/e 289.240.

Dodecanoic acid (4-methoxy-phenyl)-amide:[3]



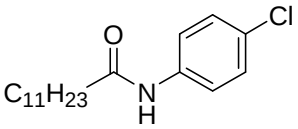
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.38 (d, *J* = 4.14 Hz, 2H), 7.05 (br s, 1H, -NH), 7.10 (d, *J*= 4.14 Hz, 2H), 3.78 (s, 3H), 2.32 (t, *J* = 7.56 Hz, 2H), 1.74-1.69 (m, 2H), 1.589-1.1587 (m, 2H), 1.38-1.20 (m, 14H), 0.87 (t, *J* = 6.84 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 171.10, 156.30, 130.87, 121.66 (C×2), 114.09 (C×2), 55.51, 37.68, 32.03, 29.58 (C×2), 29.47, 29.36, 29.31, 29.27, 25.69, 22.66, 14.11; GC-MS m/e 305.235.

Dodecanoic acid (4-fluoro-phenyl)-amide:[4]



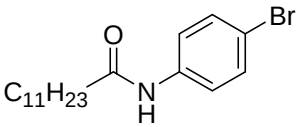
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.48-7.44 (m, 2H), 7.29 (br s, 1H, -NH), 7.01-6.98 (m, 2H), 2.33 (t, *J* = 7.56 Hz, 2H), 1.73-1.698 (m, 2H), 1.36-1.25 (m, 16H), 0.87 (t, *J* = 6.84 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 171.42, 159.27 (d, *J* = 241.84 Hz, 4-F-C), 133.89, 121.60 (d, *J* = 8.05 Hz *meta* to 4-F, C×2), 115.55 (d, *J* = 23.04 Hz, *ortho* to 4-F, C×2), 37.64, 31.87, 29.58 (C×2), 29.45, 29.35, 29.30, 29.25, 25.60, 22.66, 14.09; GC-MS m/e 293.215.

Dodecanoic acid (4-chloro-phenyl)-amide:[5]



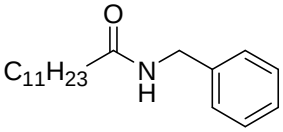
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.46 (d, *J* = 6.87 Hz, 2H), 7.34 (br s, 1H, -NH), 7.25 (d, *J*= 6.87 Hz, 2H), 2.33 (t, *J* = 7.56 Hz, 2H), 1.72-1.68 (m, 2H), 1.40-1.21 (m, 16H), 0.87 (t, *J* = 13.74 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 171.52, 136.49, 129.06, 128.93 (C×2), 120.99 (C×2), 37.73, 31.87, 29.58 (C×2), 29.45, 29.34, 29.30, 29.23, 25.54, 22.66, 14.09; GC-MS m/e 309.185.

Dodecanoic acid (4-bromo-phenyl)-amide:[6]



^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.42 (br s, 4H), 7.09 (br s, 1H, -NH), 2.34 (t, *J* = 7.56 Hz, 2H), 1.74-1.69 (m, 2H), 1.59-1.56 (m, 2H), 1.36-1.20 (m, 14H), 0.87 (t, *J* = 14.46 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 171.57, 137.00, 131.86 (C×2), 121.33 (C×2), 116.65, 37.73, 31.87, 29.57 (C×2), 29.45, 29.34, 29.30, 29.23, 25.52, 22.65, 14.09; GC-MS m/e 353.135.

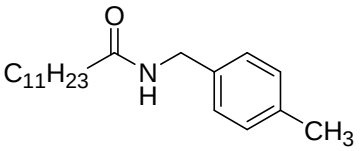
Dodecanoic acid benzylamide:[7]



^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.35-7.32 (m, 2H), 7.28-7.27 (m, 3H), 5.68 (br s, 1H, -NH), 4.42 (d, *J*= 5.46 Hz, 2H), 2.20 (t, *J*= 7.56 Hz, 2H), 1.67-1.62 (m, 2H), 1.30-1.25 (m, 16H), 0.87 (t, *J* = 6.90 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 172.84,

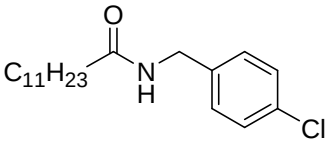
138.28, 128.70 (C×2), 127.83 (C×2), 127.50, 43.59, 36.83, 31.90, 29.59 (C×2), 29.48, 29.34, 29.32, 25.76, 22.67, 14.12; GC-MS m/e 289.240.

Dodecanoic acid 4-methyl-benzylamide:



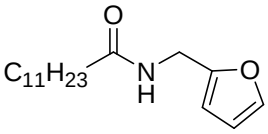
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.16 (d, *J* = 8.25 Hz, 2H), 7.13 (d, *J* = 8.25 Hz, 2H), 5.67 (br s, 1H, -NH), 4.39 (d, *J*= 5.46 Hz, 2H), 2.33 (s, 3H), 2.18 (t, *J*= 7.56 Hz, 2H), 1.66-1.61 (m, 2H), 1.30-1.20 (m, 16H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 172.89, 137.19, 135.34, 129.34 (C×2), 127.83 (C×2), 43.32, 36.83, 31.88, 29.58(C×2), 29.46, 29.31(C×2), 29.29, 25.75, 22.66, 21.07, 14.10; GC-MS m/e 303.255.

Dodecanoic acid 4-chloro-benzylamide:



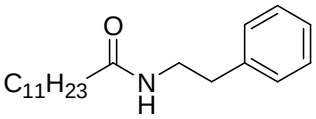
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.29 (d, *J* = 8.25 Hz, 2H), 7.20 (d, *J* = 8.25 Hz, 2H), 5.75 (br s, 1H, -NH), 4.40 (d, *J*= 6.18 Hz, 2H), 2.20 (t, *J*= 7.56 Hz, 2H), 1.67-1.62 (m, 2H), 1.30-1.25 (m, 16H), 0.88 (t, *J* = 6.60 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 173.06, 137.02, 133.28, 129.13 (C×2), 128.81 (C×2), 42.83, 36.78, 31.91, 29.60(C×2), 29.49, 29.34(C×2), 29.31, 25.73, 22.69, 14.13; GC-MS m/e 323.200.

Dodecanoic acid (furan-2-ylmethyl)-amide:



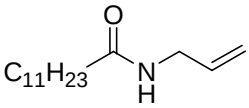
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.35 (d, *J* = 1.14 Hz, 1H), 6.32-6.31(m, 1H), 6.22 (d, *J* = 2.76 Hz, 1H), 5.81 (br s, 1H, -NH), 4.42 (d, *J*= 5.52 Hz, 2H), 2.19 (t, *J*= 7.56 Hz, 2H), 1.65-1.60 (m, 2H), 1.34-1.20 (m, 16H), 0.87 (t, *J* = 6.84 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 172.83, 151.38, 142.13, 110.43, 107.36, 36.67, 36.41, 31.88, 29.58(C×2), 29.45, 29.31(C×2), 29.24, 25.62, 22.66, 14.10; GC-MS m/e 279.220.

Dodecanoic acid phenethyl-amide:[8]



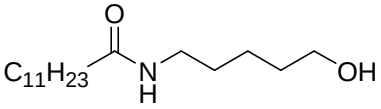
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.31 (t, *J* = 4.36 Hz, 2H), 7.23 (t, *J* = 4.36 Hz, 1H), 7.19 (d, *J*= 4.36 Hz, 2H), 5.52 (br s, 1H, -NH), 3.53-3.50 (m, 2H), 2.81 (t, *J* = 6.90 Hz, 2H), 2.11 (t, *J* = 7.50 Hz, 2H), 1.59-1.55 (m, 2H), 1.31-1.25 (m, 16H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 173.09, 138.91, 128.72(C×2), 128.57(C×2), 126.44, 40.44, 36.67, 36.81, 35.68, 31.87, 29.57, 29.45, 29.32, 29.29, 29.23, 25.72, 22.65, 14.09; GC-MS m/e 303.255.

Dodecanoic acid allylamide:



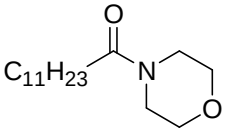
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 5.86-5.81 (m, 1H), 5.55 (br s, 1H, -NH), 5.19-5.12 (m, 2H), 3.89-3.87 (m, 2H), 2.19 (t, *J* = 7.56 Hz, 2H), 1.66-1.61 (m, 2H), 1.30-1.21 (m, 16H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 172.92, 134.36, 116.25, 41.82, 36.80, 31.87, 29.57 (C×2), 29.45, 29.32, 29.29 (C×2), 25.75, 22.65, 14.09; GC-MS m/e 239.225.

Dodecanoic acid (5-hydroxy-pentyl)-amide:



^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 5.65 (br s, 1H, -NH), 3.64 (t, *J* = 13.26 Hz, 2H), 3.27-3.24 (m, 2H), 2.15 (t, *J* = 7.56 Hz, 2H), 2.00 (br s, 1H, -OH), 1.63-1.57 (m, 4H), 1.55-1.51 (m, 2H), 1.43-1.38 (m, 2H), 1.29-1.25 (m, 16H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 173.31, 62.50, 39.26, 36.89, 32.16, 31.88, 29.59(C×2), 29.49, 29.41, 29.35, 29.31 (C×2), 25.82, 23.01, 22.66, 14.10; GC-MS m/e 285.265.

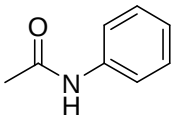
1-Morpholin-4-yl-dodecan-1-one:[9]



^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 3.66 (d, *J* = 3.48 Hz, 4H), 3.61 (s, 2H), 3.46 (s, 2H), 3.32-3.27 (m, 2H), 1.63-1.60 (m, 2H), 1.30-1.25 (m, 16H), 0.87 (t, *J* = 6.9 Hz, 3H);

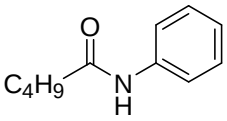
^{13}C NMR (150.92 MHz, $CDCl_3$) δ 171.81, 66.85, 66.59, 45.95, 41.75, 33.03, 31.80, 29.50 (C×2), 29.39, 29.36, 29.32, 29.22, 25.16, 22.57, 14.01; GC-MS m/e 269.235.

N-Phenyl-acetamide:[10]



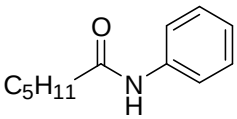
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.63 (br s, 1H, -NH), 7.50 (d, *J* = 7.80 Hz, 2H), 7.30 (t, *J* = 7.80 Hz, 2H), 7.09 (t, *J* = 7.80 Hz, 1H), 2.15 (s, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 168.55, 137.88, 128.91 (C×2), 124.25, 119.92(C×2), 24.50; GC-MS m/e 135.060.

Pentanoic acid phenylamide:[11]



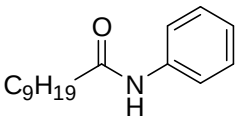
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 8.49 (br s, 1H, -NH), 7.53 (d, *J* = 7.92 Hz, 2H), 7.23 (t, *J* = 7.92 Hz, 2H), 7.05 (t, *J* = 7.92 Hz, 1H), 2.32 (t, *J* = 7.56 Hz, 2H), 1.69-1.62 (m, 2H), 1.37-1.31 (m, 2H), 0.88 (t, *J* = 6.72 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 172.35, 138.08, 129.08 (C×2), 123.94, 120.14 (C×2), 37.12, 27.69, 22.21, 13.64; GC-MS m/e 177.115.

Hexanoic acid phenylamide:[12]



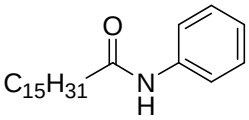
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.51 (d, *J* = 7.56 Hz, 2H), 7.41 (br s, 1H, -NH), 7.30 (t, *J* = 7.56 Hz, 2H), 7.09 (t, *J* = 7.56 Hz, 1H), 2.35-2.33 (m, 2H), 1.74-1.69 (m, 2H), 1.34-1.31 (m, 4H), 0.90 (t, *J* = 5.52 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 171.60, 137.93, 128.92 (C×2), 124.12, 119.80 (C×2), 37.73, 31.38, 25.31, 22.39, 13.90; GC-MS m/e 191.130.

Decanoic acid phenylamide:[13]



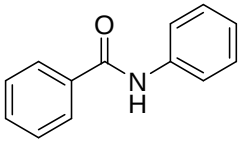
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.51 (d, *J* = 8.04 Hz, 2H), 7.31 (t, *J* = 8.04 Hz, 2H), 7.29 (br s, 1H, -NH), 7.09 (t, *J* = 8.04 Hz, 1H), 2.34 (t, *J* = 7.56 Hz, 2H), 1.74-1.69 (m, 2H), 1.37-1.20 (m, 12H), 0.87 (t, *J* = 6.90 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 171.45, 137.94, 128.95 (C×2), 124.12, 119.74 (C×2), 37.83, 31.83, 29.42, 29.36, 29.25 (C×2), 25.62, 22.64, 14.09; GC-MS m/e 247.190.

Hexadecanoic acid phenylamide:[14]



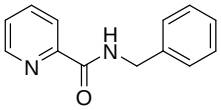
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.51 (d, *J* = 7.80 Hz, 2H), 7.31 (t, *J* = 7.80 Hz, 2H), 7.14 (br s, 1H, -NH), 7.09 (t, *J* = 7.80 Hz, 1H), 2.35 (t, *J* = 7.56 Hz, 2H), 1.74-1.70 (m, 2H), 1.31-1.25 (m, 24H), 0.87 (t, *J* = 6.90 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 171.56, 137.91, 128.96 (C×2), 124.13, 119.73 (C×2), 37.85, 31.91(C×2), 29.67 (C×2), 29.64, 29.60, 29.47, 29.34 (C×2), 29.26, 25.62, 22.68(C×2), 14.11; GC-MS m/e 331.290.

N-Phenyl-benzamide:[15]



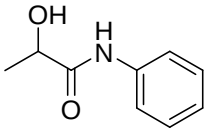
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 8.11 (d, *J* = 7.72 Hz, 1H), 7.94 (br s, 1H, -NH), 7.86 (d, *J* = 7.72 Hz, 2H), 7.63 (d, *J* = 7.72 Hz, 2H), 7.52 (t, *J* = 7.72 Hz, 1H), 7.48-7.45 (m, 2H), 7.37-7.34 (m, 1H), 7.16-7.13 (m, 1H); ^{13}C NMR (150.92 MHz, $CDCl_3$): δ 165.82, 137.87, 134.93, 133.67, 131.82, 130.15, 129.06 (C×2), 128.75, 128.44, 127.01, 124.56, 120.22; GC-MS m/e 197.085.

Pyridine-2-carboxylic acid benzylamide:[16]



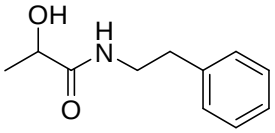
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 8.51 (d, *J* = 4.14 Hz, 1H), 8.40 (br s, 1H, -NH), 8.23 (d, *J* = 8.28 Hz, 1H), 7.87-7.82 (m, 1H), 7.41-7.40 (m, 1H), 7.37-7.35 (m, 2H), 7.34-7.32 (m, 2H), 7.27 (t, *J* = 7.56 Hz, 1H), 4.67 (d, *J* = 5.52 Hz, 1H); ^{13}C NMR (150.92 MHz, $CDCl_3$): δ 164.14, 149.75, 147,99, 138.15, 137.26, 128.61(C×2), 127.76(C×2), 127.37, 126.11, 122.25, 43.38; GC-MS m/e 212.092.

2-Hydroxy-N-phenyl-propionamide:[17]



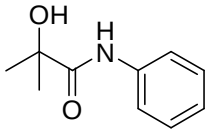
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 8.70 (br s, 1H, -NH), 7.49 (d, *J* = 7.78 Hz, 2H), 7.28 (t, *J* = 7.78 Hz, 2H), 7.10 (t, *J* = 7.78 Hz, 1H), 4.34 (br s, 1H, -OH), 4.29-4.25 (m, 1H), 1.45 (d, *J* = 6.90 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 173.38, 136.87, 128.93 (C×2), 124.65, 119.96 (C×2), 68.53, 20.88; GC-MS m/e 165.080.

2-Hydroxy-N-phenethyl-propionamide:[18]



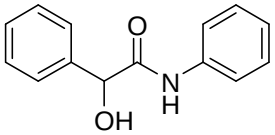
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.27 (t, *J* = 7.14 Hz, 2H), 7.19 (t, *J* = 7.14 Hz, 1H), 7.16 (d, *J* = 7.14 Hz, 2H), 7.02 (br s, 1H, -NH), 4.64 (br s, 1H, -OH), 4.14-4.11 (m, 1H), 3.50-3.40 (m, 2H), 2.81-2.74 (m, 2H), 1.33 (d, *J* = 6.84 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 175.23, 138.41, 128.52 (C×2), 128.43 (C×2), 126.37, 67.96, 40.07, 35.47, 20.92; GC-MS m/e 193.110.

2-Hydroxy-2-methyl-N-phenyl-propionamide:[19]



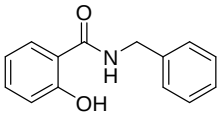
^{1}H NMR (399.78 MHz, $CDCl_3$, TMS): δ 8.77 (br s, 1H, -NH), 7.54 (d, *J* = 7.57 Hz, 2H), 7.30 (t, *J* = 7.57 Hz, 2H), 7.10 (t, *J* = 7.57 Hz, 1H), 3.17 (br s, 1H, -OH), 1.52 (br s, 6H); ^{13}C NMR (100.52 MHz, $CDCl_3$) δ 174.50, 137.40, 128.96 (C×2), 124.34, 119.62 (C×2), 74.06, 27.82; GC-MS m/e 179.095.

2-Hydroxy-2,N-diphenyl-acetamide:[20]



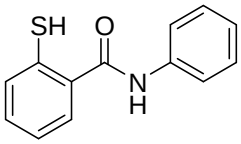
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 8.30 (br s, 1H, -NH), 7.78-7.28 (m, 10H), 5.09 (s, 1H), 3.83 (br s, 1H, -OH); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 170.12, 139.23, 137.01, 128.99 (C×2), 128.86 (C×2), 128.76, 126.80 (C×2), 124.68, 119.80 (C×2), 74.23; GC-MS m/e 227.095.

N-Benzyl-2-hydroxy-benzamide:[21]



^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 12.31 (br s, 1H, -NH), 7.40-7.38 (m, 1H), 7.37-7.36 (m, 2H), 7.35-7.34 (m, 2H), 7.33-7.31 (m, 2H), 6.98 (d, *J* = 8.28 Hz, 1H), 6.81 (t, *J* = 7.98 Hz, 1H), 6.60 (br s, 1H, -OH), 4.62 (d, *J* = 5.52 Hz, 2H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 169.81, 161.63, 137.39, 134.35(C×2), 128.91(C×2), 127.91(C×2), 125.33, 118.68 (C×2), 114.09, 43.69 ; GC-MS m/e 227.092.

2-Mercapto-N-phenyl-benzamide:[22]



^{1}H NMR (600.17 MHz, DMSO-d_6, TMS): δ 10.60 (br s, 1H, -NH), 7.82-7.77 (m, 4H), 7.56-7.54 (m, 1H), 7.44-7.38 (m, 3H), 7.18 (t, *J* = 8.22 Hz, 1H), 3.37(br s, 1H, -SH); ^{13}C NMR (150.92 MHz, DMSO-d_6): δ 166.62, 139.78, 137.37, 135.60, 132.38, 129.69 (C×2), 129.42, 127.31, 127.18, 124.92, 121.05 (C×2); GC-MS m/e 229.055.

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[4] A. Ammendola, T. Wieber, A. Wuzik, M. Lang, *U.S. Patent* 20090192192 A1, 2009.

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Chapter 3

Heterogeneous Catalysis of Nb_2O_5 for Direct Amidation of Esters

3.1. Introduction

Amides are ubiquitous and important functional groups in natural and synthetic organic compounds, such as pharmaceutically and biologically important compounds.[1] Amides can be prepared from the reaction of amines with carboxylic acids,[2] esters[3-9] or amides (transamidation).[10] Conventionally, the reaction of carboxylic acids with amines is performed via an activated carboxylic acid derivatives, such as carboxylic acid anhydrides or acyl chlorides, or using stoichiometric amount of condensation reagents,[1c] which generates large amount of unwanted co-products. Recently, atom-efficient catalytic methods for direct amidation of carboxylic acids with amines have been developed.[5] Considering the corrosive nature of carboxylic acids, direct amidation of less corrosive esters with amines can be a promising alternative method of amide production in chemical industry.

Several non-catalytic methods are reported for direct amidation of esters with amines using large amount of promoters, which suffer from low atom efficiency due to generation of stoichiometric amount of unwanted co-products.[3] To overcome these problems, homogeneous catalytic methods[4-8] have also been developed for amidation of esters with amines, but the reported methods suffer from drawbacks, including limited substrate scope, high catalyst loading (> 10 mol% with respect to substrate), and need of additives. For example, the catalytic methods with *N*-heterocyclic carbine,[4a] K_3PO_4,[4b] and organo-base,[4c,4d] tolerate only amino alcohols as amines. Although $Sb(OEt)_3$,[5a] $Zr(O\textit{t}\text{-}Bu)_4$,[5b] triazabicyclo[4.4.0]dec-5-ene,[5c] and ionic liquids[5d] are effective catalysts for the amidation of ester with various amines, these systems require high catalyst loading. Recently, sodium methoxide[6] and $La(OTf)_3$[7] have been reported as more effective catalysts for amidation of esters with various amines, though these methods are not effective for the amidation with less reactive amines such as aniline. Ru-[8a] and Ir-complexes[8b] catalyze direst amidation from esters and amines driven by hydrogen-transfer-type mechanism with liberation of H_2. These excellent homogeneous catalytic systems suffer from difficulties in catalyst reuse and catalyst/product separation, necessities of solvent and additives. A few heterogeneous catalysts (montmorillonite clay[9a,9b] and Al_2O_3[9b]) catalyzed the reaction of methyl benzoate with NH_3 to give benzamide and benzonitrile. However, the yields of the amide were low and substrate

scope of various esters and amines was not reported. Thus, it is highly desired to develop a reusable heterogeneous catalytic method for direct amidation from various esters and amines under additive-free and solvent-free conditions.

