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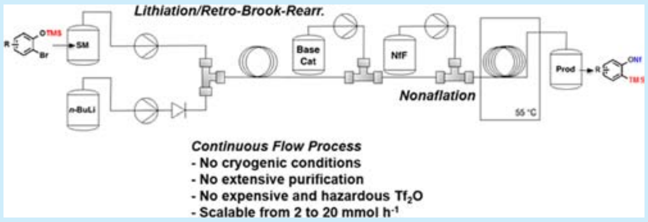
Continuous-Flow Synthesis of Trimethylsilylphenyl Perfluorosulfonate Benzyne Precursors

Boris Michel and Michael F. Greaney*

School of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, U.K.

S *Supporting Information*

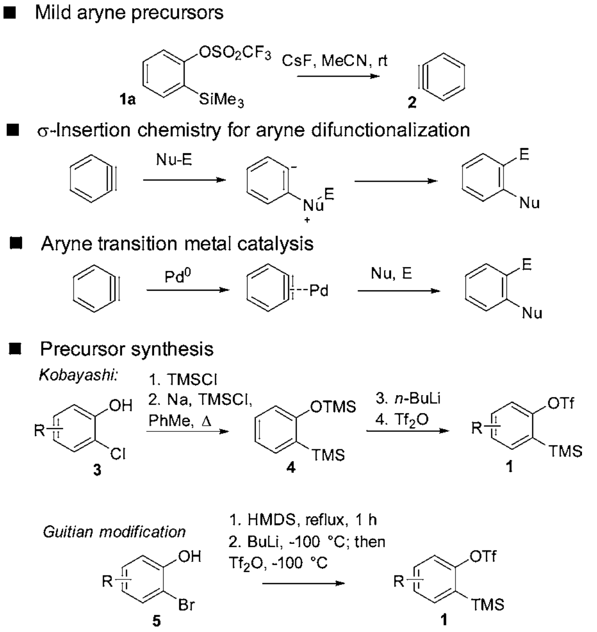
ABSTRACT: 2-(Trimethylsilyl)phenyl perfluorosulfonated aryne precursors may now be accessed using flow chemistry, enabling the fast preparation of pure compounds with no requirement for low temperature lithiation or column chromatography. The process has been adapted to novel nonaflate precursors, utilizing the cheaper and more user-friendly nonaflyl fluoride reagent. The resultant nonaflates are shown to successfully participate in a range of aryne reaction classes.



The introduction of 2-(trimethylsilyl)phenyl triflates, **1**, as benzyne precursors that function under mild conditions has led to a resurgence in aryne chemistry.[1] Triggered by fluoride at room temperature or above, these precursors have dramatically expanded the range of reactions possible using the strained triple bond.[2] Transformations that were previously restricted in scope (e.g., aryne σ-insertion processes) or unknown (e.g., transition-metal-catalyzed aryne chemistry) with classical precursors have now grown into powerful methods for arene and heteroarene synthesis. These new reactions have powered applications in natural product synthesis, materials science, and polymer synthesis.[3]

The accessibility of precursors **1** is central to the viability of the aryne field. The parent triflate **1a** is commercially available,[4] whereas analogues generally must be synthesized. The synthesis of **1** is usually achieved through a variant of Kobayashi's initially reported method,[1] which uses a retro-Brook rearrangement of a 2-(trimethylsilyloxy)phenyl halide as the key step (Scheme 1). In a particularly step-efficient modification, Guitián and co-workers replaced the sodium in refluxing toluene protocol with a low temperature lithiation, using *n*-BuLi at −100 °C in THF.[5] The phenoxide arising from retro-Brook rearrangement may then be trapped with triflic anhydride (Tf_2O) in situ.[6] Despite the step efficiency, the route suffers the drawback of cryogenic conditions (−100 °C) limiting both applicability and scalability of the chemistry. In our experience, both the lithiation and the trifluoromethylsulfonation step produce a number of side products that can be difficult to remove from the product. In addition, small amounts of triflic acid generated by the degradation of triflic anhydride can enable cationic polymerization of the THF reaction solvent, further complicating purification.

Scheme 1. Benzyne Generation from 2-Trimethylsilylphenyl Triflates



Our continued interest in aryne chemistry[7] motivated us to address the limitations in the synthesis of these starting materials through the application of continuous flow chemistry. The obvious advantages of microscale processing are the enhanced surface-to-volume ratio, leading to excellent mass and heat transport. By utilizing flow chemistry's precise temperature and mixing control, it was hoped that the problematic side reactions of the *n*-BuLi-initiated retro-Brook step could be addressed, eliminating the requirement for tedious column chromatography.[8] Furthermore, flow processing segregates toxic, corrosive, sensitive, or otherwise obnoxious chemicals (e.g., *n*-BuLi and Tf_2O) from the operator,[9] which require the utmost care and (often cumbersome) process management to

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use under batch conditions. Optimization of this delicate reaction followed by further in-line reactions[10] was expected to be rapid and cost-effective due to the innate repeatability and small scale of flow systems.[11] A final advantage of a continuous system is the facile scaling up/out of the system by simply running the optimized reaction for longer; thereby removing synthetic bottlenecks and enabling the important process of discovery to take over.

