Alcohol Functionalization

2-Fluoro-5-nitrophenyldiazonium: A Novel Sanger-Type Reagent for the Versatile Functionalization of Alcohols

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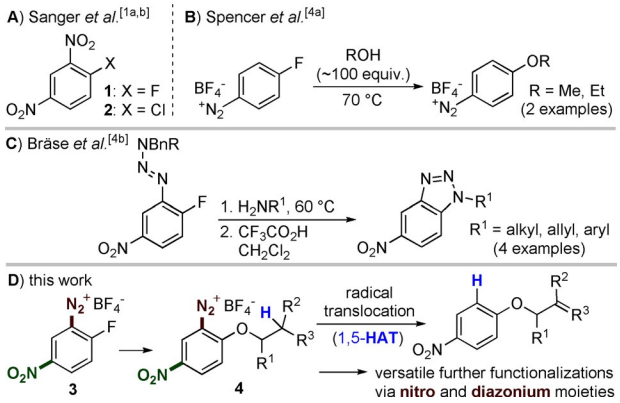
Abstract: As a novel Sanger-type reagent, 2-fluoro-5-nitrophenyldiazonium tetrafluoroborate enabled the versatile functionalization of primary and secondary aliphatic alcohols. Based on a mild nucleophilic aromatic substitution of the fluorine atom under unprecedented, base-free conditions, the diazonium unit on the aromatic core of the resulting aryl-alkyl ether could be employed for such diverse transformations as radical C–H activation and cyclization, as well as palladium catalyzed cross-coupling reactions.

Sanger-type reagents have a long history in organic chemistry,[1] and it is now 75 years ago that Frederick Sanger introduced 1-fluoro-2,4-dinitrobenzene (**1**) for the labeling of terminal amino groups in peptides (Scheme 1 A).[1a] Since then, the dinitro-benzenes **1** and **2**—representing key derivatives—have been widely used,[2] with recent applications in such diverse fields as water analysis,[2a] photosensitization,[2b] and medicinal chemistry.[2c] Given this vast potential, it was interesting to note that among the Sanger reagents, the free diazonium derivative **3** has not yet been studied (Scheme 1 D). While the increased reactivity of **3** compared to **1** and **2** could enable substitutions with even weakly nucleophilic reagents like aliphatic alcohols under mild conditions, such substitution on the aromatic core of **3** would have to proceed under acidic or at most neutral conditions due to the reactivity of the diazonium unit.[3] Generally, nucleophilic aromatic substitutions on diazonium salts are yet rare in literature with few synthetic applications,[4] whereas drawbacks arise from the necessity to use the nucleophile as solvent (Scheme 1 B)[4a] or the requirement to protect the diazonium unit as a triazene (Scheme 1 C).[4b] On the other hand, the presence of a diazonium group on an aryl-alkyl ether such as **4** would enable a broad range of further functionalizations,[5,6] which cannot be achieved with the traditional dinitro substitution pattern.



Scheme 1. Functionalization strategies based on Sanger-type reagents bearing a free or protected diazonium unit.

Among these diazonium-based functionalizations, a particularly valuable group are radical translocation reactions,[7] which have recently been studied by Baran and co-workers,[7a] Ragains and co-workers,[7b,c] and Studer and co-workers.[7d] Upon aryl radical generation from the diazonium unit, hydrogen atom transfer was observed from the 7-position in an alkyl side chain, thereby enabling remote functionalization. The related aryl radical induced hydrogen atom transfer from 5-positions (1,5-HAT), which was one of our research objectives (Scheme 1 D), has earlier been investigated by Murphy et al.[7e] as well as Curran and Xu.[7f] This approach, however, yet requires multistep syntheses for the precursors, whereas the strategy via **3** could directly provide the desired reactants **4**.

In the present work, we show that the exceptional reactivity of the Sanger-type reagent **3** enables a single step access to a broad range of aryl-alkyl ethers **4** under so far unknown, base-free conditions.[8] The diazonium and the nitro group present in **4** can be employed for manifold further transformations including radical translocations to allyl ethers as well as various further *intra* and *inter*molecular C–C bond formations.

