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tert-Butyldimethylsilyloxytrichloromethylmethane—readily accessible and robust protecting group for (hetero)aryl aldehydes

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Abstract

The *tert*-butyldimethylsilyloxytrichloromethylmethane (TBSTCM) substituent serves as a readily accessible masking group for aromatic and heteroaromatic aldehydes. The TBSTCM substituent is compatible with a range of common reagents and offers several strategic advantages over alternative aldehyde protecting groups.

During our recent investigations into new synthetic applications involving trichloromethylcarbinols,[1] we found that detrichloromethylation of aryl and alkenyl trichloromethyl carbinols could occur under specific reaction conditions, thereby revealing the corresponding aldehyde (Fig. 1, from **3** to**1**).[2] With this in mind, we reasoned that if the chemically vulnerable carbinol hydroxyl group could be shielded as a silyl ether, the resultant silyloxytrichloromethylmethane might serve as a stable masked aldehyde with strategic applications in multistep synthesis. Such a role would require that the silyloxytrichloromethylmethane be readily installed and efficiently converted back to the original aldehyde.

Kister and Mioskowski recently reported a method for the single-step preparation of trimethylsilyl-protected trichloromethylcarbinols using trichloromethyl-trimethylsilane under mild conditions.[3] Although this method offers excellent yields of the TMS-protected trichlorocarbinols, the susceptibility of the TMS ether to common reagents makes these products undesirable as potential masked aldehydes in most common reactions. We reasoned that the TBS analog would offer superior durability along with a comparable propensity for an unprecedented one-pot desilylation–detrichloromethylation to regenerate the aldehyde in the presence of a fluoride source (Fig. 1).

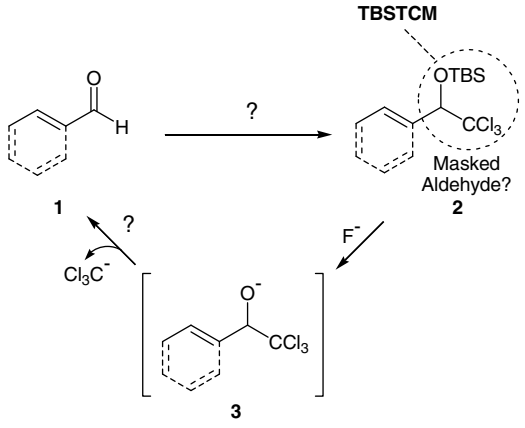

Fig. 1. Considerations in the installation and removal of the *tert*-butyldimethylsilyloxytrichloromethylmethane (TBSTCM) group.

All classes of aldehydes are efficiently converted to *tert*-butyldimethylsilyloxytrichloromethylmethane (TBSTCM) analogs using a modification of the Corey–Link aldehyde trichloromethylation procedure.[4] Addition of sodium trichloroacetate, TBSCl, and imidazole to the aldehyde in DMF affords the desired compounds in excellent yields (Fig. 2). This approach serves as an alternative to the Mioskowski procedure, but offers the advantage of

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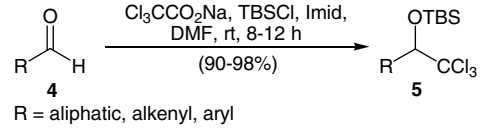

Fig. 2. One-step conversion of aldehydes to TBSTCM derivatives.

commercially available reagents. It is notable that aldol reactions of enolizable substrates do not occur under these conditions.

We screened numerous solvents and reaction temperatures in the presence of TBAF in THF, HF–pyridine, or triethylamine trihydrofluoride to evaluate the capacity of aryl, alkenyl, and aliphatic TBSTCM groups to undergo deprotection to the corresponding aldehydes. As expected, aliphatic TBSTCM groups were readily desilylated, however the ensuant saturated trichloromethylalkoxides were stable to all attempted detrichloromethylation conditions. Trichloromethylallylic alkoxides, furnished by the desilylation of the alkenyl substrates, also proved resistant to trichloromethide elimination. These compounds undergo significant but incomplete detrichloromethylation only in *tert*-butanol at elevated temperature over several days. However, aryl TBSTCM groups were rapidly and cleanly converted to the corresponding aldehydes by simply treating the substrates with 1.1 equiv of TBAF (1 M in THF) in DMF at 50 °C for 9–12 h (Fig. 3). The enhanced propensity of aryl TBSTCM substituents to undergo detrichloromethylation is presumably due to their greater thermodynamic driving force for extending conjugation relative to alkenyl substrates.

