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Z-Stereoselective Aza-Peterson Olefinations with Bis(trimethylsilane) Reagents and Sulfinyl Imines

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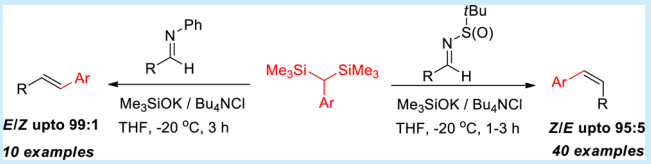
Supporting Information

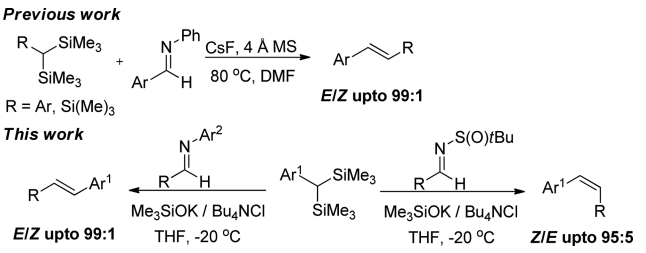
ABSTRACT: Highly stereoselective aza-Peterson olefinations from bench-stable α,α-bis(trimethylsilyl)toluene reagents and N-substituted imines have been achieved using $TMSO^-/Bu_4N^+$ as Lewis base activator in THF. Remarkably, and for the first time, *N*-*t*-butanesulfinyl imines were utilized for the synthesis of *Z*-stilbenes with excellent selectivities, while *N*-aryl imines generated *E*-stilbenes under identical reaction conditions. The protocol proved general for numerous examples with low molecular weight byproducts formed. The origin of the *Z*-selectivity is proposed to be a result of diastereoselective addition to *N*-*t*-butanesulfinyl imines followed by *syn*-elimination of an in situ formed hypervalent silicate.



Olefins are ubiquitous structural motifs in biologically relevant entities and serve as versatile precursors for a diverse range of chemical transformations that produce pharmaceutical and industrially important organic compounds.[1] New strategies for the facile synthesis of stereochallenging alkenes remain a considerable focus of research. Selective access to either the *E*- or *Z*-isomer of an alkene is often the decisive factor in the success of any alkene synthesis method. Among the olefin-forming transformations, selective preparation of *E*-isomers has been established the most, while the corresponding methods to access the thermodynamically less favorable *Z*-alkenes remain a challenge.[2,3] Several transformations have been introduced to address this issue, including hydrogenation,[4] alkyne reductive coupling[5] or carbocupration,[6] cross-metathesis,[7] terminal-to-internal olefin isomerization,[8] and photocatalytic *E*-to-*Z* isomerization.[9] A general synthesis of *Z*-olefins is available from the Wittig reaction variant in which *N*-sulfonyl imines are used instead of carbonyl electrophiles.[10]

The Peterson olefination (PO) reaction offers a superior atom economy advantage over the Wittig reaction as it produces noncrystalline low molecular weight silicon byproducts.[11] Yet, stereocontrol has always been the Achilles heel of the PO reaction, especially for direct alkene synthesis (i.e., without isolation of silyl−alcohol intermediates).[1,11] Arguably, this limiting factor, in addition to the necessity to preform α-silyl carbanions using a strong base, has restricted its more widespread use. In an effort to address these limitations, we have recently reported stereoselective aza-PO reactions utilizing bench-stable bis(trimethylsilane) reagents and *N*-phenyl imines to produce thermodynamically favored *E*-alkenes with excellent selectivities (Scheme 1).[12] Despite this success, the significant limitation for silicon-based olefination reactions is that no direct (without β-hydroxysilane isolation) *Z*-selective method currently exists. As such, we were stimulated to identify a *Z*-favoring electrophile, and our attention was drawn to the potential use of *N*-*t*-butanesulfinyl imines (Ellman imines) as substrates for aza-PO reactions.[13] To the best of our knowledge, *t*-butanesulfinyl imines have not been previously utilized for any olefination transformations. They are commonly used in diastereoselective organometallic addition reactions for the synthesis of chiral amines, with high selectivity attributed to either the formation of a metal-chelated closed six-membered ring or open (non-chelating) transition states.[13] We have recently demonstrated diastereoselective addition of benzyltrimethylsilanes to *N*-*t*-butanesulfinyl imines using Me_3SiO^-/Bu_4N^+ in THF to promote the addition reaction.[14,15]

