Ethers from esters; from exceptional transformation to synthetic method

Ivana Palej Jakopović,*[a] Samra Kapić,[a] Sulejman Alihodžić,[a] and Vitomir Šunjić[b]

[a] *Fidelta Ltd., Department of Chemistry, Prilaz baruna Filipovića 29, Zagreb, HR-10000, Croatia*
[b] *Croatian Academy of Sciences and Arts, Zrinski trg 11, Zagreb, HR-10000, Croatia*
E-mail: samra.kapic@glpg.com

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

Abstract

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

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

Table of Contents

1. Introduction

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

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

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

2. Overview of Traditional and Less Known Methods

Extensive reviews on the traditional ether-forming reactions are available. [9, 10] Here will be presented general comments on the well-known methods.

Alkylation of an alkoxy anion with an alkylhalide/sulfonate under basic conditions, known as the Williamson synthesis,[11,12] is the most frequently used method for the preparation of ethers. Several *O*-alkylation reactions are variants of Williamson ether synthesis. Most of them are known for a long time, such as alkylation by olefins[13] by dialkyl phosphates,[14] by aldehydes,[15] and by nitro compounds.[16] The major drawback of this method has been viewed as its unsuitability for base sensitive compounds and the generation of stoichiometric amount of inorganic waste, although this second issue seems to have been overcome by a catalytic etherification developed by Strauss and co-workers.[17]

The Ullmann ether synthesis is a reaction, in which a phenol is coupled to an aryl halide to create a diaryl ether in the presence of a copper compound.[18-20] Recently, it was found that addition of relatively cheap ligands (diamines, aminoalcohols, diketones, diols) made this reaction catalytic. Progress has been made by combination of mili-scale processing and microwave heating for the Cu-catalyzed Ullmann etherification in chemical synthesis, providing improved catalytic activity.[21] Also efficient, regio- and chemoselective, reusable, and heterogeneous nano CuO-catalyzed Ullmann type C–O/C–S cross coupling of aryl halide with phenol/thiophenol has been demonstrated at room temperature.[22]

The Mitsunobu reaction represents a number of substitution reactions of primary and secondary alcohols with various nucleophiles, mediated by a redox system consisting of trialkyl- or triarylphosphine and dialkyl azidodicarboxylate.[23-26] This reaction rears different faces when applied in the laboratory and large-scale syntheses. First, it is famous for its scope and power, but also for its separation headaches. Because of so many separation strategies used, the Mitsunobu reaction has been described as "a microcosmos for the new field of strategy level separation".[27] Despite the poor atom economy, this reaction is popular in organic synthesis at various scales because of its broad scope, stereospecificity and mild reaction conditions.

Dehydrative allylation of primary and secondary alcohols to afford ethers are mediated by various palladium catalysts.[28,29] There are many variants of inter- and intramolecular allylations of conjugated double bond, where Pd (II) promotes the addition of alcohols to the coordinated C=C bond.[30,31] The palladium catalyzed etherification of allylic alcohols with phenols is promoted by Ti(IV) isopropoxide, and formation of a transient allyl titanate leading to an η3-allylpalladium intermediate is supported by the formation of diallyl and diisopropyl ethers in the absence of a phenol.[32] Interestingly, we have successfully applied Pd-catalyzed *O*-alkylation of complex macrocyclic alcohols by allyl-tert-butylcarbonate.[33, 34]

Diaryl ethers,[9,35] aryl alkyl ethers[36] and enol ethers[37] can be synthesized by means of a palladium-catalyzed Buchwald-Hartwig reaction. Broad application of this metal-catalyzed coupling reaction has mainly been achieved by developing ever more effective ligands for the catalytic complexes, starting from dinitrogen ligands to mono- and bidentate phosphines, and π-

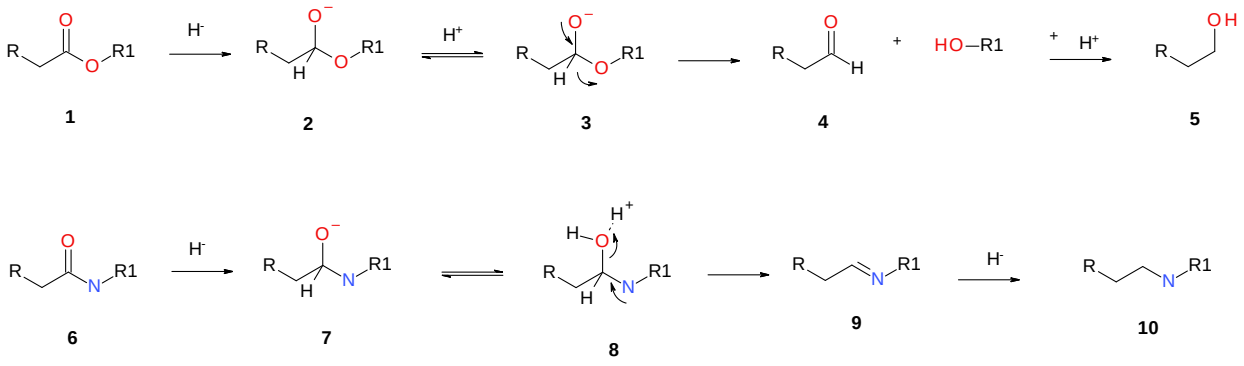
donor alkenes, dba (dibenzylideneacetone) in particular.[38] Recent progress in this reaction include use of bimetallic heterogeneous catalyst [39] and heterocyclic carbenes as ligands.[40]

The Mukaiyama method involves an oxido-reductive condensation *via* alkoxydiphenyldiphosphines, or diphenylphosphinite esters, generated *in situ* from chlorodiphenylphosphines and alcohols, 2,6-dimethylbenzoquinine and phenols.[41,42] The reaction proceeds at low temperatures and under neutral conditions to afford alkyl-aryl ethers in high yields.[43] In 2000 Maruoka and co-workers published a procedure of etherification of benzyl and allylic alcohols by use of the *in situ* prepared complex $MeAl(NTf_2)_2$ as a catalyst.[44] Interestingly, this efficient dimerization of allylic and benzylic alcohols seems not to have been widely introduced since the first report.

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

3. Reduction of Esters to Ethers

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



Scheme 1

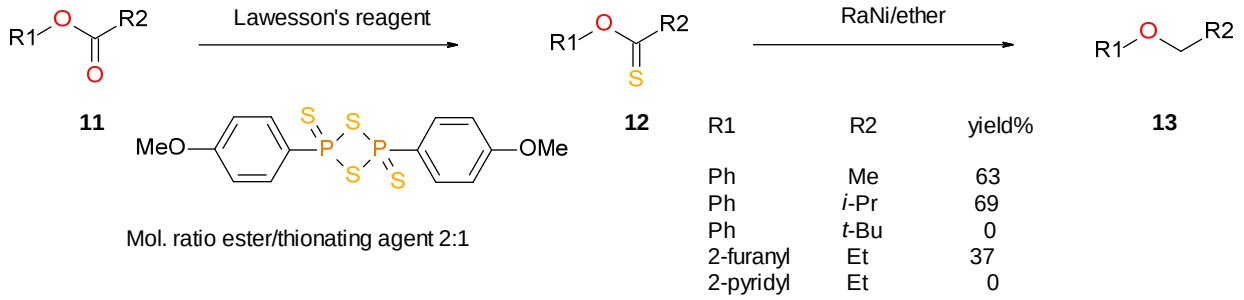
Esters are reduced to alcohols since OR_1 is a better leaving group than OH; elimination of R_1-OH preferred, while amides are reduced to *sec*-amines since elimination of H_2O is preferred.

Protonation of the tetrahedral anionic intermediate **2**, formed on hydride ion addition to ester **1**, affords hydroxyl and alkoxy group in **3**, the later one being a much better leaving group. Intermediary aldehyde **4** is then reduced to the second mole of alcohol **6**. With amides, instead, hydride ion addition and protonation precedes *via* elimination of water in **8** and formation of imine **9** which is then reduced in the second step to the *sec*-amine **10**. From *sec*-amides an intermediary *tert*-imonium ion is formed which is easily reduced to *tert*-amines.

Most of the methods that follow, in particular the catalytic ones, are based on the principle of diminished leaving ability of alkoxy group in favor of the intermediary second, better leaving unit formed from the carbonyl group.

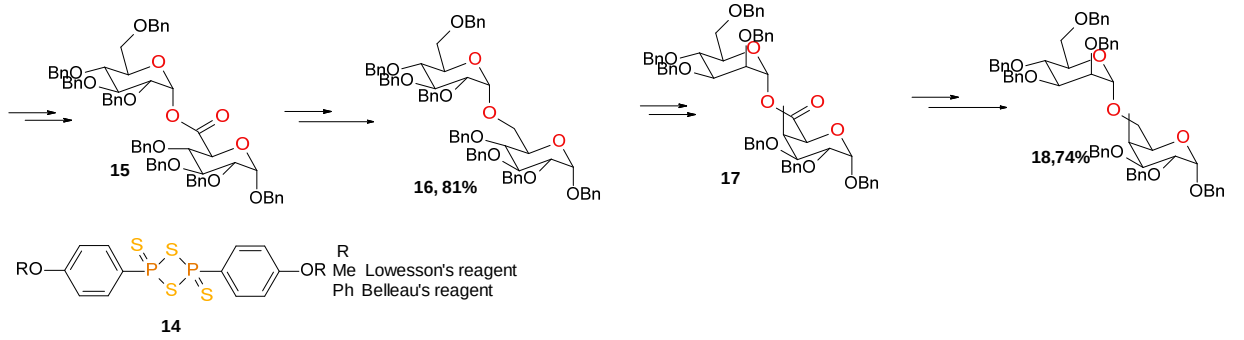
3.1. Reductions *via* thiocarbonylation /hydrogenation

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



Scheme 2

Thionating agent **14** is easily available from P_2S_5 and anisole, but thionation of esters in xylene is completed at reflux temperature over a longer period of time. The later conditions limit application of this method to thermally stable esters. In the next step reduction is completed in a few minutes using RaNi/H_2 in a shaker at -15 ^oC.

