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Silyloxide-Promoted Diastereoselective Addition of Aryl and Heterocyclic Trimethylsilanes to *N-tert*-Butanesulfinylimines

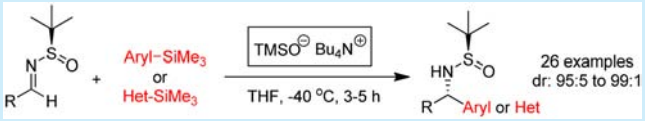
Manas Das[†] and Donal F. O'Shea*[,§,†,‡]

[†]Department of Pharmaceutical and Medicinal Chemistry, Royal College of Surgeons in Ireland, 123 St. Stephen's Green, Dublin 2, Ireland

[‡]School of Chemistry and Chemical Biology, University College Dublin, Dublin 4, Ireland

Supporting Information

ABSTRACT: The addition of a broad variety of substituted aromatic and heterocyclic silanes to chiral *N-tert*-butanesulfinylimines has been achieved providing 1,1-diaryl and diheterocyclic substituted sulfinamides with excellent diastereoselectivity in all cases. Employing Me_3SiO^-/Bu_4N^+ as the Lewis base activator for silicon allowed a general procedure for all silane reagents, including the less reactive aromatic derivatives. Evidence that the diastereoselective additions occur via an open transition state is presented.



Functionalized chiral α-branched amines are ubiquitous structural motifs in innumerable natural products, biologically active compounds, and pharmaceuticals. Specifically, enantiopure aryl- and diarylmethylamines are paramount in many drugs and drug candidates, such as the third-generation antihistamine agent levocetrizine,[1] opioid receptor agonist SNC-80,[2] and the antiplatelet aggregation drug clopidogrel[3] (Figure 1).

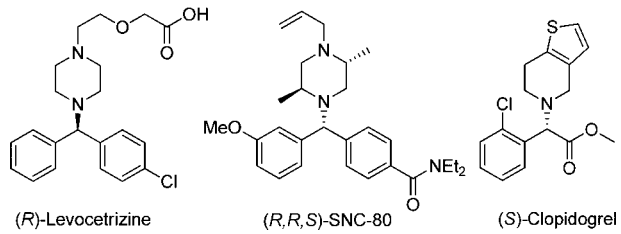


Figure 1. Representative examples of drugs containing diarylmethylamine and arylmethylamine moieties.

General strategies for the asymmetric synthesis of such amines are therefore highly compelling, though formidable challenges remain to achieving this. The asymmetric nucleophilic addition of aryl and heterocyclic organometallic reagents to imine electrophiles represents one such approach, and recently Pd-catalyzed arylation of imines has also been reported.[4,5] An attractive alternative approach would be the diastereoselective addition of aryl or heterocyclic organometallics to chiral imines, which has been explored for several nucleophilic substrates.[6] To date, the organometallics of choice for diastereoselective aryl addition reactions have been either Li, Mg, or B.[7−9] The use of in situ generated reactive organometallics such as Li or Mg can be limiting in substrate scope, and while selective additions of the less reactive arylboronic acids have been successfully achieved, they require the use of rare transition-metal Rh or Pd with specialized ligands in order to activate the pro-nucleophile. An attractive middle ground in the reactivity spectrum is the use of aryl and heterocyclic trimethylsilanes, which are readily available as bench stable reagents. If their reactivity can be unlocked they offer huge potential as masked aromatic and heterocyclic carbanion reagents.[10] We recently reported that the Lewis base Me_3SiO^-/Bu_4N^+ can promote their carbanion reactivity, but the ability to utilize these reagents with chiral imines remains unexplored. To the best of our knowledge, no reports of aryl or heterocyclic trimethylsilane additions to chiral imines have been previously published.[11] Herein, we report such additions for the first time using an array of aryl and heteroaryl *N-tert*-butanesulfinylaldimines (Ellman imines) as chiral imines.[6a]

