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Synthesis of Arenesulfonyl Fluorides via Sulfuryl Fluoride Incorporation from Arynes

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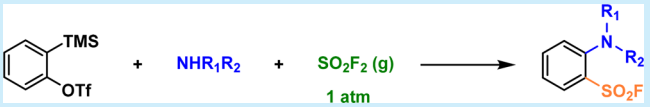
Supporting Information

ABSTRACT: Transition-metal-free multicomponent reactions involving aryne precursors, secondary amines, and sulfuryl fluoride are reported herein. Zwitterionic intermediates formed from the reaction of arynes with amine nucleophiles can capture SO_2F_2 under mild conditions, offering a novel and practical protocol for the synthesis of 2-dialkyl-, 2-alkylaryl-, or 2-diarylamino-substituted arenesulfonyl fluoride derivatives in good to excellent yields.



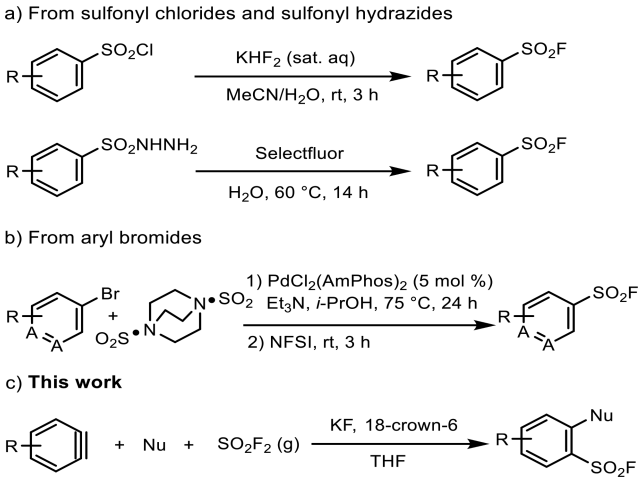
Aromatic amines are abundant in biologically active molecules.[1] Among numerous aromatic amines, *o*-aminoarenesulfonyl derivatives exhibit a wide range of pharmacological activities like antitumor,[2] antiviral,[3] antihypertensive,[4] diuretic,[5] antipsychotic,[6] and anti-inflammatory[2] properties. Therefore, much research effort has been focused on the development of efficient synthetic methods for 2-amino-substituted arenesulfonyl derivatives.[7]

Sulfonyl fluorides have received significant attention due to their unique utility in the fields of chemistry[8] and chemical biology.[9] In comparison to other aryl sulfonyl halides, aryl sulfonyl fluorides possess considerable stability toward reduction[10] and hydrolysis,[11] often resulting in increased chemoselectivity.[12] These characteristics make them privileged motifs in novel drug discovery efforts.[9] Recently, considerable research effort has been focused on new applications of arenesulfonyl fluorides, such as ^{18}F-radiolabeling,[13] deoxyfluorination,[14] click reaction,[15] and sulfonamide preparation.[16]

However, despite the importance of sulfonyl fluorides, direct synthetic approaches toward them have been limited.[8] Sulfonyl compounds are often used as starting materials for sulfonyl fluorides, as found in the reactions of potassium bifluoride with sulfonyl chlorides and Selectfluor with sulfonyl hydrazides (Scheme 1, a).[12,17] Recently, Willis et al. reported a Pd-catalyzed one-pot synthesis of arenesulfonyl fluorides from aryl bromides (Scheme 1, b).[18] This process involves transition-metal-catalyzed sulfonylation of aryl bromides using 1,4-diazabicyclo[2.2.2]octane−bis(sulfur dioxide), followed by treatment of the sulfinate with a fluorine source, e.g., *N*-fluorobenzenesulfonimide (NFSI). The tolerance of this two-step reaction to diverse functional groups is noteworthy; nevertheless, an alternative transition-metal-free synthetic protocol is more desirable. We herein report the development of an efficient protocol to obtain arenesulfonyl fluorides without using transition-metal-based reagents (Scheme 1, c).

