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Homogeneous Catalysis

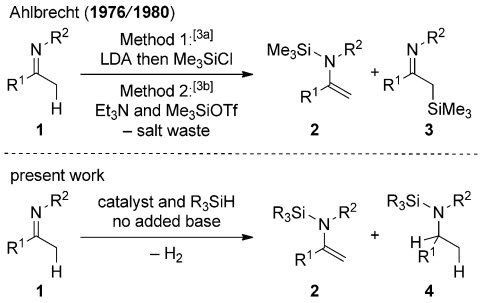
Direct Catalytic Access to N-Silylated Enamines from Enolizable Imines and Hydrosilanes by Base-Free Dehydrogenative Si–N Coupling

Julia Hermeke, Hendrik F. T. Klare, and Martin Oestreich*[a]

Abstract: A procedure for the synthesis of otherwise difficult-to-make N-silylated enamines, that is masked enamines derived from primary amines, is reported. The approach is based on formation of a silyliminium ion and subsequent abstraction of the acidified α-proton rather than α-deprotonation of the enolizable imine followed by reaction with an electrophilic silicon reagent. The silicon electrophile, stabilized by a sulfur atom, is generated by cooperative activation of an Si–H bond at the Ru–S bond of a tethered ruthenium(II) thiolate complex. After transfer of the silicon cation onto the imine nitrogen atom, the remaining ruthenium(II) hydride fulfills the role of the base. Deprotonation and release of dihydrogen close the catalytic cycle. The net reaction is a dehydrogenative Si–N coupling of enolizable imines and hydrosilanes.

N-Silylated enamines are essentially nitrogen analogs of O-silylated enols (=silyl enol ethers), but the chemistry of this uncommon compound class is by far less developed.[1] The Si–N bond serves as a placeholder for an N–H bond, and N-monosilylated enamines are, as such, precursors of otherwise unstable N-unsubstituted enamines that tautomerize preferentially to the corresponding imine. Hence, protection of the N–H group opens the door to enamine reactivity from combinations of primary rather than secondary amines and enolizable carbonyl compounds.[2] A few broadly applicable procedures for their preparation are known,[1] including the methods starting from imines that were elaborated by Ahlbrecht and co-workers a long time ago (**1**→**2**, Scheme 1, top).[3,4] These differ in base (complete[3a] versus partial[3b] deprotonation) and silicon electrophile, and Method 2 is superior to Method 1 in terms of chemoselectivity [N- (**1**→**2**) preferred over C-silylation (**1**→**3**)].

Ahlbrecht's methods are reliable, and even the use of silyl triflates is not a limitation anymore since those with typical substitution patterns are nowadays commercially available. What might be viewed as a disadvantage is the accumulation of stoichiometric salt as a result of the deprotonation/silylation



Scheme 1. Preparation of N-silylated enamines from imines by deprotonation/electrophilic substitution (top) and dehydrogenative coupling (bottom). LDA = lithium diisopropylamide and Tf = trifluoromethanesulfonyl.

sequence. That waste could be avoided in a direct dehydrogenative coupling of imines and hydrosilanes (**1**→**2**, Scheme 1, bottom), but such a reaction has not been described yet.[8] Our laboratory recently developed a catalytic dehydrogenative coupling of enolizable carbonyl compounds and hydrosilanes that directly produces silyl enol ethers along with dihydrogen (not shown).[9] Referring back to the aforementioned analogy, we anticipated that this method would be applicable to enolizable imines.[10] The overall process hinges on the ability of tethered ruthenium complexes $\mathbf{5}^+[BAr^F{}_4]^-$[11] (with Ar^F = 3,5-bis(trifluoromethyl)phenyl, Scheme 2, top) to formally split the Si–H bond of **6** into a hydride and a sulfur-stabilized silicon cation ($\mathbf{5}^+ \rightarrow [\mathbf{7}^+]^{\ddagger} \rightarrow \mathbf{8}^+$, Scheme 2, middle).[12] The activation step $[\mathbf{7}^+]^{\ddagger}$ is a σ-bond metathesis of the Si–H and Ru–S bonds. Intermediate $\mathbf{8}^+$ is an excellent source of electrophilic silicon, and its transfer onto Lewis basic sites is facile. With imine **1** as the Lewis base, silyliminium ion $\mathbf{9}^+$ forms immediately, releasing the ruthenium hydride **10** (Scheme 2, bottom). Complex **10** usually acts as a base ($\mathbf{9}^+ \rightarrow \mathbf{2}$, right) rather than a hydride donor ($\mathbf{9}^+ \rightarrow \mathbf{4}$, left); this counterintuitive behavior is documented in several dehydrogenative bond-forming reactions,[9,10,12] and hydride transfer has so far only been seen in the absence of acidic hydrogen atoms.[13] Abstraction of an acidified α-hydrogen atom in $\mathbf{9}^+$ would then afford the desired N-silylated enamine **2** and dihydrogen. We disclose here the direct synthesis of **2** from enolizable imines **1** based on this strategy.

