NHC-Catalyzed Chemo- and Regioselective Hydrosilylation of Carbonyl Derivatives

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Abstract: The hydrosilylation of carbonyl derivatives has been explored by the activation of diphenylsilane in the presence of a catalytic amount of an N-heterocyclic carbene (NHC). Presumably, a hypervalent silicon intermediate featuring strong Lewis acid character allows dual activation of both the carbonyl moiety and the hydride at the silicon center. Reduction under mild conditions could be accomplished using this organocatalytic process. Some interesting selectivities have been encountered.

Key words: hydrosilylation, N-heterocyclic carbenes, organocatalysis, reduction, green chemistry

Hydrosilylation of carbonyl derivatives is an essential functional group transformation in synthetic organic chemistry.[2] However, to date, the reaction is usually achieved using noble metal catalysts (Rh, Pt, Ru),[3] or greener and cheaper metal complexes involving copper[4] or iron.[5] Nevertheless, the cost of the catalysts and/or leaching are still challenges to be solved for efficient hydrosilylation. Hence, the development of effective metal-free organocatalyzed processes for the hydrosilylation of carbonyl derivatives is important and has attracted growing interest.[6]

Since we have shown that the Si–H bond can be activated by N-heterocyclic carbenes (NHCs) and harnessed for the hydrosilylation of olefins,[7] we decided to also explore the NHC-catalyzed reduction of carbonyls. Such a process has been described recently with poly-NHC particles, but, to the best of our knowledge, no molecular equivalent has been reported.[8] The formation of a more Lewis acidic hypervalent silicon intermediate[9] could promote dual activation of the carbonyl as well as the hydride. Herein, we report our results.

First, we optimized the hydrosilylation/desilylation sequence with acetophenone (**1a**) as a model system to give phenylethanol (**2a**). A range of azolium salts were selected as precursors of NHCs (Figure 1). The corresponding carbenes were generated in situ by deprotonation of azolium salts **A**–**E** with either *t*-BuOK or NaH. Diphenylsilane was found to be the best hydride source for this transformation. Tetrabutylammonium fluoride (TBAF) was added at the end of the reaction in order to isolate the alcohols. Sodium hydroxide (2 M solution) could also be used, but TBAF was selected for our study.

Thiazolylidene (from **A**) and ICy (from **B**) did not allow the formation of **2a** (Table 1, entries 1 and 2). Under the same conditions, IPr (from **C**) gave rise to the desired product in 15% yield (Table 1, entry 3). SIMes (from **D**) was more active (60%; Table 1, entry 4). The best candidate was the triazolylidene derived from **E**, which yielded 93% **2a** (Table 1, entry 5).

Because *t*-BuOK also activates the silane and leads to reduction in the absence of carbene (Table 1, entry 6),[10] it was necessary to make sure that the catalytic activity derived from carbene activation. For this purpose, a base-free sample[11] of **F** was tested and it was found that performing the reaction under these conditions also led to a productive outcome (Table 1, entry 7). This result shows that NHCs are indeed able to catalyze the hydrosilylation of ketones. We believe there is an incentive to use NHCs rather than *t*-BuOK because they are not as strong Brønsted bases and chiral versions can be made.

Nonetheless, in order to sidestep this issue, we switched to non-nucleophilic NaH for the deprotonation of **E**. This modification resulted in lower yield (77%; Table 1, entry 8), however, it was improved when *N*,*N*-dimethylformamide (DMF) was used as solvent (94%; Table 1, entry 9). Interestingly, the amount of silane could be decreased to 0.6 equivalents without loss of activity (90%; Table 1, entry 10), which suggests that the two hydrides on the silane are available for the hydrosilylation process. As expected, no reaction took place in the absence of NHC or base (Table 1, entries 11 and 12).

