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Di-*tert*-butylisobutylsilyl, Another Useful Protecting Group

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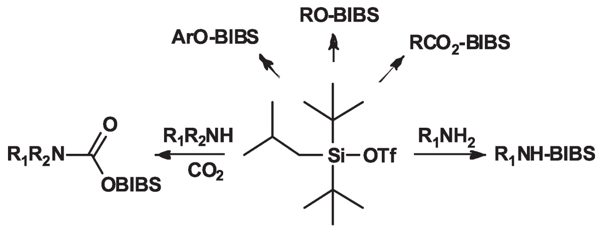
ABSTRACT



Di-*tert*-butylisobutylsilyl Triflate (BIBSOTf)
many examples

The di-*tert*-butylisobutylsilyl (BIBS) protecting group offers new possibilities for synthetic processes because of its steric bulk, robustness of its derivatives, and other special properties.

The protection of oxygen-containing functionality by various tertiary silyl groups has contributed greatly to the progress of synthetic chemistry over the past four decades, thanks to the availability of a whole series of silyl halides and triflates and a range of mild conditions for deprotection.[1] Although the prototypical trimethylsilyl group[2] is too labile for widespread use, a series of other silyl groups consisting of triethyl- (TES), isopropyldimethyl- (DMIS),[3] *tert*-butyldimethyl- (TBS),[4] triisopropyl- (TIPS),[5] *tert*-butyldiphenyl- (TBDPS) silyl[6] offers a range of robustness (gradually increasing).[7] The very bulky tri-*tert*-butylsilyl does not appear to be of comparable utility because it is difficult to prepare in quantity, very difficult to attach, even to a hydroxyl group, and resistant to cleavage.[8] In this paper, we discuss a silyl protecting group which is intermediate between tri-*tert*-butyl and the more useful TBS, TIPS, and TBDPS groups, specifically the di-*tert*-butylisobutylsilyl group (BIBS).

BIBS triflate (BIBSOTf, **3**) was readily prepared from inexpensive isobutyltrichlorosilane (**1**)[9] on a 20 g scale (Scheme 1). Isobutyltrichlorosilane (**2**) was treated with 2 equiv of *tert*-BuLi in heptane at 23 °C. Another equivalent of *tert*-BuLi in heptane was added, and the mixture was heated at reflux to form the BIBSH (**2**) by hydride transfer. This silane was then converted to BIBSOTf (**3**)[10] by reaction with 1 equiv of triflic acid at 23 °C (70% overall yield for two steps).

The BIBS group can be especially useful for protecting acidic hydroxyl groups, for example, phenols, because

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(9) Isobutyltrichlorosilane: $35/100 g from Gelest, Inc.

(10) BIBSOTf is a colorless nonfuming liquid, MW 348.14, density 1.25 g/mL at 23 °C, bp 91−93 °C/2 mmHg.

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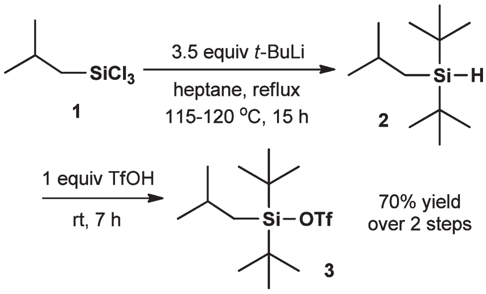
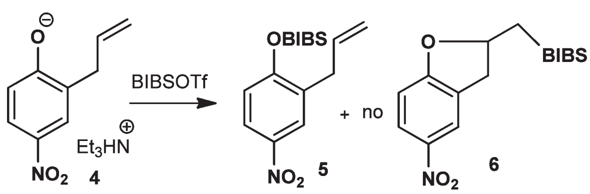
Scheme 1. Preparation of BIBSH and BIBSOTf



Di-*tert*-butylisobutylsilyl Triflate (BIBSOTf)

such BIBS ethers are much more stable than the TBS, TIPS, or TBDPS counterparts. We found that phenol BIBS ethers can be obtained in high yields, but that the rates of formation vary considerably depending on the acidity of the phenol. For example, 4-nitrophenol can be converted in 97% yield to the BIBS ether in CH_2Cl_2/Et_3N at 23 °C in 1 h, but the corresponding reaction with phenol itself is very slow and requires the use of the potassium salt in THF at reflux for > 12 h. The order of silylation reaction rates for a series of phenols with BIBSOTf was found to be 4-NO_2-C_6H_4 > 4-CO_2Me-C_6H_4 > 4-Br or 4-I-C_6H_4 > C_6H_5. The much faster reaction rate with 4-nitrophenoxide may be due to the availability of a reaction pathway via solvent-separated ions rather than contact ion pairs. We were not able to find evidence of a special electron transfer pathway using 2-allyl-4-nitrophenol as probe (Scheme 2). The only reaction product in the silylation reaction with BIBSOTf was the normal silyl ether **5**, and none of the phenoxy radical trapping product **6** was detected.

