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Catalytic Reductive Alcohol Etherifications with Carbonyl-Based Compounds or CO_2 and Related Transformations for the Synthesis of Ether Derivatives

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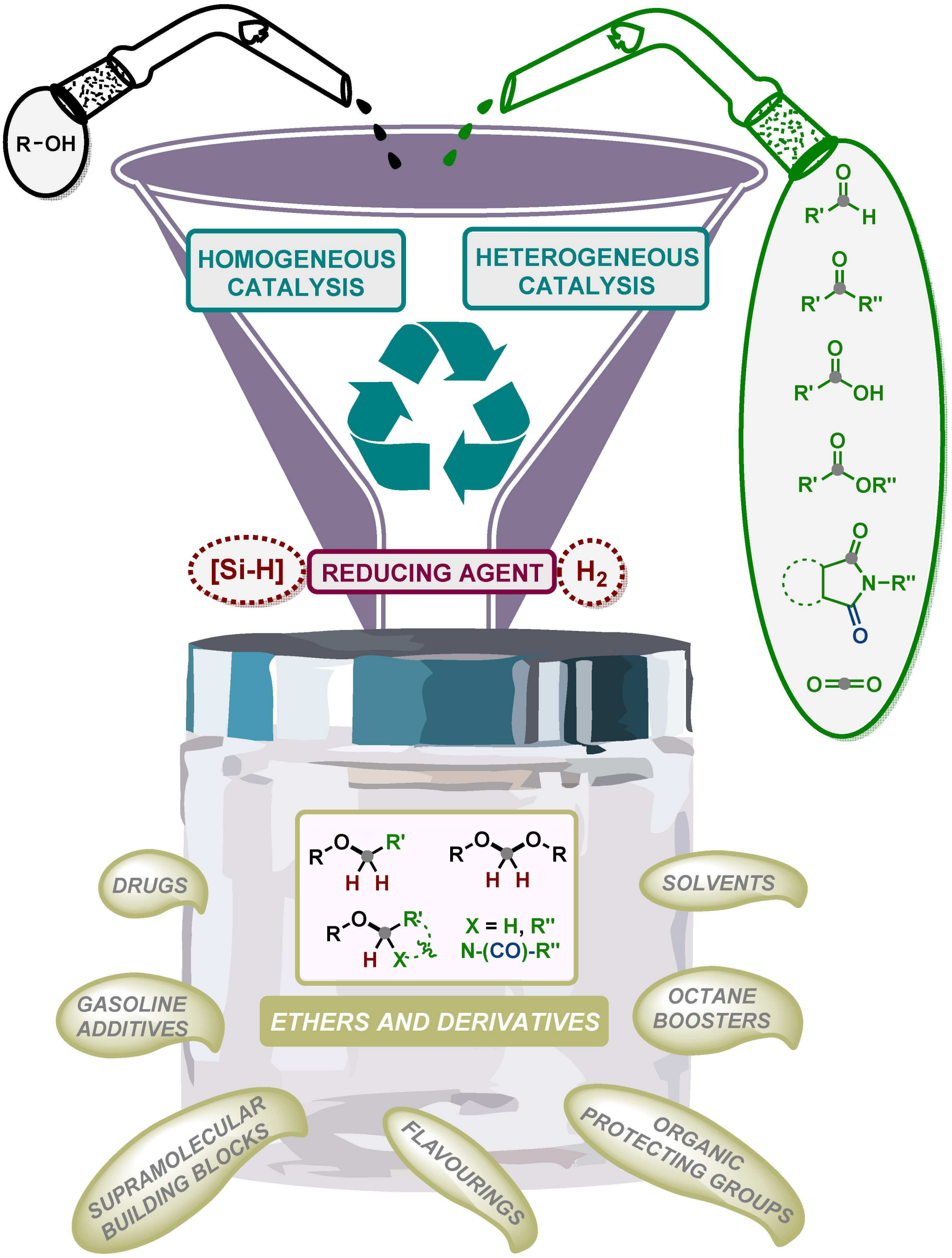

Ether derivatives have myriad applications in several areas of chemical industry and academia. Hence, the development of more effective and sustainable protocols for their production is highly desired. Among the different methodologies reported for ether synthesis, catalytic reductive alcohol etherifications with carbonyl-based moieties (aldehydes/ketones and carboxylic acid derivatives) have emerged in the last years as a potential tool. These processes constitute appealing routes for the selective production of both symmetrical and asymmetrical ethers (including O-heterocycles) with an increased molecular complexity. Likewise, ester-to-ether catalytic reductions and hydrogenative alcohol etherifications with CO_2 to dialkoxymethanes and other acetals, albeit in less extent, have undergone important advances, too. In this Review, an update of the recent progresses in the area of catalytic reductive alcohol etherifications using carbonyl-based compounds and CO_2 have been described with a special focus on organic synthetic applications and catalyst design. Complementarily, recent progress made in catalytic acetal/ketal-to-ether or ester-to-ether reductions and other related transformations have been also summarized.

1. Introduction

Ethers are pivotal compounds for the chemical industry as they present a wide range of applications in bulk and fine chemistry (Figure 1).[1] For example, ether functionality is found in many bioactive compounds, fragrances, flavorings, natural products, solvents, or polymers, a large variety of applications that highlight the great relevance of this functional group.[1] In addition, ether function is key in supramolecular chemistry being present in the structure of crown-ethers or cryptands.[1a] Moreover, ethers are commonly used as protecting groups in organic chemistry, given their chemical inertness.[1b] Interestingly, in the last years, biomass-derived ethers have aroused a large interest due to their applications as surfactants, fuel additives, or lubricants, among others.[1e,g,h] The variety of applications of ethers, together with the possibility of obtaining this class of compounds from biomass platform chemicals, has encouraged scientists working in organic chemistry and catalysis to make efforts towards the development and improvement of sustainable protocols for their synthesis (Scheme 1).

Since its discovery in the 1850s, the Williamson reaction is considered as the most common organic methodology for ether synthesis (Scheme 1A).[2] In a typical Williamson etherification, an S_N2 reaction between an alkoxide anion and a highly electrophilic reagent takes place. However, the requirement of a large excess of strong bases and the use of toxic alkylhalides seriously limit its application, as a lot of waste is intrinsically generated.[2] In addition, hindered ethers are not accessible through this protocol, since elimination takes place when secondary or tertiary alkyl halides are employed.

As a greener alternative to the Williamson reaction, related alcohol alkylations with dialkylcarbonates via $B_{AL}2$ mechanism have been also noticed but result in not economically viable processes.[3]

Another classical method for ether synthesis, although less commonly employed, is the Mitsunobu reaction (Scheme 1B).[4] In this methodology a primary or secondary alcohol reacts with a nucleophile (a phenol or an alcohol with a strong electron-withdrawing group attached to the carbon) mediated by stoichiometric amounts of a redox combination of a trialkyl or triaryl phosphine and a dialkyl azodicarboxylate.[4] Despite being a synthetically valuable protocol, typically proceeding through inversion of stereochemistry, it is far from being desirable from the sustainability viewpoint.

More recently, catalytic cross-coupling protocols involving phenols have been developed.[5] Copper-mediated Ullman-type[6] and Chan-Lam couplings,[6a,7] as well as palladium-catalyzed Buchwald–Hartwig arylations,[8] have become useful reactions for accessing usually aryl ethers. Although being efficient methods, they present important limitations such as their narrow applicability or the requirement of toxic reagents, base excess, and/or sophisticated ligands working under specific conditions (Scheme 1C).

A practical methodology widely employed for obtaining mainly linear symmetrical ethers is the acid-mediated bimolecular dehydration of alcohols, also known as the direct etherification of alcohols (Scheme 1D).[1e,g,h,2b] Linear ethers can be obtained from primary alcohols with strong acids (i. e., H_2SO_4) at high temperatures. In fact, Et_2O is nowadays produced in industry by ethanol dehydration.[2b] Gratifyingly, in the last years, improved catalytic procedures with homogeneous and heterogeneous Lewis and/or Brønsted acid catalysts have been successfully developed.[1e,g,h,9] The main drawback of this methodology is again its reduced applicability, as it is almost limited to primary alcohols to avoid alcohol dehydration to olefin and subsequent alcohol-to-olefin hydroaddition, olefin hydration, and/or oligomerization.[1g] Although some efforts have been made to design acid catalysts able to control selectivity towards asymmetrical ethers through this protocol,[9d,e] in general it is still only practical for obtaining symmetrical ethers.[1e,g]

Complementarily, the addition of an alcohol to an olefin or alkyne, so-called hydroalcoxylation or hydroetherification reaction, is a useful methodology mainly employed for the synthesis

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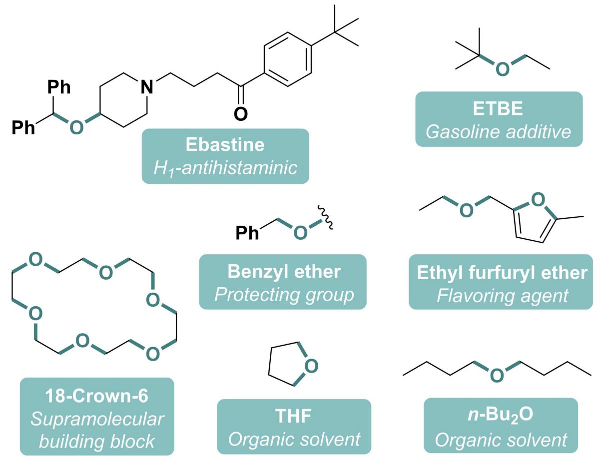

Figure 1. Some examples of ethers with relevant applications. ETBE = ethyl *tert*-butyl ether. THF = tetrahydrofuran.

of branched asymmetrical ethers (Scheme 1E).[10] This reaction, commonly applied also intramolecularly for the synthesis of O-heterocycles, is an atom-economical approach for ether synthesis.[10] Traditionally, these reactions proceed under strong acidic conditions, which implies an inherent generation of large amounts of waste and corrosion problems of the reactors.[2b] To circumvent these problems, homogeneous and heterogeneous Lewis and/or Brønsted acid catalysts have played an important role for improving ether production by hydroalcoxylation reactions.[10]

It is important to note that the hydroalcoxylation protocol presents two main challenges: avoiding the formation of side products (alkene isomerization or dimerization/oligomerization and alcohol dehydration) and controlling the selectivity (Markovnikov vs. anti-Markovnikov).[1g,2b,10] Taking into account the side product formation and Markovnikov preference, hydroalcoxylation is a practical protocol for the production of asymmetrical ether derivatives, coming from the addition of primary alcohols onto highly substituted olefins.[1g,10] In fact, branched ethers such as *t*-butyl methyl ether or ethyl *t*-butyl ether are commonly produced through this etherification procedure.[1g,10]

In addition, it is also interesting to highlight the ring opening of epoxides with alcohols as a practical protocol for accessing β-hydroxy ethers or polyethers, with high relevance in polymer industry.[11]

More specific protocols for ether synthesis such as the catalytic transfer vinylation,[12] alcohol addition to tosylhydrazones,[13] or alcohol phosphorylation[14] have been also reported. Moreover, emerging methodologies in modern synthetic organic chemistry are also being applied to ether production. Thus, protocols based on catalytic C–H activation[15] or electrosynthesis[16] have been recently developed. In addition, an elegant dialkyl ether construction through a Ni-catalyzed cross-coupling,[17] Cu-catalyzed hindered ether synthesis mediated by radicals,[18] and the organophotoredox-catalyzed decarboxylative methodology[19] are worth mentioning.

Seeking alternative protocols for ether synthesis that meet the requirements of sustainability and wide range of applicability is a main goal of current organic synthesis and

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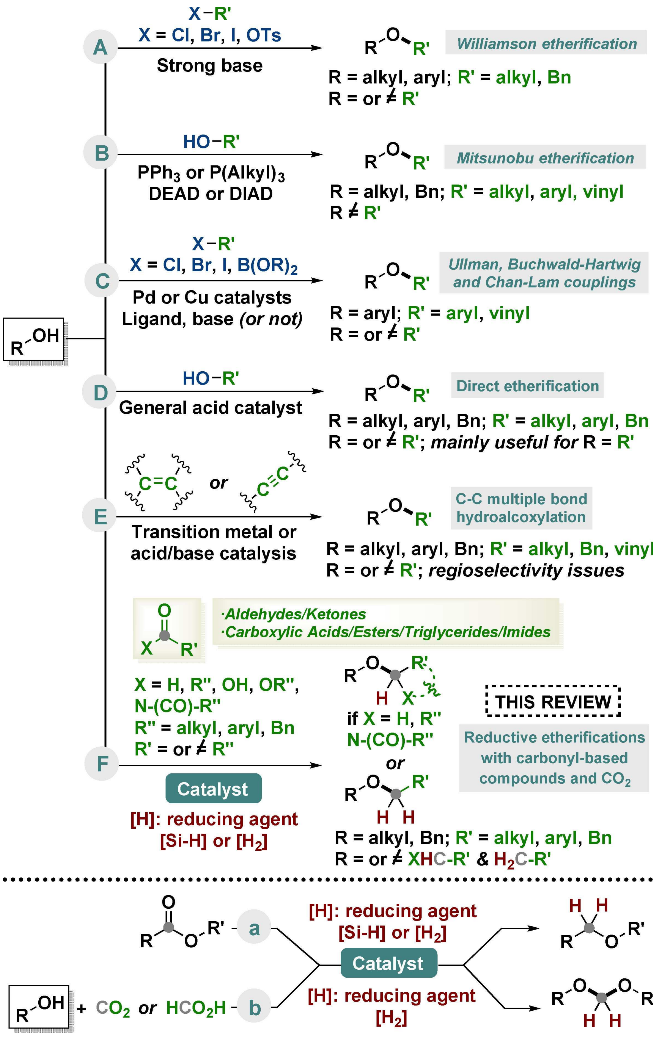


Scheme 1. Top: (A–E) general methods for obtaining ethers from alcohols. Bottom: some related catalytic transformations also included in this Review, such as (a) ester-to-ether reductions and (b) hydrogenative alcohol etherifications with CO_2 or formic acid to dialcoxymethane ethers (cyclic acetals can be obtained from diols). Bn = benzyl. DEAD = diethyl azodicarboxylate. DIAD = diisopropyl azodicarboxylate.

catalysis.[20] In this context, chemists are more and more focusing their attention in reductive protocols that allow the use of accessible reagents such as carbonyl-based compounds.[1e,g,h,5c,21] Analogously to the development of amine *N*-alkylation reductive protocols, like reductive amination,[22] typically employing aldehydes or ketones, or the more challenging reductive *N*-alkylation with carboxylic/carbonic acid derivatives,[23] reductive etherification of alcohols has more recently emerged as an attractive strategy. In reductive etherification,[1e,g] in principle an alcohol acts as a nucleophile reacting with an oxidized alkyl source (aldehydes/ketones, carboxylic acids/esters, imides, and even triglycerides) in the presence of a suitable reducing agent to afford an ether product (Scheme 1F).[1e,g,h,5c,21] At this point is important to mention that there is no evidence of an intermolecular reductive etherification involving phenols, probably due to the low nucleophilic character of the oxygen atom in this case.[24]

Traditionally, non-catalytic routes employing (over) stoichiometric amounts of metal hydrides and/or an excess of Lewis/Brønsted acids that generate large amounts of waste have proved to be effective for the reductive alcohol etherification.[2b,25] Obviously, important efforts have been dedicated to the development of catalytic protocols that allow more sustainable transformations.[1e,g,h,5c,21] In this direction, several contributions have been reported from the homogeneous or heterogeneous catalysis areas employing different reducing agents (mainly hydrosilane-based compounds or molecular hydrogen). These processes constitute convenient strategies to perform alcohol etherifications using readily available carbonyl-based compounds as alkyl sources.[1e,g,h,5c,21] In addition, reductive etherifications involving the use of alcohol surrogates (i.e., silyl-protected derivatives) or the reductive homocoupling of carbonyl-based compounds have been also developed.[5c,21] Interestingly, all these procedures constitute an appealing tool for the selective production of not only symmetrical, but also asymmetrical ethers with high molecular complexity.[1e,g,h,5c,21] In this sense, the huge variety of ether structures that can be synthesized with these reductive processes directly benefits from the wide range of aldehydes, ketones, and carboxylic acid derivatives available.

Intimately related with the reductive etherification of alcohols employing carboxylic acid derivatives, ethers can also be obtained by the direct reduction of esters (Scheme 1a).[26] This is a highly attractive method considering the availability of esters from renewable sources.[27] The ester-to-ether transformation was proved first using well-stablished non-catalytic procedures in the presence of (over)stoichiometric amounts of metal hydrides or thiocarbonylating reagents.[26,28] Owing to the great interest of this transformation and the large advances that catalytic reduction homogeneous and heterogeneous areas have achieved in the last years, several catalyzed protocols have been already reported. Nevertheless, catalytic strategies for ester-to-ether reduction are still rather undeveloped, due to the major tendency of esters to afford alcohols under reductive conditions, instead of the corresponding ethers.[26a,29] In the section 3 of this Review, recent advances reported from both catalysis areas dealing with ester-to-ether transformation are carefully addressed, given the close relationship of this reaction with reductive alcohol etherifications using carboxylic acid derivatives.

Similarly, protocols employing CO_2 or formic acid as C_1 alkyl source in the presence of alcohols and hydrogen have been also reported for accessing mainly dialkoxymethane ethers, but also other related acetal derivatives (Scheme 1b).[30] Those compounds constitute a relevant class of ether-type derivatives with several applications.[30,31] This represents a new manner of CO_2 valorization through its conversion into formaldehyde oxidation level derivatives in the presence of benign molecular hydrogen.[30,32] It is important to highlight that the use of carbon dioxide as C_1 alkylating agent entails great benefits as it is a non-toxic, cheap, and widely abundant chemical source.[23,33] Furthermore, the activation of this extremely stable molecule from the thermodynamic and kinetic viewpoints is considered nowadays a great challenge of modern chemistry.[34]

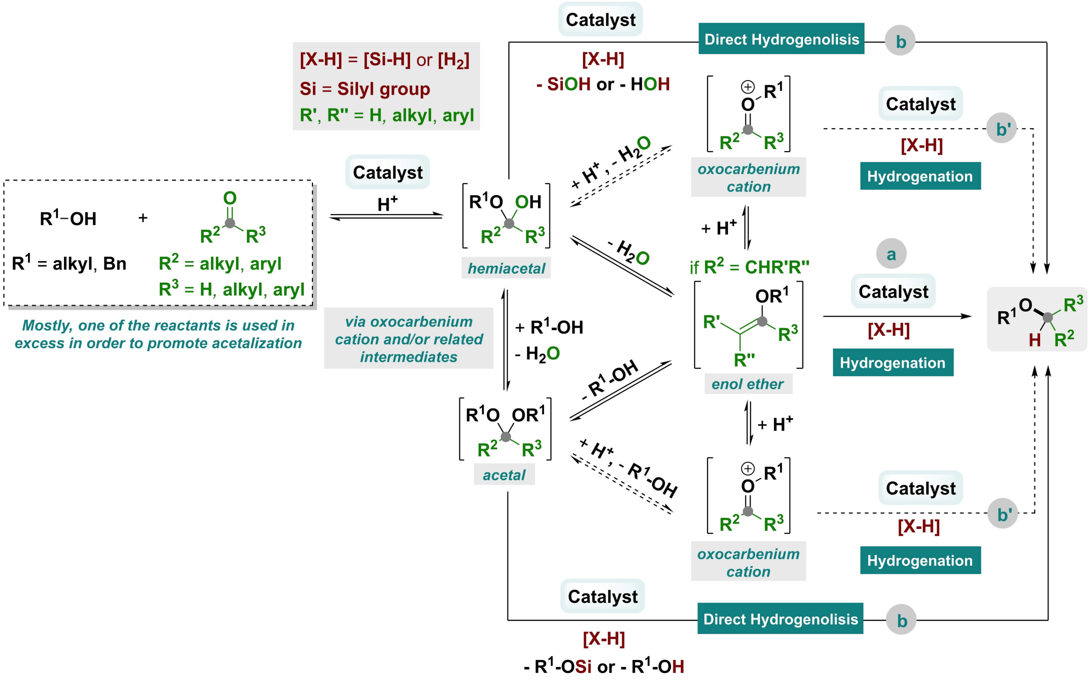
This Review offers an updated account of the advances made in the area of catalytic reductive alcohol etherification employing carbonyl compounds, carboxylic acid derivatives, and CO_2 as alkylating sources. Likewise, other associated processes entailing reductive etherification of alcohol surrogates or a self-etherification of the carbonyl-based source are also adequately discussed. Whereas more traditional non-catalytic methods are not included herein, both catalytic homogeneous as well as heterogeneous examples are summarized with a special emphasis in catalyst developments and organic synthetic applications. Reductive protocols employing as hydride source silicon-compounds bearing a Si–H bond (hydrosilanes, hydrosiloxanes, and alcoxyhydrosilanes) or H_2 are exclusively showcased here.

Other related etherification examples using hydroboranes[35] or alcohols (via Meerwein–Ponndorf–Verley)[36] as reducing agents are not discussed in this work. Complementarily, related catalytic transformations such as the acetal/ketal-to-ether[37] and ester-to-ether[26,29b] reductions are also addressed.

2. Reductive Etherification of Alcohols or Surrogates with Aldehydes/Ketones

Reductive alcohol etherification with carbonyl compounds as alkyl sources and employing external reductors (Si–H reagents or H_2) is a practical reaction for the straightforward synthesis of ethers.[1e,g,h,5c,21] Aldehydes and ketones have high accessibility, low price, easy handling, and widespread structural diversity, making this protocol a valuable synthetic alternative for the direct obtaining of a huge variety of complex symmetrical/asymmetrical ethers, including O-heterocycles.[1b,2b] Hence, a large interest has developed in the last years in both heterogeneous and homogeneous catalysis areas for designing suitable catalysts systems and optimizing reaction conditions for this transformation.

In this part of the Review, inter- and intramolecular catalytic protocols reported up to date for the reductive etherification of alcohols or surrogates (i.e., silyl-protected alcohols) with carbonyl compounds are described in detail. Related transformations, such as reductive self-etherification of carbonyl compounds and acetal/ketal-to-ether reductions, are also commented here. The general mechanism commonly proposed for this transformation is illustrated in Scheme 2.[1g,25a,38] First, the acid-catalyzed formation of a hemiacetal or acetal intermediate is proposed, with both species in equilibrium through an oxocarbenium ion or a related intermediate.[38a,j] For (hemi)acetals containing at least one α-H, loss of water or R^1OH generates the corresponding enol ether intermediate, in equilibrium with an oxocarbenium ion, which is easily reduced to the desired ether (path a). In the case of carbonyl compounds with no α-H, (hemi)acetal intermediates might undergo a direct hydrogenolysis to the corresponding ether derivative (path b).[1g,38b–d,f,g,i] It has also been suggested that direct hydrogenolysis, and/or related pathways, can entail the



Scheme 2. Catalytic reductive etherification of alcohols with aldehydes/ketones in the presence of an external reductor (i.e., Si–H reagent or H_2). Hemiacetal, acetal, enol ether, and oxocarbenium ion derivatives are considered as the main potential intermediates (enol ether derivative can be only formed if the carbonyl source has at least one α-hydrogen). Is important to note that depending on the reducing agent employed some of the depicted steps could be slightly different.

formation of an oxocarbenium ion intermediate by protonation of the (hemi)acetal and subsequent water/R^1OH release, followed by its catalytic reduction to give the desired ether (path b′).[25a,38a,c,g,39]

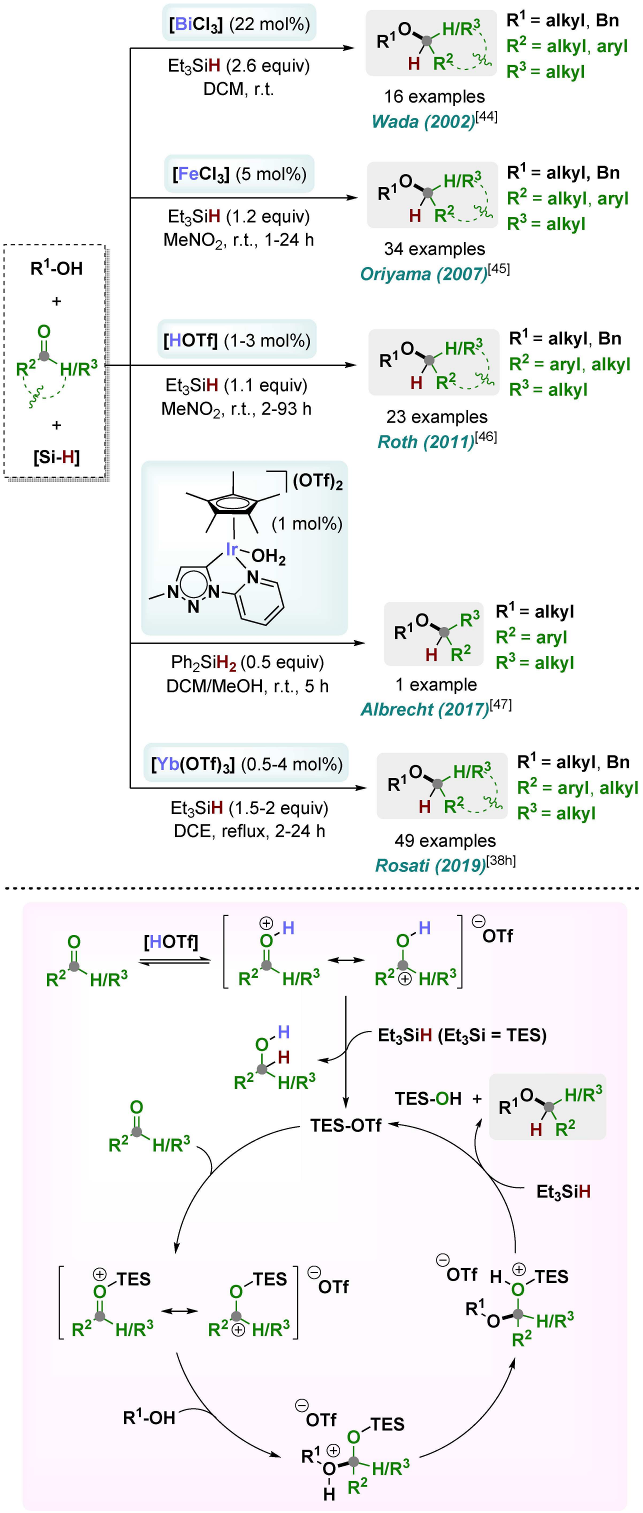
In addition, formation of symmetrical ethers as side products can be explained by the reduction of the carbonyl compound to the corresponding alcohol, and subsequent reductive etherification with its carbonyl analogue.[1g,38b,40] Moreover, ether formation could also proceed by an acid-catalyzed bimolecular dehydration of two different alcohols.[1g,41] This process could afford either the desired ether or other symmetrical ethers. In order to favor the reductive etherification pathway, reaction conditions are fine-tuned to drive the (hemi) acetal formation through the use of an excess of the alcohol or the carbonyl compound in acidic media.

