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Zinc-catalyzed Reduction of Aldehydes with a Hydrosilane Leading to Symmetric Ethers and Silyl Ethers

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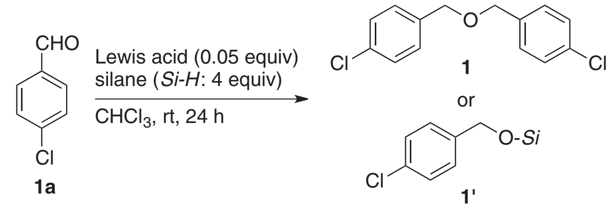
The efficient reductive etherification of aromatic or aliphatic aldehydes using a reducing system that combines $Zn(OTf)_2$ with either TMDS or Et_3SiH is described. The present reducing system can also be applied to the hydrosilylation of aromatic aldehydes having either a strong electron-withdrawing group or a pyridine ring.

Synthesis of ethers is one of the most widely investigated methods in organic chemistry. Among the various methods available, the Williamson ether synthesis and its modification under basic conditions have been widely developed for this purpose.[1] As a further extension of this method, several groups have demonstrated the combination of a Lewis or Brønsted acid with a hydrosilane such as BF_3–Et_3SiH,[2] $TrClO_4$–Et_3SiH,[3] TMSI or TMSOTf–Et_3SiH,[4] $BiCl_3$ or $BiBr_3$–Et_3SiH,[5] SbI_3–$PhSiH_3$,[6] $FeCl_3$–Et_3SiH,[7] I_2–PMHS [poly(methylhydrosiloxane)],[8] TfOH–Et_3SiH,[9] and $Cu(OTf)_2$–TMDS (1,1,3,3-tetramethyldisiloxane)[10] to promote the reductive homocoupling of carbonyl compounds or heterocoupling of carbonyl compounds with silyl ethers, which yields symmetric or unsymmetrical ethers. Reducing systems consisting of a zinc catalyst and a hydrosilane have also recently been used in a variety of functional group transformations involving the hydrosilylation of ketones,[11] deoxygenation of carbonyl compounds[12] or amides,[13] and reductive amination.[14]

In this context, during further research on the reductive transformation of a typical functional group with a carbon–oxygen bond by using a reducing system that combined an indium compound with a hydrosilane,[15] we found that unlike conventional conversions using a zinc catalyst, as shown above, a $Zn(OTf)_2$–TMDS or Et_3SiH reducing system promoted the reductive coupling of aromatic and aliphatic aldehydes, affording symmetric ethers. This type of reducing system could also be applied to the hydrosilylation of aromatic aldehydes with a pyridine ring. In this letter, we report the preliminary results of this transformation.

The reduction of *p*-chlorobenzaldehyde (**1a**) with a zinc catalyst and a hydrosilane was initially examined as a model reaction (Table 1).[16] For example, when the reaction was conducted with 0.05 equiv of $ZnCl_2$ and 4 equiv (*Si–H*) of Et_3SiH in $CHCl_3$ at room temperature, the reduction proceeded in a clean manner to produce the unexpected symmetric ether **1** in 60% yield, with the corresponding silyl ether **1′** in 20% yield (Entry 1). ZnI_2 was ineffective for the reduction, and most of the starting aldehyde was recovered (Entry 2). By contrast, a relatively strong Lewis acid among the zinc catalysts, $Zn(OTf)_2$, showed high catalytic activity for this reduction (Entries 3–5). $PhSiH_3$ and TMDS as a hydrosilane showed moderate to good selectivity, respectively, but a polymer-like PMHS did not afford the desired product (Entry 6). When the reduction was conducted in a typical coordinate solvent such as CH_3CN and THF, unfortunately, a small amount of silyl ether was obtained without the ether. On the other hand, when a similar reaction was performed using $InBr_3$ instead of the zinc catalyst, the corresponding silyl ether **1′** was selectively obtained (Entry 7). Consequently, a reducing system composed of 5 mol % of $Zn(OTf)_2$ and 4 equiv of TMDS in $CHCl_3$ provided the best result, but with the isolation of either the ether or the silyl ether, the conditions using Et_3SiH were also acceptable.

