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A general protocol for efficient construction of perfluoro-*tert*-butyl alkynes with (perfluoro-*tert*-butyl)propiolic acid†

Zhiqiang Wei,‡ Guangxing Gu,‡ Wei Zhang, Yanchuan Zhao * and Jinbo Hu *

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The perfluoro-*tert*-butyl group (PF*t*B) stands out, in part, due to its unparalleled analytical capabilities, as an indispensable functional group for sensing and imaging within biological systems. Although previously we have accomplished the introduction of the perfluoro-*tert*-butyl group into sp^3-and sp^2-carbons, the perfluoro-*tert*-butylation of sp-carbon remains a challenging task. In this study, we develop a versatile method to construct structurally diverse PF*t*B-substituted alkynes, utilizing (perfluoro-*tert*-butyl)propiolic acid (PF*t*PA) as a new reagent. PF*t*PA is easy to synthesize and can undergo Pd/Cu-catalyzed decarboxylative coupling with a wide array of (aryl, alkyl, alkenyl, and alkynyl) halides and triflates. This synthetic protocol is not only high-yielding but also compatible with various functional groups. Furthermore, we demonstrate the potential of this new synthetic protocol by developing a ^{19}F-labeled probe that is proficient in distinguishing analytes with distal chiral centers.

Introduction

The incorporation of fluorine-containing groups is crucial in the development of pharmaceuticals, pesticides, and high-performance materials.[1–7] In spite of the scarcity of organofluorine compounds in nature, fluorinated compounds play a vital role in NMR (nuclear magnetic resonance)[8] and MRI (magnetic resonance imaging).[9] Among various fluorinated groups, the perfluoro-*tert*-butyl (PF*t*B) group holds particular significance in these detection techniques.[10–23] As part of our ongoing research efforts, our team reported the perfluoro-*tert*-butylation of sp^3-carbon by *in situ* generation of the perfluoro-*tert*-butyl carbanion from the reaction between 1,1-dibromo-2,2-bis(trifluoromethyl)ethylene (DBBF) and CsF.[24] More recently, we reported the perfluoro-*tert*-butylation of sp^2-carbon using perfluoro-*tert*-butyl phenyl sulfone and arynes.[25] However, despite these advancements, the direct perfluoro-*tert*-butylation of sp-carbon remains a formidable challenge. On the one hand, the copper-mediated perfluoro-*tert*-butylation of alkynes failed to yield the desired products (Fig. 1a; for details, see the ESI†). This outcome can be attributed to the fact that the reactivity of (perfluoro-*tert*-butyl)copper is very much different from that of (trifluoromethyl)copper.[26–28] On the other hand, the perfluoro-*tert*-butylation of 1-chloroethynylated compounds using $(CF_3)_3CCs$ (generated from the highly toxic perfluoroisobutylene[29–35] and CsF) is known to be only

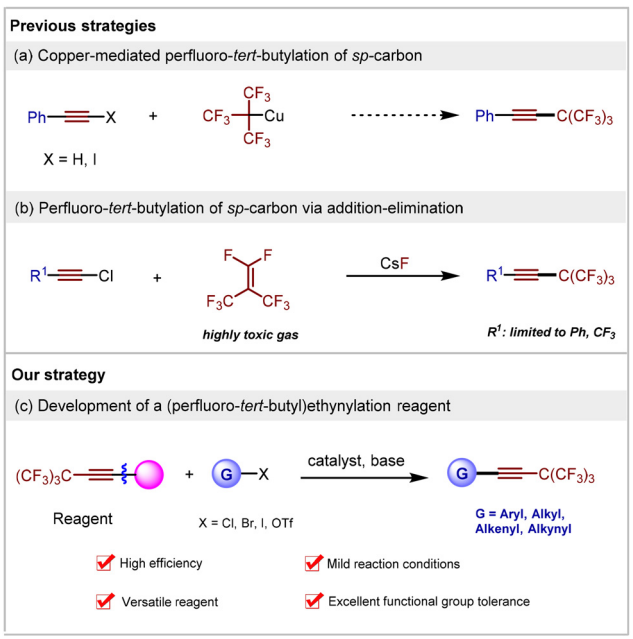

Fig. 1 Strategies for the synthesis of perfluoro-*tert*-butylated alkynes.