Based on an established protocol[9] for the preparation of diazonium tetrafluoroborates under water-free conditions, facile access to decagram quantities of **3** in high yield and purity was obtained without the need for costly and time-consuming purification methods. Subsequently, a series of experiments was conducted to identify optimized conditions for the nucleophilic substitution (Scheme 2).

Owing to the above-mentioned sensitivity of aromatic diazonium salts to even weakly basic conditions,[5a,10] we were

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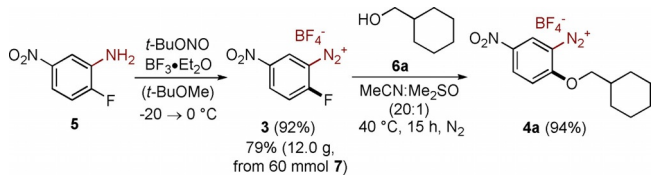


Scheme 2. Preparation of diazonium salt **3** and optimized conditions for nucleophilic substitution.

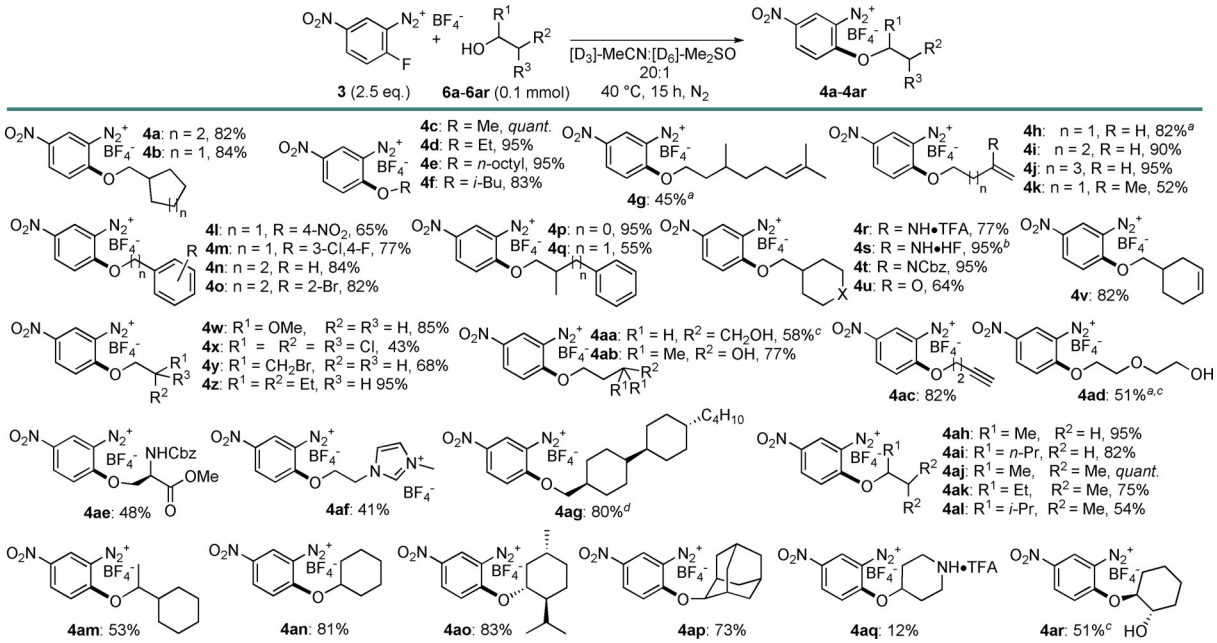
pleased to find that the desired substitution of **3** with cyclohexylmethanol (**6a**) to give **4a** can be achieved in a neutral to weakly acidic environment, which is undoubtedly enabled by the exceptional reactivity of **3** at the ring position bearing the fluorine atom.[4a]

In this context, it should be noted that diazonium tetrafluoroborates are known to be far less dangerous than their analogous chloride or bromide salts and can be safely isolated even at kilogram scale.[11] However, they may be explosive if they have excessive nitrogen content.[10] To unambiguously show that diazonium salt **3** exhibits sufficient stability, a small quantity of this compound was heated to 100 °C for 30 min and the resulting material was analyzed by LC/MS and ^{1}H NMR spectroscopy. Both analytical methods did not point to major decomposition (< 10%) of the compound. During optimization, the addition of a small amount of dry dimethylsulfoxide (5 vol%) to dry acetonitrile turned out as beneficial to achieve high yields of ether **4a** using 2.5 equivalents of the—perspectively—more readily available reactant **3**.