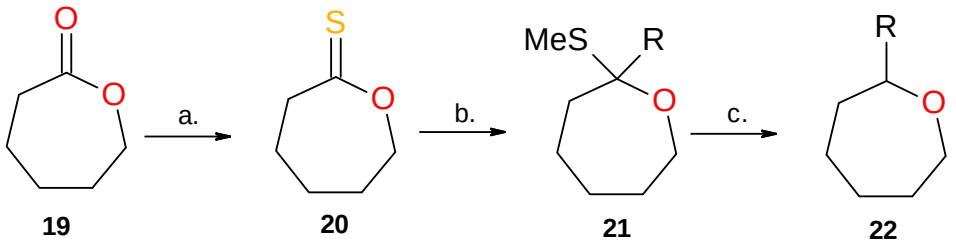


Scheme 3

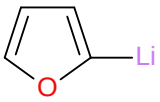
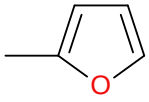
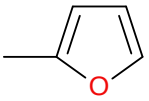
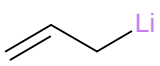
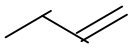
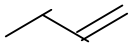
This method has been used in preparation of disaccharides from the corresponding acetal-esters, bound at 1, 6-position by an ether bond (Scheme 3).[51]

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

It is interesting that Belleauove's reagent (**14**, R=Ph) and some of its congeners proved particularly effective in preparation of thiolactones from lactones, and then, in turn, in preparation of cyclic ethers and their α-alkylated analogs (Scheme 4).[52]



19 **20** **21** **22**

Entry	nucleophile (RM)	Addition product (**21**)	yield (%)	Reduction product (**22**)	yield%
1	MeLi	R = Me	83	R = Me	85
2	PhLi	R = Ph	86	R = Me	97
3			92		90
4			86		85

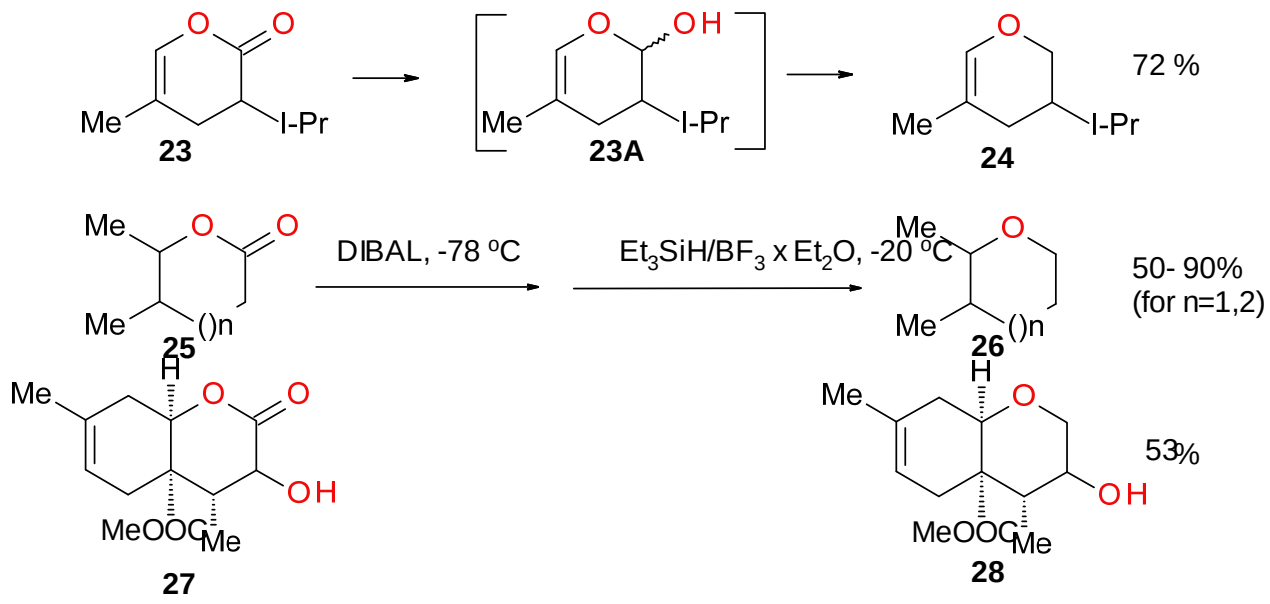
Reaction conditions: a. Belleau's reagent, toluene, reflux, 1 h; b. RM/MeI, THF, -78 °C; c. Ph_3SnH, AIBN, toluene, reflux, 20-25 min.

Scheme 4

Intermediary thionolactones **20** are quenched in a Grignard-type reaction by organometallic nucleophiles and MeI affording alkylated thioacetals. Reductive desulfurization by triphenyltin hydride (Ph_3SnH) affords α-alkylated cyclic ethers **22**. This method has been used in preparation of the key building blocks in the total synthesis of brevetoxine and lautasine.[52]

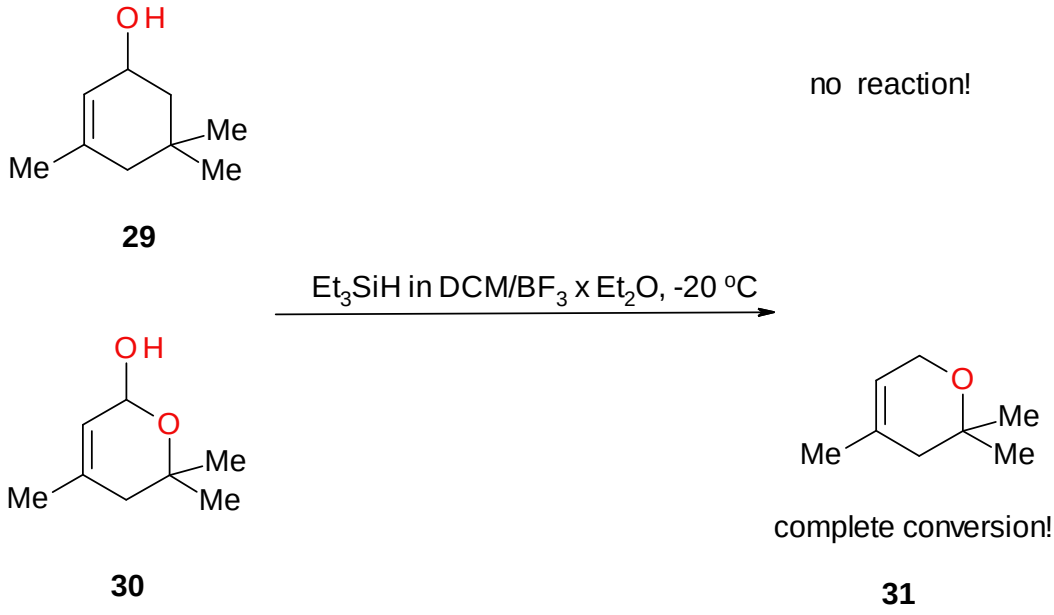
3.2. Reduction by complex hydrides

An early reported two-step method of reduction of lactones to cyclic ethers uses DIBAL in combination with $Et_3SiH/BF_3.Et_2O$ complex (Scheme 5).[53]



Scheme 5

This reaction can be stopped under controlled conditions at the level of the cyclic lactole (hemiacetal), which is an intermediate. Thus, intermediary lactol **30** was isolated in quantitative yield and reduced to **31** by $Et_3SiH/BF_3.Et_2O$ in DCM at -20 °C, (Scheme 6). On the contrary, the allylic OH group in **29** cannot be hydrogenolized by this complex reagent (Scheme 6).

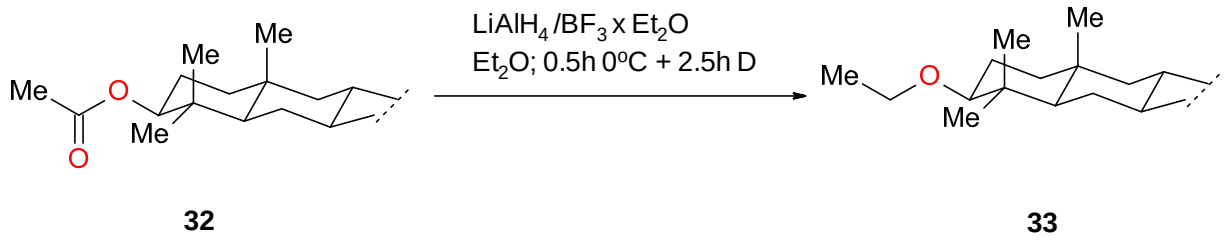


Scheme 6

3.3. Reduction by hydride X BF_3 complexes

There is only one report on the reduction of esters to ethers by $LiAlH_4$-$AlCl_3$ reagent **54**. The authors observed that the molar ratio $LiAlH_4/AlCl_3$ was highly important in determining the yield of the ether. However, the yields of ethers were low (7-15%), and this reagent has not found much application.