State Key Laboratory of Fluorine and Nitrogen Chemistry and Advanced Materials, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Ling-Ling Road, Shanghai 200032, China.
E-mail: jinbohu@sioc.ac.cn, zhaoyanchuan@sioc.ac.cn

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‡These authors contributed equally to this work.

limited to phenyl- and trifluoromethyl-substituted alkynes (Fig. 1b).[36] To efficiently construct structurally diverse PF*t*B-substituted alkynes, we envisioned a new synthetic strategy, that is, a (perfluoro-*tert*-butyl)ethynylation reagent should be developed to undergo cross-coupling with various organic halides and triflates (Fig. 1c).

Results and discussion

With these considerations in mind (Fig. 1), we designed a previously unknown compound, (perfluoro-*tert*-butyl)propiolic acid (PF*t*PA), as a new (perfluoro-*tert*-butyl)ethynylation reagent.[37–39] To synthesize PF*t*PA, we initiated our investigation by conducting perfluoro-*tert*-butylation of benzyl 3-bromopropiolate (BBP) (Fig. 2a). The ester group in BBP enhances its electrophilicity, thus facilitating the addition–elimination reaction between a nucleophile and BBP.[40,41] We used our previously developed protocol to generate the perfluoro-*tert*-butyl anion from DBBF and CsF,[24] and performed the perfluoro-*tert*-butylation of BBP (on a 100 mmol scale). The addition–elimination product [3-(perfluoro-*tert*-butyl)benzyl propiolate, PF*t*BP] was obtained in 90% yield (Fig. 2a). The subsequent facile hydrolysis of PF*t*BP afforded PF*t*PA in 87% yield (Fig. 2b). In addition to its straightforward preparation, PF*t*PA is a stable and nonvolatile liquid with a long shelf-life time, which enables the easy handling of this new reagent in organic synthesis.

Having the PF*t*PA reagent in hand, we then optimized the reaction conditions for (perfluoro-*tert*-butyl)ethynylation by using 4-iodobiphenyl (**S1**) as a model substrate. Since transition metal-catalyzed decarboxylative cross-coupling reactions generally demand high temperatures,[42,43] our initial trial for the decarboxylative (perfluoro-*tert*-butyl)ethynylation was performed at 100 °C, by using DMSO as a solvent and K_2CO_3 as a base. Encouragingly, after 12 hours, we observed that the desired product **1** was formed in 15% yield (Table 1, entry 1). Switching the solvent from DMSO to DMF increased the yield dramatically to 99% (Table 1, entry 2). However, when we decreased the reaction temperature to 80 °C, only a trace amount of the product **1** was detected (Table 1, entry 3). Inspired by the common use of organic bases in Sonogashira coupling,[44,45] we added *N*,*N*-diisopropylethylamine (DIPEA) instead of K_2CO_3, which boosted the yield of **1** to 99% even at

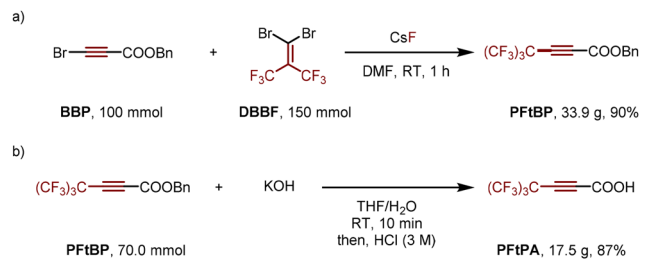
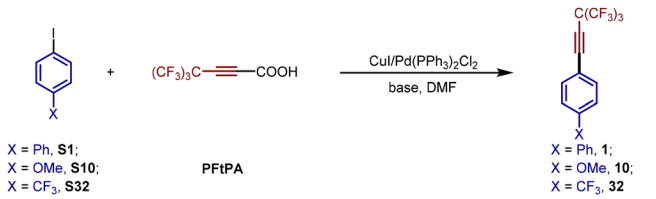


Fig. 2 Preparation of (perfluoro-*tert*-butyl)propiolic acid (PF*t*PA).

