Development of Environmentally Benign Catalysts for the Dehydrative Synthesis of Nitriles, Beckmann Rearrangement and Transesterification

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Contents

Chapter 1

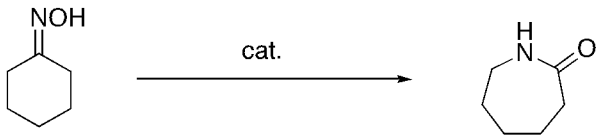
Introduction and General Summary

Green chemistry is a movement for the purpose of minimizing the hazards and maximizing the efficiency of any chemical processes.[1] Green chemistry is an overarching philosophy of chemistry, rather than a subdiscipline. It applies to organic chemistry, inorganic chemistry, biochemistry, analytical chemistry, and even physical chemistry. It is distinct from environmental chemistry which focuses on chemical phenomena in the environment.

Attempts are being made not only to quantify the greenness of a chemical process but also to factor in other variables such as chemical yield, the price of the substrates and reagents, safety in handling of chemicals, hardware demands, energy profile and ease of product workup and purification.

Atom efficiency is one of the important concepts in green chemistry.[2] Atom efficiency describes the conversion efficiency of a chemical process in terms of all of the atoms involved. In an ideal chemical process, the amount of starting materials or reactants equals the amount of all products generated and no atom is wasted. Atom efficiency can be written as Eq. (1). A catalytic Beckmann rearrangement is an example of a potentially very atom-efficient reaction [Eq. (2)].

$$\text{Atom Efficiency (\%)} = \frac{\text{Desired Product (g)}}{\text{All Reactants (g)}} \times 100\ (\%) \qquad (1)$$

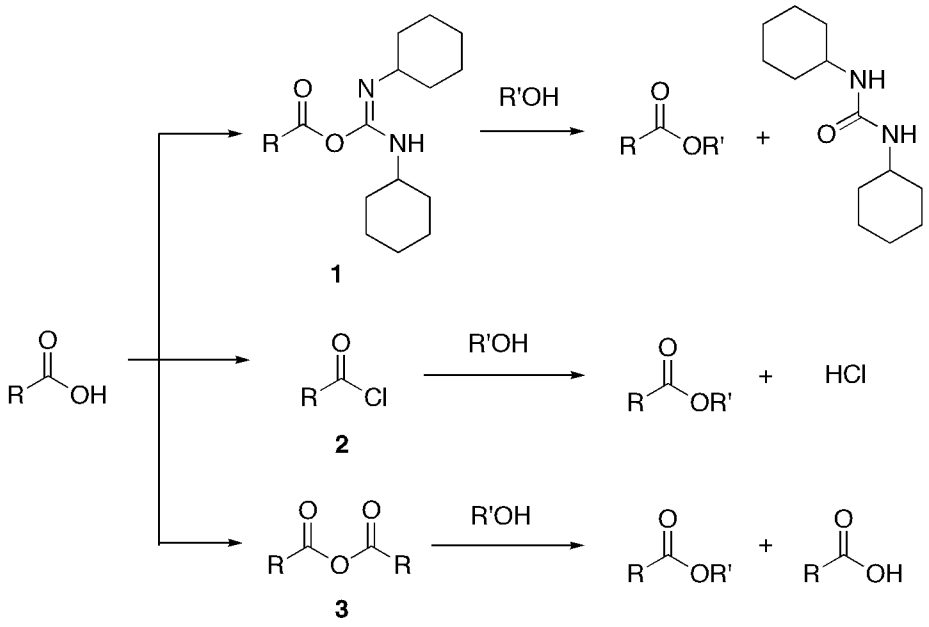


(2)

Atom Efficiency = 100%

Atom efficiency can be improved by careful selection of the starting materials and a catalyst system. For example, the ester condensation reaction between carboxylic acids and alcohols, which is one of the most fundamental organic reactions, usually requires the conversion of carboxylic acids to active acyl

intermediates, such as active esters (1), acid chlorides (2) or acid anhydrides (3), for the reaction to proceed smoothly (Scheme 1). Consequently, these methods show low atom efficiency, since an equimolar amount of byproduct is formed after the reaction. Therefore, the catalytic direct condensation between carboxylic acids and alcohols to esters has been desired as an ideal method improving atom economy and environmental safety.



Scheme 1. Esterification betwwen Carboxylic Acids and Alcohols

We have investigated the development of various catalytic transformations of carbonyl groups such as esters,[3] amide,[4] and acetals,[5] to realize environmentally benign synthesis. However, many organic reactions still need to be improved. This thesis describes the development of catalysts for the dehydrative nitrile-synthesis, the Beckmann rearrangement and the transesterification, which are important and fundamental organic reactions in the laboratory and industry.

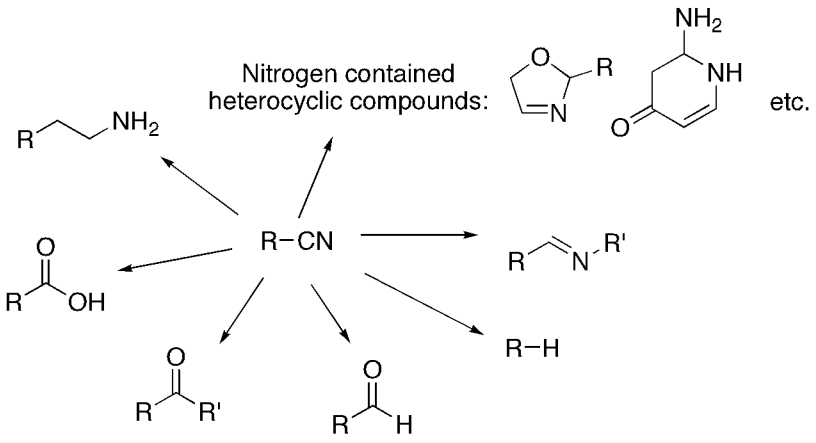
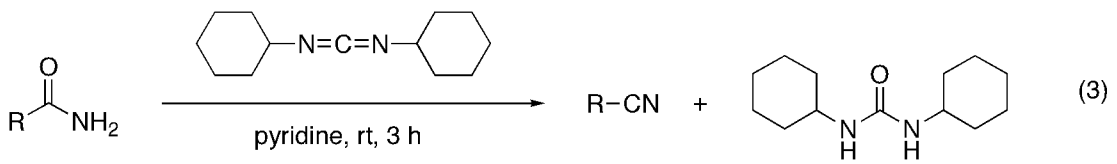


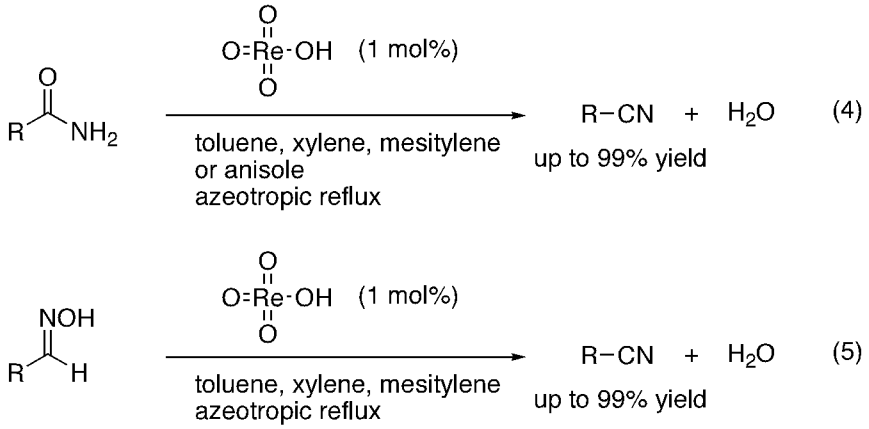
Figure 1. Transformation of nitriles to various functional groups.

Chapter 2 describes dehydrative nitrile synthesis. Nitrile compounds are widely used as synthetic intermediates in material transformation, since this functional group can be easily transformed to various other functional groups (Fig. 1). One of the most important methods for the synthesis of nitriles is the dehydration of primary amides. The dehydration of primary amides generally requires excess amounts of dehydrating media such as P_2O_5, PCl_5, or $SOCl_2$. N,N-Dicyclohexylcarbodiimide (DCC) is also used as a mild reagents for this reaction [Eq. (3)].[6] However, these classical methods are conducted under harsh conditions in acidic or basic media, or involve tedious workup procedures to remove large amounts of byproduct derived from the dehydrating reagent [i.e. N,N-dicyclohexylurea in Eq. (3)]. In addition, these processes show extremely low atom efficiency.

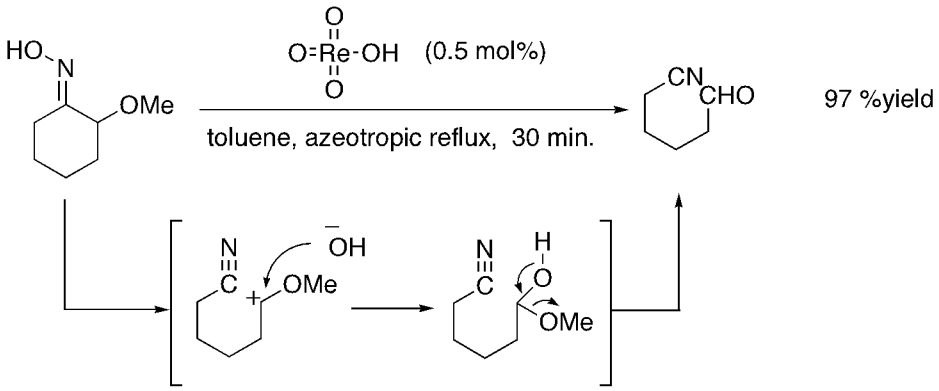


(3)

Therefore, with regard to green chemistry, we investigated the catalytic dehydration synthesis of nitriles, and found that perrhenic acid was an efficient catalyst for the dehydration of primary amides [Eq. (4)].[7] This process gave a wide variety of nitriles in high yield, and only a stoichiometric amount of water was obtained as a byproduct. In addition, this new catalytic system can be applied to gram-scale synthesis without further modifications, and perrhenic acid is reusable.



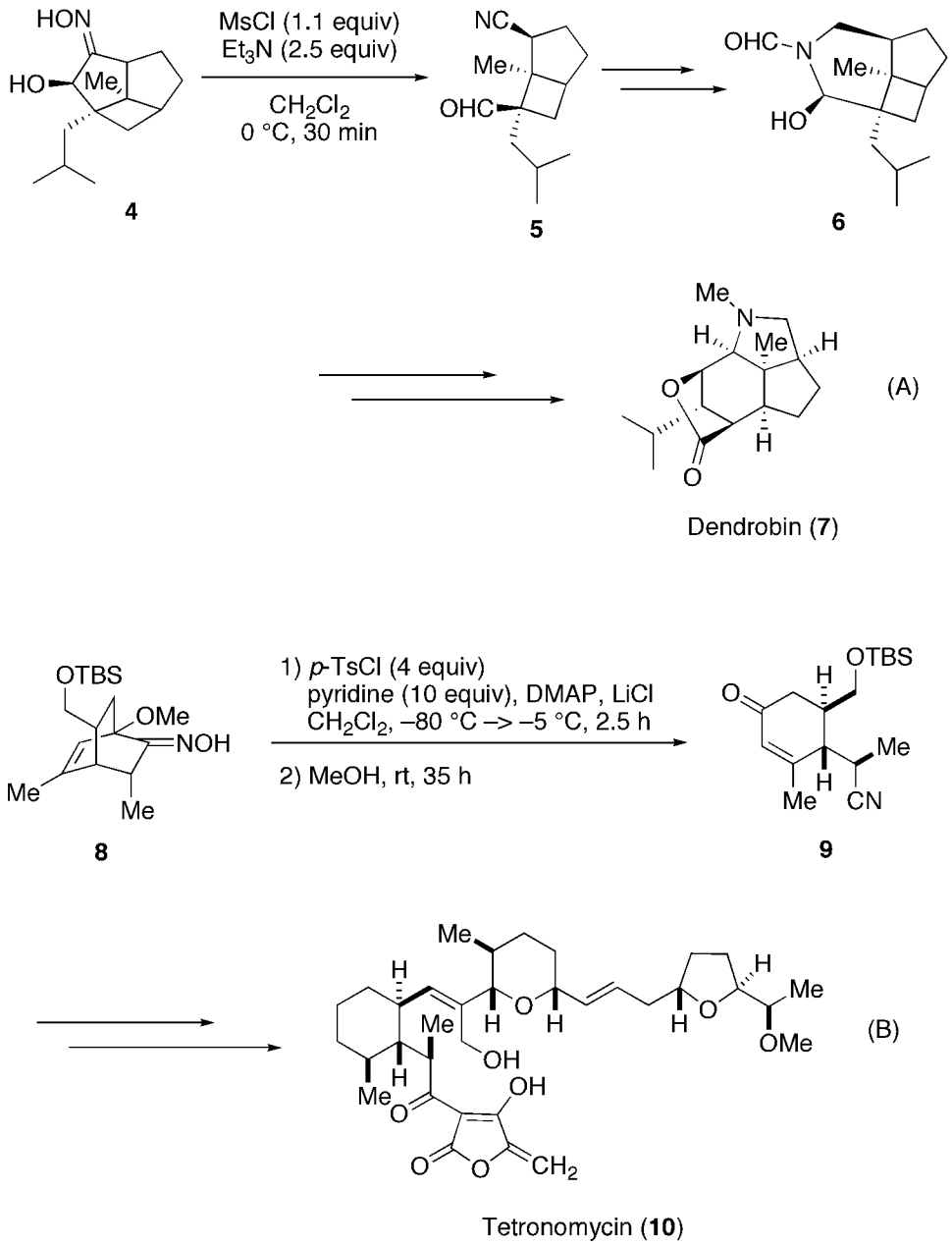
The dehydration of aldoximes with an appropriate dehydrating agent is an alternative method for the synthesis of nitriles. Perrhenic acid can be used for this dehydraiton reaction and gives the corresponding nitriles in excellent yields [Eq. (5)].[7]



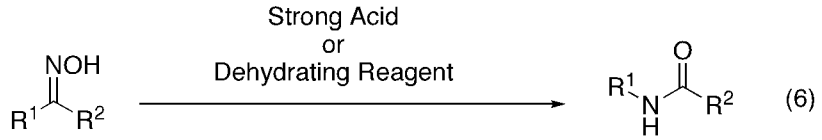
Scheme 2. Beckmann Fragmentation Catalyzed by $(HO)ReO_3$

Furthermore, this catalysis can be applied to the Beckmann fragmentation of ketoximes (Scheme 2).[7b] Beckmann fragmentation of cyclic ketoximes bearing an electron-donating group at the α position is particularly useful for organic synthesis, since synthetically useful functional groups such as cyano and carbonyl groups can be stereoselectively introduced to the products.[8] For this reason, this reaction is frequently used in the total synthesis of natural compounds. For example, in the total synthesis of dendrobine (7), Heathcock and Connoly reported intermediate 5, which has a nitrile and an aldehyde in its structure, was synthesized from ketoxime 4 by Beckmann fragmentation [Scheme 3(A)].[9a] An acyltetronic acid fragment 9 of tetronomycin (10) was stereoselectively synthesized by the Beckmann fragmentation of ketoxime 8 by Yoshii et al. in 1989 [Scheme 3(B)].[9b] Although this reaction is useful in organic synthesis, in most of the examples reported to date it is carried out with stoichiometric dehydrating reagents under basic conditions. On the other hand, rhenium (VII) catalysis enables this reaction to proceed smoothly under mild conditions.

