Sc(OTf)₃ 催化的 δ -三氟甲基- δ -芳基-双取代对亚甲基苯醌和硫醇的反应: 高效合成二芳基甲烷硫醚化合物

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摘要 报道了一种 δ -三氟甲基- δ -芳基-二取代的对亚甲基苯醌和硫醇参与的 1,6-共轭加成反应. 在 5 mol% 三氟甲基磺酸铈催化的条件下, 得到了结构多样化的含有三氟甲基四级碳中心的二芳基甲烷硫醚. 反应具有良好的官能团兼容性和底物范围. 此外, 烷基硫醇和苄硫醇也适用于该反应. 鉴于二芳基甲烷硫醚骨架以及三氟甲基在生物活性分子中的重要性, 发展的含有三氟甲基取代四级碳中心的二芳基甲烷硫醚的高效合成方法将为生物活性分子的发现提供一条简洁、高效的策略.

关键词 δ -三氟甲基- δ -芳基-二取代; 对亚甲基苯醌; 二芳基甲烷; 硫醚; 1,6-共轭加成

Sc(OTf)₃-Catalyzed 1,6-Conjugate Addition of Thiols to δ -CF₃- δ -aryl-disubstituted *para*-Quinone Methides: Efficient Construction of Diarylmethane Thioethers

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Abstract An efficient and practical 1,6-conjugate addition reaction of δ -CF₃- δ -aryl-disubstituted *para*-quinone methides with thiols has been described. This approach provides a straightforward access to structurally diverse diarylmethane thioethers bearing CF₃-substituted quaternary stereocenters using 5 mol% Sc(OTf)₃ as catalyst. The reaction has an excellent functional-group tolerance, and displays a broad scope with respect to both δ -CF₃- δ -aryl-disubstituted *para*-quinone methides and thiophenols. Moreover, alkyl thioalcohols and benzylmercaptan have proven to be suitable substrates. Diarylmethane thioethers belong to an important structural scaffold that widely exists in a number of bioactive molecules and trifluoromethyl group has a profound effect on physiological properties of organic molecules. Therefore, the efficient method for the synthesis of

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diarylmethane thioethers bearing CF₃-substituted quaternary stereocenters might provide a powerful strategy for the discovery of biologically interesting agents.

Keywords δ -CF₃- δ -aryl-disubstituted; *para*-quinone methides; diarylmethane; thioethers; 1,6-conjugate addition

1 Introduction

Sulfur-containing compounds belong to an important structural scaffold that are present in a wide range of natural products, drugs, and bioactive compounds as organosulfur compounds.^[1] Moreover, organosulfur compounds are extensively used in asymmetric synthesis as catalysts or auxiliaries,^[2] and they have been widely applied as key intermediates in the total synthesis of natural products and in the field of agrochemicals and material science.^[3] Great efforts have been devoted to their construction over past decades.^[4] Among them, the synthesis of diarylmethyl thioethers and derivatives has attracted more and more attention from chemists and pharmacists because of their various biological activities, such as potassium channel inhibitory activity, antitumor, antimalarial, and antidepressant activities (Figure 1).^[5] Therefore, the development of practical and efficient methods for the construction of diarylmethyl thioethers and derivatives is highly desired and will provide a powerful strategy for the discovery of biologically interesting molecules.

Figure 1 Representative biologically active diarylmethyl thioethers and derivatives

para-Quinone methides (*p*-QM) have been recognized as important reactive intermediates in 1,6-conjugate addition reactions owing to their strong dipolar character and the thermodynamic driving force to undergo rearomatization.^[6] As a result, the reaction of *p*-QMs with various nucleophiles is one of the most powerful strategies for the synthesis of diarylmethanes given that *p*-QM substrates typically contain a mono-aryl substitution at the δ -position.^[7] A few examples have been demonstrated in the synthesis of diarylmethyl thioethers and derivatives through 1,6-conjugate addition of *p*-QMs with sulfur reagents.^[8] However, these reaction focused on the synthesis of diarylmethyl thioethers

and derivatives with a tertiary stereocenter. Recently, δ -CF₃- δ -aryl-disubstituted *p*-QMs and δ -CN- δ -aryl-disubstituted *p*-QMs were proved to be isolable and storable substrates.^[9] Structurally diverse diarylmethenes bearing quaternary stereocenters were obtained in good yields under different reaction conditions. As we know, the incorporation of trifluoromethyl groups into organic molecules has a profound effect on their lipophilicity, permeability, and metabolic stability.^[10] The presence of a trifluoromethyl group in diarylmethyl thioethers and derivatives might have positive effects on the biological properties of parent molecules. Herein, we present an effective 1,6-conjugate addition process of δ -CF₃- δ -aryl-disubstituted *p*-QMs with aromatic and aliphatic thiols, affording structurally diverse diarylmethane thioethers bearing CF₃-substituted quaternary stereocenters in excellent yields (Scheme 1).

Scheme 1 Synthesis of δ -CF₃- δ -aryl-disubstituted *p*-QMs and diarylmethane thioethers

2 Results and discussion

Initially, the direct addition of δ -CF₃- δ -phenyl-disubstituted *p*-QM **1a** and thiophenol **2a** was selected as the model reaction for optimization (Table 1). No expected product was observed when the reaction was conducted in acetone without any additive (Entry 1). To our delight, the target product **3a** was obtained in good yield when the reaction was conducted in the presence of catalytic amount of Brønsted acids such as *p*-toluenesulfonic acid (PTSA), trifluoroacetic acid (TFA) and (PhO)₂POOH (Entries 2~4). Moreover, the reaction proceeded smoothly and the desired product **3a** was obtained with 46% yield using Lewis acid Fe(OTf)₂ as catalyst (Entry 5). Further investigation of Lewis acids indicated that Sc(OTf)₃ was more efficient with respect to both yield and reaction time,^[11] delivering the

desired product in 93% yield within 0.1 h (Entries 6~10). The solvent effect was next evaluated. When $\text{Sc}(\text{OTf})_3$ was used as catalyst, the product **3a** was obtained in good yields when the reactions were performed in CH_2Cl_2 , $\text{CH}_2\text{Cl}-\text{CH}_2\text{Cl}$, tetrahydrofuran (THF), EtOAc, and toluene (Entries 11~15). Therefore, the optimal condition was established as: $\delta\text{-CF}_3\text{-}\delta\text{-phenyl-disubstituted } p\text{-QM } \mathbf{1a}$ (0.1 mmol), thiophenol **2a** (0.12 mmol), $\text{Sc}(\text{OTf})_3$ (5 mol%), acetone (1.0 mL), and room temperature.

