ChemPubSoc Europe
DOI: 10.1002/cctc.201501172
CHEMCATCHEM Communications

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

Md. A. Ali,[a] Sondomoyee K. Moromi,[a] Abeda S. Touchy,[a] and Ken-ichi Shimizu*[a, b]

In the 20 types of heterogeneous and homogenous catalysts screened, Nb_2O_5 showed the highest activity for the synthesis of *N*-phenylsuccinimide by dehydrative condensation of succinic anhydride and aniline. Nb_2O_5 was used in the direct imidation of a wide range of carboxylic anhydrides with NH_3 or amines with various functional groups and could be reused. Kinetic studies showed that the Lewis acid Nb_2O_5 catalyst was more water tolerant than both the Lewis acidic oxide TiO_2 and the homogeneous Lewis acid $ZrCl_4$, which resulted in higher yields of imides through the use of Nb_2O_5.

Cyclic imides and their derivatives are an important class of substrates for biological and chemical applications;[1,2] they are used as intermediates in the industrial production of drugs, dyes, and polymers.[1a,b,2] However, sustainable methods for the synthesis of cyclic imides from readily available starting materials are limited. General methods for the synthesis of cyclic imides include the dehydrative condensation of dicarboxylic acids[3] or their anhydrides[3f,4,5,6] with an amine under harsh conditions (250–380 °C, ≈33.0 MPa)[3a,b] or under microwave heating[5,6] and the cyclization of an amic acid with the help of acidic reagents or in the presence of an excess amount of a promoter (e.g., Lewis acid, base, dehydrating agent). These methods suffer from drawbacks such as low atom efficiency, limited substrate scope, production of stoichiometric amounts of byproducts, and the need for special procedures (e.g., microwave heating). New synthetic routs from nitriles,[7] halides,[8] alkynes,[9] arylboronic acids,[10] aromatic amides,[11] aliphatic amides,[12] and cyclic amines[13] have been developed, but these homogeneous catalytic methods have drawbacks such as low atom efficiency, narrow substrate scope, the use of toxic reagents or additives, and difficulties in catalyst/product separation and catalyst reuse. For example, a reusable heterogeneous catalytic system of Pd/C[8d] suffers from the need for the use of halides and CO as less environmentally benign reagents. One of the most effective synthesis routes to cyclic imides by dehydrogenative coupling of diols and amines (or nitriles) catalyzed by a Ru complex[1a,14] still suffers from limited substrate scope of the diols and amines.

Catalytic synthesis of cyclic imides by condensation of cyclic anhydrides with amines is one of the most desirable routes. A few catalytic methods performed with the use of $TaCl_5/SiO_2$[15a,b] or 1,4-diazabicyclo[2.2.2]octane (DABCO)[15c] are reported to synthesize cyclic imides from cyclic anhydrides with amines. These methods[15] suffer from some drawbacks, including a limited substrate scope, no results on catalyst reuse, and the need for high catalyst loadings and special methods (e.g., microwave heating).[15a,b] Potentially, the reaction can be catalyzed by a Lewis acid, but the co-presence of water as a 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 recently reported that Nb_2O_5 acts as a water-tolerant Lewis acid catalyst for the direct imidation of dicarboxylic acids with amines[17] and the direct amidation of esters with amines.[18] We reported our preliminary results on the synthesis of cyclic imides from cyclic anhydrides,[17] but detailed catalytic properties such as substrate scope and kinetic studies were not reported. Herein, we report a general catalytic method for the direct synthesis of cyclic imides from cyclic anhydrides 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; the Lewis acid characteristics of Nb_2O_5 are reported in our previous studies.[17–19]

