Ethers from esters; from exceptional transformation
to synthetic method

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DOI: http://dx.doi.org/10.3998/ark.5550190.p008.960

Abstract
Most ether-bond forming reactions based on traditional methods or modifications thereof require strongly acidic or basic conditions and often harsh reaction conditions. Reduction of esters to ethers has been regarded as an impracticable method, generally affording alcohols as the principal products. Only recently, original, mostly catalytic methods for reduction of esters to ethers have been reported, which proceed under mild conditions and are compatible with many functional groups present in the substrate ester molecule. These reactions are considered as a valuable alternative to traditional methods, and specific protocols have been reported. An account of the progress in this synthetic methodology is given.

Keywords: Reduction, silylation, Lewis acids, esters, ethers lactones, cyclic ethers

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1. Introduction

Reactions that form carbon-oxygen bond in ethers belong to the most important transformations in organic chemistry because of the ubiquitous presence of this bond in natural and synthetic compounds. The ether bond is very stable and not easily synthesized; bond energy amounts to 360 kJ/mol, and is even higher than the single C-C bond (350 kJ/mol).\(^1\) It is therefore not surprising that formation of C-O-C bond requires either highly reactive, specifically activated partners or promotion by strong acids and bases at elevated temperatures. Some synthetic methods for ethers have been developed over the decades and have become “named reactions” such as Williamson, Mitsunobu, Mukaiyama and Maruoka synthesis. Traditionally, activation is achieved either by strong acids or bases or more recently by intermediary formation of organometallic species from the reacting esters. All these methods are characterized by the reaction couple nucleophile-electrophile, activated by more or less sophisticated agents, from protons to organometallic species.

A recent mini-review on selective reduction of carboxylic acid derivatives by catalytic hydrosilylation pays attention to the reduction of various derivatives of carboxylic acids.\(^2\) Selectivity is referred to chemo-selectivity in the presence of other reducible functionalities such as aldehydes, ketones, imines, nitriles, nitro compounds, and multiple C-C bonds. In another mini-review recent developments in the homogeneous hydrogenation of carboxylic acid esters were highlighted.\(^3\) However only the process which leads to alcohols were discussed, and limited practicability of various sophisticated transition metal complexes revealed. An interesting aspect of selective reduction of esters is their partial reduction to aldehydes, which are known as more reactive species under a variety of reducing conditions. It is general knowledge that aldehydes are reactive intermediates in the reduction of esters to ethers, and are present, if at all, at a very low steady-state concentration. Some recent papers report on progress in a controlled catalytic reduction of esters to aldehydes.\(^4\)-\(^6\)

In this review methods are presented for reduction of esters to ethers, which have an obvious advantage of using esters as easily available precursors, and are compatible with most sensitive groups, either free or protected. For a long period reduction of esters to ethers was uninvestigated due to the undesired course of this reaction. It is common knowledge that acyclic esters are reduced by complex hydrides to two mole equivalents of alcohols, and lactones to diols, in contrast to reduction of amides to dialkylamines and lactams to cyclic amines.\(^7\),\(^8\) In view of easy synthetic access to esters and lactones, their selective hydrogenation to acyclic, non-symmetric esters, and cyclic ethers of various ring-sizes, is of upmost synthetic importance. Recent papers have indeed shown that the mechanism of ester hydrogenation by complex hydrides or silanes can be controlled by Lewis acids and some organometallic species, and preferred formation of ethers has been achieved. Here we report some original methods for completion of the reduction of esters to ethers, their potential to become useful synthetic methods, and we discuss some mechanistic aspects of these reactions.
2. Overview of Traditional and Less Known Methods

Extensive reviews on the traditional ether-forming reactions are available. Here will be presented general comments on the well-known methods.

Alkylation of an alkoxy anion with an alkylhalide/sulfonate under basic conditions, known as the Williamson synthesis, is the most frequently used method for the preparation of ethers. Several O-alkylation reactions are variants of Williamson ether synthesis. Most of them are known for a long time, such as alkylation by olefins, dialkyl phosphates, by aldehydes, and by nitro compounds. The major drawback of this method has been viewed as its unsuitability for base sensitive compounds and the generation of stoichiometric amount of inorganic waste, although this second issue seems to have been overcome by a catalytic etherification developed by Strauss and co-workers.