Arynes have been recognized as valuable intermediates and have been utilized in several interesting synthetic transformations.[19] In particular, multicomponent reactions

Scheme 1. Synthetic Routes to Arenesulfonyl Fluorides



(MCRs) of arynes afforded diverse 1,2-disubstituted benzene derivatives under transition-metal-free conditions.[20] Typically, nucleophiles add to arynes generating zwitterion intermediates, which are readily trapped by electrophiles. Sharpless et al. reported an extremely useful employment of sulfuryl fluoride (SO_2F_2) for efficient construction of aryl fluorosulfates from phenol derivatives, while *N*-disubstituted sulfamoyl fluorides form secondary alkylamines in the presence of a base.[12] We envisioned that SO_2F_2 can be captured by the reactive zwitterions generated from the reaction of arynes, producing sulfonyl fluorides. We report herein a new SO_2F_2 incorporation reaction via MCRs using arynes and nucleophiles including secondary amines.

First, we investigated various known nucleophiles for the three-component reaction of arynes in the presence of sulfuryl

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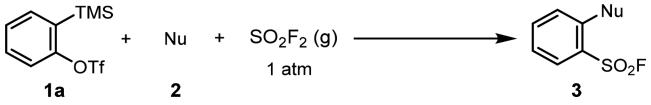
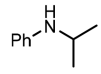
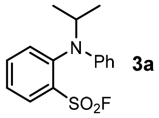
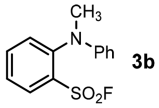
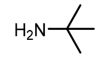
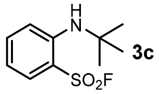
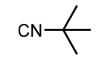
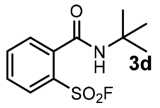
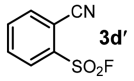
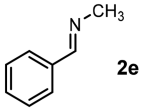
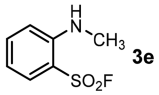
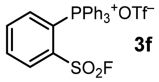
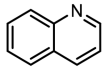
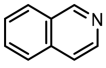
fluoride (Table 1). Several nucleophiles like isocyanides,[21] amines,[22] imines,[23] *N*-heterocycles,[24] and phosphines[25] have previously been used for MCRs with arynes. We screened various nucleophiles using 2-(trimethylsilyl)phenyl triflate (**1a**) as a model substrate, following the procedure reported for each nucleophile. When *N*-isopropylaniline (**2a**) was added to **1a** in THF at room temperature in 1 atm SO_2F_2 atmosphere, sulfonyl fluoride derivative **3a** was obtained in 53% yield. To see if the reaction works with a primary amine nucleophile, a reaction with either methylamine (**2b**) or *tert*-butylamine (**2c**) was investigated. The reaction using methylamine (**2b**) did not afford the desired three-component product because of further reaction with another aryne. Even though 2-(trimethylsilyl)-phenyl triflate (**1a**) disappeared completely, the reaction afforded 2-(methyl(phenyl)amino)benzenesulfonyl fluoride (**3b**) as a major product in 10% yield along with other side products. However, the reaction with *tert*-butylamine (**2c**) furnished 2-(*tert*-butylamino)benzenesulfonyl fluoride (**3c**) in 70% yield. Interestingly, when *tert*-butyl isocyanide (**2d**) was used as a nucleophile, 2-(*tert*-butylamidocarbonyl)-benzenesulfonyl fluoride (**3d**) and 2-cyanobenzenesulfonyl fluoride (**3d′**) were obtained in 67% and 20% yields, respectively. When we treated **1a** with *N*-benzylidenemethylamine (**2e**), we obtained 2-(*N*-methylamino)benzenesulfonyl fluoride (**3e**) in 70% yield, apparently from the hydrolysis of the resultant iminium ion after the desired three-component reaction. When triphenylphosphine (**2f**) was used as a nucleophile, (2-(fluorosulfonyl)phenyl)triphenylphosphonium triflate (**3f**) was furnished in 75% yield. Unfortunately, for *N*-heterocyclic nucleophiles like quinoline and isoquinoline, no product was formed. Since the reaction with *N*-isopropylaniline proceeded effectively, we have investigated various amine derivatives for the generation of diversely substituted *o*-aminoarenesulfonyl fluorides, which can be used for the synthesis of important drug intermediates.