With optimized conditions available, an evaluation of scope and limitations was carried out. Selected results from a large series of experiments conducted on 0.1 mmol scale are summarized in Scheme 3 (see also Supporting Information). Due to the sensitivity of the diazonium unit, the reactions were performed in deuterated solvent followed by direct analysis of the reaction mixture by ^{1}H NMR spectroscopy using an internal standard.

As shown by the broad range of examples, primary and secondary aliphatic alcohols with side chains bearing alkenes, alkynes, aromatics, alcohols, ethers, fluoro, chloro, and bromo substituents, nitro, ester as well as urethane groups are well tolerated. For protonated amines, a sufficiently large distance between the positive charge and the hydroxyl group is required (compare **4r** vs. **4aq**), thereby showing that amino alcohols can be selectively functionalized at the alcohol unit, while the otherwise more nucleophilic amine is protected by simple protonation. An attempt with a *N*-Boc (*tert*-butyloxycarbonyl) protected amino alcohol led to in situ deprotection, most probably due to the liberated hydrofluoric acid, to give **4s**. To underline synthetic applicability, **4a** was also synthesized on gram scale (6.10 mmol, 2.13 g, 94% yield, > 95% purity). Generally, washing the diazonium intermediate **4** with diisopropyl ether, followed by filtration or careful decantation provided the diazonium salt in sufficiently high purity for subsequent reactions in the same vessel. Concerning the stability of the diazonium compounds, **3** and **4a** could be stored in a desiccator at room temperature for several months without noticeable decomposition.

Limitations of the reaction scope, which also give insights into the characteristics of the novel Sanger type reagent, are as follows. While steric demand in the β-positions of secondary alcohols **6** is largely acceptable (e.g., **4al**), tertiary alcohols such as *tert*-butanol do not undergo the substitution reaction with **3**. This is also true for deactivated, less nucleophilic alcohols such as 2,2,2-trifluoroethanol. Allylic alcohols and activated benzylic alcohols (e.g., benzhydrol, furfuryl alcohol), in con-



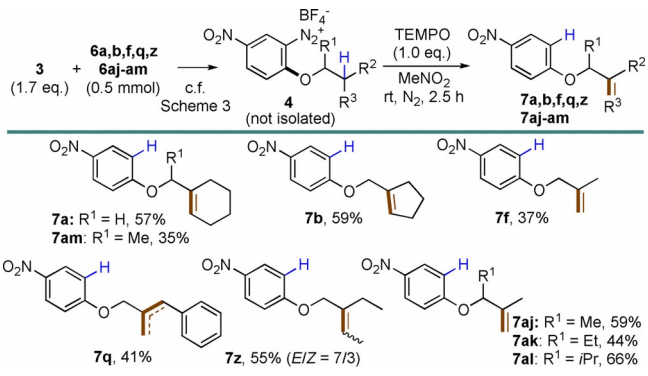
Scheme 3. Scope of primary and secondary alcohols suitable for nucleophilic substitution of **3**. Yields determined using dimethyl sulfone as internal standard. [a] Reaction performed at 0 °C. [b] *N*-Boc protected amino alcohol used as reactant **6s**. [c] 1 equiv. of **3** used. [d] $CDCl_3$ added to the reaction.

trast, provided complex product mixtures, thereby pointing to the leaving group properties of the diazonium-substituted 4-nitrophenolate.

Regarding phenols, which are reliable substrates for diaryl ether synthesis when combined with the classical Sanger reagents **1** and **2** (Scheme 1),[2a,12] such starting materials either led to no reaction with **3** (if acceptor-substituted; e.g., 4-nitrophenol) or to complex product mixtures (if donor-substituted; e.g., 4-methoxyphenol). The latter case can be rationalized by competing azo coupling between **3** and the phenol, as well as aryl radical formation due to the reductive properties of the phenol.

