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Selective Catalytic sp^3 C–O Bond Cleavage with C–N Bond Formation in 3-Alkoxy-1-propanols

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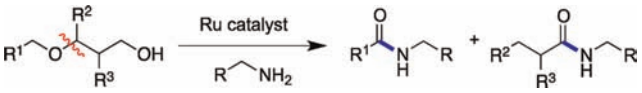
ABSTRACT



The ruthenium catalyzed selective sp^3 C–O cleavage with amide formation was reported in reactions of 3-alkoxy-1-propanol derivatives and amines. The cleavage only occurs at the C3–O position even with 3-benzyloxy-1-propanol. Based on the experimental results, O-bound and C-bound Ru enolate complexes were proposed as key intermediates for the unique selective sp^3 C–O bond cleavage in 3-alkoxy-1-propanols.

Selective C–O bond activation in ethers is scientifically challenging and has great potential in organic synthesis. Since the pioneering Ni-catalyzed arylation of aryl or vinyl ethers by Wenkert et al.,[1] much attention has been paid to the catalytic sp^2 C–O bond activation of aryl ethers for the potential substitution of aryl halides in the C–C and C–N bond formation reactions.[2,3] Compared to sp^2 C–O bond activation, few cases of catalytic activation of etheric sp^3 C–O bonds have been reported.[3c,4–8] Most examples are with strained cyclic ethers,[5] alkyl C–O bonds with good leaving groups such as OTs and OMs,[6] or relatively reactive sp^3 C–O bonds of allyl or benzyl ethers.[7,8] Selective activation of unstrained and unactivated etheric C–O bonds is highly challenging due to the relatively high bond dissociation energy of the sp^3 C–O bond and difficulty in distinguishing two different sp^3 C–O bonds in ethers.[8]

Transition metal catalyzed oxidative amide synthesis directly from alcohols and amines, without any oxidative preparation of aldehydes, carboxylic acids, and acyl

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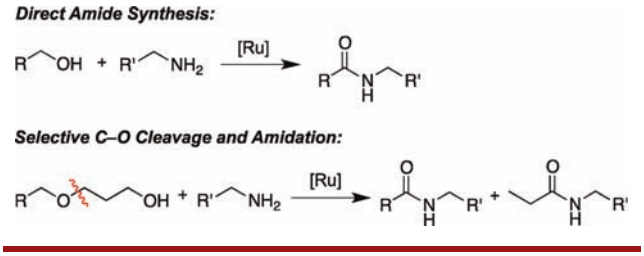
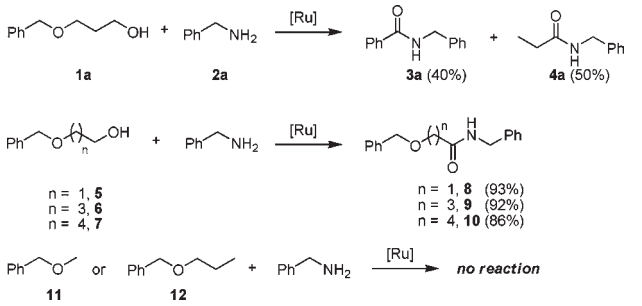
halides, has been recently highlighted as a highly atom economical transformation that generates hydrogen as the sole byproduct.[9,10] Our group has been involved in the area by developing *N*-heterocyclic carbene (NHC) based Ru catalytic systems.[11,12] While investigating the scope of the reaction, we found that sp^3 C−O cleavage in alkyl ethers occurred in the reactions of 3-alkoxy-1-propanol derivatives and an amine with concurrent formation of C−N bonds (Scheme 1). To the best of our knowledge, this is the first catalytic C−N bond formation via sp^3 C−O bond cleavage. Interestingly, the cleavage occurred selectively in the C3−O position in 3-alkoxy-1-propanols even with 3-benzyloxy-1-propanol.