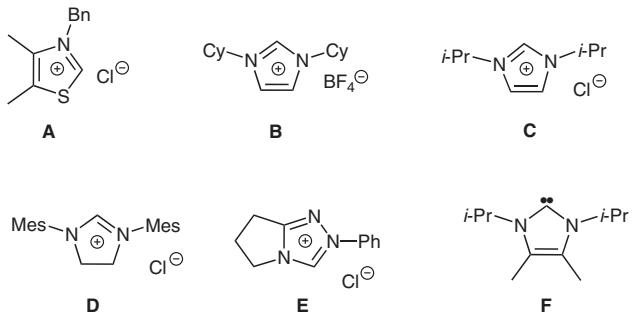

Figure 1

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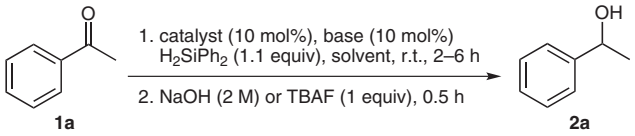
With the optimized conditions in hand (Table 1, entry 10), we investigated the scope of the reaction. Acetophenone derivatives were selected to screen the impact of phenyl ring substituents. Substrates **1b–e**, bearing electron-withdrawing or electron-donating groups, gave good to excellent yields of the corresponding alcohols **2b–e** (Table 2, entries 2–5). High chemoselectivity was observed since nitrile (**1c**)[12] or ester moieties (**1d**)[13,6a,10b] were not reduced. 2-Naphthyl methyl ketone **1f** quantitatively delivered **2f** (Table 2, entry 6). Propiophenone **1g** was efficiently reduced in five hours (Table 2, entry 7). Reduction of cyclic aromatic ketones **1h** and **1i** required stoichiometric amounts of diphenylsilane to reach completion (Table 2, entries 8 and 9). Epoxychalcone **1j** was chemoselectively reduced to the epoxyalcohol **2j** in 92% yield, leaving the reactive oxirane untouched (Table 2, entry 10).

Table 1 Reduction of **1a**

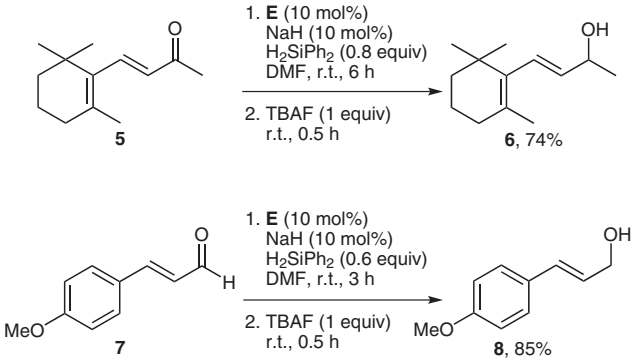


Entry	Catalyst	Base	Solvent	Yield (%)[a]
1	**A**	*t*-BuOK	THF	0
2	**B**	*t*-BuOK	THF	0
3	**C**	*t*-BuOK	THF	15
4	**D**	*t*-BuOK	THF	60
5	**E**	*t*-BuOK	THF	93
6	–	*t*-BuOK	THF	95
7	**F**	–	THF	54
8	**E**	NaH	THF	77
9	**E**	NaH	DMF	94
10[c]	**E**	NaH	DMF	92 (90)[b]
11	–	NaH	DMF	0
12	–	–	DMF	0

[a] Calculated from NMR spectra using Ph_3CH as internal standard.
[b] Isolated yield given in parentheses.
[c] H_2SiPh_2 (0.6 equiv) was used.

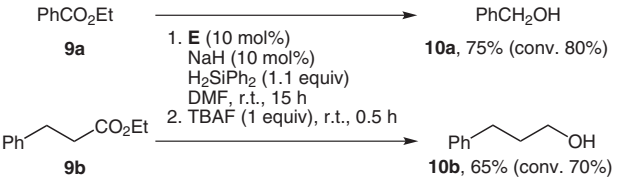
The selectivity against the reduction of alkene was highlighted by the efficient formation of alcohol **2k**, in which the olefin remained untouched, in 81% yield (Table 2, entry 11). Cyclohexyl methyl ketone was reduced sluggishly, and **2l** was isolated in 83% yield after one day with a stoichiometric amount of silane (Table 2, entry 12). The presence of an amino group did not hamper the process since **2m** was obtained in 85% yield (Table 2, entry 13). The reduction of norcamphor **1n** proceeded with complete diastereoselectivity in favor of the *endo*-alcohol **2n** (Table 2, entry 14). This method has been successfully extended to the reduction of N-Boc-protected imine **3**, leading to the formation of carbamate **4** in 75% yield (Table 2, entry 15). Such a transformation is generally not possible under transition-metal catalysis due to the reactivity of the carbamoyl group.[14]

We then turned our attention to unsaturated carbonyl compounds. To our delight, β-ionone **5** was regioselectively reduced to the 1,2-adduct **6** in 74% yield. No 1,4- or 1,6-adduct was observed (Scheme 1). Aldehydes reacted with NHCs to form the corresponding Breslow intermediates.[15] This process is fast and reversible but can be favored under protic conditions.[15e] Under our conditions, (*E*)-*p*-methoxycinnamaldehyde (**7**) was chemoselectively reduced to form the allylic alcohol **8** exclusively in 85% yield.