As listed in Table 1, 20 types of heterogeneous and homogeneous catalysts were screened for the model imidation of equimolar amounts of succinic anhydride and aniline under solvent-free conditions at 140 °C for 15 h (Table 1). Note that the reaction hardly proceeded under catalyst-free conditions (Table 1, entry 1). Thus, Table 1 shows the results of catalytic imidation. First, we screened 12 types of simple metal oxides (Table 1, entries 2–13). Among the metal oxides tested, Nb_2O_5 showed the highest yield (90 %) of the corresponding imide, *N*-phenylsuccinimide. The hydrate of Nb_2O_5, called niobic acid (Table 1, entry 3), gave a lower yield (22 %) than Nb_2O_5. Two of the oxides having Lewis acidity (ZrO_2 and TiO_2)[19,20] showed moderate yields of 59–65 % (Table 1, entries 4 and 5). 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 (Table 1, entry 14), HBEA zeolite (Table 1, entry 16), and water-tolerant Brønsted acid catalysts

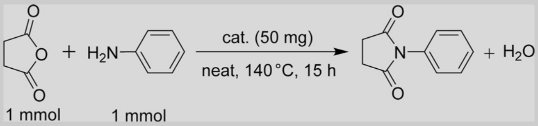
---

[a] *M. A. Ali, S. K. Moromi, Dr. A. S. Touchy, Prof. Dr. K.-i. Shimizu*
Institute for Catalysis
Hokkaido University
N-21, W-10, Sapporo (Japan)
E-mail: kshimizu@cat.hokudai.ac.jp

[b] *Prof. Dr. K.-i. Shimizu*
Elements Strategy Initiative for Catalysis and Batteries
Kyoto University
Katsura, Kyoto 615-8520 (Japan)

Supporting Information for this article is available on the WWW under http://dx.doi.org/10.1002/cctc.201501172.

Table 1. Catalyst screening for the synthesis of cyclic imides from anhydrides.



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

[a] Determined by GC.

including HZSM5 zeolite with a SiO_2/Al_2O_3 ratio of 300 (Table 1, entry 15) and commercial acidic resins (Table 1, entries 17 and 18).[21] These solid acids gave low to moderate yields (31–60 %) of *N*-phenylsuccinimide. Finally, we tested homogeneous Lewis acids[22] (Table 1, entries 19–21) including the water-tolerant Lewis acid[22c,d] scandium(III) trifluoromethanesulfonate [$Sc(OTf)_3$; Table 1, entry 20]. These homogeneous catalysts gave low yields of the product (18–44 %).

With the most effective catalyst (i.e., Nb_2O_5), we tested the model reaction in the absence and in the presence of different solvents (Table S1, Supporting Information). We found that if the reaction was performed under solvent-free conditions, the product was obtained in a higher yield than if the reaction was performed in a solvent such as toluene or *o*-xylene.

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

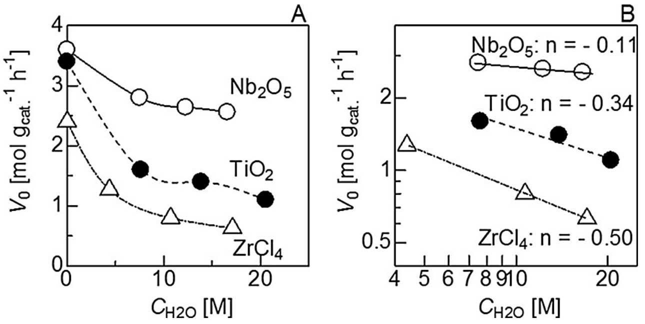


Figure 1. Initial rate for imidation of succinic anhydride (1 mmol) with aniline (1 mmol) in the presence of H_2O (0, 1, 3, and 5 mmol) catalyzed by 50 mg of Nb_2O_5, TiO_2, or $ZrCl_4$ as a function of the initial concentration of water.

