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Organic Synthesis

Highly Selective Addition of a Broad Spectrum of Trimethylsilane Pro-nucleophiles to *N-tert*-Butanesulfinyl Imines

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Abstract: Addition of organotrimethylsilane reagents to chiral *N-tert*-butanesulfinyl imines can be achieved in good yields and with excellent diastereoselectivities by employing $TMSO^-/Bu_4N^+$ as a Lewis base activator in THF. A variety of aliphatic, aromatic, heteroaromatic and organometallic chiral imines were utilised as electrophiles for the synthesis of enantioenriched *N-tert*-butanesulfinyl amides. Remarkably, the same sets of reaction conditions could be used with a highly diverse range of bench-stable organotrimethylsilane reagents, which highlights the generality and robustness of this methodology.

Introduction

The diastereoselective addition of organometallic reagents to chiral imines is arguably one of the more successful methodologies to deliver a diverse range of enantiomerically enriched amines.[1] The value of this synthetic approach is clear for medicinal chemistry discovery programs and for the production of drugs and drug candidates.[2] Over the last decade, an increasing collection of strategies based upon the chiral imines generated from *tert*-butanesulfinamide with numerous organometallic nucleophiles have been successfully developed (Figure 1).[3] Nucleophiles containing metals such as lithium, magnesium, zinc, indium, silicon and boron, with a very broad range of reactivity, have been utilised.[3b–g] The distribution of metal pro-nucleophiles is, as would be expected, diverse, with the more reactive organometallics containing Li, Mg, Zn or In requiring in situ formation and immediate use with the imine substrate. Only Si and B offer the possibility to start from a bench-stable pro-nucleophile, but these systems differ in that boron reagents need in situ transmetallation with either Rh or Pd to achieve the required reactivity. Silicon reagents alone are unique as they are bench-stable and do not require in situ transmetallation to participate in addition reactions. It is evident from the literature that the broadest substrate scope exists for the more reactive organometallics such as lithium, magnesium and zinc, whereas for silicon the focus has been more towards the most reactive nucleophiles such as cyanide, the trifluoromethyl anion and related derivatives (Figure 1).[4] The expansion of TMS pro-nucleophiles to a broader range of organo-substrates would be of value as they are readily available bench-stable reagents, which allows for their direct use in typical medicinal chemistry formats.[3a] A factor of equal importance to utilising bench-stable pro-nucleophiles would be to have a common set of reaction conditions in which these reagents could be used. We recently reported that the Lewis base Me_3SiO^- as its Bu_4N^+ salt, in THF, can promote the carbanion reactivity of organo-TMS reagents for addition to carbonyls.[5] In a preliminary study, it was found that the addition of aromatic and heterocyclic silanes to chiral *N-tert*-butanesulfinyl imines could be achieved with excellent diastereoselectivity.[6] In this account, these additions have been expanded to encompass a broad spectrum of TMS reagents, covering

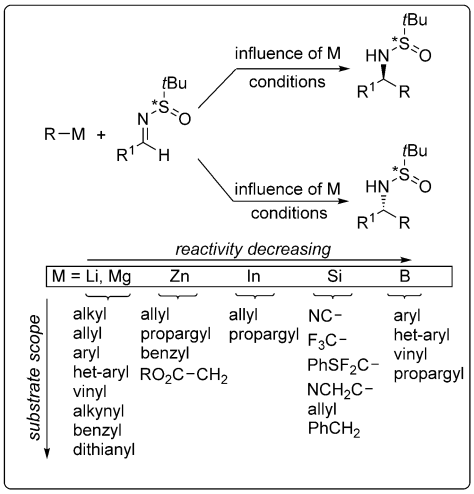

Figure 1. Diastereoselective addition of organometallics to chiral *N-tert*-butanesulfinyl imines.

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a wide span of reactivity, using a single set of reaction conditions.