2.1. Using Si–H compounds as reducing agent

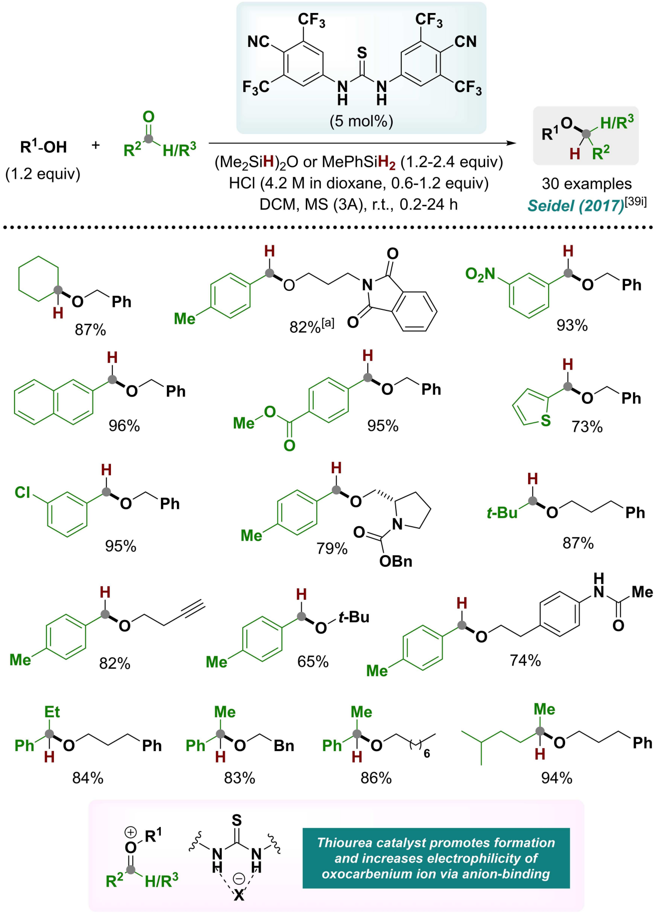
Hydrosilanes and related Si–H reagents are considered one of the most selective, easy-to-handle, and least toxic class of reductors in organic chemistry.[42] These compounds are characterized by polar Si–H moieties, being highly chemoselective and mild hydride sources for carbonyl group reduction, even in the presence of aromatics and other common reducible functionalities.[21a,43] Obviously, these reagents also present the disadvantage of generating equimolecular amounts of waste products, which makes them not the preferred choice in industrial applications for sustainability reasons. Moreover, most of the catalysts employing these reducing agents are homogeneous systems, more difficult to reuse; another drawback to achieve more sustainable processes. However, due to the easy applicability of these reagents, they have been broadly employed in catalytic reductive etherification of alcohols or surrogates (i.e., silyl-activated alcohols) with carbonyl compounds, or related reductive transformations for C–O bond building, albeit mainly in the context of small-scale laboratory reactions. With these strategies, direct formation of a widespread collection of ether-type derivatives can be accomplished with high levels of efficiency.

In 1972, Doyle et al. first showed a reduction of aldehydes/ketones with a hydrosilane (i.e., Et_3SiH) in alcoholic acidic media directly affording asymmetrical ethers.[25a] However, a molar excess of a strong Brønsted acid, such as sulfuric or trifluoroacetic acid, was required. After this contribution, several catalysts able to perform silane-mediated reductive etherifications between non-protected alcohols and aldehydes/ketones have been reported.

In this respect, Scheme 3 illustrates the described protocols to date for the intermolecular alcohol reductive etherification catalyzed by Lewis/Brønsted acids or transition metals. In 2002, Wada et al. developed the first catalytic method for symmetrical/asymmetrical ether production from alcohols and carbonyl reagents in the presence of Et_3SiH as reductor (Scheme 3, see also Scheme 6D).[44] In this work, $BiCl_3$ was used as catalyst for efficiently performing reductive etherification of alkyl and benzyl alcohols with aromatic or aliphatic carbonyl



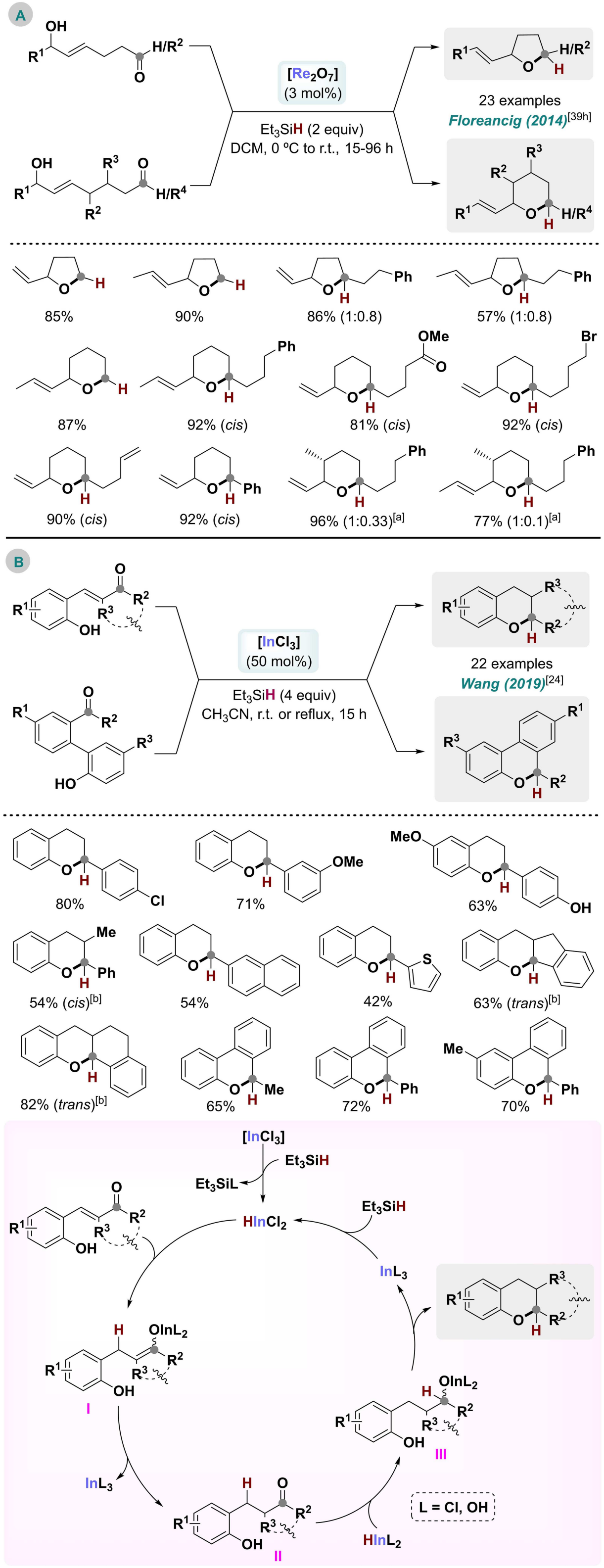
Scheme 3. Top: Lewis/Brønsted acid- or transition metal-catalyzed alcohol reductive etherifications using aldehydes/ketones and hydrosilanes. Bottom: mechanism proposed by Roth and co-workers[46] for the HOTf-catalyzed etherification of alcohols with carbonyl compounds. DCM = dichloromethane. OTf = trifluoromethanesulfonate. DCE = 1,2-dichloroethane.



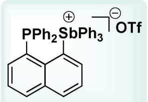
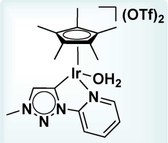
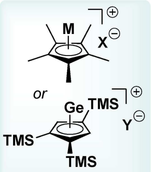
Scheme 4. Synthesis of unsymmetrical ethers by reductive etherification with anion-binding catalysis. MS = molecular sieves. [a] Run with a thiourea having Br atoms instead of CN groups.

substrates at room temperature. As expected, phenol or carboxylic acid groups were not affected under this reaction conditions.[44]

Five years later, a similar $FeCl_3$-catalyzed reductive etherification protocol was developed by Oriyama and co-workers (Scheme 3).[45] More than 30 ether derivatives were obtained, and improved results were achieved in comparison with the methodology of Wada et al. for aliphatic aldehydes or ketones. Later on, Roth and co-workers described a triflic acid-catalyzed version for the same transformation.[46] By using 1 mol% of HOTf and 1.1 equiv. of Et_3SiH, a wide range of asymmetrical ethers were accessed in up to 88% isolated yield (Scheme 3, see also Scheme 6H). Notably, even a hindered tertiary alkyl alcohol, such as *tert*-butanol, was successfully etherified for the first time. In terms of mechanism, the authors propose that, initially, triethylsilane trifluoromethanesulfonate (TES–OTf) is generated from triflic acid, carbonyl substrate and Si–H reductor as the real active species able to activate the carbonyl group towards nucleophilic attack by the alcohol (Scheme 3, bottom). Subsequently, proton transfer and reduction with Et_3SiH affords the ether and silanol by-product, regenerating the TES–OTf catalyst.[46]



Scheme 5. O-heterocycle synthesis. (A) Re_2O_7-catalyzed allylic alcohol transposition/intramolecular reductive etherification sequence. Diastereoselectivity ratio (*cis/trans*) in parentheses, calculated by ^1H NMR spectroscopy relative to the hydrogens placed in 2,5- or 2,6-positions. [a] Using a substrate with a pre-existing stereocenter as enantiopure compound. (B) Intramolecular reductive etherification of keto phenols in the presence of $InCl_3$. [b] In this case, *cis/trans* configuration refers to the hydrogens placed in 2,3-position. Isolated yields are given.

	Aldehyde/ketone	Catalyst	[Si-H] (equiv)	
A	R^1 = alkyl, aryl R^2 = H	[Ph_3CClO_4] (5 mol%)	Et_3SiH (1)	3 examples *Mukaiyama (1985)*[54]
B	R^1 = alkyl, aryl R^2 = H	[TMS-OTf] (2.8 mol%)	$(Me_2SiH)_2O$ (1)	7 examples *Palomo (1986)*[71]
C	R^1 = alkyl, aryl R^2 = H, alkyl	[$BiBr_3$] (1-3 mol%)	Et_3SiH (1.2)	8 examples *Komatsu (1997)*[57]
D	R^1 = alkyl, aryl R^2 = H, alkyl	[$BiCl_3$] (11 mol%)	Et_3SiH (1.3)	6 examples *Wada (2002)*[44]
E	R^1 = aryl R^2 = H, alkyl	[$M(OTf)_3$] [M: Sc, Bi, Ga, Al] (2-4 mol%)	Et_3SiH (1)	8 examples *Laali (2009)*[72]
F	R^1 = alkyl, aryl R^2 = H, alkyl	[I_2] (2.5 mol%)	PMHS (3)	16 examples *Yadav (2010)*[73]
G	R^1 = alkyl R^2 = alkyl	[$InBr_3$] (5 mol%)	$PhSiH_3$ (1.3) or Et_3SiH (4)	6 examples *Sakai (2011)*[74a]
H	R^1 = alkyl, aryl R^2 = H, alkyl	[HOTf] (1 mol%)	Et_3SiH (1.1)	13 examples *Roth (2011)*[46]
I	R^1 = alkyl, aryl R^2 = H, alkyl	[$Cu(OTf)_2$] (1-5 mol%)	$(Me_2SiH)_2O$ (0.6-3)	10 examples *Chen & Lemaire (2012)*[75]
J	R^1 = alkyl, aryl R^2 = H	[$Zn(OTf)_2$] (5 mol%)	Et_3SiH (4) or $(Me_2SiH)_2O$ (2)	10 examples *Sakai (2013)*[74b]
K	R^1 = alkyl, aryl R^2 = H	[$In(OTf)_3$] (10 mol%)	Et_3SiH (4)	15 examples *Mineno (2014)*[76]
L	R^1 = alkyl, aryl R^2 = H, alkyl	[$Fe_3O(AcO)_6$] or [$FeCl_3$] (2 mol%) [TMS-Cl] (8 mol%)	Et_3SiH (1.05)	19 examples *Leino (2015)*[66]
M	R^1 = alkyl, aryl R^2 = H	 (3 mol%)	Et_3SiH (3)	15 examples *Hudnall (2016)*[77]
N	R^1 = alkyl, aryl R^2 = H, alkyl	[Mo/C] (0.1 mol%)	Me_2PhSiH (1.2)	15 examples *Lohr & Marks (2017)*[78]
O	R^1 = aryl R^2 = H, alkyl aryl	 (0.1 mol%)	Ph_2SiH_2 (2)	6 examples *Albrecht (2017)*[47]
P	R^1 = alkyl, aryl R^2 = H	[$UO_2(OTf)_2$] (1 mol%)	Et_3SiH (1.2)	19 examples *Cantat (2019)*[79]
Q	R^1 = alkyl R^2 = H, alkyl	 [M: Si, Ge] (0.050-0.01 mol%)	Et_3SiH (1)	3 examples *Fritz-Langhals (2020)*[68]

Scheme 6. Reductive homocoupling of carbonyl compounds to symmetrical ethers. **X** = $B(Ar^F)_4$, $B(SiCl_3)_4$, $Al[OC(CF_3)_3]_4$. **Y** = $B(Ar^F)_4$, $B(SiCl_3)_4$.

Albrecht and co-workers reported in 2017 an Ir complex-catalyzed reductive etherification of methanol and 4-fluoroacetophenone to synthesize 1-fluoro-4-(1-methoxyethyl)benzene in the presence of diphenylsilane (Scheme 3, see also Scheme 6O).[47] Finally, $Yb(OTf)_3$ was reported by Rosati et al. in 2019 as an efficient and general Lewis acid catalyst for performing alcohol reductive etherifications with aldehydes/ketones.[38h] In the presence of Et_3SiH, a wide range of ethers were produced from alkyl/propargyl or benzyl alcohols and aromatic/aliphatic aldehydes or aliphatic ketones (Scheme 3).

In addition, in 2017 Seidel and co-workers reported a metal-free protocol[39i] in which a readily accessible thiourea organocatalyst, in cooperation with HCl, promoted reductive etherification via anion-binding catalysis[48] (Scheme 4). It is suggested that the presence of the thiourea enhances the Brønsted acid-promoted generation of the oxocarbenium ion and/or its equilibrium concentration, as well as its electrophilic character, as a consequence of thiourea interaction with the corresponding counter anion.[39i] Regarding substrate scope, either benzylic or 1°/2°/3° aliphatic alcohols undergo efficient reductive coupling with aromatic/aliphatic aldehydes or ketones using 1,1,3,3-tetramethyldisiloxane (TMDS) or $MePhSiH_2$. Notably, the protocol was fully compatible with the presence of different functionalities including ether, halides, nitro, nitrile, ester, alkenyl, or alkynyl, among others. Moreover, satisfactory ether yields were obtained from reductive etherifications involving more challenging aromatic ketones.[39i]

Interestingly, intramolecular reductive etherification protocols give place to O-heterocycle derivatives, which are the core of many natural products and compounds with relevant biological activities.[49] Early non-catalytic examples for the synthesis of O-heterocycles via reductive intramolecular condensation between alcohols and carbonyl moieties were developed by Nicolau et al.[25b,c] and Colobert, Solladié, Carreño and co-workers.[25d,e] Most of these methods were used in the context of natural product synthesis and consisted of the combination of triethylsilane and stoichiometric amounts of trimethylsilyl trifluoromethanesulfonate (TMS–OTf).

In a catalytic context, Roth and co-workers described in 2011 an example of reductive cyclization for 2-methyltetrahydrofuran formation.[46] The same year, Chandrasekhar et al. applied a similar strategy for obtaining a *cis*-2,6-disubstituted tetrahydropyran, using $BF_3 \cdot Et_2O$ as catalyst, via one-pot deketalization/intramolecular cyclization sequence, as key step for synthesizing (−)-centrolobine.[50]

Later, two general protocols for O-heterocycle synthesis through intramolecular reductive etherification have been described (Scheme 5). In 2014, the group of Floreancig developed an elegant Re_2O_7-catalyzed method for the straightforward synthesis of a wide range of cyclic ethers in the presence of Et_3SiH as reductor (Scheme 5A).[39h] In this work, an allylic alcohol transposition coupled with a direct reductive condensation, affords tetrahydrofurans and tetrahydropyrans in up to 96% isolated yield. The authors propose as key steps of the mechanism the ionization of the hemiacetal intermediate to afford the corresponding cyclic oxocarbenium ion and its reduction. As consequence of an increased access to the formation of the oxocarbenium ion, five-membered rings were produced faster than six-membered ones, and 2° allylic alcohols reacted faster than 1°.[39h] In addition, ketones exhibited improved reactivity compared with aldehydes. Interestingly, when ketones are involved, a new stereocenter is formed in the process, thus offering possibilities of stereocontrol. While a total *cis* diastereoselectivity was observed for tetrahydropyran formation (relative to 2,6-positions), tetrahydrofurans were obtained with poorer diastereoselectivity (referred to 2,5-positions).

Furthermore, reductive cyclization on substrates bearing pre-existing chiral centers was studied, giving place to tetrahydropyrans with excellent 2,6-*cis* stereochemical selectivities. It is interesting to note that the chemical nature of the Si-based hydride employed directly influences on the stereocontrol degree. In fact, when less reactive Ph_3SiH is used, an improved diastereoselectivity was obtained for the same starting material.[39h]

Five years later, Wang and co-workers designed another strategy for the production of O-heterocycles through the intramolecular reductive etherification of keto phenol compounds using $InCl_3$ as catalyst and Et_3SiH as reductor (Scheme 5B).[24] More specifically, a wide range of substituted 2-aryl chromans were obtained from 2-hydroxychalcones, as well as 6*H*-benzo[*c*]chromenes from the corresponding keto phenol derivatives in moderate to excellent isolated yields (42–93 %). In the case of substrates having a prochiral carbon stereocenter, reductive cyclization showed a total diastereoselectivity relative to 2,3-positiions. Up to date, this contribution represents the only known method for a reductive etherification using phenols as substrates.[24] In terms of mechanism (see Scheme 5B, bottom), an initial transmetalation is proposed between Et_3SiH and $InCl_3$ to form $HInL_2$ hydride. The hydride undergoes Michael addition to a 2-hydroxychalcone to generate an indium enolate (**I**), which through isomerization and hydride 1,2-addition leads to **III**. Finally, an intramolecular cyclization affords the chroman product and final transmetalation regenerates $HInL_2$ species.[24]

Complementarily to the reductive etherification protocols between alcohols and carbonyl compounds, silyl-activated analogues such as alkoxy(hydro)silanes or alkylsilyl ethers have been employed as alcohol surrogates in these reactions. These methods are less attractive alternatives from the sustainability viewpoint due to the required previous synthesis of the silyl-activated derivative.[51] However, owing to the broad presence of alkylsilyl-based protecting groups in organic chemistry and natural product synthesis, the reductive etherification methods of silyl-protected alcohols have a high synthetic value for accessing alkyl ethers.[21b,51,52] Remarkably, trimethylsilyl-protected alcohols are commonly employed in selective protecting group manipulations for the synthesis of glycoconjugates, where triethylsilane-mediated catalytic reductive etherifications constitute a key step.[21b,52] These specific works mostly focused on carbohydrate chemistry are not discussed here.[21b,52,53]

In Table 1 are summarized the catalytic protocols described in the literature for the reductive etherification of Si-activated alcohols with carbonyl compounds. By applying these methodologies, both symmetric and asymmetric ether derivatives can be accessed. Usually, Lewis/Brønsted acids or organometallic complexes have been employed as catalysts.

Original work in this field was disclosed by Mukaiyama and co-workers in 1985 (entry 1).[54] In this publication, trityl perchlorate (Ph_3CClO_4) as catalyst, in combination with Et_3SiH as reducing agent, promoted the reductive coupling of different alkoxytrimethylsilanes with aldehydes/ketones. Thereafter, other Lewis acids such as TMS–I, TMS–OTf, and $BiBr_3$ were reported from 1987 to 2002 by Olah, Prakash and co-workers,[55] Nishizawa and co-workers,[56] Komatsu et al.,[57] and Hosomi and co-workers[58] (entries 2–6) as efficient catalysts for the same transformation. Notably, the example from Hosomi and co-workers was the first where the alkoxy(hydro)silane is employed as both alcohol surrogate and reducing agent, being hence a more atom-efficient protocol (entry 6).[58]

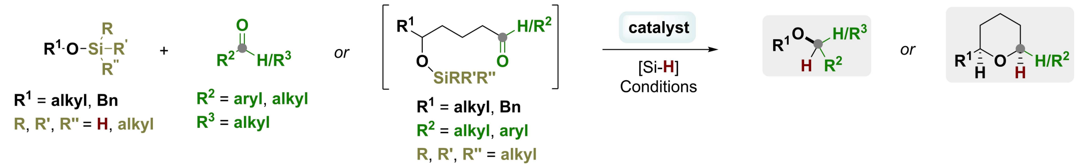
In 2002, joined contributions from Bajwa, Jiang and co-workers[59,60] reported two protocols for ether preparation from alkoxysilanes or alkoxyhydrosilanes and carbonyl compounds (entries 7 and 8). In these cases, $BiBr_3$ alone[59] or in combination with $Cl(i\text{-}Pr)_2SiH$[60] is used as catalyst system for the reductive etherification of silyl-activated alcohols. Herein, authors propose Et_3SiBr or $Cl(i\text{-}Pr)_2SiBr_3$ species, formed respectively from $BiBr_3$/Et_3SiH[59] or $BiBr_3$/$Cl(i\text{-}Pr)_2SiH$[60] combinations, as the active catalytic species.

One year later, Evans et al. and Hinkle et al. described the first catalytic intramolecular version of this transformation (entry 9).[39d–f] In their work, a stereoselective synthesis of several *cis*-2,6-disubstituted tetrahydropyrans was efficiently accomplished via $BiBr_3$-initiated reductive etherification of δ-trialkylsilyloxy substituted ketones.[39d–f] Interestingly, the synthetic applicability of this methodology was showcased by performing the total synthesis of the antibiotic (−)-centrolobine, involving a reductive cyclization of a δ-trialkylsilyloxy aryl ketone derivative as key step.[39e] In addition, authors also provided convincing evidence to assume that Brønsted acid HBr, in-situ generated from hydrosilane reduction of $BiBr_3$, constitutes the real catalyst in the etherification process.[39e] These observations are clearly in disagreement with the ones previously supposed by Bajwa et al. in 2002.[59]

From 2003 to 2008 different Lewis acid systems such as $Cu(OTf)_2$, $B(C_6F_5)_3$, $FeCl_3$, and $InCl_3$ were employed by Hung and co-workers,[61] Chandrasekhar et al.,[62] Oriyama and co-workers,[63] and Xu, Lai et al.[64] as efficient catalysts for etherification reactions of silyl-activated alcohols (entries 10–14). In these contributions, mainly Et_3SiH (entries 10, 12, and 13)[61,63] but also the hydrosiloxane PMHS (entry 11)[62] were employed as reducing agents, and trimethylsilyl (TMS)[61–63] or *tert*-butyldimethylsilyl (TBS)[63b] were used as alcohol surrogates. Triethoxysilane could be employed as both silyl activated alcohol and reducing agent (entry 14).[64]

Later on, Argouarch et al. reported in 2012 a dicarbonyl pentamethylcyclopentadienyl iron complex as active photocatalyst for obtaining unsymmetrical ethers through reductive etherification of dialkoxymethylsilanes (used either as reductor and silylated alcohol) and aldehydes (entry 15).[65] Following the trend of iron-based catalysts, the group of Leino developed in 2015 a general protocol for reductive coupling of TMS–alcohol

Table 1. Catalytic reductive etherification of silyl-protected alcohols (also known as alkoxysilanes or alkylsilyl ethers) with aldehydes or ketones as alkyl source.



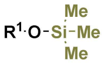
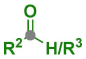
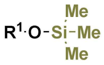
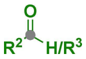
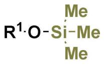
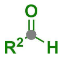
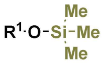
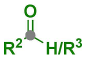
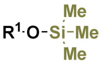
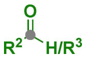
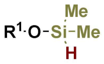
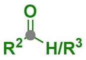
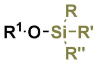
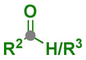
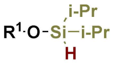
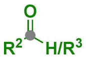
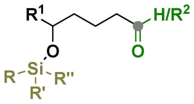
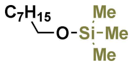
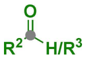
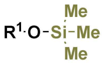
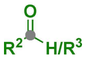
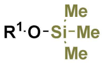
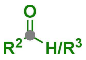
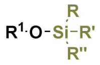
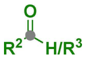
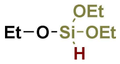
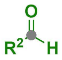
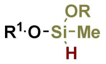
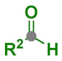
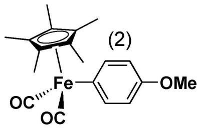
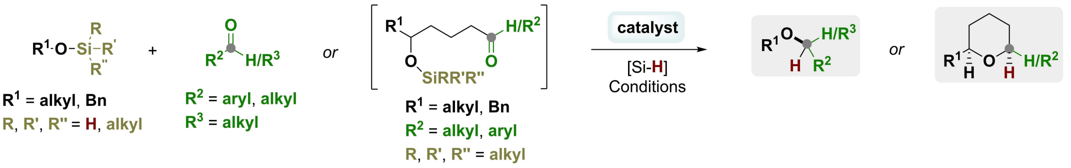
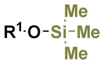
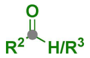
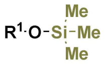
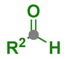
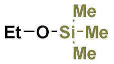
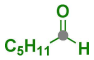
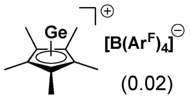
Entry[a]	Alkoxysilane	Alkyl source	Catalyst (mol %)	Si–H (equiv.)	Reaction Conditions	Scope	Ref.
1	 $\mathrm{R^1{-}O{-}Si(Me)_3}$ R¹ = 1°, 2°-alkyl, Bn		Ph_3CClO_4 (5)	Et_3SiH (1)	DCM, 0 °C, 10 min	9 ex.	[54]
2[b]	 $\mathrm{R^1{-}O{-}Si(Me)_3}$ R¹ = 1°, 2°-alkyl		TMS–I (5)	Me_3SiH (1.1)	DCM, 0 °C, 10 min	12 ex.	[55a]
3[b]	 $\mathrm{R^1{-}O{-}Si(Me)_3}$ R¹ = 3°-alkyl		TMS–I (5)	Me_3SiH (1.25)	DCM, −78 °C to RT, 5–6 h	12 ex.	[55b]
4	 $\mathrm{R^1{-}O{-}Si(Me)_3}$ R¹ = 1°, 2°, 3°-alkyl, Bn		TMS–OTf (10)	Et_3SiH (1.2)	DCM, −78 to 0 °C, 12 h	22 ex.	[56]
5	 $\mathrm{R^1{-}O{-}Si(Me)_3}$ R¹ = 1°-alkyl, Bn		$BiBr_3$ (1–3)	Et_3SiH (1)	MeCN, RT, 5 min–20 h	10 ex.	[57]
6[c]	 $\mathrm{R^1{-}O{-}SiH(Me)_2}$ R¹ = 1°, 2°-alkyl, Bn		TMS–I (5–20)	$(OR^1)SiH(Me)_2$ (1.1–1.2)	DCM, 0 °C to RT, 2–36 h	20 ex.	[58]
7	 $\mathrm{R^1{-}O{-}SiRR'R''}$ R¹ = 1°, 2°-alkyl R, R', R'' = alkyl, Ph		$BiBr_3$ (6.7)	Et_3SiH (1.5)	MeCN, RT, 10–30 min	7 ex.	[59]
8[c]	 $\mathrm{R^1{-}O{-}SiH(\text{i-Pr})_2}$ R¹ = 1°, 2°-alkyl		$BiBr_3$ (7.7) +Cl(*i*-Pr)$_2$SiH (10)	$(OR^1)SiH(\text{i-Pr})_2$ (0.8)	MeCN, RT, 10 min	9 ex.	[60]
9	 R¹ = 1°-alkyl, Bn R, R', R'' = alkyl		$BiBr_3$ (5–20)	Et_3SiH (1.2–2)	MeCN, RT	13 ex.	[39d-f]
10			$Cu(OTf)_2$ (0.5–10)	Et_3SiH (1.1)	DCM, RT to reflux, 2–24 h	11 ex.	[61]
11	 $\mathrm{R^1{-}O{-}Si(Me)_3}$ R¹ = 1°, 2°-alkyl, Bn		$B(C_6F_5)_3$ (1)	PMHS (2)	DCM, RT, 5 h	17 ex.	[62]
12	 $\mathrm{R^1{-}O{-}Si(Me)_3}$ R¹ = 1°, 2°, 3°-alkyl, Bn		$FeCl_3$ (5)	Et_3SiH (1.2)	$MeNO_2$, −20 °C to RT, 10 min–4 h	22 ex.	[63a]
13	 $\mathrm{R^1{-}O{-}SiRR'R''}$ R¹ = 1°, 2°, 3°-alkyl R, R', R'' = alkyl, Ph		$FeCl_3$ (5)	Et_3SiH (1.2–2.4)	$MeNO_2$ or MeCN, −20 °C to RT, 10 min–4 h	24 ex.	[63b]
14[c]	 $\mathrm{Et{-}O{-}SiH(OEt)_2}$	 R² = aryl	$InCl_3$ (10)	$(EtO)_3SiH$ (1.5)	TMS–Cl (1.5 equiv.), DCM, RT, 3 h	5 ex.	[64]
15[c]	 $\mathrm{R^1{-}O{-}SiH(OR)Me}$ R¹ = Me, Et R = R¹		 (2)	$(MeO)_2MeSiH$ or $(EtO)_2MeSiH$ (1.5)	DCM, hν, 4 h	14 ex.	[65]

