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Selective Catalytic Synthesis of Unsymmetrical Ethers from the Dehydrative Etherification of Two Different Alcohols

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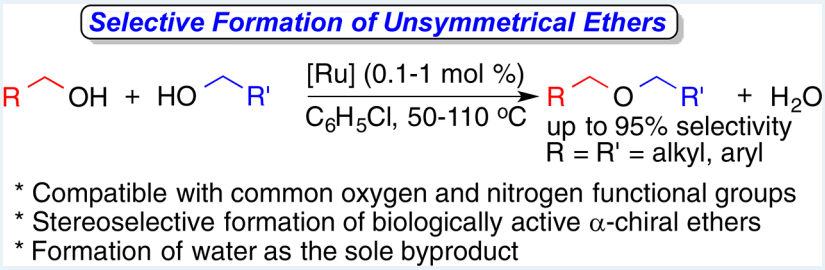
Supporting Information



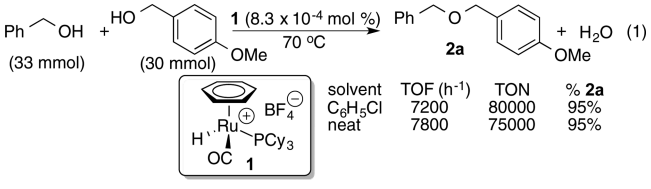
ABSTRACT: The cationic ruthenium−hydride complex $[(C_6H_6)(PCy_3)(CO)RuH]^+BF_4^-$ catalyzes selective etherification of two different alcohols to form unsymmetrically substituted ethers. The catalytic method exhibits a broad substrate scope while tolerating a range of heteroatom functional groups in forming unsymmetrical ethers, and it is successfully used to directly synthesize a number of highly functionalized chiral nonracemic ethers.

KEYWORDS: *dehydration, alcohol, ether, ruthenium catalyst*

The dehydration of alcohol is a fundamentally important organic transformation that is being widely used for the synthesis of ether compounds in both industrial and academic laboratory settings.[1] In industrial-scale processes, strong Brønsted acid and heterogeneous acid catalysts are commonly used to form symmetrically substituted ethers.[2] The Williamson ether synthesis has long been used to prepare unsymmetrically substituted ethers,[3] but the method presents major problems in large-scale synthesis due to the formation of copious amount of salt byproducts resulting from the use of inorganic base and organic halide and alkoxide substrates. To overcome these shortcomings, many transition-metal-catalyzed etherification methods have been developed in recent years. Seminal catalytic etherification methods include: Pd- and Cu-catalyzed Ullmann-type synthesis of aryl-substituted ethers,[4] Mitsunobu-type etherification,[5] reductive condensation of ketones and esters,[6] hydroalkoxylation of alkenes,[7] and oxidative C−H alkoxylation of arenes.[8] Soluble metal catalysts have also been successfully employed for the direct etherification of benzylic and propargylic alcohols.[9] Because these catalytic methods typically require reactive reagents and prefunctionalized substrates, they are often problematic in tolerating base-sensitive functional groups and lead to wasteful byproducts. The development of a broadly applicable catalytic alcohol etherification method remains an important goal particularly for the synthesis of unsymmetrically substituted ethers.

During the course of investigations on the ruthenium-catalyzed dehydrative C−H coupling reactions of alcohols,[10] we observed the formation of ether products especially when an excess amount of alcohol substrate was employed. To ascertain the origin of ether formation, we have begun to explore the alcohol dehydration reaction by using a well-defined cationic ruthenium hydride catalyst $[(C_6H_6)(PCy_3)(CO)RuH]^+BF_4^-$ (**1**).[11] Herein we disclose a highly selective synthesis of unsymmetrical ethers from direct etherification of two different alcohols. The catalytic method tolerates a range of heteroatom functional groups while generating water as the sole byproduct.