Catalysis by rhenium (VII) oxo complexes can realize the atom-economical dehydration synthesis of nitriles. The experimental details are described in Chapter 2.



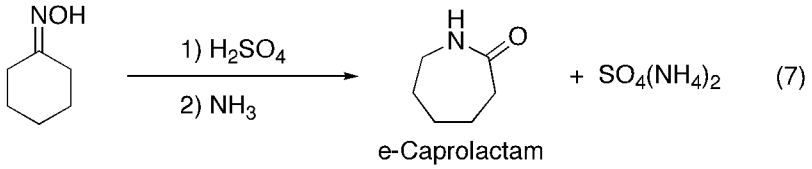
Scheme 3. Application of Beckmann Fragmentation to Total Synthesis of 7 and 10

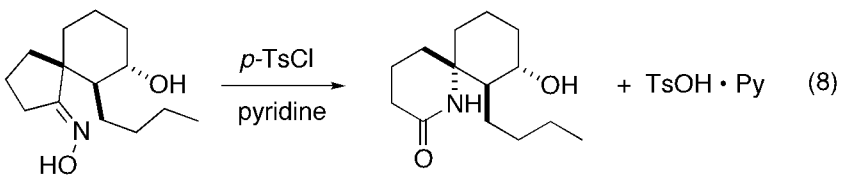


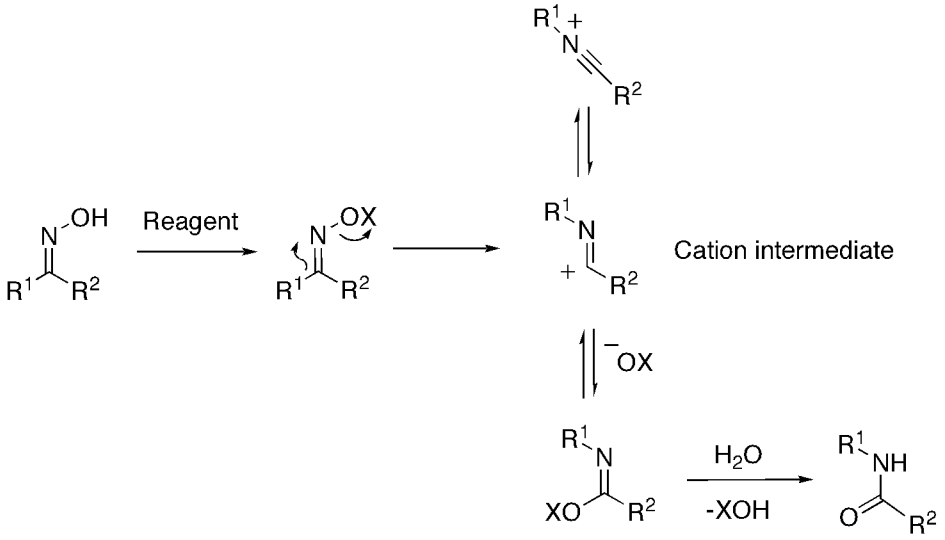
Reagents: H_2SO_4, $POCl_3$, PCl_5, *p*-TsCl

- Large amounts of byproducts are obtained.
- Acid sensitive substrates can not be used.

Chapter 3 describes cyanuric chloride-catalyzed Beckmann rearrangement.[10] Beckmann rearrangement is a powerful tool for the synthesis of amides and lactams [Eq. (6)].[11] This reaction traditionally requires high reaction temperatures and strongly acidic and dehydrating media. For example, fuming sulfuric acid is used in the industrial synthesis of ε-caprolactam, which is a key intermediate in the production of nylon-6 [Eq. (7)], and a method that involves p-toluenesulfonyl (Ts) as a leaving group under basic conditions is frequently used as a standard reaction condition [Eq. (8)].[12] Since there is a problem with the removal of unnecessary substances that originate from the reagents, and in the application of this procedure to substrates that are unstable under acidic conditions, many attempts have been made to change this from a stoichiometric to a catalytic reaction from the perspective of atom economy. Many catalyst reaction systems using Lewis acid or a metal catalyst have been reported.[13]





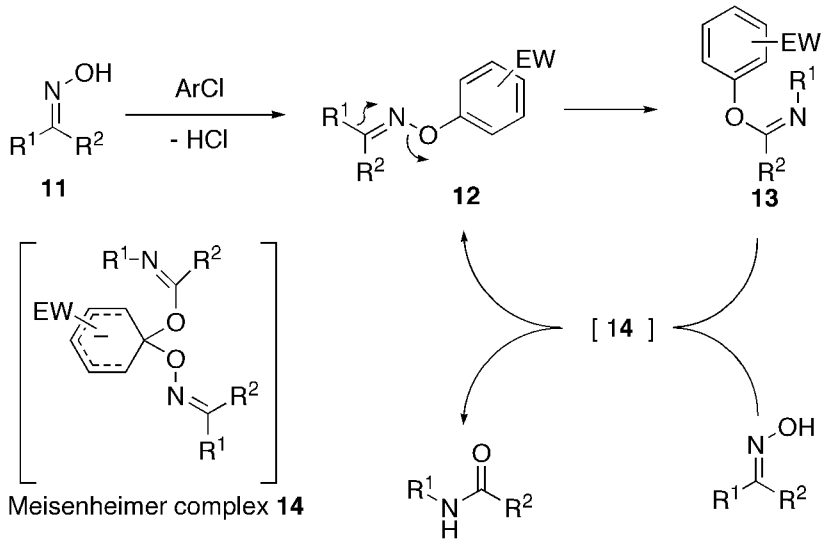


Scheme 4. Mechanism of Beckmann Rearrangement

Withdrawal of the hydroxyl group of oximes serves as a driving force to promote Beckmann rearrangement (Scheme 4). Therefore, it is important to activate a hydroxyl group efficiently. For example, there are methods that involve replacing the proton of a hydroxyl group by a good leaving group such as a tosyl group, or activating a hydroxyl group directly using Lewis acids. Lewis acids can serve as a catalyst, since the chemical nature of Lewis acids does not change and activity is maintained even though the reaction progresses. On the other hand, a tosyl group cannot be used as a catalyst because it is converted into a sulfonic acid after leaving an oxime or imidate. However, if there is a compound that can react with an oxime again and return to a leaving group, then such a compound may also be useful in Beckmann rearrangement as a catalyst. We tried to develop a catalytic Beckmann rearrangement by a new method of using a leaving group to catalytically withdraw a hydroxyl group.

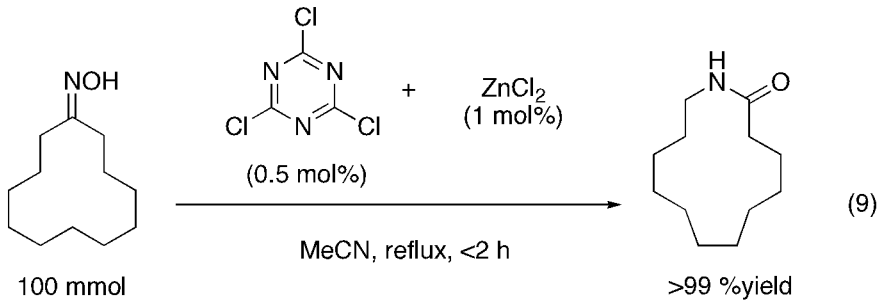
In 1951, Lampert and Bordwell reported that the Beckmann rearrangement of O-picrylbenzophenone oxime gave benzanilide through hydrolysis of a common intermediate, picryl N-phenylbenzimidate, under heating conditions in aqueous

solvents.[14] Intrigued by this reaction mechanism, we expected that chloroarenes bearing several strong electron-withdrawing groups might catalytically promote Beckmann rearrangement via the corresponding O-aryl ketoxime (12) and the Meisenheimer complex (14) which is obtained by the nucleophilic attack of ketoximes (11) to the O-aryl imidate intermediate (13) (Scheme 5).

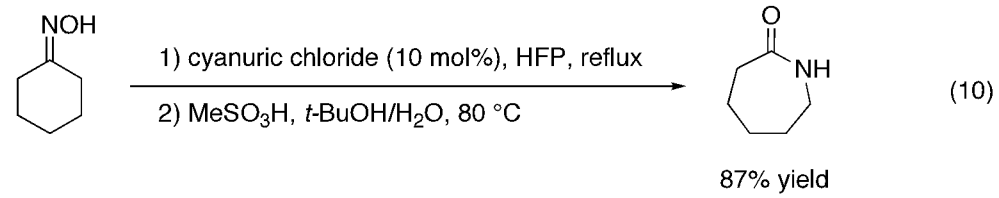


Scheme 5. New Strategy for Organocatalyzed Beckmann Rearrangement

Initially, we examined several chloroarenes as catalysts for Beckmann rearrangement in acetonitrile under reflux conditions. As a result, cyanuric chloride exhibited the highest catalytic activity. Furthermore, the catalytic use of $ZnCl_2$ as Lewis acid led to a significant increase in reactivity, and gave amides and lactams in quantitative yield [Eq. (9)].

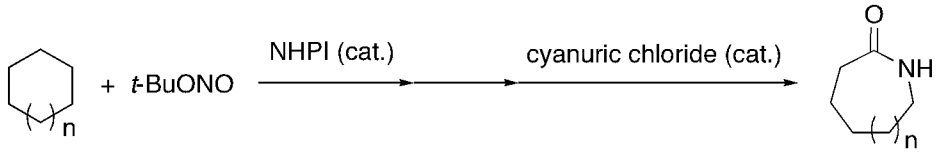


The utility of catalysis by cyanuric chloride was advanced by Ishii et al.[15] The Beckmann rearrangement of cyclohexanone oxime was improved with the use of cyanuric chloride in 1,1,1,3,3,3-hexafluoro-2-propanol (HFP), and ε-caprolactam was obtained in 87% yield [Eq. (10)]. Furthermore, the one-pot synthesis of lactams from cycloalkanes has been realized using N-hydroxyphthalimide (NHPI) and cyanuric chloride as key catalysts [Eq. (11)].



(10)

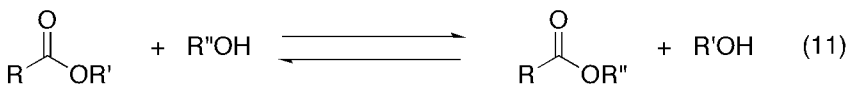
87% yield



(11)

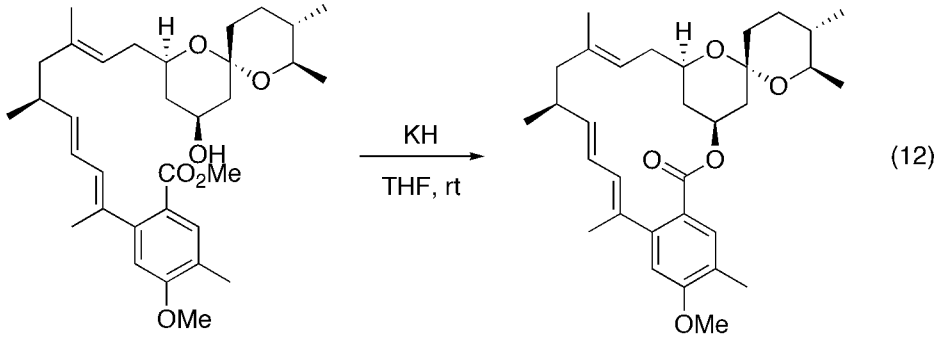
n = 1: 73% yield
n = 7: 72% yield

Chapter 4 describes the La(O–i-Pr)$_3$-catalyzed transesterification [Eq. (11)] of carboxylic esters with alcohols. The ester moiety is one of the most ubiquitous functional groups in chemistry, plays an important role in biology and act as both a key intermediate and/or a protecting group in organic transformations.[16] On some occasions, transesterification is more advantageous than ester synthesis from carboxylic acids and alcohols.[17] For instance, some carboxylic acids are only slightly soluble in organic solvents and accordingly are difficult to subject to homogeneous esterification, whereas esters are commonly soluble in most of organic solvents.

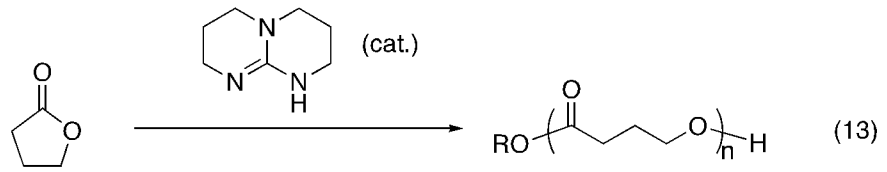


(11)

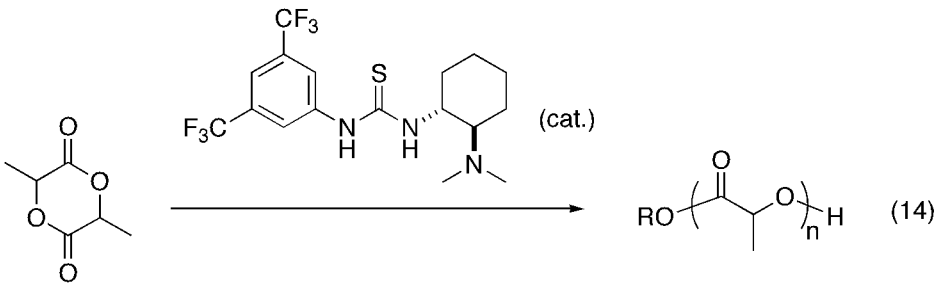
Transesterification is a powerful method for synthesizing a variety of organic esters.[16,17] In total synthesis, ester-to-ester transformation is used as a method for macrolactonization [Eq. (12)].[18] Transesterification is used not only in pure organic synthesis but also in polymerization, i.e. ring-opening of lactones and lactides [Eqs. (13) and (14)].[19]



(12)



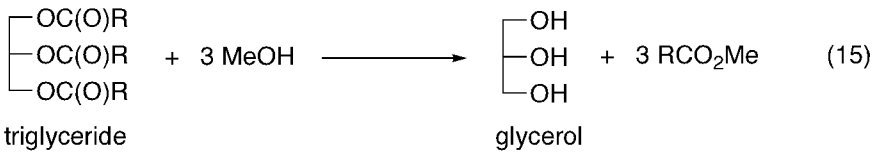
(13)



(14)

Besides its utility in the laboratory, this reaction also plays an important role in various industrial processes. The production of esters of oils and fats is very important and transesterification processes were described early in this century. Triglycerides are an important class of biological molecules that store chemical energy as the glycerol esters of long-chain fatty acids to fuel subsequent metabolism by the organism. The transesterification of triglycerides with methanol yields three methyl

esters of fatty acid chains of various lengths and saturation, as well as glycerol, as in Eq. (15). The combustion properties of long-chain fatty acid methyl esters make them a renewable source of energy known as biodiesel, the production of which is of current interest as an alternative diesel fuel.[20]



Typically, transesterification is catalyzed by a variety of protic and Lewis acids,[21] organic and inorganic bases,[22] and enzymes.[23] However, many of these reported catalysts require a large excess of one of the reactants to shift the equilibrium to the product side. Moreover, some of these reagents, particularly organotin compounds, are highly toxic. The growing interest in green chemistry has led to the development of a new generation of protocols which are aimed at a 1:1 stoichiometry between the ester and alcohol reactants under mild conditions. Thus, we were encouraged to develop a generally applicable, efficient transesterification procedure that involved simple operations and nontoxic reagents.