Results and Discussion

To determine the generality of trimethylsilane reactivity and addition diastereoselectivity under Me_3SiO^-/Bu_4N^+ activation, 17 chiral imines **1a–q** and 28 trimethylsilane reagents **2–4**, **5a,b**, **6a–j**, **7a,b**, **8a,b**, **9**, **10a–h** were investigated (for structures see Figures 2 and 3).

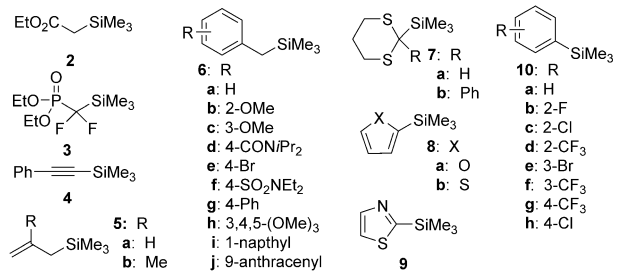


Figure 2. Structures of organotrimethylsilanes **2–10**.

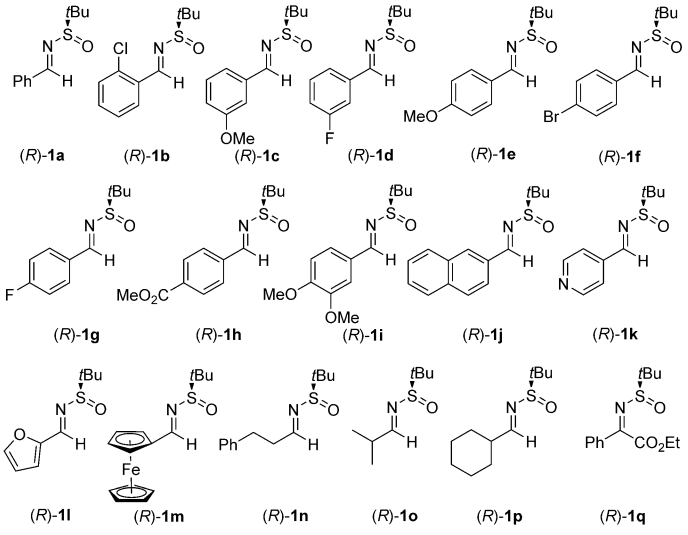
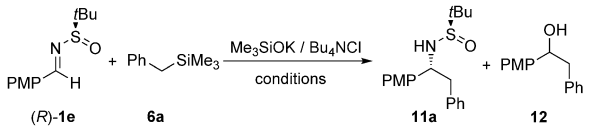


Figure 3. Structures of *N-tert*-butanesulfinyl imines **1a–q**.

The chiral imines used included aliphatic, aromatic, heteroaromatic, organometallic and ethyl benzoate derivatives with the organotrimethylsilanes having ethylacetate, difluoro(methyl)-phosphonate, alkynyl, allyl, benzyl, dithiane, heteroaryl and aryl substituents. For the initial screen to identify optimal reaction conditions, (*R*)-*N*-(4-methoxybenzylidene)-2-methylpropane-2-sulfinamide, (*R*)-**1e**, was chosen as the model imine in reaction with benzyltrimethylsilane **6a** (Table 1). The treatment of the imine (*R*)-**1e** and **6a** with 0.5 equivalents TMSOK/Bu_4NCl in dry THF at room temperature resulted in approximately 50% conversion of the imine, forming the *N-tert*-butanesulfinyl amine adduct **11a** (35%, 84:16 d.r.) with the side product alcohol **12**

Table 1. Optimisation of reaction conditions with benzyltrimethylsilane.[a]



