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COMMUNICATION

Synthesis of ethers from esters *via* Fe-catalyzed hydrosilylation†

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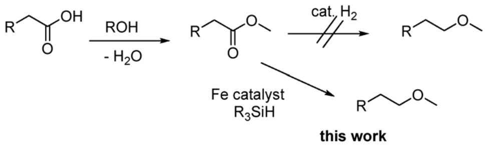
Triiron dodecacarbonyl allows for the selective reduction of esters into the corresponding ethers. This protocol has a wide substrate scope. In addition, cholesteryl pelargonate has been reduced under the reaction conditions with an excellent yield.

Aliphatic and aromatic ethers represent valuable building blocks for fine chemicals as well as polymers and dyes.[1] In addition, this structural motif is also found in a number of pharmaceuticals and agrochemicals. The most common approach for the synthesis of ethers makes use of nucleophilic substitution reactions of alkoxides with alkyl halides/sulfonates under basic conditions (Williamson synthesis).[2] In addition, acid-promoted condensations of alcohols,[3] and for aromatic ethers Buchwald–Hartwig cross-coupling reactions are frequently applied.[4] Despite these achievements, the development of novel methods for the synthesis of ethers continues to be an active area of research.[5] Among the different possible starting materials for ether synthesis, carboxylic esters constitute promising candidates. It is well known that they can be prepared in a benign manner. Subsequent catalytic hydrogenation would allow for a salt-free synthesis of ethers. Unfortunately, so far a general methodology for this transformation is not known (Scheme 1).

Instead, recent work showed that the corresponding alcohols are obtained.[6] On the other hand, the reduction of esters and thioesters to ethers is feasible using stoichiometric amounts of $LiAlH_4$,[7] DIBAL[8] or organotin hydrides.[9] Drawbacks of these protocols are the price of the reductants, necessity of additives, air and moisture sensitivity of the stoichiometric organometallic reagents. Regarding their reduction potential, organosilanes are in between highly reactive metal hydrides and inert hydrogen. Advantageously, their activity can be controlled both by the substituents on the silicone centre as well as by catalysts, *e.g.* transition metal complexes, Lewis acids or Lewis bases.



Scheme 1 Possible synthesis of ethers from esters.

Due to the unique chemo- and regioselectivity of silanes, more recently catalytic hydrosilylations have become increasingly popular in organic synthesis.[10,11] Unfortunately, similar to catalytic hydrogenations the majority of the known transition metal-based catalysts in hydrosilylations lead only to alcohols.[12] Nevertheless, few examples of catalytic hydrosilylation to ethers with Mn,[13] Ti,[14] Ru[15] and In-based[16] catalysts are known. However, still these procedures need further improvement as they use either expensive silanes such as $PhSiH_3$ or large amounts of catalysts or have limited substrate scope.

Recently, Fe-based complexes allowed for considerable inventions in catalysis.[17,18] Apart from the abundant availability of iron, the often low toxicity and the bio-mimetic nature of the pre-catalysts make iron an ideal candidate for catalysis.[19] Based on our previous studies of the reduction of carboxylic amides to amines and esters to alcohols,[20,21] herein we report the first iron-catalyzed hydrosilylation of esters to ethers.

Initially, the reaction of 2-phenethyl acetate to give the ether **1** was investigated as a model system to identify and optimize critical reaction parameters (Table 1). Apart from testing different pre-catalysts and ligands also various silanes were employed. By performing the reaction in toluene at 100 °C in the absence of any catalyst no conversion was observed (Table 1, entry 1). Similarly, in the presence of 10 mol% of different iron(II) salts and complexes no activity is found (Table 1, entries 2–5, 9 and 10). However, applying tetramethyldisiloxane (TMDS) in the presence of plain $Fe_3(CO)_{12}$ the reaction gave the desired (2-ethoxyethyl)benzene **1** in 90% yield (Table 1, entry 8). In addition to TMDS, other silanes such as $PhSiH_3$, Ph_2SiH_2, $(EtO)_3SiH$, and PMHS were also tested for this reduction. From a mechanistic point of view it is important to note that in none of the latter cases appreciable activity was found using triiron dodecacarbonyl as a catalyst (Table 1, entries 11, 16–18). Other previously reported Zn(II)- and Cu(II)-based catalysts were also applied in the model reaction but again in none of the cases any activity was observed (Table 1, entries 12–14). With respect to the mechanism, we believe that this iron-catalyzed reduction of esters to ethers proceeds similarly to the reduction of amides recently proposed by Nagashima and co-workers.[22] At first, thermolysis of $Fe_3(CO)_{12}$ should generate the coordinatively unsaturated $Fe(CO)_3$ fragment which is believed to be the "real" active species in the catalytic cycle. This fragment is formed more easily from the triiron cluster compared to $Fe(CO)_5$ and $Fe_2(CO)_9$ or other iron carbonyl complexes (Table 1, entries 6–10). Subsequent double oxidative addition of the Si–H groups of TMDS will form