It has been reported that $La(O\text{-}i\text{-}Pr)_3$ and $La(OTf)_3$ are efficient catalysts for the transesterification of carboxylic esters in alcoholic solvent.[24,25] The active complex in the methanolysis of esters was proposed to be a methoxy-bridged dimeric structure (15) (Fig. 2).[25b] Complex 15 acts as a bifunctional catalyst which can activate both an ester and alcohol at the same time, and the reaction proceeds through transition state 16 shown in Fig. 1.

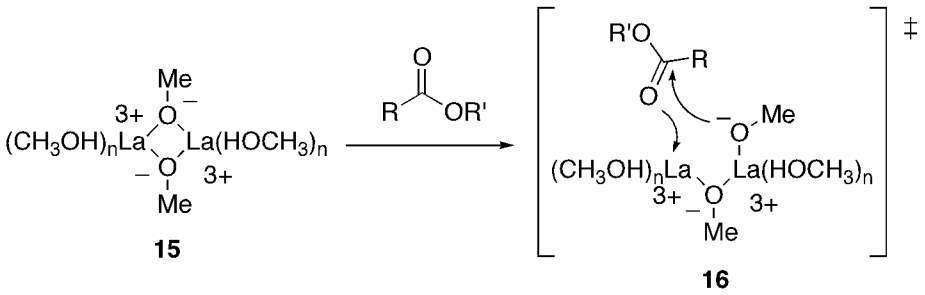
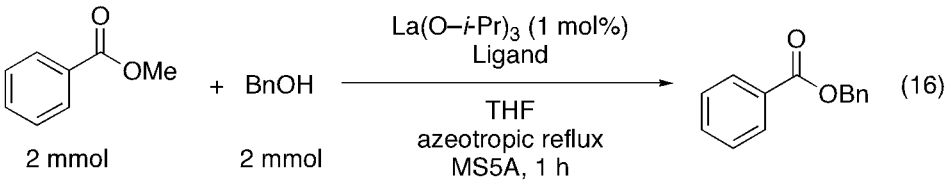
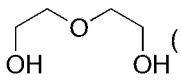


Figure 2. La(III) complex-catalyzed methanolysis of carboxylic esters.

Intrigued by this report, we focused on using ligands as a template for constructing bimetallic or polymetallic catalysts of La(O–i-Pr)$_3$ to increase the reactivity of transesterification.[26] As a result, we found that the reactivity of La(O–i-Pr)$_3$-catalyzed transesterification can be controlled by the ligand. Transesterification of methyl benzoate with benzyl alcohol in the presence of 1 mol% of La(O–i-Pr)$_3$ and diethylene glycol at azeotropic reflux with the removal of methanol gave benzyl benzoate in 77% yield [Eq. (16)].



Ligand	Yield (%)
none	35
 (1 mol%)	77

This catalytic system may be suitable for asymmetric reactions if the reactivity and structure of the catalyst can be controlled by a chiral ligand.

In summary, along the concept of green chemistry, we have developed the efficient synthetic processes, which are perrhenic acid-catalyzed dehydrative synthesis of nitriles, cyanuric chloride-catalyzed Beckmann rearrangement and $La(O\text{–}i\text{-}Pr)_3$–diethylene glycol complex-catalyzed transesterification. These newly developed synthetic methods can contribute to the improvement of the atom efficiency of the respective reactions. The details of the research and discussions are presented in the following chapters.

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24 For $La(O\text{–}i\text{-}Pr)_3$-catalyzed transesterification, see: T. Okano, K. Miyamoto, J. Kiji, Chem. Lett. 1995, 246.

25 For methanolysis of esters using $La(OTf)_3$, see: (a) A. A. Neverov, T. McDonald, G. Gibson, R. S. Brown, Can. J. Chem. 2001, 79, 1704. (b) J. S. W. Tsang, A. A. Neverov, R. S. Brown, J. Am. Chem. Soc. 2003, 125, 1559.

26 (a) K. Yabu, S. Masumoto, S. Yamasaki, Y. Hamashima, M. Kanai, W. Du, D. P. Curran, M. Shibasaki, J. Am. Chem. Soc. 2001, 123, 9908. (b) N. Kato, D. Tomita, K. Maki, M. Kanai, M. Shibasaki, J. Org. Chem. 2004, 69, 6128.

Chapter 2

Perrhenic Acid-Catalyzed Dehydration from Primary Amides, Aldoximes, N-Monoacylureas and α-Substituted Ketoximes to Nitrile Compounds.

Abstract: The dehydration reaction of primary amides is one of the most fundamental methods for the synthesis of nitriles, and the development of environmentally benign catalytic reaction processes is needed. We surveyed a variety of metal catalysts and found that perrhenic acid was extremely effective for the dehydration of not only primary amides but also aldoximes. Typically, 1 mol% of perrhenic acid gave the corresponding nitriles from amides or aldoximes under azeotropic reflux conditions with the removal of water in toluene or mesitylene. In addition, perrhenic acid is an extremely efficient catalyst for the Beckmann fragmentation of α-substituted ketoximes to functionalized nitriles. This new catalytic system can be applied to the gram-scale synthesis of nitriles without further modifications.

Introduction

The synthetic importance of the dehydration of primary aliphatic and aromatic amides to their corresponding nitriles has been thoroughly documented.[1,2] Most classical methods require the use of stoichiometric or excess amounts of highly reactive dehydrating reagents and harsh conditions in acidic or basic media, or involve tedious workup procedures. More recently, several methods for the dehydration of primary amides under milder conditions have been developed.[3] In 1990, Watanabe et al.[3a] found that dichlorotris(triphenylphospane)ruthenium (1 mol%) catalyzes the dehydration of primary amides in the presence of urea derivatives (1 equiv) in diglyme at 180 °C. In 1996, Mioskowaki et al.[3b] developed the paraformaldehyde-catalyzed (490 mol%) water-transfer reaction of primary amides in a formic acid/acetonitrile mixture. In 1999, Bose et al.[3c,d] reported the first catalytic dehydration of primary amides in the absence of any additives except for a catalyst. Unfortunately, this method requires a large amount of highly toxic dibutyltin oxide (25–35 mol%[3c] or 37 mol%[3d]) as a catalyst.

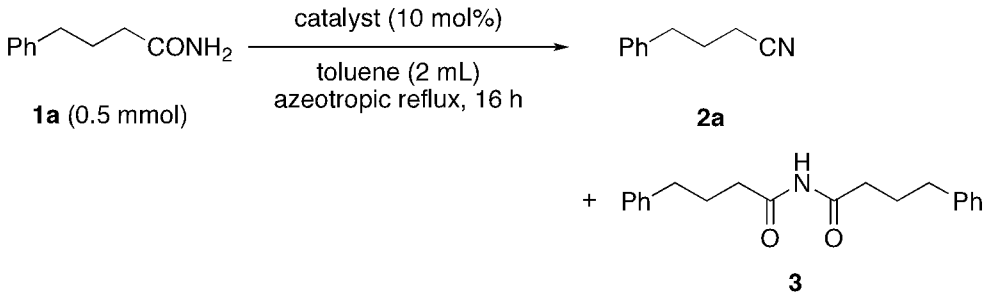
In our continuous studies on the development of various catalytic dehydration reactions in the absence of any additives except for catalyst, such as direct amide condensation,[4] direct ester condensation,[5] and the dehydration of alcohols,[6] we were interested in nitrile synthesis by catalytic dehydration reactions. We describe in this chapter perrhenic acid as an extremely active catalyst not only for dehydration reaction of primary amides and aldoximes but also for the Beckmann fragmentation of α-substituted ketoximes to synthesize various nitrile compounds.[7]

Results and Discussion

Dehydration reaction of primary amides. We first investigated the catalytic activities (10 mol%) of various metal salts, metal alkoxides, metal oxides, and

organometallic compounds that promote the model reaction of 4-phenylbutyramide (1a) in toluene at azeotropic reflux with the removal of water (Dean–Stark apparatus) for 16 hours (Table 1). Commercially available trimethylsilylperrhenate[8] was the most effective catalyst for this reaction (Table 1, entry 1), and a 65–70 wt% aqueous solution of perrhenic acid and anhydrous rhenium(VII) oxide exhibited higher catalytic activities than other metal compounds (Table 1, entries 2 and 3), whereas rhenium(VI) and rhenium(IV) oxides were inert (Table 1, entries 11 and 12). Since trimethylsilylperrhenate and rhenium(VII) oxide are very moisture-sensitive and highly expensive, we chose aqueous perrhenic acid (which is easy to handle and less expensive than trimethylsilylperrhenate) as a practical dehydration catalyst. Interestingly, dibutyltin oxide was almost inert under the same conditions (Table 1, entry 9).[3c,d]

Table 1. Dehydration of 4-Phenylbutyramide (1a) Catalyzed by Metal Compounds



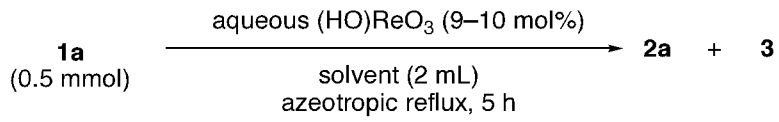
Entry	Catalyst	1a/2a/3
1	$(Me_3SiO)ReO_3$	15:82:3
2	$(HO)ReO_3$[a]	19:78:3
3	$(ReO_3)_2O$	62:32:6
4	$Zr(OiPr)_4$	77:23:0
5	$Hf(OtBu)_4$	82:12:0
6	$WOCl_3$	81:14:5
7	MoO_2Cl_2	81:11:8
8	$Ti(OiPr)_4$	89:11:0
9	Bu_2SnO	99:1:0
10	$VO(OiPr)_3$	100:0:0
11	ReO_3	100:0:0
12	ReO_2	100:0:0
13	$[RuCl_2(p\text{-cymene})]_2$	100:0:0

a) A 65–70 wt% solution of perrhenic acid (9–10 mol%) in water.

We next investigated the solvent effect on the dehydration reaction of 1a catalyzed by aqueous perrhenic acid (9–10 mol%) under azeotropic reflux conditions (Table 2). The yield of the corresponding nitrile (2a) was increased in the order toluene < chlorobenzene < o-xylene (Table 2, entries 2–4). Anisole was also a good

solvent, but its polarity slightly lowered the catalytic activity of perrhenic acid (Table 2, entry 1). The dehydration of 1a occurred smoothly only at temperatures above 125 °C. The addition of molecular sieves to the reaction mixture disturbed the dehydration.

Table 2. Solvent Effect on the Dehydration of 4-Phenylbutyramide (1a) Catalyzed by Aqueous Perrhenic Acid



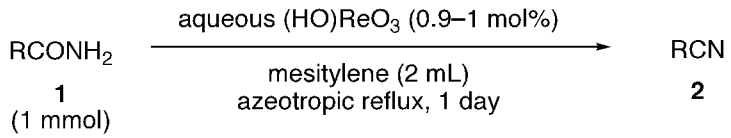
Entry	Solvent	t [°C][a]	1a/2a/3
1	Anisole	165	11:85:4
2	o-xylene	155	7:91:2
3	PhCl	140	9:89:2
4	Toluene	125	62:36:2
5	Heptane	110	98:2:0
6	EtCN	110	95:5:0
7	Dioxane	110	91:9:0

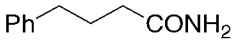
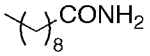
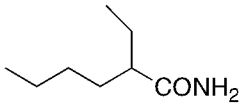
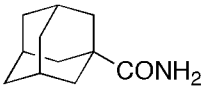
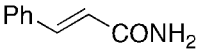
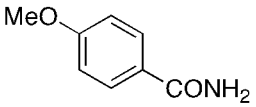
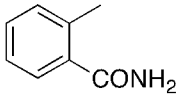
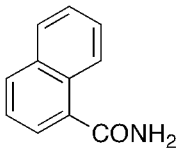
a) Bath temperature.

To explore the generality and scope of the above perrhenic acid-catalyzed dehydration reaction, various structurally diverse primary amides were examined (Table 3). The use of perrhenic acid (1 mol%) under azeotropic reflux conditions in mesitylene was adequate for dehydrating not only aliphatic amides but also aromatic amides. The catalyst could be quantitatively recovered from the reaction mixture by the distillation of products and solvents. For example, the catalyst was reused for the dehydration of o-toluamide (1g) more than three times with no loss of catalytic activity (Table 3, entry 7). This reusability of perrhenic acid is synthetically equal to >300 of TON. The reaction was successful for sterically congested amides such as

1-adamantanecarboxamide (1d) and 1g (Table 3, entries 4 and 7). The reaction of 3-ethylhexnamide (1c) was carried out in toluene in the presence of trimethylsilylperrhenate because the boiling point of the corresponding nitrile 2c is close to that of mesitylene (Table 3, entry 3). Anisole was effective as a solvent for the reaction of a less soluble amide such as 1-naphthalenecarboxamide (1h) in mesitylene (Table 3, entry 8).

