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Chemoselective Formation of Unsymmetrically Substituted Ethers from Catalytic Reductive Coupling of Aldehydes and Ketones with Alcohols in Aqueous Solution

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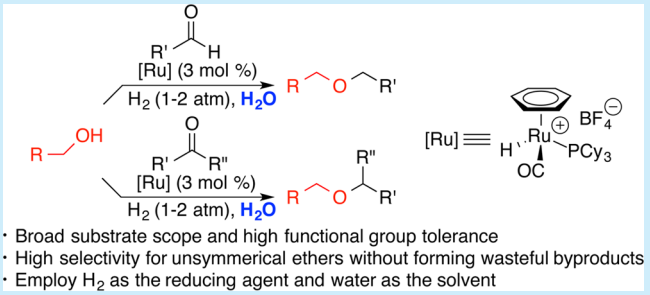
Supporting Information

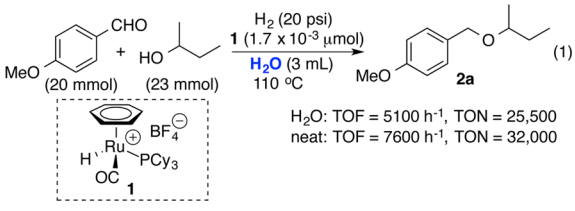
ABSTRACT: A well-defined cationic Ru−H complex catalyzes reductive etherification of aldehydes and ketones with alcohols. The catalytic method employs environmentally benign water as the solvent and cheaply available molecular hydrogen as the reducing agent to afford unsymmetrical ethers in a highly chemoselective manner.



Etherification of oxygenated organic compounds is an ubiquitous organic transformation in both industrial and fine chemical syntheses.[1] Strong Brønsted acid and heterogeneous acid catalysts are commonly employed for industrial-scale etherification of alcohols,[2] while the Williamson ether synthesis has long been used for laboratory-scale synthesis of unsymmetrically substituted ethers.[3] Seminal catalytic C−O bond formation methods such as Ullmann- and Mitsunobu-type coupling reactions have been extensively utilized for the synthesis of aryl-substituted ethers.[4] More recently, a number of highly effective catalytic methods for unsymmetrical ethers have been developed from use of hydroalkoxylation of alkenes[5] and oxidative C−H alkoxylation of arenes.[6] The reductive etherification of carbonyl compounds has also been shown to be a synthetically powerful etherification method, but this method requires a stoichiometric amount of silane as the reducing agent.[7] Despite such remarkable progress, these catalytic etherification methods pose major synthetic and environmental problems in that they employ reactive reagents such as inorganic acids and organic alkoxide substrates, which result in the formation of copious amounts of wasteful byproducts. From the viewpoint of achieving green and sustainable catalysis, the development of an efficient and broadly applicable catalytic etherification process that does not form any wasteful byproducts remains a high priority goal, particularly for the synthesis of unsymmetrically substituted ethers.[8]

We recently discovered that a well-defined cationic ruthenium hydride complex $[(C_6H_6)(PCy_3)(CO)RuH]^+BF_4^-$ (**1**) is a highly selective catalyst precursor for the etherification of two different alcohols to form unsymmetrically substituted ethers.[9] While this etherification provides unsymmetrical ethers without forming any wasteful byproducts, it was not effective for the coupling between electronically similar or sterically demanding aliphatic alcohols, as it gave a mixture of symmetrical and unsymmetrical ethers. In an effort to extend the scope of the etherification reaction, we explored the analogous reductive coupling reactions of carbonyl compounds. Herein, we report a highly chemoselective formation of unsymmetrically substituted ether products from the reductive coupling of aldehydes and ketones with alcohols. The "green" features of the catalytic method are that it employs cheaply available molecular hydrogen as the reducing agent, tolerates a number of common functional groups, and uses environmentally benign water as the solvent.