Table 1 Reaction condition optimization^a

Entry	Catalyst	Solvent	Time/h	Yield ^b
1	—	Acetone	24	<5
2	PTSA	Acetone	5	85
3	TFA	Acetone	24	69
4	(PhO) ₂ POOH	Acetone	12	75
5	$\text{Fe}(\text{OTf})_2$	Acetone	48	46
6	$\text{Fe}(\text{OTf})_3$	Acetone	24	70
7	$\text{Cu}(\text{OTf})_2$	Acetone	24	75
8	$\text{Sc}(\text{OTf})_3$	Acetone	0.1	93
9	$\text{Bi}(\text{OTf})_3$	Acetone	12	88
10	AgOTf	Acetone	12	50
11	$\text{Sc}(\text{OTf})_3$	CH_2Cl_2	0.3	91
12	$\text{Sc}(\text{OTf})_3$	$\text{CH}_2\text{ClCH}_2\text{Cl}$	0.3	91
13	$\text{Sc}(\text{OTf})_3$	THF	0.3	90
14	$\text{Sc}(\text{OTf})_3$	EtOAc	05	87
15	$\text{Sc}(\text{OTf})_3$	Toluene	0.3	91

^a Reaction conditions, unless otherwise specified: a solution of **1a** (0.1 mmol), **2a** (0.12 mmol), catalyst (0.005 mmol) in solvent (1.0 mL) at room temperature for indicated time period. ^b Isolated yield.

With the optimized conditions in hand, the 1,6-conjugate addition of $\delta\text{-CF}_3\text{-}\delta\text{-aryl-disubstituted } p\text{-QMs } \mathbf{1}$ with thiophenol **2a** was first verified (Table 2). In general, the reaction with a broad range of $\delta\text{-CF}_3\text{-}\delta\text{-aryl-disubstituted } p\text{-QMs}$ proved to be highly efficient, affording the corresponding diarylmethyl thioethers **3a~3p** in high yields (90%~95% yield). A number of $\delta\text{-CF}_3\text{-}\delta\text{-aryl-disubstituted } p\text{-QMs}$ bearing different substituents on the $\delta\text{-aryl}$ ring were compatible with the reaction conditions, providing the desired products **4a~4l** in excellent yields. $\delta\text{-CF}_3\text{-}\delta\text{-aryl-disubstituted } p\text{-QMs}$ with electron-withdrawing and electron-donating substituents at the *o*-, *m*-, and *p*-positions of the aryl moiety were also tolerated in this transformation. Moreover, $\delta\text{-CF}_3\text{-}\delta\text{-naphthoyl-disubstituted } p\text{-QM } \mathbf{1m}$ was suitable substrate, giving the product in 95% yield. The 1,6-conjugate addition process was also effective with $\delta\text{-CF}_3\text{-}\delta\text{-heteroaryl-disubstituted } p\text{-QMs } \mathbf{1n}$ and **1o**. $\delta\text{-CF}_3\text{-}\delta\text{-aryl-disubstituted } p\text{-QM } \mathbf{1p}$ bearing 2,6-diisopropyl moieties at α positions participated in the reaction smoothly, affording the product in 90% yield. With the simple and mild reaction conditions, functional groups like halogens,

electronically varied aryl moieties, and heterocyclic rings were readily accommodated.

Table 2 Scope of $\delta\text{-CF}_3\text{-}\delta\text{-aryl}$ disubstituted *p*-QMs

The scope of thiols **2** was next explored and the results were summarized in Table 3. Benzenethiols with electron-donating and withdrawing substituents on the benzene ring were employed to give indolin-3-ones (**4a**~**4d**) in high yields (93%~97% yields). Benzenethiols with substitutions at the *m*- and *p*-positions (**4e** and **4f**) of the phenyl moiety were also compatible with the reaction conditions. The reaction of **1a** with 2-naphthalenethiol proceeded smoothly, affording the corresponding diarylmethyl thioether **4g** in 93% yield. The excellent results prompted us to further explore 1,6-conjugate addition of δ -CF₃- δ -phenyl-disubstituted *p*-QM **1a** with alkyl thioalcohols. To our delight, a series of alkyl thioalcohols and benzylmercaptan also underwent the reaction, leading to the desired diarylmethyl thioethers **4h**, **4i**, **4j** and **4k** in 91%~96% yields.

Table 3 Scope of thiols

3 Conclusions

In summary, an efficient 1,6-conjugate addition process of δ -CF₃- δ -aryl-disubstituted *p*-QMs with thiols has been described. Using 5 mol% of Sc(OTf)₃ as catalyst, structurally diverse diarylmethane thioethers bearing CF₃-substituted quaternary stereocenters were obtained in high yields. The reaction proceeded under mild conditions and displayed excellent functional group tolerance. Moreover, the reaction exhibits a broad substrate scope with respect to both δ -CF₃- δ -aryl-disubstituted *para*-quinone methides and thiophenols. In addition, alkyl thioalcohols and benzylmercaptan have proven to be suitable substrates. Diarylmethane thioethers belong to an important structural scaffold that widely exists in a number of bioactive molecules, and trifluoromethyl group has a profound effect on the physiological properties of organic molecules. Therefore, this method would provide a powerful strategy for the discovery of biologically interesting agents.

4 Experimental section

4.1 General information

Proton nuclear magnetic resonance (¹H NMR) spectra, carbon nuclear magnetic resonance (¹³C NMR) spectra, and fluorine nuclear magnetic resonance (¹⁹F NMR) spectra were recorded at 500, 126, and 471 MHz, respectively. The solvent peak was used as a reference value, for ¹H NMR: CDCl₃ δ 7.26; for ¹³C NMR: CDCl₃ δ 77.23. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel GF254 plates. Column chromatography was carried out on silica gel (200~300 mesh). HRMS were carried out on an Orbitrap analyzer.

4.2 Substrate preparation

To a solution of aromatic aldehyde **S1** (2.0 mmol, 1.0 equiv.) in anhydrous tetrahydrofuran (THF) at 0 °C under N₂ was added TMSCF₃ (2.4 mmol, 1.2 equiv) and tetrabutylammoniumfluoride (TBAF) (2.4 mmol, 2.4 mL, 1.0 mol/L in THF, 1.2 equiv.) dropwise. Then the reaction was warmed to room temperature and monitored by TLC until the complete conversion. The mixture was quenched dropwise by a saturated aqueous NH₄Cl solution (5 mL). The organic layer was extracted with ethyl acetate (15 mL $\times$ 3) and the combined organic layers were washed with saturated aqueous NaCl solution, dried over anhydrous MgSO₄, filtered and removed under vacuum. The residue was purified by a column chromatography on silica gel using ethyl acetate/petroleum ether as eluent to give the desired product **S2**. The product **S2** was dissolved in hexafluoroisopropanol (HFIP) (5 mL), and TfoH (0.05 equiv.) and PhOH (3.0 equiv.) were added to the solution. The mixture was heated to reflux and monitored by TLC until the complete conversion. Then the reaction was quenched by saturated aqueous NaHCO₃ solution (10 mL). The organic layer was extracted with CH₂Cl₂ (15 mL $\times$ 3) and the combined organic layers were washed with saturated aqueous NaCl solution, dried over anhydrous MgSO₄, fil-