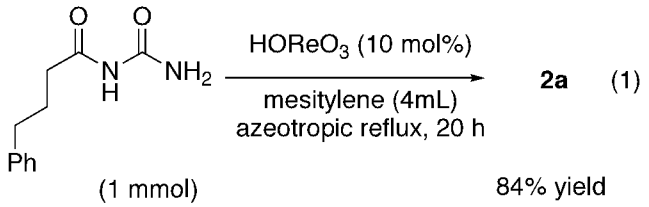
Table 3. Dehydration Reaction of Primary Amides Catalyzed by Aqueous Perrhenic Acid



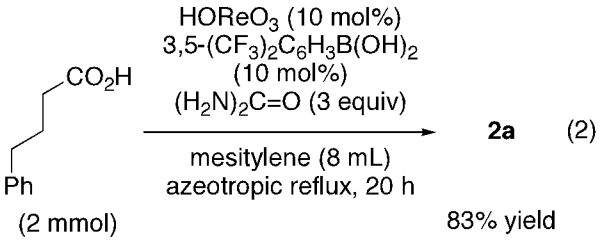
Entry	Primary amides		2 (%)[a]
1		1a	2a, 91
2		1b	2b, 54 (81[b])
3		1c	2c, 79[c]
4		1d	2d, 84
5		1e	2e, 64
6		1f	2f, 91
7[d]		1g	2g, >99 (1st run) 2g, >99 (2nd run) 2g, >99 (3rd run)
8		1h	2h, 93[e]

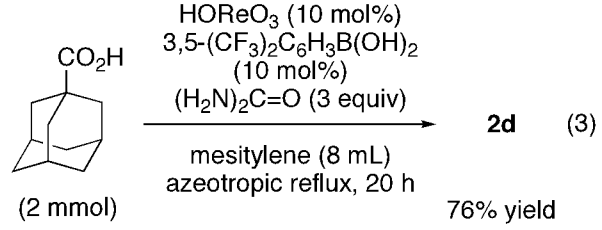
a) Isolated yield. b) $(Me_3SiO)ReO_3$ (1 mol%) for 2 days. c) $(Me_3SiO)ReO_3$ (10 mol%), toluene. d) Perrhenic acid (1 mol%) was reused. e) Anisole.

Recently, we reported the catalytic synthesis of N-acylureas through the direct condensation of carboxylic acids with ureas using 3,5-bis(trifluoromethyl)phenylboronic acid as a catalyst.[4c] We envisaged that a fragmentation reaction of N-monoacylureas to nitriles might proceed in the presence of perrhenic acid. In fact, N-(4-phenylbutyryl)urea was transformed to nitrile 2a via primary amide 1a as an intermediate by heating in mesitylene at azeotropic reflux in the presence of 10 mol% of perrhenic acid [Eq. (1)].



Furthermore, we succeeded in a one-pot synthesis of nitriles from the corresponding carboxylic acids and urea in the presence of a catalytic amount of 3,5-bis(trifluoromethyl)phenylboronic acid and perrhenic acid. Thus, 2a and 2g were obtained in good yields [Eqs. (2) and (3)]. This means that we can use urea as a synthetic equivalent of ammonia.



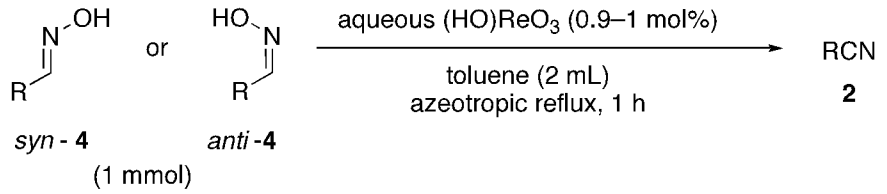


Dehydration reaction of aldoximes. Dehydration of aldoximes with an appropriate dehydrating agent is an alternative method for the synthesis of nitriles.[9] Recently, Yang and Chang reported that the catalytic dehydration of aldoximes can be promoted efficiently with $[RuCl_2(p\text{-cymene})]_2$ (3 mol%).[9a] However, this reaction requires molecular sieves (2 wt equiv) to increase the reaction rate. According to our comparative experiment in Table 1, entry 13, $[RuCl_2(p\text{-cymene})]_2$ was inert for the dehydration of primary amides. Furthermore, in 1993, Narasaka et al. reported that Bu_4NReO_4 is a good catalyst for the dehydration of aldoximes to nitriles in the presence of TfOH.[10] Although they gave an example of the dehydration of aldoximes, the yield of the obtained nitrile is not satisfactory. In their catalytic system, TfOH is necessary as a co-catalyst to activate Bu_4NReO_4, and therefore it is not suitable for acid-sensitive substrates. Thus, we interested in the catalytic activity and scope of perrhenic acid for the dehydration of aldoximes to nitriles.

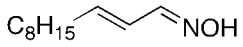
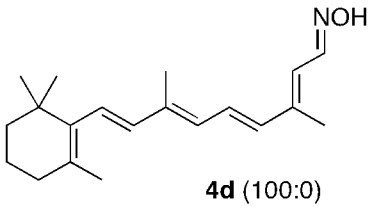
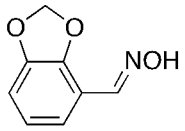
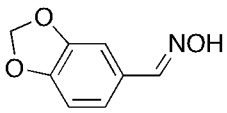
The dehydration reaction was examined with various structurally diverse aldoximes in the presence of aqueous perrhenic acid (1 mol%) under azeotropic reflux conditions in toluene or mesitylene (Table 4). The reaction was complete in less than 1 h for all aliphatic and aromatic substrates, except nicotinaldoxime (4l), and the corresponding nitriles were isolated in good to excellent yields. Sterically congested aldoximes such as cyclohexanecarbaldoxime (4b) (Table 4, entry 2), o-methoxybenzaldoxime (4e) (Table 4, entry 5), α-naphthalenecarbaldoxime (4j) (Table 4, entry 10), and mesitylenecarbaldoxime (4k) (Table 4, entry 11) were more reactive than less hindered aldoximes such as undecanaldoxime (4a) (Table 4, entry 1), and m- and p-methoxybenzaldoximes (4f and 4g respectively) (Table 4, entries 6 and 7): the former were dehydrated at reflux in toluene, whereas the latter were dehydrated at reflux in mesitylene. trans-2-Undecanaldoxime (4c) and all-trans-retinaldoxime (4d)[9a] were readily converted into their corresponding nitriles in high yield with partial inversion of the double bond (Table 4, entries 3 and 4). The present method was useful for acid-sensitive substrates such as

2,3-(methylenedioxy)benzaldoxime (4h) and 3,4-(methylenedioxy)benzaldoxime (4i) (Table 4, entries 8 and 9). Furthermore, perrhenic acid could be used as a dehydration catalyst in the presence of basic nitrogen-containing compounds: aldoxime 4l was smoothly dehydrated with the catalyst system to give pyridine-3-carbonitrile (2r) in 84% yield (Table 4, entry 12).

Table 4. Catalytic Dehydration of Aldoximes to Nitriles

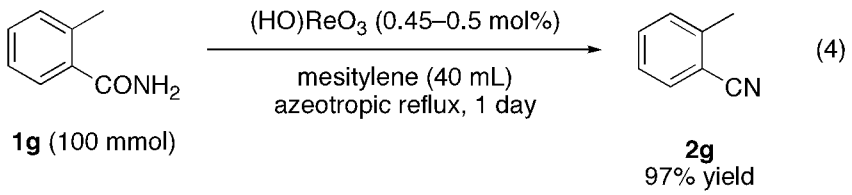


syn - **4** (1 mmol) *anti* -**4**

Entry	Aldoxime (syn/anti)	2 (%)[a]
1	n-$C_{10}H_{21}$CH=NOH 4a (0:100)	2i, >99[b]
2	cyclo-C_6H_{11}CH=NOH 4b (63:37)	2j, 91
3	 **4c** (97:3)	2k, 91[c]
4	 **4d** (100:0)	2l, 91[d],[e]
5	o-(MeO)C_6H_4CH=NOH 4e (100:0)	2m, 94[b]
6	m-(MeO)C_6H_4CH=NOH 4f (100:0)	2n, 86[b]
7	p-(MeO)C_6H_4CH=NOH 4g (100:0)	2f, 97[b]
8	 **4h** (100:0)	2o, 95[b]
9	 **4i** (100:0)	2p, 99[b]
10	1-NaphCH=NOH 4j (100:0)	2h, 98
11	2,4,6-$Me_3C_6H_2$CH=NOH 4k (100:0)	2q, >99
12	3-pyridylCH=NOH 4l (100:0)	2r, 84[b],[f]

a) Isolated yield. b) Mesitylene. c) The E/Z ratio of the product was 92:8. d) o-Xylene, 2 h. e) The isolated product was > 98% all-trans. f) 3 h.

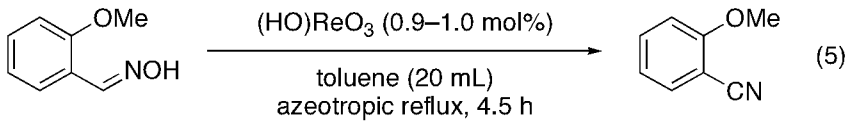
Application of the dehydration reaction to a large-scale process. The applicability of the present protocol to a large-scale process was investigated. Complete dehydration of amide 1g (100 mmol) and aldoxime 4e (40 mmol) was observed in the presence of aqueous perrhenic acid (<1 mol%), and the corresponding nitriles (2g and 2m) were isolated in high yield [Eqs. (1) and (2)].



1g (100 mmol)

2g
97% yield

(4)



4e (40 mmol)

2m
91% yield

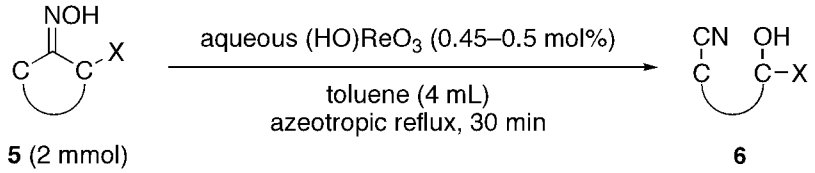
(5)

The Beckmann fragmentation of α-substituted ketoximes. The Beckmann fragmentation of α-substituted cyclic ketoximes is a powerful tool for the synthesis of functionalized nitriles.[11] However, most of the examples reported to date require the use of stoichiometric dehydrating or acidic reagents, and only a few reports have referred to the catalytic reaction.[12] For example, in 1983, Nishiyama and Itoh found that a catalytic amount of trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) promotes the Beckmann fragmentation of β-trimethylsilylketoxime acetates to unsaturated nitriles.[12a] The substrates of this catalytic system are limited to β-trialkylsilylated ketoximes because the silyl cation is required for regeneration of the catalyst. Since the activation step of fragmentation is the same as in the dehydration of aldoximes, we expected that perrhenic acid might effectively promote the fragmentaion of ketoximes bearing an electron-donating group at the α-position.

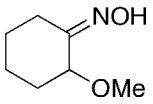
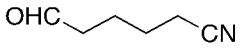
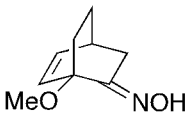
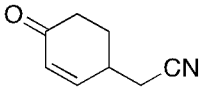
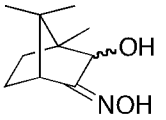
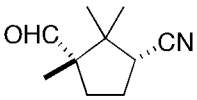
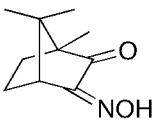
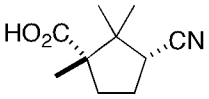
The Beckmann fragmentation of several ketoximes was examined in the

presence of 0.5 mol% of perrhenic acid under azeotropic reflux in toluene for 30 min (Table 5). As a result, the corresponding nitriles were obtained in excellent yield without any other side products. The use of $[RuCl_2(p\text{-cymen})]_2$,[9a] Bu_2SnO,[3c,d] and Me_3SiOTf[12a] instead of perrhenic acid as a catalyst showed no activity for the Beckmann fragmentation of 5a.

Table 5. Beckmann Fragmentation of α-Substituted Ketoximes



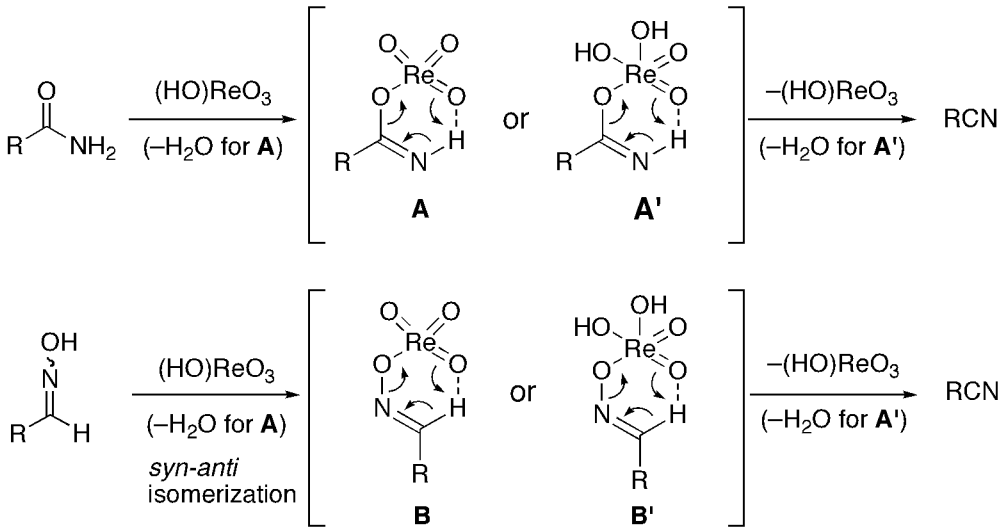
5 (2 mmol) **6**

Entry	Ketoxime		Product		Isolation yield (%)
1[a]		5a		6a	97
2		5b		6b	>99
3		5c		6c	>99
4		5d		6d	93

a) $[RuCl_2(p\text{-cymene})]_2$,[9a] Bu_2SnO,[3c, d] and Me_3SiOTf[12a] were inert.

Consideration of the reaction mechanism for the dehydration of primary amides and aldoximes catalyzed by perrhenic acid. Based on the reactivities of primary amides and aldoximes in perrhenic acid-catalyzed dehydrations, we propose the mechanism shown in Scheme 1. The reaction of the substrates and

perrhenic acid leads to six-membered cyclic transition states A and B (upon dehydration) or to the analogous transition states A' and B' (without dehydration).[3c,d] Dehydration of primary amides and aldoximes to produce nitriles should be promoted by the selective coordination of rhenium(VII) oxo complexes with their oxygen atoms. In contrast, coordination of the catalyst with the nitrogen atom of primary amides should give the corresponding imides (3). Therefore, the oxophilicity of rhenium(VII) oxo complexes is a significant factor in obtaining nitriles as major products.[13,14] The high reactivity of sterically congested aldoximes and the low reactivity of less hindered aldoximes can be explained through B and B', which is generated from a syn isomer of aldoximes. Syn/anti isomerization of aldoximes is known to occur under thermal or acidic conditions.[15] Therefore, the reactivity of aldoximes for this dehydration may depend on their syn/anti equilibrium under these reaction conditions. In the case of Beckmann fragmentation, the reaction mechanism could be explained by the idea that an oxygen atom on rhenium attacks the cationic carbon atom at the α-position of ketoximes instead of the proton in transition states B and B'. It is not clear why trimethylsilylperrhenate is more active than perrhenic acid and rhenium(VII) oxide. Pure perrhenic acid has not been isolated because it exists preferentially as a dimeric species $O_3ReOReO_3$ under anhydrous conditions,[16] whereas trimethylsilylperrhenate is monomeric. Therefore, monomeric rhenium(VII) oxo species may be more active than dimeric or oligomeric complexes.



