Advanced Synthesis & Catalysis

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**To be cited as:** *Adv. Synth. Catal.* 10.1002/adsc.201900281

**Link to VoR:** http://dx.doi.org/10.1002/adsc.201900281

10.1002/adsc.201900281

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

# Reductive etherification of aldehydes and ketones with alcohols and triethylsilane catalysed by Yb(OTf)3: an efficient one-pot benzylation of alcohols

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Received:((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

**Abstract.** The one-pot synthesis of symmetrical and unsymmetrical ethers from aldehydes and ketones can be conveniently performed using $Yb(OTf)_3$ as catalyst and triethylsilane as reducing agent in presence of alcohols. This methodology leads to the synthesis of ether derivatives with good yields. Notably, this process resulted a useful tool to protect alcohols as benzyl ether derivatives using differently substituted benzaldehydes as protecting agents under mild conditions. A plausible mechanism was also proposed.

Abstract Text----Continued

**Keywords:** Reductive etherification; Ytterbium triflate; Unsymmetrical ethers; Benzylation of alcohols; Reduction; C-O bond formation.

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## Introduction

Ethers are an important class of compounds with an extensive range of applications and uses. As functional group it is represented in a large variety of organic compounds: from simple cyclic and acyclic alkyl ethers used as organic solvents (diethyl ether, 1,4-dioxane, tetrahydrofuran and 2-methyltetrahydrofuran) and cyclicalkyl ethers based on the 1,2-ethanediol unit, defined as crown ethers,[1] to structurally diversified ethers in which it is possible to find many important pharmacologically active natural occurring and synthetic products such as, for instances, morphinanes, tetrahydrocannabinols, conicolderivatives,[2] ebastine,[3] nonactin,[4] tetrahydropyran andisochroman derivatives,[5] tetrahydrofuran derivatives,[6] etc. Cyclic monoterpenoid ethers form a large group of odorous substances,[7] both natural and synthetic, and they occur as ingredients in perfume, many brands of mouthwash and cough suppressant[8]and as insecticide.[9] Due to their volatility certain ethers, such as *tert*-butyl methyl ether, are used instead of tetraethyllead as anti-knock additives for motor fuel.[10] Some ethers, especially benzyl ethers, were widely used in synthetic organic chemistry especially as protecting groups of the alcohol moiety in multistep synthesis.[11]

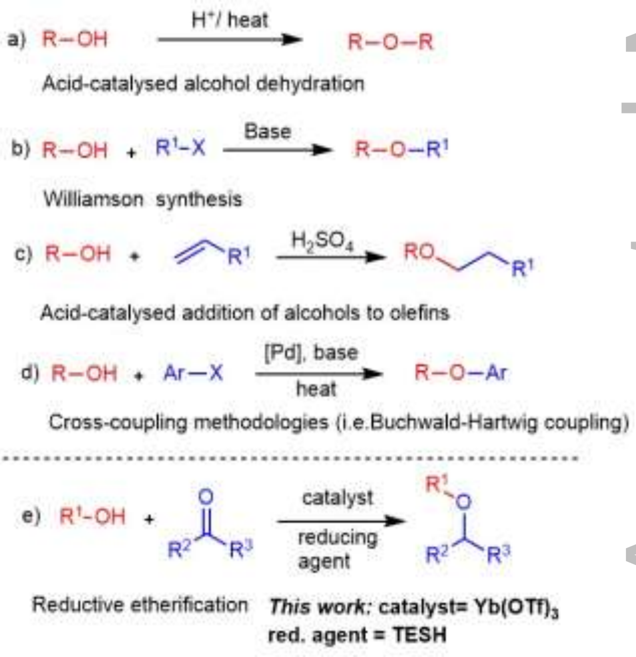

**Figure 1.** Examples of etherification processes.

For these reasons the development of a convenient and efficient method for the synthesis of ether derivatives takes on significant meaning.

Traditionally ethers can be obtained from primary alcohols with sulphuric acid at elevated temperature. The method is effective for generating symmetrical

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ethers, but not unsymmetrical ones, since either OH can be protonated, which would give a mixture of products (Figure 1a). For example diethyl ether is industrially produced by dehydration of ethanol at 140 °C.[12] The Williamson synthesis involves the reaction of an alkoxide ion obtained from an alcohol with a primary alkyl halide via an $SN_2$ type reaction and it is most often accomplished by the use of strong base (Figure 1b).[12] The conversion of primary alcohols into ethers can be obtained by dissolution in sulphuric acid and subsequent addition of the corresponding olefin (Figure 1c).

Through this synthetic process *tert*-amyl methyl ether and *tert*-butyl methyl ether are produced.[12]

Recently, cross-coupling reaction have been employed to synthesize ethers through palladium-catalyzed Buchwald-Hartwig.[13] and copper-catalyzed Cham-Lam and Ulmann couplings.[14] Neverthless these methodologies are usually restricted to the synthesis of aryl ethers (Figure 1d).

A novel strategy for the synthesis of sterically hindered ethers have been recently proposed by Kürti at al. that employs the copper-catalyzed radical etherification. [15]

Catalytic hydrogenation of aldehydes and ketones in alcoholic acidic media appears to provide the most general and convenient route to symmetrical and unsymmetrical ethers (Figure 1e). However, hydrocarbon formation competes with ether production, and yields are low when aldehydes are reduced or when the alcohol used is larger than propyl.[16]

An interesting improvement of this methodology was recently reported by Soós et al. that described the auto-tandem catalysis with frustrated Lewis pairs and $H_2$ as reducing agent for reductive etherification of aldehydes and ketones.[17]

Among the plethora of synthetic protocols for the preparation of ethers *via* catalytic hydrogenation, a very promising method for the production of symmetrical and unsymmetrical ethers is represented by silane-mediated reductive etherification that generally requires acid catalysis.

The reducing ability of organosilanes together with their superior handling has attracted growing attention because they can essentially reduce all reducible organic functional groups including alcohols,[18] carbonyl derivatives,[19] alkyl or aryl halides,[20] olefins[21] and amides.[22]

Triethylsilane (TESH) is the more commonly used organosilane in reductive process of carbonyl groups (aldehydes and ketones) in the presence of an acid promoter.[23]

In particular, the reductive etherification of carbonyl compounds with alkoxysilanes and TESH was studied as an innovative synthesis of symmetrical and unsymmetrical ethers. This reaction can be promoted by Lewis acids such as trityl perchlorate,[24] trimethylsilyl iodide,[25] trimethylsilyltrifluoromethanesulfonate,[26] bismuth bromide,[27] copper triflate,[28] tris(pentafluorophenyl)borane,[29] iron (III) chloride.[30]

However, these reactions require an annoying step-by-step procedure or a longer reaction time related to the preparation and the use of alkoxysilanes as reagents.

On the other hand, in 1972 Doyle et al. reported a one pot preparation of ethers through the reduction of aldehydes and ketones by trialkylsilanes in alcoholic acidic media.[31] In this procedure a large excess of concentrated sulphuric or trifluoroacetic acids was used as acid catalyst.

