

Fluorination

Fluorination Triggers Fluoroalkylation: Nucleophilic Perfluoro-*tert*-butylation with 1,1-Dibromo-2,2-bis(trifluoromethyl)ethylene (DBBF) and CsF

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Abstract: Perfluoro-*tert*-butylation reaction has long remained a challenging task. We now report the use of 1,1-dibromo-2,2-bis(trifluoromethyl)ethylene (DBBF) as a practical reagent for perfluoro-*tert*-butylation reactions for the first time. Through a consecutive triple-fluorination process with DBBF and CsF, the $(\text{CF}_3)_3\text{C}^-$ species can be liberated and observed, which is able to serve as a robust nucleophilic perfluoro-*tert*-butylating agent for various electrophiles. The power of this synthetic protocol is evidenced by the efficient synthesis of structurally diverse perfluoro-*tert*-butylated molecules. Multiple applications demonstrate the practicability of this method, as well as the superiority of perfluoro-*tert*-butylated compounds as sensitive probes. The perfluoro-*tert*-butylated product was successfully applied in ^1H - and ^{19}F -magnetic resonance imaging (MRI) experiment with an ultra-low field (ULF) MRI system.

Owing to the unique properties of fluorine, fluorine-containing organic compounds have played essential roles in pharmaceuticals, agrochemicals, and advanced materials.^[1,2] At present, the upsurge of structural diversity amplifies the need for more complex fluorine-containing motifs. Despite rapid advances in a plethora of methodologies, the structural diversity is still limited, which cannot keep up with the growing demand for novel motifs.^[2,3] In fact, monofluorinated and trifluoromethylated molecules predominate in the cur-

rently developed fluorochemicals, presumably because of the well-developed fluorination and trifluoromethylation methodologies.^[2,4] It is critical to explore new structures and strategies to expand the toolbox for the incorporation of fluorine. In this context, perfluoro-*tert*-butylation is definitely a potential new territory for exploration. The perfluoro-*tert*-butyl (PFtB) group $\text{C}(\text{CF}_3)_3$ is intriguing, not only because it is more electron-withdrawing than the CF_3 group,^[5] but also on account of its strong conformational bias and steric effect.^[6] Thus, the introduction of PFtB group into molecules could be an attractive choice for chemists and may have diversified applications in many other fields. Importantly, nine fluorine atoms in one PFtB group would show a strong singlet signal in ^{19}F NMR, suggesting its promising applications as a sensitive probe in molecular imaging.^[7]

However, perfluoro-*tert*-butylation has been much less explored due to the lack of efficient and practical reagents (Scheme 1 a). Traditionally, the construction of PFtB group was mainly based on the use of perfluoroisobutylene (PFIB), which is a highly toxic gas and should be handled with extreme caution.^[8,9] An alternative strategy for generating $(\text{CF}_3)_3\text{C}^-$ species is the deprotonation of 2-hydroperfluoroisobutane, yet the volatile nature of starting material greatly restricts the application of this protocol.^[10] On the other hand, perfluoro-*tert*-butyl halides have been utilized to introduce the PFtB group. In this context, the use of $\text{C}(\text{CF}_3)_3\text{I}$ can be traced back to 1966,^[11] and the photoinduced radical perfluoro-*tert*-butylation was described by Yajima in 1998.^[12] In 1998, an Arbuzov type reaction between an amido phosphite and $\text{C}(\text{CF}_3)_3\text{Br}$ was developed.^[13] Unfortunately, these processes showed very limited scope and applications.^[14] Consequently, perfluoro-*tert*-butylation reactions are now facing