Our group has studied amide bond formation from amines and amides using heterogeneous Lewis acidic catalysts.[10] Recently, we reported the first example of direct synthesis of cyclic imines from dicarboxylic acids and amines by Nb_2O_5 as reusable Lewis acid catalyst. In the course of our continuous efforts on Lewis acid catalysis of metal oxides, we have found that Nb_2O_5 is an effective and reusable catalyst for direct amidation of esters with amines. Herein we report the first successful example of a reusable catalyst for direct synthesis of amide from various esters and amines. The method has higher activity than recent homogeneous catalytic methods.[6,7] Infrared (IR) spectroscopic and kinetic results suggest that the high catalytic efficiency of Nb_2O_5 can be due to activation of ester by Lewis acid sites of Nb_2O_5 with base-tolerant nature.

3.2. 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$^+$-1 capillary column (Frontier Laboratories Ltd.) using N_2 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 μm, Kanto Chemical Co. Ltd.). Molecular sieves 3Å were dehydrated at 100 °C in oven.

Catalyst preparation

Niobic acid ($Nb_2O_5 \cdot nH_2O$, HY-340) was kindly supplied by CBMM. Nb_2O_5 (surface area = 54 m^2 g^{-1}) was prepared by calcination of niobic acid at 500 °C for 3 h. MgO (JRC-MGO-3), TiO_2 (JRC-TIO-4), CeO_2 (JRC-CEO-3), H^+-type BEA zeolite (HBEA) with SiO_2/Al_2O_3 ratio of 25 (JRC-Z-HB25) were supplied from Catalysis Society of Japan. HZSM-5 with SiO_2/Al_2O_3 ratio of 300 was purchased from N.E. CHEMCAT. SiO_2

(Q-10, 300 m^2 g^{-1}) was supplied from Fuji Silysia Chemical Ltd. $ZrO_2 \cdot nH_2O$ was prepared by hydrolysis of zirconium oxynitrate 2-hydrate in water by aqueous NH_4OH solution, followed by filtration of precipitate, washing with water three times, and drying at 200 °C. ZrO_2, ZnO, SnO_2, MoO_3, and WO_3 were prepared by calcination (500 °C, 3 h) of the hydrous oxides: $ZrO_2 \cdot nH_2O$, $ZnO \cdot nH_2O$ (Kishida Chemical), H_2SnO_3 (Kojundo Chemical Laboratory Co., Ltd.), H_2MoO_4 (Kanto Chemical), H_2WO_4 (Kanto Chemical). γ-Al_2O_3 and θ-Al_2O_3 were 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_2 composite) were purchased from Aldrich. Fe^{3+}-exchanged K-10 (Fe^{3+}-mont)[10b] was prepared by treating the clay with aqueous solution of $FeCl_3 \cdot 6H_2O$ 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^{3+}-mont (0.46 wt%) was determined by ICP analysis. Scandium(III) trifluoromethanesulfonate, $Sc(OTf)_3$, and $La(OTf)_3$ were purchased from Tokyo Chemical Industry. $ZrCl_4$ and sodium methoxide (NaOMe) was purchased from WAKO.

In situ IR

In situ IR spectra were recorded using a JASCO FT/IR-4200 equipped with an MCT detector.[11] 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 -50 ± 5 °C. The sample was pressed into a 40 mg of self-supporting wafer (ϕ = 2 cm) and mounted into the IR cell with CaF_2 windows. Spectra were measured accumulating 15 scans at a resolution of 4 cm^{-1}. 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 -50 ± 5 °C. Then, the sample was exposed to 1.2 Pa of ethyl acetate at -50 ± 5 °C for 500 s, followed by evacuation for 500 s. Then a differential IR spectrum, with respect to the reference spectrum, was recorded at -50 ± 5 °C.

Catalytic tests. We did not use “anhydrous” solvent but used as-received solvent. The heterogeneous catalysts, stored under ambient conditions and the catalyst surface is dehydrated at 200 °C for 0.5 h under the flow of N_2 before the reaction.

Typically, methyl benzoate (1 mmol) and aniline (1.5 mmol) in 50 mg of Nb_2O_5 were added to a reaction vessel (pyrex cylinder) with a reflux condenser and a magnetic starter. The reaction mixture was heated at 140 °C under N_2 atmosphere and stirred at 400 rpm. A funnel containing 0.2 g of molecular sieves 3 Å (MS3Å) on a cotton plug is placed in the upper side of the cylinder surrounded by a reflux condenser.

After completion of the reaction, 2-propanol (4 mL) was added to the mixture, and the Nb_2O_5 catalyst was separated by centrifugation. For the catalytic tests in Table 3.1, Figure 3.2 and Figure 3.3, 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 3.3 and 3.4, the product was isolated by column chromatography. Then, the resulting product was identified using GCMS, ^{1}H-NMR, and ^{13}C-NMR analyses.

NMR and GC-MS analysis

^{1}H and ^{13}C NMR spectra were recorded using at ambient temperature by JEOL-ECX 600 operating at 600.17 and 150.92 MHz respectively with tetramethylsilane as an internal standard. All chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. All chemical shifts are reported relative to tetramethylsilane and *d*-solvent peaks (77.00 ppm, chloroform), respectively. Abbreviations used in the NMR experiments: s, singlet d, doublet; t, triplet; q, quartet; m, multiplet. Structure of the reported cyclic imides was identified by spectral comparison with literature data or analogous to literature data.

3.3. Results and discussion

Catalyst screening

We screened various catalysts, including metal oxides and conventional heterogeneous and homogeneous acid catalysts, for a model reaction of 1 mmol of methyl benzoate with 1.5 mmol of aniline at 140 °C under solvent-free conditions for 30 h. We used a reaction vessel equipped with a funnel, containing 0.2 g of molecular sieves 3 Å pellets (MS3Å) on a cotton plug, surmounted by a reflux condenser. For the model reaction, we adopted a less reactive amine (aniline), because there are no successful reports of the catalytic amidation of esters with aniline. Table 3.1 lists the yield of the corresponding amide, benzanilide. The thermal reaction in the absence of catalyst resulted in 0% yield of the amide (entry 1). We tested 16 types of simple metal oxides (entries 2-17) including

hydrates (entries 3,7). Among the oxide catalysts, Nb_2O_5 showed the highest yield (88%) of the amide. A hydrate of Nb_2O_5, niobic acid (entry 3), gave lower yield (22%) than Nb_2O_5. TiO_2 (anatase) was the secondary effective catalyst. SnO_2, Ta_2O_5, $ZrO_2 \cdot nH_2O$, ZrO_2, ZnO, and CeO_2 gave low yields of 4-15%, and other oxides such as alumina, MoO_3, SiO_2, and basic oxides (MgO, CaO) showed quite low yields of 0-2%. Well known acidic catalysts such as Fe^{3+}-exchanged montmorillonite K10 clay (Fe^{3+}-mont),[39,40] H^+-exchanged zeolites (HZSM-5 and HBEA) and commercial acidic resin catalysts (Amberlyst-15 and Nafion-SiO_2) showed low yields of 0-4%. Homogeneous Lewis acids, such as $Sc(OTf)_3$ (entry 23) and $ZrCl_4$ (entry 24) were also less effective than Nb_2O_5. $La(OTf)_3$ (entry 25), as one of the most effective homogeneous catalyst reported for this reaction,[7] gave lower yield of the amide (38%) than Nb_2O_5 under the standard conditions at 140 °C. The reaction by $La(OTf)_3$ at lower temperature (70 °C) was also ineffective.

With the most effective catalyst, Nb_2O_5, we optimized reaction conditions. The time course of the standard reaction (Figure 3.S1 in the Supporting Information) shows that the conditions without MS3Å for 30 h gave lower yield (73%) than the standard conditions. The reaction with MS3Å in the reaction mixture resulted in lower yield (33%) than the standard conditions with MS3Å inside the reflux condenser.

Performance of Nb_2O_5-catalyzed amidation

Table 3.2, the turnover number (TON) with respect to the Lewis acid site of Nb_2O_5 was 303. This value was more than two orders of magnitude higher than those of recently reported homogenous catalyst for the direct amidation[6] of esters with amines) and 118 times higher than TBD (another well established homogenous catalyst[5c]). Nb_2O_5 also shows 6.8 times larger TON than that of TiO_2. As discussed in the above section, the higher catalytic efficiency of Nb_2O_5 can be due to the higher base-tolerance and higher Lewis acid activation of the C=O bond by Nb_2O_5 than TiO_2.

We studied the reusability of Nb_2O_5 for the reaction of methylbenzoate (1 mmol) with *n*-octylamine (1.1 mmol) at standard condition. After the reaction (Table 3.3, entry 8), the catalyst was separated from the mixture by centrifugation, followed by washing with acetone, and by drying at 90 °C for 3 h and then the catalyst was pre-heated at 200 °C for 0.5h under N_2. 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 three times

without loosing its catalytic activity (Figure 3.3). These results indicate that Nb_2O_5 acts as a reusable heterogeneous catalyst for this reaction.

Then, we studied generality of the present direct amidation of esters with amines by Nb_2O_5. As listed in Table 3.3, aniline (entry 1) and its derivative with electron-withdrawing group (entry 2), benzyl amines (entries 3,4), heteroaromatic amine (entries 5,6), and aliphatic amines (entries 7-10) with various functional groups (pheny and hydroxyl groups) reacted with methyl benzoate to give the corresponding amide in good to high isolated yields (62-95%).

Table 3.4 shows the results of Nb_2O_5–catalyzed amidation of various esters with benzylamine. Methyl benzoate (entry 1) and its derivative with electron withdrawing group (entry 2), linear aliphatic esters (entries 3-5) with different functional groups (phenyl, -C=C and hydroxyl groups), and heteroaromatic esters (entries 7-10), and cyclic esters (entries 11,12) including DL-lactide (entry 12), underwent amidation with benzyl amine to give the corresponding amides in good to high isolated yields (70-95%). Summarizing the results in Table 3.3 and Table 3.4, we can conclude that the present method is generally effective for direct amidation of various esters with various amines.

Base-tolerant catalysis of Nb_2O_5 for amidation

To study acid-base interaction between the substrate (ester) and the catalyst surface, we carried out IR measurements of a model ester, ethyl acetate, adsorbed on the surface of pre-dehydrated catalysts (Nb_2O_5, γ-Al_2O_3, TiO_2) with different catalytic activity. Note that Lewis acidic nature of these catalysts were confirmed in our previous IR study of pyridine adsorption on various metal oxides.[12] To prevent the dissociation of the ethyl acetate to acetate adspecies, the ester was adsorbed at low temperature (-50 °C). As expected, the IR spectra of ethyl acetate adsorbed on these catalysts (Figure 3.1) showed no bands due to acetate ion but C=O stretching band of the molecularly adsorbed ethyl acetate. The band for Nb_2O_5 centred at lower wavenumber (1697 cm^{-1}) than those of γ-Al_2O_3 (1705 cm^{-1}) and TiO_2 (1712 cm^{-1}). Additionally, the C=O band for Nb_2O_5 had a shoulder at lower wavenumber region (1650-1660 cm^{-1}). These results indicate that the Lewis acid site (Nb^{5+} cation) of Nb_2O_5 interact more strongly with the carbonyl oxygen of the ester than those of the other Lewis acidic oxides (γ-Al_2O_3 and TiO_2). Considering this fact, the higher catalytic activity of Nb_2O_5 than the other oxides can be discussed as

follows. The strong acid-base interaction between the Nb^{5+} site and carbonyl oxygen increases electrophilicity of the C=O group, which can result in high reactivity of the adsorbed ester with a nucleophile (amine).

To study an additional reason why Nb_2O_5 shows higher catalytic activity than other Lewis acidic catalysts, we carried out kinetic study. Figure 3.1 shows the effect of aniline concentration on the initial rate of the amidation of 1 mmol methylbenzoate with 1.6, 2.0, 3.1 or 4.9 mmol aniline at 140 °C (Figure 3.2). We adopted TiO_2 and $La(OTf)_3$ as control heterogeneous and homogeneous catalysts, respectively. For TiO_2 and $La(OTf)_3$, the reaction rates decreased with increase in the concentration of aniline. The reaction orders with respect to aniline are -3.9 and -8.8 for TiO_2 and $La(OTf)_3$, respectively, indicating that these catalysts are not tolerant to basic conditions. Considering Lewis acidic nature of these catalysts, the large negative values can be explained as follows. The basic molecules, such as amines, in the solution can suppress Lewis acidity of the catalyst by hindering coordination of esters. In the case of a homogeneous Lewis acid, $La(OTf)_3$, strong basic conditions can irreversibly decompose the Lewis acid, which can result in larger negative impact of basic conditions on the catalytic activity. In contrast, the activity of Nb_2O_5 did not markedly depend on the concentration of aniline, and the reaction order with respect to aniline was -0.5. This indicates that Nb_2O_5 has higher tolerance to basic conditions than TiO_2 and $La(OTf)_3$. The base-tolerant character of the Nb^{5+} Lewis acid sites of niobium oxide is consistent with our previous report of imide synthesis.[11]

3.4. Conclusion

We have demonstrated a novel, versatile and sustainable method for direct amidation of esters with various amines using Nb_2O_5 as a reusable, inexpensive, and commercially available heterogeneous catalyst. This simple and atom-efficient method is effective for various functionalities and is applicable to challenging substrates such as anilines and α-hydroxyesters. For amidation, the active Lewis acid site of Nb_2O_5, has higher tolerance to the co-present basic molecules (anilines) than the heterogeneous Lewis acid catalysts for the amidation (anatase TiO_2) and shows higher TON than other homogeneous (NaOMe, TBD) and heterogenous (anatase TiO_2) catalyst.

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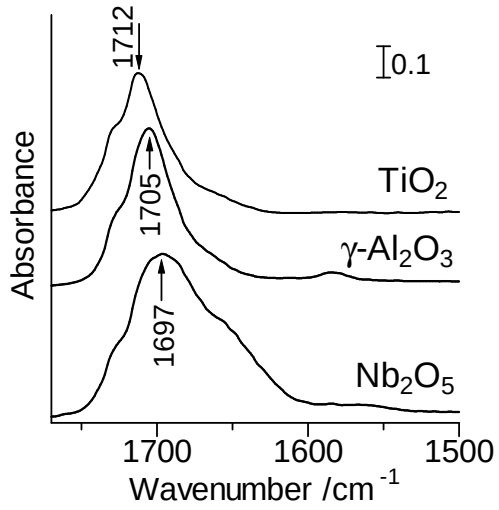


Figure 3.1. IR spectra of ethyl acetate adsorbed on Nb_2O_5, TiO_2, and γ-Al_2O_3 at - 50 ^oC.

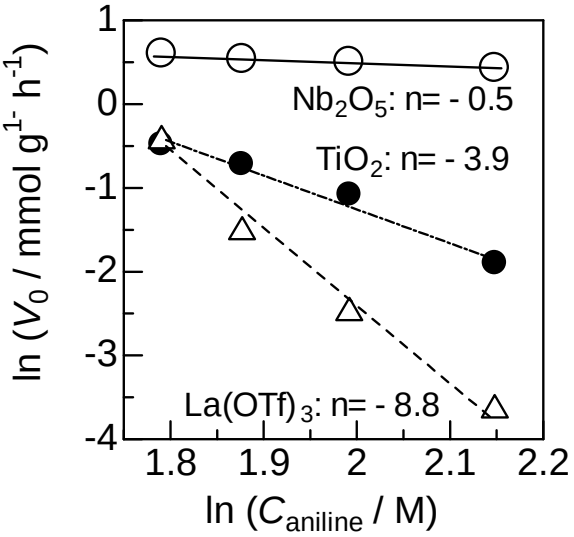


Figure 3.2. Initial rate for amidation of methylbenzoate (1 mmol) with aniline (1.6, 2.0, 3.1 or 4.9 mmol) catalyzed by Nb_2O_5 and TiO_2 as a function of the initial concentration of aniline.

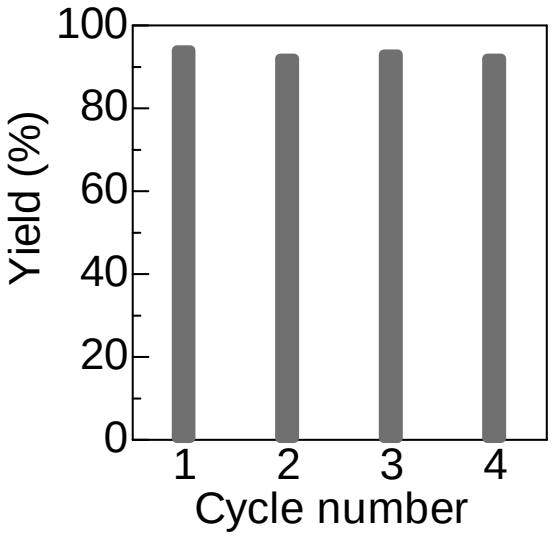


Figure 3.3. Reusability of Nb_2O_5 (50 mg) for amidation of methylbenzoate (1 mmol) with *n*-octylamine (1.1 mmol) catalyzed by Nb_2O_5 under neat condition for 30 h.

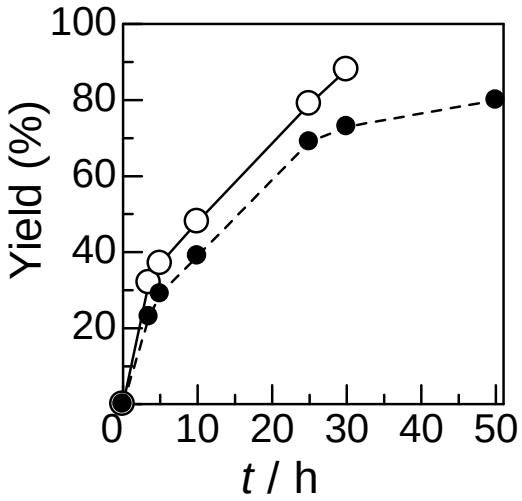
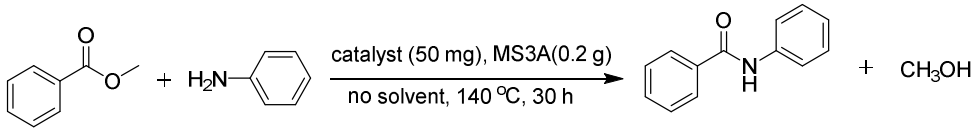


Figure 3.S1. Time-yield profiles for amidation of methylbenzoate (1 mmol) with aniline (1.5 mmol) catalyzed by Nb_2O_5 (50 mg) in presence (○) and absence (●) of molecular sieves 3 Å (MS3Å, 0.2 g) inside the reflux condenser.

Table 3.1. Catalyst screening for amidation of methyl benzoate with aniline.[a]



1mmol 1.5 mmol

Entry	Catalyst	Yield [%][b]
1	Blank	0
2	Nb_2O_5	88
3	$Nb_2O_5 \cdot nH_2O$	22
4	TiO_2	40
5	SnO_2	15
6	Ta_2O_5	5
7	$ZrO_2 \cdot nH_2O$	5
8	ZrO_2	4
9	ZnO	4
10	CeO_2	3
11	θ-Al_2O_3	2
12	γ-Al_2O_3	1
13	MoO_3	0
14	WO_3	1
15	SiO_2	1
16	CaO	0
17	MgO	0
18	Fe^{3+}-mont	0
19	HBEA	4
20	HZSM-5	0
21	Amberlyst-15	0
22	Nafion-SiO_2	1
23	$Sc(OTf)_3$	22
24	$ZrCl_4$	10
25	$La(OTf)_3$	38 (0)[c]

26	NaOMe	50

[a] Catalyst was preheated at 200 °C under N_2 for 30 min.

[b] GC yields.

[c] 70 °C

Table 3.2. Heterogeneous (upper part) and homogeneous (lower part) catalysts for the amidation of methylbenzoate (1mmol) with aniline (1.5mmol) at 140 °C under neat condition.

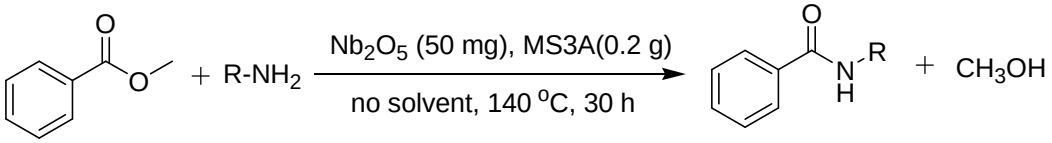
catalyst	[LA][a] /mmol g^{-1}	*t* [h]	Yield [%]	TOF / h^{-1}	TON
Nb_2O_5	0.058	30	88	10.9[b]	303[b]
TiO_2	0.083	30	40	1.6[b]	48[b]
$La(OTf)_3$	-	30	38	0.07[c]	2.2[c]
NaOMe	-	30	50	0.01[c]	0.27[c]

[a] The number of Lewis acid sites on the surface of oxides Nb_2O_5 and TiO_2 estimated by pyridine adsorption at 200 °C, which were reported in ref. [12].

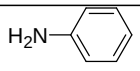
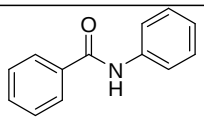
[b] Based on the number of Lewis acid sites on the oxides.

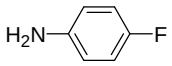
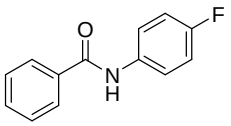
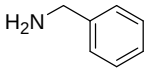
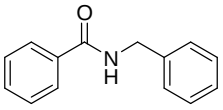
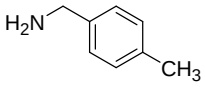
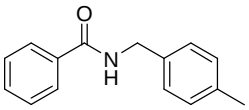
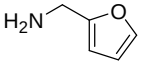
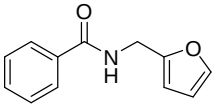
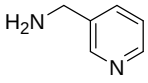
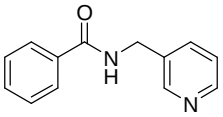
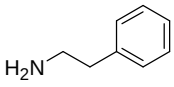
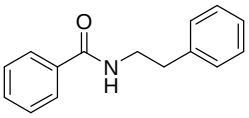
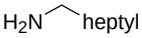
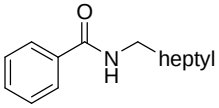
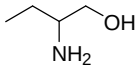
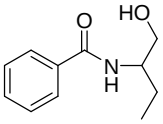
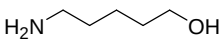
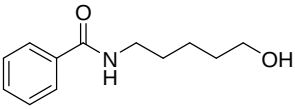
[c] Based on molecular weight.