We initially examined the catalytic activity of **1** for the etherification reaction of two different benzylic alcohols. Thus, the treatment of benzyl alcohol (33 mmol) and 4-methoxybenzyl alcohol (30 mmol) in the presence of the catalyst **1** (0.25 μmol, 8.3×10^{-4} mol %) in chlorobenzene (3 mL) at 70 °C resulted in the selective formation of the unsymmetrical ether 4-OMe-$C_6H_4CH_2OCH_2Ph$ (**2a**)(95%) over the symmetrical ones (4-OMe-$C_6H_4CH_2)_2O$ (5%) and $(PhCH_2)_2O$ (<1%) (eq 1). The initial turnover frequency



(TOF) of 7200 h^{-1} after 30 min and the turnover number (TON) of 80 000 after 12 h were measured from using both

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GC and NMR spectroscopic methods. The etherification reaction under neat conditions without using solvents also led to a comparable selectivity for **2a** (TOF = 7800 h^{-1} and TON = 75 000). The catalyst **1** exhibited distinctively high activity and selectivity in forming the unsymmetrical ethers among screened metal catalysts, and the activity of a number of Brønsted acid catalysts was quite low under the similar conditions (Table S1, Supporting Information (SI)).

Encouraged by unusually high selectivity toward the formation of unsymmetrical ethers, we next used the catalyst **1** to explore the scope of the etherification reaction (Table 1).

Table 1. Synthesis of Unsymmetrically Substituted Ethers[a]

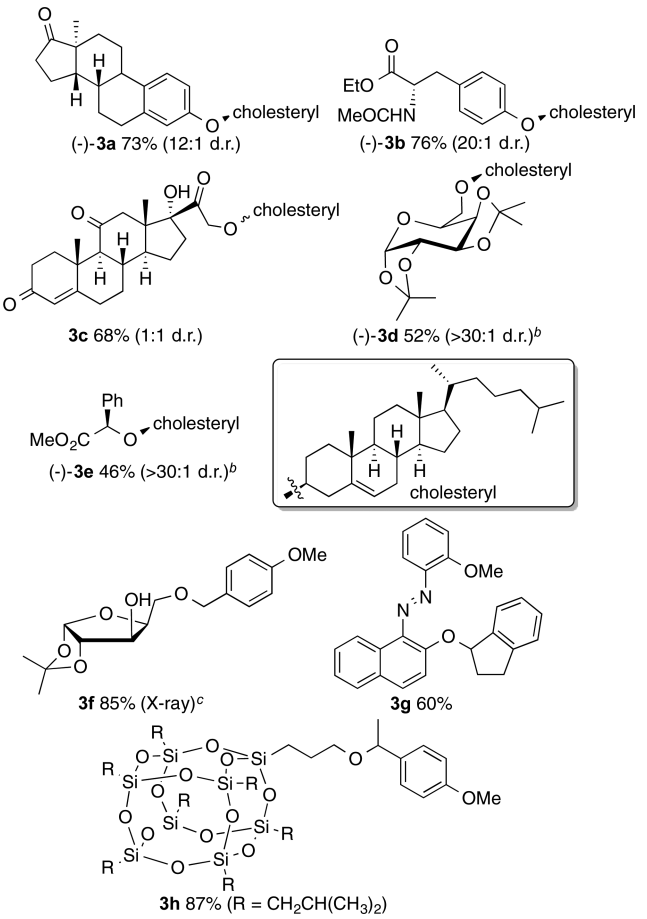
entry	R-OH	R'-OH	product	temp (°C)	t (h)	yd (%)
1		$PhCH_2OH$	**2b**	50	3	89
2		$PhCH(Me)OH$	**2c**	50	3	93
3		$PhCH(Me)CH_2CH_2OH$	**2d**	70	4	87
4		$PhCH_2OH$	**2e**	50	3	91
5		$PhCH(CH_3)OH$	**2f**	50	3	87
6		*p*-OMe-$C_6H_4CH(Me)OH$	**2g**	50	3	88
7	X = H	*p*-OMe-$C_6H_4CH_2OH$	X = H **2h**	50	2	94
8	X = OMe	$PhCH(Me)OH$	**2i**	50	2	91
9	X = H	$PhCH(Me)CH_2CH_2OH$	**2j**	50	3	92
10	X = H	$MeO_2CCH_2(CH_3)CH_2OH$	**2k**	50	4	91
11[b]	n = 1	1-hexanol	**2l**	25	8	87
12[b]	n = 1	*p*-Cl-C_6H_4OH	**2m**	25	8	85
13[b]	n = 1	*p*-OMe-C_6H_4OH	**2n**	25	8	94
14[b]	n = 2	*p*-OMe-C_6H_4OH	**2o**	25	8	91
15	X = H	1-hexanol	**2p**	70	8	79
16	X = Cl	1-hexanol	**2q**	70	8	81
17	X = Me	$PhCH(Me)OH$	**2r**	50	6	92
18	X = OMe	$NCCH_2CH_2OH$	**2s**	60	6	83
19		1-(1-naphthyl)ethanol	**2t**	60	8	80
20	n = 1		**2u**	80	8	82[c]
21	n = 3		**2v**	80	8	86[c]
22			**2w**	70	8	78[c]
23	n = 1		**2x**	50	3	87
24	n = 2		**2y**	50	3	81