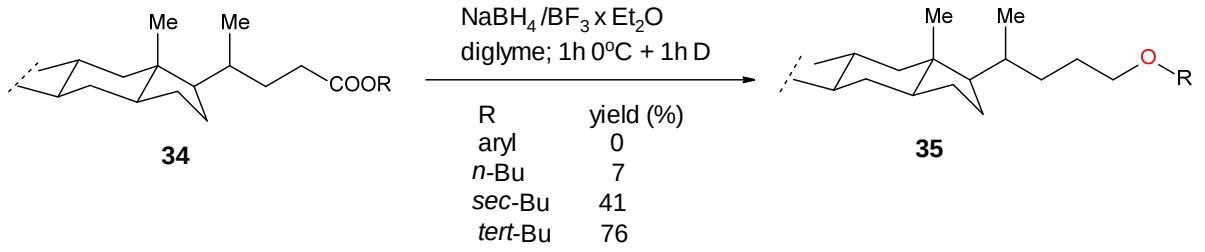
Reduction of esters to ethers by the complex $LiAlH_4/BF_3.Et_2O$ was first described by Pettit *et* al.[55,56] During hydrogenation of 3β-acetoxy derivative of 5α-cholestane **32** the authors observed formation of ether **33** (Scheme 7).



32 **33**

Scheme 7

Soon after the authors observed that this reduction is not specific for the acetoxy group, and completed reduction of esters **34** to ethers **35**, whereby the complex $NaBH_4/BF_3.Et_2O$ proved equally useful (Scheme 8). [57]



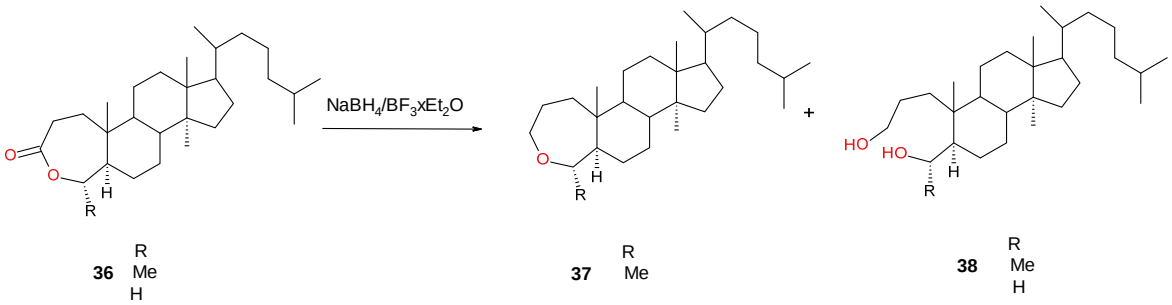
34 **35**

R	yield (%)
aryl	0
n-Bu	7
sec-Bu	41
tert-Bu	76

Scheme 8

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

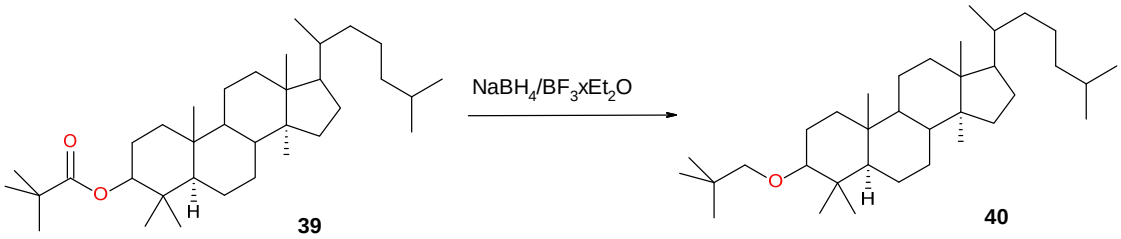
The same reducing complex proved less effective in reduction of lactones **36** to ethers **38**; lactone **36** (R=Me) afforded a mixture of lactone **37** (44%) and diol (42%), while less sterically crowded lactones (R=H) afforded diol as the only product, (Scheme 9).[58,59]



36 R = Me, H **37** R = Me **38** R = Me, H

Scheme 9

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

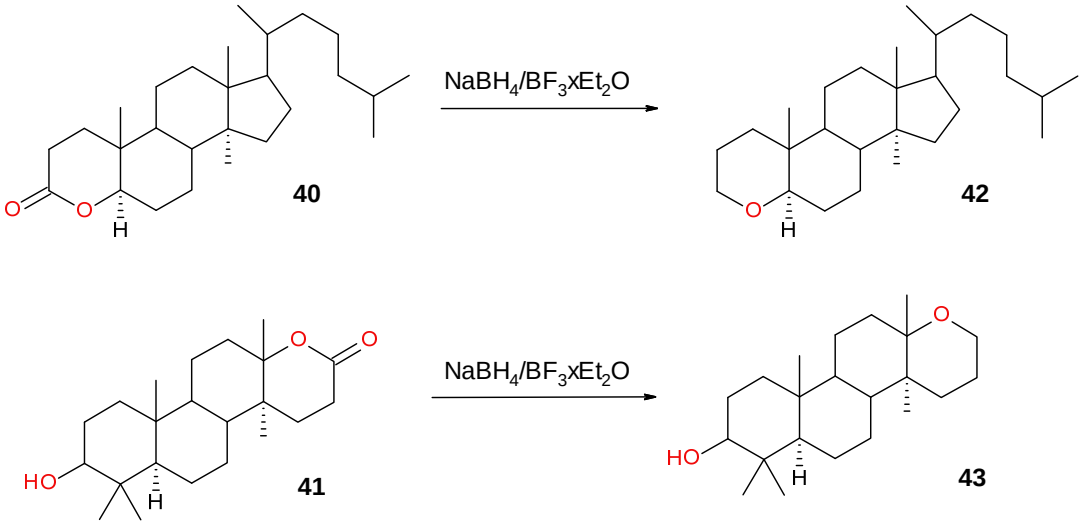


39 **40**

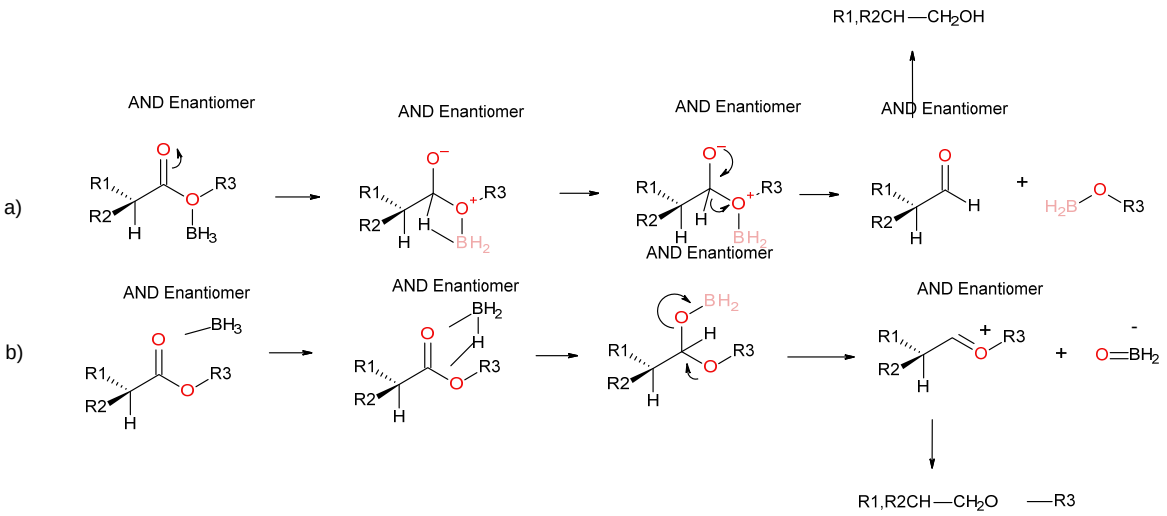
Scheme 10

Conformationally stable δ-lactones **40**, **41** were reduced to tetrahydrofuran derivatives **42**, **43** in 75% and 44% yield, respectively (Scheme 11).[58]

Progress in this approach has been achieved by Morra and Pagenkopf, who prepared strong Lewis acids $BF_2OTf.OEt_2$.[60] It is well known that coordination of Lewis acids to the carbonyl group plays an important role in a number of reactions, such as ene-ractions,[61] addition of silanes and stananes to aldehydes and conjugated enones,[62] Diels-Alder reactions,[63] and aldol reactions; [64] The authors concluded the coordinating ability of the Lewis acid to the carbonyl oxygen can orient reduction of esters to ethers. This effect of Lewis acids is outlined in the Scheme 12.