Table 1 Survey of reaction conditions[a]



Entry	Base	Pd (equiv.)	*T* (°C)	Time (h)	Yield[b] (%)
1[c]	K_2CO_3	0.05	100	12	15
2	K_2CO_3	0.05	100	12	>99
3	K_2CO_3	0.05	80	12	Trace
4	DIPEA	0.05	80	12	>99
5	DIPEA	0.05	RT	12	90
6	DIPEA	0.05	RT	24	>99
7	DIPEA	0.03	RT	24	>99
8[d]	DIPEA	0.03	RT	24	91
9[d]	DIPEA	0.05	RT	24	>99
10[e]	DIPEA	0.05	RT	24	82
11[e]	DIPEA	0.05	40	24	93
12[e]	DIPEA	0.05	60	24	>99
13[e]	**DIPEA**	**0.05**	**60**	**12**	**>99**

[a] Reaction conditions: **S1** (0.3 mmol, 1.0 equiv.), PF*t*PA (0.36 mmol, 1.2 equiv.), base (0.6 mmol, 2.0 equiv.), CuI (0.015 mmol, 5 mol%), DMF (3.0 mL). [b] Determined by ^{19}F NMR spectroscopy using trifluoromethoxybenzene as an internal standard. [c] DMSO was used as the solvent. [d] 1-Iodo-4-methoxybenzene (**S10**) was used instead of **S1**. [e] 1-Iodo-4-(trifluoromethyl)benzene (**S32**) was used instead of **S1**. Note: DIPEA = *N*,*N*-diisopropylethylamine.

80 °C (Table 1, entry 4). Remarkably, when the reaction was performed at room temperature, the product **1** was still formed in 90% yield (Table 1, entry 5). This suggests that the electron-withdrawing ability of the (perfluoro-*tert*-butyl)ethynyl group might facilitate the decarboxylation process. Extending the reaction time to 24 hours led to a full conversion of 4-iodobiphenyl (**S1**) and gave a near quantitative yield of product **1** (Table 1, entry 6). For substrate **S1**, a 3 mol% of palladium catalyst loading still resulted in 99% yield of product **1** (Table 1, entry 7). However, when 1-iodo-4-methoxybenzene (**S10**) was used as a substrate under identical reaction conditions, the yield of product **10** decreased to 91% (Table 1, entry 8). This decrease can be attributed to the slower reaction rates with the electron-rich substrate, resulting in incomplete conversion of **S10**. To ensure complete substrate conversion, we figured out that a 5 mol% of palladium catalyst loading was optimal for the reaction (Table 1, entry 9). For the electron-deficient aryl iodide 1-iodo-4-(trifluoromethyl)benzene (**S32**), the reductive elimination step can be sluggish and thus requires elevated temperature.[46] As expected, increasing the temperature to 60 °C concurrently improved the reaction yield and reduced the reaction time to 12 hours (Table 1, entries 11–13).

Having established our optimal reaction conditions (as shown in Table 1, entry 13), we proceeded to investigate the substrate scope of the (perfluoro-*tert*-butyl)ethynylation of aryl iodides. As illustrated in Fig. 3, in most cases, the product yields were over 90%, regardless of the electronic and steric

