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Autocatalytic Carbonyl Arylation through In-Situ Release of Aryl Nucleophiles from *N*-Aryl-*N'*-Silyldiazenes

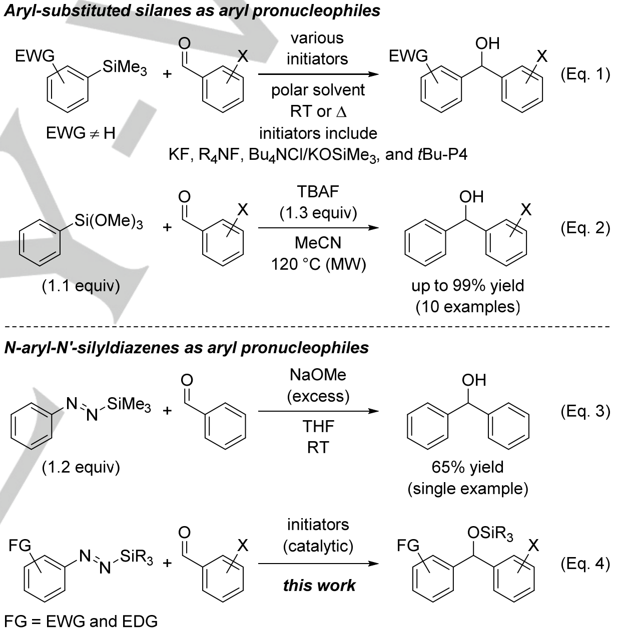
Clément Chauvier[+], Lucie Finck[+], Elisabeth Irran, and Martin Oestreich*

Dedicated to Professor Rolf Huisgen on the occasion of his 100th birthday
and 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 alkali metal silanolates, resulting in desilylation and loss of N_2. Catalytic quantities of those Lewis bases initiate the transfer of the aryl nucleophile from the diazene to carbonyl and carboxyl compounds with superb functional-group tolerance. The aryl alkaline metal can be decorated with electrophilic substituents such as methoxycarbonyl or cyano as well as halogen groups. The synthesis of an 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 not imaginable anymore.[1] Usual methods of their preparation include reductive metalation and halogen–metal exchange of aryl halides, and the resulting polar organometallic reagents can be converted into one another by transmetalation. These procedures are not always chemoselective, and the high reactivity of those nucleophiles is often detrimental to their functional-group tolerance. Especially Knochel and co-workers 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 their 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 silicon atom;[6] even parent Ph–$SiMe_3$ does not react[7,6e] (Scheme 1, Eq. 1). That gap was closed with the more electrophilic Ph–$Si(OMe_3)$ and $Bu_4N^+F^-$ (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–SiR_3) that 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–SiR_3 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, did not witness any further development. The present work shows how this approach can be turned into a *catalytic* process with excellent functional-group tolerance in both the diazene and the carbonyl compound, including transformations of a difunctional building block (Scheme 1, Eq. 4).



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; R = alkyl or aryl group. *t*Bu-P4 = 3-*tert*-butylimino-1,1,1,5,5,5-hexakis(dimethylamino)-3-{[tris(dimethylamino)phosphoranylidene]amino}-$1\lambda^5,3\lambda^5,5\lambda^5$-1,4-triphosphazadiene (Schwesinger base); TBAF = tetrabutylammonium fluoride.

We began our investigation with 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 (H_2O) ≈ 16.5] and the less basic silanolate Me_3SiOLi[11] [pK_a (H_2O) ≈ 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 salt of trimethylsilanol, respectively;[11] full conversion was reached in less than five minutes accompanied by vigorous evolution of N_2 (entries 3 and 4). The same outcome was obtained with 5.0 mol% Me_3SiONa but yields dwindled with 1.0

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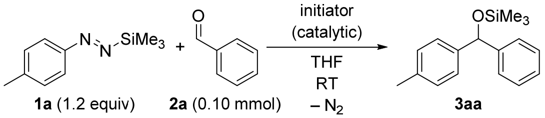
mol% Me_3SiONa or Me_3SiOK even at prolonged reactions times (entries 5–7). These results emphasize the influence of the alkali metal cation in this reaction. Polar co-solvents such as *N*-methylpyrrolidone (NMP) accelerated the already fast reactions. For completion, we included fluoride sources such as CsF and anhydrous TMAF into our screening. CsF did promote the aryl transfer yet at low reaction rate (entry 8) while essentially no conversion was seen with the poorly soluble ammonium fluoride (entry 9).