Table 1. continued



Entry[a]	Alkoxysilane	Alkyl source	Catalyst (mol %)	Si–H (equiv.)	Reaction Conditions	Scope	Ref.
16	 R^1 = 1°, 2°-alkyl, Bn		$Fe_3O(AcO)_6$ or $FeCl_3$ (2) + TMS–Cl (4)	Et_3SiH (1.05)	AcOEt, RT, 0.5–1 h	18 ex.	[66]
17	 R^1 = 2°-alkyl, glycosyl homoglycosyl	 R^2 = aryl	TMS–OTf (10–20)	PMHS (0.25–0.5)	DCM, −70 to −30 °C	16 ex.	[67]
18			 (0.02)	Et_3SiH (1)	CD_2Cl_2, RT	1 ex.	[68]

[a] In entries 1, 2, 11, 16, and 18, Si-alcohol and carbonyl substrate are added equally. In entries 3, 8, 12, 14, and 17 the limiting reagent is the alkoxysilane while for entries 5–7, 10, 13, and 15 the limiting reagent is the carbonyl source. In entry 4, for aldehydes alkoxysilane is the limiting reagent while for ketones it is the carbonyl compound. In all cases, the amount of Si–H reductor is referred to the limiting reagent. [b] TMS–I catalyst is generated in situ from powered iodine and hexamethyldisilane. [c] Alkoxysilane also acts as the reducing agent. TMS = trimethylsilyl. PMHS = polymethylhydrosiloxane. TBAF = tetra-*n*-butylammonium fluoride. $Ar^F = C_6F_5$.

derivatives with aldehydes/ketones employing iron(III) oxoacetate or chloride, in combination with TMS–Cl, as catalyst system (entry 16).[66]

Finally, two examples of this reductive transformation were presented last year. On the one hand, Mong and co-workers designed a general procedure for the reductive etherification of different trimethylsilyl-protected glycosides or polyols with benzaldehyde or 2-naphthylaldehyde using PMHS as hydride source and TMS–OTf as catalyst (entry 17).[67] By applying this methodology sequentially, several TMS-protected substrates prepared by alcohol silylation without isolation[53c] can be converted to the corresponding benzyl and naphthylmethyl ethers avoiding common transilylation side reactions.[67] On the other hand, Fritz-Langhals et al. synthesized a novel cationic germanium complex $[Cp^*Ge]B(Ar^F)_4$ able to catalyze the reductive coupling between ethoxytrimethylsilyl and hexanal in the presence of triethylsilane as reductor (entry 18).[68]

Apart from inter- and intramolecular reductive etherifications between alcohols or surrogates and carbonyl compounds, reductive self-coupling of aldehydes/ketones into symmetrical ethers has been also explored (Scheme 6). In fact, this reaction has been performed with some of the previously described catalysts for the related reductive transformations (see Schemes 3 and 5 and Table 1). Doyle et al. reported in 1974 an original non-catalytic example affording symmetrical ethers through carbonyl compounds reduction with Et_3SiH in trifluoroacetic acid media.[69] In 1976, subsequent attempts employing 33–50 mol% of $BF_3{\cdot}Et_2O$ as Lewis acid were also described by the same group.[70] After such early contributions, a significant number of mostly homogeneous catalysts have been reported for this reaction (Scheme 6). Since the work of Mukaiyama and co-workers in 1985 using trityl perchlorate as catalyst in combination with Et_3SiH to form symmetrical ethers from aldehydes (Scheme 6A),[54] different Lewis/Brønsted acid catalyst systems were proven to be effective in this etherification process (Scheme 6B–L). Thereby, TMS–OTf,[55a] $BiBr_3$, $BiCl_3$, $M(OTf)_3$ (with M = Sc, Bi, Ga, or Al), I_2, $InBr_3$, HOTf, $Cu(OTf)_2$, $Cu(OTf)_2$, $Zn(OTf)_2$, $In(OTf)_3$, and $Fe_3O(AcO)_8$ or $FeCl_3$ in combination with TMS–Cl were independently reported from 1986 to 2015 by the groups of Palomo,[71] Komatsu,[57] Wada,[44] Laali,[72] Yadav,[73] Sakai,[74] Roth,[46] Chen and Lemaire,[75] Mineno,[76] and Leino[66] as active catalysts for this reaction. In most of the cases, both aldehydes and ketones worked well under the reaction conditions affording symmetrical ethers in good to excellent yields. Because of the high chemoselectivity offered by Si–H reductors, aromatic moieties were successfully tolerated.

Interestingly, in 2016 Hudnall and co-workers presented the synthesis of a novel stibonium triflate salt and its successful application as a Lewis acid catalyst for the reductive coupling of a broad range of aromatic/aliphatic aldehydes with Et_3SiH as reductor (Scheme 6M).[77] Spectroscopic and computational studies revealed that the interaction between a highly Lewis acidic antimony(V) center and the Lewis basic oxygen from the aldehyde is key to polarize the C=O bond.

A year later, Lohr, Marks and co-workers described the only heterogeneously catalyzed example for this reaction (Scheme 6N).[78] In this contribution, a carbon-supported dioxomolybdenum (Mo/C) material in combination with Me_2PhSiH as the reducing agent was able to perform reductive coupling of several aldehydes/ketones, including aromatic examples, into symmetrical ethers.

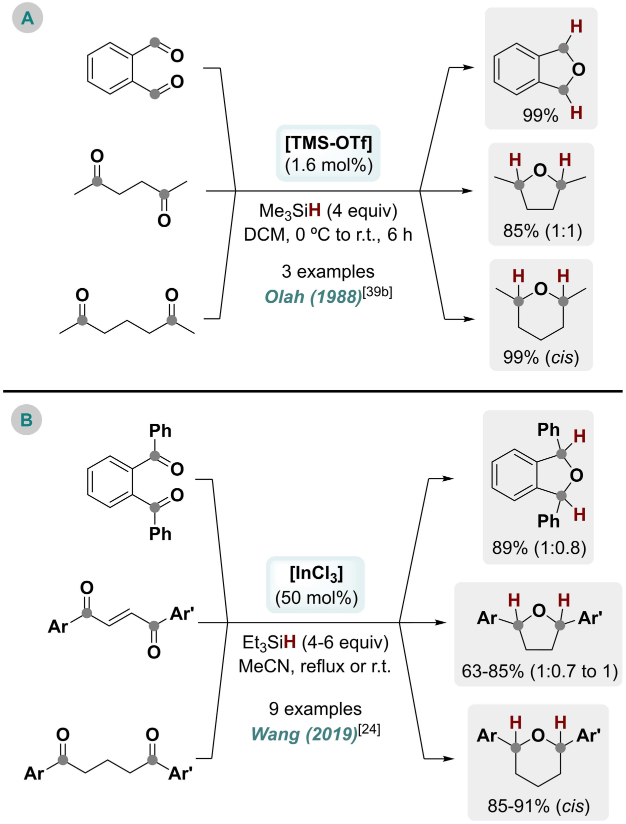
Between 2017–2020, three additional systems were presented as efficient catalysts for promoting carbonyl compounds reductive homocoupling. First, Albrecht et al. studied a meso-ionic carbene iridium complex bearing a triazolylidene-pyridyl ligand, as catalyst for symmetrical ether production from aromatic aldehydes/ketones (Scheme 6O, see also Scheme 3).[47] Using diphenylsilane as hydride source and 0.1 mol% of the Ir-complex, different dibenzyl ethers could be accessed at room temperature. In 2019, Cantat and co-workers published that a uranyl(VI) triflate [$UO_2(OTf)_2$] catalyst in combination with Et_3SiH as reductor was effective to form a wide range of symmetrical ethers from aldehydes at 20 °C (Scheme 6P).[79] This contribution clearly evidences that highly oxidized species, such as uranyl (VI), are stable and fully compatible with the presence of reducing agents. Indeed, during aldehyde group reduction the integrity of the U=O bond is not compromised.

Finally, last year Fritz-Langhals et al. synthesized novel cationic Si^{II} and Ge^{II} compounds and successfully applied them as catalysts in oxidative coupling of silanes to siloxanes and simultaneous reductive self-etherification of aldehydes/ketones to afford ethers (Scheme 6Q).[68]

Interestingly, reductive etherification using dicarbonylic compounds to afford O-heterocycles is also known. To date, there are two reported contributions in the literature of this specific transformation. In 1988, Olah and co-workers showed that catalytic amounts of TMS–OTf in combination with trimethylsilane, efficiently promote the production of O-based heterocycles from the corresponding dicarbonyls (Scheme 7A).[39b] While a total lack of stereoselectivity was observed for the formation of a five-membered ring, cyclization of 2,6-heptadione generated the desired *cis*-heterocycle quantitatively. Similar results were reported in 2019 by Wang et al. by employing $InCl_3$ as catalyst and triethylsilane as reducing agent (Scheme 7B).[24] In this case, reductive cyclization of 1,2-dibenzoylbenzene produced 1,3-dihydrobenzofuran with 89% yield and 1:0.8 *trans*/*cis* molar ratio. Several 2,6-diaryl-substituted tetrahydrofurans were synthesized from α,β-unsaturated ketocarbonyls in moderate to good yields (63–85%) with rather negligible stereoselectivity. By contrast, 1,5-dicarbonyl substrates afforded the desired 2,6-diaryl-substituted tetrahydropyrans with total *cis* stereoselectivity.[24]

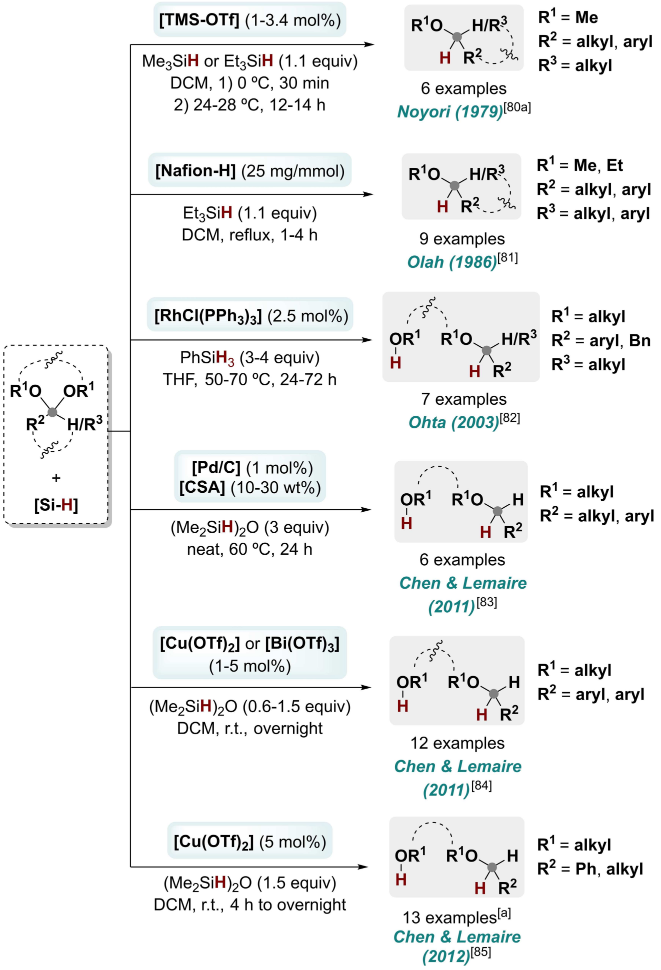
2.1.1. Acetal/ketal-to-ether reduction using Si–H reagents

It is known that acetals/ketals are key intermediates in the reductive etherification between alcohols and aldehydes/ketones (see Scheme 2). Hence, several examples performing acetal/ketal-to-ether[37] catalytic reduction have been reported in the literature using homogeneous and heterogeneous catalysis (Scheme 8). Originally, in 1979 Noyori and co-workers developed a TMS–OTf-catalyzed method for the hydrogenolysis of acetals/ketals in the presence of hydrosilanes.[80] Later on, Olah et al. described that Nafion-H and triethylsilane efficiently promote the reductive cleavage of acetals/ketals to the desired ethers.[81] Remarkably, in this contribution a one-pot methodology for the reductive conversion of carbonyl compounds into ethers using orthoformates as alcohol surrogates was also developed.



Scheme 7. O-heterocycles from reductive condensation of dicarbonyl compounds catalyzed by (A) TMS–OTf or (B) $InCl_3$. Isolated yields are given. In parentheses is shown the diastereoselectivity ratio (*trans*/*cis*), calculated by ^1H NMR spectroscopy, relative to the hydrogens placed in 2,5- or 2,6-positions.

Following these two seminal examples, in 2003 Ohta et al. presented that the $RhCl(PPh_3)_3$ complex is able to catalyze the reductive cleavage of C–O bond in acetals/ketals to produce ethers (Scheme 8).[82] Some years later, Pd/C in combination with (*R*)-10-camphorsulfonic acid (CSA; 10–30 wt%) as additive were employed by Chen, Lemaire and co-workers to promote the reductive conversion of several acetals into ethers using TMDS as reducing agent.[83] With this method, some glycerol acetal derivatives were reacted, although the selectivity between 1°- and 2°-alkyl ethers was rather low. The same year, also Chen, Lemaire and co-workers presented another methodology employing catalytic amounts of $Cu(OTf)_2$ or $Bi(OTf)_3$ to smoothly convert aromatic/aliphatic acetals into ethers at room temperature.[84] Notably, this system showed high chemoselectivities performing the effective reduction of acetals with hydroxy, nitro, nitrile, or ester groups unaltered (Scheme 8). Finally, in 2012 Chen, Lemaire and co-workers applied the previously reported conditions for the regioselective ring cleavage of hexopyranosyl acetals.[85] Interestingly, depending on the 4,6-*O*-(benzyl/alkyl)idine glycosyl acetal employed, the 4- or 6-regioisomer was obtained as main ether product in each case (Scheme 8).



Scheme 8. Acetal/ketal-to-ether catalytic reductions using silanes. CSA = (*R*)-10-camphorsulfonic acid. [a] Glycosyl acetals are used. Depending on the substrate, 4- or 6-ether regioisomer is detected as the main product.

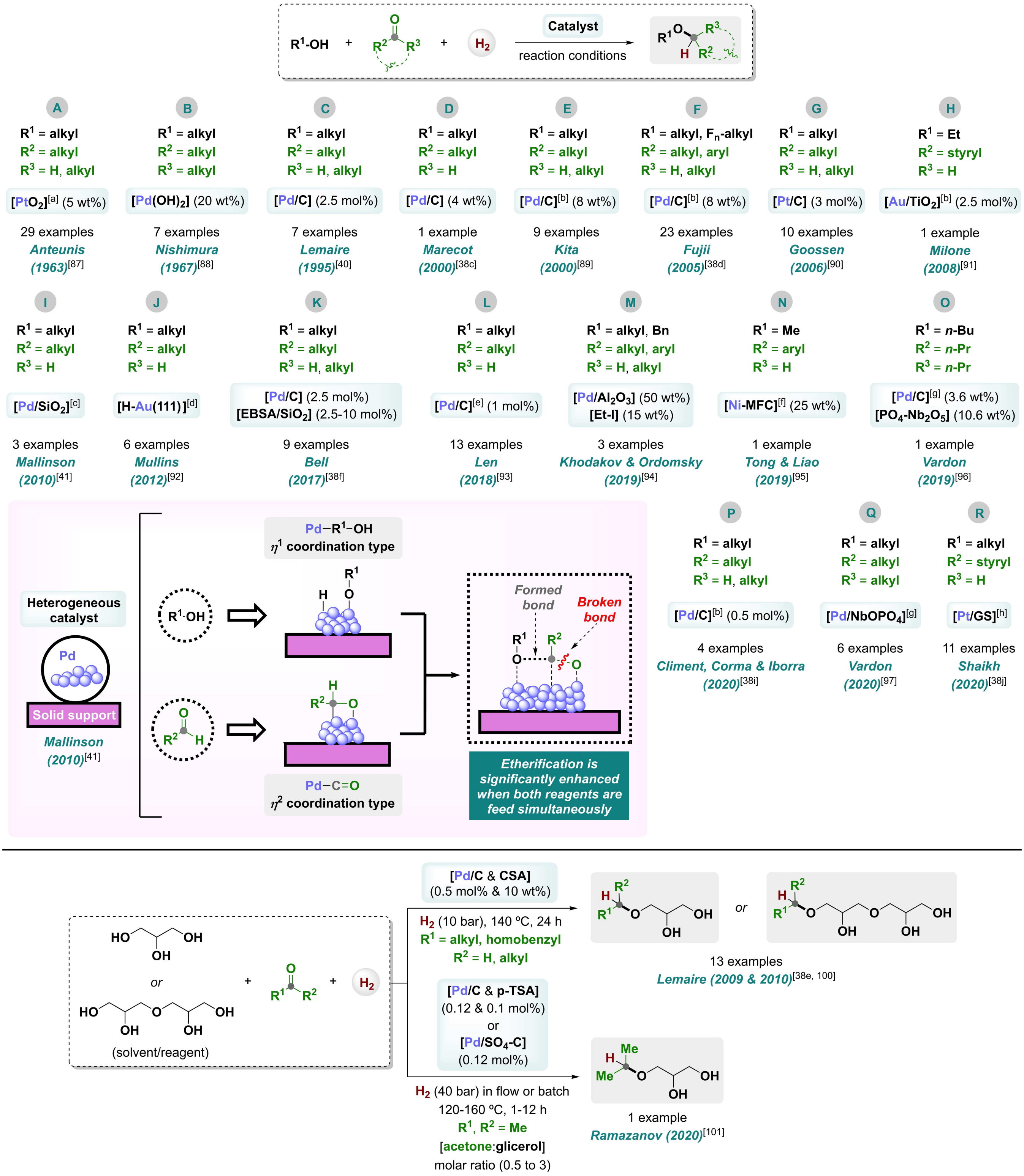
2.2. Using molecular hydrogen as reducing agent

As it has been exposed, Si-based reducing agents present an important synthetic applicability related with its high accessibility, easy handling, low toxicity, and remarkable chemoselectivity.[21a,42,43] However, these reagents present some important disadvantages from a sustainable perspective, as they require tedious work-ups and cause non-negligible waste production. Therefore, the use of molecular hydrogen as benign reductor constitutes a more practical and greener alternative that offers potential applications for large-scale synthesis.[42a,86] Yet, no high levels of (chemo)selectivity are reached generally compared to Si–H reductors. Moreover, it also should be remarked that safety issues need to be always considered when employing hydrogen as reducing agent. However, plenty of either small-scale or industrial solutions exist nowadays for handling this issue with safety guarantees.

Thus, H_2 has been studied as a clean reducing agent in reductive couplings between alcohols and carbonyl compounds, mainly catalyzed by heterogeneous systems, which is an additional advantage from the sustainability point of view, although some homogeneous catalysts have been also described.[1e,g,h] From the heterogeneous field, in 1963 Anteunis and co-workers described the first example of a reductive etherification between alcohols and carbonyl compounds employing H_2 (Scheme 9A).[87] In this work, authors make use of Adam's catalyst PtO_2 to perform the reductive coupling of aliphatic carbonyl substrates using the alcohol as solvent, at RT and 1 bar of H_2. Unfortunately, strong acidic conditions were required for acetalization steps. Four years later, the group of Nishimura reported the $Pd(OH)_2$-catalyzed synthesis of ethers from cyclohexanones and a large-excess of alcohol (Scheme 9B).[88]

After these former contributions, in 1995 Lemaire and co-workers developed a Pd/C-catalyzed protocol for the synthesis of asymmetric ethers from aliphatic alcohols and aldehydes/ketones (Scheme 9C).[38b,40] Here, the employment of either the alcohol or the carbonyl source as solvent helps hemiacetal formation, suggested to be a key step. Unfortunately, the protocol was no selective towards aromatic ring hydrogenation. Closely related with this work, in 2000 Marecot and co-workers carried out further mechanistic studies on butyl octyl ether production from octanal and butanol using a Pd/C system in which the charcoal support has been treated with nitric acid (Scheme 9D).[38c] The acidic treatment was required for promoting the acid-catalyzed acetal formation. The authors proved that the Pd nanomaterial is responsible for acetalization, enol ether formation, and subsequent hydrogenation into the ether. Interestingly, the lower reactivity observed for an aldehyde with no α-H (i.e., pivaldehyde) is explained by its impossibility of forming the enol ether.[38c] Later, contributions from Kita, Fuji and co-workers reported a H_2-bubbling methodology for the synthesis of ethers from aliphatic 1°/2° alcohols and aldehydes/ketones with Pd/C (Scheme 9E,F).[38d,89] Remarkably, only 2-fold excess of the carbonyl partner is needed and water removal accelerates the etherification process. In the second of these works, the protocol was applied for accessing to highly valuable alkyl fluoroalkyl ethers for the first time and one example of an alkyl aryl ether was obtained in poor yields.[38d] Similarly to the study of Marecot and co-workers, authors concluded that acidic- or even neutral-type Pd/C catalyst is effective to promote either acetalization, enol ether formation, if possible, and hydrogenation, or direct hydrogenolysis of hemiacetal/acetal intermediates.

In 2006, a Pt/C-catalyzed reductive etherification protocol was published by the group of Goossen affording symmetrical/asymmetrical dialkyl ethers in good to excellent isolated yields (73–92%, Scheme 9G).[90] Either 1°/2° alcohols were coupled with aldehydes/ketones by using a small excess of the alcohol (2–4 equiv. vs. carbonyl reagent) at 50 °C and 1 bar of H_2. Once again, the presence of aromatic groups was not compatible with the reductive process. Two years later, Milone et al. showed that Au/TiO_2 promotes the synthesis of cinnamyl ethyl ether from cinnamaldehyde hydrogenation in flow and in the presence of ethanol (Scheme 9H).[91] The acidity of TiO_2 matrix and pre-reduction of the supported gold catalyst at 200 °C, improved the selectivity to the desired allyl ether.



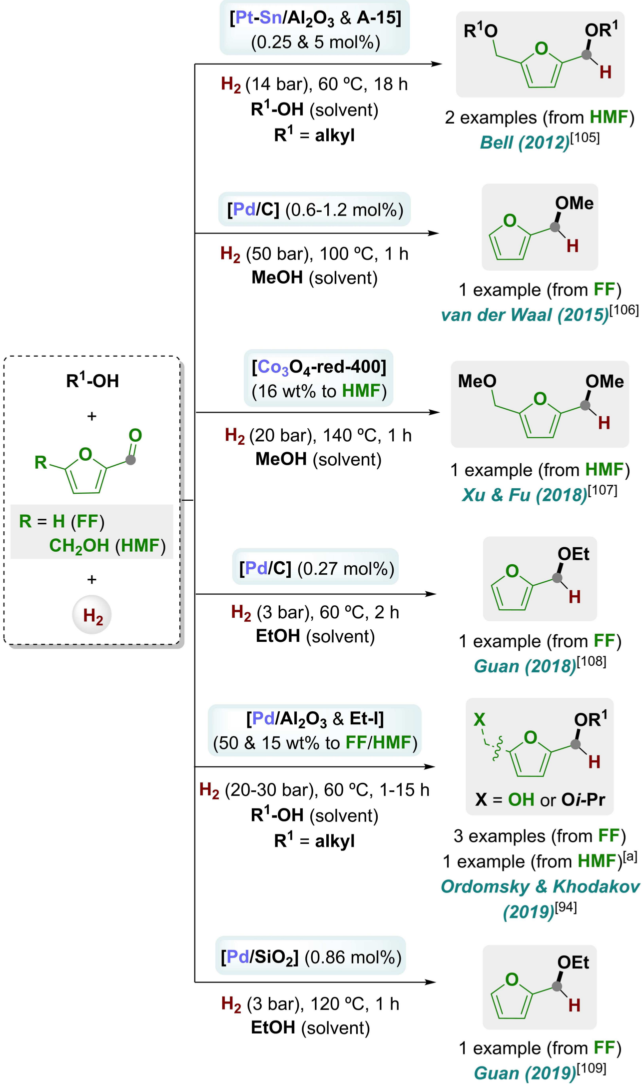
Scheme 9. Heterogeneously catalyzed reductive etherification of alcohols (top) or glicerol/di-glycerol (bottom) using aldehydes/ketones and H_2. [a] Reactions were performed in HCl (2.5 M) media. In all cases, amounts of catalyst expressed as mol% or wt% are referred to the limiting reagent (normally the carbonyl compound). [b] Reactions were performed in a batch reactor under a H_2 bubbling. [c] Catalytic experiments were performed under continuous H_2 flow and using a liquid feed of reactants with a W/F ($g_{cat}\,g^{-1}{}_{feed}\,h^{-1}$) values from 0.25 to 2 h. [d] H adatom-covered Au(111) single-crystal sample was employed as catalyst. Self-etherification of aldehydes into symmetrical ethers was also carried out. [e] Reactions were performed in a continuous-flow system with a H_2 flow of 0.6 mL min^{-1}. [f] Ni-MFC catalyst was obtained after N_2-pyrolysis of a 2D Ni-based MOF at 500 °C. [g] Experiments under continuous H_2 flow and using a liquid feed composed by equimolar amounts of both reagents were also carried out with the same catalyst system. [h] In Pt/GS catalyst, GS is a green cellulosic support obtained from the jute plant (*Corchorus genus*) stem. EBSA = 4-ethylbenzesulfonic acid. *p*-TSA = *p*-toluenesulfonic acid.

In 2010, Mallinson and co-workers used SiO_2 as a support for stabilizing Pd nanoparticles (NPs) able to promote reductive etherifications between aliphatic alcohols and aldehydes under continuous H_2-flow (Scheme 9I).[41] Remarkably, improved levels of efficiency were reached if the alcohol and aldehyde were fed simultaneously at equimolar ratios, as the simultaneous co-adsorption of η^1-coordinated alkoxide and η^2-adsorbed aldehyde are required to achieve optimum rates of ether formation. Moreover, etherification process is highly sensitive to metal NPs morphology.[41] After, Mullins and co-workers studied the tunable reductive coupling of alcohols with aldehydes, as well as the self-etherification of aldehydes, on H adatom-covered Au(111) crystals at low temperatures (Scheme 9J).[92]

From 2017 to 2019, several groups independently described several Pd-based methodologies for reductive etherification. In 2017, Bell and co-workers used Pd/C in combination with silica-supported 4-ethylbenzesulfonic acid (EBSA)/SiO_2, for the production of ethers with fuel lubricant properties via alcohol reductive etherifications with carbonyl compounds from biomass origin (Scheme 9K).[38f] Next, Len and co-workers reported in 2018 a Pd/C-catalyzed continuous flow process for the general reductive etherification of several bio-based alcohols and aldehydes into symmetrical/asymmetrical dialkyl ethers (Scheme 9L).[93] Finally, in 2019 a Pd–I bifunctional catalyst was developed by Khodakov, Ordomsky and co-workers for the mild and aromatic ring tolerant reductive etherification (Scheme 9M, see also Scheme 10).[94] In this work, the authors defined that heterolytic dissociation of H_2 can occur on the surface of alumina-supported Pd NPs modified with iodine species. This process in-situ generates Brønsted acid sites that are fully responsible of the etherification.