Scheme 1. Stereoselective Aza-Peterson Olefinations



In this work, our motivation for investigating *N*-*t*-butanesulfinyl imines as carbonyl replacement electrophiles was the potential for diastereoselective addition, through a chelating six-membered transition state, brought about by interaction of the silicon of the α-silyl carbanion with the oxygen of the sulfinyl imine (Figure 1). This intramolecular oxygen−silicon activation would induce hypervalency on Si, thereby facilitating an olefin-forming *syn*-elimination step with participation of the six-membered ring guiding the outcome toward the thermodynami-

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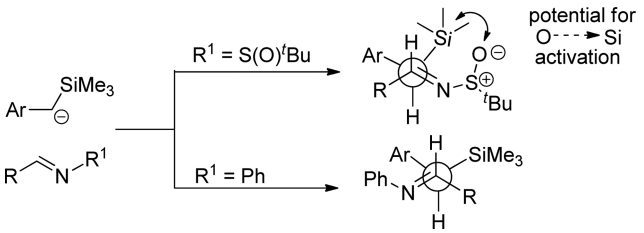


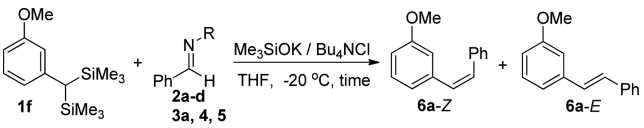
Figure 1. Possible addition profiles when using *N*-*t*-butanesulfinyl imine and *N*-phenyl imine electrophiles.

cally less stable *Z*-isomers. This would contrast with an open nonchelating addition model for the *N*-phenyl imine electrophiles, which delivers the thermodynamically favored *trans*-isomers (Figure 1).

At the outset, the reaction conditions of Me_3SiO^-/Bu_4N^+ in THF were chosen to match those previously successfully used in our addition reactions.[14] As it would be beneficial to have both *E*- and *Z*-isomers accessible from a single set of conditions (and allow direct comparison), these conditions were also applied to a number of *N*-aryl imine reactions, some of which have been previously observed to give high *E*-selectivity using CsF/DMF.[12] In this initial study, 13 bis(trimethylsilane) reagents **1a**−**m**, five *N*-aryl imines **2a**−**e**, and 19 *N*-*t*-butanesulfinyl imines **3a**−**s** were used (for structures, see Figures S1−S3).[16]

Before investigating the *Z*-selectivity, it was first confirmed that changing silicon activation from a fluoride source in DMF to Me_3SiO^- in THF did not impact the high *E*-selectivity with *N*-phenyl-substituted imines. Reaction of ((3-methoxyphenyl)-methylene)bis(trimethylsilane) **1f** and *N*-phenyl imine **2a** in the presence of 1.5 equiv of Me_3SiOK/Bu_4NCl in THF at −20 °C provided the target alkene **6a** in 87% yield with a *Z*/*E* ratio of 1:99, which was consistent with our previous results using CsF in DMF (Table 1, entry 1).[12] To determine the influence, if any, of

