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Article

Regioselective Aromatic Perfluoro-*tert*-butylation Using Perfluoro-*tert*-butyl Phenyl Sulfone and Arynes

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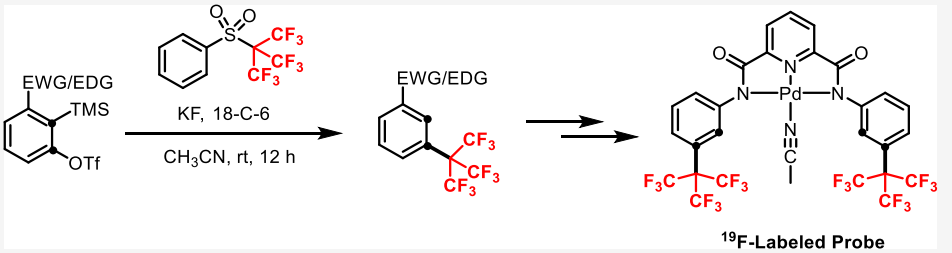

ABSTRACT: The selective introduction of perfluoro-*tert*-butyl group (PFtB, the bulkier analogue of CF_3 group) into arenes has long been sought after but remains a formidable task. We herein report the first general synthetic protocol to realize aromatic perfluoro-*tert*-butylation. The key to the success is the identification of PFtB phenyl sulfone as a new source of PFtB anion, which reacts with arynes in a highly regioselective manner to afford perfluoro-*tert*-butylated arenes in high yields. The application of the method is demonstrated by the preparation of sensitive ^{19}F-labeled NMR probes with an extraordinary resolving ability.

INTRODUCTION

Fluorine-containing compounds are widely used in the development of pharmaceuticals, agrochemicals, liquid crystalline materials, and molecular imaging agents, among others.[1,2] During the past decade, there has been an increasing awareness of the importance of densely trifluoromethylated moieties [$(CF_3)_2CX$ (X = H, F, OH, CF_3, etc.)]. The common feature of these moieties is that the central carbon atom is connected to two or more trifluoromethyl substituents. Two representative moieties conforming to this definition are the *α*,*α*-bis(trifluoromethyl)carbinol (BTFC) and heptafluoroisopropyl (HFIP) groups, which have been widely explored to impart favorable steric, electronic, and hydrophobic properties to parent molecules. For instance, the BTFC group is essential for the potent activity of a number of drug molecules for the treatment of cancer, diabetes, and inflammation (Figure 1a).[3] The HFIP group is privileged in agrochemical discovery, the exploration of which has led to a series of well-known pesticides, such as Flubendiamide[4a] and Pyrifluquinazon (Figure 1b).[4b] Owing to its unique electronic properties, the HFIP has been employed to tune the performance of chiral catalysts (Figure 1c), enabling a variety of asymmetric reactions with high efficiency and enantioselectivity.[5] These intriguing applications highlight the great potential to harness densely trifluoromethlyated moieties to pursue unique properties that are otherwise difficult or impossible to achieve. Among fluorinated moieties bearing multiple CF_3 substituents, the perfluoro-*tert*-butyl (PFtB) group occupies a special position as it possesses the largest structural bulkiness and the strongest electron-withdrawing capability. In addition, the nine chemically equivalent fluorine atoms render PFtB superior to others in acting as a sensitive ^{19}F label in molecular sensing and imaging (Figure 1d).[6] Despite the growing interest in exploring the unique function of the PFtB moiety, methods to synthesize perfluoro-*tert*-butylated compounds are very limited.[7] Recently, our group has developed a new method for the generation of $(CF_3)_3C^-$ anion via the reaction between 1,1-dibromo-2,2-bis(trifluoromethyl)ethylene (DBBF) and CsF (Scheme 1a).[8] This approach avoids the use of toxic gaseous chemicals.[7a−f]