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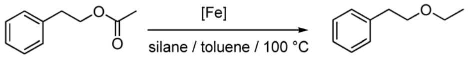
Table 1 Iron-catalyzed hydrosilylation of 2-phenylethyl acetate: variation of catalysts and optimization of reaction conditions[a]

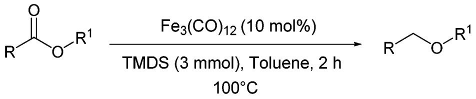


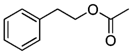
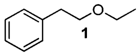
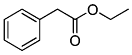
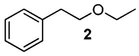
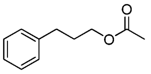
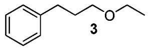
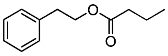
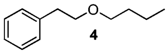
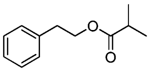
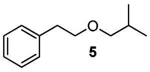
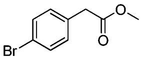
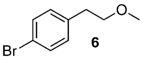
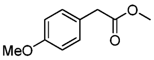
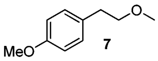
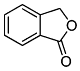
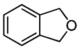
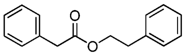
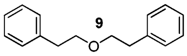
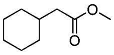
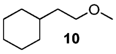
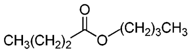
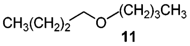
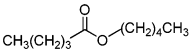
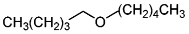
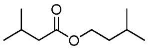
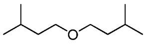
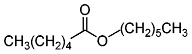
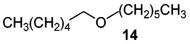
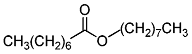
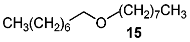
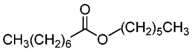
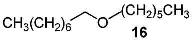
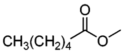
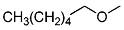
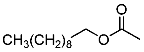
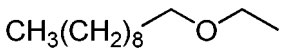
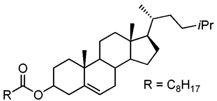
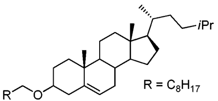
1

Entry	Catalyst [mol%]	Silane	Solvent	Yield[b] [%]
1	—	TMDS[c]	Toluene	—
2	$Fe(OAc)_2$ (10)	TMDS	Toluene	—
3	$Fe(BF_4)_2{\cdot}6H_2O$ (10)	TMDS	Toluene	—
4	$Fe(OTf)_2$ (10)	TMDS	Toluene	—
5	$Fe(NO_3)_2$ (10)	TMDS	Toluene	—
6	$Fe(CO)_5$ (10)	TMDS	Toluene	10
7	$Fe_2(CO)_9$ (10)	TMDS	Toluene	25
8	**$Fe_3(CO)_{12}$ (10)**	**TMDS**	**Toluene**	**90**
9	$Fe(CO)_3(COT)$ (10)	TMDS	Toluene	—
10	$CpFe_2(CO)_4$ (10)	TMDS	Toluene	—
11	$Fe_3(CO)_{12}$ (10)	PMHS[d]	Toluene	35
12	$Zn(OAc)_2$ (10)	$(EtO)_2MeSiH$	Toluene	—
13	$Zn(OTf)_2$ (10)	TMDS	Toluene	—
14	$Cu(OTf)_2$ (10)	TMDS	Toluene	—
15	$Fe_3(CO)_{12}$ (10)	Ph_2SiH_2	Toluene	32
16	$Fe_3(CO)_{12}$ (10)	Et_3SiH	Toluene	5
17	$Fe_3(CO)_{12}$ (10)	$PhMe_2SiH$	Toluene	19
18	$Fe_3(CO)_{12}$ (10)	Ph_2MeSiH	Toluene	15
19	$Fe_3(CO)_{12}$ (5)	TMDS	Toluene	78
20	$Fe_3(CO)_{12}$ (2.5)	TMDS	Toluene	33
21	**$Fe_3(CO)_{12}$ (10)**	**TMDS**	***p*-Xylene**	**90**
22	$Fe_3(CO)_{12}$ (10)	TMDS	Dioxane	61