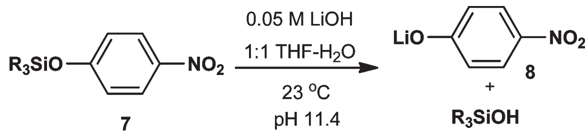
Scheme 2. Probe for a Phenoxy Radical Pathway



The BIBS ethers of phenols are readily cleaved to the free phenols by treatment with *n*-Bu_4NF in THF. They are promising as synthetic intermediates because they are stable to silica gel column chromatography or to rapid washing with cold water at pH 3–9. They can also be cleaved in aqueous hydroxide solutions, but they are considerably more stable than other silyl ethers. We have measured the rates of hydrolysis of a series of 4-nitrophenol silyl ethers **7** in aqueous THF with the results that are summarized in Table 1.

The much greater stability of the BIBS ether **7** relative to the TBS or TIPS ethers provides guidance for applications in multistep synthesis. Protection of a phenolic oxygen by

Table 1. Rates of Hydrolysis of a Series of 4-Nitrophenyl Silyl Ethers

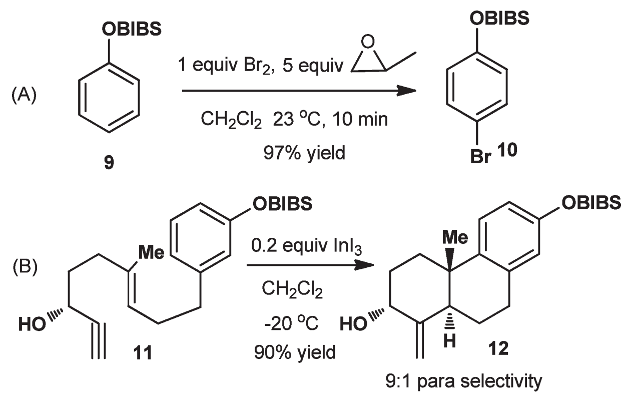


R_3Si	$t_{1/2}$ (min)[a]	relative rate[b]
t-Bu_2-*i*-Bu	1096	1.0
t-Bu_2-*n*-Bu	189	5.26
t-Bu_2-Me	28.7	34.6
i-Pr_3	0.75	1316
t-Bu-Me_2	0.09	10526

[a] Rates measured spectrophotometrically using 4-nitrophenolate (**8**) absorption at 403 nm. [b] E_a for hydrolysis of the BIBS ether was measured as 18.4 kcal/mol by rate studies over a range of temperatures.

the BIBS group also provides steric bulk which can assist in the direction of aromatic substitution, as shown by the examples in Scheme 3. The efficient position-selective indium-promoted cationic polycyclization of a phenolic BIBS ether **11** was recently reported from this laboratory.[11]

Scheme 3. Examples of Phenolic BIBS Ethers



The BIBS ether of 2-bromophenol (**13**) was obtained in crystalline form and subjected to single crystal X-ray diffraction analysis, which yielded the structure shown in Figure 1. In this structure, a gearing effect of several methyl groups in the BIBS subunit is evident as well as strong steric shielding not only around the silicon atom but also of the attached oxygen.

Carboxylic acids are readily transformed into the corresponding BIBS esters simply and cleanly by stirring with 1.5 equiv of Et_3N and 1 equiv of BIBSOTf at room temperature in CH_2Cl_2 solution for ca. 5 h. BIBS esters are unusually stable for silyl esters and can be chromatographed on silica gel. In ethereal solution, they are unchanged by washing with water at pH 3–9. Cleavage of the BIBS esters to the corresponding carboxylic acids can be

(11) Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 9724.