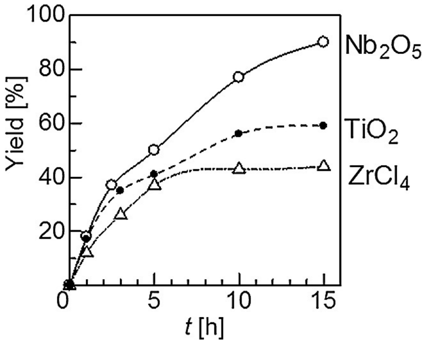
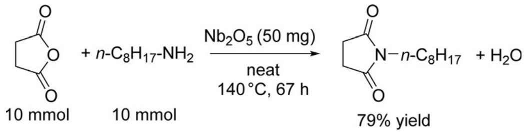


Figure 2. Time–yield profiles for the imidation of succinic anhydride (1 mmol) with aniline (1 mmol) catalyzed by 50 mg of Nb_2O_5, TiO_2, or $ZrCl_4$.

Next, we studied the effectiveness of the Nb_2O_5-catalyzed imidation of carboxylic anhydrides with amines. The results of a gram-scale reaction are shown in Scheme 1. The reaction of succinic anhydride (10 mmol) with *n*-octylamine (10 mmol) in the presence of Nb_2O_5 (50 mg) for 67 h gave the corresponding imide in 79 % yield. Previously, we reported the number of surface Lewis acid sites on the Nb_2O_5 catalyst by pyridine ad-



Scheme 1. A gram-scale reaction of succinic anhydride with *n*-octylamine in the presence of Nb_2O_5.

sorption IR spectroscopy at 200 °C.[17,19] The turnover number (TON) with respect to the Lewis acid sites of Nb_2O_5 (0.056 mmol g^{-1}) was calculated to be 2820.

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

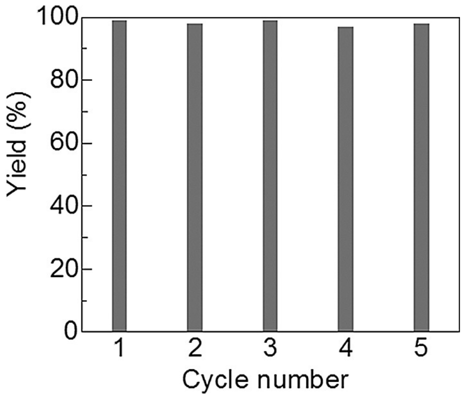
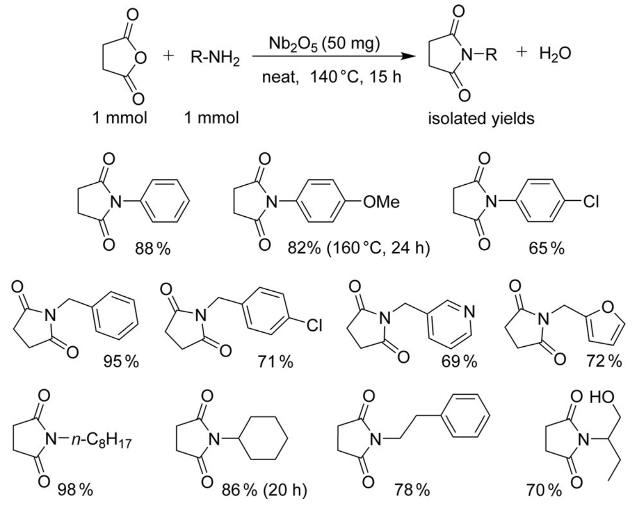
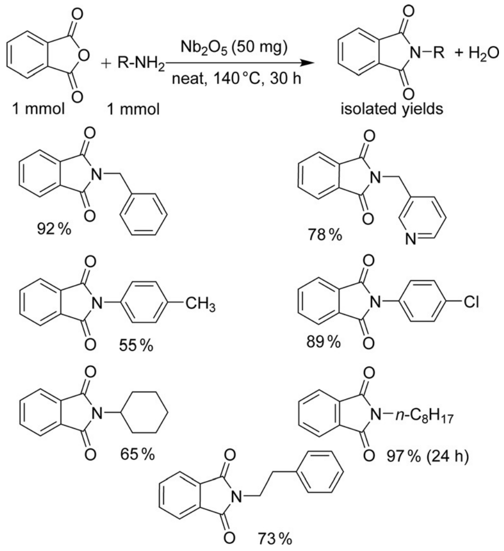


Figure 3. Reuse of Nb_2O_5 for the imidation of succinic anhydride with *n*-octylamine under the conditions shown in Scheme 2.

