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Alkoxyhydrosilane-facilitated cross-etherification reaction of secondary benzyl alcohol with aliphatic alcohol: synthesis of unsymmetrical dialkyl ethers†

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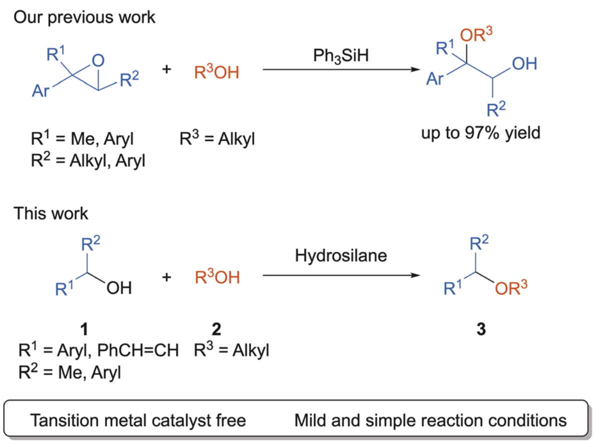
Alkoxyhydorosilane is found to be an effective mediator for the cross-etherification reaction between two distinct alcohols, namely, a secondary benzyl alcohol and an aliphatic alcohol, providing the unsymmetrical dialkyl ethers in good-to-high yields. The reaction is also successfully applied to the lignin model compound, which is an important renewable non-fossil organic carbon source. Initial mechanistic studies indicated that the carbocation derived from benzyl alcohol was formed under the present reaction conditions.

Alcohol is an inexpensive and environmental benign compound which can be obtained from biomass. Compared to fossil resources, alcohol is a sustainable resource, and its direct use in bulk and fine chemicals is of increasing interest. As environmental issues are growing concern, finding efficient, atom-economical, and step-economical strategies for the directly conversion of distinct alcohols into unsymmetrical dialkyl ethers, which are crucial structural units in many natural products and pharmaceutical,[1] is a major challenge in organic chemistry. Many research groups have reported the reaction using various catalysts.[2–10]

Organosilane compounds have enormous practical advantages due to its non-toxic, environmentally benign nature, and high-abundance in the Earth's crust. Recently, many research groups have focused on the study of the Lewis acidity of neutral tetracoordinated silane compounds.[11–14] In 2015, Tilley and Bergman group has reported that bis(perfluorocatecholato) silane, catalyzed hydrosilylation and silylcyanation reactions with aldehydes.[12] Greb group and Inoue group also independently reported the electron-deficient tetraalkoxysilane compounds catalyzed the hydrodefluorination of 1-adamantylfluoride.[13,14] Recently, our groups reported that Ph_3SiH showed the catalytic activity for the synthesis of β-alkoxy alcohols *via* epoxide ring-opening reaction with aliphatic alcohol (Scheme 1 up).[15] As a part of our ongoing study using hydrosilane, we found that alkoxyhydrosilane serves as a Lewis acid in the direct cross-etherification reaction between secondary benzyl alcohols and aliphatic alcohols (Scheme 1 down). In this paper, we disclose a synthesis of the unsymmetrical dialkyl ethers using two distinct alcohols. The reactions proceeded smoothly with the aid of alkoxyhydrosilane mediator to produce the corresponding dialkyl ethers in good-to-high yields.

We started with the optimization of the reaction conditions for the cross-etherification reaction using 1-(*p*-tolyl)ethanol (**1a**) with EtOH (**2a**) as a solvent in the presence of organosilane at 85 °C for 24 h (Table 1). After many trials,[16] we identified that the $(EtO)_2MeSiH$ (4.0 equiv.) provided the desired ether **3aa** in 95% isolated yield (entry 1). The choice of $(EtO)_2MeSiH$ is particularly important. When Ph_3SiH, which works as the Lewis acid catalyst toward the ring-opening reaction of epoxide to afford the β-alkoxyalcohols,[15] was employed, **3aa** was not formed, and **1a** was recovered (entry 2). $(EtO)_3SiH$, $(EtO)_4Si$,



Scheme 1 Our recent work and this work.