On the other hand, direct incorporation of PFtB into arenes has long been sought after but still remains a formidable challenge. In 1989, Toltaya and co-workers revealed that the reaction between $(CF_3)_3CCs$ (from highly toxic perfluoroisobutylene) and diphenyl-λ^3-chlorane ($Ph_2Cl^+X^-$) afforded perfluoro-*tert*-butylbenzene in 43% yield (Scheme 1b), representing a rare example of aromatic perfluoro-*tert*-butylation.[9] Although the PFtB group can be introduced via the S_NAr-type substitution, the approach is only applicable for highly electron-deficient aryl fluorides.[8] As a consequence, synthetic strategies allowing access to functionalized perfluoro-*tert*-butylated arenes remain elusive. Herein, we report a

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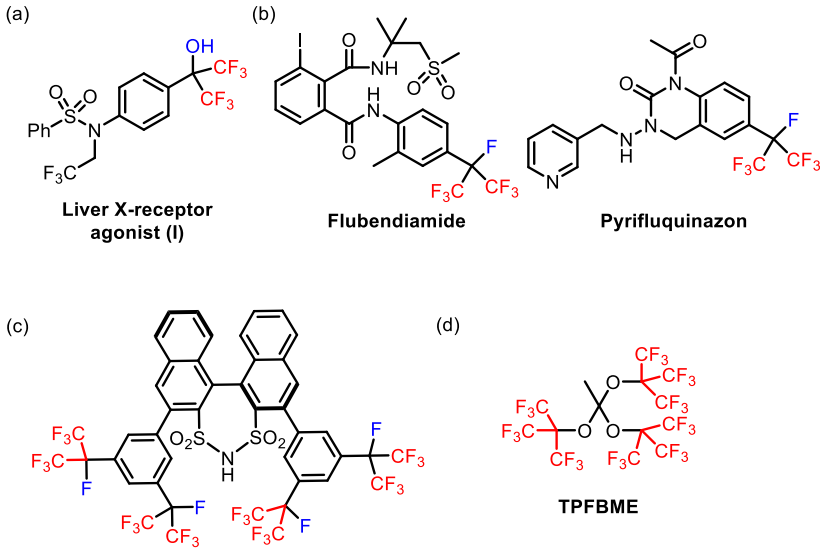
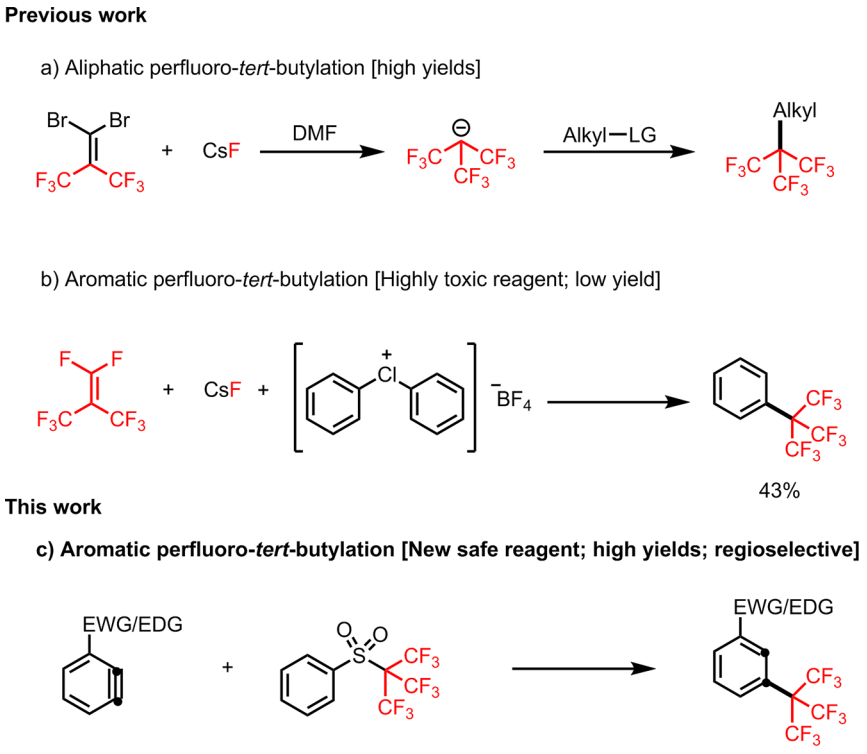


Figure 1. Densely trifluoromethylated compounds in different applications.