Scheme 1. Proposed Mechanism for the Dehydration of Primary Amides and Aldoximes to from Nitriles

Conclusion

We have described several noteworthy features of new catalysts for the dehydration not only of primary amides and aldoximes but also of N-monoacylureas. Furthermore, we have also demonstrated that rhenium(VII) oxo complexes efficiently catalyze the Beckmann fragmentation of α-substituted ketoximes. These reactions proceed under essentially mild conditions, and the catalyst is recoverable and reusable. This protocol can be readily applied to large-scale processes with high efficiency and selectivity, making it an economical and environmentally benign process for the preparation of nitriles.

Experimental

General Methods. Infrared (IR) spectra were recorded on a JASCO FT/IR-460 plus spectrometer. ^{1}H NMR spectra were measured on a Varian Gemini-2000 spectrometer (300 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the scale, multiplicity (s = single; d = doublet; t = triplet; m = multiplet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a Varian Gemini-2000 spectrometer (75 MHz). Chemical shifts were recorded in ppm from the solvent resonance ($CDCl_3$ at 77.0 ppm). High-resolution mass spectral analysis (HRMS) was performed at the Chemical Instrument Room, Research Center for Material Science, Nagoya University. Microanalyses were performed at the Chemical Instrument Room, Research Center for Material Science, Nagoya University. For preparative column chromatography, Merck silica gel 60 (0.040–0.063 mm) was used. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Trimethylsilylperrhenate was purchased from Gelest-Azmax. Perrhenic acid (65–70 % in water, 99.999+ %) and rhenium(VII) oxide were purchased from Aldrich.

Procedure for Preparing for Primary Amides (Table 3). (Method A)[17] To a stirred solution of 10 mmol of nitrile in 10 mL of DMSO, cooled in an ice bath, are added 30% 1.2 mL of H_2O_2 and 0.2 g of anhydrous K_2CO_3. The mixture is allowed to warm up to room temperature. After 5 min. distilled water (50 mL) is added, cooling applied, after the product was precipitated, the white solid was separated by filteration and washed successively with water, and dried over under reduced pressure.

(Method B) To a stirred solution of aqueous NH_3 (1.5 mL, 20 mmol), triethylamine

(2.9 mL, 15 mmol) and a catalytic amount of DMAP in 10 mL of MeCN was slowly added acyl chloride (10 mmol) at 0 °C. The mixture was allowed to come to room temperature. After completion of reaction, organic layer was extracted with EtOAc from aqueous HCl layer and aqueous $NaHCO_3$ layer, and washed with brine, dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the residue was purified by column chromatography on silica gel to give pure product.

(Method C) 1.2 equiv of Oxalyl chloride (1.04 mL, 12 mmol) was added to the suspension of 10 mmol of carboxylic acid and catalytic amount of DMF in dichloromethane at 0 °C, and the mixture was allowed to come to room temperature. After completion of reaction, a large part of solvent was evaporated, and the crude product was purified by column chromatography on silica gel to give pure prodeuct.

4-Phenylbutamide (1a), 1-Naphtylcarboxamide (1h) are prepared by method A and commercially available.

Decanamide (1b) was prepared by method B and commercially available.

2-Ethylhexanamide (1c) was prepared by method C and commercially available.

1-Adamantanecarboxamide (1d), Cinnamamide (2e), 4-Methoxybenzamide (1f) and o-Toluamide (1g) are purchased from Acros–Organics, TCI, Japan, and Sigma–Aldrich Japan.

Representative Procedure for Preparing Aldoximes (Table 4). To a solution of hydroxylamine hydrochloride (2.6 g, 37 mmol) in 4 mL of water were added aldehyde (30 mmol) and solution of sodium carbonate (2.0 g, 18.7 mmol) in water, and the mixture was stirred at room temperature. After completion of reaction, organic layer was separated and washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel to give pure product.

(E)-Undec-2-enal oxime (4c). a syn/anti mixture (The ratio of syn/anti

was 97/3 determined by ^{1}H NMR spectra.). IR (neat) 3205, 3067, 2925, 2855, 1649, 1465, 1336, 1117, 976 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) for syn-4c δ 7.73 (d, J = 9.0 Hz, 1H), 7.59 (bs, 1H), 6.16–5.99 (m, 2H), 2.16 (q, J = 6.9 Hz, 2H), 1.44–1.27 (m, 12H), 0.88 (t, J = 6.6 Hz, 3H); for anti-4c δ 7.04 (d, J = 9.3 Hz, 1H), 6.72 (dd, J = 9.6, 15.6 Hz, 1H), 6.12 (dt, J = 6.9, 15.6 Hz, 1H), 2.19 (q, J = 7.2 Hz, 2H), 1.44–1.27 (m, 12H), 0.88 (t, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) for syn-4c δ 151.7, 142.8, 123.6, 32.7, 31.8, 29.3, 29.2, 29.1, 28.6, 22.6, 14.0; for anti-4c δ 148.7, 144.2, 118.6, 32.8, 31.7, 29.3, 29.1 (2C), 28.5, 22.6, 14.0; HRMS (FAB) calcd for $C_{11}H_{21}NO$ [(M+H)$^+$] 184.1701, found 184.1700.

2,3-Methylenedioxybenzaldoxime (4h). IR (KBr) 3264, 2986, 2908, 2785, 1498, 1463, 1309, 1253, 1222, 1201, 1082, 1028, 968, 927 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.14 (s, 1H), 6.96–6.83 (m, 3H), 6.07 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 146.0, 145.1, 121.8, 121.1, 114.5, 109.5, 101.5 ; HRMS (FAB) calcd for $C_8H_7NO_3$ [(M+H)$^+$] 166.0504, found 166.0500.

Undecanaldoxime (4a)[18] and all-trans-Retinaldoxime (4d)[9a] are known compounds. The spectroscopic properties were identical to those reported in the literature.

Cyclohexanecarbaldoxime (4b), o-Mthoxybenzaldoxime (4e), m-Mthoxybenzaldoxime (4f), p-Mthoxybenzaldoxime (4e), 3,4-Methylenedioxybenzaldoxime (4i). 1-Naphtaldoxime (4j), 2,4,6-trimethylbenzaldoxime (4k) and Nicotinaldoxime (4l) were commercially available.

General Procedure for The Dehydration of Primary Amides and Aldoximes (Tables 3 and 4). A solution of primary amides (1 mmol) or aldoximes (1 mmol), perrhenic acid (65–70 wt% solution in water, 0.009–0.010 mmol, 0.9–1.0 mol%), and solvent (2 mL) was heated at azeotropic reflux with the removal of water. After several hours, the mixture was cooled to ambient temperature and saturated

aqueous $NaHCO_3$ was added. The organic layer was extracted with ethyl acetate and dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel.

The following products are commercially available: 4-Phenylbutyronitrile (2a), Decanenitrile (2b), 2-EthylHexanenitrile (2c), 1-adamantanecarbonitrile (2d), cinnamonitrile (2e), 4-Methoxybenzonitrile (2f), o-Tolunitrile (2g), 1-Naphtonitrile (1h), Undecanenitrile (2i), Cyclohexanecarbonitrile (2j), 2-Methoxybenzonitrile (2m), 3-Methoxybenzonitrile (2n), 3,4-Methylenedioxybenzonitrile (2p), 2,4,6-Trimethylbenzonitrile (2q), Nicotinonitrile (2r).

The following products have been previously reported: (E)-1-Cyano-1-decene (2k)[19], 3,7-Dimethyl-9-(2′,6′,6′,-trimethyl-1′-cyclohexen-1′-yl)-2,4,6,8-nonatetraenenitrile (2l)[9a], 2,3-Methylenedioxybenzonitrile (2o).[20]

Procedure for Preparation of N-Carbamoyl-4-phenylbutanamide. A mixture of 4-phenylbutanoic acid (131 mg, 2 mmol), urea (132 mg, 2.2 mmol) and 3,5-bis(trifluoromethyl)phenylboronic acid (25.8 mg, 0.1 mmol) in toluene (10 mL) was heated at azeotropic reflux with removal of water. After reaction completed, the resulting mixture was cooled to ambient temperature and washed with saturated aqueous ammonium chloride and satulated aqueous $NaHCO_3$, and the product was extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$, The solvent was evaporated, and the residue was purified by flash column chromatography on silica gel to give pure product in 92% yield. IR(KBr) 3378, 3327, 3229, 1655, 1418, 1183, 1095, 696 cm^{-1}; ^1H NMR (300 MHz, THF-d8) δ 9.68 (s, 1H), 7.98 (s, 1H), 7.26–7.11 (m, 5H), 6.70 (s, 1H), 2.63 (t, J=7.5 Hz, 2H), 2.29 (t, J=7.5, 2H), 1.92 (quintet, J=7.5 Hz, 2H)); ^{13}C NMR (75 MHz, THF-d_8) δ 175.0, 155.4, 142.6, 129.2, 129.1, 126.6, 36.4, 35.9, 27.3; HRMS (FAB) calcd for $C_{11}H_{15}N_2O_2$ [(M+H)$^+$]

168.1025, found 168.1013.

Procedure for Dehydration of N-Carbamoyl-4-phenylbutanamide. A mixture of N-Carbamoyl-4-phenylbutanamide, perrhenic acid (65–70 wt% solution in water, 0.09–0.10 mmol, 9.0–10 mol%), and mesitylene (4 mL) was heated at azeotropic reflux with the removal of water. After 20 hours, the mixture was cooled to ambient temperature and saturated aqueous $NaHCO_3$ was added. The organic layer was extracted with ethyl acetate and dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel to give 1a in 84% yield.

Procedure for One-Pot Synthesis of Nitriles from Carboxylic Acids and Ureas. A mixture of carboxylic acid, urea (46.0 mg, 6 mmol), 3,5-bis(trifluoromethyl)phenylboronic acid (51.6 mg, 0.2 mmol, 10 mol%), perrhenic acid (65–70 wt% solution in water, 0.09–0.10 mmol, 9.0–10 mol%), and mesitylene (8 mL) was heated at azeotropic reflux with the removal of water. After 1 day, the mixture was cooled to ambient temperature and saturated aqueous $NaHCO_3$ was added. The organic layer was extracted with ethyl acetate and dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel to give pure product.

Procedure for Preparation of To a mixture of ketone (13 mmol) and 2.3 equiv of hydroxylamine hydrochloride (2.0 g, 30 mmol) in 18 mL of methanol, 9mL of aqueous solution of sodium acetate trihydrate (4.5 g, 32.5 mmol) was adde at rt. The mixture was then refluxed until all starting material consumed. The reaction mixture was poured into saturated aqueous $NaHCO_3$, the organic layer was extracted with ethyl acetate and washed with brine. Drying of combined extracts over $MgSO_4$, followed by evaporative concentration, and flash chromatography on silica gel gave the pure

product.

2-Methoxycyclohexanone oxime (5a) is a known compound.[21]

1-Methoxybicyclo[2.2.2]oct-5-en-2-one oxime (5b) was prepared from 1-Methoxybicyclo[2.2.2]oct-5-en-2-one:[22] IR (KBr) 3230, 2970, 1613, 1422, 1112, 1015 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (bs, 1H), 6.36 (d, J=3.6 Hz, 2H), 3.54 (s, 3H), 2.83 (bs, 1H), 2.43 (dd, J=2.5, 17.8 Hz, 1H), 2.26 (dt, J=18.0, 3.1 Hz, 1H), 1.90–1.81 (m, 1H), 1.75–1.64 (m, 2H), 1.57–1.50 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 134.5, 131.5, 79.2, 52.7, 31.3, 30.0, 29.1, 24.8; HRMS (FAB) calcd for $C_9H_{14}NO_2$ [(M+H)$^+$] 168.1025, found 168.1013.

Bicyclo[2.2.2]heptan-2-one-3-hydroxy-4,7,7-trimethyl oxime (5c) and 3-(hydroxyimino)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (5d) are commercially compounds.

General Procedure for Beckmann Fragmentation of Ketoximes (Table 5). A solution of ketoximes (2 mmol), perrhenic acid (65–70 wt% solution in water, 0.009–0.010 mmol, 0.45–0.50 mol%), and toluene (4 mL) was heated at azeotropic reflux with the removal of water for 30 min. The resulting mixture was purified by flash column chromatography on silica gel to afford pure products.

5-Cyanopentanal (6a),[23] 3-Formyl-2,2,3-trimethyl-cyclopentanecarbonitrile (6c)[24] and 3-Cyano-1,2,2-trimethylcyanopentanecarboxylic acid (8)[25] are known compoubds.

(4-Oxo-cyclohex-2-enyl)acetonitrile (6b). IR(neat) 2954, 2870, 2247, 1682, 1390, 1252 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.82 (dt, J=10.2, 2.4 Hz, 1H), 6.12 (dd, J=1.9, 10.0 Hz, 1H), 2.93–2.83 (m, 1H), 2.63–2.54 (m, 3H), 2.44 (ddd, J=5.1, 12.0, 17.1 Hz, 1H), 2.34–2.24 (m, 1H), 1.90 (ddt, J=10.0, 13.0, 4.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6, 149.1, 130.8, 117.3, 36.1, 32.9, 28.2, 22.5; HRMS (FAB) calcd for $C_8H_{10}NO$ [(M+H)$^+$] 136.0762, found 136.0762.

