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N-Heterocyclic Olefin Catalyzed Silylation and Hydrosilylation Reactions of Hydroxyl and Carbonyl Compounds

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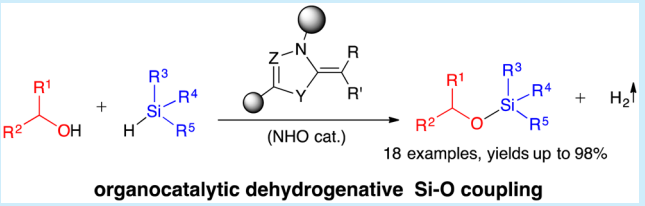
Supporting Information

ABSTRACT: N-Heterocyclic olefins (NHOs), the alkylidene derivatives of N-heterocyclic carbenes (NHCs), have recently emerged as a new family of promising organocatalysts with strong nucleophilicity and Brønsted basicity. The development of a novel method is shown using NHOs as efficient promoters for the direct dehydrogenative silylation of alcohols or hydrosilylation of carbonyl compounds. Preliminary results of the first NHO-promoted asymmetric synthesis are also discussed.

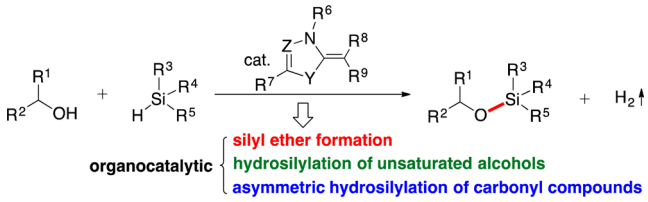


Silyl ethers are commonly used for a diverse range of synthetic applications in protection chemistry,[1] silicon polymer chemistry,[2] surface coating chemistry,[3] and hybrid organic–inorganic materials.[4] In terms of atom economic and environmentally benign synthesis of silyl ethers, the stoichiometric base-promoted reactions between alcohols and halosilanes are less advantageous than the dehydrogenative coupling reactions between alcohols and hydrosilanes, as the latter are typically mediated by catalysts and only generate hydrogen gas as the sole byproduct.[5] Over the past two decades, this type of chemical transformation has been extensively studied with various transition metal complexes[6] and main group Lewis acid/base catalysts.[7] Most notably, Oestreich[8] and Grubbs[9] have reported elegant studies in which they used simple and inexpensive catalysts such as alkali *tert*-butoxide[8] or hydroxide[9] to promote dehydrogenative silylation reactions of alcohols. With the rapid development of organosilicon chemistry, however, new catalytic methods with better efficiency, selectivity, and functional group tolerance are always in demand.

Cui and Gao recently demonstrated the effectiveness of NHCs[10] as Brønsted bases to activate a range of alcohols for coupling reactions with hydrosilanes to form silyl ethers with excellent outcomes.[5] Zhao et al.[11] also reported NHC-catalyzed hydrosilylation of styryl and propargyl alcohols with intriguing mechanistic insights. While NHCs have been shown to activate organosilicon reagents for a wide variety of chemical transformations,[12] the aforementioned studies[5,11] remain the only two *organocatalytic* examples of this dehydrogenative Si–O coupling reaction to date.

Our group has recently developed a number of new synthetic applications[13] for NHOs, an emerging class of NHC-derived organocatalysts with enhanced nucleophilicity and Brønsted basicity.[13,14] Several studies showed that, similar to NHCs, NHOs could also coordinate to the hydroxyl group to activate alcohols for nucleophilic reactions.[13b,14c,e] Based on this, we envisioned that NHOs could serve as suitable organocatalysts for the dehydrogenative coupling reactions of alcohols and hydrosilanes. Herein, we report the development of such a novel NHO-catalyzed silyl ether formation method.