Table 1. Examinations of reaction conditions

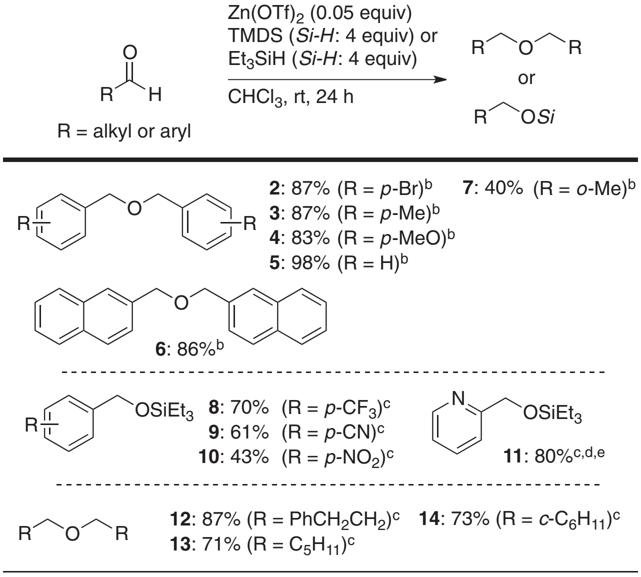


Entry	Lewis acid	Silane	Yield/%[a]	
			1	**1′**
1	$ZnCl_2$	Et_3SiH	60	20
2	ZnI_2	Et_3SiH	NR	
3	$Zn(OTf)_2$	Et_3SiH	60	trace
4	$Zn(OTf)_2$	$PhSiH_3$	66[b]	ND
5	$Zn(OTf)_2$	TMDS	88 (78)	trace
6	$Zn(OTf)_2$	PMHS	NR	
7[c]	$InBr_3$	Et_3SiH	trace	(84)

[a]GC (isolated) yield. [b]The starting aldehyde was recovered in 25% yield. [c]Bath temperature: 60 °C, reaction time: 1 h.

With the optimized conditions found in Table 1, the scope of this reaction was examined with aromatic aldehydes containing a variety of functional groups (Table 2).[17] In all cases using aromatic aldehydes having either a relatively weak electron-withdrawing group such as a halogen or an electron-donating group such as a methyl or methoxy substituent, the etherification proceeded smoothly, producing the corresponding symmetric ethers **2**–**4** in good yields. When the reaction was conducted with 2-naphthaldehyde or benzaldehyde, the corresponding ethers **5** and **6** were obtained in good yields. On the other hand, the use of benzaldehyde with an *o*-methyl substituent led to a decrease in the yield and recovery of the starting aldehyde, probably due to steric hindrance.[18] By contrast, when the reaction was carried out using benzaldehydes with a strong electron-withdrawing group such as a trifluoromethyl, cyano, or nitro group, contrary to our expectation, the corresponding silyl ether derivatives **8**–**10** were selectively obtained via hydrosilylation.[19] Interestingly, although a pyridine ring with a basic

Table 2. Zinc-catalyzed reduction of aromatic or aliphatic aldehydes[a]

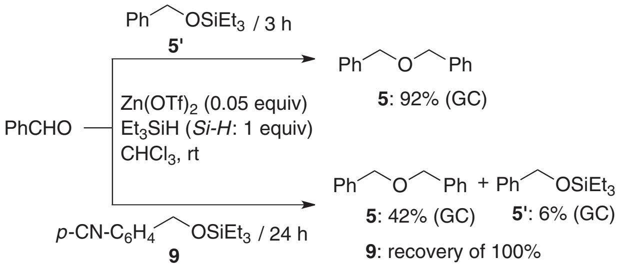


2: 87% (R = *p*-Br)[b] **7**: 40% (R = *o*-Me)[b]
3: 87% (R = *p*-Me)[b]
4: 83% (R = *p*-MeO)[b]
5: 98% (R = H)[b]
6: 86%[b]
8: 70% (R = *p*-CF$_3$)[c]
9: 61% (R = *p*-CN)[c]
10: 43% (R = *p*-NO$_2$)[c]
11: 80%[c,d,e]
12: 87% (R = PhCH$_2$CH$_2$)[c] **14**: 73% (R = *c*-C$_6$H$_{11}$)[c]
13: 71% (R = C$_5$H$_{11}$)[c]

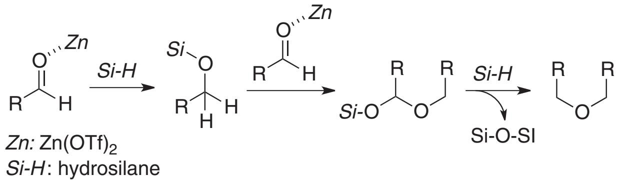
[a]Isolated yield. [b]TMDS was used. [c]Et$_3$SiH was used. [d]Temp: 65 °C. [e]Zn(OTf)$_2$: 0.2 equiv.

nitrogen atom generally deactivates a Lewis acid catalyst to preclude the desired functional group conversion, chloroform reflux conditions in the presence of 0.2 equiv of Zn(OTf)$_2$ gave the silyl ether derivative **11** in good yield. With the noted exception of some examples with a complicated transition-metal complex involving Fe,[20a,20b] Ru,[20c] Rh,[20d] Ni,[20e] and Cu,[20f,20g] this was a unique example of the hydrosilylation of an aromatic aldehyde with a pyridine ring by the combination of a typical metal catalyst, zinc triflate, and an easy-to-handle hydrosilane.[21] However, hydrosilylation of other heteroaromatic aldehydes such as pyrrole-2-carboxaldehyde and furfural did not proceed. This Zn(OTf)$_2$–Et$_3$SiH reducing system could also be applied to the reduction of aliphatic aldehydes. Without reference to a steric obstacle next to a carbonyl group, in all cases, the desired etherification proceeded in a clean manner to give the symmetric ether derivatives **12**–**14** in good yields. Unfortunately, the Zn(OTf)$_2$–TMDS or Et$_3$SiH reducing system did not promote the reductive coupling of an aromatic ketone.