Table 1. MCRs Involving Arynes, Nucleophiles, and SO_2F_2[a]



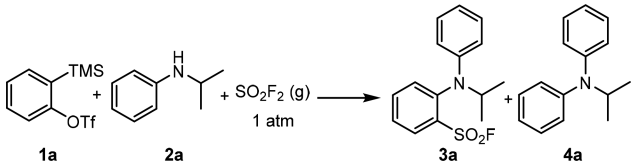
1a **2** **3**

entry	nucleophile	product	yield (%)
1	 **2a**	 **3a**	53
2	H_2N-CH_3 **2b**	 **3b**	10
3	 **2c**	 **3c**	70
4	 **2d**	 **3d**  **3d′**	67, 20
5	 **2e**	 **3e**	70
6	PPh_3 **2f**	 **3f**	75
7		n.d.[b]	–
8		n.d.[b]	–

[a]Reaction conditions: **1a**, nucleophile, KF, 18-crown-6, and THF under SO_2F_2 atmosphere (1 atm). [b]Not detected.

We proceeded to further optimize the reaction conditions for the three-component reactions using *N*-isopropylaniline (**2a**) as a representative nucleophile. We chose compound **1a** as the aryne precursor and carried out reactions at −10 °C under 1 atm SO_2F_2 atmosphere, following Yoshida's and Biju's CO_2 capture procedure.[22] The results are collected in Table 2.

Table 2. Reaction Optimization[a]



1a **2a** **3a** **4a**

entry	F^- source (equiv)	additive (equiv)	solvent	**3a**[b] (%)	**4a**[b] (%)
1	CsF (4.5)		CH_3CN	0	0
2	KF (4.5)		THF	0	0
3	TBAF (4.5)		THF	0	29
4	TBAT (4.5)		THF	0	24
5	CsF (4.5)	18-crown-6 (4.5)	CH_3CN	3	39
6	KF (4.5)	18-crown-6 (4.5)	CH_3CN	7	38
7	KF (4.5)	18-crown-6 (4.5)	MTBE	3	3
8	KF (4.5)	18-crown-6 (4.5)	DME	66	26
9	KF (4.5)	18-crown-6 (4.5)	THF	78	21
10[c]	KF (4.5)	18-crown-6 (4.5)	THF	68	29
11[d]	KF (4.5)	18-crown-6 (4.5)	THF	36	53
12	KF (3.0)	18-crown-6 (3.0)	THF	82	18
13[e]	KF (3.0)	18-crown-6 (3.0)	THF	60	35
14[f]	KF (3.0)	18-crown-6 (3.0)	THF	0	11

[a]Reaction conditions: **1a** (1.5 equiv), **2a** (1.0 equiv, 0.25 mmol) and solvent (2.5 mL) at −10 °C under SO_2F_2 atmosphere (1 atm) for 24 h. [b]Determined by GC analysis with dodecane as an internal standard. [c]Reaction was performed at 0 °C. [d]Reaction was performed at 25 °C. [e]**1a** (1.0 equiv, 0.25 mmol), **2a** (1.5 equiv). [f]Fluorosulfuryl imidazolium salt (1.0 equiv) was used instead of SO_2F_2 under Ar atmosphere (1 atm).

First, examination of diverse fluoride sources revealed that the reactivity highly depends upon the fluoride source. No product was obtained from the reactions using KF or CsF (entries 1 and 2). When tetrabutylammonium fluoride (TBAF) or tetrabutylammonium difluorotriphenylsilicate (TBAT) was used as the fluoride source, the protonated product, *N*-isopropyl-*N*-phenylaniline (**4a**), was obtained as the only product (entries 3 and 4).[26] However, the desired three-component reaction product **3a** was formed in a small amount when 18-crown-6 was used as an additive along with KF or CsF in acetonitrile (entries 5 and 6, respectively). Still, the protonated product **4a** was formed in a significant amount. Reaction in methyl *tert*-butyl ether gave a very low yield of both the desired product **3a** (3%) and **4a** (3%) (entry 7).