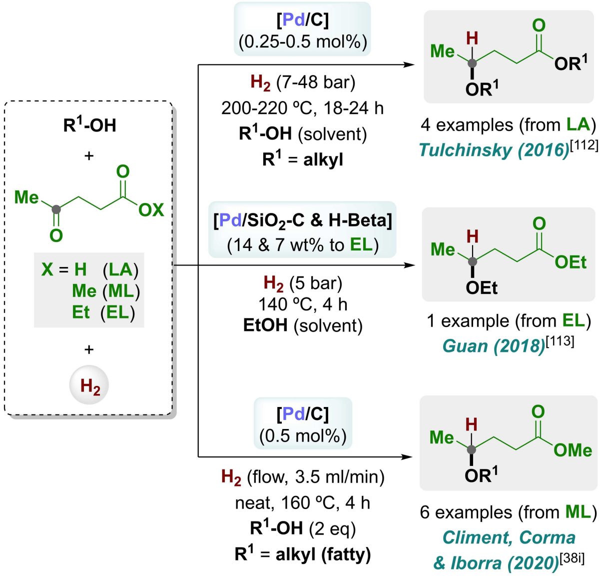
Apart from Pt, Pd, and Au based catalysts, also nickel was recently disclosed as an active metal for promoting reductive etherifications. Tong, Liao et al. developed a Ni-based material, designed as Ni-MFC, for the selective production of 2-methoxy-4-(methoxymethyl)phenol from vanillin and MeOH (Scheme 9N).[95] In this work, optimum Ni catalyst was fabricated from N_2-pyrolysis of a 2D Ni-MOF ($[Ni(tia)(H_2O)_2]_\infty$) [tia^{2-} = 5-(*1H*-1,2,3-triazol-1-yl) isophthalate] at 500 °C.

During 2019 and 2020, four additional contributions in the area of heterogeneous hydrogenative etherifications were described (Scheme 9O–R). First, Vardon and co-workers developed a catalytic process for synthesizing of 4-butoxyheptane (4-BH) through the reductive etherification of 1-butanol and 4-heptanone in equimolecular amounts, both in batch and continuous flow (Scheme 9O).[96] In this work, they employed a Pd/C material in combination with an acid solid such as phosphated niobic acid (PO_4-Nb_2O_5), as catalytic system showing improved thermal stability, excellent regenerability, and 4-BH productivity at 190 °C. Interestingly, the authors determined, through a fuel-property-first approach, that 4-BH is a biomass-derived advantaged oxygenate diesel blendstock, meeting with essential diesel fuel properties and health/safety requirements.[96] In the following year, Climent, Corma, Iborra and co-workers developed an additive-free Pd/C-mediated reductive etherification, under H_2 bubbling in a batch reactor, for the production of biolubricants using building blocks from biomass (Scheme 9P, see also Scheme 11).[38i] By employing only 0.5 mol% of Pd catalyst at 160 °C, several aliphatic ketones and aldehydes were reductively coupled with two equivalents of octanol.



Scheme 10. Furfuryl alkyl ethers from heterogeneously catalyzed hydrogenative etherifications between HMF or FF and aliphatic alcohols. A-15 = Amberlyst-15. [a] Concomitant formation of 5-(isopropoxymethyl) furfuryl alcohol and 2,5-bis(isopropoxymethyl)furan (X=OH or O*i*-Pr) was observed.

Closely related with their previous achievements, in 2020 Vardon and co-workers carried out the design of a single-phase Pd nanocatalyst for diesel bioblendstocks production (Scheme 9Q).[97] More specifically, a novel niobium phosphate-supported Pd material (Pd/$NbOPO_4$) was outlined as an effective catalyst either for batch and flow solvent-free production of branched dialkyl ethers (C_7–C_{15}) through hydrogenative etherification at 190 °C. Interestingly, the Pd/$NbOPO_4$ system outperformed the results obtained for 4-BH synthesis when compared with Pd/PO_4-Nb_2O_5 analogue.[97] Finally, a contribution from Shaikh et al. showcased the synthesis of a "dip-



Scheme 11. Alkyl 4-alkoxypentanoates from Pd-catalyzed hydrogenative etherifications between levulinic acid (LA), methyl or ethyl levulinate (ML, EL), and alcohols.

catalyst" bearing Pt NPs stabilized on a green cellulose-based matrix (Pt/GS) and its application for the selective synthesis of cinnamylalkyl ethers via reductive etherification (Scheme 9R).[38j] Remarkably, aromatic and alkene functionalities in cinnamaldehyde were fully tolerated with this system.

Glycerol is a common by-product in soap manufacture and fatty acid/ester production from vegetable oils.[98] In the last years, the growing interest in the production of biodiesel in EU and US has caused a remarkable increase in the access to glycerol. Hence, an impressive number of glycerol applications, as an additive, as a raw material or for the production of energy, have been already presented. In addition, obtaining high-value-added chemicals from glycerol is a desired goal.[1e,99] In this context, a few number of catalytic protocols for the *O*-alkylation of glycerol with carbonyl compounds and H_2 have been reported in the literature (Scheme 9, bottom).[1e]

From 2009 to 2010, Lemaire and co-workers presented that [Pd/C] in combination with a Brønsted acid (CSA) as additive, constitutes a suitable catalyst system for the synthesis of 1-*O*-alkyl glycerol or diglycerol monoethers using aldehydes/ketones and the polyol as a solvent/reagent.[38e,100] In addition to the work by Lemaire and co-workers, last year Maksimov et al. developed a protocol for the catalytic synthesis of glycerol monoisopropyl ether through the flow hydrogenation of glycerol/acetone mixtures at 120–160 °C.[101] In this work, either Pd/C in combination with *p*-TSA, or a Pd/SO_4-C bifunctional material, were employed as effective systems for the production of the target compound. Remarkably, the glycerol monoethers (GMEs) obtained in these protocols constitute highly interesting compounds due to its applications in cosmetics, cleaning formulations, pharmacy, and personal care, among others.[1e,99]

The fast depletion of fossil fuels and the climate change consequences derived from its use, make a paradigm shift imperative also in chemical industry. It is required the development of new and sustainable catalytic processes for employing renewable resources,[102] and here, biomass constitutes an excellent alternative to fossil fuels.[27a,c,d,f,h,103] In this context, 5-hydroxymethylfurfural (HMF) and furfural (FF), efficiently produced through an acid-promoted dehydration of biomass lignocellulose fractions, constitute platform molecules that can be converted into valuable chemicals.[1g,h,27a,c,d,f,h,103a,b,104] Among the derivatives accessed from HMF or FF valorization, furfuryl alkyl ethers are considered primary commodities since they can be employed as bio-diesel compounds, pesticides, pharmaceuticals, flavor and aroma components, and others.[1g,h,27a,c,d,f,h,103a,b,104]

In the last decade, furfuryl alkyl ethers, including 5-(methoxymethyl)furfuryl alcohol, 2,5-bis(ethoxymethyl)furan, 2-methoxymethylfuran, 2-ethoxymethylfuran, among others, have been produced from HMF or FF either via hydrogenation/direct etherification sequence or by a reductive etherification. When comparing both strategies, the one-pot reductive etherification strategy is considered as the most direct and elegant approach.[1g,h,104]

Thus, in the last years several protocols have been developed for the synthesis of furfuryl alkyl ethers from HMF or FF and alcohols through this one-pot reductive strategy (Scheme 10). In 2012, Bell and co-workers described the first example for the direct production of 2,5-bis(alkoxymethyl)furans through reductive etherification between alcohols and HMF.[105] In this work, alumina-supported Pt_1Sn_1 alloy together with the acidic resin A-15 is presented as the most effective catalyst combination. Besides, a sequential dehydration/reductive etherification of D-(−)-fructose to produce 2,5-bis(alkoxymethyl)furans in reasonable yields was performed, showing the great potential of the methodology (Scheme 10).[105] Following this seminal example, van der Waal et al. screened a series of commercially available metal heterogeneous catalysts for the synthesis of furfuryl methyl ether (FME) via reductive etherification of furfural.[106] In particular, Pd/C was proved to be the most competitive system among all the samples tested.

In 2018, Xu, Fu and co-workers presented a non-noble metal based nanocatalyst (Co_3O_4 reduced at 400 °C) for making 2,5-bis(methoxymethyl)furan from HMF under relatively mild conditions (Scheme 10).[107] Similar to the report by Bell and co-workers, here the authors also designed a two-step method for the preparation of the targeted ether directly from fructose. The same year, a Pd/C-based synthesis of furfuryl ethyl ether via reductive etherification of FF in ethanol was reported by Wang et al.[108] Additionally, SiO_2- or TiO_2-supported Pd NPs systems were studied too, but in all cases, worse catalytic results were afforded. Detailed kinetic investigations pointed to the acetal 2-(diethoxymethyl)furan as the key intermediate, which undergoes hydrogenolysis into furfuryl ethyl ether.[108]

In 2019, two more Pd-catalyzed strategies for the synthesis of furfuryl alkyl ethers were reported (Scheme 10). In the first of them, Ordomsky, Khodakov and co-workers undertook a superficial modification of Pd/Al_2O_3 catalyst by treatment with small amounts of Et–I (Scheme 10, see also Scheme 9M).[94] The novel designed bifunctional heterogeneous Pd–I catalyst showed high efficiency in HMF and FF reductive etherifications using excess of aliphatic alcohols at mild conditions. Finally, Guan and co-workers presented the Pd/SiO_2-catalyzed reductive etherification between furfural and ethanol to give furfuryl ethyl ether.[109] Here, the absence of sodium cations in the Pd material is key for avoiding furan ring hydrogenation and driving selectivity to the reductive etherification process (Scheme 10).

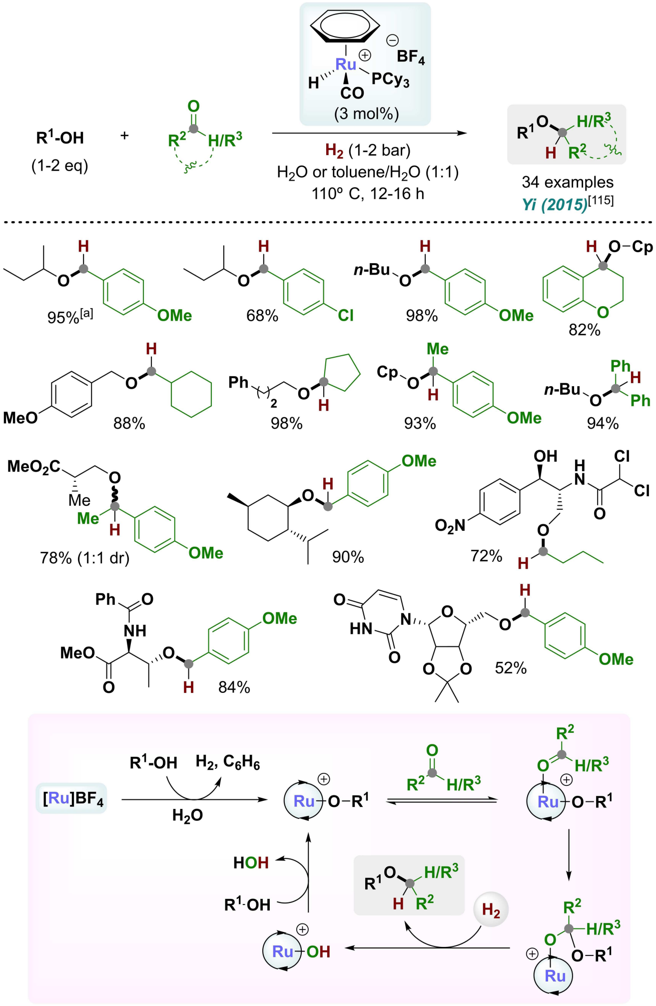
Levulinic acid (LA) is a world-wide demanded platform chemical (>2000 Tm per year) obtained from HMF (see above), and, hence, produced from the acid hydrolysis of lignocellulosic biomass.[27a,c,d,f,h,103,110] The high interest in the valorization of this compound is explained by its chemical versatility, as it presents two functionalizable groups: a carbonyl and a carboxylic acid group.[27a,c,d,f,h,103] In this section of the Review, transformations implying LA or alkyl levulinate derivatives (ML and EL) that entail the reductive functionalization of the carbonyl group will be discussed.[103c] On the other hand, processes involving the reaction of both functional groups to afford 2-methyltetrahydrofuran in one pot will be discussed in Section 3.

Reductive etherification processes between LA or its esters (ML or EL) and alcohols directly generate 4-alkoxypentanoates, compounds with potential applications as renewable solvents, fuel additives, and surfactant precursors.[111] In Scheme 11 are displayed the three catalytic methodologies, all involving Pd-heterogeneous catalysis, reported for this transformation up to date.

In 2016, the group of Tulchinsky reported the first example of alkyl 4-alkoxypentanoates synthesis via Pd/C-catalyzed simultaneous esterification/reductive etherification of LA.[112] The reaction was performed with alcohols in excess at high temperatures (200–220 °C) obtaining four different etherified esters in moderate to good yields (54–77 %). Two years later, Guan and co-workers showed that a combination of a silica-modified carbon-supported palladium nanocatalyst (Pd/SiO_2-C) and H-BETA zeolite as acidic co-catalyst efficiently catalyzes the synthesis of ethyl-4-ethoxypentanoate (in 93 % yield) from EL and ethanol as solvent.[113] Finally, last year Climent, Corma, Iborra and co-workers described an elegant strategy for the reductive etherification of ML and several fatty alcohols.[38i] In this protocol, selectivities to alkyl 4-alkoxypentanoates up to >99 % were obtained employing Pd NPs supported on a slightly acidic activated carbon as catalyst, atmospheric H_2-flow, 160 °C, and just 2-fold excess of the fatty alcohol.

As it has been shown, efficient reductive etherification methods with carbonyl compounds and alcohols using hydrogen as reducing agent have been widely developed employing heterogeneous catalysts (see Schemes 9–11). Most of these systems present the large advantage of being reusable catalysts. However, a limitation of many of them is encountered when aromatic compounds are reacted, due to the great tendency of nanostructured metal-based systems to reduce aromatic fragments. By contrast, there are only a few examples of homogeneous catalysts for the same transformation totally compatible with aromatic moieties.

As an early example, Fleming and Bolker demonstrated in 1976 that reductions of benzaldehyde-alcohol mixtures with $Co_2(CO)_8$ as catalyst using high pressures of syngas (CO/H_2, >160 bar), yielded ethers as main products with no aromatic ring reduction.[38a] Indeed, some years before, Wender et al. had observed dibenzyl ether formation in the reduction of benzaldehyde using syngas and cobalt-carbonyl complexes.[114] After these earlier observations, two homogeneous general protocols for this reaction have been more recently reported. In 2015, the group of Yi described a novel well-defined cationic $[(C_6H_6)(PCy_3)(CO)RuH]BF_4$ complex as a highly active and chemoselective catalyst [turnover number (TON) = 32000 and turnover frequency (TOF) = 7600 h^{-1} under neat conditions] for the reductive condensation of alcohols with aliphatic/aromatic aldehydes/ketones into unsymmetrical ethers using water as solvent (Scheme 12).[115] Employing this strategy, a wide range of complex substituted ether compounds could be obtained in moderate to excellent isolated yields (52–98 %). Additionally, the synthetic versatility of the protocol was further demonstrated by the etherification of several biologically active alcohols with high structural complexity (Scheme 12). Regard-



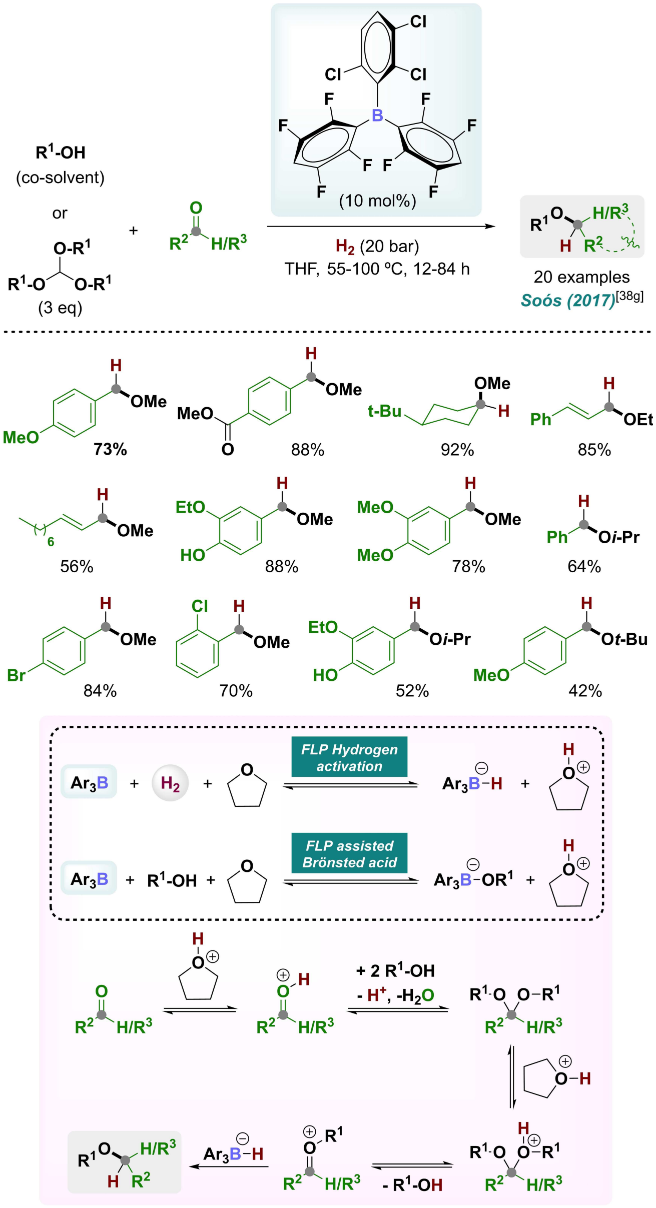
Scheme 12. Ru-catalyzed reductive etherification of alcohols with aldehydes/ketones and H_2 for the synthesis of unsymmetrical ethers. Isolated yields are given. Cp = cyclopentyl. [a] TON = 32000 and TOF = 7600 h^{-1} were reached using alcohol as the solvent.

ing the mechanism, the authors suggest an initial formation of a cationic Ru-alkoxy species, followed by a nucleophilic addition of the alkoxy fragment to the carbonyl source to give a hemiacetoxy intermediate (Ru-acetal species). Finally, this intermediate reacts with H_2 to afford the ether and the cationic complex.[115]

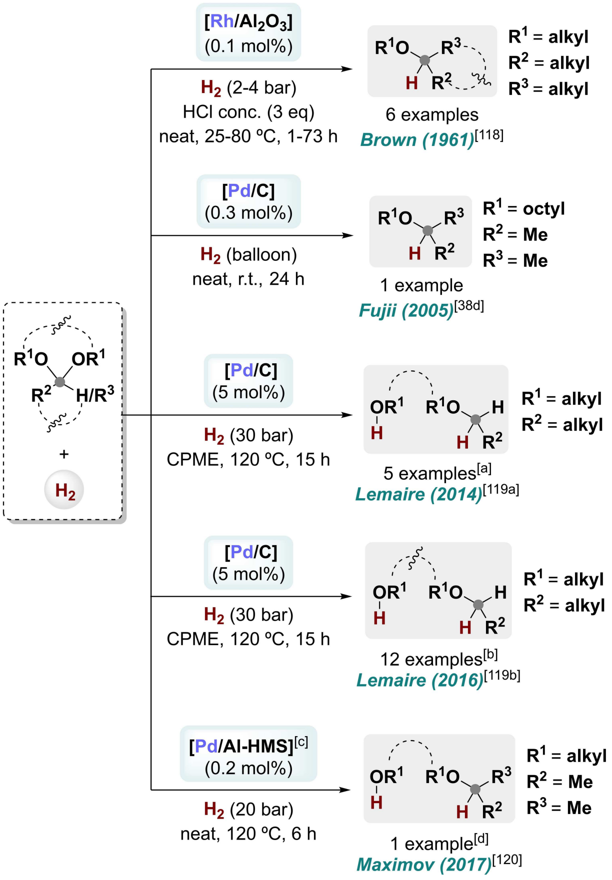
Two years later, an elegant protocol for the frustrated Lewis pair (FLP)-catalyzed reductive etherification of alcohols or orthoformiates with aldehydes/ketones to afford asymmetrical ethers was delineated by Soós and co-workers (Scheme 13, see also Scheme 15A).[38g] Notably, small amounts of the borane catalyst (10 mol%), without the requirement of additional acids, are able to promote acetalization/acetal hydrogenation sequence under relatively mild conditions (55–100 °C and 20 bar H_2). Different aliphatic alcohols or orthoformiates were reductively coupled with both aromatic and aliphatic aldehydes, or aliphatic ketones, affording ethers in up to 88 % yield with good tolerance to reducible groups such as halogens, stryril, or carboxyester groups.[38g] Even common vanillin ether motifs, industrially accessed by multi-step processes, could be obtained in remarkable yields by this FLP protocol. In this case, authors propose that a joint action of the Lewis acid (borane) and a soft O-based Lewis base (i. e., THF solvent) in the presence of H_2 and R^1–OH generate a strong Brønsted acid species able to promote acetalization and related processes, as well as a borohydride. Finally, the borohydride reduces the oxocarbenium cation, affording the ether derivative (Scheme 13).[38g]

2.2.1. Acetal/ketal-to-ether reduction using molecular hydrogen

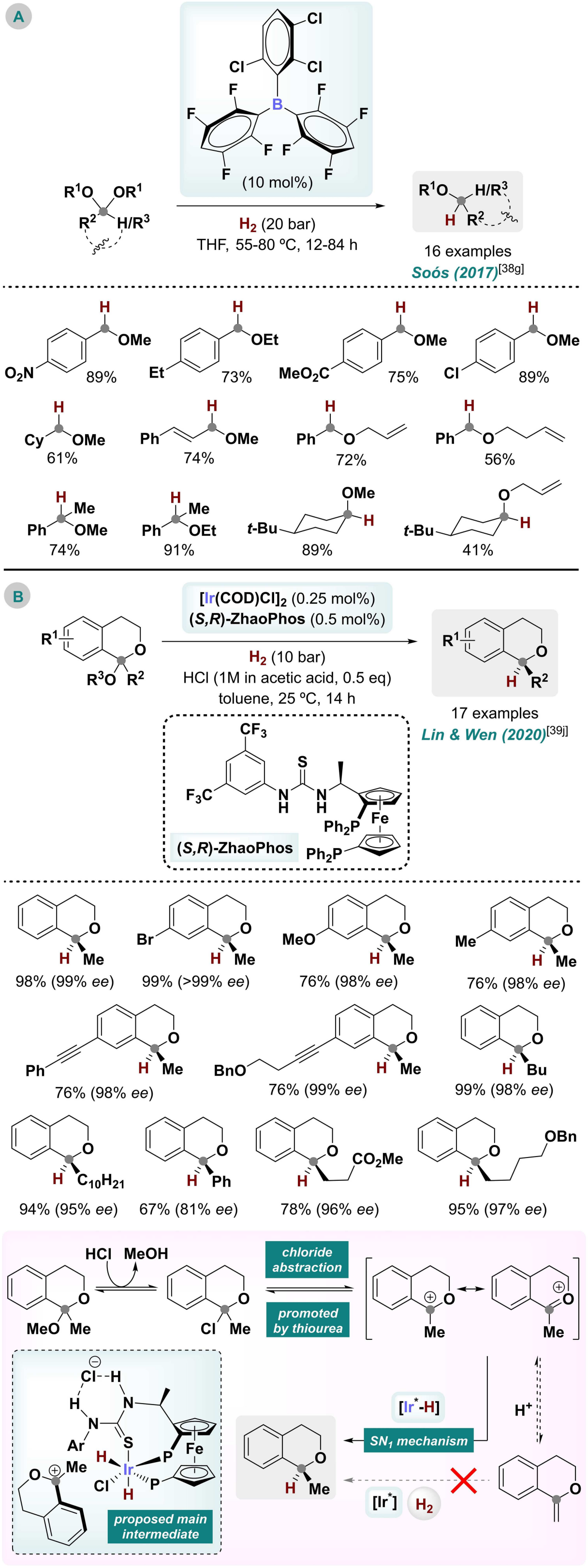
Molecular hydrogen has also been employed for performing catalytic acetal/ketal-to-ether[37] reductions either with heterogeneous and homogeneous systems (Schemes 14 and 15).



Scheme 13. Hydrogenative etherification of alcohols/orthoformates with aldehydes/ketones catalyzed by an FLP. ^1H NMR yields are given.



Scheme 14. Heterogeneous acetal/ketal-to-ether hydrogenations. [a] Alkyl glucoside-4,6-*O*-acetals are exclusively used affording a mixture of 4- and 6-alkyl-regioisomers in a (1 : 2.5-3) molar ratio. [b] A mixture of five- and six-membered pentylidene sorbitan acetals were exclusively used affording mixtures of sorbitan 3-, 5-, and 6-*O*-ether regioisomers in a different molar ratio. [c] Al-HMS = Al-containing hexagonal mesoporous silica with a molar ratio (SiO_2/Al_2O_3 = 19.7). [d] This work was focused on solketal hydrogenolysis into glycerol isopropyl ether.



Scheme 15. (A) FLP-catalyzed acetal/ketal-to-ether reduction. ^1H NMR yields are given. (B) Enantioselective formation of chiral isochromans from acetals via asymmetric Ir-catalyzed hydrogenation. Isolated yields are given. COD = 1,5-cyclooctadiene.