The Ullmann ether synthesis is a reaction, in which a phenol is coupled to an aryl halide to create a diaryl ether in the presence of a copper compound. Recently, it was found that addition of relatively cheap ligands (diamines, aminooalcohols, diketones, diols) made this reaction catalytic. Progress has been made by combination of milli-scale processing and microwave heating for the Cu-catalyzed Ullmann etherification in chemical synthesis, providing improved catalytic activity. Also efficient, regio- and chemoselective, reusable, and heterogeneous nano CuO-catalyzed Ullmann type C–O/C–S cross coupling of aryl halide with phenol/thiophenol has been demonstrated at room temperature.

The Mitsunobu reaction represents a number of substitution reactions of primary and secondary alcohols with various nucleophiles, mediated by a redox system consisting of trialkyl- or triarylphosphate and dialkyl azidodicarboxylate. This reaction rears different faces when applied in the laboratory and large-scale syntheses. First, it is famous for its scope and power, but also for its separation headaches. Because of so many separation strategies used, the Mitsunobu reaction has been described as “a microcosmos for the new field of strategy level separation”. Despite the poor atom economy, this reaction is popular in organic synthesis at various scales because of its broad scope, stereospecificity and mild reaction conditions.

Dehydrative allylation of primary and secondary alcohols to afford ethers are mediated by various palladium catalysts. There are many variants of inter- and intramolecular allylations of conjugated double bond, where Pd (II) promotes the addition of alcohols to the coordinated C=C bond. The palladium catalyzed etherification of allylic alcohols with phenols is promoted by Ti(IV) isopropoxide, and formation of a transient allyl titanate leading to an η3-allylpalladium intermediate is supported by the formation of dialyl and diisopropyl ethers in the absence of a phenol. Interestingly, we have successfully applied Pd-catalyzed O-alkylation of complex macrocyclic alcohols by allyl-tert-butylocarbonate.

Diaryl ethers, aryl alkyl ethers and enol ethers can be synthesized by means of a palladium-catalyzed Buchwald-Hartwig reaction. Broad application of this metal-catalyzed coupling reaction has mainly been achieved by developing ever more effective ligands for the catalytic complexes, starting from dinitrogen ligands to mono- and bidentate phosphines, and π-
donor alkenes, dba (dibenzylideneacetone) in particular.\textsuperscript{38} Recent progress in this reaction include use of bimetallic heterogeneous catalyst \textsuperscript{39} and heterocyclic carbenes as ligands.\textsuperscript{40}

The Mukaiyama method involves an oxido-reductive condensation via alkoxydiphenyldiphosphines, or diphenylphosphinite esters, generated \textit{in situ} from chlorodiphenyldiphosphines and alcohols, 2,6-dimethylbenzoquinine and phenols.\textsuperscript{41,42} The reaction proceeds at low temperatures and under neutral conditions to afford alkyl-aryl ethers in high yields.\textsuperscript{43} In 2000 Maruoka and co-workers published a procedure of etherification of benzyl and allylic alcohols by use of the \textit{in situ} prepared complex MeAl(NTf\textsubscript{2})\textsubscript{2} as a catalyst.\textsuperscript{44} Interestingly, this efficient dimerization of allylic and benzylic alcohols seems not to have been widely introduced since the first report.

Synthesis of ethers from alcohols and carbonyl compounds, aldehydes or ketones, under reductive conditions has been reported by Lemaiere et al.\textsuperscript{45,46} and claimed by Fujii et al.\textsuperscript{47,48} The original method, however, required high pressure of hydrogen, over 40 atm, and a dilute solution of substrate, below 0.2 M, leading to many side-products. An improved protocol for reductive coupling of alcohols and carbonyl compounds under a hydrogen atmosphere is reported.\textsuperscript{48} To achieve high yields and conversions, this operationally simple method requires continuous elimination of water, and apparently has only certain limitation in the presence of other reducible groups.

