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Lewis acid-promoted carbonyl addition of 1,3-bis(silyl)propenes

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ABSTRACT

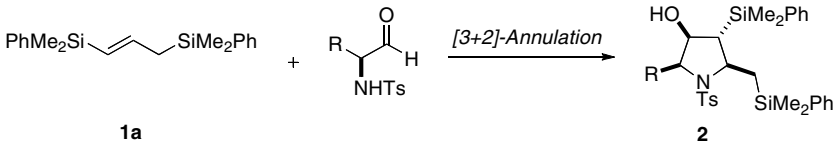
A novel synthetic protocol for Lewis acid-promoted addition of 1,3-bis(silyl)propenes to *N*-phenyl glyoxylamide and ethyl glyoxylate is developed. The reaction does not appear to be influenced by the steric bulk of the 1,3-bis(silyl)propenes, and represents a new approach to vinylation of glyoxylates; the products are obtained in good yields.

Allylsilanes are synthetically versatile precursors to enantioenriched building blocks for natural product synthesis.[1] Lewis acid-promoted addition of allylsilanes to aldehydes and ketones is an efficient method for stereoselective C–C bond formation,[2-4] and they can also be used as a synthetic equivalent of 1,2-[5,6] and 1,3-[7-9] dipoles in stereoselective annulation reactions. Recently, we reported an expansion of allylsilane technology, namely that 1,3-bis(silyl)propene **1a** can participate in a highly stereoselective [3+2] annulation reaction with α-amino aldehydes to provide densely functionalized pyrrolidines **2** (Scheme 1).[10]

In contrast, the use of vinylsilanes as nucleophiles in addition to carbonyl compounds is relatively rare,[11,12] presumably due to their low inherent nucleophilicity. Based on this precedent, we were interested in examining the efficiency of silane **1a**[13] as a nucleophile recognizing that its structural features include both vinyl- and allylsilane moieties and that this dual reactivity would allow for an efficient addition to carbonyl compounds. To this end, we report a novel Lewis acid-catalyzed addition of 1,3-bis(silyl)propene **1a** to glyoxylamide **3a**[14] and glyoxylate **3b**, which represents a conceptually distinct approach to vinylation of glyoxylates, as well as providing access to functionalized allylsilanes (Scheme 2).

Initial attempts were directed toward developing optimal reaction conditions for the successful addition of silane **1a** to *N*-phenyl glyoxylamide **3a** (Table 1). In view of our previous success in promoting the [3+2] annulation reaction of silane **1a** with α-amino aldehydes, we began our investigation by employing $MeAlCl_2$ as the Lewis acid. Disappointingly, neither aluminum-based bidentate Lewis acids nor $BF_3{\cdot}Et_2O$ furnished the desired product (entries 1 and 2).

Further screening[15] of both monodentate and chelating Lewis acids revealed that excess $SnCl_4$ successfully promoted addition of silane **1a** to glyoxylamide **3a** to give **4a** together with *O*-desilylated product **5** in low yield (entry 3). Both prolonged reaction time and increased reaction temperature resulted in the formation of **6**, the result of a protodesilylation[16] of **1a** followed by addition of the so-formed allylsilane to amide **3a**. In order to preclude this



1a 2

Scheme 1. [3+2]-Annulation of α-amino aldehydes.

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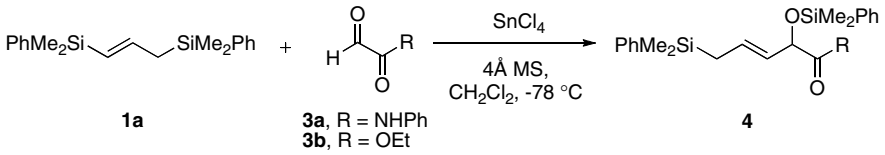
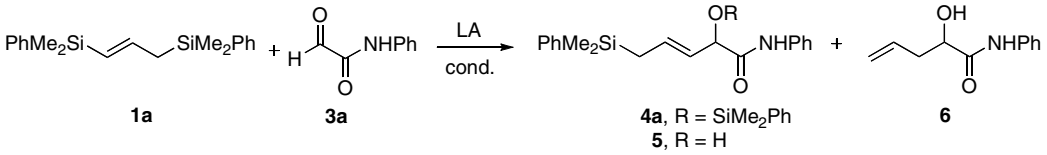


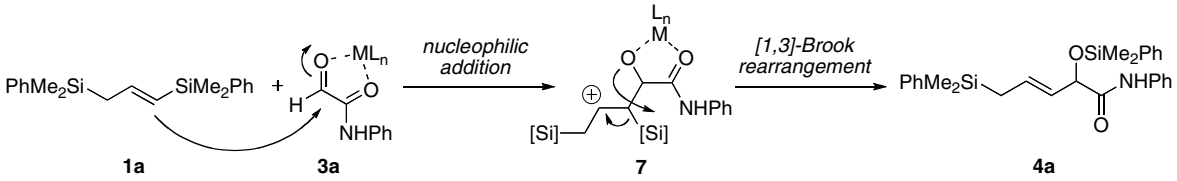
Scheme 2. Addition of silane **1a** to glyoxylamide **3a** and glyoxylate **3b**.