Iwanami et al. in 2007 proposed the use 5 mol% of anhydrous $FeCl_3$ as catalyst in nitromethane under argon atmosphere for the one pot preparation of ethers through the reductive etherification of aldehydes and ketones with alcohols in the presence of triethylsilanes.[32]

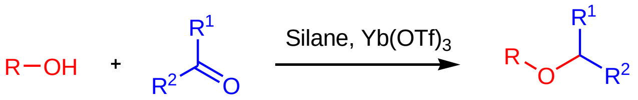
Roth et al. in 2011 proposed the use of triflic acid (1 mol%) as catalyst in nitromethane or dichloromethane for the reductive coupling of carbonyl compounds with O-, S-. and N-nucleophile in the presence of triethylsilanes.[33]

Hence, the reductive etherification of aldehydes and ketones could offer a viable alternative with improved results to the traditional synthesis of ethers, which are characterized by several drawbacks.

Furthermore, the reductive etherification of aldehydes and ketones can benefit of the wide overview of aldehydes and ketones offering considerable synthetic potential, especially for the synthesis of unsymmetrical ethers.

## Results and Discussion

In this work we report a one-pot synthesis of symmetrical and unsymmetrical ethers starting from ketones (or aldehydes) and alcohols in the presence of a silane and Ytterbium triflate as catalyst, as proposed in the scheme 1. Ytterbium triflate is known to be a useful mild, versatile, and environmentally friendly Lewis acid catalyst.[34]



**Scheme 1.** General reaction of reductive etherification catalysed by $Yb(OTf)_3$.

In order to examine the feasibility of this process, preliminary experiments were carried out using reaction conditions similar to the reported in the literature. Triethylsilane (TESH, 2 equiv) was chosen as reductive agent in the presence of $Yb(OTf)_3$ (4 mol%) and 1,2-dichloroethane as solvent since it has proven to be an excellent solvent in reactions

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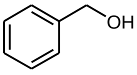
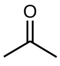
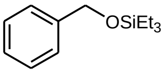
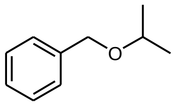
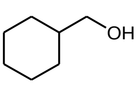
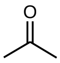
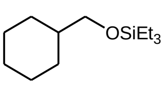
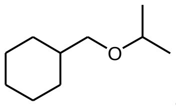
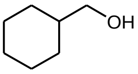
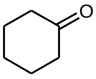
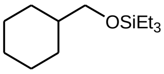
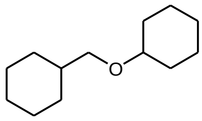
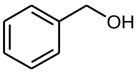
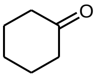
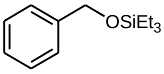
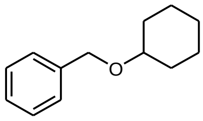
catalyzed by Yb(OTf)$_3$.[35] Benzyl alcohol (**1a**) and cyclohexylmethanol (**1b**) were used as primary alcohols in the reductive etherification reaction of acetone (**2a**) or cyclohexanone (**2b**) respectively (Table 1).

With an equimolar ratio of alcohol and ketone the reaction did not take place at room temperature and it resulted slow when carried out at reflux temperature.

Although this reaction has led to the desired products **4a** and **4b**, the reaction yields are completely inadequate (Table 1, entries 1-3). The reason for this low yield, can be explained by the greater volatility of the acetone (**2a**) (b.p. = ~56 °C) respect to 1,2-dichloroethane (b.p. = ~80 °C). In order to overcome the decrease of acetone concentration due to evaporation at reflux temperature, an excess of acetone (**2a**) (4 equiv) was required. This precaution allowed to increase the reaction yield up to 53% after 24 hours (Table 1, entry 5). It is important to note that all the experiments led also to the alkoxysilanederivatives of the starting alcohols. Interestingly, the TLC analysis showed a particularly ongoing of the reactions over the time with the alkoxysilaneintermediates (**3a** and **3b**) increasing in concentration at the beginning of the reaction (Table 1, entries 1 and 4). With the progress of the reaction time, the alkoxysilane tended to decrease in intensity while unsymmetrical ether derivatives (**4a** and **4b**) slowly increased as a result. After 24 hours the main product were the unsymmetrical ether derivatives.

The decrease of the alkoxysilane intermediates in favour of the unsymmetrical ether derivative, leads us to hypothesize its role as a reaction intermediate. Indeed, as mentioned above, several reductive etherifications of aldehydes and ketones use preformed alkoxysilanes obtained by known methods as starting products.

**Table 1.** Reductive etherification of ketones with alcohols and TESH (2 equiv) in 1,2-dichloroethane at reflux in the presence of Yb(OTf)$_3$ (4 mol %).

| Entry | Alcohol (ROH) | Ketone [equiv] | | Time (h) | ROSiEt$_3$ (yield %)$^a$ | | Unsymmetrical ether (yield %)$^a$ | |
|---|---|---|---|---|---|---|---|---|
| 1 |  **1a** |  **2a** | [1] | 2 |  **3a** | (13) |  **4a** | (7) |
| 2 | | | [1] | 24 | | (7) | | (18) |
| 3 |  **1b** |  **2a** | [1] | 24 |  **3b** | (4) |  **4b** | (11) |
| 4 | | | [4] | 2 | | (32) | | (37) |
| 5 | | | [4] | 24 | | (11) | | (53) |
| 6 |  **1b** |  **2b** | [1] | 24 |  **3b** | (5) |  **4c** | (57) |
| 7 | | | [2] | 24 | | (11) | | (71) |
| 8 |  **1a** |  **2b** | [2] | 24 |  **3a** | (5) |  **4d** | (75) |

$^a$Isolated yields

This would mean that the reaction took place in two different pathways where the initial reductive phase of the ketone was followed (or occurred simultaneously) by the formation of the triethyl silyl ether of the starting alcohol; subsequently the latter would turn into the final ether at a low speed. This would explain the slow disappearance of the alkoxysilane intermediate in favour of the unsymmetrical ether.

As shown in Table 1, the use of cyclohexanone (**2b**) overcame the problem related to the volatility of acetone and lead to the unsymmetrical ether **4c** already with 1 equivalent of ketone (Table 1, entry 6). A further improvement of the reaction yields of the unsymmetrical ethers **4c** and **4d** was obtained when 2 equivalents of cyclohexanone (**2b**) were used with the starting alcohols **1a** and **1b** respectively (Table 1, entries 7 and 8). It is important to note that, relatively to the type of reaction conditions, silane reagents can be converted to a disiloxane[23,30] or a silanol.[31]

In our process the use of ytterbium triflate as Lewis acid catalyst led to the formation of hexaethyldisiloxane as byproduct.