Scheme 1

To our delight, alcohols **10a** and **10b** were obtained in 75 and 65% yields, respectively, from esters **9a** and **9b** (Scheme 2). The reactions proceeded smoothly with stoichiometric amounts of silane, although longer reaction times were needed compared to the reaction with ketones.

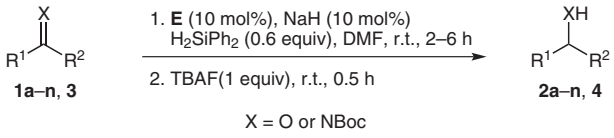


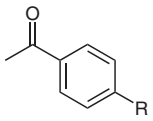
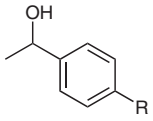
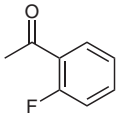
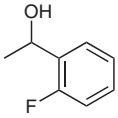
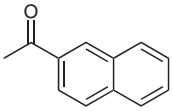
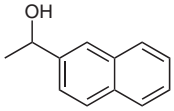
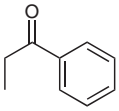
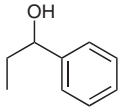
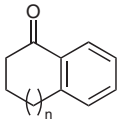
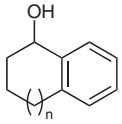
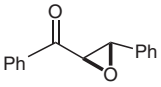
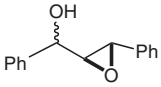
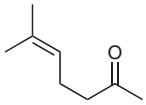
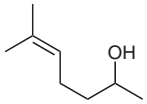
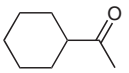
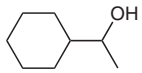
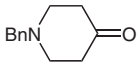
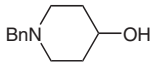
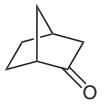
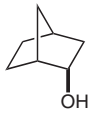
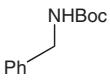
Scheme 2

The reduction of ethyl benzoylacetate (**11a**) was investigated, but no reaction was observed even when 1.1 equivalent of diphenylsilane was used (Scheme 3). Acetophenone was added to this reaction mixture in order to assess whether the catalytic activity was maintained in the presence of **11a**; under these conditions, no reaction occurred, indicating that inactivation of the catalyst had occured. We surmised that the acidic protons might protonate the NHC. When cyclopropyl derivative **11b** was submitted to the reduction conditions, 1,3-diol **12** was obtained in 25% yield and further improved to 82% with two equivalents of diphenylsilane. The selective reduction

of the ketone group was not observed. This contrasts with the selective reduction of ketone **1d** in a shorter reaction time with the same amount of silane (Table 1, entry 4). We postulated a fast reduction of the ketone group in **11b**, leading to the corresponding alkoxysilane with a hydride suitably positioned for intramolecular transfer onto the ester group.[16]

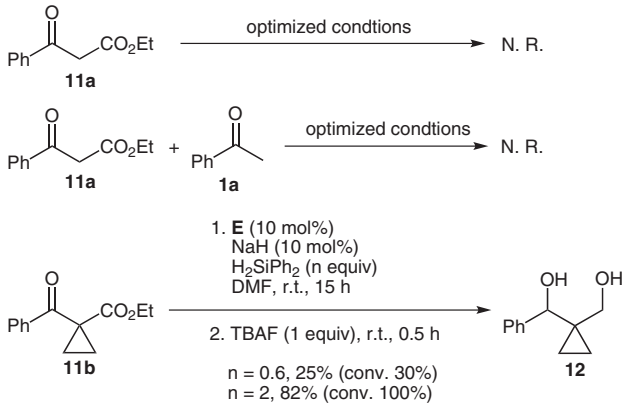
Table 2 Scope of the Reduction Process



Entry	Substrate		Product		Yield (%)[a]
1		**1a**; R = H		**2a**	90
2		**1b**; R = OMe		**2b**	99
3		**1c**; R = CN		**2c**	83
4		**1d**; R = CO_2Me		**2d**	99
5		**1e**		**2e**	87
6		**1f**		**2f**	99
7		**1g**		**2g**	87
8[b]		**1h** (n = 0)		**2h**	90
9[b]		**1i** (n = 1)		**2i**	89
10		**1j**		**2j**	92[c]
11		**1k**		**2k**	81
12[b]		**1l**		**2l**	83
13		**1m**		**2m**	85
14		**1n**		**2n**	68
15		**3**		**4**	75

[a] Isolated yield.
[b] H_2SiPh_2 (1.1 equiv) was used in 24 h.
[c] Ratio *syn*/*anti* = 2.5:1 based on ^1H NMR analysis of the crude reaction mixture.