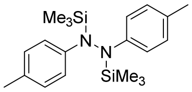
Table 1: Selected examples of the optimization.



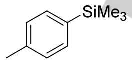
1a (1.2 equiv) **2a** (0.10 mmol) **3aa**

Entry	Initiator	mol%	Time	Yield [%][a]
1	*t*BuOLi	10	1 h	91
2	Me_3SiOLi	10	1 h	> 95
3	Me_3SiONa	10	< 5 min	98 (70)[b]
4	Me_3SiOK	10	< 5 min	90
5	Me_3SiONa	5	< 5 min	> 95
6	Me_3SiONa	1	20 h	6
7	Me_3SiOK	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] Isolated yield on a 0.40 mmol scale after flash chromatography on silica gel in parentheses. TMAF = tetramethylammonium fluoride.



4a

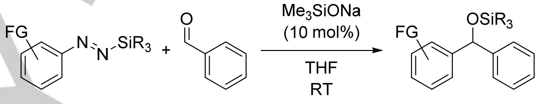


5a

It is important to note that hydrazine **4a** had never been detected by GLC analysis in those experiments. This would emerge from the addition of the aryl nucleophile across the N=N double bond of the diazene followed by silylation.[12] This 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% Me_3SiONa in THF at room temperature as the standard procedure. Diazenes with silyl groups other than Me_3Si were examined (**1b**–**d**; Table 2, entries 1–3). It was only the Me_2PhSi-substituted derivative **1d** that behaved similarly to **1a**, affording the silyl ether **3da** in 86% yield. Conversely, **1b** with a Et_3Si group and **1c** with a *t*$BuMe_2Si$ group exhibited either low or no conversion of benzaldehyde. However, little re-optimization showed that Me_3SiOK instead of Me_3SiONa promotes the 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 Me_3Si-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 the aryl transfers from diazenes **1g**, **1h**, and **1n** containing sensitive functional groups (CO_2Me in **3ga**, CN in **3ha**, and NO_2 in **3na**). Even the transfer of aryl nucleophiles containing a bromo or iodo groups 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 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).

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



1b–o (1.2 equiv) **2a** (0.40 mmol) **3ba–oa**

Entry	Diazene	SiR₃	FG	Silyl ether	Yield [%][a]
1[a]	**1b**	$SiEt_3$	4-Me	**3ba**	76
2[b]	**1c**	Si*t*$BuMe_2$	4-Me	**3ca**	68
3	**1d**	$SiMe_2Ph$	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_2Me	**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] Me_3SiOK instead of Me_3SiONa. [b] Me_3SiOK/18-crown-6 (1.0:1.2 molar ratio) instead of Me_3SiONa.