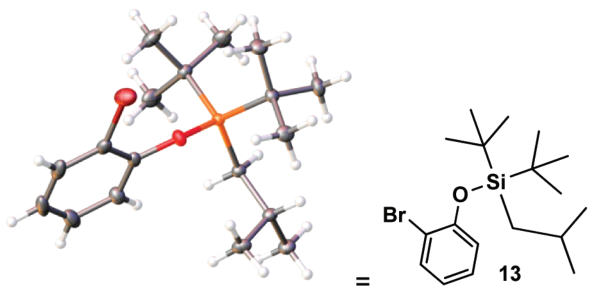
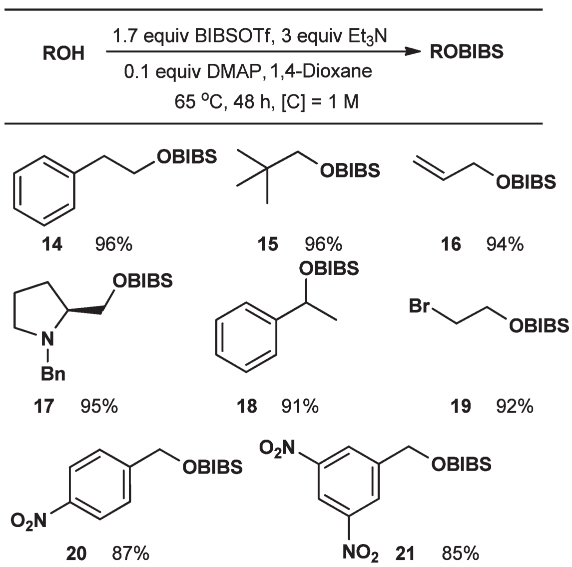


Figure 1. X-ray structure of (2-bromophenoxy) di-*tert*-butylisobutylsilane.

effected by 1 M LiOH in 1:1 THF/H_2O at room temperature or *n*-Bu_4NF in THF.

The silylation of primary and secondary hydroxyl groups by BIBSOTf (1.7 equiv) and Et_3N (3 equiv) can be accomplished generally but requires heating to 65 °C in 1,4-dioxane for ca. 48 h using an initial concentration of the alcohol of 1 M. Some representative examples of such protection reactions are shown in Scheme 4. Deprotection occurs upon treatment with *n*-Bu_4NF in THF.

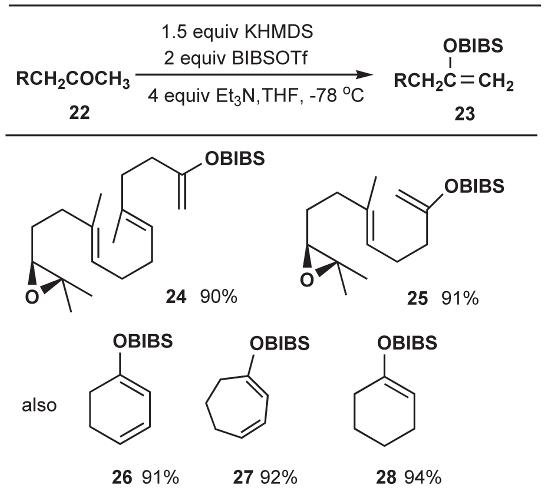
Scheme 4. BIBS Ethers of Alcohols



We also report that BIBSOTf is useful for the conversion of a variety of methyl ketones to 1-alkenyl-2-BIBS ethers (i.e., terminal enol ethers; see **22** → **23**) with excellent selectivity. The optimum conditions for effecting this reaction involve the successive addition of 1.5 equiv of potassium hexamethyldisilazane to 1 equiv of ketone in THF solution at −78 °C, followed by 2 equiv of BIBSOTf and 4 equiv of Et_3N. The vinyl silyl ethers shown in Scheme 5 were prepared selectively in this way. This method also allowed the selective synthesis of a group of cyclic vinyl enol BIBS ethers.

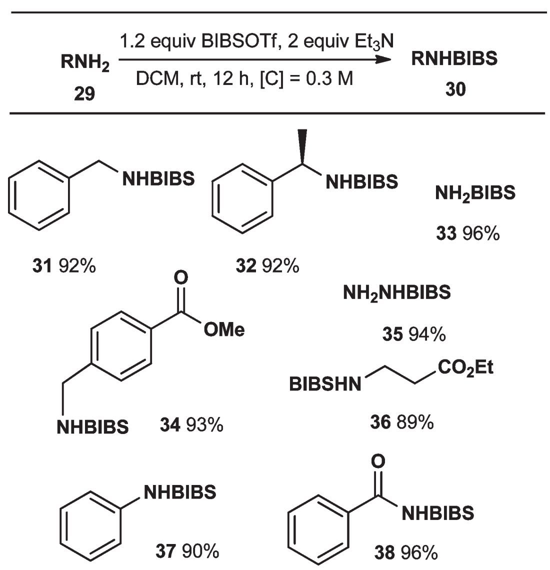
Primary amino groups **29** can be protected as *N*-mono-BIBS derivatives **30** by treatment with BIBSOTf and Et_3N