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Chapter 3

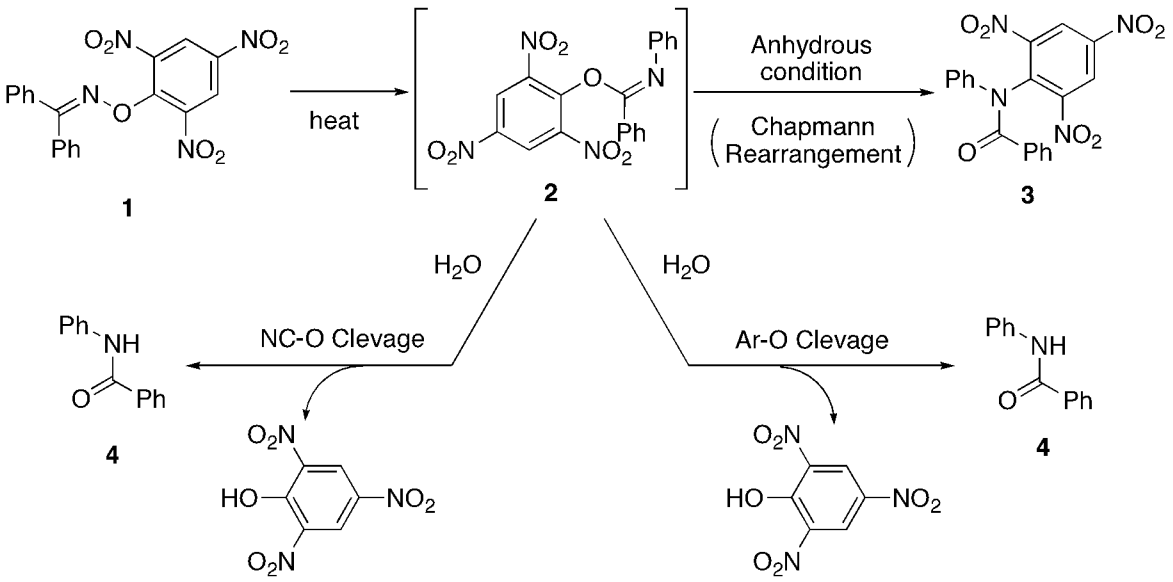
Cyanuri Chloride as a Mild and Active Beckmann Rearrangement Catalyst

Abstract: More environmentally benign alternative to current chemical processes are highly desirable. Beckmann rearrangement is one of the most important amide synthetic transformations. Although numerous methods for the catalytic Beckmann rearrangement have already been explored and developed, there are few successful examples under mild conditions. We describe the first general organocatalytic Beckmann rearrangement under mild conditions. Commercially available cyanuric chloride was an extremely active catalyst for the Beckmann rearrangement of ketoximes. Furthermore, the addition of acids such as HCl and $ZnCl_2$ are effective as co-catalysts of cyanuric chloride. For example, azacyclotridecan-2-one, which is synthetically valuable as a starting material of nylon-12, has been prepared in quantitative yield by the Beckmann rearrangement of cyclododecanone oxime (100 mmol scale) catalyzed by cyanuric chloride (0.5 mol%) and $ZnCl_2$ (1 mol%).

Introduction

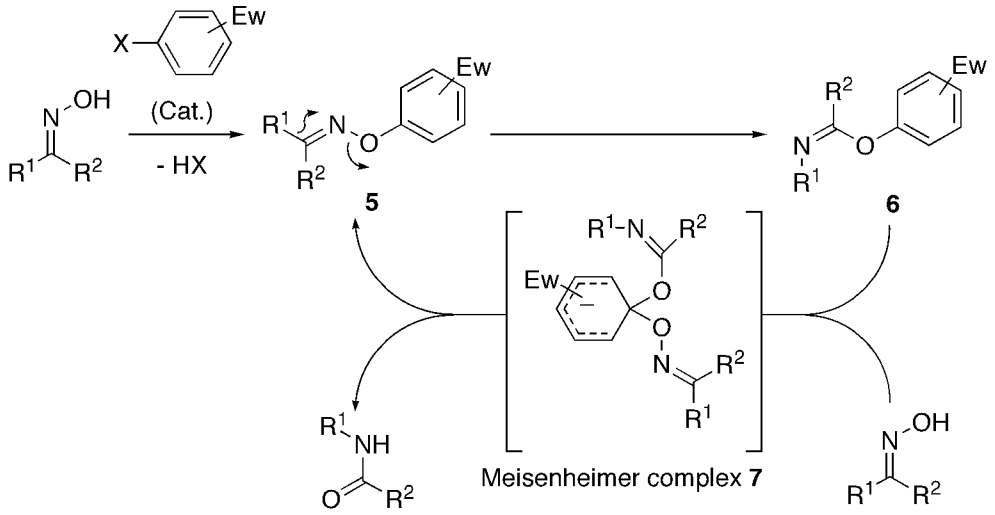
The Beckmann rearrangement is commonly used in organic chemistry to transform ketoximes into amides.[1,2] The reaction generally requires high reaction temperatures and strongly acidic and dehydrating media.[1,2] Thus, this reaction leads to large amount of byproducts and cannot be used with sensitive substrates. I described in this chapter that 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride, 9a)[3,4] is a highly effective catalyst for the Beckmann rearrangement under reflux in acetonitrile or nitromethane. To the best my knowledge, this is the first example of an organocatalytic Beckmann rearrangement.

The Beckmann rearrangemnt of O-picrylbenzophenone oxime (1) is known to give N-picrylbenzamide (3) and benzamide (4) via a common intermediate, picryl N-phenylbenzimidate (2), under heating conditions in anhydrous and aqueous solvents, respectively (Scheme 1).[5] Product 3 is formed through a 1,3-shift of the picryl cation of 2 (Ar–O or NC–O cleavage).



Scheme 1. Beckamn Rearrangement o 1

If the above Beckmann rearrangement is performed in the presence of excess benzophenone oxime in the place of water in an anhydrous solvent, 1 may be reproducted with 4 through the nucleophilic attack of benzophenone oxime to 2 (Ar–O cleavage). On the basis of this assumption, a new strategy for organocatalyzed Beckmann rearrangement was proposed, as shown in Scheme 2. We expected that chloroarenes bearing several strong electron-withdrawing groups, such picryl chloride (8a), might catalytically promote Beckmann rearrangement via the corresponding O-aryl ketoxime 5, O-aryl imidate intermediate 6, and Meisenheimer complex 7.[6]



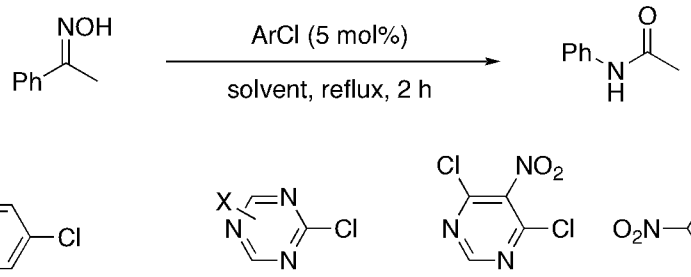
Scheme 2. A New Strategy for Organocatalyzed Beckmann Rearangement

Results and Discussion

First, several chloroarenes (5 mol%) were examined as catalysts for the Beckmann rearrangement of acetophenone oxime in acetonitrile under reflux conditions for 2 h (Table 1). As expected, the use of 8a gave acetanilide in 45% yield. 8a was the most active catalyst among chlorobenzenes bearing electron-withdrawing groups (e.g, entries 2 and 3). By further screening of chloroarenes, we found that

cyanuric chloride 9a was much more effective than 8a (entry 4). In contrast, 4,6-dimethoxy-2-chloro-1,3,5-triazine (9b) was inert (entry 5). This result can be easily understood by the electron-donating effect of the two methoxy groups. Although 4,6-dichloro-5-nitropyridine (10) and 2-chloro-3,5-dinitoropyridine (11) were also as effective as 8a (entries 7 and 8), 9a exhibited outstanding catalytic activity. The solvent effect was also investigated (entries 8–11). Polar and nucleophilic solvents, such as acetonitrile and nitromethane, were suitable for this catalysis.

Table 1. ArCl-Catalyzed Beckamnn Rearrangement of Acetophenone Oxime[a)]



8a: X = 2,4,6-$(NO_2)_3$ **9a**: X = 4,6-Cl_2 **10** **11**
8b: X = 2,6-(NO_2)-4-CN **9b**: X = 4,6-$(OMe)_2$
8c: X = 2,6-(NO_2)-4-CF_3

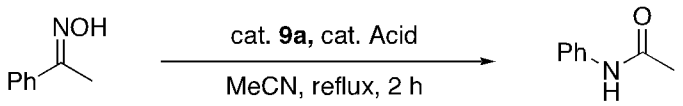
entry	ArCl	solvent (bp)	yield (%)
1	8a	MeCN (82 °C)	43
2	8b	MeCN (82 °C)	15
3	8c	MeCN (82 °C)	0
4	9a	MeCN (82 °C)	100
5	9b	MeCN (82 °C)	0
6	10	MeCN (82 °C)	58
7	11	MeCN (82 °C)	44
8	9a	MeCN (82 °C)	100
9	9a	1,4-dioxane (101 °C)	5
10	9a	acetone (56 °C)	16
11	9a	toluene (110 °C)	8

a) The rearrangement of acetophenone oxime (2 mmol) was carried out in a solvent (4 mL) in presence of 5 mol% of ArCl

Next, several Lewis acids and Brønsted acids were examined as cocatalysts for 9a to firther increase the catalytic activity of 9a. Representative results are shown in Table 2. The Beckmann rearrangement of acetophenone oxime proceeded quantitatively in the presence of 9a (2 mol%) and mild Lewis acids (2 mol%), such as

$ZnCl_2$, $FeCl_3$, $CoCl_2$, and $BiCl_3$, within 2 h (entries 2–5). However, this rearrangement was quit slow in the presence of 2 mol% of 9a without any cocatalysts (entry 1). Furthermore, these weak Lewis acids and Brønsted acids were inert or less active for this rearrangement in the absence of 9a (entries 2–5 and 11). Brønsted acids, such as TsOH and HCl, were also effective, but less effective than the above Lewis acids (entries 10 and 11). Therefore, less-expensive $ZnCl_2$ was the best choice as a cocatalyst for 9a. The addition of more than 2 equive of $ZnCl_2$ per 9a further activates the rearrangement (entries 12–14). Thus, the rearrangement gave acetanilide in 97%yield within 2 h in the presence of 9a (1 mol%) and $ZnCl_2$ (2 mol%) (entry 13).

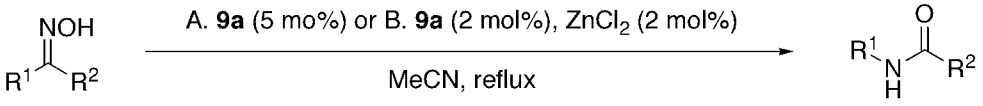
Table. 2 Effect of Acids as Cocatalysts on the 9a-Catalyzed Beckmann Rarrangement of Acetophenone Oxime[a)]



entry	9a (mol%)	acid (mol%)	yield (%)	entry	9a (mol%)	acid (mol%)	yield (%)
1	2		31	9	2	$CuCl_2$ (2)	10
2	2	$ZnCl_2$ (2)	100 [0][b)]	10	2	TsOH (2)	69
3	2	$FeCl_3$ (2)	100 [0][b)]	11	2	HCl (2)[c)]	50 [3][b)]
4	2	$CoCl_2$ (2)	100 [0][b)]	12	1	$ZnCl_2$ (1)	67
5	2	$BiCl_3$ (2)	100 [13][b)]	13	1	$ZnCl_2$ (2)	97
6	2	$GeCl_4$ (2)	83	14	1	$ZnCl_2$ (3)	98
7	2	$FeCl_2$ (2)	49	15	1	$FeCl_3$ (2)	59
8	2	$MgCl_2$ (2)	32	16	1	$CoCl_2$ (2)	70

a) The rearrangement of acetophenone oxime (5 mmol) was carried out in MeCN (10 mL). b) The results in the absence of 9a are indicated in brackets. c) 4 M HCl solution in 1,4-dioxane.

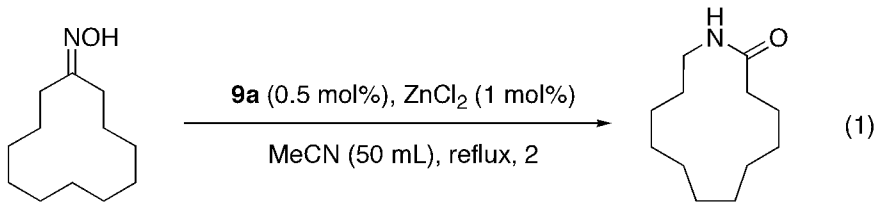
Table 3. Generality and Scope of The Beckmann Rearrangement Catalyzed by 9a or 9a–$ZnCl_2$[a)]



entry	R^1	R^2	time (h), yield (%)[b)]	
			condition A	condition B
1	Ph	Me	2, 97	2, 99
2	o-(MeO)C_6H_4	Me	1, 98	1, 99
3	m-(MeO)C_6H_4	Me	6, 93	2, 96
4	p-(MeO)C_6H_4	Me	2, 94	1, 99
5	p-FC_6H_4	Me	4, 92	2, 97
6	3,4-(CH_2O_2)C_6H_3[c)]	Me		2, 98
7	2-naphthyl	Me	4, 96	2, 98
8	Ph	i-Pr		1, 97[d)]
9	Ph	$(CH_2)_2CO_2Me$		2, 95
10	C_8H_{17}	Me	4, 94	2, 96
11	i-Pr	i-Pr		1, 97
12	$(CH_2)_{11}$		1, 98	1, 97
13	$(CH_2)_{10}$			1, 95
14	$(CH_2)_9$			1, 96
15	$(CH_2)_7$			6, 27
16	$(CH_2)_5$		2, 30[e)]	

a) The rearrangement of ketoxime (2 mmol) was carried out in MeCN (4 mL). b) Isolated yield. c) 3,4-Methylenedioxyphenyl. d) N-Phenylisobutyramide and N-isopropylbenzamide were obtained in 49 and 48%, respectively. e) 10 mol% of 9a was used.

To explore the generality and scope of the Beckmann rearrangement catalyzed by 9a or 9a–$ZnCl_2$, representative ketoximes as substrates were examined under reflux conditions in acetonitrile (Table 3). Not only aromatic but also aliphatic ketoximes were smoothly rearranged of under both conditions A and B. In particular, the rearrangement of most substrates was complete within 2 h under condition B. Acetal and ester groups in ketoximes were tolerable under these conditions (entries 6 and 9). Large cycloalkanone oximes were also very reactive and were trans formed to the corresponding lactams, whoch were useful as starting materials for nylons.[7] Unfortunately, the reaction of six- to eight-menbered cycloalkanone oximes gave the desired lactams in poor yield (entries 15 and 16).



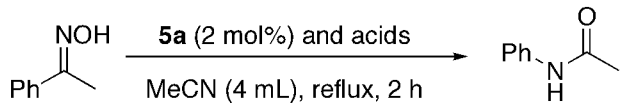
100 mmol >99% yield (1)

The applicability of the present protocol to a large-scale process was examined. The Beckmann rearrangement of cyclododecanone oxime (100 mmol) was complete within 2 h in the presence of 9a (0.5 mol%) and $ZnCl_2$ (1 mol%) (eq. 1).