tered and removed under vacuum. The residue was purified by a column chromatography on silica gel using ethyl acetate/petroleum ether as eluent to give the desired product **S3**. The product **S3** was dissolved in CH_2Cl_2 , and DDQ (1.1 equiv.) and PTSA (0.01 equiv.) were added to the solution at room temperature. Upon completion, the reaction was concentrated and purified by a flash column chromatography to give the desired product **1**.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-phenylethylidene)cyclohexa-2,5-dien-1-one (**1a**): ^1H NMR (500 MHz, CDCl_3) δ : 7.62~7.53 (m, 1H), 7.57~7.41 (m, 3H), 7.35~7.13 (m, 2H), 6.73 (s, 1H), 2.11 (d, $J=1.2$ Hz, 3H), 1.91 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ : 186.9, 138.7, 138.5, 137.4 (q, $J=30.3$ Hz), 134.5, 133.3, 132.7, 130.4, 130.2, 129.4, 128.4, 123.3 (q, $J=276.0$ Hz), 16.9, 16.4; ^{19}F NMR (471 MHz, CDCl_3) δ : -52.89. HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{14}\text{F}_3\text{O}$ $[\text{M}+\text{H}]^+$ 279.0991, found 279.0995.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-(4-fluorophenyl)ethylidene)cyclohexa-2,5-dien-1-one (**1b**): ^1H NMR (500 MHz, CDCl_3) δ : 7.58 (s, 1H), 7.52~7.38 (m, 2H), 7.34~7.18 (m, 2H), 6.73 (s, 1H), 2.11 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ : 186.7, 164.5, 162.0, 138.8, 138.8, 136.2 (q, $J=30.7$ Hz), 134.8, 133.0, 132.3, 132.2, 130.4, 123.1 (q, $J=276.3$ Hz), 115.8, 115.6, 16.9, 16.5; ^{19}F NMR (376 MHz, CDCl_3) δ : -53.18, -111.12. HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{13}\text{F}_4\text{O}$ $[\text{M}+\text{H}]^+$ 297.0897, found 297.0892.

4-(1-(4-Chlorophenyl)-2,2,2-trifluoroethylidene)-2,6-dimethylcyclohexa-2,5-dien-1-one (**1c**): ^1H NMR (400 MHz, CDCl_3) δ : 7.56~7.51 (m, 1H), 7.49~7.41 (m, 2H), 7.19 (d, $J=8.3$ Hz, 2H), 6.67 (s, 1H), 2.09 (d, $J=1.1$ Hz, 3H), 1.91 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ : 187.0, 139.2, 139.1, 136.1 (q, $J=30.6$ Hz), 135.0, 133.1, 131.8, 131.2, 130.4, 130.0, 123.2 (q, $J=276.0$ Hz), 17.1, 16.7; ^{19}F NMR (376 MHz, CDCl_3) δ : -52.89. HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{13}\text{ClF}_3\text{O}$ $[\text{M}+\text{H}]^+$ 313.0602, found 313.0612.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-(*p*-tolyl)ethylidene)cyclohexa-2,5-dien-1-one (**1d**): ^1H NMR (400 MHz, CDCl_3) δ : 7.55 (s, 1H), 7.27 (d, $J=7.0$ Hz, 2H), 7.14 (d, $J=7.9$ Hz, 2H), 6.75 (s, 1H), 2.43 (s, 3H), 2.10 (d, $J=1.3$ Hz, 3H), 1.91 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ : 187.2, 139.8, 138.7, 138.5, 137.9 (q, $J=30.1$ Hz), 134.4, 133.8, 130.7, 129.2, 123.5 (q, $J=276.2$ Hz), 21.6, 17.1, 16.7; ^{19}F NMR (376 MHz, CDCl_3) δ : -53.18. HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{16}\text{F}_3\text{O}$ $[\text{M}+\text{H}]^+$ 293.1148, found 293.1155.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-(4-isopropylphenyl)ethylidene)cyclohexa-2,5-dien-1-one (**1e**): ^1H NMR (400 MHz, CDCl_3) δ : 7.56 (d, $J=1.3$ Hz, 1H), 7.31 (d, $J=8.1$ Hz, 2H), 7.16 (d, $J=8.0$ Hz, 2H), 6.77 (s, 1H), 2.98 (dt, $J=13.8, 6.9$ Hz, 1H), 2.10 (d, $J=1.2$ Hz, 3H), 1.91 (s, 3H), 1.30 (d, $J=6.9$ Hz, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ : 187.2, 150.6, 138.6, 138.5, 138.0 (q, $J=60.0, 29.9$ Hz), 134.4, 133.8, 130.8, 130.5, 130.1, 126.6, 123.5 (q, $J=276.2$ Hz), 34.2, 24.0, 17.1, 16.7; ^{19}F NMR (376 MHz, CDCl_3) δ : -52.75. HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{20}\text{F}_3\text{O}$ $[\text{M}+\text{H}]^+$ 321.1461, found 321.1467.

4-(1-(4-(Tert-butyl)phenyl)-2,2,2-trifluoroethylidene)-2,

6-dimethylcyclohexa-2,5-dien-1-one (**1f**): ^1H NMR (400 MHz, CDCl_3) δ : 7.56 (d, $J=1.3$ Hz, 1H), 7.50~7.42 (m, 2H), 7.17 (d, $J=8.1$ Hz, 2H), 6.78 (d, $J=0.6$ Hz, 1H), 2.10 (d, $J=1.2$ Hz, 3H), 1.92 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ : 187.3, 152.9, 138.7, 138.1 (q, $J=29.9$ Hz), 134.5, 133.9, 130.8, 130.3, 125.5, 123.56 (d, $J=276.2$ Hz), 35.1, 31.5, 17.2, 16.7; ^{19}F NMR (376 MHz, CDCl_3) δ : -52.73. HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{22}\text{F}_3\text{O}$ $[\text{M}+\text{H}]^+$ 335.1617, found 335.1619.