When 3-benzyloxy-1-propanol (**1a**) was reacted with benzyl amine (**2a**) using an (NHC)Ru-based catalytic system for the oxidative amide synthesis from alcohols and amines,[11a] to our surprise, *N*-benzylbenzamide (**3a**) and *N*-benzylpropionamide (**4a**) were isolated in 40% and 50% yields, respectively, instead of the expected amide (Scheme 2). Noticeably, the C3−O bond was selectively cleaved with concurrent C−N bond formation instead of the more activated benzylic C−O bond. Inspired by the result, we focused on identifying the key structure for this unique C−O bond cleavage. 2-Benzyloxy-1-ethanol (**5**), 4-benzyloxy-1-butanol (**6**), and 5-benzyloxy-1-pentanol (**7**) were also tested under the same conditions, but only uncleaved corresponding amides **8**−**10** were obtained in excellent yields (Scheme 2). In the cases of benzyl methyl ether (**11**) and benzyl propyl ether (**12**), no reaction happened (Scheme 2). These results indicated that a 3-alkoxy-1-propanol skeleton is necessary to result in the C−O bond cleavage.

Scheme 1



Scheme 2. Selective C−O Bond Cleavage in 3-Alkoxy-1-propanol[a]



[a] 1.0 equiv of alcohol or ether and 1.1 equiv of amine were used. [Ru] = 2.5 mol % $[RuCl_2(p\text{-cymene})]_2$, 5 mol % *N*,*N*-diisopropylimidazolium bromide (**13**), 5 mol % pyridine, and 15 mol % NaH.

This catalytic C−O bond cleavage and amidation reaction of 3-benzyloxy-1-propanol (**1a**) with benzyl amine (**2a**) was further optimized (Table S1, Supporting Information). After extensive screening, an optimized catalytic system was identified as 5 mol % $[RuCl_2(benzene)]_2$, 5 mol % **13**, 5 mol % acetonitrile, and 45 mol % NaH and used for the following study. With the optimized conditions in hand, the substrate scope of the reaction was studied (Table 1). 3-Benzyloxy-1-propanol (**1a**) reacted smoothly with **2a** to give **3a** and **4a** in 88% and 78% isolated yields, respectively (entry 1). 3-Methoxy-1-propanol (**1b**) gave **4a** in 71% yield, and the other possible product, *N*-benzylformamide, was not observed (entry 2). (NHC)Ru-catalyzed formamide formation with methanol and amines has not been successful until now.[11] 3-Ethoxy-1-propanol (**1c**) yielded 51% of **3c** and 70% of **4a** under open reaction conditions and an Ar flow (entry 3). The Ru catalyzed direct amide syntheses have been reported to perform under open conditions and an Ar flow to facilitate removal of H_2.[11,12] As the boiling point of in situ generated ethanol, a likely C−O bond cleavage product, is low, the reaction was run in a sealed tube. Considerable improvement was achieved for **3c** (75% in a closed system vs 51% in an open system), and a comparable result was obtained for **4a** (70% in a closed system vs 71% in an open system) (entry 3). These results suggested that either an open or a closed system does not considerably affect the efficiency of the C−O bond cleavage. Substrates **1d**−**h** were selected to evaluate the effect of substituents on the C1−C3 positions. A comparable yield of **3a** with **1a** was obtained if 3-benzyloxy-2-methyl-1-propanol (**1d**) was used (entry 4), while a slightly lower yield was observed in the case of 3-benzyloxy-2-phenyl-1-propanol (**1e**) (entry 5). However, C2-disubstituted 3-benzyloxy-2,2-dimethyl-1-propanol (**1f**) was not reactive for the C−O cleavage (entry 6). Only 5% of the corresponding amide *N*-benzyl 3-benzyloxy-2,2-dimethyl-1-propionamide was isolated. These results demonstrated that at least a hydrogen should exist at the C2 carbon of 3-alkoxy-1-propanol. A methyl substituent on the C3 position (**1g**) was effective for the C−O bond cleavage (entry 7). Substrate **1h** with a methyl group on the C1 position worked well to

