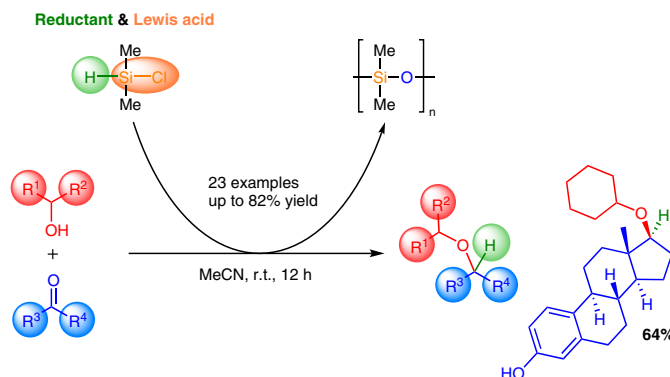


Ether Synthesis through Reductive Cross-Coupling of Ketones with Alcohols Using Me_2SiHCl as both Reductant and Lewis Acid

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Abstract We report that a Lewis acidic silane, Me_2SiHCl , can mediate the direct cross-coupling of a wide range of carbonyl compounds with alcohols to form dialkyl ethers. The reaction is operationally simple, tolerates a range of polar functional groups, can be utilized to make sterically hindered ethers, and is extendable to sulfur and nitrogen nucleophiles.

Key words silanes, Lewis acid, ketones, alcohols, ethers, reductive coupling

Dialkyl ethers are important compounds in organic synthesis because of their widespread applications in medicinal chemistry and their occurrence in many natural products and materials.¹ Traditionally, dialkyl ethers have been formed through the nucleophilic displacement of (pseudo)halogens with an alkoxide through the Williamson ether synthesis.² However, this procedure has been limited by the harsh reaction conditions and by the need to convert more common hydroxyl groups into better leaving groups (e.g., Br, OTs) prior to ether bond formation. Moreover, the Williamson procedure is inherently limited when sterically congested electrophiles and alkoxides are utilized because of the formation of side-products through elimination processes. While recent creative approaches have addressed some of the traditional limitations of the Williamson ether synthesis,^{3–6} a practical procedure that enables direct access to dialkyl ethers, including sterically congested ones, remains to be developed. In particular, a method that employs common starting materials and simple reagents would likely find broad application in synthesis.

A straightforward approach to unsymmetrical ether synthesis proceeds through the reductive cross-coupling of broadly available carbonyls and alcohols under reducing

conditions.^{6b,7} In particular, protocols using silanes as reductants benefit from operationally simple procedures and low toxicity, both of which are attractive features for laboratory-scale synthesis. Unfortunately, besides some exceptions,^{1d,8,9} most of the reports in this area have employed preformed silyl ethers as substrates, thus limiting the step-economy and practicality of these reactions.^{10,11} In 2011, Roth and co-workers reported the most general solution to the direct cross-coupling of carbonyls and alcohols using a silane reductant.⁹ Using triflic acid as a catalyst and inex-

Table 1 Optimization Studies^a

Entry	Reductant (equiv)	Acid or additive (equiv)	Solvent	GC yield (%) ^b
1	Et_3SiH (1.1)	TfOH (0.03)	MeNO_2	22
2	Et_3SiH (1.1)	TfOH (0.03)	MeCN	56
3	Et_3SiH (1.1)	Me_2SiHCl (0.03)	MeCN	7
4	Et_3SiH (1.1)	–	MeCN	0
5	Me_2SiHCl (1.1)	–	MeCN	89 (79)
6	Ph_2SiHCl (1.1)	–	MeCN	49
7	$i\text{Pr}_2\text{SiHCl}$ (1.1)	–	MeCN	25
8	$t\text{Bu}_2\text{SiHCl}$ (1.1)	–	MeCN	3
9	Me_2SiHCl (1.1)	–	MeNO_2	50
10	Me_2SiHCl (1.1)	–	DCM	52
11	Me_2SiHCl (1.1)	–	CHCl_3	24

^a Cyclohexanone (0.25 mmol), solvent (0.5 mL).

^b Yields based on GC-FID analysis using dodecane as a standard; yields of isolated products are given in parentheses.

pensive Et_3SiH as a reducing agent, they were able to cross-couple a wide range of carbonyl compounds with alcohols, as well as with N- and S-nucleophiles. However, their protocol gave low yields with ketone substrates and could not be extended to the preparation of branched dialkyl ethers, despite the wide occurrence of these sterically congested motifs in organic synthesis.

In this letter, we report that a Lewis acidic silane, Me_2SiHCl , can mediate the direct cross-coupling of a wide range of carbonyl compounds with alcohols to form dialkyl

ethers, including sterically congested secondary-secondary ethers.

As part of our program aiming at developing selective reductions of oxygen-containing substrates using silanes and Lewis acids,¹² we undertook the development of a practical reductive cross-coupling of carbonyls and alcohols. As a starting point, we selected the coupling of a ketone and a primary alcohol, because this transformation is challenging to accomplish using state of the art protocols (Table 1). Accordingly, when we applied the conditions reported by

Table 2 Alcohol Substrate Scope^a

$ \begin{array}{c} \text{R}^1-\text{C}(=\text{O})-\text{R}^2 + \text{HO}-\text{R}^3 + \begin{array}{c} \text{Me} \\ \\ \text{H}-\text{Si}-\text{Cl} \\ \\ \text{Me} \end{array} \xrightarrow[\text{r.t., 12 h}]{\text{MeCN}} \begin{array}{c} \text{R}^3 \\ \\ \text{R}^1-\text{C}-\text{O}-\text{R}^2 \\ \\ \text{H} \end{array} \\ (1.1 \text{ equiv}) \qquad (1.1 \text{ equiv}) \end{array} $					
Entry	Product	Yield (%)	Entry	Product	Yield (%)
1		79	8		51
2		59	9		45
3		66	10		75 / 66 ^d
4		64	11		82
5		52	12 ^c		50
6		74	13 ^c		54
7 ^b		42			

^a Isolated yields; ketone (0.25 mmol).