Table 3.3. Scope of amines with methylbenzoate.[a]



1 mmol 1.5 mmol

Entry	Amine	Product	Yield [%][b]
1			86

2			62
3			95
4[c]			75
5			69
6			66
7			91
8[d]			92
9			67
10			71

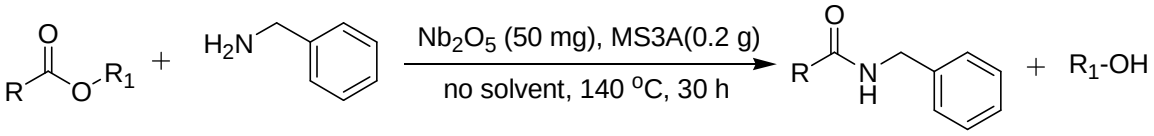
[a] Catalyst was preheated at 200 °C under N_2 for 30 min.

[b] isolated yields.

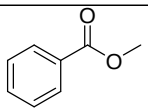
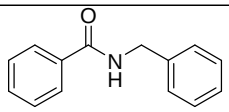
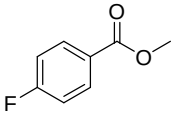
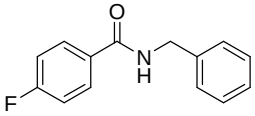
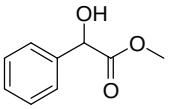
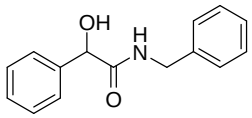
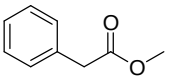
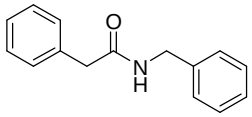
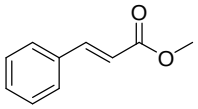
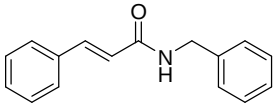
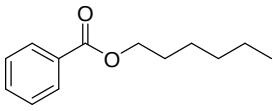
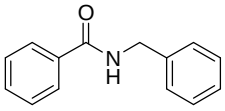
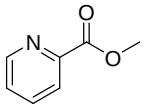
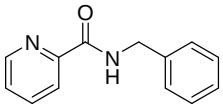
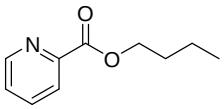
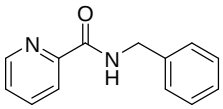
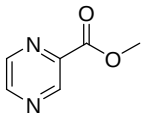
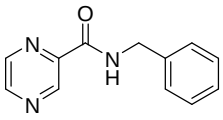
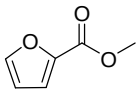
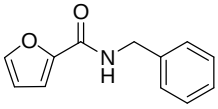
[c] 160 ˚C.

[d] 1.1 mmol n-octylamine.

Table 3.4. Scope of different esters with benzylamine.[a]



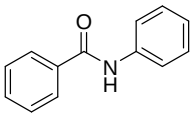
1 mmol 1.5 mmol

Entry	Ester	Product	Yield [%][b]
1			95
2			71
3			82
4[c]			80
5[c]			74
6			70
7			91
8			88
9			90
10			87

[a] Catalyst was preheated at 200 °C under N_2 for 30 min. [b] isolated yields. [c] 160 °C.

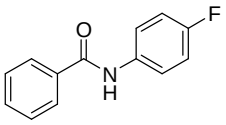
NMR and GC-MS analysis:

***N*-Phenyl-benzamide:[1]**



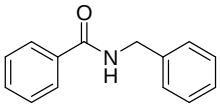
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.93 (br s, 1H, -NH), 7.85 (d, *J*= 7.62 Hz, 2H), 7.64 (d, *J*= 7.62 Hz, 2H), 7.53 (t, *J*= 7.62 Hz, 1H), 7.45 (t, *J*= 7.56 Hz, 2H), 7.35 (t, *J*= 7.56 Hz, 2H), 7.14 (t, *J* = 7.56 Hz, 1H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 165.77, 137.90, 134.96, 131.79, 129.05 (C×2), 128.74 (C×2), 127.00 (C×2), 124.54, 120.22 (C×2); GC-MS m/e 197.080.

***N*-(4-Fluoro-phenyl)-benzamide:[2]**



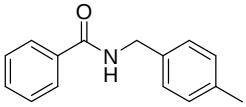
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.86-7.85 (m, 2H), 7.83 (br s, 1H, -NH), 7.60-7.58 (m, 2H), 7.56-7.54 (m, 1H), 7.50-7.47 (m, 2H), 7.08-7.04 (m, 2H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 165.73, 159.56 (d, *J* = 245.30 Hz, 4-F-C), 134.71, 133.86, 131.95, 128.82 (C×2), 126.98 (C×2), 122.09 (d, *J* = 6.91 Hz *meta* to 4-F, C×2), 115.75 (d, *J* = 23.03 Hz, *ortho* to 4-F, C×2); GC-MS m/e 215.070.

***N*-Benzyl-benzamide:[3]**



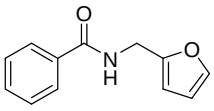
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.78 (t, *J* = 5.74 Hz, 2H), 7.51-7.49 (m, 1H), 7.43 (t, *J*= 5.74 Hz, 2H), 7.36 (d, *J*= 5.74 Hz, 4H), 7.32-7.28 (m, 1H), 6.38 (br s, 1H), 4.66 (d, *J* = 5.52 Hz, 2H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 167.31, 138.13, 134.43, 131.56, 128.85 (C×2), 128.60 (C×2), 127.94 (C×2), 127.69, 126.92 (C×2), 44.17; GC-MS m/e 211.090.

***N*-(4-Methyl-benzyl)-benzamide:[3]**



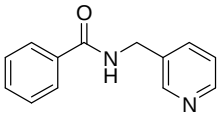
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.77 (t, *J* = 7.56 Hz, 2H), 7.49-7.47 (m, 1H), 7.41 (t, *J*= 7.56 Hz, 2H), 7.24 (d, *J*= 8.28 Hz, 2H), 7.16 (d, *J*= 7.56 Hz, 2H), 6.41 (s, 1H), 4.60 (d, *J* = 5.46 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 167.24, 137.36, 135.10, 134.45, 131.46 (C×2), 129.43 (C×2), 128.55 (C×2), 127.94 (C×2), 126.90 (C×2), 43.92, 21.08; GC-MS m/e 225.110.

_N_-Furan-2-ylmethyl-benzamide:[4]



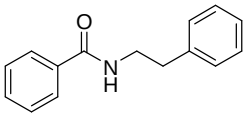
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.78 (d, *J* = 7.08 Hz, 2H), 7.49 (t, *J* = 7.08 Hz, 1H), 7.41 (t, *J*= 7.08 Hz, 2H), 7.36 (s, 1H), 6.55 (br s, 1H), 6.31 (m, 2H), 4.63 (s, 2H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 167.29, 151.10, 142.27, 134.08, 131.60, 128.54 (C×2), 126.97 (C×2), 110.49, 107.68, 36.99; GC-MS m/e 201.075.

_N_-Pyridin-3-ylmethyl-benzamide:[5]



^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 8.44-8.39 (m, 2H), 7.85 (t, *J* = 6.54 Hz, 2H), 7.80 (t, *J* = 6.54 Hz, 2H), 7.62 (d, *J*= 8.25 Hz, 1H), 7.48-7.43 (m, 1H), 7.34 (t, *J* = 8.25 Hz, 2H), 7.18-7.16 (m, 1H), 4.54 (d, *J*= 5.82 Hz, 1H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 167.75, 148.73, 148.27, 135.58, 134.21, 134.21, 133.85, 131.49, 128.34, 126.99 (C×2), 123.48, 41.16; GC-MS m/e 212.091.

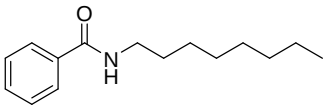
_N_-Phenethyl-benzamide:[6]



^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.69 (t, *J* = 7.76 Hz, 2H), 7.48-7.44 (m, 1H), 7.39 (t, *J*= 7.76 Hz, 2H), 7.32 (t, *J*= 7.76 Hz, 2H), 7.25-7.22 (m, 3H), 6.20 (br s, 1H),

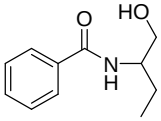
3.73-3.70 (m, 2H), 2.93 (t, *J* = 7.56 Hz, 2H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 167.45, 138.87, 134.62, 131.36, 128.79 (C×2), 128.68 (C×2), 128.52 (C×2), 126.77 (C×2), 126.57, 41.10, 35.67; GC-MS m/e 225.110.

_N_-Octyl-benzamide:[7]



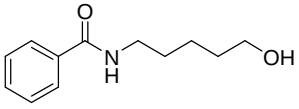
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.75 (t, *J* = 7.06 Hz, 2H), 7.48 (t, *J* = 7.06 Hz, 1H), 7.41 (t, *J* = 7.06 Hz, 2H), 6.19 (br s, 1H, -NH), 3.46-3.43 (m, 2H), 1.62-1.58 (m, 2H), 1.37-1.22 (m, 10H), 0.87 (t, *J* = 6.96 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 167.51, 134.86, 131.26, 128.50 (C×2), 126.80 (C×2), 40.11, 31.76, 29.65, 29.26, 29.18, 26.98, 22.60, 14.05; GC-MS m/e 233.170.

_N_-(1-Hydroxymethyl-propyl)-benzamide:[8]



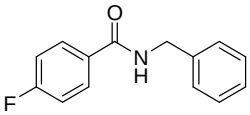
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.95 (d, *J* = 7.20 Hz, 2H), 7.48-7.44 (m, 1H), 7.40 (t, *J* = 7.20 Hz, 2H), 4.48 (t, *J*= 8.22 Hz, 2H), 4.27-4.24 (m, 1H), 4.06 (t, *J*= 7.56 Hz, 2H), 1.79-1.73 (m, 1H), 1.66-1.58 (m, 1H), 1.00 (t, *J* = 7.56 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 163.57, 131.23 (C×2), 128.27 (C×2), 128.23, 127.80, 72.13, 67.83, 28.56, 9.93; GC-MS m/e 193.110.

_N_-(5-Hydroxy-pentyl)-benzamide:[9]



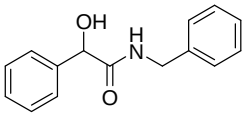
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.76 (d, *J* = 7.53 Hz, 2H), 7.44-7.40 (m, 1H), 7.35 (t, *J* = 7.53 Hz, 2H), 7.01 (s, 1H), 4.27 (s, 1H), 3.58 (t, *J*= 6.18 Hz, 2H), 3.40-3.37 (m, 2H), 1.60-1.52 (m, 4H), 1.41-1.36 (m, 2H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 167.93, 134.40, 131.20, 128.30 (C×2), 126.85 (C×2), 62.08, 39.86, 31.89, 29.07, 22.99; GC-MS m/e 207.120.

***N*-Benzyl-4-fluoro-benzamide:[10]**



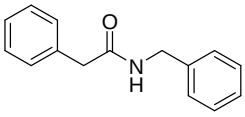
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.82-7.77 (m, 2H), 7.36-7.28 (m, 5H), 7.06 (t, *J* = 8.52 Hz, 2H), 6.63 (br s, 1H, -NH), 4.59 (t, *J* = 5.40 Hz, 2H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ δ 166.34, 164.68 (d, *J* = 251.03 Hz, 4-F-C), 138.03, 130.48, 129.29 (d, *J* = 9.20 Hz *meta* to 4-F, C×2), 128.73 (C×2), 127.82 (C×2), 127.59, 115.52 (d, *J* = 21.88 Hz, *ortho* to 4-F, C×2), 44.11; GC-MS m/e 229.090.

***N*-Benzyl-2-hydroxy-2-phenyl-acetamide:[11]**



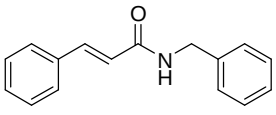
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.38-7.27 (m, 8H), 7.15 (d, *J* = 6.90 Hz, 2H), 5.68 (s, 1H), 4.99 (s, 1H), 4.41-4.33 (m, 2H), 3.91 (s, 1H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 172.21, 139.36, 137.62, 128.76 (C×2), 128.65 (C×2), 128.56 (C×2), 127.53 (C×2), 126.75 (C×2), 74.06, 43.37; GC-MS m/e 241.110.

***N*-Benzyl-2-phenyl-acetamide:[1]**



^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.34 (t, *J* = 6.84 Hz, 2H), 7.30-7.27 (m, 6H), 7.17 (d, *J* = 7.56 Hz, 2H), 5.73 (s, 1H), 4.40 (d, *J* = 6.18 Hz, 2H), 3.62 (s, 2H); ^{13}C NMR (150.92 MHz, $CDCl_3$): δ 170.85, 138.07, 134.71, 129.42 (C×2), 129.03 (C×2), 128.62 (C×2), 127.44 (C×2), 127.39 (C×2), 43.79, 43.53; GC-MS m/e 225.110.

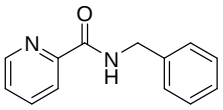
***N*-Benzyl-3-phenyl-acrylamide:[10]**



^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.65 (d, *J* = 15.12 Hz, 1H), 7.49-7.46 (m, 2H), 7.35-7.31 (m, 8H), 6.43 (d, *J* = 15.12 Hz, 1H), 6.17 (br s, 1H, -NH), 4.54 (d, *J* = 6.18 Hz,

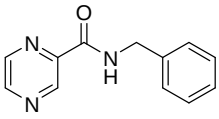
2H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 165.80, 141.33, 138.13, 134.71, 129.66, 128.76 (C×2), 128.69 (C×2), 127.86 (C×2), 127.76 (C×2), 127.51, 120.39, 43.79; GC-MS m/e 237.115.

Pyridine-2-carboxylic acid benzylamide:[12]



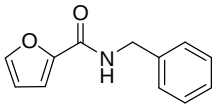
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 8.52 (d, *J* = 6.21 Hz, 1H), 8.37 (br s, 1H, -NH), 8.23 (d, *J* = 6.21 Hz, 2H), 7.86-7.83 (m, 1H), 7.42-7.40 (m, 1H), 7.37-7.33 (m, 4H), 7.28 (t, *J* = 6.54 Hz, 1H), 7.09 (t, *J* = 6.54 Hz, 1H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 164.20, 149.83, 148.05, 138.19, 137.33, 128.67 (C×2), 127.82 (C×2), 127.44, 126.16, 122.33, 43.46; GC-MS m/e 212.090.

Pyrazine-2-carboxylic acid benzylamide:[13]



^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 9.45 (d, *J* = 2.76 Hz, 1H), 8.74 (d, *J* = 2.76 Hz, 1H), 8.50 (t, *J* = 2.76 Hz, 1H), 8.15 (br s, 1H, -NH), 7.36-7.34 (m, 4H), 7.32-7.28 (m, 1H), 4.68 (d, *J* = 6.18 Hz, 2H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 162.85, 147.30, 144.52, 144.39, 142.49, 137.70, 128.77 (C×2), 127.86 (C×2), 127.66, 43.49; GC-MS m/e 213.090.

Furan-2-carboxylic acid benzylamide:[12]



^{1}H NMR (399.78 MHz, $CDCl_3$, TMS): δ 7.41-7.40 (m, 1H), 7.36-7.32 (m, 5H), 7.14-7.13 (m, 1H), 6.71 (br s, 1H, -NH), 6.49-6.48 (m, 1H), 4.60 (d, *J* = 8.94 Hz, 2H); ^{13}C NMR (100.52 MHz, $CDCl_3$): δ 158.24, 147.78, 143.86, 137.92, 128.70 (C×2), 127.84 (C×2), 127.57, 114.39, 112.13, 43.09; GC-MS m/e 201.070.

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Chapter 4

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

4.1. Introduction

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 narro 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 °C, P=~ 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.

4.2. Experimental Section

General

Commercially available organic compounds (from Tokyo Chemical Industry or Aldrich) were used without further purification. GC (Shimadzu GC-14B) and GCMS (Shimadzu GCMS-QP2010) analyses were carried out with Ultra ALLOY$^{+\ -1}$ capillary column (Frontier Laboratories Ltd.) using nitrogen 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 on Cica-Reagent silica gel 60 (70-230 mesh).

Catalyst preparation

Niobic acid ($Nb_2O_5{\cdot}nH_2O$, HY-340) was kindly supplied by CBMMI. Nb_2O_5 (surface area = 54 $m^2\ g^{-1}$) was prepared by calcination of niobic acid at 500 °C for 3 h. MgO (JRC-MGO-3), TiO_2 (JRC-TIO-4), CeO_2 (JRC-CEO-3) and H^+-type MFI zeolite (HMFI) with a SiO_2/Al_2O_3 ratio of 90 (JRC-Z5-90H) were supplied from Catalysis Society of Japan. SiO_2 (Q-10, 300 $m^2\ g^{-1}$) was supplied from Fuji Silysia Chemical Ltd. ZnO, SnO_2 , MoO_3, and WO_3 were prepared by calcination (500 °C, 3 h) of the hydrous oxides: $ZnO{\cdot}nH_2O$ (Kishida Chemical), H_2SnO_3 (Kojundo Chemical Laboratory Co., Ltd.), H_2MoO_4 (Kanto Chemical), and H_2WO_4 (Kanto Chemical). γ-Al_2O_3 was prepared by calcination of γ-AlOOH (Catapal B Alumina purchased from Sasol) for 3 h at 900 °C. $ZrO_2{\cdot}nH_2O$ was prepared by calcination (500 °C for 3 h) of $ZrO_2{\cdot}nH_2O$ prepared by hydrolysis of zirconium oxynitrate 2-hydrate in water by aqueous NH_4OH solution, followed by filtration of precipitate, washing with water three times, and drying at 100 °C.

Montmorillonite K10 clay and a sulfonic resins (Amberlyst-15® and nafion-SiO_2 composite) were purchased from Aldrich. Scandium(III) trifluoromethanesulfonate, $Sc(OTf)_3$, and ytterbium(III) trifluoromethanesulfonate, $Yb(OTf)_3$, were purchased from Tokyo Chemical Industry. $HfCl_4$ was purchased from WAKO. $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ was prepared by titrating $H_3PW_{12}O_{40}$ (Nippon Inorganic Color and Chemicals Co.) by aqueous solution of Cs_2CO_3 (0.10 mol dm^{-3}) with vigorous stirring. After centrifuging and drying the precipitate at 80 °C, the precipitate was aged at 200 °C for 3 h in air.

In situ IR

In situ IR spectra were recorded using a JASCO FT/IR-4200 equipped with an MCT detector. The 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 (ϕ = 2 cm) and mounted into the IR cell with CaF_2 windows. Spectra were measured accumulating 15 scans at a resolution of 4 cm^{-1}. After in situ pre-evacuation of the sample at 500 °C for 0.5 h, a reference spectrum of the sample disc (Nb_2O_5, γ-Al_2O_3 or TiO_2) 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.

General Procedure for the Synthesis of Cyclic Imides

Solvent we used was not “anhydrous” one but as-received one which was stored under ambient conditions. The catalysts, stored under ambient conditions, were used for catalytic reactions without any pretreatment. Hence, the surface of metal oxides is hydrated before the reaction.

Typically, succinic acid (1 mmol) and *n*-octylamine (1 mmol) in 2.5 mL hexane and 50 mg of Nb_2O_5 were added to an oven dried reaction vessel with a reflux condenser and a magnetic starter. The reaction mixture was heated to reflux under N_2 atmosphere and stirred at 400 rpm. After completion of the reaction, 2-propanol/acetone (0.5 g/0.5 g) was added to the mixture, and the Nb_2O_5 catalyst was separated by centrifugation. For the

catalyst screening test (Table 4.1) and kinetic study (Table 4.2), the reaction mixture was analyzed by GC, and yield of the products was determined based on succinic acid using *n*-dodecane as an internal standard. For the reactions in Tables 4.3-4.5 the crude product was isolated by using column chromatography except for entries 2 and 9 in Table 4.5 (recrystallization). For the products in equation 1, the product was isolated by extraction with $CHCl_3/H_2O$. Then, the resulting product was identified using GCMS, ^{1}H-NMR and ^{13}C-NMR analyses by comparison with literature data.[1-22]

For the reactions in Table 4.4, equation 1 and entries 1 and 2 in Table 4.5, we used a reaction vessel equipped with a funnel, containing 0.2 or 0.3 g of molecular sieves 4 Å (pellets) on a cotton plug, surmounted by a reflux condenser.

For the reaction of dicarboxylic acids with NH_3 (equation 1), we used a stainless autoclave with a glass inner tube (dead space of 28 cm^3). Molecular sieves 4 Å pellets (0.2 g) were placed on a cotton plug at the upper side of the glass tube. After being sealed, the reactor was flushed with NH_3 and charged with 3 bar NH_3, followed by heating at 140 °C.

NMR and GC-MS analysis

^{1}H and ^{13}C NMR spectra were recorded using at ambient temperature by JEOL-ECX 600 operating at 600.17 and 150.92 MHz respectively with tetramethylsilane as an internal standard. All chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. All chemical shifts are reported relative to tetramethylsilane and *d*-solvent peaks (77.00 ppm, chloroform), respectively. Abbreviations used in the NMR experiments: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Structure of the reported cyclic imides was identified by spectral comparison with literature data or analogous to literature data.