### 3. Reduction of Esters to Ethers

As mentioned in the Introduction, esters are reduced to alcohols accompanied with a split of the C-O bond, whereas amides are reduced to amines with the C-N bond retained. A mechanistic explanation for different reduction products of these two carboxylic acid derivatives is presented (Scheme 1).

\begin{equation}
\begin{array}{c}
\text{O} \\
\text{R} \quad \text{OR}_1 \quad \text{1} \\
\end{array}
\begin{array}{c}
\text{H} \\
\text{2} \\
\end{array}
\begin{array}{c}
\text{H} \\
\text{3} \\
\end{array}
\begin{array}{c}
\text{H} \\
\text{H} \\
\text{R} \quad \text{O} \quad \text{R}_1 \quad \text{4} \\
\end{array}
\begin{array}{c}
\text{H} \\
\text{5} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{R} \quad \text{N} \quad \text{R}_1 \quad \text{6} \\
\end{array}
\begin{array}{c}
\text{H} \\
\text{7} \\
\end{array}
\begin{array}{c}
\text{H} \\
\text{8} \\
\end{array}
\begin{array}{c}
\text{H} \\
\text{R} \quad \text{N} \quad \text{R}_1 \quad \text{9} \\
\end{array}
\begin{array}{c}
\text{H} \\
\text{10} \\
\end{array}
\end{equation}

\textbf{Scheme 1}

Esters are reduced to alcohols since OR\textsubscript{1} is a better leaving group than OH; elimination of R\textsubscript{1}-OH preferred, while amides are reduced to sec-amines since elimination of H\textsubscript{2}O is preferred.
Protonation of the tetrahedral anionic intermediate 2, formed on hydride ion addition to ester 1, affords hydroxyl and alkoxy group in 3, the later one being a much better leaving group. Intermediary aldehyde 4 is then reduced to the second mole of alcohol 6. With amides, instead, hydride ion addition and protonation precedes via elimination of water in 8 and formation of imine 9 which is then reduced in the second step to the sec-amine 10. From sec-amides an intermediary tert-imonium ion is formed which is easily reduced to tert-amines. Most of the methods that follow, in particular the catalytic ones, are based on the principle of diminished leaving ability of alkoxy group in favor of the intermediary second, better leaving unit formed from the carbonyl group.

3.1. Reductions via thiocarbonylation /hydrogenation

A few years after Lawesson’s report on a new method for thionation of esters into thionoesters,49 Bradshaw and co-workers developed the method reduction of intermediary thionosters to ethers.50 This two-step transformation of esters to ethers is outlined below (Scheme 2).

![Scheme 2](image)

Thionating agent 14 is easily available from P$_2$S$_5$ and anisole, but thionation of esters in xylene is completed at reflux temperature over a longer period of time. The later conditions limit application of this method to thermally stable esters. In the next step reduction is completed in a few minutes using RaNi/H$_2$ in a shaker at -15 °C.

![Scheme 3](image)
This method has been used in preparation of disaccharides from the corresponding acetal-esters, bound at 1, 6-position by an ether bond (Scheme 3).\textsuperscript{51}

It was observed that Lawesson's reagent (14, R=Me) reacts at elevated temperatures, due to its low solubility in most organic solvents at low temperatures, giving many side-products. Its more soluble analogue, X (R=Ph), named Belleauove's reagent, can be used at low temperatures in benzene, chloroform, and DME. On hydrogenation of intermediary thionosters, 1, 6-ethers were obtained in 70-85% yield.

It is interesting that Belleauove’s reagent (14, R=Ph) and some of its congeners proved particularly effective in preparation of thiolactones from lactones, and then, in turn, in preparation of cyclic ethers and their $\alpha$-alkylated analogs (Scheme 4).\textsuperscript{52}

![Scheme 4](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>nucleophile (RM)</th>
<th>Addition product (21)</th>
<th>yield (%)</th>
<th>Reduction product (22)</th>
<th>yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeLi</td>
<td>R = Me</td>
<td>83</td>
<td>R = Me</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>PhLi</td>
<td>R = Ph</td>
<td>86</td>
<td>R = Me</td>
<td>97</td>
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<tr>
<td>3</td>
<td>$\text{Li}O$</td>
<td>$\text{Li}O$</td>
<td>92</td>
<td>$\text{Li}O$</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>$\text{Li}$</td>
<td>$\text{Li}$</td>
<td>86</td>
<td>$\text{Li}$</td>
<td>85</td>
</tr>
</tbody>
</table>

Reaction conditions: a. Belleau's reagent, toluene, reflux, 1 h; b. RM/Mel, THF, -78 °C; c. Ph$_3$SnH, AIBN, toluene, reflux, 20-25 min.