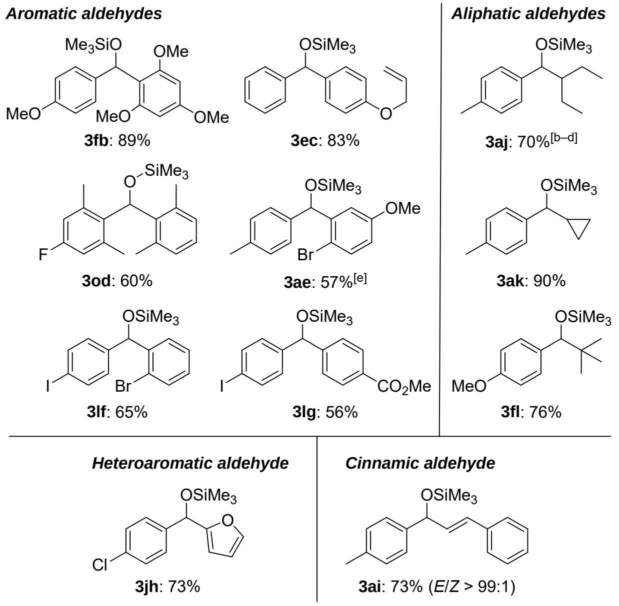
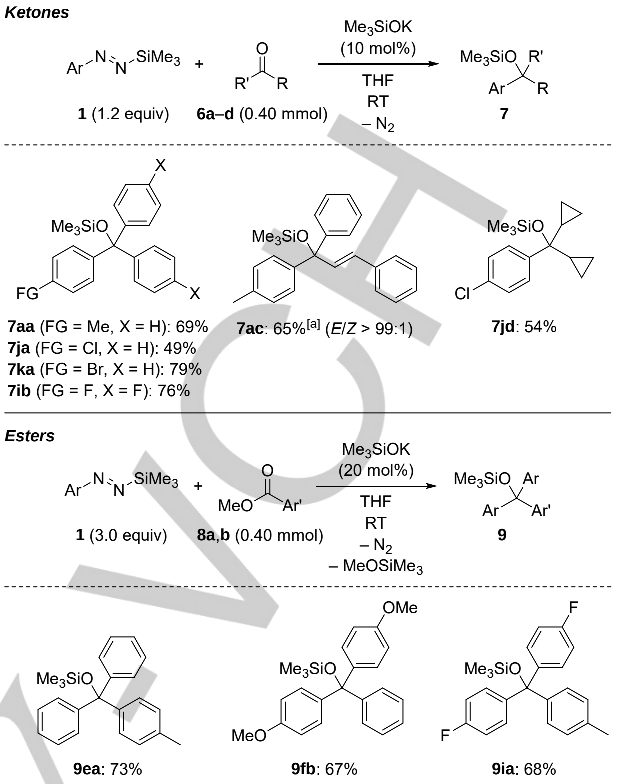


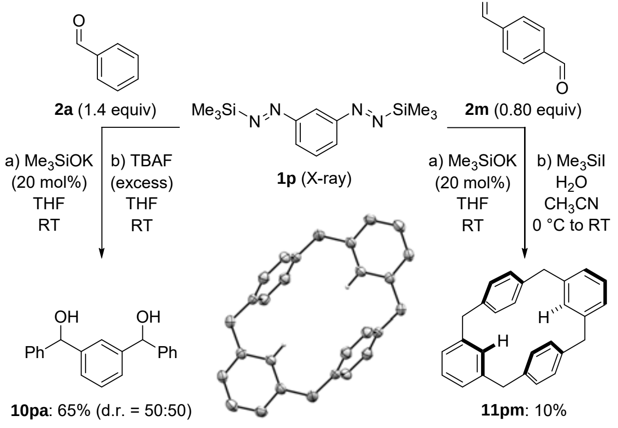
Figure 1. Scope II: Various diazene/aldehyde combinations.[a] [a] Unless noted otherwise, the reactions were performed on a 0.40 mmol scale with 10 mol% Me_3SiONa in THF at room temperature. [b] Me_3SiOK instead of Me_3SiONa. [c] Formed along with the corresponding silyl enol ether in 30% yield. [d] Yield determined by NMR spectroscopy using CH_2Br_2 as an internal standard. [e] The reaction was performed on a 1.8 mmol scale with 5.0 mol% Me_3SiONa in THF at room temperature.

Less electrophilic ketones were also competent substrates but, as is 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 Me_3SiOK as the initiator (Scheme 2, top). No reaction or low conversion were observed with Me_3SiOLi and Me_3SiONa, presumably because of the low reactivity of 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- (**7ac**, 65%) and the 1,4-adduct (6%). Moreover, modification of the reaction setup with a higher loading of Me_3SiOK (20 mol%) and slow addition of the diazene (3 equiv) to a solution of a methyl benzoates **8** and THF even allowed for a 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 also diagnostic of the in-situ formation of highly reactive aryl anions.[14]



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

Our next plan was to explore the possibility as to whether the diazene platform would also enable reactions of aryl dinucleophiles.[15] For this, we synthesized the 1,3-bismetalated 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, crystalline deep blue 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% Me_3SiOK afforded diol **10pa** in 65% yield after deprotection with TBAF (Scheme 3, left).