[a]Reaction conditions: ROH (1.2 mmol), R′OH (1.0 mmol), C_6H_5Cl (2 mL), and **1** (1 mol %). [b]ROH (1.0 mmol) and R′OH (1.2 mmol). [c]The product yield is determined by GC.

High selectivity toward the formation of unsymmetrical ether products **2** was observed between aliphatic and benzylic alcohols, with typically <5% of symmetrical ethers and other side products. In most cases, >90% selectivity toward the formation of unsymmetrical ethers was readily achieved by using a slight excess amount of one of the alcohol substrates (1.2 equiv). Both couplings between aliphatic and benzylic alcohols and between two benzylic ones occurred at a moderate temperature (entries 1−10), while the coupling of indanol with phenol derivatives gave the ether products **2m**−**2o** at room temperature (entries 12−14). The coupling of phenol derivatives with both aliphatic and benzylic alcohols selectively afforded the corresponding aryl-substituted ethers **2p**−**2s** (entries 15−18). Intramolecular coupling of α,ω-diols selectively formed cyclic ethers **2u**−**2y** (entries 20−24). Analytically pure ether products are isolated after a column chromatography on silica gel. It should be emphasized that the selective formation of unsymmetrical ethers is quite rare; in a recent report, catalytic coupling between two aliphatic alcohols has been found to give a mixture of ethers, hemiacetal, and ester products.[12]

To further demonstrate its synthetic utility, we next examined the etherification of highly functionalized, biologically active alcohol substrates (Table 2). The treatment of

Table 2. Synthesis of Highly Functionalized Unsymmetrical Ethers[a]



[a]Reaction conditions: alcohol (1.0 mmol), alcohol (1.0 mmol), toluene/C_6H_5Cl (1:1, 3−4 mL), **1** (3−5 mol %), 80−110 °C, 12−16 h. [b]C_6H_5Cl (3 mL). [c]CH_2Cl_2/C_6H_5Cl (1:1, 4 mL).

functionalized phenolic substrates, estrone and *N*-acetyltyrosine ethyl ester, with (−)-cholesterol led to the diastereoselective formation of the corresponding α-chiral ether products (−)-**3a** and (−)-**3b**, respectively. In both cases, the ether products are formed with the retention of stereochemistry on the cholesterol carbon. Because the phenolic C−O bond is considerably stronger than the aliphatic ones, the exclusive C−O bond cleavage on cholesterol substrate is expected in forming these ether products. In contrast, the analogous coupling of cholesterol with cortisone yielded a 1:1 diastereomeric mixture of the products **3c**, resulting from the epimerization of the alcoholic carbon. The analogous coupling with a protected (−)-pyranose and (*R*)-methyl mandelate also gave the corresponding ether products, (−)-**3d** and (−)-**3e** respectively, in a highly diastereoselective fashion and with the stereoretention on the cholesterol carbon. A highly diastereoselective

