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Ruthenium-catalyzed reduction of *N*-alkoxy- and *N*-hydroxyamides

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1. Introduction

N-Alkoxy- and *N*-hydroxyamides (hydroxamic acids and their derivatives) have been widely used as biologically active compounds [1-3] as well as versatile synthetic intermediates [4]. In the synthesis of β -lactams [5] and compounds derived from *O*-alkyl oximes [6], the alkoxy groups of the alkoxyamide moieties are utilized as protecting groups, and Li [5a,7], $\text{Cp}_2\text{TiCl}_2/\text{Zn}$ (or Mn) [5d], H_2 -Pd/C and TiCl_3 [5b,c], TiCl_3 only [8] and SmI_2 [6] have been employed as reductants in conventional methods for deprotection. *N*-Hydroxyamides can be reduced by titanium complexes as well [5b-d]. As non-metal reductants, *t*-butyldimethylsilyl triflate/triethylamine [9] and an organic neutral super-electron donor [10] have also been reported. These reactions occur via single-electron transfer and require a stoichiometric amount of metals, metal complexes or organic reductants.

During the course of our investigation on the reactions of Weinreb amides in the presence of ruthenium complexes, we found that the N-O bond cleavage occurred efficiently to afford the corresponding deprotected amides. We report here a novel catalytic reduction of *N*-alkoxyamides using a simple $\text{RuCl}_3/\text{Zn-Cu}$ /alcohol system, which was also found to be effective for the reduction of *N*-hydroxyamides.

2. Results and discussion

2.1. Optimization of Reaction Conditions

Initially, *N*-methyl-*N*-methoxybutyramide (**1a**), which is known as a Weinreb amide [4a], was treated with 5 mol% of $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ and 30 mol% of Zn-Cu couple in MeOH at 80 °C under an argon atmosphere. The reduction proceeded to give the deprotected product, *N*-methylbutyramide (**2a**), in 76% NMR yield after 24 h (Eq. (1)).

(Eq. (1))

The catalytic activity of other ruthenium complexes such as $[\text{RuCl}_2(\text{CO})_3]_2$, $\text{RuCl}_2(\text{PPh}_3)_3$, $[\text{RuCl}_2(1,5\text{-cyclooctadiene})]_n$, $[\text{RuCl}_2(2,5\text{-norbornadiene})]_n$, $[\text{Cp}^*\text{RuCl}_2]_2$ (Cp^* = pentamethylcyclopentadienyl), $\text{RuCl}_4(2,2'\text{-bipyridine})$, $[\text{RuCl}_2(\text{C}_6\text{H}_6)]_2$, and $[\text{RuCl}_2(p\text{-cymene})]_2$ was examined in the presence of Zn-Cu in MeOH. In most cases, the yields were less than 30% and none

were comparable to RuCl_3 . In the absence of Zn-Cu, $\text{Ru}(\text{C}_6\text{H}_6)(\text{methyl acrylate})_2$ [11], a zerovalent complex, was employed for the reaction in toluene at 130 °C for 24 h. However, this resulted in a low yield (21%). We also attempted the reactions with additives such as monodentate/bidentate nitrogen or phosphorous ligands (5–10 mol%) under the same reaction conditions as in Eq. (1); however, lower yields of the product (12–46%) were obtained in all cases.

Next we examined the effects of various solvents and reaction temperatures (Table 1). The use of EtOH instead of MeOH gave a slightly higher yield of **2a** (Entry 2) and raising the bath temperature to 100 °C gave the best result of 97% (Entry 3). Secondary alcohols such as 2-PrOH and 2-BuOH were also effective; however, these lowered the yield as compared to that of EtOH (Entries 4 and 5). The presence of a certain amount of water ($\text{EtOH}:\text{H}_2\text{O} = 10:1$) considerably inhibited the reduction (Entry 6).