Originally, the group of Sigmund noted in the 1920s that acetals are converted into ethers using Ni/SiO_2 catalyst.[116] Several decades later, Gorin described a methodology for the hydrogenolysis of carbohydrate cyclic ketals using copper chromite as catalyst.[117] However, both protocols demanded very harsh conditions to proceed. In 1961, Howard and Brown developed the first catalytic method for ketal-to-ether hydrogenolysis effective under mild reaction conditions (25–80 °C, 2–4 bar H_2) (Scheme 14).[118] Using Rh/Al_2O_3 and strong acid conditions, different aliphatic ethers could be obtained from the hydrogenation of its corresponding ketals. Later on, Fujii et al. (2005)[38d] and Lemaire and co-workers (2014 and 2016)[119] independently described some catalytic strategies for the hydrogenolysis of acetal/ketal derivatives to ethers. In all cases, Pd/C without acid additives, was employed as the most suitable system (Scheme 14). By applying those strategies, Lemaire described the reduction of pure alkyl glucoside-4,6-*O*-acetals into mixtures of 4- and 6-alkyl-regioisomer glucoside ethers[119a] or the reduction of pentylidene sorbitan acetal mixtures into 3-, 5-, and 6-*O*-ether regioisomer combinations.[119b] Finally, in 2017 Maximov and co-workers developed a Pd/Al-HMS bifunctional nanomaterial able to perform direct solketal hydrogenolysis for producing glycerol alkyl ethers (Scheme 14).[120] Related to this contribution, in 2020 they also showed that Pd/C in combination with *p*-TSA or Pd/SO_4-C alone (see Scheme 9, bottom) are active for the same transformation.[101]

A smaller number of examples for acetal/ketal-to-ether hydrogenation have been reported at the homogeneous side. As an early example, in 1976, Fleming and Bolker described that $Co_2(CO)_8$ catalyzes ether production from aromatic acetals by using syngas under harsh conditions.[38a] Apart from this, in 2017 Soós and co-workers developed the first metal-free strategy for the hydrogenative cleavage of acetal/ketals into ethers by using an FLP as catalyst (Scheme 15A, see also Scheme 13).[38g] In this work, authors demonstrated how a boron molecular catalyst is capable to perform the hydrogenolysis, likely via oxocarbenium cation, of a wide range of aromatic/aliphatic acetals (including some ketals), under mild conditions with a broad substrate scope and high tolerance towards several reducible functionalities (nitro, halogens, non-activated olefins, and esters) (Scheme 15A). In addition, no side reactions occurred in the reductive cleavage of allyl/homoallyl acetals what makes the authors suggest that FLP-reduction of acetal/ketals seems to be synchronous "S_N2-like".[38g]

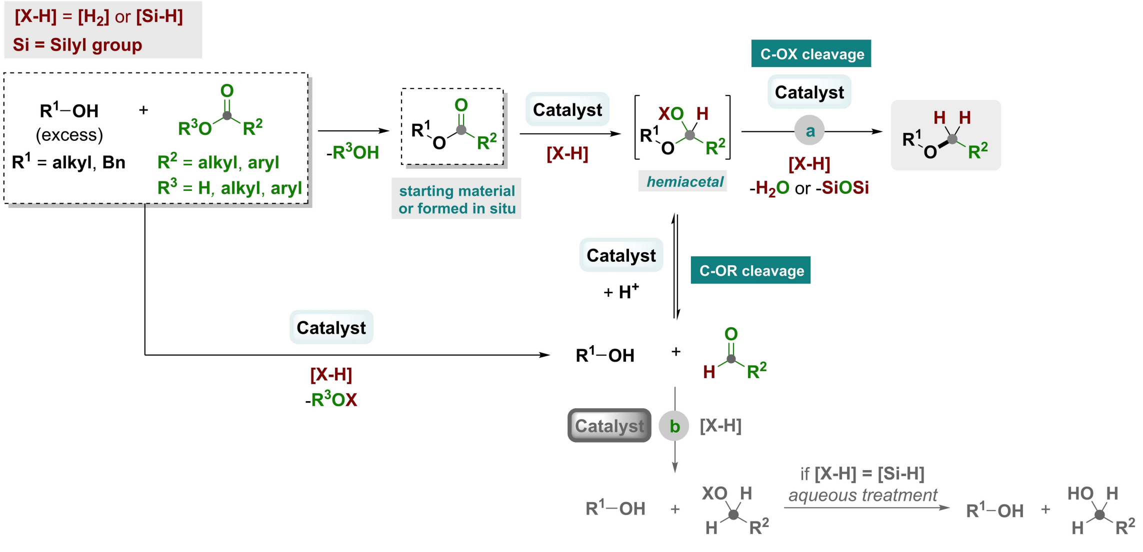
Finally, Lin, Wen and co-workers described last year a very interesting acid-mediated strategy for the enantioselective hydrogenation of ketals into chiral isochromans via ionic reduction of the in-situ formed oxocarbenium ions (Scheme 15B).[39j] $[Ir(COD)Cl]_2$ complex in combination with a bifunctional thiourea-based chiral diphosphine [(*S*,*R*)-ZhaoPhos] was employed as highly efficient catalyst (TON up to 8600). Using this system at 25 °C and H_2 (10 bar), and in the presence of HCl (0.5 equiv.), a wide range of 1-substituted chiral isochromans could be obtained from acetals with good to excellent isolated yields (67–99 %) and enantioselectivities (*ee* up to 99 %) with high tolerance to other reducible groups such as internal alkyne, halogen or ester.[39j] In terms of mechanism, the isochroman acetal is first converted into the corresponding α-chloroether that subsequently undergoes chloride abstraction, affording a reactive oxocarbenium cation. The formation of this cationic species is promoted by anion-binding interaction between the thiourea group and the substrate.[39i,48] Finally, the asymmetric hydrogenation of the in-situ generated oxocarbenium ion produces the chiral isochroman with excellent yield and enantioselectivity. Interestingly, isotope-labeling experiments with deuterated solvents demonstrated a fast equilibrium between the oxocarbenium ion and the enol ether intermediate, suggesting a "S_N1-like" hydrogenation mechanism (Scheme 15B).[39j]

3. Reductive Etherification of Alcohols with Carboxylic Acid Derivatives

As an alternative to carbonyl compounds, carboxylic acid derivatives have been also used as alkyl partners in reductive *O*-alkylation of alcohols (Scheme 1F).[1e,g] This kind of alkylating agents are highly desirable due to their large availability (in some cases they are biomass-derived feedstocks) and great stability. However, it is their high stability what makes the activation of these compounds a great challenge.[23,26,29] Hence, the number of examples in which carboxylic acid derivatives are used as alkylating agents in reductive etherification of alcohols is still scarce, in comparison with aldehydes/ketones.[1e,g] The increased stability of carboxylic acid derivatives is explained by the fact that they are compounds in a high oxidation state, presenting a carbonyl function less electrophilic than the one of carbonyl compounds. For carboxylic acids or esters, commonly employed in these reactions, the electron donor effect of –OH/–OR groups cause the inactivation of the carbonyl function towards the typical hydride attack required in these processes.[23,26,29]

Furthermore, in this part of the Review the examples of ester-to-ether reduction will be also discussed, considering the intimate relationship of this reaction with the reductive etherification using carboxylic acid derivatives as alkylating partners (Scheme 1a).[26,29b]

In Scheme 16 is depicted the reaction mechanism proposed for both of these reactions. Here, the ester is either the starting material, in the case of ester-to-ether reduction,[121] or the first formed intermediate, when employing carboxylic acid derivatives as alkylating agents.[121d,122] In the latter case, the esterification between the alcohol, normally in excess, and the carboxylic acid derivative affords the ester. In both kinds of transformations, there is a first reduction of the ester to a hemiacetal intermediate.[121,122] Analogously to the mechanism proposed in Scheme 2 for carbonyl compounds as alkylating agents, the hemiacetal can afford the desired ether through a second reduction, by either direct hydrogenolysis or via oxocarbenium cation and/or enol ether intermediates (Scheme 16a).[121,122] This pathway is commonly designed in carboxylic acid derivatives chemistry as a C–OX cleavage pathway, in clear contrast with a C–OR cleavage pathway in which the hemiacetal is in equilibrium with an aldehyde plus an alcohol.[23,26,29,121f] In addition, the same aldehyde/alcohol mixture of products can be formed by the direct reduction of the carboxylic acid derivative employed as alkylating agent. If the aldehyde reduction occurs (Scheme 16b, grey), it would mean the formation of a mixture of alcohols, considered, in the context of a reductive etherification, secondary undesired products. Obviously, in the case of employing an excess of R^1–OH, C–OX cleavage pathway can be favored, avoiding selectivity problems.[121d,122b–d] Hence, ester-to-ether reduction can entail more selectivity issues considering that the alcohol is



Scheme 16. Pathway a: General accepted mechanism for the catalytic reductive etherification of alcohols with carboxylic acid derivatives or ester-to-ether reduction in the presence of an external reductor (i.e., Si–H reagents or H_2), implying a C–OX cleavage. Pathway b: Mixture of alcohols formation, via C–OR cleavage, as possible secondary products in the reductive etherification with carboxylic acid derivatives or ester-to-ether reduction.

present in equimolecular amounts to the aldehyde. In addition, it must be considered the possibility that the alcohol mixture (R^1–OH and R^2–CH_2OH) undergoes direct etherification to afford the desired ether, generally in the presence of acid catalysis.[121d,122d]

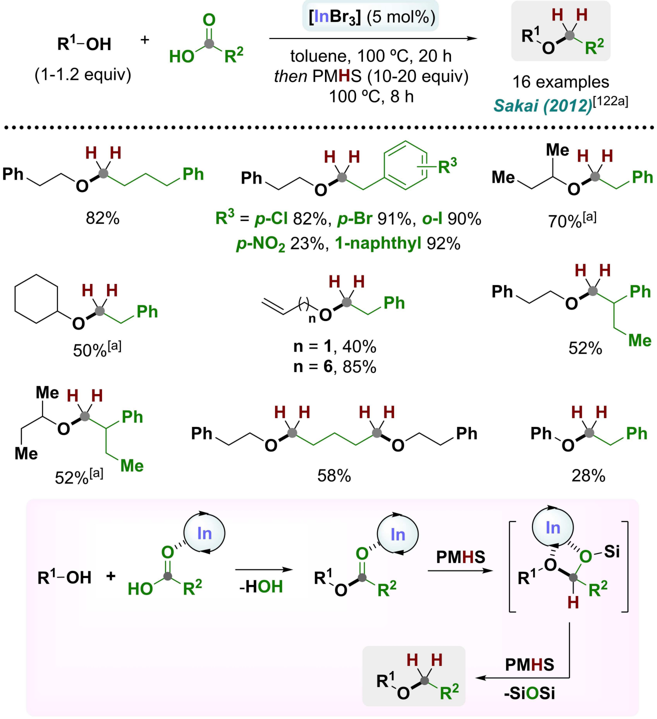
As it has been commented, the first hydride attack to the ester to afford the hemiacetal intermediate is the most challenging step in this transformation.[26,29] The recent design of more powerful reduction catalyst systems employing suitable strategies to activate these unactivated substrates has caused lately a considerable development in these specific transformations.[26,29] In this part of the Review we will comment these advances referred to the use of either Si–H compounds or H_2 as reducing agents.

3.1. Using Si–H compounds as reducing agent

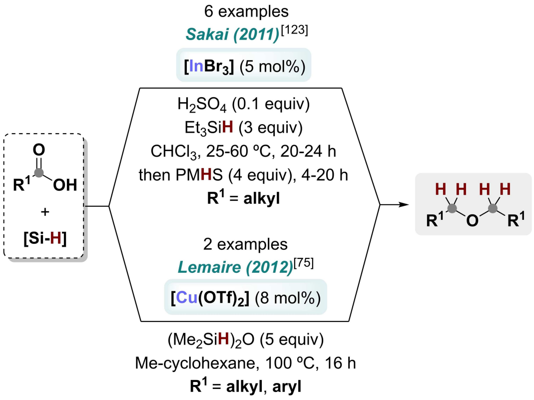
Similarly to reductive etherification protocols with carbonyl compounds, hydrosilanes/hydrosiloxanes[42] have been also employed as convenient reducing agents in the case of using carboxylic acid derivatives as alkyl sources or ester-to-ether reduction.[26,29b] In comparison with molecular hydrogen,[26a,29a,c,d,g,h] these hydride sources present certain affinity to promote the C–OX cleavage pathway, enabling the selective synthesis of ethers.[26,29b] Obviously, from the point of view of sustainability Si–H reagents present as drawback the large generation of by-products. Furthermore, there are only examples of homogeneous catalysts, more difficult to reuse than heterogeneous, employing these reducing agents, which certainly is another negative feature from the sustainability perspective. However, due to its large selectivity, Si–H compounds can be considered practical solutions for small-scale reactions.

Up to date, there is only one example of catalytic reductive etherification of alcohols with carboxylic acid derivatives using Si–H reagents.[122a] In 2012 Sakai et al. developed a widely applicable, one-pot esterification-deoxygenation protocol for the reductive *O*-alkylation of alcohols with carboxylic acids, using $InBr_3$ as a Lewis acid catalyst and PMHS as reducing agent (Scheme 17).[122a] The principal advantages of this methodology are the employment of alcohol and the carboxylic acid in equal amounts, as well as a large functional group tolerance. However, this protocol requires the use of low-steric-demanding alcohols with high nucleophilicity and does not tolerate benzoic acid type compounds. The authors propose a mechanism in which $InBr_3$ catalyzes the ester formation followed by hydrosilylation and C–OSi bond cleavage to afford the ether.[122a]

Related to this type of transformation, it is important to highlight the reductive self-etherification of carboxylic acid derivatives reported by Sakai et al.[123] and Lemaire and co-workers.[75] In 2011, Sakai et al. reported a protocol to achieve the one-pot conversion of a carboxylic acid into a symmetrical ether (Scheme 18).[123] The procedure consisted in a first treatment of the carboxylic acid with $InBr_3$ and H_2SO_4 as catalysts and Et_3SiH as reducing agent to obtain an ester followed by the addition without isolation of PMHS to obtain the final ether. It was applied to only aliphatic carboxylic acids and afforded ethers in moderate to very good yields (50–86 %).[123] In the following year, Lemaire and co-workers proved that this transformation was not $InBr_3$ specific and reported two more examples of reductive carboxylic acid self-etherification catalyzed by $Cu(OTf)_2$ and using TMDS as reducing agent (Scheme 18).[75] Despite the limited scope of the reaction, it was possible for the first time to use benzoic acid as starting material in this type of transformation and the corresponding ether was obtained with 91 % isolated yield.



Scheme 17. $InBr_3$-catalyzed reductive etherification of alcohols with carboxylic acids and PMHS. Yields of isolated products are given. [a] Using H_2SO_4 (0.1 equiv.).



Scheme 18. Lewis acid-catalyzed reductive self-coupling of carboxylic acids into symmetrical ethers.

Interestingly, Lemaire and co-workers published the same year the intramolecular version of this transformation.[124] In this work the authors could obtain a variety of five- and six-membered O-heterocycles from highly-available 3-substituted glutaric acid or 2-substituted succinic acid derivatives (Scheme 19). Tetrahydropyran (THP) derivatives were obtained in better yields in comparison with tetrahydrofuran (THF) ones. Remarkably, a seven-membered oxepan derivative could be synthesized in good yield.[124]

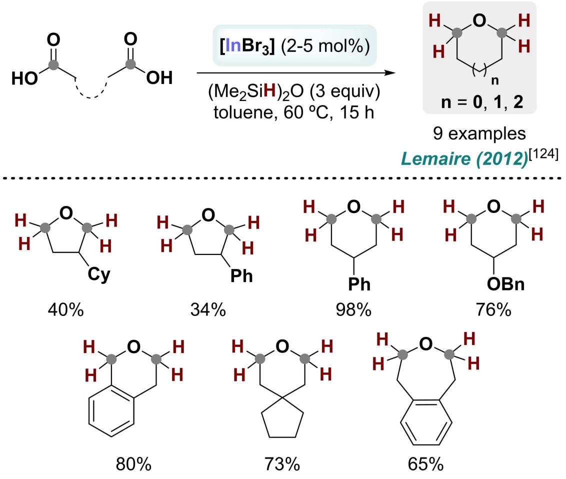
3.1.1. Ester-to-ether reduction using Si–H reagents

Ester-to-ether reduction is a straightforward process for the convenient synthesis of ethers[26,29b] due to the easy preparation and large availability of esters.[27] Indeed, this reaction has been more widely studied and several catalysts have been described as active systems for obtaining ethers from esters using Si–H compounds as reducing agents.[26,29b]

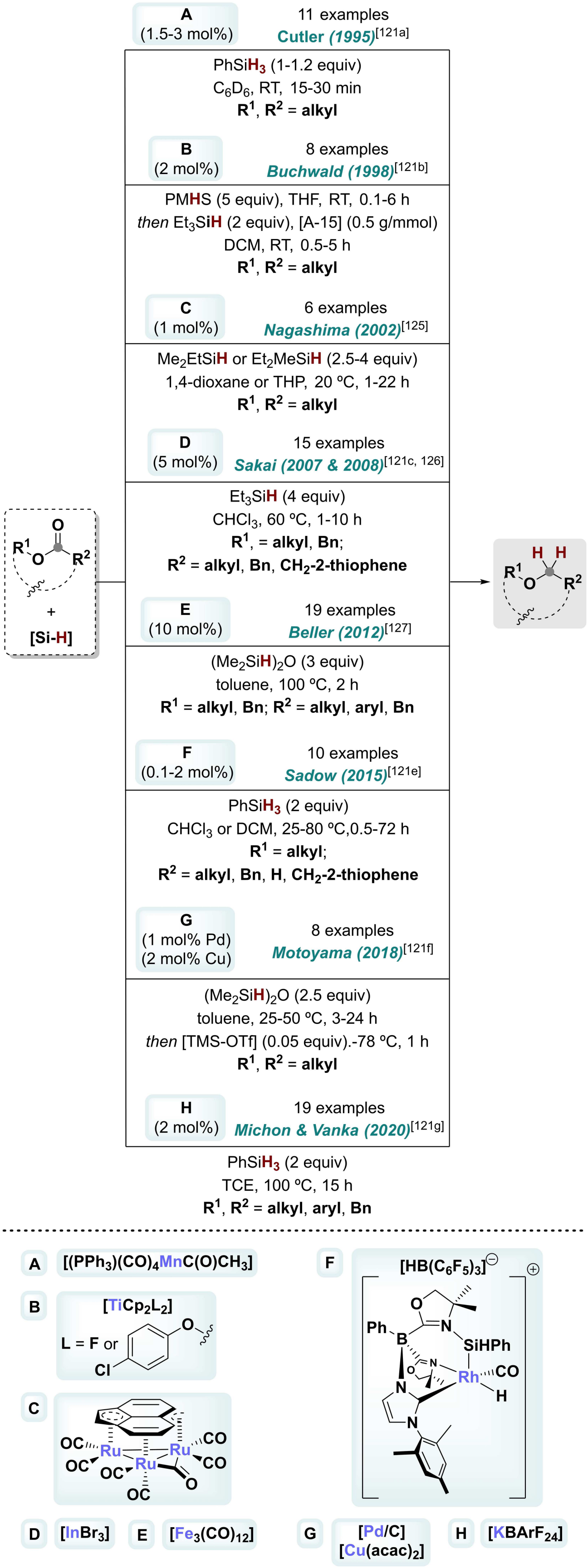
Pioneering work in this area was reported by Cutler and co-workers in 1995.[121a] In this work, the authors are able to reduce esters to ethers in the presence of $PhSiH_3$ and a manganese acetyl complex as homogeneous pre-catalyst, photochemically or thermally activated (Scheme 20A).

In 1998 Buchwald et al. reported the first method for reducing five- and six-membered lactones to ethers (Scheme 20B).[121b] This protocol involved a two-step process in which lactones were first transformed into lactols by treatment with a titanium complex in the presence of PMHS. In a second step, the lactol was converted into the corresponding cyclic ether by treatment with Amberlyst-15 and Et_3SiH.

Nagashima and co-workers studied in 2002 the reduction of esters using an organometallic tri-ruthenium cluster activated with a hydrosilane as catalyst (Scheme 20C).[125] In this work, the authors tried to optimize the reaction conditions to control the C–OSi versus C–OR selectivity in order to obtain the desired ether or alcohol. They determined that the specific combination



Scheme 19. O-heterocycles from intramolecular reductive coupling of dicarboxylic acids. Yields of isolated products are given.



Scheme 20. Ester-to-ether catalytic reductions using Si–H compounds. TCE = 1,1′,2,2′-tetrachloroethane. acac = acetylacetonate. $BArF_{24}$ = tetrakis[(3,5-trifluoromethyl)phenyl]borate.

of Et_2MeSiH as hydrosilane and THP as solvent favors ether selectivity for linear ethers, whereas lactones afforded cyclic ethers with total selectivities employing Me_2EtSiH and 1,4-dioxane conditions.[125]

The first Lewis acid-catalyzed ester-to-ether reduction was reported by Sakai et al. in 2007, using $InBr_3$ as catalyst and Et_3SiH as reducing agent (Scheme 20D).[121c,126] Employing this protocol, the authors obtained 20 ethers, linear and cyclic, with good yields and demonstrated a good functional group tolerance including unsaturated fatty esters. However, this method was limited for benzoic esters or acetates in which the –OAc group is attached to a secondary carbon bonding to a phenyl group or conjugated double bond. Mechanistic studies suggest that the reaction proceeds through radical intermediates.[121c,126]

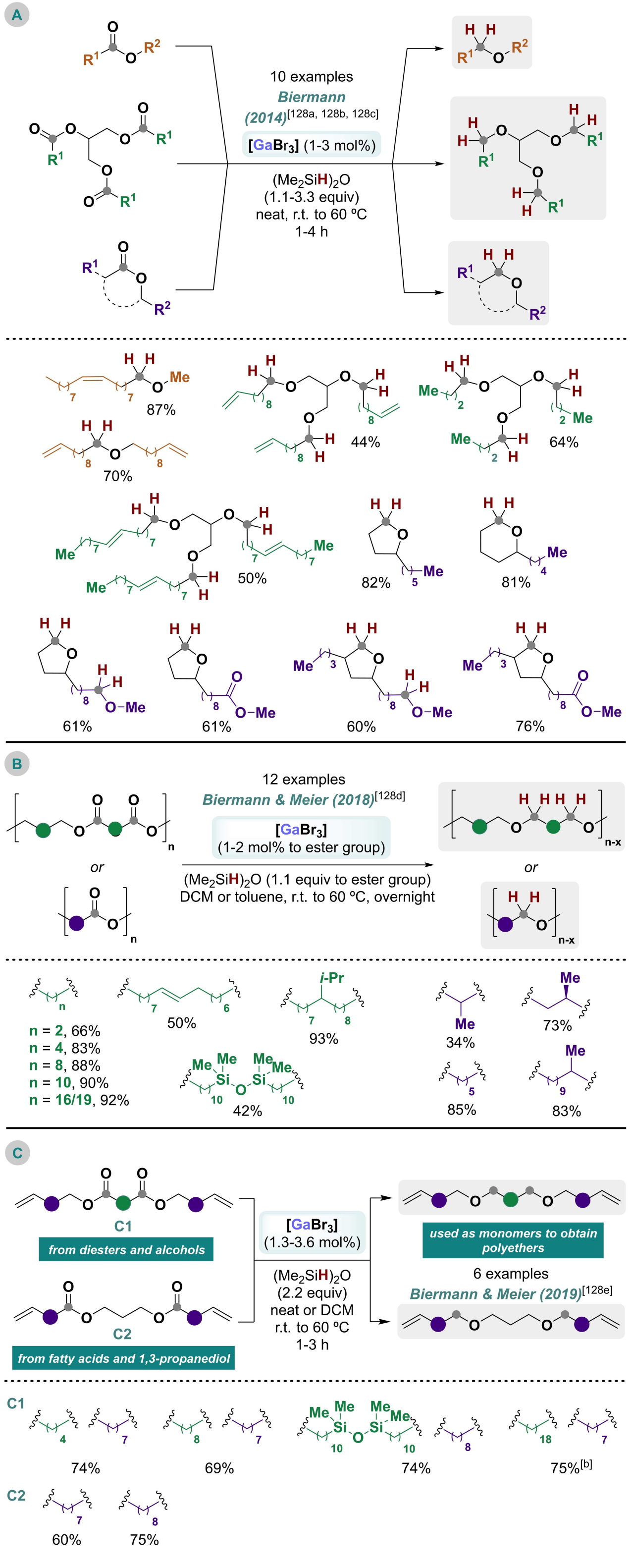
Interestingly, in 2012 Beller and co-workers reported a catalytic system based on an earth-abundant iron complex, $Fe_3(CO)_{12}$, as pre-catalyst and TMDS as hydride source for the ester-to-ether reaction (Scheme 20E).[127] In this work, 16 linear esters and an aryl lactone could be selectively reduced to the corresponding ethers in moderate to excellent yields (50–90 %). The synthetic value of the developed protocol was demonstrated by the reduction of cholesteryl nonanoate, a steroid-derived ester, to the corresponding ether in high yield and showing tolerance towards alkene function.[127]

In 2015, Sadow et al. reported a zwitterionic rhodium silylene complex as an active catalyst for the deoxygenation of esters to ethers in the presence of $PhSiH_3$ (Scheme 20F).[121e] Under optimized conditions, 10 examples, including formate esters, afforded the corresponding ethers with up to 93 % yield.

More recently, in 2018, Motoyama and co-workers showed that a system based on the combination of Pd/C and $Cu(acac)_2$ was able to reduce lactones to silyl acetals employing TMDS as reducing agent (Scheme 20G).[121f] The silyl acetal intermediates were further transformed into the corresponding ethers by the addition of TMS–OTf in catalytic amounts at −78 °C. Applying this strategy, several five-, six-, and seven-membered cyclic ethers were obtained in very good to excellent isolated yields (78–99 %), and one example of open-chain ether was reported.

Last year, Michon, Vanka et al. achieved a metal-free deoxygenation of esters to ethers employing a fluorinated borate catalyst and $PhSiH_3$ as reductor (Scheme 20H).[121g] With this protocol, a wide range of esters were converted into the corresponding ethers, including two benzoate derivatives. Mechanistic investigations revealed the relevant role that non-covalent interactions between the catalyst, hydrosilanes, and ether play in this reaction.[121g]

The large synthetic potential of ester-to-ether reduction was demonstrated in a series of works published by Biermann, Meier and co-workers from 2014 to 2019 (Scheme 21).[128] As it has been previously commented, ester functionality is present in relevant biomass compounds such as triglycerides or fatty esters, main components of oils and fats.[27] Furthermore, polyesters are also highly relevant polymers in chemical industry with many applications as plastics or textiles.[27g,129] Hence, developing new methodologies for obtaining ethers



Scheme 21. $GaBr_3$-catalyzed reductions using TMDS as hydride source: (A) fatty esters, triglycerides, or lactones to the corresponding ether derivatives; (B) polyesters to polyethers; (C) diesters to aliphatic diether monomers. Yields of isolated products are given.

from these abundant raw materials is a topic of interest nowadays.

