

The first catalytic Sakurai reaction of *N*-alkoxycarbonylamino sulfones with allyltrimethylsilane

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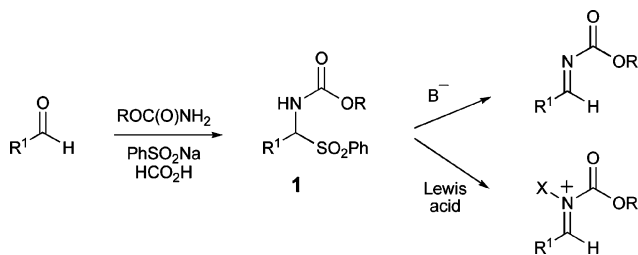
We report the first catalytic Sakurai reaction of *N*-alkoxycarbonylamino sulfones with allylsilanes. The allylation reaction of *N*-alkoxycarbonylamino phenylsulfones with allyltrimethylsilane proceeded smoothly with low catalyst loading of bismuth triflate (2.0 mol%) to afford the corresponding protected homoallylic amines in moderate to very good yields (up to 96%).

The development of new methods for the preparation of homoallylic amines is an important area of synthetic efforts. Homoallylic amines are extremely important as biologically active molecules.¹ Among the variety of synthetic methods so far reported, the Lewis acid-catalyzed reaction of imines with allylsilanes provides an efficient route for the synthesis of homoallylic amines. Catalytic allylation reactions have been reported by several groups as an efficient method to prepare homoallylic amines.² However, imines in general tend to be unstable during the purification process. Therefore, methods involving the *in situ* generation of imines are highly attractive, among which the one-pot allylation of imines, have been proposed.³ Yet, most Lewis acids cannot be used in this reaction because they deactivate or decompose in the presence of the amine and water produced during imine formation. Very reactive *N*-acyliminiums, easily prepared from stable precursors, provide an attractive alternative. Scheme 1 illustrates the preparation of the *N*-acylimine precursor from corresponding aldehydes.⁴ *N*-Alkoxycarbonyl imines have been prepared from basic treatment of the *N*-alkoxycarbonylamino sulfones **1**; and the corresponding *N*-alkoxycarbonyl iminium derivatives have been prepared by the use of a Lewis acid with

1 (Scheme 1).⁵ This approach has previously been used for highly enantioselective amine syntheses.⁶ We wish to report herein the first catalytic Sakurai reaction of *N*-alkoxycarbonylamino sulfones with allylsilanes. Alkoxycarbonyl protected homoallylic amines are obtained efficiently in the presence of 2–5 mol% of Bi(OTf)₃·4H₂O. To the best of our knowledge, a catalytic version of this reaction has never been reported. The only reported allylation reaction from *N*-alkoxycarbonylamino sulfones involves a Lewis acid like TiCl₄ or SnCl₄ used in a stoichiometric quantity or in large excess.^{5a,7}

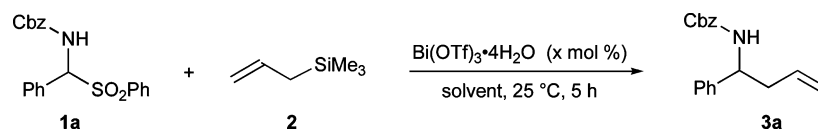
Recently, several laboratories have disclosed significant advances regarding rare-earth and lanthanide triflates as catalysts for allylation reactions.⁸ High catalytic activity, low toxicity, moisture and air tolerance make lanthanide triflates valuable catalysts. Bismuth compounds provide a good alternative as they have recently attracted attention due to their low toxicity, low cost, and good stability.⁹ Bismuth salts have been reported as catalysts for opening of epoxides,¹⁰ Mukaiyama-aldol reactions,¹¹ Mannich-type reactions,¹² formation of acetals,¹³ Friedel–Crafts reactions,¹⁴ and Fries and Claisen rearrangements.¹⁵ Bi(OTf)₃ is particularly attractive because it is commercially available or can be easily prepared from commercially available compounds.¹⁶ We recently reported the Bi(OTf)₃-catalyzed allylation reaction of a variety of aldimines generated *in situ* using aldehydes, amines, and allyltrimethylsilane in a three-component reaction.¹⁷ One drawback of this method could be eventual formation of homoallylic alcohol as a trace by-product. These results encouraged us to pursue an alternative approach using *N*-alkoxycarbonylamino phenylsulfones as stable imine precursors.