4.3. Results and discussion

First, the reaction between 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 4.1). Under the conditions where the reaction hardly proceeded in absence of catalyst (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 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 (3-11%). As listed in Table 4.2, 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 infrared (IR) result of the CO adsorbed on the Nb^{5+} Lewis acid site on the pre-hydrated 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 carbonyl oxygen of a carboxylic group, we measured in situ IR spectrum of acetic acid adsorbed on Nb_2O_5. The spectrum (Figure 4.S1 in the supporting information) shows the C=O stretching band of the adsorbed acetic acid ($\upsilon_{C=O}$) at lower wavenumber (1686 cm^{-1}) than that on non Lewis acidic oxide, SiO_2 (1703 cm^{-1}). This indicates the activation of carbonyl group by Nb^{5+} Lewis acid site. The Lewis acid-base interaction depends on highest occupied molecular orbital (HOMO) level of a nucleophile (base) and lowest unoccupied molecular orbital (LUMO) level of an electrophile (acid); the smaller HOMO-LUMO gap results in a more stable Lewis acid-base complex.[20c,21] Figure 4.S3 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 carbonyl oxygen 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 4.2). 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), indicating 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, indicating 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 4.2, the $\upsilon_{C=O}$ IR band of the adsorbed acetic acid on Nb_2O_5 appeared at lower wavenumber than those on TiO_2 (1695 cm^{-1}) and γ-Al_2O_3 (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 4.1, 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 4.3). 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 varieties of aliphatic and aromatic amines with various functional groups reacted with equimolar amount of succinic acid to give the *N*-substituted succinimde derivatives in good to high isolated yield. Linear-, branched- and cyclo-alkyl amines (entry 1-4), aliphatic amines with phenyl (entry 5), hydroxyl (entry 6), C≡C- (entry 7) groups, benzyl amines with electron-rich and electron-poor ring (entries 9-11), heteroaromatic amines (entries 12,13) and anilines with different substituents (CH_3O-, Cl-, SH-) were tolerant, resulting in good to high isolated yields of the *N*-aryl imides (74-98%). Next, we tested reactions of *n*-octylamine with various dicarboxylic acids, including less reactive ones (Table 4.4). Although the reaction with glutaric acid under the standard conditions gave 69% yield of the corresponding imide, the uses of 1.2 equivalent of amine and 0.2 g of 4Å molecular sieve (MS4A) pellets, placed at the upper side of the reaction vessel, resulted in 84% yield (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 acids or anhydrides (Table 4.5). Using aqueous solution of methylamine, phensuximide (an anticonvulsant) and *N*-methylmaleimide were prepared in high yields (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-quinolonephthalimide (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). 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, phthalimide in good to excellent isolated yields (71-94%).

4.4. Conclusion

We have reported that cyclic imides can be synthesized directly from various dicarboxylic acid or anhydrides with various amines, hydroxylamine or ammonia 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 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 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.

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[23] After 3 h of the standard reaction (entry 2 in Table 1), 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.

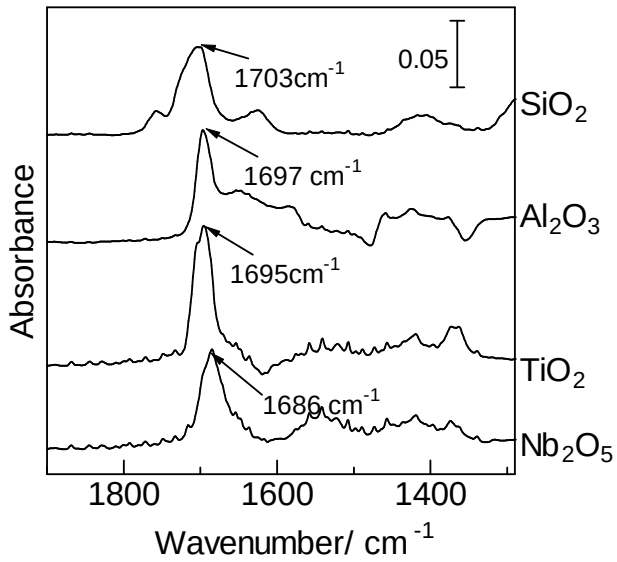
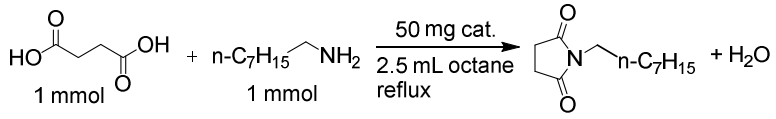


Figure 4. S1. IR spectra of acetic acid adsorbed on metal oxides at -75 ºC.



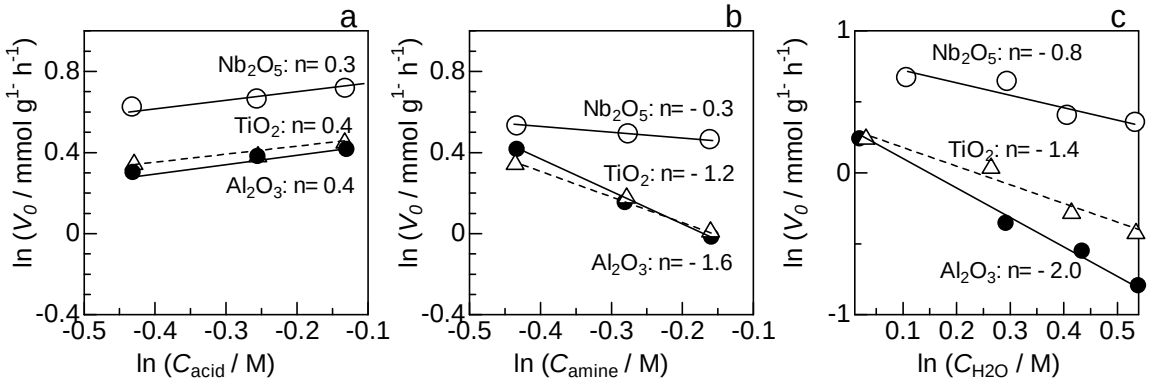
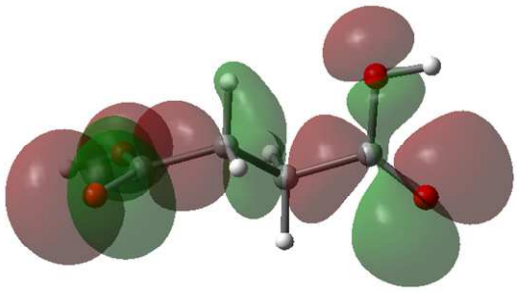
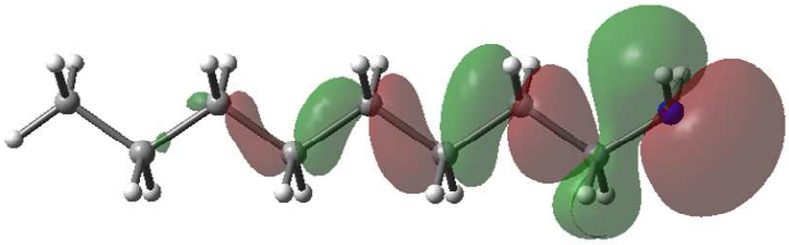


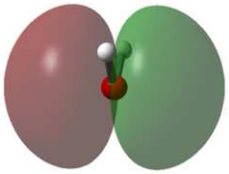
Figure 4.S2. Initial rate for cyclic imidation of succinic acid with *n*-octylamine by (○) Nb_2O_5, (Δ) TiO_2 or (●) γ-Al_2O_3 as a function of the initial concentration of (a) succinic acid (C_{acid} = 0.37 to 0.74 M), (b) *n*-octylamine (C_{amine} = 0.37 to 0.69 M) and (c) water (C_{H2O} = 1.1 to 3.4 M).



(a) succinic acid (ε = -7.45 eV)



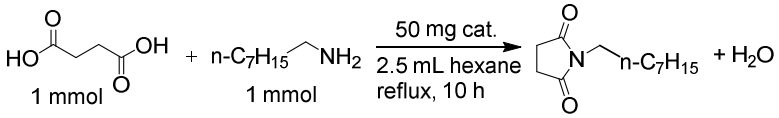
(b) *n*-octylamine (ε = -6.23 eV)



(c) H_2O (ε = -7.96 eV)

Figure 4.S3. MO distributions and energy levels of the HOMOs of (a) succinic acid, (b) *n*-octylamine, and (c) H_2O. Number in parenthesis is orbital energy in eV unit. 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), indicating that a Lewis acid can interact with nitrogen atom of *n*-octylamine in preference to carbonyl oxygen of succinic acid.

Table 4.1. Catalyst screening for synthesis of cyclic imide



Ent	Catalyst	Yield [%][a]
1	no catalyst	<1
2	Nb_2O_5	99, 99,[b] 98,[c] 95,[d]
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	3
16	$Cs_{2.5}H_{0.5}PW_1$	3
17	Amberlyst-1	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

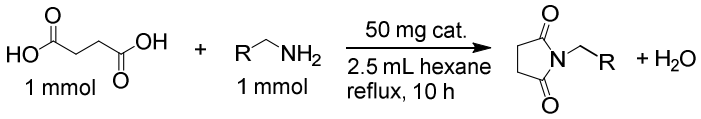
Table 4.2. Summary of IR and kinetic results.

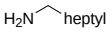
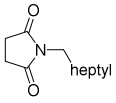
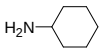
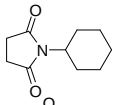
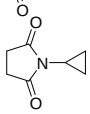
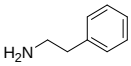
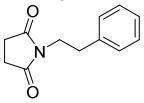
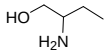
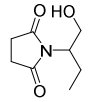
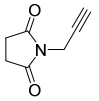
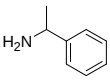
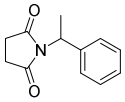
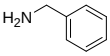
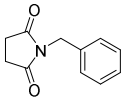
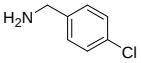
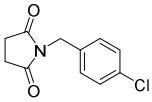
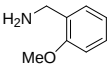
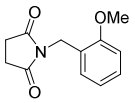
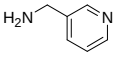
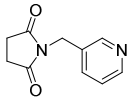
Catalyst	[LA] [a] /mmol g^{-1}	$\upsilon_{C=O}$ [b] / cm^{-1}	n_{acid} [c]	n_{amine} [d]	n_{H2O} [e]	TON[f]
Nb_2O_5	0.058	1686	0.3	-0.3	-0.8	341
TiO_2	0.083	1695	0.4	-1.2	-1.4	147
γ-Al_2O_3	0.148	1697	0.4	-1.6	-2.0	70
$Sc(OTf)_3$	2.0[g]	-	-	-	-	0.5

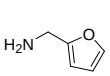
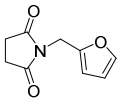
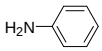
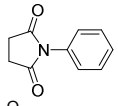
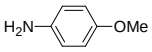
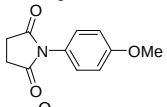
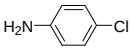
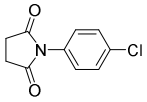
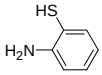
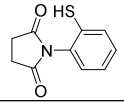
[a] The number of Lewis acid sites on the surface of oxides estimated by pyridine adsorption at 200°C (from ref [18]). [b] Position of $\upsilon_{C=O}$ IR band of adsorbed acetic acid (Figure 4.S1). [c] Reaction order with respect to succinic acid (Figure 4.S2a). [d]

Reaction order with respect to *n*-octylamine (Figure 4.S2b). [e] Reaction order with respect to water (Figure 4.S2c). [f] TON with respect to Lewis acid site. [g] Based on molecular weight of $Sc(OTf)_3$.

Table 4.3. Synthesis of succinimides from different amines by Nb_2O_5.

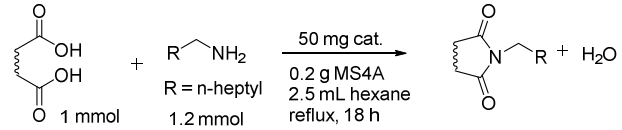


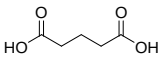
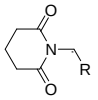
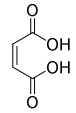
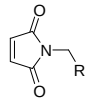
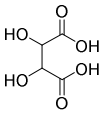
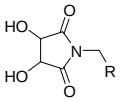
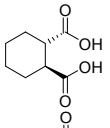
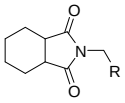
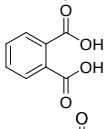
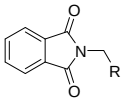
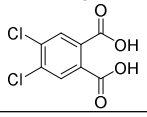
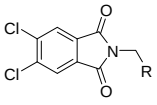
Entry	Amine	Product	Yield [%][a]
1			98
2			80
3[b]			95
4			74
5			97
6[b]			75
7[b,c]			98
8[b,c]			81
9[d]			95
10[b]			85
11[b]			92
12			90

13[b,d]			82
14			90
15			88
16			78
17			91

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

Table 4.4. Cyclic imidation of dicarboxylic acids with n-octylamine by Nb_2O_5.

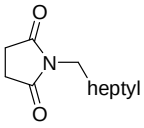


Entry	Acid	Product	Yield [%][a]
1[b]			84
2			68
3[c]			77
4[c]			91
5			98
6[b]			88

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

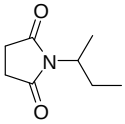
NMR and GCMS analysis:

1-Octyl-pyrrolidine-2,5-dione:[1]



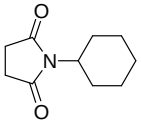
Purified by column chromatography (hexane/ethylacetate = 3:2); white solid, 98% yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 3.35 (t, *J* = 6.84 Hz, 2H), 2.57-2.52 (m, 4H), 1.42 (s, 2H), 1.15-1.11 (m, 10H), 0.74 (t, *J* = 4.14 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 177.03 (C×2), 38.54, 31.45, 28.82 (C×2), 27.87(C×2), 27.41, 26.55, 22.31, 13.77; GC-MS m/e 211.010.

1-sec-Butyl-pyrrolidine-2,5-dione:[2]



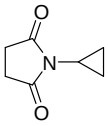
Purified by column chromatography (hexane/ethylacetate = 3:2); colorless oil, 80% yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 4.09-4.03 (m, 1H), 2.63-2.58 (m, 4H), 1.92-1.84 (m, 1H), 1.70-1.63 (m, 1H), 1.30 (d, *J* = 6.84 Hz, 3H), 0.78 (t, *J* = 7.56 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 177.39 (C×2), 49.62, 27.91 (C×2), 25.71, 17.26, 10.05; GC-MS m/e 155.095.

1-Cyclohexyl-pyrrolidine-2,5-dione:[3]



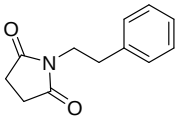
Purified by column chromatography (hexane/ethylacetate = 1:4); off white, 95% yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 3.98-3.95 (m, 1H), 2.69-2.64 (m, 4H), 2.16-2.02 (m, 2H), 2.88-2.81 (m, 2H), 1.66-1.58 (m, 3H), 1.32-1.12 (m, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 177.42 (C×2), 51.72, 28.74 (C×2), 28.07 (C×2), 25.86 (C×2), 25.01; GC-MS m/e 181.010.

1-Cyclopropyl-pyrrolidine-2,5-dione:



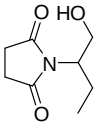
Purified by column chromatography (hexane/ethylacetate = 1:9); white solid, 72% yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 2.69-2.65 (m, 4H), 2.58-2.53 (m, 1H), 0.96-0.90 (m, 4H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 177.44 (C×2), 27.61 (C×2), 21.68, 4.31(C×2); GC-MS m/e 139.100.

1-Phenethyl-pyrrolidine-2,5-dione:[3]



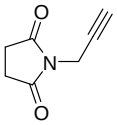
Purified by column chromatography (hexane/ethylacetate = 1:1); white solid, 97% yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.29 (t, *J* = 8.22 Hz, 2H), 7.23-7.17 (m, 3H), 3.74 (t, *J* = 6.18 Hz, 2H), 2.88 (t, *J* = 8.22 Hz, 2H), 2.68-2.64 (m, 4H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 176.98(C×2), 137.70, 128.80 (C×2), 128.70 (C×2), 126.67, 39.90, 33.49, 28.04 (C×2); GC-MS m/e 203.100.

1-(1-Hydroxymethyl-propyl)-pyrrolidine-2,5-dione:



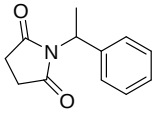
Purified by column chromatography (hexane/ethylacetate = 1:1); pale yellow solid, 75% yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 4.13-4.11 (m, 1H), 3.99-3.96 (m, 1H), 3.76-3.74 (m, 1H), 3.12-3.11 (m, 1H), 2.74-2.72 (m, 4H), 1.82-1.75 (m, 2H), 0.87 (t, *J* = 7.56 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 178.36(C×2), 62.15, 56.09, 28.00(C×2), 20.80, 10.64; GC-MS m/e 171.020.

1-Prop-2-ynyl-pyrrolidine-2,5-dione:[4]



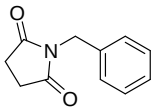
Purified by column chromatography (hexane/ethylacetate = 2:3); white solid, 98% yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 4.26 (d, *J* = 2.76 Hz, 2H), 2.78-2.74 (m, 4H), 2.20 (t, *J* = 2.76 Hz, 1H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 175.69 (C×2), 76.54, 71.24, 28.11 (C×2), 27.59; GC-MS m/e 137.100.

1-Benzyl-pyrrolidine-2,5-dione:[5]



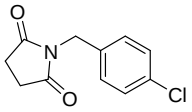
Purified by column chromatography (hexane/ethylacetate = 4:1); off white solid, 95% yield.^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.39 (d, *J* = 6.84 Hz, 2H), 7.31 (t, *J* =4.14 Hz, 2H), 7.28 (t, *J* = 1.38 Hz, 1H), 4.65 (s, 2H), 2.71-2.69 (m, 4H); ^{13}C NMR (150.92 MHz, $CDCl_3$): δ 176.82(C×2), 135.74, 128.89(C×2), 128.60(C×2), 127.93, 42.35, 28.16(C×2); GC-MS m/e 189.020.

1-(1-Phenyl-ethyl)-pyrrolidine-2,5-dione:[3]



Purified by column chromatography (hexane/ethylacetate = 1:3); colorless oil, 75% yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.44 (d, *J* = 7.56 Hz, 2H), 7.30 (t, *J* = 7.56 Hz, 2H), 7.25 (t, *J* = 7.56 Hz, 1H), 5.43-5.39 (m, 1H), 2.63-2.58 (m, 4H), 1.80 (d, *J* = 7.56 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$): δ 176.91(C×2), 139.50, 128.27(C×2), 127.66, 127.49(C×2), 50.13, 27.94(C×2), 16.39; GC-MS m/e 203.100.

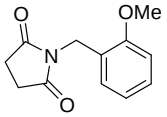
1-(4-Chloro-benzyl)-pyrrolidine-2,5-dione:[6]



Purified by column chromatography (hexane/ethylacetate = 2:3); off white solid, 85% yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.34 (d, *J* = 6.89 Hz, 2H), 7.28 (d, *J* = 6.89 Hz, 2H), 4.61 (s, 2H), 2.74-2.71 (m, 4H); ^{13}C NMR (150.92 MHz, $CDCl_3$): δ

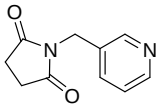
176.74(C×2), 134.17, 133.98, 130.43(C×2), 128.81 (C×2), 41.70, 28.18(C×2); GC-MS m/e 223.800.

1-(2-Methoxy-benzyl)-pyrrolidine-2,5-dione:[6]



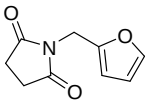
Purified by column chromatography (hexane/ethylacetate = 3:2); white solid, 92% yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.20-7.24 (m, 1H), 7.11 (d, *J* = 7.56 Hz, 1H), 6.91-6.86 (m, 2H), 4.74 (s, 2H), 3.85 (s, 3H), 2.78-2.63 (m, 4H)**;** ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 176.85(C×2), 157.09, 128.83, 128.54, 123.31, 120.30, 110.43, 55.40, 37.59, 28.19(C×2); GC-MS m/e 219.010.

1-Pyridin-3-ylmethyl-pyrrolidine-2,5-dione:[5]



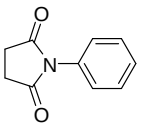
Purified by column chromatography (hexane/ethylacetate = 3:2); white solid, 90% yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 8.65 (d, *J* = 2.04 Hz, 1H), 8.54-8.53 (m, 1H), 7.74-7.71(m, 1H), 7.25-7.23(m, 1H), 4.67(s, 2H), 2.74-2.72 (m, 4H); ^{13}C NMR (150.92 MHz, $CDCl_3$): δ 176.59(C×2), 150.19, 149.35, 136.74, 131.40, 123.51, 39.86, 28.15(C×2); GC-MS m/e 190.100.

1-Furan-2-ylmethyl-pyrrolidine-2,5-dione:[7]



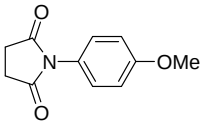
Purified by column chromatography (hexane/ethylacetate = 4:1); brown solid, 82% yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.32 (m, 1H), 6.34 (d, *J* = 2.76 Hz, 1H), 6.30-6.29 (m, 1H), 4.68 (s, 2H), 2.73 (s, 4H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 176.40 (C×2), 148.63, 142.45, 110.44, 109.12, 34.95, 28.13 (C×2); GC-MS m/e 179.020.

1-Phenyl-pyrrolidine-2,5-dione:[8]



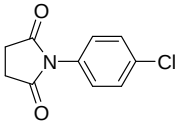
Purified by column chromatography (hexane/ethylacetate = 2:3); light pink solid, 90% yieid. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.48 (t, *J* = 7.56 Hz, 2H), 7.40 (t, *J* = 7.56 Hz, 1H), 7.28 (d, *J* = 7.56 Hz, 2H), 2.90 (s, 4H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 176.14 (C×2), 131.97, 129.20 (C×2), 128.65, 126.45 (C×2), 28.41 (C×2); GC-MS m/e 175.100.

1-(4-Methoxy-phenyl)-pyrrolidine-2,5-dione:[9]



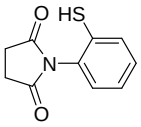
Purified by column chromatography (hexane/ethylacetate = 1:2); light pink solid, 88% yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.20-7.16 (m, 2H), 6.99-6.96 (m, 2H), 3.82 (s, 3H), 2.87-2.84 (m, 4H); ^{13}C NMR (150.92 MHz, $CDCl_3$): δ 176.47 (C×2), 159.50, 127.65 (C×2), 124.41, 114.52 (C×2), 55.46, 28.33 (C×2); GC-MS m/e 205.020.

1-(4-Chloro-phenyl)-pyrrolidine-2,5-dione:[10]



Purified by column chromatography (hexane/ethylacetate = 3:2); off white solid, 96% yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.39-7.37 (m, 2H), 7.20-7.17 (m, 2H), 2.83 (s, 4H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 175.86 (C×2), 134.45, 130.30, 129.41 (C×2), 127.65 (C×2), 28.37; GC-MS m/e 209.800.