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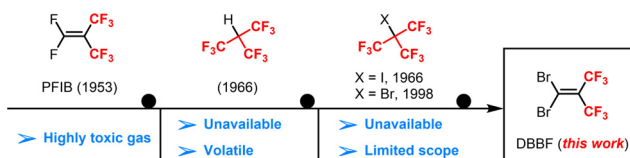
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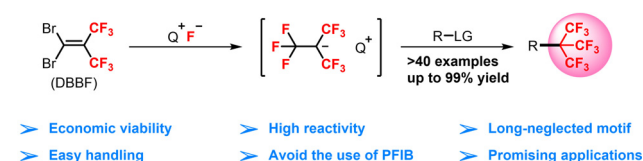
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(a) Development of perfluoro-*tert*-butylation reactions



(b) Perfluoro-*tert*-butylation with DBBF in the presence of fluoride ions (*this work*)



Scheme 1. Access to perfluoro-*tert*-butylated molecules.

three major challenges: 1) the need for tractable reagents; 2) the need for broad substrate scope, and 3) the need for safe operation. Herein, we report our recent success in the development of a readily accessible and highly reactive perfluoro-*tert*-butylation reagent and its synthetic applications.

Previously, we developed a C1-to-C3 fluorocarbon elongation reaction by adopting an anionic homologation strategy.^[15] The highly efficient transformation of fluoroalkene intermediates prompted us to build complex polyfluorinated motifs via simple alkenes. We envisioned that a *gem*-bis(trifluoromethyl)ethylene with two leaving groups would undergo triple fluoride additions to release $(\text{CF}_3)_3\text{C}^-$ species (Scheme 1b). In this context, three requirements were taken into account when designing the structure of *gem*-bis(trifluoromethyl)ethylene reagent bearing two leaving groups: 1) efficient generation of $(\text{CF}_3)_3\text{C}^-$ species; 2) economic viability of large-scale production; and 3) easy handling of the reagent. Considering the higher leaving ability of Br^- than that of F^- and the enhanced nucleophilicity of fluoride ion in polar aprotic solvents, we speculated that an efficient in situ generation of $(\text{CF}_3)_3\text{C}^-$ species could be accomplished by using the combination of 1,1-dibromo-2,2-bis(trifluoromethyl)ethylene (DBBF)^[16] and fluoride ions. It is noteworthy that DBBF is a colorless liquid at room temperature and can be easily accessible from hexafluoroacetone (a bulky fluorochemical), thus making it an attractive reagent for perfluoro-*tert*-butylation reactions.

With DBBF in hand,^[16] we started our investigation by treating 4-phenylbenzyl bromide (**1a**) with DBBF in the presence of KF as a fluoride source in DMF to examine the generation and transfer of $(\text{CF}_3)_3\text{C}^-$ (Table 1). To our delight, the desired product **3a** was observed in 20 % yield (entry 1) with 61 % of DBBF being unconverted (for details, see Table S1 in the Supporting Information). The combination of KF/18-Crown-6 resulted in the complete consumption of

DBBF and a higher yield of **3a** (entry 2), suggesting that the nucleophilicity of fluoride ion is crucial for the generation of $(\text{CF}_3)_3\text{C}^-$ and the formation of the desired product. Further investigation of fluoride salts and solvents identified CsF as an optimal fluoride source and DMF as a suitable solvent (entries 3–7). After an extensive optimization of other reaction parameters (for details, see Supporting Information), we were pleased to find that, when DBBF (1.5 equiv) and CsF (5.0 equiv) were stirred in DMF for 2 hours, the perfluoro-*tert*-butylated product **3a** was obtained in 93 % isolated yield (entry 10). Notably, the product **3a** was observed in 72 % yield when the reaction occurred at 80 °C in 20 minutes, which promises the potential application of this protocol in ^{18}F -isotope radiolabeled synthesis (entry 11).

