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Addition of benzyltrimethylsilane to imines triggered by tetrabutylammonium fluoride

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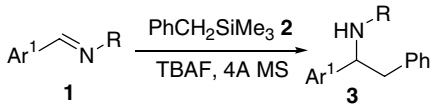
Abstract—The addition of benzyltrimethylsilane **2** to imines **1** triggered by TBAF in the presence of 4A molecular sieves gave rise to the corresponding α-benzylated amines **3** in good yields. Moderate to high diastereoselectivity was obtained in the reactions of *tert*-butanesulfinyl imines with **2**.

Organosilane reagents have found their wide-range uses in organic synthesis.[1] Sakurai–Hosomi reaction,[2] the reaction of an allylsilane with a carbonyl compound under Lewis acid conditions or in the presence of fluoride ions, is among the most popular protocols.[3] The reaction has also been extended to aza-analogies.[4,5] In spite of the success of allylation of C=N bond using allylsilane derivatives under Sakurai–Hosomi reaction conditions, few examples reported so far the reaction of imines with benzylsilane **1** in the presence of fluoride though the reaction of **1** with aldehyde catalyzed by TBAF was investigated previously.[6]

We have investigated the reaction of allylsilane with imines triggered by fluoride anion.[5] Further studies showed that benzyltrimethylsilane also reacted with imines in the presence of *n*-tetrabutylammonium fluoride (TBAF) and 4A molecular sieves to give the corresponding benzylated products. Herein, we would like to report our preliminary results.

The reaction of imine **1a** with benzylsilane **2** in the presence of 5 mol % of TBAF and 4A MS in THF under reflux provided benzylated product **3a** in 72% yield (Eq. 1).



1 **3** (1)

As it is shown in the reaction of allylsilane with imines, the presence of a molecular sieve is crucial. No reaction took place in the absence of it.[5] Screening of the solvents showed that many solvents are suitable (solvent, temperature, yield: THF, reflux, 72%; CH_2Cl_2, reflux, 72%; hexane, reflux, 62%; toluene, 85 °C, 59%). However, complex products were given when the reaction was run in DMF.

Under the above condition, several imines were tested (Table 1). All *N*-aryl imines derived from arylaldehydes gave good yields (entries 1–5), while imine **1f** with a benzyl substituent at N-atom failed to give the product. The electronic property of the substituent on either phenyl rings has little influence on the yield.

Many bioactive molecules, including some medicines, contain $BnCH^*–NH_2$ subunit with chiral carbon center.[7] One of the easiest ways to prepare compounds containing such a subunit is the addition of benzyl reagents to imines. Chiral sulfinyl group as an excellent chiral auxiliary and activator of the C=N bond for nucleophilic addition has widely been used in organic synthesis, since

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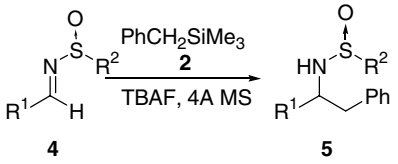
Table 1. Reaction of Imines **1** with benzylsilane **2** in the presence of TBAF[a]

Entry	Imine **1**	Ar	R	Yield[b] (%)
1	**1a**	Ph	Ph	**3a**, 72
2	**1b**	*p*-$MeOC_6H_4$	Ph	**3b**, 70
3	**1c**	Ph	*p*-$MeOC_6H_4$	**3c**, 65
4	**1d**	*p*-ClC_6H_4	Ph	**3d**, 71
5	**1e**	Ph	*p*-ClC_6H_4	**3e**, 74
6	**1f**	*p*-$MeOC_6H_4$	Bn	0

[a] The reaction proceeded on a 0.5 mmol scale in 2 mL THF at reflux, molar ratio of **1**:**2**:TBAF = 1:1.5:0.05, and 200 mg of 4A MS was added.
[b] Isolated yield based on imine **1**.

Davis and Ellman pioneered using chiral *p*-toluenesulfinyl and *tert*-butanesulfinyl groups in imine chemistry.[8] Thus, sulfinylimines **4** were tested in this fluoride-triggered benzylation reaction (Eq. 2). However, sulfinylimine **4a** derived from racemic *p*-tolylsulfinamide reacted with benzylsilane **2** in THF at 40 °C in the presence of 5 mol % TBAF gave no desired product. When the amount of TBAF increased to 15 mol %, 20% of product **5a** as well as complex by-products was delivered, which may have produced through competitive α-deprotonation followed by unknown transformations under basic condition.[9] Side-reactions were greatly depressed and the yield of product **5a** increased to 68% if the reaction run in THF at −40 °C and 30 mol % of TBAF was used. The ^{1}H NMR spectrum of the product showed two peaks at δ 2.37 (s) and 2.39 (s) with a ratio of 82:18, which corresponds to 64% de. Higher de value was provided if imine derived from *t*-butylsulfinamide was used. A de value of 85% was given when imine **4b** reacted with **2** in THF at −60 °C. Under this optimized condition, several sulfinimines were used and the results are compiled in Table 2.