**Scheme 4**

Intermediary thionolactones 20 are quenched in a Grignard-type reaction by organometallic nucleophiles and MeI affording alkylated thioacetals. Reductive desulfurization by triphenyltin hydride (Ph$_3$SnH) affords $\alpha$-alkylated cyclic ethers 22. This method has been used in preparation of the key building blocks in the total synthesis of brevetoxine and lautasine.\textsuperscript{52}

### 3.2. Reduction by complex hydrides

An early reported two-step method of reduction of lactones to cyclic ethers uses DIBAL in combination with Et$_3$SiH/BF$_3$.Et$_2$O complex (Scheme 5).\textsuperscript{53}
Scheme 5

This reaction can be stopped under controlled conditions at the level of the cyclic lactole (hemiacetal), which is an intermediate. Thus, intermediary lactol 30 was isolated in quantitative yield and reduced to 31 by Et$_3$SiH/ BF$_3$.Et$_2$O in DCM at -20 °C, (Scheme 6). On the contrary, the allylic OH group in 29 cannot be hydrogenolized by this complex reagent (Scheme 6).

Scheme 6
3.3. Reduction by hydride X BF$_3$ complexes

There is only one report on the reduction of esters to ethers by LiAlH$_4$-AlCl$_3$ reagent 54. The authors observed that the molar ratio LiAlH$_4$/AlCl$_3$ was highly important in determining the yield of the ether. However, the yields of ethers were low (7-15%), and this reagent has not found much application.

Reduction of esters to ethers by the complex LiAlH$_4$/BF$_3$.Et$_2$O was first described by Pettit et al.55,56 During hydrogenation of 3β-acetoxy derivative of 5α-cholestane 32 the authors observed formation of ether 33 (Scheme 7).

Soon after the authors observed that this reduction is not specific for the acetoxy group, and completed reduction of esters 34 to ethers 35, whereby the complex NaBH$_4$/BF$_3$.Et$_2$O proved equally useful (Scheme 8).57

Arylesters did not give ethers, and the yield for alkyl esters varied with the structure of the alcohol unit.

The same reducing complex proved less effective in reduction of lactones 36 to ethers 38; lactone 36 (R=Me) afforded a mixture of lactone 37 (44%) and diol (42%), while less sterically crowded lactones (R=H) afforded diol as the only product, (Scheme 9).58,59

![Scheme 7](image_url)

![Scheme 8](image_url)
This example has for the first time shown beneficial effect of perturbation by the neighboring group in the alcohol unit on reduction directed to ethers. Another interesting example represents reduction of sterically crowded ester 39, which under conditions shown in the Scheme give in 70-80% yield the neopentyl ether 40, which proved unavailable by Williamson ether synthesis (Scheme 10).58

Conformationally stable $\delta$-lactones 40, 41 were reduced to tetrahydrofuran derivatives 42, 43 in 75% and 44% yield, respectively (Scheme 11).58

Progress in this approach has been achieved by Morra and Pagenkopf, who prepared strong Lewis acids BF$_2$OTf.OEt$_2$.60 It is well known that coordination of Lewis acids to the carbonyl group plays an important role in a number of reactions, such as ene-reactions,61 addition of silanes and stananes to aldehydes and conjugated enones,62 Diels-Alder reactions,63 and aldol reactions;64 The authors concluded the coordinating ability of the Lewis acid to the carbonyl oxygen can orient reduction of esters to ethers. This effect of Lewis acids is outlined in the Scheme 12.
Whereas path (a) leads to formation of alcohols, on the path (b) the split of the C-O bond is precluded and ethers are formed. Along the route (a) in the first step borane is coordinated to the sp³ O-atom, followed by the transfer of the hydride ion to the carbonyl C-atom, elimination of alkoxyborane accompanied by intermediary formation of aldehyde, which in the fast step is reduced to alcohol. On the route (b) borane is in the first step coordinated to carbonyl sp² O-atom, then on transfer of hydride ion the best leaving group became oxoborane. In the last and fast step oxonium ion is reduced to ether. It is assumed that steric strain driven by the substituents on the R₃ group precludes formation of an intermediary complex on the route (a) and
favors the complex on the route (b). Along both paths in the last step the hydride ion is transferred, affording two molar equivalents of alcohol in the first case and one molar equivalent of ether in the second one.

