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

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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.

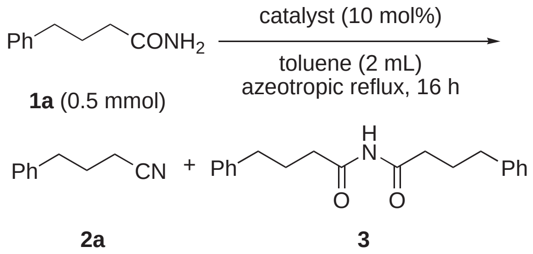
The synthetic importance of the dehydration of primary aliphatic and aromatic amides to their corresponding nitriles has been thoroughly documented.[1,2] Most classical methods require the use of stoichiometric or excess amounts of highly reactive dehydrating reagents and harsh conditions in acidic or 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(triphenylphosphine)ruthenium (1 mol %) catalyzes the dehydration of primary amides in the presence of urea derivatives (1 equiv) in diglyme at 180 °C. In 1996, Mioskowski et al.[3b] developed the paraformaldehyde-catalyzed (490 mol %) water-transfer reaction of primary amides in a formic acid/acetonitrile mixture. In 1999, Bose and Jayalakshmi[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 here 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 h (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 rhe-

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	$Zr(O\textit{i}Pr)_4$	77:23:0
5	$Hf(O\textit{t}Bu)_4$	82:12:0
6	$WOCl_3$	81:14:5
7	MoO_2Cl_2	81:11:8
8	$Ti(O\textit{i}Pr)_4$	89:11:0
9	Bu_2SnO	99:1:0
10	$VO(O\textit{i}Pr)_3$	100:0:0
11	ReO_3	100:0:0
12	ReO_2	100:0:0
13	$[RuCl_2(\textit{p}\text{-cymene})]_2$	100:0:0

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

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

$$\underset{(0.5\ \mathrm{mmol})}{\mathbf{1a}} \xrightarrow[\substack{\text{solvent (2 mL)}\\ \text{azeotropic reflux, 5 h}}]{\substack{\text{aqueous (HO)ReO}_3\\ (9\text{–}10\ \text{mol\%})}} \mathbf{2a} + \mathbf{3}$$

Entry	Solvent	t/°C[a)]	**1a/2a/3**
1	Mesitylene	175	2:96:2
2	Anisole	165	11:85:4
3	*o*-Xylene	155	7:91:2
4	PhCl	140	9:89:2
5	Toluene	125	62:36:2
6	Heptane	110	98:2:0
7	EtCN	110	95:5:0
8	Dioxane	110	91:9:0

a) Bath temperature.

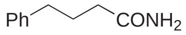
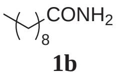
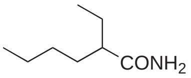
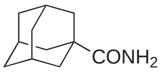
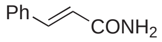
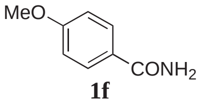
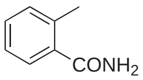
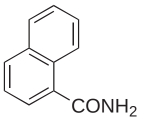
nium(VI) and rhenium(IV) oxides were inert (Table 1, Entries 11 and 12). Since trimethylsilylperrhenate and rhenium(VII) oxide are very moisture-sensitive and highly expensive, we chose aqueous perrhenic acid (which is easy to handle and less expensive than trimethylsilylperrhenate) as a practical dehydration catalyst. Interestingly, dibutyltin oxide was almost inert under the same conditions (Table 1, Entry 9).[3c,d]

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 < mesitylene (Table 2, Entries 1 and 3–5). Anisole was also a good solvent, but its polarity slightly lowered the catalytic activity of perrhenic acid (Table 2, Entry 2). The dehydration of **1a** occurred smoothly only at temperatures above 125 °C. The addition of molecular sieves to the reaction mixture disturbed the dehydration.

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 2-ethylhexanamide (**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).

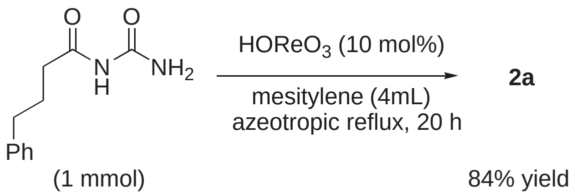
Table 3. Dehydration Reaction of Primary Amides Catalyzed by Aqueous Perrhenic Acid

$$\underset{\substack{\mathbf{1}\\(1\ \mathrm{mmol})}}{\mathrm{RCONH_2}} \xrightarrow[\substack{\text{mesitylene (2 mL)}\\ \text{azeotropic reflux, 1 day}}]{\substack{\text{aqueous (HO)ReO}_3\\ (0.9\text{–}1\ \text{mol\%})}} \underset{\mathbf{2}}{\mathrm{RCN}}$$