Subsequently, a wide variety of structurally diverse electrophiles were examined to illustrate the reliability of this new perfluoro-*tert*-butylation method (Table 2).^[22] Benzyl bromides bearing different substituents on the aromatic ring, such as phenyl (**3a**), halogens (**3c**, **3d**, **3n**, and **3o**), nitrile (**3e**, **3k**), nitro (**3f**, **3g**), acyl (**3h**, **3i**), sulfonyl (**3j**), and esters (**3q**, **3u**, and **3v**), were well tolerated under standard conditions. Additionally, substrates containing medicinally relevant heterocycles, including quinolone (**3s**), naphthalene (**3t**), benzothiophene (**3w**), thiophene (**3x**), and pyridine (**3y**, **3z**), were all successfully employed to afford the desired perfluoro-*tert*-butylated products in excellent yields. Geranyl bromide was also subjected to the reaction, giving the desired product in good yield (**3aa**). In addition, allyl chloride (**3ab**) and benzyl chlorides (**3ac**, **3ad**) were also viable in this reaction, probably due to the Cl/Br halogen exchange with bromide ions which were released from DBBF. Perfluoro-*tert*-butylated sulfide and selenide were also produced from the corresponding chlorides with ease (**3ae**, **3af**). Besides the different bromides and chlorides, alkyl iodides were also viable substrates in this perfluoro-*tert*-butylation reaction (**3ag–3aq**). Several functionalities that can undergo further transformations were tolerated, including allyl (**3ah**), ester (**3aj**), lactams (**3ak**, **3ao**), and azide (**3am**). Moreover, bioactive molecules such as ivabradine and idebenone derivatives could also be readily converted to the perfluoro-*tert*-butylated derivatives (**3ak** and **3aq**). To further explore the generality of this method, electron-deficient arenes were applied in the reaction to form perfluoro-*tert*-butylated arenes via the $\text{S}_{\text{N}}\text{Ar}$ -type reactions (**3ar–3at**).

To confirm the existence of the perfluoro-*tert*-butyl anion $[(\text{CF}_3)_3\text{C}^-]$ in the reaction system, the preparation of “ $\text{CsC}(\text{CF}_3)_3$ ” was carried out, which was monitored by ^{19}F NMR spectroscopy (Figure 1a). We combined DBBF (0.6 mmol) and CsF (2.0 mmol) in DMF, and stirred for 1 h at room temperature. A broad singlet at around -43.2 ppm was observed (using CCl_3F as an internal standard at 0.0 ppm), which matched the previously reported data^[17] and was assigned as the “ $\text{CsC}(\text{CF}_3)_3$ ” species. It is noteworthy that the “ $\text{CsC}(\text{CF}_3)_3$ ” species was relatively stable and could be stored at -20°C for at least 50 hours without loss of reactivity for perfluoro-*tert*-butylation of the model substrate **1a** (Figure 1b). To better understand the generation and stability of $(\text{CF}_3)_3\text{C}^-$ species, preliminary computational studies were conducted using DFT calculations (for details, see Supporting

Table 1: Survey of reaction conditions.

Entry ^[a]	x	Fluoride salt ^[b]	Solvent ^[c]	Yield [%] ^[b]
1	1.0	KF (3.3 equiv)	DMF	20
2	1.0	KF/18-C-6 (3.3 equiv)	DMF	51
3	1.0	CsF (3.3 equiv)	DMF	80
4	1.0	TBAF (3.3 equiv)	DMF	4
5	1.0	TBAT (3.3 equiv)	DMF	0
6	1.0	CsF (3.3 equiv)	MeCN	68
7	1.0	CsF (3.3 equiv)	THF	0
8	1.2	CsF (3.8 equiv)	DMF	90
9	1.5	CsF (5.0 equiv)	DMF	> 99
10 ^[d]	1.5	CsF (5.0 equiv)	DMF	99 (93 ^[d])
11 ^[e]	1.5	CsF (5.0 equiv)	DMF	72

[a] Unless otherwise noted, **1a** (0.2 mmol, 1.0 equiv), fluoride salt, **2**, and solvent (0.1 M) were stirred in a dry sealed PE tube in glove box at room temperature for 4 h. [b] Yields were determined by ^{19}F NMR with PhOCF_3 as an internal standard. [c] 2 h. [d] Isolated yield. [e] The reaction was at 80 °C, 20 min. 18-C-6 = 18-Crown-6, TBAF = tetrabutylammonium fluoride, TBAT = tetrabutylammonium difluorotriphenylsilicate.