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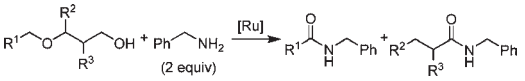
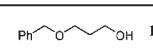
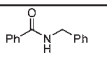
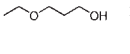
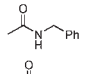
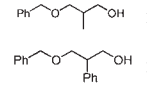
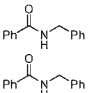
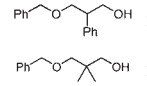
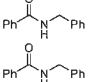
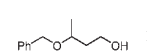
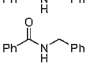
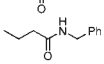
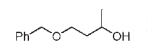
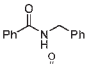
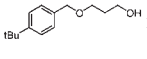
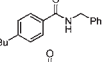
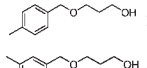
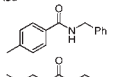
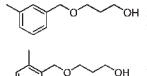
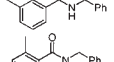
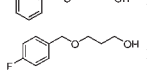
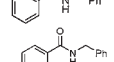
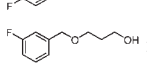
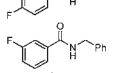
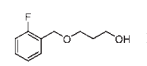
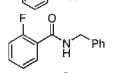
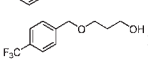
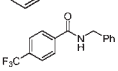
Table 1. Selective sp^3 C−O Bond Cleavage with C−N Bond Formation[a]



entry	alcohol		amide[b]			amide[b]		
1		**1a**		**3a**	88		**4a**	78
2		**1b**						71
3		**1c**		**3c**	51 (75[c])			70 (71[c])
4		**1d**			86		**4d**	65
5		**1e**			77		**4e**	56
6		**1f**			0		**4f**	0
7		**1g**			69		**4g**	80
8		**1h**			82			
9		**1i**		**3i**	92			83
10		**1j**		**3j**	88			79
11		**1k**		**3k**	89			77
12		**1l**		**3l**	60			80
13		**1m**		**3m**	68			68
14		**1n**		**3n**	62			60
15		**1o**		**3o**	20			66
16		**1p**		**3p**	41			60

[a] Reaction conditions: **1** (1.0 equiv), **2a** (2.0 equiv), 2.5 mol % $[RuCl_2(benzene)]_2$, 5 mol % **13**, 5 mol % acetonitrile, and 45 mol % NaH, toluene, reflux, 24 h. [b] Isolated yields were reported. [c] The reaction was carried out in a sealed tube at 115 °C.

generate **3a**. However, the other part, likely, a cleaved secondary alcohol, 2-butanol (or ketone, 2-butanone), cannot participate in the amidation reaction. We could not detect 2-butanol, 2-butanone, or any C_4-related compound, presumably due to the low boiling points of the possible products. Later in Scheme 5, we identified cleaved alcohols and an ester product from **1e**.

Only alkoxy groups are efficient for this transformation. Other groups such as 3-phenoxy-, 3-mesyloxy-, and 3-acetoxy- were not effective. Since those electron-deficient groups were not reactive, the electronic effect on the alkoxy group was investigated with **1a** derivatives with different substituents on the phenyl group (entries 9−16, Table 1). Both electron-donating and -withdrawing substituents can afford the product **4a** in 60−83% yields. Substrates with more electron-rich alkoxy groups showed better reactivity (entries 9−12). Therefore, electronic properties affected

Table 2. Reactivity with Different Amines[a]

entry	amine		amide[b]			amide[b]		
1		**2b**		**3ab**	76		**4ab**	66
2		**2c**		**3ac**	71		**4ac**	52
3		**2d**		**3ad**	70		**4ad**	65
4		**2e**		**3ae**	81		**4ae**	73
5		**2f**		**3af**	21		**4af**	21
6		**2g**		**3ag**	60		**4ag**	45
7		**2h**		**3ah**	61		**4ah**	50
8		**2i**		**3ai**	58		**4ai**	66

[a] Reaction conditions: **1a** (1.0 equiv), **2** (2.0 equiv), 2.5 mol % $[RuCl_2(benzene)]_2$, 5 mol % **13**, 5 mol % acetonitrile, and 45 mol % NaH, toluene, reflux, 24 h. [b] Isolated yields were reported.

