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可见光促进合成三氟甲基取代的四氢呋喃和四氢吡喃

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摘要 利用相对廉价易得、操控简便的三氟甲基磺酰氯为三氟甲基自由基前体, 在可见光催化下通过非活化烯烃的自由基 1,2-烷氧基-三氟甲基化反应实现了一系列三氟甲基化的四氢呋喃和四氢吡喃化合物的高效合成.
关键词 三氟甲基磺酰氯; 四氢呋喃; 四氢吡喃; 可见光; 烷氧-三氟甲基化

Visible-Light Promoted Preparation of Trifluoromethylated Tetrahydrofuran and Tetrahydropyran

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Abstract An efficient protocol for facile access to trifluoromethylated tetrahydrofuran and tetrahydropyran has been developed under visible light irradiation conditions via radical 1,2-alkoxyl-trifluoromethylation of unactivated alkene. It features the use of readily commercially available and operatively simple trifluoromethanesulfonyl chloride as a trifluoromethyl radical source, thus making the protocol potentially appealing for practical preparation.
Keywords trifluoromethanesulfonyl chloride; tetrahydrofuran; tetrahydropyran; visible light; alkoxyl-trifluoromethylation

1 Introduction

Tetrahydrofuran and tetrahydropyran are essential motifs of many natural products and bioactive molecules.[1] Thus, their synthesis has attracted many research efforts over the last several decades.[2] On the other hand, the trifluoromethyl group has recently emerged as a greatly useful tool in pharmaceutical[3] and agrochemical[4] sciences due to its unique beneficial effects for enhancing chemical and metabolic stability, bioavailability, and interaction with biologically relevant targets.[5] Therefore, it is highly desirable to develop efficient methods for introducing trifluoromethyl groups[6] into tetrahydrofurans and tetrahydropyrans for potential drug and agrochemical discovery.[7] In this respect, intramolecular 1,2-alkoxyl-trifluoromethylation of unactivated alkene[8] represents a particularly convenient way for accessing various sorts of trifluoromethylated tetrahydrofurans and tetrahydropyrans using different sources of trifluoromethyl radicals, such as Togni's reagents,[9] Umemoto reagents,[10] and trifluoromethyl halides (Scheme

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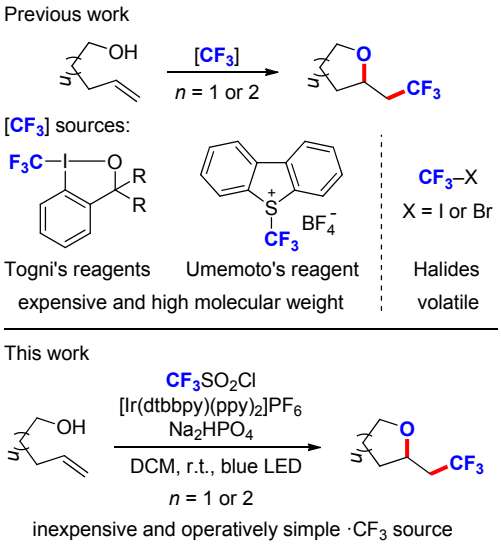
1).[11] However, both of the former two types of reagents are relatively expensive and high molecular weights, while the last one is volatile, all of which render these sources uneconomical and impractical for large scale preparations. In contrast, the readily commercially available trifluoromethanesulfonyl chloride (TfCl, CF_3SO_2Cl) is relatively inexpensive, of much lower molecular weight, and is a liquid at ambient temperature, all of which make it an ideal trifluoromethyl radical precursor.[12] As our continuing interest in fluorine chemistry,[13] we herein report an efficient and practical protocol for preparation of a variety of trifluoromethylated tetrahydrofurans and tetrahydropyrans using TfCl-participated 1,2-alkoxyl-trifluoromethylation of unactivated alkene under mild visible-light promoted conditions (Scheme 1).[14]



Scheme 1 Preparation of tetrahydrofuran and tetrahydropyran via 1,2-alkoxyl-trifluoromethylation of alkene