Table 1. Imine Stereoeffects on Aza-Peterson Olefinations[a]



entry	R	imine	time (h)	yield[b] (%)	*Z*/*E*[c]
1	Ph	**2a**	3	87	1/99
2	*p*-$MeOC_6H_4$	**2b**	3	76	1/99
3	*p*-$CF_3C_6H_4$	**2c**	3	84	1/99
4	3,5-$(CF_3)_2C_6H_3$	**2d**	3	85	1/99
5	(*R*)-S(O)*t*Bu	**3a**	2	89	95/5
6	(*S*)-S(O)*t*Bu	**3a**	2	88	95/5
7	(±)-S(O)*t*Bu	**3a**	2	86	95/5
8	SO_2Me	**4**	4[d]	51	65/35
9	SO_2*p*-MeC_6H_4	**5**	4[d]	63	45/55

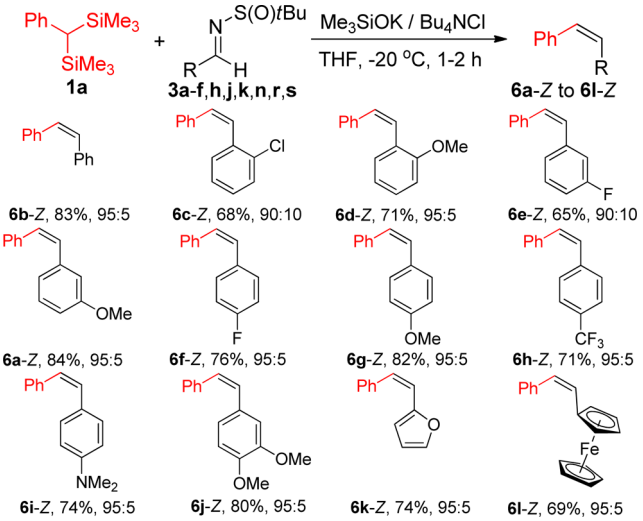
[a]Reaction conditions: bis(silanes) (0.8 mmol), imine (0.4 mmol), and Me_3SiOK/Bu_4NCl (0.6 mmol). [b]Yield of the isolated product after chromatography. [c]Determined by ^1H NMR. [d]Reaction warmed to 0 °C for 2 h.

electronic effects of the *N*-aryl group on the stereochemical outcome of the reaction, *N*-*p*-methoxyphenyl **2b**, *N*-*p*-trifluoromethylphenyl **2c**, and bis(trifluoromethyl)phenyl **2d** substituted imines were used in the reaction with **1f** under the same conditions. In each case, the product *Z*/*E* ratio remained unchanged at 1:99, with only minor variations in yields (entries 2−4). These results pointed toward *N*-aryl sterics influencing the reaction course toward highly selective *E* product.

Next, (*R*)-*N*-benzylidene-2-methylpropane-2-sulfinamide, (*R*)-**3a**, was chosen as electrophile in the reaction with **1a** under identical conditions. To our delight, a complete inversion of the stereo-outcome was obtained, with alkene **6a** obtained in 89% yield with a *Z*/*E* ratio of 95:5 (entry 5). Using either the *S*-isomer or a racemic mixture of sulfinyl imine **3a** had no effect on *Z*/*E* ratio (entries 6 and 7). A survey of the two sulfonyl imines **4** and **5** was next performed to compare their influence on the stereochemical outcome of the reaction. When methylsulfonyl imine **4** was treated with **1f** in the presence of 1.5 equiv of Me_3SiOK/Bu_4NCl in THF, alkene **6a** was formed in 51% yield with a poor *Z*/*E* ratio of 65:35 (entry 8). Employing *p*-toluenesulfonyl imine **5** under the same reaction conditions produced the product alkene **6a** in 63% yield, having little *Z*/*E* selectivity (45:55), which is a comparable result to that seen with benzaldehyde (entry 9).[12] This dramatic difference between sulfinyl and sulfonyl imines is pertinent as *p*-toluenesulfonyl imines are excellent substrates for the formation of *Z*-alkenes in the Wittig reaction.[10c] Together, these initial results indicated that *N*-phenyl imine and *rac*-*N*-*t*-butanesulfinyl imines could be used for *E*- and *Z*-selective olefination, respectively, in the presence of 1.5 equiv of Me_3SiOK/Bu_4NCl at −20 °C in THF.