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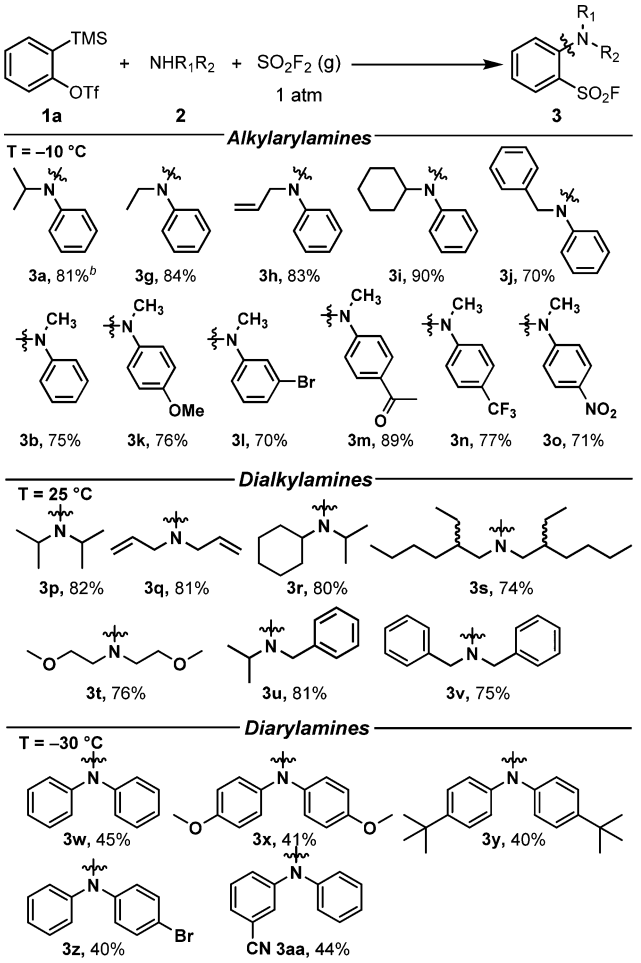
However, reaction in dimethoxyethane (DME) yielded 66% of the desired product **3a** and 26% of **4a** (entry 8). The reaction in tetrahydrofuran (THF) improved the yield of the desired product significantly (entries 9 and 12). The selectivity for the three-component product, compared with the protonation product, was also dependent on temperature (entries 9−11). Warming the reaction to room temperature yielded more of the protonated product **4a**, presumably due to rapid proton transfer from the ammonium salt intermediate at higher temperatures (entry 11). Use of 4.5 equiv of KF did not provide better selectivity for the desired product than that of 3.0 equiv KF (entries 9 and 12). Use of excess amine (1.5 equiv) under otherwise the same reaction conditions did not improve the selectivity or the yield (entry 13). When fluorosulfuryl imidazolium salt was employed instead of SO_2F_2, which is a more reactive fluorosulfating reagent for amines and phenols, only a small amount of **4a** was formed without any desired fluorosulfonyl product (entry 14).[27]

With the optimized reaction conditions in hand, various secondary amines, such as alkylarylamines, dialkylamines, and diarylamines, were examined as nucleophiles in the three-component reactions. Scheme 2 shows that different reaction temperatures had to be employed to provide high yields of the desired products, depending on the amine substituents. We found that the choice of the reaction temperature should be based on the propensity for proton ransfer of the intermediate aryl anion. Reactions involving alkylarylamines like *N*-isopropyl-, *N*-ethtyl-, *N*-allyl-, *N*-cyclohexyl-, and *N*-benzylaniline were conducted at −10 °C and afforded the desired products in 81, 84, 83, 90, and 70% yields, respectively. *N*-Methylaniline and diversely substituted (*p*-methoxy, *m*-bromo, *p*-acetyl, *p*-trifluoromethyl, and *p*-nitro) *N*-methylanilines afforded the desired products in 75, 76, 70, 89, 77, and 71% yields, respectively. Reactions employing dialkylamines were carried out at 25 °C and furnished the *o*-dialkylamino-substituted benzenesulfonyl fluorides in good (74−82%) yields. The reaction of diisopropylamine in the presence of sulfuryl fluoride proceeded efficiently, affording the desired product in 82% yield. Reaction involving diallylamine or *N*-isopropylcyclohexylamine also proceeded smoothly with 81 and 80% yields, respectively. Even sterically demanding bis(2-ethylhexyl)amine participated well in the three-component reaction to give the desired product in 74% yield. Bis(methoxyethyl)amine, benzylisopropylamine, and dibenzylamine all emerged as good substrates for the coupling reactions, furnishing 76, 81, and 75% yields, respectively. Unfortunately, reactions involving cyclic amines like piperidine and pyrrolidine proceeded directly with SO_2F_2, instead of with the aryne to give *N*-sulfamoyl fluorides. In the reactions involving diarylamines, we discovered that THF participated as a nucleophile, presumably due to its higher nucleophilicity than the diarylamines. Therefore, the solvent was switched to DME.[28] Due to the higher acidities of diarylammonium salts, their reactions produced more protonated compounds at high temperatures; therefore, the reactions were conducted at −30 °C, and somewhat reduced yields were obtained due to the decreased activity at low temperatures. The reactions were well-tolerated, however, regardless of the substituents on the diarylamines, such as electron-donating methoxy and *tert*-butyl groups and electron-withdrawing bromo and cyano groups. Notably, a variety of functional groups, including allyl, methoxy, bromo, carbonyl, trifluoromethyl, nitro, and cyano groups, survived the reaction conditions.