Scheme 1. NHOs Activate Alcohols for Nucleophilic Reactions



The synthetic utility of this catalytic process could also be expanded to the reductive hydrosilylation of unsaturated alcohols or carbonyl compounds with high efficiency (Scheme 1). Additionally, we were able to induce moderate to good *enantioselectivity* to the latter type of hydrosilylation reaction using a chiral NHO catalyst or chiral alcohol auxiliaries. This paves the way to future stereoselective synthesis of silyl ethers[4c,6e,15] or kinetic resolution of alcohols,[6c,16] which can be induced by the inherently tunable structure of chiral NHO catalysts, a potential advantage over established methods using simpler Brønsted bases.[8,9]

Thus, we started the investigation with the coupling reaction between a simple nonactivated primary alcohol **1a** and

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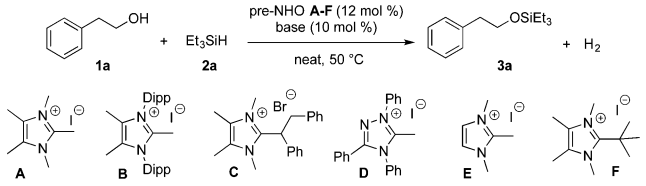
Table 1. Screening of NHO Catalysts[a]



entry[a]	base	precatalyst	time (h)	yield[b] (%)
1	NaO^{t}Bu	**A**	24	36
2	NaO^{t}Bu	**B**	24	**80**
3	KO^{t}Bu	**B**	24	69
4	KHMDS	**B**	24	55
5	Cs_2CO_3	**B**	24	20
6	DBU	**B**	24	25
7	NaO^{t}Bu	–	24/120	12/27
8	–	**B**	24/72	trace/5
9	NaO^{t}Bu	**C**	24	47
10	NaO^{t}Bu	**D**	24	6
11	Cs_2CO_3	**D**	24	31
12	NaO^{t}Bu	**E**	24	14
13	NaO^{t}Bu	**F**	24/72	16/17
14	$NaOCH_2CH_2Ph$	**B**	24	78

[a]Reaction conditions: NHO precursor (0.06 mmol) and base (0.05 mmol) and then alcohol **1a** (0.5 mmol) and silane **2a** (1.0 mmol) at 50 °C. [b]Yield of the isolated product.

triethylsilane (**2a**) in the presence of a range of NHO catalysts (Table 1, formed *in situ* from their precursors **A**–**F** and a base; also see mechanism in Figure 1).[13b,17] To our delight, most of the screened catalysts afforded silyl ether products with the clear formation of H_2 gas. During the optimization of the solvent system, we found that reactions using neat conditions interestingly led to comparable or better results than the ones with solvents. A quick optimization of the base on the best performing precatalyst **B** showed that sodium *tert*-butoxide was the most suitable base for catalyst generation (entries 2–6, Table 1).[18] The same base was used with all the other precatalysts with varying outcomes. Phenylethanolate salt could also trigger the reaction to give similar outcomes (entry 14).

Triazolium salt **D** (entries 10–11, Table 1) was less efficient in comparison to imidazolium precatalysts **A**–**C**, probably due to the low nucleophilicity of the generated NHO that its parent triazolylidene NHC was known to possess.[19] $C_{4,5}$-unsubstituted imidazolium **E** (entry 12, Table 1) gave a complicated reaction mixture with poor product yield, supporting our previous prediction that abnormal NHC (*a*NHC)[20] formation might be an issue for this type of framework.[14a] It is interesting that the observed activity trend of catalysts **A**–**E** differs from their analogous NHCs previously studied by Cui/Gao and Zhao et al.[5,11] This can be related to the fact that the active sites of NHOs are *exocyclic*[14a] rather than on the NHC ring. Control studies (entries 7–8, Table 1), where just NaO^{t}Bu[8] or the precatalyst **B** was used,[17] gave unsatisfactory results even after prolonged reaction times. It suggested that the formation of NHO catalyst was crucial for the promotion of this reaction. Similarly, we observed poor results with the *tert*-butylated precursor **F** (entry 13), which agreed well with the fact that no active NHO catalyst could form from precursor **F**.[13a]

Conceptually, the NHO catalyst can either activate the alcohol or the hydrosilane substrate to promote the reaction as suggested by Zhao et al.[11] on the NHC-catalyzed hydrosilylation of alcohols. We used ^{1}H NMR to monitor the progress of the NHO-catalyzed dehydrogenative coupling reaction to gather more mechanistic insights (Figure 1).[17] C_6D_6 was used as a reaction medium for the NMR study with the anticipation that this nonpolar solvent would not influence the reaction pathway.