The established reaction conditions were next evaluated by employing a broad range of aryl **3a**−**f**,**h**,**j**,**k**,**n**, heteroaryl **3r**, and organometallic **3s** *N*-*t*-butanesulfinyl imines with (phenylmethylene)bis(trimethylsilane) **1a** (Scheme 2). *Z*-

Scheme 2. *Z*-Selective PO with *N*-*t*-Butanesulfinylimines[a]



[a]Yield of the isolated product after chromatography; *Z*/*E* determined by ^1H NMR.

Selective olefination of electron-neutral, -rich, and -poor aryl imines having *o*-, *m*-, or *p*-substitution or bisubstitution worked very well, providing the corresponding alkenes *Z*-**6a** to *Z*-**6j** in high yields and with excellent range of *Z*/*E* ratios from 90:10 to 95:5. Pharmaceutically important heteroatomatic furan is also compatible with the protocol to produce the corresponding alkene *Z*-**6k** in 74% yield. Ferrocenyl imine **3s** was utilized for the first time in stereoselective olefination, providing alkene *Z*-**6l** in 69% yield and *Z*/*E* ratio of 95:5 (Scheme 2). Having successfully explored various *N*-*t*-butanesufinyl imines, the influence of diversely substituted bis(trimethylsilane) reagents **1b**,**d**−**f**,**h**,**j**,**k**

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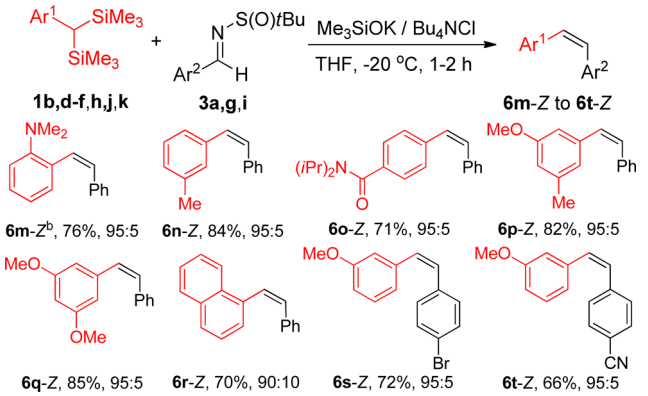
with imines **3a,g,i** was examined (Scheme 3). Pleasingly, each reaction was successful with good *Z*/*E* ratios in spite of the varying substitution patterns.

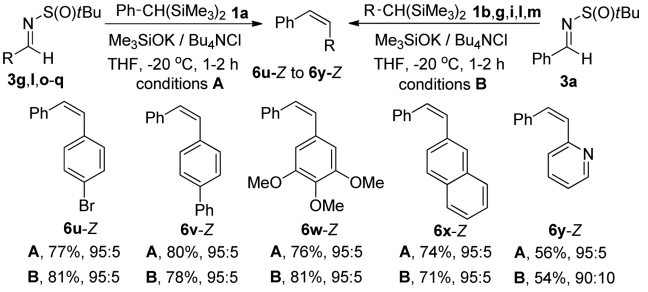
Scheme 3. *Z*-Selective Olefination[a]



[a]Yield of the isolated product after chromatography; *Z*/*E* determined by ^{1}H NMR. [b]Reaction performed at −20 to −10 °C.