Biermann et al. explored in 2014 several Lewis acids as catalysts for the reduction of fatty esters, triglycerides and lactones to the corresponding ethers (Scheme 21A).[128c] It was determined that $GaBr_3$ in the presence of TMDS could catalyze very efficiently the selective reduction of esters to ethers at very mild conditions, with good selectivities respect to the alcohol product, and tolerating alkene function. Interestingly, the system demonstrated also selectivity to the reduction of a lactone in the presence of a linear ester.[128c] In addition, the reduction of high oleic sunflower oil[128b] and 10-undecenyl 10-undecenoate, a fatty ester derived from castor oil,[128a] was achieved using the same catalytic system at mild conditions. These processes have high potential to afford glyceryl trialkyl ethers with applications as surfactants or polyether monomers.[1e,99]

Polyethers are important polymers in chemical industry with very interesting properties such as high stability. They are commonly obtained in industry by ring-opening polymerization of epoxides.[11] Hence developing alternative and sustainable methods for acceding these compounds is very interesting, especially if they can be obtained from available polyesters.[27g,129] In 2018, Biermann, Meier and co-workers applied the $GaBr_3$/TMDS system to the reduction of aliphatic polyesters with different chain length to obtain the corresponding polyethers (Scheme 21B).[128d]

In the context of polyether synthesis, another relevant approach consists in introducing the ether moiety in the corresponding monomer by the ester-to-ether reduction, before polymerization step.[27g,129] Biermann, Meier et al. applied this strategy employing their $GaBr_3$/TMDS catalytic reductive protocol to fatty acid-derived ω,ω'-unsaturated diene diesters to obtain the target diethers (Scheme 21C), which later were polymerized.[128e]

3.2. Using molecular hydrogen as reducing agent

As it has been commented previously, hydrogen is the most desirable reducing agent, as it only produces water as by-product and it is highly available and affordable.[42a,86] Hence, this large advantage from the sustainability viewpoint clearly balances the safety cautions that must be considered, especially in an industrial context, when employing this reagent. Thus, in the last years, efforts have been directed to the development of catalytic systems able to perform the ether synthesis via reductive etherification of alcohols with carboxylic acid derivatives and employing hydrogen as reducing agent.[1e,g,h]

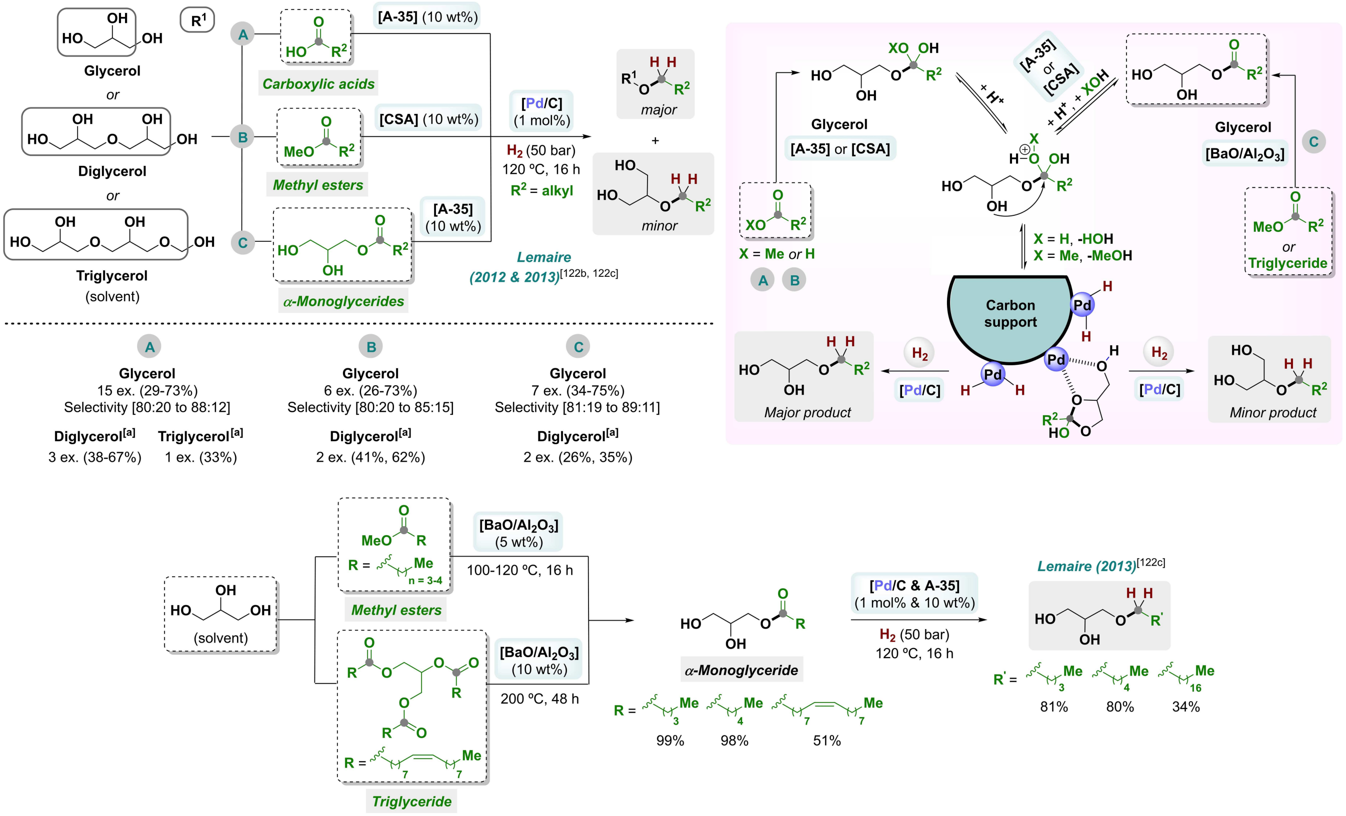
The first example of reductive *O*-alkylation of alcohols with carboxylic acid derivatives using H_2 as reductant was reported by Lemaire and co-workers in 2012 and 2013.[122b,c] They developed a method for obtaining poly(glycerol)monoethers, amphiphilic compounds of high interest as a consequence of their surfactant, antimicrobial, and antitumor properties.[1e,99] In this protocol, a mixture of an acid catalyst (Amberlyst-35 or CSA) to catalyze the esterification or transesterification and Pd/C as hydrogenating system was employed.[122b,c] Thus, 1-*O*-alkyl (di)glycerol ethers and one example of 1-*O*-alkyl triglycerol ether were prepared via the reductive alkylation of glycerol derivatives with carboxylic acids (Scheme 22, top, left, A),[122b] methyl esters (Scheme 22, top, left, B)[122c] and α-monoglycerides (Scheme 22, top, left, C)[122c] with low to high yields and good selectivities towards 1-*O*-alkyl glycerol ether versus 2-*O*-alkyl glycerol ether.

Furthermore, they reported a two-step protocol consisting in a first BaO-Al_2O_3-catalyzed transesterification of methyl valerate, methyl hexanoate, or high-oleic sunflower refined oil with glycerol to obtain the corresponding α-monoglyceride. Without isolation, the α-monoglyceride was subjected to the reductive etherification in the presence of glycerol excess to obtain the corresponding 1-*O*-alkyl glycerol ether (Scheme 22, bottom).[122c]

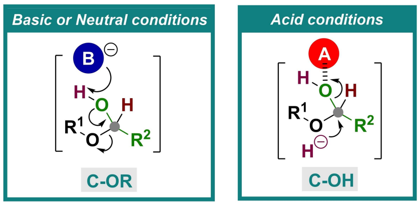
Mechanistic investigations were performed and they revealed that the key intermediate in this reaction is a five-membered cyclic hemi-*ortho* ester (Scheme 22, top, right).[122b,c] Different tests showed that the third OH function in this intermediate is coordinating to Pd and, hence, plays a crucial role favoring the Pd preferential cleavage of the secondary C–O bond over the primary one. This is the determining factor explaining the 1-*O*-alkyl glycerol ether selectivity. With this method, highly abundant carboxylic acid derivatives and alcohols can be used as starting materials for obtaining glycerol monoethers,[122b,c] traditionally synthesized through much more undesirable methods such as Williamson etherification or acid-catalyzed direct etherification.[1e,99]

After the early works by Lemaire and co-workers, focused on the use of glycerol-type alcohols, other more general synthetic methodologies for the reductive etherification using hydrogen have emerged. Most of the early homogeneous catalytic systems developed for the hydrogenation of carboxylic acid derivatives had as requisite performing in basic conditions.[23b,29a,c,d,g,h] Therefore, in these conditions, the hemiacetal intermediate deprotonation is followed by a C–OR cleavage pathway, which finally affords the alcohols mixture (Scheme 16 and 23, left). In the last two decades, several catalytic systems able to hydrogenate carboxylic acid derivatives in acidic conditions have been developed.[23,29a,c,d,g,h,130] In these conditions the C–OX pathway, C–OH in the case of H_2 as reducing agent, can be clearly favored and, hence, these systems are much more suitable for catalyzing reductive etherification (Scheme 23, right).

One of the most studied homogeneous catalytic systems with remarkable activities for hydrogenative transformations of carboxylic acid derivatives in acidic media, is based on ruthenium or cobalt complexes with Triphos ligand (1,1,1-tris(diphenylphosphinomethyl)).[23,29a,c,d,g,h,130] In 2015, Beller and co-workers reported the $Ru(acac)_3$/Triphos/$Al(OTf)_3$ catalytic system for the hydrogenative *O*-alkylation of primary alcohols with benzoic acids/esters or aliphatic acids (Scheme 24).[121d] The protocol was limited to primary alcohols and, in the case of esters, the substituent of the carboxylate group (–OR^1) and the alcohol (R^1OH) in excess should be the same structure.



Scheme 22. Top, left: Pd/C-catalyzed reductive etherification of glycerol-type alcohols with (A) carboxylic acids, (B) methyl esters, and (C) α-monoglycerides. Bottom: BaO/Al_2O_3-catalyzed transesterification of methyl esters or triglycerides with glycerol to afford α-monoglycerides, followed by Pd/C-catalyzed hydrogenation to the corresponding 1-*O*-alkylglycerol ether derivative. Top, right: reaction mechanism. Yields of isolated products are given. Selectivity between 1-*O*- and 2-*O*-alkylglycerol ethers determined by ^{1}H NMR spectroscopy is given in parentheses. [a] When diglycerol or triglycerol were used, the selectivity between 1-*O*- and 2-*O*-alkyl(poly)glycerol monoethers could not be determined. A-35 = Amberlyst-35.

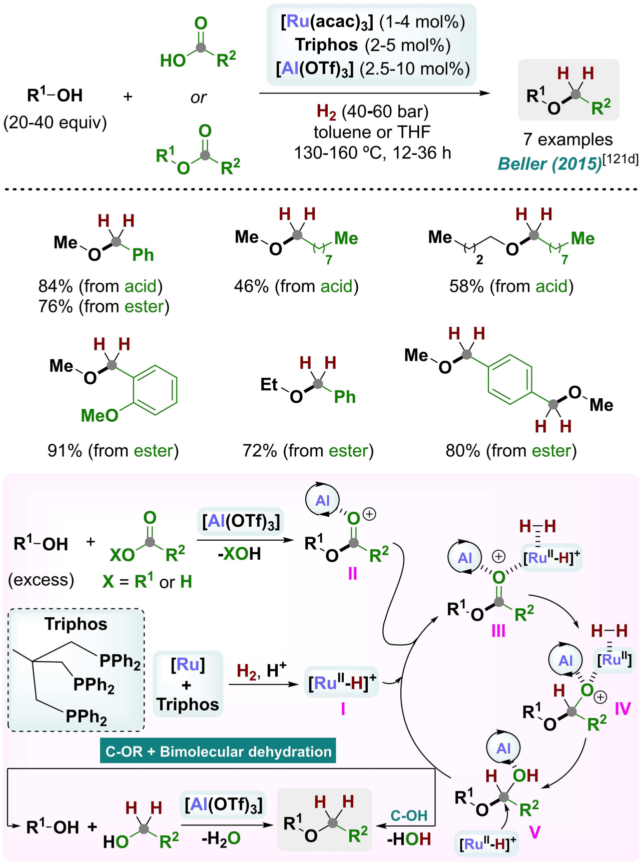


Scheme 23. Hemiacetal intermediate (C–OR) cleavage favored in basic/neutral conditions (left) versus hemiacetal (C–OH) cleavage favored in acid conditions (right).

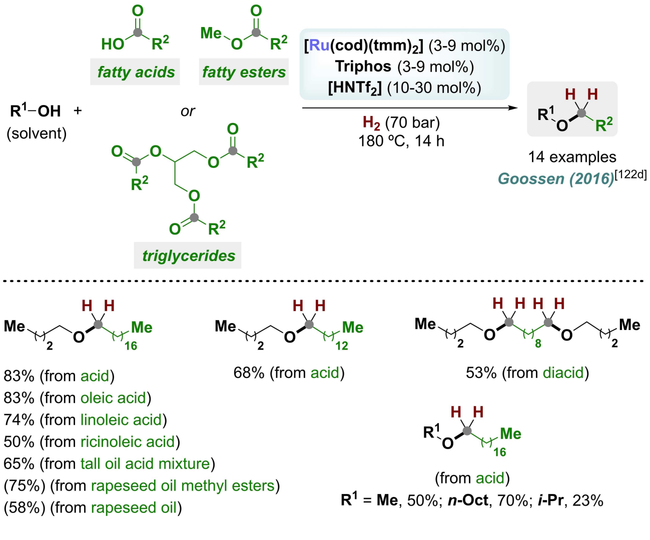
Based on experimental evidence, the authors propose a mechanism (Scheme 24, bottom) in which the ruthenium complex should be activated through the formation of a Ru^{II} hydrido complex [Ru^{II}–H^+] **I**. In first term, $Al(OTf)_3$ catalyzes an initial esterification step to afford the corresponding ester, which can be reduced to the hemiacetal intermediate **V** by Ru/acid catalysis.[121d] The authors propose that this intermediate can be further hydrogenated through a C–OH pathway to afford the ether. In addition, they also consider the possibility of a C–OR pathway followed by acid catalyzed bimolecular dehydration to explain the ether formation.[121d]

One year later, in 2016, Goossen et al. published a very related catalytic system based on the combination Ru-(cod)(tmm)$_2$/Triphos/$HNTf_2$ (cod = 1,5-cyclooctadiene, tmm = 2-methylallyl) for the reductive *O*-alkylation of alcohols with fatty acids/esters and triglycerides (Scheme 25).[122d] This system operates at harsher conditions of 180 °C and 70 bar H_2, but it is able to mediate the cross-coupling of a variety of natural occurring carboxylic acid derivatives, including methyl esters and triglycerides, with primary alcohols. It does not show selectivity towards alkene hydrogenation and, hence, converts complex carboxylic acid/ester mixtures into simple ethers in one step.[122d]

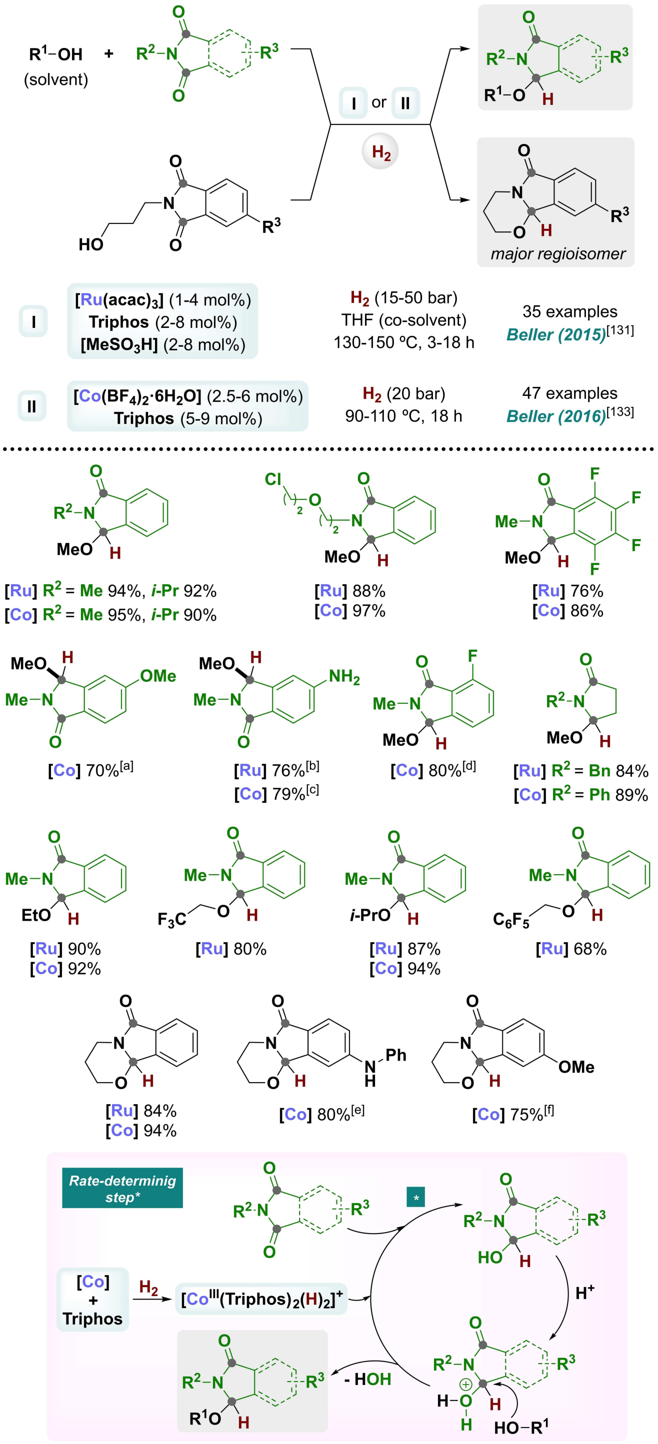
Further organic synthetic application of a Ru/Triphos system in hydrogenative alcohol etherification was reported by Beller and co-workers in 2016 (Scheme 26).[131] In this work the authors were able to perform the *O*-alkylation of a variety of alcohols using imides, phthalimides, and succinimides as alkylating agents. This methodology, which employed a $Ru(acac)_3$/Triphos/$MeSO_3H$ catalytic system in the presence of an excess of alcohol, gave access to a broad variety of heterocycles with isoindolinone and pyrrolidinone structures, privileged scaffolds in medicinal chemistry.[132] Moreover, in 2017, the same authors showed that the related $Co(BF_4)_2 \cdot 6H_2O$/Triphos catalytic system was able to mediate this transformation at milder temperatures



Scheme 24. Ru-catalyzed hydrogenative synthesis of ethers from alcohols and carboxylic acids/esters, and its proposed mechanism. Yields of isolated products are given.



Scheme 25. Ru-catalyzed hydrogenative etherification between 1° alcohols and fatty acids/esters or triglycerides. Yields of isolated products are given. GC yields are given in parentheses. Rapeseed oil = 51–71 % oleic acid (OA), 15–30 % linoleic acid (LA), 5–14 % linoleic acid (LN). Tall oil acids = 47 % OA, 34 % LA, 2 % LN, 2 % palmitic acid (PA). tmm = trimethylenemethane.



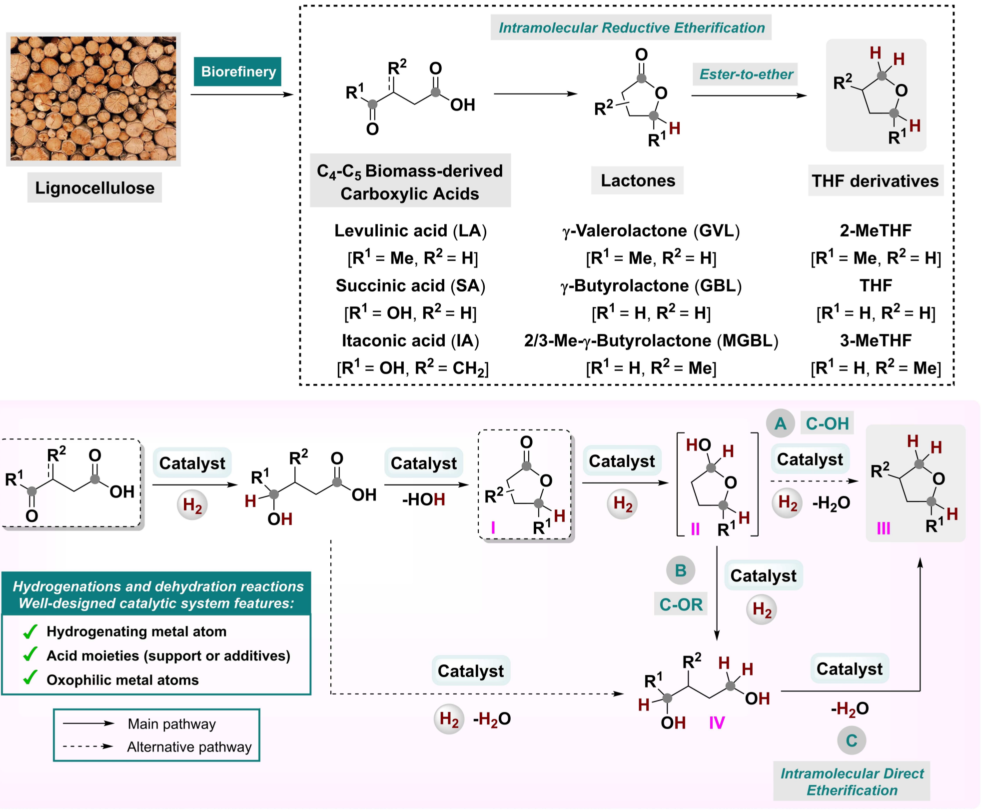
Scheme 26. Metal-catalyzed reductive *O*-alkylation of alcohols using imides as alkyl sources. Yields of isolated products are given. [a] Minor regioisomer was isolated in 29 % yield, selectivity major/minor 2.4 : 1. [b] Selectivity major/minor 15.7 : 1. [c] Selectivity major/minor > 99 : 1. [d] Minor regioisomer was isolated in 6 % yield, selectivity major/minor 11.5 : 1. [e] Selectivity major/minor 8 : 1. [f] Minor regioisomer was isolated in 15 % yield, selectivity major/minor 3.5 : 1.

(Scheme 26).[133] With both catalytic systems, a good tolerance to aromatic ring as well as many functional groups, such as halogens, was demonstrated. Remarkably, in the case of aromatic ring substituted phthalimides, good to excellent selectivities to one of the regioisomers were shown. In addition, the intramolecular version of this transformation afforded tricyclic heterocycles with up to 94% isolated yield.[131,133] In the case of cobalt catalytic system, kinetic and mass spectrometric studies revealed the $[Co^{III}(Triphos)_2(H)_2]^+$ complex as a crucial intermediate for the rate-limiting imide bond hydrogenation to the hemiaminal intermediate.[133]

In a context of more and more development of catalytic systems for the challenging hydrogenation of carboxylic acid derivatives, alternative reductive etherifications of more accessible feedstocks have emerged.[27a,c,d,f,h,103] Hence, in the last years, many examples of hydrogenative etherifications in which the alcohol is formed in situ from a more oxidized functionality, either a carbonyl compound or another carboxylic acid derivative, have appeared and they will be commented in this Review.[27a,c,d,f,h,103]

It is important to highlight that this transformation is mainly associated with the intramolecular conversion of platform molecules, bearing C_4–C_5 carboxylic acid structure, in cyclic ethers presenting a variety of applications as solvents, monomers or fuel additives.[27a,c,d,f,h,103] More specifically, levulinic (LA),[110] succinic (SA),[134] and itaconic (IA)[135] acids and its ester derivatives (Scheme 27, top) are the carboxylic acid derivatives, obtained by biorefinery processes applied to lignocellulose that have been used in these transformations affording THF derivatives.[27a,c,d,f,h,103] These mono- and dicarboxylic acids are considered among the top carbohydrate-derived organic starting materials named by the US Department of Energy.[136] Therefore, obtaining ethers with important applications from these compounds, while using hydrogen as reducing agent, is a relevant topic.

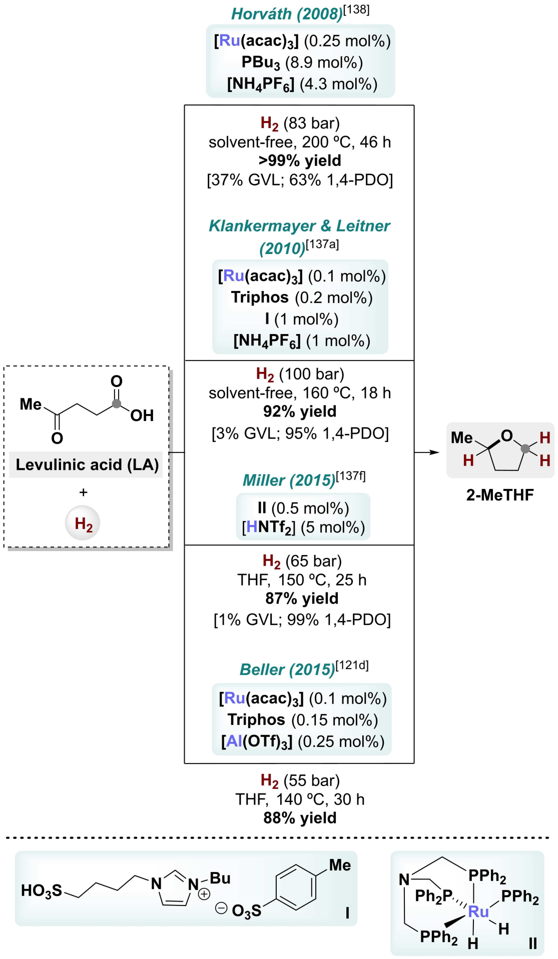
Generally, the intramolecular hydrogenative etherification of these derivatives takes place through a two-step mechanism.[137] In first place, there is a hydrogenation of the carbonyl function, in the case of LA, or one of the carboxyl groups, for IA or SA, that affords an alcohol able to give the corresponding lactone through esterification. In a second step, the corresponding lactone undergoes ester-to-ether hydrogenation to give the THF derivative (Scheme 27, top). Scheme 27, bottom shows a more detailed mechanism normally proposed for the intramolecular reductive etherification of this kind of compounds.[137] Analogously to the general mechanism of reductive etherification using carboxylic acid derivatives (Scheme 16, see above), the key intermediate here is the cyclic hemiacetal **II** that can be further hydrogenated by the C–OH pathway to form the desired ether **III** (Scheme 27, bottom, A).[137a,c] However, in the case of these compounds, mechanistic investigations point out the C–OR pathway to give a 1,4-diol **IV** followed by an intramolecular direct etherification as the most



Scheme 27. Top: General scheme describing the sequential synthesis of THF derivatives from lignocellulose through intramolecular reductive etherifications of levulinic acid (LA), succinic acid (SA), and itaconic acid (IA). Synthesis of THF derivatives from direct hydrogenation of γ-valerolactone (GVL), γ-butyrolactone (GBL), and 2/3-methyl-γ-butyrolactone (MGBL) is also considered. Bottom: General proposed mechanism for the intramolecular reductive etherification of LA, SA, and IA.

probable via to explain the ether formation (Scheme 27, bottom, B and C).[137] Considering this reaction mechanism, the catalytic systems normally reported as active for this kind of transformations present as main requisites: being able of activate hydrogen and presenting acid properties that enable the direct etherification of 1,4-diols. Moreover, catalytic systems presenting oxophilic atoms able to activate the stable carbonyl function of carboxylic acid moiety also favor these transformations.[27a,c,d,f,h,103]

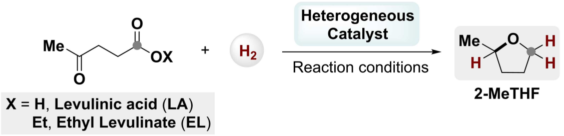
Taking into account these requisites, several homogeneous catalytic systems have been described for the LA intramolecular hydrogenative etherification to afford 2-MeTHF (Scheme 28). All these systems are composed by a Ru complex with a phosphine type ligand in the presence of an acid additive. Early investigations were reported in 2008 by Horváth and co-workers and employed Ru(acac)$_3$/PBu$_3$/NH$_4$PF$_6$ as catalytic system for this reaction.[138] Later on, Klankermayer, Leitner and co-workers,[137a,c] Miller and co-workers,[137f] and Beller and co-workers,[121d] used improved systems consisting on ruthenium complexes with tridentate phosphines (Triphos or N-Triphos^{Ph}).[23,29a,c,d,g,h,130] Remarkably, Horváth,[138] Klankermayer and Leitner[137a,c] and Miller[137f] works demonstrate the formation of γ-valerolactone (GVL) and, above all, 1,4-pentanediol (1,4-PDO) when the catalytic system was used in the absence of the acid co-catalysts, confirming the proposed mechanism.[137c]



Scheme 28. Homogeneously catalyzed intramolecular LA reductive etherification to produce 2-MeTHF. Yield of isolated product is given. Results of the reactions conducted in the absence of acid co-catalysts are given between brackets. GVL = γ-valerolactone. 1,4-PDO = 1,4-pentanediol.

Obviously, developing more sustainable heterogeneous catalytic systems that allow the valorization of a platform chemical such as LA to 2-MeTHF is a topic of interest nowadays considering the easier possibility of reusing these systems.[27a,c,d,f,h,103] Seminal work in this area was reported by Hixon and co-workers in 1947.[139] These authors obtained for the first time 2-MeTHF from LA as a secondary product when they were investigating a two-step process for synthesizing 1,4-PDO from LA using Ni-Raney and Cu$_2$Cr$_2$O$_5$. Since then, important efforts have been made, mainly in the last decade, and several nanostructured catalysts have been described for obtaining 2-MeTHF from LA or its derived ester ethyl levulinate (EL) (Scheme 29). In this sense, solid materials have been carefully designed in order to optimize this complex transformation by introducing in their structure bifunctional features, as well as acid properties. Moreover, a deep investigation of crucial reaction parameters has also been performed.

