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Graphical Abstract

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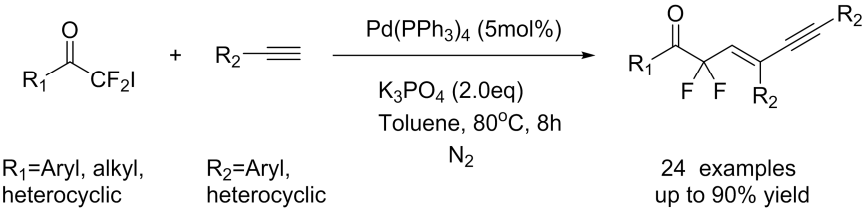

R_1=Aryl, alkyl, heterocyclic

R_2=Aryl, heterocyclic

24 examples
up to 90% yield

Abstract: A palladium-catalyzed one-pot difunctionalization of alkynes with α,α-iododifluoroacetones is introduced for the synthesis of difluorinated 1,3-enynes. The reaction proceeds through the radical addition of $RCOCF_2$ radical to alkynes and subsequent Sonogashira coupling with the same alkynes to give the 1,3-enyne products with high regio and stereoselectivity.

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ABSTRACT

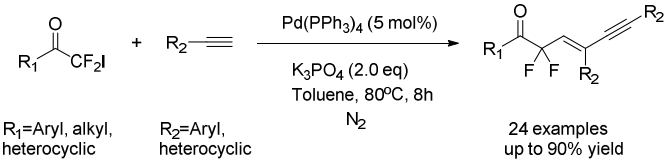
A palladium-catalyzed one-pot difunctionalization of alkynes with α,α-iododifluoroacetones is introduced for the synthesis of difluorinated 1,3-enynes. The reaction proceeds through the radical addition of $RCOCF_2$ radical to alkynes and subsequent Sonogashira coupling with the same alkynes to give the 1,3-enyne products with high regio and stereoselectivity.

1. Introduction

Since the organofluorine compounds have specific biological activity such as lipid solubility and metabolic stability in medicinal chemistry and thermal stability in materials chemistry [1], the novel strategies for introducing fluorine or fluorine-containing groups into organic compounds have attracted much attention and significant progress in this field has taken place in the past few decades [2]. Specifically, the increasing number of CF_2-containing drugs [3] have stimulated considerable interest in exploring new methods for the synthesis of CF_2-containing compounds [4]. Transition-metal-mediated difluoroalkylation becomes a hot research topic in current organofluorine chemistry [5]. It is high desired to develop novel protocols for the transition-metal-mediated difluoroalkylation of different substrates to construct structurally diverse CF_2-containing compound library in the terms of both synthetic and medicinal aspects.

As we know, alkynes are ubiquitous building blocks in chemical industries and their functionalization continues to attract attention [6]. However, the alkyne difunctionalization of fluoroalkyl species is still a challenge task. Nevado [7] and Chaładaj [8] groups reported palladium-catalyzed three-component reactions of terminal alkynes or internal alkynes, boronic acids, and perfluoroalkyl iodides for the synthesis of trisubstituted or tetrasubstituted perfluoroalkyl-containing alkenes respectively. Liang and coworkers disclosed a palladium-catalyzed three-component reaction of terminal alkynes, arylboronic acids and ethyl iododifluoroacetate to construct a variety of gem-difluoroalkylated alkenes [9]. Our group recently developed a method for palladium-catalyzed three-component reaction of aryl alkynes, arylboronic acids and α,α-iododifluoroacetones for access to benzoyldifluoromethyl-2,2-diphenylethylenes [10]. The processes mentioned above are multicomponent reactions involving radical fluoroalkylation of an alkyne followed by a cross-coupling reaction with a boronic acid.

An interesting alkyne difunctionalization "two-component" reaction of perfluoroalkyl iodides and alkynes has been described by Wu and coworkers to synthesize perfluoroalkylated enynes under palladium catalysis [11]. 1,3-Enyne is an scaffold could be found in drugs, such as Terbinafine [12] and also could serve as an important building block for organic synthesis and materials science due to C-C unsaturated bond [13]. Consistent with our interest in the development of methods for the preparation of structurally diverse CF_2-containing compounds with the building block α, α-iododifluoroacetones [14], we sought to explore the alkynes difunctionalization with α, α-iododifluoroacetones and alkynes. Herein, we reported a palladium-catalyzed one-pot reaction of α,α-iododifluoroacetones and alkynes involving the radical addition and subsequent Sonogashira coupling reaction to give difluorinated 1,3-enyne compounds with high region and stereoselectivities (Scheme 1).



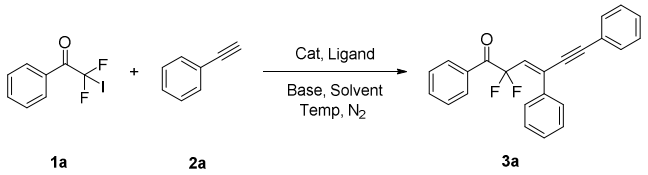
Scheme 1 Palladium-catalyzed one-pot reaction.

2. Result and disscussions

2.1 The optimization of reaction conditions

Initially, α,α-iododifluoroacetone **1a** and phenylacetylene **2a** were chosen as the model substrates for the optimization of reaction conditions. The reaction was conducted in 1,4-dioxane at 80 ºC with K_2CO_3 as the base and catalyzed by $Pd(PPh_3)_4$ under the nitrogen. To our delight, the desired product 2,2-difluoro-1,4,6-triphenylhex-3-en-5-yn-1-one **3a** was obtained in moderate yield (Table 1, entry1). The yield was not improved when other Pd catalysts, such as $Pd(PPh_3)_2Cl_2$, $PdCl_2$, $Pd_2(dba)_3$ or $Pd(OAc)_2$ was used (Table 1, entries 2-5). Therefore, $Pd(PPh_3)_4$ was chosen as suitable catalyst for the one-pot reaction. The addition of ligand to the reaction did not lead to significant change in the reaction yields (Table 1, entries 6 and 7). Screening of the solvent and base (Table 1, entries 8-13) demonstrated that K_3PO_4 and toluene are the most suitable base and solvent for the reaction, giving the target product **3a** in 92% yield at 80 ºC (Table 1, entry 12). Increasing or decreasing the temperature failed to improve the yield of **3a** (Table 1, entries 14 -16).