In conclusion, we have demonstrated the ability of NHCs to catalyze the metal-free hydrosilylation of aldehydes, ketones, esters and ketimines.[17] This organocatalyzed reaction exhibits high selectivity. All of the hydrides on the silicon atom can be transferred. We are currently investigating the mechanism for this transformation and the ability of chiral NHCs to promote an enantioselective variant of the reaction.



Scheme 3

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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Analytical data for some typical examples: Compound **2c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.0 Hz, 2 H), 7.47 (q, *J* = 8.0 Hz, 2 H), 4.93 (q, *J* = 6.0 Hz, 1 H), 2.31 (br s, 3 H), 1.47 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.2, 132.3, 126.1, 118.9, 111.0, 70.0, 25.4. Compound **2d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.0 Hz, 2 H), 7.40 (q, *J* = 8.0 Hz, 2 H), 4.92 (q, *J* = 6.4 Hz, 1 H), 3.88 (s, 3 H), 2.49 (br s, 1 H), 1.47 (d, *J* = 6.4 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1, 151.1, 129.8, 129.1, 125.3, 69.9, 52.1, 25.3. Compound **2h**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 5.6 Hz, 1 H), 7.29–7.22 (m, 3 H), 5.24 (t, *J* = 6.0 Hz, 1 H), 3.06 (m, 1 H), 2.82 (m, 1 H), 2.53–2.44 (m, 1 H), 1.99–1.90 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.0, 143.3, 128.3, 126.7, 124.9, 124.2, 76.4, 35.9, 29.8. Compound **2j** (*syn*/*anti*, 2.5:1): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.27 (m, 20 H, *syn* and *anti*), 5.00 (t, *J* = 2.0 Hz, 1 H, *anti*), 4.73 (t, *J* = 4.2 Hz, 1 H, *syn*), 4.17 (d, *J* = 2.0 Hz, 1 H, *anti*), 4.04 (d, *J* = 2.0 Hz, 1 H, *syn*), 3.34 (dd, *J* = 4.2, 2.0 Hz, 1 H, *syn*), 3.32 (dd, *J* = 2.8, 2.0 Hz, 1 H, *anti*), 3.01 (d, *J* = 4.2 Hz, 1 H, *syn*), 2.85 (d, *J* = 2.4 Hz, 1 H, *anti*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.2 (*syn*), 139.4 (*anti*), 136.6 (*anti*), 136.4 (*syn*), 128.8 (*syn*), 128.7 (*anti*), 128.6 (*syn* and *anti*), 128.5 (*syn*), 128.4 (*anti*), 128.3 (*syn* and *anti*), 126.7 (*anti*), 126.3 (*syn*), 125.8 (*syn* and *anti*), 73.5 (*syn*), 71.3 (*anti*), 65.9 (*syn*), 65.1 (*anti*), 57.0(*syn*), 55.2 (*anti*). Compound **2l**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.54 (m, 1 H), 1.84–1.67 (m, 5 H), 1.30–0.91 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 72.4, 45.1, 28.7, 28.4, 26.5, 26.2, 26.1, 20.4. Compound **4**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.24 (m, 5 H), 4.90 (br s, 1 H), 4.31 (d, *J* = 4.8 Hz, 2 H), 1.47 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9, 139.0, 128.6, 127.5, 127.3, 79.5, 44.7, 28.4. Compound **6**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.04 (d, *J* = 16.0 Hz, 1 H), 5.48 (dd, *J* = 16.0, 6.8 Hz, 1 H), 4.35 (sext., *J* = 6.4 Hz, 1 H), 1.97 (t, *J* = 6.4 Hz, 2 H), 1.66 (s, 3 H), 1.62–1.51 (m, 3 H), 1.44 (m, 2 H), 1.32 (d, *J* = 6.0 Hz, 3 H), 0.98 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.6, 136.6, 128.8, 127.5, 69.5, 39.4, 33.9, 32.7, 28.7, 28.6, 23.6, 21.3, 19.2. Compound **12**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.26 (m, 5 H), 4.1 (s, 1 H), 3.74 (d, *J* = 11.6 Hz, 2 H), 3.19 (d, *J* = 11.6 Hz, 1 H), 2.92 (br s, 1 H), 0.73–0.62 (m, 3 H), 0.48–0.44 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.1, 128.2, 127.5, 126.2, 79.7, 68.4, 27.5, 9.8, 8.0.