Finally, we studied the substrate scope for the present catalytic system. Scheme 2 shows the results of the imidation of succinic anhydride (1 mmol) with different amines (1 mmol). Under the standard solvent-free conditions with the use of 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 (e.g., H-, MeO-, Cl-) in the *para* position, benzylamines, heteroaromatic amines with pyridyl and furanyl groups, linear and cyclic aliphatic amines, and amines with phenyl and hydroxy groups were all converted into the corresponding *N*-aryl imides in good to high yields (65–98%).



Scheme 2. Substrate scope for imidation of succinic anhydride with different amines.



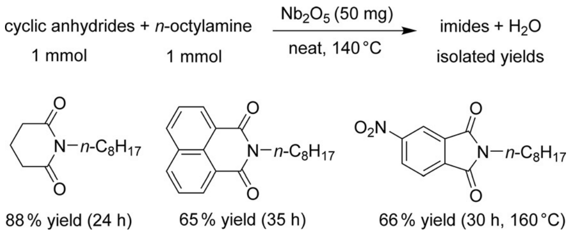
Scheme 3. Synthesis of phthalimides from phthalic anhydride and various primary amines.

The method was also effective for the direct synthesis of phthalimides from readily available phthalic anhydride and equimolar amounts of amines (Scheme 3). Benzyl amine, heteroaromatic amine, anilines with electron-rich and electron-poor groups, cyclohexylamine, phenylethylamine, and *n*-octylamine were all converted into the corresponding *N*-substituted phthalimides in moderate to high yields (55–92%).

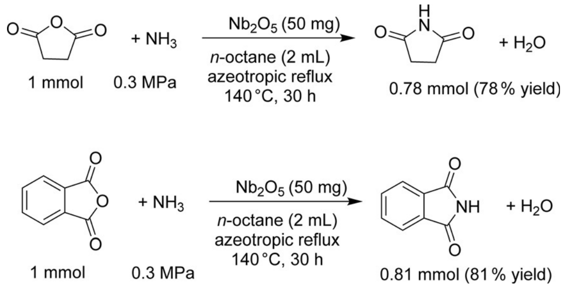
Scheme 4 shows the reactions of *n*-octylamine with various cyclic anhydrides. Gluteric anhydride, 1,8-naphthalic anhydride, and 4-nitrophthalic anhydride were all transformed into the corresponding *N*-substituted cyclic imides in moderate to high yields (65–88%).

Notably, unsubstituted cyclic imides were also synthesized from cyclic anhydrides and ammonia under azeotropic reflux conditions in *n*-octane (Scheme 5). The reactions of succinic anhydride and phthalic anhydride in a closed stainless reactor under NH_3 pressure (0.3 MPa) at 140 °C resulted in succinimide in 78% yield and phthalimide in 81% yield, respectively.

Summarizing the above results, we can conclude that the present method involving the use of a catalytic amount of Nb_2O_5 is widely applicable to the direct imidation of various



Scheme 4. Synthesis of *N*-substituted cyclic imides from cyclic anhydrides with *n*-octylamine.



Scheme 5. Imidation of cyclic anhydrides and ammonia.

carboxylic anhydrides with ammonia or amines with various functional groups. To our knowledge, this is the first general catalytic method for the synthesis of imides from carboxylic anhydrides and amines by using a reusable catalyst.

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

Acknowledgements

This work was supported by Grant-in-Aids for Scientific Research B from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan (26289299), a MEXT program "Elements Strategy Initiative to Form Core Research Center", and a Grant-in-Aid for Scientific Research on Innovative Areas "Nano Informatics" from Japan Society for the Promotion of Science (JSPS) (25106010).