(2)

It can be seen from Table 2 that good de was given for all reactions, 86% de being the best (Table 2, entries 6 and 10).[10] Imines derived from arylaldehydes gave the products in higher yields than that derived from aliphatic aldehydes (Table 2, entries 3–6 vs entries 7–11), even for imine **4k** derived from heteroarylaldehyde (Table 2, entry 11). It is interesting to note that CH_3CN is better than THF when imines derived from arylaldehydes were substrates (Table 2, entries 7–11). It is the same as for the reaction of imines **1** that the electronic property of the substituent on phenyl ring has no effect on the yield (Table 2, entry 8 vs entries 9 and 10).

It appears that this benzylation reaction was also initiated by fluoride.[5] However, the yields of the reaction using benzylsilane **2** were lower than that using allylsilane, which may reflect the difference in reactivity between benzylsilane and allylsilane.

Table 2. The reaction of sulfinylimines **4** with **2** in the presence of TBAF[a]

Entry	Imine **4**	R^1	R^2	Yield[b] (%)	de[e] (%)
1[c]	**4a**	*i*-Propyl	*p*-Tolyl	**5a**, 68	64
2[c]	**4b**	*i*-Propyl	*t*-Butyl	**5b**, 63	85
3[c]	**4c**	*n*-Propyl	*t*-Butyl	**5c**, 38	83
4[c]	**4d**	*s*-Butyl	*t*-Butyl	**5d**, 49	63
5[c]	**4e**	$PhCH_2CH_2$	*t*-Butyl	**5e**, 40	65
6[c]	**4f**	*t*-Butyl	*t*-Butyl	**5f**, 31	86
7[d]	**4g**	PhCH=CH	*t*-Butyl	**5g**, 68	59
8[d]	**4h**	Ph	*t*-Butyl	**5i**, 85	77
9[d]	**4i**	4-F–C_6H_4	*t*-Butyl	**5i**, 73	72
10[d]	**4j**	4-$MeOC_6H_4$	*t*-Butyl	**5j**, 66	86
11[d]	**4k**	2-Furyl	*t*-Butyl	**5k**, 67	69

[a] The reaction was run on a 0.25 mmol scale, molar ratio of **4**:**2**:TBAF = 1:2:0.3, and 200 mg of 4A MS was added.
[b] Isolated yield based on imine **4**.
[c] Run at −60 °C in THF.
[d] Run at −45 °C in CH_3CN.
[e] Determined by 300 MHz ^{1}H NMR.

In conclusion, benzylation of imines using benzyltrimethylsilane in the presence of TBAF has been developed.[11] Good de was provided when sulfinimines were used. Further studies on fluoride-initiated reactions as well as the applications of benzylsilane in organic synthesis are in progress.

Acknowledgments

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10. A product with 74% de was obtained when optical **4h** reacted with **2** at −20 °C.
11. Typical procedure for benzylation of imine **4**: The mixture of imine **4j** (60 mg, 0.25 mmol), benzyltrimethylsilane **2** (82 mg, 0.5 mmol), and THF (1.5 mL) was added dropwise to the solution of 4A MS (200 mg), TBAF (75 μL of 1 M solution in THF), and CH_3CN (1.5 mL) at −45 °C while stirring. After the reaction was completed (monitored by TLC), the reaction mixture was filtered on a short silica gel column. The solvent was removed and the residue was purified by chromatography to give **5j** in 66% yield with 86% de. The major isomer of ^1H NMR (300 MHz, $CDCl_3$): δ 1.13 (s, 0.63H, minor), 1.15 (s, 8.37H, major), 2.98 (m, 1H), 3.28 (m, 1H), 3.49 (br, 1H), 3.78 (s, 2.79H, major), 3.80 (s, 0.21H, minor), 4.54 (m, 1H), 6.82 (d, $J = 9.0$ Hz, 2H). 7.00 (m, 2H), 7.15–7.20 (m, 5H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 159.1, 137.6, 133.7, 129.6, 128.4, 128.2, 126.4, 60.2, 55.8, 55.2, 43.5, 22.5. IR (cm^{-1}): 3142 (m, NH), 1036 (s, S=O). MS *m*/*z* (EI): 332 (M+1). Anal. Cacld for $C_{19}H_{25}NO_2S$: C, 68.85; H, 7.60; N, 4.23. Found: C, 68.76; H, 7.52; N, 4.22.