Table 1 Screening of optimal conditions.[a]



Entry	Catalyst	Temp	Base	Solvent	Yield (%)[b]
1	$Pd(PPh_3)_4$	80 ºC	K_2CO_3	1,4-dioxane	60
2	$Pd(PPh_3)_2Cl_2$	80 ºC	K_2CO_3	1,4-dioxane	32
3	$PdCl_2$	80 ºC	K_2CO_3	1,4-dioxane	50
4	$Pd_2(dba)_3$	80 ºC	K_2CO_3	1,4-dioxane	30
5	$Pd(OAc)_2$	80 ºC	K_2CO_3	1,4-dioxane	24
6[c]	$Pd(PPh_3)_4$	80 ºC	K_2CO_3	1,4-dioxane	53
7[d]	$Pd(PPh_3)_4$	80 ºC	K_2CO_3	1,4-dioxane	59
8	$Pd(PPh_3)_4$	80 ºC	Et_3N	1,4-dioxane	40
9	$Pd(PPh_3)_4$	80 ºC	Cs_2CO_3	1,4-dioxane	32
10	$Pd(PPh_3)_4$	80 ºC	K_3PO_4	1,4-dioxane	65
11	$Pd(PPh_3)_4$	80 ºC	K_3PO_4	CH_3CN	30
12	$Pd(PPh_3)_4$	80 ºC	K_3PO_4	Toluene.	92
13	$Pd(PPh_3)_4$	80 ºC	K_3PO_4	DMF	40
14	$Pd(PPh_3)_4$	40 ºC	K_3PO_4	Toluene.	trace
15	$Pd(PPh_3)_4$	60 ºC	K_3PO_4	Toluene.	30
16	$Pd(PPh_3)_4$	90 ºC	K_3PO_4	Toluene.	89

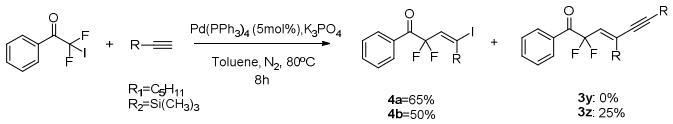
[a] Conditions: α, α-iododifluoroacetone **1a** (1.0 mmol), phenylacetylene **2a** (2.0 mmol), base (2.0 mmol), toluene (2.0 ml), catalyst (5% mmol), 80 ºC under N_2 for 8h; [b] GC yield; [c] Ligand (dppf, 10mol%) was added; [d] Ligand ($P(o\text{-anisyl})_3$, 10mol%) was added.

2.2 Substrates scope

With the optimized reaction conditions in hand, both α,α-iododifluoroacetones and alkynes were explored for this one-pot reaction (Table 2). The synthesis of various α,α-iododifluoroacetones was accomplished according to Colby's reported procedure [14[a]]. Overall, the α,α-iododifluoroacetones bearing electron-donating or electron-withdrawing groups on the benzene ring are compatible with the reaction conditions, thus providing the *E*-isomers of difluorinated 1,3-enynes **3a**−**3g** as major products in high yields. Among them, the substrates with electron-withdrawing groups gave relatively lower yields of the corresponding products (**3f** and **3g**) than others. The heterocyclic 2-iodo-2,2-difluoroketones **1h** and **1i** were also suitable fluorination agents for this one-pot reaction. Furthermore, when aliphatic 2-iodo-2,2-difluoroketone **1j** was employed, the one-pot reaction was also performed well to give the desired products **3j** in high yield. While in the case of 1-([1,1'-biphenyl]-4-yl)-2,2-difluoro-2-iodoethan-1-one **1k**, the corresponding product **3k** was obtained in 55% yield. Moreover, other fluorinated agents like ICF_2CO_2Et and $C_6F_{13}I$, reacted with **2a** smoothly to give the expected enyne products **3x** and **3y** in 90% yield and 70% yield respectively, which shows the generality of this one-pot reactions.

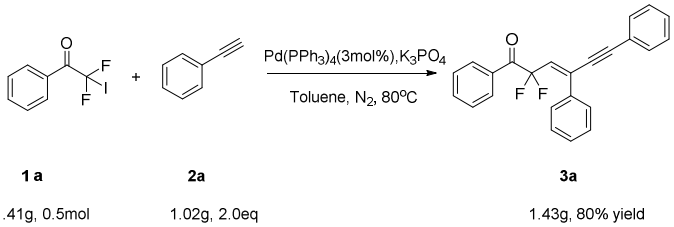
The scope of alkynes were investigated next using 2,2-difluoro-2-iodo-1-phenylethanone **1a** as partner. The reaction was revealed to be compatible with a broad range of alkynes, including various phenylacetylenes, 1-ethynylcyclohex-1-ene and 2-ethynylthiophene (Table 2). Phenylacetylene substituted with an electron-donating group or halo substituents provided the corresponding products **3l**-**3s** in good to high yields. It is worth mentioning that when 1-ethynyl-4-(trifluoromethyl) benzene was subjected to the reaction, only *E*-isomer of the product **3t** was obtained in good yield. Thienyl substituted acetylene can also afford the enyne products with good yield (**3u**, 75%). The reaction with substrate 1-cyclohexenyl substituted acetylene gave **3v** in excellent yield (90%). Moreover, the one-pot reaction of 2,2-difluoro-2-iodo-1-(thiophen-2-yl)ethan-1-one and 1-ethyl-4-ethynylbenzene was also examined, and the desired difluorinated 1,3-enyne **3w** was isolated in 68% yield.

When aliphatic alkynessuch as 1-hepyne or trimethylsilylacetyleneas was used as partner in this one-pot reaction, we found that the addition products were obtained as major products respectively. (Scheme 2).



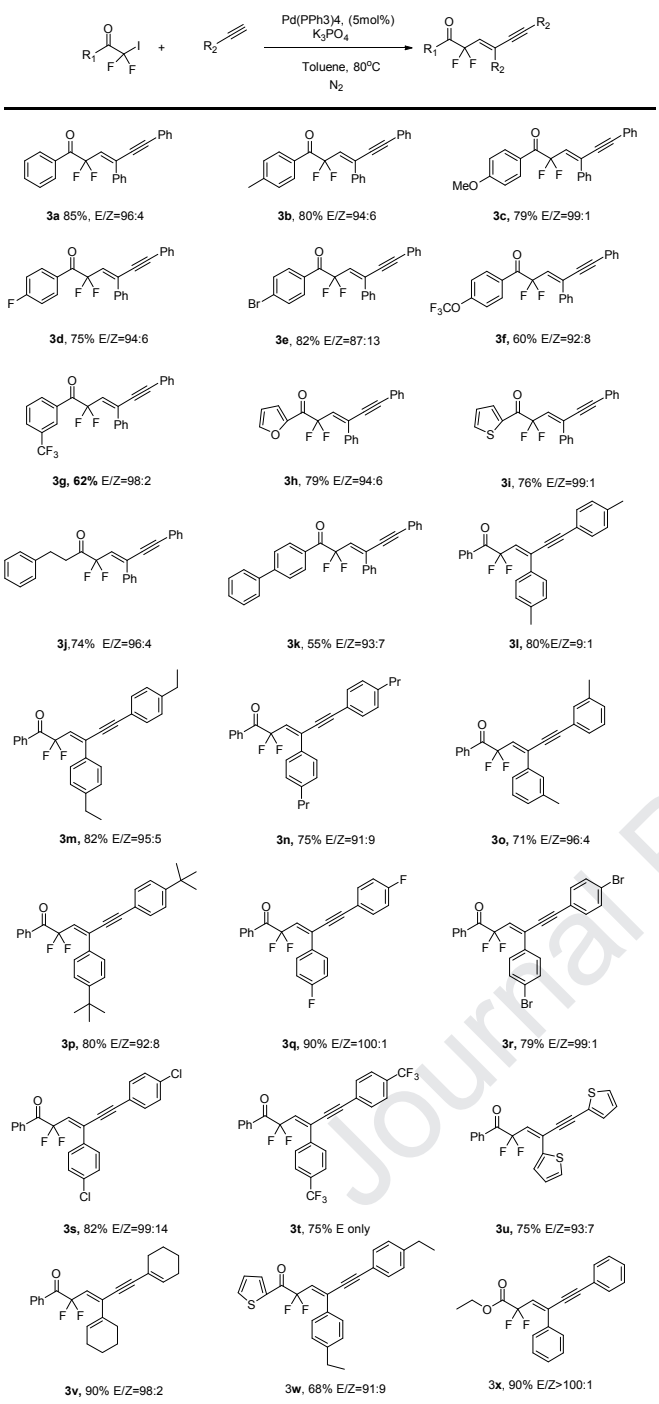
Scheme 2 Reaction of **1a** and alkyl alkynes.