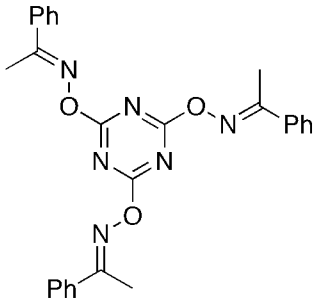
To ascertain that the present organocatalytic Beckmann rearrangement occurred via O-aryl ketoxime 5, the rearrangement of acetophenone oxime was attempted in the presence of 2 mol% of 5a in place of 9a (Table 4). 5a was almost inert in the absence of acids. On the other hand, 5a acted as an organocatlyst in the presence of HCl (6 mol%) or $ZnCl_2$ (2 mol%). Finally, this rearrangement was extremely accelerated by the combined use of 5a (2 mol%), HCl (6 mol%) and $ZnCl_2$ (2 mol%) (see entry 2, Table 2). These experimental results suggested that HCl, whitch is generated in situ from ketoximes and 9a by nucleophilic substitution, plays a very important role in this organocatalysis of 9a: HCl and $ZnCl_2$ probably promote the rearrangemnt of 5a by their chelation with nitrogen atoms of 5a and substituted

oxime.[4b]

Table 4. Beckmann Rearrangement of Acetophenone Oxime Catalyzed by 5a and Acids



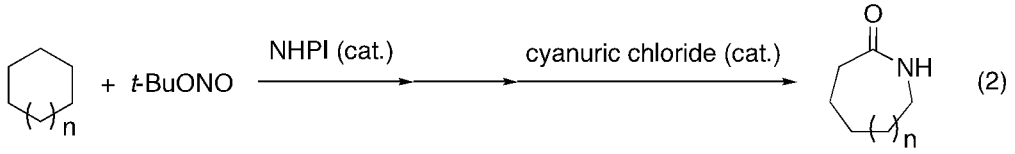
acids (mol%)	yield (%) of acetanilide
–	2
HCl (6)	68
$ZnCl_x$ (2)	12
HCl (6) + $ZnCl_x$ (2)	96



5a

Conclusion

In summary, we have realized the first general organocatalytic Beckmann rearrangement of ketoximes into amides. Commercially available 9a was the most effective organocatalyst, and acids such as HCl and $ZnCl_2$ were effective as cocatalysts for 9a. The utility of this catalysis of cyanuric chloride has advanced by the research of Ishii et. al.[8] The Beckmann rearrangement of cyclohexanone oxime was improved using cyanuric chloride in 1,1,1,3,3,3-hexafluoro-2-propanole (HFP), and ε-caprolacatm was obtained in 87% yield. Furthermore, one-pot synthesis of lacatms from cycloalkanes has been realized by using N-hydroxyphthalinide (NHPI) and cyanuric chloride as key catalyst [Eq. (2)].



(2)

n = 1: 73% yield
n = 7: 72% yield

Experimental

General Methods. Infrared (IR) spectra were recorded on a JASCO FT/IR-460 plus spectrometer. ^{1}H NMR spectra were measured on a Varian Gemini-2000 spectrometer (300 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the scale, multiplicity (s = single; d = doublet; t = triplet; m = multiplet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a Varian Gemini-2000 spectrometer (75 MHz). Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm). High-resolution mass spectral analysis (HRMS) was performed at the Chemical Instrument Room, Research Center for Material Science, Nagoya University. Microanalyses were performed at the Chemical Instrument Room, Research Center for Material Science, Nagoya University. For preparative column chromatography, Merck silica gel 60 (0.040–0.063 mm) was used. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. In experiments that required dry solvent, acetonitirile, nitromethane, toluene, and acetone were purchased from TCI or Wako as the "anhydrous" and stored over 4A molecular sieves. 1,4-Dioxane was freshly distilled from sodium. Other simple chemicals were analytical-grade and obtained commercially.

Representative Procedure for Preparing Ketoximes. To a suspension of ketone (30 mmol) and 2.3 equiv of hydroxylamine hydrochloride (69 mmol) in 40 mL of MeOH, 2.5 equiv of sodium acetate trihydrate in 20 mL of water was added at room temperature, and the mixture was refluxed for 1 h. After completion of reaction, the mixture was cooled to 0 °C and neutralized with saturated aqueous sodium hydrogen carbonate, and diluted with ether. The organic layer was separated, washed successively with brine and dried over anhydrous magnesium sulfate. The solvent

was removed in vacuo, and the obtained product was purified in good yield by distillation or sublimation under reduced pressure.

Acetophenone Oxime (entry 1, Table 3): Purchased from TCI, Japan.

o-Methoxyacetophenone Oxime (entry 2, Table 3):[9] IR (film) 3221, 2925, 1599, 1579, 1493, 1460, 1435, 1270, 1246, 1025, 917, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (br, 1H), 7.34–7.28 (m, 2H), 6.90–6.97 (m, 2H), 3.83 (s, 3H), 2.23 (s, 3H).

m-Methoxyacetophenone Oxime (entry 3, Table 3):[9] IR (film) 3250, 3076, 3003, 2938, 2835, 1600, 1579, 1488, 1464, 1454, 1429, 1302, 1231, 1040, 1006, 942, 855, 783, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.07 (br, 1H), 7.33–7.25 (m, 1H), 7.22–7.18 (m, 2H), 6.95–6.91 (m, 1H), 3.84 (s, 3H), 2.29 (s, 3H).

p-Methoxyacetophenone Oxime (entry 4, Table 3):[9] IR (KBr) 3244, 2926, 1607, 1577, 1512, 1311, 1249, 1182, 1024, 922, 837, 822, 599 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.90 (br, 1H), 7.58 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 3.83 (s, 3H), 2.27 (s, 3H).

p-Fluoroacetophenone Oxime (entry 5, Table 3): Purchased from Across Organics.

1-(benzo[d][1,3]dioxol-5-yl)ethanone Oxime (entry 6, Table 3):[9] IR (KBr) 2922, 1735, 1498, 1448, 1302, 1228, 1036, 944, 807 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.18 (d, J = 1.5 Hz, 1H), 7.10 (dd, J = 1.5, 8.1 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 5.99 (s, 3H), 2.24 (s, 3H).

1-(Naphthalen-2-yl)ethanone Oxime (entry 7, Table 3):[9] IR (KBr) 3215, 3053, 2911, 1597, 1503, 1448, 1420, 1384, 1307, 1196, 1132, 1017, 925, 825, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (br, 1H), 7.88–7.83 (m, 4H), 7.51–7.48 (m, 3H), 2.40 (s, 3H).

Isobutyrophenone Oxime (entry 8, Table 3):[10] a cis- and trans-isomeric mixture (44:56); IR (KBr) 3267, 2968, 2930, 1456, 1384, 1314, 1019, 946, 770, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.65 (br, 0.44H), 9.30 (br, 0.56H), 7.45–7.24 (m,

5H), 3.60 (septet, J = 7.2 Hz, 0.44 H), 2.83 (septet, J = 6.9 Hz, 0.56H), 1.21 (d, J = 7.2 Hz, 2.64H), 1.13 (d, J = 6.9 Hz, 3.36H).

Methyl 4-(Hydroxyimino)-4-phenylbutanoate (entry 9, Table 3):[11] E/Z ratio = 90 : 10; IR (film) 3404, 3057, 2952, 1737,1497, 1439, 1284, 1201, 1174, 937, 762, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) for (E)-isomer δ 8.81 (br, 1H), 7.63–7.59 (m, 2H), 7.57–7.40 (m, 3H), 3.66 (s, 3H), 3.10–3.16 (m, 2H), 2.56–2.65 (m, 2 H); ^1H NMR (300 MHz, $CDCl_3$) for (Z)-isomer δ 7.63–7.60 (m, 2H), 7.45–7.37 (m, 3H), 3.68 (s, 3H), 2.89 (t, J = 7.4 Hz, 2H), 2.66–2.57 (m, 2H).

2-Decanone Oxime (entry 10, Table 3):[10] E/Z ratio = 76 : 24; IR (KBr) 3236, 2925, 2856,1665, 1465, 1368, 1113, 956, 722 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) for (E)-isomer δ 7.90–7.60 (br, 1H), 2.17 (t, J = 7.5 Hz, 2H), 1.86 (s, 3H), 1.52–1.47 (br, 2H), 1.27 (br, 10H), 0.90–0.86 (m, 3H); ^1H NMR (300 MHz, $CDCl_3$) for (Z)-isomer δ 7.90–7.60 (br, 1H), 2.36 (t, J = 7.5 Hz, 2H), 1.87 (s, 3H), 1.27 (br, 10H), 0.90-0.86 (m, 3H).

Diisopropylketone Oxime (entry 11, Table 3):[11] IR (KBr) 3312, 2924, 1656, 1462, 1385, 1365, 1117, 1022, 934, 867, 762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.72 (br, 1H), 3.21 (septet, J = 6.9 Hz, 1H), 2.57 (septet, J = 6.9 Hz, 1H), 1.16 (d, J = 6.9 Hz, 6H), 1.13 (d, J = 6.9 Hz, 6H).

Cyclododecanone Oxime (entry 12, Table 3):[14] Purchased from Sigma–Aldrich Japan.

Cycloundecanone Oxime (entry 13, Table 3):[15] IR (KBr) 2924, 2859, 1637, 1474, 935, 729 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.36–2.27 (m, 4H), 1.79 (q, J = 6.3 Hz, 2H), 1.70–1.62 (m, 2H), 1.48–1.42 (m, 12H).

Cyclodecanone Oxime (entry 14, Table 3):[15,16] IR (KBr) 3266, 2920, 2861, 1472, 1434, 949, 935 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.44 (t, J = 6.6 Hz, 2H), 1.83–1.71 (m, 4H), 1.59–1.42 (m, 10H).

Cyclooctanone Oxime (entry 15, Table 3): Purchased from Sigma-–Aldrich Japan.

Cyclohexanone Oxime (entry 16, Table 3): Purchased from TCI, Japan.

Representative Procedure for the Beckmann Rearrangement of Ketoximes (Table 3). (Condition A) The mixture of ketoxime (2 mmol) and 5 mol% of cyanuric chloride 9a (18.41 mg, 0.1 mmol) in 4 mL of dry MeCN was refluxed. After completion of reaction, it was quenched with saturated aqueous sodium hydrogen carbonate. The organic layer was extracted with ethyl acetate, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel to give the corresponding amide in high yield. (Condition B) The mixture of ketoxime (2 mmol) and 2 mol% of cyanuric chloride 9a (7.36 mg, 0.04 mmol) and $ZnCl_2$ (5.45 mg, 0.04 mmol) in 4 mL of dry MeCN was refluxed. After completion of reaction, it was quenched with saturated aqueous sodium hydrogen carbonate. The organic layer was extracted with ethyl acetate, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel to give the corresponding amide in high yield.

Acetanilide (entry 1, Table 3):[9] IR (KBr) 3293, 3155, 1657, 1597, 1555, 1500, 1434, 1369, 1322, 1264, 755, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.40 (br, 1H), 7.36–7.26 (m, 2H), 7.10 (t, J = 7.2 Hz, 1H), 2.17 (s, 3H).

o-Methoxyacetanilide (entry 2, Table 3):[9] IR (KBr) 3250, 2924, 1654, 1541, 1496, 1458, 1252, 1117, 1025, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.36 (dd, J = 1.8, 7.8 Hz, 1H), 7.76 (br, 1H), 7.07–6.92 (m, 2H), 6.87 (dd, J = 1.8, 8.1 Hz, 1H), 3.88 (s, 3H), 2.20 (s, 3H).

m-Methoxyacetanilide (entry 3, Table 3):[9] IR (KBr) 3257, 2924, 2853, 1664, 1607, 1562, 1494, 1417, 1282, 1155, 1051, 860, 766, 688 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (br, 1H), 7.28–7.18 (m, 2H), 6.96 (d, J = 8.1 Hz, 1H), 6.61 (dd, J = 2.1, 8.0 Hz, 1H), 3.80 (s, 3H), 2.17 (s, 3H).

p-Methoxyacetanilide (entry 4, Table 3):[9] IR (KBr) 3242, 2924, 2853,

1743, 1647, 1606, 1512, 1246, 1030, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J = 9.0 Hz, 2H), 7.07 (brs, 1H), 6.86 (d, J = 9.0 Hz, 2H), 3.79 (s, 3H), 2.16 (s, 3H).

p-Fluoroacetanilide (entry 5, Table 3):[9] IR (KBr) 3290, 3071, 2923, 2853, 1662, 1617, 1559, 1507, 1402, 1235, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (dd, J = 4.8, 9.0 Hz, 2H), 7.18 (brs, 1H), 7.01 (d, J = 9.0 Hz, 2H), 2.17 (s, 3H).

3,4-Methylendioxyacetanilide (entry 6, Table 3);[9] IR (KBr) 3326, 2923, 1742, 1662, 1546, 1486, 1444, 1238, 1181, 1039, 814 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, J = 1.2 Hz, 1H), 7.11 (br, 1H), 6.75-6.74 (m, 2H), 5.95 (s, 2H), 2.15 (s, 3H).

N-(2-Naphthyl)acetamide (entry 7, Table 3):[9] IR (KBr) 3283, 1668, 1589, 1561, 1471, 1396, 1281, 858, 816, 746 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (br, 1H), 7.76–7.80 (m, 4H), 7.46–7.40 (m, 3H), 2.24 (s, 3H).

N-Isopropylbenzamide (entry 8, Table 3):[17] IR (KBr) 3299, 2971, 1632, 1347, 1289, 1170, 1137, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78–7.74 (m, 2H), 7.51–7.38 (m, 3H), 6.11 (br, 1H), 4.28 (m, 1H), 1.26 (d, J = 6.6 Hz).

N-Phenylisobutyramide (entry 8, Table 3):[18] IR (KBr) 3433, 3302, 2968, 1661, 1600, 1549, 1442, 1309, 758, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (br, 1H), 7.55–7.08 (m, 5H), 2.51 (septet, J = 6.9 Hz, 1H), 1.26 (d, J = 6.9 Hz, 6H).

Methyl 4-oxo-4-(phenylamino)butanoate (entry 9, Table 3):[9] IR (KBr) 3360, 2924, 2853, 1724, 1685, 1597, 1543, 1500, 1445, 1404, 1365, 1312, 1244, 1216, 1167, 761, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (brs, 1H), 7.52–7.10 (m, 5H), 3.72 (s, 3H), 2.77 (t, J = 6.6 Hz, 2H), 2.67 (t, J = 6.6 Hz, 2H).

N-Octylacetamide (entry 10, Table3):[9] IR (film) 3289, 3088, 2956, 2856, 1652, 1558, 1465, 1438, 1370, 723, 603 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.49 (br, 1H), 3.26–3.19 (m, 2H), 1.97 (s, 3H), 1.51–1.44 (m, 2H), 1.27 (br, 10H), 0.88 (t, J = 6.3 Hz, 3H).

N-Isopropylisobutyramide (entry 11, Table 3):[18] IR (KBr) 3297, 2970, 2933, 2873, 1644, 1551, 1366, 1244, 1179, 1096, 699 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$) δ 5.23 (br, 1H), 4.13–4.02 (m, 1H), 2.28 (septet, J = 6.9 Hz, 1H), 1.14 (d, J = 6.9 Hz, 12H).

