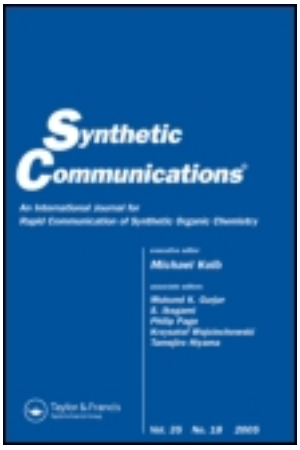

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Scandium Triflate as an Efficient and Recyclable Catalyst for the Deprotection of Tert-Butyl Aryl Sulfonamides

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Scandium Triflate as an Efficient and Recyclable Catalyst for the Deprotection of Tert-Butyl Aryl Sulfonamides

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Abstract: A mild and efficient method for deprotection of *tert*-butyl sulfonamide groups utilizing $Sc(OTf)_3$ as deprotecting reagent has been developed. A variety of *tert*-butyl aryl sulfonamides used under these conditions gave the corresponding primary sulfonamides in high yields. The Lewis acid catalyst could be fully recovered and reused with maintained activity after the reactions.

Keywords: Scandium triflate, sulfonamide, deprotection, catalyst

Acid labile protecting groups are important in organic synthesis.[1,2] Among them, the *tert*-butyl group is commonly used for protection of a large variety of functional groups, e.g., acids,[3] alcohols,[4] phenols,[5] and sulfonamides.[6] The sulfonamide and acylated sulfonamide groups are of great importance in medicinal chemistry as carboxylic acid bioisosteres[7,8] and are widely used in many bioactive compounds, e.g., AT_1 antagonists,[9] endothelin antagonists,[10] and factor Xa antagonists.[7] In the synthetic routes to these drugs the *tert*-butyl group is frequently used as protection of the sulfonamide.[6,9,11–15] The unmasking of the sulfonamide from the *tert*-butyl protection is generally executed with strong protic acids,

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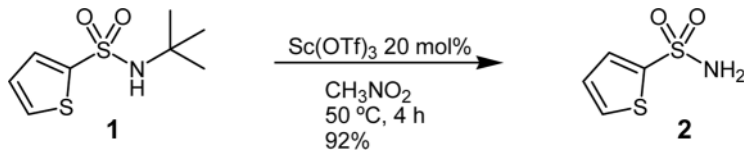
e.g., HCl,[6,16] H_2SO_4,[17] or more commonly TFA.[1,2,9,11–15] In addition, long reaction times are often required for full conversion, i.e., from 6 h to 18 h. These harsh conditions, when applied in a medicinal chemistry program of complex target molecules, could sometimes be limiting to the diversity of the structures.

Environmental concerns call for reaction processes that avoid hazardous as well as harmful reagents and solvents.[18] The importance of catalysis for organic transformations has been increased, since catalysts are generally used in small quantities and often recovered and reused.[19] Lewis acid catalyzed reactions are of great interest in synthetic organic chemistry, and unique reactivities, selectivities, and mild reaction conditions can be achieved.[20] Recently our group reported BCl_3 as a mild and selective Lewis acid alternative to the protic acids as a deprotection reagent for *tert*-butyl solfonamides.[21] Unfortunately, BCl_3, like most Lewis acids, decompose or are deactivated in the presence of water and therefore require a dry environment or an excess of the reagent to ensure full deprotection. Scandium triflate is considered a new type of Lewis acid that differs from typical Lewis acids such as $AlCl_3$, BF_3, and $TiCl_4$.[22,23] Thus, unlike most Lewis acids scandium triflate can act as a Lewis acid in water solutions and does not undergo decomposition or deactivation. The water stability and solubility makes the scandium triflate an ideal reagent for recycling that can be recovered without loss of activity.[24]

