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Letter

Cine-Substitutions at Five-Membered Hetarenes Enabled by Sulfonium Salts

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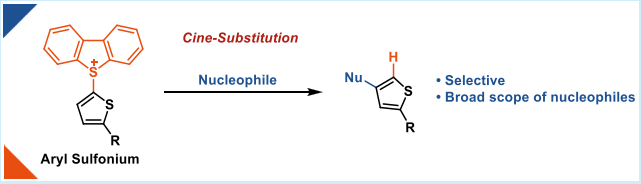
ABSTRACT: We report a nucleophilic substitution reaction of five-membered hetarylsulfonium salts that results in a change of the substitution pattern on the arene. The products of these *cine*-substitutions are hard to access synthetically otherwise. The sulfonium salts that serve as starting materials are generated by a highly site-selective C–H functionalization reaction.



Substitution reactions on arenes that change the substitution pattern when a non-hydrogen leaving group is replaced give access to potentially valuable molecules with a constitution that is often hard to access otherwise. Even site-selective C–H functionalization reactions, in the best case, dictate which single position is functionalized as a consequence of the reaction mechanism, so that the other positions are not easily accessible for functionalization. Despite the high potential utility of reactions that change the substitution pattern, such *cine*- and *tele*-substitutions are rare.[1−3] Here we report *cine*-substitution reactions of electron-rich hetarylsulfonium salts with various nucleophiles. The starting materials are readily accessible through site-selective C–H functionalization,[4] and the physicochemical properties, namely, the ability to form ylides, distinguish the sulfonium leaving groups used in this chemistry from other (pseudo)halides. The unusual reactivity is enabled by the ability of the sulfonium salt to function both as a cationic pseudo-Michael acceptor and as a leaving group, which together with the exquisite site selectivity for C–H functionalization sets it apart from other leaving groups in current arene substitution reactions. Hence, the method allows for the synthesis of constitutional isomers to which there is no other straightforward access with alternative methods.

Depending on whether a functional group is introduced at the position adjacent to the position of a leaving group or a position further away, aromatic substitution reactions are classified as *cine*- or *tele*-substitutions, respectively (Figure 1a).[5] In combination with a site-selective C–H functionalization reaction, a *cine*-substitution reaction would double the number of isomers that are accessible selectively. However, no general *cine*-substitution reaction is currently available. Reactions that proceed via an aryne intermediate through an elimination–addition mechanism lose the positional information on the starting material substituents in the aryne intermediate and therefore usually produce mixtures of *cine*- and *ipso*-substitution products.[6] Addition of nucleophiles to electron-poor arenes, for

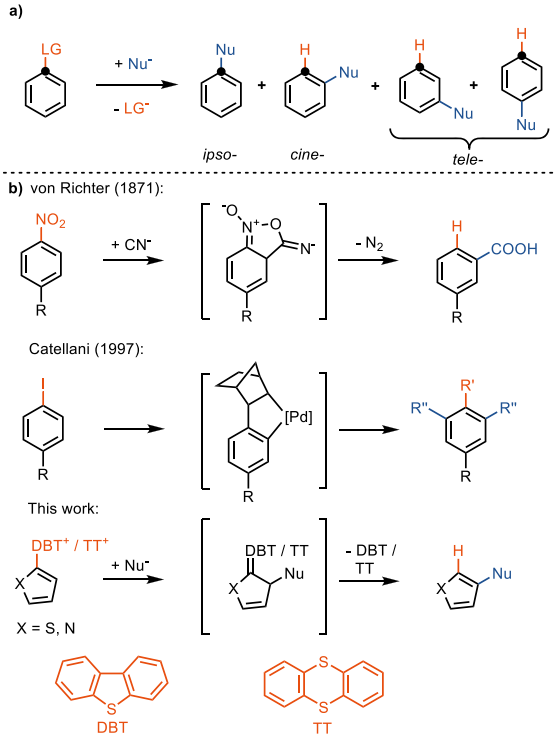


Figure 1. (a) Nomenclature of aromatic substitution of a leaving group (LG) with a nucleophile (Nu^-) and (b) methods available for *cine*-substitution.