Scheme 2. Scope of Secondary Amines[a]



[a]Reaction conditions for the reactions employing alkylarylamine: **1a** (1.5 equiv), amine (1.0 equiv), KF (3.0 equiv), 18-crown-6 (3.0 equiv), and THF (2.5 mL) at −10 °C under SO_2F_2 atmosphere (1 atm) for 24 h. Reaction conditions for the reactions employing dialkylamine: **1a** (1.0 equiv), amine (1.5 equiv), KF (3.0 equiv), 18-crown-6 (3.0 equiv), and THF (2.5 mL) at 25 °C under SO_2F_2 atmosphere (1 atm) for 24 h. Reaction conditions for the reactions employing diarylamine: **1a** (1.5 equiv), amine (1.0 equiv), KF (3.0 equiv), 18-crown-6 (3.0 equiv), and DME (0.5 mL) at −30 °C under SO_2F_2 atmosphere (1 atm) for 24 h. [b]77% yield was obtained on a 1 mmol scale reaction.

To investigate the scope of the aryne part, we investigated substituted aryne precursors for the three-component reactions (Table 3). Using *N*-isopropylaniline (**2a**) as a model nucleophile, we examined the reactions of various functionalized arynes. The reaction with 4-methylbenzyne (**1b**) proceeded well, affording **5a** and **5a′** in a 1.3:1 ratio and 80% yields. While high regioselectivity (10:1) was observed with 6-methylbenzyne (**1c**), the yield (46%) was lower than that of the reaction with 4-methylbenzyne.[22,29] Symmetrical aryne precursors like dimethoxy (**1d**) and naphthyl (**1e**) derivatives afforded single products in 86 and 80% yields, respectively. Decreased yield (35%) was obtained with 4-fluorobenzyne (**1f**), providing **5e** and **5e′** in 4.2:1 ratio.

To probe the reaction mechanism, reactions of **1a** with *N*-sulfamoyl fluorides were performed under the optimized conditions in an Ar atmosphere (Scheme 3). As mentioned above, cyclic secondary alkylamines like pyrrolidine, piperidine,

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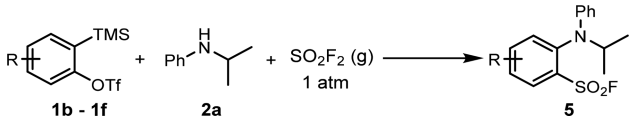
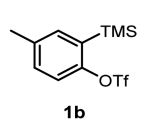
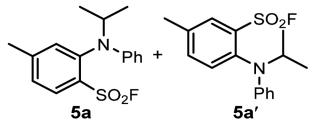
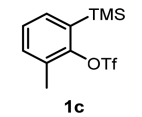
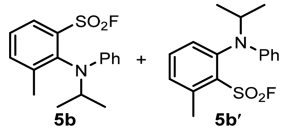
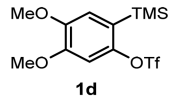
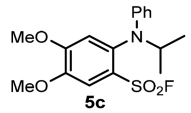
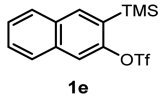
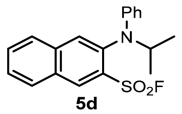
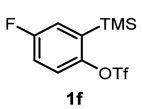
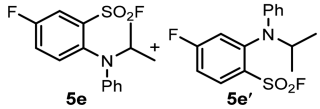
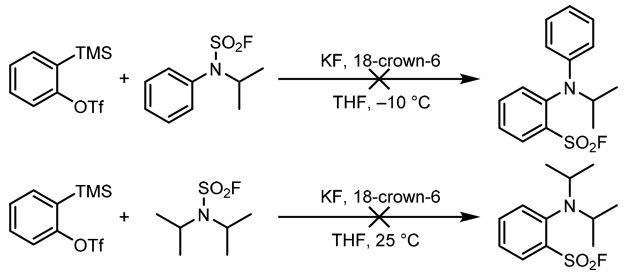
Table 3. Scope of Arynes[a]