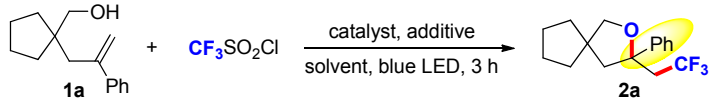
2 Results and discussion

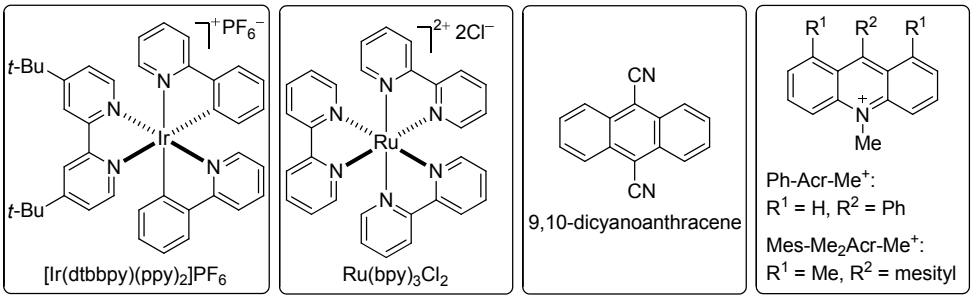
Our investigation began with **1a** as a model substrate under our previously employed conditions[15] for generation of trifluoromethyl radical: photosensitizer [Ir(dtbbpy)-(ppy)$_2$]PF_6 (1 mol%), trifluoromethyl radical source CF_3SO_2Cl (1.5 equiv.), basic additive Na_2HPO_4• $12H_2O$ (2 equiv.), and solvent EtOAc under blue LED (light-emitting diode) irradiation. To our delight, the desired trifluoromethylated tetrahydrofuran **2a** was successfully obtained, albeit in low yield (Table 1, Entry 1, 36%). Next, several common solvents (Table 1, Entries 2～11) were screened and chlorinated solvents generally performed better than others. In addition, dichloromethane (DCM) was slightly superior to 1,2-dichloroethane (Table 1, Entries 2 and 3, 70% and 68%, respectively). In order to further improve the reaction efficiency, then the effect of different inorganic bases as additives was examined (Table 1, Entries 12～15). Unfortunately, all these bases were inferior to the original Na_2HPO_4. Another common photosensitizer Ru(bpy$_3$)Cl_2• $6H_2O$[14c] was also examined but only low yield of desired product **2a** (Table 1, Entry 16) was observed. This result was not unexpected given its relatively low reduction capability (E_{red} = −0.81 V and −0.96 V vs SCE for excited states of $Ru(bpy_3)^{2+}$ and $[Ir(dtbbpy)(ppy)_2]^+$, respectively).[14e] In addition, several organic photoredox catalysts,[14j] such as 9,10-dicyanoanthracene, Ph-Acr-Me$^+$ ClO_4^-, and Mes-Me$_2$Acr-Me$^+$ ClO_4^-, were explored (Table 1, Entries 17～19). Unfortunately, none of them provided comparable efficiency with the Ir-based photocatalyst, possibly due to different reaction mechanisms. Therefore, the optimal reaction conditions were identified as follows: [Ir(dtbbpy)-(ppy)$_2$]PF_6 (1 mol%), CF_3SO_2Cl (1.5 equiv.), and Na_2HPO_4•$12H_2O$ (2 equiv.) in dichloromethane (DCM) (2 mL) under blue LED irradiation, in which the desired product was obtained in 55% isolated yield on a 0.2 mmol scale (Table 2).

With the optimized conditions in hand, the substrate scope of the current alkoxyl-trifluoromethylation reaction was subsequently explored (Table 2). Substrates bearing electron-donating or electron-withdrawing groups on the *meta*- or *para*-positions of the alkenyl phenyl rings were tolerated to afford desired trifluoromethylated tetrahydrofurans **2b**～**2f** in 45%～70% isolated yields. The sterically bulky substrates **1g** and **1h** possessing a 2-methyl substituted phenyl ring and a 1-naphtharene ring also worked well, leading to products **2g** and **2h**, respectively. A labile benzothiophene ring in substrate **1i** survived the reaction conditions to provide product **2i** in 40% yield. Noteworthy is that gem-dialkyl-substituted alkene **1j** and mono-alkyl-substituted alkenes **1k** and **1l** were also applicable in the reaction, giving rise to corresponding products in moderate to high yields. In addition, alkenols **1m** and **1n** bearing only one aryl substituent on the tether also underwent the reaction smoothly, albeit in apparently no diastereoselectivity. Most importantly, substrates **1o**～**1q** with one-carbon-longer tethers were workable under the same conditions to deliver trifluoromethylated tetrahydropyrans **2o**～**2q** in good to excellent yields and low diastereoselectivity. Furthermore, substrate **1r** featuring a phenyl-fused tether was also compatible with the reaction conditions to give tetrahydrobenzopyran **2r** in moderate yield. The successful formation of trifluoromethylated tetrahydropyran under our conditions is in agreement with literature reports, which indicates that visible-light photoredox catalyzed conditions are more robust and versatile than other conditions in terms of the scope for cyclic ether products.[9~11,16]

