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Stereoselective Peterson Olefinations from Bench-Stable Reagents and N-Phenyl Imines

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Abstract: The synthesis of bench-stable α , α -bis(trimethylsilyl)toluenes and tris(trimethylsilyl)methane is described and their use in stereoselective Peterson olefinations has been achieved with a wide substrate scope. Product stereoselectivity was poor with carbonyl electrophiles (*E/Z* ~1:1 to 4:1) though this was significantly improved by employing the corresponding substituted *N*-benzylideneaniline (up to 99:1) as an alternative electrophile. The olefination byproduct was identified as *N*,*N*-bis(trimethylsilyl)aniline and could be easily separated from product by aqueous acid extraction. Evidence for an autocatalytic cycle has been obtained.

In the synthetic olefination toolbox the Peterson olefination, in spite of its great value, remains one of the lesser utilized methods for the conversion of carbonyls to alkenes.^[1] The transformation is considered as a silicon analogue of the Wittig reaction with the reaction of α -silyl carbanions **2** (typically generated by deprotonation of **1** using strong lithium or magnesium bases) with carbonyls providing the alkene product **3** and trimethylsilyl oxide byproduct (Scheme 1, route a).^[2] Intermediate



Scheme 1. Peterson olefination.

 β -hydroxysilanes can be isolated when the silyl carbanion used is not stabilized (e.g. R=alkyl), which upon treatment with either base or acid can deliver the corresponding (*E*)- or (*Z*)-



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alkene stereoselectively.^[3] For stabilized α -silyl carbanions (e.g. R=Ar) these intermediates are not isolated and stereocontrol has yet to be achieved making it a less attractive approach for such reactions.^[4] A further disincentive to its use is that the silyl anion **2** must be first generated often with strong bases under nontrivial conditions prior to the addition of the aldehyde.

Yet, if solutions to these two issues were in hand, an inherent advantage of the Peterson olefination is its superior atom economy over the Wittig reaction as it produces low molecular silicon byproduct in the carbon-carbon double-bond-forming step rather than crystalline triphenylphosphine oxide.^[5] An alternative approach to the generation of the α -silyl carbanions that does not require strong bases is to use geminal bis(trimethyl silanes) 4 as starting substrates and a fluoride source to promote generation of the α -silyl carbanion precursor 5 (Scheme 1, route b). Bis(silanes) 4 are bench stable (analogous to the Wittig phosphonium salt), yet they have received very limited use due to the lack of a general route for their synthesis.^[4e-g,6] The use of bis(silanes) as Peterson olefination reagents offers an additional advantage in that they eliminate the need to pre-form the carbanion species as it is generated in situ in the presence of the aldehyde.

In this report we illustrate a new general two-step approach for the synthesis of α, α -bis(trimethylsilyl)toluenes **7**a-h from their corresponding toluenes using identical synthetic conditions for both steps. We have developed methods for their use in olefination reactions and shown, for the first time, how stereocontrol can be achieved by the use of aniline-derived *N*-aryl imine electrophiles. In addition this method is extended to the complementary tris(trimethylsilane) **9**, which opens a new route to vinyl trimethylsilanes; these compounds are in themselves important substrates for cross-coupling transformations in alkene synthesis.^[7]

Synthesis of (arylmethylene)bis(trimethylsilanes) **7a-h** was achieved by the regioselective benzylic metalation of the parent toluene by using BuLi, KOtBu, and TMP(H) in THF (LiNK conditions)^[8] and TMSCI quench to form the substituted benzylsilanes **6a-h** with a repeat of these conditions providing the desired olefination reagents (Scheme 2, top panel). Introduction of a sensitive bromine functional group, which would not be tolerant of the chemistry required for the geminal bis(silane) synthesis, was achieved from **7a** to give *p*-bromo derivative **7i** in a high 83% yield (Scheme 2, left bottom panel). Tris(trimethylsilyl)methane **9** was generated by deprotonation

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Scheme 2. Synthesis of (arylmethylene)bis(trimethylsilanes) 7 a-i and tris(trimethylsilyl)methane 9.

of bis(trimethylsilyl)methane **8** and TMSCI quench (Scheme 2, right bottom panel).