Scheme 1. Synthesis of PFtB Compounds



solution to the unmet need for aromatic perfluoro-*tert*-butylation, wherein a highly efficient and regioselective coupling between $(CF_3)_3C^-$ anion and arynes has been achieved (Scheme 1c).

RESULTS AND DISCUSSION

Inspired by the success of copper-mediated fluoroalkylation reactions,[10−12] we set out our investigation by screening conditions for aromatic perfluoro-*tert*-butylation using the PFtB copper species, which can be generated through the reaction between CsF and DBBF in the presence of CuBr. Various coupling partners, such as arylboronic acids, aryl iodide, and diazonium and diaryliodonium salts, were then attempted to react with PFtB copper either directly or under oxidative coupling conditions; however, no perfluoro-*tert*-butylated product was observed (for details, see Supporting Information), suggesting a chemical behavior distinct from that of the well-documented "CF_3Cu" species. Our group has long been engaged in developing synthetic applications of highly reactive intermediates. One intriguing intermediate that attracted our special attention was aryne,[13] the unique reactivity of which had been explored to achieve aromatic trifluoromethylation[13a] and fluorination.[13b] In light of these studies, we next attempted the perfluoro-*tert*-butylation of arynes by using the 2-(trimethylsilyl)phenyl triflate (**1′**) as the benzyne precursor (Scheme 2a).[14] In this reaction, the PFtB anion was first prepared through the nucleophilic fluorination

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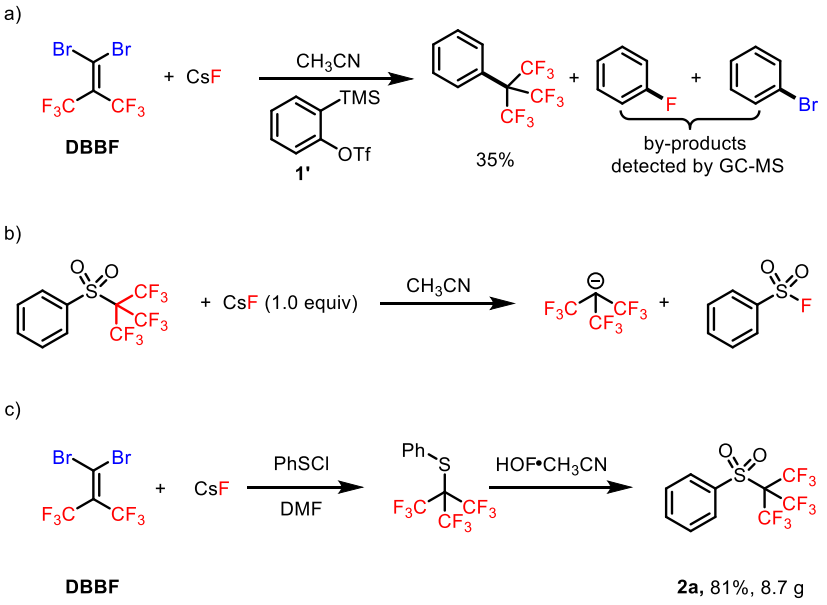
J. Am. Chem. Soc. 2022, 144, 22281−22288

Scheme 2. Synthetic Routes for Perfluoro-*tert*-butylated Compounds



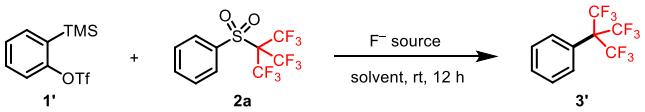
of DBBF in acetonitrile followed by the addition of **1′**. To our delight, the target product was produced in 35% yield when the mixture was stirred for 12 h at room temperature. A close inspection of the reaction mixture through gas chromatography−mass spectrometry analysis revealed the formation of bromobenzene and fluorobenzene as the major byproducts (Scheme 2a). These observations indicated that fluoride and bromide anions could compete with the PFtB anion to react with benzyne (in situ generated from **1′**), decreasing the efficiency of the desired reaction. Having identified the bottleneck of the reaction, we turned our attention to the development of a sulfone-based reagent that was envisioned to give access to the clean PFtB anion without concomitant halide ions.[15] By design, the reaction of PFtB phenyl sulfone (**2a**) with an equal amount of metal fluoride would afford the desired PFtB anion, with the non-interfering benzenesulfonyl fluoride being formed as the only byproduct (Scheme 2b). The reagent **2a** was prepared in 8.7 g scale by the oxidation of PFtB phenyl sulfide (Scheme 2c).