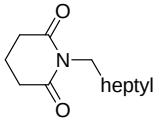
1-(2-Mercapto-phenyl)-pyrrolidine-2,5-dione:



Purified by column chromatography (hexane/dichloromethane = 2:3); off white solid, 91% yield. ^{1}H NMR (600.17 MHz, DMSO-d_6, TMS): δ 12.36 (s, S-H, 1H), 8.08 (d, *J* =

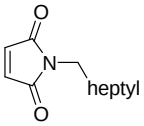
7.54 Hz, 1H), 7.96 (d, *J* = 7.54 Hz, 1H), 7.51 (t, *J* = 7.54 Hz, 1H), 7.44 (t, *J* = 7.54 Hz, 1H), 3.37 (t, *J* = 6.90 Hz, 2H), 2.87 (t, *J* = 6.90 Hz, 2H); ^{13}C NMR (150.92 MHz, DMSO-d_6, TMS): δ 173.64, 171.02, 153.12, 135.24, 126.54, 125.37, 122.68, 122.57, 32.83, 29.29; GC-MS m/e 207.110.

1-Octyl-piperidine-2,6-dione:



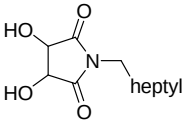
Purified by column chromatography (hexane/ethylacetate = 1:1); white solid 84 % yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 3.72 (t, *J* = 5.76 Hz, 2H), 2.63 (t, *J* = 6.18 Hz, 4H), 1.98-1.89 (m, 2H), 1.49-1.46 (m, 2H), 1.30-1.19 (m, 10H), 0.86 (t, *J* = 6.18 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$): δ 172.47 (C×2), 39.66, 32.89 (C×2), 31.77, 29.23, 29.16, 28.00, 26.93, 22.61, 17.19, 14.07; GC-MS m/e 225.175.

1-Octyl-pyrrole-2,5-dione:[11]



Purified by column chromatography (hexane/dichloromethane = 2:3); brown solid, 68 % yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 6.68 (s, 2H), 3.50 (t, *J* = 6.90 Hz, 2H), 1.59-1.54 (m, 2H), 1.27-1.24 (m, 10H), 0.86 (t, *J* = 6.90 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$): δ 170.90 (C×2), 134.01 (C×2), 37.92, 31.73, 29.13, 29.07, 28.53, 26.73, 22.60, 14.06; GC-MS m/e 209.110.

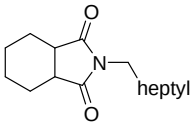
3,4-Dihydroxy-1-octyl-pyrrolidine-2,5-dione:[12]



Purified by column chromatography (hexane/dichloromethane = 2:3); white solid, 77% yield. ^{1}H NMR (600.17 MHz, DMSO-d_6, TMS): δ 6.29-6.26 (m, 2H), 4.35-4.32 (m, 2H), 1.51-1.47 (m, 2H), 1.33-1.17 (m, 12H), 0.89 (t, *J* = 6.84 Hz, 3H); ^{13}C NMR (150.92 MHz,

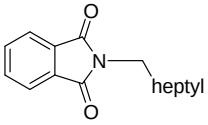
DMSO-d_6): δ 175.64 (C×2), 75.24 (C×2), 38.54, 32.12, 29.45, 29.42, 27.97, 27.06, 23.00, 14.88; GC-MS m/e 243.100.

2-Octyl-hexahydro-isoindole-1,3-dione:



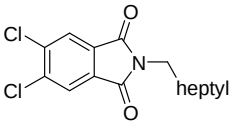
Purified by column chromatography (hexane/ethylacetate = 2:3); grey solid, 91 % yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 3.46 (t, *J* = 7.56 Hz, 2H), 2.84-2.80 (m, 2H), 1.86-1.83 (m, 2H), 1.75-1.70 (m, 2H), 1.56-1.52 (m, 2H), 1.45-1.39 (m, 2H), 1.28-1.22 (m, 12H), 0.86 (t, *J* = 4.80 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 179.86 (C×2), 39.68 (C×2), 38.52, 31.73, 29.12, 29.09, 27.71, 26.82, 23.76 (C×2), 22.60, 21.60 (C×2), 14.07; GC-MS m/e 265.205.

2-Octyl-isoindole-1,3-dione:[13]



Purified by column chromatography (hexane/dichloromethane = 2:3); white solid, 98% yield. ^{1}H NMR (600.17 MHz, DMSO-d_6, TMS): δ 7.91-7.89 (m, 2H), 7.88-7.86 (m, 2H), 3.59 (t, *J* = 6.90 Hz, 2H), 1.63-1.60 (m, 2H), 1.29-1.24 (m, 10H), 0.87 (t, *J* = 6.90 Hz, 3H); ^{13}C NMR (150.92 MHz, DMSO-d_6): δ 168.89 (C×2), 135.31 (C×2), 132.52 (C×2), 123.92 (C×2), 38.30, 32.11, 29.45, 29.42, 28.78, 27.16, 22.98, 14.86; GC-MS m/e 259.010.

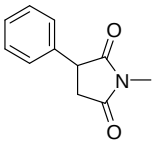
5,6-Dichloro-2-octyl-isoindole-1,3-dione:



Purified by column chromatography (hexane/ethylacetate = 2:3); off white solid 88 % yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.91 (s, 2H), 3.66 (t, *J* = 7.56 Hz, 2H), 1.67-1.62 (m, 2H), 1.30-1.20 (m, 10H), 0.87 (t, *J* = 6.90 Hz, 3H); ^{13}C NMR (150.92 MHz,

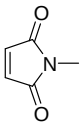
$CDCl_3$): δ 166.43 (C×2), 138.75 (C×2), 131.27 (C×2), 125.28 (C×2), 38.53, 31.73, 29.12, 29.08, 28.44, 26.80, 22.59, 14.05; GC-MS m/e 327.075.

1-Methyl-3-phenyl-pyrrolidine-2,5-dione:[5]



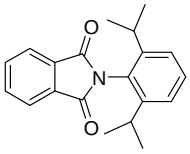
Purified by column chromatography (hexane/dichloromethane = 1:2); grey solid, 92 % yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.37 (t, *J* = 4.34 Hz, 2H), 7.31 (t, *J* = 4.34 Hz, 1H), 7.22 (d, *J* = 4.34 Hz, 2H), 4.06-4.01 (m, 1H), 3.23-3.18 (m, 1H), 3.07 (s, 3H), 2.87-2.81 (m, 1H); ^{13}C NMR (150.92 MHz, $CDCl_3$): δ 177.79, 176.21, 137.03, 129.17 (C×2), 127.93, 127.34 (C×2), 45.91, 37.09, 25.18.; GC-MS m/e 189.075.

1-Methyl-pyrrole-2,5-dione:[14]



Purified by recrystallization [after completion the reaction, 2 mL 2-propanol was added to the mixture and then the Nb_2O_5 catalyst was separated by filtration and solvent was removed using rotary evaporator, remaining solid was dissolved in minimum volume of warm hexane/ethyl acetate (1:4) mixture and slowly cooled down to room temperature to allow recrystallization; finally filttered out and washed with chilled hexane and dried under vaccum] ; white solid, 88 % yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 6.72 (s, 2H), 3.02 (s, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$): δ 170.77 (C×2), 134.14 (C×2), 23.60; GC-MS m/e 111.035.

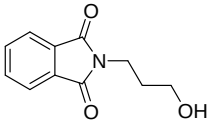
2-(2,6-Diisopropyl-phenyl)-isoindole-1,3-dione:[15]



Purified by column chromatography (hexane/dichloromethane = 1:2); white solid, 80 % yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.96-7.95 (m, 2H), 7.78-7.77(m, 2H), 7.46

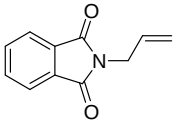
(t, *J* = 8.28 Hz, 1H), 7.30 (d, *J* = 7.56 Hz, 2H), 2.74- 2.71 (m, 2H), 1.18(d, *J* = 6.84 Hz, 12H); ^{13}C NMR (150.92 MHz, $CDCl_3$): δ 168.13 (C×2), 147.17 (C×2), 134.30 (C×2), 131.76 (C×2), 130.11, 126.78, 123.86 (C×2), 123.74 (C×2), 29.22 (C×2), 23.89 (C×4); GC-MS m/e 307.157.

2-(3-Hydroxy-propyl)-isoindole-1,3-dione:[16]



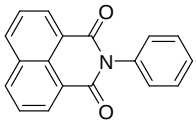
Purified by column chromatography (hexane/ethylacetate = 2:1); white solid, 92 % yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.84-7.82 (m, 2H), 7.75-7.73 (m, 2H), 3.84 (t, *J* = 6.18 Hz, 2H), 3.66 (t, *J* = 5.52 Hz, 2H), 3.19 (s, 1H), 1.90 (p, *J* = 6.18 Hz, 2H); ^{13}C NMR (150.92 MHz, $CDCl_3$): δ 168.49 (C×2), 133.79 (C×2), 131.66 (C×2), 122.99 (C×2), 58.96, 34.25, 31.07; GC-MS m/e 205.010.

2-Allyl-isoindole-1,3-dione:[17]



Purified by column chromatography (hexane/dichloromethane = 2:3); off white solid, 98 % yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.87-7.84 (m, 2H), 7.74-7.70 (m, 2H), 5.90-5.85 (m, 1H), 5.26-5.18 (m, 2H), 4.29 (d, *J* = 2.70 Hz, 2H); ^{13}C NMR (150.92 MHz, $CDCl_3$): δ 167.92 (C×2), 133.97, 132.09 (C×2), 131.50 (C×2), 123.30 (C×2), 117.73, 40.03; GC-MS m/e 187.063.

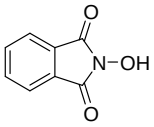
2-Phenyl-benzo[de]isoquinoline-1,3-dione:[18]



Purified by column chromatography (hexane/dichloromethane = 1:2); white solid, 97 % yield. ^{1}H NMR (600.17 MHz, DMSO-d_6, TMS): δ 8.61-8.54 (m, 4H), 7.97-7.94 (m, 2H), 7.58-7.56 (m, 2H), 7.51- 7.49 (m, 1H), 7.44 (d, *J* = 7.56 Hz, 2H); ^{13}C NMR (150.92 MHz,

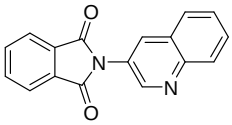
DMSO-d_6): δ 164.62 (C×2), 137.07, 136.28, 135.36 (C×2), 133.38, 132.40, 131.65 (C×2), 130.04 (C×2), 129.77, 129.67, 129.10, 128.45, 128.16, 123.52; GC-MS m/e 273.075.

2-Hydroxy-isoindole-1,3-dione:[19]



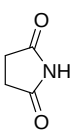
Purified by column chromatography (hexane/dichloromethane = 1:2); grey solid, 85 % yield. ^{1}H NMR (600.17 MHz, DMSO-d_6, TMS): δ 10.84 (s, 1H of -OH), 7.90 (s, 4H); ^{13}C NMR (150.92 MHz, DMSO-d_6): δ 164.96 (C×2), 135.47 (C×2), 129.67 (C×2), 123.91 (C×2); GC-MS m/e 163.025.

2-Quinolin-3-yl-isoindole-1,3-dione:[20]



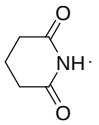
Purified by recrystallization [after completion the reaction, 2 mL 2-propanol was added to the mixture and then the Nb_2O_5 catalyst was separated by filtration and solvent was removed using rotary evaporator, remaining solid was dissolved in minimum volume of warm hexane/ethyl acetate (1:4) mixture and slowly cooled down to room temperature to allow recrystallization; finally filttered out and washed with chilled hexane and dried under vaccum] grey solid, 93 % yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 9.07 (d, *J* = 2.76 Hz, 1H), 8.32 (d, *J* = 2.76 Hz, 1H), 8.18 (d, *J* = 8.94 Hz, 1H), 8.01-7.98 (m, 2H), 7.89 (d, *J* = 8.22 Hz, 1H), 7.85-7.82 (m, 2H), 7.80-7.76 (m, 1H), 7.62-7.60 (m, 1H); ^{13}C NMR (150.92 MHz, $CDCl_3$): δ 166.93 (C×2), 147.78 (C×2), 146.64, 134.78 (C×2), 132.78, 131.55, 130.24, 129.12, 128.06, 127.62, 127.41, 125.60, 124.02(C×2); GC-MS m/e 274.075.

Pyrrolidine-2,5-dione:[21]



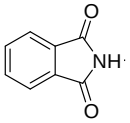
Purified by extraction (after completion the reaction, 2 mL 2-propanol was added to the mixture and then the Nb_2O_5 catalyst was separated by filtration; filtrate was quenched by H_2O and extracted with $CHCl_3$×3; combined organic layer was washed by $NaHCO_3$ solution and dried over $NaSO_4$; finally concentrated using rotary evaporatoer); white solid, 79 % yield. ^{1}H NMR (600.17 MHz, DMSO-d_6, TMS): δ 11.09 (br s, 1H), 2.62 (s, 4H); ^{13}C NMR (150.92 MHz, DMSO-d_6): δ 180.39 (C×2), 30.48 (C×2); GC-MS m/e 99.030.

Piperidine-2,6-dione[22]



Purified by extraction (after completion the reaction, 2 mL 2-propanol was added to the mixture and then the Nb_2O_5 catalyst was separated by filtration; filtrate was quenched by H_2O and extracted with $CHCl_3$×3; combined organic layer was washed by $NaHCO_3$ solution and dried over $NaSO_4$; finally concentrated using rotary evaporatoer); greenish solid, 91 % yield. ^{1}H NMR (600.17 MHz, DMSO-d_6, TMS): δ 10.66 (br s, 1H), 2.47 (t, *J* = 6.51 Hz, 4H), 1.85 (p, *J* = 6.51 Hz, 2H); ^{13}C NMR (150.92 MHz, DMSO-d_6): δ 174.58 (C×2), 32.25 (C×2), 18.08; GC-MS m/e 113.010.

Isoindole-1,3-dione:



Purified by extraction (after completion the reaction, 2 mL 2-propanol was added to the mixture and then the Nb_2O_5 catalyst was separated by filtration; filtrate was quenched by H_2O and extracted with $CHCl_3$×3; combined organic layer was washed by $NaHCO_3$ solution and dried over $NaSO_4$; finally concentrated using rotary evaporatoer); white solid, 94 % yield. ^{1}H NMR (600.17 MHz, DMSO-d_6, TMS): δ 11.37 (br s, 1H), 7.84 (s, 4H); ^{13}C NMR (150.92 MHz, DMSO-d_6): δ 170.18 (C×2), 135.26 (C×2), 133.55 (C×2), 123.87 (C×2); GC-MS m/e 147.035.

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Chapter 5

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

5.1. Introduction

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] and 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 atom-efficient synthesis of cyclic imides via dehydrogenative coupling of diols and amines catalyzed by a Ru complex[1a,14] still suffers from limited substrate scope of diols and amines.

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 the first 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]

5.2. Experimental

General

Commercially available organic compounds (from Tokyo Chemical Industry or Sigma-Aldrich) were used without further purification. GC (Shimadzu GC-2014) and GCMS (Shimadzu GCMS-QP2010) analyses were carried out with Ultra ALLOY$^+$-1 capillary column (Frontier Laboratories Ltd.) using N_2 and He as the carrier. 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 μm, Kanto Chemical Co. Ltd.).

Catalyst preparation

Niobic acid ($Nb_2O_5 \cdot nH_2O$, HY-340) was kindly supplied by CBMM. Nb_2O_5 (surface area = 54 m^2 g^{-1}) was prepared by calcination of niobic acid at 500 °C for 3 h. MgO (JRC-MGO-3), TiO_2 (JRC-TIO-6, rutile, 100 m^2 g^{-1}), CeO_2 (JRC-CEO-3), and H^+-type BEA zeolite (HBEA) with SiO_2/Al_2O_3 ratio of 25 (JRC-Z-HB25) were supplied from Catalysis Society of Japan. HZSM5 zeolite with SiO_2/Al_2O_3 ratio of 300 was purchased from N.E. CHEMCAT. SiO_2 (Q-10, 300 m^2 g^{-1}) was supplied from Fuji Silysia Chemical Ltd. ZrO_2, ZnO, SnO_2, Ta_2O_5 and CaO were prepared by calcination (500 °C, 3 h) of the hydrous oxides: $ZrO_2 \cdot nH_2O$, $ZnO \cdot nH_2O$ (Kishida Chemical), H_2SnO_3 (Kojundo Chemical Laboratory), $Ta_2O_5 \cdot nH_2O$ (Mitsuwa Chemicals) and $Ca(OH)_2$ (Kanto Chemical). γ-Al_2O_3 was prepared by calcination of γ-AlOOH (Catapal B Alumina purchased from Sasol) for 3 h at 900 °C. Montmorillonite K10 clay and sulfonic resins (Amberlyst-15® and Nafion-SiO_2 composite) were purchased from Sigma-Aldrich. Fe^{3+}-exchanged K-10 (Fe^{3+}-mont) was prepared by treating the clay with aqueous solution of $FeCl_3 \cdot 6H_2O$ 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^{3+}-mont (0.46 wt%) was determined by ICP analysis. The heterogeneous catalysts were stored under ambient conditions. Scandium(III) trifluoromethanesulfonate, $Sc(OTf)_3$ (Tokyo Chemical Industry), $HfCl_4$ (WAKO) and $ZrCl_4$ (WAKO) were purchased.

Catalytic tests

Typically, succinic anhydride (1 mmol), aniline (1 mmol) and 50 mg of Nb_2O_5 were added to a reaction vessel (pyrex cylinder) with a reflux condenser and a magnetic stirrer. Then, the cylinder was heated at 140 °C under N_2 atmosphere with stirring at 400 rpm. After completion of the reaction, 2-propanol (4 mL) was added to the mixture, and the Nb_2O_5 catalyst was separated by centrifugation. For the catalytic tests in Table 5.1, Table 5.S1, Figures 5.1, 5.2, and 5.3, the reaction mixture was analyzed by GC, and yields of the products were determined using *n*-dodecane as an internal standard. For the reactions in Schemes 5.1, 5.2, 5.3, and 5.4, the product was isolated by column chromatography, and the resulting product was identified using GCMS, ^{1}H-NMR and ^{13}C-NMR analyses.

For the reaction of succinic anhydride or phthalic anhydrides in *n*-octane (2 mL) as solvent with NH_3 (Scheme 5.4), we used a stainless autoclave with a glass inner tube (28 cm^3). Molecular sieves 4 Å pellets (0.2 g) were placed on a cotton plug at the upper side of the glass tube. After being sealed, the reactor was flushed with NH_3 and charged with 3 bar NH_3, followed by heating the lower side of the autoclave at 140 °C under refluxing of *n*-octane.

NMR and GC-MS analysis

^{1}H and ^{13}C NMR spectra were recorded using at ambient temperature by JEOL-ECX 600 and JEOL-ECX 400 operating at 600.17 and 399.78 for ^{1}H MHz; and 150.92 MHz 100.52 MHz for ^{13}C with tetramethylsilane as an internal standard. All chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. All chemical shifts are reported relative to tetramethylsilane and *d*-solvent peaks (77.00 ppm, chloroform), respectively. Abbreviations used in the NMR experiments: s, singlet; d, doublet; t, triplet; q, quartet; m,

multiplet. Structure of the reported cyclic imides was identified by spectral comparison with literature data or analogous to literature data.

5.3. Results and Discussion

As listed in Table 5.1, 20 types of the heterogeneous and homogeneous catalysts were screened for the model imidation of the equimolar amount of succinic anhydride and aniline under neat conditions at 140 °C for 15 h (Table 5.1). Note that the reaction hardly proceeded in the catalyst-free conditions (entry 1). Thus, Table 5.1 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%). With the most effective catalyst (Nb_2O_5), we tested the model reaction in the absence and the presence of different solvent (Table 5.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 5.1A 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 5.1B 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 5.2 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 5.1), the result in Figure 5.2 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 $ZrCl_4$. Next, we studied effectiveness of the Nb_2O_5-catalyzed imidation of carboxylic anhydrides with amines. Figure 5.3 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. Finally, we studied substrate scope for the present catalytic system. Scheme 5.1 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-, and 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 5.2). 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 5.3 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 5.4). 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.

5.4. Conclusion

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 atom-efficient and simple method is the first 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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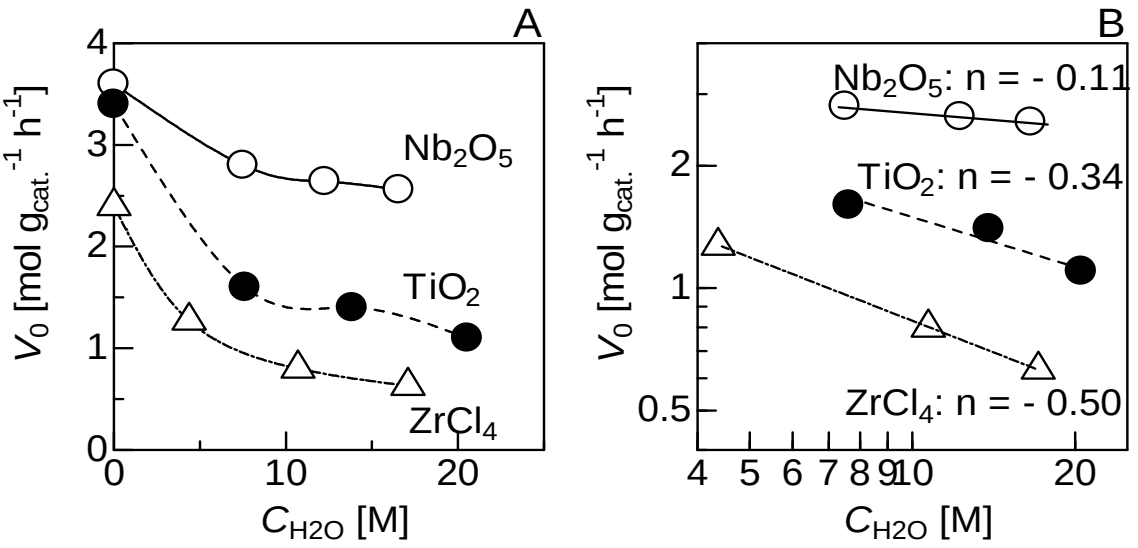


Figure 5.1. Initial rate for imidation of succinic anhydride (1 mmol) with aniline (1 mmol) in the presence of H_2O (0, 1, 3 and 5 mmol) catalyzed by 50 mg of Nb_2O_5, TiO_2 or $ZrCl_4$ as a function of the initial concentration of water.