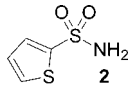
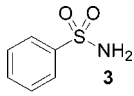
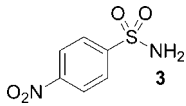
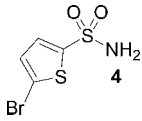
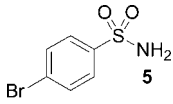
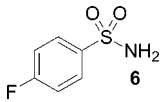
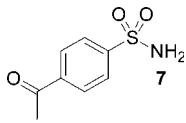
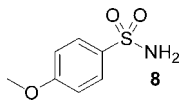
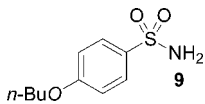
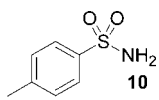
We therefore felt prompted to explore the use of scandium triflate as a recyclable and mild reagent for the deprotection of *tert*-butyl sulfonamides. As a model substrate *N-tert*-butylthiophene-2-sulfonamide **1**, encompassing a nucleophilic aromatic ring system, was used (Scheme 1). The sulfonamide **1** is traditionally deprotected with pure TFA at ambient temperature over night.[1,2,9,11–15] This condition was used as a starting point for our investigation. With the addition of 20 mol% of scandium triflate, the reaction was completed in 1 h at RT and gave a 90% yield (entry 1, Table 1). Different solvents were thereafter evaluated as replacement for the strong acid, TFA.

Acetonitrile, dichloromethane, dioxane, ethyl acetate, and nitro methane were all used with 20 mol% of scandium triflate at ambient temperature. Notably, the highly polar nitro methane[28] was the only solvent that gave full conversion of the substrate after 24 h (79% yield, entry 2, Table 1). The



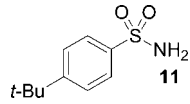
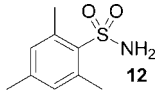
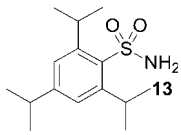
Scheme 1.

Table 1. Deprotection of *N-tert*-butyl aryl sulfonamides and amides with Scandium triflate

Entry	Product	Temp (°C)	Time (h)	Isolated yield (%)	Mp (°C)	Lit. Mp (°C)
1[a]	 **2**	rt	1	90		
2		rt	24	79	146–147	147[5]
3		50	4	92,89,95,90[b]		
4	 **3**	50	5	84	155–157	155–158[25]
5	 **3**	50	3	89	179–181	178–180[26]
6	 **4**	50	6	85	141–142	144[14]
7	 **5**	50	4	95	165–166	169–170[7]
8	 **6**	50	4	92	124–125	123[15]
9	 **7**	50	3	95	176–178	178–179[20]
10	 **8**	50	5	87	110–112	116[27]
11	 **9**	50	4	84	110–111	103–105[25]
12	 **10**	50	3	92	143–144	142–143[25]

(*continued*)

Table 1. Continued

Entry	Product	Temp (°C)	Time (h)	Isolated yield (%)	Mp (°C)	Lit. Mp (°C)
13	 **11**	50	5	96	136–138	1138–138.5[8]
14	 **12**	50	7	94	144–146	141–142[19]
15	 **13**	50	5	96	108–110	119–119.6[21]

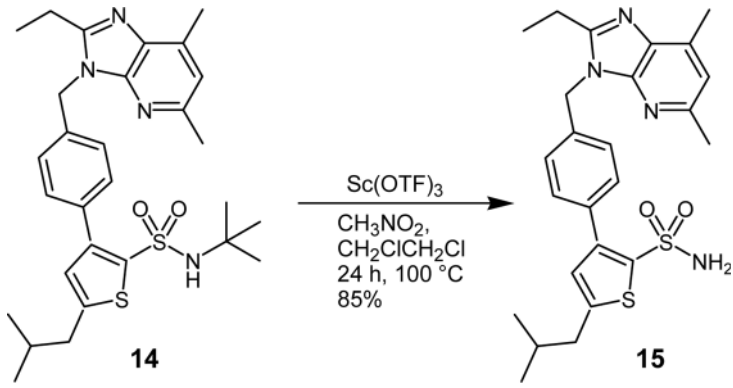
[a]TFA as solvent.
[b]Yield of consecutive reactions with recycled scandium triflate.

long reaction time could be decreased if the reaction mixture was heated slightly. At 50°C the reaction was completed in 4 h and the sulfonamide **2** was isolated in 92% yield (entry 3, Table 1).