Initially, we screened various solvents for the Sakurai reaction of *N*-alkoxycarbonylamino sulfones with allyltrimethylsilane in the presence of Bi(OTf)₃·4H₂O. *N*-Benzyloxycarbonylamino phenylsulfone **1a** was chosen as model substrate for the following studies (Scheme 2). Interestingly, when **1a** was treated with 2 mol% Bi(OTf)₃·4H₂O in dichloromethane (1.3 equiv. allyltrimethylsilane, 25 °C, 5 h), the corresponding Cbz-protected homoallylic amine **3a** was isolated in moderate yield (73%) (Table 1, entry 1). An increase of the quantity of the allyltrimethylsilane used led to an increased yield, albeit with a lower catalyst loading (Table 1, entry 2). Only 2 mol% of the catalyst with 1.5 equivalents of allyltrimethylsilane **2** was necessary to obtain the homoallylic amine **3a** in excellent yield (Table 1, entry 3). Among various solvents tested, dichloromethane and acetonitrile furnished the expected product in the highest yield (Table 1, entries 3–7). Because of the poor solubility in acetonitrile of many *N*-alkoxycarbonylamino sulfones **1** presented here (Table 2), dichloromethane was selected as the solvent of choice.



Scheme 1 *N*-Alkoxycarbonylamino sulfones as precursors of *N*-alkoxycarbonyl imine derivatives.

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Scheme 2 $\text{Bi}(\text{OTf})_3$ -catalyzed Sakurai reactions involving *N*-benzyloxycarbonylamino phenylsulfone **1a** and allyltrimethylsilane.

Table 1 Allylation of *N*-benzyloxycarbonylamino phenylsulfone **1a** with allyltrimethylsilane using $\text{Bi}(\text{OTf})_3 \cdot 4\text{H}_2\text{O}$ as catalyst^a

Entry	x mol% $\text{Bi}(\text{OTf})_3$	Allylsilane 2 (equiv.)	Solvent	Yield 3a (%) ^b
1	2	1.3	CH_2Cl_2	73
2	1	1.5	CH_2Cl_2	80
3	2	1.5	CH_2Cl_2	96
4	2	1.5	Et_2O	0
5	2	1.5	THF	43
6	2	1.5	MeCN	94
7	2	1.5	PhMe	16

^a All new compounds were characterized by ^1H NMR, ^{13}C NMR spectroscopy and mass spectroscopy. ^b Isolated yields after purification by column chromatography.

Given that the same reaction does not occur in the presence of N^1, N^1, N^8, N^8 -tetramethylnaphthalene-1,8-diamine proton sponge® (1 equiv. of **1a**, 1.5 equiv. of allyltrimethylsilane **2**, 0.02 equiv. of $\text{Bi}(\text{OTf})_3 \cdot 4\text{H}_2\text{O}$, 0.06 equiv. of proton sponge®, 25 °C, 28 h, 99% recovery of **1a**) but still proceeds with K_2CO_3 used as a proton scavenger (1 equiv. of **1a**, 1.5 equiv. of allyltrimethylsilane **2**, 0.02 equiv. of $\text{Bi}(\text{OTf})_3 \cdot 4\text{H}_2\text{O}$, 0.06 equiv. K_2CO_3 , 25 °C, 19 h, 62% of **3a**) does not indicate unambiguously that triflic acid is involved in the mechanism. However, when HOTf is used as the catalyst, the reaction proceeds to afford the expected product **3a**, indicating that HOTf is also an effective catalyst for the transformation (1 equiv. of **1a**, 1.5 equiv. of allyltrimethylsilane **2**, 0.06 equiv. of HOTf, 25 °C, 4 h, 67% of **3a**). Also, Me_3SiOTf might be involved as a catalyst in our conditions since it appears to be an effective catalyst as well (1 equiv. of **1a**, 1.5 equiv. of allyltrimethylsilane **2**, 0.06 equiv. of Me_3SiOTf , 25 °C, 5 h, 82% of **3a**). Since the chemical yields of the 6% HOTf and Me_3SiOTf -catalyzed reactions are lower than when using 2% $\text{Bi}(\text{OTf})_3 \cdot 4\text{H}_2\text{O}$ (compare with Table 1, entry 3), a bismuth(III) salt is likely to be involved as a Lewis acid. More detailed investigations on the mechanism of this transformation are in progress.