A systematic investigation of reaction conditions for the addition of furan-2-yltrimethylsilane **2a** to model imine (*R*)-*N*-(4-bromobenzylidene)-2-methylpropane-2-sulfinamide (*R*)-**1a** was first carried out (Table 1). The treatment of TMSOK/Bu_4NCl with **2a** and the imine (*R*)-**1a** in THF at rt resulted in modest 34% yield of the *N-tert*-butanesulfinylamine adduct **3a** with 92:8 dr (entry 1). Changing the solvent from THF to toluene, heptane, or CH_2Cl_2 under similar reaction conditions failed to produce the desired product **3a** (entries 2−4). Temperature dependence was next explored as a means to improve the reaction outcome. Lowering the temperature to 0 °C in toluene gave the addition product **3a** in 36% yield with dr of 90:10 (entry 5), whereas in THF, **3a** was obtained in 54% yield and with 94:6 dr (entry 6). A further yield improvement for the reaction to 80% was obtained by lowering the temperature to −40 °C in THF, with a dr of 97:3 (entry 7). When the reaction was performed at −78 °C for 6 h, the yield was reduced to 33% with slight improved dr of 99:1 (entry 8). Using these conditions the reaction of (*S*)-**1a** was also effective, producing the opposite configuration at the chiral carbon

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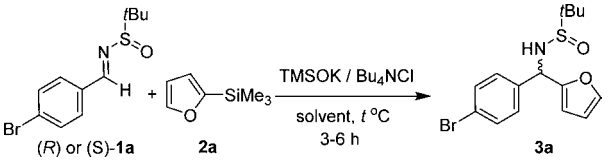
Table 1. Optimization of Furan-2-yltrimethylsilane Additions



entry	1a	solvent	temp (°C)	% yield[a]	dr[b]
1	*R*	THF	rt	34	92:8
2	*R*	PhMe	rt	trace	
3	*R*	heptane	rt	nd	
4	*R*	CH_2Cl_2	rt	nd	
5	*R*	PhMe	0	36	90:10
6	*R*	THF	0	54	94:6
7	*R*	THF	−40	80	97:3[c]
8	*R*	THF	−78	33	99:1
9	*S*	THF	−40	75	99:1[c]

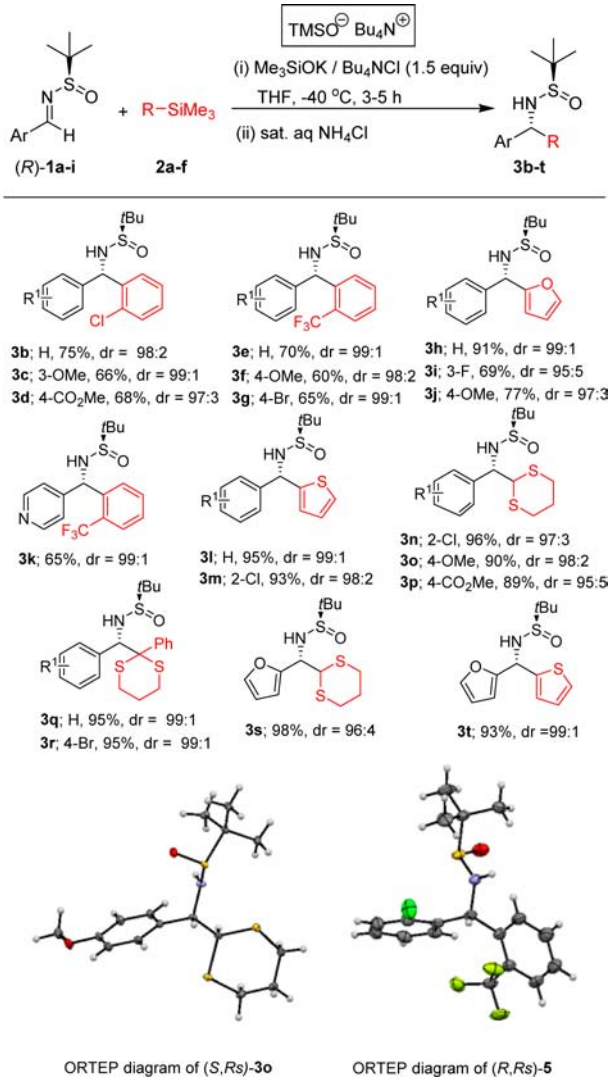
[a]Yield of product after chromatography. [b]Determined by HPLC and ^{1}H NMR analysis of crude product. [c]Difference attributed to incomplete HPLC baseline separation.