Azacyclotrideca-2-one (entry 12, Table 3):[9] IR (KBr) 3299, 2931, 2854, 1639, 1546, 1448, 1059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.31 (dd, J = 6.0, 10.8 Hz, 2H), 2.22–2.18 (m, 2H), 1.70–1.64 (m, 2H), 1.51–1.48 (m, 2H), 1.32 (br, 14H).

Azacyclododecan-2-one (entry 13, Table 3):[19] IR (KBr) 3313, 2926, 1639, 1545, 1466 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.25–2.20 (m, 2H), 1.74–1.54 (m, 4H), 1.47–1.26 (m, 14H).

Azacycloundecan-2-one (entry 15, Table 3):[20] IR (KBr) 3307, 2929, 1638, 1551, 1463, 689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.33 (dd, J = 5.4, 11.1 Hz, 2H), 2.23–2.18 (m, 2H), 1.78–1.32 (m, 14H).

Azacyclononan-2-one (entry 15, Table 3):[9] IR (KBr) 3313, 2927, 1646, 1541, 1447, 1155, 1031, 797, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.63 (br, 1H), 3.38–3.35 (m, 2H), 2.44 (t, J = 6.3 Hz, 2H), 1.80–1.62 (m, 6H).

ε-Caprolactam (entry 16, Table 3):[9] IR (KBr) 3211, 3075, 2928, 2856, 1654, 1486, 1438, 1417, 1365, 1198, 1125, 823 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.05 (br, 1H), 3.21 (t, J = 6.3 Hz, 2H), 2.47 (t, J = 5.7 Hz, 2H), 1.80–1.62 (m, 6H).

Preparation of O-2,4,6-Tris(1-phenylethylideneaminoxy)-1,3,5-triazine (5a). To a stirred solution of acetophenone oxime (2.04 g, 15 mmol) and 9a (922 mg, 5 mmol) in 10 mL of dry MeCN, triethylamine (2.23 mL, 16 mmol)was added at room temperature. After 5a was precipitated, the white solid was separated by filtration, and washed successively with ether, water and dried under reduced pressure (>90% yield). Mp 155–156 °C; IR (KBr) 2923, 1578, 1552, 1459, 1355, 1105, 1077, 886, 755, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 8.1 Hz, 6H), 7.47–7.43 (m, 9H), 2.56 (s, 9H); cm^{-1}; ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5 (3C), 163.4 (3C), 134.8 (3C), 130.8 (3C), 128.6 (6C), 127.3 (6C), 14.8 (3C). Anal. Calcd for $C_{27}H_{24}N_6O_3$: C, 67.49; H, 5.03; N, 17.49; Found: C, 67.04; H, 4.91; N, 17.23.

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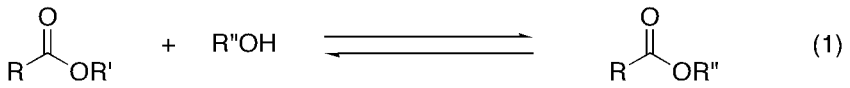
Chapter 4

Ligand Effect of Diethyleneglycol Derivatives on $La(O\text{–}i\text{-}Pr)_3$-Catalyzed Transesterification of Carboxylic Esters with Alcohols

Abstract: Transesterification is one of the most important reactions in organic synthesis. Besides its utility in the laboratory, this reaction also plays a significant role in various industrial processes. While several useful and reliable transesterification methods have been reported, only a few examples have achieved the stoichiometric transesterification of esters with alcohols in a 1: 1 ratio under catalytic conditions. We investigated the $La(O\text{–}i\text{-}Pr)_3$-catalyzed transesterification of esters with a stoichiometric amount of alcohols, and found that diethylene glycol was an efficient ligand of $La(O\text{–}i\text{-}Pr)_3$.

Introduction

Transesterification is an important synthetic method in the laboratory as well as in industrial processes.[1] This transformation takes place via an alkoxy moiety exchange between an ester and an alcohol (Eq. 1). Since this reaction is an equilibrium process, a large excess amounts of one of alcohols is usually required to shift the equilibrium to the product side. The growing interest in green chemistry has led to the development of a new generation of protocols that are aimed at a 1:1 stoichiometry between the ester and alcohol reactants under mild conditions. While several procedures catalyzed by a variety of protic and Lewis acids,[2] organic and inorganic bases,[3] enzymes[4] have been developed, only a few examples have achieved stoichiometric transesterification under catalytic conditions. Recently, the mild and neutral esterification of carboxylic acids with alcohols in a 1:1 molar ratio catalyzed by bulky ammonium sulfonate has been developed in our laboratory.[5] We were also interested in the development of an environmentally benign alternative esterification process.



(1)

It has been reported that $La(O\text{–}i\text{-}Pr)_3$ and $La(OTf)_3$ are efficient catalysts for the transesterification of carboxylic esters in alcoholic solvents.[6,7] The active complex of the methanolysis of esters was proposed to be a methoxy-bridged dimeric structure (1) (Fig. 1).[7b] Complex 1 acts as a bifunctional catalyst which can activate both esters and alcohols at the same time, and the reaction proceeds through transition state 2 shown in Fig. 1.

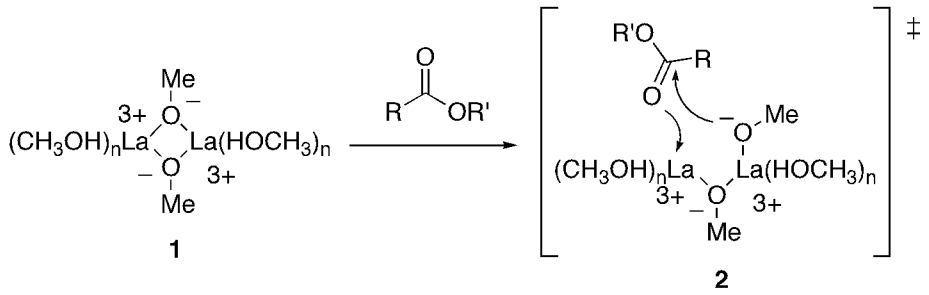


Figure 1. La(III) complex-catalyzed methanolysis of carboxylic esters.

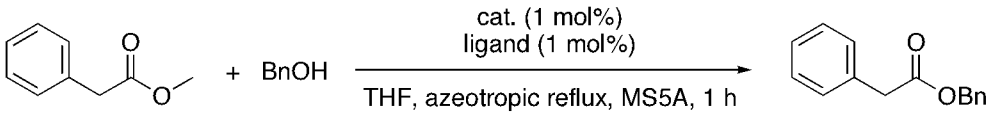
Intrigued by this chapter, we focused on using ligands as a template for constructing bimetallic or polymetallic catalysts of La(O–i-Pr)$_3$ to increase the reactivity of transestrification.[8]

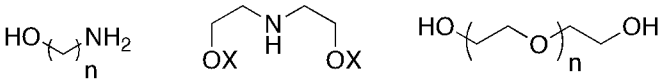
Results and Discussion

We initially confirmed that La(O–i-Pr)$_3$ was catalytically active for transesterification between methyl phenylacetate and benzyl alcohol in a 1 : 1 molar ratio in THF under azeotropic reflux with the removal of methanol in the presence of MS5A. La(O–i-Pr)$_3$ was an effective catalyst for this reaction even by use of reactants in a 1 : 1 ratio (Table 1, entry 1). On the other hands, Ti(O–i-Pr)$_3$ and Yb(O–i-Pr)$_3$ gave no desired products under the same conditions (Table 1, entries 2 and 3), and La(OTf)$_3$, which is an effective catalyst for the methanolysis of esters, did not show catalytic activity under these conditions (Table 1, entry 4). Next, to examine the efficiency of a ligand on lanthanum(III), various ligands such as phosphines, phosphine oxides, amines and alcohols, we examined. Aminoalcohol 3b slightly accelerated the reactivity (Table 1, entry 6), and the use of diethanolamine (4a) and diethylene glycol (5a) proved to be effective for the desired transformation and provided benzyl phenylacetate in respective yields of 73% and 79% (Table 1, entries 9 and 11). When we switched to dimethylamino ether (4b) or changed the length of the

linker moiety of glycols (5c and 5d), the activation effect by the ligand was lower than with 4a and 5a.

Table 1. Ligand Effects on the La(O–i-Pr)$_3$-catalyzed Transesterification of Methyl Phenylacetate with Benzyl Alcohol[a)]





3a: n = 2
3b: n = 3
3c: n = 4
3d: n = 5

4a: OX = OH
4b: OX = OMe

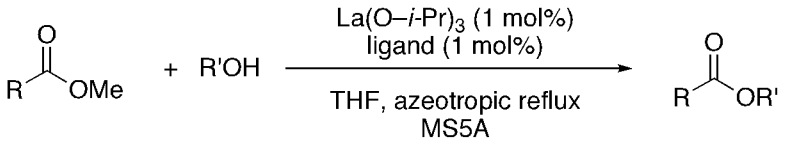
5a: n = 1
5c: n = 2
5d: n = 3

entry	Cat.	Ligand	yield (%)
1	La(O–i-Pr)$_3$	–	58
2	Ti(O–i-Pr)$_3$	–	0
3	Yb(O–i-Pr)$_3$	–	0
4	La(OTf)$_3$	–	0
5	La(O–i-Pr)$_3$	3a	43
6	La(O–i-Pr)$_3$	3b	66
7	La(O–i-Pr)$_3$	3c	29
8	La(O–i-Pr)$_3$	3d	28
9	La(O–i-Pr)$_3$	4a	73
10	La(O–i-Pr)$_3$	4b	55
11	La(O–i-Pr)$_3$	5a	79
12	La(O–i-Pr)$_3$	5b	65
13	La(O–i-Pr)$_3$	5c	51

a) Reaction conducted in THF (4 mL) in the presence of methyl phenylacetate (2 mmol) and benzyl alcohol (2 mmol) at azeotropic reflux with the removal of methanol using MS5Å mounted on a Soxhlet extractor.

To explore the generality and scope of the transesterification catalyzed by $La(O\text{–}i\text{-}Pr)_3$ in the presence of a catalytic amount of ligand, several combinations of esters and alcohols were examined (Table 2). The transesterification of methyl phenylacetate and methyl benzoate with benzyl alcohol using ligand 5a gave the corresponding esters in good yield at 1 h and 3 h, respectively (Table 2, entries 1 and 3). A striking difference in the activation effect by ligands was observed between 4a and 5a when benzoate, which shows low reactivity for transesterification, was used as a starting ester (Table 2, entries 2 and 4). This catalysis was applicable to reactions with alcohols with a long alkyl chain such as n-octanol (Table 2, entry 5) and secondary alcohols such as cyclohexanol (Table 2, entry 6).

Table 2. Scope and Generality of Transesterification Catalyzed by $La(O\text{–}i\text{-}Pr)_3$ in the Presence of Catalytic Amount of Ligand[a)]



Entry	R	R'	ligand	Time (h)	yield
1	$PhCH_2$	$PhCH_2$	5a	1	79
2	Ph	$PhCH_2$	–	1	35
3			5a	1	77
4			5a	3	81
5			4a	1	55
6	Ph	n-C_8H_{17}	5a	8	98
7		cycl-C_6H_{11}	5a	15	64

Conclusion

In summary, we found that La(O–i-Pr)$_3$-catalyzed transesterification can be controlled by the ligand, and diethylene glycol is an efficient ligand of La(O–i-Pr)$_3$ for transesterification of ester and alcohol in a 1:1 molar ratio. As La^{3+}-diethylene glycol complex is undissolved in the solvent, the catalyst might be a polymetallic structure of La^{3+} aggregated with diethylene glycol. Further investigation of the details of the reaction mechanism and the design of a proper ligand might make it possible to improve the reactivity of transesterification. This catalytic system which is controlled by the ligand may be suitable for use in an asymmetric reaction, such as kinetic resolution of alcohols[9] and the asymmetric ring-opening of epoxides,[10] using chiral ligands.

Experimental

General Methods. Infrared (IR) spectra were recorded on a JASCO FT/IR-460 plus spectrometer. ^{1}H NMR spectra were measured on a Varian Gemini-2000 spectrometer (300 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the scale, multiplicity (s = single; d = doublet; t = triplet; m = multiplet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a Varian Gemini-2000 spectrometer (75 MHz). Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm). High-resolution mass spectral analysis (HRMS) was performed at the Chemical Instrument Room, Research Center for Material Science, Nagoya University. Microanalyses were performed at the Chemical Instrument Room, Research Center for Material Science, Nagoya University. For preparative column chromatography, Merck silica gel 60 (0.040–0.063 mm) was used. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. $La(Oi\text{-}Pr)_3$ was purchased from Soekawa Chemicals. In experiments that required dry solvent, tetrahydrofuran was purchased from Kanto Chemical Co. as the "dehydrated stabilizer free". Methyl esters and alcohols as substrates were distilled from CaH_2 and stored under Nitrogen. Other simple chemicals were analytical-grade and obtained commercially.

Representative Procedure for the Transesterification of Methyl Esters and Alcohols (Table 2). To a mixture of $La(O\text{–}i\text{-}Pr)_3$ (6.32 mg, 0.02 mmol) in anhydrous THF was added diethylene glycol (1.87 μL, 0.02 mmol) at room temperature, and the mixture was stirred for 1 h. To this mixture were added 2 mmol of alcohol and methyl ester and the mixture was refluxed under the removal of

methanol using MS5Å mounted on a Soxhlet extractor for several hours. After the reaction mixture was allowed to come to room temperature, it was diluted with hexane and a few drops of water and anhydrous magnesium sulfate were added. The mixture was filtered and the solvent was then evaporated. The crude product was purified by column chromatography on silica gel to give the corresponding ester.

The following products are commercially available: Benzyl phenylacetate (Table 2), Benzyl benzoate (Table 2).

The following products have been previously reported: n-Octyl benzoate (Table 2)[11], Cyclohexyl benzoate (Table 2)[12].

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Publication List

1. Rhenium(VII) Oxo Complexes as Extremely Active Catalysts in the Dehydration of Primary Amides and Aldoximes to Nitriles.
Kazuaki Ishihara, Yoshiro Furuya, Hisashi Yamamoto
Angew. Chem. Int. Ed. 2002, 41, 2983.

2. Cyanuric Chloride as a Mild and Active Beckmann Rearrangement Catalyst.
Yoshiro Furuya, Kazuaki Ishihara, Hisashi Yamamoto
J. Am. Chem. Soc. 2005, 127, 11240.

3. Perrhenic Acid-Catalyzed Dehydration from Primary Amides, Aldoximes, N-Monoacylureas and α-Substituted Ketoximes to Nitrile Compounds.
Yoshiro Furuya, Kazuaki Ishihara, Hisashi Yamamoto
Bull. Chem. Soc. Jpn. 2007, in press.

4. Ligand Effect of Diethyleneglycol Derivatives on La(O–i-Pr)$_3$-Catalyzed Transesterification of Caboxylic Esters with Alcohols.
Kazuaki Ishihara, Yoshiro Furuya
In preparation.

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