Protection and deprotection of both activated and deactivated benzaldehydes (Table 1, entries 1–4), naphthaldehyde (entry 5), and heteroaromatic aldehydes (entries 6–8) proceed smoothly.[5,6] The resultant products are subjected to a simple aqueous workup, then readily purified by passing through a short plug of silica.

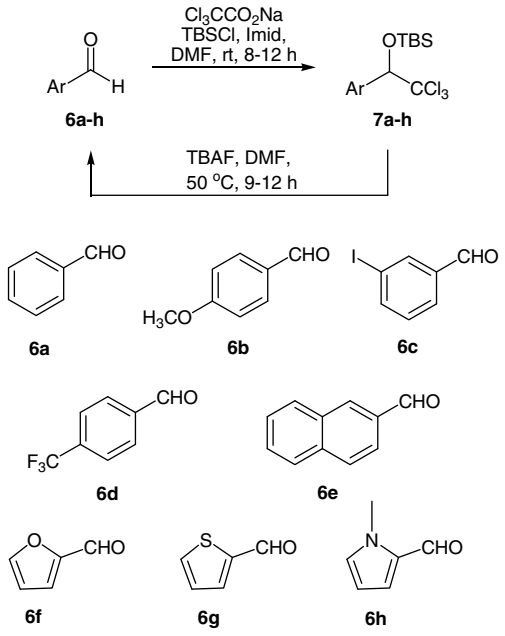

Fig. 3. Established conditions for the protection and deprotection of aryl aldehydes **6a**–**h**.

Table 1
Yields for the protection of aldehydes **6a**–**h** and deprotection of aryl TBSTCM derivatives **7a**–**h**

Entry	Aldehyde	Protection yield[a] (%)	Deprotection yield[a] (%)
1	**6a**	96	92
2	**6b**	97	94
3	**6c**	97	92
4	**6d**	96	92
5	**6e**	95	93
6	**6f**	90	90
7	**6g**	90	91
8	**6h**	94	95

[a] Isolated yield of chromatographically purified product.

Having established optimal conditions for the protection and deprotection of aryl aldehydes, we investigated the compatibility of the TBSTCM substituent in **7a** toward a variety of common reaction conditions (Table 2). The TBSTCM group possesses excellent thermal stability (entry 1) and is compatible with common reductants (entries 4–6) and oxidants (entries 7 and 8). We were pleased to find that the TBSTCM functionality shows resistance to both Brönsted acidic and basic conditions (entries 2 and 3) despite the presence of the silyloxy group. The reduced Lewis basicity of the TBSTCM oxygen atom, resulting from the proximal trichloromethyl group, may contribute to the hydrolytic stability and diminished propensity for trans-silylation. The protecting group is also suitable in reactions involving LDA, Grignard reagents, and organocuprates (entries 9–11). The only investigated conditions incompatible with the TBSTCM substituent were those involving fluoride, which generates the corresponding trichloromethyl carbinol, and alkyl lithium reagents[7] or Lewis acids that result in decomposition (entries 12 and 13).