Another presentation of the mechanistic difference in reduction in the presence of protons and Lewis acids is given in the Scheme 13. Direction of reduction to ethers can be controlled by coordination of the strong Lewis acid to the O-atom of the carbonyl group.

Scheme 13

A characteristic of the route (b) is transformation of the carbonyl O-atom on coordination into the best nucleophilic group, and parallel formation of an alkyl-oxonium ion, which is hydrogenated in the last step. This mechanism indicates that strong Lewis acids can preclude collapse of the tetrahedral intermediate, as in the route (a), and reorient the reaction towards elimination of the complex bearing the former carbonyl O-atom.

In order to demonstrate stability of the Lewis acids BF₃.Et₂O (X=Ms, Tf) the authors have determined equilibrium constants for the routes (a) and (b) in the Scheme 14. Both equilibria were achieved in few minutes at ambient temperature.⁶⁰

Scheme 14

Using the strongest Lewis acid BF₂OTf.OEt₂ the authors completed reduction of the series of esters 44 to ethers 45 (Table 1). In most cases, however, selectivity was low; formation of larger
quantities of alcohols 46 and smaller quantities of silylesters 47 were observed. Presently, this method seems limited to relatively simple aliphatic esters, and requires optimization of reaction conditions in view of the high reactivity of BF$_2$OTf.OEt$_2$ complex.

**Table 1. Reduction of esters with varying steric crowding**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R$^1$</th>
<th>R$^2$</th>
<th>Time (h)</th>
<th>Conditions</th>
<th>Ether (%)</th>
<th>Alcohol (%)</th>
<th>Silylether (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph(CH$_2$)$_3$</td>
<td>Me</td>
<td>28</td>
<td>A</td>
<td>50</td>
<td>41</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B</td>
<td>62</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Ph(CH$_2$)$_3$</td>
<td>i-Pr</td>
<td>72</td>
<td>A</td>
<td>47</td>
<td>44</td>
<td>6</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>B</td>
<td>58</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Ph(CH$_2$)$_3$</td>
<td>t-Bu</td>
<td>120</td>
<td>A</td>
<td>47</td>
<td>47</td>
<td>4</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>B</td>
<td>57</td>
<td>42</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Ph(CH$_2$)$_3$</td>
<td>H</td>
<td>24</td>
<td>A</td>
<td>46</td>
<td>48</td>
<td>3</td>
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<td>B</td>
<td>62</td>
<td>36</td>
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</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>Ph(CH$_2$)$_2$</td>
<td>48</td>
<td>A</td>
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<td></td>
<td></td>
<td></td>
<td>B</td>
<td>70</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Ph(CH$_2$)$_3$</td>
<td>Ph(CH$_2$)$_2$</td>
<td>72</td>
<td>A</td>
<td>67</td>
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<td></td>
<td></td>
<td></td>
<td>B</td>
<td>71</td>
<td>26</td>
<td>0</td>
</tr>
</tbody>
</table>

Reaction conditions: A = TMSOTf (6 equiv.), BF$_3$.OEt$_2$ (1.2 equiv.); B = TMSOTf (1.2 equiv.), BF$_3$.OEt$_2$ (1.8 equiv.), reduced pressure (40 mmHg), 2h.

**3.4. Reductions by silanes and Lewis acids**

Corriu and co-workers$^{65}$ reported in an early paper on hydrosilylation of esters by trialkoxysilanes, in the presence of CsF and in the absence of solvent, a method to afford alcohols in 65-90% yield.