[a] Reaction conditions: ester (1.0 mmol), catalyst, silane (3 mmol), solvent (3 mL), 2 h, 100 °C. [b] Determined by GC with hexadecane as an internal standard. [c] TMDS = tetramethyldisiloxane. [d] 1 mmol PMHS = 0.06 mL.

Table 2 Iron-catalyzed reduction of esters[a]



Entry	Esters	Ethers	Yield[b] [%]
1		 **1**	85[c]
2		 **2**	85
3		 **3**	78
4		 **4**	70
5		 **5**	70
6		 **6**	75
7		 **7**	70
8		 **8**	60
9		 **9**	85
10		 **10**	50
11		 **11**	60
12		 **12**	70
13		 **13**	70
14		 **14**	71
15		 **15**	72
16		 **16**	70
17		 **17**	73
18		 **18**	70
19	 **19a**	 **19b**	70

[a] Reaction conditions: esters (1 mmol), $Fe_3(CO)_{12}$ (10 mol%), TMDS (3 mmol), toluene (3 mL). [b] All are isolated yields except entries 8, 11–17 (here GC yields were obtained using hexadecane as an internal standard). [c] In all the cases of isolated yields, the silane was destroyed after the reaction by adding 3 mL of 2 M solution of sodium hydroxide for 3 h. Then, the products were purified by column chromatography.

a disilaferracyclic intermediate. Hydrosilylation of the carbonyl group of the ester forms the O-silylated species. After reductive eliminations the desired ether and siloxane are produced. This proposed catalytic cycle is in agreement with the special activity of TMDS compared to monosilanes.

Once suitable reaction conditions were identified for the model system, next the scope and limitations of this first iron-catalyzed reduction of esters to ethers were explored. As shown in Table 2, 19 different aromatic and aliphatic esters are reduced smoothly to the corresponding ethers (Table 2). Different aromatic, aliphatic, and alicyclic esters are reduced under the optimized reduction conditions to give the respective ethers in 50–85% yield. In none of the cases we observed the formation of alcohols. Comparing entries 6 and 7 in Table 2 there is no difference between electron-withdrawing and electron-donating substituents on the aryl ring. As shown by the reduction of benzofuranone it is also possible to synthesize cyclic ethers by this methodology (Table 2, entry 8). From a synthetic point of view the synthesis of non-symmetric aliphatic ethers using this iron catalyst is interesting, too (Table 2, entries 11–18). Expediently, the model reaction was easily scaled up to the 50 mmol-scale to provide 90% of the desired product. After having demonstrated the synthesis of various aliphatic ethers in good yield we investigated the reduction of different steroid esters. As an example the hydrosilylation of cholesteryl nonanoate, also called cholesteryl pelargonate, was performed (Table 2, entry 19). The starting material is an industrially applied liquid crystal material, which is also used for cosmetic applications.

In the presence of 10 mol% triiron dodecacarbonyl selective reduction of the ester group took place without touching the double bond and provided the corresponding ether in 70% isolated yield. In summary, we developed the first iron-catalyzed reduction of esters to ethers using TMDS and plain iron carbonyl complexes. Moderate to good yields of 19 different ethers were obtained starting from aromatic, aliphatic and alicyclic esters. Clearly, this procedure can be still further improved with respect to substrate scope and reaction conditions. Nevertheless, we believe it represents a significant step towards the development of a general methodology for the challenging transformation of esters into ethers.

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