After extensive screening, HOF·CH_3CN (prepared from F_2 gas) was identified as the only viable reagent for efficient oxidation of PFtB sulfide (Scheme 2c).[16] As no organic byproduct was formed during oxidation, compound **2a** was easily obtained by simple workup without the need of column chromatography. The differential scanning calorimetry plot indicates that the melting point of **2a** is 59 °C. Probably due to the high fluorine content, **2a** is prone to undergo sublimation at high temperatures such that storage in a sealed vial is preferred (for the crystal structure of **2a**, see Supporting Information).

With sulfone reagent **2a** in hand, we next screened the reaction conditions for the perfluoro-*tert*-butylation of arynes.

Acetonitrile was identified as the optimal solvent for this reaction, giving perfluoro-*tert*-butylbenzene (**3′**) in 61% yield (Table 1, entry 1), whereas the desired transformation did not occur in less-polar solvents such as tetrahydrofuran and ethyl acetate (Table 1, entries 2−3). No perfluoro-*tert*-butylated product was observed when KF was used in place of CsF, probably due to the reduced nucleophilicity of fluoride ion (Table 1, entry 4). When 18-crown-6 (18-C-6) was added to

Table 1. Survey of Reaction Conditions[a]



entry	solvent	**2a** (equiv)	"F⁻" source	"F⁻" (equiv)	yield of **3′** (%)[b]
1	CH_3CN	1.0	CsF	3.0	61
2	THF	1.0	CsF	3.0	0
3	EtOAc	1.0	CsF	3.0	0
4	CH_3CN	1.0	KF	3.0	0
5	CH_3CN	1.0	KF + 18-C-6	3.0	70
6	CH_3CN	1.0	KF + Dicy-18-C-6	3.0	68
7	CH_3CN	1.2	KF + 18-C-6	3.0	72
8	CH_3CN	1.4	KF + 18-C-6	3.0	77
9	CH_3CN	1.6	KF + 18-C-6	3.0	78
10	**CH_3CN**	**1.4**	**KF + 18-C-6**	**2.4**	**81**
11	CH_3CN	1.4	KF + 18-C-6	2.6	80

[a]Reaction conditions: **1′** (0.1 mmol, 1.0 equiv), solvent (2.0 mL). [b]Determined by ^{19}F NMR spectroscopy using trifluoromethoxybenzene as an internal standard. Note: Dicy-18-C-6 denotes dicyclohexyl-18-crown-6; 18-C-6 denotes 18-crown-6.

enhance the reactivity of KF, the yield was improved to 70% (Table 1, entry 5). The use of other ion-chelating agents, such as dicyclohexyl-18-crown-6 (Dicy-18-C-6), did not further improve the efficiency of the reaction (Table 1, entry 6). The reaction yield was found to gradually increase when we added more **2a**, indicating that an excess amount of PFtB anion was beneficial to trap the fleeting benzyne intermediate effectively (Table 1, entries 7−9). The highest yield of **3′** was achieved by finely tuning the amount of reagent **2a** (1.4 equiv) and the fluoride activator (2.4 equiv). It is noteworthy that all the fluoride ions were consumed by reagent **2a** and the benzyne precursor **1′** under the conditions such that the side product fluorobenzene was not observed.