Trichlorosilane, activated by photochemical excitation, has been shown to reduce esters to ethers.$^{66-68}$ For the series of alkyl esters reduction to ethers in 80-100% yield is reported. In analogy to addition of silanes to the carbonyl group, the mechanism of reduction was proposed (Scheme 15).$^{68}$

**Scheme 15**
Important modification of this procedure, which requires \( \gamma \)-rays induction, was achieved by the combined use of TiCl₄ and TMSOMs.⁶⁹ In Table 2 results are shown for the selected group of esters 48 to ethers 49. One observes the use of a molar excess of Et₃SiH and TMSOTf, and 50% mol excess of TiCl₄, presenting a less attractive aspect of this method.

**Table 2. Reduction of ester 1a to ether 2a with Et₃SiH in the presence of TiCl₄**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Et₃SiH (mol)</th>
<th>TiCl₄ (mol)</th>
<th>TMSOTf (mol)</th>
<th>AgOTf (mol)</th>
<th>TMSCl (mol)</th>
<th>Yield (%)</th>
<th>48</th>
<th>49</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.0</td>
<td>3.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>27</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5.0</td>
<td>1.5</td>
<td>0.5</td>
<td>-</td>
<td>-</td>
<td>35</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>5.0</td>
<td>1.5</td>
<td>1.5</td>
<td>-</td>
<td>-</td>
<td>65</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5.0</td>
<td>1.5</td>
<td>3.0</td>
<td>-</td>
<td>-</td>
<td>81</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>5.0</td>
<td>1.5</td>
<td>3.0</td>
<td>-</td>
<td>-</td>
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<td>6</td>
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<td>-</td>
<td>3.0</td>
<td>-</td>
<td>-</td>
<td>88</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>5.0</td>
<td>1.5</td>
<td>-</td>
<td>3.0</td>
<td>-</td>
<td>63</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>5.0</td>
<td>1.5</td>
<td>-</td>
<td>3.0</td>
<td>3.0</td>
<td>76</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Additionally, in this reaction the yield of ethers does not exceed 80%, and larger quantities of non-reacted ester are found.

Hydrosilylation reactions were initially not catalyzed by transition metals and led to prim-alcohols.⁷⁰-⁷³ Catalyzed hydrosilylations giving prim-alcohols⁷⁴-⁷⁷ have also been reported by Cutler and co-workers⁷⁸ who reported first hydrosilylation of esters to ethers (Scheme 16).

![Scheme 16](image-url)

**Scheme 16**
This reaction is characterized by formation of precatalytic complexes I and II and their intervention into formation of silyl acetals, which in the second step undergo hydrogenolysis. This reaction is very fast and the yields are 80-95%. A problem remains in preparation of the catalyst which is preferentially available by photochemical activation then by thermal reaction. Nagashima and co-workers\textsuperscript{79} have introduced in this reaction a new catalytic system consisting of a trirhuteniumcarbonyl cluster and aromatic ligands as bridges, structures 52 and 53 (Scheme 17).

Preparation of catalytic complexes 52 and 53 was reported previously\textsuperscript{80} and monitoring of reaction by NMR has shown intermediary formation of silyl acetals, analogous to that shown in the Scheme 16. Complex 53 proved completely selective in formation of ether 56, at room temperature and in a short reaction time. In the same paper the authors have studied selectivity of 53 in reduction of some other esters and lactones to ethers.\textsuperscript{79} It turned out that reduction of lactones to cyclic ethers proceeds with significantly higher selectivity then for acyclic ethers, and that the later can be reduced with higher selectivity in dioxane then in tetrahydrofuran.

It was also observed that the trirhutenium complex 52 in the presence of hydrosilane can selectively catalyze the split of the C-O bond of the O-\textit{t}Bu group in carbamates, carbonates, esters and ethers.\textsuperscript{81} Due to its efficiency and selectivity this reaction is suggested as a new deprotection method for the O-\textit{t}Bu group.