We set out to develop a usable process that would not require any significant investment in sophisticated microscale reactor equipment. We addressed the key retro-Brook step first, using the syringe-pump flow scheme set out in Figure 1. This reaction system was assembled using cheap and readily available flangeless fittings, PTFE microtubing and Y- or T-unions. We chose TMS capped phenols (**6**) as the starting point for continuous flow synthesis as their batch synthesis via HMDS treatment of phenols is extremely facile, requiring simple heating and subsequent evaporation. We were pleased to find that initial attempts at flow retro-Brook rearrangement of **6** were successful, with a reaction temperature of −78 °C in THF affording usable yields of the phenol **7a**. There were problems with reproducibility, however, as the flow rate was impacted by degradation of *n*-BuLi to gaseous butane in THF while in a syringe pump at room temperature. A solvent change to diethyl ether, in which *n*-BuLi is more stable, removed this issue, but the lower polarity and coordination behavior of Et_2O slowed the reaction down significantly at −78 °C. We solved this problem by conducting the flow lithiation at room temperature, a process that would not be feasible in batch, affording **7a** in 92% yield as a pure compound following filtration through a pad of silica and concentration. The method proved general for a range of substrates, yielding the product phenols (**7a**−**e**) in excellent yields (Scheme 2). We were interested in extending the method to substrates containing two halogens (**6f** and **6g**), as the bromine atom in the final aryne precursors would represent a useful directing group and point of further functionalization. Initial application of our optimized flow conditions to these substrates led to selectivity problems; lithiation of (2,6-dibromo)phenoxytrimethylsilane in Et_2O at temperatures between 0 or 25 °C led to additional lithiation of the second halide atom and thus to side products that required time-consuming column chromatography to remove. Lowering the temperature to −78 °C gave no reaction at all in Et_2O, but was productive in THF. By loading the substrate in THF and *n*-BuLi in Et_2O we could circumvent the issue of *n*-BuLi degradation while still maintaining the activating properties of THF upon mixing the two solutions at −78 °C. The reactions then proceeded to completion, producing pure **7f** (76% yield) and **7g** (75% yield).

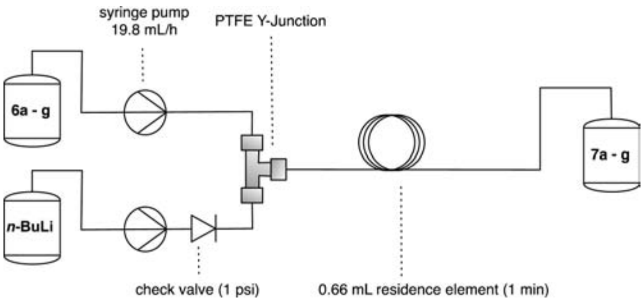
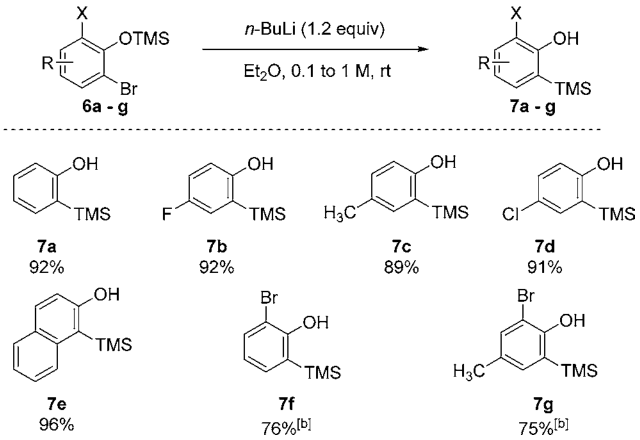


Figure 1. Schematic for continuous flow retro-Brook rearrangement.

