A novel solid-phase equivalent to the triflate group and its application to traceless linking and cross-coupling-release strategies†

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A solid-phase version of the triflate group has been developed and its use demonstrated in traceless linking of aromatics and cross-coupling release strategies.

The upsurge in use of solid-phase organic synthesis (*e.g.* combinatorial chemistry and robotic parallel synthesis) has inspired the search for more versatile polymer supported reagents and linkers. "Traceless" linkers have proved particularly challenging but a number of successful strategies have been developed.[1] In this communication we wish to report a novel polymer linker that behaves like a "triflate" group.

Organic triflates (trifluoromethane sulfonates) are widely employed in synthesis, effectively converting an OH group into a leaving group. Conversion of phenols into triflates renders the Ar–O bond sufficiently electron deficient (weak) to permit insertion of transition metals (such as Pd(0)) and their chemistry is akin to that of aryl bromides. As such there is a wealth of chemistry available. We,[2] and others, have used this chemistry for the deoxygenation of phenols by conversion to triflate and reduction with Pd(0)/HCOO⁻.[3] A polymer supported "triflate" equivalent would provide a means of attaching aryl residues (through phenolic OH) and removal from the resin in a traceless fashion (leaving Ar–H), or by employing other transition metal catalysed processes. An example of one such triflate equivalent has been reported by Holmes using a perfluoroalkylsulfonate.[4]

We wished to develop a solid-phase triflate equivalent using robust and simple chemistry and focused on aryl sulfonates. Polymer supported (simple) phenyl sulfonates have been employed in attempts to perform related chemistry but limited success was achieved.[5] The catalytic process required for reduction or cross-coupling relies on Pd(0) insertion into the Ar–O bond. Successful reactions require this bond to be weakened by either electron withdrawing groups on the Ar or on the sulfonate ester. Efficient reductive cleavage was therefore only observed when electron withdrawing groups were present on the aryl residue.

A more detailed solution phase study has been carried out by Cabri[6] who examined the effect of electron withdrawing groups on the sulfonate, ranking efficiency $CF_3 > p\text{-}FAr > Ar$, indicating the potential for polyfluorophenyl sulfonates. To establish the number of fluorines required for efficient Pd(0) insertion we performed further solution phase model reactions using 2,4-difluorophe-

nylsulfonyl chloride and pentafluorophenylsulfonyl chloride. The corresponding esters were prepared from phenylphenol and reduced using standard (for triflates) conditions (Pd(OAc)$_2$, dppp, HCOOH, Et$_3$N, 100 °C). Both reactions proceeded smoothly to give biphenyl as the only product (Scheme 1). The rates of the reactions were significantly different with the 2,4-difluorophenyl sulfonate requiring 6 h. The reaction employing the pentafluorophenyl sulfonate, in contrast, was complete in less than 1 h. This result indicates that 2 fluorine substituents are sufficient to enable reduction (Pd insertion) on electron-neutral residues, but the more powerfully electron deficient sulfonate permits reaction under milder conditions.

These model sulfonates are, of course, unsuitable for attachment to a solid support and require an additional linking functionality. We chose to link to a solid support *via* a carboxylic acid derivative, reasoning that the link group could serve also as a further electron withdrawing group, and that the synthesis of a suitable precursor would be straightforward. Di-acid chloride **1** was smoothly prepared following the procedure described by Fielding[7] starting from pentafluorobenzoic acid. Reaction of **1** with methanol at room temperature for 30 min gave the ester **2** (from reaction with the carboxylic acid chloride only) and this compound was used in a further solution state model analogous to that described previously (Scheme 2). Triflate equivalent **2** was reacted with phenylphenol to give **3** which was reduced under standard conditions. The reaction was complete in 3 h, giving biphenyl as the sole product.
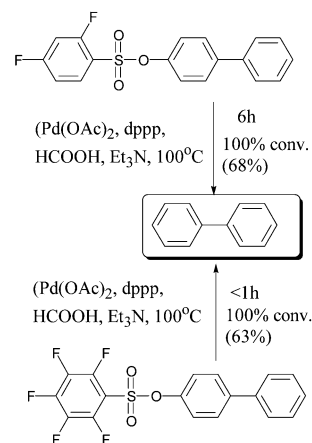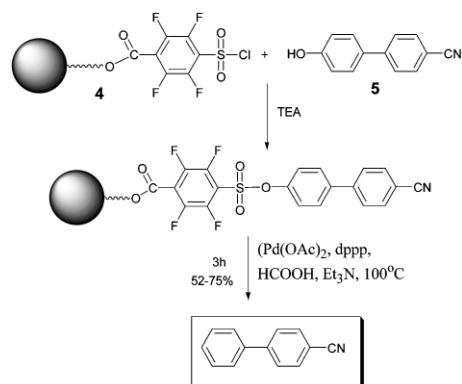
Scheme 1 Model studies towards a triflate-equivalent based on fluoroaryl sulfonates.
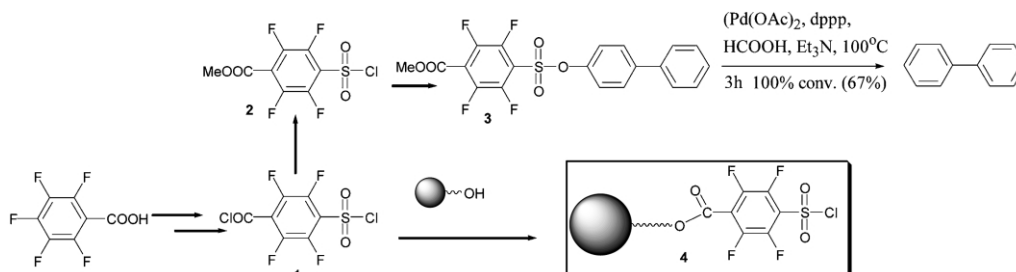
Scheme 2 Synthesis of solid-phase (polymer supported) triflate equivalent and a related molecular derivative.