We initially screened the catalyst activity of the ruthenium complex **1** for the reductive coupling reaction of 2-butanol with 4-methoxybenzaldehyde (eq 1). While searching for a suitable set



of conditions, we were delighted to discover that H_2 (1−2 atm) can be used as the reducing agent and water as the solvent. Under these conditions, complex **1** was found to exhibit distinctively high activity and selectivity in forming the ether product **2a** among screened ruthenium and acid catalysts, as analyzed by both GC and NMR spectroscopic methods (Table S1, Supporting Information (SI)). Since most reductive etherifications of carbonyl compounds require a stoichiometric amount of silane or borane as the reducing agent,[7] our catalytic

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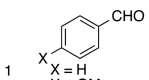
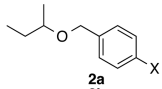
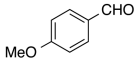
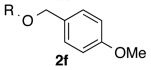
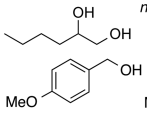
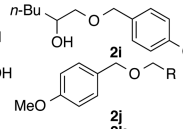
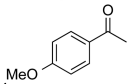
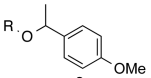
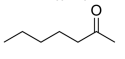
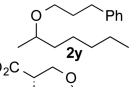
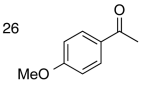
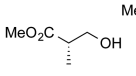
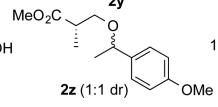
method on using molecular H_2 is quite beneficial from both synthetic and environmental points of view.

We measured the catalytic activity of **1** for the etherification reaction. In a Fisher−Porter pressure bottle, the treatment of 4-methoxybenzaldehyde (20 mmol) with 2-butanol (23 mmol) and H_2 (20 psi) in the presence of **1** (1.7×10^{-3} μmol) in water (3 mL) was stirred at 110 °C. The initial turnover frequency (TOF) of 5100 h^{-1} after 30 min and the turnover number (TON) of 25500 after 18 h were obtained as measured by both GC and NMR spectroscopic methods. The etherification reaction under neat conditions led to a considerably higher activity for **2a** (TOF = 7600 h^{-1} and TON = 32000). The salient feature of the catalytic method is that it employs cheaply available H_2 as the reducing agent in an aqueous solution.

Substrate scope of the etherification reaction was explored by using the catalyst **1** (Table 1). Both aliphatic and aryl-substituted aldehydes readily reacted with both primary and secondary alcohols to form the ether products **2** (entries 1−13). In the case of 1,2-hexanediol, exclusive etherification to the primary alcohol

Table 1. Etherification of Alcohols with Aldehydes and Ketones[a]

entry	carbonyl compd	alcohol	product(s)	time (h)	yield (%)
1	 X = H		 **2a**	12	82
2	X = OMe		**2b**	12	95[b]
3	X = OBn		**2c**	12	97
4	X = Cl		**2d**	12	68
5	X = NHCOMe		**2e**	12	85
6		R-OH	 **2f**	12	98
7	R = *n*-Butyl		**2g**	16	95[b]
8	R = Cyclopentyl R = (*R*)-$CH_2CHMeCO_2Me$		(*R*)-**2h**	16	91[b]
9			 **2i**	16	91[b]
10	R-CHO R = *i*-Butyl		**2j**	12	86
11	R = Cyclohexyl		**2k**	12	88
12	*n*-$C_5H_{11}CHO$	Ethanol	**2l**	12	71
13	*c*-$C_6H_{11}CHO$	1-Butanol	**2m**	12	76
14		R-OH	 **2n**	16	88
15	R = *n*-Butyl		**2o**	16	93
16	R = Cyclopentyl R = Bn		**2p**	16	55
17		R-OH	 **2q**	16	94
18	R = *n*-Butyl		**2r**	16	92
19	R = $CH_2C_6H_4$-4-OMe		**2s**	16	65
20		R-OH	 **2t**	16	89
21	R = *n*-Butyl		**2u**	16	82
22	 n = 2	R-OH	 **2v**	16	85
23	n = 2	R = *n*-Butyl	**2w**	12	80
24	n = 1	R = $CH_2CH_2CH_2Ph$	**2x**	16	98
25		$PhCH_2CH_2CH_2OH$	 **2y**	16	55[b]
26			 **2z** (1:1 dr)	16	78[b]

[a]Reaction conditions: carbonyl compound (1.0 mmol), alcohol (2.0 mmol), toluene/H_2O (v/v = 1:1, 3 mL), **1** (3 mol %), 110 °C. [b]Reaction in pure water (3 mL).

was observed in yielding the ether product **2i** (entry 9). The coupling between aliphatic alcohol and aldehyde substrates was sluggish, leading to a lower yield than with benzylic ones (entries 12 and 13). In this case, extending the reaction time to 24 h did not increase the product yield significantly.