Scheme 11

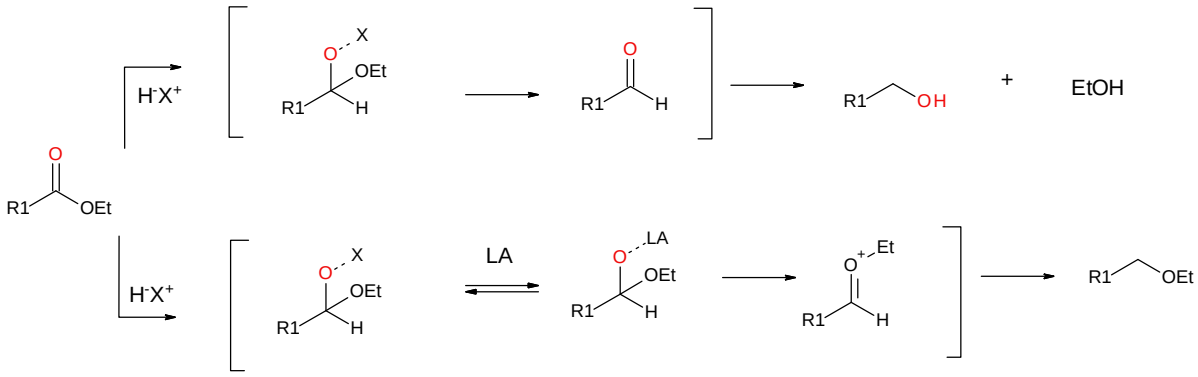


Scheme 12

Whereas path (a) leads to formation of alcohols, on the path (b) the split of the C-O bond is precluded and ethers are formed. Along the route (a) in the first step borane is coordinated to the sp^3 *O*-atom, followed by the transfer of the hydride ion to the carbonyl C-atom, elimination of alkoxyborane accompanied by intermediary formation of aldehyde, which in the fast step is reduced to alcohol. On the route (b) borane is in the first step coordinated to carbonyl sp^2 *O*-atom, then on transfer of hydride ion the best leaving group became oxoborane. In the last and fast step oxonium ion is reduced to ether. It is assumed that steric strain driven by the substituents on the R_3 group precludes formation of an intermediary complex on the route (a) and

favors the complex on the route (b). Along both paths in the last step the hydride ion is transferred, affording two molar equivalents of alcohol in the first case and one molar equivalent of ether in the second one.

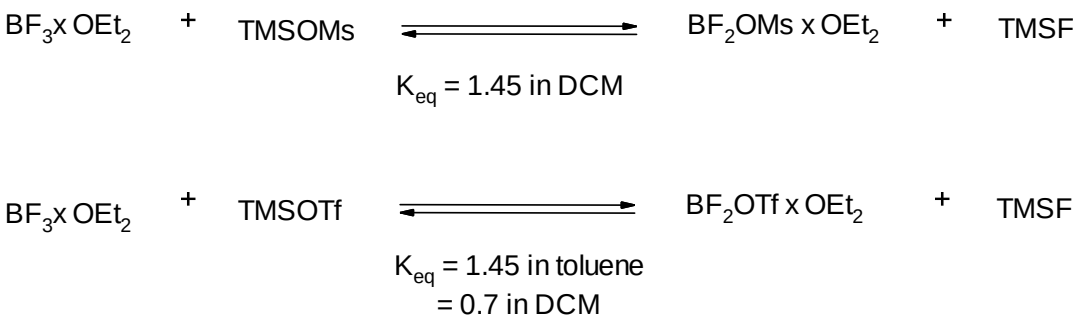
Another presentation of the mechanistic difference in reduction in the presence of protons and Lewis acids is given in the Scheme 13. Direction of reduction to ethers can be controlled by coordination of the strong Lewis acid to the *O*-atom of the carbonyl group.



Scheme 13

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

In order to demonstrate stability of the Lewis acids $BF_3.Et_2O$ (X=Ms, Tf) the authors have determined equilibrium constants for the routes (a) and (b) in the Scheme 14. Both equilibria were achieved in few minutes at ambient temperature.[60]

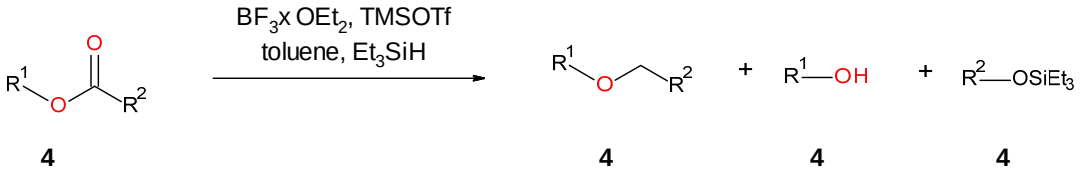


Scheme 14

Using the strongest Lewis acid $BF_2OTf.OEt_2$ the authors completed reduction of the series of esters **44** to ethers **45** (Table 1). In most cases, however, selectivity was low; formation of larger

quantities of alcohols 46 and smaller quantities of silylesters **47** were observed. Presently, this method seems limited to relatively simple aliphatic esters, and requires optimization of reaction conditions in view of the high reactivity of $BF_2OTf.OEt_2$ complex.

Table 1. Reduction of esters with varying steric crowding



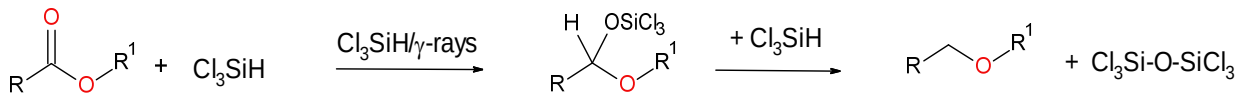
Entry	R^1	R^2	Time (h)	Conditions	Ether (%)	Alcohol (%)	Silylether (%)
1	$Ph(CH_2)_3$	Me	28	A	50	41	8
				B	62	36	0
2	$Ph(CH_2)_3$	i-Pr	72	A	47	44	6
				B	58	40	0
3	$Ph(CH_2)_3$	t-Bu	120	A	47	47	4
				B	57	42	0
4	$Ph(CH_2)_3$	H	24	A	46	48	3
				B	62	36	0
5	Me	$Ph(CH_2)_2$	48	A	52	-	-
				B	70	-	-
6	$Ph(CH_2)_3$	$Ph(CH_2)_2$	72	A	67	20	9
				B	71	26	0

Reaction conditions: A = TMSOTf (6 equiv.), $BF_3.OEt_2$ (1.2 equiv.); B = TMSOTf (1.2 equiv.), $BF_3.OEt_2$ (1.8 equiv.), reduced pressure (40 mmHg), 2h.

3.4. Reductions by silanes and Lewis acids

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

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



Scheme 15

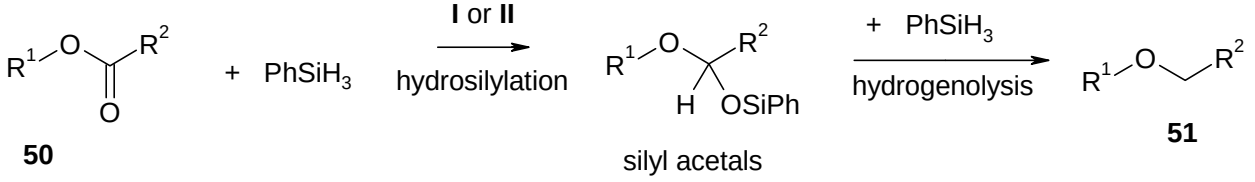
Important modification of this procedure, which requires γ-rays induction, was achieved by the combined use of $TiCl_4$ and TMSOMs.[69] In Table 2 results are shown for the selected group of esters **48** to ethers **49**. One observes the use of a molar excess of Et_3SiH and TMSOTf, and 50% mol excess of $TiCl_4$, presenting a less attractive aspect of this method.

Table 2. Reduction of ester 1a to ether **2a** with Et_3SiH in the presence of $TiCl_4$

Entry	Et_3SiH (mol)	$TiCl_4$ (mol)	TMSOTf (mol)	AgOTf (mol)	TMSCl (mol)	Yield (%) **48**	**49**
1	5.0	3.0	-	-	-	27	61
2	5.0	1.5	0.5	-	-	35	54
3	5.0	1.5	1.5	-	-	65	14
4	5.0	1.5	3.0	-	-	81	-
5	5.0	1.5	3.0	-	-	58	-
6	5.0	-	3.0	-	-	-	88
7	5.0	1.5	-	3.0	-	63	-
8	5.0	1.5	-	3.0	3.0	76	-

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

Hydrosilylation reactions were initially not catalyzed by transition metals and led to prim-alcohols.[70-73] Catalyzed hydrosilylations giving prim- alcohols[74-77] have also been reported by Cutler and co-workers[78] who reported first hydrosilylation of esters to ethers (Scheme 16).