After identifying the optimal reaction conditions (Table 1, entry 10), we next examined the substrate scope of the current aromatic perfluoro-*tert*-butylation reaction (Table 2). When

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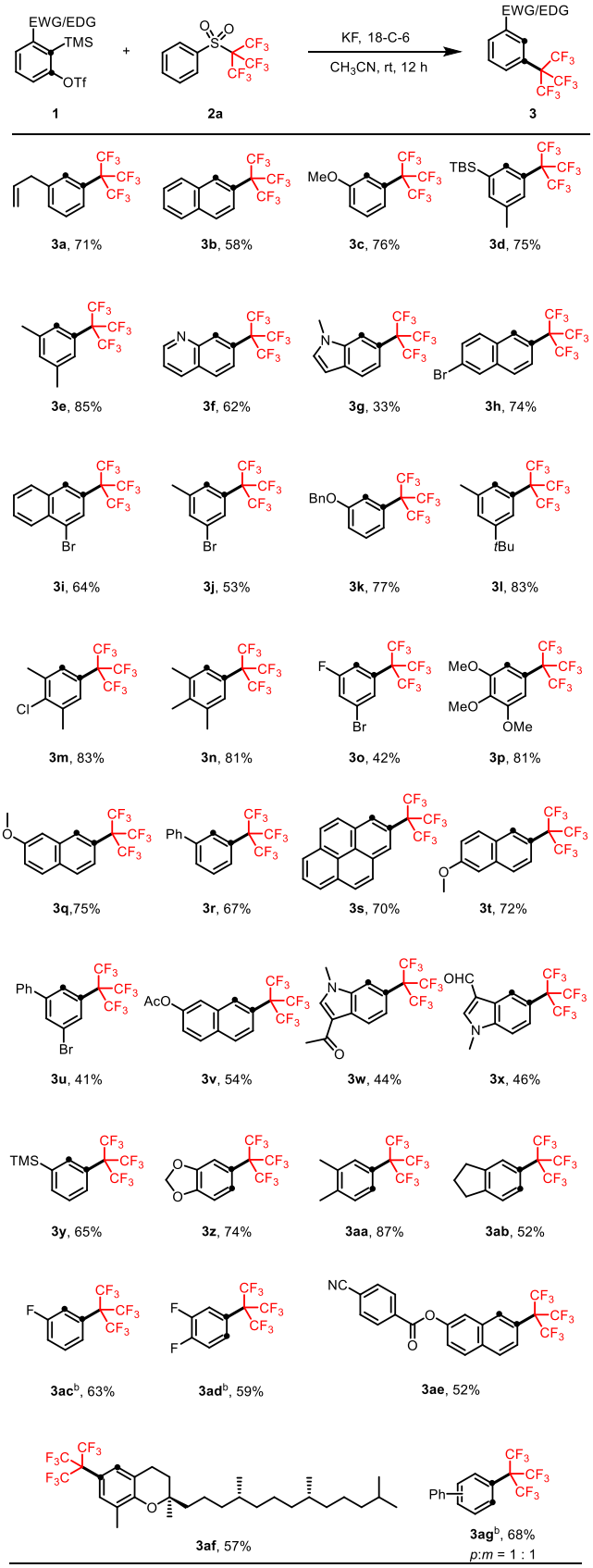
Table 2. Perfluoro-*tert*-butylation of Arynes[a]



[a]Reaction conditions: **1** (0.2 mmol, 1.0 equiv), **2a** (0.28 mmol, 1.4 equiv), KF (0.48 mmol, 2.4 equiv), 18-C-6 (0.48 mmol, 2.4 equiv), CH_3CN (4.0 mL). [b]Determined by ^{19}F NMR spectroscopy using trifluoromethoxybenzene as an internal standard.