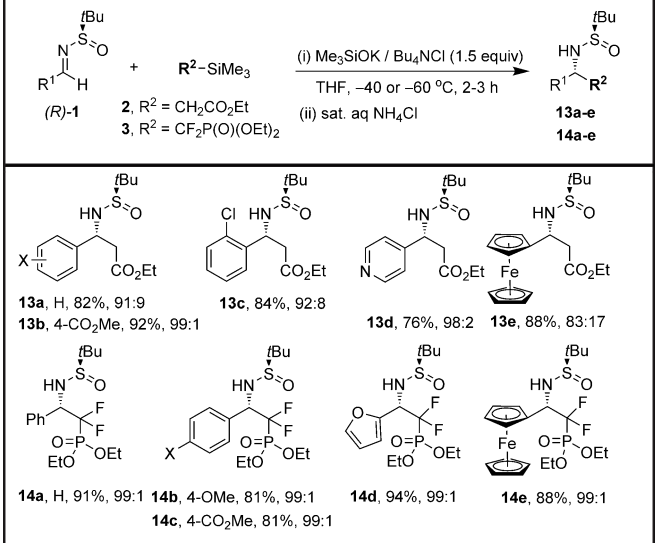
Entry	mol%	Solvent	*T* [°C]	*t* [h]	Conv. [%]	Yield [%][b] **11a/12**	d.r.[c] (1*R*:1*S*)
1	50	THF	rt	6	50	35/10	84:16
2	100	THF	rt	3	90	63/23	84:16
3	150	THF	rt	3	100	81/15	84:16
4	150	THF	0	5	100	86/trace	85:15
5	150	THF	−40	5	100	92/nd	90:10
6	150	THF	−78	5	100	91/nd	90:10

[a] PMP = *p*-methoxyphenyl; nd = Not detected. [b] Yield after chromatography. [c] Determined by ^1H NMR spectroscopy and HPLC.

generated in a 10% yield (Table 1, entry 1). A plausible explanation for the formation of side product **12** is the partial decomposition of (*R*)-**1e** to *p*-anisaldehyde, which concomitantly reacted with **6a**. In an attempt to achieve complete conversion of imine, 1 equivalent of activator TMSOK/Bu_4NCl was used, resulting in ~90% imine conversion with **11a** obtained in higher yield and with same diastereoselectivity (63%, 84:16 d.r.), but the yield of the alcohol **12** also increased to 23% (entry 2). A complete conversion of imine was accomplished with the formation **11a** (81%, 84:16 d.r.) and **12** (15%) when 150 mol% TMSOK/Bu_4NCl was utilised (entry 3). The temperature dependence of the reaction was investigated next; encouragingly, with 1.5 equivalents of TMSOK/Bu_4NCl at 0 °C in THF, complete conversion was achieved with **11a** obtained in 86% yield (85:15 d.r.) and **12** formed in only trace amounts (entry 4). Further lowering the temperature to −40 °C improved the yield of **11a** to 92% and the d.r. to 90:10 with no alcohol **12** detected in the crude product (entry 5). A similar result was obtained when the reaction was performed at −78 °C (entry 6). The absolute configuration of the major diastereomer of *N*-sulfinyl amine **11a** was determined to be ($1R,R_S$) by comparison with reported literature data.[7] The conclusions from this study were to use 1.5 equivalents of TMSOK/Bu_4NCl and temperatures of −40 °C or below to assess the addition reactivity and selectivity performance of trimethylsilanes **2–10**.

Addition to imines is a convenient route to β-amino acids, which are an important class of building blocks for the synthesis of natural products and pharmaceutical agents.[8] In addition, they are the underlying monomers of β-peptides, which have received considerable attention owing to their unique structural properties and valuable biological activities.[9] As such, the addition of ethyl-2-(trimethylsilyl)acetate **2** to aryl, heteroaryl and ferrocenyl (*R*)-imines was investigated (Table 2). Owing to the high reactivity of **2**, the chosen reaction temperature was −60 °C, which gave the corresponding *N*-sulfinyl β-

Table 2. Addition of diethyl (difluoro(trimethylsilyl)methyl)phosphonate and ethyl-2-(trimethylsilyl)acetate to *N-tert*-butanesulfinyl imines[a]



[a] Yield after chromatography; d.r. determined by ^{1}H NMR or ^{19}F NMR spectroscopy or HPLC.