(Table 1)

The effects of reductants were also examined (Table 2). Even in the absence of a reductant, the reaction proceeded to give 13% of **2a** (Entry 1). Although 5 mol% of Zn-Cu did not operate well (Entry 2), both conversion and yield were critically improved by using more than 15 mol% (Entries 3 and 4). Either Zn or Mg did not compare with Zn-Cu (Entries 5 and 6).

(Table 2)

2.2. Scope of Substrates

The optimized reaction conditions found above were applied to several *N*-alkoxyamides (Table 3). Decreasing the precatalyst loading to 2 mol% slightly lowered the yield (Entry 2), whereas decreasing to 1 mol% resulted in substantially low conversion (54%) and yield (34%) (Entry 3). Relatively bulky *N*-methyl-*N*-methoxypivalamide (**1b**) was converted to *N*-methylpivalamide (**2b**) in 24 h (Entry 4). *N*-Methyl-*N*-methoxybenzamide (**1c**) afforded *N*-methylbenzamide (**2c**) in high yield (Entry 5). In addition, the reaction of *N*-methoxybutyramide (**1d**) having an amide proton proceeded smoothly to give butyramide (**2d**) (Entry 6). A benzyloxy protected amide,

N-methyl-*N*-benzyloxybutyramide (**1e**), also afforded **2a** (Entry 7) with the formation of benzyl alcohol (65%) and benzaldehyde (21%), whereas the reaction of *N*-methyl-*N*-isopropoxybutyramide (**1f**) was sluggish, probably because of steric hindrance (Entry 8). The reduction was also found to be applicable to *N*-hydroxyamides **1g-i**, resulting in **2a**, *N*-phenylbutyramide (**2e**), and **2d**, respectively (Entries 9–11). Although all the substrates converted in these cases, the yields varied from moderate to high depending on the substituents on the nitrogen atoms.

(Table 3)

The present method was applied to β -substituted- α,β -unsaturated *N*-methoxyamides (Table 4) [12]. The deprotection proceeded as well, but hydrogenation of the olefin moiety occurred simultaneously. When *N*-methyl-*N*-methoxycrotonamide (**3a**) was employed, there was a low yield of *N*-methylcrotonamide (**4a**), whereas in the case of *N*-methyl-*N*-methoxycinnamamide (**3b**), the yield of deprotected product **4b** was up to 93% after 6 h and that of deprotected/hydrogenated product **2f** was 6% (Entry 2) [13]. In the both cases, the formation ratios of **4** : **2** were high at the early stage (3 h), and the highest yields of **4** were observed after 6 h. The yields of **4** decreased after 24 h along with the further formation of **2**. Whereas the conversions of the substrate **3b** and the total yields of the products **4b** and **2f** are well balanced (Entry 2), the conversions of **3a** are approximately 15–30% higher than the total yields of **4a** and **2a** (Entry 1). The imbalance may be attributable to the strong coordination of π -acidic α,β -unsaturated amides **3a** and/or **4a** to ruthenium, by which they cannot be detected as free amides. The aforementioned changes in the yields of the products **4** and **2** with time, and the fact that hydrogenated products of **3** without deprotection were not formed during the course of the reactions, indicate that the deprotection rather than the hydrogenation from **3** proceeds preferentially to afford **4**, and then the hydrogenation of **4** would follow.

(Table 4)

2.3. Possible Reaction Mechanisms

To elucidate the role of the solvent molecule in the catalytic cycle, the reduction of **1h** was performed in 2-octanol at 100 °C for 6 h (Eq. (2)). As a result, 2-octanone was formed in 45% NMR yield along with the formation of deprotected amide **2e** in 86% NMR yield. Although a small amount of 2-octanone (9%) was detected even in the absence of **1h** under the same reaction conditions as in Eq. (2), these results imply the participation of the solvent as a hydrogen donor in the catalytic cycle of the reduction.