the aryne precursor **1a** was used as the substrate, perfluoro-*tert*-butylation occurred at the position meta to the original substituent, giving product **3a** exclusively. This observation is intriguing because the addition to arynes often leads to the formation of a mixture of regioisomeric products that are difficult to separate. The meta-regioselectivity was universally found in perfluoro-*tert*-butylation of various ortho-substituted arynes (**1a**−**1y**), regardless of the electronic properties of the substituents.[17,18] We attribute the unique selectivity to the extraordinary steric bulkiness of the PFtB group, which overrides the electronic and distortional bias of the carbon−carbon triple bond of aryne intermediates.[19] Consistent with this assumption, density functional theory calculations reveal that the *A*-value for PFtB is 6.109 kcal/mol, which is larger than that of the *tert*-butyl group (5.704 kcal/mol).[20] The unique steric property of the PFtB group was also evident in the regioselectivity observed in the nucleophilic addition onto 3-silylbenzyne (such as **1y**), where the PFtB anion was found to be the only known nucleophile that led to the exclusive formation of the meta-functionalized product (for details, see Supporting Information, page 37). It is also noteworthy that the sterically controlled nucleophilic addition was previously observed for the arynes with *tert*-butyl substituents;[19] however, the scope of the reaction was found to be narrow. In contrast, our current regioselective perfluoro-*tert*-butylation method is applicable to the functionalization of arynes bearing diverse substituents, such as allyl (**3a**), methoxy (**3c**), *tert*-butyldimethylsilyl (**3d**), bromide (**3h**−**3j**), benzyloxy (**3k**), *tert*-butyl (**3l**), chloride (**3m**), ester (**3v**), carbonyl (**3w**), aldehyde (**3x**), and trimethylsilyl (**3y**) groups. Polysubstituted (**3e**, **3n**, **3p**) and fused ring-containing (**3s**) aryne precursors were also suitable substrates. In all these cases, excellent regioselectivities were observed. When the substituent was distal to the triple bond of aryne, a 1:1 mixture of regioisomeric product was obtained (**3ag**), in which the steric effect of the PFtB group was no longer dominating. This perfluoro-*tert*-butylation reaction also proceeded smoothly, with substrates bearing a range of heterocyclic motifs, including quinoline (**3f**) and indole (**3g**). The application of the current method in the modification of bioactive molecules was demonstrated by the introduction of the PFtB group to the scaffold of vitamin E (**3af**).

Recently, 3,5-diheptafluoroisopropylated ligands and catalysts have been increasingly explored to enhance the reaction rate and the selectivity of asymmetric reactions.[5] As a moiety with larger steric hindrance compared to the HFIP, the introduction of PFtB to the ligand and catalyst would open up exciting new possibilities. By using 2-(trimethylsilyl)-1,3-phenylene bis(trifluoromethanesulfonate) (**4**) as a domino benzyne precursor,[21] two PFtB groups were simultaneously introduced, giving 1,3-bis(perfluoro-*tert*-butyl)benzene (**5**) in 72% yield (Scheme 3). The availability of perfluoro-*tert*-butylated compounds shown in Table 2 and Scheme 3 would allow chemists to systematically evaluate the properties of PFtB, which may lead to the discovery of new reactivities and functions.

Considering the superior NMR detectability of the PFtB group, we next explored the utility of our method in the preparation of high-performance ^{19}F-labeled probes. Recognition-enabled chromatographic ^{19}F NMR has recently