On the basis of literature reports, we propose a possible reaction pathway for the alkoxyl-trifluoromethylation reaction (Scheme 2). First, the photosensitizer Ir(III) complex is converted to its excited state Ir(III)* under blue LED irradiation, which subsequently reduces TfCl to provide trifluoromethyl radical and Ir(IV).[17] Next, the trifluoromethyl radical adds to alkene **1** to provide alkyl radical **I**. This radical **I** is subsequently oxidized by Ir(IV) to form carbocation **II**, thus regenerating the initial Ir(III) complex. Finally, the desired product **2** is forged upon intramolecularly

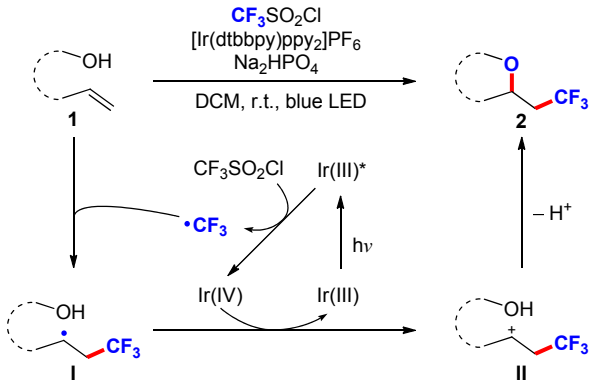
Table 1 Optimization of reaction conditions[a]





Entry	Catalyst	Additive	Solvent	Yield/%
1	$[Ir(dtbbpy)(ppy)_2]PF_6$	$Na_2HPO_4•12H_2O$	EtOAc	36
2	**$[Ir(dtbbpy)(ppy)_2]PF_6$**	**$Na_2HPO_4•12H_2O$**	**DCM**	**70**
3	$[Ir(dtbbpy)(ppy)_2]PF_6$	$Na_2HPO_4•12H_2O$	DCE	68
4	$[Ir(dtbbpy)(ppy)_2]PF_6$	$Na_2HPO_4•12H_2O$	CH_3CN	44
5	$[Ir(dtbbpy)(ppy)_2]PF_6$	$Na_2HPO_4•12H_2O$	PhF	36
6	$[Ir(dtbbpy)(ppy)_2]PF_6$	$Na_2HPO_4•12H_2O$	DMF	21
7	$[Ir(dtbbpy)(ppy)_2]PF_6$	$Na_2HPO_4•12H_2O$	DMSO	Messy
8	$[Ir(dtbbpy)(ppy)_2]PF_6$	$Na_2HPO_4•12H_2O$	THF	39
9	$[Ir(dtbbpy)(ppy)_2]PF_6$	$Na_2HPO_4•12H_2O$	1,4-Dioxane	26
10	$[Ir(dtbbpy)(ppy)_2]PF_6$	$Na_2HPO_4•12H_2O$	Cyclohexane	Messy
11	$[Ir(dtbbpy)(ppy)_2]PF_6$	$Na_2HPO_4•12H_2O$	MeOH	39
12	$[Ir(dtbbpy)(ppy)_2]PF_6$	$NaHCO_3$	DCM	55
13	$[Ir(dtbbpy)(ppy)_2]PF_6$	Na_2CO_3	DCM	56
14	$[Ir(dtbbpy)(ppy)_2]PF_6$	$KHCO_3$	DCM	49
15	$[Ir(dtbbpy)(ppy)_2]PF_6$	K_2CO_3	DCM	31
16	$Ru(bpy)_3Cl_2•6H_2O$	$Na_2HPO_4•12H_2O$	DCM	45
17	9,10-Dicyanoanthracene	$Na_2HPO_4•12H_2O$	DCM	20
18	Ph-Acr-Me^+ ClO_4^-	$Na_2HPO_4•12H_2O$	DCM	13
19	Mes-Me_2Acr-Me^+ ClO_4^-	$Na_2HPO_4•12H_2O$	DCM	28

[a] Conditions: **1a** (0.1 mmol), catalyst (1 mol%), CF_3SO_2Cl (1.5 equiv.), and additive (2 equiv.) in solvent (1 mL) under blue LED irradiation for 3 h. Yields were based on ^{19}F NMR spectroscopy using *α,α,α*-trifluorotoluene as an internal standard.



Scheme 2 Mechanistic proposal

trapping the carbocation with the alkoxyl group followed by facile deprotonation.