Reductive alkylation of aldehydes to ethers is related to ester reduction, since it uses trialkylsilanes in the presence of a catalytic quantity of Fe (III) ions and trimethylsilyl ethers as alkylating agents (Scheme 18).\textsuperscript{82}
Scheme 18

By this two-step one-pot reductive alkylation aromatic aldehydes can also be alkylated, though the yields are somewhat lower. The obvious advantages of the method are the cheap catalyst and short reaction time under mild conditions. A development of this method involves the application of InBr$_3$/Et$_3$SiH as the catalytic system.$^{83}$ Selection of the solvents and optimization of the reaction conditions is presented (Table 3).

Table 3. Optimization of the reaction conditions for reduction of 60 to 61

<table>
<thead>
<tr>
<th>Entry</th>
<th>InX$_3$</th>
<th>R$_3$SiH</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>InBr$_3$</td>
<td>Et$_3$SiH</td>
<td>CHCl$_3$</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>InBr$_3$</td>
<td>Et$_3$SiH</td>
<td>PhH</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>InBr$_3$</td>
<td>Et$_3$SiH</td>
<td>PhMe</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>InBr$_3$</td>
<td>Et$_3$SiH</td>
<td>THF</td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>InBr$_3$</td>
<td>Et$_3$SiH</td>
<td>MeCN</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>InBr$_3$</td>
<td>Et$_3$SiH</td>
<td>CHCl$_3$</td>
<td>NR</td>
</tr>
<tr>
<td>7</td>
<td>In(OTf)$_3$</td>
<td>Et$_3$SiH</td>
<td>CHCl$_3$</td>
<td>Trace</td>
</tr>
<tr>
<td>8</td>
<td>IN(OAc)$_3$</td>
<td>Et$_3$SiH</td>
<td>CHCl$_3$</td>
<td>NR</td>
</tr>
<tr>
<td>9</td>
<td>InBr$_3$</td>
<td>(EtO)$_3$SiH</td>
<td>CHCl$_3$</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>InBr$_3$</td>
<td>PhMe$_2$SiH</td>
<td>CHCl$_3$</td>
<td>94</td>
</tr>
</tbody>
</table>

NR = no reaction
Chloroform was found to be the best solvent; benzene and toluene were nearly as good, whereas reaction in THF and MeCN did not proceed. When the reaction was attempted in the presence of InCl₃, In(OAc)₃ and In(OTf)₃ no product was observed. Best results were obtained with 0.05 equiv. of InBr₃ and 4 equiv. of Et₃SiH in chloroform. The authors suggested the mechanism shown below (Scheme 19).

![Scheme 19](image)

This process includes the following steps; (i) initial transmetalation between InBr₃ and Et₃SiH, (ii) formation of a radical intermediate, consecutive split of the H atom from Et₃SiH and formation of the radical ether product, (iii) and in the final step the indium radical species is regenerated.

In a following paper, the authors have applied this method to selected esters (Table 4).
Table 4. Reduction of esters to ethers by InBr$_3$/Et$_3$Si

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ester 60</th>
<th>Time (h)</th>
<th>Ether 61</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>1</td>
<td>61</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>1</td>
<td>61</td>
<td>69</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>3</td>
<td>61</td>
<td>61</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>4</td>
<td>61</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>10</td>
<td>61</td>
<td>71</td>
</tr>
<tr>
<td>6</td>
<td>R = n-Pr</td>
<td>1</td>
<td>61</td>
<td>71</td>
</tr>
<tr>
<td>7</td>
<td>R = i-Pr</td>
<td>10</td>
<td>61</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>R = cyclopropyl</td>
<td>10</td>
<td>61</td>
<td>53</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>1</td>
<td>61</td>
<td>89</td>
</tr>
<tr>
<td>10</td>
<td>R = 4-NO$_2$C$_6$H$_4$</td>
<td>6</td>
<td>61</td>
<td>62</td>
</tr>
</tbody>
</table>

The results demonstrate compatibility of the process with the presence of the nitro group, bromine atom and thiophene ring, and revealed that sterically crowded groups in the alcohol do not hinder the reduction. 5-And 6-membered lactones are reduced to cyclic ethers in high yields. The same authors$^{85,86}$ reported on another aspect of catalytic deoxygenation of esters by InBr$_3$/R$_3$SiH. In the first paper sequential preparation of symmetrical ethers has been accomplished (Scheme 20).$^{85}$
**Scheme 20**