With the olefination reagents in hand their use in the fluoride-promoted reaction with aldehydes was explored to identify optimal activation conditions and record the effects of substituents on product E/Z selectivity (Table 1). It was found that reaction of **7 d** with benzaldehyde proceeded smoothly in either THF or DMF when using tetrabutylammonium fluoride (TBAF), tetrabutylammonium difluorotriphenylsilicate (TBAT), or

Table 1. Screening of olefination reaction conditions with carbonyls.						
$\begin{array}{c} & & & \\ & & & & \\ & & & \\ & & & \\ & & & & \\ & & & \\ & & & \\ & & & & \\ & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ &$						
Entry	7/9	Solvent	Ar	<i>T</i> [°C]	Yield [%]	$E/Z^{[a]}$
1	7 d	THF	Ph	RT ^[b]	10 a /56	56:44
2	7 d	THF	Ph	70 ^[b]	10 a /77	54:46
3	7 d	DMF	Ph	80 ^[e]	10 a /82	51:49
4	7 d	THF	$4-BrC_6H_4$	70 ^[b]	10 b /74	52:48
5	7 d	THF	$4-MeOC_6H_4$	70 ^[b]	10 c /77	52:48
6	7 d	THF	$4-MeC_6H_4$	70 ^[b]	10 d /64	53:47
7	7 d	THF	2-naphthyl	70 ^[b]	10 e /73	47:53
8	7 d	THF	(E)-PhCH=CH	70 ^[b]	10 f /89	50:50
9	7 d	THF	4-CNC ₆ H ₄	70 ^[b]	10 g /70	51:49
10	7 a	THF	4-MeOC ₆ H ₄	RT ^[d]	10 h /70	53:47
11	7 g	THF	$4-MeOC_6H_4$	RT ^[b]	10 i/64	80:20
12	9	THF	Ph	70 ^[f]	11 a /85	80:20
13	9	THF	Ph	RT ^[g]	11 a /65	75:25
[a] <i>E/Z</i> ratio determined by ¹ H NMR spectroscopy of the crude product. Fluoride source. [b] TBAT. [c] CsF. [d] TBAF. [e] 1 equiv CsF used. [f] 20 mol% TBAT used. [g] 20 mol% TBAF used.						

CsF, respectively, giving the stilbene product in each case but with virtually no stereoselectivity (Table 1, entries 1–3).

Reaction with other aldehydes showed no significant change in product E/Z ratio, which is consistent with previous reports (Table 1, entries 4–9).^[4] Similar results were obtained with **7a** when using TBAF as an activator (entry 10). Only derivative **7g** containing an electron-withdrawing group and the tris(trimethylsilyl)methane **9** showed moderate 80:20 E/Z selectivities (entries 10–13).^[4d,9] While the lack of stereocontrol is a major drawback, monitoring of the reaction by ¹H NMR spectroscopy in [D₈]THF revealed that hexamethyldisiloxane was the reaction byproduct, which as a low-boiling solvent (98 °C) can be readily removed (Table 1, Supporting Information).

As neither substrate nor reaction conditions had any significant general influence on the stereochemical outcome of the reaction, a new approach was sought to gain stereocontrol. Previously reported computational studies on the Peterson olefination mechanism have described that, in the absence of a coordinating counter ion, the addition step was rate-limiting and as such it should be sensitive to steric and electronic influences.^[10] In an effort to exert such influences in a general manner, (*E*)-*N*-benzylideneanilines were chosen as alternative electrophiles to aldehydes which could be readily generated by their condensation with inexpensive aniline (Table 2).^[11]

Table 2. Optimization of olefination conditions with N-phenyl imines.						
$\begin{array}{c} N \xrightarrow{Ph} \\ Ph \xrightarrow{H} \\ Ph \xrightarrow{H} \\ F \xrightarrow{(10 \text{ mol}\%)} \\ SiMe_3 \\ SiMe_3 \\ Solvent, MS 4Å, 7 \\ 7d, 9 \end{array} \xrightarrow{Ph} \xrightarrow{Ph} \\ Ph \xrightarrow{H} \\ SiMe_3 \\ SiMe_3 \\ aqueous acid extractable \\ extractable \\ \end{array}$						
Entry	7 d/9	Fluoride	Solvent	7 [°C]	Yield [%]	$E/Z^{[a]}$
1						
1 '	7 d	TBAT	THF	70	10 a /15	94:6
2	7 d 7 d	TBAT CsF ^[b]	THF DMF	70 RT ^[c]	10 a /15 10 a /59	94:6 97:3
2 3	7 d 7 d 7 d	TBAT CsF ^[b] CsF ^[c]	THF DMF DMF	70 RT ^[c] 80	10 a/15 10 a/59 10 a/77	94:6 97:3 96:4
2 3 4	7 d 7 d 7 d 9	TBAT CsF ^(b) CsF ^[c] CsF ^[b]	THF DMF DMF DMF	70 RT ^[c] 80 80	10 a/15 10 a/59 10 a/77 11 a/83	94:6 97:3 96:4 99:1