amino ester derivatives **13a–e** in good yields and with moderate to excellent diastereoselectivities of 83:17 to 99:1. This method offers an alternative to the ester enolate addition for the synthesis of chiral β-amino esters.[10] The absolute configuration of the major isomer of sulfinamide **13a** was assigned as (1*R*,R_S) by comparison with the previously reported data and **13b–e** were assigned by analogy.[10a]

Organophosphorus compounds are important substrates in the study of biochemical processes as isosteres of β-amino acids.[11a] It is well documented that β-aminophosphonic acids have shown diverse biological and biochemical properties, such as, antibacterial activity, enzyme inhibition, activity as haptens for catalytic antibodies, and anti-HIV activity.[11b,c] Few efficient asymmetric synthetic methods are available for the preparation of chiral β-aminophosphonic acid derivatives.[11b] As such, the diethyl (difluoro(trimethylsilyl)methyl)phosphonate **3** was synthesized from diethyl (bromodifluoromethyl)-phosphonate through a lithium halogen exchange and TMSCl quench and its addition performance investigated (see the Supporting Information). Additions of **3** were carried out at −40 °C to the five different sulfinyl aldimines (*R*)-**1a,e,h,l,m**, transforming them to their corresponding *N*-sulfinyl amines **14a–e** with good yields and excellent diastereoselectivities (Table 2). The absolute configuration of the major isomer of product **14a** was determined to be (1*S*,R_S) by single-crystal X-ray structure analysis (Figure 4).[12] The absolute configurations for **14b–e** were assigned to be same as **14a** by analogy.

Chiral propargylic and homoallylic amines have great value as structural subunits and key synthetic intermediates in organic synthesis.[13] To date, several approaches to these useful amines have been recorded.[14,15] Among them, the most common route is nucleophilic 1,2-addition of alkyne or allyl nucleophiles to imines using Lewis acids or transition-metal com-

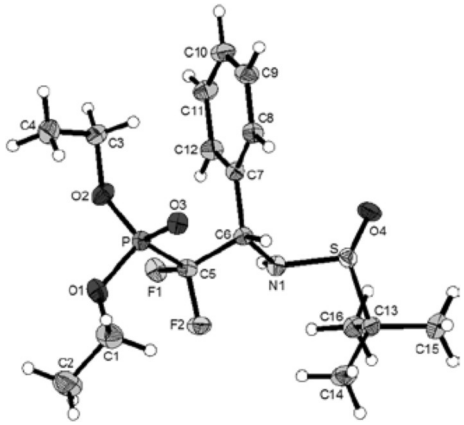
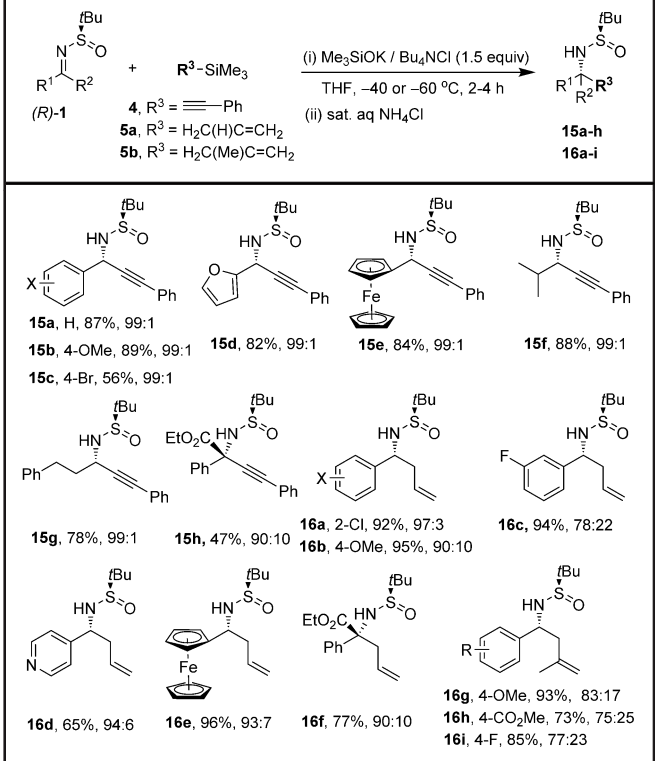