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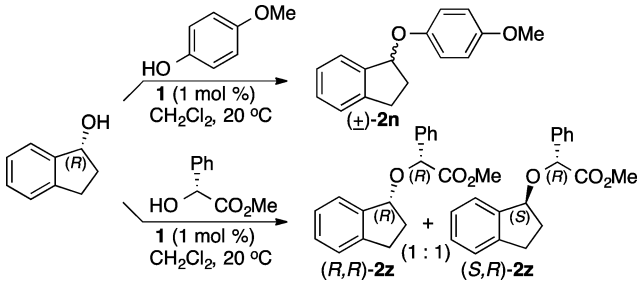
formation of the chiral nonracemic ether products with stereoretention on the cholesterol carbon implicates a S_Ni type of mechanism on the ether formation step.[13]

The etherification of a protected furanose with 4-methoxybenzyl alcohol selectively formed the corresponding ether product **3f**, the structure of which was determined by X-ray crystallography (Figure S3, SI). The etherification of functionalized organic materials, Sudan red G (a dye molecule) and a silsesquioxanyl alcohol (a nanomaterial precursor), has also been achieved by employing benzylic alcohols to form **3g** and **3h**, respectively. The catalytic etherification method provides an operationally simple, practical protocol for the stereoselective formation of α-chiral ethers while tolerating a range of common functional groups.

We performed the following experiments to probe mechanistic insights. First, we examined the coupling of a number of phenol derivatives with chiral alcohols to probe stereochemical outcome in forming these unsymmetrical chiral ethers. Thus, the treatment of an optically active (*R*)-1-indanol with 4-methoxyphenol at room temperature yielded the product (±)-**2n** in a racemic form (Scheme 1). In a control experiment, the complete racemization of (*R*)-1-indanol occurred within 10 min in the presence of **1** as monitored by the optical rotation of the reaction mixture.

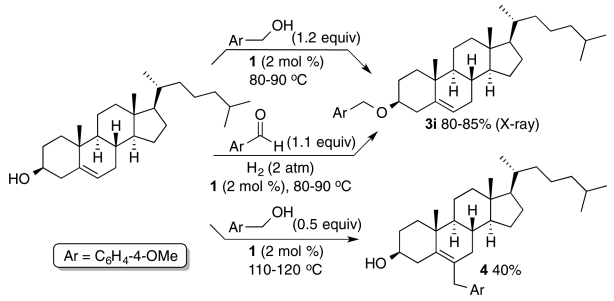
Scheme 1. Etherification Reaction of (*R*)-Indanol with 4-Methoxyphenol and (*R*)-Methyl Mandelate



The analogous coupling of (*R*)-1-indanol with (*R*)-methyl mandelate afforded a 1:1 diastereomeric mixture of the products (*R*,*R*)-**2z** and (*S*,*R*)-**2z** in 73% yield, which is the result of the selective epimerization of (*R*)-1-indanol. In this case, the diastereomeric mixture was readily separated by a simple column chromatography, and the absolute stereochemistry of each ether product was firmly established by comparing its optical rotation with the literature values.[14] In a separate experiment, the coupling of racemic (±)-1-indanol with (*R*)-methyl mandelate also formed the same diastereomeric mixture of ether products. In a control experiment, the etherification of indanol alone proceeded smoothly to give the symmetrical indanyl ether product, whereas the etherification of methyl mandelate did not occur under the similar reaction conditions. These results indicate that the epimerization of chiral alcohol is faster than the ether formation and that the unsymmetrical ether product is formed from selective C−O bond cleavage of a more reactive indanol substrate.

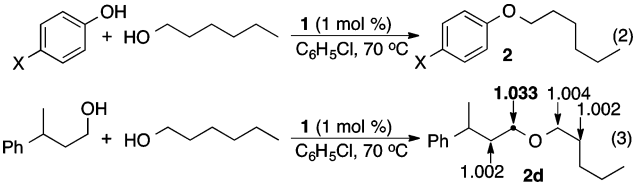
To demonstrate chemoselectivity on the etherification versus the dehydrative alkylation, we next examined the coupling of (−)-cholesterol with 4-methoxybenzyl alcohol (Scheme 2). The treatment of (−)-cholesterol with 4-methoxybenzyl alcohol led to the selective formation of the ether product **3i** at a relatively low temperature (80−90 °C), without any