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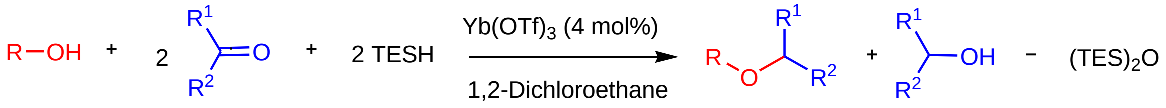
Thus, the use of two equivalents of cyclohexanone (**2b**) lead to the formation of 1 equiv. of cyclohexanol as a consequence of the reductive process. For this reasons, it is necessary to adjust the stoichiometry of the reaction adequately as proposed in Scheme 2.



**Scheme2.** Stoichiometric ratio of reagents and by-products for the reductive etherification catalysed by $Yb(OTf)_3$.

In order to optimize the synthetic procedure, the reaction of benzyl alcohol (**1a**) and cyclohexanone (**2b**) has been chosen as test reaction. Firstly, was evaluated the efficiency of different silanes as reducing agents. The results evidenced the efficiency of TESH as reducing agent over triisopropylsilane and triphenylsilane providing the unsymmetrical ether **4d** with yield of 75, 30 and 34 % respectively.
Interestingly, the more significant optimization involved the catalyst load (Table 2). Indeed, higher yields of ether **4d** were obtained when the catalyst load was decreased to 0.5 mol % proving the high catalytic efficiency of $Yb(OTf)_3$. The formation of unsymmetrical ether **4d** was not observed when the reaction was carried out in the absence of catalyst thus confirming the importance of acid catalysis in this synthetic process.

**Table 2.** Reductive etherification reaction of cyclohexanone (**2b**) with benzyl alcohol (**1a**) using different ratio of catalyst and TESH after 24 hours at reflux.

| Entry | **2b** [equiv] | TESH [equiv] | $Yb(OTf)_3$ (mol %) | Yield **4d** (%)[a] |
|---|---|---|---|---|
| 1 | 2.0 | 2.0 | 4 | 75 |
| 2 | 2.0 | 1.5 | 4 | 77 |
| 3 | 2.0 | 1.5 | 8 | 74 |
| 4 | 2.0 | 1.5 | 2 | 75 |
| 5 | 2.0 | 1.5 | 1 | 80 |
| 6 | 2.0 | 1.5 | 0.5 | 93 |
| 7 | 2.0 | 1.5 | 0.5 | 76[b] |
| 8 | 1.5 | 1.5 | 0.5 | 75 |
| 9 | 1.0 | 1.0 | 0.5 | 45 |
| 10 | 1.0 | 2.0 | 0.5 | 69 |
| 11 | 2.0 | 4.0 | 0.5 | 43 |
| 12 | 2.0 | 1.5 | 0.2 | 29 |
| 13 | 2.0 | 1.5 | -- | -- |

[a] Isolated yield. [b] Reaction time: 12 h.

On the other hand, the amount of TESH can be decreased to 1.5 equivalent whereas 2 equivalents of cyclohexanone (**2b**) are required to obtain higher performances of the reductive etherification process (Table 2, entries 2-6). In particular, the best yield was obtained using 2 equivalents of cyclohexanone (**2b**) 1.5 equivalents of TESH and 0.5 mol % of $Yb(OTf)_3$ (Table 2, entry 6).

In order to establish the optimal reaction media, benzyl alcohol (**1a**) and cyclohexanone (**2b**) were used in a new set of experiments under optimized reaction conditions using different types of solvents (Table 3).
The use of solvent with low boiling point such as dichloromethane led to a drastic decrease in the formation of ether **4d** (Table 3, entry 2). On the other hand, high boiling point solvents such as acetonitrile (Table 3, entry 3) and toluene (Table 3, entry 4) provided even worse yields; also the use of nitromethane, reported by Iwanami as an optimal reaction media in the reductive etherification process,[30,32] was unsuccessful affording only to 55% of yield of **4d** (Table 3, entry 5).

**Table 3.** Reaction of benzyl alcohol (**1a**) (1 equiv) and cyclohexanone (**2b**) (2 equiv) with $Yb(OTf)_3$ (0.5 mol %) and TESH (1.5 equiv) after 24 hours at reflux.

| Entry | Solvent | Yield [%][b] |
|---|---|---|
| 1 | 1,2-Dichloroethane | 93 |
| 2 | Dichloromethane | 33 |
| 3 | Acetonitrile | 19 |
| 4 | Toluene | 21 |
| 5 | Nitromethane | 55 |
| 6 | 1,4-Dioxane | -- |
| 7 | Tetrahydrofuran | -- |
| 8 | Neat [a)] | 21 |

[a)] The reaction was carried out at 90 °C. [b] Isolated yield.

The formation of **4d** did not occur when 1,4-dioxane (Table 3, entry 6) or tetrahydrofuran (Table 3, entry 7) were used as reaction solvents. From a sustainability point of view, the best solvent is “no solvent” but unfortunately, the reaction under solvent free condition (Table 3, entry 8) yielded only 21% of **4d**. Thus, 1,2-dichloroethane is confirmed to be the best reaction solvent for this synthetic approach. This observation was reported also by Laali in 2009 during an investigation about the influence of Lewis acid and solvent in the hydrosilylation of aldehydes and ketones with triethylsilane.[36]
To evaluate the catalyst efficiency of $Yb(OTf)_3$ over other possible catalysts, several metals triflate and $AlCl_3$ were tested under optimal reaction conditions. For this purpose, reductive etherification reaction of

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cyclohexanone (**2b**) with benzyl alcohol (**1a**) and TESH (1.5 equiv.) was performed in the presence of 0.5 mol % of catalyst (La(OTf)$_3$, Mg(OTf)$_2$, Zn(OTf)$_2$, Cu(OTf)$_2$, AgOTf and AlCl$_3$). All tested catalysts promoted the formation of ether **4d** with isolated yields lower than obtained by Yb(OTf)$_3$. In particular, AlCl$_3$ resulted the less efficient catalyst giving an isolated yield of 24%. Among the tested catalysts, the use of Zn(OTf)$_2$ should be highlighted. Although it promoted the formation of ether **4d** with 81% of isolated yield, it can be considered as a possible candidate as catalyst in view of its low cost and less toxicity over other metals.

Once the optimal conditions had been established, we next focused on the scope of the method.

Under our best reaction conditions, benzyl alcohol (**1a**) and cyclohexylmethanol (**1b**) led to the formation of the ethers **4d** and **4c** with an increment up to 93% and 84 % respectively (Table 4, entries 1 and 2).

When cyclohexanol (**1c**) was used as secondary alcohol (Table 4, entry 3) the symmetrical dicyclohexyl ether **4e** was obtained with a yield of 91%.