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)]

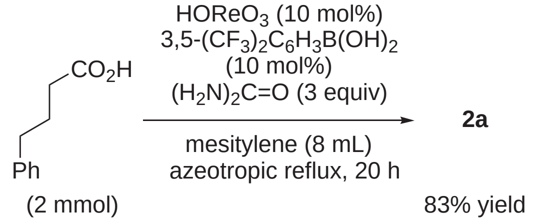
a) Isolated yield. b) $(Me_3SiO)ReO_3$ (1 mol %) was used as a catalyst. The reaction time was prolonged to 2 days. c) $(Me_3SiO)ReO_3$ (10 mol %) was used as a catalyst in toluene in place of mesitylene. d) Perrhenic acid (1 mol %) was reused. e) Anisole was used in place of mesitylene.

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).

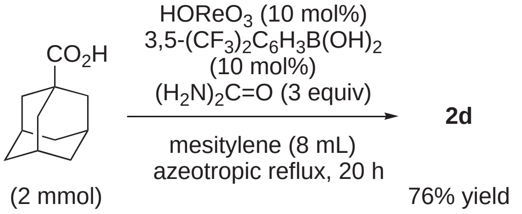


(1)

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.



(2)

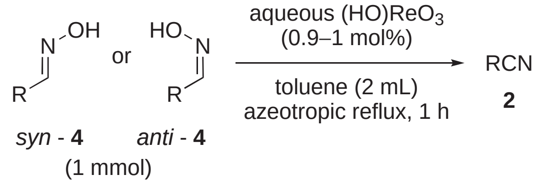


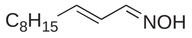
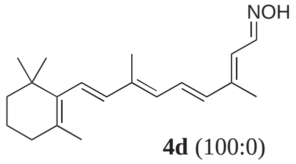
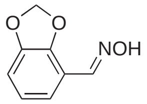
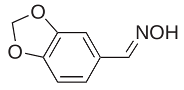
(3)

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-Undecenaldoxime (**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



Entry	Aldoxime (*syn*/*anti*)	**2**/%[a)]
1	$n\text{-}C_{10}H_{21}CH{=}NOH$ **4a** (0:100)	**2i**, >99[b)]
2	$cyclo\text{-}C_6H_{11}CH{=}NOH$ **4b** (63:37)	**2j**, 91
3	 **4c** (97:3)	**2k**, 91[c)]
4	 **4d** (100:0)	**2l**, 91[d),e)]
5	$o\text{-}(MeO)C_6H_4CH{=}NOH$ **4e** (100:0)	**2m**, 94[b)]
6	$m\text{-}(MeO)C_6H_4CH{=}NOH$ **4f** (100:0)	**2n**, 86[b)]
7	$p\text{-}(MeO)C_6H_4CH{=}NOH$ **4g** (100:0)	**2f**, 97[b)]
8	 **4h** (100:0)	**2o**, 95[b)]
9	 **4i** (100:0)	**2p**, 99[b)]
10	1-NapCH=NOH **4j** (100:0)	**2h**, 98
11	$2,4,6\text{-}Me_3C_6H_2CH{=}NOH$ **4k** (100:0)	**2q**, >99
12	3-Pyridylch=NOH **4l** (100:0)	**2r**, 84[b),f)]

a) Isolated yield. b) Mesitylene was used in place of toluene. c) The *E*/*Z* ratio of the product was 92:8. d) *o*-Xylene was used in place of toluene. The reaction time was prolonged to 2 h. e) The isolated product was >98% all-*trans*. f) The reaction time was prolonged to 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. 4 and 5).

$$\underset{(100\ \text{mmol})}{\mathbf{1g}} \xrightarrow[\text{mesitylene (40 mL)}\ \ \text{azeotropic reflux, 1 day}]{(\text{HO})\text{ReO}_3\ \ (0.45\text{–}0.5\ \text{mol\%})} \underset{97\%\ \text{yield}}{\mathbf{2g}} \qquad (4)$$

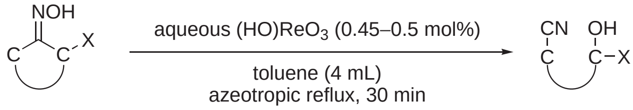
$$\underset{(40\text{ mmol})}{\mathbf{4e}} \xrightarrow[\substack{\text{toluene (20 mL)} \\ \text{azeotropic reflux, 4.5 h}}]{\substack{\text{(HO)ReO}_3 \\ (0.9\text{–}1.0\text{ mol\%})}} \underset{91\%\text{ yield}}{\mathbf{2m}} \qquad (5)$$

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, Itoh, and co-workers 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.

