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Brønsted acid catalyzed transoximation reaction: synthesis of aldoximes and ketoximes without use of hydroxylamine salts

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The transoximation reaction enables the transfer of oxime to a carbonyl compound and is catalyzed by transoximase in the pupae of silkworm. Inspired by this bio-synthetic pathway, we achieved the transoximation of oximes to aldehydes and ketones catalyzed by Brønsted acid under mild conditions. Hydroxylamine salt, which necessitates a stoichiometric amount of base, was not required. NMR analysis clarified that this reaction proceeded through hydroxylamines generated by the successive hydrolysis of oxime in situ. In addition, an environmentally benign method for catalytic transoximation was demonstrated in aqueous medium on a one hundred gram, scale and the reaction filtrate containing the catalyst was recovered and reused over 10 times.

Introduction

Oximes are useful and important key intermediates in the generation of nitriles via dehydration[1] and amides via Beckmann rearrangement[2]. In particular, ε-caprolactam is produced from cyclohexanone oxime to provide a source of nylon 6 on an industrial scale. The dehydration of aldehydes and ketones with hydroxylamine is the typical synthetic method for oximes.[3] However, hydroxylamine is explosive and unstable, and fatal explosions occurred in oxime manufacturing plants in 1999 in the U.S. and in 2000 in Japan.[4] To reduce these risks, hydroxyloxime is often converted to various salt forms using acids such as hydrogen chloride, sulfuric acid, or phosphoric acid. The use of these salts for oxime synthesis requires the use of stoichiometric amounts of base, resulting in the generation of large amounts of byproducts such as ammonium sulfate (Figure 1(b)). Ammoximation using titanosilicate heterogeneous catalyst (TS-1) is an alternative method used in specific oxime syntheses (e.g., cyclohexanone oxime and methylethyl ketone oxime (MEKO)) on an industrial scale to avoid the direct use of hydroxylamine.[5] However, TS-1 is not available commercially and is difficult to prepare.

Transoximation is a transamination reaction that occurs in the pupae of silkworm. Yamafuji *et al.* reported that this transoximation reaction is catalyzed by transoximase and converts pyruvic acid oxime to acetone and acetaldehyde to form acetone oxime and acetaldoxime at pH 5-6 and 37 °C (Figure 1(a)).[6] They suggested that the reaction mechanism involves pyridoxal phosphate as a co-enzyme of transoximase, and that pyridoxal phosphate oxime is produced as an intermediate (Figure 1(a)).[7] Interestingly, neither hydroxylamine nor nitrous acid were observed during the transoximation, suggesting that the oximes were transformed to carbonyl compounds without proceeding through the hydroxylamine as an intermediate.[8] This is reasonable in vivo because hydroxylamine is highly toxic to organisms. Non-enzymatic transoximations from acetone oxime to aldehydes and ketones respectively, are catalyzed by acid catalysts such as formic acid, acetic acid, and sulfuric acid.[9] However, this approach requires harsh conditions and specialized equipment, and acetone derived from acetone oxime is selectively released to outside as a gas in order to prevent the retro reaction. Another example of transoximation is for the purpose of de-oximation and is often used to de-protect the oxime to give the desired carbonyl compound.[10]

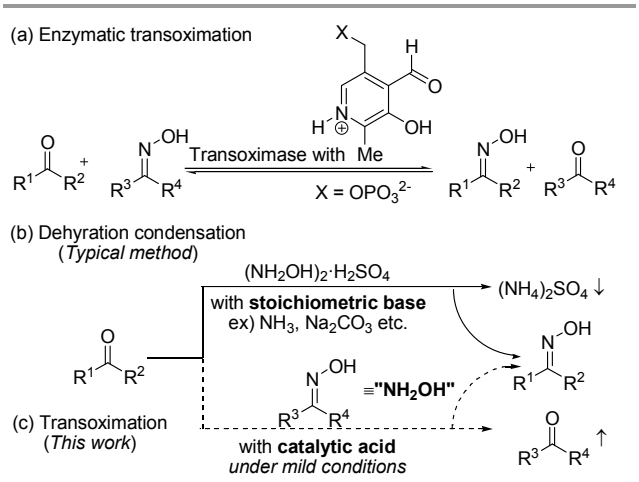

Figure 1. (a) Biological transoximation observed in the pupae of silkworm. (b) Oxime synthesis by typical dehydration condensation. (c) Catalytic transoximation.