**Table 5.** One-pot synthesis of ethers from various carboxylic acids and phenylethyl alcohol

<table>
<thead>
<tr>
<th>Entry</th>
<th>Silane (equiv.)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td><img src="image1" alt="Product 1" /></td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td><img src="image2" alt="Product 2" /></td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td><img src="image3" alt="Product 3" /></td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td><img src="image4" alt="Product 4" /></td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td><img src="image5" alt="Product 5" /></td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td><img src="image6" alt="Product 6" /></td>
<td>48</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td><img src="image7" alt="Product 7" /></td>
<td>71</td>
</tr>
</tbody>
</table>
In the first step unprecedented reductive dimerization of two carboxylic acids 62 to produce ester derivatives 63 by combination of the catalyst involving InBr$_3$ and sulfuric acid is achieved. A sequential conversion of the in-situ formed ester to symmetrical ethers was accomplished in the same pot by indium-catalyzed deoxygenation of the ester with a hydrosilane.$^{86}$ In the second paper $^{86}$ the authors have developed “a widely applicable and direct method” of etherification from carboxylic acid and an alcohol by indium-catalyzed deoxygenation of the transient esters to ethers 64. They also demonstrated remarkable tolerance of the catalytic system in the presence of several functional groups including alkenes, halogens, nitro group and heterocyclic unit, Table 5.

A plausible mechanism for the indium-catalyzed reductive deoxygenation of esters en route to ethers is presented in the Scheme 21.$^{85}$

\[
\begin{align*}
\text{O}^\text{In} & \quad \text{R}^1\text{O}^\text{In} \quad + \quad \text{R}^2\text{OH} \\
\text{Si-H} & \quad \text{H}_2\text{O} \quad \text{Si-O}^\text{Si}
\end{align*}
\]

Scheme 21

According to this mechanism InBr$_3$ has several roles, the first being to promote the condensation of a carboxylic acid and an alcohol and to subsequently activate the ester formed in-situ to facilitate hydrosilylation by a silane. The silyl acetal thus generated is then again activated by InBr$_3$ transforming the corresponding ether by the second hydrosilylation and desiloxylolation.

4. Conclusions

Undoubtedly, development of new methods for the reduction of esters to ethers and further improvement of existing protocols are on the horizon. Understanding the mechanism of these particular reactions may have will certainly lead to a focused, rational improvement in the procedures. The evolution from exceptional transformation to useful reaction and /or synthetic method has followed the general evolution from rare to applicable synthetic methods. Although there is no single synthetic method which can be universally applied, ether functionality can now be synthesized by a wide range of available methods. Each method has its unique advantages and limitations, which must be carefully considered when choosing which method to use for a specific starting material.
5. Acknowledgment

We thank Dr. Phil Dudfield and Dr. Gregory Bar for a critical reading of the manuscript. Ivan Grgicevic is acknowledged for his technical assistance.

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Authors Biographies

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Vitomir Šunjić graduated in chemistry in 1963, and completed his Ph.D. in 1969 at the University of Zagreb. He spent his postdoctoral with Prof. Vlado Prelog in 1969-1970 at ETH, Zurich. After four years at the Institute of Chemistry, University of Zagreb he joined Compagnia di Ricerca Chimica (Udine, Italy) from 1975-1982. Then he was elected as senior scientist at Rudjer Bošković institute in Zagreb where he was active from 1982-2003, founded in 1988 Laboratory for Stereoselective Catalysis and Biocatalysis (CATBIO), and headed Department of Chemistry from1998-2003. From 1988 he was appointed professor of organic chemistry at Faculty of Mathematics and Natural Sciences, University of Zagreb. From 2003-2008 he joined PLIVA research institute. V. Šunjić is author or coauthor of over 230 papers, three books, and has applied for over 60 patents. In the period 1996-2002 he was elected member of ESOC.
Committee, and from 2001-2003 acted as the President of this Committee. He was awarded in 1990 by National price for research in chemistry, and in 1996 by the National Academy price for research in organic chemistry. From 2012 he is elected member of Croatian Academy of Sciences and Arts.

**Graphical Abstract**