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A 'triflate-like' tetrafluoroarylsulfonate linker for multifunctional solid-phase organic synthesis†

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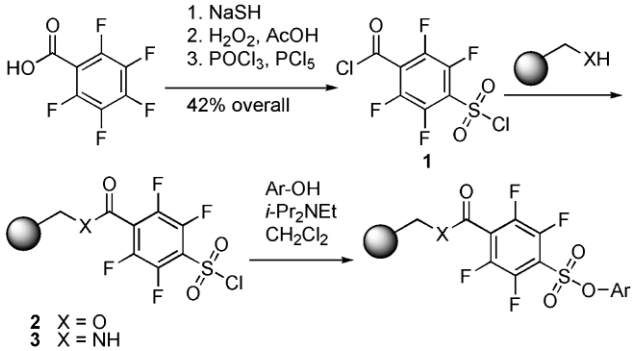
Received (in Cambridge, UK) 1st June 2004, Accepted 16th July 2004
First published as an Advance Article on the web 29th July 2004

An arylsulfonate solid-phase linker is suitable for 'traceless' synthesis and Pd(0) catalyzed cross-coupling reactions.

The majority of solid-phase linkers were originally developed in the context of peptide synthesis. Now that combinatorial chemistry targets a wide variety of small molecules,[1] alternative cleavage strategies have evolved. Among the most powerful are (1) 'cyclative cleavage',[2] whereby an intramolecular cyclization effects compound release; (2) 'traceless' synthesis,[3] in which the point of attachment is replaced by an innocuous C–H bond, and (3) 'multifunctional' linkers,[4] which yield different products depending on the cleavage conditions. Here, we report an inexpensive 'triflate-like' linker, capable of both traceless *and* multifunctional cleavage.

Our premise was based on the conversion of phenols to sulfonates that are precursors to arylpalladium intermediates. On solid-phase, this was first accomplished by Wustrow.[5] The reaction of phenols with a benzenesulfonic acid resin yielded immobilized sulfonates, which under transfer hydrogenation conditions underwent 'traceless' cleavage to the deoxygenated aromatic. However, due to the low activation from a simple benzenesulfonate, extended reaction times at high temperature were needed and yields were variable. A significant advance was Holmes' perfluoroalkylsulfonate linker[6] with nonaflate-like reactivity, and good yields were demonstrated for both transfer hydrogenation and Suzuki–Miyaura cross-coupling. Nevertheless, this linker takes five steps to prepare from an expensive starting material (£9 per mmol from Aldrich), and the final loading is only ~0.3 mmol g^{-1}. We believed that combining the Wustrow and Holmes approaches in a *perfluoro*arylsulfonate linker would overcome these shortcomings.

The known bis-acid chloride **1** (Scheme 1) was readily prepared in three steps[7] from inexpensive pentafluorobenzoic acid (£0.40 per mmol, Aldrich), and immobilized *via* either an ester or amide linkage to afford polystyrene-tetrafluoroarylsulfonate (PS-TAS) linkers **2** and **3** (loading ~0.9 mmol g^{-1}) respectively. These were briefly mentioned[8] in a previous patent, but as reagents for preparing reactive acylating agents from carboxylic acids rather than the present Pd(0)-catalyzed applications.

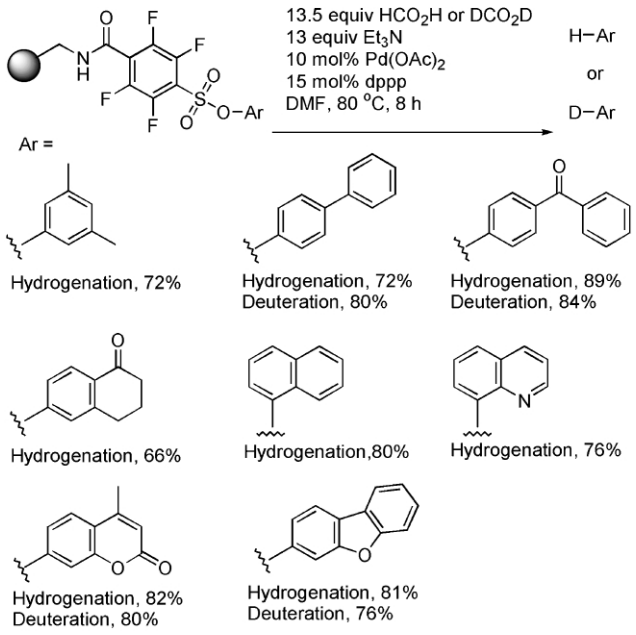


Scheme 1 Synthesis of the PS-TAS linkers and phenol attachment.