Structurally simple precatalyst **A**, 2-phenylethanol (**1a**), and methyldiphenylsilane (**2c**, in ratio 0.12:1:2) were used in the study, as they have a minimal number of overlapping signals. The NMR spectra (**I**–**III**; see full extended version in the SI)[17] in Figure 1b clearly showed the coordination of the hydroxyl group to the NHO catalyst before the reaction took place. Based on previous studies[13,14c,e] of NHO-catalyzed reactions and recent knowledge on the similar NHC-promoted dehydrogenative alcohol-silane couplings,[5,11] we proposed that the reaction occurred through a mechanistic pathway depicted in Figure 1a. The *in situ* generated NHO catalyst (**A′**) acted as a Brønsted base to coordinate to the hydroxyl group of the alcohol substrate (**4**) and activated it for the Si–O bond formation (**5**). The resulting hypervalent[21] silyl hydride (**6**) reacted with the NHO precursor **A** to regenerate the catalyst and afford the silyl ether product.

In addition to the NMR experiments, high-level *ab initio* calculations on a model system lend further support for the proposed mechanism (see p S17 in the SI for details). Specifically, the highest barrier for this proposed reaction pathway is about 120 kJ mol^{-1}, which is in the right ballpark based on the observed duration of these reactions. The overall process is thermodynamically favorable ($\Delta G < -100$ kJ mol^{-1}).

With the optimized reaction conditions established (see optimization studies on silane substrates in Table S1 in the SI), we further extended the scope of this NHO-catalyzed Si–O coupling reaction to a range of alcohols (Scheme 2). Several primary benzylic or nonactivated alcohols reacted smoothly to afford products **3a**–**d** and **3g**–**j** in high to excellent yields.

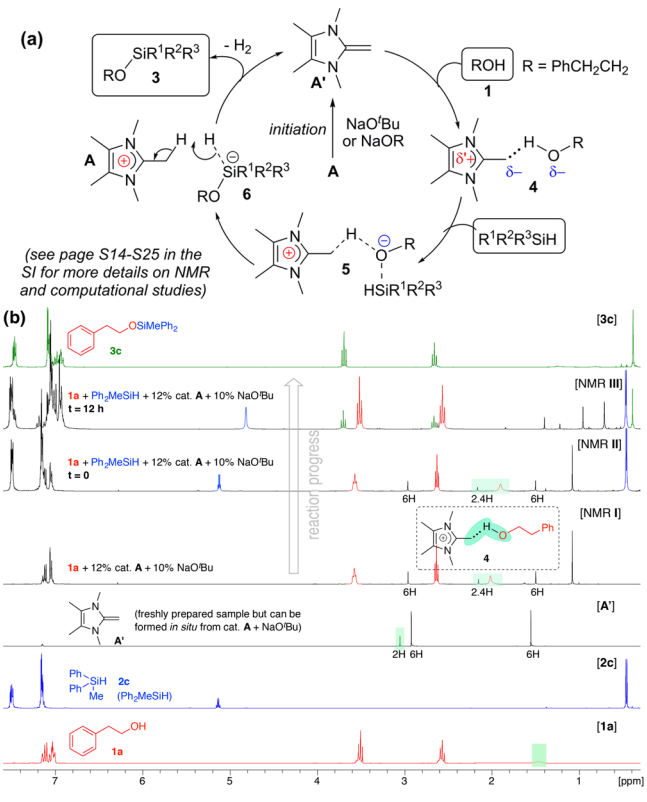


Figure 1. Mechanistic studies of the NHO-promoted Si–O coupling reaction (^{1}H NMR, 25 °C, C_6D_6, 400 MHz).