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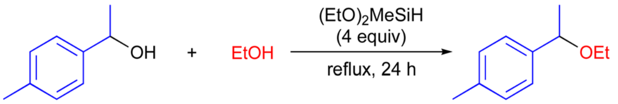
Table 1 Optimisation of the reaction conditions[a]



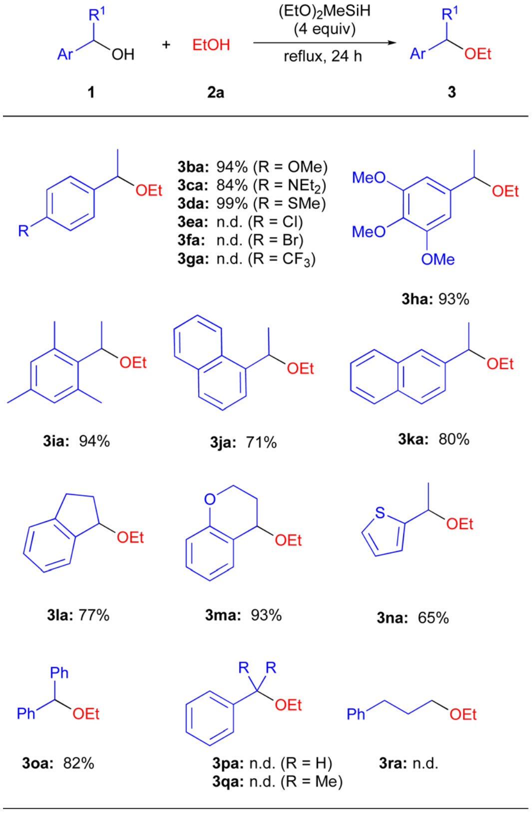
1a 2a 3aa

Entry	Variation from the standard conditions	Yield of **3aa**[b] (%)
1	None	95[c]
2	Ph_3SiH instead of $(EtO)_2MeSiH$	0
3	$(EtO)_3SiH$ instead of $(EtO)_2MeSiH$	0
4	$(EtO)_4Si$ instead of $(EtO)_2MeSiH$	0
5	$(EtO)_2Me_2Si$ instead of $(EtO)_2MeSiH$	7
6	$(EtO)_2MePhSi$ instead of $(EtO)_2MeSiH$	0
7	$MePh_2SiH$ instead of $(EtO)_2MeSiH$	38
8	Me_2PhSiH instead of $(EtO)_2MeSiH$	0
9	Ph_4Si instead of $(EtO)_2MeSiH$	0
10	3.0 equiv. of $(EtO)_2MeSiH$	67[c]
11	60 °C instead of 85 °C	18[c]
12	No $(EtO)_2MeSiH$	0

[a] The reaction was carried out using **1a** (0.50 mmol) and hydrosilane (4 equiv.) in **2a** (2.5 mL) for 24 h in reflux. [b] The yield of **3aa** was determined by NMR analysis using pyrazine as an internal standard. [c] Isolated yield.

$(EtO)_2Me_2Si$ and $(EtO)_2MePhSi$ were not effective for the reaction (entries 3–6). $MePh_2SiH$ afforded **3aa** in only 38% yield, while Me_2PhSiH and Ph_4Si were not effective for this reaction (entries 7–9). When the amount of $(EtO)_2MeSiH$ reduced from 4.0 equivs to 3.0 equivs, **3aa** was obtained in 67% yield (entry 10). At 60 °C, the reaction proceeded slowly to afford **3aa** in only 18% yield (entry 11) When $(EtO)_2MeSiH$ was removed from the reaction system, **3aa** was not formed and **1a** was recovered almost quantitatively (entry 12).[17–19]