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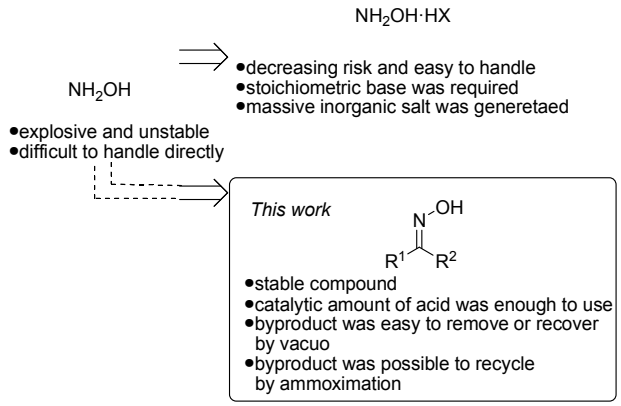


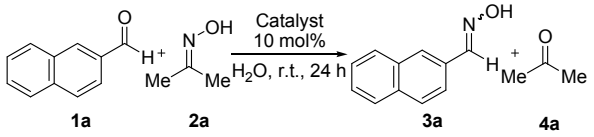
Figure 2. Convenience and usefulness for use of oxime instead of hydroxylamine salt to synthesize oxime

In 2011, Burés and Vilarrasa *et al.* reported de-oximation via transoximation using diacetyl as a receptor and $AuBr_3$ as the catalyst under neutral conditions.[11] In contrast, oximation via catalytic transoximation to prepare oxime remains poorly developed, despite the existence of transoximases in nature. We were inspired by bio-synthetic pathways to explore catalytic transoximation for several reasons: 1) transoximation could allow the use of stable oximes instead of dangerous hydroxylamine, 2) some oximes are inexpensively produced industrially by, for example, ammoximation, 3) carbonyl compounds generated from oxime as byproducts are easily removed by vaporization, 4) depending on the type of byproducts generated, the target oxime can be regenerated industrially using TS-1 catalyst,[12] and 5) the reaction mechanism of the acid-catalyzed reaction remains poorly understood (Figure 2). Herein, we attempted Brønsted acid-catalyzed transoximation to aldehydes and ketones under mild conditions, and studied the catalytic mechanisms (Figure 1(c)). Furthermore, we established a methodology for reuse of the homogeneous catalyst.

Results and discussion

Initially, we attempted the transoximation of 2-naphthaldehyde **1a** (1.0 equiv.) with acetone oxime **2a** (1.5 equiv.) using various Brønsted acids (10 mol%) at room temperature (23°C) (Table 1). No product was obtained in the absence of acid catalyst, and carboxylic acids and sulfonic acids gave moderate yields (entries 1-7). The use of perchloric acid (70 wt% $HClO_4$ aq ≈ 2.39 $H_2O/HClO_4$, mol/mol) as a Brønsted acid catalyst provided a good yield (entry 8). We next examined various oximes **2** with aldehyde **1a** using $HClO_4$ at room temperature (Table 2). Acetaldoxime **2b** gave a trace amount of product, whereas no reaction occurred in the presence of 4-pyridinealdoxime **2c** (entries 2, 3). The use of MEKO **2d** provided a slightly increased yield compared to **2b**, but cyclohexanone oxime **2e** provided a lower yield (entries 4, 5). To our delight, the best yield was obtained using ethyl acetohydroxamate **2g** (entry 7). Interestingly, transoximation proceeded in the presence of just 9.4 ppm water in dichloromethane as the solvent (entry 8). However, we chose MEKO **2d** as an oxime source and water as the solvent because MEKO **2d** is inexpensive, commercially available, and widely used as a peel-preventing antioxidant in paints and lacquers.[13] Moreover