A gram-scale reaction of **1a** and **2a** was also carried out under the standard reaction conditions to give **3a** in 80% yield even though the amount of Pd catalyst was lowered to 3 mol % of substrate **1a** (Scheme 3).



Scheme 3 Gram-scale reaction

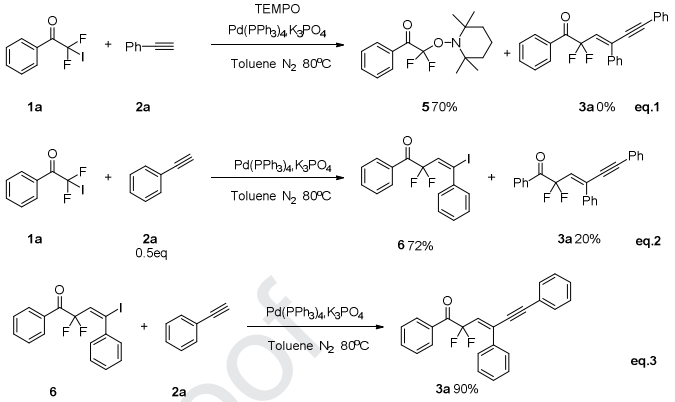
Table 2 Reaction scope of α,α-iododifluoroacetones and alkynes [a]



[a] Condition: α,α-iododifluoroacetones (1.0 mmol), terminal alkene (2.0mmol, base (2.0mmol), toluene (2.0 ml), catalyst 5mol% , 80□ under N_2 for 8h; [b] Isolated yield.

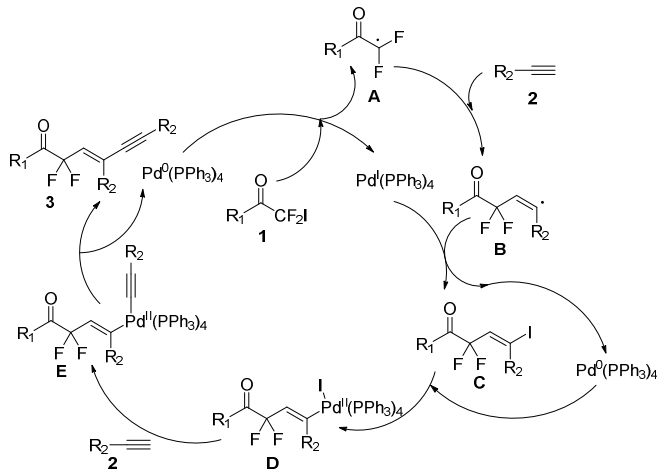
3. Control experiments and mechanism investigation

Several control reactions were carried out to understand the reaction mechanism (Scheme 4). When 1.2 equiv. of TEMPO (2,2,6,6-tetramethyl-1-oxylpiperidine) was added into the reaction system, no desired product **3a** was obtained; instead, compound **5** and Ph-$COCF_2H$ were detected in 56% and 27% yield respectively (^{19}F NMR δ -57.24 for compound **1a**, δ -71.42 for compound **5**, δ -121.44 for compound Ph-$COCF_2H$, see the Supporting Information). (Scheme 4, eq. 1). The result shows that a gem-difluoroalkyl radical addition pathway might be involved in the reaction pathway. Then, we decreased the ratio of **1a** and **2a** to 1: 0.5 and quenched the reaction in just half an hour. The radical adduct product **6** was found to be major product (72% yield) accompanied with 20% yield of the desired product **3a** (Scheme 4, eq. 2). Moreover, the coupling reaction of the adduct product **6**and **2a** proceeded well under the $Pd(PPh_3)_4$-catalytic system to give the product **3a** in 90% yield (Scheme 4, **eq. 3**). These results indicated that the radical adduct product might be formed in the reaction process and involved in the formation of the desired difluorinated 1,3-enynes.



Scheme 4 Control experiments

On the basis of the result of the control experiments above and previous literature reports [15] , a plausible reaction mechanism is proposed (Scheme 5). First, the reaction of α, α-iododifluoroacetones **1** and $Pd^0(PPh_3)_4$ gives benzoyldifluoroalkyl ($RCOCF_2$) radical **A** and $Pd^I(PPh_3)_4$ through the single electron transfer. The $RCOCF_2$ radical **A** then adds to the alkyne **2** to generate alkyl radical **B** which reacts with $Pd^I(PPh_3)_4$ to give vinyl iodide **C**. Subsequently, the intermediate **D** is formed from vinyl iodide **C** and $Pd^0(PPh_3)_4$ through the typical oxidative addition and then reacts with alkyne **2** to give the intermediate **E**. Finally, the intermediate **E** goes through reductive elimination to afford the final difluorinated 1,3-enyne product **3** and $Pd^0(PPh_3)_4$.



Scheme 5 Plausible mechanism of the reaction

4.Conclusion

In conclusion, a palladium-catalyzed ligand-free one-pot method for the construction of difluorinated 1,3-enynes from α,α-iododifluoroacetones and alkynes were reported. This method demonstrated broad substrates scope and high region and stereoselectivities. Mechanistic investigation indicated that a

$RCOCF_2$ radical and radical adduct product are involved in the one-pot reaction pathway.

5. Experimental section

5.1 General Information

All reagents were commercially available and used without further purification unless indicated otherwise. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin layer chromatorgraphy (TLC) carried out on GF254 plates (0.25 mm layer thickness) using UV light as visualizing agent. Flash chromatography was performed with 200-300 mesh silica gels.

All NMR spectra were recorded on a Bruker Avance 500 (resonance frequencies 500 MHz for ^{1}H and 125 MHz for ^{13}C) equipped with a 5 mm inverse broadband probe head with z-gradients at 295.8 K with standard Bruker pulse programs. The samples were dissolved in 0.6 mL CDCl3 (99.8% D.TMS). Chemical shifts were given in values of δH and δC referenced to residual solvent signals (δH 7.26 for ^{1}H, δC 77.0 for ^{13}C in $CDCl_3$). Data are presented in the following space: chemical shift, multiplicity, coupling constant in hertz (Hz), and signal area integration in natural numbers. ^{19}F NMR was recorded on an Agilent MR 400 spectrometer ($CFCl_3$ as an external standard and low field is positive). ^{1}H, ^{13}C and ^{19}F multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), triplet of doublets (td), multiplet (m), and broad resonance (br). High-resolution mass spectra (HRMS) (Compounds **3a**, **3c**, **3r**, **3p**) were recorded under electron impact conditions using a MicroMass GCT CA 055 instrument and recorded on a MicroMass LCTTM spectrometer. High-resolution mass spectra (HRMS) (Other Compound **3b**-**3w**) was recorded on a Bruker micro-TOF-QII time of flight massspectrometer with electrospray ionization.