Bimetallic nanosized materials operating through a cooperative or sequential mechanism are among the most studied catalysts for this transformation. In fact, the first example of a direct process affording 2-MeTHF from LA was reported by Bozell et al. in 2000 employing a Pd–Re/C material as catalyst (Scheme 29A).[140] In 2011, Chang, Hwang and co-workers published the first example of material based on the combination of copper and nickel as hydrogenating metals (Scheme 29B).[141] More specifically, the authors reported a Cu–Ni/SiO$_2$ material with high copper loadings, containing Cu NPs of around 20 nm, and highly dispersed Ni NPs that act as promoters. This material affords 2-MeTHF from LA, via GVL, with large selectivity and stability. Several years later, Arias et al. published a nanomaterial with the same metal combination but employing Al$_2$O$_3$ as support (Scheme 29C).[137e] In this example, the material is composed by Ni–Cu mixed particles where both metals act synergistically to hydrogenate LA to 2-MeTHF in good yields. The authors assign Ni the role of promoting activity, whereas Cu is needed to achieve a good selectivity to the ether derivative. In addition, the role of *i*-PrOH as both solvent and hydrogen transfer agent was demonstrated for this system.[142] In 2019, Han, Chen and co-workers reported a Cu–Ni/Al$_2$O$_3$-ZrO$_2$ catalytic system affording the highest yields of 2-MeTHF (>99%) obtained up to date through the LA reductive etherification with H$_2$ (Scheme 29K).[143] In this work, it is demonstrated the bimetallic synergy, as Cu favors 2-MeTHF selectivity, while Ni is key for GVL hydrogenolysis to take place. Another key point explaining the high efficiency of this system are the optimum properties of the designed support, characterized by a mesoporous structure, with large area and important acidic properties.[143] Similarly to previous Cu–Ni based materials active for this reaction, high hydrogen pressures and $T > 200\,°C$ are required to achieve good selectivities towards 2-MeTHF versus GVL. More recently, Wang, Li, Huang and co-workers published the last example of a Cu–Ni nanocatalyst able to afford 2-MeTHF in excellent yields from LA



	Heterogeneous Catalyst	Reaction conditions **product yield**	
A	[Pd-Re/C]	H_2 (103 bar) 240 °C continuous-flow **83%**	*Bozell (2000)*[140]
B	[Cu-Ni/SiO_2]	H_2 (25 bar) 265 °C continuous-flow **89%**	*Chang & Hwang (2011)*[141]
C	[Cu-Ni/Al_2O_3]	H_2 (40 bar) *i*-PrOH, 250 °C 20 h **80%**	*Arias (2015 & 2016)*[137e, 142]
D	[Pt-Mo/H-BETA]	H_2 (50 bar) H_2O, 130 °C 24 h **86%**	*Kaneda (2016)*[145]
E	[Ru/GO]	H_2 (25 bar) 1,4-dioxane, 275 °C continuous-flow **50%**	*Chang & Hwang (2016)*[148]
F	[Cu/Al_2O_3-SiO_2]	H_2 (30 bar) solvent-free, 250 °C continuous-flow **65%** (from **EL**)	*Zheng & Zhu (2016)*[149]
G	[Co/ZrO_2]	H_2 (40 bar) 1,4-dioxane, 230 °C 8 h **77%** (from **EL**)	*Fan & Zhu (2018)*[150]
H	[Ru/C] [Re/C] [$Nb_3(PO_4)_5$]	H_2 (50 bar) H_2O, 180 °C **28%**	*Galletti (2018)*[147]
I	[Co/SiO_2]	H_2 (30 bar) solvent-free, 225 °C continuous-flow **70%**	*Mihályi (2019)*[151]
J	[Ni/SiO_2]	H_2 (30 bar) solvent-free, 250 °C continuous-flow **56%**	*Mihályi (2019)*[152]
K	[Cu-Ni/Al_2O_3-ZrO_2]	H_2 (30 bar) 2-BuOH, 220 °C 10 h **>99%**	*Han & Chen (2019)*[143]
L	[Ru-Zr/Al-SBA-15][a]	H_2 (1 bar) solvent-free, 400 °C continuous-flow **81%**	*Thiripuranthagan (2020)*[146]
M	[Cu-Ni/Al_2O_3]	H_2 (40 bar) *n*-hexane, 180 °C 4 h **98%** (from **LA**, **EL**)	*Wang, Li & Huang (2020)*[144]

Scheme 29. Intramolecular reductive etherification of LA or EL into 2-MeTHF mediated by heterogeneous catalysis. GO = graphene oxide. [a] (Si/Al = 25).

and EL (Scheme 29M).[144] The authors designed a Cu–Ni/Al_2O_3 material in which a Cu–Ni synergy is established, entailing a LA-to-GVL step catalyzed by Ni and a Cu-catalyzed GVL-to-2-MeTHF reduction. The acidic properties of the Al_2O_3 support also play an important role in this reaction. In addition, several mechanistic investigations, including density functional theory (DFT), indicated the crucial role of the non-polar solvent used in this reaction (*n*-hexane) facilitating H_2 solubility and GVL adsorption. This material showed activity at the mildest reported temperature of 180 °C for this kind of catalysts.[144]

Apart from Cu–Ni bimetallic materials, it is interesting to highlight the Pt–Mo/H-BETA system reported by Kaneda and co-workers for the LA intramolecular etherification to 2-MeTHF at mild conditions (130 °C) and in good yields (Scheme 29D).[145] In this work, the authors show that the material is composed by Pt^0 NPs acting synergistically with Mo^{VI} oxide clusters to achieve the hydrogenation of LA to 1,4-PDO, which, in the presence of the acidic support, is able to cyclodehydrate to afford 2-MeTHF.[145]

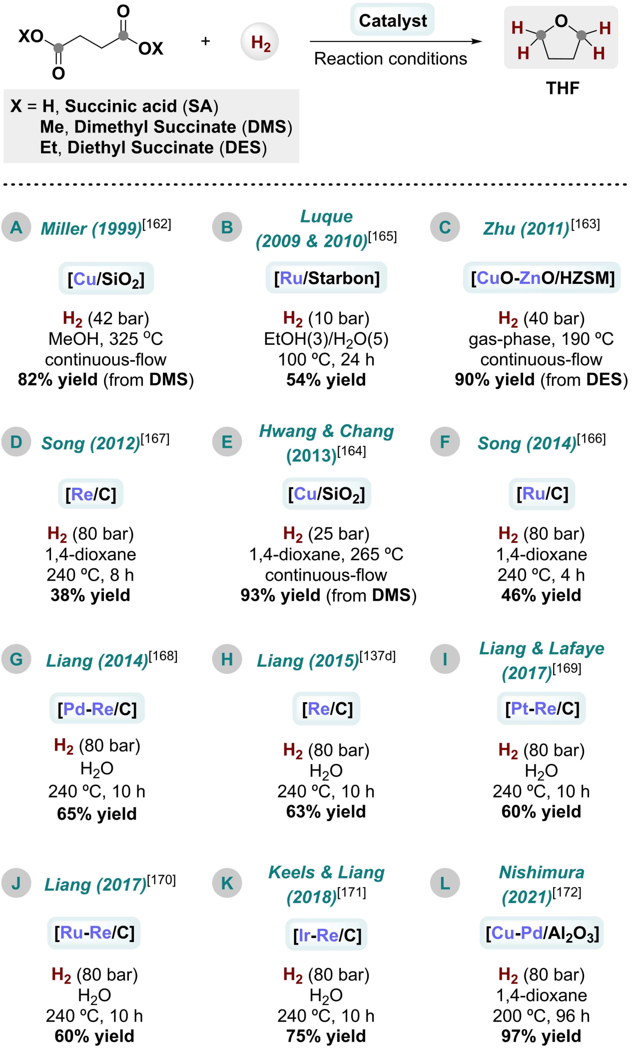
In addition, other Ru-based bimetallic materials, such as Ru–Zr/Al-SBA-15 reported by Thiripuranthagan et al. (Scheme 29L),[146] or the combination of Ru and Re commercial catalysts in the presence of $Nb_3(PO_4)_6$ as acid component (Scheme 29H),[147] studied by Galletti and co-workers, have been also reported as catalysts for this transformation.

Several monometallic nanomaterials have also been described for this relevant reaction. In 2016, Chang, Hwang et. al. described a Ru/GO system as catalyst for LA to 2-MeTHF hydrogenation (Scheme 29E).[148] Here, the graphene oxide support appears to be crucial for the selectivity to 2-MeTHF due to its acid properties and the major dispersion of Ru nanoparticles, in comparison with a regular carbon support. Interestingly, the same year Zheng,Zhu and co-workers described a Cu/Al_2O_3–SiO_2 nanocatalyst active for the hydrogenative etherification of EL into 2-MeTHF (Scheme 29F).[149] Key features of this system are related with the support properties, enabling the stabilization of smaller Cu NPs, as well as providing better stability and acid properties to the material. In 2018, Fan, Zhu and co-workers reported the reductive EL conversion to 2-MeTHF in good yields and in the presence of H_2, using a Co/ZrO_2 material as catalyst (Scheme 29G).[150] Finally, in 2019 Mihályi and co-workers published two nanostructured materials, Co/SiO_2,[151] and Ni/SiO_2,[152] as active catalysts for LA hydrogenation to 2-MeTHF (Scheme 29I,J). In the case of Co/SiO_2, a bifunctional behavior was identified attributing the success of the system to the combination of Co^0 metal sites, able to hydrogenate, and CoO_x Lewis acid sites, able to dehydrate, at $T \geq 225$ °C.[151]

Succinic acid and their diester derivatives [dimethyl succinate (DMS) and diethyl succinate (DES)] are platform chemicals obtained from glucose through a fermentation process.[27a,c,d,f,h,103a,b,134,136] Moreover, these kind of compounds can also be synthesized from petroleum derivatives, and are intimately related with maleic acid or maleates, only differing with succinic in a C=C double bond.[27a,c,d,f,h,103a,b,134,136] Considering the easy availability of these compounds, their heterogeneously catalyzed intramolecular reductive etherification to directly obtain THF has awakened a notable interest in catalytic community. Early examples of this transformation correspond to two patents reporting the activity of bimetallic nanomaterials.[153] Marbry et al. as well as Schwartz patented in 1985 and 1995, respectively, a Pd–Re/C[153a] and a Ru–Re/C[153b] systems active for obtaining THF from succinic acid in aqueous media and in the presence of hydrogen. Chaudhari and co-workers also reported in the early 2000s two bimetallic catalysts combining Ru either with Co[154] or with Re[155] for the hydrogenation of succinic acid or maleic acid to THF in aqueous media.

Other early examples of this reaction were described in the 1990s and employed as catalysts Cu-based solid materials. The work from Trimm and co-workers should be highlighted,[156] who studied the activity of several copper catalysts such as Cu-Raney,[156a,b] Cu/$CuCr_2O_4$, Cu/SiO_2, or Cu/ZnO[156c] for the DMS gas-phase hydrogenation to THF. In these works, it was shown that Cu/ZnO catalyzed the direct formation of THF from DMS. In addition, a relevant catalytic system based on a Cu–Zn–Al–O composite was described by Zhang et al. for the hydrogenation of diethyl maleate to THF in 1998.[157] This key work defined that Cu^0 surface centers promote the THF formation, while Cu^I centers are selective for the formation of γ-butyrolactone (GBL) and 1,4-butanediol (1,4-BDO) from the diester.

Dimethyl or diethyl maleate hydrogenation to THF using copper-based heterogeneous catalysts has been further studied along the years, although the interest in this reaction has lately decayed due to the petroleum origin of this compound.[27a,c,d,f,h,103a,b] Several systems based on $Cu_2Cr_2O_5$,[158] Cu/ZnO extruded with γ-Al_2O_3,[159] Cr-Cu–B/γ-Al_2O_3,[160] and Cu/SiO_2[161] have been described by Chaudhari et al., Kraushaar-Czarnetzki and co-workers, Qiao, Fan and co-workers, and Zhang and co-workers for hydrogenative synthesis of THF from dialkyl maleates.[158–161] On the other hand, more examples concerning hydrogenation of SA or dialkyl succinates to THF have been reported due to the biomass origin of this compound.[27a,c,d,f,h,103a,b,134] Among the most recent work focused on Cu-based catalysts, the group of Miller published a Cu/SiO_2 system with high area and acidity for the DMS direct and selective hydrogenation to THF, without detecting GBL or 1,4-BDO as intermediates (Scheme 30A).[162] More recently, Zhu and co-workers reported a CuO/ZnO material in combination with H-Y zeolite[137b] and the CuO-ZnO/H-ZSM bifunctional system,[163] both active for the vapor-phase hydrogenation of DES to THF (Scheme 30C). In this case, the authors clearly stablished the need of zeolite acidity to catalyze the 1,4-BDO cyclodehydration to THF. In 2013, Hwang, Chang and co-workers developed a Cu/SiO_2 catalyst affording THF from DMS in good yields in the absence of acid additives (Scheme 30E).[164] It was showed that the presence of Cu^0 centers with a size diameter of 11 nm in this material was crucial for achieving a good THF selectivity.



Scheme 30. THF synthesis from the heterogeneously catalyzed intramolecular reductive etherification of succinic acid (SA), dimethyl succinate (DMS), or diethyl succinate (DES).

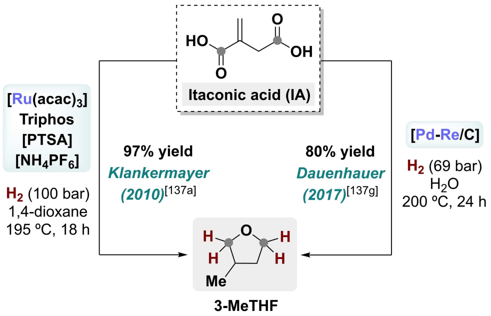
Succinic acid hydrogenation has also been reported with Ru monometallic on carbon-type supports catalysts by Luque et al. and Song and co-workers. More specifically, Luque et al. published a Ru/Starbon® nanomaterial active and stable for SA hydrogenation in aqueous conditions, in which ruthenium low particle size and high dispersion are crucial features (Scheme 30B).[165] Song and co-workers reported two active catalysts for this reaction based on Ru/C, in which the support was a carbon composite (Scheme 30F).[166] In these works, better selectivities for THF, although moderate, were obtained in the case of materials containing smaller Ru nanoparticles. Analogously to ruthenium catalysts, several Re-based materials with carbon-type supports have been described for hydrogenating SA to THF. Song et al. reported in 2012 a Re/C material with a similar support to the one used by the same group with Ru and affording also moderate yields of THF (Scheme 30D).[167] In 2015, Liang and co-workers published another Re/C material for the aqueous media-catalyzed SA hydrogenation to THF (Scheme 30H).[137d] The authors studied that the system efficiency was better in the case of materials with a larger Re dispersion. They could identify GBL and 1,4-BDO as reaction intermediates.

Recent reports of bimetallic nanocatalysts for, mainly aqueous media, hydrogenation of SA to THF have been also published. In this area, the work of Liang and co-workers should be noted, who designed a series of materials combining Re either with Pd (Scheme 30G),[168] Pt (Scheme 30I),[169] Ru (Scheme 30J)[170] or Ir (Scheme 30K)[171] supported on carbon materials for SA hydrogenation to THF. For these materials, it is showcased a synergic effect caused by the key interaction of Re with the other metal and the requirement of high temperatures to promote THF formation versus 1,4-BDO. Finally, this year the group of Nishimura reported a Cu–Pd/γ-Al_2O_3 material able to give THF in good yields from SA in dioxane (Scheme 30L).[172] In this work, it was demonstrated the important role of γ-Al_2O_3 support providing Lewis acid sites, and strongly interacting with Cu, for achieving good THF selectivities.

Another dicarboxylic acid obtained from glucose fermentation and whose intramolecular reductive etherification has also been studied, although in less extent, is IA (Scheme 31).[27a,c,d,f,h,103a,b,135,136] In first place, Klankermayer and co-workers described a homogeneous catalytic system, similar to the one described for LA, to afford 3-MeTHF from IA in good yields.[137a,c] The system was composed by a Ru/Triphos complex in the presence of acid additives. More recently, Dauenhauer and co-workers reported a Pd–Re/C material as an active catalyst for the same reaction.[137g,h] The IA hydrogenation to 3-MeTHF was studied in the context of the desing of a synthetic route to obtain isoprene from glucose by fermentation/intramolecular reductive etherification/dehydrodecyclization. The authors described a Pd–Re interaction in this material resulting in a synergistic effect required for catalyzing the ring opening of the 2/3-methyl-γ-butyrolactone, that it is the rate-limiting step of this complex transformation. Moreover, the acid properties of the carbon support and ReO_x were also crucial for the success of the catalyst. In addition, the feasibility of the process starting from mesaconic acid, an isomer of IA, was also proposed by the same authors.[173]

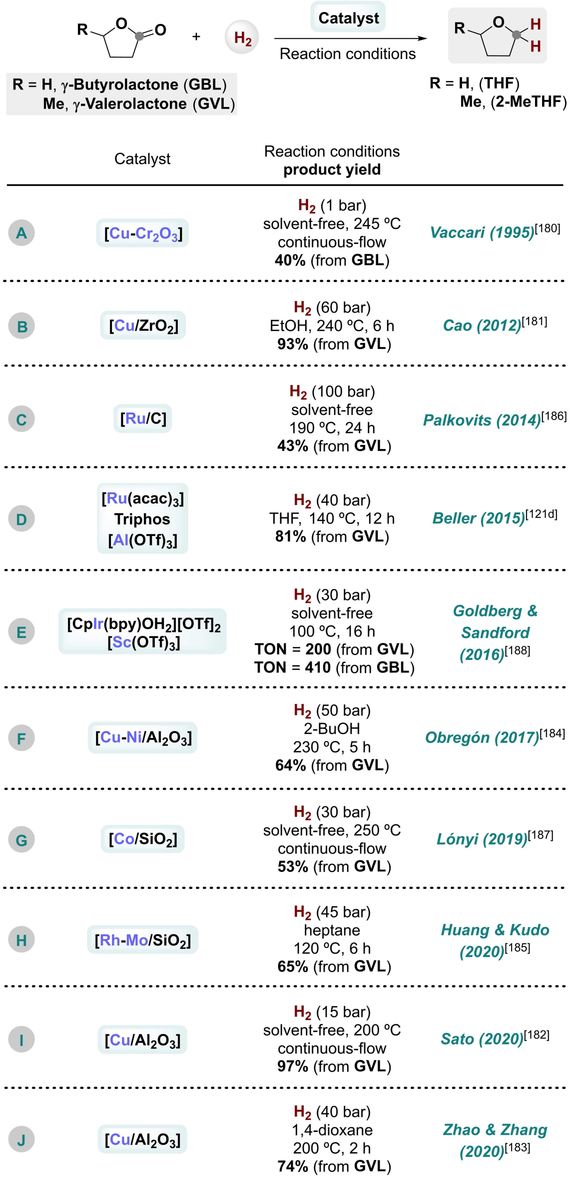
3.2.1. Ester-to-ether reduction with molecular hydrogen

As we previously discussed, other related process that has been explored for the convenient synthesis of ether derivatives is the ester-to-ether hydrogenation. Pioneer work of this reaction was published in 1964 by Edward and Ferland, that reported the hydrogenation of six-membered lactones to cyclic ethers with PtO_2 in acidic conditions.[174] The large accessibility of five-membered lactones such as GVL and GBL,[27a,c,d,f,h,103,175] as well as the fact that these compounds are more prone to undergo a dehydrocyclization pathway (see Scheme 27, bottom) have helped many protocols for their hydrogenation to 2-MeTHF and THF to emerge (Scheme 32).



Scheme 31. Catalytic intramolecular reductive etherification of IA into 3-MeTHF. PTSA = *p*-toluenesulfonic acid.

Although nowadays GBL can be considered a platform chemical affordable from the hydrogenation of succinic acid, traditionally it has been obtained from the dehydrogenation of 1,4-BDO, normally synthesized from petroleum derivatives.[27a,c,d,f,h,103a,b] Hence, in the 1990s of the last century there was a strong interest in studying catalytic systems for the hydrogenation of this compound to THF. Several patents based on multimetallic materials, such as Pd–Ag–Re,[176] Ru–Re–Sn/C,[177] or Pt–Re–Sn/C,[178] and copper chromite catalysts[179] were reported for this reaction. In addition, in 1995, Vaccari and co-workers studied a series of copper chromite catalysts, determin-



	Catalyst	Reaction conditions product yield	
A	[Cu-Cr_2O_3]	H_2 (1 bar) solvent-free, 245 °C continuous-flow **40%** (from **GBL**)	*Vaccari (1995)*[180]
B	[Cu/ZrO_2]	H_2 (60 bar) EtOH, 240 °C, 6 h **93%** (from **GVL**)	*Cao (2012)*[181]
C	[Ru/C]	H_2 (100 bar) solvent-free 190 °C, 24 h **43%** (from **GVL**)	*Palkovits (2014)*[186]
D	[Ru(acac)$_3$] Triphos [Al(OTf)$_3$]	H_2 (40 bar) THF, 140 °C, 12 h **81%** (from **GVL**)	*Beller (2015)*[121d]
E	[CpIr(bpy)OH_2][OTf]$_2$ [Sc(OTf)$_3$]	H_2 (30 bar) solvent-free 100 °C, 16 h **TON = 200** (from **GVL**) **TON = 410** (from **GBL**)	*Goldberg & Sandford (2016)*[188]
F	[Cu-Ni/Al_2O_3]	H_2 (50 bar) 2-BuOH 230 °C, 5 h **64%** (from **GVL**)	*Obregón (2017)*[184]
G	[Co/SiO_2]	H_2 (30 bar) solvent-free, 250 °C continuous-flow **53%** (from **GVL**)	*Lónyi (2019)*[187]
H	[Rh-Mo/SiO_2]	H_2 (45 bar) heptane 120 °C, 6 h **65%** (from **GVL**)	*Huang & Kudo (2020)*[185]
I	[Cu/Al_2O_3]	H_2 (15 bar) solvent-free, 200 °C continuous-flow **97%** (from **GVL**)	*Sato (2020)*[182]
J	[Cu/Al_2O_3]	H_2 (40 bar) 1,4-dioxane 200 °C, 2 h **74%** (from **GVL**)	*Zhao & Zhang (2020)*[183]

Scheme 32. Catalytic hydrogenation of GBL and GVL to THF and 2-MeTHF, respectively. bpy-OMe = 4,4′-dimethoxy-2,2′-bipyridine. Cp* = pentamethylcyclopentadienide.

ing that a Cu-Cr_2O_3 material with large amounts of Cu(0) afforded THF from GBL in moderate yields (Scheme 32A).[180]

More recently, a stronger interest in GVL hydrogenation to 2-MeTHF has been developed, due to the easy access of this compound from lignocellulosic biomass.[27a,c,d,f,h,103,175] In 2012, Cao and co-workers designed a Cu/ZrO_2 nanomaterial for selectively obtaining 2-MeTHF from GVL, avoiding 1,4-PDO formation (Scheme 32B).[181] In this work the authors elucidated that lower calcination temperatures (up to 400 °C) were essential to achieve a material with the correct copper dispersion and acid sites that enables a good 2-MeTHF selectivity. Although kinetic studies pointed to a direct GVL hydrogenation, they could not discard a dehydration pathway through 1,4-PDO.

Two other copper-based materials have been described as active catalysts for this reaction during 2020 (Scheme 32I,J). Both examples, published by Sato and co-workers[182] and Zhao, Zhang and co-workers[183] were based on a Cu/Al_2O_3 material in which the presence of acid sites is again crucial for achieving a good selectivity to 2-MeTHF. In the case of the material used by Sato and co-workers, they determined that calcination temperatures lower than 700 °C afforded materials with larger copper particles and optimum acid properties for the selective formation of 2-MeTHF, instead of the diol.[182]

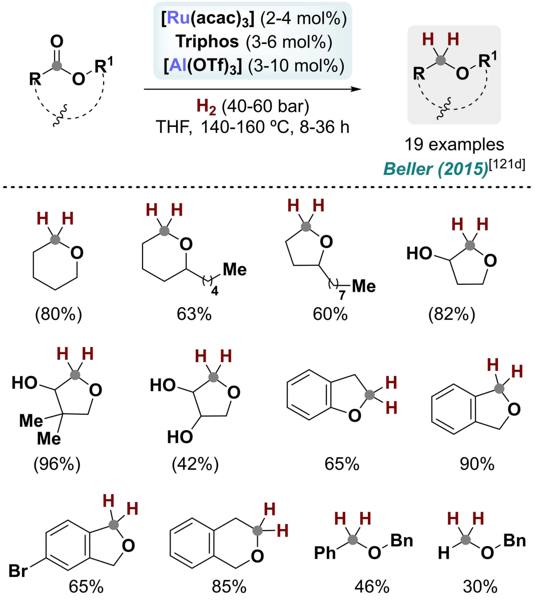
Similarly to the catalysts described for LA hydrogenation (see Scheme 29C), Obregón et al. described in 2017 a Cu–Ni/Al_2O_3 material active for the hydrogenation of GVL to 2-MeTHF (Scheme 32F).[184] In this work the authors demonstrated that Cu–Ni interactions as well as catalyst acidity are crucial factors in this reaction. Last year, Huang, Kudo et al. reported another bimetallic catalyst based on a Rh–Mo/SiO_2 material that achieved a low-temperature (120 °C) hydrogenation of GVL to THF in heptane (Scheme 32H).[185] Here, the good selectivity to 2-MeTHF versus 2-pentanol was achieved as a consequence of the bimetallic cooperation. This cooperation is responsible of: a reduction in hydrogenating activity by the partial coverage of Rh particles, an increase in Lewis acid properties of the material by the oxygen vacancies of reduced Mo and a strong adsorption of the substrate at the Rh–Mo interface.[185] In addition, Palkovits and co-workers[186] and Lónyi and co-workers[187] described monometallic materials of Ru/C and Co/SiO_2, respectively, as active catalysts for this reaction affording 2-MeTHF with moderate selectivities through hydrogenation to 1,4-PDO followed by cyclodehydration (Scheme 32C,G).