In order to verify the effect on a chiral centre of the starting alcohol, the optically active (S)-(+)-2-octanol (**1d**) (98% ee) was taken into consideration. Unfortunately, the unsymmetrical ether **4f** was obtained in a very low yield (35%) (Table 4, entry 4). An improvement of the reaction yield to 62% was observed by increasing the amount of catalyst to 4 mol % and TESH to 2 equivalents (Table 4, entry 5). It is important to highlight that in this case 29% of starting alcohol **1d** was recovered. The optical rotation of the unsymmetrical ether **4f** was measured, and it was found to be $[\alpha]^{25}_{D}$=+10.8°, a value in accordance with the literature ($[\alpha]^{20}_{D}$=+9.7°).[37]

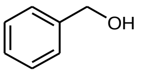
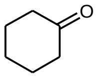
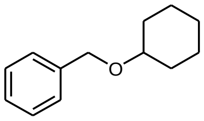
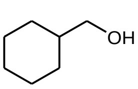
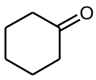
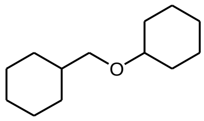
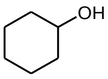
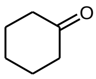
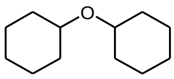
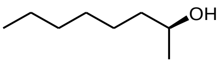
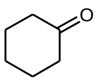
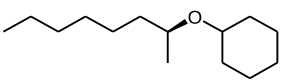
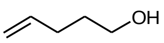
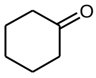
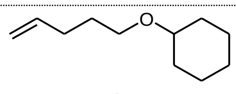
Under our reaction conditions isolated double bound is not reduced, as verified by the use of 4-penten-1-ol (**1e**) that led to the ether **4g** with a low yield of 39% (Table 4, entry 6). Also in this case when the reaction was performed with 4 mol % of catalyst and 2 equivalents of TESH, the ether **4g** was obtained with higher yield (71 %, Table 4, entry 7).

Tertiary alcohol such as 2-phenyl-2-propanol (**1f**) was totally non-reactive also increasing the amount of catalyst and TESH (Table 4, entries 8 and 9). In this case, it was possible to isolate the dicyclohexyl ether **4e** as a result of the reaction of cyclohexanone (**2b**) with the cyclohexanol (**1c**) formed as a consequence of the reduction of cyclohexanone (**2b**).

Similar result was obtained with the use of 4-*tert*-buthylphenol (**1g**) that led again to the formation of dicyclohexyl ether **4e** (Table 4, entry 10) and the corresponding triethylsilyl ether derivative of **1g** in 71% yield. This fact confirms the observation reported by Iwanami and coll. that described as bulky silyl derivative of tertiary alcohols and phenols are respectively less reactive or non-reactive at all when employed as starting materials in the reductive process with benzaldehyde and TESH in the presence of FeCl$_3$.[30b]

In order to confirm this trend and verify the chemoselectivity of this reductive process, 2-(4-hydroxyphenyl)ethanol (**1h**), containing also a primary hydroxy group, was used as starting material. Interestingly, this reaction was effective at the concentration of 0.5 mol % of Yb(OTf)$_3$ and 1.5 equivalents of TESH, and afforded compound **4h** (72%, Table 4, entry 11) in which the chemoselective etherification of the alcoholic group and the silylation of the phenolic group occurred at the same time.

**Table 4.** Reductive etherification of ketones or aldehydes with alcohols and TESH in the presence of Yb(OTf)$_3$ after 24 hours.

| Entry | Alcohol | Ketone/aldehyde [eq] | Ether | TESH [eq] | Yb(OTf)$_3$ (mol %) | Yield (%)[a] |
|---|---|---|---|---|---|---|
| 1 |  **1a** |  **2b** [2] |  **4d** | 1.5 | 0.5 | 93 |
| 2 |  **1b** |  **2b** [2] |  **4c** | 1.5 | 0.5 | 84 |
| 3 |  **1c** |  **2b** [2] |  **4e** | 1.5 | 0.5 | 91 |
| 4<br>5 |  **1d** |  **2b** [2] |  **4f** | 1.5<br>2.0 | 0.5<br>4.0 | 35<br>62 |
| 6<br>7 |  **1e** |  **2b** [2] |  **4g** | 1.5<br>2.0 | 0.5<br>4.0 | 39<br>71 |

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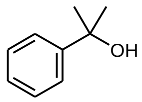
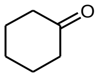
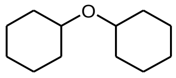
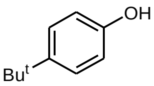
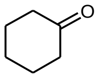
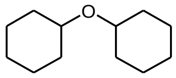
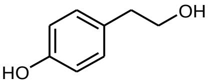
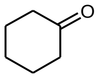
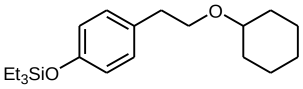
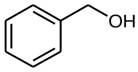
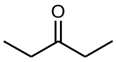
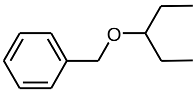
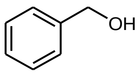
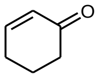
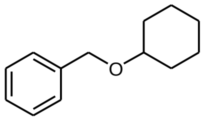
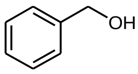
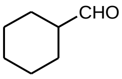
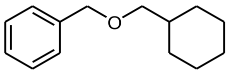
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 8<br>9 |  **1f** |  **2b** | [2] |  **4e** | 1.5<br>2.0 | 0.5<br>4.0 | 74<br>88 |
| 10 |  **1g** |  **2b** | [2] |  **4e** | 1.5 | 0.5 | 56 |
| 11 |  **1h** |  **2b** | [2] |  **4h** | 1.5 | 0.5 | 72 |
| 12<br>13 |  **1a** |  **2c** | [2] |  **4i** | 1.5<br>2.0 | 0.5<br>4.0 | 49<br>74 |
| 14<br>15 |  **1a** |  **2d** | [1] |  **4d** | 1.5<br>2.0 | 0.5<br>4.0 | 44<br>70 |
| 16<br>17 |  **1a** |  **2e** | [2]<br>[2] |  **4j** | 1.5<br>2.0 | 0.5<br>4.0 | 42<br>22 |

[a] Isolated yield

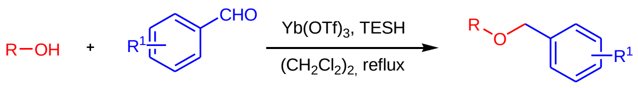
This result confirms the very high and effective chemoselectivity of our reaction when both alcoholic and phenolic groups are present in the starting material.

When 3-pentanone (**2c**) was used in the reaction with benzyl alcohol (**1a**), the corresponding ether **4i** was obtained in low yield (49 %, Table 4, entry 12). Again, the increase of catalyst amount to 4 mol % and TESH to 2 equivalents allowed a little improvement in the reaction yield (74%, Table 4, entry 13).

As reported in the literature, C-C double bond of *α,β*-unsaturated ketones can be selectively reduced to saturated ketone by TESH in the presence of $(Ph_3P)_3RhCl$.[21b] In this case, the reductive etherification of 2-cyclohexenone (**2d**) and benzyl alcohol performed in the presence of $Yb(OTf)_3$ and TESH gave, after 24 hours, the ether **4d** (table 4, entry 14 and 15) demonstrating that also the reduction of the C-C double bond occurred under our reaction conditions.