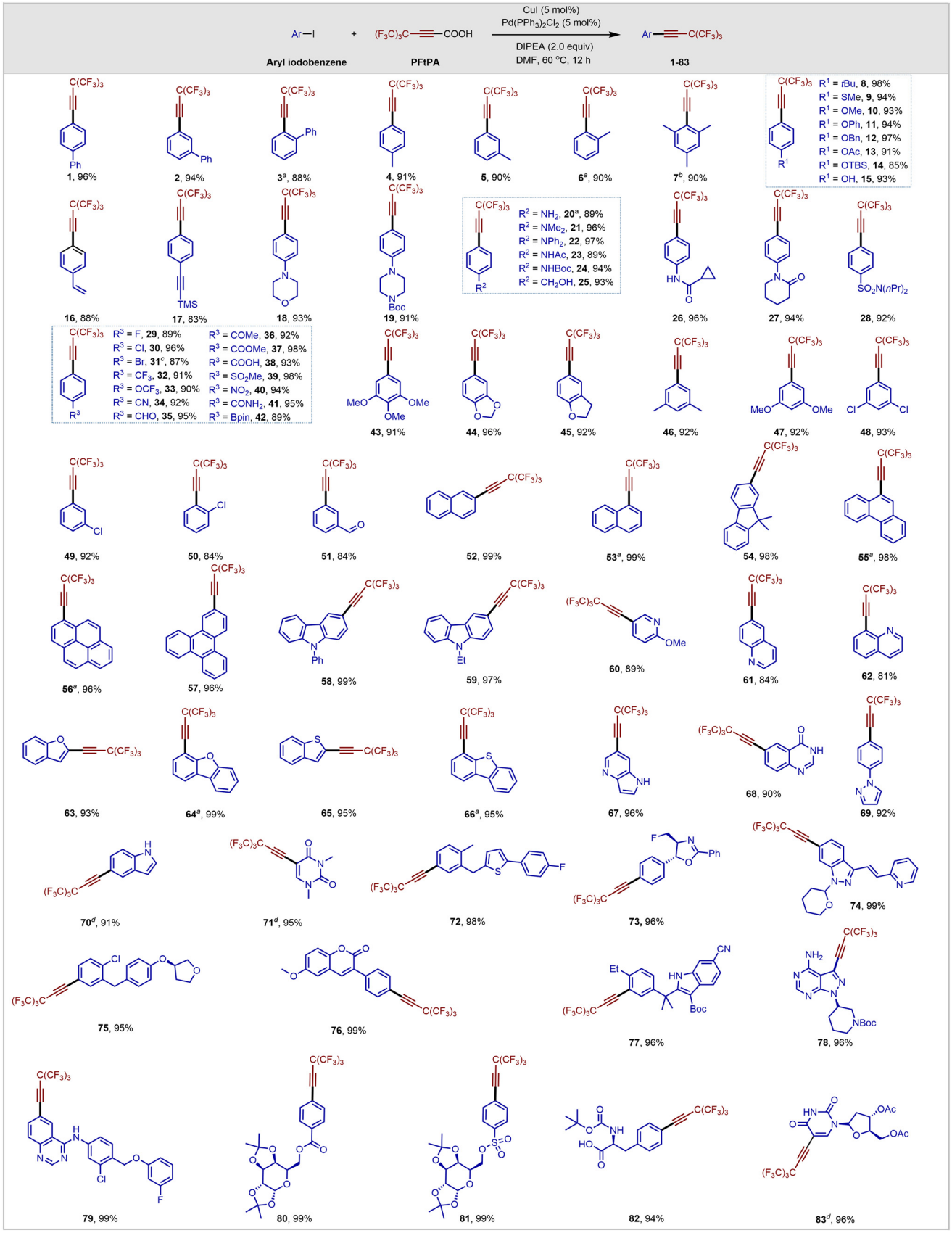


Fig. 3 (Perfluoro-*tert*-butyl)ethynylation of aryl iodides. Reaction conditions: unless otherwise mentioned, ArI (0.30 mmol, 1.0 equiv.), PF*t*PA (0.36 mmol), and DMF (3.0 mL) were used. [a]The reaction time is 24 h. [b]The reaction temperature is 100 °C. [c]The reaction temperature is 25 °C. [d]The reaction temperature is 80 °C.

