Nucleophilic Addition

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

Clément 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

silicon atom;[6] even the parent Ph-SiMe₃ does not react[6e, 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
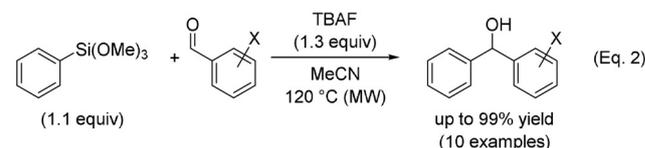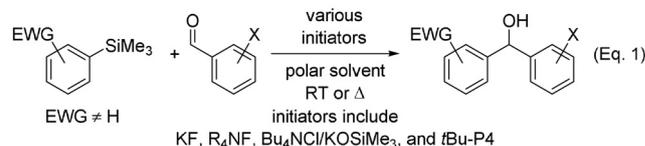
N-aryl-N′-silyldiazenes as aryl pronucleophiles

FG = EWG and EDG
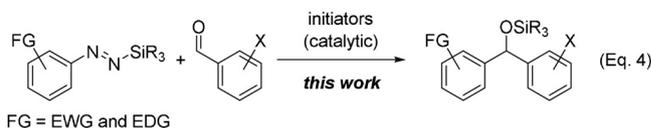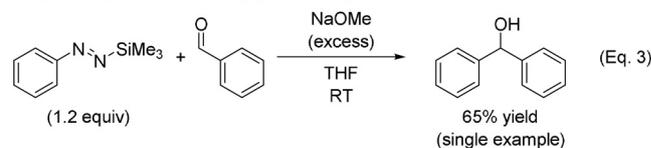
Scheme 1. Silicon-based aryl pronucleophiles in transition-metal-free 1,2-addition to aldehydes (alcohols after hydrolysis). EWG = electron-withdrawing group, EDG = electron-donating group, FG = functional group, X = aryl substituent. MW = microwave irradiation, R = alkyl or aryl group, *t*Bu-P4 = 3-*tert*-butylimino-1,1,1,5,5,5-hexakis(dimethylamino)-3-{[tris(dimethylamino)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 (H$_2$O) ≈ 16.5] and the less basic silanolate Me$_3$SiOLi[11] [pK_a (H$_2$O) ≈ 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 N$_2$ (entries 3 and 4). The same outcome was obtained with 5.0 mol% Me$_3$SiONa but yields dwindled with 1.0 mol% Me$_3$SiONa or Me$_3$SiOK 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% Me$_3$SiONa in THF at room temperature as the standard procedure. Diazenes with silyl groups other than Me$_3$Si were examined (**1b–d**; Table 2, entries 1–3). It was only the Me$_2$PhSi-substituted derivative **1d** that behaved similarly to **1a**, affording the silyl ether **3da** in 86% yield. Conversely, **1b**, which has a Et$_3$Si group, and **1c**, which has a *t*BuMe$_2$Si group, led to either low or no conversion of benzaldehyde. However, a little re-optimization showed that Me$_3$SiOK instead of Me$_3$SiONa 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 Me$_3$Si-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 (CO$_2$Me in **3ga**, CN in **3ha**, and NO$_2$ 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.
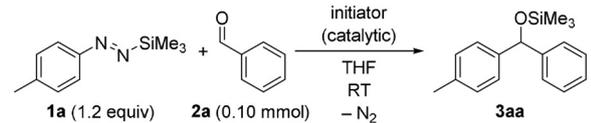
Entry	Initiator	mol%	Time	Yield [%][a]
1	*t*BuOLi	10	1 h	91
2	Me$_3$SiOLi	10	1 h	>95
3	Me$_3$SiONa	10	<5 min	98 (70)[b]
4	Me$_3$SiOK	10	<5 min	90
5	Me$_3$SiONa	5	<5 min	>95
6	Me$_3$SiONa	1	20 h	6
7	Me$_3$SiOK	1	20 h	58
8	CsF	10	20 h	60
9	TMAF	10	20 h	trace

[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.
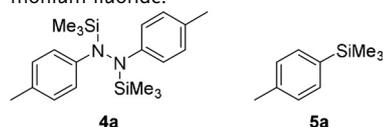

Table 2: Scope I: Variation of the silyl and aryl groups of the diazene.