For a better understanding of the reaction pathway for the etherification, several experiments were conducted (Scheme 1). When the heterocoupling of benzaldehyde with benzyl triethylsilyl ether **5′**, which was prepared from benzyl alcohol and Et$_3$SiCl, was initially carried out with 1 equiv of Et$_3$SiH in the presence of Zn(OTf)$_2$, the reduction proceeded smoothly to afford the corresponding ether **5** in nearly quantitative yield. However, when the reaction was carried out without either Zn(OTf)$_2$ or 1 equiv of Et$_3$SiH, the heterocoupling did not occur. These results strongly implied that the silyl ether was the intermediate through the reduction series and showed that a combination of the zinc catalyst and the hydrosilane was indispensable for this etherification. Moreover, when the coupling of benzaldehyde with an isolated benzylsilyl ether having a cyano group **9** was conducted under same conditions, a mixture of **5** and **5′** was obtained, with quantitative recovery of **9**.



Scheme 1. Heterocoupling of benzaldehyde with a silyl ether.



Scheme 2. Plausible reaction path for the etherification.

On the basis of these results, a plausible reaction path for the etherification is shown in Scheme 2. As with the etherification using a conventional reducing system, the reaction of the silyl ether, which was formed by hydrosilylation, with an activated aldehyde initially produced a silylated hemiacetal, followed by a second reduction of the acetal with another hydrosilane to afford the corresponding symmetric ether. Further, for the formation of the silyl ether, it seemed that introduction of a strong electron-withdrawing group on the benzene ring remarkably lowered the nucleophilicity of the in situ formed silyl ether, which led to the preclusion of a subsequent addition.

In conclusion, we found an efficient dimerization of aromatic or aliphatic aldehydes via a Zn(OTf)$_2$–TMDS or Et$_3$SiH reducing system that aids the preparation of symmetric ethers. We also found that the present reducing system could be applied to the hydrosilylation of aromatic aldehydes having either a strong electron-withdrawing group or a pyridine ring.

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16 General procedure for etherification of aldehydes: To a freshly distilled $CHCl_3$ solution (0.60 mL) in a screw-capped vial under N_2 atmosphere were successively added a magnetic stirrer bar, an aldehyde (1.0 mmol), $Zn(OTf)_2$ (0.050 mmol, 18 mg), and TMDS (4.0 mmol, 350 µL) or Et_3SiH (4.0 mmol, 600 µL). The vial was sealed with a cap contained a PTFE septum. During stirring of the reaction mixture, the reaction was monitored by TLC until consumption of the starting aldehyde. After 24 h, the resulting mixture was directly subjected to silica gel without the common work-up, and was purified by flash column chromatography (hexane–AcOEt) to give the corresponding ether or silyl ether. Selected spectral data for the formed ether or silyl ether: Bis(4-chlorobenzyl)ether (**1**): ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.47 (s, 4H), 7.29–7.33 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 71.4, 128.6, 129.0, 133.4, 136.5; MS (EI): m/z 266 (M^+). 2-Triethylsiloxymethylpyridine (**11**): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.68 (q, 6H, $J = 8.0$ Hz), 0.99 (t, 9H, $J = 8.0$ Hz), 4.85 (s, 2H), 7.12 (t, 1H, $J = 5.0$ Hz), 7.53 (d, 1H, $J = 8.0$ Hz), 7.68 (t, 1H, $J = 8.0$ Hz), 8.49 (d, 1H, $J = 5.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 4.3, 6.6, 65.6, 119.9, 121.6, 136.4, 148.5, 161.2; MS (EI): m/z 223 (M^+).

17 When the crude product was measured with GC, a trace amount of the corresponding silyl ether was observed. However, we could not isolate them by a common purification.

18 According to the reviewer comments, when the reaction was carried out with 1-naphthaldehyde, the corresponding ether was isolated in 57%. The result also showed that a steric hindrance around an aldehyde group had an effect to a decrease in the yield.

19 When the reaction was carried out with the substrate having a CF_3 group, a trace amount of the corresponding ether was observed.

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21 In comparison with this reducing system, when pyridine-2-carboxaldehyde was treated with $InBr_3$ and triethylsilane, the expected etherification did not occur, see ref 15e.