$PhSiH_3$ + (L)(CO)Mn(CO)CH_3 (L= CO, PPh_3) → (L)$(CO)_3$Mn-SiR_3 **I**; → (L)(CO)$MnH(SiR_3)_2$ **II**

$(PPh_3)(CO)MnC(O)CH_3$ catalyzed hydrosilylation by $PhSiH_3$

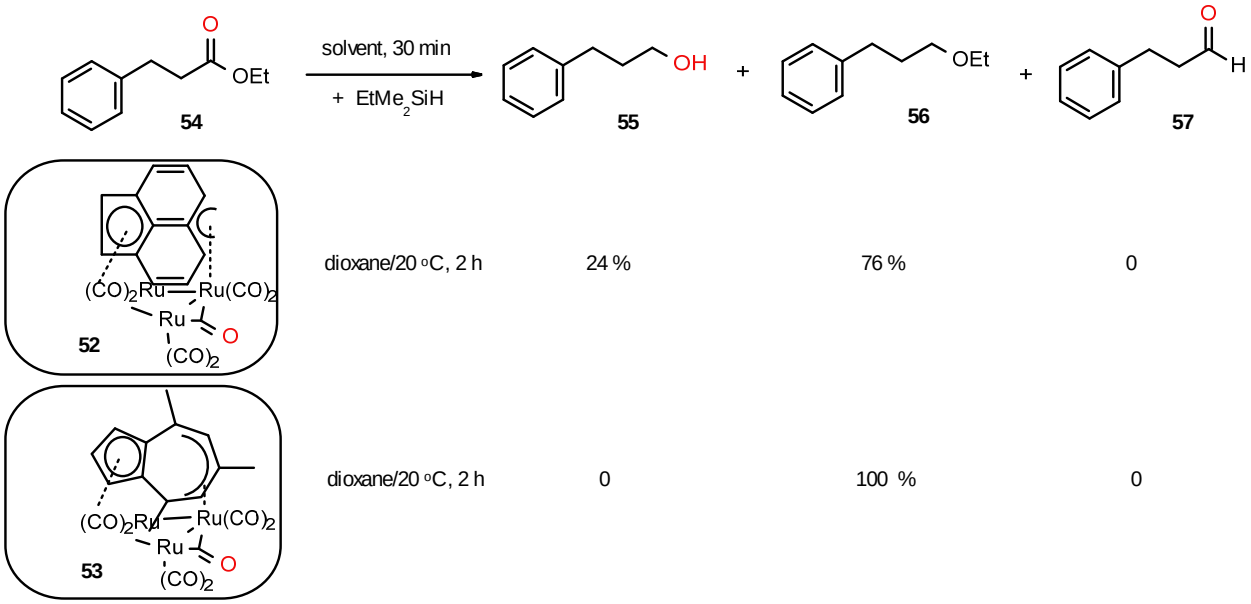
Ester	Conversion of estera, min	Ether, NMR yield%
Me-COOMe, Et	15	85
Me-COOi-Pr	30	95
$Me(CH_2)_4$-COOEt	30	81
Cyclohexyl-COOMe	25	89

Scheme 16

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

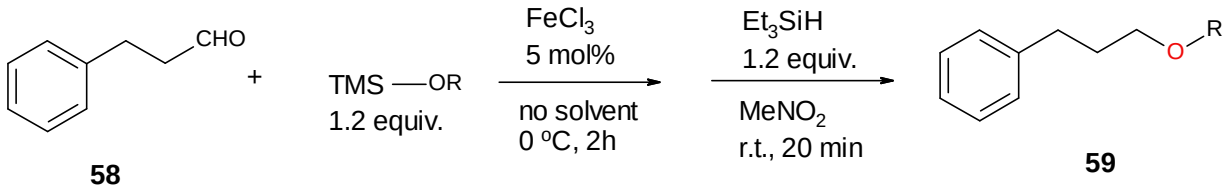
Preparation of catalytic complexes **52** and **53** was reported previously[80] and monitoring of reaction by NMR has shown intermediary formation of silyl acetals, analogous to that shown in the Scheme 16. Complex **53** proved completely selective in formation of ether **56**, at room temperature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

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



Scheme 17

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



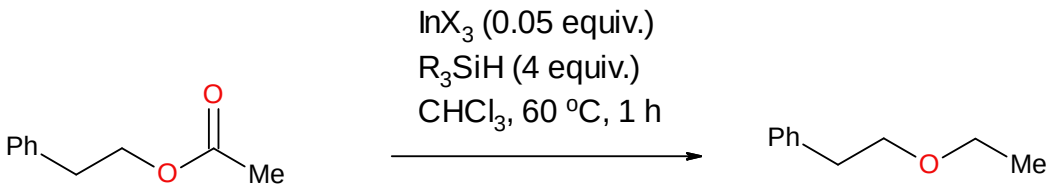
58 **59**

R	Yield%
benzyl	85
n-Bu	89
cyclohexyl	70
t-Bu	33

Scheme 18

By this two-step one-pot reductive alkylation aromatic aldehydes can also be alkylated, though the yields are somewhat lower. The obvious advantages of the method are the cheap catalyst and short reaction time under mild conditions. A development of this method involves the application of $InBr_3/Et_3SiH$ as the catalytic system.[83] Selection of the solvents and optimization of the reaction conditions is presented (Table 3).

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

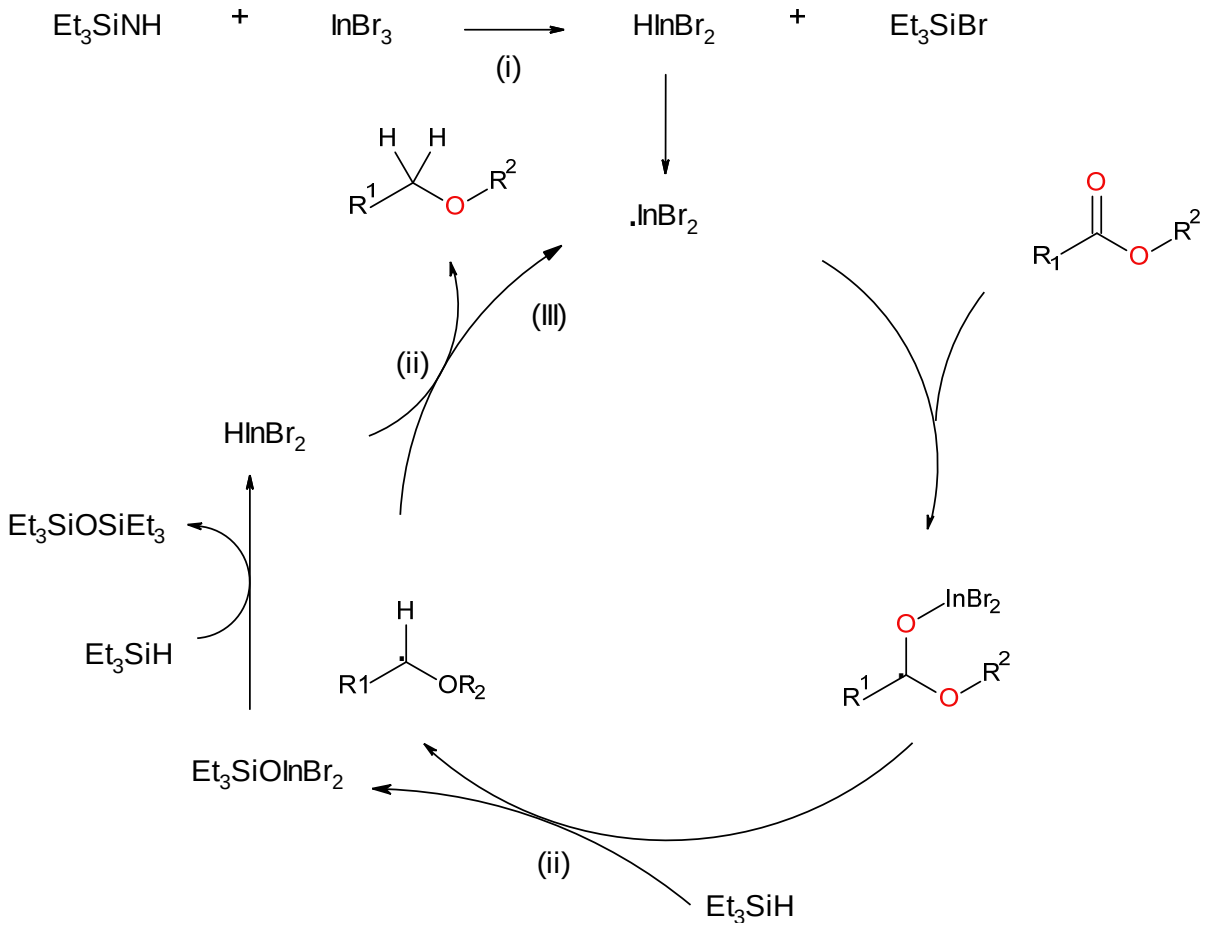


60 (1 equiv.) **61**

Entry	InX_3	R_3SiH	Solvent	Yield (%)
1	$InBr_3$	Et_3SiH	$CHCl_3$	99
2	$InBr_3$	Et_3SiH	PhH	90
3	$InBr_3$	Et_3SiH	PhMe	85
4	$InBr_3$	Et_3SiH	THF	NR
5	$InBr_3$	Et_3SiH	MeCN	4
6	$InBr_3$	Et_3SiH	$CHCl_3$	NR
7	$In(OTf)_3$	Et_3SiH	$CHCl_3$	Trace
8	$IN(OAc)_3$	Et_3SiH	$CHCl_3$	NR
9	$InBr_3$	$(EtO)_3SiH$	$CHCl_3$	10
10	$InBr_3$	$PhMe_2SiH$	$CHCl_3$	94

NR = no reaction

Chloroform was found to be the best solvent; benzene and toluene were nearly as good, whereas reaction in THF and MeCN did not proceed. When the reaction was attempted in the presence of $InCl_3$, $In(OAc)_3$ and $In(OTf)_3$ no product was observed. Best results were obtained with 0.05 equiv. of $InBr_3$ and 4 equiv. of Et_3SiH in chloroform. The authors suggested the mechanism shown below (Scheme 19).