3 Summary

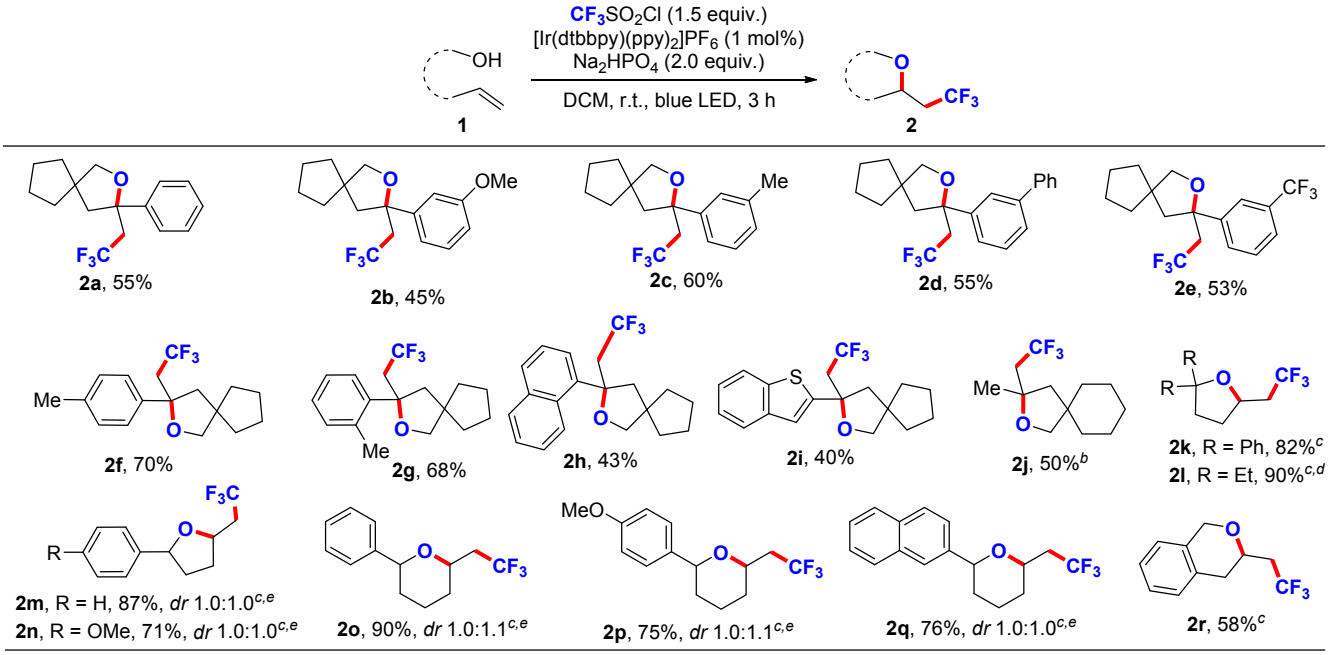
In sum, we have prepared a range of trifluoromethylated tetrahydrofurans and tetrahydropyrans using relative inexpensive and atom-economical trifluoromethanesulfonyl chloride as the trifluoromethyl radical source for radical 1,2-alkoxyl-trifluoromethyaltion of unactivated alkene under mild visible-light irradiation conditions. This practical protocol may find wide applications in discovering novel drugs and agrochemicals.

4 Experimental section

4.1 General information

All reactions were carried out under argon using Schlenk techniques. Unless otherwise noted, reagents were purchased at the commercial quality and used without further purification. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 GF254 plates. Flash column chromatography was performed using Tsingdao silica gel (60, particle size 0.040～0.063 mm). Visualization on TLC was achieved by use of UV light (254 nm), $KMnO_4$, or iodine stain. NMR spectra were recorded

Table 2 Substrate scope[a]



[a] Conditions: **1** (0.2 mmol), $[Ir(dtbbpy)(ppy)_2]PF_6$ (1 mol%), CF_3SO_2Cl (1.5 equiv.), and $Na_2HPO_4•12H_2O$ (2 equiv.) in DCM (2 mL) under blue LED irradiation for 3 h, unless otherwise noted. Yields were isolated ones, unless otherwise noted. [b] Reaction time: 1 h. [c] Reaction Time: 1.5 h. [d] Yield was based on ^{19}F NMR spectroscopy using α,α,α-trifluorotoluene as an internal standard. [e] Diastereomeric ratio was determined based on quantitative ^{13}C NMR spectra of inseparable mixtures of both diastereomers.

on a Bruker DPX 400/500 spectrometers at 400/500 MHz for ^1H NMR, 100/125 MHz for ^{13}C NMR, and 376 MHz for ^{19}F NMR in $CDCl_3$ with tetramethylsilane (TMS) as internal standard. ^{19}F NMR spectra were recorded on a Bruker DPX 400 MHz spectrometer ($CFCl_3$ as an external reference). Mass spectrometric data were obtained using a "Bruker Apex IV RTMS".