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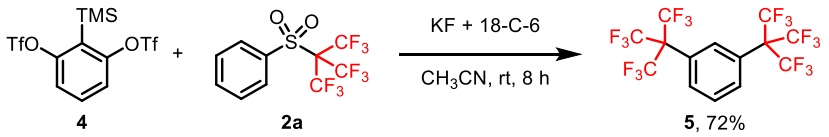
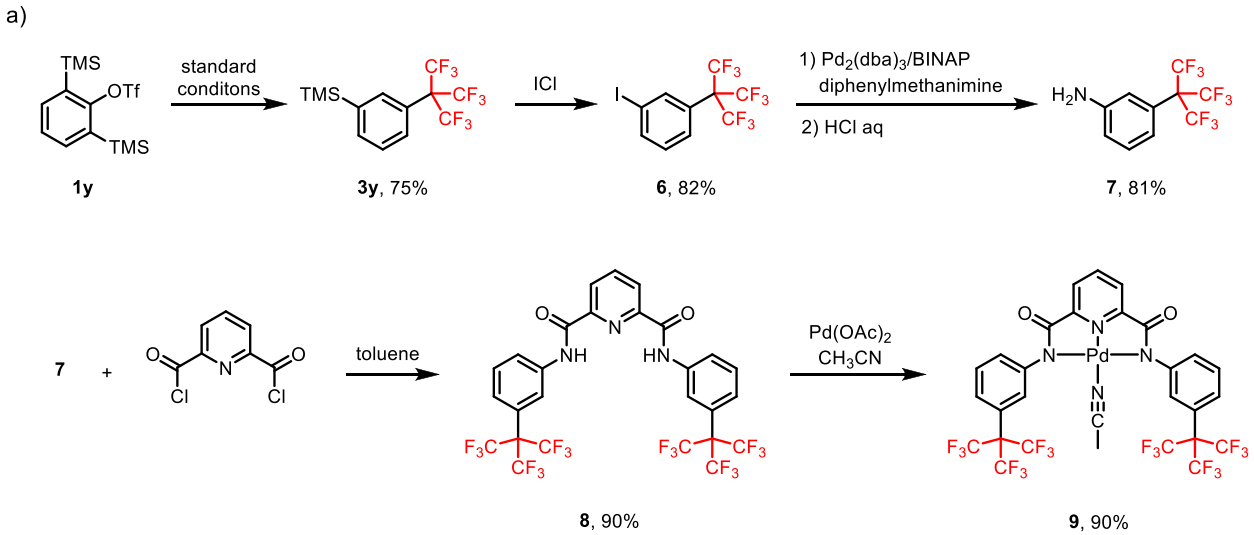
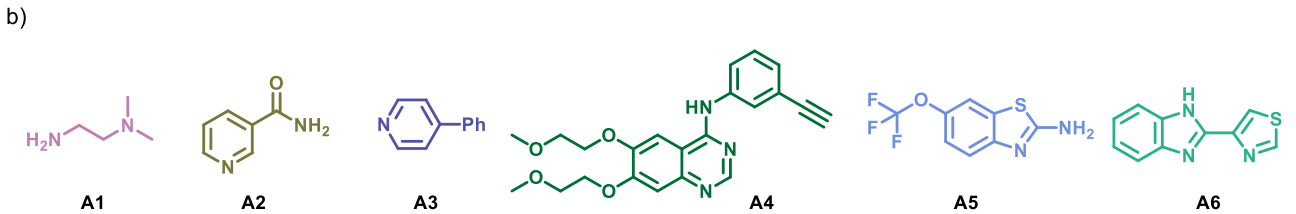
Scheme 3. Synthesis of 1,3-Bis(perfluoro-*tert*-butyl)benzene