Gratifyingly, the reaction of **7d** in either THF with TBAT at reflux or DMF/CsF at RT gave the product **10a** in modest yield but with dramatically improved *E/Z* selectivity of 94:6 (Table 2, entries 1 and 2). The product yield was found to improve to 77% when the reaction was carried out in DMF at 80°C using 30 mol% CsF (entry 3). Applying similar conditions, the tris(trimethylsilyl)methane **9** gave **11a** in a 83% yield and *E/Z* ratio of 99:1 (entry 4). Following the reaction course of **7d** with *N*-benzylideneaniline in [D₇]DMF showed that 1,1,1-trimethyl-*N*-phenyl-*N*-(trimethylsilyl)silanamine **12** was produced as a by-product during the course of the reaction (see the Supporting Information). Compound **12** was readily separable from the alkene product by aqueous acid extraction during which it was seen to desilylate and generate aniline.

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The generality of E-product selectivity was investigated using ten different olefination reagents 7a-i and 9, with thirteen different N-phenyl imines chosen to reflect differing electronic and steric factors (Table 3). Remarkably, the excellent E

Table 3 imines.	Stereocl	nemistry control in	Peterson ole	efination with	N-phenyl
$R \xrightarrow{SiMe_3} + Ar \xrightarrow{H} H \xrightarrow{CsF, MS 4Å, DMF} Ar \xrightarrow{R} R$ SiMe ₃ + Ar $H \xrightarrow{SiMe_3} + Ar^1$ 9: R = SiMe ₃ + SiMe ₃ + CsF, MS 4Å, DMF Ar $Ar \xrightarrow{R} R$ 10c, f, h-w: R = Ar ¹ 11b-j: R = SiMe ₃					
Entry	7/9	Ar	Product	Yield [%]	$E/Z^{[a]}$
1	7a	Ph	10j	79	92:8
2	7 a	4-MeOC ₆ H ₄	10 h	60	91:9
3	7 b	2-CIC ₆ H ₄	10 k	83	98:2
4	7 b	ferrocenyl	101	82	99:1
5	7 c	2-CIC ₆ H ₄	10 m	71	98:2
6	7 d	4-MeOC ₆ H ₄	10 c	62	92:8
7	7 d	(<i>E</i>)-PhCH=CH	10 f	71	91:9
8	7 e	2-naphthyl	10 n	53	99:1
9	7 e	$4-FC_6H_4$	10 o	73	95:5
10	7 f	3-MeOC ₆ H ₄	10 p	89	99:1
11	7 f	ferrocenyl	10 q	41	99:1
12	7 g	Ph	10 r	77	99:1
13	7 g	$4-FC_6H_4$	10 s	69	99:1
14	7 h	$4-BrC_6H_4$	10 t	68	99:1
15	7 h	4-MeOC ₆ H ₄	10 u	83	99:1
16	7 i	$4-FC_6H_4$	10 v	87	99:1
17	7 i	2-MeOC ₆ H ₄	10 w	11	99:1
18	9	2-CIC ₆ H ₄	11 b	71	97:3
19	9	3-MeOC ₆ H ₄	11 c	73	99:1
20	9	$4-BrC_6H_4$	11 d	51	99:1
21	9	$4-FC_6H_4$	11 e	56	99:1
22	9	4-MeOC ₆ H ₄	11 f	61	99:1
23	9	$4-Me_2NC_6H_4$	11 g	60	99:1
24	9	4-MeOC(O)C ₆ H ₄	11 h	44	99:1
25	9	2-naphthyl	11 i	70	99:1
26	9	ferrocenyl	11 j	47	97:3
[a] E/Z ratio determined by ¹ H NMR spectroscopy of the crude product.					

selectivity was observed in all reactions with the stilbene products 10 obtained in E/Z ratios ranging from 91:9 to 99:1 (Table 3, entries 1-17) and substituted trimethyl(styryl)silanes 11 ranging from 97:3 to 99:1 (entries 18–26).