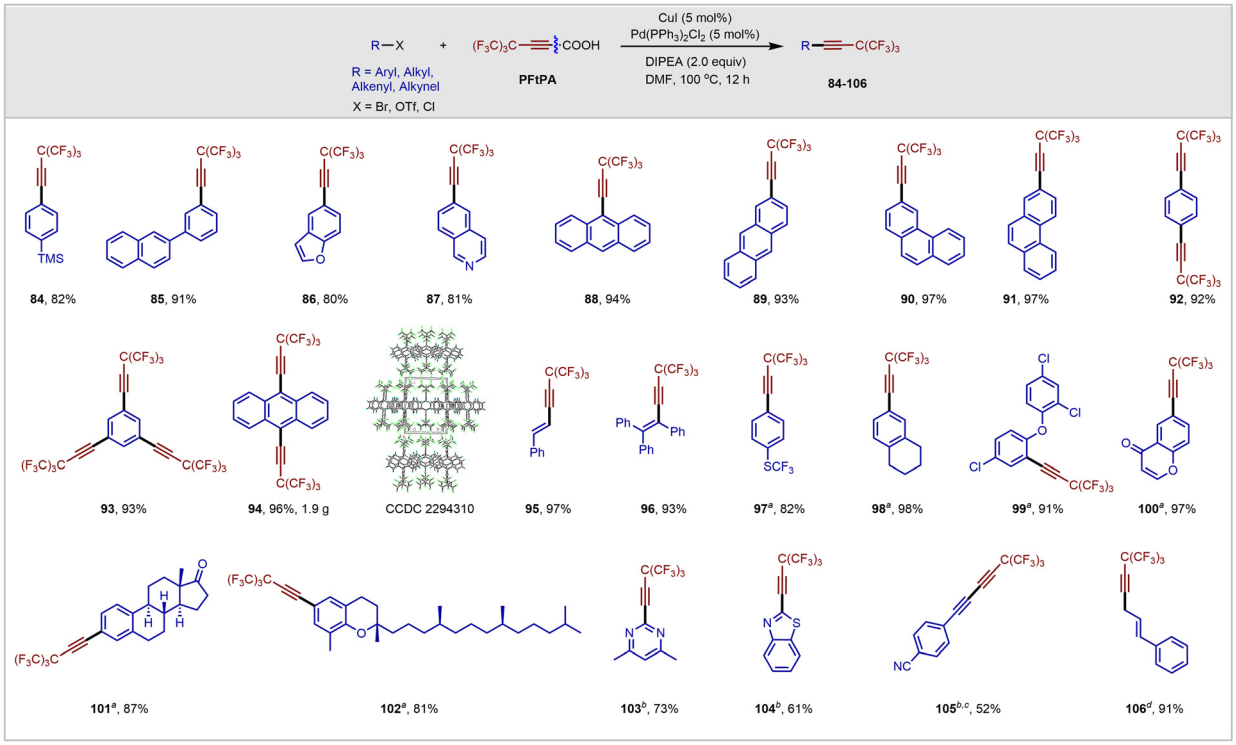


Fig. 4 (Perfluoro-*tert*-butyl)ethynylation of bromides, triflates and chlorides. Reaction conditions: ArBr (0.3 mmol, 1.0 equiv.), PF*t*PA (0.36 mmol, 1.2 equiv.), DMF (3.0 mL). [a]X = OTf. [b]X = Cl. [c]The reaction temperature is 60 °C. [d]No Pd catalyst and at RT.

nature of substrates. A wide array of aryl iodides, ranging from monosubstituted ones bearing electron-neutral, -rich, or -deficient groups (positioned at *ortho*, *meta*, or *para*) to polysubstituted ones, were all suitable substrates for the reaction, giving the desired products under mild reaction conditions. This method showcases impressive tolerance of various functional groups, including *tert*-butyl (**8**), methylthio (**9**), methoxy (**10**), phenoxy (**11**), benzyloxy (**12**), acetyloxy (**13**), OTBS (**14**), hydroxyl (**15**, **25**), C=C double bond (**16**), C≡C triple bond (**17**), and boronic ester (**42**) groups. Moreover, substrates featuring diverse heterocyclic patterns (**58–71**), such as carbazole (**58**, **59**), pyridine (**60**), benzofuran (**63**, **64**), and more, all underwent the desired transformation smoothly. Notably, the procedure effectively supported (perfluoro-*tert*-butyl)ethynylation of the derivatives of bioactive molecules, underscoring its potential in the pharmaceutical realm, with canagliflozin (**72**) and ibrutinib intermediate (**78**) standing out as prominent examples.

Encouraged by these outcomes, we broadened our scope to probe the reactivity of substrates such as aryl bromides (**84–94**), triflates (**97–102**), and chlorides (**103**, **104**). The results are shown in Fig. 4. The structure of product **94** was confirmed by its single crystal X-ray diffraction analysis (CCDC 2294310†). Furthermore, this synthetic protocol also enabled the (perfluoro-*tert*-butyl)ethynylation of cinnamyl (**106**), alkenyl (**95**, **96**) and alkynyl (**105**) halides, and all these substrates exhibited remarkable compatibility with the (perfluoro-*tert*-butyl) ethynylation, which supports the versatility of our synthetic protocol in late-stage functionalization of complex molecules.