Table 2: Substrate scope for the perfluoro-*tert*-butylation reaction.^[a]

$\text{R-X} + \text{BrC}(\text{CF}_3)_2 \xrightarrow[\text{DMF, RT}]{\text{CsF}} \text{R-C}(\text{CF}_3)_3$		1	2	3
a. Alkyl Bromides				
3a , 93%	3b , 75%	3c , R = Cl, 91% 3d , R = Br, 96%	3e , 92%	3f , R = <i>p</i> -NO ₂ , 95% 3g , R = <i>m</i> -NO ₂ , 89%
3h , R = H, 97% ^a 3i , R = Me, 93%	3j , 90%	3k , 91%	3l , 89%	3m , 98%
3n , 92%	3o , 93%	3p , 90%	3q , 94%	3r , 97%
3s , 85%	3t , 93%	3u , R = Me, 94% 3v , R = <i>t</i> Bu, 96%	3w , 89%	3x , 88%
3y , 86%	3z , 92%	3aa , 82% ^b	3ab , 99% ^b	3ac , 83% ^c
b. Alkyl, Sulfonyl, and Selenenyl Chlorides				
3ad , 89% ^c	3ae , 72% ^d	3af , 70% ^d	3ag , 94% ^b	3ah , 93% ^c
3ai , 88% ^c	3aj , 95% ^c	3ak , 72% ^c	3al , R = Bn, 97% ^c 3am , R = N ₃ , 73% ^c (>99% ^b)	3an , 90% ^c
3ao , 81% ^c	3ap , 94% ^c	3aq , 67% ^e	3ar , 92%	3as , 74% ^b
c. Alkyl Iodides				
3at , 64% ^b	3au , 74% ^b	3av , 74% ^b	3aw , 74% ^b	3ax , 74% ^b
d. S_NAr-Type				
3ay , 74% ^b	3az , 74% ^b	3ba , 74% ^b	3bb , 74% ^b	3bc , 74% ^b

Unless otherwise mentioned, substrate (0.3 mmol, 1.0 equiv), CsF (227.9 mg, 1.5 mmol, 5.0 equiv) and DMF (3 mL) were added to a dry sealed PE tube, then DBBF (144.8 mg, 0.45 mmol, 1.5 equiv) was added, the mixture was stirred at room temperature for 2 h. The yields are isolated yields.

[a] Reaction performed on 4.0 mmol scale. [b] Yields were determined by ¹⁹F NMR with PhOCF₃ as an internal standard. [c] CsF (9.3 equiv) and DBBF (3.0 equiv) were used. [d] Substrate was added to the pre-prepared "CsC(CF₃)₃". [e] Tetrabutylammonium iodide (2.0 equiv) was used, MeCN (3 mL) instead of DMF, 6 h. For more experimental details, see Supporting Information.