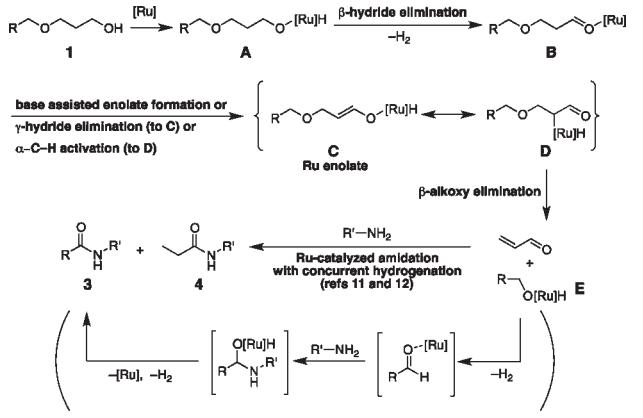
this reaction and electron-deficient alkoxy groups are less favored for the C−O cleavage.

Different amines were also screened (Table 2). Sterically less hindered primary aliphatic and benzyl amines worked effectively. Electronically different benzylamines did not significantly affect the yields, unlike electronically different 3-benzyloxy-1-propanols (entry 1 in Table 1 and entries 1−2 in Table 2). Sterically hindered primary amines and secondary amines gave lower yields as previously reported in the oxidative amidation from alcohols and amines.[9−11]

Due to the unique reactivity of 3-alkoxy-1-propanols, requirement of at least one hydrogen on the β-carbon of the OH group, and well-reported dehydrogenation of alcohols to carbonyl compounds by Ru complexes, we proposed the involvement of a Ru enolate complex in the process. Bergman et al. isolated Ru enolate complexes of both O- and C-bound forms.[13] It is proposed that subsequent β-alkoxy elimination, after generation of a C-bound Ru enolate complex, could explain the selective sp^3 C−O bond cleavage (Scheme 3). The first step is the generation of Ru alkoxide complex **A**, followed by β-hydride elimination of **A** to give Ru-bound aldehyde species **B**. **B** can be deprotonated to generate O-bound Ru enolate species **C**, which can be further isomerized to C-bound Ru enolate **D**. Alternatively, **C** could be formed by γ-hydride elimination of **B**. **D** could be also directly generated by α-C−H activation of **B**.[14] The role of a catalytic amount of NaH is not clear. We think that it is related to the generation of

(13) Hartwig, J. F.; Andersen, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 5670.

Scheme 3. Proposed Mechanism



an active catalytic intermediate or/and assistance to formation of Ru enolate complexes. It was previously reported that an active catalytic intermediate for the direct amide synthesis, $[Ru]H_2$ or [Ru], could be formed from $[Ru]Cl_2$ and an alkoxide generated by a strong base and a primary alcohol.[11c] β-Alkoxy elimination occurred to yield **E** and acrolein (or Ru-bound acrolein), which reacted further with an amine to give amides **3** and **4** as reported.[11,12]

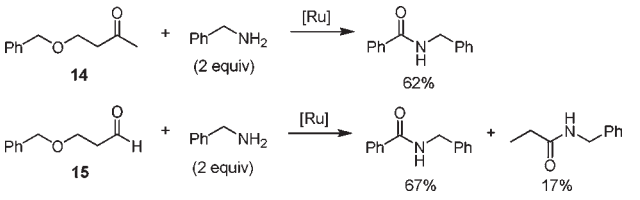
For further investigation, substrates **14** and **15** having a carbonyl group instead of an OH group were subjected to the reaction conditions. The two substrates also showed the selective C–O bond activation leading to the formation of the cleaved amides in good, but less, yields than 3-alkoxy-1-propanols, presumably due to the more facile Ru-binding to oxygen through **A** when starting from alcohols (Scheme 4).[11] Involvement of imines was ruled out as the reaction conditions are basic and no imine was observed.