center with a measured dr of 99:1 (entry 9). Together, these results suggest that the use of TMSOK/Bu_4NCl in THF at −40 °C would be the optimal conditions to explore the general scope of this method.

The established reaction conditions were next evaluated by examining the addition of six structurally and electronically different aryl and heterocyclic trimethylsilane reagents to a range of 11 *N*-*t*ert-butaneslfinylimines (see the Supporting Information, Tables 1 and 2, for structures). Addition of silanes **2a**−**f** to electron-neutral, electron-poor, and electron-rich aromatic imines **1a**−**i** was achieved in good yields and with near-perfect diastereoselectivities in most cases. *Ortho*-, *meta*-, and *para*-substituted arylimines and -silanes all performed well under the reaction conditions, providing the diversely substituted diarylsulfinamides **3b**−**g** (Table 2). Moreover, 1-aryl-1-heteroaromatic sulfinamides **3h**−**m** were obtained, showing tolerance for both pyridine and furan rings participating as either the electrophilic or nucleophilic components of the reaction. Nonaromatic dithiane heterocycles performed equally well, giving **3n**−**r** with excellent yields and selectivities. The procedure was also successful for synthesis of 1,1-diheterocyclic substituted sulfinamides **3s**,**t** containing either dithiane, furan, or thiophene rings. In general, the substituent tolerance was broad with, for instance, ester functionality of **3d**, trifluoromethyl of **3e**, and bromo group of **3g** unaffected by the reaction conditions. The absolute configuration of the generated stereocenter was determined to be *S* for **3o** by single-crystal X-ray analysis (Table 2).

Encouraged by these results, the addition of aryl and heterocyclic trimethylsilanes to ferrocenyl imine (*R*)-**1j** was explored, as chiral aminoferrocene derivatives have been of long-standing interest as catalysts for numerous transformations (Table 3).[12] To the best of our knowledge, this is the first reported addition of trimethylsilane reagents to ferrocenyl *N*-*tert*-butanesulfinylaldimines. In all cases, the addition proceeded in high yields and with excellent diastereoselectivities to give the products **4a**−**d** (Table 3). Single-crystal X-ray analysis confirmed the absolute stereochemistry of the newly formed carbon center in **4a** to be *S*, formed with the same sense of stereroinduction observed in the structure of **3o** (Table 3).

Table 2. Aryl and Heterocyclic Trimethylsilane Addition to *N*-(*tert*-Butanesulfinyl)aldimines[a]



[a]dr determined by HPLC and ^{1}H NMR analysis of crude product; yield of product after chromatography.

To gain insight into the mode of diastereosective induction, a comparative study was conducted using chiral imine (*R*)-**1h** and three *o*-(trifluoromethyl)arene organometallics with either Li, Mg, or Si as the metal/metalloid (Table 4). It has previously been reported that arylorganolithium additions with *N*-*t*ert-butanesulfinylimines in THF operate through an open noncoordinating transition state, whereas Grignard reagents in hydrocarbon solvents add via a chelated six-membered transition state.[7a,c,d] A consequence of the different transition states is that the opposite diastereofacial selectivity for the additions is obtained. With this knowledge in hand, it was of interest to determine whether the silicon pro-nucleophiles under our reaction conditions gave stereoinduction comparable to a Li or Mg organometallic. Addition of (2-(trifluoromethyl)-phenyl)lithium to (*R*)-**1h** in THF at −78 °C gave the sulfinamide **5** with a dr of 90:10 and the absolute *R* configuration at carbon for the predominate isomer (Table 4, entry 1). In contrast, addition of (2-(trifluoromethyl)phenyl)-magnesium bromide to (*R*)-**1h** in toluene at 0 °C produced **5** with a dr of 1:99 with the *S* configuration for the generated