Figure 4. ORTEP diagram of **14a** (thermal ellipsoids are drawn on the 50% probability level).

plexes as catalysts.[3d] However, reports on the Lewis base mediated stereoselective reaction of alkynes with chiral sulfinimines are rare.[16] The importance of homoallylic amines is emphasised by the prevalence of chiral α-branched amines in natural products, biologically active molecules, and ligands.[17] Among the strategies developed, diastereoselective allyl addition to chiral sulfinyl imines has received major attention.[18] With appropriate allyl metal reagents as the nucleophiles, reactions can be carried out stereoselectively and provide enantio-

Table 3. Addition of acetylenic and allylic trimethylsilanes to *N-tert*-butanesulfinyl imines[a]



[a] Yield after chromatography; d.r. determined by ^{1}H NMR or ^{19}F NMR spectroscopy or HPLC.

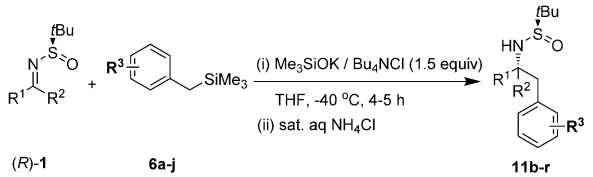
pure amines effectively. The fluoride-promoted addition of allyltrimethylsilane to racemic sulfinyl imines has been previously reported.[4e]

For this study, trimethyl(phenylethynyl)silane **4**, allyltrimethylsilane **5a**, and trimethyl(2-methylallyl)silane **5b** were chosen as pro-nucleophile substrates. The generality of the reaction with respect to imine substrates was challenged with 12 derivatives **1a**,**b**,**d**–**h**,**l**,–**o**,**k**,**q**, which included alkyl, aryl, heteroaryl and ferrocenyl aldimines and the activated ketimine **1q**. In all cases, the desired propargylic (**15a**–**h**) and homoallylic (**16a**–**i**) sulfinyl amines were obtained in moderate to very good yields (Table 3). In general, the d.r. values for phenylethynyl additions (ranging from 99:1 to 89:11) were consistently higher and better than those of the allyl additions (ranging from 94:6 to 75:25). The absolute configuration of the major isomer of sulfinamides **15e** and **16a** were determined to be (1*S*,R_S) and (1*R*,R_S), respectively, by comparison with reported literature data.[15e,18b]

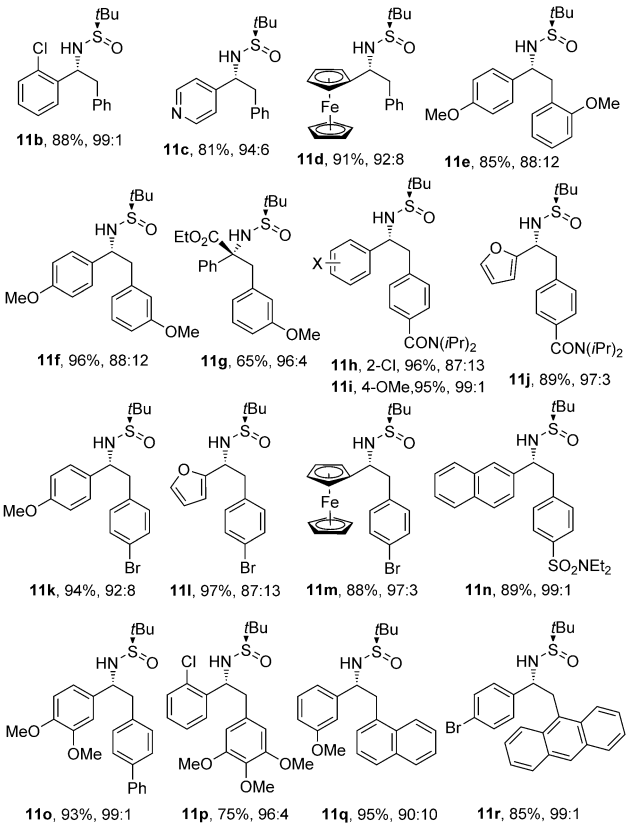
Synthetic routes to substituted chiral homobenzyl amines have been a subject of interest over the past decade owing to the presences of this structural motif in many pharmaceuticals and biologically active compounds.[19] A valuable method to prepare chiral amine compounds containing such a subunit is the addition of benzyl organometallic reagents to chiral sulfinyl imines. To date, the use of mixed Mg/Zn organometallics have been successfully utilised for benzyl additions.[7,20] The fluoride-promoted addition of unsubstituted benzylsilane **6a** to racemic imines has been previously reported.[4f]