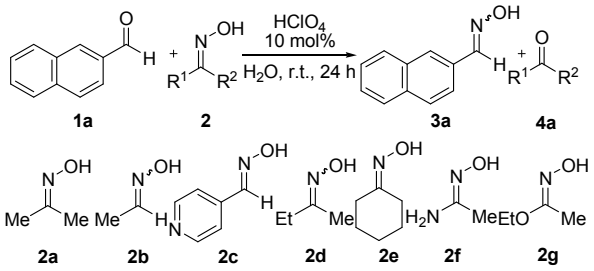
Table 1. Optimization of reaction conditions[a]



Entry	Catalyst	*E*/*Z*[b]	Yield (%)[c]
1	-	-	0
2	HCOOH	97/3	27
3	AcOH	95/5	22
4	TFA	98/2	66
5	H_2SO_4	99/1	88
6	TfOH	98/2	73
7	TsOH	99/1	73
8[d]	$HClO_4$	99/1	90
9	$HIO_4{\cdot}2H_2O$	99/1	44

a) Reaction conditions: **1a** (0.64 mmol), **2a** (0.96 mmol), catalyst (10 mol%) in H_2O (0.20 M) at r.t. for 24 h. b) *E*/*Z* ratio was determined by ^1H NMR from crude mixtures. c) Isolated yield. d) 70 wt% $HClO_4$ aq. was used.

Table 2. Scope of the oxime partners[a]



Entry	Oxime	*E*/*Z*[b]	Yield (%)[c]
1	**2a**	99/1	90
2	**2b**	99/1	26
3	**2c**	-	0
4	**2d**	99/1	92
5	**2e**	99/1	85
6	**2f**	-	0
7	**2g**	99/1	96
8[d]	**2g**	97/3	96
9[e]	**2d**	99/1	84

a) Reaction conditions: **1a** (0.64 mmol), **2** (0.96 mmol), 70 wt% $HClO_4$ aq. (10 mol%) in H_2O (0.20 M) at r.t. for 24 h. b) *E*/*Z* ratio was determined by ^1H NMR from crude mixtures. c) Isolated yield. d) CH_2Cl_2 (9.4 ppm H_2O measured by Karl-Fisher titration was contained) was used as a solvent instead of H_2O. e) $HClO_4$ was loading 5 mol%.

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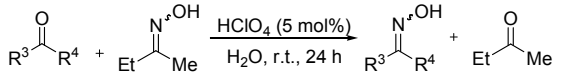
2d could be synthesized via ammoximation by TS-1, Ti-WWW,[12] which could avoid to use indirect hydroxylamine salts for the preparation.

Having optimized the reaction conditions, we investigated the utility and scope of various aldehydes and ketones (Table 3). The reaction of aldehydes **1a**-**1l** gave products **3a**-**3l** in high yield (entries 1-12). The reactions proceeded in the presence of aliphatic aldehydes, as well as in the presence of aromatic aldehydes with electron-donating and electron-withdrawing groups. Depending on the substrate, some products were obtained as solids and could be isolated by simple filtration, followed by washing with water (entries 4-10, 12). Under the same conditions used for aldehydes, ketone substrates were less reactive. However, the reaction of various ketones with 10 or 30 mol% $HClO_4$ in H_2O or EtOH under reflux provided good yields (entries 13-18). Notably, 2-chloroacetophenone **1o** was smoothly converted to **3o** without displacement of the chlorine atom at the α-position, similar to an S_N2 reaction (entry 15). The yield of aromatic ketone oximes **3m**, **3o**, **3p** were improved when **2g** was used instead of **2d** (entries 13, 15, 16). In addition, H_2SO_4 was also shown effective catalyst activity as well as $HClO_4$ (entries 1, 3, 4, 14 and Table S3).