When cyclohexanecarboxaldehyde (**2e**) was reacted with benzyl alcohol in the presence of 0.5 mol % of $Yb(OTf)_3$ and 1.5 equivalents of TESH, benzyl cyclohexylmethyl ether **4j** was obtained with a yield of 42% (Table 4, entry 16). Effectively, cyclohexanecarboxaldehyde (**2e**) undergoes reduction leading to the corresponding alcohol more rapidly than ketone does. Hence, the presence of higher level of cyclohexylmethyl alcohol (**1b**) increases the possibility of competition with benzyl alcohol (**1a**). The result is the formation of the corresponding bis(cyclohexylmethyl) ether as by-product (40%). The increase of catalytic amount of $Yb(OTf)_3$ to 4 mol % and TESH to 2 equivalents improved this trend leading to the ether **4j** with a lower yield (Table 4, entry 17). On the contrary, the formation of bis(cyclohexylmethyl) ether increased to 52%.

The use of aromatic aldehydes, such as benzaldehyde and its derivatives, in this reductive etherification, is particularly intriguing because it would lead directly to the synthesis of the benzyl ether derivatives of alcohols (Scheme 3). Benzyl ethers and substituted benzyl derivatives are important functional groups in synthetic organic chemistry and they are widely used as useful protecting groups of the hydroxyl function.[11]



**Scheme 3.** Direct conversion of alcohols into benzyl ether derivatives by reductive etherification of benzaldehyde derivatives.

Traditionally, the synthesis of benzyl ethers is performed by the use of benzyl halides under the influence of bases.[38] The use of benzyl halides is the main drawback of these procedures. Indeed, a reagent such as benzyl bromide is a strong lachrymator and also intensely irritating to skin and mucous membranes.

In table 5 are summarized the results obtained by reductive etherification of benzaldehyde and its derivatives. When 2 equivalents of benzaldehyde

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were used in the presence of benzyl alcohol the symmetric ether **4k** was obtained with quantitative yield (Table 5, entry 1). The first important observation is that the reductive etherification of benzaldehyde proceeds more rapidly than ketones. When benzaldehyde was decreased to 1.5 equivalents, the ether **4k** was obtained with high yields and resulted quantitative after 24 hours (Table 5, entries 2 and 3). The use of 2 equivalents of benzaldehyde is not favourable when the target is an unsymmetrical ether. Indeed, the formation of benzyl alcohol as a result of the reduction of benzaldehyde lead to a competition with the starting alcohol. Thus, when cyclohexylmethyl alcohol **1b** was used with 2 equivalents of benzaldehyde (**2f**) the formation of ether **4j** (74%, Table 5, entry 4) was accompanied by the formation of dibenzyl ether **4k** (22%) as by-product. The decrease of benzaldehyde to 1.5 equivalents lead to a good yield of 89% of ether **4j** after 4 hours (Table 5, entry 5) against the formation of only 10% of dibenzyl ether **4k**. No yield increase was observed by a prolonged reaction time of 24 hours (Table 5, entry 6). The use of 4-nitrobenzaldehyde (**2g**) and 4-chlorobenzaldehyde (**2h**) was particularly useful to clarify some aspects of the reaction mechanism. The presence of a strong electron withdrawing group, such as the nitro group, in the *para* position of benzaldehyde caused a great decrease of the reaction yield, that remained low also after 24 hours (**4l**, Table 5, entries 7 and 8). Despite its electronegativity, the chlorine in the *para* position did not affect the reaction yield (**4m**, Table 5, entry 9). Other functional groups, such as methyl, nitrile and trifluoromethyl in the *para* position of benzaldehyde, are well tolerated. Thus, aldehydes **2i**, **2j** and **2k** gave good yields when reacted with benzyl alcohol (Table 5, entries 10, 11 and 12). However, in the case of 4-formylbezonitrile (**2j**), the nitrile group influenced negatively the reaction in terms of duration, similarly to the nitro group of **2g**, as reported above.

Also functionalized benzyl alcohols, such as the 2-bromo- (**1i**) and the 3-methoxy- (**1j**), reacted with benzaldehyde (**2f**) affording the final ether **4q** and **4r** with a yield of 68 and 93% in 4 hours, respectively (Table 5, entries 13 and 14).

The use of 2-(4-hydroxyphenyl)ethanol (**1h**) confirmed the regioselectivity of this process, obtaining the unsymmetrical ether **4sa** with good yield (Table 5, entry 15). In this case the phenolic triethylsilylether functional group is not stable and over the time it undergoes decomposition to the unprotected ether **4sb** (Table 5, entry 16). Despite the use of an excess of triethylsilane, after 24 hours the ether **4sb** resulted the main product (Table 5, entry 17).

The use of (2*S*)-2-octanol (**1i**), gave the corresponding benzyl ether **4t** with high yield (ee [%]: 97.4) (Table 5, entry 18). Interestingly, 4-penten-1-ol (**1e**) gave the ether **4u** with a high yield of 92% (Table 5, entry 19).

Propargyl alcohol (**1k**) resulted less reactive than other primary alcohol, leading to the ether **4v** with low reaction yield (Table 5, entry 20); furthermore, the formation of a considerable amount of dibenzyl ether **4k** was observed. Also in this case, tertiary alcohol such as 2-phenyl-2-propanol (**1f**) resulted totally non-reactive (Table 5, entry 21), instead, leading only to the dibenzyl ether **4k**. Interestingly, ethyl 3-hydroxybutanoate (**1l**), was converted to the benzyl derivative **4w** with an isolated yield of 65% after 24 hours (Table 5, entry 22).

With our procedure it was possible synthesize ether **4x**, which usually require multistep reaction,[39] starting from 3-bromopropanol (**1m**) and benzaldehyde (**2f**). In this case, a slow addition of benzaldehyde (**2f**) solution in dichloroethane, during 6 hours, was required to prevent the excessive formation of dibenzyl ether (**4k**) as by-product. Thus, the ether **4x** was obtained with a yield of 63% in 8 hours. (Table 5, entry 23).

The use of alcohol **1n**[40] confirmed the role of steric hindrance on the reactivity of alcohols. Indeed, the high steric hindrance of the phthalimido group on C-2 of alcohol **1n** leads to a considerable decrease in reactivity and, after 24 hours, only 26% of ether **4y** was obtained (Table 5, entry 24). Similarly, also the silyl ether intermediate **3d** is affected by the steric hindrance effect of the phthalimido group and it can be recovered with a yield of 25% after 24 hours.

A particular mention should be done about the use of 7-oxooctanoic acid **2l**, that reacted with benzyl alcohol (**1a**) under the same optimized reaction condition of aromatic aldehydes. In this case, the presence of a free carboxylic group is well tolerated; furthermore, the reaction seems to be faster than usually ketones do and, after 6 hours, the final ether **4z** was obtained with 67% of yield (Table 5, entry 25).