4.2 General procedure for the synthesis of **3a**-**3w**

An oven-dried tube was charged with K_3PO_4 (2.0 mmol, 2.0 equiv), and $Pd(PPh_3)_4$ (0.05 mmol, 5 mol %). The tube was evacuated and backfilled with nitrogen (repeated three times).Then, α,α-iododifluoroacetones **1** (1.0 mmol, 1.0 equiv) dissolved in toluene (3.0 mL), and terminal alkyne **2** (2.0 mmol, 2.0 equiv) were added into the tube. The reaction mixture was stirring at 80 °C for 4-12h. After completion of the reaction (as indicated by TLC), the reaction is quenched with the appropriate amount of water, and the reaction mixture was extracted with ethyl acetate (3*10 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, concentrated in vacuum and the crude residue was purified by silica-gel column chromatography (petroleum ether/EtOAc =200:1) to afford desired the product **3a**-**3w**.

5.3 (*E*)-2,2-difluoro-1,4,6-triphenylhex-3-en-5-yn-1-one (**3a**)

Pale yellow sticky liquid ; yield=85% ; ^{1}H NMR (500MHz,$CDCl_3$) :δ 7.78 (d, *J* = 7.8 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.43 (dd, *J* = 7.6, 1.7 Hz, 2H), 7.37 (t, *J* = 7.9 Hz, 2H), 7.32 (m, 4H), 7.25 (m,4H), 6.57 (t, *J*=12.8Hz, 1H); ^{13}C NMR (125MHz, $CDCl_3$): δ187.19 (t,^{2}'$J_{C\text{-}F}$=29.38Hz), 135.58, 134.07, 133.96 (t,$^3J_{C\text{-}F}$=9.375Hz), 131.84, 129.75, 129.73, 129.71, 129.12, 128.79, 128.43, 128.09, 127.59(t, $^2J_{C\text{-}F}$=26.875Hz), 126.69, 122.19, 114.73 (t, $^1J_{C\text{-}F}$=246.25Hz), 93.66, 89.32; ^{19}F NMR (376Hz,$CDCl_3$): δ -88.25 (d, *J*=11.28Hz, 2F); HRMS (EI-TOF) calculated[M]+for $C_{24}H_{16}F_2O$: 358.1169,found: 358.1165.

5.4 (*E*)-2,2-difluoro-4,6-diphenyl-1-(p-tolyl)hex-3-en-5-yn-1-one (**3b**)

Pale yellow sticky liquid ; yield=80% ; ^{1}H NMR (500MHz,$CDCl_3$) :δ 7.81 (d, *J* = 5 Hz, 2H), 7.72 (dd, *J* = 13.3,7.4 Hz, 1H), 7.43 (d, *J* = 5Hz, 3H), 7.30-7.23 (m, 6H), 6.85 (d, J=10Hz, 2H), 6.56 (t, *J*=13.0Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$): δ186.81 (t, ^{2}'$J_{C\text{-}F}$=28.75Hz), 145.24, 135.64, 133.80 (t, $^3J_{C\text{-}F}$=9.375Hz), 131.83, 129.94, 129.18, 129.08, 129.05, 128.78, 128.42, 128.05, 127.71 (t, $^2J_{C\text{-}F}$=26.875Hz),122.24, 122.19, 114.82 (t, $^1J_{C\text{-}F}$=246.25Hz), 93.53, 89.43, 21.81; ^{19}F NMR (376Hz,$CDCl_3$): δ -89.30 (d, *J*=12.06Hz, 2F); HRMS (ESI-TOF) calculated[M+H]+for $C_{25}H_{18}F_2O$: 373.1404,found: 373.1399

5.5 (*E*)-2,2-difluoro-1-(4-methoxyphenyl)-4,6-diphenylhex-3-en-5-yn-1-one (**3c**).

Pale yellow sticky liquid ; yield=79% ; ^{1}H NMR (500MHz,$CDCl_3$) :δ 7.81(d, *J* = 9Hz, 2H), 7.43 (t, *J* = 8 Hz, 2H), 7.33-7.25 (m, 8H), 6.86 (d, *J* = 9Hz, 2H), 6.56 (t, *J*=13.0Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$): δ185.70 (t, ^{2}'$J_{C\text{-}F}$=29.18Hz), 164.26, 135.66, 133.63 (t,$^3J_{C\text{-}F}$=8.875Hz), 132.32, 131.80, 129.02, 128.97, 128.73, 128.39, 127.98, 127.77 (t, $^2J_{C\text{-}F}$=26.56Hz), 124.70, 122.25, 114.88 (t, $^1J_{C\text{-}F}$=246.93Hz), 113.73, 93.41, 89.45, 55.54; ^{19}F NMR (376Hz,$CDCl_3$): δ -88.52 (d, *J*=13.16Hz,2F); HRMS (EI-TOF) calculated [M]+for $C_{25}H_{18}F_2O_2$:389.1275, found: 388.1276

5.6 (*E*)-2,2-difluoro-1-(4-fluorophenyl)-4,6-diphenylhex-3-en-5-yn-1-one (**3d**)

Pale yellow sticky liquid; yield=75%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (dd, *J* = 8.5,5.5Hz, 2H), 7.43 (d, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 7.6 Hz, 4H), 7.24 (d, *J* =5 Hz, 4H); 7.04 (t, *J* = 7.5 Hz, 2H), 6.56 (t, *J* = 12.75Hz, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ185.6 (t, ^{2}'$J_{C\text{-}F}$=29.375Hz), 166.20 (d, ^{1}''$J_{C\text{-}F}$=256.25Hz), 135.52, 134.16 (t, ^{3}'$J_{C\text{-}F}$=9.375Hz), 132.55 (d ,^{3},''$J_{C\text{-}F}$=10Hz), 131.85, 129.21, 129.18, 128.80, 128.45, 128.21, 128.12, 127.37(t, $^2J_{C\text{-}F}$=26.875), 122.12, 115.72 (d, ^{2}''$J_{C\text{-}F}$=21.25Hz) ,114.68 (t, $^1J_{C\text{-}F}$ =246.25), 93.88, 89.19; ^{19}F NMR (376 MHz, $CDCl_3$): δ -88.15 (d, *J* = 11.28Hz, 2F), δ-102.54(m, 1F); HRMS (ESI-TOF) calculated $[M+H]^+$ for $C_{24}H_{15}F_3O$: 376.1153，found: 377.1154