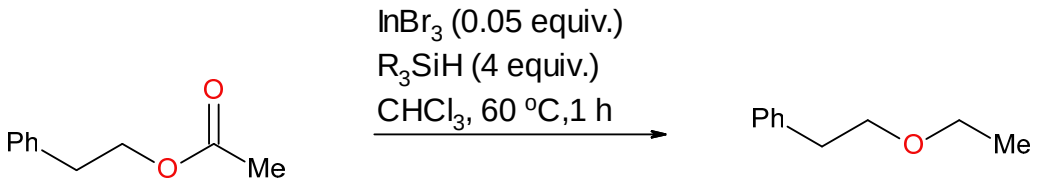


Scheme 19

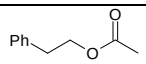
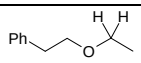
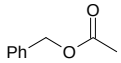
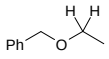
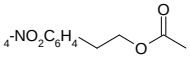
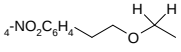
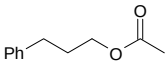
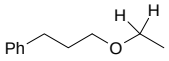
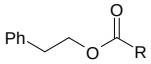
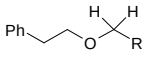
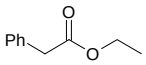
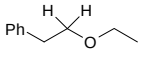
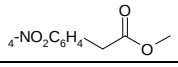
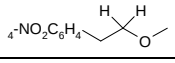
This process includes the following steps; (i) initial transmetalation between $InBr_3$ and Et_3SiH, (ii) formation of a radical intermediate, consecutive split of the H atom from Et_3SiH and formation of the radical ether product, (iii) and in the final step the indium radical species is regenerated.

In a following paperi[84] the authors have applied this method to selected esters (Table 4).

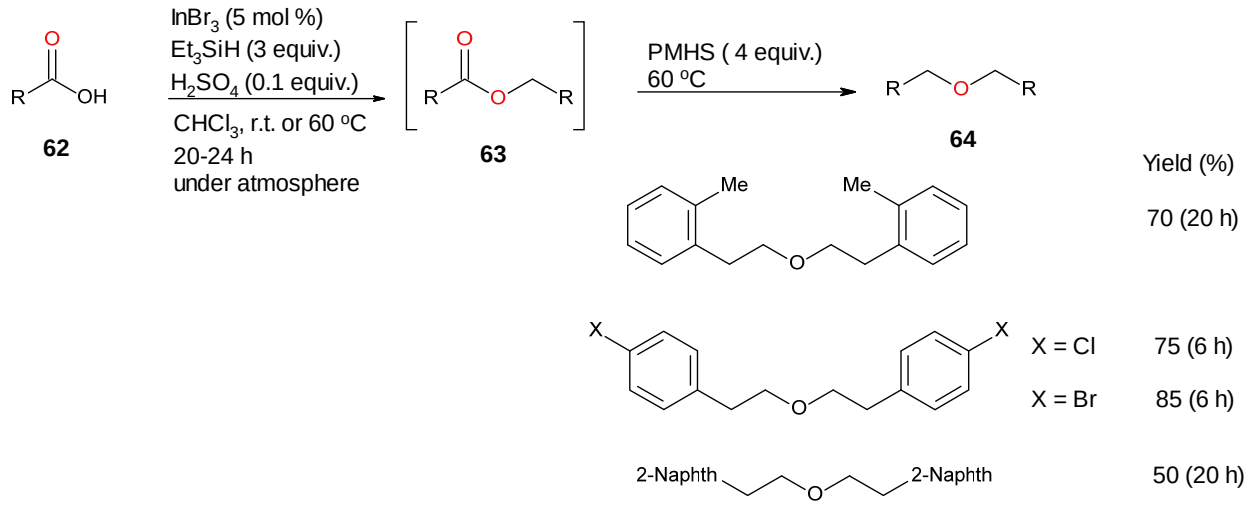
Table 4. Reduction of esters to ethers by $InBr_3/Et_3Si$



60 **61**

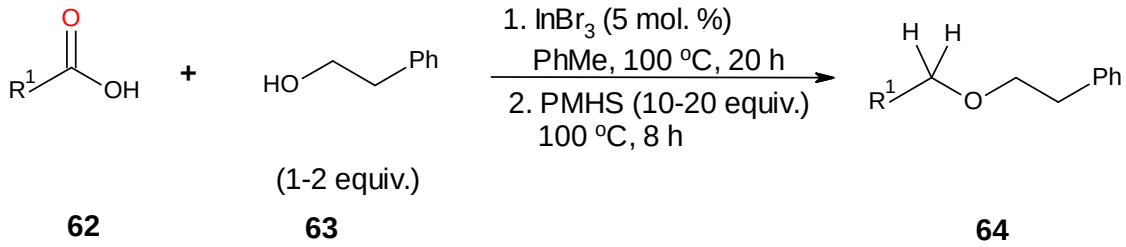
Entry	Ester **60**	Time (h)	Ether **61**	Yield (%)
1		1		92
2		1		69
3		3		61
4		4		89
5	 R = *n*-Pr	10	 R = *n*-Pr	71
6	R = *i*-Pr	1	R = *i*-Pr	71
7	R = *t*-Bu	10	R = *t*-Bu	30
8	R = cyclopropyl 1h	10	R = cyclopropyl 2h	53
9		1		89
10		6		62

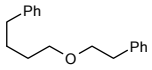
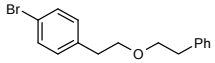
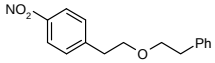
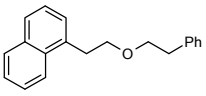
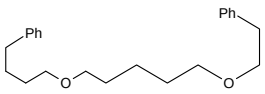
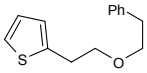
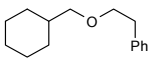
The results demonstrate compatibility of the process with the presence of the nitro group, bromine atom and thiophene ring, and revealed that sterically crowded groups in the alcohol do not hinder the reduction. 5-And 6-membered lactones are reduced to cyclic ethers in high yields. The same authors[85,86] reported on another aspect of catalytic deoxygenation of esters by $InBr_3/R_3SiH$. In the first paper sequential preparation of symmetrical ethers has been accomplished (Scheme 20).[85]



Scheme 20

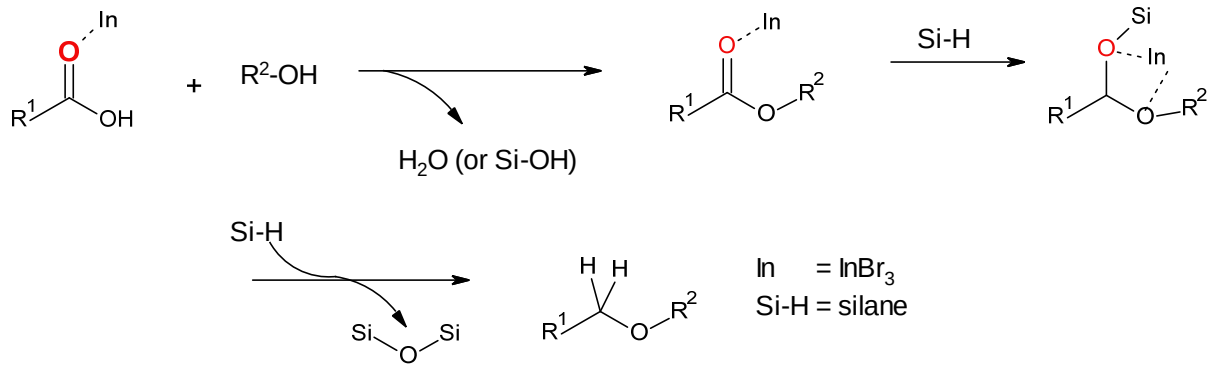
Table 5. One-pot synthesis of ethers from various carboxylic acids and phenylethyl alcohol



Entry	Silane (equiv.)	Product	Yield (%)
1	10		82
2	15		91
3	15		45
4	10		92
5	20		58
6	15		48
7	10		71

In the first step unprecedented reductive dimerization of two carboxylic acids **62** to produce ester derivatives **63** by combination of the catalyst involving $InBr_3$ and sulfuric acid is achieved. A sequential conversion of the *in-situ* formed ester to symmetrical ethers was accomplished in the same pot by indium-catalyzed deoxygenation of the ester with a hydrosilane.[86] In the second paper [86] the authors have developed "a widely applicable and direct method" of etherification from carboxylic acid and an alcohol by indium-catalyzed deoxygenation of the transient esters to ethers **64**. They also demonstrated remarkable tolerance of the catalytic system in the presence of several functional groups including alkenes, halogens, nitro group and hererocyclic unit, Table 5.

A plausible mechanism for the indium-catalyzed reductive deoxygenation of esters en route to ethers is presented in the Scheme 21. [85]



Scheme 21

According to this mechanism $InBr_3$ has several roles, the first being to promote the condensation of a carboxylic acid and an alcohol and to subsequently activate the ester formed *in situ* to facilitate hydrosilylation by a silane. The silyl acetal thus generated is then again activated by $InBr_3$ transforming the corresponding ether by the second hydrosilylation and desiloxylation.