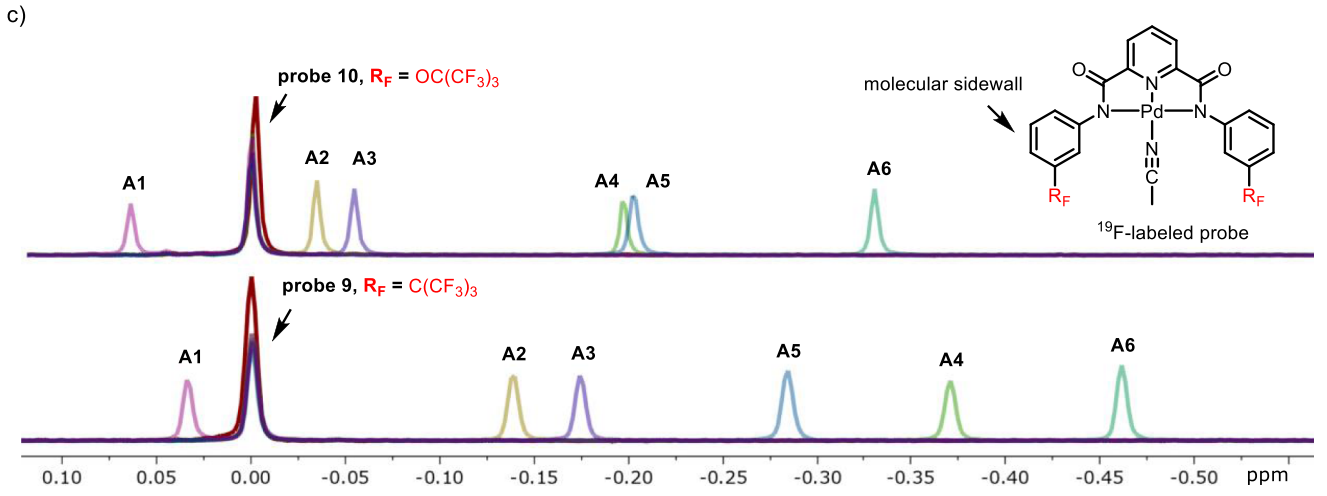


Figure 2. Synthesis and applications of highly sensitive ^{19}F probes. (a) Synthetic route for a ^{19}F probe with 18 chemically equivalent fluorine atoms. (b) Chemical structures of analytes. (c) Comparison between the performance of $-OC(CF_3)_3$- and $-C(CF_3)_3$-labeled ^{19}F probes. Note: the ^{19}F chemical shifts of **9** and **10** were adjusted to 0 ppm for a clear comparison between the performances. The spectra in dark red were obtained by dissolving the probe compound **9** or **10** in $CDCl_3$ without adding analytes.

attracted increasing attention, wherein the reversible interactions between a ^{19}F-labeled probe and analytes produce chromatogram-like ^{19}F signals of discrete chemical shifts.[22] The chemosensing nature of the approach allows signal enhancement to be achieved by incorporating more chemically equivalent fluorine atoms. The use of perfluoro-*tert*-butoxy-lated probes has enabled the detection of target analytes at nanomolar concentrations, paving new avenues for the application of densely fluorinated compounds in detection.[23] Direct installation of the PFtB group into the aromatic sidewall of the probe is highly preferred because this would bring ^{19}F atoms closer to the bound analyte to promote more

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pronounced perturbations on ^{19}F chemical shifts. However, access to these probes is hampered by the lack of viable methods for aromatic perfluoro-*tert*-butylation. To prepare a PFtB-labeled probe and examine its resolving ability, **3y** prepared via our aryne chemistry was first converted to aryl iodine **6** (Figure 2a). The corresponding PFtB-labeled aniline was obtained through a palladium-catalyzed amination, which further reacted with pyridine-2,6-dicarbonyl dichloride to afford ligand **8**. Metalation of **8** with $Pd(OAc)_2$ gave the target probe **9** (Figure 2a). Notably, the bound acetonitrile of **9** can be readily replaced by various nitrogen-containing analytes, inducing characteristic changes in the ^{19}F chemical shifts.[22c,23b,24]

We next evaluated the performance of probe **9** through the detection of a series of biologically relevant analytes. As shown in Figure 2c, the newly generated ^{19}F signals are well separated, allowing highly sensitive and unambiguous detection of all 6 analytes in complex mixtures. Unlike the analogous probe **10** bearing $OC(CF_3)_3$ moieties, the detection window of probe **9** is much wider. Compared to the $OC(CF_3)_3$ group, the conformational flexibility of PFtB is significantly reduced, which is envisioned to promote through-space interactions between the analyte and ^{19}F atoms. This unique feature enables probe **9** to discriminate between challenging analytes (Figure 2b,c, **A4** and **A5**), which are not resolvable by probe **10**. These observations indicate that PFtB is a promising moiety that has great potential for advancing NMR-based detection and imaging.

CONCLUSIONS

In summary, we have developed a general synthetic approach to access functionalized perfluoro-*tert*-butylated arenes via nucleophilic addition of PFtB anion to arynes. PFtB phenyl sulfone has been identified as a superior source for PFtB anion, which avoids the concomitant formation of the interfering side products. The bulky PFtB anion is found to attack preferentially the less-hindered carbon atom of the aryne intermediate, leading to meta-functionalized products exclusively. This excellent regioselectivity not only allows facile product purification but also provides new insights into aryne chemistry. It is further demonstrated that the use of the PFtB group significantly enhances the resolving ability of ^{19}F-labeled probes, enabling the unambiguous multicomponent analysis of complex mixtures. Further explorations of the unique applications of perfluoro-*tert*-butylated arenes are underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c10479.

Experimental details, optimization of the reaction conditions, procedures for the synthesis of substrates and products, and the spectroscopic data of the new compounds (PDF)

Accession Codes

CCDC 2218235 contains 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, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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