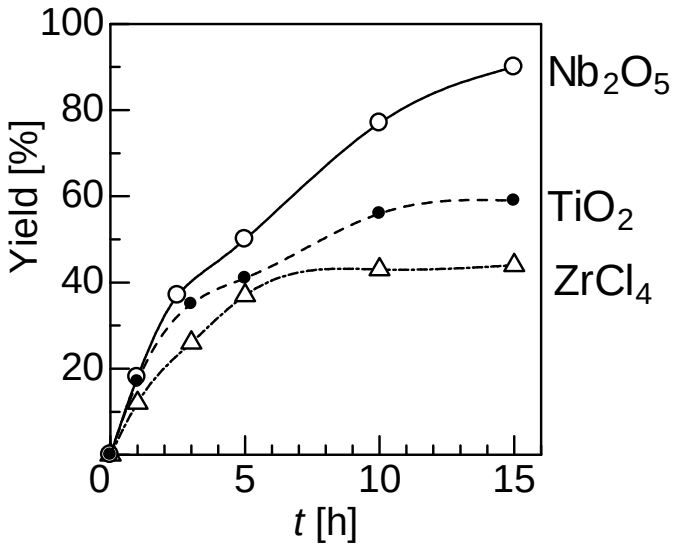


Figure 5.2. Time-yield profiles for imidation of succinic anhydride (1 mmol) with aniline (1 mmol) catalyzed by 50 mg of Nb_2O_5, TiO_2 or $ZrCl_4$.

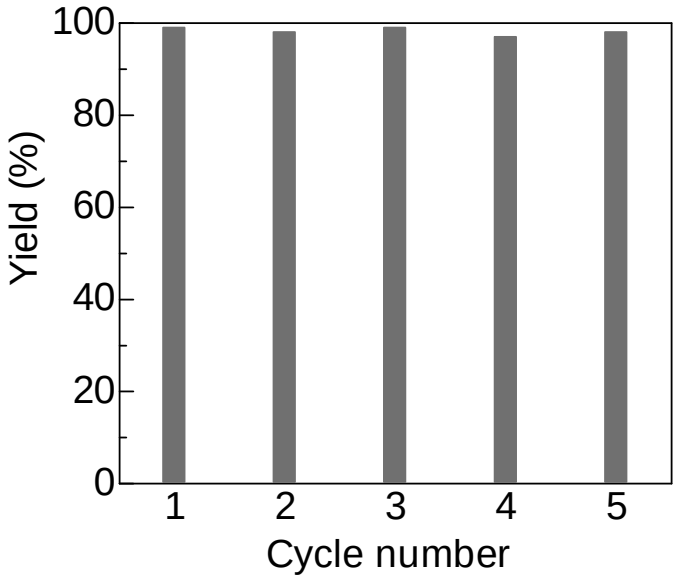
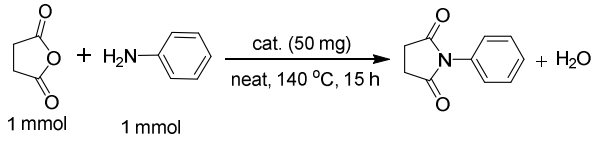


Figure 5.3. Reuse of Nb_2O_5 for imidation of succinic anhydride with *n*-octylamine under the conditions in Scheme 1.

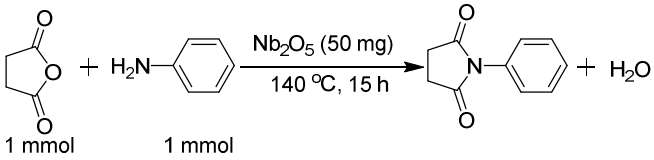
Table 5.1. Catalyst screening for synthesis of cyclic imide from anhydrides.



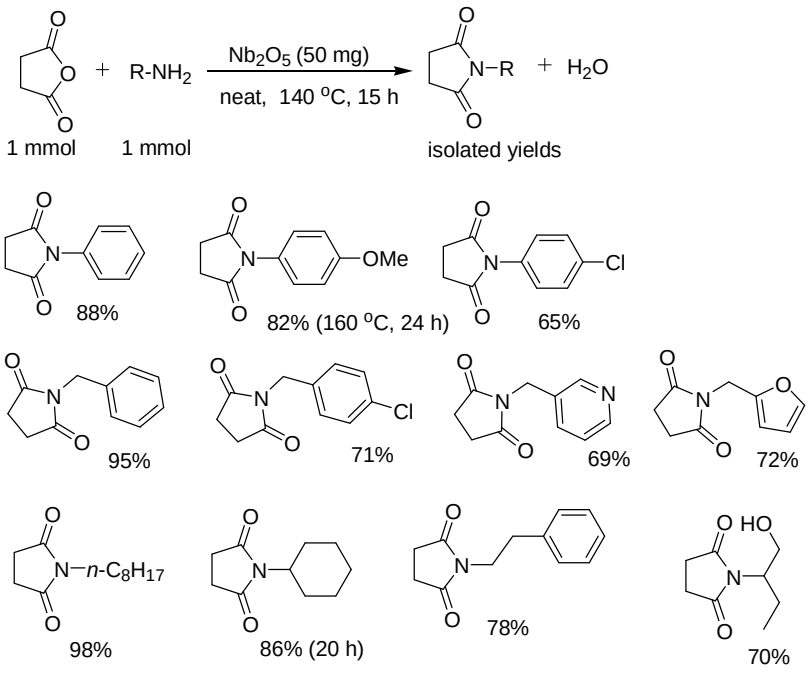
Entry	Catalyst	GC yield
1	blank	<1
2	Nb_2O_5	90
3	niobic acid	22
4	ZrO_2	65
5	TiO_2	59
6	SnO_2	45
7	Ta_2O_5	42
8	ZnO	38
9	γ-Al_2O_3	17
10	SiO_2	16
11	CeO_2	15
12	MgO	15

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

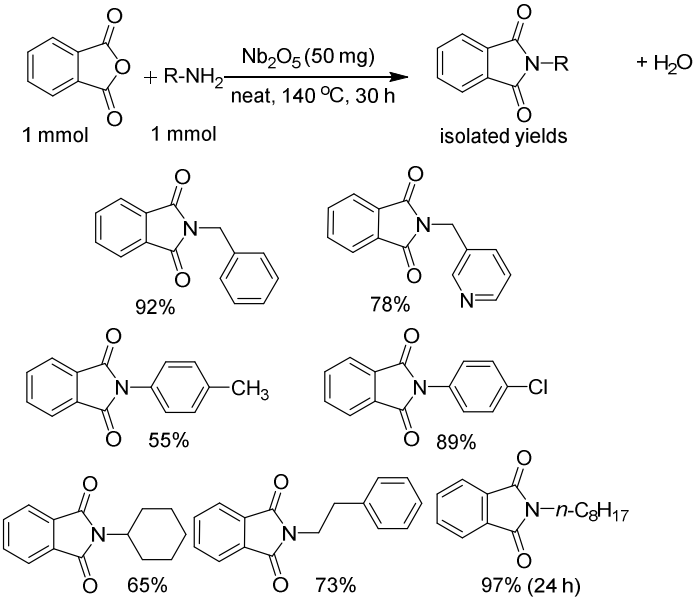
Table 5.S1. Solvent screening



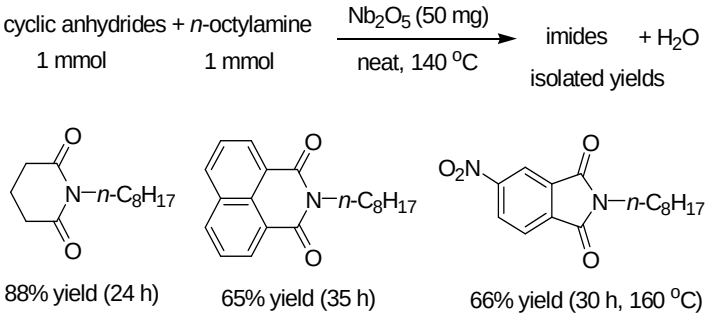
Entry	Solvent	GC yield [%] [a]
1	*n*-hexane	10
2	*n*-octane	35
3	toluene	68
4	*o*-xylene	80
5	neat	90



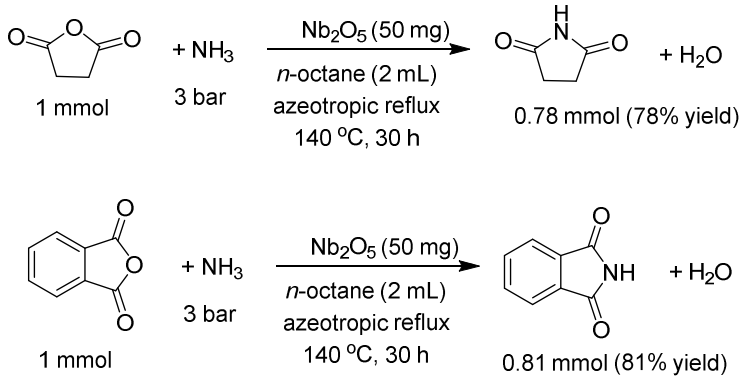
Scheme 5.1. Substrate scope for imidation of succinic anhydride with different amines.



Scheme 5.2. Synthesis of phthalimides from phthalic anhydride and various primary amines.



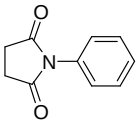
Scheme 5.3. Synthesis of *N*-substituted cyclic imide from cyclic anhydrides with *n*-octylamine.



Scheme 5.4. Imidation of cyclic anhydride and ammonia.

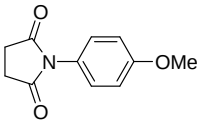
NMR and GC-MS analysis:

1-Phenyl-pyrrolidine-2,5-dione:[1]



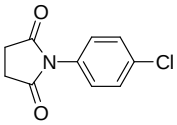
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.48 (d, *J* = 7.32 Hz, 2H), 7.40 (t, *J* = 7.32 Hz, 1H), 7.28 (t, *J* = 7.32 Hz, 2H), 2.90 (s, 4H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 176.16 (C×2), 129.26 (C×2), 128.66, 128.59, 126.44 (C×2), 28.40 (C×2); GC-MS m/e 175.180.

1-(4-Methoxy-phenyl)-pyrrolidine-2,5-dione:[1]



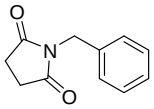
^{1}H NMR (399.78 MHz, $CDCl_3$, TMS): δ 7.19 (d, *J* = 8.93 Hz, 2H), 6.98 (d, *J* = 8.93 Hz, 2H), 3.82 (s, 3H), 2.88 (m, 4H); ^{13}C NMR (100.52 MHz, $CDCl_3$): δ 176.47 (C×2), 159.52, 127.65 (C×2), 124.42, 114.54 (C×2), 55.48, 28.35 (C×2); GC-MS m/e 205.201.

1-(4-Chloro-phenyl)-pyrrolidine-2,5-dione:[1]



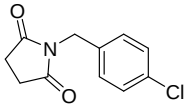
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.45 (d, *J* = 5.16 Hz, 2H), 7.25 (d, *J* = 5.16 Hz, 2H), 2.90 (s, 4H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 175.86 (C×2), 134.39, 130.24, 129.39 (C×2), 127.63 (C×2), 28.35 (C×2); GC-MS m/e 209.620.

1-(1-Phenyl-ethyl)-pyrrolidine-2,5-dione:[2]



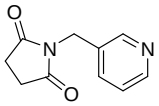
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.40-7.38 (m, 2H), 7.32-7.27 (m, 3H), 4.65 (s, 2H), 2.70 (s, 4H); ^{13}C NMR (150.92 MHz, $CDCl_3$): δ 176.85 (C×2), 135.75, 128.92 (C×2), 128.62 (C×2), 127.96, 42.38, 27.94 (C×2); GC-MS m/e 189.210.

1-(4-Chloro-benzyl)-pyrrolidine-2,5-dione:[3]



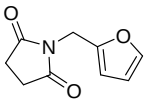
^{1}H NMR (399.78 MHz, $CDCl_3$, TMS: δ 7.33 (d, *J* = 7.69 Hz, 2H), 7.27 (d, *J* = 7.69 Hz, 2H), 4.61 (s, 2H), 2.71 (s, 4H); ^{13}C NMR (100.52 MHz, $CDCl_3$): δ 176.73 (C×2), 134.17, 133.96, 130.43 (C×2), 128.80 (C×2), 41.70, 28.18 (C×2); GC-MS m/e 223.650.

1-Pyridin-3-ylmethyl-pyrrolidine-2,5-dione:[2]



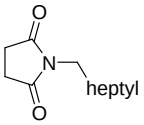
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS: δ 8.65 (d, *J* = 2.16 Hz, 1H), 8.54-8.53 (m, 1H), 7.75-7.71 (m, 1H), 7.25-7.24 (m, 1H), 4.67 (s, 2H), 2.73 (s, 4H); ^{13}C NMR (150.92 MHz, $CDCl_3$): δ 176.59 (C×2), 150.11, 149.28, 136.72, 131.37, 123.48, 39.81, 28.12 (C×2); GC-MS m/e 190.195.

1-Furan-2-ylmethyl-pyrrolidine-2,5-dione:[1]



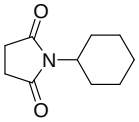
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.32 (d, *J* = 3.66 Hz, 1H), 6.32 (d, *J* = 3.66 Hz, 1H), 6.29 (t, *J* = 3.66 Hz, 1H), 4.65 (s, 2H), 2.71 (s, 4H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 176.37 (C×2), 148.50, 142.19, 110.25, 108.84, 34.70, 27.93 (C×2); GC-MS m/e 179.170.

1-Octyl-pyrrolidine-2,5-dione:[1]



^{1}H NMR (399.78 MHz, $CDCl_3$, TMS): δ 3.35 (t, *J* = 7.31 Hz, 2H), 2.57 (s, 4H), 1.45-1.40 (s, 2H), 1.18-1.13 (m, 10H), 0.74 (t, *J* = 6.87 Hz, 3H); ^{13}C NMR (100.52 MHz, $CDCl_3$) δ 177.04 (C×2), 38.52, 31.44, 28.81 (C×2), 27.85 (C×2), 27.40, 26.55, 22.30, 13.76; GC-MS m/e 211.300.

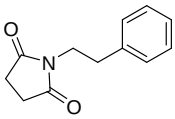
1-Cyclohexyl-pyrrolidine-2,5-dione:[2]



^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 3.99-3.94 (m, 1H), 2.65 (s, 4H), 2.15-2.10 (m, 2H), 1.83-1.81 (m, 2H), 1.66-1.56 (m, 2H), 1.32-1.20 (m, 4H); ^{13}C NMR (150.92 MHz,

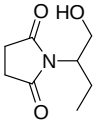
$CDCl_3$) δ 177.34 (C×2), 51.43, 28.47 (C×2), 27.82 (C×2), 25.61 (C×2), 24.77; GC-MS m/e 181.230

1-Phenethyl-pyrrolidine-2,5-dione:[2]



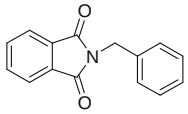
^{1}H NMR (399.78 MHz, $CDCl_3$, TMS): δ 7.31-7.27 (m, 2H), 7.23-7.20 (m, 3H), 3.76-3.72 (m, 2H), 2.90-2.86 (m, 2H), 2.65 (s, 4H); ^{13}C NMR (100.52 MHz, $CDCl_3$) δ 176.96 (C×2), 137.70, 128.78 (C×2), 128.49 (C×2), 126.65, 39.88, 33.49, 28.03 (C×2); GC-MS m/e 203.230.

1-(1-Hydroxymethyl-propyl)-pyrrolidine-2,5-dione:[1]



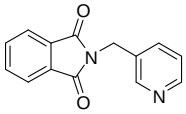
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 4.16-4.11 (m, 1H), 4.01-3.97 (m, 1H), 3.78-3.75 (m, 1H), 2.74-2.73 (m, 4H), 1.86-1.75 (m, 2H), 1.21-1.20 (m, 1H) 0.91-0.86 (m, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 178.36 (C×2), 62.25, 56.09, 28.02 (C×2), 20.83, 10.66; GC-MS m/e 171.190.

2-Benzyl-isoindole-1,3-dione:[4]



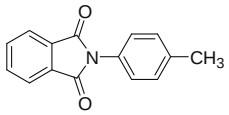
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.83-7.82 (m, 2H), 7.68-7.67 (m, 2H), 7.58-7.56 (m, 2H), 7.42 (d, *J* = 7.56 Hz, 2H), 7.30 (t, *J* = 7.56 Hz, 2H), 7.25 (d, *J* = 6.84 Hz, 1H), 4.84 (m, 2H); ^{13}C NMR (150.92 MHz, $CDCl_3$): δ 165.95 (C×2), 136.28, 133.90 (C×2), 132.01 (C×2), 128.60 (C×2), 128.53 (C×2), 127.74, 123.25 (C×2), 41.51; GC-MS m/e 237.250.

2-Pyridin-3-ylmethyl-isoindole-1,3-dione:[2]



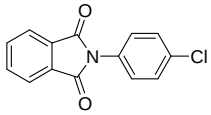
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 8.71 (d, *J* = 1.80 Hz, 1H), 8.53-8.52 (m, 1H), 7.85-7.84 (m, 2H), 7.78-7.76 (m, 1H), 7.73-7.772 (m, 2H), 7.25-7.24 (m, 1H), 4.86 (s, 2H); ^{13}C NMR (150.92 MHz, $CDCl_3$): δ 167.73 (C×2), 149.98, 149.19, 136.36 (C×2), 134.12 (C×2), 131.91, 131.84, 123.48 (C×2), 123.42, 39.01; GC-MS m/e 238.240.

2-p-Tolyl-isoindole-1,3-dione:[5]



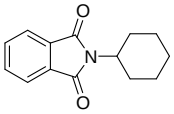
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.95-7.94 (m, 2H), 7.79-7.77 (m, 2H), 7.31 (s, 4H), 2.41 (s, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$): δ 167.43 (C×2), 138.18, 134.30 (C×2), 131.78 (C×2), 129.76 (C×2), 128.91, 126.44 (C×2), 123.67 (C×2), 21.20; GC-MS m/e 237.250.

2-(4-Chloro-phenyl)-isoindole-1,3-dione:[6]



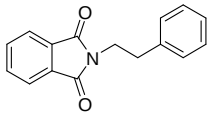
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.96-7.95 (m, 2H), 7.81-7.80 (m, 2H), 7.48 (d, *J* = 8.94 Hz, 2H), 7.41 (d, *J* = 8.22 Hz, 2H); ^{13}C NMR (150.92 MHz, $CDCl_3$): δ 166.96 (C×2), 134.55 (C×2), 133.78, 131.56 (C×2), 130.14, 129.28 (C×2), 127.64 (C×2), 123.83 (C×2); GC-MS m/e 257.670.

2-Cyclohexyl-isoindole-1,3-dione:[5]



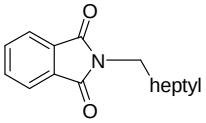
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.82-7.80 (m, 2H), 7.70-7.68 (m, 2H), 4.11-4.10 (m, 1H), 2.22-2.19 (m, 2H), 1.88-1.85 (m, 2H), 1.74-1.71 (m, 3H), 1.38-1.28 (m, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$): δ 168.38 (C×2), 133.66 (C×2), 131.99 (C×2), 122.92 (C×2), 50.80, 29.79 (C×2), 25.94 (C×2), 25.04; GC-MS m/e 229.270.

2-Phenethyl-isoindole-1,3-dione:[7]



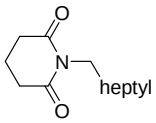
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.82-7.81 (m, 2H), 7.69-7.68 (m, 2H), 7.29-7.24 (m, 4H), 7.20 (t, *J* = 6.90 Hz, 1H), 3.92 (t, *J* = 7.56 Hz, 2H), 2.98 (t, *J* = 8.28 Hz, 2H); ^{13}C NMR (150.92 MHz, $CDCl_3$): δ 168.06 (C×2), 137.91, 133.81 (C×2), 131.95, 128.76 (C×2), 128.47 (C×2), 126.55 (C×2), 123.12 (C×2), 39.18, 34.52; GC-MS m/e 251.270.

2-Octyl-isoindole-1,3-dione:[8]



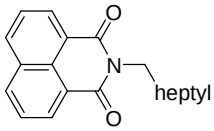
^{1}H NMR (399.78 MHz, $CDCl_3$, TMS): δ 7.85-7.80 (m, 2H), 7.73-7.68 (m, 2H), 3.67 (t, *J* = 7.35 Hz, 2H), 1.71-1.63 (m, 2H), 1.38-1.23 (m, 10H), 0.87 (t, *J* = 4.59 Hz, 3H); ^{13}C NMR (100.52 MHz, $CDCl_3$): δ 168.13 (C×2), 133.57 (C×2), 131.96 (C×2), 122.87 (C×2), 37.81, 31.55, 28.94, 28.39, 26.65, 25.14, 22.40, 13.85; GC-MS m/e 259.340.

1-Octyl-piperidine-2,6-dione:[1]



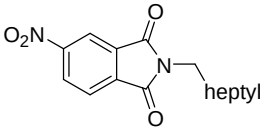
^{1}H NMR (399.78 MHz, $CDCl_3$, TMS): δ 3.73 (t, *J* = 7.56 Hz, 2H), 2.64 (t, *J* = 6.90 Hz, 4H), 1.95-1.91 (m, 2H), 1.50-1.47 (m, 2H), 1.31-1.23 (m, 10H), 0.87 (t, *J* = 7.56 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$): δ 172.35 (C×2), 39.51, 32.76 (C×2), 31.65, 31.44, 29.11, 29.04, 26.81, 22.49, 17.08, 13.94; GC-MS m/e 225.320.

2-Octyl-benzo[de]isoquinoline-1,3-dione:[9]



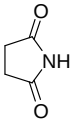
^{1}H NMR (399.78 MHz, $CDCl_3$, TMS): δ 8.49-8.43 (m, 2H), 8.11-8.05 (m, 2H), 7.68-7.62 (m, 2H), 4.11 (t, *J* = 7.79 Hz, 2H), 1.75-1.67 (m, 2H), 1.44-1.22 (m, 10H), 0.87 (t, *J* = 3.67 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$): δ 163.65 (C×2), 133.39 (C×2), 131.13, 130.70 (C×2), 127.63, 126.54 (C×2), 122.32 (C×2), 40.20, 31.60, 29.13, 29.03, 27.90, 26.96, 22.43, 13.90; GC-MS m/e 309.402.

