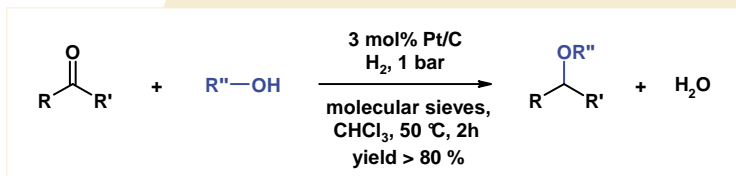


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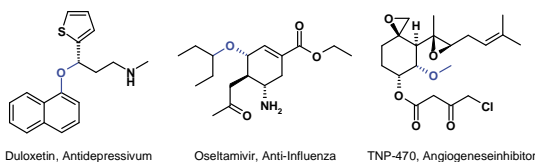
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The unsymmetrical ether moieties are among the most abundant substructures in organic molecules. Traditionally, they are prepared via the Williamson ether synthesis, despite the need for strong bases and the inevitable formation of stoichiometric amounts of salts as byproducts. We herein present a practical, waste-minimized protocol for the synthesis of unsymmetrical ethers using a special Pt/C-catalyst that allows the reductive etherification of ketones and alcohols under atmospheric hydrogen pressure. In this transformation, only water is formed as byproduct, which is trapped by molecular sieves. The synthetic interest of this new protocol is demonstrated by the wide range of ketones and both primary and secondary alcohols that can be transformed under these conditions.

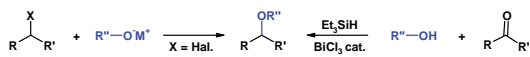


The Synthesis of unsymmetrical Ethers

Many organic molecules contain ether functionalities as demonstrated by the examples below.

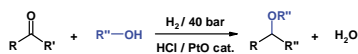


The Williamson ether synthesis represents the most widely used synthetic entry to this substrate class. However, it cannot be considered to be environmentally benign as it requires the use of stoichiometric amounts of strong bases as well as equimolar amounts of salts are formed as by-products.



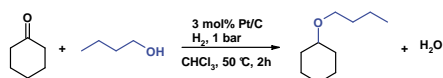
Catalytic Reductive Etherification of Ketones with Alcohols

In contrast to the widely used reductive amination, an analogous ether synthesis from carbonyl compounds and alcohols under reductive conditions has never become established as a standard tool for ether synthesis. This can be attributed to the fact that previously reported reductive etherification procedures are limited to short-chain primary alcohols and are impractical for laboratory use. All of these processes despite the need for either strong acids or a high hydrogen pressure and call for a large excess of one of the substrates, usually as a solvent for the other.



As a consequence, related procedures were favored in which the reductant is either a silane, or an alkoxysilane pre-formed with the alcohol substrate, thus sacrificing the atom economy of the overall process (see scheme above).

A protocol that allows the coupling of carbonyl compounds with a wider range of alcohols in the presence of hydrogen as the reducing agent, under conditions suitable for everyday laboratory use, would be of high synthetic interest. In order to develop such a method, we chose the coupling of cyclohexanone with 1-butanol as a model reaction. We started our catalyst development with a 1:2 mixture of the ketone and the alcohol in a chloroform solution at a temperature of 50 °C using Pt/C as a catalyst.



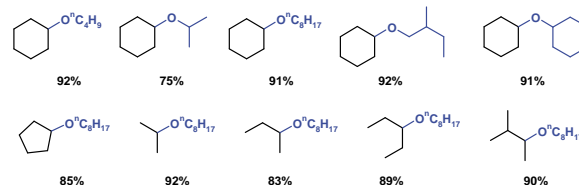
Entry	Catalyst	Ratio	Temp (°C)	Yield (%)
1 ^b	Pt/C ^c	1:2	50	22
2	Pt/C ^c	1:2	50	68
3	Pd/C	1:2	50	34
4	Rh/C	1:2	50	2
5	Pt/Al ₂ O ₃	1:2	50	0
6	Pt/C ^d	1:2	50	84
7	Pt/C ^d	1:2	40	28
8	Pt/C ^d	1:2	60	46
9	Pt/C ^d	1:4	50	87
10	Pt/C ^d	1:1.5	50	79
11	Pt/C ^d	1:1	50	72

Reaction conditions: 1.00 mmol cyclohexanone, given amount of butan-1-ol, 0.03 mmol cat., H₂ (1 bar), 500 mg MS 3 Å, 4.00 mL CHCl₃, 50°C, 2h; ^b without molecular sieves; ^c 10% Pt/C; Acros; Pt/C; Degussa R-type; 5% Pt/105 R/D

These initial experiments gave only low yields until we discovered the detrimental effect of water on the transformation: adding molecular sieves to the reaction mixture to remove the water by-product increased the yields to a preparatively useful level. Under these conditions most metals on solid supports tested displayed almost no catalytic activity, but we were pleased to find that a specific type of 5% platinum on charcoal catalyst (Degussa R-type: F 105 R/D) resulted in a high conversion.

Chloroform was found to be the best solvent, while coordinating solvents, e.g. tetrahydrofuran, or plain hydrocarbons were less effective. We also optimized the reaction stoichiometry and found that already with a 1:1 ratio of the substrates, reasonable yields were obtained. A small excess of the alcohol component (1.5-2 equiv) gave slightly better yields, while an increase of the amount of alcohol beyond two equivalents did not lead to any further improvement.

We applied the optimized protocol to a number of alcohols and ketones to investigate the scope of the reaction. A reasonably wide range of both substrates could be obtained in good yields. Selected examples are shown below.



As it had been our initial aim to increase the reducing power of the catalyst system to a maximum achievable, it is not surprising that only those functionalities were tolerated which are inert towards reducing conditions, and do not react with carbonyl compounds. In order to make this protocol accessible to an even larger range of compounds, future work will be directed at tuning the hydrogenation catalyst to improve substrate tolerance while retaining its high reactivity towards the reductive etherification.

We thank Degussa AG and Umicore AG for generous donations of the catalysts.

Literature and Further Reading (see also www.chemie.uni-kl.de/goossen)

- [1] L. J. Goossen, C. Linder, *Synlett* **2006**, 3489.
- [2] a) W. Williamson, *Justus Liebigs Ann. Chem.* **1851**, 77, 37; b) J. March, in *Advanced Organic Chemistry* 3rd ed.: Wiley; New York: **1992**, 386.
- [3] a) S. Gomez, J. A. Peters, T. Maschmeyer, *Adv. Synth. Catal.* **2002**, 344, 1037; b) P. N. Rylander, in *Catalytic Hydrogenation over Platinum Metals* Academic Press; New York: **1967**, 291.
- [4] V. Bethmont, F. Fache, M. Lemaire, *Tetrahedron Lett.* **1995**, 36, 4235.
- [5] a) M. P. Doyle, D. J. DeBruyn, D. A. Kooista, *J. Am. Chem. Soc.* **1972**, 94, 3659; b) M. Wada, S. Nagayama, K. Mizutani, R. Hiroi, N. Miyoshi, *Chem. Lett.* **2002**, 248; c) T. Suzuki, K. Ohashi, T. Oriyama, *Synthesis* **1999**, 9, 1561.
- [6] a) S. Hatakeyama, H. Mori, K. Kitano, H. Yamada, M. Nishizawa, *Tetrahedron Lett.* **1994**, 35, 4367; b) J. Kato, N. Iwasawa, T. Mukaiyama, *Chem. Lett.* **1985**, 743; c) M. B. Sassaman, K. D. Kotian, G. K. S. Prakash, G. A. Olah, *J. Org. Chem.* **1987**, 52, 4314.