4-(1-([1,1'-Biphenyl]-4-yl)-2,2,2-trifluoroethylidene)-2,6-dimethylcyclohexa-2,5-dien-1-one (**1g**): ^1H NMR (400 MHz, CDCl_3) δ : 7.74~7.64 (m, 4H), 7.60 (s, 1H), 7.49 (t, $J=7.5$ Hz, 2H), 7.41 (t, $J=7.3$ Hz, 1H), 7.35 (d, $J=7.9$ Hz, 2H), 6.84 (s, 1H), 2.13 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ : 187.1, 142.4, 140.0, 137.4 (q, $J=30.3$ Hz), 134.7, 133.6, 131.6, 130.6, 129.1, 128.1, 123.4 (q, $J=276.2$ Hz), 17.1, 16.7; ^{19}F NMR (376 MHz, CDCl_3) δ : -52.58. HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{18}\text{F}_3\text{O}$ $[\text{M}+\text{H}]^+$ 355.1304, found 355.1313.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-(4-methoxyphenyl)ethylidene)cyclohexa-2,5-dien-1-one (**1h**): ^1H NMR (400 MHz, CDCl_3) δ : 7.54 (d, $J=1.3$ Hz, 1H), 7.20~7.10 (m, 2H), 7.02~6.92 (m, 1H), 6.78 (s, 2H), 3.87 (s, 3H), 2.09 (d, $J=1.1$ Hz, 3H), 1.91 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ : 187.2, 160.7, 138.5, 138.4, 137.7 (q, $J=30.1$ Hz), 134.4, 133.9, 132.2, 130.8, 123.5 (q, $J=278.1$ Hz), 113.9, 55.6, 17.2, 16.7; ^{19}F NMR (376 MHz, CDCl_3) δ : -52.91. HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{16}\text{F}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 309.1097, found 309.1105.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-(3-fluorophenyl)ethylidene)cyclohexa-2,5-dien-1-one (**1i**): ^1H NMR (400 MHz, CDCl_3) δ : 7.53 (d, $J=0.7$ Hz, 1H), 7.44 (td, $J=8.0, 5.9$ Hz, 1H), 7.23~7.12 (m, 1H), 7.01 (dd, $J=17.2, 8.3$ Hz, 2H), 6.67 (s, 1H), 2.10 (d, $J=1.0$ Hz, 3H), 1.91 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ : 187.0, 163.7, 161.3, 139.2 (d, $J=16.6$ Hz), 135.7 (q, $J=59.4, 30.5$ Hz), 135.0, 133.0, 130.3, 126.2, 123.2 (q, $J=275.8$ Hz), 117.5 (d, $J=22.4$ Hz), 116.6 (d, $J=20.9$ Hz), 17.1, 16.7; ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ : -57.66, -116.69. HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{13}\text{F}_4\text{O}$ $[\text{M}+\text{H}]^+$ 297.0897, found 297.0888.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-(*m*-tolyl)ethylidene)cyclohexa-2,5-dien-1-one (**1j**): ^1H NMR (400 MHz, CDCl_3) δ : 7.55 (s, 1H), 7.37~7.24 (m, 2H), 7.08~6.98 (m, 2H), 6.72 (s, 1H), 2.41 (s, 3H), 2.09 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ : 187.2, 138.7, 138.5, 138.3, 137.7 (q, $J=30.2$ Hz), 134.4, 133.6, 132.7, 130.7, 130.3, 128.3, 127.5, 123.4 (q, $J=276.1$ Hz), 21.5, 17.1, 16.7; ^{19}F NMR (376 MHz, CDCl_3) δ : -52.83. HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{16}\text{F}_3\text{O}$ $[\text{M}+\text{H}]^+$ 293.1148, found 293.1155.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-(3-methoxyphenyl)ethylidene)cyclohexa-2,5-dien-1-one (**1k**): ^1H NMR (500 MHz, CDCl_3) δ : 7.54 (d, $J=0.9$ Hz, 1H), 7.37 (t, $J=8.0$ Hz, 1H), 7.05~6.97 (m, 1H), 6.82 (d, $J=7.6$ Hz, 1H), 6.77 (s, 1H), 6.73 (s, 1H), 3.84 (s, 3H), 2.10 (d, $J=1.0$ Hz, 3H), 1.90 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ : 187.2, 159.6, 138.9, 138.7, 137.3 (q, $J=30.4$ Hz), 134.6, 134.1,

133.6, 130.6, 129.7, 123.4 (q, $J=276.0$ Hz), 122.8, 115.9, 115.1, 55.6, 17.1, 16.6; ^{19}F NMR (471 MHz, CDCl_3) δ : -53.25. HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{16}\text{F}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 309.1097, found 309.1090.

4-(1-(3,5-Dimethylphenyl)-2,2,2-trifluoroethylidene)-2,6-dimethylcyclohexa-2,5-dien-1-one (**11**): ^1H NMR (400 MHz, CDCl_3) δ : 7.52 (d, $J=1.3$ Hz, 1H), 7.07 (s, 1H), 6.82 (s, 2H), 6.71 (s, 1H), 2.34 (s, 6H), 2.07 (d, $J=1.2$ Hz, 3H), 1.88 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ : 187.2, 138.6, 138.4, 138.2, 138.1 (q, $J=30.3$ Hz), 134.3, 133.8, 132.7, 131.2, 130.7, 127.9, 123.5 (q, $J=276.1$ Hz), 21.4, 17.1, 16.6; ^{19}F NMR (376 MHz, CDCl_3) δ : -52.85. HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{18}\text{F}_3\text{O}$ $[\text{M}+\text{H}]^+$ 307.1304, found 307.1313.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-(naphthalen-2-yl)ethylidene)cyclohexa-2,5-dien-1-one (**1m**): ^1H NMR (400 MHz, CDCl_3) δ : 7.98~7.86 (m, 3H), 7.75 (s, 1H), 7.66~7.53 (m, 3H), 7.36 (d, $J=8.3$ Hz, 1H), 6.77 (s, 1H), 2.14 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ : 187.2, 138.9, 137.6 (q, $J=30.3$ Hz), 134.8, 133.6, 133.4, 132.7, 130.7, 130.4, 128.5, 128.3, 128.0, 127.6, 127.3, 127.2, 123.5 (q, $J=276.2$ Hz), 17.2, 16.6; ^{19}F NMR (376 MHz, CDCl_3) δ : -52.55. HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{16}\text{F}_3\text{O}$ $[\text{M}+\text{H}]^+$ 329.1148, found 329.1150.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-(furan-2-yl)ethylidene)cyclohexa-2,5-dien-1-one (**1n**): ^1H NMR (400 MHz, CDCl_3) δ : 7.59 (dd, $J=5.1, 1.2$ Hz, 1H), 7.53 (d, $J=1.1$ Hz, 1H), 7.15 (dd, $J=5.1, 3.6$ Hz, 1H), 7.10 (d, $J=3.3$ Hz, 1H), 6.99 (s, 1H), 2.10 (d, $J=1.2$ Hz, 3H), 1.96 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ : 187.2, 139.0, 138.89, 136.7, 133.7, 130.3, 130.3 (q, $J=31.7$ Hz), 130.2, 127.5, 122.9 (q, $J=276.3$ Hz), 17.2, 16.7; ^{19}F NMR (376 MHz, CDCl_3) δ : -53.94. HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{12}\text{F}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 269.0784, found 269.0792.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-(thiophen-2-yl)ethylidene)cyclohexa-2,5-dien-1-one (**1o**): ^1H NMR (500 MHz, CDCl_3) δ : 7.59 (dd, $J=5.1, 1.1$ Hz, 1H), 7.53 (d, $J=1.1$ Hz, 1H), 7.15 (dd, $J=5.1, 3.6$ Hz, 1H), 7.10 (d, $J=3.4$ Hz, 1H), 6.99 (s, 1H), 2.10 (d, $J=1.0$ Hz, 3H), 1.95 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ : 187.2, 139.0 (d, $J=15.0$ Hz), 136.6 (d, $J=2.6$ Hz), 133.7, 132.8, 130.3 (q, $J=3.1$ Hz), 130.3 (q, $J=31.7$ Hz), 130.2, 127.5, 122.9 (q, $J=276.2$ Hz), 17.1, 16.7; ^{19}F NMR (471 MHz, CDCl_3) δ : -53.97. HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{12}\text{F}_3\text{OS}$ $[\text{M}+\text{H}]^+$ 285.0555, found 285.0563.

2,6-Diisopropyl-4-(2,2,2-trifluoro-1-(4-methoxyphenyl)ethylidene)cyclohexa-2,5-dien-1-one (**1p**): ^1H NMR (400 MHz, CDCl_3) δ : 7.48 (s, 1H), 7.20 (d, $J=8.5$ Hz, 2H), 6.98 (d, $J=8.7$ Hz, 2H), 6.74 (s, 1H), 3.87 (s, 3H), 3.17 (dt, $J=13.7, 6.8$ Hz, 1H), 3.04 (dt, $J=13.7, 6.9$ Hz, 1H), 1.16 (d, $J=6.9$ Hz, 6H), 0.95 (d, $J=6.9$ Hz, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ : 185.3, 160.6, 148.1, 137.7 (q, $J=30.0$ Hz), 134.7, 132.2, 130.3, 128.9 (q, $J=220.0$ Hz), 127.1, 125.0, 122.3, 113.9, 55.5, 27.3, 27.1, 22.1, 21.9; ^{19}F NMR (376 MHz, CDCl_3) δ : -52.79. HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{24}\text{F}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 365.1723, found 365.1655.