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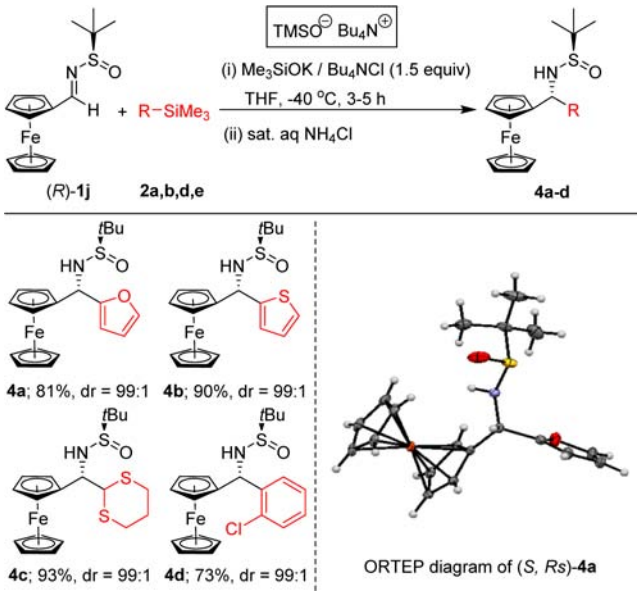
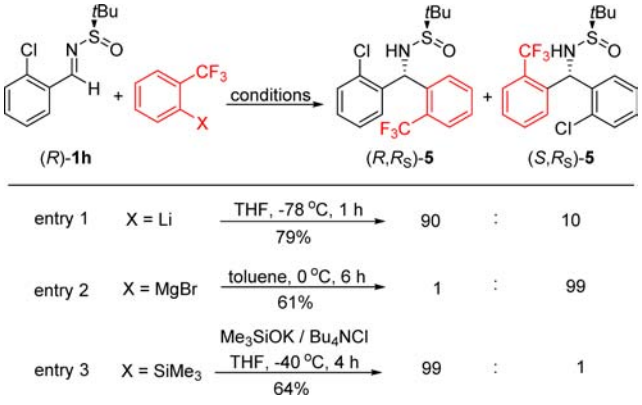
Table 3. Addition to Ferrocenyl Imine[a]



[a]dr determined by HPLC and ^{1}H NMR analysis of crude product; yield of product after chromatography.

Table 4. Comparative Study of Aryl Li, Mg, and Si Reagents



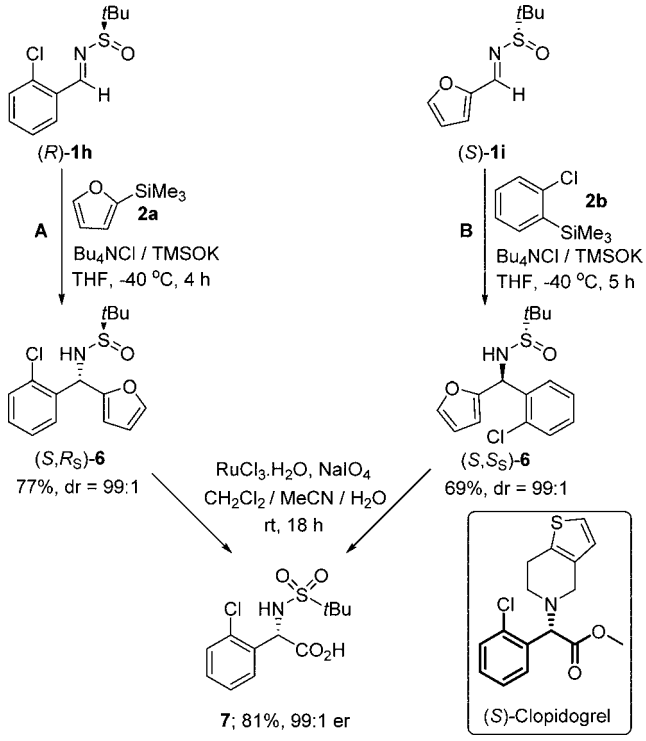
[a]dr determined by HPLC and ^{19}F NMR analysis of crude product; yield of product after chromatography.

