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An Acid-Stable *tert*-Butyldiarylsilyl (TBDAS) Linker for Solid-Phase Organic Synthesis

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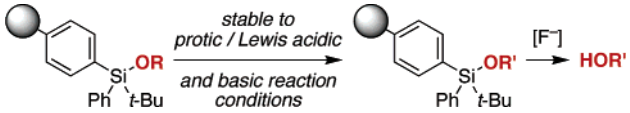
ABSTRACT



A new, robust *tert*-butyldiarylsilyl (TBDAS) linker has been developed for solid-phase organic synthesis. This linker is stable to both protic and Lewis acidic reaction conditions, overcoming a significant limitation of previously reported silyl linkers. Solid-phase acetal deprotection, olefination, asymmetric allylation, and silyl protecting group deblocking reactions have been demonstrated with TBDAS-linked substrates.

An important ongoing challenge in solid-phase organic synthesis is the development of new linkers for attaching substrates to solid supports.[1] Ideally, a linker should withstand a wide variety of reaction conditions used to process the attached substrates, yet also be cleaved under specific, mild, chemoselective conditions that do not degrade the products. A variety of silyl ether linkers have been developed for this purpose on the basis of the pioneering work of Frechet[2] and the extensive use of silyl protecting groups in solution-phase synthesis. Linkers having an "all-carbon" attachment to the solid support have been particularly useful. Examples include the aryldiisopropylsilyl linker **1**[3] and *n*-alkyldiisopropylsilyl linkers such as **2**[4,5] (Figure 1). In general, these linkers are stable to a variety of reaction conditions and can be cleaved orthogonally with fluoride reagents.

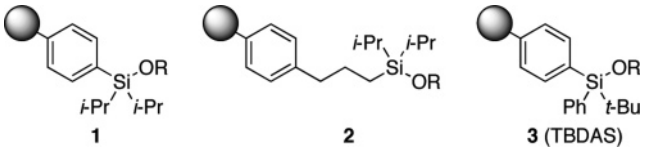


Figure 1. Silyl ether linkers with all-carbon attachments to the solid support.

In the course of our research program in the diversity-oriented synthesis (DOS) of natural product-based libraries,[6] we required a linker that was stable to strong protic and Lewis acidic conditions to carry out reactions such as acetal deprotections, Lewis acid-catalyzed cycloadditions, and aldehyde addition reactions. Encouraged by preliminary experiments with triisopropylsilyl-protected alcohols as solution-phase analogues, we explored the utility of **2** in such

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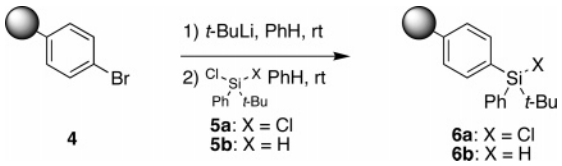
reactions on polystyrene beads.[7] Unfortunately, the linker was degraded significantly under acidic conditions (e.g., TsOH), resulting in premature cleavage of the substrates from the solid support. We report herein our solution to this problem, entailing the synthesis and evaluation of a new, robust *tert*-butyldiarylsilyl (TBDAS) linker **3**.[8]

By analogy to the *tert*-butyldiphenylsilyl (TBDPS) protecting group for alcohols,[9] we envisioned that the TBDAS linker **3** would be significantly more stable to acids than **1** or **2**. Moreover, since the solution-phase analogues of **1** and **2** are uncommon, we recognized that the direct correspondence between **3** and the well-established TBDPS protecting group would offer a further advantage with respect to predicting the stability of the linker and the reactivity of TBDAS-linked substrates.

Our initial approach to **3** involved lithiation of bromopolystyrene resin **4**[2,7] (Scheme 1), followed by treatment with

Scheme 1. Synthesis of the TBDAS Linker.