Our primary interest was to determine the level of generality for highly selective additions for an extensive series of substituted benzyltrimethylsilanes. As such, the electronically and structurally diverse silanes **6a**–**j** were chosen as nucleophilic substrates and were tested against a wide range of aryl-, heteroaryl- and ferrocenyl-substituted *N-tert*-butanesulfinyl aldimines and an activated ketimine (Table 4).

Table 4. Benzyl group addition to *N-tert*-butanesulfinyl imines.[a]



(*R*)-**1** **6a-j** **11b-r**



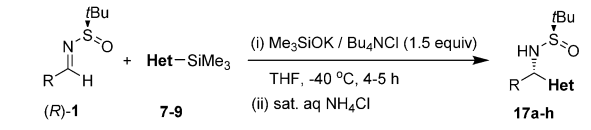
[a] Yield after chromatography; d.r. determined by ^{1}H NMR spectroscopy and HPLC.

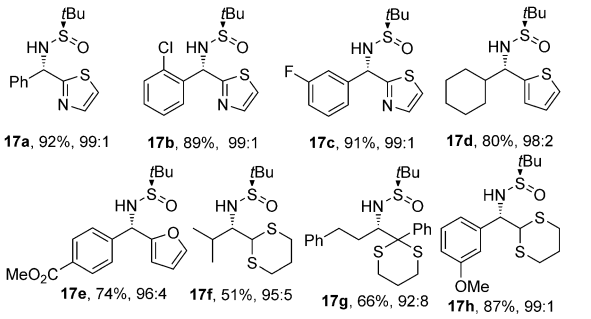
Remarkably, all reactions were successful under the one set of reaction conditions with all the desired products **11b**–**r** obtained. Of note is the predominately high d.r. values with over 75% of sulfinyl amides obtained with diastereomeric ratios of 90:10 or above (Table 4). Product **11g**, obtained with a d.r. of 96:4, is of particular relevance as a precursor to α-amino acids with quaternary stereogenic centres. The absolute configuration of the major isomer of sulfinamide **11b** was determined to be (1*R*,R_S) by analytical correlation with the literature data[7] and, by analogy, the other examples have been assigned identical stereochemistry.

Diastereoselective nucleophilic addition of heteroaryls to *N-tert*-butanesulfinyl imines has been previously examined in the literature by utilising lithium and magnesium reagents.[21] Recently, we have reported the selective addition of heterocyclic trimethylsilanes to aryl *N-tert*-butanesulfinyl imines.[6] This initial study has now been expanded to include 2-(trimethylsilyl)thiazole substrates and aliphatic imines. Thiazole additions are useful as one-carbon homologating procedures as their conversion to a formyl group is readily achievable.[22] Thiazole additions performed very well to produce the desired aryl thiazole sulfonamides **17a**–**c** each with excellent 99:1 diastereoselectivity (Table 5). Pleasingly, addition of other aromatic and non-aromatic heterocycles to cyclohexyl-, isopropyl- and 3-phenylpropane-substituted imines also gave products **17d**, **f** and **g**, respectively, with high d.r. values (Table 5).