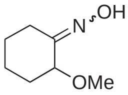
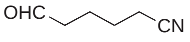
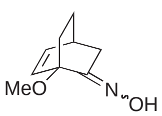
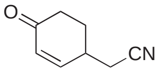
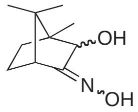
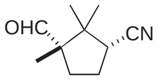
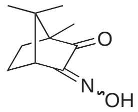
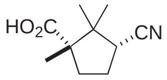
The Beckmann fragmentation of several ketoximes was examined in the presence of 0.5 mol % of perrhenic acid under azeotropic reflux in toluene for 30 min (Table 5). As a result, the corresponding nitriles were obtained in excellent yield without any other side products. The use of $[RuCl_2(p\text{-cymene})]_2$,[9a]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

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

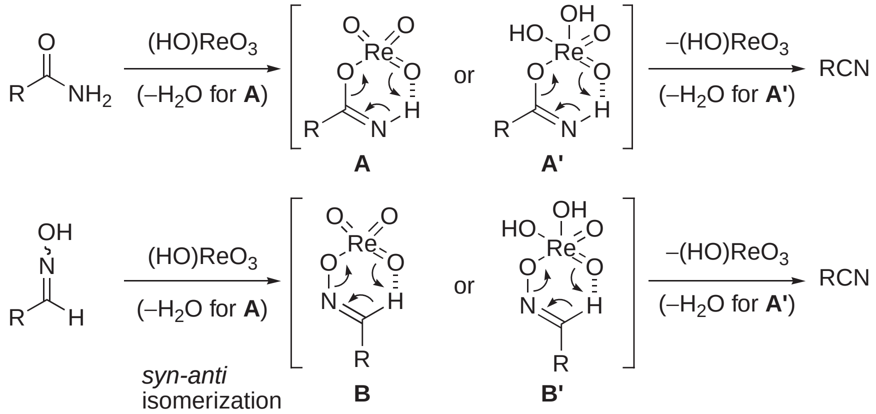
Table 5. Beckmann Fragmentation of α-Substituted Ketoximes



5 (2 mmol) **6**

Entry	Ketoxime		Product		Isolated 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.



Scheme 1. Proposed mechanism for the dehydration of primary amides and aldoximes to form nitriles.

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.

Conclusion

We have reported here 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 acidic but nearly neutral 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. 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). Tetramethylsilane was used as an internal standard (δ 0.00 ppm). ^{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. Primary amides **1a**–**1h** are commercially available. The following obtained nitriles are commercially available: **2a**–**2j**, **2m**, **2n**, and **2p**–**2r**. The following obtained nitriles are known compounds: **2k**,[17] **2l**,[9a] and **2o**.[18] Aldoximes **4b**, **4c**, **4e**–**4g**, and **4i**–**4l** are commercially available. Aldoxime **4d** was prepared by the known method.[9a] The following aldoxime is a known compound: **4a**.[19] Ketoximes **5c** and **5d** are commercially available. Ketoxime **5a** is a known compound.[20] The following obtained nitriles are known compounds: **6a**,[21] **6c**,[22] and **6d**.[23]

(*E*)-Undec-2-enal Oxime (4c). This compound was prepared by known method[9a] and obtained in 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 (brs, 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-Methylenedioxybenzaldehyde Oxime (4h). This compound was prepared by known method.[9a] 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.

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.

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}; ^{1}H NMR (300 MHz, THF-d_8) 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, $J = 7.5$ Hz, 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 h, 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 1-Methoxybicyclo[2.2.2]oct-5-en-2-one Oxime (5b). To a mixture of 1-methoxybicyclo[2.2.2]-oct-5-en-2-one[24] (2.0 g, 13.2 mmol) and hydroxylamine hydrochloride (2.12 g, 30.3 mmol) in 18 mL of methanol, 9 mL of aqueous solution of sodium acetate trihydrate (4.53 g, 33.0 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 **5b** in 36% yield. IR (KBr) 3230, 2970, 1613, 1422, 1112, 1015 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (brs, 1H), 6.36 (d, $J = 3.6$ Hz, 2H), 3.54 (s, 3H), 2.83 (brs, 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.

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.

(4-Oxocyclohex-2-enyl)acetonitrile (6b). IR(neat) 2954, 2870, 2247, 1682, 1390, 1252 cm^{-1}; ^{1}H 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, 1H); ^{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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