The etherification of ketones also proceeded smoothly to give the α-substituted ether products. The aryl-substituted ketones with both primary and secondary alcohols led to the corresponding ether products **2n−x** (entries 14−24). The coupling with a linear aliphatic ketone was found to be considerably slower than with benzylic ketones (entry 25). The treatment of a chiral alcohol with 4-methoxyacetophenone led to a 1:1 diastereomeric mixture of ether product **2z** (entry 26). In most cases, using 2 equiv of alcohol substrate (second equivalent alcohol is served as the hydrogen donor) was found to be convenient for forming the ether products, but 1 equiv of alcohol substrate can be used with H_2 (1−2 atm) without sacrificing the product yields. In addition, a 1:1 toluene/H_2O was used as the solvent system in most cases, and pure water was used for water-soluble substrates. The catalytic method achieves a highly chemoselective etherification of aldehydes and ketones without using any reactive reagents, and employs environmentally sustainable and cheaply available alcohol substrates.

To further illustrate the synthetic versatility of the catalytic method, we next surveyed the etherification reaction of functionalized alcohol substrates of biological importance (Figure 1). The etherification of (−)-menthol and 2′,3′-

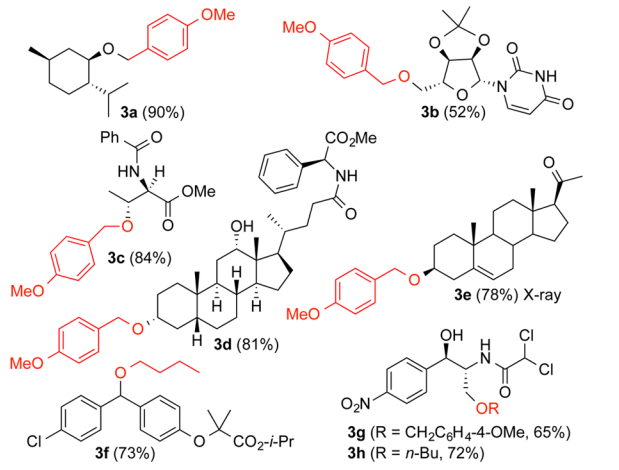


Figure 1. Etherification biologically active alcohols with aldehydes. Reaction conditions: alcohol (1.0 mmol), aldehyde (1.0 mmol), H_2 (1 atm), C_6H_5Cl (2 mL), **1** (3 mol %), 110 °C.

isopropylidenedeoxyuridine with 4-methoxybenzaldehyde smoothly formed the ether product **3a** and **3b** without any epimerization or side products. The etherification reaction of an amino acid and steroid derivatives with 4-methoxybenzaldehyde also proceeded predictively to give the products **3c−e**, while displaying high chemoselectivity toward the ether product formation. An aliphatic aldehyde was successfully used for fenofibrate and chloroamphenicol, where in the latter case, a selective etherification to the primary alcohol was achieved over the secondary one in forming the ether product **3h**. In these cases, a nonprotic solvent chlorobenzene was found to be most suitable for the coupling reaction, as the substrates become insoluble in toluene/H_2O solvent. The structure of **3e** was determined by X-ray crystallography (Figure S6, SI).