(Eq. (2))

Taking these observations into consideration, three possible reaction mechanisms are proposed as shown in Scheme 1. In each mechanism, either a zerovalent ruthenium complex or a divalent ruthenium hydride complex is supposed to be involved as a catalytically active species. Zerovalent ruthenium complexes such as Ru(1,5-cyclooctadiene)(1,3,5-cyclooctatriene), Ru(benzene)(1,3-cyclohexadiene) [14] and Ru{P(OMe)₃}(dimethyl muconate)₂ [15] are known to be formed from RuCl₃·3H₂O in the presence of Zn and appropriate ligands in an alcoholic solvent, and divalent ruthenium hydride species can be generated under the similar reaction conditions as well [15]. In Path A, *N*-alkoxy- or *N*-hydroxyamide **1** coordinates to zerovalent ruthenium species **5** to form **6**, and oxidative addition of the N-O bond occurs to give divalent ruthenium species **7** having amidato and alkoxo (or hydroxo) ligands [16]. At this stage, the alkoxo (or hydroxo) ligand may exchange with an external alcohol used as a solvent. The subsequent β-hydrogen elimination from **8** gives ruthenium amidate hydride species **9** along with an aldehyde (or ketone), and reductive elimination from **9** affords **10**, from which the deprotected product **2** is dissociated to regenerate **5**. The result using a zerovalent complex, Ru(C₆H₆)(methyl acrylate)₂, mentioned in section 2.1 may support Path A, while the yield of the product was low.

On the other hand, both Paths B and C involve only divalent ruthenium species. In Path B, divalent ruthenium hydride species **11** is formed initially, and subsequent coordination of **1** to ruthenium gives **12**. Elimination of alcohol (or water) via weak N-O bond cleavage, followed by the reaction with EtOH, liberates **2** along with the formation of **14**, from which β-hydrogen elimination proceeds to regenerate **11**. In Path C, another type of N-O bond cleavage occurs from **12**, where the

hydride ligand migrates to nitrogen to form **2** and **15**. To evaluate the validity of Paths B and C, the reactions of **1a** using ruthenium hydride complexes, $\text{RuHCl}(\text{PPh}_3)_3$ and $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$, as a precatalyst (5 mol%) in the absence of Zn-Cu in MeOH at 80 °C for 24 h were performed. As a result, the yields of the deprotected product **2a** were low (10% and 9%, respectively); however, since the presence of phosphorous ligands tends to lower the yield as mentioned in section 2.1, these results may be still reasonable even if the reaction proceeds via Path B or C.

Although all of these mechanisms can explain most of the obtained experimental results, the relatively low yield of 2-octanone as compared to that of **2e** in Eq. (2) is unexpected, because the yields of these compounds should be nearly equal according to the mechanisms proposed above. This fact indicates that other mechanisms may be concurrently involved in the present reaction. In any case, it appears to be difficult to elucidate the mechanism at this stage.

(Scheme 1)

3. Conclusions

We have developed a novel ruthenium-catalyzed reduction of *N*-alkoxy- and *N*-hydroxyamides to give corresponding amides. A simple $\text{RuCl}_3/\text{Zn-Cu}/\text{alcohol}$ system, without the addition of ligands, exhibited a high catalytic activity. In the reduction of *N*-hydroxyamides, the alcoholic solvent was found to function as a hydrogen donor. The present method does not require a stoichiometric amount of metals or metal complexes as reductants, and may complement the reported procedures which proceed via single-electron transfer.

4. Experimental section

4.1. General

$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ was purchased from Furuya Metal. $[\text{RuCl}_2(\text{CO})_3]_2$ and $[\text{RuCl}_2(p\text{-cymene})]_2$ were obtained from Strem and Sigma-Aldrich, respectively. Other ruthenium catalysts, $\text{RuCl}_2(\text{PPh}_3)_3$ [17], $[\text{RuCl}_2(1,5\text{-cyclooctadiene})]_n$ [18], $[\text{RuCl}_2(2,5\text{-norbornadiene})]_n$ [19], $[\text{Cp}^*\text{RuCl}_2]_2$ [20], $\text{RuCl}_4(2,2'\text{-bipyridine})$ [21], $[\text{RuCl}_2(\text{C}_6\text{H}_6)]_2$ [22], $\text{Ru}(\text{C}_6\text{H}_6)(\text{methyl acrylate})_2$ [11], and Zn-Cu [23] were prepared as described in the literature. *N*-Alkoxy- and *N*-hydroxyamides were prepared by the