Finally, GVL hydrogenation has also been studied using two homogeneous systems (Scheme 32D,E). On the one hand, Beller and co-workers reported in 2015 the Ru$(acac)_3$/Triphos/Al$(OTf)_3$ system, also used for the hydrogenative etherification of alcohols with carboxylic acids/esters, as an active catalyst for obtaining 2-MeTHF from GVL in good yields (Scheme 32D).[121d] One year later, Goldberg, Sandford and co-workers published that an Ir complex in the presence of Sc$(OTf)_3$ as acid additive was able to hydrogenate GVL to 2-MeTHF, as well as GBL to THF through the hydrogenation to diol followed by dehydration (Scheme 31E).[188]

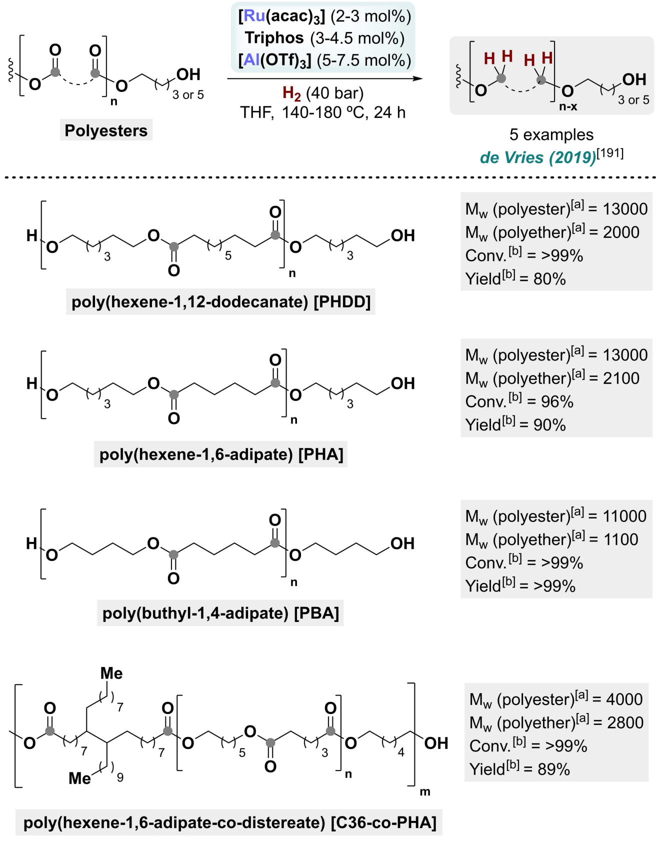
It is interesting to note that the hydrogenation of 2-methyl-γ-butyrolactone (MGBL), potentially obtained from IA, to 3-MeTHF has also been reported using nanostructured materials in several patents.[189] Moreover, maleic anhydride hydrogenation to THF has been more studied with heterogeneous catalysts, mainly based on copper.[190] However, these works will not be commented here as anhydrides hydrogenation to ethers are out of the scope of this Review.

In addition to these protocols focused on the synthesis of THF derivatives from C_4–C_5 carboxylic acids (LA, SA, and IA) and their related esters (GVL, GBL, and MGBL), more versatile synthetic approaches for the production of ethers with larger structural diversity from the hydrogenation of esters are desired.[26] In this context, to date the only catalytic protocol for promoting a more general ester-to-ether hydrogenation was developed by Beller and co-workers in 2015 (Scheme 33, see also Scheme 24).[121d] Here, authors make use of the well-developed Ru/Triphos system, in combination with Al$(OTf)_3$ as acid cocatalyst, for the deoxygenative hydrogenation of more than 15 lactones (including aromatic, aliphatic, and more sensitive α-hydroxy lactones) to obtain cyclic ethers with up to 96% yield. Furthermore, two more challenging linear esters could be hydrogenated to the desired ethers but in modest yields (Scheme 33).[121d] Concerning the mechanism, and as it was already discussed in Scheme 24, authors defend that a hydrogenation process involving selective C–OH cleavage of the hemiacetal intermediate might be a reasonable pathway. However, a C–OR cleavage of the hemiacetal into the alcohols followed by an acid-promoted direct etherification has also to be deemed taking into account the more favored unimolecular dehydration pathway in lactones in comparison with acyclic substrates.[121d]

Finally, the same Ru-based catalyst combination was applied by de Vries and co-workers in 2019 for promoting polyester-to-polyether hydrogenations (Scheme 34).[191] As we



Scheme 33. Ru-catalyzed ester-to-ether hydrogenations. Yields of isolated products are given. GC yields are given in parentheses.



Scheme 34. Polyester-to-polyether hydrogenations catalyzed by Ru/Triphos/Al(OTf)$_3$ system. [a] Molecular weights [g mol^{-1}] were determined by gel permeation chromatography (GPC). [b] Determined by NMR spectroscopy. Conversion refers to the ester groups converted, and yield was calculated considering the theoretical conversion of all ester groups to ether groups.

previously discussed in Section 3.1, this transformation has a direct application for plastic waste chemical recycling into value-added compounds[27g,129] and novel materials due to the high stability and improved properties of polyethers.[11] In this contribution, several industrial-grade polyesters including poly(hexene-1,12-dodecanate) [PHDD], poly(hexene-1,6-adipate) [PHA], poly(buthyl-1,4-adipate) [PBA] and poly(hexene-1,6-adipate-co-distereate) [C36-co-PHA] were efficiently hydrogenated to the corresponding ether oligomers at 140–180 °C and 40 bar H_2.[191] Interestingly, experimental investigations support a sequential mechanism mainly driven by a C–OR ester group hydrogenation, followed by the Al(OTf)$_3$-catalyzed direct etherification of the formed alcohols.[191] Notably, Klankermayer and co-workers recently reported a related protocol for the hydrogenative depolymerization of waste polyesters to the corresponding diols using a similar Ru-based molecular system.[192] In this case, HNTf$_2$ was employed as acid additive, and a C–OR bond cleavage pathway was also clearly demonstrated since alcohols are obtained as the main products.

4. Alcohol Hydrogenative Etherifications with CO_2 or HCO_2H to Dialkoxymethane Ethers and Related Acetals

Carbon dioxide levels in the atmosphere have steadily increased since the beginning of industrialization.[193] Anthropogenic emissions, mainly coming from combustion of petroleum-derived fuels and industrialized processes, are the main factors explaining this increase.[193] Nowadays, this is one of the biggest problems of humankind owing to its impact on Earth's climate change. Hence, there is an obvious interest in the development of technologies for the capture and utilization of CO_2.[193] Furthermore, the employment of carbon dioxide as feedstock in chemical industry is also clearly associated with a more sensible resource management and a renewable carbon economy, both concepts needed for a more sustainable industry.[193] However, owing to CO_2 kinetic inertness and thermodynamic stability, its activation is currently one of the greatest challenges of modern chemistry.[34]

In this context, important efforts have been made for designing transformations to produce valuable organic molecules using CO_2 as starting material.[34] Recently, catalytic protocols for *N*-methylation of amines using CO_2 as C_1 building block in the presence of a reducing agent have emerged.[23,33] Likewise for amines, the selective CO_2 reduction with H_2 in the presence of alcohols can give direct access to dialkoxymethane ethers (DAM) and related acetals, a relevant class of ether-type compounds.[30–32]

More specifically, so-called oxymethylene ethers (OMEs) constitute valuable feedstocks as useful chemical intermediates and building blocks.[30,31] In addition, mainly dimethoxymethane (DMM, referred to as OME_1 or methylal) as the first of the family, but also diethoxymethane (DEM) and poly(oxymethylene) dimethyl ethers (OME_x), present important applications as fuels or fuel additives.[30,31] Properties of these compounds such as their high viscosity, low vapor pressure, and high cetane number and oxygen contents explain their capacity for reducing soot generation during combustion in diesel engines.[30,31] Moreover, DMM is also applied as an environmentally-benign solvent in the fine-chemical industry.

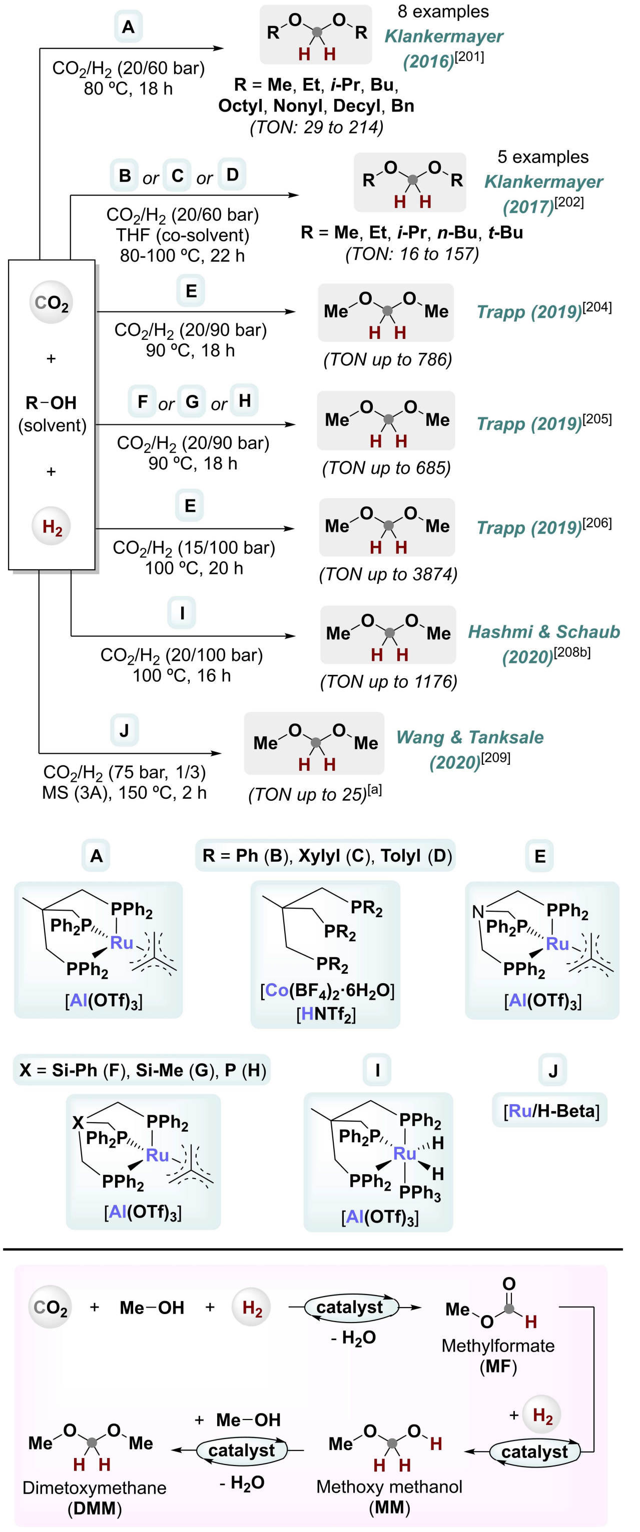
Apart from all the mentioned applications, DAMs are also interesting from the viewpoint of being formaldehyde surrogates.[30,31] In fact, formaldehyde can be easily obtained from these compounds by simple hydrolysis. Therefore, the synthesis of DAMs from CO_2/H_2 is a way of hydrogenating carbon dioxide selectively to the formaldehyde stage.[30] This is a very challenging transformation, taking into account the easy hydrogenation of an aldehyde in the conditions usually employed for CO_2 hydrogenation. Hence, CO_2 hydrogenation to acetal followed by hydrolysis is a highly desirable strategy for obtaining formaldehyde, a pivotal compound for industry.[30] Formaldehyde is world-wide produced in >20 million tons per year and currently is synthesized through the catalytic gas-phase oxidation of methanol at high temperatures (Formox process).[194] Alternatively, transition metal- or FLP-catalyzed CO_2 reductions in the presence of hydrosilanes[195] or hydroboranes[196] have been explored to afford bis(silyl) or bis(boryl) acetals, also formaldehyde surrogates as less sustainable processes.

At this point is also worth mentioning that several methodologies relying on dimethyl ether (DME) production from CO/H_2[197] or CO_2/H_2[34h,m,197b,198] have been developed. In general, such processes are mediated by heterogeneous hybrid acid catalysts, mainly based on Cu-ZnO/γ-Al_2O_3 and related systems, able to promote two main steps: (a) hydrogenation of CO or CO_2 to methanol and (b) DME generation from an acid-catalyzed direct etherification of the above-formed methanol. Although those protocols are in close relationship with the ones commented on here and represent exceptional advances in the area of CO or CO_2 hydrogenations, they are not going to be discussed in detail as they are far from the scope of this Review, more focused on a synthetic organic perspective. Moreover, several excellent Reviews dealing with this interesting topic have been recently reported.[34h,m,197a,b,198]

DAM derivatives are normally synthesized via redox-inefficient routes involving methanol oxidation steps or from dangerous formaldehyde.[30,194,199] For example, DMM is industrially produced by the Formox process followed by the acid-catalyzed acetalization of formaldehyde with methanol.[30,194,199a,c,e,f] In this section the advances in the synthesis of DAMs through the more benign reductive etherification of alcohols with CO_2 in the presence of hydrogen are discussed.[30,32]

In Scheme 35 (top) are summarized the handful number of catalytic systems able to mediate such hydrogenative alcohol etherifications with CO_2/H_2. In general, most of the catalysts are homogeneous complexes (Scheme 35A–H) whose structure is based in a molecularly-defined ruthenium or cobalt Triphos [1,1,1-tris(diphenyl-phosphinomethyl)ethane][130a] or related systems, in combination with the suitable acid cocatalyst. Notably, Triphos and derivatives have been presented in the last decade as key ligands in many transition metal-catalyzed hydrogenative transformations involving carboxylic/carbonic acid derivatives or CO_2.[23,29a,c,d,g,h,33,130,200]

Pioneering work in the area of DAM production from CO_2/H_2 and alcohols was reported in 2016 by Klankermayer and coworkers.[201] In this example, a well-defined Ru(Triphos)(tmm) complex in the presence of $Al(OTf)_3$ as acid cocatalyst was shown to be an active system (Scheme 35A). By using this catalyst system, which exhibited a clear dependence between its performance and the increase of the ratio additive/Ru-complex, TONs up to 214 for DMM were obtained at 80 °C and CO_2/H_2 20:60 bar with the concomitant formation of methyl formate (MF) as by-product. In addition, the protocol could be also executed for the reductive etherification of different aliphatic 1°/2° alcohols, yielding DAMs with TONs from 29 to 118. Interestingly, mechanistic investigations showed that MF and methoxy methanol (MM) are central intermediates in the process (Scheme 35, bottom). Based on these data, a sequential route for DMM production was proposed implying: (a) MF formation from CO_2 hydrogenation to formic acid followed by esterification with methanol; (b) hydrogenation of MF to MM; (c) final transetherification of MM with excess methanol to afford DMM.[201]



Scheme 35. Top: catalytic etherification of alcohols with CO_2/H_2 into dialkoxymethane ethers. TONs were determined by ^1H NMR spectroscopy. [a] TON was determined by GC. Bottom: reaction pathway for the DMM production from CO_2/H_2/MeOH.[201]

One year later, the group of Klankermayer developed an elegant non-noble metal-based protocol for DMM synthesis from methanol and CO_2/H_2 employing a related cobalt system (Scheme 35B).[202] In this case, a suitable combination of $Co(BF_4)_2 \cdot 6H_2O$, Triphos, and $HNTf_2$ as acid additive, was used as catalyst system to produce DMM with TONs up to 92 at 100 °C. Interestingly, DMM TONs could be further improved by using related tailored cobalt catalysts with a parent Triphos aromatic ring substituted (Scheme 35C,D).[202] Apart from methanol, other aliphatic alcohols afforded the desired DAM using the Co/Triphos/$HNTf_2$ system (TONs from 16 to 109), albeit with worse results than the ones obtained with the more active ruthenium catalyst.[202] Very recently, Wei, Jiao and co-workers studied by DFT the mechanism involved in the DMM production from CO_2/H_2/MeOH with this cobalt system.[203]

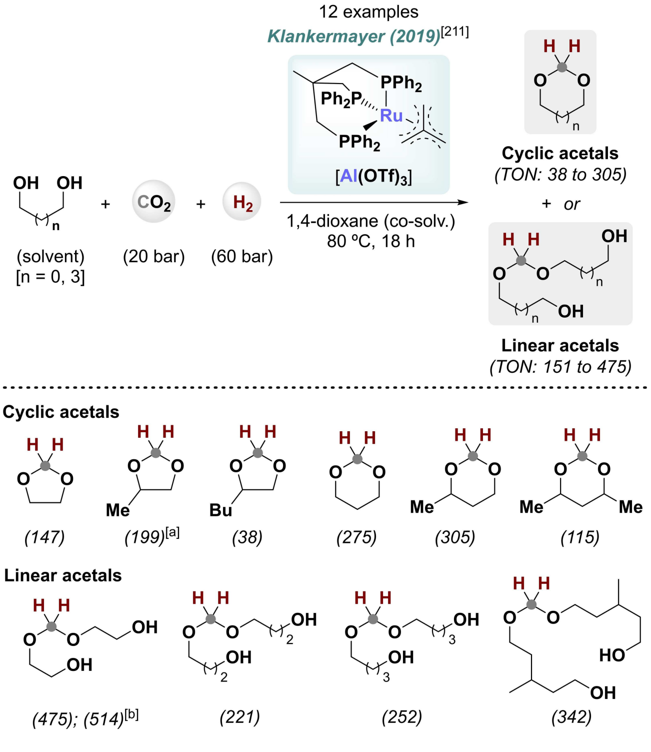
After those inspiring contributions, a new protocol for this transformation was developed by Trapp and co-workers in 2019.[204] In this piece of work, the authors performed a systematic study evaluating the activity of a series of catalysts with different synthesized tripodal ligands and employing different reaction parameters. As a result of this study, a well-defined Ru(N-Triphos^{Ph})(tmm) complex in the presence of $Al(OTf)_3$ (Scheme 35E) was reported as the most active system for DMM production from CO_2/H_2, reaching a TON of 786 at 90 °C.[204] These excellent results encouraged the authors to further extend their study to related backbone-modified tripodal ligands bearing a silicon (F and G, where R=Si–Ph and Si–Me, respectively) or phosphorous (H, where R=P) as apidal constituents.[205] Among the different systems, Ru(^{Me}Si-Triphos^{Ph})(tmm), in combination with $Al(OTf)_3$, (Scheme 35G) afforded the best results for DMM (TON = 685), albeit without surpassing the more active system (Scheme 35E).[205] Very connected with these investigations, the same group showcased the power that multivariate modelling optimization can offer in order to further improve the efficiency of a catalytic process.[206] By the application of this theoretical approach, based on modelling and prediction of the conditions optimally accounting for parameter interaction, allowed them to obtain TON values up to 3874 for DMM production from CO_2/H_2 and methanol with Ru(N-Triphos^{Ph})(tmm) complex and $Al(OTf)_3$ in a high excess with respect to the ruthenium catalyst (Scheme 35E).[206,207]

Last year, Hashmi, Schaub et al. conducted complementary investigations showcasing the enhancing effect of additives in the catalytic efficiency of the stablished Ru(Triphos)(tmm) system[201] in this reaction.[208] In this work, a related $RuH_2(Triphos)(PPh_3)$ complex was synthesized and applied, in combination with $Al(OTf)_3$ as acid cocatalyst, for DMM synthesis from CO_2/H_2/MeOH, reaching TON values up to 1176 with a 70 % selectivity to DMM (Scheme 35I).[208b] Considering such improved results, authors proposed that PPh_3 has a potential role for avoiding catalyst deactivation pathways. Indeed, Ru(Triphos)(tmm)]/[$Al(OTf)_3$ system (Scheme 35A) in combination with 4-fold excess of PPh_3 with respect to Ru, did not show catalyst degradation towards formation of cationic RuH$(CO)_2$(Triphos)OTf.[208b] In addition, this enlarged activity is likewise attributed to the fact that PPh_3 acts as a precursor of in situ formed Lewis-acidic phosphonium salts [PPh_3CH_2OH]OTf. Besides, it was also showcased that Ru(Triphos)(tmm)]/[$Al(OTf)_3$ system, in combination with PPh_3 and HCO_2H as additives, allowed the recyclability of the system through the suppression of catalyst deactivation pathways such as the formation of [RuH$(CO)_2$(Triphos)]OTf species. These findings potentially pave the way towards the application of these protocols in long-term sustainable continuous processes.[208b]

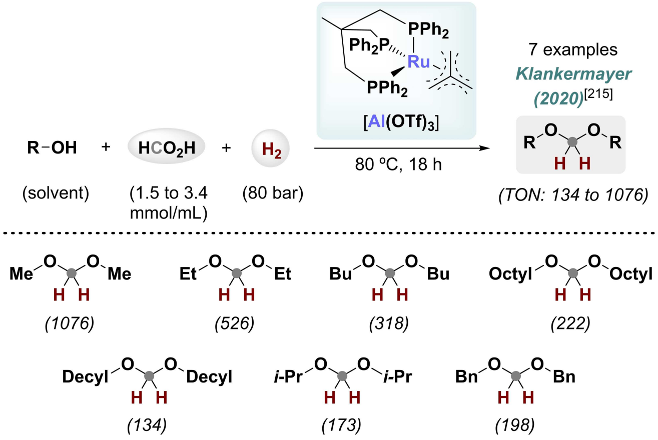
Finally, Wang, Tanksale and co-workers reported in the same year the first heterogeneously catalyzed synthesis of DMM from CO_2/H_2 and methanol.[209] In this contribution, different weight [%] amounts of Ru NPs were supported on zeolite H-BETA (with a molar ratio $SiO_2/Al_2O_3 = 38$). More specifically, 3 %Ru/H-BETA material (Scheme 35J) was revealed as the best catalyst affording a TON of 25 for DMM (OME_1) production at 150 °C and 2 h under 75 bar of CO_2/H_2 (1 : 3) mixture. Kinetic studies showed that selectivity towards DMM versus MM improved in the presence of molecular sieves, due to a detrimental effect of water. Deuterium labelling experiments pointed out formaldehyde as a feasible intermediate in this transformation.[209]

Remarkably, this group also developed an elegant example of a liquid-phase DMM production from syngas and methanol.[210] In that case, Ru–Ni/H-BETA nanocatalyst was shown as an active system for the formal hydrogenative etherification of methanol to DMM via an initial CO hydrogenation to formaldehyde, followed by its acetalization with methanol.[210]

In 2019, the group of Klankermayer reported the reductive etherification of a variety of biomass derived diols with CO_2/H_2 for the sustainable construction of a larger family of linear and cyclic acetals using a similar procedure to the previously reported by themselves (Scheme 36).[211] Cyclic acetals such as



Scheme 36. Cyclic and linear acetals from catalytic reductive etherification of diols with CO_2/H_2. TONs were determined by ^1H NMR spectroscopy. [a] Linear acetal was also obtained with a TON of 68. [b] Reaction without 1,4-dioxane.



Scheme 37. Ru-catalyzed hydrogenative etherification of alcohols using HCO_2H as C_1 source for the synthesis of DAM. TONs were determined by ^1H NMR spectroscopy.

1,3-dioxane or 1,3-dioxepane are compounds of current significance presenting a wide range of chemical applications, such as their use as solvents. In addition, cyclic and linear acetals can be utilized as building blocks for the synthesis of polymers with high water solubility (polyoxymethylenes) and can be considered formaldehyde surrogates.[212] The targeted compounds could be efficiently produced using Ru(Triphos)(tmm)/$Al(OTf)_3$ catalyst (Scheme 36) at 80 °C, with TONs up to 514. In fact, if the formation of both cyclic/linear acetal is considered together, a combined TON of up to 622 could be reached, demonstrating the high efficiency of the process.[211] A variety of diols could be employed with a linear/cyclic selectivity depending on the number of carbon atoms between both hydroxy groups.

Formic acid (FA) is a practical feedstock, liquid under ambient conditions.[213] It is produced industrially by a two-step procedure consisting of a first reaction of CO and methanol affording MF, followed by hydrolysis. In addition, FA can also be produced from CO_2 through its selective hydrogenation or by biomass oxidation.[213] Since many years ago, FA has interesting applications such as mild transfer hydrogenation agent,[214] and more recently, it has been revealed as a practical hydrogen storage material.[213] Moreover, its utilization as C_1 alkyl source for reductive alkylation processes in the presence of nucleophiles (i.e., *N*-methylamine synthesis) has undergone important advances, too.[23] In this context, similarly to CO_2, FA has also been employed as C_1 alkyl partner in alcohol hydrogenative etherifications.

Last year, Klankermayer and co-workers developed the only hydrogenative protocol for alcohol etherification using FA as C_1 feedstock (Scheme 37).[215] In this work, the authors employed Ru(Triphos)(tmm)/$Al(OTf)_3$ catalytic system (Scheme 35A) for obtaining several dialkoxymethylene ethers from 1°/2° alcohols and FA. In these conditions, DMM was obtained with TONs up to 1076. Remarkably, it was showed that FA concentration in the methanolic solution had an important impact on the overall process.[215] A notable decrease in the DMM yield was detected when $[FA] < 3.4$ M was employed, which limits the applicability of the process. Despite this limitation, this is a very interesting protocol as FA is an environmentally benign reagent with easier handling and better storage properties than CO_2.

5. Conclusions and Outlook

In the last century, a wide range of applications for ether-type compounds have been encountered in both fine and bulk chemical industries. Hence, synthetic and catalytic communities have been encouraged to develop new protocols for the synthesis of these compounds. Our contribution with this Review has aimed to perform a general summary of the existing methodologies for ether synthesis through catalytic reductive etherification using alcohols and carbonyl-based reagents (aldehydes, ketones, and carboxylic acid derivatives). In the last decade, a significant growth in the number of reports based on this kind of methodologies has been noticed. The growing interest in these protocols is explained by the fact that they enable the access to ethers with a high structural variety, owing to the large available diversity of carbonyl compounds, carboxylic acid derivatives, and alcohols. Moreover, both symmetrical and asymmetrical ethers can be obtained through this methodology, in comparison with other common methodologies such as the acid-promoted direct etherification which only gives access selectively to symmetrical ethers.

In this Review, we have also included related reductive transformations such as the etherification using silyl-activated alcohols and carbonyl compounds, the self-coupling of carbonyl compounds, or the acetal-to-ether reduction. Interestingly, the existing examples of the more challenging reductive ester-to-ether transformation have been also summarized herein. Moreover, in this work we have also presented the examples of alcohol hydrogenative etherifications with CO_2 or formic acid to give dialkoxymethane ethers or related acetals. The high stability of CO_2 and the fact that the obtained acetals can be considered formaldehyde surrogates make this transformation of high interest.

Remarkably, biomass-derived compounds include a variety of carbonyl-type derivatives (i.e., 5-hydroxymethylfurfural, levulinic acid). Due to the high availability of these compounds and the interesting applications of their ether derivatives, reductive etherification protocols using these biomass carbonyl sources as starting materials are especially interesting and constitute an important part of this Review.

Along this work, we have shown the described protocols for reductive etherification employing as reducing agents either Si–H reagents or molecular hydrogen. Although Si–H reductors have proved to be practical from the point of view of requiring mild conditions and exhibiting excellent selectivities, they present the disadvantage of generating large amounts of waste products. For this reason, the future development of this field should be more directed towards developing protocols based on the use of H_2 as sustainable reducing agent. In this sense, more efficient hydrogenating catalysts able to afford good selectivities to the ether need to be designed either in homogeneous as in heterogeneous fields. This is especially important for reactions employing carboxylic acid derivatives or CO_2 as well as ester-to-ether reduction, considering that these are more oxidized and stable derivatives compared with carbonyl compounds. If an analysis of the catalysts described throughout the Review, and the main mechanistic pathways proposed, is made, it can be concluded that generally acidic catalysts or catalytic systems acting under acidic conditions are required to achieve good selectivities to the ether product. Therefore, this key point needs to be considered when designing new and better homogeneous and heterogeneous systems. In the homogeneous area, big efforts should be dedicated to the synthesis of new tailored ligands allowing for more active systems. On the other hand, in the heterogeneous field, the rational design of new nanomaterials with functional supports and enhanced interactions between the metal nanoparticle, nanocluster, or single atoms and the support should be an interesting point for finding active solid catalytic systems. Moreover, another important point for a future design of more sustainable reductive etherification protocols is performing a careful selection of feedstocks, either carbonyl-based compounds or alcohols. Designing ethers with interesting applications synthesized by reductive etherification from starting materials such as CO_2, carbonyl-type reagents/alcohols obtained from biomass or as secondary products of important industrial processes, is also an important focus for chemists working in this field.

From our point of view, the development of new reductive methodologies for ether synthesis that enable obtaining ethers with higher levels of structural complexity is a hot topic for synthetic and catalytic communities. We expect that this Review serves as an inspiration for researchers in these fields willing to develop new reductive etherification processes and better understand their nature.

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Conflict of Interest

The authors declare no conflict of interest.

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