With the optimized reaction conditions in hand, we investigated a variety of secondary benzyl alcohols **1** using EtOH (**2a**) (Scheme 2). It was found that benzyl alcohols **1b–1d** and **1h** containing electron-donating substituents in the aryl ring, including MeO, Et_2N, and MeS efficiently underwent the present etherification reactions to give the corresponding dialkyl ethers **3ba–3da** and **3ha** in 84–99% isolated yields, while benzyl alcohols **1e–1g** containing electron-withdrawing substituents including Cl, Br, and CF_3 in the aryl ring did not give the corresponding ethers **3ea–3ga**.[20] 1-Mesitylethanol (**1i**) was suitable substrates for the present reaction conditions, affording the ether **3ia** in 94% yield. In addition, naphthyl alcohols **1j–1k** and cyclic alcohols **1l–1m** effectively participated in the direct etherification reactions with **2a** to produce the expected products **3ja–3ma** in 71–93% yields. 1-(1-Thiophene) ethanol **1n** and diphenylmethanol **1o** were also applicable in this reaction, affording **3na** and **3oa** in 65% and 82% yields. Unfortunately, the primary benzylic alcohol **1p** was recovered in quantitatively, suggesting the primary carbocation was not formed in the precent reaction conditions. In addition, tertiary benzyl alcohols **1q** and aliphatic alcohol **1r** were also unreactive under the applied reaction conditions.[20]

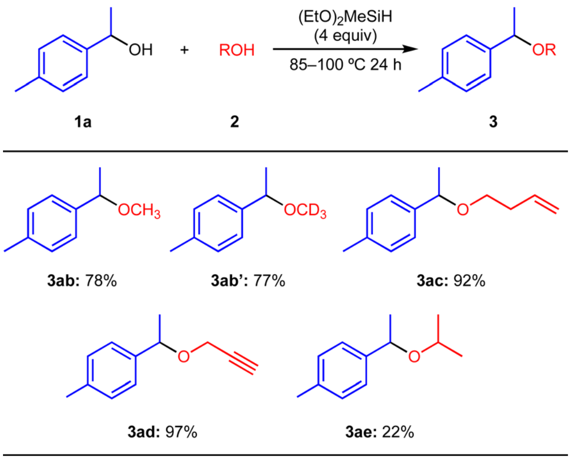


Scheme 2 Substrate scope for the etherification reaction of various benzyl alcohols **1** with **2a**.

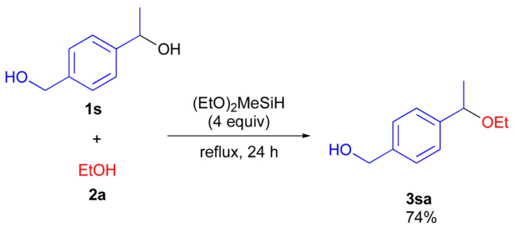
Next, we examined the substrate scope of the etherification reaction between **1a** and various aliphatic alcohols **2**, as shown in Scheme 3. The reaction using MeOH (**2b**) afforded **3ab** in 78% isolated yield. MeOH-d_4 (**2b′**) can be applied to the present reaction and **3ab′** was obtained in 77% yield. Terminal alkene (**2c**) and alkyne groups (**2d**) were tolerated in the present reaction conditions, affording the products **3ac** and **3ad** in 92% and 97%, respectively. i-PrOH (**2e**) induced less efficient etherification even at reflux conditions (**3ae**, 22% isolated yield).[21] *t*-BuOH (**2f**) did not give the ether **3af**.

To demonstrate the synthetic utility of the etherification reaction, chemoselective reaction using diol **1s** having both primary and secondary hydroxy moieties was performed (Scheme 4). The reaction of **1s** with **2a** reacted selectively at the secondary hydroxy site to give **3sa** in high yield.

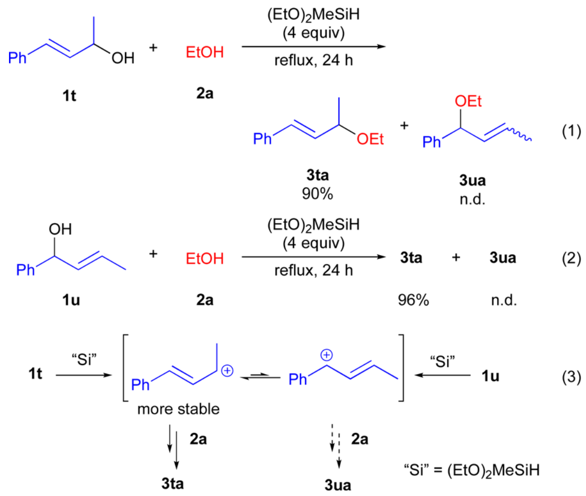
To obtain the mechanistic insight into this reaction, several control experiments were carried out under the optimized reaction conditions (Scheme 5). Initially, we carried out the reaction using cinnamyl alcohol **1t** with **2a** gave the **3ta** in 90% yield, whereas **3ua** was not detected (eqn (1)). In addition, when **1u** was used, **3ta** was obtained in 96% yield as a sole product (eqn (2)). We assumed that the formation of **3ta** is more favourable than **3us** due to the stability of carbocations (eqn (3)). Next, we examined the reaction using chiral alcohol (*S*)-**1j** (97% ee) (Scheme 6). Treatment of (*S*)-**1j** with **2a** in the presence of $(EtO)_2MeSiH$ gave the ether **3ja** in 84% isolated yield with 14% ee. In addition, no racemization of the isolated ether **3ja**