We began our investigation with testing selected Ru–S complexes $\mathbf{5}^+[BAr^F{}_4]^-$ and various hydrosilanes **6** (Table 1). The choice of **6** is determined by the size of the pocket that both the thiolate and phosphine ligands create around the Ru–S bond, and Me_2PhSiH (**6a**) had been found to be a good fit be-

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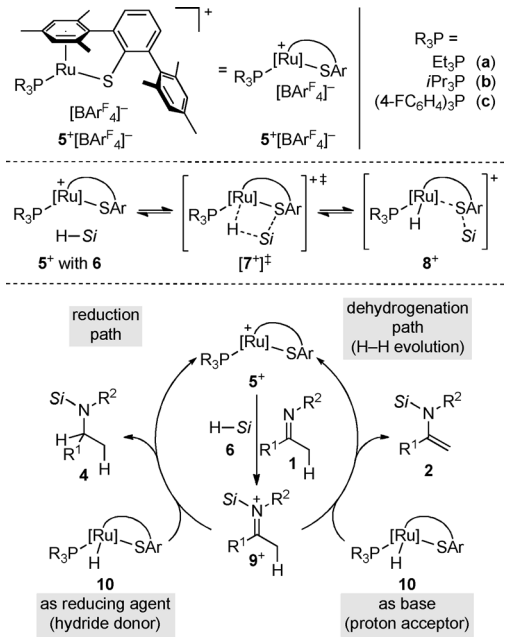


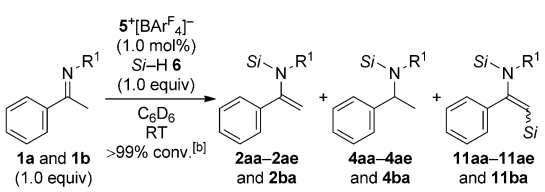
Scheme 2. Catalyst (top), cooperative Si–H bond activation (middle), and concept of dehydrogenative enamine formation from imines (bottom). Ar^F = 3,5-bis(trifluoromethyl)phenyl and *Si* = R_3Si = triorganosilyl.

fore.[9,10,12a,13] Enolizable imines **1a** and **1b** were employed as model substrates, and three representative complexes **5a**$^+$–**5c**$^+$ with sterically and electronically different phosphine ligands were used as catalysts. For N-phenylimine **1a** as substrate, low loadings of all three Ru–S complexes **5**$^+$ were found to promote the dehydrogenative coupling at room temperature (entries 1–3). However, the reaction times were markedly dependent on the steric and electronic situation at the Ru–S bond in **5**$^+$. The electron-rich phosphines form more reactive complexes than the electron-deficient phosphine[14] with the deprotonation/loss of dihydrogen event likely to be rate-determining, but increased steric bulk also decelerates the reaction (hours with *i*Pr_3P versus minutes with Et_3P). The chemoselectivity was generally high when the reaction was run in an open system to release dihydrogen (**1a**→**2aa**, entries 1–3),[15] and the reduction path could be completely suppressed using **5b**$^+$ (entry 2). It is worth noting that we identified a minor component, the C-silylated N-silylated enamine **11aa**, as the result of a twofold dehydrogenative coupling. The N-silylated enamine **2aa** is a nucleophile itself that reacts with the silicon electrophile to yield a C-silylated silyliminium ion that, in turn, is deprotonated to reestablish the enamine functional group (not shown).[16,17] Traces of **11aa** are seen with the bulkier catalysts **5b**$^+$ and **5c**$^+$ (entries 2 and 3), and these proportions did not change in the presence of excess hydrosilane **6a** (2.0 equiv or more). However, as evident from the substrate screening below, **11** forms in substantial amounts from imines with sterically hindered substituents at the imine nitrogen atom. Hence, imine **1** and enamine **2** compete for the silicon electrophile in these cases.