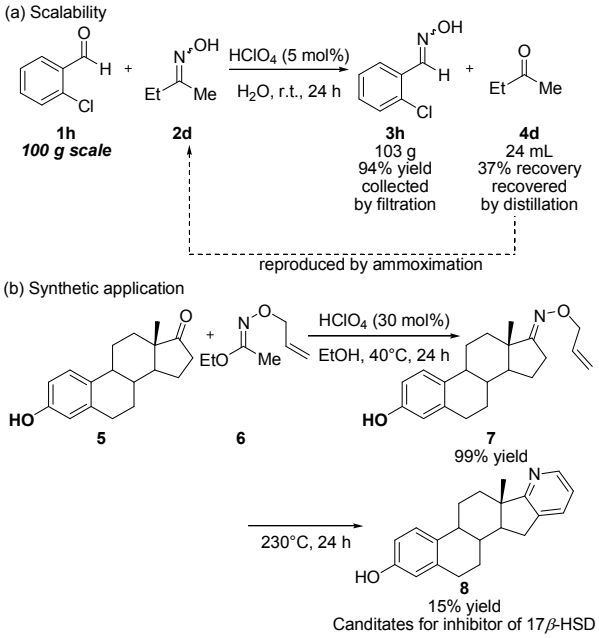
Table 3. Scope of aldehydes and ketones for catalytic transoximation on gram scale[a]



1 **2d** **3** **4d**

Entry	R^3	R^4	**1**	**3**	*E*/*Z*[b]	Yield %[c]
1	2-$C_{10}H_7$	H	**1a**	**3a**	99/1	95 (94)[d]
2	C_6H_5	H	**1b**	**3b**	99/1	91
3	4-$MeOC_6H_4$	H	**1c**	**3c**	92/8	99 (81)[d]
4	4-$CF_3C_6H_4$	H	**1d**	**3d**	99/1	92 (91)[d]
5	4-FC_6H_4	H	**1e**	**3e**	99/1	90
6	4-ClC_6H_4	H	**1f**	**3f**	99/1	90
7	3-ClC_6H_4	H	**1g**	**3g**	99/1	97
8	2-ClC_6H_4	H	**1h**	**3h**	99/1	95
9	C_6H_5CH=CH	H	**1i**	**3i**	52/48	98
10	$C_6H_5CH_2CH_2$	H	**1j**	**3j**	99/1[e]	93
11[f]	C_9H_{19}	H	**1k**	**3k**	54/46[e]	85
12	2-thienyl	H	**1l**	**3l**	99/1	95
13[g]	C_6H_5	Me	**1m**	**3m**	99/1	74 (93)[h]
14[i]	C_9H_{19}	Me	**1n**	**3n**	76/24[e]	82 (76)[j]
15[g]	C_6H_5	CH_2Cl	**1o**	**3o**	88/12[e]	70 (97)[h]
16[g]	C_6H_5	C_6H_5	**1p**	**3p**	-	41 (97)[k]
17[i]	-$(CH_2)_5$-		**1q**	**3q**	-	93
18[i]	C_6H_5CH=CH	Me	**1r**	**3r**	64/36[e]	84

a) Reaction conditions: **1** (11 mmol, gram scale), **2d** (1.5 equiv.), $HClO_4$ (5 mol%) in H_2O (0.20 M) at r.t. b) *E*/*Z* ratio was determined by ^1H NMR. c) Isolated yield. d) 5 mol% H_2SO_4 was used instead of $HClO_4$. e) This means the ratio of major and minor isomer. f) 10 mol% $HClO_4$ was used at 40°C. g) 30 mol% $HClO_4$ was used in EtOH at reflux. h) **2g** was used instead of **2d** with 5 mol% $HClO_4$ at r.t. i) 10 mol% $HClO_4$ was used at reflux. j) 10 mol% H_2SO_4 was used instead of $HClO_4$. k) **2g** was used instead of **2d** at 40°C.