The use of ^{19}F-labeled probes in chemosensing is growing in popularity, primarily due to their ability to rapidly distinguish between structurally similar analytes and chiral entities with high fidelity.[47–53] We were particularly intrigued by the high sensitivity of the (perfluoro-*tert*-butyl)ethynyl group when used as a ^{19}F label, which prompted us to delve into its potential for chirality sensing. For our exploration, we chose the cyclopalladium complex-type probe as our model system. Recent studies have shown that these probes often contain a bound acetonitrile, which can be easily replaced by various analytes.[54,55] When chiral amines are present, distinctive ^{19}F NMR signals emerge, with each signal having a unique chemical shift that corresponds to individual enantiomers. Nonetheless, a lingering challenge is the differentiation of analytes with distant chiral centers using the previously developed CF_3-labeled probe (Fig. 5, **probe 2**). One appealing solution involved embedding the (perfluoro-*tert*-butyl)ethynyl group into the probe structure. This strategic alteration places the ^{19}F atom closer to the chiral center, which was not discernable by the CF_3 group. Additionally, having nine identical fluorine atoms would augment sensitivity, yielding intensified ^{19}F signals and reducing data acquisition durations. The designed probe was conveniently synthesized, with a pivotal step involving the novel (perfluoro-*tert*-butyl)ethynylation of pyridyl bromide **S107**. This was followed by a C–H palladation, yielding the desired probe in 90% yield (Fig. 5A). For evaluation purposes, we utilized analytes that are known to be challenging. Amines with a β-chirality center or those carrying similar groups linked to their chirality