With N-benzylimine **1b** as substrate, the product distribution changes dramatically under otherwise identical conditions (Table 1, entries 4–6). To our surprise, catalysts **5a**$^+$ and **5c**$^+$ furnished the N-silylated amine (**1b**→**4ba**, entries 4 and 6) whereas **5b**$^+$ still provided the desired N-silylated enamine with excellent chemoselectivity (**1b**→**2ba**, entry 5). As a result of the sterically less hindered benzyl group in **1b**, formation of **11ba** was hardly seen, if at all. The effect of the phosphine ligand on the reaction path is absolutely remarkable: **5b**$^+$ with the bulky electron-donating phosphine produces the N-silylated enamine (**1b**→**2ba**) and **5c**$^+$ with the electron-withdrawing phosphine exclusively yields the N-silylated amine (**1b**→**4ba**).

With optimal catalyst **5b**$^+$ in hands, we tested representative triorganohydrosilanes **6b**–**6e** (Table 1, entries 7–10). EtMe_2SiH is as good as Me_2PhSiH (**6a** and **6b**, entries 2 and 7). Conversely, any other hydrosilane **6c**–**6e** was too bulky to undergo the σ-bond metathesis at the Ru–S bond in **5b**$^+$ (entries 8–10). While this was expected for Et_3SiH (**6c**) and Ph_3SiH

Table 1. Optimization of reaction conditions for the synthesis of N-silylated enamines **2** from enolizable imines **1**.[a]



Entry	R 5^+	R^1 Imine	*Si*–H Hydrosilane	*t* [h]	Ratio **2/4/11**[c]	Yield [%][d]
1	Et **5a**$^+$	Ph **1a**	Me_2PhSiH **6a**	0.25	90:10:0 **2aa**:**4aa**:**11aa**	quant
2	*i*Pr **5b**$^+$			12	97:0:3 **2aa**:**4aa**:**11aa**	quant[e] (79)[f]
3[g]	Ar[h] **5c**$^+$			60	84:10:6 **2aa**:**4aa**:**11aa**	97
4	Et **5a**$^+$	Bn **1b**	Me_2PhSiH **6a**	0.5	13:86:1 **2ba**:**4ba**:**11ba**	quant
5	*i*Pr **5b**$^+$[i]			12	93:2:5 **2ba**:**4ba**:**11ba**	90
6	Ar[h] **5c**$^+$[i]			12	0:>99:0 **2ba**:**4ba**:**11ba**	95
7	*i*Pr **5b**$^+$	Ph **1a**	EtMe_2SiH **6b**[j]	4	>99:0:0 **2ab**:**4ab**:**11ab**	quant
8[k]			Et_3SiH **6c**	48	>99:0:0 **2ac**:**4ac**:**11ac**	8[l]
9[k]			MePh_2SiH **6d**	48	0:>99:0 **2ad**:**4ad**:**11ad**	1[l]
10[k]			Ph_3SiH **6e**	48	– **2ae**:**4ae**:**11ae**	0[l]