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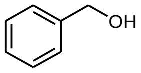
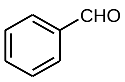
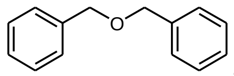
**Table 5.** Reductive etherification reaction of aromatic aldehydes with alcohols in the presence of $Yb(OTf)_3$ (0.5 mol %) and TESH (1.5 equiv).

| Entry | Alcohol | Ketone/aldehyde [eq] | | Ether | Time(h) | Yield(%)a |
|---|---|---|---|---|---|---|
| 1 |  **1a** |  **2f** | [2.0] |  **4k** | 4 | >99 |
| 2 | | | [1.5] | | 4 | 87 |
| 3 | | | [1.5] | | 24 | 99 |

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10.1002/adsc.201900281

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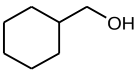
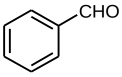
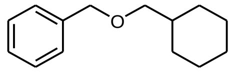
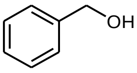
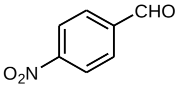
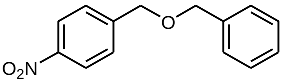
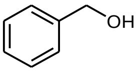
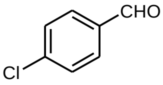
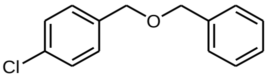
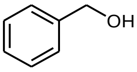
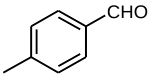
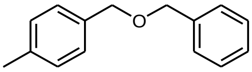
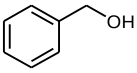
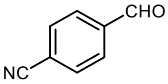
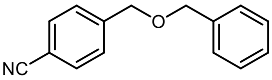
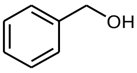
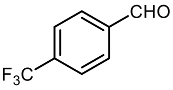
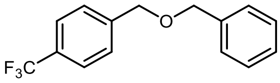
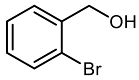
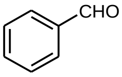
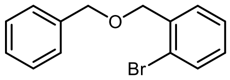
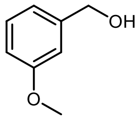
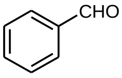
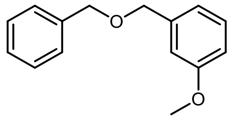
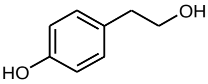
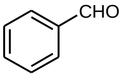
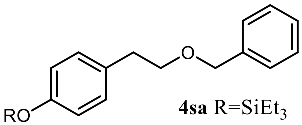
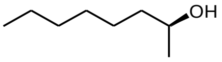
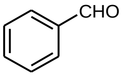
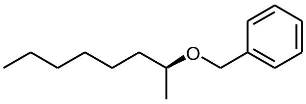
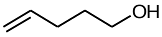
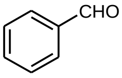
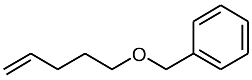
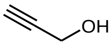
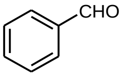
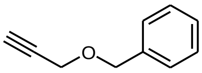
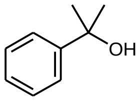
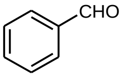
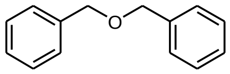
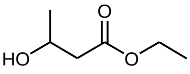
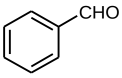
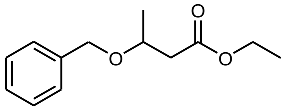
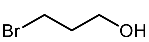
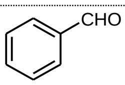
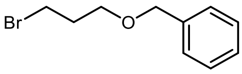
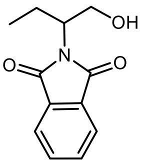
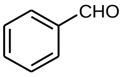
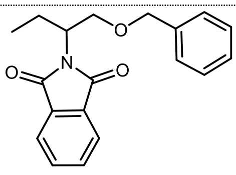
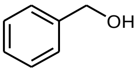
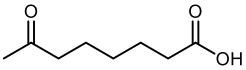
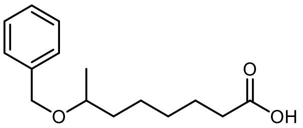
|---|---|---|---|---|---|---|
| 4 |  **1b** |  **2f** | [2.0] |  **4j** | 18 | 74 |
| 5 | | | [1.5] | | 4 | 89 |
| 6 | | | [1.5] | | 24 | 87 |
| 7 |  **1a** |  **2g** | [1.5] |  **4l** | 4 | 30 |
| 8 | | | [1.5] | | 24 | 43 |
| 9 |  **1a** |  **2h** | [1.5] |  **4m** | 6 | 85 |
| 10 |  **1a** |  **2i** | [1.5] |  **4n** | 4 | 81 |
| 11 |  **1a** |  **2i** | |  **4o** | 24 | 65 |
| 12 |  **1a** |  **2k** | |  **4p** | 6 | 82 |
| 13 |  **1i** |  **2f** | |  **4q** | 4 | 68 |
| 14 |  **1j** |  **2f** | |  **4r** | 4 | 93 |
| | | | | | | **4sa**/**4sb** |
| 15 |  **1h** |  **2f** | [1.5] |  **4sa** R=$SiEt_3$<br>**4sb** R=H | 3 | 62/23 |
| 16 | | | [1.5] | | 6 | 24/57 |
| 17 | | | [2.5] | | 24 | 7/78 |
| 18 |  **1d** |  **2f** | [1.5] |  **4t** | 4 | 91 |
| 19 |  **1e** |  **2f** | [1.5] |  **4u** | 3 | 92 |
| 20 |  **1k** |  **2f** | [1.5] |  **4v** (+ **4k**, 48%) | 24 | 47 |
| 21 |  **1f** |  **2f** | [1.5] |  **4k** | 24 | 68 |
| 22 |  **1l** |  **2f** | [1.5] |  **4w** | 24 | 65 |
| 23 |  **1m** |  **2f** | |  **4x** | 8 | 63 |
| 24 |  **1n** |  **2f** | |  **4y** | 24 | 27 |
| 25 |  **1a** |  **2l** | |  **4z** | 6 | 67 |

[a] Isolated yield

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## Mechanistic hypothesis

Based on our results and the data reported in the literature, aplausible mechanism of this reductive etherification process catalysed by $Yb(OTf)_3$ can be proposed. Although some mechanistic aspects ofthe reductive etherification of aldehydes and ketones with alkoxysilane derivatives and silaneswere reported, as proposed by Laali and Coll.,[36] in our knowledge there is not mechanistic information about the direct reductive etherification of aldehydes and ketones with alcohols and silanes catalysed by Lewis acids. The mechanism proposed by Laali entails the formation of a triflate-hydride-triethylsilonium metal species [***a***] (Figure 2) which is then capable of reacting in the presence of nucleophiles. In our case, the presence of alcohol involves a competition with ketone (or aldehyde), generating two possible pathways leading to the related silylonium derivatives [***b***] and [***c***].

