

Nucleophilic Addition

Autocatalytic Carbonyl Arylation through In Situ Release of Aryl Nucleophiles from *N*-Aryl-*N'*-SilyldiazenesClément Chauvier[†], Lucie Finck[†], Elisabeth Irran, and Martin Oestreich*

In memory of Rolf Huisgen and dedicated

to Professor Reinhard Brückner on the occasion of his 65th birthday

Abstract: A method for the catalytic generation of functionalized aryl alkali metals is reported. These highly reactive intermediates are liberated from silyl-protected aryl-substituted diazenes by the action of Lewis basic alkali metal silanolates, resulting in desilylation and loss of N₂. Catalytic quantities of these Lewis bases initiate the transfer of the aryl nucleophile from the diazene to carbonyl and carboxyl compounds with superb functional-group tolerance. The aryl alkali metal can be decorated with electrophilic substituents such as methoxycarbonyl or cyano as well as halogen groups. The synthesis of a previously unknown cyclophane-like [4]arene macrocycle from a 1,3-bisdiazene combined with a 1,4-dialdehyde underlines the potential of the approach.

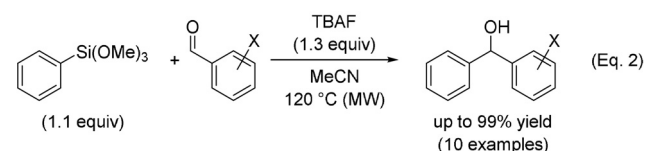
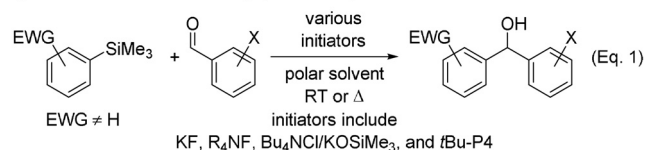
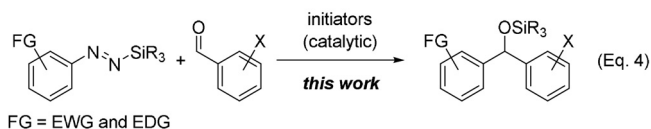
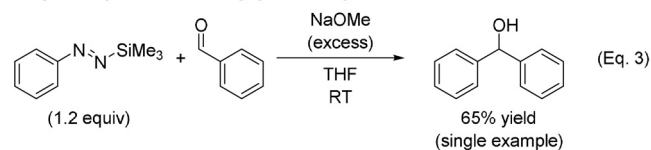
Synthetic chemistry without aryl nucleophiles based on lithium, magnesium (Grignard), and zinc is difficult to imagine.^[1] The usual methods for their preparation include reductive metalation and halogen–metal exchange of aryl halides, and the resulting polar organometallic reagents can be interconverted by transmetalation. These procedures are not always chemoselective, and the high reactivity of the nucleophiles is often detrimental to their functional-group tolerance. In particular, Knochel and co-workers have provided viable solutions to these problems, thereby turning polyfunctionalized zinc and Grignard reagents into everyday chemicals.^[2–4]

An alternative to these reactive compounds are easy-to-handle and storable less polarized aryl pronucleophiles based on silicon, mainly the trimethylsilyl derivatives.^[5] Aside from the fact that these are typically accessed from one of the aforementioned reagents, their fluoride- or alkoxide-promoted activation for aryl transfer to aldehydes is only applicable to electron-deficient aryl groups attached to the

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silicon atom;^[6] even the parent Ph-SiMe₃ does not react^[6c,7] (Scheme 1, Eq. 1). This gap was closed with the more electrophilic Ph-Si(OMe)₃ and Bu₄N⁺F⁻ (TBAF) as the Lewis basic activator (Scheme 1, Eq. 2).^[8] To overcome this limitation, we considered the related activation of *N*-aryl-*N'*-silyldiazenes (Ar-N=N-SiR₃), which can be readily synthesized in two steps from aryl hydrazines with no need for aryl halides.^[9] We envisioned that Lewis base activation of Ar-N=N-SiR₃ could unleash a reactive aryl nucleophile equivalent by desilylation and denitrogenation. This conceptual framework was formulated by Bottaro forty years ago (Scheme 1, Eq. 3), yet with no demonstration of its synthetic value and using NaOMe as an overstoichiometric activator.^[10] This seminal contribution has been largely overlooked and, hence, has not witnessed any further development. The present work shows how this approach can be turned into a catalytic

Aryl-substituted silanes as aryl pronucleophiles

*N*-aryl-*N'*-silyldiazenes as aryl pronucleophiles

Scheme 1. Silicon-based aryl pronucleophiles in transition-metal-free 1,2-addition to aldehydes (alcohols after hydrolysis). EWG = electron-withdrawing group, EDG = electron-donating group, FG = functional group, X = aryl substituent. MW = microwave irradiation, R = alkyl or aryl group, tBu-P4 = 3-*tert*-butylimino-1,1,1,5,5,5-hexakis(dimethylamino)-3-[[tris(dimethylamino)phosphoranylidene]amino]-1λ⁵,3λ⁵,5λ⁵-1,4-triphosphazadiene (Schwesinger base), TBAF = tetrabutylammonium fluoride.