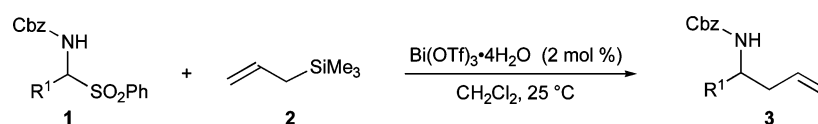
Several examples of $\text{Bi}(\text{OTf})_3 \cdot 4\text{H}_2\text{O}$ -catalyzed Sakurai reactions of various *N*-benzyloxycarbonylamino phenylsulfones **1** with allyltrimethylsilane are summarized in Table 2.† *N*-Benzyloxycarbonylamino sulfones **1** derived from differently substituted benzaldehydes were reacted with allyltrimethylsilane in dichloromethane at room temperature (Scheme 3). The corresponding homoallylic amines **3** were obtained in moderate to

good yields (Table 2, entries 1–9). Sulfones derived from several electron-rich aromatic aldehydes led to the desired products in good to very good yields (Table 2, entries 1–3), including starting with *o*-substituted benzaldehyde (Table 2, entries 1 and 3). The reaction was efficient using electron-deficient benzaldehyde-derived sulfones and the corresponding homoallylic amines **3** were obtained with moderate to good yields (Table 2, entries 4–9). Benzyloxycarbonylamino sulfone **1j** could be selectively prepared from *p*-acetyl benzaldehyde and subsequently allylated to give **3j** with an overall complete aldehyde vs. ketone selectivity (Table 2, entry 9). In addition, heteroaromatic aldehyde derived sulfone **1k** could also serve as a substrate in this reaction, albeit giving the corresponding homoallylic amine in a moderate yield (Table 2, entry 10). Aliphatic aldehydes led to a moderate to good yield of **3** (Table 2, entries 11–15). For selected substrates, higher yields were obtained when using a catalyst loading of 5 mol% instead of 2 mol% with 5 equiv. of allyltrimethylsilane in dichloromethane at reflux (Table 2, entries 3, 10, 13, and 14).

In summary, we have found that the Sakurai reaction of *N*-benzyloxycarbonylamino sulfones **1** proceeds smoothly with allyltrimethylsilane in the presence of a catalytic amount of $\text{Bi}(\text{OTf})_3 \cdot 4\text{H}_2\text{O}$. This method offers several advantages including mild reaction conditions, low catalyst loading (2–5 mol%), and no formation of by-products. To the best of our knowledge, this is the first report of a catalytic Sakurai reaction of *N*-alkoxycarbonylamino sulfones with allyltrimethylsilane. Moreover, our process involves an environmentally benign, cheap, and easy to handle catalyst. The homoallylic amine, already protected as a Cbz derivative, is smoothly obtained under mild conditions. Because of its numerous benefits, the $\text{Bi}(\text{OTf})_3 \cdot 4\text{H}_2\text{O}$ protocol should find utility in the synthesis of biologically active compounds. Research is under way to demonstrate other significant applications of this $\text{Bi}(\text{OTf})_3 \cdot 4\text{H}_2\text{O}$ -catalyzed Sakurai reaction.