4. Conclusions

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

5. Acknowledgment

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

6. References

1. Blanksby, S. J.; Ellison, G. B. "Bond Dissociation Energies of Organic Molecules" in *Acc Chem. Res*. **2003**, *36*, 255–263. http://dx.doi.org/10.1021/ar020230d
2. Addis, D.; Das, S.; Junge, K.; Beller, M. *Angew. Chem. Int. Ed*. **2011**, *50*, 6004. http://dx.doi.org/10.1002/anie.201100145
3. Clarke, M. L. *Catal. Sci. Technol*. **2012**, (2), 2418. http://dx.doi.org/10.1039/C2CY20601C
4. Igarashi M.; Mizuno R, Fuchikami, T. *Tetraheron Lett*. **2001**, *42*, 2149. http://dx.doi.org/10.1016/S0040-4039(01)00094-6
5. Cheng, C.; Brookhart, M. *Angew. Chem. Int. Ed*. **2012**, *51*, 9422. http://dx.doi.org/10.1002/anie.201205154
6. Li, H.; Misal Castro, L. C.; Zheng, J.; Roisnel, T.; Dorcet, V.; Sortais, J.-B.; Darcel, C. *Angew. Chem. Int. Ed.* **2013**, *52*, 8045. http://dx.doi.org/10.1002/anie.201303003
7. March, J.; March's Advanced Organic Chemistry, Reaction, Mechanims and Structure, 6th ed.; Wiley&Sons, New York, 2007, pp. 529.
8. Sawyer, J. S. *Tetrahedron* **2000**, *56*, 5045 http://dx.doi.org/10.1016/S0040-4020(00)00257-X
9. Frlan, R.; Kikelj, D. *Synthesis* **2006**, *14*, 2271. http://dx.doi.org/10.1055/s-2006-942440
10. Williamson, A.W. *J. Chem. Soc*. **1852**, *4*, 229. http://dx.doi.org/10.1039/QJ8520400229
11. Bugget,N. Comprehensive Organic Synthesis, Barton, D.; Ollis, W. D.; Eds.; Pergamon Oxford 2000, Vol. 1, 799.
12. March, J.; March's Advanced Organic Chemistry, Reaction, Mechanims and Structure, 5th ed.; Wiley&Sons, New York. 2001, p. 477.
13. Callahan, F. M.; Anderson, G. W.; Paul, R.; Zimmerman, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 201. http://dx.doi.org/10.1021/ja00885a020
14. Kashman, Y. *J. Org. Chem*. **1972**, *37*, 912. http://dx.doi.org/10.1021/jo00971a021
15. Torii, S.; Takagishi, S.; Inokuchi, T.; Okumoto, H. *Bull. Chem. Soc. Jpn*. **1987**, (60), 775. http://dx.doi.org/10.1246/bcsj.60.775

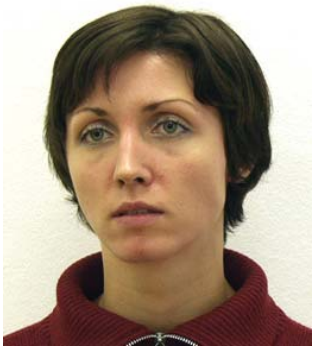
16. Sammers, P. G.; Thetford, D.; Voyle, M. *J. Chem. Soc. Chem. Commun*. **1987**, 1373. http://dx.doi.org/10.1039/C39870001373
17. Bagnell, L; Cablewski, T.; Strauss, C. R. *Chem. Commun*. **1999**, 283. http://dx.doi.org/10.1039/A808980I
18. Ullmann F.; Sponagel P. *Chem. Ber*. **1905**, *38*, 2211. http://dx.doi.org/10.1002/cber.190503802176
19. Ullmann, F. Bielecki, J. *Chem. Ber.* **1901**, *34*, 2174. http://dx.doi.org/10.1002/cber.190103402141
20. Ullmann, F. *Chem. Ber*. **1903**, *36*, 2382. http://dx.doi.org/10.1002/cber.190303602174
21. Benaskar, F.; Patil, N. G.; Engels, V.; Rebrov, E. V.; Meuldijk, J.; Hulshof, L. A.; Hessel, V.; Wheatley, A. E. H.; Schouten, J. C. *Chem. Eng. J*. 2012, *207–208*, 426. http://dx.doi.org/10.1016/j.cej.2012.06.147
22. Babu, S. G.; Karvembu, R. *Tetrahedron Lett*. **2013**, *54* 1677. http://dx.doi.org/10.1016/j.tetlet.2013.01.063
23. Mitsunobu, O.; Comprehensive Organic Synthesis, Trost, B. M.; Fleming, I. Eds.; Pergamon New York, 1991, Vol. 6.
24. Kumara Swamy, K. C.; Bhuvan Kumar, N.N.; Balaraman E.; Pavan Kumar, K.V.P. *Chem. Rev.* **2009**, *109*, 2551. http://dx.doi.org/10.1021/cr800278z
25. Shi, J.; Hughes, D. L.; McNamara, J. M. *Tetrahedron Lett*. **2003**, *44*, 3609. http://dx.doi.org/10.1016/S0040-4039(03)00728-7
26. Guanti, G.; Banfi, L.; Basso, A.; Bevilacqua, E.; Bindanza, L.; Riva, R. *Tetrahedron: Asymmetry* **2004**, *15*, 2889. http://dx.doi.org/10.1016/j.tetasy.2004.07.040
27. Dandapani S.; Curran, D. P. *Chem. Eur. J*. **2004**, *10*, 3130. http://dx.doi.org/10.1002/chem.200400363
28. Zumpe, F. L.; Kazmaier, U. *Synthesis* **1999**, 1785. http://dx.doi.org/10.1055/s-1999-3598
29. Muzart, J. *Tetrahedron* **2005**, *61*, 5955. http://dx.doi.org/10.1016/j.tet.2005.04.002
30. Hosokawa, T.; Shinohara, T.; Ooka, Y.; Murahashi, S.-I. *Chem. Lett*. **1989**, 2001. http://dx.doi.org/10.1246/cl.1989.2001
31. Miller, K. J.; Kitagawa, T. T.; Abu-Omar, M. M. *Organometallics* **2001**, *20*, 4403. http://dx.doi.org/10.1021/om0103097
32. Satoh, T.; Ikeda, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1997**, *62*, 4877. http://dx.doi.org/10.1021/jo970534r
33. Palej Jakopović, I.; Kragol, G.; Forrest, A. K.; Frydrych, C. S. V; Štimac, V.; Kapić ,S.; Matanović´ Škugor, M.; Ilijaš, M.; Čipčić Paljetak, H.; Jelić, D.; Holmes, D. J.; Hickey, D.

M. B.; Verbanac, D.; Eraković Haber, V.; Alihodžić , S. *Bioorg. Med. Chem.* **2010**, *18*, 6578–6588.
http://dx.doi.org/10.1016/j.bmc.2010.07.007
34. Kapić, S.; Č ipčić Paljetak, H.; Palej Jakopović, I.; Fajdetić, A.; Ilijaš, M.; Štimac, V.; Brajša, K.; Holmes, D. J.; Berge J.; Alihodžić, S. *Bioorg. Med. Chem.* **2011**, *19*, 7281–7298.
http://dx.doi.org/10.1016/j.bmc.2011.07.010
35. Burgos, C. H.; Barder, T. E.; Huang, X.; Buchwald, S. L. *Angew. Chem. Int. Ed*. **2006**, *45*, 4321.
http://dx.doi.org/10.1002/anie.200601253
36. (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, (31), 805.
http://dx.doi.org/10.1021/ar9600650
(b) Hartwig, J. F. *Acc. Chem. Res*. **1998**, *31*, 852.
http://dx.doi.org/10.1021/ar970282g
37. Dehli, J. R.; Legros, J.; Bolm, C. *Chem. Commun*. **2005**, 973.
http://dx.doi.org/10.1039/B415954C
38. Olivera R.; SanMartin R.; Churruca, F.; Dominguez, E. *J. Org. Chem*. **2002**, *67*, 7215.
http://dx.doi.org/10.1021/jo025767j
39. Lipschutz, H. B.; Nihan, D. M.; Vinogradova E.; Taft, B. R.; Bošković, Ž. V. *Org. Letters* **2008**, *10*, 4279.
http://dx.doi.org/10.1021/ol801676u
40. Akkoca, M.; Gurbuza, N.; Cetinkayab, E.; Ozdemir, I. *Synlett* **2008**, 1781.
http://dx.doi.org/10.1055/s-2008-1078548
41. Shi, Y.-J.; Hughes, D. L.; McNamara, J. M.; *Tetrahedron Lett*. **2003**, *44*, 3609.
http://dx.doi.org/10.1016/S0040-4039(03)00728-7
42. Shintou, T.; Mukayama, T. *Chem. Lett.* **2003**, *32*, 984.
http://dx.doi.org/10.1246/cl.2003.984
Ibid. **2003**, *32*, 1100.
http://dx.doi.org/10.1246/cl.2003.1100
43. Shintou, T.; Mukaiyama, T. *J. Am. Chem. Soc*. **2004**, *126*, 7359.
http://dx.doi.org/10.1021/ja0487877
44. Ooi, T.; Ichikawa, H.; Itagaki, Y.; Maruoka, K. *Heterocycles*, **2000**, *52*, 575.
http://dx.doi.org/10.3987/COM-99-S99
45. Bethmont, V.; Fache F.; Lemaire, M. *Tetrahedron Lett*. **1995**, *36*, 4235.
http://dx.doi.org/10.1016/0040-4039(95)00730-Z
46. Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.
http://dx.doi.org/10.1021/cr000664r
47. Fujii, Y.; Furugaki, H.; Kita K.; Morimoto, H.; Uno, M.; Kajihara, Y. U.S. Pat 6011071 (2000), Prior. Appl. Jpn. Patent JP 95118309, 17 May, 1995. Chem. Abstr. **1997**, *126*, 61873.
48. Fujii ,Y.; Furukaga, H.; Tamura, E.; Yano, S.; Kita, K. *Bull. Chem. Soc. Jpn*. **2005**, *78*, 456.