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process with excellent functional-group tolerance with respect to both the diazene and the carbonyl compound, including transformations of a difunctional building block (Scheme 1, Eq. 4).

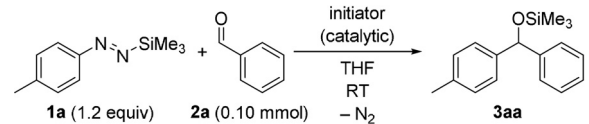
We began our investigation by testing various initiators in the reaction of 4-tolyl-substituted diazene **1a** and benzaldehyde (**2a**) in THF (Table 1). Lithium salts such as the alkoxide *t*BuOLi [pK_a (H₂O) \approx 16.5] and the less basic silanolate Me₃SiOLi^[11] [pK_a (H₂O) \approx 12.7] both initiated the reaction at room temperature, affording the silyl ether **3aa** in high yields within one hour (entries 1 and 2). With the same initiator loading of 10 mol%, improved reaction kinetics were achieved with the sodium and potassium salts of trimethylsilanol;^[11] full conversion was reached in less than five minutes, accompanied by vigorous evolution of N₂ (entries 3 and 4). The same outcome was obtained with 5.0 mol% Me₃SiONa but yields dwindled with 1.0 mol% Me₃SiONa or Me₃SiOK even at prolonged reactions times (entries 5–7). These results emphasize the influence of the alkali metal cation in this reaction. Polar co-solvents such as *N*-methylpyrrolidone (NMP) accelerated the already fast reactions. For completion, we included fluoride sources such as CsF and anhydrous TMAF into our screening. CsF did promote the aryl transfer but with a low reaction rate (entry 8), while essentially no conversion was seen with the poorly soluble ammonium fluoride (entry 9).

It is important to note that hydrazine **4a** was never detected by GLC analysis in those experiments. This would arise from the addition of the aryl nucleophile across the N=N double bond of the diazene followed by silylation.^[12] This result suggests that the aldehyde substrate outcompetes the diazene as the electrophile. The silylated arene **5a**, which formally arises from the silylation of the corresponding aryl anion, did usually form in trace amounts, likely because of the

slight excess of the diazene reagent **1a** employed. In turn, compounds **4a** and **5a** were the major products of the alkoxide-initiated degradation of **1a** in the absence of the aldehyde substrate (see the Supporting Information for details).

To demonstrate the scope of the new method, we continued with 10 mol% Me₃SiONa in THF at room temperature as the standard procedure. Diazenes with silyl groups other than Me₃Si were examined (**1b–d**; Table 2, entries 1–3). It was only the Me₂PhSi-substituted derivative **1d** that behaved similarly to **1a**, affording the silyl ether **3da** in 86% yield. Conversely, **1b**, which has a Et₃Si group, and **1c**, which has a *t*BuMe₂Si group, led to either low or no conversion of benzaldehyde. However, a little re-optimization showed that Me₃SiOK instead of Me₃SiONa promotes aryl transfer from **1b** to benzaldehyde, and **3ba** was isolated in 76% yield. The reaction of sterically more hindered **1c** required the addition of 18-crown-6, and the “more naked” silanolate and alkoxide intermediate enabled the formation of the silyl ether **3ca** in 68% yield. We also prepared a wide range of Me₃Si-substituted diazenes with functionalized aryl groups (**1e–o**; Table 2, entries 4–14). Without exception, these reacted in good yields under the standard setup. The successful reaction of electron-rich **1f** to silyl ether **3fa** closes an important gap (cf. Scheme 1, top). Further notable examples include aryl transfers from diazenes **1g**, **1h**, and **1n**, which contain sensitive functional groups (CO₂Me in **3ga**, CN in **3ha**, and NO₂ in **3na**). Even the transfer of aryl nucleophiles containing a bromo or iodo group, as in **1k** and **1l** (competing halogen–metal exchange), or a fluorine substituent in the *ortho* position, as in **1m** (competing β -elimination/aryne formation), proceeded in high yields. These examples highlight the chemoselectivity of the method and its orthogonality with classical carbonyl arylations. The productive combination of these diazenes and a broad range of aromatic, heteroaromatic, and cinnamic aldehydes (**2b–i**) is

Table 1: Selected examples from the optimization.