5-Nitro-2-octyl-isoindole-1,3-dione: [10]



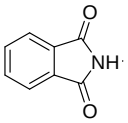
^{1}H NMR (399.78 MHz, $CDCl_3$, TMS): δ 8.66 (d, *J* = 1.56 Hz, 1H), 8.61-8.59 (m, 1H), 8.04 (d, *J* = 7.31 Hz, 1H), 3.73 (t, *J* = 7.31 Hz, 2H), 1.72-1.65 (m, 2H), 1.33-1.22 (m, 10H), 0.87 (t, *J* = 6.43 Hz, 3H); ^{13}C NMR (100.52 MHz, $CDCl_3$) δ 166.25, 165.96, 151.68, 136.56, 133.53, 129.14, 124.33, 118.58, 38.78, 31.71, 29.09, 29.06, 28.41, 26.80, 22.58, 14.04; GC-MS m/e 304.340.

Pyrrolidine-2,5-dione:[1]



^{1}H NMR (600.17 MHz, DMSO-d_6, TMS): δ 11.00 (br s, 1H), 2.60 (s, 4H); ^{13}C NMR (150.92 MHz, DMSO-d_6): δ 180.41 (C×2), 30.46 (C×2); GC-MS m/e 99.080.

Isoindole-1,3-dione:[1]



^{1}H NMR (600.17 MHz, DMSO-d_6, TMS): δ 11.38 (br s, 1H), 7.86 (s, 4H); ^{13}C NMR (150.92 MHz, DMSO-d_6): δ 170.20 (C×2), 135.28 (C×2), 133.55 (C×2), 123.90 (C×2); GC-MS m/e 147.130.

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Chapter 6

Fe^{3+}-exchanged clay catalyzed transamidation of amides with amines under solvent-free condition

6.1. Introduction

The amide bond is a fundamental component of biological and synthetic polymers (i.e., proteins and nylons) and constitutes an important functional group in organic chemistry.[1] The most common way to make an amide bond is based on the coupling of activated carboxylic acid derivatives and amines, but there are limitations such as the lability of the activated acid derivatives and tedious procedures.[2,3] Among various catalytic methods of amide bond formation,[4] transamidation of amides with amines is potentially an attractive alternative method of the direct amidebond formation. Due to the high stability of carboxyamide groups, thermal transamidation requires high temperatures (>180^{o}C) or microwave heating, which leads to a limited substrate scope.[5,6] Enzyme- mediated tr ansformation is also known, but it has limited scope and requires highly evolved enzymes as well as long reaction time.[7] To overcome these detriments new homogeneous[8–17] and heterogeneous[18–20] catalysts for transamidation are recently reported. Stahl[8,9] and Mayers[10] reported pioneering works and showed possibility of transamidation under mild conditions, but the methods suffer from low yield or use of excess amount of activation reagents. Recently, Beller (copper acetate)[11] and Williams[12,13] (hydroxylamine hydrochloride and zirconocene dichloride) have developed effective homogeneous catalysts for transamidation. However, these homogeneous catalysts suffer from difficulty in catalyst recycle, necessity of the solvent, and low turnover number (TON). Our group reported the first successful example of heterogeneous catalysis for transamidation under solvent-free conditions using CeO_2 as reusable catalyst.[19] More recently, Akamanchi et al. reported sulfated tungstate as a solid catalyst, but it required solvent and the reusability was not studied.[20]

As part of our continuing interests in the heterogeneous catalysis for transamidation[19] and heterogeneous Lewis acid catalysis,[21,22] we report herein the efficient transamidation of amides with amines under solvent-free condition using Fe^{3+}-exchanged montmorillonite (Fe-mont). We will show that Fe-mont as a cheap and reusable heterogeneous catalyst exhibits higher activity and wider substrate scope than CeO_2.

6.2. Experimental

General

The GC (Shimadzu GC-14B) and GCMS (Shimazu GCMS-QP2010) analyses were carried out with Ultra ALLOY capillary column UA^{+}-5 (Frontier Laboratories Ltd.) using nitrogen as the carrier gas. Commercially available organic compounds (from Tokyo Chemical Industry or Kanto Chemical) were used without further purification.

Catalyst

Montmorillonite K-10 clay was purchased from Sigma–Aldrich. The basal (001) reflection was not observed in the XRD pattern of K-10, which confirms the delamination of the layered structure of the montmorillonite. Fe^{3+}-exchanged K-10 (Fe^{3+}-mont) was prepared by treating the support with aqueous solution of $FeCl_3 \cdot 6H_2O$ 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-mont (0.46 wt%) was determined by ICP analysis. CeO_2 (JRC-CEO3) was supplied from the Catalysis Society of Japan. SiO_2 (Q-10) was supplied from Fuji Silysia Chemical Ltd. Fe_2O_3 was purchased from Wako Pure Chemical Industries.

Typical procedures of catalytic reactions

A typical procedure for transamidation of benzamide with *n*-octylamine is as follows. Fe-mont (121.4 mg, 1.0 mol% Fe-mont with respect to benzamide) was added to the mixture of benzamide (1.0 mmol), *n*-octylamine (1.1 mmol) in a reaction vessel equipped with a condenser under N_2. The resulting mixture was vigorously stirred at 140 °C. The reaction mixture was analyzed by GC. Conversion and yield of the products were determined based on benzamide and *n*-octyl benzamide using dodecane as an internal standard. After completion of the reaction, acetone (2 g) was added to the mixture, and then the Fe-mont catalyst was separated by centrifugation. The crude product was isolated by column chromatography and the resulting product was identified by GCMS, ^{1}H-NMR and ^{13}C-NMR analyses.

In-situ IR

In situ IR spectra were recorded at 160 °C using a JASCO FT/IR-4200 equipped with a quartz IR cell connected to a conventional flow reaction system. The sample was pressed into a 30 mg of self-supporting wafer and mounted into the quartz IR cell with CaF_2 windows. Spectra were measured accumulating 10 scans at a resolution 4 cm^{-1} in a flow of He. A reference spectrum of the catalyst wafer under He was subtracted from each spectrum. For the introduction of acetamide to the IR disc, the liquid compound was injected under a He flow preheated at 200 °C, respectively, which was fed to the in situ IR cell. Then, the IR disk was purged with He gas for 1200 s, and IR measurement was carried out.

NMR and GC-MS analysis

^{1}H and ^{13}C NMR spectra were recorded using at ambient temperature by JEOL-ECX 600 operating at 600.17 and 150.92 MHz respectively with tetramethylsilane as an internal standard. All chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. All chemical shifts are reported relative to tetramethylsilane and *d*-solvent peaks (77.00 ppm, chloroform), respectively. Abbreviations used in the NMR experiments: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Structure of the reported cyclic imides was identified by spectral comparison with literature data or analogous to literature data.

6.3. Results and discussion

We performed the reaction of benzamide and n-octylamine as a model reaction to optimize the catalytic parameters. Table 6.1 summarizes the results of the initial catalyst screening test under the solvent-free condition (140 °C, 30 h, under N_2) using different catalysts including CeO_2. Note that CeO_2 showed the highest activity for transamidation among 11 kinds of metal oxides tested in our previous study.[19] Among the catalysts in Table 6.1, Fe-mont showed the highest yield of the corresponding alkylamide. Thermal transamidation hardly proceeded without any catalyst at 140 °C. Using Femont, increase in the amide/amine ratio from 1/1.1 to 1.1/1 resulted in a decrease of the yield from 98% to 69%. This result suggests stronger interaction of amide with the active site (Fe^{3+} Lewis acid site) than amine during the reaction. From the time–yield profile (Fig. 6.S1), we

adopted the reaction time of 30 h. Stoichiometric amount of NH_3 is produced and is mostly present in gas phase. Using Fe-mont as the most effective catalyst, we studied reusability and general applicability of this catalytic system. Table 6.2 shows the isolated yield of the products for the transamidation of different amides with n-octylamine by 1 mol % of Fe-mont. Transamidation of benzamide with n-octylamine (entry 1) resulted in 100% conversion of amides and excellent yield (98%) of the products. ICP-AES analysis of the solution confirmed that the content of Fe in the solution was below the detection limit. Figure 6.1 shows the result of catalyst reuse. For each successive use, the catalyst was washed with acetone three times to remove the products, followed by centrifugation and by drying in air. The catalyst was reused at least four times without marked loss of its activity. As shown in Table 6.2 (entries 2–8), benzamides, benzylamide and phenyl acrylamide were also tolerated with 100% conversion and high isolated yield (85–96%). Heteroaromatic amides (entries 9–12) were also tolerated giving 100% conversion and high yield (85–95%). The aliphatic amides, acetamide and n-butyramide, also gave excellent yield of 95–96% (entries 13–15). For the first time, we succeeded in the transamidation of lactamide (entries 16) and 2-hydroxy-2-methyl-propionamide (entry 17) with n-octylamine (92–99% yield). Table 6.3 lists the results for the transamidation of benzamide and aliphatic amides with various amines. Transamidation of benzamide with various amines (aniline, 4-methylaniline, morpholine and cyclohexylamine) resulted in 100% conversion and good yields (entries 1–4). Various aliphatic amides were also tolerated (entries 6–9). Some of the previously reported systems did not tolerate the transamidation of acetamide with aniline possibly because of the low nucleophilicity of anilines as well as low reactivity of a acetamide. In contrast, 0.2 mol % of Fe-mont catalyzed the reaction with 86% yield (entry 10), corresponding to TON of 428 and turnover frequency (TOF) of 14.3. These are the highest values for this reaction by comparing with the previous catalytic systems (Table 6.4). These values are more than 46 times higher than that of $Cu(OAc)_2$ catalyzed reaction[11] (TON = 9 for the same reaction). Table 6.4 includes the result for the transamidation of acetamide with aniline by 0.2 mol % of Fe-mont at lower temperature (toluene reflux conditions). After 25 h the yield reached 98%, corresponding to TON of 490. Recently, Akamachi et al.[20] reported that sulfated tungstate (0.4 g, S-loading not reported) showed 88% yield for the

transamidation of acetamide with aniline for 12 h under toluene reflux conditions. The TOF per tungsten atom for sulfated tungstate (0.6 h^{-1}) was lower than the TOF per Fe atom for Fe-mont (19.6 h^{-1}). Finally we discuss a possible role of Fe^{3+} cation in the catalytic cycle. Using in situ IR, we studied the adsorption complexes formed by the introduction of acetamide on Fe-mont and SiO_2(non-Lewis acidic standard compound) at 160 °C. Acetamide(1 lL) was injected to He flow preheated at 200 °C, which was fed to the catalyst disc in the IR cell. IR spectra due to adsorbed species are shown in Figure 6.2. The main bands at 1661 cm^{-1} (for Fe-mont) and 1666 cm^{-1} (for SiO_2) are characteristic to the carbonyl stretching vibration of adsorbed acetamide species.[19] The band for Fe-mont is observed at lower wave number than that for SiO_2, indicating a weakened C=O bond strength in acetamide species on Fe-mont. This suggests that carbonyl oxygen of acetamide interacts with Lewis acid (Fe^{3+}), resulting in an increase in electrophilicity of the amide. Considering the previously reported mechanism of Lewis acid (Cu or Zr)-catalyzed transamidation[11,13] combined with our previous result of pyridine adsorption IR that Fe-mont has Lewis and Brønsted acid sites,[21] a possible catalytic cycle is shown in Scheme 6.1. The catalytic cycle starts with the activation of amide by Lewis acid (Fe^{3+}) site. The adsorbed amide undergoes an addition of the amine species to the amide carbon atom to give the N-alkyl amide.

6.4. Conclusion

We have demonstrated that Fe-mont acts as an effective heterogeneous catalyst for the transamidation of amides and amines. This novel catalysis provides a clean, convenient and practical route for the direct N-alkyl/N-phenyl amides synthesis in view of the following advantages. (1) The reaction proceeds smoothly and effectively under solvent free condition. (2) The catalyst is readily available, cheap, stable, reusable and a non-polluting solid that offers easy handling and ready work-up. (3) The present method is applicable in the synthesis of various N-alkyl amides, including useful aliphatic, aromatic and hetero-aromatic amides, with aliphatic, aromatic, hetero-atomic and cyclic amines in high yields and shows higher TON and TOF than previous methods.

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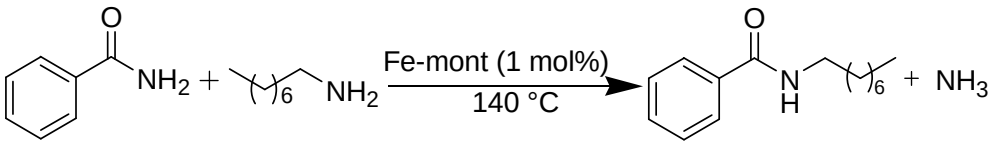


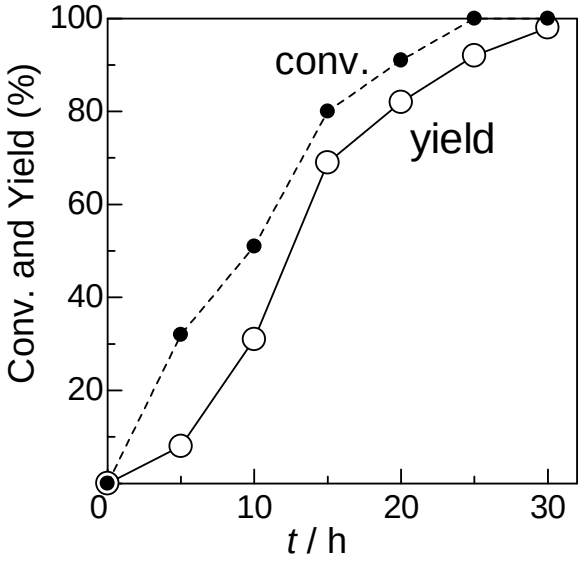


Figure 6.S1. Conversion of n-octylamine (●) and yield of the product (○) for reaction of benzamide and n-octylamine by Fe-mont (1 mol%) at 140 °C under N_2.

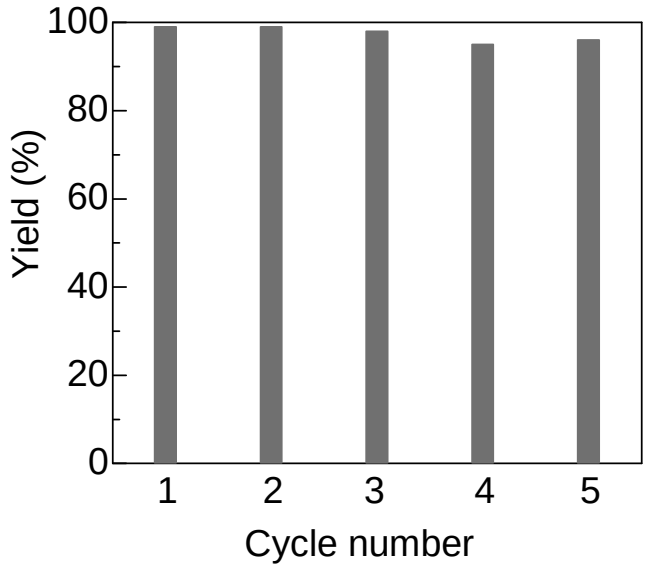


Figure 6.1. Reusability of Fe-mont (1.0mol%) for transamida-tion of benzamide (1.0 mmol) with *n*-octylamine (1.1 mmol) at 140 °C (t = 30h).

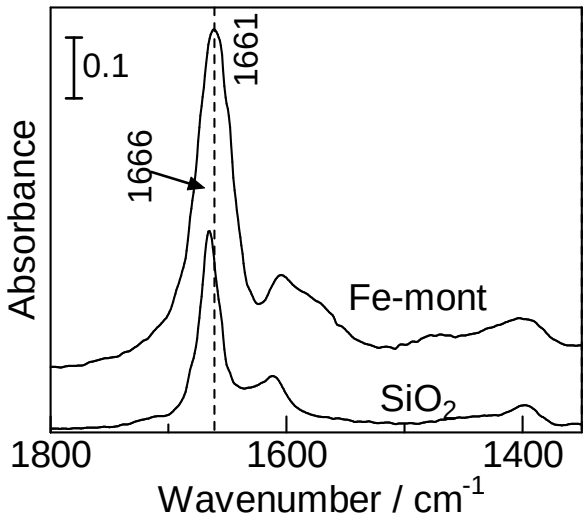
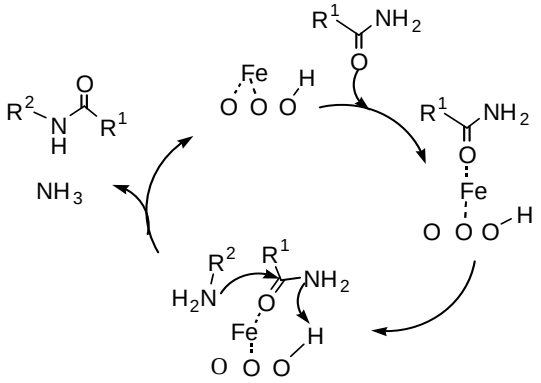
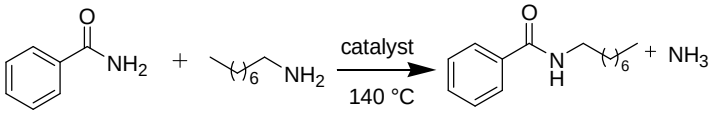


Figure 6.2. IR spectra of acetamide adsorbed on Fe-mont and SiO_2 at 160 ^oC.



Scheme 6.1. Possible catalytic cycle of transamidation by Fe-mont. O denotes the anionic oxygen atom on the clay surface.

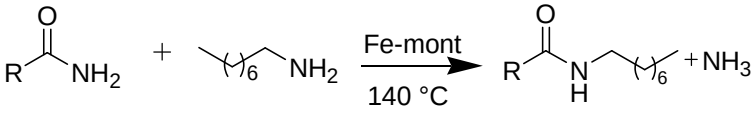
Table 6.1. Transamidation of benzamide with *n*-octayl amine by various catalysts.[a]

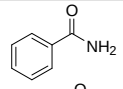
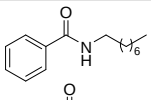
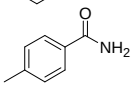
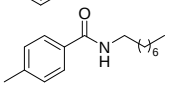
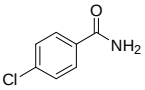
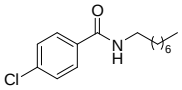
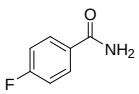
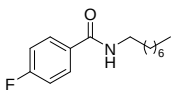
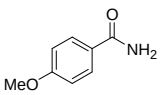
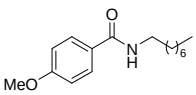


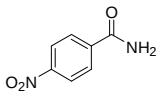
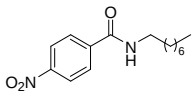
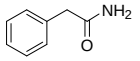
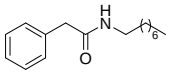
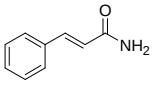
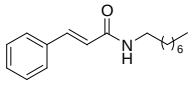
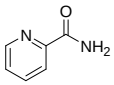
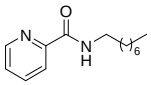
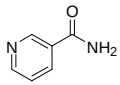
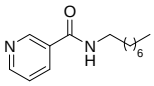
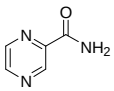
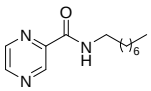
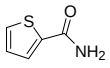
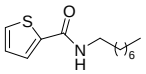
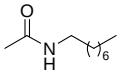
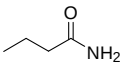
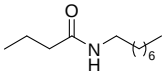
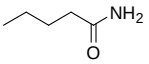
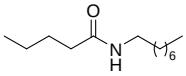
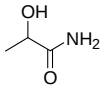
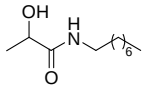
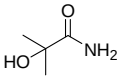
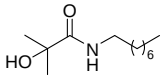
Catalyst	Yield (%)
Fe-mont	99
CeO_2	79
Fe_2O_3	9
$FeCl_3{\cdot}6H_2O$	34
Blank	<1

[a] Conditions: benzamide (1.0 mmol), *n*-octylamine (1.1 mmol), catalyst (1 mol%), 140 ^{o}C, 30 h. Yield of *n*-octyl benzamide was determined by GC.

Table 6.2. Transamidation of various amides with *n*-octylamine.[a]

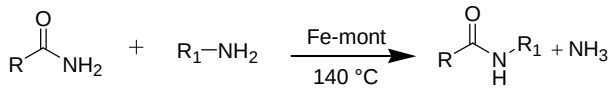


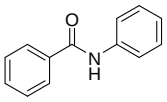
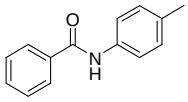
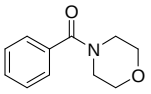
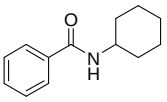
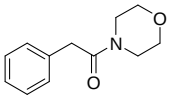
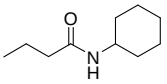
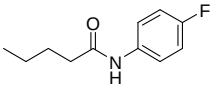
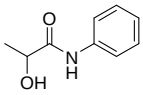
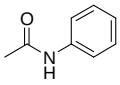
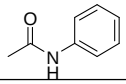
Entry	Amide	Product	yield (%)
1			98
2[b]			87
3			85
4			90
5			90

6[b]			90
7			89
8			96
9			85
10			87
11[b]			95
12[b]			92
13			95
14			95
15			96
16			92
17			99

[a] Conditions: amide (1.0mmol), n-octylamine (1.1 mmol), Fe-mont (1 mol%), 140 ^{o}C. [b] Amide / *n*-octylamine = 1.0 mmol /1.0 mmol.