4.2 General procedure for visible light promoted alkoxyl-trifluoromethylation of alkene

To a 5-mL single-necked tube equipped with a magnetic stir bar were added compound **1** (0.2 mmol), $[Ir(dtbbpy)(ppy)_2]PF_6$ (1.8 mg, 0.002 mmol) and $Na_2HPO_4•12H_2O$ (143 mg, 0.4 mmol). Then the reaction tube was evacuated with oil pump and back-filled with argon three times. After addition of anhydrous DCM (2 mL) and CF_3SO_2Cl (32 μL, 0.3 mmol) under argon atmosphere, the reaction tube was sealed. And the mixture was stirred under the irradiation with blue LED for appropriate time (1～3 h). Upon completion, the solvent was removed directly under reduced pressure to afford the crude product, which was purified by flash column chromatography to afford the desired product.

3-Phenyl-3-(2,2,2-trifluoroethyl)-2-oxaspiro[4.4]nonane (**2a**):[9d] Colourless oil, 55% yield. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.47～7.41 (m, 2H), 7.39～7.33 (m, 2H), 7.31～7.25 (m, 1H), 3.83 (d, J=8.3 Hz, 1H), 3.69 (d, J=8.3 Hz, 1H), 2.69 (q, J=10.7 Hz, 2H), 2.43 (d, J=12.8 Hz, 1H), 2.32 (d, J=12.7 Hz, 1H), 1.84～1.73 (m, 1H), 1.71～1.43 (m, 5H), 1.43～1.19 (m, 2H).

3-(3-Methoxyphenyl)-3-(2,2,2-trifluoroethyl)-2-oxaspiro[4.4]nonane (**2b**):[9d] Colourless oil, 45% yield. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.27 (t, J=8.0 Hz, 1H), 7.05 (dd, J=2.6, 1.7 Hz, 1H), 6.98 (ddd, J=7.7, 1.8, 1.0 Hz, 1H), 6.81 (ddd, J=8.2, 2.6, 0.9 Hz, 1H), 3.87～3.80 (m, 4H), 3.70 (d, J=8.3 Hz, 1H), 2.68 (q, J=10.7 Hz, 2H), 2.42 (d, J=12.7 Hz, 1H), 2.31 (d, J=12.8 Hz, 1H), 1.85～1.72 (m, 1H), 1.72～1.44 (m, 5H), 1.43～1.33 (m, 1H), 1.32～1.21 (m, 1H).

3-(*m*-Tolyl)-3-(2,2,2-trifluoroethyl)-2-oxaspiro[4.4]-nonane (**2c**):[9d] Colourless oil, 60% yield. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.25～7.15 (m, 3H), 7.08～7.03 (m, 1H), 3.79 (d, J=8.3 Hz, 1H), 3.66 (d, J=8.3 Hz, 1H), 2.65 (q, J=10.7 Hz, 2H), 2.38 (d, J=12.8 Hz, 1H), 2.36 (s, 3H), 2.29 (d, J=12.7 Hz, 1H), 1.84～1.69 (m, 1H), 1.70～1.42 (m, 5H), 1.39～1.29 (m, 1H), 1.29～1.18 (m, 1H).

3-([1,1'-Biphenyl]-3-yl)-3-(2,2,2-trifluoroethyl)-2-oxaspiro[4.4]nonane (**2d**):[9d] Colourless oil, 55% yield. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.67～7.65 (m, 1H), 7.60 (d, J=7.4 Hz, 2H), 7.51～7.30 (m, 6H), 3.82 (d, J=8.3 Hz, 1H), 3.69 (d, J=8.4 Hz, 1H), 2.71 (q, J=10.7 Hz, 2H), 2.45 (d, J=12.7 Hz, 1H), 2.34 (d, J=12.8 Hz, 1H), 1.84～1.70 (m, 1H), 1.70～1.40 (m, 5H), 1.41～1.29 (m, 1H), 1.33～1.19 (m, 1H).