An important feature of any new synthetic method is robustness, as its use will often be in the hands of a nonexpert. To showcase the generality of the current method, a dual synthetic strategy was chosen to prepare five representative alkenes **6u−y** (Scheme 4). Under conditions **A**, **1a** was reacted

Scheme 4. Dual Synthetic Strategy[a]

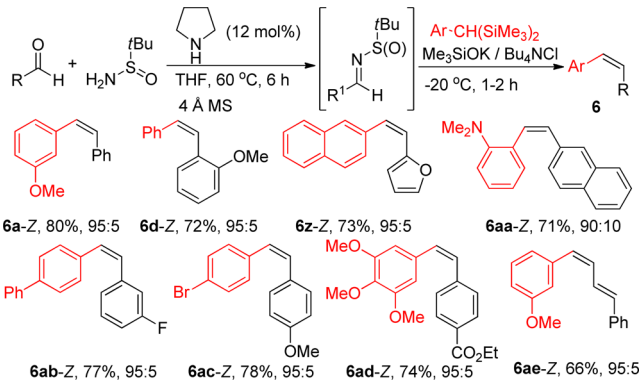


[a]Yield of the isolated product after chromatography; *Z*/*E* determined by ^{1}H NMR.

with five different imines **3g,l,o−q**, providing the corresponding alkenes in good yields with excellent *Z*-selectivities. In dual conditions **B**, five different bis(trimethylsilanes) **1b,g,i,l,m** were employed with **3a** to produce the same alkenes. Yields and *Z*-selectivity for both approaches show comparable results, many of which are within the range of experimental error. Of specific note, bis(trimethylsilane)pyridine derivative **1m** and its *N*-*t*-butanesulfinyl analogue **3q** were both compatible with this process (Scheme 4).

To streamline the *Z*-alkene synthesis from aldehydes, a one-pot approach was adopted (Scheme 5). Reaction of aldehyde and 2-methylpropane-2-sulfinamide in THF with pyrrolidine catalyst generated the sulfinyl imine.[17] Imine formation was monitored by TLC, and upon completion, the temperature was lowered to −20 °C, bis(trimethylsilane) added, and the reaction carried out as previously described. Eight diversely substituted alkenes were produced in good yields while maintaining the excellent *cis*-selectivity (Scheme 5). It could be anticipated that this approach would be of specific importance for library generation of *Z*-

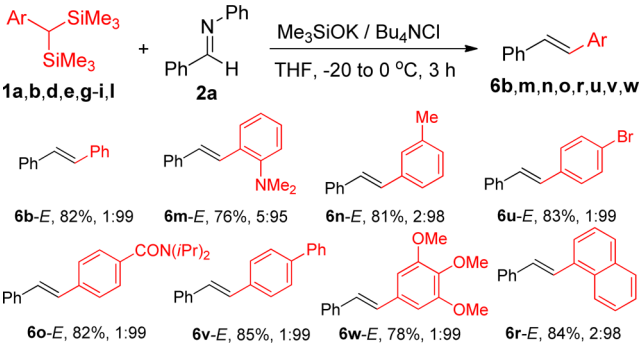
Scheme 5. One-Pot *Z*-Selective Aza-PO from Aldehydes[a]



[a]Reaction conditions: aldehyde (0.4 mmol), sulfinamide (0.44 mmol), bis(silanes) (0.8 mmol), and Me_3SiOK/Bu_4NCl (0.7 mmol); *Z*/*E* determined by ^{1}H NMR.

alkenes via high-throughput synthesis. As it would be a unique advantage to have a single silicon activation to produce both *Z*- and *E*-isomers, the use of Me_3SiO^-/Bu_4N^+ with *N*-phenyl imines was next evaluated. Eight bis(trimethylsilanes) were successfully tested with sulfinyl imine **2a**, providing alkenes **6b,m−o,r,u−w** in high yields and with ratios ranging from 5:95 to 1:99 (Scheme 6).

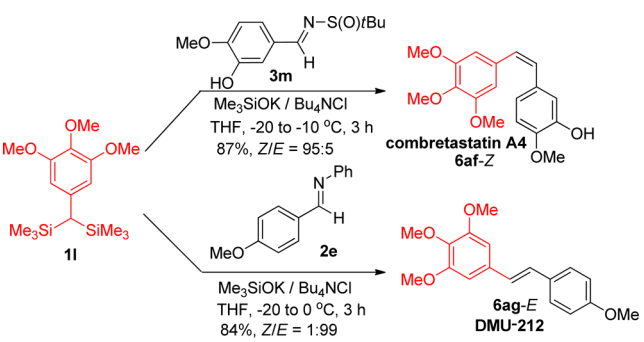
Scheme 6. *E*-Selective Olefination[a]



[a]Yield of the isolated product after chromatography; *Z*/*E* determined by ^{1}H NMR.