Entry	Diazene	SiR$_3$	FG	Silyl ether	Yield [%]
1[a]	**1b**	SiEt$_3$	4-Me	**3ba**	76
2[b]	**1c**	Si*t*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] Me$_3$SiOK instead of Me$_3$SiONa. [b] Me$_3$SiOK/18-crown-6 (1.0:1.2 molar ratio) instead of Me$_3$SiONa.
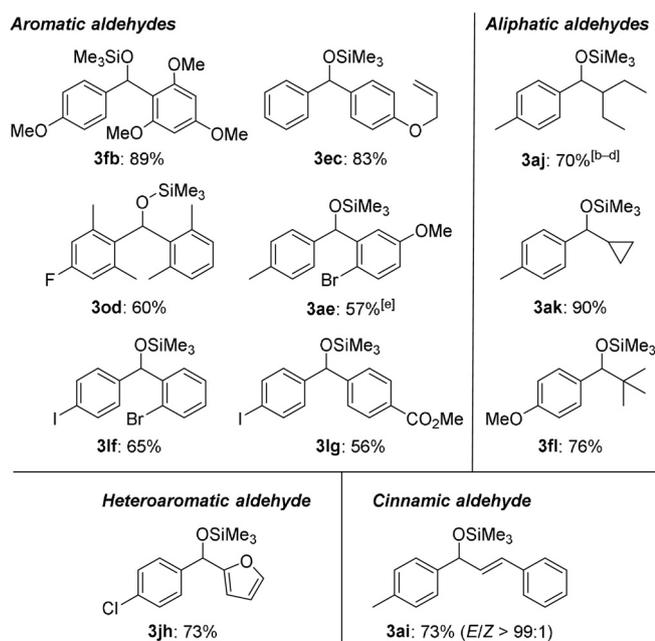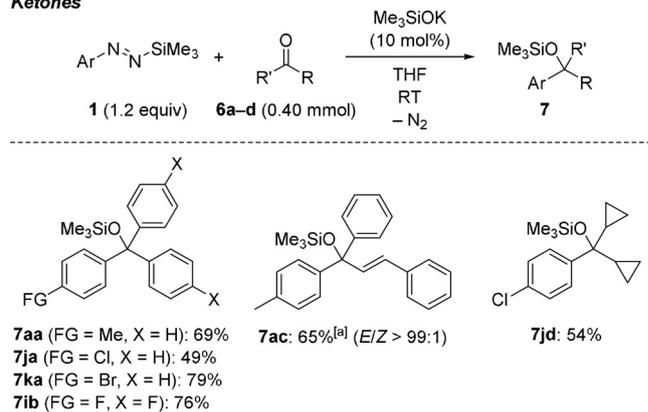
Figure 1. Scope II: Various diazene/aldehyde combinations.[a]
[a] Unless noted otherwise, the reactions were performed on
a 0.40 mmol scale with 10 mol% Me$_3$SiONa in THF at room temper-
ature. [b] Me$_3$SiOK instead of Me$_3$SiONa. [c] Formed along with the
corresponding silyl enol ether in 30% yield. [d] Yield determined by
NMR spectroscopy using CH$_2$Br$_2$ as an internal standard. [e] The
reaction was performed on a 1.8 mmol scale with 5.0 mol% Me$_3$SiONa
in THF at room temperature.