5.7 (*E*)-1-(4-bromophenyl)-2,2-difluoro-4,6-diphenylhex-3-en-5-yn-1-one（**3e**）

Pale yellow sticky liquid ; yield=82% ; ^{1}H NMR (500MHz,$CDCl_3$) :δ 7.66 (d, *J* = 8.5, 2H), 7.56 (d, *J* = 8.5Hz, 2H), 7.48(dd, *J* =7.6,1.5Hz, 2H), 7.36 (t, *J* = 7.5Hz, 4H), 7.295-7.284 (m, 4H), 6.56 (t, *J*=12.5Hz, 1H); ^{13}C NMR (125MHz, $CDCl_3$): δ186.26(t, ^{2}'$J_{C\text{-}F}$=30Hz), 135.44, 134.27 (t, $^3J_{C\text{-}F}$=10Hz), 131.86, 131.81, 131.07, 130.53, 129.58, 129.28, 129.21, 128.84, 128.46, 128.16, 127.88 (t, $^2J_{C\text{-}F}$=26.875Hz), 122.08, 114.58 (t, $^1J_{C\text{-}F}$=244.375Hz), 94.01, 89.14; ^{19}F NMR (376Hz,$CDCl_3$): δ -88.15 (d, *J*=12.78Hz, 2F); HRMS (ESI-TOF) calculated[M+H]+for $C_{24}H_{15}F_2BrO$: 437.0353, found: 437.0352

5.8 (*E*)-2,2-difluoro-4,6-diphenyl-1-(4-(trifluoromethoxy)phenyl)hex-3-en-5-yn-1-one (**3f**)

Pale yellow sticky liquid ; yield=60% ; ^{1}H NMR (500MHz,$CDCl_3$) :δ 7.86 (d, *J* = 5 Hz, 2H), 7.48 (d, *J* = 5Hz, 2H), 7.38-7.34 (m, 4H), 7.30-7.26 (m, 4H), 7.23(d, *J*=10Hz, 2H), 6.60 (t, *J*=12.75Hz, 1H); ^{13}C NMR (125MHz, $CDCl_3$): δ185.75 (t, ^{2}'$J_{C\text{-}F}$=30Hz), 153.20, 135.50, 134.30 (t, $^3J_{C\text{-}F}$=9.375Hz), 131.84, 131.77, 129.96, 129.23, 129.18, 128.76, 128.43, 128.12, 127.14, 126.92 (t, $^2J_{C\text{-}F}$=27.5Hz), 122.32 (q, *J*=258.3Hz), 122.01, 114.59(t, $^1J_{C\text{-}F}$=246.25Hz), 93.99, 89.08; ^{19}F NMR (376Hz,$CDCl_3$): -57.54(s, 3F), δ -88.12 (d,*J*=15.04Hz, 2F); HRMS (ESI-TOF) calculated $[M+H]^+$ for $C_{25}H_{15}F_5O_2$: 443.1070,found: 443.1070

5.9 (*E*)-2,2-difluoro-4,6-diphenyl-1-(3-(trifluoromethyl)phenyl)hex-3-en-5-yn-1-one (**3g**)

Pale yellow sticky liquid; yield=62%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, *J* = 10Hz, 1H), 7.87(s, 1H), 7.79 (d, *J* = 10 Hz,1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.13 (dd, *J* =7.8,1.6Hz, 2H); 7.34-7.30 (m, 3H), 7.25-7.17(m, 4H), 6.57 (t, *J* = 12.5Hz, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ186.16 (t, $^{2'}J_{C-F}$=30Hz), 135.39, 134.49 (t, $^{3'}J_{C-F}$=10Hz), 132.51, 132.42, 131.85, 131.30, 131.04, 130.24(q, $^{1''}J_{C-F}$=3.75Hz), 129.40, 129.21, 128.97, 128.77, 128.43, 128.20, 127.05 (t, $^{2}J_{C-F}$=27.5Hz), 123.285 (q, $^{1''}J_{C-F}$=261.25Hz), 122.03, 114.50 (t, $^{1}J_{C-F}$ =245.62Hz), 94.13, 88.89; ^{19} F NMR (376 MHz, $CDCl_3$): δ -62.95 (s, 3F), δ-87.84 (d, *J*=11.28Hz, 2F); HRMS (ESI-TOF) calculated [M+H]+ for $C_{25}H_{15}F_5O$: 427.1121, found: 427.1118

5.10 (*E*)-2,2-difluoro-1-(furan-2-yl)-4,6-diphenylhex-3-en-5-yn-1-one (**3h**)

Pale yellow sticky liquid; yield=79%; ^{1}H NMR (500 MHz, $CDCl_3$): δ7.64 (d, *J*=8.45Hz, 2H), 7.55 (d, *J*=8.6Hz, 2H), 7.47 (d, *J* =6.25Hz, 2H), 7.35 (d, *J*=7.25Hz, 3H), 7.28 (d, *J*=5.35Hz, 4H), 6.59 (t, *J* = 12.5Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 186.24 (t, $^{2'}J_{C-F}$=29.785Hz), 135.42, 134.25 (t, $^{3}J_{C-F}$=9.68Hz), 131.84, 131.79, 131.05, 129.54, 129.24, 129.17, 128.81, 128.43, 128.13, 127.24 (t, $^{2}J_{C-F}$=27.25Hz), 126.67, 122.07 ,114.56 （t, $^{1}J_{C-F}$=246.12Hz）, 93.96, 89.10; ^{19}F NMR (376 MHz, $CDCl_3$): δ-91.97 (d, *J* = 13.16Hz, 2F)； HRMS (ESI-TOF) calculated [M+H]+ for $C_{22}H_{15}F_2O_2$:349.1040， found：349.1040

5.11 (*E*)-2,2-difluoro-4,6-diphenyl-1-(thiophen-2-yl)hex-3-en-5-yn-1-one(**3i**)

Pale yellow sticky liquid; yield=76%; ^{1}H NMR (500 MHz, $CDCl_3$): δ7.77 (s, 1H), 7.71 (d, *J*=5Hz, 1H), 7.44 (d, *J* =5Hz, 2H), 7.36-7.28 (m, 8H), 7.11 (t, *J*=5Hz, 1H), 6.52 (t, *J* = 15Hz,1H)； ^{13}C NMR (125 MHz,$CDCl_3$): 180.84 (t, $^{2}J_{C-F}$=31.25Hz), 138.14, 136.18, 135.60, 135.43, 134.35 (t, $^{3}J_{C-F}$=8.75Hz), 131.85, 129.14, 129.06, 128.71, 128.51, 128.44, 128.09, 126.99 (t, $^{2}J_{C-F}$=25.625Hz), 122.16, 114.63 （t, $^{1}J_{C-F}$=248.125）, 93.86, 89.37; ^{19}F NMR (376 MHz, CDCl3): δ-89.96 (d, *J* = 15.04Hz, 2F)； HRMS (ESI-TOF) calculated [M+H]+ for $C_{22}H_{14}F_2OS$:365.0812， found：365.0807.