Scheme 2. Formation of Unsymmetrical Ether vs Alkylation Products



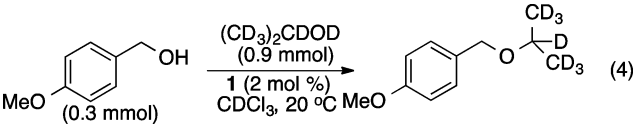
significant racemization on the alcohol carbon. The same ether product **3i** was also formed when (−)-cholesterol was reacted with 4-methoxybenzaldehyde in the presence of H_2 (2 atm) under otherwise similar reaction conditions. The structure of **3i** was confirmed by X-ray crystallography (Figure S4, SI). In contrast, the formation of the olefin alkylation product **4** became prevalent at a higher temperature (110−120 °C) under the previously reported conditions.[10] The results further illustrate the importance of selective benzylic C−O bond cleavage in yielding both ether and alkylation products.

To probe electronic effects on the ether formation, we compared the rates of the ether formation for a series of *para*-substituted phenol derivatives *p*-X-C_6H_4OH with 1-hexanol (eq 2). The Hammett plot from the relative rates versus σ_p led to a negative ρ value of −1.3 ± 0.2 (X = OCH_3, CH_3, H, Br, Cl) (Figure S2, SI). The observation of a strong promotional effect by the electron-releasing group on phenol is consistent with a nucleophilic displacement of the coordinated alcohol via an electrophilic ruthenium−phenoxy species.



The $^{12}C/^{13}C$ carbon isotope effect was successfully measured from the coupling reaction of (±)-3-phenyl-1-butanol with 1-hexanol by employing Singleton's NMR technique (eq 3).[15] The pronounced carbon isotope effect on the α-carbon of **2d** was observed when the ^{13}C ratio of the product **2d** at 85% conversion was compared to the ones obtained from three low conversions [(^{13}C at 85% conversion)/(average of ^{13}C at 14% conversion) at C(1) = 1.033] (Table S2, SI). The data are consistent with a rate-limiting step involving the C−O bond formation on the ether product.

To examine H/D exchange pattern on ether formation, we monitored the reaction of a benzyl alcohol with 2-propanol-d_8 by NMR (eq 4). The treatment of 4-methoxybenzyl alcohol



(0.3 mmol) with 2-propanol-d_8 (0.9 mmol, 99% D) and **1** (2 mol %) in $CDCl_3$ (0.4 mL) led to the preferential formation of the unsymmetrical ether product, 4-OMe-$C_6H_4CH_2OCD$-

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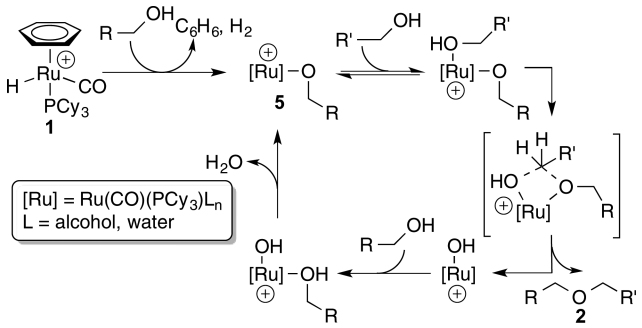
$(CD_3)_2$ over $(4\text{-OMe-}C_6H_4CH_2)_2O$ (10:1) within 1 h at room temperature but without any significant deuterium exchange to benzylic positions (Figure S1, SI).[16] The absence of H/D exchange to benzylic position is inconsistent with a mechanistic path via a reversible alcohol-to-aldehyde dehydrogenation.