Keywords: amination · ketones · Lewis acids · niobium · primary amines

[1] a) S. Muthainh, S. H. Hong, *Synlett* **2011**, 1481 – 1485; b) M. K. Hargreaves, J. G. Pritchard, H. R. Dave, *Chem. Rev.* **1970**, *70*, 439 – 469; c) A. M. Crider, T. M. Kolczynski, K. M. Yates, *J. Med. Chem.* **1980**, *23*, 324 – 326.

[2] a) K. H. Chae, Y. H. Kim, *Adv. Funct. Mater.* **2007**, *17*, 3470 – 3476; b) G. Chen, X. Zhang, S. Zhang, T. Chen, Y. Wu, *J. Appl. Polym. Sci.* **2007**, *106*, 2808 – 2816.

[3] a) J. Fraga-Dubreuil, G. Comak, A. W. Taylora, M. Poliakoff, *Green Chem.* **2007**, *9*, 1067 – 1072; b) A. Da Settimo, G. Primofiore, F. Da Settimo, F. Simorini, C. La Motta, A. Martinelli, E. Boldrini, *Eur. J. Med. Chem.* **1996**, *31*, 49 – 58; c) C. J. Perry, Z. Parveen, *J. Chem. Soc. Perkin Trans. 1* **2001**, 512 – 521; d) B. Martin, H. Sekljic, C. Chassaing, *Org. Lett.* **2003**, *5*, 1851 – 1853; e) J. A. Seijas, M. P. Vazuez-Tato, C. Gonzalez-Bande, M. M. Maontserrat, B. Pacios-Lopez, *Synthesis* **2001**, *7*, 0999 – 1000; f) N. B. Mehta, A. P. Phillips, F. F. Lui, R. E. Brooks, *J. Org. Chem.* **1960**, *25*, 1012 – 1015.

[4] a) P. Y. Reddy, S. Kondo, T. Toru, Y. Ueno, *J. Org. Chem.* **1997**, *62*, 2652 – 2654; b) Z.-G. Le, Z.-C. Chen, Y. Hu, Q.-G. Zheng, *Synthesis* **2004**, *7*, 995 – 998; c) C. D. Chu, Y. H. Qi, W. Hao, *Catal. Commun.* **2007**, *8*, 1527 – 1530; d) K. Li, C. Yuan, S. Zheng, Q. Fang, *Tetrahedron Lett.* **2012**, *53*, 4245 – 4247; e) D. N. Garad, S. D. Tanpure, S. B. Mhaske, *Beilstein J. Org. Chem.* **2015**, *11*, 1008 – 1016; f) A. A. M. Abdel-Aziz, *Eur. J. Med. Chem.* **2007**, *42*, 614 – 626.

[5] a) E. Benjamin, Y. Hijji, *Molecules* **2008**, *13*, 157 – 169; b) K. Sugamoto, Y.-i Matsushita, Y-h Kameda, M. Suzuki, T. Matsui, *Synth. Commun.* **2005**, *35*, 67 – 70.

[6] a) T. Vidal, A. Petit, A. Loupy, R. N. Gedye, *Tetrahedron* **2000**, *56*, 5473 – 5478; b) S. K. Upadhyay, S. R. K. Pingali, B. S. Jursic, *Tetrahedron Lett.* **2010**, *51*, 2215 – 2217.

[7] H. Takaya, K. Yoshida, K. Isozaki, H. Terai, S.-I. Murahashi, *Angew. Chem. Int. Ed.* **2003**, *42*, 3302 – 3304; *Angew. Chem.* **2003**, *115*, 3424 – 3426.

[8] a) J. R. Martinelli, D. A. Watson, D. M. M. Freckmann, T. E. Barder, S. L. Buchwald, *J. Org. Chem.* **2008**, *73*, 7102 – 7107; b) H. Cao, H. Alper, *Org. Lett.* **2010**, *12*, 4126 – 4129; c) X. Wu, S. Oschatz, M. Sharif, A. Flader, L. Krey, M. Beller, P. Langer, *Adv. Synth. Catal.* **2013**, *355*, 3581 – 3585; d) M. V. Khedkar, S. R. Khan, D. N. Sawant, D. B. Bagal, B. M. Bhanage, *Adv. Synth. Catal.* **2011**, *353*, 3415 – 3422.