4.3 General procedure for 1,6-aza-conjugate addition of anilines to δ -cyano substituted *para*-quinone methides

To a solution of **1** (0.1 mmol, 1.0 equiv.) in acetone (1.0 mL) was successively added **2** (0.12 mmol, 1.2 equiv.) and $\text{Sc}(\text{OTf})_3$ (0.005 mmol, 0.05 equiv.) at room temperature. It was stirred at the same temperature and monitored by TLC until complete conversion. The reactants were then concentrated and purified by flash column chromatography, using ethyl acetate/petroleum ether ($V:V=2:98$) as eluent to obtain the desired product **3**.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-phenyl-1-(phenylthio)ethyl)phenol (**3a**): 36.5 mg, 94% yield. ^1H NMR (400 MHz, CDCl_3) δ : 7.44~7.38 (m, 2H), 7.29~7.25 (m, 3H), 7.24~7.19 (m, 1H), 7.09~7.06 (m, 4H), 7.05 (s, 2H), 4.73 (s, 1H), 2.20 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ : 152.2, 138.8, 137.6, 130.6, 130.5, 130.3, 129.9, 129.5, 128.2, 128.0, 127.8, 126.8 (q, $J=283.6$ Hz), 122.3, 67.1 (q, $J=51.4, 25.9$ Hz), 16.2; ^{19}F NMR (471 MHz, CDCl_3) δ : -64.14. HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{18}\text{F}_3\text{OS}$ $[\text{M}-\text{H}]^-$ 387.1036, found 387.1033.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-(4-fluorophenyl)-1-(phenylthio)ethyl)phenol (**3b**): 39.6 mg, 95% yield. ^1H NMR (500 MHz, CDCl_3) δ : 7.40~7.33 (m, 2H), 7.25~7.21 (m, 1H), 7.09 (d, $J=4.6$ Hz, 4H), 7.02 (s, 2H), 6.99~6.90 (m, 2H), 4.71 (s, 1H), 2.20 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ : 163.2, 161.2, 152.3, 137.6, 134.7, 132.2, 130.6, 130.4, 129.6, 128.3, 126.7 (q, $J=283.3$ Hz), 122.5, 114.8 (d, $J=21.4$ Hz), 66.7 (q, $J=26.1$ Hz), 16.2; ^{19}F NMR (471 MHz, CDCl_3) δ : -64.38, -113.96. HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{17}\text{F}_4\text{OS}$ $[\text{M}-\text{H}]^-$ 405.0942, found 405.0941.

4-(1-(4-Chlorophenyl)-2,2,2-trifluoro-1-(phenylthio)ethyl)-2,6-dimethylphenol (**3c**): 38.9 mg, 92% yield. ^1H NMR (500 MHz, CDCl_3) δ : 7.33 (d, $J=8.5$ Hz, 2H), 7.25~7.21 (m, 3H), 7.14~7.06 (m, 4H), 7.01 (s, 2H), 4.72 (s, 1H), 2.20 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ : 152.4, 137.6, 137.5, 134.0, 131.7, 130.5, 130.2, 129.7, 129.4, 128.3, 128.0, 126.6 (q, $J=566.7, 283.3$ Hz), 122.5, 66.7 (q, $J=26.0$ Hz), 16.2; ^{19}F NMR (471 MHz, CDCl_3) δ : -64.30. HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{17}\text{F}_3\text{ClOS}$ $[\text{M}-\text{H}]^-$ 421.0646, found 421.0645.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-(phenylthio)-1-(*p*-tolyl)ethyl)phenol (**3d**): 37.0 mg, 92% yield. ^1H NMR (500 MHz, CDCl_3) δ : 7.30 (d, $J=8.0$ Hz, 2H), 7.24~7.19 (m, 1H), 7.09 (m, 6H), 7.04 (s, 2H), 4.69 (s, 1H), 2.35 (s, 3H), 2.19 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ : 152.1, 137.8, 137.5, 135.8, 130.7, 130.6, 130.2, 130.0, 129.4, 128.6, 128.1, 126.9 (q, $J=283.4$ Hz), 122.3, 67.1 (q, $J=25.6$ Hz), 21.2, 16.2; ^{19}F NMR (471 MHz, CDCl_3) δ : -64.15. HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{20}\text{F}_3\text{OS}$ $[\text{M}-\text{H}]^-$ 401.1192, found 401.1191.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-(4-isopropylphenyl)-1-(phenylthio)ethyl)phenol (**3e**): 40.5 mg, 94% yield. ^1H NMR (500 MHz, CDCl_3) δ : 7.29 (d, $J=8.2$ Hz, 2H), 7.22~7.18 (m, 1H), 7.10 (d, $J=8.4$ Hz, 2H), 7.08 (s, 2H), 7.07~7.02 (m, 4H), 4.70 (s, 1H), 2.90 (dt, $J=13.8, 6.9$

Hz, 1H), 2.21 (s, 6H), 1.26 (d, $J=6.9$ Hz, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ : 152.1, 148.7, 137.6, 136.0, 130.8, 130.7, 130.2, 129.9, 129.3, 128.1, 126.9 (q, $J=571.7$, 278.4 Hz), 125.9, 122.3, 67.1 (q, $J=25.8$ Hz), 33.9, 24.1, 24.1, 16.20; ^{19}F NMR (471 MHz, CDCl_3) δ : -64.22. HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{24}\text{F}_3\text{OS}$ $[\text{M}-\text{H}]^-$ 429.1505, found 429.1512.

4-(1-(4-(tert-Butyl)phenyl)-2,2,2-trifluoro-1-(phenylthio)ethyl)-2,6-dimethylphenol (**3f**): 41.3 mg, 93% yield. ^1H NMR (500 MHz, CDCl_3) δ : 7.31~7.25 (m, 4H), 7.22~7.18 (m, 1H), 7.10 (s, 2H), 7.07~7.00 (m, 4H), 4.71 (s, 1H), 2.21 (s, 6H), 1.33 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ : 152.1, 151.0, 137.6, 135.6, 130.7, 129.3, 128.0, 126.6 (q, $J=287.1$ Hz), 124.7, 122.3, 67.1 (q, $J=26.0$ Hz), 34.7, 31.5, 16.2; ^{19}F NMR (471 MHz, CDCl_3) δ : -64.23. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{26}\text{F}_3\text{OS}$ $[\text{M}-\text{H}]^-$ 443.1662, found 443.1661.