Diastereoselective addition of aryl organometallics to chiral imines, as a route to diarylmethyl amines, has been explored for several nucleophilic substrates.[3b] To date, the organometallics of choice for diastereoselective aryl addition reactions have been either Li, Mg or B.[23] Although more recently, the silyloxide-promoted addition of *ortho*-substituted aryltrimethylsilanes to *N-tert*-butanesulfinyl imines has been communicated.[6] The substrate breadth for these additions has now been expanded to *ortho*-, *meta*- and *para*-substituted aryltrimethylsilanes. We were delighted to find that, in most cases, the desired diaryl-

Table 5. Addition of heterocyclic trimethylsilanes to aliphatic and aryl *N*-*tert*-butanesulfinyl imines.[a]

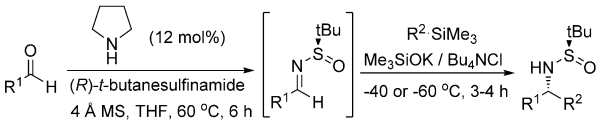




[a] Yield after chromatography; d.r. determined by ^{1}H NMR spectroscopy or HPLC.

sulfinamides **18a–k** were obtained in moderate to good yields (Table 6). Products were obtained with consistently high diastereoselectivities, all being higher than a 90:10 ratio. The activation of phenyltrimethylsilane under these conditions was unsuccessful, which marks the current reactivity limit for this methodology.

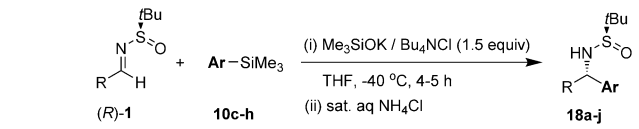
To stream-line the method, a one-pot approach from the starting aldehyde was developed. An amino catalytic process for in situ preparation of sulfinyl imine was performed by using a catalytic amount of pyrrolidine in THF to effect the condensation of aldehyde and (*R*)-2-methylpropane-2-sulfinamide via an iminium ion intermediate.[24] Chiral imine formation was monitored by TLC and upon completion the reaction mixture was adjusted to −40 °C or −60 °C and the trimethylsilane addition carried out as previously described. To showcase the robustness of this approach, the substituted sulfinamides **11b**, **13b**, **15d**, **17h**, **17i** and **18l** were produced in good yields and with excellent diastereoselectivities (Scheme 1). It could be anticipated that this approach would be of specific importance for library generation by high-throughput synthesis.

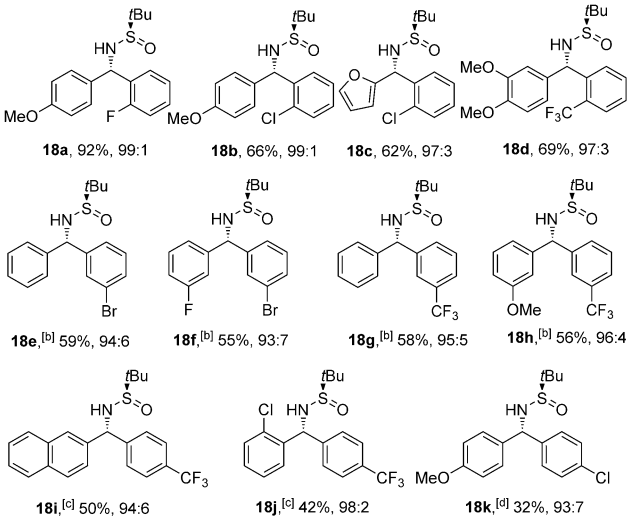


11b; R^1 = 2-ClC_6H_4; R^2 = $CH_2C_6H_5$;85%; d.r. = 99:1
13b; R^1 = 4-$MeO_2CC_6H_4$; R^2 = CH_2CO_2Et; 83%; d.r. = 99:1
15d; R^1 = 2-furyl; R^2 = ≡—Ph; 74%; d.r. = 99:1
17h; R^1 = 3-$OMeC_6H_4$; R^2 = 1,3-dithiane; 87%; d.r. = 98:2
17i; R^1 = ferrocenyl; R^2 = 2-furyl; 73%; d.r. = 99:1
18l; R^1 = 4-BrC_6H_4; R^2 = 2-$CF_3C_6H_4$; 62%; d.r. = 99:1

Scheme 1. One-pot approach from aldehydes.