While further investigation is required to fully explain the Nphenyl imine stereocontrol two influential differences between the imine and carbonyl reaction pathways would be the increased sterics involved in the addition of 13 and the effect of the phenyl(trimethylsilyl)amide leaving group 17. Loss of 17 could be envisaged 1) following the formation of the carbanion 15 by an 1,3-aza-Brook-type rearrangement of 14 or 2) following the concerted formation of the substituted 1-aza-2-silacyclobutane 16 (Scheme 3).^[12] Completion of the reaction cycle with the formation of 12 as a byproduct indicates the possibility of an autocatalytic cycle in which 17 reacts with starting material 7 to generate 12 and 13 (Scheme 3).^[13] This was confirmed by the reaction of **7 d** with *N*-benzylideneaniline by using one equivalent of 17 (generated by the reaction of 1,1,1trimethyl-N-phenylsilanamine with NaH) to promote the reac-



mmunication

Scheme 3. Mechanistic cycle.

tion. The expected stilbene product 10a was obtained with an identical E/Z selectivity as observed with the CsF-promoted reaction (Scheme 3, inset). This we believe is the first demonstration of an autocatalytic Peterson reaction.

While the synthesis of N-benzylideneanilines could be considered trivial it does add an additional synthetic step to the overall process. As such, a one-pot method was developed which first conducted the aldehyde/aniline condensation in DMF following which the bis(silane) reagent was added and olefination performed in situ. Using 7 b, d, and f as representative bis(silanes), this approach worked well with the stilbenes 10 a, 10 x, y isolated in comparable yield and E-selectivity as the approach outlined above (Scheme 4).



Scheme 4. One-pot (E)-selective synthesis of stilbenes.

In summary, a new general two-step synthesis of α, α -bis(trimethylsilyl)toluenes and tris(trimethylsilyl)methane has been developed providing access to bench-stable Peterson olefination reagents. Poor E/Z selectivity was obtained in their reaction with aldehydes but when the corresponding substituted N-benzylideneanilines were employed as electrophiles high E selectivity was observed for a wide range of substrates. Identification of the reaction byproduct as aqueous extractable N,N-bis(trimethylsilyl)aniline maintains the advantage of Peterson olefinations in generating a readily removable byproduct.

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Evidence for an autocatalytic cycle has been established with the olefin forming leaving group being capable of propagating the reaction. As the use of imine electrophiles for aza-Peterson olefinations has not been previously studied, the scope of this approach is currently being further explored in conjunction with additional mechanistic investigations.

Experimental Section

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General procedure for the olefination of (benzyl)bis(trimethylsilane) with *N*-phenyl imines

A solution of (benzyl)bis(trimethylsilane) (0.48 mmol) and substituted N-benzylideneaniline (0.40 mmol) in anhydrous DMF (2.0 mL) with 4 Å molecular sieves was treated with CsF (0.12 mmol) under N₂ and the resulting solution was heated at 80 °C until the reaction reached completion. The reaction mixture was quenched with water. The residue was extracted with diethyl ether (20 mL×3). Organic layers were combined and washed with water and brine, dried over anhydrous sodium sulfate, and concentrated. Purification by silica gel chromatography eluting with petroleum ether/ ethyl acetate gave the corresponding alkene. The *E/Z* ratios for the alkene products were determined by ¹H NMR spectroscopic analysis.

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Keywords: bench-stable reagents • imines • organic synthesis • Peterson olefination • stereoselectivity

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A mild method for *E*-selective Peterson olefinations is described. Bench-stable α , α -bis(trimethylsilyl)toluenes and tris-(trimethylsilyl)methane are used as reagents in reaction with substituted *N*-phenyl imines (see scheme).

RSiMe ₃	N ^{Ph}	CsF	⇒ R
+ SiMe ₃		C, DMF	Ar V
R = Ar, Si(Me) ₃	/		<i>E/Z</i> 99:1

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