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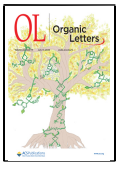

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example *ortho* to a nitro group, is possible, but nitrite is not a sufficiently good leaving group, so *cine*-substitutions with the elimination of nitrous acid are rare.[3] A special example of a *cine*-substitution—limited to cyanide addition to nitroarenes for the synthesis of benzoic acids—is the von Richter reaction[7] (Figure 1b), which circumvents the elimination of nitrite by intramolecular attack of the nitro group onto the cyano group after addition, followed by rearrangement and loss of dinitrogen to yield benzoic acids.[7b−d]

In the Catellani reaction[8] (Figure 1b), a norbornene cocatalyst enables *ortho* functionalization, typically of aryl iodides, through palladium catalysis. The reaction has great potential and utility but is still limited to a rather small number of functional groups and typically results in functionalization of both *ortho* positions unless other carefully placed substituents are present.[8] The most substantial difference between the few available reported methods and the approach disclosed here is the lack of available methods to prepare the starting materials selectively in the former case. Therefore, even if *cine*-substitution is achievable in a few reactions, the initial C−H functionalization to prepare their starting materials still results in more than one constitutional isomer for most methods and most arenes.

We propose a *cine*-substitution that proceeds by the initial addition of the nucleophile to the arylsulfonium salt, enabled by its cationic charge, which results in sulfur ylide **II** (Figure 2a).

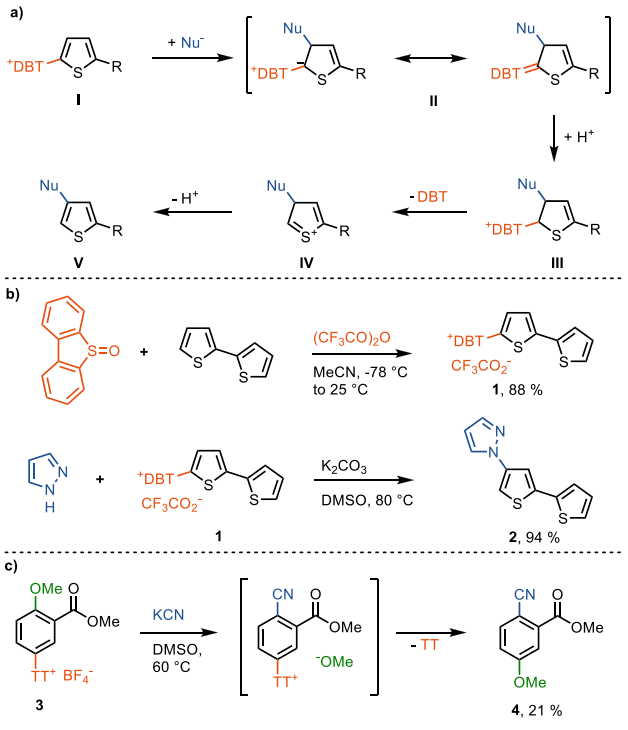

Figure 2. (a) Proposed mechanism of *cine*-substitution. (b) Substitution of a dibenzothiophenium salt. (c) Mechanistic control experiments with an unsuitable substrate.