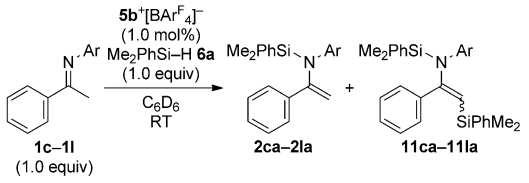
[a] All reactions were performed according to the General Procedure (see the Supporting Information for details). [b] Determined by ^{1}H NMR spectroscopy using 1,2,4,5-tetramethylbenzene as internal standard. [c] Determined by ^{1}H NMR spectroscopy. [d] Combined NMR yield determined by using 1,2,4,5-tetramethylbenzene as internal standard. [e] In situ formation of coordinatively unsaturated **5b**$^+$[BAr^F_4]$^-$ from the corresponding air-stable chloride complex by treatment with $NaBAr^F_4$ furnished the same result within the experimental error; in this way, it was not necessary to handle oxygen-sensitive catalyst **5b**$^+$[BAr^F_4]$^-$ in a glovebox. [f] Isolated yield on a 1.5 mmol scale. [g] Reaction with 2.0 mol% catalyst loading results in same ratio and yield in 12 h. [h] Ar = 4-FC_6H_4. [i] Catalyst loading of 2.0 mol% required for these reaction times. [j] 2.0 equiv due to its volatility. [k] 80 °C. [l] Conversion.

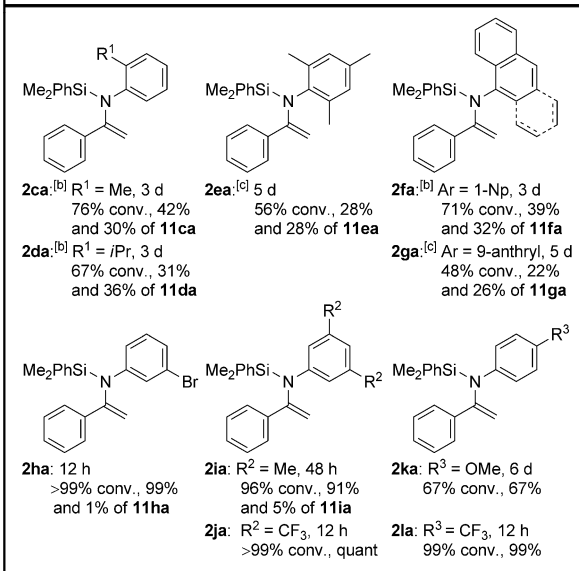
(**6e**),[9,10,12a,13] the inability of **5b**$^+$ (with iPr$_3$P) to split the Si–H bond in MePh$_2$SiH (**6d**) was not. The fact that both **5a**$^+$ (with Et$_3$P) and **5c**$^+$ [with (4-FC$_6$H$_4$)$_3$P] do mediate the activation of this particular hydrosilane[14] is evidence for the importance of the size of the phosphine ligand in catalysts **5**$^+$. Elevated temperatures did not make any difference.

The optimized procedure was then applied to acetophenone-derived imines **1c**–**1l** with various aryl groups at the imine nitrogen atom (Table 2). Gratifyingly, the N-silylated amines **4c**–**4l** did not form in any of these examples. However, the aforementioned twofold dehydrogenative coupling leading to **11** became a serious side reaction with imines **1** having a sterically less accessible nitrogen atom (**1**→**2**→**11**). As a result, N-arylimines **1c**–**1g** with an *ortho*-substituent or a *peri*-position afforded C-silylated N-silylated enamines **11ca**–**11ga** in quantities similar to those of desired **2ca**–**2ga**. Imines **1ha**–**1la** not crowded around the nitrogen atom reacted smoothly to yield the N-silylated enamines **2ha**–**2la**. CF$_3$-substituted N-arylimines **1j** and **1l** reacted faster than the OMe-substituted congener **1k**. Electron-withdrawing substituents at the N-aryl group make the imine nitrogen atom of **1** less basic but also destabilize the silyliminium ion intermediate **9**$^+$, thereby facilitating the (potentially rate-determining) deprotonation step. Adjusting the reaction time also allowed for decent conversion of imine **1k** with an electron-donating group (67% conversion in days versus full conversion in hours).