Scheme 1. Scalability and synthetic application

Oxime **3h** shows antifungal activity against *Candida*.[14] To investigate applications of catalytic transoximation, a large-scale synthesis of **3h** using **1h** (100 g) was performed in water (0.71 L, 1.0 M) with 5 mol% $HClO_4$ at r.t. (≈ the reaction mixture became 0.68 wt% $HClO_4$ aqueous solution) (Scheme 1(a)). The reaction proceeded under very mild temperatures of 23-25 °C. After 24 h, 103 g of the product **3h** was easily isolated by filtration of the reaction mixture. Methyl ethyl ketone **4d** (MEK) was recovered as a byproduct from the filtrate by distillation, which can be reused to make MEKO by ammoximation without the need for hydroxylamine salts.[12]

We next investigated a synthetic application of this approach (Scheme 1(b)). 17*β*-Hydroxysteroid dehydrogenases (17*β*-HSD) are an important class of steroidogenic enzymes that regulate the bioavailability of active estrogens and androgens.[15] Compound **8** is a candidate inhibitor of 17*β*-HSD. Here, precursor **7** of compound **8** was directly synthesized in 99% yield on a 2-gram scale by an *O*-allyl transoximation reaction using *O*-allyl oxime **6** without the need to prepare *O*-allyl hydroxylamine[16] or to perform selective *O*-allylation of estrone oxime. Compound **7** could be converted to **8** at 230°C under neat conditions.[15]

Confirmation of the generation of hydroxylamine in-situ is important and would help us understand the reaction mechanism of catalytic transoximation, since hydroxylamine was not detected during transoximation by transoximase.[8] We endeavored to confirm the presence or absence of hydroxylamine in-situ by directly monitoring the transoximation of aldehyde **1a** using ethyl *O*-(4-

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fluorobenzoyl)acetohydroxamate **5g** by ^{19}F NMR (Figure S3-S6). A new small peak derived from *O*-(4-fluorobenzoyl)-hydroxylamine was observed at -102 ppm 15 minutes after the start of the reaction and lead us to predict that this catalytic transoximation proceeded via the hydroxylamine by hydrolysis of the oxime.

Next, we surveyed the hydrolytic behavior of oxime **2g** using $HClO_4$ as the catalyst by quantifying the generation of ethyl acetate to clarify the transoximation mechanism (Figure 3, Table 4).[17] When 20 mol% $HClO_4$ was added to **2g** (1.0 equiv.) in d_2-CD_2Cl_2, the yield of ethyl acetate **4g** was 23%, similar to the catalytic amount (20 mol%) (entry 1). Further addition of $HClO_4$ (20 mol%) promoted the reaction immediately, and the yield of **4g** increased to 42%. Although the addition of water (20 mol%) had no effect, the addition of 20 mol% aldehyde **1a** restarted the reaction, and the reaction continued until **1a** was consumed (Figure 1). This result indicated that $HClO_4$ as a catalyst did not turn over for the hydrolysis of **2g** when used in catalytic amounts, but that the catalyst was regenerated by the aldehyde. We assumed that water would play an important role in transoximation because the reaction did not proceed in the presence of molecular sieves which remove water from the reaction mixture (entry 2). However, even the presence of adequate water did not promote the reaction and the product yield was comparable to the catalytic amount (entry 3). These observations suggest that $HClO_4$ was inactive following the hydrolysis of **2g** either because 1) $HClO_4$ directly reacted with **2g** and was not regenerated or 2) $HClO_4$ formed a salt with NH_2OH generated by hydrolysis of **2g** and was thus deactivated. To determine which of these possibilities was correct, we performed hydrolysis experiments in ^{18}O-labeled water ($H_2{}^{18}O$) with $H^{16}ClO_4$ (1.0 equiv.). ^{18}O-labeled **4g** was quantified by GC-MS and we found that the carbonyl oxygen of **4g** originated from water, which meant that $HClO_4$ did not react with **2g** directly (entry 4). Furthermore, the reaction was very sluggish when $HClO_4{\cdot}NH_2OH$ was used as the catalyst, but interestingly the reaction started quickly as soon as aldehyde **1a** was added to the reaction mixture (entry 5). Therefore, we found that the initial presence of water and aldehyde played important roles for $HClO_4$ to function as a catalyst.