Entry	Initiator	mol%	Time	Yield [%] ^[a]
1	<i>t</i> BuOLi	10	1 h	91
2	Me ₃ SiOLi	10	1 h	> 95
3	Me ₃ SiONa	10	< 5 min	98 (70) ^[b]
4	Me ₃ SiOK	10	< 5 min	90
5	Me ₃ SiONa	5	< 5 min	> 95
6	Me ₃ SiONa	1	20 h	6
7	Me ₃ SiOK	1	20 h	58
8	CsF	10	20 h	60
9	TMAF	10	20 h	trace

[a] Determined by calibrated GLC analysis with tetracosane as an internal standard. [b] Yield of isolated product on a 0.40 mmol scale after flash chromatography on silica gel in parentheses. TMAF = tetramethylammonium fluoride.

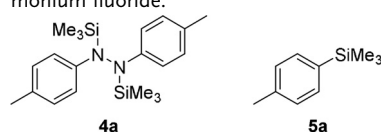
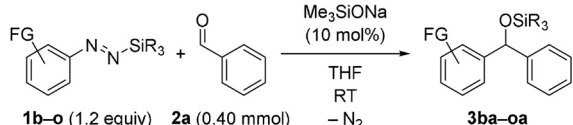


Table 2: Scope I: Variation of the silyl and aryl groups of the diazene.



Entry	Diazene	SiR ₃	FG	Silyl ether	Yield [%]
1 ^[a]	1b	SiEt ₃	4-Me	3ba	76
2 ^[b]	1c	Si <i>t</i> BuMe ₂	4-Me	3ca	68
3	1d	SiMe ₂ Ph	4-Me	3da	86
4	1e	SiMe ₃	H	3ea	72
5	1f	SiMe ₃	4-OMe	3fa	82
6 ^[a]	1g	SiMe ₃	4-CO ₂ Me	3ga	80
7	1h	SiMe ₃	4-CN	3ha	72
8	1i	SiMe ₃	4-F	3ia	99
9	1j	SiMe ₃	4-Cl	3ja	81
10	1k	SiMe ₃	4-Br	3ka	87
11	1l	SiMe ₃	4-I	3la	83
12	1m	SiMe ₃	2-F	3ma	65
13 ^[a]	1n	SiMe ₃	3-NO ₂	3na	67
14	1o	SiMe ₃	2,5-Me ₂ , 4-F	3oa	73

[a] Me₃SiOK instead of Me₃SiONa. [b] Me₃SiOK/18-crown-6 (1.0:1.2 molar ratio) instead of Me₃SiONa.

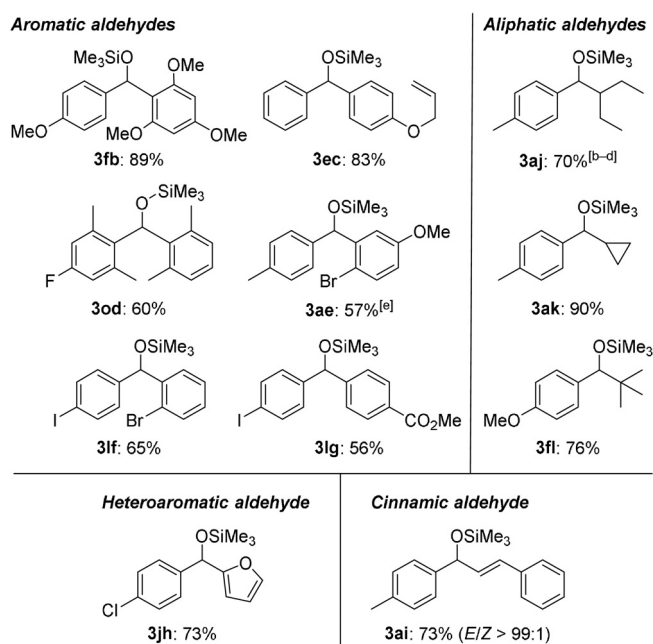
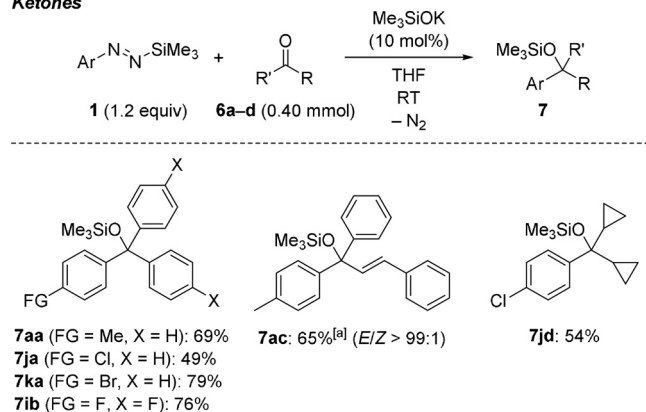


Figure 1. Scope II: Various diazene/aldehyde combinations.^[a]
[a] Unless noted otherwise, the reactions were performed on a 0.40 mmol scale with 10 mol% Me₃SiONa in THF at room temperature. [b] Me₃SiOK instead of Me₃SiONa. [c] Formed along with the corresponding silyl enol ether in 30% yield. [d] Yield determined by NMR spectroscopy using CH₂Br₂ as an internal standard. [e] The reaction was performed on a 1.8 mmol scale with 5.0 mol% Me₃SiONa in THF at room temperature.