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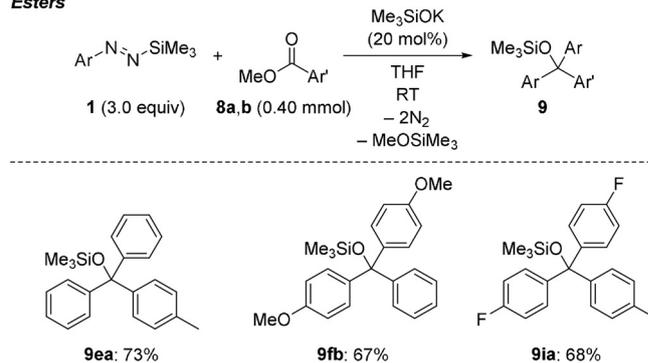along with the corresponding 1,4-adduct in 6% yield.

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 Me$_3$SiOK as the initiator (Scheme 2, top). No reaction or
low conversion were observed with Me$_3$SiOLi and
Me$_3$SiONa, 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 Me$_3$SiOK (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 unprece-
dented 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]

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-bismetalated benzene equiv-
alent **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% Me$_3$SiOK
afforded diol **10pa** in 65% yield after deprotection with
TBAF (Scheme 3, left).

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-difunc-
tional **1p** and terephthalaldehyde (**2m**) with its 1,4-substitu-
tion 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$_3$SiOK 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
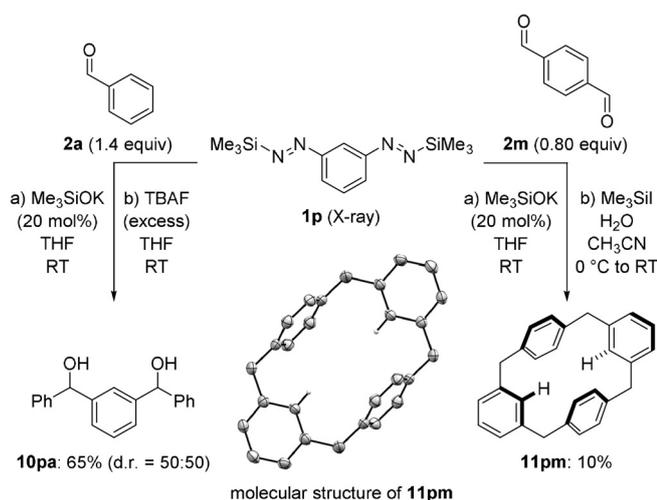
Scheme 3. Scope IV: Equivalent of an aryl bisnucleophile in the reaction with an aldehyde (left) or a dialdehyde (right); molecular structure of a cyclophane-like [4]arene macrocycle (middle, thermal ellipsoids are shown at the 50% probability level and all hydrogen atoms except the two pointing toward the center are omitted for clarity).

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 **11 pm** was confirmed by X-ray diffraction[16] (Scheme 3, middle) and shows a 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^{-1} (see the Supporting Information for details). Compound **11 pm** is the simplest unfunctionalized member of an emerging class of hybrid macrocycles[22] that currently comprises 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
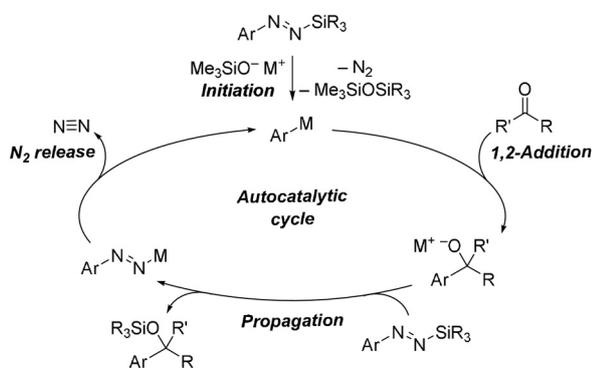
Scheme 4. Proposed autocatalytic cycle. M = alkali metal, R and R′ = alkyl or aryl, Ar = aryl.

the diazene reagent. This step then propagates the catalytic cycle.

To summarize, we have shown 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$_3$SiOM (with M = Li, Na, and K)[11] species as initiators, whereas Barbier reactions typically rely on overstoichiometric amounts of reducing metals. Aside from its excellent functional-group tolerance, this new method differs from established ones in that it is halide-free, starting from aryl hydrazines rather than aryl halides.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest.

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