entry	aryne precursor	product(s)	yield (ratio)
1			80% (1.3:1)[b]
2			46% (10:1)[b]
3			86%
4			80%
5			35% (4.2:1)[b]

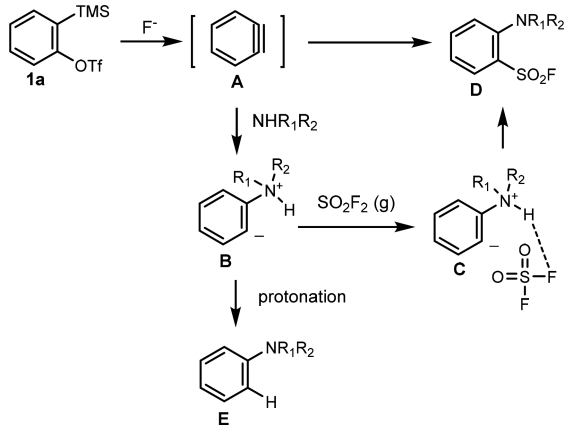
[a]Reaction conditions: aryne precursor (1.5 equiv), **2a** (1.0 equiv, 0.25 mmol), KF (4.5 equiv), 18-crown-6 (4.5 equiv), and THF (2.5 mL) at −10 °C under SO_2F_2 atmosphere (1 atm) for 24 h. [b]The regioisomer ratio was determined by ^{1}H NMR analysis.

Scheme 3. Reactions of Aryne Precursors with *N*-Sulfamoyl Fluorides



azepane, 1,2,3,4-tetrahydroisoquinoline, and morpholine gave *N*-disubstituted sulfamoyl fluorides upon reaction with SO_2F_2. In the reactions in Scheme 3, the desired product was not obtained in either case, suggesting the involvement of the three-component reactions. Based on these results, a plausible reaction mechanism was proposed (Scheme 4). Nucleophilic attack of the secondary amine on the aryne, generated in situ from **1a** in the presence of a fluoride source, would lead to the formation of a zwitterionic intermediate **B**, which would react with SO_2F_2 to provide the desired arenesulfonyl fluoride **D** or with a proton from the ammonium salt to yield the protonated side product **E**. We envisioned that a strong hydrogen bond between the proton of the ammonium salt and SO_2F_2 as shown in **C** led to the desired three-component reaction instead of proton abstraction. This hydrogen bond would not only greatly enhance the electrophilic nature of SO_2F_2 but also place the

Scheme 4. Proposed Mechanism



sulfuryl fluoride in an appropriate position for nucleophilic capture.

In conclusion, we have developed a novel transition-metal-free protocol for the direct synthesis of arenesulfonyl fluorides via incorporation of fluorosulfonyl group to arynes. This multicomponent reaction works efficiently with 1 atm of sulfuryl fluoride under mild conditions, producing diversely substituted 2-aminoarenesulfonyl fluoride derivatives in good to excellent yields. With a wide range of functional group compatibility, various secondary amines, including dialkylamines, alkylarylamines, and diarylamines, underwent the three-component reaction with good selectivity. With this new sulfuryl fluoride incorporation reaction in hand, diverse nucleophiles can also be utilized for the direct synthesis of sulfonyl fluoride derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03610.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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