In an effort to detect catalytically relevant species, a 1:1 mixture of the complex **1** (0.1 mmol) and 4-methoxybenzyl alcohol (0.14 mmol) in CD_2Cl_2 (0.6 mL) was monitored by NMR. After 10 min at room temperature, the appearance of a new species was observed along with the formation of free benzene molecule (δ 7.26 ppm on ^{1}H NMR), as indicated by a new Ru−H signal at δ −10.95 ppm on ^{1}H NMR and a phosphine peak at δ 72.4 ppm by $^{31}P\{^1H\}$ NMR. We tentatively assign the new set of peaks to an arene-coordinated Ru−H complex $[(4\text{-OMe-}C_6H_4CH_2OH)(PCy_3)(CO)\text{-}RuH]^+BF_4^-$, in light of the previously observed arene exchange reaction of **1**.[17]

On the basis of these observations, we present a working mechanistic hypothesis for the selective formation of unsymmetrical ethers (Scheme 3). We propose that a cationic Ru-alkoxy species **5**, initially generated from the deprotonation of the alcohol substrate, is the key intermediate species for the etherification reaction. Both carbon isotope effect and Hammett data implicate the preferential C−O bond cleavage from a more reactive alcohol substrate. A rapid epimerization of an optically active indanol also supports the notion for the selective C−O bond cleavage from a more reactive alcohol substrate. To explain the retention of stereochemistry on the less reactive alcoholic carbon, we suggest a S_Ni type of nucleophilic displacement mechanism for the formation of α-chiral ethers.[13] As indicated by the Hammett study of phenol substrates, the acidity of alcoholic substrate may be an important factor in promoting the formation of Ru-alkoxy species **5** from the deprotonation of a less reactive, more basic alcohol substrate. The coordination of another alcohol substrate and the liberation of water byproduct would facilitate the regeneration of the alkoxy species **5**. Still, many aspects on how the catalyst can mediate a high degree of selectivity remain unresolved, and detailed kinetic and computational studies are warranted to elucidate the mechanism of unsymmetrical ether formation.[18]

Scheme 3. Working Mechanistic Hypothesis for Unsymmetrical Ether Formation



In summary, we successfully developed a highly selective catalytic method for the direct etherification of two different alcohols. A well-defined cationic ruthenium-hydride catalyst exhibits uniquely high chemo- and stereoselectivity toward the formation of unsymmetrically substituted and highly functionalized α-chiral ethers. We anticipate that the catalytic method would provide an operationally simple tool for synthesizing functionalized ethers without using any reactive reagents or protecting groups.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and methods, characterization data, and NMR spectra of organic products. 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.

■ ACKNOWLEDGMENTS

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■ REFERENCES

(1) Reviews: (a) Mitsunobu, O. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, J., Eds.; Pergamon Press: New York, 1991; Vol. *6*, pp 1−31. (b) Lee, C.; Matunas, R. In *Comprehensive Organometallic Chemistry III*, Crabtree, R. H., Mingos, D. M. P., Eds.; Elsevier: Boston, 2007, Vol. *10*, pp 649−693.

(2) (a) Olah, G. A.; Molnár, A. *Hydrocarbon Chemistry*, 2nd ed.; Wiley: Hoboken, NJ, 2003. (b) Klier, K.; Beretta, A.; Sun, Q.; Feeley, O. C.; Herman, R. G. *Catal. Today* **1997**, *36*, 3−14. (c) Nowak, I.; Ziolek, M. *Chem. Rev.* **1999**, *99*, 3603−3624. (d) Tanabe, K.; Hölderich, W. F. *Appl. Catal.* **1999**, *181*, 399−434.

(3) (a) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; Wiley: New York, 2001. (b) Baggett, N. In *Comprehensive Organic Chemistry*, Barton, D., Ollins, W. D., Eds.; Pergamon Press: Oxford, 1979; Vol. *1*.

(4) (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400−5449. (c) Maligres, P. E.; Li, J.; Krska, S. W.; Schreier, J. D.; Raheem, I. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 9071−9074.

(5) (a) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428−2439. (b) Sze-But, T. Y.; Toy, P. H. *Chem.—Asian J.* **2007**, *2*, 1340−1355. (c) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450−1460. (d) Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. P. *Chem. Rev.* **2009**, *109*, 2551−2651.

(6) (a) Shintou, T.; Mukaiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 7359−7367. (b) Sakai, N.; Moriya, T.; Konakahara, T. *J. Org. Chem.* **2007**, *72*, 5920−5922.