Protonation of the ylide results in the formation of a sulfonium salt (intermediate **III**), from which elimination of DBT produces the final product (**V**). Dissociation of DBT from **III** should be favored for arenes that stabilize the ensuing positive charge, for example electron-rich hetarenes such as thiophenes. In line with our proposal, treatment of sulfonium salt **1** (Figure 2b), which is accessible by selective C−H functionalization from 2,2′-bithiophene, with nucleophiles such as pyrazole results in clean *cine*-substitution. The execution of the reaction is simple, as it does not need any additives, catalysts, or transition metals and is tolerant of air and moisture. The reaction is applicable to thiophenes, thienothiophenes, imidazopyridines, and naphthalene derivatives, which undergo *cine*-substitution with various nucleophiles (Figure 3). Although furan could also stabilize the ensuing positive charge, *cine* products of furan-derived DBT salts were not detected, possibly because of the lower stability of those sulfonium salts. Substrates that would not stabilize a cationic intermediate analogous to intermediate **IV**, such as simple six-membered mononuclear arenes, did not react at all or underwent side reactions. In the case of thianthrenium salt **3** (Figure 2c), a double nucleophilic substitution was observed, resulting in the replacement of the methoxy group for a cyano substituent and subsequent substitution of the thianthrenium group for the previously released methoxide. The nucleophilic substitution of the methoxy group shows that addition of a nucleophile to the arylsulfonium salt is possible, even though no *cine*-substitution was observed.

The reaction works well with cyanide, which is used as its potassium salt, as well as with a broad scope of nitrogen nucleophiles that possess pK_a values between 10 and 20 in DMSO, such as imides, triazoles, pyrazoles, imidazoles, hydantoins, and pyridones (Figure 3). The nucleophile can be used as the potassium salt directly if it is available (e.g., K-phthalimide) or can be generated in situ from its corresponding acid by deprotonation with a base as weak as potassium carbonate. In the substitutions with ambident nucleophiles such as 1,2,4-triazoles (compounds **9**, **15**, **18**, and **22**) and pyridone (compound **23**) single products were obtained, while substitution with benzotriazole (compounds **6** and **12**) produced two isomers resulting from reaction of the benzotriazolate at the 1- or 2-position (see the Supporting Information). The major isomer was obtained in pure form and is shown in Figure 3. With weaker nucleophiles such as benzene sulfinate (pK_a = 7 in DMSO[9]) and acetylacetonate (pK_a = 13 in DMSO[9]) no reactions with the sulfonium salts were observed. The reaction of strongly basic nucleophiles such as alkoxide (pK_a(MeOH) = 29 in DMSO[9]) with sulfonium salts results in products of the cleavage of the endocyclic C−S bond of the sulfonium leaving group or products of *ipso*-substitution, while *ipso*-substitution was not observed in any of the reactions shown in Figure 3. Presumably such basic nucleophiles attack on the sulfur atom and subsequently undergo reductive elimination, breaking either the exocyclic C−S bond (to produce *ipso*-substitution products) or the endocyclic C−S bond.[4e] In protic solvents the nucleophilicity and pK_a of alkoxides decrease, allowing *cine*-alkoxylation to take place in alcoholic solution (compound **24**, Figure 3). The sulfonium leaving group can be dibenzothiophene, thianthrene, or diphenyl sulfide. Electron-rich heterocycles are best functionalized using dibenzothiophenation, but otherwise the more reliable thianthrenation is preferred. For particularly electron-rich and oxidation-sensitive 2-methoxynaphthalene and anthracene, the less reactive diphenyl sulfoxide was used to generate the sulfonium salt. Independent of the choice of the leaving group, single isomers were observed in the C−H functionalization step. Many products accessible by *cine*-substitution, such as the compounds shown in Figure 3, would require multiple steps to be synthesized otherwise. For example, in thiophenes the 2-position is usually the most reactive position, causing electrophilic reactions, radical reactions, and many metal-catalyzed C−H functionalization reactions to occur at the 2-position,[10] while