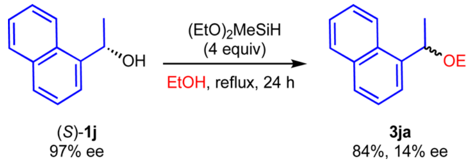
Scheme 3 Substrate scope for the etherification reactions of **1a** with various primary alcohols **2**.



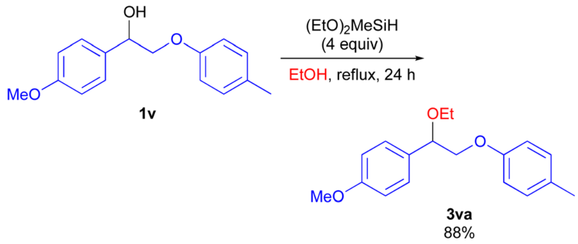
Scheme 4 Chemoselective etherification reaction of **1s**.



Scheme 5 The reaction using alcohols **1t** and **1u**.



Scheme 6 The reaction using chiral alcohol (*S*)-**1j**.



Scheme 7 Synthetic application for the etherification reaction of lignin model **1v**.

(14% ee) was observed when the enantio-rich ether **3ja** was exposed to the present reaction conditions.[22] These results indicated the formation of the carbocations derived from secondary benzyl alcohols **1** during the reaction course, although more detailed studies are required for a definitive understanding of the exact mechanism of the present reaction.

Lignin is an important renewable non-fossil organic carbon source.[23,24] The selective C(sp^3)–O bond functionalization of diol or polyol derivatives could offer a sustainable approach to gain valuable oxygen-containing feedstock chemicals from lignin biomass. To demonstrate the synthetic utility of the (EtO)$_2$MeSiH system, the cross-etherification using lignin model compound was performed (Scheme 7). Compound **1v** was converted to the corresponding products **3va** in 88% yield.

Conclusions

We reported that (EtO)$_2$MeSiH mediated cross-etherification reactions between secondary benzyl alcohol and aliphatic alcohol furnished unsymmetrical dialkyl ethers in good-to-high yields. Initial mechanistic studies suggested that the carbocation derived from benzyl alcohol was formed and subsequently, aliphatic alcohol attacked the *in situ* formed carbocation to afford the desired product. Further transformations catalyzed/mediated by organosilane and mechanistic studies are currently in progress in our laboratory.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

T. H. and M. H. directed the project. T. H. conceived the idea, designed the experiments and wrote the manuscript. T. H., Y. M., Y. O., and S. T. performed the experiments. All the authors participated in the preparation of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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16 For details, see the ESI†

17 The reaction using mixed solvents (EtOH/DMF and EtOH/acetone) did not give the ether product **3aa** and **1a** was recovered quantitatively.

18 Di(1-phenylethyl)ether did not converted to the **3aa** in the present reaction conditions.

19 In the reaction mixture, formation of the siloxane derived from $(EtO)_2MeSiH$ was confirmed.

20 The starting materials **1e**, **1f**, **1g**, **1q**, and **1r** were recovered in quantitatively.

21 In this reaction, the starting material **1a** was recovered in 41% and **3aa** was not detected at all.

22 The reaction using 4-vinylbiphenyl with **2a** in the present of $(EtO)_2MeSiH$ did not gave the desired ether product at all and the polymerization of styrene derivative was observed.

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