5.12 (*E*)-4,4-difluoro-1,6,8-triphenyloct-5-en-7-yn-3-one(**3j**)

Pale yellow sticky liquid; yield=74%; ^{1}H NMR (500 MHz, CDCl3): δ7.43 (d, *J* = 10Hz, 2H), 7.41-7.38 (m, 2H), 7.36 (d, *J* =5Hz, 3H), 7.32 (t, *J*=5Hz, 3H), 7.24 (t, *J*=7.4Hz, 2H), 7.18 (t ,*J*=7.5Hz, 1H), 7.08 (d, *J* = 5Hz, 2H), 6.33 (t, *J* = 15Hz,1H); ^{13}C NMR (125 MHz,CDCl3): 198.26 (t, $^{2}J_{C-F}$=30.62Hz), 140.13, 135.97, 134.29 (t, $^{3}J_{C-F}$=9.375Hz), 131.84, 129.18, 129.14, 128.72, 128.58, 128.44, 128.32 ,128.28, 126.62 (t, $^{2}J_{C-F}$=26.875Hz), 126.36, 122.19, 113.97 （t, $^{1}J_{C-F}$=246.87Hz）, 93.91, 89.17, 38.51, 28.69; ^{19}F NMR (376 MHz, $CDCl_3$): δ-95.14 (d, *J* = 12.7 Hz, 2F)； HRMS (ESI-TOF) calculated $[M+H]^+$ for $C_{26}H_{20}F_2O$: 387.1560， found：386.1559

5.13 (*E*)-1-([1,1'-biphenyl]-4-yl)-2,2-difluoro-4,6-diphenylhex-3-en-5-yn-1-one（**3k**）

Pale yellow sticky liquid; yield=55%; ^{1}H NMR (500MHz, $CDCl_3$) :δ 7.88(d, *J* = 5 Hz, 2H), 7.62 (d, *J* = 5Hz, 4H), 7.49-7.39 (m, 6H), 7.34-7.31 (m, 4H), 7.28(s, 2H) 7.25 (s, 1H), 6.60 (t, *J*=12.5Hz, 1H); ^{13}C NMR (125MHz, $CDCl_3$): δ186.76 (t, $^{2'}J_{C-F}$=23.75Hz), 146.67, 139.52, 135.61, 133.95 (t, $^{3}J_{C-F}$=9.375Hz), 131.83, 130.51, 130.48, 130.36, 129.09, 129.03, 128.79, 128.70, 128.55, 128.40, 128.07, 127.29, 127.20 (t, $^{2}J_{C-F}$=53.75Hz), 122.19, 114.79 (t, $^{1}J_{C-F}$=243.93Hz), 93.68, 89.35; ^{19}F NMR (376Hz, $CDCl_3$): δ -88.45 (d, *J*=15.04Hz, 2F); HRMS (ESI-TOF) calculated$[M+H]^+$for $C_{30}H_{20}F_2O$: 435.1560,found: 435.1555

5.14 (*E*)-2,2-difluoro-1-phenyl-4,6-di-p-tolylhex-3-en-5-yn-1-one(**3l**)

Pale yellow sticky liquid, yield: 80%, ^{1}H NMR (500 MHz, CDCl3): δ7.78 (d, *J* = 7.5Hz, 2H), 7.54(t, *J*=7.25Hz, 1H), 7.37 (t, *J*=7.75Hz, 2H), 7.31 (d, *J*=8Hz, 2H), 7.13 (dd, *J* = 15.7, 8.0 Hz, 4H), 7.04 (d, *J*=8Hz, 2H), 6.51 (t, *J*=12.75Hz, 1H), 2.235 (s, 6H); ^{13}C NMR (125MHz, $CDCl_3$): 187.29 (t, $^{2'}J_{C-F}$=29.18Hz), 139.34, 139.14, 134.14 (t, $^{3}J_{C-F}$=9.625Hz), 133.96, 132.81, 131.87, 131.73, 129.70, 129.17, 128.75, 128.71, 128.34, 126.72 (t, $^{2}J_{C-F}$=22.5Hz), 119.18, 114.80 (t, $^{1}J_{C-F}$=246.06Hz), 93.68, 88.99 21.56, 21.33; ^{19}F NMR (376 MHz, $CDCl_3$): δ -88.18 (d, *J* = 12.8Hz, 2F)； HRMS (ESI-TOF) calculated [M+H]+ for $C_{26}H_{20}F_2O$: 387.1560， found：387.1562

5.15 (*E*)-4,6-bis(4-ethylphenyl)-2,2-difluoro-1-phenylhex-3-en-5-yn-1-one(**3m**)

Pale yellow sticky liquid , yield: 82%, ^{1}H NMR (500 MHz, CDCl3): δ7.75 (d, *J* = 8Hz, 2H), 7.52 (t, *J*=7.5Hz, 1H), 7.36-7.33 (m, 4H), 7.14 (dd, *J*=10.6, 8.2Hz, 4H), 7.05 (d, *J*=8 Hz, 2H), 6.52 (t, *J*=12.75Hz, 1H), 2.64-2.59 (m, 4H), 1.24-1.89 (m, 6H); ^{13}C NMR (125MHz, $CDCl_3$): 187.28 (t, $^{2'}J_{C-F}$=28.75Hz), 145.63, 145.48, 134.15 (t, $^{3}J_{C-F}$=9.375Hz), 133.90, 133.03, 131.96, 131,85, 129.61, 128.87, 128.32, 127.98, 127.53, 126.81 (t, $^{2}J_{C-F}$=26.875Hz), 119.44, 114.79 (t, $^{1}J_{C-F}$=245.625Hz), 93.71, 88.99, 28.88, 28.70, 15.45,15.27; ^{19}F NMR (376 MHz, CDCl3): δ -88.91 (d, *J* = 11.50Hz, 2F)； HRMS (ESI-TOF) calculated [M+H]+ for $C_{28}H_{24}F_2O$: 415.1873， found：415.1874

5.16 (*E*)-2,2-difluoro-1-phenyl-4,6-bis(4-propylphenyl)hex-3-en-5-yn-1-one (**3n**)

Pale yellow sticky liquid , yield: 75%, ^{1}H NMR (500 MHz, $CDCl_3$): δ7.74 (d, *J* = 5Hz, 2H), 7.52 (t, *J*=7.5Hz, 1H), 7.36-7.33 (m, 4H), 7.12 (dd, *J*=11.9,8.2Hz, 4H), 7.02 (d, *J*=8.2Hz, 2H), 6.53 (t, *J*=12.6Hz, 1H), 2.57-2.54 (m, 4H), 1.65-1.57 (m, 4H), 0.93 (dt,*J*=21.8,7.3Hz, 6H); ^{13}C NMR (125MHz, $CDCl_3$): 187.18 (t, $^{2'}J_{C-F}$=29.375Hz), 144.41, 143.97, 134.17 (t, $^{3}J_{C-F}$=10Hz), 133.90, 132.98, 131.93, 131,76, 129.61, 128.81, 128.60, 128.31, 128.13, 126.90 (t, $^{2}J_{C-F}$=27.5Hz), 119.45, 114.75 (t, $^{1}J_{C-F}$=245.62Hz), 93.72, 89.00, 38.00, 37.84, 24.44, 24.29, 13.83, 13.73; ^{19}F NMR (376 MHz, CDCl3): δ -87.72 (d, *J* = 11.28Hz, 2F)； HRMS (ESI-TOF) calculated [M]+ for $C_{30}H_{28}F_2O$: 443.2186， found：443.2180