similar procedure reported previously [24,25]. Dehydrated EtOH was purchased from Wako Pure Chemical Industries. Other dehydrated solvents were obtained from Wako, Nacalai Tesque and Sigma-Aldrich. Other chemicals were also commercially available and were used without further purification. All reactions were performed under an argon atmosphere. Flash column chromatography was performed using silica gel SILICYCLE SiliaFlash F60 (40-63 μm , 230-400 mesh). NMR spectra were recorded on either a JEOL AL-400 (400 MHz (^1H), 100 MHz (^{13}C)) or a Bruker AV-300N (300 MHz (^1H), 75 MHz (^{13}C)) spectrometer. Chemical shift values (δ) were expressed relative to SiMe_4 . IR measurements (ATR) were carried out using a JASCO FT/IR-6100 spectrometer. Elemental analysis was obtained using a J-SCIENCE LAB JM-10 analyzer. Mass spectra were recorded on either a JEOL JMS-T100LC or a SHIMADZU GCMS-QP5050 spectrometer.

4.2. Preparation of *N*-methoxyamides **1a-d**, **3a-b**

A procedure for *N*-methyl-*N*-methoxybutyramide (**1a**) is representative. Dry pyridine (8.90 mL, 110 mmol) was added dropwise to a mixture of *N,O*-dimethylhydroxylamine hydrochloride (5.36 g, 55 mmol) and butyryl chloride (5.19 mL, 50 mmol) in CH_2Cl_2 (150 mL) at 0 $^\circ\text{C}$ under argon. The reaction mixture was warmed up to room temperature and stirred for 2 h. The solvent was evaporated to give a white solid, to which a saturated brine and a 1:1 mixture of $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$ were added for extraction. The aqueous layer was further extracted by a 1:1 mixture of $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$ three times. The combined organic layer was dried over MgSO_4 , filtered, and the solvent was evaporated to dry. Purification by flash column chromatography (eluent: hexane/ethyl acetate = 1:1) afforded **1a** (3.89 g, 29.7 mmol) as a colorless oil in 59% yield. Spectral data were consistent with those reported previously [26].

Compounds **1b-d** and **3a-b** were prepared in the same manner, and the spectral data for *N*-methyl-*N*-methoxypivalamide (**1b**) [27], *N*-methyl-*N*-methoxybenzamide (**1c**) [28], *N*-methyl-*N*-methoxycrotonamide (**3a**) [29] and *N*-methyl-*N*-methoxycinnamamide (**3b**) [30] were in accordance with those in the literature.

4.2.1. *N*-methoxybutyramide (**1d**)

Colorless oil. IR spectrum (ATR): 3195, 2967, 1661, 1519, 1057 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz): δ 9.98 (br s, 1H, NH), 3.67 (s, 3H, OCH_3), 2.04 (br t, $J = 6.9$ Hz, 2H, CH_2CO), 1.66-1.54 (m, 2H, CH_2), 0.88 (t, $J = 7.2$ Hz, 3H, CH_3). ^{13}C NMR (CDCl_3 , 75 MHz): δ 171.0 ($\text{C}=\text{O}$), 63.9 (NOCH_3), 34.8 ($-\text{CH}_2\text{CO}-$), 18.8 (CH_2), 13.5 (CH_3). MS (EI) m/z 117 (M^+).

4.3. Preparation of *N*-benzyloxyamide **1e** and *N*-isopropoxyamide **1f**

A procedure for *N*-methyl-*N*-benzyloxybutyramide (**1e**) is representative. A solution of *N*-methyl-*N*-hydroxybutyramide (1.00 mL, 8.3 mmol), anhydrous K_2CO_3 (1.52 g, 11 mmol) and benzyl bromide (1.31 mL, 11 mmol) in dry acetone (25 mL) was stirred for 12 h at 75 °C under argon. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 and washed with a 1 M solution of NaOH. The two layers were separated and the aqueous layer was extracted three times with CH_2Cl_2 . The combined organic layer was dried over MgSO_4 , filtered and the solvent was evaporated to dry. Purification by flash column chromatography (eluent: hexane/ethyl acetate = 10:1) afforded **1e** (1.35 g, 6.51 mmol) as a colorless oil in 79% yield. Compound **1f** was prepared in the same manner.