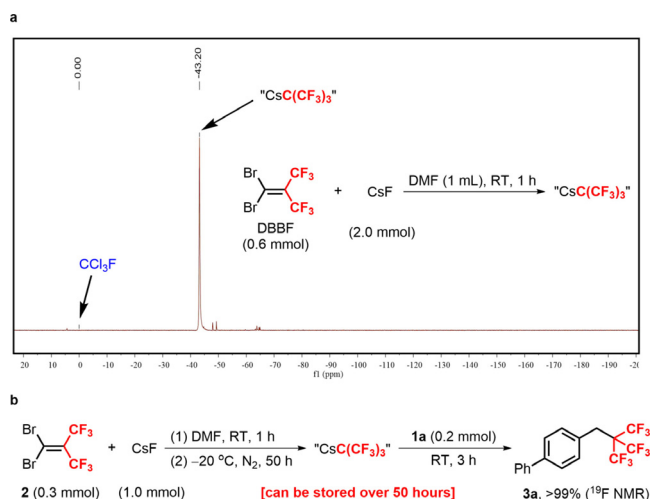


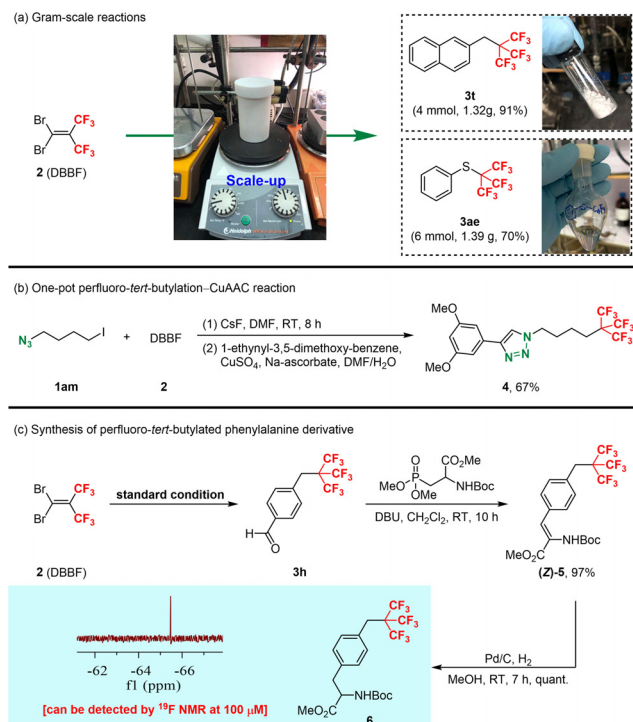
Figure 1. a) ^{19}F NMR monitoring of the reaction. b) Perfluoro-*tert*-butylation of **1a** with pre-prepared “ $\text{CsC}(\text{CF}_3)_3$ ”.

Information). In PFIB, the carbon atom of CF_2 unit possesses a partial positive charge, rendering it the preferred site for nucleophilic attack by a fluoride ion. In addition, the existence of negative hyperconjugation is also justified (for details, see Supporting Information), which contributes to the stability of $(\text{CF}_3)_3\text{C}^-$ anion.^[18]

To demonstrate the synthetic practicability and robustness of this protocol, gram-scale synthesis and other synthetic applications were carried out. As shown in Scheme 2, the reaction can be scaled up to 4 or 6 mmol, affording perfluoro-*tert*-butylated products **3s** and **3ad** in 91 % and 70 % yield, respectively. By using **1am** as the substrate, the perfluoro-*tert*-

butylation reaction was applied without purification in a copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction to produce the PFtB-labeled triazole (**4**), which is potentially useful in drug discovery (Scheme 2b). To further demonstrate the synthetic utility of the method, the perfluoro-*tert*-butylated phenylalanine derivative (**6**) was readily obtained by a simple HWE olefination of **3h** and a subsequent hydrogenation (Scheme 2c). Notably, 100 μM concentration of the phenylalanine derivative (**6**) was sufficient to observe a sharp singlet by ^{19}F NMR spectroscopy within 1 minute due to nine chemically equivalent fluorine atoms (for details, see Supporting Information), providing a powerful tool for monitoring the distribution of PFtB-labeled compounds in biological systems.^[7,19]

In a final demonstration of the potential use of PFtB-labeled compounds as probes in molecular imaging (Figure 2), a 3D-printed phantom was used for magnetic resonance imaging (MRI) experiment with an ultra-low field (ULF) MRI system utilizing Superconducting Quantum Interference Device (SQUID) as the detector (Figure 2a).^[20] Indeed, ^{19}F -MRI is an emerging field which compensates for the shortcomings and fill the information gaps left by ^1H -MRI or other diagnostic tools because of its high sensitivity (84 % relative to ^1H).^[21] Compared with high field MRI (static magnetic field $B_0 > 1.5$ T), ULF MRI with typical B_0 strength below 250 μT has many advantages, such as low cost, minimized susceptibility artifacts, enhanced T_1 contrast between cancerous and benign tissues, and imaging in the presence of metal.^[21] The static field B_0 in this experiment was chosen to be 123 μT corresponding to the Larmor frequencies (f_L) of 4924 Hz for ^{19}F and 5236 Hz for ^1H . The high-sensitivity and wide-bandwidth SQUID sensor enables the simultaneous acquisition of ^{19}F and ^1H signals which are excited by the same excitation pulse B_1 .