5.17 (*E*)-2,2-difluoro-1-phenyl-4,6-di-m-tolylhex-3-en-5-yn-1-one(**3o**)

Pale yellow sticky liquid , yield: 75%, ^{1}H NMR (500 MHz, CDCl3): δ7.66 (d, *J* = 7.5Hz, 2H), 7.46 (t, *J*=7.5Hz,1H), 7.29 (t, *J*=7.5Hz, 2H), 7.18-7.11 (m, 3H), 7.08-7.03 (m, 3H), 6.94 (d, *J*=6.5Hz, 1H); 6.87 (s, 1H), 6.47 (t, *J*=12.25Hz,1H), 2.24 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$): 185.98 (t, $^{2'}J_{C-F}$=28.75Hz), 164.55, 135.95, 133.92 (t, $^{3}J_{C-F}$=8.75Hz), 132.59, 132.52, 133.07, 129.30, 129.24, 129.01, 128.84, 128.74, 128.66, 128.26, 128.05 (t, $^{2}J_{C-F}$=26.875Hz), 126.95, 124.99, 122.53, 115.17 (t, $^{1}J_{C-F}$=247.5Hz),114.02, 93.70, 89.74, 55.81, 55.80; ^{19}F NMR (376 MHz, $CDCl_3$): δ -88.91 (d, *J* = 11.50Hz, 2F); HRMS (EI-TOF) calculated [M]+ for $C_{26}H_{20}F_2O$:386.1482， found：386.1478

5.18 (*E*)-4,6-bis(4-(tert-butyl)phenyl)-2,2-difluoro-1-phenylhex-3-en-5-yn-1-one(**3p**)

Pale yellow sticky liquid, yield: 80%, ^{1}H NMR (500 MHz, $CDCl_3$): δ7.62 (d, *J* = 7.5Hz, 2H), 7.45(t, *J*=7.5Hz, 1H), 7.29 (t, *J*=7Hz, 3H), 7.24 (s, 1H), 7.18 (s, 1H), 7.14 (d, J=8.5Hz, 2H), 7.06 (d, *J*=8Hz, 2H), 6.45 (t, *J*=12.5Hz, 1H), 1.23 (s, 9H), 1.22 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$): 187.24 (t, $^{2'}J_{C-F}$=28.93Hz), 152.45, 152.36, 133.98 (t, $^3J_{C-F}$=9.93Hz), 133.81, 132.70, 131.98, 131.59, 129.45, 128.61, 128.22, 126.95 (t, $^2J_{C-F}$=26.875Hz), 125.40, 124.94, 119.21, 114.67 (t, $^1J_{C-F}$=245.125Hz), 93.56, 88.88, 34.86, 34.70, 31.24,31.13; ^{19}F NMR (376 MHz, $CDCl_3$): δ -87.41 (d, *J* = 12.78Hz, 2F)；HRMS (ESI-TOF) calculated [M+H]+ for $C_{32}H_{32}F_2O$: 471.2499， found：471.2498.

5.19 (*E*)-2,2-difluoro-4,6-bis(4-fluorophenyl)-1-phenylhex-3-en-5-yn-1-one(**3q**)

Pale yellow sticky liquid , yield: 90%, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.8Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.34 (t, *J* = 7.0 Hz, 4H), 7.18-7.15 (m , 2H), 6.95 (t, *J* = 7.5 Hz, 2H), 6.87 (t, *J*=10Hz, 2H) , 6.49 (t, *J* = 12.8Hz, 1H) ; ^{13}C NMR (125 MHz, CDCl3): δ187.11 (t, $^{2'}$*JC-F*=30Hz), 163.12 (d, $^{1'''}J_{C-F}$=248.75Hz), 163.03 (d,$^{1'''}$J$_{C-F}$=250Hz), 134.20, 133.85, 133.79, 132.72 (t, $^3J_{C-F}$=9.375Hz), 131.68, 130.75, 130.68, 128.50, 127.72 (t, $^2J_{C-F}$=26.875Hz), 115.58 (d, $^{2''}J_{C-F}$=85Hz), 115.2 (d, $^{2'''}J_{C-F}$=85Hz), 114.66 (t, $^1J_{C-F}$=246.875Hz), 92.69, 88.83; ^{19}F NMR (376 MHz, CDCl3): δ -89.42 (d, *J* = 12.5 Hz, 2F), -109.95 (s, 1F), -112.41 (s, 1F); HRMS (ESI-TOF) calculated [M+H]+ for $C_{24}H_{14}F_4O$: 395.1059,found:395.1055

5.20 (*E*)-4,6-bis(4-bromophenyl)-2,2-difluoro-1-phenylhex-3-en-5-yn-1-one (**3r**)

Pale yellow sticky liquid ; yield=79% ; ^{1}H NMR (500MHz,$CDCl_3$) :δ 7.84(d, *J* = 7.5Hz, 2H), 7.59 (t, *J* = 7.25Hz, 1H), 7.46-7.39 (m, 6H), 7.35(d, *J* = 8.5Hz, 2H), 7.14 (d, *J* = 8.5Hz, 2H), 6.57 (t, *J*=13.0Hz, 1H); ^{13}C NMR (125MHz, $CDCl_3$): δ187.19 (t, $^{2'}J_{C-F}$=30.625Hz), 134.34, 133.21, 132.49 (t, $^3J_{C-F}$=9.375Hz), 131.92, 131.79, 131.61, 131.36, 130.31, 129.84, 128.59, 128.10 (t, $^2J_{C-F}$=26.25Hz), 123.72, 123.56, 120.89, 114.69 (t, $^1J_{C-F}$=247.5Hz), 92.83, 89.76; ^{19}F NMR (376Hz, $CDCl_3$): -89.76 (d, *J*=12.74Hz, 2F); HRMS (ESI-TOF) calculated[M+H]+for $C_{24}H_{16}F_2OBr_2$: 517.9339, found:517.9336

5.21 (*E*)-4,6-bis(4-chlorophenyl)-2,2-difluoro-1-phenylhex-3-en-5-yn-1-one(**3s**)

Pale yellow sticky liquid ; yield=82% ; ^{1}H NMR (500MHz,$CDCl_3$) :δ 7.84(d, *J* = 7.5Hz, 2H), 7.58 (t, *J* = 7.5Hz, 1H), 7.41 (t, *J* = 7.75Hz, 2H), 7.35(d, *J* = 8.5Hz, 2H), 7.29 (t, *J* = 8.5Hz, 2H), 7.25-7.19 (m, 4H), 6.57 (t, *J*=13.0Hz, 1H); ^{13}C NMR (125MHz, $CDCl_3$): δ187.16 (t, $^{2'}J_{C-F}$=30Hz), 135.43, 135.30, 134.35,133.89, 133.06, 132.51 (t, $^3J_{C-F}$=9.375Hz), 131.62, 130.11, 129.83, 128.87, 128.60, 128.41, 128.13 (t, $^2J_{C-F}$=24.375Hz), 120.47, 114.71 (t, $^1J_{C-F}$=247.5Hz), 92.77, 89.81; ^{19}F NMR (376Hz,$CDCl_3$): -88.80 (d, *J*=13.16Hz, 2F); HRMS (ESI-TOF) calculated[M+H]+for $C_{24}H_{16}F_2OCl_2$: 427.0468,found: 427.0459.