3-(2,2,2-Trifluoroethyl)-3-(3-(trifluoromethyl)phenyl)-2-oxaspiro[4.4]nonane (**2e**):[9d] Colourless oil, 53% yield. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.72 (s, 1H), 7.62 (d, J=7.8 Hz, 1H), 7.54 (d, J=7.8 Hz, 1H), 7.48 (t, J=7.7 Hz, 1H), 3.84 (d, J=8.4 Hz, 1H), 3.69 (d, J=8.4 Hz, 1H), 2.79～2.62 (m, 2H), 2.43～2.33 (m, 2H), 1.86～1.73 (m, 1H), 1.73～1.43 (m, 5H), 1.40～1.16 (m, 2H).

3-(*p*-Tolyl)-3-(2,2,2-trifluoroethyl)-2-oxaspiro[4.4]-nonane (**2f**):[9d] Colourless oil, 70% yield. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.29 (d, J=7.9 Hz, 2H), 7.13 (d, J=7.8

Hz, 2H), 3.78 (d, J=8.3 Hz, 1H), 3.64 (d, J=8.3 Hz, 1H), 2.65 (q, J=10.8 Hz, 2H), 2.38 (d, J=12.7 Hz, 1H), 2.33 (s, 3H), 2.27 (d, J=12.8 Hz, 1H), 1.84～1.68 (m, 1H), 1.70～1.39 (m, 5H), 1.40～1.26 (m, 1H), 1.29～1.17 (m, 1H).

3-(*o*-Tolyl)-3-(2,2,2-trifluoroethyl)-2-oxaspiro[4.4]-nonane (**2g**):[9d] Colourless oil, 68% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.74～7.63 (m, 1H), 7.23～7.07 (m, 3H), 3.79 (d, J=8.4 Hz, 1H), 3.60 (d, J=8.4 Hz, 1H), 2.93～2.63 (m, 2H), 2.40～2.31 (m, 5H), 1.90～1.78 (m, 1H), 1.75～1.44 (m, 5H), 1.47～1.22 (m, 2H).

3-(Naphthalen-1-yl)-3-(2,2,2-trifluoroethyl)-2-oxaspiro-[4.4]nonane (**2h**): Colourless oil, 43% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96～7.81 (m, 3H), 7.78 (d, J=8.2 Hz, 1H), 7.54～7.43 (m, 3H), 3.88 (d, J=8.4 Hz, 1H), 3.70 (d, J=8.3 Hz, 1H), 3.16～2.89 (m, 2H), 2.71～2.58 (m, 2H), 1.96～1.83 (m, 1H), 1.77～1.53 (m, 5H), 1.57～1.43 (m, 1H), 1.45～1.33 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.75, 134.87, 129.82, 129.64, 128.53, 125.82, 125.64 (q, J=278.9 Hz), 125.41, 125.06, 124.75, 123.56, 83.30～83.05 (m), 77.79, 53.30～52.90 (m), 51.59, 45.06 (q, J=26.0 Hz), 38.33, 36.76, 24.95, 24.77; ^{19}F NMR (376 MHz, $CDCl_3$) δ: －60.54; HRMS (ESI) calcd for $C_{20}H_{22}F_3O$ $[M+H]^+$ 335.1617, found 335.1613.

3-(Benzo[*b*]thiophen-3-yl)-3-(2,2,2-trifluoroethyl)-2-oxaspiro[4.4]nonane (**2i**): Colourless oil, 40% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.93～7.87 (m, 1H), 7.85～7.78 (m, 1H), 7.50 (s, 1H), 7.46～7.33 (m, 2H), 3.86 (d, J=8.4 Hz, 1H), 3.74 (d, J=8.3 Hz, 1H), 3.00～2.85 (m, 2H), 2.61 (d, J=12.8 Hz, 1H), 2.42 (d, J=12.7 Hz, 1H), 1.93～1.79 (m, 1H), 1.78～1.43 (m, 5H), 1.43～1.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.79, 139.56, 136.51, 124.13, 124.11, 123.41, 122.93, 122.90, 82.35 (q, J=2.0 Hz), 78.54, 51.38, 50.78, 44.17 (q, J=26.1 Hz), 38.28, 37.31, 24.84, 24.76; ^{19}F NMR (376 MHz, $CDCl_3$) δ: －61.01; HRMS (ESI) calcd for $C_{18}H_{20}F_3OS$ $[M+H]^+$ 341.1181, found 341.1190.

3-Methyl-3-(2,2,2-trifluoroethyl)-2-oxaspiro[4.5]decane (**2j**): Colourless oil, 50% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.79 (dd, J=11.9, 3.9 Hz, 1H), 3.68 (dd, J=11.9, 5.1 Hz, 1H), 2.87～2.72 (m, 2H), 2.06～1.96 (m, 2H), 1.85～1.81 (m, 3H), 1.58～1.32 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 125.22 (q, J=279.0 Hz), 68.76～68.65 (m), 66.02 (br s), 49.91 (br s), 49.44 (q, J=27.2 Hz), 39.69, 35.06, 34.46, 31.48, 26.20, 21.66, 21.60; ^{19}F NMR (376 MHz, $CDCl_3$) δ: －59.79; HRMS (ESI) calcd for $C_{12}H_{20}F_3O$ $[M+H]^+$ 237.1461, found 237.1459.