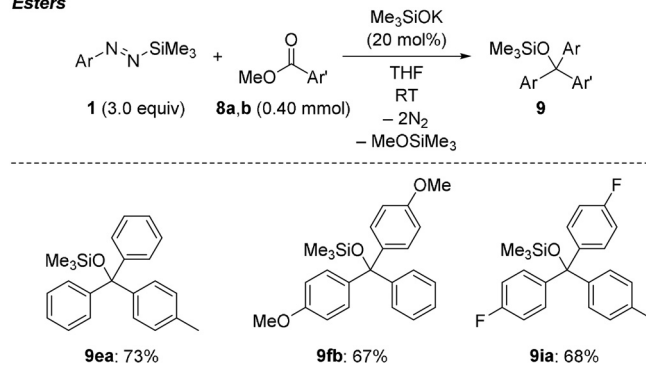
further evidence of this (Figure 1). Enolizable aldehydes were not compatible but α -branched 2-ethylbutyraldehyde (**2j**) yielded the silyl ether **3aj** in 70% yield along with the silyl enol ether in 30% yield. Other aliphatic aldehydes **2k** and **2l** reacted with high chemoselectivity to furnish **3ak** and **3fl** in good yields (Figure 1).

Less electrophilic ketones were also competent substrates but, as in the case of enolizable acetophenone, deprotonation was the predominant pathway to afford the corresponding silyl enol ether in 60% yield (not shown, see the Supporting Information). Conversely, **6a-d** reacted in the planned way with Me₃SiOK as the initiator (Scheme 2, top). No reaction or low conversion were observed with Me₃SiOLi and Me₃SiONa, presumably because of the low reactivity of the intermediate tertiary alkoxide, and hence its inability to maintain catalytic turnover. Unlike the 1,2-selective aryl transfer to *trans*-cinnamaldehyde (**2i**→**3ai**, Figure 1), the reaction of the aryl nucleophile with *trans*-chalcone (**6c**) led to the formation of both the 1,2-adduct (**7ac**, 65%) and the 1,4-adduct (6%). Moreover, modification of the reaction setup with a higher loading of Me₃SiOK (20 mol%) and slow addition of the diazene (3 equiv) to a solution of a methyl benzoates **8** and THF even enabled two-fold aryl transfer to give the tertiary silyl ethers **9** in reasonable yields (Scheme 2, bottom). To the best of our knowledge, this is an unprecedented catalytic arylation of unactivated carboxylic acid derivatives with non-stabilized carbanion equivalents.^[13] We note here that the occurrence of this nucleophilic addition is

Ketones



Esters



Scheme 2. Scope III: Ketones and esters as electrophiles. [a] Formed along with the corresponding 1,4-adduct in 6% yield.

also diagnostic of the in situ formation of highly reactive aryl anions.^[14]

Our next plan was to explore whether the diazene platform would also enable reactions of aryl dinucleophiles.^[15] For this, we synthesized the 1,3-bismetallated benzene equivalent **1p** from 1,3-diaminobenzene in 26% yield over three steps (see the Supporting Information for details and crystallographic characterization^[16]). The bisdiazene **1p** is a storable deep-blue crystalline solid with decent thermal stability (up to 130 °C). The reaction of **1p** and benzaldehyde (**2a**, 1.4 equiv) in the presence of 20 mol% Me₃SiOK afforded diol **10pa** in 65% yield after deprotection with TBAF (Scheme 3, left).

The fact that **10pa** had been employed as a precursor of porphinoic macrocycles^[17] inspired us to make use of building block **1p** in the practical assembly of otherwise difficult-to-prepare macrocycles. The idea was to combine 1,3-difunctional **1p** and terephthalaldehyde (**2m**) with its 1,4-substitution pattern, hoping that the alternate 1,3/1,4 motifs of the rings would result in cyclization rather than polymerization to poly(diarylcarbinols). The reaction of **1p** and 0.80 equiv **2m** initiated with 20 mol% Me₃SiOK led to a complex product mixture of polymeric and oligomeric material, from which a tetrameric macrocyclic compound could be identified by HRMS analysis.^[18] Defunctionalization of the crude residue, that is removal of the silyl ethers by a reported procedure,^[19] considerably simplified the analysis and allowed the isolation of the unknown cyclophane-like [4]arene macrocycle **11pm** in

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