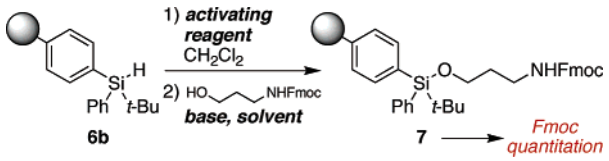


tert-butyldichlorophenylsilane **5a**, which is commercially available, albeit at relatively high cost.[10] A large molar excess of **5a** was used, both to drive the silylation reaction to completion and to reduce the amount of anticipated intrabead cross-linking. The support-bound silyl chloride **6a** was then treated with *N*-Fmoc-β-alaninol and imidazole in CH_2Cl_2. We were encouraged to find that standard Fmoc quantitation[11] indicated 38% alcohol loading. However, in view of the expensive dichlorosilane **5a** required, we elected to pursue a second-generation approach to provide more practical access to the TBDAS linker.

Thus, we synthesized the known monochlorosilane **5b**[12] by addition of *t*-BuLi to dichlorophenylsilane. The freshly prepared and distilled monochlorosilane was then used to silylate lithiated bromopolystyrene to afford the shelf-stable silyl hydride resin **6b**. After significant optimization, linker loading levels of 1.03−1.39 mequiv/g were achieved (Si elemental analysis), corresponding to a 60−81% yield relative to the initial bromine loading level (see Supporting Information). Residual bromine was also detected at 0−10% of the initial loading level (Br elemental analysis).[13] Additives such as HMPA, CuCN,[14] or TMSCN[15] did not increase the loading level.

We then evaluated various methods of activating the silyl hydride resin **6b** for alcohol loading (Table 1) including

Table 1. Activation of the Silyl Hydride Resin **6b** and Alcohol Loading



activating reagent	base[e]	solvent	yield (%)[f]
NBS[a]	Et_3N, DMAP	CH_2Cl_2	69
NBS[a]	Et_3N, DMAP	DMF	21
NBS[a]	imidazole	CH_2Cl_2	78
NBS[b]	imidazole	CH_2Cl_2	73
TfOH[c]	2,6-lutidine	CH_2Cl_2	0
trichloroisocyanuric acid[a]	imidazole	CH_2Cl_2	23[g]
1,3-dichloro-5,5-dimethyl-hydantoin[d]	imidazole	CH_2Cl_2	93−100

[a] Performed with 2 equiv. [b] Performed with 10 equiv. [c] Performed with 6 equiv. [d] Performed with 12 equiv. [e] Base (8−12 equiv) was added to the washed resin in the solvent indicated, followed by 3 equiv of *N*-Fmoc-β-alaninol. [f] Yields determined by Fmoc quantitation, relative to Si loading level determined by elemental analysis. [g] Not optimized.

N-bromosuccinimide,[16] triflic acid,[17] and trichloroisocyanuric acid.[4] The best results were achieved via chlorination using 1,3-dichloro-5,5-dimethylhydantoin,[5b] which afforded highly efficient loading of *N*-Fmoc-β-alaninol (Fmoc quantitation) relative to the silyl hydride loading level.[18]

We also investigated loading of the TBDAS linker onto brominated polystyrene SynPhase L-Series Lanterns,[19] which were lithiated, silylated, chlorinated, and loaded with *N*-Fmoc-β-alaninol as described above. Elemental analysis indicated 16−19 μequiv of Si per Lantern (45−55% yield based on the initial Br loading level). Residual bromine was detected at 5.7−6.7 μequiv of Br per Lantern (16−19%).[20] Fmoc quantitation indicated 13−18 μequiv of alcohol loaded per Lantern (37−52% overall yield). Although these yields are lower than those achieved using the polystyrene beads above,

(7) Polymer Laboratories: PL-PBS Resin, 150−300 μm, 25% *p*-bromostyrene, 1% divinylbenzene, 2.0 mequiv Br/g.

(8) For a report of an amide-linked anilino-*tert*-butylphenylsilyl linker, see: Mullen, D. G.; Barany, G. *J. Org. Chem.* **1988**, *53*, 5240−5248.