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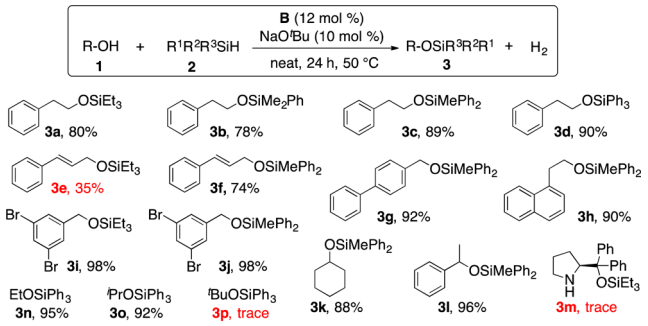
Scheme 2. Alcohol Substrate Scope



Secondary alcohols also worked well with methyldiphenylsilane to form silyl ether products **3k**–**l**. Diphenylprolinol only gave the coupled product **3m** in trace amounts. The selectivity of the method toward bulky alcohols can be best represented with products **3n**–**3p**, where the NHO catalyst was shown to be inactive with tertiary alcohols.[18]

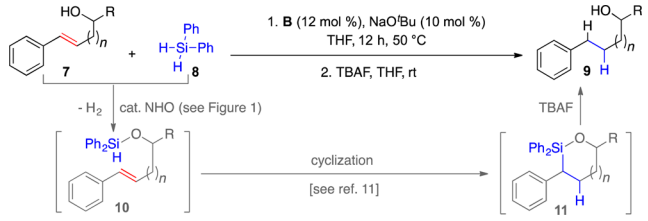
It was expected that benzylic or allylic alcohols should give better reaction outcomes than the nonactivated substrates (Scheme 2). Hence, the unusually poor results (**3e**–**f**) with cinnamyl alcohol took us by surprise. Studies from Zhao et al.[11] hinted that this unsaturated substrate might be prone to react with the silane in a reductive hydrosilylative fashion to form a mixture of saturated alcohol and its silyl ether. Indeed, careful analysis of these reaction mixtures revealed evidence of these byproducts being formed, which led to lower yields of the target dehydrogenative coupled products **3e**–**f**.

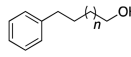
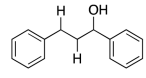
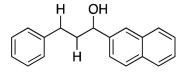
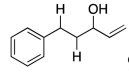
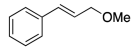
The side reactions on these unsaturated alcohol substrates are actually of significant synthetic value, as organocatalytic hydrosilylation of alkenols has been rarely encountered in organic chemistry.[11a] Thus, we set out to investigate the promotion of this type of reaction by NHO catalysts (Table 2) using the dihydro-diphenylsilane (**8**) to allow for the hydrosilylation. Under optimized conditions,[17] the unsaturated alcohols were first treated with the newly developed Si–O coupling reaction conditions and subsequently carried through silyl deprotection with TBAF. Pleasingly, most of the tested unsaturated substrates (**7a**–**b**, **7d**–**f**) gave reduced alcohol derivatives in good to high yields.[17]

Presumably, these reactions proceeded through the formation of alkoxydiphenylsilane (**10**) and cyclic intermediates **11**,[11] which were afterward unmasked by TBAF to produce saturated alcohol products **9a**–**9f**. When the distance between the hydroxyl group and the C–C double bond increased (**7a**–**c**, Table 2), the cyclization reaction became less favored, leading to a significant decrease in product yields. The hydrosilylation also seemed to be regioselective at the conjugate double bond (**7f**). Without the hydroxyl functionality (**7g**) the hydrosilylation did not take place.

The NHO-catalyzed hydrosilylation reaction on carbonyl compounds, previously studied with a solid-supported NHC catalyst by Tan et al.,[22] was also investigated (Scheme 3a). Trialkylsilanes (**2a**, **2e**) only reacted to give the products **13a**–**b** in poor yields. However, catalyst **B** could efficiently catalyze the reductive hydrosilylation of several aldehydes and ketones to form silyl ether products **13c**–**h** with other active silanes. We have also synthesized and used chiral NHO precursor **G** (Scheme 3b) to catalyze the hydrosilylation reaction between triphenylsilane (**2e**) and acetophenone (**14**). Gratifyingly, after subsequent desilylation with TBAF, we were able to obtain (*R*)-1-phenylethanol (**15**) in good yield and with some enantioselectivity. Although the stereoselectivity induced by this chiral NHO is unsatisfactory, this marked the first *asymmetric* reaction catalyzed by a chiral NHO. Studies on other chiral NHOs with stereogenic centers on the exocyclic olefin-carbons to improve the stereoselectivity of these NHO-catalyzed reactions are ongoing in our group.