While primary and secondary aliphatic amines mainly showed triazene formation resulting from nucleophilic attack on the diazonium unit,[13] the outcomes with anilines depend (as those for phenols) on the actual substitution pattern. Donor-substituted anilines (e.g., *N*,*N*-diethyl-1,4-phenylenediamine) again act as reductants and partners for azo coupling to yield complex mixtures. Interestingly, acceptor-substituted anilines provided benzotriazoles via substitution of the fluorine atom and cyclization involving the diazonium unit (see Scheme 1 C and the Supporting Information).[4b]

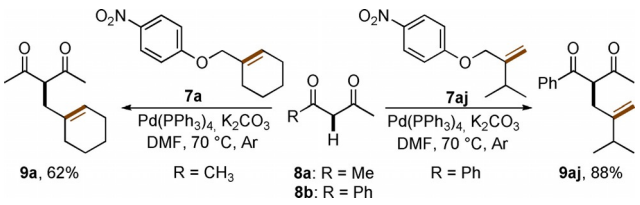
Based on the straightforward accessibility of aryl-alkyl ethers **4** from various primary and secondary alcohols **6**, we then turned to the first field of application. To evaluate the feasibility of radical translocation reactions, nine aryl-alkyl ethers (**4a**,**b**,**f**,**q**,**z** and **4aj**–**am**) were prepared on a 0.5 mmol scale, purified by washing with diisopropyl ether, and subsequently submitted to a reaction with (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) (1.0 equiv.) to induce aryl radical generation. Via hydrogen atom transfer a new double bond is introduced in the side chain (Scheme 4). Within the optimization of the radical translocation step, it turned out that the conditions originally reported by Baran and co-workers[7a] cannot be directly applied, but that a parallel addition of aryl-alkyl ether **4** and TEMPO to the reaction mixture is necessary to reach useful yields for the alkenes **7** (see the Supporting Information for details and mechanism). Notably, this transformation is the first example of an olefination by C–H activation to yield activated aryl-allyl ethers.



Scheme 4. Two-step synthesis of activated allylic alcohols **7** from **3** and **6** involving a radical translocation reaction.

A control experiment with the *n*-butyl substituted aryl ether (**4**, $R^1 = R^2 = H$, $R^3 = Et$, Scheme 4) revealed that, if no particular position in the alkyl chain is activated by alkyl substitution, then hydrogen atom transfer will preferably occur from the β (1,5-HAT) and to a lesser extent from the α position (1,4-HAT) with a ratio of 2.2:1 (28 and 13% yield). The fact that 1,5-hydrogen atom transfer step is reasonably fast, can be estimated from an experiment in which the cyclohexylmethyl substituted ether **4a** (Scheme 3) was treated with three equivalents of iodide instead of TEMPO. Although trapping of aryl radicals by iodide is known to proceed with high rate constants around 10^{10} s^{-1},[5a] only 27% of the Sandmeyer product (the aryl iodide) were obtained, whereas 37% of the reaction products could be directly related to hydrogen atom transfer (see the Supporting Information for details).

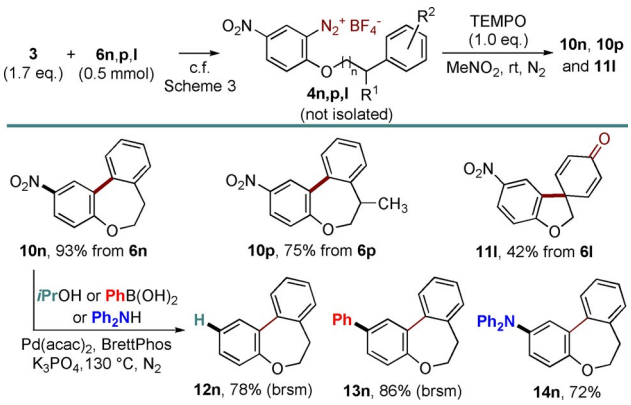
As outlined in Scheme 4, the sequence combining nucleophilic aromatic substitution of diazonium salt **3** with radical translocation is a so far unique strategy to convert aliphatic alcohols **6** into activated allylic ethers **7** in only two reaction steps. Perspectively, the corresponding alcohols may be obtained under mild conditions and with high yields via methanolytical cleavage of the 4-nitrophenyl unit as described by Takahashi and Ogasawara.[14] Compounds structurally related to **7** have further been reported to be useful for numerous applications, including allylic alkylation,[15] Claisen rearrangement,[16] and carbonyl olefination.[17] As illustrative examples, the previously prepared allylic ethers **7a** and **7aj** were further converted under Tsuji–Trost conditions[18] to transform **8a** and **8b** into the highly functionalized 1,3-diketones **9a** and **9aj** in yields of 62 and 88%, respectively (Scheme 5).