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(13) An alternative metalation with *i*-Pr(*n*-Bu)$_2$MgLi has been reported recently: Thomas, G. L.; Ladlow, M.; Spring, D. R. *Org. Biomol. Chem.* **2004**, *2*, 1679−1681. This procedure also provided efficient metalation (0.6% residual Br, elemental analysis) but did not improve net linker loading (49% yield, Si elemental analysis).

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(18) Overall loading level with **3** is comparable to the levels we achieved using **1** (62−65%, Fmoc quantitation, relative to initial Br loading level) and **2** (40−59%).

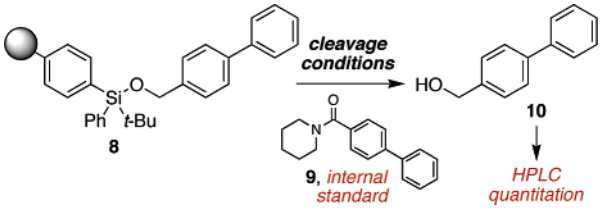
(19) Mimotopes: SynPhase PS L-Series brominated Lanterns, 35 μequiv Br/Lantern.

(20) Use of the alternative *i*-Pr(*n*-Bu)$_2$MgLi metalation procedure (ref 13) yielded Lanterns with 16.1 μequiv of residual Br (46% of initial loading, Br elemental analysis) and 12.7 μequiv of linker loading (36% yield, Si elemental analysis).

we note that the *loading level* is on par with that for commercially available Lanterns that are preloaded with other linkers (15 μequiv) and is sufficient to produce up to 7−9 mg of cleaved product (500 MW) per Lantern.

Our attention next turned to developing suitable cleavage conditions for TBDAS-linked alcohols (Table 2). Biphenylmethanol **10** was loaded onto polystyrene resin via the TBDAS linker as described above. The beads were then exposed to cleavage conditions in the presence of an internal standard **9**, and the amount of cleaved biphenylmethanol was determined by HPLC analysis.[21]

Table 2. Cleavage of a TBDAS-Linked Alcohol



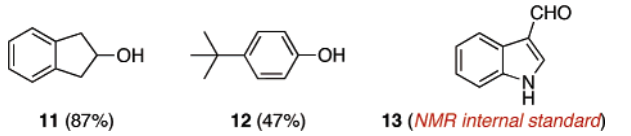
cleavage conditions	temp (°C)	time (h)	cleavage (%)[a]
HF·pyr, pyr, THF	25	17	20
HF·pyr, pyr, THF	35	31	60
HF·pyr, pyr, THF	55	16	97
Et_3N·3HF, Et_3N, THF	35	70	74
NH_4F, DMF	35	70	74
TBAF, THF	25	<1	100
TAS-F, THF	25	<1	100

[a] Percent cleavage was determined by comparison of HPLC peak integrations for **9** and **10**, adjusted for extinction coefficients, relative to Si or Fmoc quantitation of maximum loading level.

Interestingly, in contrast to **2**, hydrogen fluoride·pyridine (HF·pyr) cleavage of the TBDAS linker proceeded slowly at room temperature. However, the alcohol could be released at elevated temperature and recovered by quenching of the excess HF with TMSOMe and simple evaporation.[22] Tetrabutylammonium fluoride (TBAF) also induced rapid cleavage at room temperature, and the alcohol could be recovered in ≥90% purity by filtration through a short plug of normal-phase and reverse-phase silica gel, or by treatment with Amberlyst A15 acidic resin, to remove the residual tetrabutylammonium salts. The extremely mild tris(dimethylamino)-sulfur (trimethylsilyl)difluoride (TAS-F)[23] reagent also effected rapid, efficient cleavage, providing an alternative to TBAF for base-sensitive substrates.

The secondary alcohol **11** and the phenol **12** (Figure 2) were also successfully loaded onto and cleaved from the TBDAS linker under our standard conditions (two-step yields, NMR quantitation vs internal standard **13**).