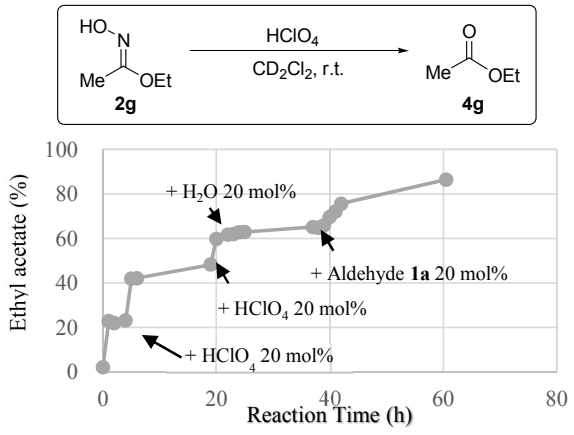
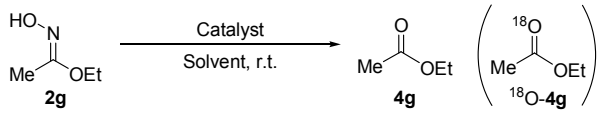


Figure 3. Hydrolysis behavior of oxime **2g** by $HClO_4$ and H_2O, aldehyde **1a**.

Table 4. Preliminary mechanistic study by hydrolysis experiments for oxime **2g**



Entry	Catalyst	Solvent	Time (h)	Yield (%)[a]
1	$HClO_4$	CD_2Cl_2	4	23 (42)[b]
2[c]	$HClO_4$	CD_2Cl_2	16	1
3	$HClO_4$	D_2O	16	23
4[d]	$HClO_4$	$H_2{}^{18}O$	10 min	> 99[e]
5	$HClO_4{\cdot}NH_2OH$	CD_2Cl_2	16	7 (> 99)[f]

a) Yield was directly determined from reaction mixtures by ^1H NMR using an internal standard. b) The parentheses means the yield after addition of 20 mol% $HClO_4$. c) MS4A (300 wt% for **2g**) was added. d) 100 mol% $HClO_4$ was loading. e) ^{18}O-labeled **4g** was obtained instead of ^{16}O-**4g**. f) The parentheses means the yield after 1.0 equiv. of **1a** was added and stirred for 4 h.

We also investigated the rate dependence of the reaction on each component in order to determine the reaction profile of catalytic transoximation (Fig. S11-14). The reaction rate had a zero-order dependence on aldehyde, oxime and water, and 1.5th-order dependence on $HClO_4$. Besides, the result of cross-over reaction shows us that more electrophilic aldehydes are better receptors and more electron-rich oximes could be more suitable donors for transoximation (Scheme S1-S3).

Based on these information, we propose a stepwise reaction mechanism for transoximation (Figure 4). Oxime **2** activated by $HClO_4$ (**A**) reacted with a trace amount of initial water and generated NH_2OH together with ester **4** (**B**). Then, complex B was dehydro-condensed with aldehyde **1** to provide protonated aldoxime (**C**) along with water. Finally, complex C generated by Brønsted acid-base reaction with oxime **2** gave the corresponding aldoxime and regenerated protonated oxime A. In addition, water generated from the dehydration condensation (**B** to **C**) was consumed during the hydrolysis process (**A** to **B**). Consequently, water was required for transoximation, although a trace amount is sufficient as an initiator.

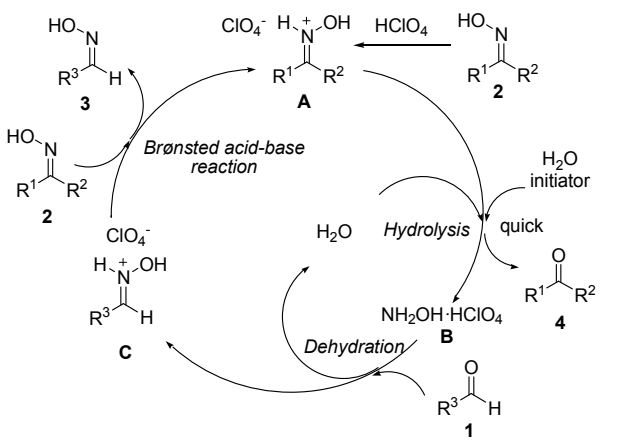


Figure 4. Proposed transoximation reaction mechanism catalyzed by $HClO_4$.