Table 6.3. Transamidation of aliphatic and aromatic amide with various amines.[a]



Entry	Product	yield (%)
1		75
2		70
3		85
4		75
5		96
6		78
7		91
8		85
9		97
10[b]		86

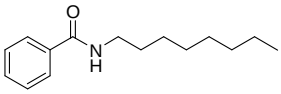
[a] Conditions: amide (1.0 mmol), amine (1.1 mmol), Fe-mont (1 mol%), 140 °C. [b] Fe-mont (0.2 mol %)

Table 6.4. Heterogeneous (upper part) and homogeneous (lower part) catalysts for the transamidation of acetamide with aniline.

catalyst	mol%	*T* (°C)	*t* (h)	yield (%)	TOF (h^{-1})	TON	ref.
Fe-mont	0.2	140	30	86	14.3	428	this study
CeO_2	0.2	140	30	11	0.4	13	this study
$PhI(OAc)_2$	5	120	24	81	1.1	27	15
$Cu(OAc)_2$	10	140	16	93	0.6	9	11
$B(OH)_3$	10	150	20	76	0.4	8	14
L-Proline	10	150	36	84	0.2	8	16

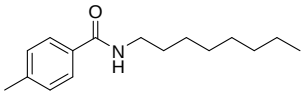
NMR and GCMS analysis:

***n*-Octyl-benzamide:**[1]



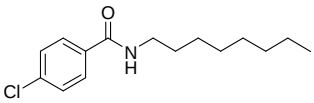
Purified by column chromatography (hexane/ethylacetate = 4:1); off white solid, 98% yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.76 (d, *J* = 7.32 Hz, 2H), 7.48 (t, *J* =7.32 Hz, 1H), 7.42 (t, *J* = 7.32 Hz, 2H), 6.19 (s, 1H), 3.46-3.43 (m, 2H), 1.62-1.58 (m, 2H), 1.37-1.26 (m, 2H), 1.31-1.26 (m, 8H), 0.88 (t, *J* = 9.00, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 167.49, 134.80, 131.19, 128.43 (C×2), 126.81 (C×2), 40.07, 31.74, 29.62, 29.24, 29.17, 26.96, 22.59, 14.04; GC-MS m/e 233.100.

4-Methyl-N-octyl-benzamide:[2]



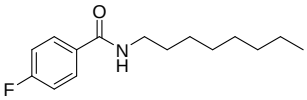
Purified by column chromatography (hexane/ethylacetate = 3:1); off white solid, 87% yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.65 (d, *J* = 7.40 Hz, 2H), 7.22 (d, *J* =7.40 Hz, 2H), 6.12 (br s, 1H), 3.43-3.42 (m, 2H), 2.39 (s, 3H), 1.61-1.58 (m, 2H), 1.30-1.29 (m, 2H), 1.28-1.25 (m, 8H), 0.87 (t, *J* = 14.46, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 167.38, 141.62, 131.96, 129.14 (C×2), 126.77 (C×2), 40.02, 31.76, 29.68, 29.27, 29.19, 26.99, 22.61, 21.39, 14.07; GC-MS m/e 247.150.

4-chloro-N-octyl-benzamide:[2]



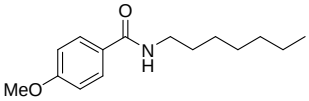
Purified by column chromatography (hexane/ethylacetate = 4:1); pale yellow solid , 85% yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.63 (d, *J* = 8.28 Hz, 2H), 7.30 (d, *J* =8.28 Hz, 2H), 7.19 (s, 1H), 3.35-3.33 (m, 2H), 1.53-1.50 (m, 2H), 1.23-1.22 (m, 2H), 1.20-1.18 (m, 8H), 0.80 (t, *J* = 14.40, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 166.41, 137.45, 133.13, 128.75 (C×2), 128.25 (C×2), 40.19, 31.76, 29.60, 29.25, 29.17, 26.97, 22.62, 14.07; GC-MS m/e 267.110.

4-Fluoro-N-octyl-benzamide:



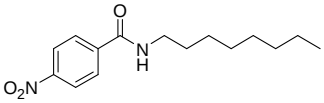
Purified by column chromatography (hexane/ethylacetate = 4:1); pale yellow solid, 90% yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.70 (d, *J* = 8.94 Hz *meta* to 4-F, 2H), 6.98 (d, *J* =8.94 Hz ortho to 4-F, 2H), 6.44 (s, 1H), 3.34-3.32 (m, 2H), 1.52-1.49 (m, 2H), 1.21-1.20 (m, 2H), 1.19-1.17 (m, 8H), 0.79 (t, *J* = 14.40, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 166.47, 164.49 (d, *J* = 250.51 Hz, 4-F-C), 130.92, 129.14 (d, *J* = 9.49 Hz, *meta* to 4-F, C×2), 115.37 (d, *J* = 22.98 Hz, *ortho* to 4-F, C×2), 40.15, 31.72, 29.57, 29.23, 29.14, 26.95, 22.56, 14.01; GC-MS m/e 251.150.

4-methoxy-N-octyl-benzamide:[2]



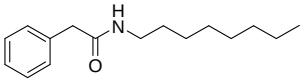
Purified by column chromatography (hexane/ethylacetate = 4:1); off white solid, 90% yield.^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.72 (d, *J* = 8.94 Hz, 2H), 6.92 (d, *J* =8.94 Hz, 2H), 6.04 (br s, 1H), 3.84 (s, 3H), 3.43-3.41 (m, 2H), 1.61-1.58 (m, 2H), 1.29-1.28 (m, 2H), 1.27-1.25 (m, 8H), 0.87 (t, *J* = 14.46, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 167.38, 162.62, 128.55(C×2), 113.66(C×2), 55.37, 40.02, 31.77, 29.73, 29.28, 29.19(C×2), 27.00, 22.61, 14.07; GC-MS m/e 263.220.

4-nitro-N-octyl-benzamide:[3]



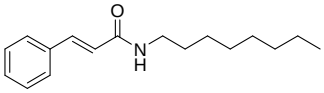
Purified by column chromatography (hexane/ethylacetate = 3.33:1); brown solid, 90 % yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 8.21 (d, *J* = 9.60 Hz, 2H), 7.86 (d, *J* =9.60 Hz, 2H), 7.19 (s, 1H), 6.24 (s, 1H), 3.40-3.39 (m, 2H), 1.57-1.55 (m, 2H), 1.22-1.221 (m, 2H), 1.21-1.20 (m, 8H), 0.80 (t, *J* = 6.84, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 165.57, 149.45, 140.52, 128.16 (C×2), 123.86 (C×2), 40.19, 31.85, 29.60, 29.33, 29.27, 27.06, 22.71, 14.17; GC-MS m/e 278.140.

N-Octyl-2-phenyl-acetamide:[2]



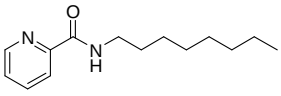
Purified by column chromatography (hexane/ethylacetate = 4:1); off white solid, 89 % yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.36 (d, *J* = 7.56 Hz, 2H), 7.35-7.7.29 (m, 1H), 7.26-7.24 (m, 2H), 5.35 (s, 2H), 3.57 (s, 2H), 3.19-3.17 (m, 2H), 1.41-1.38 (m, 2H), 1.27-1.26 (m, 2H), 1.25-1.22 (m, 8H), 0.87 (t, *J* = 14.46, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 170.82, 135.02, 129.44(C×2), 129.0 (C×2), 127.30, 43.89, 39.64, 31.70, 29.39, 29.12(C×2), 26.72, 22.59, 14.06; GC-MS m/e 247.400.

N-Octyl-3-phenyl-acrylamide:[4]



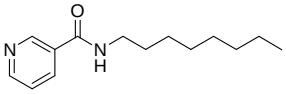
Purified by column chromatography (hexane/ethylacetate = 4:1); off white solid, 96 % yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.62 (d, *J* = 15.84 Hz, *trans*, 1H), 7.48-7.47 (s, 2H), 7.33-7.32 (m, 3H), 6.47-6.40 (m, 1H), 6.02 (br s, 1H), 3.39 (t, *J* = 5.64 Hz, 2H), 1.57-1.53 (m, 2H), 1.34-1.33 (m, 2H), 1.28-1.26 (m, 8H), 0.87 (t, *J* = 6.90, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 165.86, 140.60, 134.86, 129.48, 128.71(C×2), 127.67 (C×2), 120.90, 39.79, 31.74, 29.63, 29.25, 29.16, 26.95, 22.58, 14.04; GC-MS m/e 259.200.

Pyridine-2-carboxylic acid octylamide:[2]



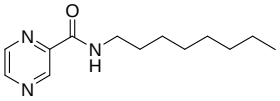
Purified by column chromatography (hexane/ethylacetate = 3:2); red solid, 85 % yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 10.37 (d, *J* = 6.00 Hz, 1H), 10.04 (d, *J* = 6.00 Hz, 1H), 9.93 (br s, 1H), 9.69-9.67 (m, 1H), 9.27-9.25 (m, 1H), 5.32-5.29 (m, 2H)**,** 3.49-3.47 (m, 2H)**,** 3.16-3.15 (m, 2H)**,** 3.13-3.11 (m, 8H)**,** 2.71 (t, *J* = 6.00 Hz, 3H)**;** ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 164.09, 149.97, 147.89, 137.21, 125.90, 122.05, 39.36, 31.70, 29.55, 29.19, 29.09, 26.91, 22.53, 13.98; GC-MS m/e 234.300.

N-Octyl-nicotinamide:[5]



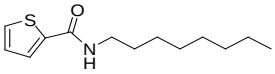
Purified by column chromatography (hexane/ethylacetate = 3:2); grey solid, 87 % yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 8.96 (d, *J* = 3.30 Hz, 1H), 8.70 (d, *J* = 3.30 Hz, 1H), 8.12-8.11 (m, 1H), 7.38-7.36 (m, 1H), 6.48 (br s, 1H), 3.47-3.44 (m, 2H), 1.65-1.60 (m, 2H), 1.39-1.35 (m, 2H), 1.33-1.26 (m, 8H), 0.87 (t, *J* = 13.74 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 165.56, 152.02, 147.72, 135.07, 130.48, 123.45, 40.20, 31.73, 29.53, 29.21, 29.15, 26.94, 22.58, 14.04; GC-MS m/e 234.100.

Pyrazine-2-carboxylic acid octylamide:[2]



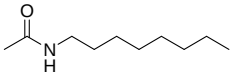
Purified by column chromatography (hexane/ethylacetate = 4:1); off white solid, 95 % yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 9.34 (d, *J* = 1.71 Hz, 1H), 8.67 (d, *J* = 1.71 Hz, 1H), 8.44 (s, 1H), 7.75 (br s, 1H), 3.42-3.40 (m, 2H), 1.58-1.54 (m, 2H), 1.32-1.23 (m, 2H), 1.22-1.19 (m, 8H), 0.80 (t, *J* = 6.84 Hz, 3H) ; ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 162.79, 147.08, 144.55, 144.35, 142.40, 39.44, 31.73, 29.51, 29.20, 29.13, 26.91, 22.57, 14.03; GC-MS m/e 235.020.

Thiophene-2-carboxylic acid octylamide:[2]



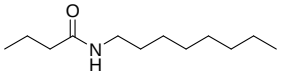
Purified by column chromatography (hexane/ethylacetate = 4:1); off white solid, 92 % yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.63 (d, *J* = 5.74 Hz, 1H), 7.42 (d, *J* = 5.74 Hz, 1H), 7.02 (t, *J* = 5.74 Hz, 1H), 6.99 (br s, 1H), 3.39-3.37 (m, 2H), 1.59-1.57 (m, 2H), 1.26-1.25 (m, 2H), 1.25-1.23 (m, 8H), 0.86 (t, *J* = 13.74, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 162.04, 139.39, 129.50, 127.75, 127.41, 39.99, 31.63, 29.51, 29.15, 29.05, 26.85, 22.48, 13.93; GC-MS m/e 239.020.

N-Octyl-acetamide:[6]



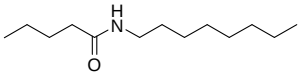
Purified by column chromatography (hexane/ethylacetate = 4:1); off white solid, 95 % yieid. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 6.41 (br s, 1H), 3.20 (m, 2H), 1.97 (s, 3H), 1.49 (m, 2H), 1.48-1.27 (m, 10H), 0.87 (t, *J* = 6.58 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 170.23, 39.53, 31.61, 29.35, 29.11, 29.04, 26.79, 22.96, 22.45, 13.89; GC-MS m/e 171.100.

N-Octyl-butyramide:[7]



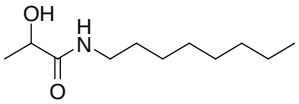
Purified by column chromatography (hexane/ethylacetate = 4:1); yellow liquid, 95 % yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 6.37 (br s, 1H), 3.23-3.21 (m, 2H), 2.17-2.14 (m, 2H), 1.67-1.64 (m, 2H), 1.51-1.47 (m, 2H), 1.29-1.20 (s, 10H), 0.94 (t, *J* = 8.94, 3H), 0.87 (t, *J* = 1.38, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 173.04, 39.30, 39.11, 31.59, 29.46, 29.10, 29.03, 26.78, 22.43, 19.09, 13.85, 13.53; GC-MS m/e 199.170.

Pentanoic acid octylamide:



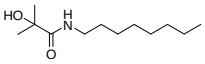
Purified by column chromatography (hexane/ethylacetate = 3:2); brown solid, 96 % yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 6.08 (br s, 1H), 3.23-3.20 (m, 2H), 2.17 (t, *J* = 7.56 Hz, 2H), 1.63-1.58 (m, 2H), 1.51-1.46 (m, 2H), 1.37-1.26 (m, 12H), 0.91 (t, *J* = 6.84 Hz, 3H), 0.87 (t, *J* = 6.90 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 173.14, 39.37, 36.41, 31.65, 29.52, 29.15, 29.08, 27.85, 26.82, 22.50, 22.29, 13.93,13.67; GC-MS m/e 213.200.

2-Hydroxy-N-octyl-propionamide:[8]



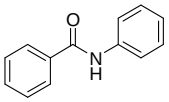
Purified by column chromatography (hexane/ethylacetate = 3:2); brown solid, 92 % yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 6.67 (br s, 1H, NH), 4.14-4.12 (m, 1H), 3.63 (br s, 1H, OH), 3.18-3.16 (m, 2H), 1.45-1.41 (m, 2H), 1.33 (d, *J* = 6.90, 3H), 1.25-1.14 (m, 10H), 0.80 (t, *J* = 6.90 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 174.68, 68.25, 39.09, 31.73, 29.48, 29.19, 29.14, 26.82, 22.57, 21.25, 14.03; GC-MS m/e 201.100.

2-Hydroxy-2-methyl-Nc-octyl-propionamide:



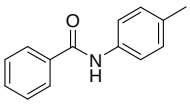
Purified by column chromatography (hexane/ethylacetate = 4:1); grey solid, 99 % yield. ^{1}HNMR (600.17 MHz, $CDCl_3$, TMS): δ 7.06 (br s, 1H, NH), 4.13 (br s, 1H, OH), 3.21 (t, *J* = 13.08, 2H), 1.50-1.49 (m, 2H), 1.42-1.41 (m, 6H), 1.29-1.27 (m, 10H), 0.87 (t, *J* = 6.90, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 176.93, 73.11, 39.15, 31.66, 29.41, 29.13, 29.07(C×2), 27.66, 26.76, 22.50, 13.95; GC-MS m/e 215.110.

N-Phenyl-benzamide:[9]



Purified by column chromatography (hexane/ethylacetate = 4:1); light pink solid, 75 % yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.81(br s, 1H), 7.78 (d, *J* = 3.4 Hz, 2H), 7.57 (d, *J* = 8.22 Hz, 2H), 7.48-7.46 (m, 1H), 7.40 (t, *J* = 7.56 Hz, 2H), 7.29 (t, *J* = 8.22 Hz, 2H), 7.09-7.07 (m, 1H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 165.73, 137, 88, 134.96, 131.83, 129.16 (C×2), 128.78 (C×2), 126.98 (C×2), 124.55 (C×2), 120.17; GC-MS m/e 197.080.

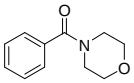
N-p-Tolyl-benzamide:[10]



Purified by column chromatography (hexane/ethylacetate = 4:1); grey solid, 70 % yield. ^{1}H NMR (600.17 MHz, CD_3CN, TMS): δ 7.86 (d, *J* =7.80 Hz, 2H), 7.53-7.52 (m, 2H), 7.51-7.46 (m, 2H), 7.17 (d, *J* = 7.80 Hz, 2H), 6.96 (d, *J* = 7.80 Hz, 1H), 6.61 (d, *J* = 8.28 Hz, 1H), 2.23 (s, 3H); ^{13}C NMR (150.92 MHz, CD_3CN) δ 165.54, 135.31, 135.03, 134.19,

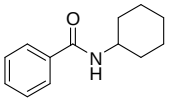
131.69, 129.53 (C×2), 128.70 (C×2), 126.96 (C×2), 115.21 (C×2), 20.88; GC-MS m/e 211.110.

N-Morpholin-4-yl-benzamide:[11]



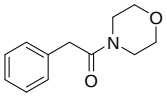
Purified by column chromatography (hexane/ethylacetate = 3:2); off white solid 85 % yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.44-7.38 (m 5H), 3.86-3.48 (m, 8H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 170.26, 135.13, 129.73, 128.40 (C×2), 126.91 (C×2), 66.71, 48.06, 42.39, 11.65; GC-MS m/e 191.220.

N-Cyclohexyl-benzamide:[12]



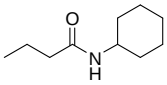
Purified by column chromatography (hexane/ethylacetate = 4:1); white solid 75 % yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 6.86 (d, *J* = 8.94 Hz, 2H), 6.61-6.58 (m, 1H), 6.53 (m, 2H), 6.38 (s, 1H), 1.16-1.13 (m, 2H), 0.89-0.85 (m, 2H), 0.78-0.75 (m, 1H), 0.57-0.51 (m, 2H), 0.39-0.31 (m, 4H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 166.58, 135.08, 131.20, 128.47(C×2), 126.78(C×2), 48.63, 33.21, 25.54 (C×2), 24.89 (C×2); GC-MS m/e 203.260.

N-Morpholin-4-yl-2-phenyl-acetamide:



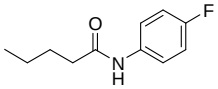
Purified by column chromatography (hexane/ethylacetate = 4:1); pale yellow solid 96 % yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.31-7.29 (m, 2H), 7.24-7.20 (m, 3H), 3.71 (s, 2H), 3.61 (s, 4H), 3.45-3.44 (m, 2H), 3.41-3.39 (m, 2H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 169.36, 134.48, 128.46 (C×2), 128.23 (C×2), 126.57, 66.40, 66.08, 46.16, 41.81, 40.41; GC-MS m/e 205.250.

N-Cyclohexyl-butyramide:[13]



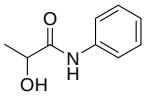
Purified by column chromatography (hexane/ethylacetate = 4:1); white solid 78 % yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 5.40 (br s, 1H), 3.69 (t, *J* = 4.14 Hz, 1H), 2.05 (t, *J* = 8.28 Hz, 2H), 1.84-1.82 (m, 2H), 1.64-1.54 (m, 5H), 1.29-1.27 (m, 2H), 1.07-1.03 (m, 3H), 0.86 (t, *J* = 6.84 Hz, 3H) ; ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 171.97, 47.94, 38.89, 33.19 (C×2), 25.47, 24.83 (C×2), 19.24, 13.64; GC-MS m/e 169.100.

Pentanoic acid (4-fluoro-phenyl)-amide:



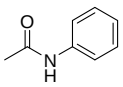
Purified by column chromatography (hexane/ethylacetate = 5:1); grey solid, 91 % yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.62 (br s, 1H), 7.46-7.44 (m, 2H), 6.98-6.95 (m, 2H), 2.32 (t, *J* = 7.56 Hz, 2H), 1.70-1.65 (m, 2H), 1.39-1.35 (m, 2H), 0.92 (t, *J* = 7.56 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 171.68, 159.22 (d, *J* = 242.96 Hz, 4 F-C), 133.94, 121.75 (d, *J* = 7.22 Hz, *meta* to 4-F, C×2), 115.46 (d, *J* = 21.28 Hz, 21.67 Hz, *ortho* to 4-F, C×2), 37.25, 27.66, 22.33, 13.74; GC-MS m/e 195.110.

2-Hydroxy-N-phenyl-propionamide:[14]



Purified by column chromatography (hexane/ethylacetate = 4:1); yellowish liquid, 85 % yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 8.56 (s, 1H), 7.52 (d, *J* = 8.94 Hz, 2H), 7.31-7.28 (m, 2H), 7.11-7.09 (m, 1H), 4.32-4.29 (m, 1H), 3.60 (br s, 1H), 1.48 (d, *J* = 6.90 Hz, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 173.01, 137.17, 129.14 (C×2), 124.74, 119.98 (C×2), 68.89, 21.19; GC-MS m/e 165.100.

N-Phenyl-acetamide:[15]



Purified by column chromatography (hexane/ethylacetate = 4:1); grey solid, 97 % yield. ^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 6.73(br s, 1H), 6.64 (d, *J* = 8.25 Hz, 2H), 6.42 (d, *J* = 8.25 Hz, 2H), 6.21 (m, 1H), 1.27 (s, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 168.54, 137.88, 128.91 (C×2), 124.25, 119.92 (C×2), 24.51; GC-MS m/e 135.070.

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Chapter 7

General Conclusion

In this research, I find out the reason, for which the Lewis acid catalyzed amide bond formation reaction usually possessed some drawbacks. Kinetic studies of the reaction support the hypothesis and showed that base tolerant Lewis acid catalyst is more effective to overcome the drawbacks for amidation of carboxylic acid with amines. So, a new base tolerant heterogeneous Lewis acidic catalytic system is developed for amide and imide bond formation reaction. The present catalytic system does not require high catalyst loading which increases the atom economy and showed higher turnover numbers than previous Lewis acid catalytic method for amidation. This newly developed simple, atom-efficient and environmentally benign method provides a practical and convenient route to synthesize amides and imides from readily available starting materials with a wide range of substrate scope.

Chapters 2-6, showed the precise examples of heterogeneous Lewis acid catalysis for the direct synthesis of amide and imide. By using this simple methodology, various important amides were synthesized from carboxylic acids and esters with amines. This atom-efficient method tolerates various functional groups and is applicable to challenging substrates such as α-hydroxycarboxylic acids and α-hydroxycarboxylic esters. For the first time, imide derivatives were synthesized from dicarboxylic acids and carboxylic anhydrides with amines and ammonia by using this heterogeneous Lewis acid catalytic system. By using this new catalytic system, amides are also synthesized by transamidation of amides with amines.

Mechanistic studies suggested that the Lewis acid site of Nb_2O_5 is more tolerant to basic molecules (amines and water as by product), present in the reaction mixture, these properties of Nb_2O_5, makes it highly effective catalyst for amidation and imidation reaction. These heterogeneous Lewis acid catalysts can be applied to other reactions involving activation of carbonyl groups in the presence of amines.

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Md. Ayub Ali