4-(1-(1,1'-Biphenyl)-4-yl)-2,2,2-trifluoro-1-(phenylthio)ethyl)-2,6-dimethylphenol (**3g**): 45.0 mg, 91% yield. ^1H NMR (500 MHz, CDCl_3) δ : 7.62 (d, $J=7.3$ Hz, 2H), 7.51 (d, $J=8.6$ Hz, 2H), 7.49~7.44 (m, 4H), 7.38 (t, $J=7.4$ Hz, 1H), 7.22 (t, $J=7.3$ Hz, 1H), 7.15~7.09 (m, 4H), 7.07 (t, $J=7.7$ Hz, 2H), 4.72 (s, 1H), 2.22 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ : 152.3, 140.6, 140.5, 137.8, 137.6, 130.7, 130.5, 129.8, 129.5, 129.0, 128.2, 127.8, 127.2, 126.8 (q, $J=283.3$ Hz), 126.4, 122.4, 67.1 (q, $J=25.7$ Hz), 16.2; ^{19}F NMR (471 MHz, CDCl_3) δ : -64.11. HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{22}\text{F}_3\text{OS}$ $[\text{M}-\text{H}]^-$ 463.1349, found 463.1346.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-(4-methoxyphenyl)-1-(phenylthio)ethyl)phenol (**3h**): 38.5 mg, 92% yield. ^1H NMR (400 MHz, CDCl_3) δ : 7.33 (d, $J=8.6$ Hz, 2H), 7.26~7.18 (m, 1H), 7.11~7.06 (m, 4H), 7.04 (s, 2H), 6.80 (d, $J=9.0$ Hz, 2H), 4.73 (s, 1H), 3.82 (s, 3H), 2.19 (s, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ : 159.1, 152.1, 137.5, 131.6, 130.7, 130.6, 130.0, 129.4, 129.3, 128.2, 126.9 (q, $J=283.4$ Hz), 122.3, 113.1, 66.9 (q, $J=25.7$ Hz), 55.5, 16.2; ^{19}F NMR (471 MHz, CDCl_3) δ : -64.3. HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{20}\text{F}_3\text{O}_2\text{S}$ $[\text{M}-\text{H}]^-$ 417.1142, found 417.1140.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-(3-fluorophenyl)-1-(phenylthio)ethyl)phenol (**3i**): 37.8 mg, 93% yield. ^1H NMR (400 MHz, CDCl_3) δ : 7.26~7.18 (m, 2H), 7.15~7.08 (m, 5H), 7.03 (s, 2H), 7.01~6.93 (m, 1H), 4.75 (s, 1H), 2.21 (s, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ : 162.0 (d, $J=245.2$ Hz), 152.2, 141.0 (d, $J=7.4$ Hz), 137.4, 130.3, 129.9, 129.5, 129.0, 129.0 (d, $J=8.0$ Hz), 128.1, 126.3 (q, $J=283.2$ Hz), 125.8, 122.3, 117.5 (d, $J=22.2$ Hz), 114.7 (d, $J=21.0$ Hz), 66.6 (q, $J=26.2$ Hz), 16.0; ^{19}F NMR (471 MHz, CDCl_3) δ : -64.23, -112.93. HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{17}\text{F}_4\text{OS}$ $[\text{M}-\text{H}]^-$ 405.0942, found 405.0939.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-(phenylthio)-1-(*m*-tolylethyl)phenol (**3j**): 37.0 mg, 92% yield. ^1H NMR (500 MHz, CDCl_3) δ : 7.24~7.17 (m, 3H), 7.17~7.12 (m, 1H), 7.10~7.06 (m, 5H), 7.04 (s, 2H), 4.69 (s, 1H), 2.30 (s, 3H), 2.20 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ : 152.1,

138.6, 137.6, 137.4, 131.0, 130.7, 130.7, 129.9, 129.4, 128.7, 128.1, 127.7, 127.5, 126.8 (q, $J=283.3$ Hz), 122.3, 67.3 (q, $J=25.6$ Hz), 21.7, 16.2; ^{19}F NMR (471 MHz, CDCl_3) δ : -63.99. HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{20}\text{F}_3\text{OS}$ $[\text{M}-\text{H}]^-$ 401.1192, found 401.1193.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-(3-methoxyphenyl)-1-(phenylthio)ethyl)phenol (**3k**): 38.5 mg, 92% yield. ^1H NMR (500 MHz, CDCl_3) δ : 7.24~7.20 (m, 1H), 7.18 (t, $J=8.1$ Hz, 1H), 7.12~7.06 (m, 4H), 7.05 (s, 2H), 7.02~6.95 (m, 2H), 6.82 (dd, $J=8.0$, 2.2 Hz, 1H), 4.73 (s, 1H), 3.73 (s, 3H), 2.19 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ : 159.0, 152.2, 140.2, 137.5, 130.6, 129.7, 129.5, 128.7, 128.2, 126.8 (q, $J=283.2$ Hz), 122.9, 122.3, 116.7, 113.4, 67.2 (q, $J=25.8$ Hz), 55.5, 16.2; ^{19}F NMR (471 MHz, CDCl_3) δ : -63.96. HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{20}\text{F}_3\text{O}_2\text{S}$ $[\text{M}-\text{H}]^-$ 417.1142, found 417.1140.

4-(1-(3,5-Dimethylphenyl)-2,2,2-trifluoro-1-(phenylthio)ethyl)-2,6-dimethylphenol (**3l**): 37.9 mg, 91% yield. ^1H NMR (500 MHz, CDCl_3) δ : 7.24~7.18 (m, 1H), 7.09~7.05 (m, 4H), 7.04 (s, 2H), 7.02 (s, 2H), 6.91 (s, 1H), 4.69 (s, 1H), 2.25 (s, 6H), 2.20 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ : 152.0, 138.5, 137.5, 137.2, 130.8, 130.7, 130.0, 129.6, 129.4, 128.1, 128.0, 126.9 (q, $J=283.4$ Hz), 67.3 (q, $J=26.0$ Hz), 21.6, 16.2; ^{19}F NMR (471 MHz, CDCl_3) δ : -63.88. HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{22}\text{F}_3\text{OS}$ $[\text{M}-\text{H}]^-$ 415.1349, found 415.1347.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-(naphthalen-2-yl)-1-(phenylthio)ethyl)phenol (**3m**): 41.6 mg, 95% yield. ^1H NMR (500 MHz, CDCl_3) δ : 7.87~7.81 (m, 2H), 7.79~7.73 (m, 2H), 7.54~7.47 (m, 3H), 7.15 (t, $J=8.0$ Hz, 1H), 7.10~7.04 (m, 4H), 6.98 (t, $J=7.7$ Hz, 2H), 4.75 (s, 1H), 2.20 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ : 152.4, 137.5, 135.7, 132.6, 132.5, 130.7, 130.5, 129.6, 129.5, 128.8, 128.7, 128.2, 127.5, 126.9, 126.8 (q, $J=283.5$ Hz), 126.4, 122.5, 67.4 (q, $J=25.8$ Hz), 16.2; ^{19}F NMR (471 MHz, CDCl_3) δ : -63.94. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{20}\text{F}_3\text{OS}$ $[\text{M}-\text{H}]^-$ 437.1192, found 437.1184.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-(furan-2-yl)-1-(phenylthio)ethyl)phenol (**3n**): 35.6 mg, 94% yield. ^1H NMR (500 MHz, CDCl_3) δ : 7.31 (dd, $J=5.2$, 1.1 Hz, 1H), 7.30~7.26 (m, 1H), 7.23 (d, $J=7.2$ Hz, 2H), 7.19 (s, 2H), 7.14 (dd, $J=10.6$, 4.7 Hz, 2H), 6.98 (dd, $J=2.5$, 1.1 Hz, 1H), 6.88 (dd, $J=5.2$, 3.7 Hz, 1H), 4.75 (s, 1H), 2.22 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ : 152.7, 142.6, 137.3, 130.7, 130.2, 130.2, 129.8, 129.5, 129.2, 128.4, 126.7, 126.3, 126.2 (q, $J=283.5$ Hz), 64.8 (q, $J=27.2$ Hz), 16.3; ^{19}F NMR (471 MHz, CDCl_3) δ : -65.55. HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{16}\text{F}_3\text{O}_2\text{S}$ $[\text{M}-\text{H}]^-$ 377.0829, found 377.0821.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-(phenylthio)-1-(thiophen-2-yl)ethyl)phenol (**3o**): 36.7 mg, 93% yield. ^1H NMR (400 MHz, CDCl_3) δ : 7.31 (dd, $J=5.2$, 1.0 Hz, 1H), 7.27 (d, $J=6.4$ Hz, 1H), 7.23 (d, $J=7.2$ Hz, 2H), 7.19 (s, 2H), 7.14 (t, $J=7.6$ Hz, 2H), 7.00~6.95 (m, 1H), 6.88 (dd, $J=5.1$, 3.7 Hz, 1H), 4.75 (s, 1H), 2.22 (s, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ : 152.6, 142.6, 137.3, 130.7, 130.2, 129.8, 129.5, 129.2, 128.4, 126.7, 126.3, 126.2 (q, $J=567.3$,