4.3.1. *N*-Methyl-*N*-benzyloxybutyramide (**1e**)

Colorless oil. IR spectrum (ATR): 2963, 1667, 1456, 1386 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz): δ 7.38-7.34 (m, 5H, arom.), 4.81 (s, 2H, NOCH_2Ph), 3.18 (s, 3H, NCH_3), 2.35 (t, $J = 7.5$ Hz, 2H, CH_2CO), 1.67-1.54 (m, 2H, CH_2), 0.90 (t, $J = 7.5$ Hz, 3H, CH_3). ^{13}C NMR (CDCl_3 , 75 MHz): δ 175.1 ($\text{C}=\text{O}$), 134.6 (Ph), 129.2 (Ph), 128.9 (Ph), 128.7 (Ph), 76.2 (NOCH_2Ph), 34.1 ($-\text{CH}_2\text{CO}-$), 34.0 (NCH_3), 18.0 (CH_2), 13.9 (CH_3). MS (ESI) m/z 230.1 ($\text{M} + \text{Na}^+$).

4.3.2. *N*-Methyl-*N*-isopropoxybutyramide (**1f**)

Colorless oil. IR spectrum (ATR): 2974, 1669, 1383, 1112 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz): δ 4.14-4.06 (m, 1H, $\text{NOCH}(\text{CH}_3)_2$), 3.16 (s, 3H, NCH_3), 2.38 (t, $J = 7.2$ Hz, 2H, CH_2CO), 1.67-1.58 (m, 2H, CH_2), 1.22 (d, $J = 6.4$ Hz, 6H, $\text{NOCH}(\text{CH}_3)_2$), 0.92 (t, $J = 7.2$ Hz, 3H, CH_3). ^{13}C NMR (CDCl_3 , 75 MHz): δ 176.3 ($\text{C}=\text{O}$), 75.6 ($\text{NOCH}(\text{CH}_3)_2$), 35.1 (NCH_3), 34.2 (CH_2CO), 20.8 ($\text{NOCH}(\text{CH}_3)_2$), 18.0 (CH_2), 14.0 (CH_3).

4.4. Preparation of *N*-hydroxyamides **1g-i**

A procedure for *N*-methyl-*N*-hydroxybutyramide (**1g**) is representative. Et₂O (12 mL) and water (6 mL) were added to the mixture of NaHCO₃ (1.26 g, 15 mmol) and *N*-methylhydroxylamine hydrochloride (0.42 g, 5.0 mmol) and the solution was vigorously stirred. Butyryl chloride (0.52 mL, 5.0 mmol) was added dropwise to the reaction mixture at 0 °C, and then the mixture was stirred at room temperature for 3 h. The organic layer was separated, and the aqueous layer was acidified with AcOH and was extracted with Et₂O three times. The combined organic layer was dried over MgSO₄, filtered, and the solvent was evaporated to dry. Purification by flash column chromatography (eluent: hexane/ethyl acetate = 2:1) afforded **1g** (0.35 g, 3.0 mmol) as a colorless oil in 60% yield. Spectral data were consistent with those reported previously [31]. Compounds **1h** and **1i** were prepared in the same manner.

4.4.1. *N*-Phenyl-*N*-hydroxybutyramide (**1h**)

Colorless plate crystal. IR spectrum (ATR): 3171, 2958, 1626 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 8.95 (br s, 1H, OH), 7.47-7.32 (m, 5H, arom), 2.28 (br s, 2H, CH₂CO), 1.72-1.61 (m, 2H, CH₂), 0.89 (t, J = 7.6 Hz, 3H, CH₃). ¹³C NMR (CDCl₃, 100 MHz): δ 168.5 (C=O), 138.4 (ipso-C of Ph), 129.2 (Ph), 126.7 (Ph), 126.6 (Ph), 34.2 (CH₂CO), 18.7 (CH₂), 13.7 (CH₃). Anal. Calcd for C₁₀H₁₃NO: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.67; H, 7.27; N, 7.71.