Scheme 2. Synthetic applications.

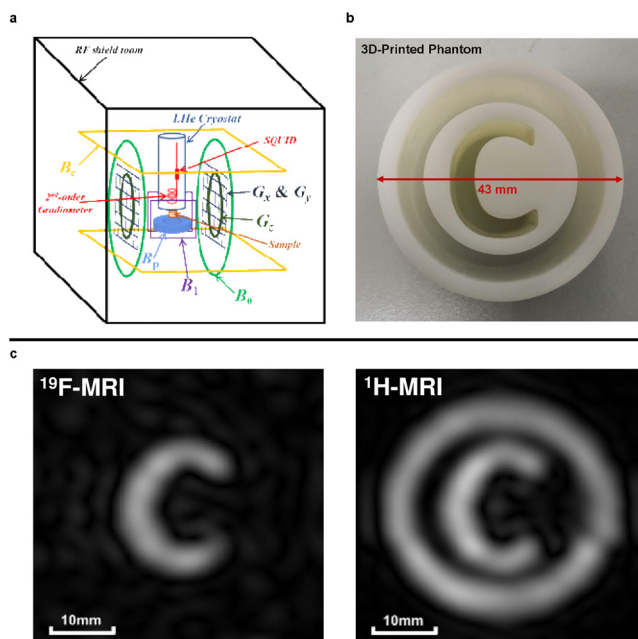


Figure 2. a) Configuration of ULF-MRI system. b) 3D-printed phantom. c) Simultaneous MR imaging of ^{19}F and ^1H at ultra-low field (ULF).

In our case, the outer “O” was filled with petroleum ether and the inner “C” contained a petroleum ether solution of **3t** (Figure 2b). Figure 2c clearly shows a bright “C”-type image from ^{19}F nuclei around 4924 Hz, while no ^1H signal can be observed. In contrast, bright images can be seen in both “C” and “O” from the ^1H nuclei around 5236 Hz, which cannot be distinguished from ^1H -MRI image. These results indicate that PFtB-labeled compounds with increased fluorine density represent potential alternatives to contrast agents for ^{19}F -MRI.

In summary, we have successfully developed an unprecedented nucleophilic perfluoro-*tert*-butylation protocol using the low-cost, operationally simple and efficient reagent DBBF. Consecutive triple fluorinations of DBBF generate observable $(\text{CF}_3)_3\text{C}^-$ species, which readily reacts with a variety of electrophiles under mild conditions. Given the ubiquity and availability of electrophiles, this method is able to provide a new class of perfluoro-*tert*-butylated molecules. The potential of these new compounds as sensitive probes has been demonstrated by simultaneous magnetic resonance imaging experiments. We anticipate that the convenient generation of $(\text{CF}_3)_3\text{C}^-$ species from DBBF promises to find further applications in many different scenarios.

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Conflict of Interest

The authors have filed a patent on the synthetic application of DBBF in the perfluoro-*tert*-butylation.

Keywords: fluorination · fluoroalkylation · imaging probes · magnetic resonance imaging · perfluoro-*tert*-butylation