Due to the unique water stability of the scandium triflate, the catalyst could be recovered after the reaction with a conventional water extraction followed by concentration and drying under vacuum. The recycled Lewis acid was then reused in a consecutive reaction. Consistent with previous findings,[29] the recycled catalyst retained its activity and gave **2** in 89% yield (95% the third and 90% the fourth time of recycling, entry 3, Table 1).

To examine the scope and limitation of the Lewis acid deprotection procedures a series of electron-rich and electron-deficient *tert*-butyl aryl sulfonamides were selected for evaluation. The preparative results are shown in Table 1. All of the *N-tert*-butyl aryl sulfonamides provided good to excellent yields with reaction times ranging from 3 to 7h. The reaction with *N-tert*-butyl-4-acetylbenzenesulfonamide, which in our previous method relying on BCl_3 was somewhat sluggish, was now very efficient and resulted in a good yield of the sulfonamide **8** (entry 9, Table 1). The two sterically hindered tri-substituted compounds **12** and **13** were straightforwardly obtained, although the tri-methylated compound needed a slightly longer reaction time to obtain full conversion (entries 14 and 15, Table 1).

To verify the deprotection method on a more complex drug-like molecule, a key intermediate in the synthesis of the ANG II agonist L-162,313[30] was used as a test molecule (Scheme 2).



Scheme 2.

Unfortunately, the *tert*-butyl protected compound **14** was not soluble in nitro methane, proven to be the most suitable solvent for the $Sc(OTf)_3$ method, therefore a 1 : 1 mixture of nitro methane:dichloroethane was used. Hence, an elevated temperature (100°C) and a longer reaction time (24 h) were required for full conversion of the starting material. Despite the increased reaction time and temperature, the reaction proceeded smoothly and the desired target compound **15** was isolated in a high yield (85%).

In summary, a mild and high-yielding method for removal of *tert*-butyl protecting group from aryl sulfonamides utilizing $Sc(OTf)_3$ has been developed. The reaction is not sensitive to moisture and provides an environmentally friendly procedure for recycling of the catalyst with preserved activity through several cycles.

EXPERIMENTAL

General

All of the *tert*-butyl protected sulfonamides were commercially available except for the starting material to the products **7** and **9** that were synthesized according to literature procedure.[13] All reagents were weighed in air and the reactions were conducted under an atmosphere of air. Analytical TLC was performed using Merck glass-backed 0.2 mm silica gel 60 F-254 plates. Visualization was done with UV light and staining with anisaldehyde solution [anisaldehyde (5.0 mL), AcOH (3.5 mL) and H_2SO_4 (6.0 mL) in EtOH (200 mL)] followed by heating. Flash column chromatography was performed on silica gel 60 (0.04–0.63 mm, E. Merck). Infrared spectra were recorded on a Perkin-Elmer Model 1605 FT-IR. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX 270 spectrometer at 270.2 and 67.8 MHz respectively.

Low-resolution mass spectra were recorded on a Varian GC-MS instrument equipped with a CP-Sil 8 CB capillary column (30 m × 0.25 mm, 0.25 μm) operating at ionization energy of 70 eV. The oven temperature was 40–300°C. Melting points were recorded on an electrothermal melting point apparatus. All the products are known from literature and gave consistent analytical data.[25–27,31–43]

General Procedure for the Deprotection of Sulfonamides with $Sc(OTf)_3$

$Sc(OTf)_3$ (0.048 g, 20 mol %) was added to a solution of *N-tert*-butyl aryl sulfonamide (1.0 mmol) in CH_3NO_2 (1.0 mL) and stirred at 50°C. After completion of the reaction, solvent was evaporated and the residue was dissolved in ethyl acetate and washed with deionized water. The organic layer was dried over $MgSO_4$, concentrated, and purified by silica-gel flash chromatography using pet.ether: acetone (3–1) to afford the desired products.[25–27,31–43]

Recovery of the $Sc(OTf)_3$

The aqueous layer was evaporated and the scandium triflate was dried under vacuum (7 mbar, 50°C, 2 h) before reuse.

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