4.4.2. *N*-Hydroxybutyramide (**1i**)

Pale yellow oil. IR spectrum (ATR): 3224, 2967, 1645 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δ 8.34 (br s, 1H), 3.49 (s, 1H), 2.13 (t, J = 7.3 Hz, 2H, CH₂CO), 1.71-1.64 (m, 2H, CH₂), 0.95 (t, J = 7.3 Hz, 3H, CH₃). ¹³C NMR (CDCl₃, 75 MHz): δ 171.8 (C=O), 34.8 (CH₂CO), 18.8 (CH₂), 13.5 (CH₃).

4.5. General procedure for ruthenium-catalyzed reduction of *N*-alkoxy- and *N*-hydroxyamides

RuCl₃·3H₂O (6.5 mg, 0.025 mmol) and Zn-Cu couple (9.8 mg, 0.15 mmol) were placed in a glass Schlenk tube which was filled with argon. Dibenzyl ether (90 μ L, 0.47 mmol, internal

standard), an *N*-alkoxy- or *N*-hydroxyamide (0.50 mmol), and dehydrated EtOH (1.0 mL) were added to the mixture in this order, and the reaction mixture was refluxed at 100 °C (bath temperature). The reaction was followed by ¹H NMR spectroscopy. NMR sample solutions were prepared by sampling the reaction mixture (0.2 mL) which was quenched under air and was mixed with CDCl₃ (0.5 mL). Conversions of substrates and yields of products were calculated based on the ratio of integral areas for substrates and products relative to that for the internal standard.

For isolation of the products, the reaction mixture was filtered to remove insoluble materials. After removal of the solvent under vacuum, the residue was extracted with ethyl acetate, and the extract was filtered again to remove insoluble materials. The filtrate was evaporated to dry, and purification by flash column chromatography (eluent: hexane/ethyl acetate) afforded the products. Spectral data for *N*-methylbutyramide (**2a**) [32], *N*-methylpivalamide (**2b**) [32,33], *N*-methylbenzamide (**2c**) [34], butyramide (**2d**) [35], *N*-phenylbutyramide (**2e**) [36], *N*-methyl-3-phenylpropanamide (**2f**) [37] and *N*-methyleinnamamide (**4b**) [38] were consistent with those reported previously.

4.5.1. *N*-Methylcrotonamide (**4a**)

Colorless oil. IR spectrum (KBr, tablet): 3286, 3096, 2962, 1626 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 6.80 (dq, *J* = 15.2, 6.8 Hz, 1H, CH₃CH=CH-), 5.76 (dq, *J* = 15.2, 1.6 Hz, 1H, CH₃CH=CH-), 5.52 (br s, NH, 1H), 2.79 (d, *J* = 4.8 Hz, 3H, NCH₃), 1.82 (dd, *J* = 6.8, 1.6 Hz, 3H, CH₃). ¹³C NMR (CDCl₃, 100 MHz): δ 166.7 (C=O), 139.6 (CH₃CH=CH-), 124.9 (CH₃CH=CH-), 26.2 (NCH₃), 17.6 (CH₃). MS (EI) *m/z* 99 (M⁺).