These results highlight that phenyl/sulfinyl imine *E*/*Z* stereocontrol is general and achievable under identical reaction conditions. This imine stereocontrolled alkene synthesis has been applied to both *Z* and *E* chemotherapeutics combretastatin A4 and DMU-212 (Scheme 7).[18,19] The reaction of ((3,4,5-

Scheme 7. *Z*-Combretastatin A4 and *E*-DMU-212



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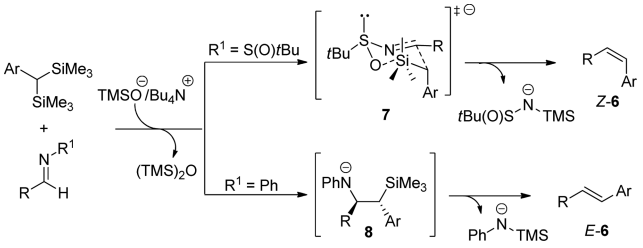
trimethoxyphenyl)methylene)bis(trimethylsilane) **1l** with sulfinylimine **3m** provided the therapeutic *Z*-**6af** in high yield and with excellent geometrical purity. Notably, the phenol group was tolerated, avoiding the need for functional group protection. Moreover, the promising anticancer agent DMU-212 was prepared from **1l** and the *E*-favoring 1-(4-methoxyphenyl)-*N*-phenylmethanimine **2e** (Scheme 7).

Identification of the exact mechanistic pivot point for *N*-sulfinyl- and *N*-phenyl imine *Z*/*E* stereocontrol requires further investigation, but some useful observational conclusions can be drawn at this stage. Based on our previous findings that addition of substituted benzyltrimethylsilanes to sulfinyl imines is highly diastereoselective,[14] it could be anticipated that (arylmethylene)-bistrimethylsilanes **1** would also be, thereby primarily setting the stereochemical outcome of the reaction at the addition step. This poses the question as to whether a four-membered 1-aza-2-silacyclobutane or a six-membered 1,2,3,6-azathiazasilinane intermediate is formed as a result of this addition. Tamao et al. have demonstrated a concerted [2 + 2] cycloreversion mechanism of substituted 1-aza-2-silacyclobutanes with retention of stereochemistry at the carbon atoms in the alkene product.[20] This would indicate that if a concerted [2 + 2] addition (as proposed for PO with carbonyls[21]) of the α-silyl carbanion with sulfinylimine was operating, the stereochemistry fixed at the addition stage would be reflected in the alkene product. Intriguingly, as *Z*-selectivity is observed for sulfinyl but not sulfonyl imines, it is also plausible that a six-membered azathiazasilinane TS (or intermediate) **7** could be operating as a lower energy alternative pathway to the four-membered azasilacyclobutane ring (Scheme 8). For *N*-aryl imines, as the

Scheme 8. Plausible Pathways for Aza-POs



thermodynamic product is being formed, addition to form the acyclic intermediate **8** with subsequent β-elimination could selectively provide the *trans*-product.

In summary, we have demonstrated highly tunable stereoselective aza-Peterson olefinations with bench-stable bis(trimethylsilanes) and imine electrophiles, with silicon activation achieved by trimethylsilyloxide in THF. Stereoselectivity of the product alkene solely depends on the nature of the imine employed. The more challenging Z-selectivity is obtained by the use of *N*-sulfinyl imine electrophiles, potentially through a unique pathway for olefination reactions. Further mechanistic investigation of both the *Z* and *E* reaction pathway(s) is ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03519.

General experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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