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Scheme 3 $\text{Bi}(\text{OTf})_3$ -catalyzed Sakurai reactions involving various *N*-benzyloxycarbonylamino phenylsulfones **1** and allyltrimethylsilane **2**.

Table 2 Allylation of *N*-benzyloxycarbonylamino phenylsulfones **1** with 1.5 equiv. allyltrimethylsilane **2** using 2 mol% Bi(OTf)₃·4H₂O as catalyst

Entry	Reactant	Product ^a	Time/h	Product	Yield (%) ^b
1			23	3b	84
2			12	3c	86
3			22	3d	62 ^c
4			24	3e	74
5			26	3f	78
6			24	3g	73
7			24	3h	78
8			43	3i	58
9			27	3j	56
10			24	3k	45 ^c
11			24	3l	73
12			44	3m	61
13			22	3n	76 ^c
14			28	3o	74 ^c
15			26	3p	74

^a All new compounds were characterized by ¹H NMR, ¹³C NMR spectroscopy and mass spectroscopy. ^b Isolated yields after column chromatography.^c The reaction was run with 5 mol% Bi(OTf)₃·4H₂O and 5 equiv. allyltrimethylsilane **2** at reflux.

Notes and references

† **General procedure for the bismuth-catalyzed Sakurai reaction:** Under an inert atmosphere of argon, the allyltrimethylsilane **2** (0.75 mmol) was added dropwise to a solution of $\text{Bi}(\text{OTf})_3 \cdot 4\text{H}_2\text{O}$ (0.01 mmol) and *N*-alkoxycarbonylamino sulfone **1** (0.5 mmol) in dry CH_2Cl_2 (1.5 mL) at 25 °C. The mixture was stirred until the reaction was completed as indicated by TLC. The reaction was quenched with distilled H_2O and extracted with EtOAc. The combined organic phases were washed with H_2O , sat. aq. NaCl, dried over MgSO_4 , and concentrated under vacuum (rotary evaporator). The crude product was purified by column chromatography (eluent hexane–EtOAc 92 : 8 to 85 : 15, or toluene). Spectral data for **3a**, **c**, **18a**, **3i**, **17a**, **3j**, **18b**, **3k**, **3f**, **3l**, **18c**, **3m**, **18d**, **3n-o**, **3f** and **3p**^{18a} agree with those previously reported in the literature. **Benzyl 1-(4-fluorophenyl)but-3-enylcarbamate (3h):** Reagents: benzyl (4-fluorophenyl) (phenylsulfonyl) methyl carbamate **1h** (201 mg, 0.5 mmol), allyltrimethylsilane **2** (121 μL , 1.5 mmol), and $\text{Bi}(\text{OTf})_3 \cdot 4\text{H}_2\text{O}$ (7 mg, 0.01 mmol). The reaction was stirred for 24 h at 25 °C. The crude product was purified by silica gel chromatography to afford 117 mg (78%) of **3h** as a colorless crystal; mp 39–41 °C; R_f = 0.90 (hexane–EtOAc = 7 : 3); IR (neat): 3421, 3326, 1698, 1642 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 7.26–7.43 (m, 5 H), 7.14–7.26 (m, 2 H), 6.96–7.04 (m, 2 H), 5.57–5.71 (m, 1 H), 5.00–5.20 (m, 5 H), 4.77 (br s, 1 H), 2.40–2.57 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ = 162.1 (d, $J_{\text{C-F}}$ = 245.5 Hz), 155.8, 138.0, 136.5, 133.6, 128.7, 128.4, 128.0 (d, $J_{\text{C-F}}$ = 7.7 Hz), 118.9, 115.6 (d, $J_{\text{C-F}}$ = 21.5 Hz), 67.0, 54.1, 41.2; ^{19}F NMR (376 MHz, CDCl_3): δ = –115.83; HRMS: m/z calcd for $\text{C}_{18}\text{H}_{19}\text{FNO}_2$ [$\text{M} + \text{H}^+$]: 300.1400, found: 300.1403.

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