- [1] a) B. Ameduri, H. Sawada, *Fluorinated Polymers*, Royal Society of Chemistry, Cambridge, **2016**; b) D. Cahard, J.-A. Ma, *Emerging Fluorinated Motifs: Synthesis Properties, and Applications*, Wiley-VCH, Weinheim, **2020**; c) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330; d) R. Berger, G. Resnati, P. Metrangola, E. Weber, J. Hulliger, *Chem. Soc. Rev.* **2011**, *40*, 3496–3508.
- [2] a) M. Inoue, Y. Sumii, N. Shibata, *ACS Omega* **2020**, *5*, 10633–10640; b) Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai, N. Shibata, *iScience* **2020**, *23*, 101467.
- [3] S. Dandapani, L. A. Marcaurelle, *Nat. Chem. Biol.* **2010**, *6*, 861–863.
- [4] a) C. Alonso, E. M. Marigorta, G. Rubiales, F. Palacios, *Chem. Rev.* **2015**, *115*, 1847–1935; b) D. E. Yerien, S. Bonesi, A. Postigo, *Org. Biomol. Chem.* **2016**, *14*, 8398–8427.
- [5] a) C.-Y. Chen, H.-K. Jiang, B.-Q. Chen, M.-L. Liang, *Acta Chim. Sin.* **1966**, *32*, 18–25; b) C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165–195.
- [6] a) P. Bisel, L. Al-Momani, M. Müller, *Org. Biomol. Chem.* **2008**, *6*, 2655–2665; b) A. K. Pandey, D. Naduthambi, K. M. Thomas, N. J. Zondlo, *J. Am. Chem. Soc.* **2013**, *135*, 4333–4363; c) S. Decato, T. Bemis, E. Madsen, S. Mecozzi, *Polym. Chem.* **2014**, *5*, 6461–6471.
- [7] For representative reviews, see: a) J.-X. Yu, V. D. Kodibagkar, W. Cui, R. P. Mason, *Curr. Med. Chem.* **2005**, *12*, 819–848; b) E. N. G. Marsh, Y. Suzuki, *ACS Chem. Biol.* **2014**, *9*, 1242–1250; c) T. M. Swager, *Angew. Chem. Int. Ed.* **2018**, *57*, 4248–4257; *Angew. Chem.* **2018**, *130*, 4325–4335; d) Z. Xu, C. Liu, S. Zhao, S. Chen, Y. Zhao, *Chem. Rev.* **2019**, *119*, 195–230.
- [8] For early synthesis of small molecules containing PFtB group using PFIB, see: a) T. J. Brice, J. D. LaZerte, L. J. Hals, W. H. Pearlson, *J. Am. Chem. Soc.* **1953**, *75*, 2698–2702; b) R. N. Haszeldine, J. M. Kidd, *J. Chem. Soc.* **1953**, 3219–3225; c) S. Andreades, *J. Org. Chem.* **1962**, *27*, 4163–4170.
- [9] For leading references on the formal perfluoro-*tert*-butylation reactions using PFIB, see: a) N. I. Delyagina, E. Y. Pervova, I. L. Knunyants, *Russ. Chem. Bull.* **1972**, *21*, 326–329; b) B. L. Dyatkin, B. I. Martynov, L. G. Martynova, N. G. Kizim, S. R. Sterlin, Z. A. Stumbrevichute, L. A. Fedorov, *J. Organomet. Chem.* **1973**, *57*, 423–433; c) S. L. Bell, R. D. Chambers, M. Y. Gribble, J. R. Maslakiewicz, *J. Chem. Soc. Perkin Trans. 1* **1973**, 1716–1720; d) Y. V. Zeifman, L. T. Lantseva, I. L. Knunyants, *Russ. Chem. Bull.* **1978**, *27*, 2362–2366; e) Y. V. Zeifman, E. G. Ter-Gabrielyan, N. P. Gambaryan, I. L. Knunyants, *Russ. Chem. Rev.* **1984**, *53*, 256–273.
- [10] a) I. L. Knunyants, S. T. Kocharyan, E. M. Rokhlin, *Russ. Chem. Bull.* **1966**, *15*, 1008–1012; b) S. T. Kocharyan, E. M. Rokhlin, Y. A. Cheburkov, I. L. Knunyants, *Russ. Chem. Bull.* **1966**, *15*, 1813.
- [11] E. P. Mochalina, B. L. Dyatkin, I. V. Galakhov, I. L. Knunyants, *Dokl. Akad. Nauk SSSR* **1966**, *169*, 1346–1349.
- [12] T. Yajima, K. Yamaguchi, R. Hirokane, E. Nogami, *J. Fluorine Chem.* **2013**, *150*, 1–7.
- [13] A. Kolomeitsev, A. Shtarev, K. Chabanenko, T. Savina, Y. Yagupolskii, A. Shtarev, K. Chabanenko, Y. Yagupolskii, M. Görg, J. Przyborowski, E. Lork, G.-V. Röschenthaler, *Chem. Commun.* **1998**, 705–706.
- [14] The reactions of $\text{C}(\text{CF}_3)_3\text{I}$ with diazomethane and ethylene were described in Ref. [11], and only one example for perfluoro-*tert*-butylation was reported in Ref. [11] and Ref. [12].
- [15] Q. Wang, C. Ni, M. Hu, Q. Xie, Q. Liu, S. Pan, J. Hu, *Angew. Chem. Int. Ed.* **2020**, *59*, 8507–8511; *Angew. Chem.* **2020**, *132*, 8585–8589.
- [16] DBBF was first synthesized by Burton et al. in 1993, but no synthetic application of DBBF has been reported. See: P. A. Morken, P. C. Bachand, D. C. Swenson, D. J. Burton, *J. Am. Chem. Soc.* **1993**, *115*, 5430–5439.
- [17] a) B. E. Smart, W. J. Middleton, W. B. Farnham, *J. Am. Chem. Soc.* **1986**, *108*, 4905–4908; b) N. I. Delyagina, S. M. Igumnov, V. F. Snegirev, I. L. Knunyants, *Russ. Chem. Bull.* **1981**, *30*, 1836–1840; c) S. M. Igumnov, N. I. Delyagina, I. L. Knunyants, *Russ. Chem. Bull.* **1986**, *35*, 1191–1193.
- [18] a) W. B. Farnham, *Chem. Rev.* **1996**, *96*, 1633–1640; b) D. A. Dixon, T. Fukunaga, B. E. Smart, *J. Am. Chem. Soc.* **1986**, *108*, 4027–4031; c) W. B. Farnham, B. E. Smart, W. J. Middleton, J. C. Calabrese, D. A. Dixon, *J. Am. Chem. Soc.* **1985**, *107*, 4565–4567; d) W. B. Farnham, D. A. Dixon, J. C. Calabrese, *J. Am. Chem. Soc.* **1988**, *110*, 2607–2611.