Scheme 5. Preparation of BIBS Enol Ethers



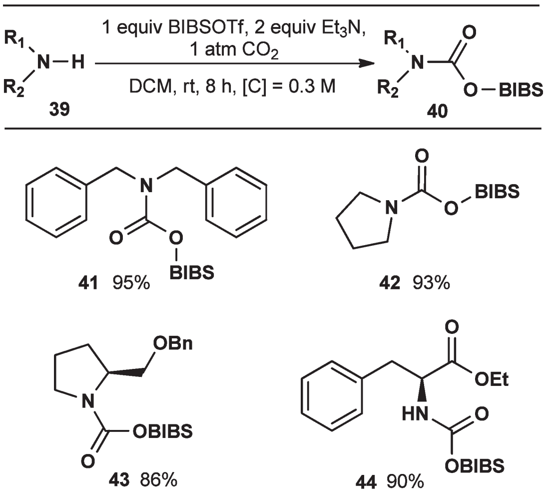
in CH_2Cl_2 at room temperature.[12] A number of examples are provided in Scheme 6. In contrast, secondary amines do not react under these conditions. These primary amines can be protected in the presence of secondary amines using the BIBSOTf-Et_3N reagent—a potentially useful device in synthesis. Deprotection of BIBS primary amine derivatives occurs upon treatment with HF/pyridine reagent in THF at 23 °C for 30 min.

Scheme 6. BIBS as a Protecting Group for Primary Amines

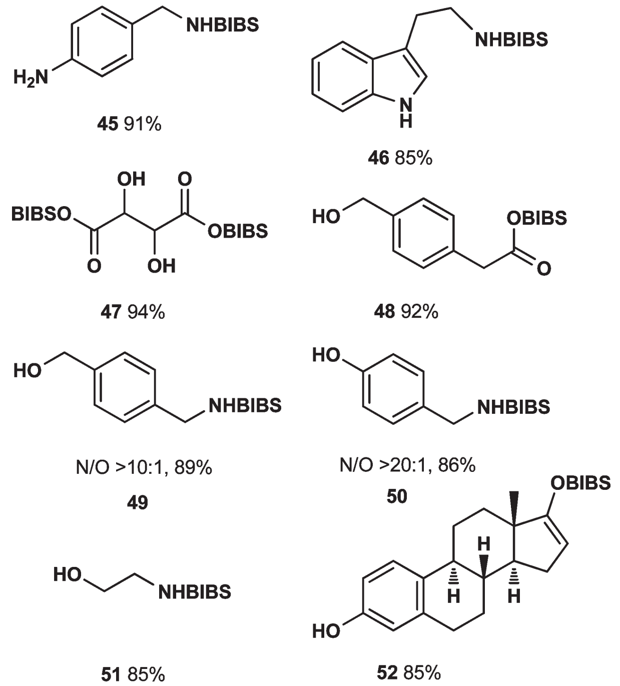


Secondary amines can be protected as BIBS carbamates by the reagent combination BIBSOTf, Et_3N, and CO_2 (1 atm) at room temperature, as indicated in Scheme 7.[13] The deprotection of BIBS carbamates of general formula $R_1R_2NCO_2BIBS$ occurs in high yield by reaction with *n*-Bu_4NF in THF at 23 °C for 1 h.

Scheme 7. Protection of Secondary Amines by BIBSOTf/CO_2



Scheme 8. Chemoselectivity



We also report on a number of other interesting cases of selectivity that have been achieved with the BIBSOTf-Et_3N reagent at 23 °C in CH_2Cl_2. The structures of the monosilylated BIBS derivatives that have been prepared selectively are shown in Scheme 8. In this collection are instances of clean discrimination between two nitrogen functions, two oxygen functions and an amino and a hydroxyl group. In the case of example **48**, only low selectivity was found when TIPSOTf was used instead of BIBSOTf.

In conclusion, the new reagent BIBSOTf provides many possibilities for the protection of functional groups in chemical synthesis. It offers significant opportunities for the more robust protection of various groups and for enhanced selectivity.

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Supporting Information Available. Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Lipshutz, B. H.; Papa, P.; Keith, J. M. *J. Org. Chem.* **1999**, *64*, 3792.