Table 1
Optimization of the reaction conditions for the addition of **1a** to *N*-phenyl glyoxylamide **3a**[a]



Entry	Lewis acid	Equiv	*T* (°C)	Time (h)	Product	Yield[b] (%)
1	$MeAlCl_2$	2	−78	24	—	—
2	$BF_3{\cdot}Et_2O$	1	−78	24	—	—
3	$SnCl_4$	1.2	−78	2.5	**4a** (**5**)	32 (12)
4	$SnCl_4$	1	−78 to −20	18	**6** (**5**)	69 (17)
5[c]	$SnCl_4$	0.15	−78	1	**4a**	89

[a] Reaction conditions: to a solution of **3a** (1.2 equiv) and **1a** (1 equiv) in CH_2Cl_2 at −78 °C was added Lewis acid, and the reaction mixture was stirred for the indicated time, see Ref. 17.
[b] Isolated yield.
[c] Reaction was conducted in the presence of 4 Å MS.

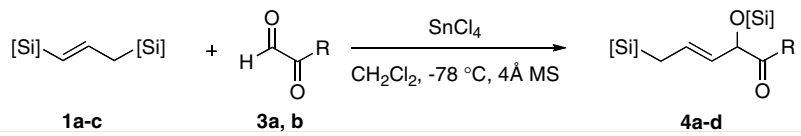


Scheme 3. Proposed mechanism for allylsilane formation.

undesired side reaction, it was found that addition of 4 Å molecular sieves to the reaction mixture together with a low reaction temperature could effectively suppress protodesilylation of silane **1a**, and using this protocol allylsilane **4a** could be obtained as the sole product in an excellent yield (entry 5).[17]

A plausible mechanism for the formation of **4a** commences with nucleophilic addition of silane **1a** to the Lewis acid-activated electrophile **3a**, furnishing the β-silicon-stabilized carbocation **7**,[18] and subsequent [1,3]-Brook rearrangement[19] yields allylsilane **4a** (Scheme 3). Thus, this reaction represents a rare example of vinylation of glyoxylates.[11] Since **1a** is a rather poor nucleophile compared to the corresponding allylsilane,[20] it is believed that bidentate Lewis acid activation of **3a** is required to promote the addition. With optimized conditions at hand, we then turned our attention to the reaction scope. Despite the fact that glyoxylamide **3a** has been used successfully in asymmetric glyoxylamide-ene reactions,[21] Sakurai allylations,[14] and vinylsilane[11] and propargylsilane[22] additions, it is not commercially available, and has to be prepared via a tedious procedure.[21] Consequently, we were interested to see whether the present reaction protocol could be applied for the addition of silane **1a** to commercially available ethyl glyoxylate **3b**, thus making it more suitable for future

Table 2
$SnCl_4$-catalyzed additions of silanes **1a–c** to **3a, b**[a]



Entry	**1** ([Si])	**3** (R)	Equiv ($SnCl_4$)	Yield of **4**[b] (%)[c]
1	**a** ($SiMe_2Ph$)	**a** (NHPh)	0.15	**a** (89)
2	**a** ($SiMe_2Ph$)	**b** (OEt)	0.3	**b** (84)
3	**b** ($SiMe_3$)	**b** (OEt)	0.3	**c** (71)
4	**c** ($SiPh_2t$-Bu)	**b** (OEt)	0.3	**d** (85)

[a] For reaction conditions, see Ref. 24.
[b] All new compounds were fully characterized by IR, ^1H, and ^{13}C NMR.
[c] Isolated yield.

applications. To our delight, increasing the catalyst loading to 30% of $SnCl_4$ together with a prolonged reaction time afforded allylsilane **4b** in 84% yield (Table 2, entry 2). Finally, the effect of different silicon substituents on the reaction outcome was investigated.[23] Interestingly, neither the less bulky silane **1b** ([Si] = $SiMe_3$) nor the more bulky silane **1c** ([Si] = $SiPh_2t$-Bu) showed significant effects on the product distribution, and the corresponding allylsilanes **4c** and **4d** were obtained in good yields (Table 2, entries 3 and 4).[24]

In summary, we have developed a novel protocol for addition of 1,3-bis(silyl)propenes to Lewis acid-activated glyoxylates resulting in vinylation. The reaction proceeds in high yields and the outcome does not appear to be influenced by the steric bulk of the trialkylsilyl moieties in silanes **1**. Further studies on the presented reaction, including asymmetric protocols, are currently underway.