283.7 Hz), 122.4, 64.8 (q, $J=54.4$, 27.2 Hz), 16.3; ^{19}F NMR (376 MHz, CDCl_3) δ : -65.57. HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{16}\text{F}_3\text{OS}_2$ $[\text{M}-\text{H}]^-$ 393.0600, found 393.0602.

2,6-Diisopropyl-4-(2,2,2-trifluoro-1-(4-methoxyphenyl)-1-(phenylthio)ethyl)phenol (**3p**): 42.7 mg, 90% yield. ^1H NMR (500 MHz, CDCl_3) δ : 7.39 (d, $J=8.7$ Hz, 2H), 7.22~7.16 (m, 1H), 7.09~7.02 (m, 4H), 7.01 (s, 2H), 6.84~6.79 (m, 2H), 4.82 (s, 1H), 3.83 (s, 3H), 3.13~3.03 (m, 2H), 1.19 (d, $J=6.9$ Hz, 6H), 1.11 (d, $J=6.9$ Hz, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ : 159.3, 149.5, 137.7, 132.8, 131.7, 131.0, 130.9, 130.1, 129.3, 128.1, 126.9 (q, $J=283.4$ Hz), 113.0, 67.3 (q, $J=25.6$ Hz), 55.5, 27.4, 22.8; ^{19}F NMR (471 MHz, CDCl_3) δ : -64.58. HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{28}\text{F}_3\text{O}_2\text{S}$ $[\text{M}-\text{H}]^-$ 473.1768, found 473.1760.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-((4-fluorophenyl)thio)-1-phenylethyl)phenol (**4a**): 38.6 mg, 95% yield. ^1H NMR (500 MHz, CDCl_3) δ : 7.39~7.36 (m, 2H), 7.28~7.26 (m, 3H), 7.05~7.00 (m, 4H), 6.75 (t, $J=8.7$ Hz, 2H), 4.76 (s, 1H), 2.20 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ : 164.8, 162.8, 152.2, 139.6, 138.6, 130.6, 130.3, 129.7, 128.6 (q, $J=82.9$ Hz), 128.1, 127.9, 125.8, 122.4, 115.4, 115.2, 67.0 (q, $J=26.1$ Hz), 16.2; ^{19}F NMR (471 MHz, CDCl_3) δ : -64.21, -111.21. HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{17}\text{F}_4\text{OS}$ $[\text{M}-\text{H}]^-$ 405.0942, found 405.0941.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-phenyl-1-((4-(trifluoromethyl)phenyl)thio)ethyl)phenol (**4b**): 44.3 mg, 97% yield. ^1H NMR (500 MHz, CDCl_3) δ : 7.41 (d, $J=7.8$ Hz, 2H), 7.34~7.27 (m, 5H), 7.15 (d, $J=8.1$ Hz, 2H), 7.02 (s, 2H), 4.73 (s, 1H), 2.20 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ : 152.4, 138.4, 137.4, 135.4, 131.29 (q, $J=32.6$ Hz), 130.5, 130.3, 128.3, 128.1, 126.7 (q, $J=283.4$ Hz), 124.1 (q, $J=272.4$ Hz), 122.6, 67.6 (q, $J=26.1$ Hz), 16.2; ^{19}F NMR (471 MHz, CDCl_3) δ : -62.9, -64.18. HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{17}\text{F}_6\text{OS}$ $[\text{M}-\text{H}]^-$ 455.0910, found 455.0907.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-phenyl-1-(*p*-tolylthio)ethyl)phenol (**4c**): 37.4 mg, 93% yield. ^1H NMR (500 MHz, CDCl_3) δ : 7.42~7.38 (m, 2H), 7.29~7.26 (m, 3H), 7.05 (s, 2H), 6.95 (d, $J=8.1$ Hz, 2H), 6.88 (d, $J=8.0$ Hz, 2H), 4.71 (s, 1H), 2.26 (s, 3H), 2.20 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ : 152.2, 139.7, 138.9, 137.5, 130.7, 130.3, 130.0, 129.0, 127.9, 127.8, 127.0, 126.8 (q, $J=283.4$ Hz), 122.3, 67.1 (q, $J=25.7$ Hz), 21.4, 16.2; ^{19}F NMR (471 MHz, CDCl_3) δ : -64.06. HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{20}\text{F}_3\text{OS}$ $[\text{M}-\text{H}]^-$ 401.1192, found 401.1192.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-((4-methoxyphenyl)thio)-1-phenylethyl)phenol (**4d**): 39.3 mg, 94% yield. ^1H NMR (500 MHz, CDCl_3) δ : 7.41~7.35 (m, 2H), 7.27~7.24 (m, 3H), 7.04 (s, 2H), 6.98 (d, $J=8.7$ Hz, 2H), 6.62~6.55 (m, 2H), 4.73 (s, 1H), 3.73 (s, 3H), 2.20 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ : 160.8, 152.1, 139.2, 138.9, 130.7, 130.3, 130.0, 127.9, 127.8, 126.9 (q, $J=283.5$ Hz), 122.3, 121.3, 113.7, 67.0 (q, $J=25.6$ Hz), 55.4, 16.2. ^{19}F NMR (471 MHz, CDCl_3) δ : -64.11. HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{20}\text{F}_3\text{O}_2\text{S}$ $[\text{M}-\text{H}]^-$ 418.1142, found 418.1141.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-phenyl-1-(*o*-tolylthio)-