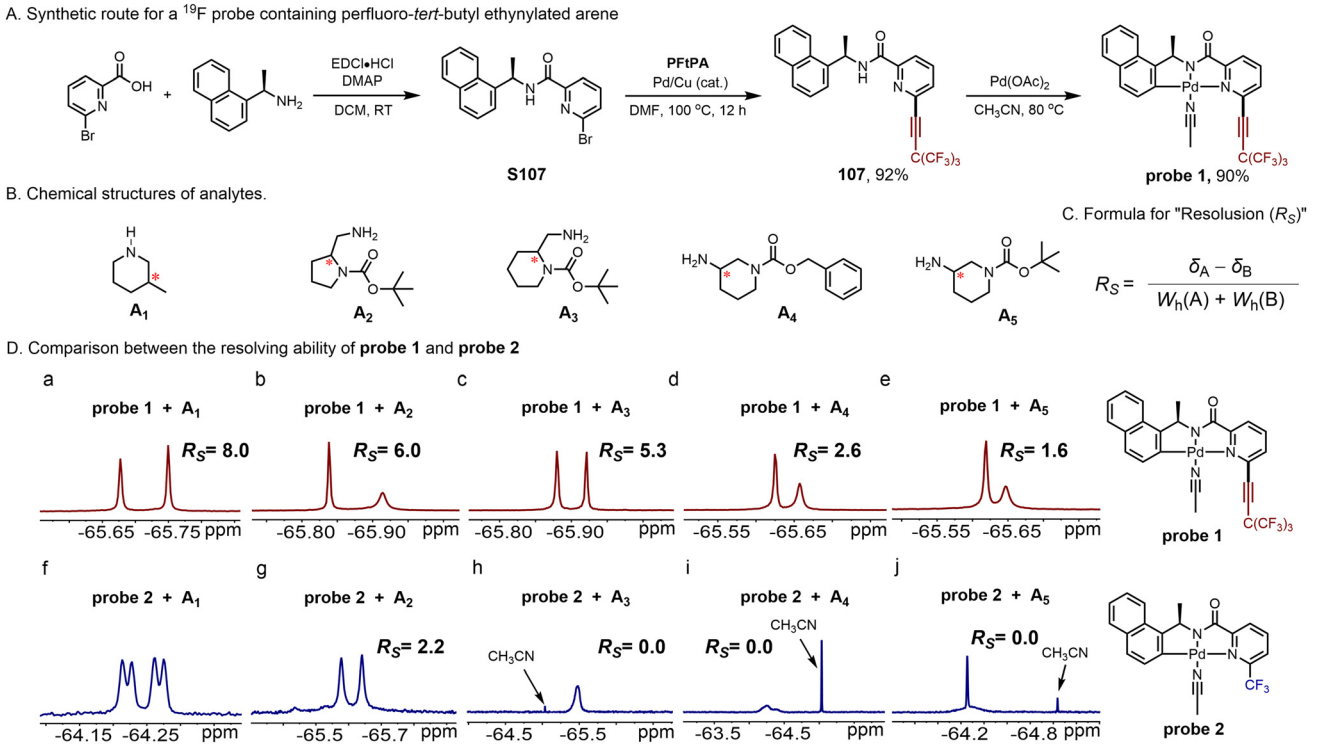


Fig. 5 Synthesis and applications of highly sensitive ^{19}F probes. (A) Synthetic route for a ^{19}F probe labeled with the (perfluoro-*tert*-butyl)ethynyl group. (B) Chemical structures of analytes. (C) Formula for "Resolution (R_s)". (D) Comparison between the resolving ability of **probe 1** and **probe 2**. (a–e) ^{19}F NMR spectra of mixtures of **probe 1** (0.5 mg, 1.9 mM) and various racemic analytes (0.3 mg, *ca.* 3.75 mM) in $CDCl_3$. (f–j) ^{19}F NMR spectra of mixtures of **probe 2** (0.5 mg, 2.5 mM) and various racemic analytes (0.3 mg, *ca.* 3.75 mM) in $CDCl_3$. Note: spectra in dark red were obtained using **probe 1**; spectra in deep blue were obtained using **probe 2**.

center were tested (Fig. 5B). To gauge the probes' resolving capacity, we introduced a metric, "resolution (R_s)", as defined by the equation shown in Fig. 5C. Herein, δ_A and δ_B depict the chemical shifts of the ^{19}F signals for a pair of enantiomers, with $W_h(A)$ and $W_h(B)$ representing their respective ^{19}F NMR signal linewidths at half-peak intensity (Fig. 5C).[56,57] Notably, a higher R_s value signifies a better resolving power. In our experiments, ^{19}F NMR spectra of racemic analytes combined with the probe in $CDCl_3$ were generated. As illustrated in Fig. 5D, analytes **A_1**–**A_5** were distinctly resolved using the (perfluoro-*tert*-butyl) ethynyl-labeled **probe 1**. In contrast, the CF_3-labeled **probe 2** either failed in resolution or produced lower R_s values. These results underscore the promising capabilities of the (perfluoro-*tert*-butyl)ethynyl group in ^{19}F NMR-based detection. The added ethynyl component situates the perfluoro-*tert*-butyl group at an optimal distance from the probe's functional site, paving the way for refining the properties of ^{19}F-labeled probes.

Conclusions

In conclusion, we have developed a new strategy for the efficient construction of structurally diverse $(CF_3)_3C$-substituted alkynes, which commences with perfluoro-*tert*-butylation of one end of alkynes, followed by the functionalization of the other end. In this process, (perfluoro-*tert*-butyl)propiolic acid (PF*t*PA), as a bridge, connects the overall construction. This strategy not only avoids the use of a highly toxic gas but also overcomes the limitations of addition–elimination reactions, enabling the (perfluoro-*tert*-butyl)ethynylation of various functional groups (aryl, vinyl, alkynyl, and alkyl) with excellent yields. This advancement significantly improves access to ^{19}F-labeled biological molecules and probes, paving the way for substantial enhancements in sensing and imaging applications. The introduction of these densely fluorinated building blocks holds immense potential for both scientific exploration and advancements in medical diagnostics. Further investigation in this direction is underway in our laboratory.

Author contributions

Z. W., G. G., Y. Z., and J. H. conceived the study and designed the synthesis as well as tests; Z. W., G. G., and W. Z. synthesized all the compounds; Z. W., G. G., Y. Z., and J. H. analyzed the data and wrote the manuscript.

Data availability

Crystallographic data for compound **94** have been deposited at the Cambridge Crystal Data Centre: CCDC 2294310. Further data supporting this study are available in the ESI.†

Conflicts of interest

There is no conflict of interest to report.

Acknowledgements

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