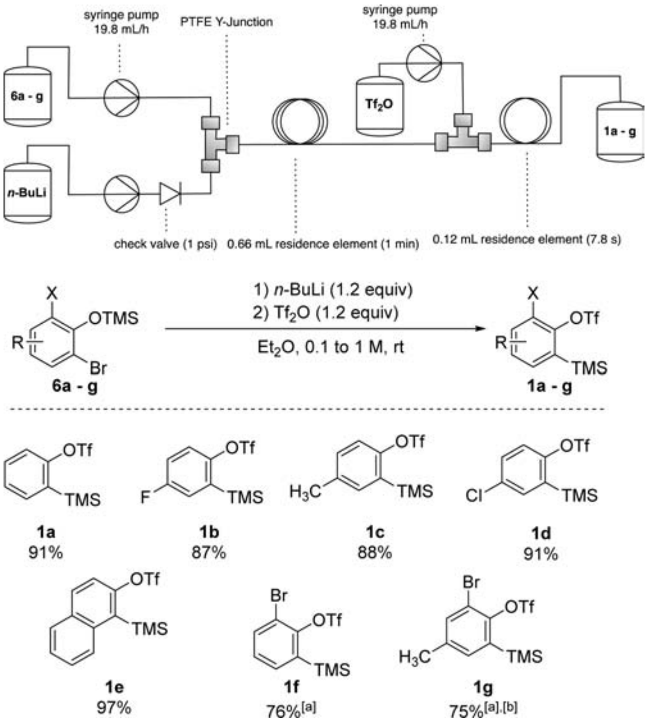
Scheme 2. Continuous Flow Synthesis of 2-Trimethylsilylphenols[a]



[a] Reaction conditions: 1 mmol of (2-bromophenoxy)trimethylsilane (1.0 M in Et_2O) and 1.2 mmol of *n*-BuLi (1.6 M in hexane) were loaded into syringes and diluted to 10 mL with the appropriate solvents. The reaction was carried out in a setup as displayed in Figure 1. [b] Substrate dissolved in THF; *n*-BuLi diluted with ether.

The linking together of multistep processes is a key advantage of flow and could be exemplified by the further reaction of the retro-Brook phenolates with Tf_2O under controlled flow conditions (Scheme 3). We added Tf_2O in Et_2O to the phenolate stream via a PTFE Y-junction and then allowed reaction in a 0.12 mL residence element for 7.8 s. All

Scheme 3. Flow Diagram and Substrate Scope for Continuous Flow Synthesis of 2-Trimethylsilylaryl Trifluoromethylsulfonates[a]



[a] For multihalogenated species an exact equivalent of *n*-butyllithium has to be used to suppress successive lithium halide exchange. [b] Containing a small amount <5% of an impurity.

substrates that underwent retro-Brook rearrangement successfully were converted to the homologous Kobayashi type benzyne precursors in excellent yields, following filtration over a pad of silica to remove inorganic side products and concentration (Scheme 3). To test the scalability of the process, we prepared 2.7 g of **1a** from bromophenol **6a** in 30 min. The product was homogeneous and required no chromatographic purification (see the Supporting Information).

Having established a flow synthesis of 2-trimethylsilyphenyl triflate aryne precursors, we then turned our attention to the triflate nucleofuge. The expense of triflic anhydride, relative to other activating groups, severely restricts its use on scale.[4] In addition, its high reactivity makes it difficult to store and handle in the research laboratory, being subject to rapid hydrolytic degradation and incompatibility with common solvents such as THF. The nonaflate group represents an attractive alternative, being cheaper[4] and far more stable in terms of its precursor reagent 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonyl fluoride (NfF). Aryl nonaflates[12] share similar reactivity to triflates as leaving groups, but are more resistant to hydrolysis. Critically, the nonaflate leaving group is non-nucleophilic—a key requirement for any functional group displaced in a benzyne-generating reaction.

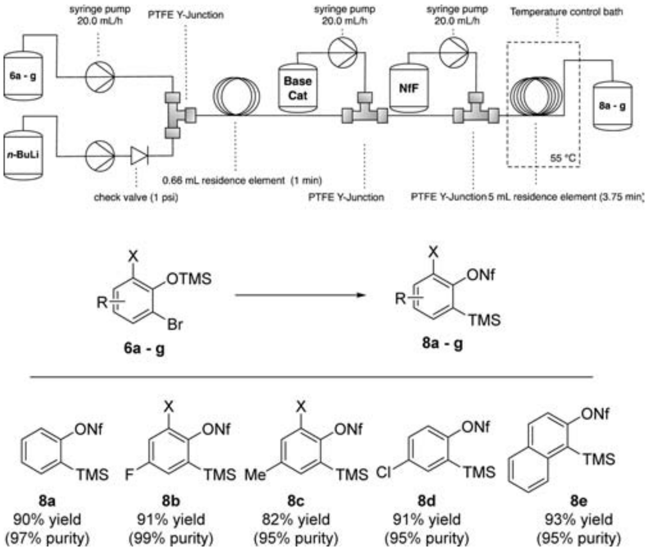
Preparing nonaflate aryne precursors presents an obvious problem, however, in that the fluoride generated from treatment of phenols **7** with NfF could generate benzyne, degrading the precursor as soon as it is formed. This potential in situ reactivity has been harnessed by Akai and co-workers, who treated 2-trimethylsilylphenols with NfF/Cs_2CO_3 in MeCN in the presence of furans.[13] The nonaflates formed in situ underwent fluoride-triggered aryne formation and Diels—Alder reaction, affording adducts in good yield. This approach is necessarily restricted to aryne transformations tolerant of the electrophilic NfF reagent and (strongly) nucleophilic phenolate component present in the reaction. We speculated that our flow synthesis could be adapted to the successful synthesis and isolation of nonaflate aryne precursors, if the displaced fluoride could be held as a tight ion-pair (e.g., LiF in Et_2O) while remaining in solution such that the flow apparatus would not block.