[9] K. M. Driller, H. Klein, R. Jackstell, M. Beller, *Angew. Chem. Int. Ed.* **2009**, *48*, 6041 – 6044; *Angew. Chem.* **2009**, *121*, 6157 – 6160.

[10] a) R. Shintani, W. L. Duan, T. Hayashi, *J. Am. Chem. Soc.* **2006**, *128*, 5628 – 5629; b) M. L. Kantam, B. Neelima, C. V. Reddy, V. Neeraja, *J. Mol. Catal. A* **2006**, *249*, 201 – 206.

[11] S. Inoue, H. Shiota, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2009**, *131*, 6898 – 6899.

[12] E. J. Yoo, M. Wasa, J. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 17378 – 17380.

[13] X. Yan, K. Fang, H. Liu, C. Xi, *Chem. Commun.* **2013**, *49*, 106650 – 10652.

[14] a) J. Zhang, M. Senthilkumar, S. Ghosh, S. Hong, *Angew. Chem. Int. Ed.* **2010**, *49*, 6391 – 6395; *Angew. Chem.* **2010**, *122*, 6535 – 6539; b) J. Kim, S. H. Hong, *Org. Lett.* **2014**, *16*, 4404 – 4407.

[15] a) S. Chandrasekhar, M. Takhi, G. Uma, *Tetrahedron Lett.* **1997**, *38*, 8089 – 8092; b) S. Chandrasekhar, M. B. Padmaja, A. Raza, *Synlett* **1999**, *10*, 1597 – 1599; c) M. M. Heravi, R. H. Shoar, L. Pedram, *J. Mol. Catal. A* **2005**, *231*, 89 – 91.

[16] a) K. Nakajima, Y. Baba, R. Noma, M. Kitano, J. N. Kondo, S. Hayashi, M. Hara, *J. Am. Chem. Soc.* **2011**, *133*, 4224 – 4227; b) K. Nakajima, R. Noma, M. Kitano, N. Ichikuni, M. Hara, *J. Phys. Chem. C* **2013**, *117*, 16028 – 16033; c) A. Corma, M. E. Domine, S. Valencia, *J. Catal.* **2003**, *215*, 294 – 304; d) Y. Romón-Leshkov, M. E. Davis, *ACS Catal.* **2011**, *1*, 1566 – 1580; e) Y. Wang, F. Wang, Q. Song, Q. Xin, S. Xu, J. Xu, *J. Am. Chem. Soc.* **2013**, *135*, 1506 – 1515.

[17] M. A. Ali, S. M. A. H. Siddiki, K. Kon, J. Hasegawa, K. Shimizu, *Chem. Eur. J.* **2014**, *20*, 14256 – 14260.

[18] M. A. Ali, S. M. A. Siddiki, K. Kon, K. Shimizu, *ChemCatChem* **2015**, *7*, 2705 – 2710.

[19] M. Tamura, K. Shimizu, A. Satsuma, *Appl. Catal. A* **2012**, *433 – 434*, 135 – 145.

[20] G. Busca, *Phys. Chem. Chem. Phys.* **1999**, *1*, 723 – 736.

[21] T. Okuhara, *Chem. Rev.* **2002**, *102*, 3641 – 3666.

[22] a) H. Lundberg, F. Tinnis, H. Adolfsson, *Chem. Eur. J.* **2012**, *18*, 3822 – 3826; b) K. Ishihara, *Tetrahedron* **2009**, *65*, 1085 – 1109; c) S. Kobayashi, K. Manabe, *Acc. Chem. Res.* **2002**, *35*, 209 – 217; d) Y. Koito, K. Nakajima, H. Kobayashi, R. Hasegawa, M. Kitano, M. Hara, *Chem. Eur. J.* **2014**, *20*, 8068 – 8075.

Received: October 27, 2015