Table 2
Reagent compatibility of **7a**

Entry	Reagent	Equiv	Conditions	Recovery[a] (%)
1	NA	NA	DMF, reflux, 12 h	98
2	1 N HCl	4	MeOH, rt, 24 h	99
3	2 N NaOH	4	THF, rt, 24 h	97
4	$LiAlH_4$	2.0	THF, rt, 12 h	96
5	DIBAL	1.2	$PhCH_3$, −78 °C	97
6	BH_3·DMS	1.5	Et_2O, rt, 24 h	96
7	PCC	2.5	DCM, rt, 12 h	88[b]
8	DMP	1.3	DMF, rt, 6 h	98
9	LDA	1.1	THF, −78 °C, 2 h	98
10	MeMgBr (3 M in Et_2O)	1.2	THF, rt, 12 h	96
11	$Bu_2Cu(CN)Li_2$·LiCl	1.5	THF, −40 °C to rt, 4 h	97
12	*n*-BuLi	1.2	THF, −78 °C, 1 h	Decomp.
13	$AlCl_3$	1.5	DCM, rt, 12 h	Decomp.

[a] Isolated recovery of chromatographically purified **7a**.
[b] No conversion to other materials or decomposition was detected.

Given the stability of TBSTCM substituent to a variety of reaction conditions and the means by which the group is removed to reveal the corresponding aldehyde, we considered several strategic advantages offered by its employment. Protected compounds **10** and **11** were prepared from **8**[8] as shown in Figure 4. It is notable that the selection of the TBSTCM group allows for the protection of both the aldehyde and the resident hydroxyl or phenol groups in an efficient single operation (e.g., conversion of **8** to **9**). Product **11** features a TBS-protected primary alcohol, phenol, and a TBSTCM masked aldehyde. Treatment of **11** with 3.5 equiv of TBAF in DMF at 50 °C affords globally deprotected **12** in excellent yield (Fig. 4A). An analogous deprotection process could prove particularly advantageous in the late stages of complex molecule syntheses.

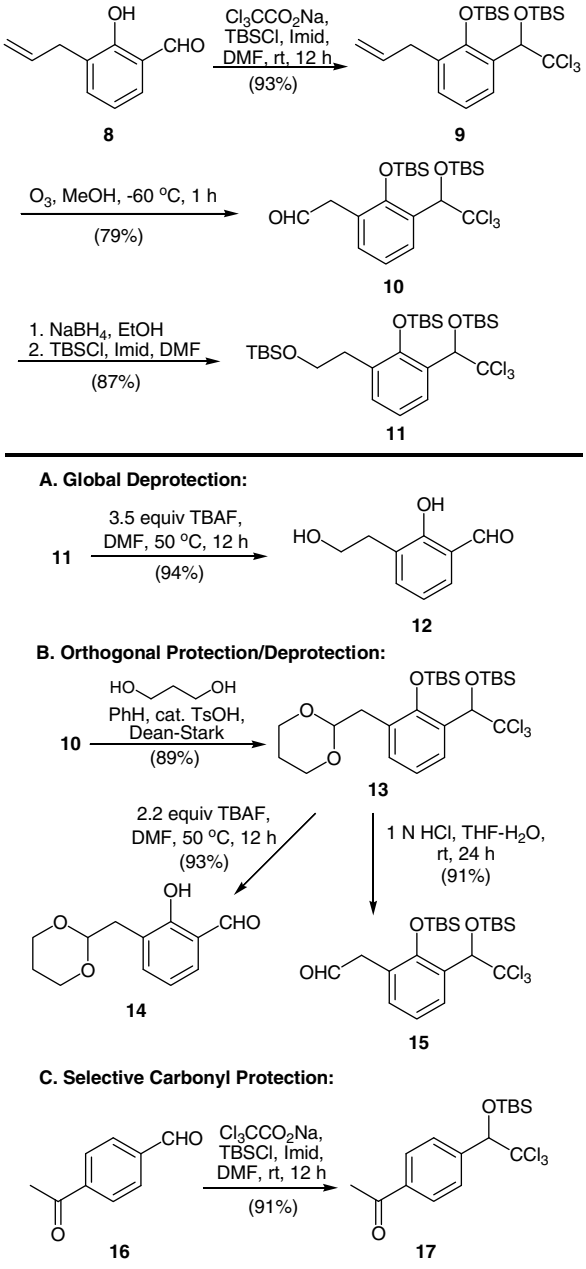

Fig. 4. Preparation of TBS-protected masked aryl aldehydes **10** and **11** and strategic applications/advantages of the TBSTCM group.