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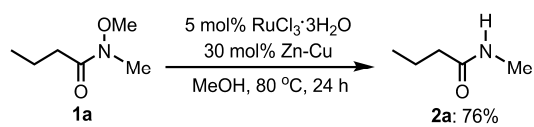
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- [12] The present method was also applied to *N*-methoxy-*N*-methylacrylamide, which has no substituent at β -position; however, polymerization of the amide appeared to occur and no deprotected compounds were detected by ^1H NMR analysis.
- [13] In these reactions, the hydrogen source would be EtOH used as a solvent, and therefore, we performed the reduction of **3a** with a small amount of EtOH (30 mol%) and DMA as a solvent at 100 °C for 24 h, in order to circumvent the hydrogenation. Although these reaction conditions suppressed the formation of deprotected/hydrogenated product **2a** (7%), the conversion of **3a** and the yield of **4a** were low as well (69% and 33% respectively).
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Eq. (1)



Eq. (2)

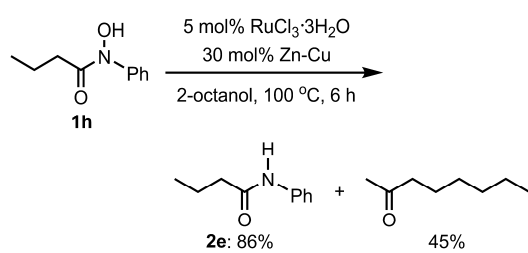
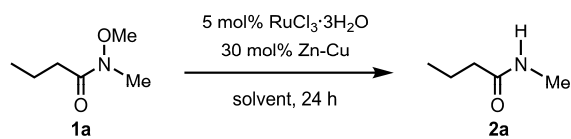


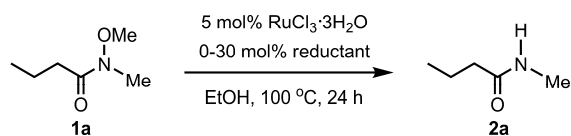
Table 1. Effects of various solvents and reaction temperatures^a

Entry	Solvent	Temp. (°C) ^b	Conversion of 1a (%) ^c	Yield of 2a (%) ^c
1	MeOH	80	76	76
2	EtOH	80	83	83
3	EtOH	100	97	97
4	2-PrOH	100	90	90
5	2-BuOH	110	78	73
6	EtOH:H ₂ O = 10:1	100	50	43

^a Reaction conditions: amide **1a** (0.50 mmol), $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ (0.025 mmol), Zn-Cu (0.15 mmol), and solvent (1.0 mL) for 24 h.

^b Bath temperature.

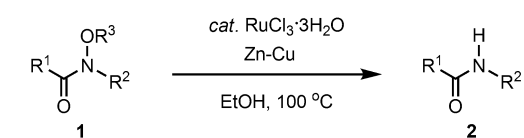
^c Determined by ¹H NMR. Dibenzyl ether was used as an internal standard.

Table 2. Effects of reductants^a

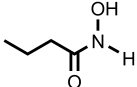
Entry	Reductant	Amount (mol%)	Conversion of 1a (%) ^b	Yield of 2a (%) ^b
1	none		16	13
2	Zn-Cu	5	33	13
3	Zn-Cu	15	91	91
4	Zn-Cu	30	97	97
5	Zn	30	100	86
6	Mg	30	50	34

^a Reaction conditions: amide **1a** (0.50 mmol), $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ (0.025 mmol), reductant (0-0.15 mmol), and EtOH (1.0 mL) at 100 °C for 24 h.

^b Determined by ^1H NMR. Dibenzyl ether was used as an internal standard.

Table 3. Reduction of several *N*-alkoxy- and *N*-hydroxyamides^a

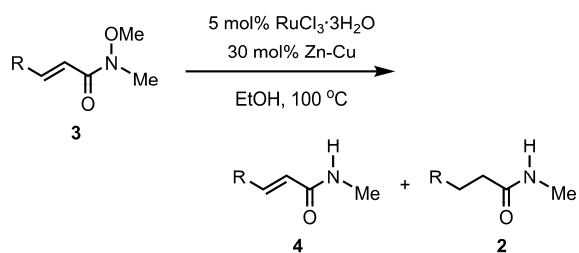
Entry	Substrate	Product	Ru Catalyst (mol%)	Time (h)	Conversion of 1 (%) ^b	Yield of 2 (%) ^{b,c}
1		1a 2a	5	6 24	94 97	94 97 (93)
2			2	24	96	90
3			1	24	54	34
4		1b 2b	5	6 24	64 100	64 >99 (95)
5		1c 2c	5	6 24	91 96	91 (85) 96
6		1d 2d	5	3	100	89 (81)
7		1e 2a	10	3	100	>99 (92)
8		1f 2a	10	6 24	41 74	41 74 (60)
9		1g 2a	5	3 20	100 100	65 74 (72)
10		1h 2e	5	4	100	98 (89)