Any aryl group other than phenyl at the imine nitrogen atom will be an exception rather than the norm. We therefore continued probing the scope of the dehydrogenative Si–N coupling using a range of differently substituted acetophenone-derived N-phenylimines under the optimized reaction conditions (Table 3). Examples include substitution in the *ortho*, *meta*, and *para* positions with electron-donating as well as withdrawing groups. Without exception, the N-silylated enamines **2ma**–**2za** and **2a′a** were obtained chemoselectively in high to excellent yields. Substrates with electron-withdrawing groups worked perfectly with this catalytic system, for example, **2ra**, **2ua**, **2va**, **2xa**, and **2a′a**. Substrates bearing strongly electron-donating groups furnished **2ma**, **2pa**, and **2sa** in good to high yields but required longer reaction times. It was only these reactions where small amounts of the N-silylated

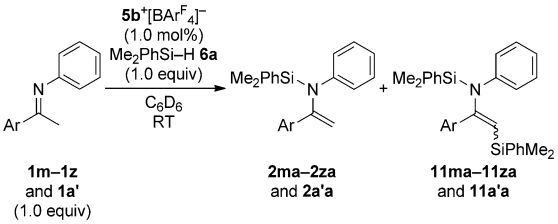
Table 2. Substrate scope I: Variation of the N-aryl moiety of acetophenone-derived imines.[a]

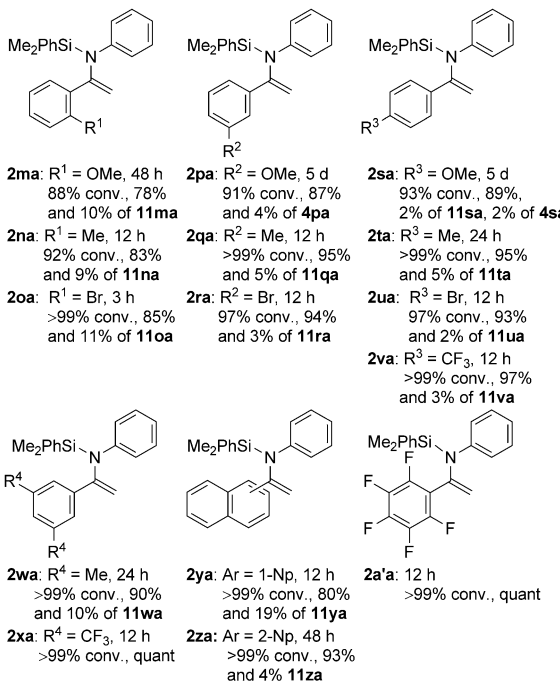




[a] All reactions were performed according to the General Procedure (see the Supporting Information for details). Conversions and NMR yields were determined by ^{1}H NMR spectroscopy using 1,2,4,5-tetramethylbenzene as internal standard. [b] Reaction with 2.0 mol% catalyst loading results in same ratio and yield. [c] Catalyst loading of 2.0 mol%.

Table 3. Substrate scope II: Variations of the substitution pattern of acetophenone-derived N-phenylimines.[a]

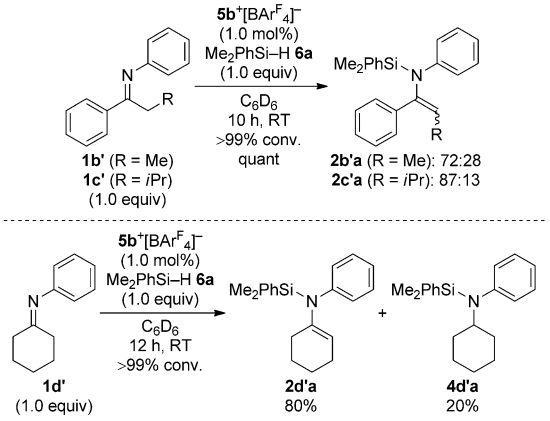




[a] All reactions were performed according to the General Procedure (see the Supporting Information for details). Conversions and NMR yields were determined by ^{1}H NMR spectroscopy using 1,2,4,5-tetramethylbenzene as internal standard.

amines **4pa** (4%) and **4sa** (2%) were detected. Steric hindrance again led to C-silylation of the N-silylated enamine (**2**→**11**) albeit to much lesser extent than seen for imines substituted at the nitrogen atom with a bulky aryl group. Hence, *ortho*-aryl- and 1-naphthyl-substituted imines **1m**–**1o** and **1y** afforded **2ma**–**2oa** and **2ya** in good yields along with **11ma**–**11oa** (≈10%) and **11ya** (19%). We also reacted selected systems **1m**–**1o** with double the amount of hydrosilane **6a** to learn whether the C-silylated N-silylated enamine would form quantitatively from hindered intermediates **2ma**–**2oa**, and we were delighted to see the high-yielding formation of **11ma**–**11oa** (see the Supporting Information for details). These electronic and steric effects are consistent with the trends discussed for the various acetophenone-derived N-arylimines (Tables 2 and 3).