A series of phenols was attached to PS-TAS linkers **2** and **3**. These reactions can be conveniently monitored by ^{19}F gel-phase NMR. Pleasingly, the sulfonate resins were efficiently cleaved in a 'traceless' manner to the deoxygenated aromatic by Pd(0)-catalyzed transfer hydrogenation (Scheme 2). As yields were consistently ~10% higher with amide linker **3**, only these results are reported. The reaction of several of these sulfonate resins was additionally carried out with deuterated formic acid, and found to be equally successful as hydrogenation.

Thus, the PS-TAS linker provides the opportunity for 'traceless' C–H incorporation at the site of cleavage, as well as site-specific isotopic labelling of aromatic compounds by deuteration. Although not investigated, these conditions should also be suitable for tritiation.

Besides hydrogenation and deuteration, we have explored the feasibility of the PS-TAS linker for effecting Pd(0)-catalyzed carbon–carbon bond formation. The Suzuki–Miyaura cross-coupling of phenylboronic acid and immobilized 7-hydroxy-4-methylcoumarin was tested with a number of catalyst/ligand systems. Among these, $PdCl_2$(dppf) and $Pd(OAc)_2$/Xphos[9] were found to give superior yields to $Pd(OAc)_2$/dppp, $PdCl_2(PPh_3)_2$, $Pd(dba)_2$ or $Pd(OAc)_2/PPh_3$. The $PdCl_2$(dppf) conditions were then applied to a set of immobilized phenols (Scheme 3), and the biaryl products isolated in good yield. An exception was 8-hydroxyquinoline, which produced a complex reaction mixture with $PdCl_2$(dppf). In this particular case, Buchwald's $Pd(OAc)_2$/Xphos yielded the desired product quinoline in 69% yield. In addition to the Suzuki–Miyaura reaction, initial results (Scheme 4) indicate the suitability of the PS-TAS linker for release of immobilized sulfonates *via* the Mizoroki–Heck cross-coupling.



Scheme 2 Transfer hydrogenation and deuteration with the PS-TAS linker. Isolated yields are given for individual sulfonate substrates.

† Electronic supplementary information (ESI) available: Experimental procedures for linker synthesis, phenol attachment, and Pd(0)-catalyzed reactions. See http://www.rsc.org/suppdata/cc/b4/b408166h/

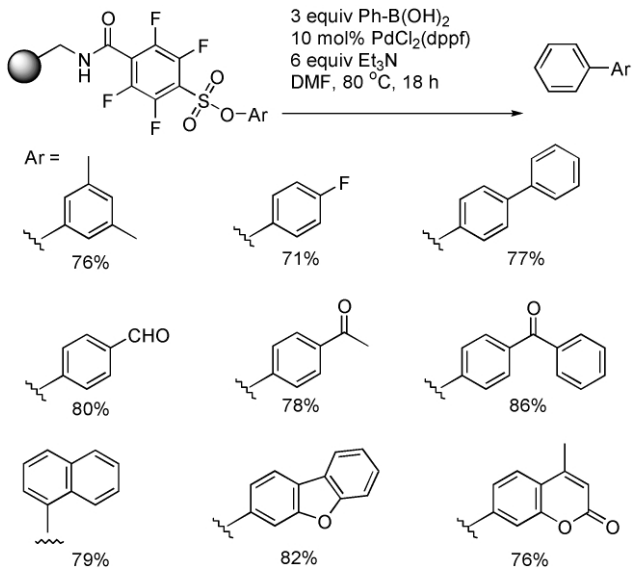
DOI: 10.1039/b408166h

To demonstrate the potential of the PS-TAS linker in multistep sequences, we targeted the solid-phase synthesis of Valsartan,[10] a selective antagonist of the angiotensin type I receptor in clinical use. Our route (Scheme 5) begins with the immobilization of 4-hydroxybenzaldehyde to the PS-TAS linker, followed by reductive amination under racemization-free conditions[11] with L-valine methyl ester. The resulting secondary amine was then acylated with valeryl chloride.