http://dx.doi.org/10.1246/bcsj.78.456
49. Pedersen, B. S.; Shheibye, S.; Clausen, K.; Lawson, S. O. *Bull. Soc. Chim. Belg*. **1978**, *87*, 223.
50. Baxter, S. L.; Bradshaw, J. S. *J. Org. Chem*. **1981**, *46*, 831. http://dx.doi.org/10.1021/jo00317a045
51. Barrett, A. G. M.; Lee, A. C. J. *Org. Chem*. **1992**, *57*, 2818. http://dx.doi.org/10.1021/jo00036a012
52. Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Kim, B. H.; Ogilvie, W. W.; Yiannikouros, G.; Prasad, C. V. C.; Veale, C. A.; Hark, R. *J. Am. Chem. Soc*. **1990**, *112*, 6263. http://dx.doi.org/10.1021/ja00173a013
53. Kraus, G. A. Frazier, K. A.; Roth, B. C.; Taschner, M. J.; Neunschwander, K. *J. Org. Chem.* **1981**, *46*, 2417. http://dx.doi.org/10.1021/jo00324a050
54. Maione, A. M.; Torrini, J. *Chemistry & Industry* **1975**, *19*, 839-40.
55. Pettit, G. R.; Kasturi, T. R. *J. Org. Chem*. **1960**, *25*, 875. http://dx.doi.org/10.1021/jo01075a635
56. Pettit, G. R.; Kasturi, T. R. *J. Org. Chem*. **1961**, *26*, 4553. http://dx.doi.org/10.1021/jo01069a086
57. Pettit, G. R.; Kasturi, T. R. *J. Org. Chem*. **1962**, *27*, 2127. http://dx.doi.org/10.1021/jo01053a054
58. Dias, J. R.; Pettit, G. R. *J. Org. Chem*. **1971**, *36*, 3485. http://dx.doi.org/10.1021/jo00822a003
59. Pettit, G. R.; Green, B.; Kasturi, T. R.; Ghatak, U. R. *Tetrahedron* **1962**, *18*, 953. http://dx.doi.org/10.1016/S0040-4020(01)92749-8
60. Morra, N. A.; Pagenkopf, B. L. S*ynthesis* **2008**, 511. http://dx.doi.org/10.1055/s-2008-1032141
61. Snieder, B. B.; *in Comprehensive Organic Chemistry*, Trost, B. M.; Fleming, I., Pergamon Press. Oxford **1991**, Vol. 2, Chapter 2.1., 527.
62. Konig, K., Neumann, W. P. *Tetrahedron Lett*. **1967**, 493-498. http://dx.doi.org/10.1016/S0040-4039(00)90536-7
63. Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev*. **1993**, *93*, 741.
64. http://dx.doi.org/10.1021/cr00018a006
65. Carreira, E. M. *in Modern Carbonyl Chemistry*, Otera J., Ed.; Wiley. Weinheim 2000, Chapter 8.
66. Boyer, J.; Corriu, R. J.; Perz, R.; Poirier, M.; Reye, M. *Synthesis* **1981**, 558. http://dx.doi.org/10.1055/s-1981-29527
67. Tsurugi, J.; Nakao, R.; Fukumoto, T. *J. Am. Chem. Soc*. **1969**, *91*, 4587. http://dx.doi.org/10.1021/ja01044a067
68. Baldwin, S.; Hant, S. A. *J. Org. Chem*. **1975**, *40*, 3885. http://dx.doi.org/10.1021/jo00914a016

69. Calas, R.; Frainet, E.; Bonastre, J. *Compt. Rend*. **1960**, *251*, 2987.
http://dx.doi.org/10.1007/978-1-4684-2142-2_23
70. Yato, M.; Homma, K.; Ishida, A. *Tetrahedron* **2001**, 57, 5353.
http://dx.doi.org/10.1016/S0040-4020(01)00420-3
71. Calas, R. *Pure Appl. Chem*. **1966**, *13*, 61
http://dx.doi.org/10.1351/pac196613010061
72. Chuit, C.; Corriu, R. J. P.; Perz, R.; Reye, C. *Synthesis* **1982**, 981.
http://dx.doi.org/10.1055/s-1982-30035
73. Corriu, R. J. P.; Perz, R.; Reye, M. *Tetrahedron* **1983**, *39*, 999.
http://dx.doi.org/10.1016/S0040-4020(01)88599-9
74. Benkeser, R. A.; Ehler, D. F. *J. Org. Chem*. **1973**, *38*, 3660.
http://dx.doi.org/10.1021/jo00960a062
75. Berk, S. C.; Kreutzer, K. A.; Buchwald, S. L. *J. Am. Chem. Soc*. **1991**, *113*, 5093.
http://dx.doi.org/10.1021/ja00013a074
76. Berk, S. C.; Buchwald, S. L. *J. Org. Chem.* **1992**, *57*, 3751.
http://dx.doi.org/10.1021/jo00040a001
77. Barr, K. J.; Berk, S. C.; Buchwald, S. L. *J. Org. Chem*. **1994**, *59*, 4323.
http://dx.doi.org/10.1021/jo00094a056
78. Bower, S.; Kristina, K. A.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1996**, *35*, 1515.
http://dx.doi.org/10.1002/anie.199615151
79. Mao, Z.; Gregg, B. T.; Cutler, A. R. *J. Am. Chem. Soc*. **1995**, *117*, 10139.
http://dx.doi.org/10.1021/ja00145a036
80. Matsubara, K.; Iura, T.; Maki, T.; Nagashima, H. *J. Org. Chem*. **2002**, *67*, 4985.
http://dx.doi.org/10.1021/jo025726n
81. Nagashima, H.; Suzuki, A.; Iura, T.; Ruy, K.; Matsubara, K. *Organometallics* **2000**, *19*, 3579.
http://dx.doi.org/10.1021/om0003887
82. Hanada, S.; Yuasa, A.; Kuriowa, H.; Motoyama, Y.; Nagashima, H. *Eur. J. Org. Chem*. **2010**, *6*, 1021.
http://dx.doi.org/10.1002/ejoc.200901279
83. Iwanami, K.; Seo, H.; Oriyama, T. *Synthesis* **2005**, 183.
http://dx.doi.org/10.1055/s-2004-834942
84. Sakai, N.; Moriya, T.; Konakahara, T. *J. Org. Chem*. **2007**, *72*, 5920.
http://dx.doi.org/doi/pdfplus/10.1021/jo070814z
85. Sakai, N.; Moriya, T.; Fujii, K.; Konakahara, T. *Synthesis* **2008**, 3533.
http://dx.doi.org/10.1055/s-0028-1083191
86. Sakai, N.; Usui, Y.; Ikeda, R.; Konakahara, T. *Adv. Synth. Catal.* **2011**, (353), 3397.
http://dx.doi.org/10.1002/adsc.201100524
87. Sakai, N.; Usui, Y.; Moriya, T.; Ikeda, R.; Konakahara, T. *Eur. J. Org. Chem.* **2012**, 4603.
http://dx.doi.org/10.1002/ejoc.201200552

Authors Biographies



Ivana Palej Jakopović, completed her PhD degree in 2011 under the supervision of Kata Majerski, Prof. and Sulejman Alihodžić, focused on the discovery of new macrolide antibiotics. She started her industrial career in PLIVA Research Institute and for several years she has been working in the field of anti-inflammatory drugs in GSK research Centre Zagreb. Currently she is working in the Scale up group in Fidelta Ltd. She is an author/co-author of seven original scientific articles published in journals quoted by CC and six patent applications.

Samra Kapić completed her Ph.D. degree in 2010 under the supervision of Prof. Vitomir Šunjić and Dr Sulejman Alihodžić, working on the discovery of new macrolide antibiotics. She started working in pharmaceutical industry in 2002 as a Synthetic Chemist at PLIVA Research Institute, since 2006 she has been working as a Senior scientist - Medicinal chemist in GSK research centre Zagreb which is now Fidelta Ltd. in the field of anti-infectives and anti-inflammation. She is an author/co-author of seven original scientific articles published in journals quoted by CC and three patent applications.

Sulejman Alihodžić completed his M.Sc. and Ph.D. degrees in 1992 and 1995, respectively, in Organic Chemistry under the supervision of Prof. Mladen Žinić at Ruđer Bošković Institute in Zagreb. From 1996 to 1998 he was a Robert A. Welch Post-doctoral Fellow at the University of North Texas where he worked with Prof. Alan P. Marchand in the area of high energy cages, aza- and diaza-crown ethers and kalixarenes. He started his industrial carrier in 1998 working in the pharmaceutical and biotech companies PLIVA, GlaxoSmithKline and Galapagos holding several leading positions including a Head of Chemistry (GSK) Zagreb. His work, focused mainly on anti-infective and anti-inflammatory research has contributed to the progression of several drug discovery projects. This is complemented by his extensive experience in the scale-up and physico-chemical profiling of NCEs. S.Alihodžić is author or coauthor of over 45 scientific papers and has applied for over 25 patents.

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

Committee, and from 2001-2003 acted as the President of this Committee. He was awarded in 1990 by National price for research in chemistry, and in 1996 by the National Academy price for research in organic chemistry. From 2012 he is elected member of Croatian Academy of Sciences and Arts.

Graphical Abstract