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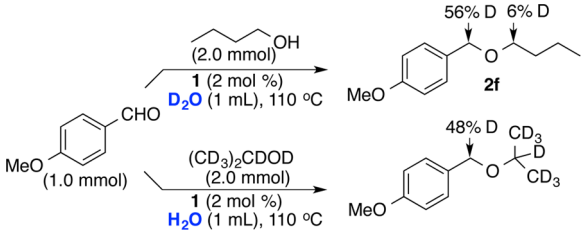
A series of kinetic experiments were performed to gain mechanistic insights for the etherification reaction. First, the H/D exchange pattern on the coupling reaction was examined. The treatment of 4-methoxybenzaldehyde with 1-butanol (2 equiv) in D_2O led to the selective deuterium incorporation to benzylic position of the product **2f** (Scheme 1). Conversely, 4-

Scheme 1



methoxybenzaldehyde with 2-propanol-d_8 (2 equiv) in H_2O gave the product with ~50% of deuterium on the benzylic position. In a control experiment, the treatment of 2-propanol with D_2O in the presence of **1** (2 mol %) led to a rapid H/D exchange to form $(CH_3)_2CHOD$ at room temperature. These results suggest that an extensive H/D exchange between the solvent molecules and the alcohol substrate led to the deuterium incorporation to the benzylic position of the ether product during the C═O hydrogenolysis step.

To probe the involvement of solvent molecules, the solvent isotope effect was measured on the catalytic reaction. The initial rates of the reaction between 4-methoxybenzaldehyde with 2-butanol (2 equiv) were separately measured in H_2O and D_2O. The first order plots showed a relatively high normal isotope effect of k_{H2O}/k_{D2O} = 2.9 ± 0.2 (Figure 2). A similar solvent

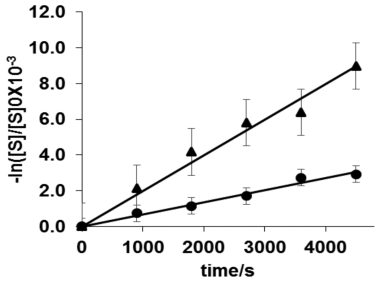


Figure 2. First-order plot of the 4-methoxybenzaldehyde (S) with 2-butanol in H_2O (▲) and in D_2O (●).

isotope effect was obtained from 2-propanol/2-propanol-d_8 (k_{PrOH}/k_{PrOD} = 2.0 ± 0.2, Figure S3, SI). A relatively large solvent isotope effect suggests that the water molecules are intricately involved in C−O bond cleavage and hydrogenolysis steps via extensive hydrogen-bonding-network interactions.[10]

To probe the electronic effect on the aldehyde substrate, we constructed a Hammett plot from measuring the rate of a series of *para*-substituted benzaldehydes *p*-X-C_6H_4CHO (X = OMe, Me, H, F, Cl) with 2-butanol. A linear correlation from the relative rate vs Hammett σ_p led to a negative ρ value of −1.6 ± 0.1 (Figure 3). The result is consistent with the notion that an electron-releasing group promotes the C−O bond hydrogenolysis step but not during the formation of hemiacetal species. Similar Hammett ρ values have been observed in the catalytic coupling reactions of arenes.[11]

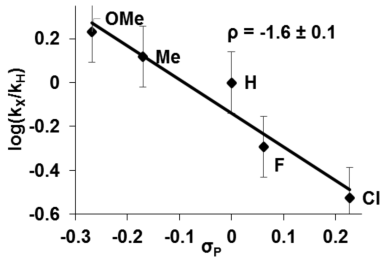
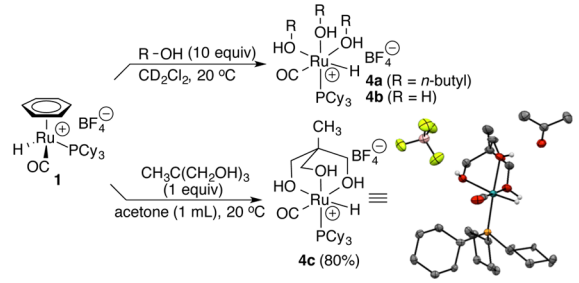


Figure 3. Hammett plot from the reaction of *p*-XC_6H_4CHO (X = OMe, Me, H, F, Cl) with 2-butanol.

To discern the structure of catalytically relevant species, we explored the reactions of **1** with alcohols and water. The treatment of the complex **1** (0.07 mmol) with excess 1-butanol (0.7 mmol) in CD_2Cl_2 (0.6 mL) led to the formation of a new Ru−H species within 30 min at room temperature (Scheme 2).