Aldehyde **10** is smoothly converted to 1,3-dioxane **13** under standard conditions (Fig. 4B). The resulting acetal may be selectively removed by treatment with 1 N HCl in THF–H_2O over 24 h. The TBSTCM group shows no degradation under these conditions, thereby exemplifying its hydrolytic stability. Alternatively, the TBSTCM substituent may be converted to aryl aldehyde **14** using TBAF in DMF without affecting the acetal. These results highlight the orthogonality of the TBSTCM and acetal carbonyl protecting groups. Another advantage of the outlined method is the high selectivity of the weakly nucleophilic trichloromethide, generated from the decarboxylation of sodium trichloroacetate in DMF, for aldehydes relative to unhindered ketones (**16**, Fig. 4C). Hence, the aryl TBSTCM group may be installed without competition from resident non-aldehyde carbonyl functionalities.

Although we have featured the aryl TBSTCM substituent as a masked aldehyde, it is important to note that silyl-protected trichloromethyl carbinols are used directly in several synthetic transformations. The increased stability of the TBS-protected trichloromethyl carbinols reported herein, relative to the typical TMS analogs, allows the former to be prepared, carried through numerous synthetic steps, then converted directly to, for example, (*Z*)-2-chloroenol ethers,[7,9] (*Z*)-1-chloroalk-1-enes, 2-chloroketones, vinyl dichlorides, terminal alkynes,[10] or 2-aryl-2-fluoro-1,1,1-trichloroethanes.[11] As such, the TBSTCM group may serve as a valuable synthetic handle or stable latent functionality independent of its application as a capable protecting group for aromatic and heteroaromatic aldehydes.

The facile installation and removal, coupled with broad reagent compatibility, make the *tert*-butyldimethylsilyloxytrichloromethylmethane group an attractive option for aryl aldehyde protection. Its possible employment in global silylation–desilylation protocols, applications requiring orthogonal carbonyl protecting groups, or the selective monoprotection of ketoaldehydes offers strategic synthetic options unavailable to many alternatives. Such masked aldehydes may also prove useful in direct transformations to unrelated functional groups.

Acknowledgment

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Supplementary data

Preparative experimental procedures, characterization data, and ^{1}H and ^{13}C spectra of compounds **7a**–**h**, **9**–**15** and **17** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.02.072.

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5. *General procedure for the preparation of monoprotected aryl aldehydes* (**7a**–**h**). To a solution of aldehyde (1 mmol) in 3.3 mL of anhydrous DMF was added sodium trichloroacetate (2 mmol) with stirring at room temperature. Initially, rapid evolution of CO_2 was observed. After 40 min, imidazole (1.5 mmol) and TBSCl (1.4 mmol) were added. After 8 h, the reaction mixture was monitored by TLC. [If starting material remained, additional sodium trichloroacetate (1 mmol) was added and the suspension was mixed rapidly for an additional 4–6 h.] The mixture was diluted with 5 mL of diethyl ether and washed with a saturated aqueous solution of ammonium chloride. Any precipitate was filtered and washed with diethyl ether (3×10 mL). The filtrate was washed two more times with ammonium chloride solution and once with brine. The organic phase was dried with anhydrous sodium sulfate and evaporated under reduced pressure. The resulting residue was eluted through a plug of silica gel with hexane/ethyl acetate to afford the corresponding monoprotected aryl aldehyde.
6. *General procedure for the deprotection of monoprotected aryl aldehydes* (**6a**–**h**). To a solution of monoprotected aryl aldehyde (1 mmol) in 2 mL of DMF with stirring at room temperature was added a 1 M solution of TBAF in THF (1.1 mmol). After heating for 9–12 h at 50 °C, the reaction mixture was cooled to room temperature and eluted through a plug of silica gel with hexane/ethyl acetate to afford the corresponding aryl aldehyde.
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