(7) (a) Sassaman, M. B.; Kotian, K. D.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1987**, *52*, 4314−4319. (b) Sakai, N.; Moriya, T.; Konakahara, T. *J. Org. Chem.* **2007**, *72*, 5920−5922. (c) Haibach, M. C.; Guan, C.; Wang, D. Y.; Li, B.; Lease, N.; Steffens, A. M.; Krogh-Jespersen, K.; Goldman, A. S. *J. Am. Chem. Soc.* **2013**, *135*, 15062−15070.

(8) (a) Wang, X.; Lu, Y.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 12203−12205. (b) Jiang, T.-S.; Wang, G.-W. *J. Org. Chem.* **2012**, *77*, 9504−9509. (c) Li, W.; Sun, P. *J. Org. Chem.* **2012**, *77*, 8362−8366. (d) Zhang, S.-Y.; He, G.; Zhao, Y.; Wright, K.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 7313−7316. (e) Chen, F.-J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 4187−4192. (f) Roane, J.; Daugulis, O. *Org. Lett.* **2013**, *15*, 5842−5845.

(9) (a) Manabe, K.; Iimura, S.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 11971−11978. (b) Sherry, B. D.; Radosevich, A. T.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 6076−6077. (c) Liu, Y.; Hua, R.; Sun, H.-B.; Qiu, X. *Organometallics* **2005**, *24*, 2819−2821. (d) Prades, A.; Corberán, R.; Poyatos, M.; Peris, E. *Chem.—Eur. J.*

2008, *14*, 11474−11479. (e) Seo, S. Y.; Yu, X.; Marks, T. J. *J. Am. Chem. Soc.* **2009**, *131*, 263−276. (f) Mitsudome, T.; Matsuno, T.; Sueoka, S.; Mizugaki, T.; Jitsukaw, K.; Kaneda, K. *Green Chem.* **2012**, *14*, 610−613.

(10) (a) Lee, D.-H.; Kwon, K.-H.; Yi, C. S. *Science* **2011**, *333*, 1613−1617. (b) Lee, D.-H.; Kwon, K.-H.; Yi, C. S. *J. Am. Chem. Soc.* **2012**, *134*, 7325−7328.

(11) Yi, C. S.; Lee, D. W. *Organometallics* **2010**, *29*, 1883−1885.

(12) (a) Gunanathan, C.; Shimon, L. J. W.; Milstein, D. *J. Am. Chem. Soc.* **2009**, *131*, 3146−3147. (b) Gunanathan, C.; Milstein, D. *Science* **2013**, *341*, 249.

(13) Selected examples of S_Ni substitution mechanism: (a) Schreiner, P. R.; Schleyer, P. R.; Hill, R. K. *J. Org. Chem.* **1994**, *59*, 1849−1854. (b) Moss, R. A.; Fu, X.; Tian, J.; Sauers, R.; Wipf, P. *Org. Lett.* **2005**, *7*, 1371−1374. (c) Gómez, H.; Polyak, I.; Thiel, W.; Lluch, J. M.; Masgrau, L. *J. Am. Chem. Soc.* **2012**, *134*, 4743−4752.

(14) Mashraqui, S. H.; Kellogg, R. M. *J. Org. Chem.* **1984**, *49*, 2513−2516.

(15) (a) Singleton, D. A.; Thomas, A. A. *J. Am. Chem. Soc.* **1995**, *117*, 9357−9358. (b) Frantz, D. E.; Singleton, D. A.; Snyder, J. P. *J. Am. Chem. Soc.* **1997**, *119*, 3383−3384.

(16) The analogous coupling of the deuterated benzyl alcohol 4-OMe-$C_6H_4CH_2OD$ with 2-propanol-d_8 gave the same ether products with identical deuterium exchange pattern. Also, the treatment of 4-methoxybenzyl alcohol with 2-propanol-d_8 without the Ru catalyst did not lead to any significant deuterium exchange between alcohols.

(17) Kwon, K.-H.; Lee, D. W.; Yi, C. S. *Organometallics* **2010**, *29*, 5748−5750.

(18) As shown in the catalyst screening (Table S1, SI), the Ru catalyst is definitely required for high activity and selectivity for unsymmetrical ethers. Also, the difference in physical properties such as boiling point and solubility between two alcohols is relatively small in most cases, and this is unlikely to affect the observed selectivity.