^b Crotyl alcohol (1.5 equiv), Me_2SiHCl (2.0 equiv).

^c 36 h.

^d Ketone (25 mmol).

Table 3 Carbonyl Substrate Scope^a

Entry	Carbonyl	Product	Yield (%)
1			75
2			70
3			70
4			59
5			76
6 ^b			54
7 ^{b,c}			64

^a For conditions see Table 2 and the Supporting Information. Isolated yields; carbonyl (0.25 mmol).

^b Me₂SiHCl (2 equiv).

^c 60 °C.

Roth and co-workers, only 22% of the desired product was obtained, along with significant amounts of side-products arising from ketone reduction and reductive dimerization. Solvent optimization then revealed that acetonitrile could improve the process, giving moderate yields of the product. At this stage, we reasoned that utilizing a chlorosilane as mediator might enable us to combine the benefits of a Lewis acid and a silane into one reagent to improve the reactivity. Gratifyingly, the use of just 1.1 equivalents of Me₂SiHCl led to product formation with a yield of 89%. Increasing the steric demand of the silane reagent had a negative impact on the reaction outcome, leading to reduced conversions. Further control reactions confirmed that acetonitrile is the solvent of choice for this transformation.

We next explored the scope of functionalized alcohol nucleophiles that can be employed under these reaction conditions (Table 2). Initially, we were pleased to note that esters, alkynes, alkenes and an imide were well tolerated under these reaction conditions. On a larger scale (25 mmol scale), the desired ether product was isolated with only a slight decrease in yield (Table 2, Entry 10). Notably, ketones reacted with sterically hindered secondary alcohols to form highly congested ethers that cannot be easily accessed by using alternative methods.^{1f,6b–c,7b–c,10b–c}

Next, we explored the functional group tolerance of the ketone substrates in the cross coupling with a sterically crowded secondary alcohol (Table 3). Again, a broad range of functional groups was tolerated, including a halogen, alkene and a carbamate. The reaction could also be employed to chemo- and stereoselectively functionalize estrone.

Lastly, we explored the possibility of using other heteroatom-based nucleophiles under our reaction conditions (Table 4). A thiol and sulfonamide nucleophile afforded good yield of the cross-coupled product. Finally, indole reacted selectively at the C3 position to give the corresponding alkylated product in good yield.

In conclusion, we have reported a practical (one single reagent) protocol for the reductive cross coupling of carbonyls and alcohols.^{13,14} The reaction distinguishes itself by a good functional group tolerance and the ability to obtain sterically congested dialkyl ethers that are otherwise hard to access. We are thus confident that this transformation will find applications in organic synthesis.

Table 4 Reductive Coupling of Carbonyls with S-, N-, and C-Nucleophiles^a

Entry	Nucleophile	Product	Yield (%)
1			69
2			79
3			62

^a Isolated yields; ketone (0.25 mmol).

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0036-1590838>.

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- (13) **General procedure for the reductive etherification reaction:** To a mixture of carbonyl (0.25 mmol) and alcohol (0.275 mmol, 1.1 equiv) in acetonitrile (0.5 mL) was added chlorodimethylsilane (0.275 mmol, 1.1 equiv) under argon. The reaction mixture was stirred at room temperature (ca. 25 °C) for 12 h. The reaction was then quenched by adding a drop of aqueous NaHCO₃ solution under air. The resulting mixture was dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (pentane/DCM or pentane/MTBE).
- (14) **(8R,9S,13S,14S,17S)-17-(Cyclohexyloxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-ol (Table 3, Entry 7):** White solid. ¹H NMR (500 MHz, CDCl₃): δ = 7.15 (d, J = 8.5 Hz, 1 H), 6.62 (dd, J = 8.5, 2.7 Hz, 1 H), 6.55 (d, J = 2.7 Hz, 1 H), 4.55 (s, 1 H), 3.49 (dd, J = 8.5, 8.5 Hz, 1 H), 3.32–3.23 (m, 1 H), 2.89–2.74 (m, 2 H), 2.31–2.21 (m, 1 H), 2.20–2.11 (m, 1 H), 2.06–1.93 (m, 2 H), 1.94–1.80 (m, 3 H), 1.79–1.69 (m, 2 H), 1.71–1.60 (m, 1 H), 1.58–1.42 (m, 3 H), 1.45–1.36 (m, 1 H), 1.39–1.10 (m, 9 H), 0.79 (s, 3 H). ¹³C NMR (125 MHz, CDCl₃): δ = 153.4, 138.5, 133.1, 126.7, 115.4, 112.7, 86.5, 77.1, 50.3, 44.2, 43.4, 38.8, 37.9, 33.3, 33.2, 29.8, 29.1, 27.3, 26.6, 26.0, 24.6, 24.5, 23.3, 11.9. HRMS (ESI⁺): m/z [M+H]⁺ calcd for C₂₄H₃₅O₂: 355.26316; found: 355.26335.