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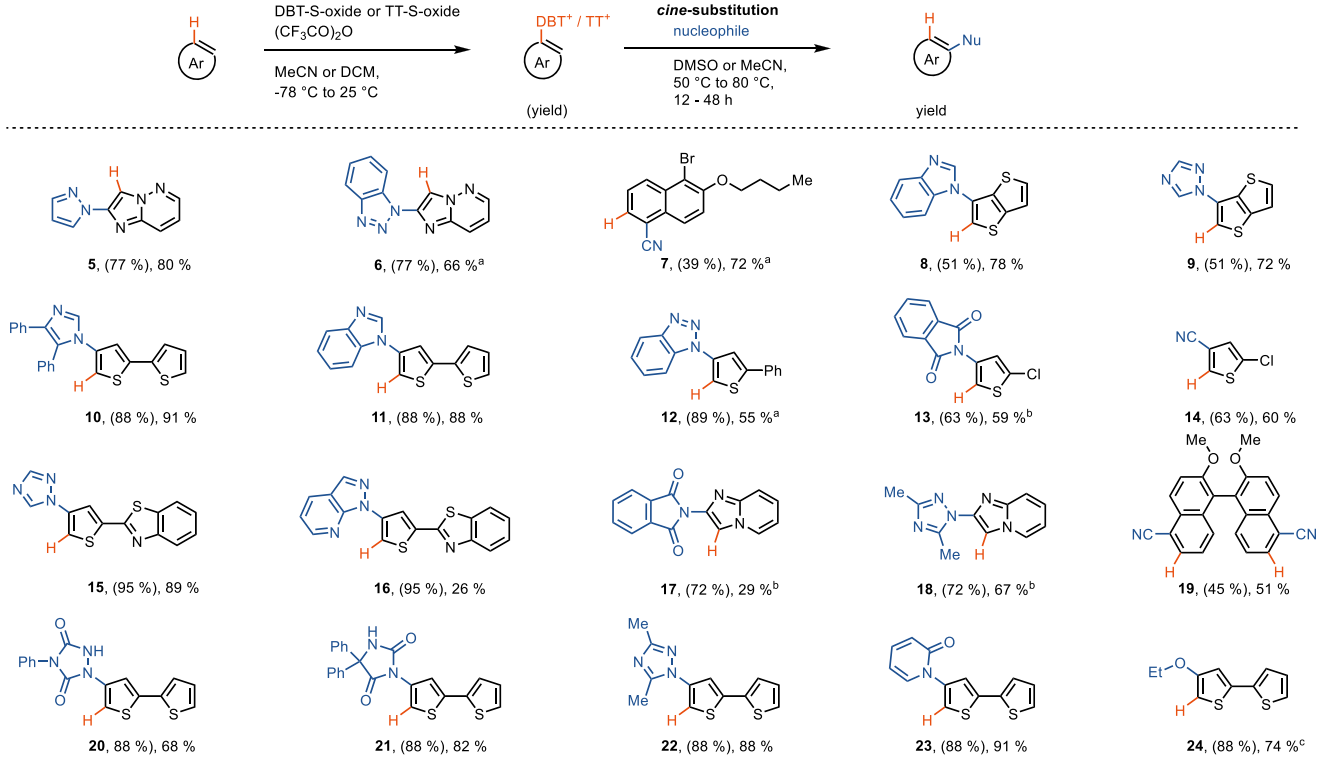

Figure 3. Products obtained by *cine*-substitution of arylsulfonium salts. Reaction conditions: Sulfonium salt (0.12−1.3 mmol, 1.0 equiv), Nucleophile−K (2.0−4.0 equiv) or Nucleophile−H (1.7−3.4 equiv) + K_2CO_3 (2.0−4.5 equiv), and the solvent (MeCN or DMSO; c = 33−150 mM) were stirred at 50−80 °C for 12−48 h. [a]*Cine*-substitution with benzotriazole reacting at its 2-position was also observed. [b]Reaction time: 3 days. [c]Solvent: EtOH, NaOtBu used instead of K_2CO_3.