Scheme 3 Traceless linking *via* reductive cleavage from polymer-supported triflate equivalent.

The final step required the attachment of the triflate to a solid support. We chose to link to the polymers using the chemistry established during the model studies and therefore selected polymer supports with hydroxyl groups. Three supports were used. The first support, based on surface-functionalised nano-beads, was developed in our laboratories and recently described.[8]

These polymer nano-beads, as prepared using microemulsion polymerisation using a polymerisable, carboxylate surfactant, comprise solid styrene-divinylbenzene co-polymer with a surface coating of carboxylic acids. Hydroxyl-functionalised nano-beads were simply prepared by reduction using LiAlH₄. Two commercial hydroxy supports, Novasyn® TG hydroxy resin and hydroxymethyl polystyrene, were also used. In typical preparations, an excess of **1** was stirred with the hydroxyl polymer support in dichloromethane for 48 h at room temperature. The polymers were isolated by filtration, washed repeatedly, and characterised by IR spectroscopy which clearly indicated the attachment *via* the formation of a carboxylic ester (1746 cm^{-1}). 4-Hydroxybiphenyl-4′-carbonitrile **5** was chosen as model phenol so that its incorporation onto the polymeric triflate equivalent could be similarly monitored by IR. Sulfonyl chloride polymers **4** were treated with an excess of **5** in DCM–TEA at room temperature for 48 h. The IR spectra of the washed, loaded polymers showed characteristic peaks for the bound carbonitrile (2228 cm^{-1}).

The reductive cleavage from the polymer supports was again achieved by treating the polymers with Pd(OAc)₂/dppp/HCOO$^-$ in DMF at 100 °C for 48 h and proceeded smoothly. All polymers gave similar perfomance. The recovered polymer showed no trace of residual nitrile groups indicating complete reductive cleavage (4-cyanobiphenyl was the only product from the reactions). Yields, calculated over all steps based on the theoretic loading capacity,
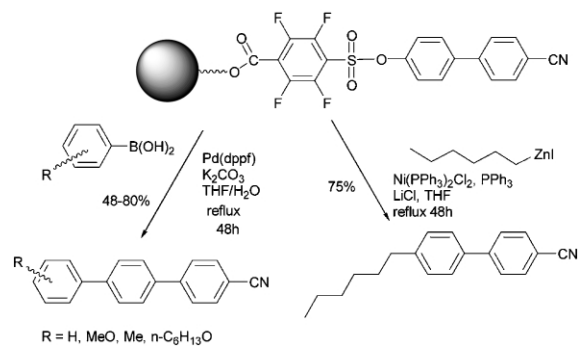
Scheme 4 Cross-coupling release strategies employing Suzuki and Negishi reactions.

were good (range 50–75%) and reproducible. The residual polymer appears to retain its "triflate equivalent" (IR) and is therefore theoretically recyclable (Scheme 3).

As mentioned previously, attachment of phenol residues to polymer support *via* a triflate linker offers potential to remove the (final) product from the residue using a range of cross-coupling chemistry. Scheme 4 shows examples of such protocols involving Suzuki[9] and Negishi reactions (again the coupled product is the only one observed, yields are based on theoretical loading capacity and are over all steps from the hydroxyl polymer).

In conclusion we have reported an easy-to-prepare polymeric "triflate" equivalent based on an electron-poor aryl sulfonate. Attachment of phenols is straightforward and removal can be achieved by palladium catalysed processes, most notably reductive cleavage (traceless linking) and cross-coupling.

Notes and references

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