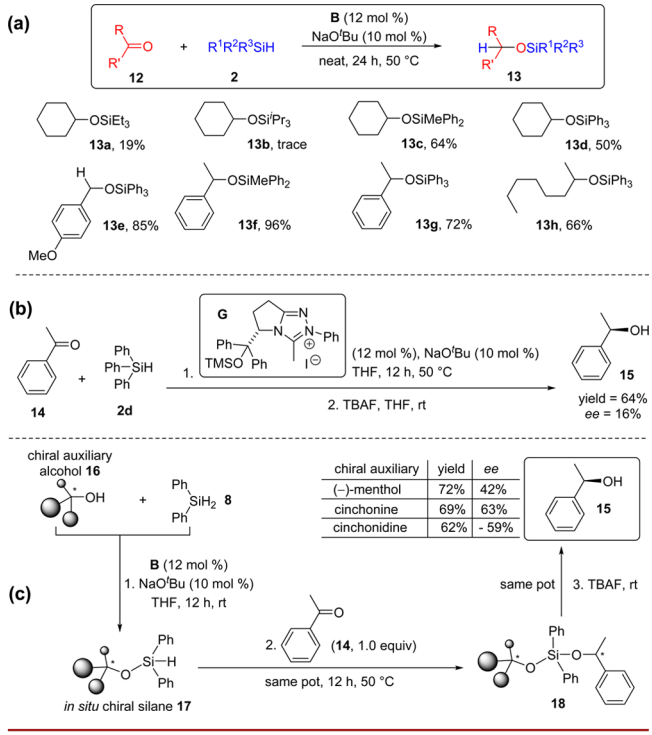
Table 2. Hydrosilylation Reactions of Unsaturated Alcohols[a]



entry[a]	n, R	product	yield[b] (%)
1	**7a**: 0, H		**9a**: 83
2	**7b**: 1, H		**9b**: 43
3	**7c**: 2, H		**9b**: trace
4	**7d**: 0, Ph	 **9d**	76
5	**7e**: 0, 2-naphthyl	 **9e**	69
6	**7f**: 0, vinyl	 **9f**	73
7	 **7g**	starting material	n.d

[a]Reaction conditions: **B** (0.12 mmol) and NaO^{t}Bu (0.10 mmol), alcohol **7** (1.0 mmol), and silane **8** (1.0 mmol) at 50 °C then TBAF (1 M, THF) at rt. [b]Yield of the isolated product.

Scheme 3. Hydrosilylation of Carbonyl Compounds



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On the other hand, this asymmetric hydrosilylation reaction could also be performed using a different strategy with a chiral auxiliary (Scheme 3c). By exploiting our Si−O coupling reaction established earlier in this work, we were able to produce chiral silane intermediates **17** *in situ* from a range of chiral alcohol auxiliaries **16**. Chiral intermediates **17** could then be used to hydrosilylate acetophenone in the same catalytic reaction system. Subsequent Si−O cleavage of **18** with TBAF afforded 1-phenylethanol (**15**) in good yields and moderate to good enantioselectivity, depending on the chiral auxiliary used (Scheme 3c). Cinchonine and cinchonidine gave almost opposite stereoselective induction as expected.

In conclusion, we have established a novel method to use N-heterocyclic olefins as efficient Brønsted base organocatalysts for the direct dehydrogenative coupling reactions of hydrosilanes and hydroxyl compounds. NHO catalysts can also trigger the reductive hydrosilylation of unsaturated alcohols and carbonyl compounds with excellent outcomes. In a preliminary study, we were able to induce *stereoselectivity* for the hydrosilylation of a ketone using chiral auxiliaries or a chiral NHO catalyst. This work not only offered a convenient method for the synthesis of silyl ethers but also advanced the synthetic utility of NHOs as a versatile class of organocatalysts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00306.

Experimental details; analytical data; NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(16) For example, see: Karatas, B.; Rendler, S.; Froehlich, R.; Oestreich, M. *Org. Biomol. Chem.* **2008**, *6*, 1435.

(17) See the Supporting Information for more details.

(18) Tertiary alcohols are not activated by NHOs; therefore, NaO^{t}Bu can be used to deprotonate the NHO precursor *in situ* (see ref 13). This feature can potentially be used in selective silylation of primary or secondary alcohols in mixtures with tertiary alcohols.

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