4,4-Diphenyl-2-(2,2,2-trifluoroethyl)tetrahydrofuran (**2k**): Colourless oil, 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.49～7.41 (m, 4H), 7.40～7.33 (m, 4H), 7.32～7.25 (m, 2H), 4.26～4.07 (m, 1H), 2.74～2.36 (m, 4H), 2.04～1.85 (m, 1H), 1.83～1.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.76, 146.29, 128.49, 128.47, 127.33, 127.26, 126.09, 126.02, 125.31 (d, J=277.5 Hz), 77.89, 54.78 (q, J=2.9 Hz), 42.68 (q, J=28.6 Hz), 38.33, 32.87; ^{19}F NMR (376 MHz, $CDCl_3$) δ: －63.88; HRMS (ESI) calcd for $C_{18}H_{18}F_3O$ $[M+H]^+$ 307.1304, found 307.1294.

4,4-Diethyl-2-(2,2,2-trifluoroethyl)tetrahydrofuran (**2l**): Colourless oil, 90% yield (based on ^{19}F NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.21～4.07 (m, 1H), 2.74～2.50 (m, 2H), 2.01～1.88 (m, 1H), 1.85～1.68 (m, 2H), 1.59～1.43 (m, 5H), 0.98～0.83 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 125.39 (q, J=277.6 Hz), 74.35, 54.96 (q, J=3.2 Hz), 42.59 (q, J=28.4 Hz), 34.50, 32.30, 31.31, 30.86, 7.92, 7.76; ^{19}F NMR (376 MHz, $CDCl_3$) δ: －63.87; HRMS (ESI) calcd for $C_{12}H_{22}F_3O$ $[M+H]^+$ 211.1304, found 211.1326.

2-Phenyl-5-(2,2,2-trifluoroethyl)tetrahydrofuran (**2m**): Colourless oil, 87% yield, *dr* 1.0∶1.0 (based on quantitative ^{13}C NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40～7.26 (m, 5H+5H), 4.80～4.64 (m, 1H+1H), 4.22～4.07 (m, 1H+1H), 2.69～2.43 (m, 2H+2H), 2.11～1.95 (m, 2H+2H), 1.95～1.81 (m, 2H+1H), 1.79～1.67 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 144.24, 144.17, 128.79, 128.76, 128.66～122.01 (m, 1C+1C), 128.04, 127.98, 125.88, 125.82, 74.18, 73.59, 54.37 (q, J=3.3 Hz), 53.97 (q, J=3.2 Hz), 42.93～42.19 (m, 1C+1C), 35.46, 35.15, 34.71, 34.26; ^{19}F NMR (376 MHz, $CDCl_3$) δ: －63.83; HRMS (ESI) calcd for $C_{12}H_{14}F_3O$ $[M+H]^+$ 231.0991, found 231.0993.

2-(4-Methoxyphenyl)-5-(2,2,2-trifluoroethyl)tetrahydro-furan (**2n**): Colourless oil, 71% yield, *dr* 1.0∶1.0 (based on quantitative ^{13}C NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30～7.21 (m, 2H+2H), 6.93～6.84 (m, 2H+2H), 4.70～4.59 (m, 1H+1H), 4.23～4.06 (m, 1H+1H), 3.80 (s, 3H+3H), 2.69～2.41 (m, 2H+2H), 2.14～1.77 (m, 3H+3H), 1.76～1.62 (m, 1H+1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 159.37, 159.33, 136.37, 136.29, 128.67～122.01 (m, 1C+1C), 127.17, 127.10, 114.11, 114.09, 73.77, 73.23, 54.37 (q, J=3.3 Hz), 53.99 (q, J=3.2 Hz), 42.93～42.18 (m, 1C+1C), 35.36, 35.08, 34.79, 34.38; ^{19}F NMR (376 MHz, $CDCl_3$) δ: －63.83; HRMS (ESI) calcd for $C_{13}H_{16}F_3O_2$ $[M+H]^+$ 261.1097, found 261.1088.