11		1i	2d	5	3	100	66 (62)
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^a Reaction conditions: amide **1** (0.50 mmol), RuCl₃·3H₂O (0.005-0.05 mmol), Zn-Cu (0.03-0.3 mmol, 6 equiv. relative to RuCl₃·3H₂O), and EtOH (1.0 mL) at 100 °C.

^b Determined by ¹H NMR. Dibenzyl ether was used as an internal standard.

^c Isolated yields are shown in parentheses.

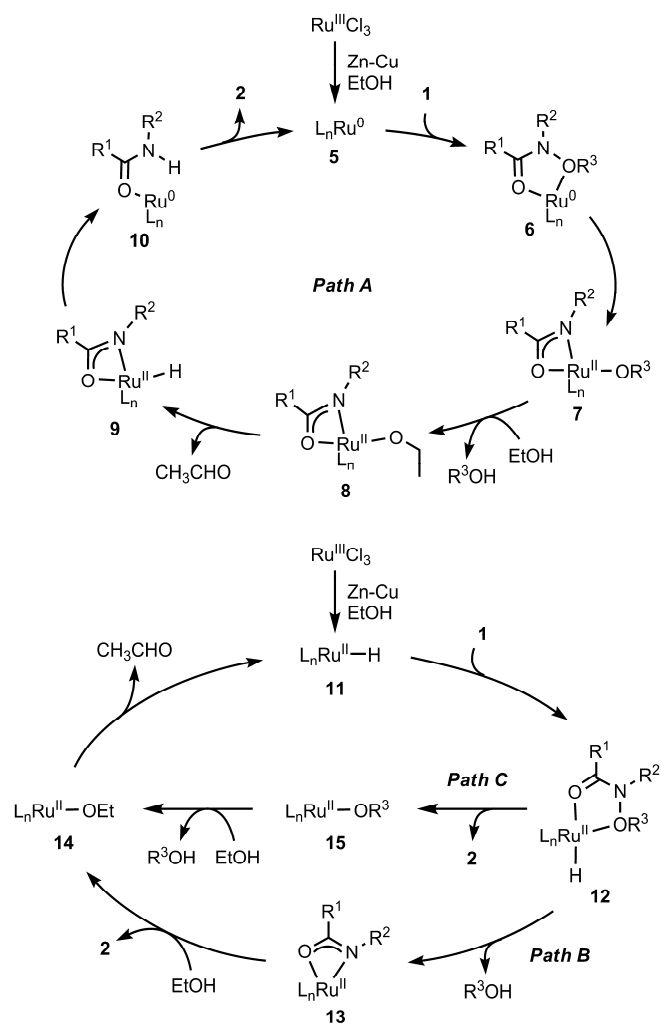
Table 4. Reduction of α,β -unsaturated *N*-methoxyamides^a

Entry	R	Substrate	Products	Time (h)	Conversion of 3 (%) ^b	Yield of 4 (%) ^{b,c}	Yield of 2 (%) ^{b,c}
1	Me	3a	4a, 2a	3	86	48	6
				6	99	56 (52)	13 (13)
				24	100	47	38
2	Ph	3b	4b, 2f	3	82	76	4
				6	99	93 (79)	6
				24	100	81	18

^a Amide **3** (0.50 mmol), $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ (0.025 mmol), Zn-Cu (0.15 mmol) and EtOH (1.0 mL) at 100 °C.

^b Determined by ^1H NMR. Dibenzyl ether was used as an internal standard.

^c Isolated yields are shown in parentheses.



Scheme 1. Possible reaction mechanisms.