Scheme 2



The appearance of a new set of peaks was observed along with the formation of free benzene molecule as monitored by NMR (^{1}H NMR: δ −18.8 (d, J_{PH} = 31.3 Hz) ppm; $^{31}P\{^1H\}$ NMR: δ 76.0 ppm). We tentatively assign the new species to the alcohol-coordinated complex $[(1\text{-butanol})_3(PCy_3)(CO)RuH]^+BF_4^-$ (**4a**), in light of the previously observed arene exchange reaction of **1**.[12] The analogous reaction with excess water also formed the water-coordinated complex **4b** (^{1}H NMR: δ −17.7 (d, J_{PH} = 30.3 Hz) ppm; $^{31}P\{^1H\}$ NMR: δ 73.0 ppm), which steadily decomposed within 1 h at room temperature. The catalytic activity of complex **4a** was found to be identical to **1** for the etherification of 4-methoxybenzaldehyde with 2-butanol under the conditions described in eq 1.

We next examined the reaction of complex **1** with diols and triols as a way to form a stable alcohol-coordinated complex. Thus, the treatment of **1** with 1,1,1-tris(hydroxymethyl)ethane in acetone at room temperature led to the triol-coordinated complex **4c**, which was isolated in 80% after recrystallization in acetone/pentane. The X-ray crystal structure of **4c** showed a distorted octahedral geometry with a facial arrangement between the triol and the ancillary ligands. A number of ruthenium−hydride complexes have been successfully utilized as catalysts for the alcohol-coupling reactions.[13]

We present a possible mechanism of the catalytic reaction on the basis of these results (Scheme 3). We propose that an unsaturated cationic Ru−alkoxy (or Ru−alcohol) species **5** is initially generated from the benzene ligand displacement and the dehydrogenation steps. In support of this notion, we have been able to detect/isolate the formation of alcohol-coordinated cationic Ru−H complex **4** from the reaction of **1** with alcohols and water. The coordination of a carbonyl substrate followed by the nucleophilic addition of an alkoxy group is envisioned for the

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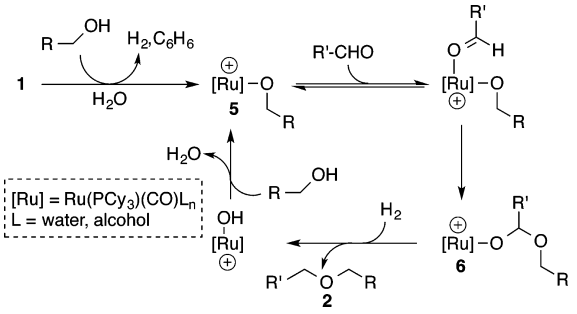
Scheme 3. Possible Mechanism for the Reductive Etherification of an Alcohol with an Aldehyde



formation of hemiacetoxy species **6**. The observed H/D exchange pattern on the α-carbon of the ether product **2** as well as a normal solvent isotope effect indicates that the solvent molecules are intricately involved in the C−O bond hydrogenolysis step. The Hammett correlation study, where the reaction is promoted by electron-releasing group of the aldehyde, supports the notion that the hydrogenolysis step is likely the turnover-limiting step of the catalytic reaction.[14]

In conclusion, we successfully developed a highly chemoselective catalytic etherification method of aldehydes and ketones with alcohols. The ruthenium hydride catalyst exhibits a uniquely high activity as well as broad substrate scope in promoting the reductive etherification reaction of carbonyl compounds in an aqueous solution without using any reactive reagents or forming wasteful byproducts. We anticipate that the catalytic etherification method provides an environmentally sustainable and cost-effective protocol for forming unsymmetrical ether compounds.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and methods, characterization and NMR spectra, and X-ray data of **3e** and **4c** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(14) In light of the recent results as described in ref 9, we have considered an alternative mechanism involving the hydrogenation of carbonyl substrate to the corresponding alcohol and the subsequent dehydrative coupling with the second alcohol substrate. Since both mechanistic pathways should involve an alcohol−ketone hydrogenation−dehydrogenation redox process and a C−O bond hydrogenolysis step, we cannot distinguish between these two pathways at the present time.

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