The intermediate [***b***] reduce the ketone to the related alcohol and then it is converted into silyl ether [***d***]. It should be noted that this reaction step should be faster than that of the intermediate [***c***], due to the greater nucleofilicity of alcohol respect to the ketone. Indeed, it was observed that the formation of silyl ether [***d***] was rather fast and that it slowly diminished over time in favour of the final ether [***g***]. The successive interaction of intermediates [***c***] and [***d***], the transposition of the triethylsilyl group and the subsequent formation of the unsymmetrical ether [***g***], are the same as proposed by Laali.[36]

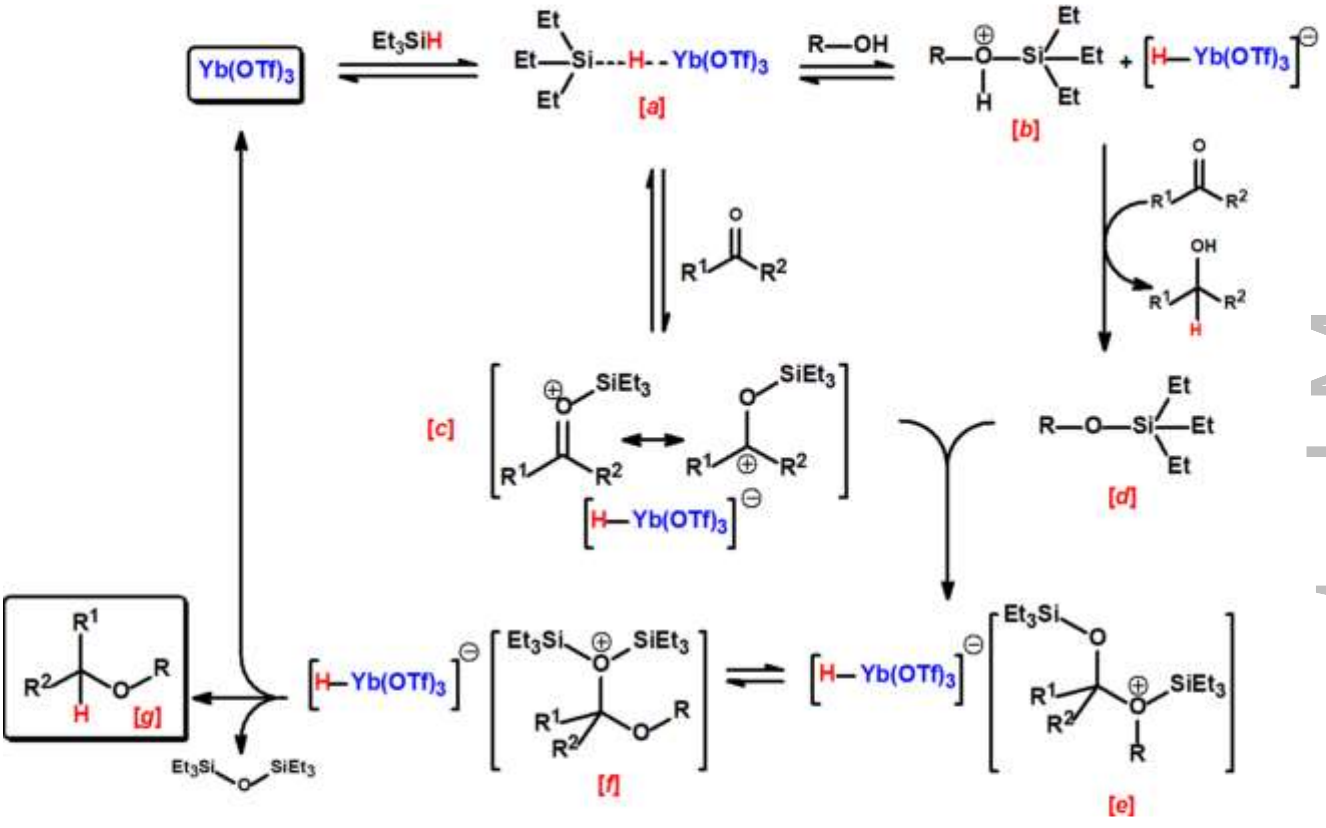

**Figure 2.** Proposed reaction mechanism of the reductive etherification catalysed by $Yb(OTf)_3$.

The observation that aromatic aldehydes generally react faster than ketones could support the proposed mechanism. Indeed, the rate of formation of the intermediate [***c***] will be greater when the stabilization of the positive charge of silylonium intermediate is effective. From this point of view, the nitro electron withdrawing group in the para position of benzaldehyde does not allow the stabilization of this intermediate by resonance. Thus, the unsymmetrical ether **4l** is obtained with low yields also after prolonged reaction time (Table 5, entries 7 and 8). On the other hand, chlorine is able to effectively stabilize the positive charge of silylonium intermediate by

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resonance giving **4m** in excellent yield (Table 5, entry 9).

To support our hypothesis, we performed an accurate and reliable monitoring of the reactions providing essential information regarding reaction kinetics and the concentration of starting material, intermediate and final compound over the time by $^1$H-NMR spectroscopy. For this purpose, we chose the reaction of cyclohexylmethanol (**1b**) with benzaldehyde (**2f**) as a model under optimal reaction conditions. Indeed, in this case starting reagent (**1b**), alkoxysilane intermediate (**3b**) and final ether (**4j**) are well recognizable in $^1$H-NMR spectra in the range of 3.3-5.0 ppm as doublets at 3.45, 3.39 and 3.34 ppm, respectively. Furthermore, the ether **4j** show also an increasing peak at 4.53 ppm as a singlet. This analysis was achieved by collection of 100 μL samples (from a 2 mmol scale reaction) over the time (4 h). A workup of the samples with a 5% $NaHCO_3$ solution was carried out to quench the reaction. Then, the reaction mixtures were analyzed by $^1$H-NMR spectroscopy. The concentration of the reaction components was estimated by the $^1$H-NMR integration and normalized in order to report the data also in graphical format (figure 3). The results obtained in this analysis support the considerations we made above about the mechanistic hypothesis showing the cyclohexylmethanol (**1b**) that undergo silylation to form the alkoxysilane intermediate **3b**. Over the time **3b** increase in concentration up to a 20 % maximal and, in turn, it is quickly consumed in favor of the ether **4j**. After 135 min, the concentration of **1b**, **3b** and **4j** is 4.6, 7.2 and 88,2%, respectively. With the progress of the reaction, TESH is oxidized to hexaethyldisiloxane. The disiloxan by-product formed in this process can be easily collected from the crude of the reaction mixture by chromatographic separation on silica gel. Depending on the progress of the reaction and the reaction conditions, hexaethyldisiloxane can be generally recovered with a yield similar or slightly higher than the yield of final ether. This is due to the use of an excess of aldehyde (or ketone) that leads also to the formation of small amount of symmetrical ethers as by-product. For instance, the hexaethyldisiloxane formed in the reaction of cyclohexylmethanol (**1b**) with benzaldehyde (**2f**) (Table 5, entry 4) was recovered with a yield of 88%, a value slightly higher than the yield of 74% of the final ether **4j**. Indeed, small amount of dibenzyl ether (**4k**) was also formed in this reaction with a yield of 9%.