Scheme 5. Tsuji–Trost reactions using activated allylic ethers **7a** and **7aj**.

Remarkably, Tsuji–Trost reactions have so far not been conducted with 4-nitrophenol as a leaving group. As a second field of application, and again exploiting the presence of the diazonium unit in the aryl-alkyl ethers **4**, we turned to radical reactions proceeding under carbon–carbon bond formation (Scheme 6). Within this study, the tricylic dibenzoxepanes **10n** and **10p** as well the spirocyclic derivate **11l** became accessible in only two steps from the alcohols **6n**, **6p**, and **6l**. As shown, the novel type of Pschorr cyclization[19] to the spirocyclic dihydrobenzofuran **11l** requires a shorter chain length ($n = 0$) and an additional nitro group ($R^2 = 4\text{-}NO_2$) in the aryl-alkyl ether **4l**.[20]

The further synthetic options arising from the presence of the nitro substituent on the aromatic core of the diazonium salt were exemplified by three transformations using dibenzoxepane **10n** as starting material (Scheme 6). In palladium-cata-



Scheme 6. Aryl-alkyl ethers **4** in Pschorr cyclizations and further transformations of the nitro group.

lyzed reactions employing BrettPhos as key ligand,[21] reduction to **12n**, aryl–aryl coupling to **13n** as well as amination to give **14n** were achieved in good to high yields. As a result, the overall strategy gives facile access to the diverse dibenzoxepanes requiring only 2 to 3 reaction steps, which is an ideal starting point for the elucidation of structure–activity relationships. Known applications of dibenzoxepanes comprise different fields of medicinal chemistry,[22a,b,c] natural product synthesis,[22d,e] and mechanistic studies,[22f,g] whereas the reported synthetic studies further underline the general interest in this compound class.[22h,i] This is also the case for the spirocyclic compound **11l**, which constitutes the key structural element of several natural products of the kadsuralignan and interiorin type, which are known for their antioxidant and anti-HIV properties.[23]

With the aim to further exploit the diazonium unit present in the aryl-alkyl ethers **4**, we also evaluated the applicability in palladium-catalyzed transformations. As shown by representative examples in the Supporting Information, transformation of **4a** under Suzuki[24] and Heck–Matsuda[25] conditions gave biphenyl and cinnamic acid derivatives in high yields of 88 and 78%, respectively. Two subsequent aryl–aryl coupling reactions, now involving the diazonium and the nitro unit, provided a *m*-terphenyl derivative.[21b,24a] Regarding a future analytical labeling of aliphatic alcohols with the novel Sanger-type reagent **3**, a valuable option also arises from the conversion of the adducts **4** into azobenzene derivatives, which can enable much easier colorimetric detection than yet achievable with traditional Sanger reagents (see the Supporting Information).

In conclusion, it has been shown that the novel Sanger-type reagent 2-fluoro-5-nitrophenyldiazonium **3** is particularly useful for the functionalization of a broad range of primary and secondary aliphatic alcohols. While the exceptionally strong electron-withdrawing character of the diazonium group enabled aromatic substitutions with weakly nucleophilic alcohols under yet unknown neutral and acidic conditions, the presence of the diazonium unit can be exploited in various further transformations. Besides C–H activation combined with radical translocation, diverse radical as well as palladium-catalyzed carbon–carbon bond formations could be carried out. These manifold synthetic options are nicely complemented by additional functionalization via the nitro aromatic group, which overall renders the novel Sanger-type reagent **3** a broadly applicable tool in organic synthesis.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: C–C bond formation · C–H activation · diazonium · nucleophilic aromatic substitution · Sanger reagent

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