With optimized procedures in hand for synthesis, loading, and cleavage of the TBDAS linker, we next investigated its stability to various reaction conditions (Table 3). The diisopropylsilyl linkers **1** and **2** were used for comparison. Thus, biphenylmethanol **10** was loaded onto polystyrene beads via each of the three linkers. The beads were exposed to "stressing" conditions and washed thoroughly. The biphenylmethanol remaining on the resin was cleaved with TBAF and quantitated by HPLC analysis relative to internal standard **9** as above.



11 (87%) **12** (47%) **13** (*NMR internal standard*)

Figure 2. Secondary alcohol and phenol were successfully loaded onto and cleaved from the TBDAS linker.

Table 3. Comparative Stability of Silyl Linkers to Various Reaction Conditions

		3	**1**	**2**
entry	stressing conditions[a]	recovered **10** (%)[c]		
1	TsOH, acetone, THF, 24 h, rt	100	17	3
2	TFA, CH_2Cl_2, 20 h, rt	85	68	8
3	BF_3·OEt_2, CH_2Cl_2, 1.5 h, −78 °C	100	69	50
4	$AlMe_3$, CH_2Cl_2, 20 h, rt	79	60	89
5[b]	K_2CO_3, MeOH, 1 h, rt	92	100	98
6	KO*t*-Bu, THF, 1 h, rt	100	96	88
7	MeLi, THF, 1 h, rt	90	69	39
8	HF (aq), CH_3CN, 24 h, rt	100	nd	nd

[a] Each reagent was used as a 0.2 M solution. [b] Used as a 0.1 M solution. [c] Average of two experiments, relative to the amount of biphenylmethanol recovered from unstressed resin. Maximum standard deviation = 5.7%. nd = not determined.

We were gratified to find that our TBDAS linker **3** is substantially more stable to protic acids than the previously reported diisopropylsilyl linkers **1** and **2** (entries 1, 2). Moreover, the TBDAS linker exhibits good stability to Lewis acids (entries 3, 4) and also performs well under basic conditions (entries 5−7). All three linkers were stable to $ZnCl_2$ and *t*-BuLi (not shown). Finally, we noted that the TBDAS linker **3** is stable to extended exposure to aqueous HF in CH_3CN (entry 8), raising the intriguing possibility of using orthogonal HF-labile protecting groups in solid-phase synthetic schemes.

To investigate the feasibility of this idea, 4-(*tert*-butyldimethylsilyloxymethyl)benzyl alcohol[24] was loaded onto polystyrene resin via the TBDAS linker and then treated with HF·pyr buffered with pyridine at room temperature (Scheme 2). The resin was washed and subjected to exhaustive acetylation. Cleavage with TAS-F in the presence of internal standard **13** provided the acetate **15a** in ≥85% purity (55%

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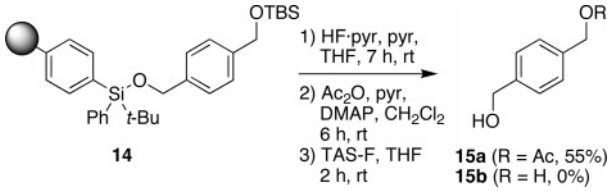
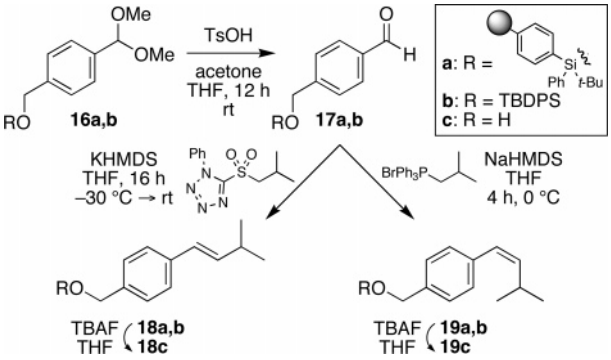
Scheme 2. Silyl Protecting Group Manipulation.



over four steps, NMR quantitation). Diol **15b**, whose presence would indicate incomplete removal of the TBS group by HF·pyr, was not detected. Thus, this experiment provides a preliminary indication that such silyl protecting group manipulations are, indeed, possible with the TBDAS linker.