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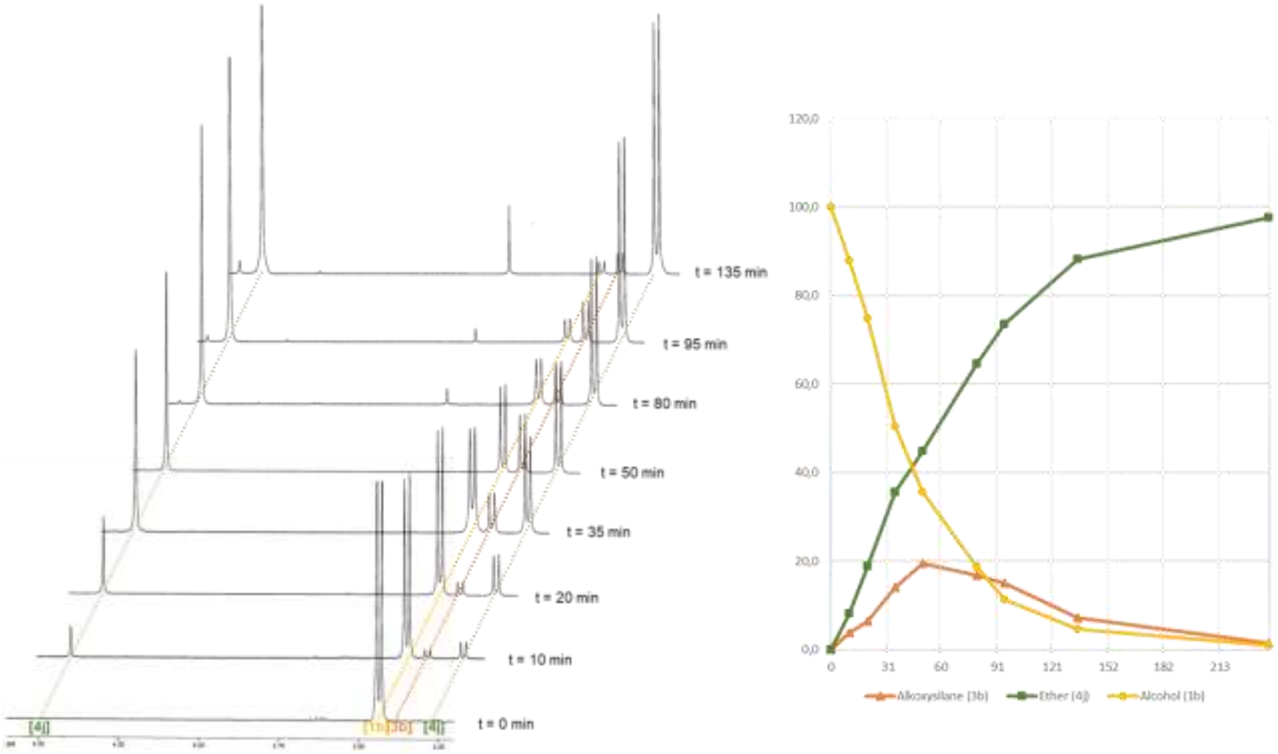

**Figure 3.** Monitoring of the reductive etherification reactions of **1b** and **2f** by $^1$H-NMR.

## Recycling experiment and scale up

In the recycling experiments benzaldehyde (**2f**) and cyclohexylmethanol (**1b**) were used under optimized reaction conditions affording to the final unsymmetrical ether **4j** with a yield of 89, 86, 87, 85 and 84% respectively.

In view of a possible industrial application, the reaction mentioned above was repeated on gram scale using 3.46 g of cyclohexylmethanol (**1b**) (30 mmol) affording the final ether **4j** with a yield of 86%.

## Conclusion

The results obtained in this investigation highlighted some important features about the reductive etherification of ketones in the presence of different alcohols through a Yb(OTf)$_3$/TESH system. The most important advantage respect to other procedures is the possibility to carry out a one pot reaction starting from alcohols and aldehydes/ketones without the need of anhydrous condition. Actually, the alkoxysilane is formed during the reductive process and it is a key intermediate in the formation of final symmetrical or unsymmetrical ethers. Among different silanes, TESH resulted to be the best reducing agent and, respect to other procedures, TESH was generally employed in 1.5-2.0 equivalents. Yb(OTf)$_3$ is an effective catalyst in the reductive etherification also at very low concentration (0.5 mol %). Less difference of reactivity between primary and secondary alcohols was observed, whereas tertiary alcohols and phenols were totally nonreactive. Several functional groups, either on alcohols or carbonyl derivatives, are well tolerated. Notably, when applied to substituted benzaldehydes, this process represents a more manageable procedure for the synthesis of benzyl ether derivatives of alcohols.

The disiloxan by-product formed in this process is more safe and can be easily collected. Also the alcohols derived from aldehydes and ketones as by-products of the reductive process could be recovered. Finally, the catalyst can be reused after drying without loss of catalytic efficiency.

## Experimental Section

### General procedure for the synthesis of symmetrical and unsymmetrical ethers

To the mixture of catalyst (Yb(OTf)$_3$ 0.5-4 mol %), triethylsilane (1.5-2.0 equiv) and alcohol (1 equiv) in 1,2-dichloroethane (4 mL/mmol), the ketone or the aldehyde (1.5-2 equiv) was added. The reaction was left at reflux under stirring for the appropriate time under air atmosphere. At the end, the reaction solvent was recovered by distillation at reduced pressure. The crude of the

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reaction was diluted with hexane and filtered on a Büchner funnel at reduced pressure to collect the solid catalyst. The recovered catalyst was washed with hexane and dried for possible reuse. Efficient and complete separation of the major reaction products was achieved by column chromatography on silica gel, eluting with *n*-hexane/dichloromethane (80:20)

## Acknowledgements

*We gratefully acknowledge the Università degli Studi di Perugia within financing program "Fondo d'Ateneo per la Ricerca di Base 2015" and Dr. Diana Persia for her helpful technical support in the laboratory.*

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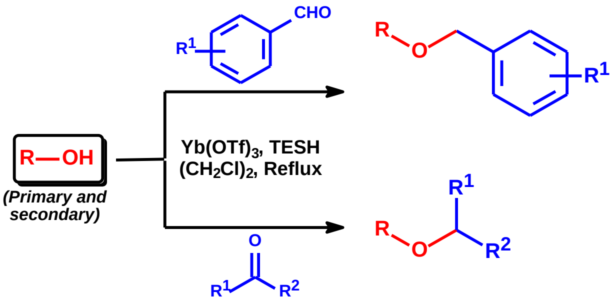

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