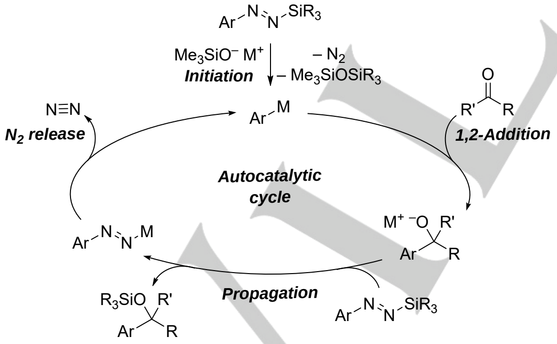


Scheme 3. Scope IV: Equivalent of an aryl bisnucleophile in the reaction with an aldehyde (left) or a dialdehyde (right); molecular structure of a cyclophane-like [4]arene macrocycle (middle, thermal ellipsoids are shown at the 50%

probability level and all hydrogen atoms except the two pointing toward the center are omitted for clarity).

The fact that **10pa** had been employed as a precursor of porphinoid 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% Me_3SiOK led to a complex product mixture of poly- 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 for the isolation of the unknown cyclophane-like [4]arene macrocycle **11pm** in 10% yield over two steps (Scheme 3, right).[20] This seemingly low yield compares well with others from difficult macrocyclizations involving aromatic precursors lacking preorganization, especially in relatively high concentration (0.1 M).[21] The molecular structure of **11pm** was confirmed by X-ray diffraction[16] (Scheme 3, middle) and shows preference for a chair-like conformation in the solid state whereas a boat-like conformation was computed to be more stable by approximately 0.5 kcal/mol (see the Supporting Information for details). Compound **11pm** is the simplest, unfunctionalized member of an emerging class of hybrid macrocycles[22] currently comprising just two derivatives.[23]

Although an in-depth mechanistic analysis is still pending, we propose the autocatalytic cycle outlined in Scheme 4. After initiation with either of the three trimethylsilanolate alkali salts the aryl alkali metal will form as a result of desilylation and loss of N_2. The in-situ-formed aryl nucleophile then adds to the carbonyl compound, forming an alkali metal alkoxide that will in turn engage in the desired degradation of the diazene reagent. This step then propagates the catalytic cycle.



Scheme 4. Proposed autocatalytic cycle. M = alkali metal; R and R' = alkyl or aryl; Ar = aryl.

To summarize, we showed that *N*-aryl-*N'*-silyldiazenes constitute a versatile platform from which various highly reactive and, at the same time, functionalized aryl nucleophiles can be released at ambient temperature. The reaction of a related bisdiazene illustrates the potential of the method to formally generate dinucleophiles. These reactive intermediates can be trapped in situ with functionalized carbonyl and carboxyl compounds. Conceptually, these arylation reactions are similar to a Barbier-like setup[24] where the polar organometallics are generated in situ, thereby avoiding their delicate preparation and handling. However, our method makes use of Me_3SiOM (with M = Li, Na, and K)[11] as initiatiors whereas Barbier reactions typically rely on overstoichiometric amounts of reducing metals. Aside from the excellent functional-group tolerance, the new protocol differs from established methods in that it is halide-free, starting from aryl hydrazines rather than aryl halides.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: autocatalysis • chemoselectivity • Lewis bases • nucleophilic addition • silicon

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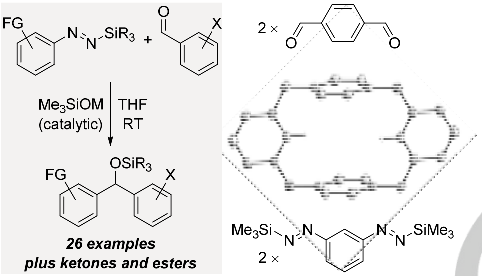
Suggestion for the Entry for the Table of Contents

COMMUNICATION

Under cover of nitrogen. Silyl-protected aryl-substituted diazenes act as masked aryl nucleophiles. By initiation with Me_3SiOM (M = Li, Na, and K) aryl transfer to carbonyl and carboxyl groups occurs at ambient temperature. This mild nucleophile generation is compatible with electron-withdrawing and -donating functional groups (FGs).



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