Next, we tested the reaction of **1e** without amines under the same reaction conditions to check whether an amine is necessary for the C–O bond cleavage (Scheme 5). C–O bond cleavage occurred as we expected from the proposed mechanism. Esterification of benzyl alcohol was observed as well as reported in other Ru-catalyzed esterifications of primary alcohols.[9,15] For 2-phenyl-1-propanol, the corresponding ester product was not observed, presumably due to steric hindrance of the substrate and transfer hydrogenations between alcohols.

In conclusion, a novel and effective ruthenium catalyzed selective sp^3 C3–O cleavage was reported in the reaction of

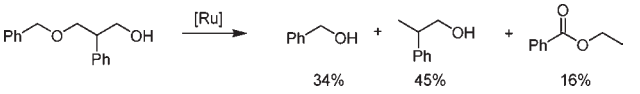
(14) (a) Takaya, H.; Ito, M.; Murahasi, S.-I. *J. Am. Chem. Soc.* **2009**, *131*, 10824. (b) Murahashi, S.-I.; Takaya, H. *Acc. Chem. Res.* **2000**, *33*, 225.

Scheme 4. C–O Bond Cleavage with a Ketone or an Aldehyde[a]



[a] Reaction conditions: **14** or **15** (1.0 equiv), **2a** (2.0 equiv), 2.5 mol % $[RuCl_2(benzene)]_2$, 5 mol % **13**, 5 mol % acetonitrile, and 45 mol % NaH, toluene, reflux, 24 h.

Scheme 5. C–O Bond Cleavage without an Amine[a]



[a] Reaction conditions: **1e** (1.0 equiv), 2.5 mol % $[RuCl_2(benzene)]_2$, 5 mol % **13**, 5 mol % acetonitrile, and 45 mol % NaH, toluene, reflux, 24 h.

3-alkoxy-1-propanol derivatives and primary or secondary amines. 3-Alkoxy-1-propanol C_3 scaffolds are required for the C–O bond cleavage. The cleavage only occurs at the C3–O position even with 3-benzyloxy-1-propanol. O- and C-bound Ru enolates were proposed as key intermediates to realize the selective sp^3 C3–O bond cleavage in 3-alkoxy-1-propanols.

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Supporting Information Available. Details of experimental procedures and characterization data. These materials are available free of charge via the Internet at http://pubs.acs.org.

(15) (a) Murahashi, S.-I. *Ruthenium in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2004. (b) Murahashi, S.-I.; Ito, K. I.; Naota, T.; Maeda, Y. *Tetrahedron Lett.* **1981**, *22*, 5327. (c) Murahashi, S.-I.; Naota, T.; Ito, K.; Maeda, Y.; Taki, H. *J. Org. Chem.* **1987**, *52*, 4319. (d) Blum, Y.; Shvo, Y. *J. Organomet. Chem.* **1984**, *263*, 93. (e) Ishii, Y.; Osakada, K.; Ikariya, T.; Saburi, M.; Yoshikawa, S. *J. Org. Chem.* **1986**, *51*, 2034. (f) Zhao, J.; Hartwig, J. F. *Organometallics* **2005**, *24*, 2441. (g) Ito, M.; Osaku, A.; Shiibashi, A.; Ikariya, T. *Org. Lett.* **2007**, *9*, 1821. (h) Murahashi, S.-I.; Kondo, K.; Hakata, T. *Tetrahedron Lett.* **1982**, *23*, 229.

The authors declare no competing financial interest.