Acknowledgments

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17. A typical experimental procedure for the preparation of **4a** is described (Table 1, entry 5). To a solution of **3a** (23.4 mg, 0.156 mmol) and silane **1a** (40.4 mg, 0.130 mmol) in CH_2Cl_2 at −78 °C containing 4 Å MS (100 mg/mmol) was added $SnCl_4$ (13 μL, 0.1 mmol, 1 M solution in CH_2Cl_2) in one portion. The resultant mixture was stirred at −78 °C until the reaction was judged complete by TLC analysis (typically 1 h for additions to **3a**, R_f (**1a**) = 0.84, 7:1 heptane/EtOAc). The reaction mixture was then quenched at −78 °C with Et_3N (0.2 mL) followed by addition of H_2O (10 mL). The mixture was extracted with EtOAc (3 × 15 mL), the organic phases dried ($MgSO_4$), and the resultant crude material purified by flash chromatography (SiO_2, 7:1 pentane/EtOAc) to provide **4a** as a colorless oil (53.2 mg, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.43 (s, 1H), 7.58–7.54 (m, 2H), 7.54–7.49 (m, 4H), 7.46–7.30 (m, 8H), 7.15–7.10 (m, 1H), 5.81 (dtd, *J* = 1.2, 8.2, 15.3, 1H), 5.43 (ddt, *J* = 1.1, 6.2, 15.1, 1H), 4.62 (d, *J* = 6.2, 1H), 1.75 (d, *J* = 8.3, 1H), 0.44 (s, 3H), 0.44 (s, 3H), 0.30 (s, 3H), 0.28 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 170.26, 138.48, 137.63, 136.69, 133.82, 133.52, 130.67, 130.36, 129.18, 128.34, 127.98, 126.53, 124.46, 119.75, 75.45, 22.18, −0.94, −1.37, −3.08, −3.15. HRMS (ESI$^+$): exact mass calcd for $C_{27}H_{33}NO_2Si_2$ [M+H]$^+$, requires *m*/*z*: 460.2122, found *m*/*z*: 460.2121.
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24. A typical experimental procedure for the preparation of **4b** is described (Table 2, entry 2). To a solution of silane **1a** (509.8 mg, 1.64 mmol) in CH_2Cl_2 containing 4 Å MS (100 mg/mmol, activated) was added freshly distilled ethyl glyoxylate (263 μL, 1.97 mmol, 80% solution in toluene, [see Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859–10860] at −78 °C followed by $SnCl_4$ (164 μL, 0.1 mmol, 1 M solution in CH_2Cl_2) and the resulting mixture was stirred for 1 h at −78 °C. Each hour, for 2 h, an additional portion of $SnCl_4$ (2 × 164 μL, 0.2 mmol, 1 M solution in CH_2Cl_2) was added. The resulting solution was stirred at −78 °C until the silane **1a** was completely consumed (1.5–2 h) as determined by TLC (R_f (**1a**) = 0.84, 7:1 heptane/EtOAc). The reaction mixture was then quenched at −78 °C with Et_3N and after warming to rt, was filtered through Celite 521, and concentrated. The crude product was purified by flash chromatography (aluminium oxide 90 active basic, 7:1 pentane/EtOAc) to provide **4b** as a colorless oil (569 mg, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.66–7.50 (m, 2H), 7.50–7.43 (m, 2H), 7.43–7.29 (m, 6H), 5.74 (dtd, *J* = 1.2, 8.2, 15.3, 1H), 5.40 (ddt, *J* = 1.1, 6.7, 15.1, 1H), 4.54 (d, *J* = 6.6, 1H), 4.20–4.00 (q, 2H), 1.72 (d, *J* = 8.3, 2H), 1.20 (t, *J* = 7.1, 3H), 0.39 (s, 3H), 0.38 (s, 3H), 0.25 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 174.18, 145.43, 139.95, 138.38, 133.73, 133.15, 131.49, 129.41, 129.27, 127.94, 127.86, 125.34, 71.93, 61.99, 22.23, 14.31, 1.01, −3.29. HRMS (ESI$^+$): exact mass calcd for $C_{23}H_{32}O_3Si_2$ [M+Na]$^+$, requires *m*/*z*: 435.1782, found *m*/*z*: 435.1781.