- [19] a) J. C. Jackson, J. T. Hammill, R. A. Mehl, *J. Am. Chem. Soc.* **2007**, *129*, 1160–1166; b) N. B. Barhate, R. N. Barhate, P. Cekan, G. Drobny, S. T. Sigurdsson, *Org. Lett.* **2008**, *10*, 2745–2747; c) B. C. Buer, B. J. Levin, E. N. G. Marsh, *J. Pept. Sci.* **2013**, *19*, 308–314; d) C. M. Tressler, N. J. Zondlo, *Org. Lett.* **2016**, *18*, 6240–6243; e) H. Meng, L. Wen, Z. Xu, Y. Li, J. Hao, Y. Zhao, *Org. Lett.* **2019**, *21*, 5206–5210.
- [20] a) J. Clarke, M. Hatridge, M. Mössle, *Annu. Rev. Biomed. Eng.* **2007**, *9*, 389–413; b) C. Liu, Y. Zhang, L. Qiu, H. Dong, H.-J. Krause, X. Xie, A. Offenhäusser, *Supercond. Sci. Technol.* **2012**, *25*, 075013.
- [21] I. Tirotta, V. Dichiarante, C. Pigliacelli, G. Cavallo, G. Terraneo, F. B. Bombelli, P. Metrangolo, G. Resnati, *Chem. Rev.* **2015**, *115*, 1106–1129.
- [22] Deposition Numbers 2042569 (for **3m**) and 2042571 (for **3ap**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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