We next carried out other representative solid-phase reactions using substrates attached to polystyrene resin via the TBDAS linker. As hoped, the acetal deprotection reaction that had originally caused premature cleavage of alkyldiisopropylsilyl linker **2** proceeded efficiently with the TBDAS-linked substrate **16a**, with no evidence of substrate cleavage (Scheme 3). The resulting resin-bound aldehyde **17a** was then

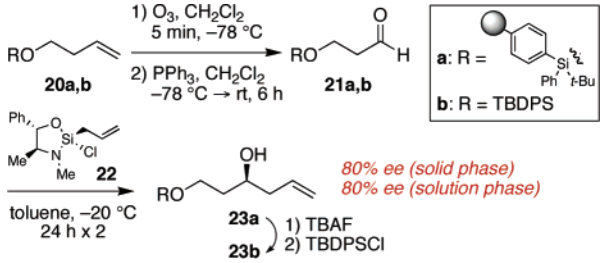
Scheme 3. Acetal Deprotection and Aldehyde Olefinations of TBDAS-Linked Substrates.



converted to (*E*)- and (*Z*)-olefins **18a** and **19a** via Julia and Wittig couplings, respectively.[25] TBAF cleavage provided the (*E*)-olefin **18c** (69% over four steps, >8.5:1 *E*/*Z*, NMR quantitation vs internal standard **10**) and the (*Z*)-olefin **19c** (74% over four steps, >20:1 *Z*/*E*). Notably, optimization of this reaction sequence was facilitated by use of the TBDPS-protected solution-phase analogues **16b**−**19b**.

We recognized that direct coupling of the TBDAS linker to the polystyrene support resulted in a stereogenic Si center that might adversely affect asymmetric reactions of support-bound substrates. Such reactions are of increasing interest for introducing stereochemical diversity, and hence increased structural diversity, in DOS. To investigate this possibility, 3-buten-1-ol was loaded onto polystyrene resin via the TBDAS linker, converted to aldehyde **21a** by ozonolysis, and then treated with Leighton's allylsilane reagent[26] **22** (Scheme 4). The resulting homoallylic alcohol **23a** was

Scheme 4. Ozonolysis and Asymmetric Allylation of TBDAS-Linked Substrates.



cleaved from the resin and then selectively protected at the primary hydroxyl group with TBDPSCl to provide **23b**. Separately, **23b** was also synthesized in solution from the TBDPS-protected analogue **21b**. We were pleased to find that Mosher ester analysis[27] of both the solid- and solution-phase synthesis-derived alcohols **23b** indicated identical levels of enantiomeric excess. Thus, the stereogenic Si center of the TBDAS linker did not adversely affect the stereoselectivity of this asymmetric allylation reaction.

In conclusion, we have developed a versatile new TBDAS linker for solid-phase organic synthesis. This linker has marked advantages over previously reported silyl linkers in that it is stable to protic and Lewis acidic reaction conditions. Furthermore, TBDPS-protected alcohols can be used as convenient solution-phase analogues for reaction development. We have demonstrated that the TBDAS linker can be cleaved under mild, chemoselective conditions to afford cleavage products in high purity and yield. The TBDAS linker is compatible with acetal deprotection, Wittig and Julia coupling, asymmetric allylation, and even silyl protecting group manipulation reactions. This new linker should be a valuable addition to the chemist's toolkit for solid-phase organic synthesis.

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Supporting Information Available: Experimental procedures and analytical data for **5b**, **6b**, **7**, **9**, **10**, **15a**, **17a**, **18c**, **19c**, **21a**, and **23a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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