2-Phenyl-6-(2,2,2-trifluoroethyl)tetrahydro-2*H*-pyran (**2o**): Colourless oil, 90% yield, *dr* 1.0∶1.1 (based on quantitative ^{13}C NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47～7.27 (m, 5H+5H), 4.76～4.65 (m, 1H+1H), 4.19～4.05 (m, 1H+1H), 2.74～2.44 (m, 2H+2H), 1.98～1.53 (m, 5H+6H), 1.54～1.38 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 144.58 (1.1C), 144.56 (1C), 128.67 (2.2C+2C), 127.85 (1.1C), 127.83 (1C), 125.94 (2.2C), 125.90 (2C), 125.36 (d, J=277.5 Hz, 1.1C+1C), 74.47 (1.1C), 74.38 (1C), 54.14～54.06 (m, 1.1C+1C), 42.83～42.13 (m, 1.1C+1C), 38.20 (1C), 38.18 (1.1C), 37.99 (1C), 37.95 (1.1C), 22.52 (1C), 22.49 (1.1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ: －63.78; HRMS (ESI) calcd for $C_{13}H_{16}F_3O$ $[M+H]^+$ 245.1148, found 245.1139.

2-(4-Methoxyphenyl)-6-(2,2,2-trifluoroethyl)tetrahydro-2*H*-pyran (**2p**): Colourless oil, 75% yield, *dr* 1.0∶1.0 (based on quantitative ^{13}C NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28 (d, J=8.5 Hz, 2H+2H), 6.91 (d, J=8.7 Hz, 2H+2H), 4.68～4.57 (m, 1H+1H), 4.17～4.04 (m, 1H+1H), 3.83 (s, 3H+3H), 2.72～2.43 (m, 2H+2H), 1.94～1.51 (m, 5H+6H), 1.51～1.36 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 159.24 (1.1C), 159.23 (1C), 136.73 (1C),

136.70 (1.1C), 127.21 (2.2C), 127.17 (2C), 125.37 (d, J=277.4 Hz, 1.1C+1C), 114.02 (2.2C+2C), 74.07 (1C), 74.00 (1.1C), 55.39 (1.1C+1C), 54.16～54.07 (m, 1.1C+1C), 42.84～42.13 (m, 1.1C+1C), 38.11 (1C), 38.09 (1.1C), 38.00 (1.1C), 37.97 (1C), 22.58 (1C), 22.55 (1.1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −63.81; HRMS (ESI) calcd for $C_{14}H_{18}F_3O_2$ $[M+H]^+$ 275.1253, found 245.1244.

2-(Naphthalen-2-yl)-6-(2,2,2-trifluoroethyl)tetrahydro-2*H*-pyran (**2q**): Colourless oil, 76% yield, *dr* 1.0∶1.0 (based on quantitative ^{13}C NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.90～7.83 (m, 3H+3H), 7.80 (s, 2H), 7.57～7.50 (m, 2H+3H), 7.48 (t, J=2.0 Hz, 1H), 4.91～4.82 (m, 1H+1H), 4.18～4.05 (m, 1H+1H), 2.72～2.43 (m, 2H+2H); 2.01～1.58 (m, 5H+6H), 1.56～1.42 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 141.90, 141.87, 133.35 (1C+1C), 133.14, 133.13, 128.56, 128.54, 128.03 (1C+1C), 127.82 (1C+1C), 126.38 (1C+1C), 126.06 (1C+1C), 125.36 (q, J=277.5 Hz, 1C+1C), 124.74, 124.68, 123.99 (1C+1C), 74.59, 74.49, 54.14～54.05 (m, 1C+1C), 42.82～42.12 (m, 1C+1C), 38.06 (1C+1C), 37.99, 37.96, 22.54, 22.49; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −63.76; HRMS (ESI) calcd for $C_{17}H_{18}F_3O$ $[M+H]^+$ 295.1304, found 295.1300.

3-(2,2,2-Trifluoroethyl)isochromane (**2r**): Colourless oil, 58% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44～7.39 (m, 1H), 7.38～7.30 (m, 2H), 7.30～7.26 (m, 1H), 4.81～4.69 (m, 2H), 4.53～4.42 (m, 1H), 3.29 (dd, J=14.5, 6.0 Hz, 1H), 3.21 (dd, J=14.5, 8.6 Hz, 1H), 2.77～2.61 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.94, 135.54, 130.81, 129.50, 128.52, 127.85, 125.44 (q, J=277.6 Hz), 63.61, 54.51 (q, J=3.1 Hz), 42.05 (q, J=28.6 Hz), 41.10; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −63.51; HRMS (ESI) calcd for $C_{11}H_{12}F_3O$ $[M+H]^+$ 217.0835, found 217.0834.

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

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