only a few methods are available for the synthesis of 3-substituted thiophenes.[11] Many compounds similar to the molecules in Figure 3 have found application in medicinal chemistry or materials science. For example, thienothiophenes substituted with nitrogen-based functional groups, similar to compounds **8** and **9**, have been used as precursors for organic semiconductors and require thienothiophenes that already carry a bromo substituent at the 3-position as starting materials for the synthesis.[12] The 3-bromothienothiophene needs to be prepared by annelation of a thiophene ring to a 3-brominated thiophene[13] because bromination of thienothiophene would result in a different substitution pattern.[14] Also, thiophenes substituted with pyrazoloquinolines at the 3-position, which were found to be antagonists of benzodiazepine receptors,[15] were synthesized from building blocks that already carry a substituent at the 3-position.[15] Imidazopyridines substitued with nitrogen at the 2-position, similar to compounds **17** and **18**, are motifs in kallikrein-7 inhibitors.[16] The 2-aminoimidazopyridine unit was synthesized in a four-step synthesis by annelation of the imidazole ring to a pyridine.[17]

When both positions adjacent to the sulfonium leaving group are blocked, *cine*-substitution cannot take place, but the substitution can still occur at a *tele* position, i.e., a position further away from the leaving group (compounds **25**−**28**; Figure 4). The attack of the nucleophile at a position further away from the leaving group is less favorable, which is evident from the reaction of the chlorothiophene-derived sulfonium salt, which undergoes *cine*-substitution (compounds **13** and **14**, Figure 3) but not nucleophilic aromatic substitution of the chlorine substitutent. Because the attack of the nucleophile at a position further away from the leaving group is less favorable, *tele*-

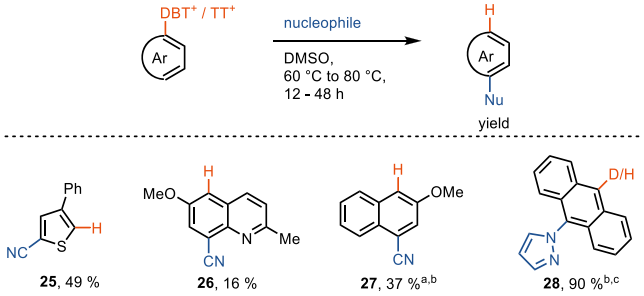

Figure 4. *Tele*-substitution of arylsulfonium salts. [a]Reaction time: 6 days. [b]The diphenylsulfonium salt was used. [c]Solvent: DMSO-d_6/D_2O (100:1 v/v); deuterium incorporation: 77%.

substitutions were observed only with strong nucleophiles such as cyanide. Also, the yields for *tele*-substitution are generally lower than for *cine*-substitution. The reaction with the symmetrical anthracene was carried out in a deuterated solvent (compound **28**; Figure 4). The incorporation of deuterium indicates that the product is predominantly formed by *tele*-substitution and not by *ipso*-substitution. The higher yield for the *tele*-substitution with the anthracene-derived sulfonium salt could be a result of a lower resonance energy of the central ring of anthracene and better stabilization of the positive charge in the cationic intermediate analogous to **IV** (Figure 2b).

This initial study demonstrates a new approach to accomplish *cine*-substitution by utilizing arylsulfonium salts as pseudo-Michael acceptors. It could be a first step to new chemistry making use of nucleophilic addition to arenes enabled by the sulfonium moiety, which can be introduced selectively in a single step. To accomplish such a goal, further expansion of the arene

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scope toward benzene derivatives would need to be achieved, likely through a different mechanistic pathway for elimination that avoids intermediate **IV** (Figure 2b). Nevertheless, the chemistry shown here can already provide arenes with unusual substitution patterns on useful but otherwise challenging to functionalize heterocycles such as imidazopyridine **6**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02067.

Detailed experimental procedures, spectroscopic characterization, and X-ray crystallographic data (PDF)

Accession Codes

CCDC 1987147−1987150 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare the following competing financial interest(s): A patent application dealing with the use of thianthrene and its derivatives for C-H functionalization has been filed (EP18204755.5, Germany), and F.B. and T.R. may benefit from royalty payments.

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