Initial observations on the flow nonaflate process established that the lithium phenolate arising from retro-Brook rearrangement of **6** in Et_2O would not react with NfF directly. No reaction was observed at all on substituting NfF for Tf_2O under the previously successful flow conditions. An optimization study (see the Supporting Information) established that amine bases could promote the reaction, with the key observation being that the nonaflation responded to nucleophilic catalysis.

We developed the flow process shown in Scheme 4, where a THF solution of excess triethylamine containing 4-pyrrolidinopyridine (3 mol %) was mixed with the stream of retro-Brook product **7** in ether. A second mixing of NfF in THF was fed into a residence element held at 55 °C for the longer time of 3.75 min.

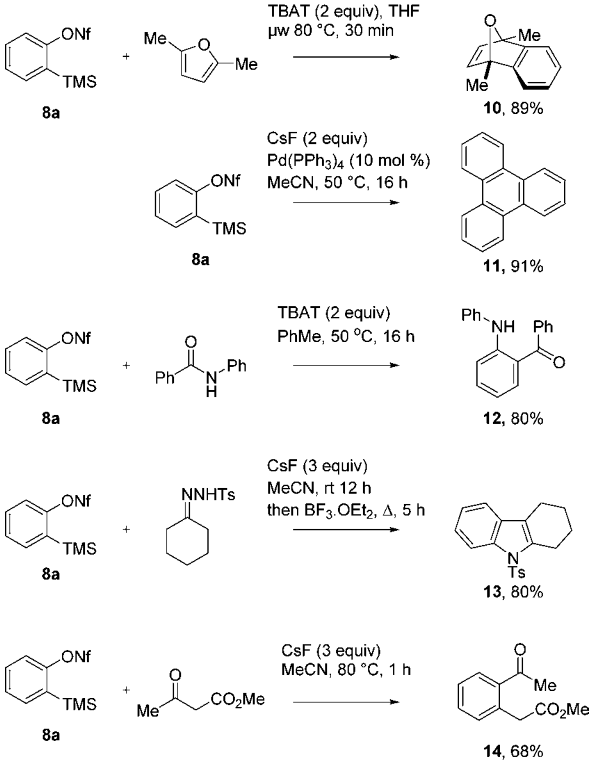
This process gave an excellent 90% yield of nonaflate **8a** in 97% purity after simple filtration through a silica plug and was scaled to produce 20 mmol of **8a** in 1 h. The flow process was applied to the synthesis of nonaflates **8a**−**e**, affording the novel aryne precursors in excellent yields and purities. A limitation was observed when using the dibromo-substituted systems that had been previously observed to react sluggishly with Tf_2O (Scheme 1, **7f** and **7g**). Nonaflation failed in these cases and would likely require temperatures higher than our solvent choice can permit in the flow apparatus.

Scheme 4. Flow Diagram and Substrate Scope for Continuous Flow Synthesis of 2-Trimethylsilyl Nonafluorobutylsulfonates



To verify that the pure nonaflates (**8**) can effectively act as general aryne precursors, we tested them in the transformations shown in Scheme 5. We were pleased to observe successful reaction in 4 + 2 cycloaddition,[14] Pd-catalyzed triphenylene synthesis,[15] amide insertion,[16] benzyne Fisher-indole synthesis,[7c] and β-keto ester insertion.[17] All reactions gave good to excellent yields that are comparable with those reported in the literature for the analogous triflates. The reactions demonstrate

Scheme 5. Nonaflate Precursors in Aryne Transformations



the compatibility of nonaflate **8a** with microwave heating, TBAT and CsF fluoride sources, transition-metal catalysis, and MeCN, THF, and toluene reaction solvents.

In conclusion, we have devised a novel continuous flow process for the synthesis of 2-(trimethylsilyl)phenyl triflate and nonaflate aryne precursors in excellent yields and purities. The flow preparation processes are scalable on a concentration range from 0.1 to 1 M and thus output 2–20 mmol of fine product per hour without further purification. We have used the cheaper and more stable reagent NfF to prepare a range of nonaflate aryne precursors in flow, and demonstrated their effectiveness in a range of aryne chemistries. Further applications of these reagents and processes in arene synthesis will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization data, and copies of spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: michael.greaney@manchester.ac.uk.

Author Contributions

The manuscript was written through contributions of both authors.

Notes

The authors declare no competing financial interest.

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