chiral carbon (entry 2). Using our developed reaction conditions, addition of [2-(trifluoromethyl)phenyl]-trimethylsilane gave **5** with dr of 99:1 in favor of the (R,R_S) diastereoisomer (Table 4, entry 3) as confirmed by single-crystal X-ray crystallography (Table 2).[13,14]

These results show that the TS for the TMSO$^-$/Bu$_4$N$^+$-promoted addition of aryltrimethylsilanes is comparable to that of Li organometallics in THF, which has been proposed to be open and nonchelating. The exact nature of the TS and the contributory role played by the Bu$_4$N$^+$ counterion remains to be fully elucidated.

The generality of the Me$_3$SiOK/Bu$_4$NCl-promoted carbanion reactivity was showcased by two complementary routes to *N*-protected (*S*)-2-chlorophenylglycine **7** as an intermediate toward the synthesis of the medicinally important pharmaceutical (*S*)-clopidogrel (Scheme 1).[3] Route A utilized (*R*)-(*N*-*tert*-butanesulfinyl)-2-chlorobenzaldimines (*R*)-**1h** and furan-2-yltrimethylsilane **2a**, which following addition reaction gave the sulfinamide **6** in 77% yield with a (S,R_S):(R,R_S) ratio = 99:1. Alternative route B comprised the addition of (2-

Scheme 1. Synthesis of Precursor to (*S*)-Clopidogrel



chlorophenyl)trimethylsilane **2b** to (*S*)-(*N*-*tert*-butanesulfinyl)-2-furaldimines (*S*)-**1i** and provided the sulfonamide **6** in 69% yield with dr of (S,S_S):(R,S_S) = 99:1. Oxidation of **6** with catalytic ruthenium trichloride and sodium periodate gave the protected amino acid product **7** in 81% yield.[15,16]

In summary, a new general Me$_3$SiOK/Bu$_4$NCl activation method has been utilized to unmask the carbanion reactivity of aryl and heterocyclic trimethylsilanes for their diastereoselective addition to chiral *N*-*tert*-butanesulfinyl imines. The procedure proved efficient for a very broad range of substrates and showed excellent functional group tolerance, with high diastereoselectivity obtained almost universally. The use of bench-stable TMS reagents avoids the need to in situ generate strongly basic Li or Mg organometallics and the use of transition metals to catalyze boron reagents. Evidence was obtained that additions were taking place via a nonchelating TS with, remarkably, stereoinduction being the same as the more practically challenging aryllithium reagents. Application to the formal synthesis of (*S*)-clopidogrel, the second most prescribed drug in 2010, has been demonstrated. Ongoing work includes expanding the trimethylsilane substrate scope and gaining further mechanistic insight into the nature of the carbanion involved in the addition step.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedures and characterization data for all products and reagents. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: donalfoshea@rcsi.ie.

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Present Address

[§]Department of Pharmaceutical and Medicinal Chemistry, Royal College of Surgeons in Ireland, 123 St. Stephen's Green, Dublin 2, Ireland.

Notes

The authors declare no competing financial interest.

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(14) The sense of stereoinduction observed for [2-(trifluoromethyl) phenyl]trimethylsilane addition was the same as that for **3o** and **4a**, implying that a common TS exists for aryl and heterocyclic trimethylsilanes.

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