Table 6. Addition of aryltrimethylsilanes to *N*-*tert*-butanesulfinyl imines.[a]





[a] Yield after chromatography; d.r. determined by ^{1}H NMR or ^{19}F NMR spectroscopy or HPLC. [b] Reaction performed at −20 °C. [c] Reaction performed at −10 °C. [d] Reaction performed at 0 °C.

For completion, some representative sulfinamides **11a–b**, **13c** and **16a–b** were transformed to their corresponding amines by acid deprotection.[23g] Selective cleavage of the sulfinyl group was accomplished in high yields without erosion of enantiomeric purity to provide the chiral amines **19a–e** (Table S3 in the Supporting Information).

A qualitative experimentally observed trimethylsilane reactivity trend from more to less reactive can be summarised as follows: **2**, **3**, **4** > **7**, **8**, **9** > **5**, **6**, > **10b,c,d** > **10e,f** > **10g,h** > **10a**. For the aryl-TMS derivatives **10**, *ortho*-substituted arenes are more reactive than *meta*- or *para*-substituted, with unsubstituted **10a** being the least reactive. It is of interest to note that diastereofacial selectivity is not related to reactivity as it was seen that it remained consistently high, for example, for both silane derivatives of type **3** and **10**. The silane derivatives that showed the widest distribution of d.r. values for differing imines were the allyl and the benzyl derivatives. However, overall, the selectivity is invariably high with the average d.r. for all 70 reactions performed being 95:5. Product analysis and literature comparison indicates that the mode of stereoinduction is common for all trimethylsilane reagents and would be consistent with operating via a non-chelating open transition state.[25]

Conclusion

A general Me_3SiO^-/Bu_4N^+ activation in anhydrous THF has been utilised to unmask the carbanion reactivity of a broad spectrum of trimethylsilane reagents, allowing their diastereoselective addition to chiral *N-tert*-butanesulfinyl imines. The procedure proved successful for a broad spectrum of substrates, showing excellent functional group tolerance, and with high diastereoselectivity obtained almost universally. These results highlight the potential of under-utilised bench-stable TMS reagents as pro-nucleophiles, which avoid the need for in situ generation of more strongly basic organometallics. This use of organo-TMS reagents in this manner offers a unified approach to chiral amines through diastereoselective *N-tert*-butanesulfinyl imines additions.

Experimental Section

General procedure for the addition of organotrimethylsilanes to *N-tert*-butanesulfinyl imines: A solution of dried Bu_4NCl (104 mg, 0.375 mmol) and TMSOK (48 mg, 0.375 mmol) in anhydrous THF (1.0 mL) at −40 or −60 °C was treated with a solution of *N-tert*-butanesulfinyl imine **1** (0.25 mmol) and organotrimethylsilane **2**–**10** (0.75 mmol) in anhydrous THF (1.5 mL) under N_2 atmosphere and the resulting solution stirred for 3–5 h. The reaction mixture was quenched with saturated ammonium chloride solution at −40 or −60 °C, warmed to room temperature, water added and extracted with diethyl ether (15 mL×3). The organic portions were combined, washed with brine, dried over anhydrous sodium sulfate and concentrated. Purification by silica gel chromatography eluting with cyclohexane/ethyl acetate afforded the corresponding *N-tert*-butanesulfinamide. The diastereomeric ratios for the products were determined by ^{1}H NMR or ^{19}F NMR spectroscopy or by HPLC analysis.

Acknowledgements

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Keywords: chiral imines · diastereoselectivity · organotrimethylsilanes · pro-nucleophiles · trimethylsilyloxide activation

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