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Finally, we tackled the recovery and reuse of the catalyst, a topic of particular interest to many synthetic chemists. Heterogeneous catalysts can often be recycled.[18, 19] We focused on recovering catalyst from reactions in which the product was conveniently purified by filtration and washed with water. Organic solvent is not required because both the reagents and byproducts dissolve in water or are liquids. We expected that the reaction filtrate could be reused repeatedly to conduct the same reaction by simply adding aldehyde and MEKO because the $HClO_4$ catalyst would remain in the filtrate as complex B. We applied this proposed approach to the synthesis of **3j** and demonstrated that the filtrate could be reused more than ten times without the need to prepare new catalyst or add additional water as a solvent (Figure 5). This approach allows the reuse of both the homogeneous catalyst and solvent (and residual staring material and reagents) if the product becomes a solid and the starting material is a liquid or consumed.

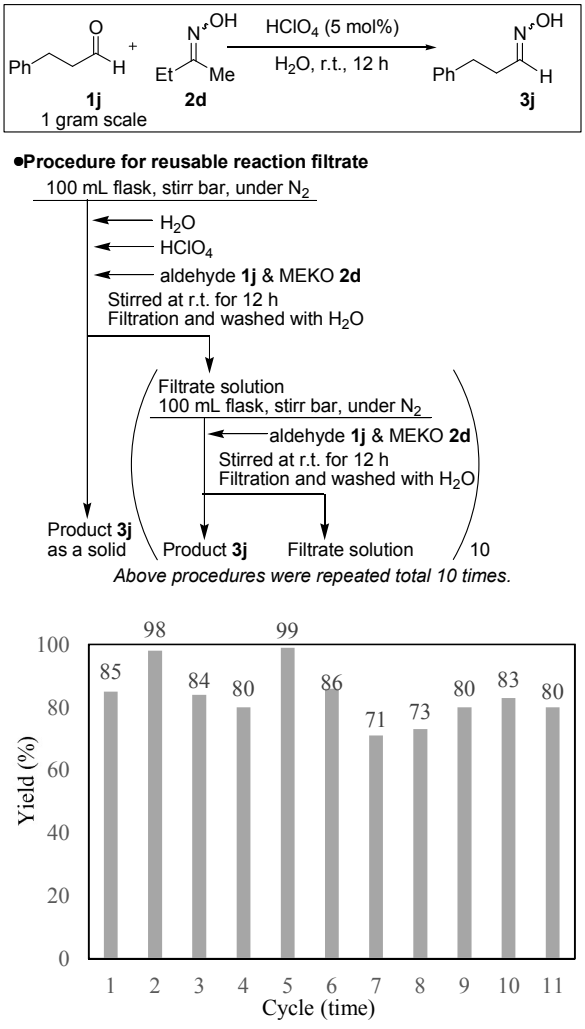

Figure 5. Recovery and reuse of reaction filtrates.

Conclusions

We achieved transoximation to aldehydes and ketones catalyzed by $HClO_4$ under mild reaction conditions. The reaction conditions were tolerated by several aromatic/aliphatic aldehyde and ketone substrates and gave the desired aldoximes in good yield. Analysis of the reaction mechanism suggested that this transoximation reaction proceeded via hydroxylamine generated by the successive hydrolysis of oxime, and both aldehyde and a trace amount of water were essential to turn over the catalyst. Moreover, we found that the homogeneous Brønsted catalyst could be reused more than ten times by reusing the reaction filtrate. These results will allow the use of stable oximes rather than hydroxylamines, which require a stoichiometric amount of base, thus avoiding the production of large amounts of inorganic salt. Research is in progress to expand this approach to other substrates.

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Inspired by bio-synthesis, we demonstrate Brønsted acid catalyzed transoximation for the synthesis of oximes without using hydroxylamine salts in water.