ethyl)phenol (**4e**): 34.2 mg, 85% yield. ^1H NMR (500 MHz, CDCl_3) δ : 7.46 (d, $J=7.4$ Hz, 2H), 7.32~7.26 (m, 3H), 7.16~7.10 (m, 2H), 7.09 (s, 2H), 6.79~6.72 (m, 1H), 6.54 (d, $J=7.7$ Hz, 1H), 4.71 (s, 1H), 2.47 (s, 3H), 2.20 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ : 152.2, 144.6, 139.1, 137.8, 130.9, 130.6, 130.3, 130.1, 130.0, 129.4 (q, $J=246.8$ Hz), 129.6, 128.0, 127.8, 125.4, 122.3, 67.1 (q, $J=25.9$ Hz), 21.2, 16.2; ^{19}F NMR (471 MHz, CDCl_3) δ : -64.40. HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{20}\text{F}_3\text{OS}$ $[\text{M}-\text{H}]^-$ 401.1192, found 401.1193.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-phenyl-1-(*m*-tolylthio)ethyl)phenol (**4f**): 37.8 mg, 94% yield. ^1H NMR (500 MHz, CDCl_3) δ : 7.44~7.38 (m, 2H), 7.30~7.26 (m, 3H), 7.05 (s, 2H), 7.02 (s, 1H), 6.97 (t, $J=7.5$ Hz, 1H), 6.94 (s, 1H), 6.78 (s, 1H), 4.70 (s, 1H), 2.20 (s, 6H), 2.13 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ : 152.2, 138.9, 138.2, 137.8, 134.5, 130.7, 130.4, 130.2, 130.2, 130.0, 127.9, 127.8, 126.8 (q, $J=283.4$ Hz), 122.30, 67.2 (q, $J=25.9$ Hz), 21.2, 16.2; ^{19}F NMR (471 MHz, CDCl_3) δ : -64.15. HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{20}\text{F}_3\text{OS}$ $[\text{M}-\text{H}]^-$ 401.1192, found 401.1190.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-(naphthalen-2-ylthio)-1-phenylethyl)phenol (**4g**): 40.8 mg, 93% yield. ^1H NMR (500 MHz, CDCl_3) δ : 7.74 (d, $J=8.0$ Hz, 1H), 7.58 (d, $J=7.9$ Hz, 1H), 7.53 (d, $J=8.9$ Hz, 2H), 7.48~7.42 (m, 4H), 7.28 (d, $J=7.3$ Hz, 3H), 7.10 (dd, $J=8.5$, 1.5 Hz, 1H), 7.08 (s, 2H), 4.70 (s, 1H), 2.18 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ : 152.3, 138.9, 138.1, 133.5, 133.4, 133.1, 130.7, 130.4, 129.9, 128.2, 128.0, 127.9, 127.9, 127.6, 127.4, 127.2, 126.2, 124.6 (q, $J=283.2$ Hz), 122.4, 67.4 (q, $J=25.9$ Hz), 16.2; ^{19}F NMR (471 MHz, CDCl_3) δ : -64.04. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{20}\text{F}_3\text{OS}$ $[\text{M}-\text{H}]^-$ 437.1192, found 437.1193.

4-(1-(Ethylthio)-2,2,2-trifluoro-1-phenylethyl)-2,6-dimethylphenol (**4h**): 32.7 mg, 96% yield. ^1H NMR (500 MHz, CDCl_3) δ : 7.44 (d, $J=7.5$ Hz, 2H), 7.33~7.24 (m, 3H), 7.00 (s, 2H), 4.67 (s, 1H), 2.31 (ddd, $J=15.1$, 9.3, 5.7 Hz, 1H), 2.23~2.19 (m, 1H), 2.17 (d, $J=9.3$ Hz, 6H), 1.05 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ : 152.1, 139.1, 130.1, 129.8, 128.1, 128.0, 127.4 (q, $J=283.3$ Hz), 122.5, 63.8 (q, $J=26.4$ Hz), 25.5, 16.3, 13.5; ^{19}F NMR (471 MHz, CDCl_3) δ : -65.34. HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{18}\text{F}_3\text{OS}$ $[\text{M}-\text{H}]^-$ 339.1036, found 339.1034.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-(isopropylthio)-1-phenylethyl)phenol (**4i**): 32.9 mg, 93% yield. ^1H NMR (500 MHz, CDCl_3) δ : 7.44 (d, $J=7.3$ Hz, 2H), 7.31~7.24 (m, 3H), 7.01 (s, 2H), 4.66 (s, 1H), 2.18 (s, 6H), 1.10 (d, $J=7.0$ Hz, 3H), 1.00 (d, $J=7.0$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ : 152.1, 139.3, 130.4, 130.3, 130.0, 128.0, 128.0, 127.2 (q, $J=282.7$ Hz), 122.4, 64.3 (q, $J=26.4$ Hz), 36.4, 25.1, 25.0, 16.2; ^{19}F NMR (471 MHz, CDCl_3) δ : -65.54. HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{20}\text{F}_3\text{OS}$ $[\text{M}-\text{H}]^-$ 353.1192, found 353.1892.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-(hexylthio)-1-phenylethyl)phenol (**4j**): 36.0 mg, 91% yield. ^1H NMR (500 MHz, CDCl_3) δ : 7.46 (d, $J=7.4$ Hz, 2H), 7.34~7.29 (m, 3H), 7.03 (s, 2H), 4.67 (s, 1H), 2.35~2.30 (m, 1H), 2.24~

2.18 (m, 7H), 1.44~1.36 (m, 2H), 1.27~1.19 (m, 4H), 1.14 (ddd, $J=11.7, 5.4, 3.1$ Hz, 2H), 0.84 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ : 152.0, 139.1, 130.2, 129.9, 128.1, 128.0, 127.4 (q, $J=566.3, 283.1$ Hz), 122.5, 63.7 (q, $J=26.4$ Hz), 31.5, 31.3, 28.6, 28.6, 22.6, 16.3, 14.2; ^{19}F NMR (471 MHz, CDCl_3) δ : -65.24. HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{26}\text{F}_3\text{OS}$ $[\text{M}-\text{H}]^-$ 395.1662, found 395.1661.

4-(1-(Benzylthio)-2,2,2-trifluoro-1-phenylethyl)-2,6-dimethylphenol (**4k**): 37.8 mg, 94% yield. ^1H NMR (500 MHz, CDCl_3) δ : 7.53 (d, $J=7.5$ Hz, 2H), 7.38~7.33 (m, 3H), 7.26~7.19 (m, 3H), 7.16~7.10 (m, 2H), 7.08 (s, 2H), 4.72 (s, 1H), 3.54 (d, $J=11.3$ Hz, 1H), 3.40 (d, $J=11.3$ Hz, 1H), 2.21 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ : 152.2, 138.8, 136.6, 130.2, 129.9, 129.8, 129.5, 128.7, 128.2, 128.2, 127.5, 127.4 (q, $J=283.2$ Hz), 122.6, 64.5 (q, $J=26.5$ Hz), 36.3, 16.2; ^{19}F NMR (471 MHz, CDCl_3) δ : -65.20. HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{20}\text{F}_3\text{OS}$ $[\text{M}-\text{H}]^-$ 401.1192, found 401.1193.

Supporting Information Copies of ^1H NMR and ^{13}C NMR spectra. The Supporting Information is available free of charge via the Internet at <http://sioc-journal.cn/>.

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