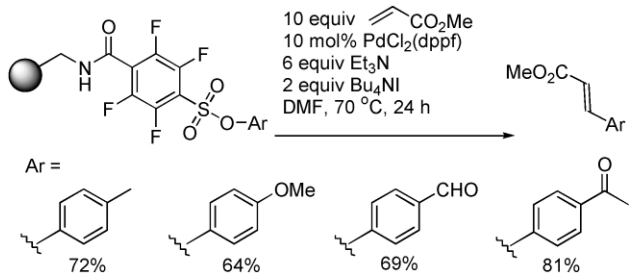
Release of Valsartan methyl ester directly by Suzuki–Miyaura cross-coupling with 2-tetrazolylphenylboronic acid was investigated, but proved to be unsuccessful. Based on literature reports[12] that the tetrazole nitrogen needs to be protected, we then employed the *N*-trityl derivative. After considerable experimentation, *N*-trityl Valsartan methyl ester was obtained in 39% for the overall four-step sequence. Alternatively, the sulfonate resin was cleaved with the less capricious 2-cyanophenyl boronic acid. Solution-phase reaction of the biaryl cyanide with trimethylsilyl azide[13] then completed the synthesis of Valsartan methyl ester.

In summary, we have developed a new tetrafluorophenylsulfonyl chloride linker, PS-TAS. This easily prepared and inexpensive resin functions as a solid-phase 'triflate' equivalent. Phenols attached to the linker as sulfonate esters can be subjected to 'traceless' cleavage by transfer hydrogenation, while Suzuki–Miyaura and Mizoroki–Heck reactions provide the opportunity for carbon–carbon bond formation during compound release. The synthesis of Valsartan methyl ester illustrates an application of the PS-TAS linker in designing multistep solid-phase sequences.

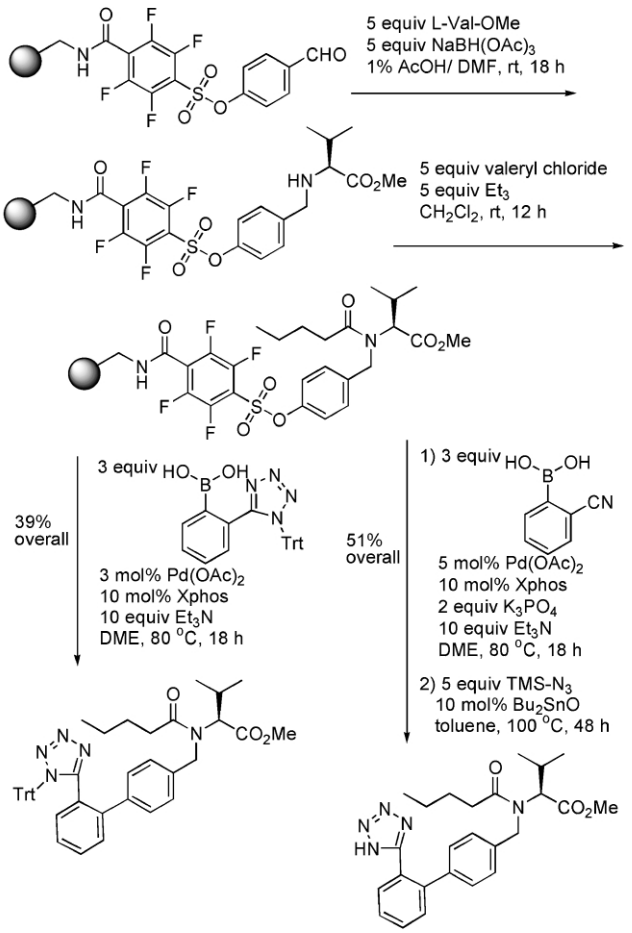
The Combinatorial Centre of Excellence was funded by an industrial consortium comprising Amersham, AstraZeneca, Glaxo-SmithKline, Lilly, Merck Biosciences, Organon, Pfizer, Roche and government funding through the JIF initiative.



Scheme 3 Application of the PS-TAS linker in Suzuki–Miyaura reactions, with isolated yields of cross-coupled products.



Scheme 4 Application of the PS-TAS linker in Mizoroki–Heck reactions, with isolated yields of cross-coupled products.



Scheme 5 Solid-phase synthesis of Valsartan methyl ester.

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