Probing the possibility of diastereocontrol in the formation of the N-silylated enamine, we subjected imines **1b′** and **1c′** to the standard reaction conditions (Scheme 3, top). Both **2b′a** and **2c′a** formed in quantitative yield and, not unexpectedly, higher steric demand of the R group had a beneficial effect on



Scheme 3. Additional substrates: Exploring control of the double bond geometry (top) and chemoselectivity in the reaction of a dialkyl imine (bottom).

the diastereoselectivity. Finally, we studied an example of a dialkyl imine, namely the N-phenylimine of cyclohexanone (Scheme 3, bottom). For **1d′**, the chemoselectivity was not as high as in all previous cases; N-silylated enamine **2d′a** and N-silylated amine **4d′a** formed in a ratio of 80:20. These initial results are promising though and set the stage for further improvement of the catalyst structure to control the alkene geometry as well as expand the substrate scope.

In summary, we disclosed here a new way for the direct catalytic preparation to N-silylated enamines from enolizable imines and hydrosilanes in high yields. The reaction proceeds at room temperature with low catalyst loadings and, importantly, does not require addition of a base, liberating dihydrogen as the sole byproduct. In situ generation of the coordinatively unsaturated catalyst allows for performing the reactions outside a glovebox. The choice of the ruthenium(II) thiolate catalyst or, more precisely, the phosphine ligand at the ruthenium(II) center, is crucial for obtaining high chemoselectivity in favor of N-silylated enamine (dehydrogenation path) over N-silylated amine (reduction path). We were able to demonstrate that structurally diverse acetophenone-derived imines participate in this reaction. By this, a rare class of enamines that are made from primary amines now becomes readily available.

Acknowledgements

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Keywords: chemoselectivity · dehydrogenative coupling · enamine compounds · homogeneous catalysis · Si–H bond activation

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[15] a) The procedure is detailed in the General Procedure in the Supporting Information; b) The rate of the addition of catalyst **5a**$^{+}$[BAr$^{F}_{4}$]$^{-}$ was found to effect the chemoselectivity but slow addition secured reproducibility.

[16] A similar reaction of N,N-dialkylated enamines with $(C_6F_5)_3SiOTf$ using Et_3N as base was reported by Dilman and co-workers: V. V. Levin, A. D. Dilman, P. A. Belyakov, A. A. Korlyukov, M. I. Struchkova, V. A. Tartakovsky, *Tetrahedron Lett.* **2005**, *46*, 3729 – 3732.

[17] An alternative pathway to arrive at C-silylated N-silylated enamines from imines could proceed through the C-silylated enamine (by a mechanism similar to that outlined in Ref. [16]) followed by its dehydrogenative Si–N coupling (cf. Ref. [10]).

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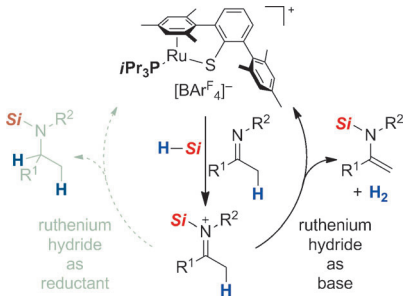

Silicon IN, hydrogen OUT: N-silylated enamines are protected enamines derived from combinations of primary rather than secondary amines and enolizable carbonyl compounds. This rare class of compounds is now directly available from imines by a dehydrogenative Si–N coupling. The catalyst generates the silicon electrophile by Si–H bond activation and also acts as a base after transfer of the silicon electrophile onto the imine nitrogen atom (see scheme, Ar^F = 3,5-bis(trifluoromethyl)-phenyl, *Si* = R_3Si = triorganosilyl).