5.22 (*E*)-2,2-difluoro-1-phenyl-4,6-bis(4-(trifluoromethyl)phenyl)hex-3-en-5-yn-1-one(**3t**)

Pale yellow sticky liquid ; yield=75% ; ^{1}H NMR (500MHz,$CDCl_3$) :δ 7.86 (d, *J* = 7.5Hz, 2H), 7.61-7.53(m, 7H), 7.44-7.41 (m, 4H), 6.68 (t, *J*=13.25Hz, 1H); ^{13}C NMR (125MHz, $CDCl_3$): δ187.20 (t, $^{2'}J_{C-F}$=29.375Hz), 138.94, 134.48, 132.09 131.91 (t, $^3J_{C-F}$=8.75Hz), 131.49, 129.86, 129.40(t, $^2J_{C-F}$=26.25Hz), 129.00, 128.66, 125.41(q, $^{2'''}J_{C-F}$=3.3Hz), 125.18 (q, $^{2''}J_{C-F}$=3.75Hz), 123.84 (q, $^{1'''}J_{C-F}$=270.41Hz), 123.73 (q, $^{1'''}J_{C-F}$=270.83Hz), 127.59 (t, $^2J_{C-F}$=26.875Hz), 126.69, 122.19, 114.64 (t, $^1J_{C-F}$=247.5Hz), 92.56, 90.50; ^{19}F NMR (376Hz, $CDCl_3$): δ -66.82(s, 3F), -62.97(s, 3F), -89.26 (d,*J*=15.04Hz, 2F); HRMS (ESI-TOF) calculated[M+H]$^+$for $C_{26}H_{14}F_8O$: 495,0995,found: 495.0990

5.23 (*E*)-2,2-difluoro-1-phenyl-4,6-di(thiophen-2-yl)hex-3-en-5-yn-1-one(**3u**)

Pale yellow sticky liquid , yield: 75%, 1H NMR (500 MHz, $CDCl_3$): δ7.77 (d, *J* = 10Hz, 2H), 7.50 (t, *J*=7.5Hz, 1H), 7.43 (s, 1H), 7.34 (t, *J*=8Hz, 3H), 7.22-7.20 (m, 1H), 7.11-7.10 (m, 1H), 7.05 (d, *J*=5Hz, 1H), 6.93(d, *J*=5Hz, 1H), 6.41 (d, *J*=13Hz, 1H); δ187.16 (t,$^{2'}J_{C-F}$=30Hz), 135.42, 135.30, 134.35,133.89, 133.06, 132.50 (t, $^3J_{C-F}$=9.375Hz), 131.62, 130.11, 129.83, 128.87, 128.60, 128.41, 128.13 (t, $^2J_{C-F}$=24.375Hz), 120.47, 114.71 (t, $^1J_{C-F}$=247.5Hz), 92.77, 89.81; ^{19}F NMR (376 MHz, $CDCl_3$): δ -88.53 (d, *J* = 13.16Hz, 2F)； HRMS (ESI-TOF) calculated $[M+H]^+$ for $C_{20}H_{12}F_2OS_2$:371.0376, found：371.0372.

5.24 (*E*)-4,6-di(cyclohex-1-en-1-yl)-2,2-difluoro-1-phenylhex-3-en-5-yn-1-one(**3v**)

Pale yellow sticky liquid , Yield: 90%, ^{1}H NMR (500 MHz, $CDCl_3$): δ8.00 (d, *J* = 7.5Hz, 2H), 7.59(t, *J*=7.5Hz, 1H), 7.45 (t, *J*=8Hz, 2H), 6.21-6.16 (m, 2H), 5.72-5.70 (m, 1H), 2.12 (d, *J*=4.5Hz, 3H),1.95-1.82 (m, 2H), 1.65-1.56 (m, 5H), 1.43-1.41 (m, 2H), 1.37-1.32 (m, 2H),1.27-1.23 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$): 186.61 (t, $^{2'}J_{C-F}$=28.12Hz), 136.93, 136.57 (t, $^3J_{C-F}$=12.5Hz), 134.04, 133.73, 133.14, 131.86, 129.99, 128.35, 126.68 (t, $^2J_{C-F}$=30Hz), 120.25, 114.75 (t, $^1J_{C-F}$=241.25Hz), 95.37, 84.94, 28.91, 25.88, 25.80, 24.67, 22.18, 21.82, 21.37, 21.06; ^{19}F NMR (376 MHz, $CDCl_3$): δ -85.37 (d, *J* = 10.52Hz, 2F)；HRMS (ESI-TOF) calculated [M+H]+ for $C_{24}H_{24}F_2O$:367.1873， found：367.1866.

5.25 (*E*)-4,6-bis(4-ethylphenyl)-2-fluoro-2-methyl-1-(thiophen-2-yl)hex-3-en-5-yn-1-one(**3w**)

Pale yellow sticky liquid , yield: 68%, ^{1}H NMR (500 MHz, $CDCl_3$): δ7.77 (d, *J* = 3Hz, 1H), 7.69 (dd, *J*=4.9, 0.7Hz, 1H), 7.35 (d, *J*=8.5Hz, 2H), 7.256 (t, *J*=6Hz, 2H), 7.14 (d, *J*=8.5Hz, 2H), 7.10-7.08 (m, 3H), 6.45 (t, *J*=13.25Hz, 1H), 2,65-2.60 (m, 4H), 1.23-1.20 (m, 6H); ^{13}C NMR (125MHz, $CDCl_3$): 180.95 (t, $^{2'}J_{C-F}$=31.87Hz), 145.62, 145.31, 138.29, 135.91, 135.26, 134.57(t, $^3J_{C-F}$=9.375Hz), 133.10, 131.84, 128.78, 128.37, 127.97, 127.51, 126.20 (t, $^2J_{C-F}$=26.875Hz), 119.43, 114.73 (t, $^1J_{C-F}$=247.5Hz), 93.89, 89.07, 28.87, 28.66, 15.34, 15.26; ^{19}F NMR (376 MHz, $CDCl_3$): δ -88.61 (d, *J* = 13.16Hz, 2F)；HRMS (ESI-TOF) calculated [M+H]+ for $C_{26}H_{22}F_2OS$:421.1438 ， found：421.1437.

5.26 Ethyl (*E*)-2,2-difluoro-4,6-diphenylhex-3-en-5-ynoate (**3x**)

Pale yellow sticky liquid , yield: 90%, ^{1}H NMR (500 MHz, $CDCl_3$): δ7.48-7.46 (m, 4H), 7.39-7.38 (m, 3H), 7.36-7.34 (m, 3H), 6.36 (t, *J*=12.25Hz, 1H), 3.94 (q, *J*=7.2Hz, 2H), 1.16(t, J=7.2Hz, 3H); ^{13}C NMR (125MHz, $CDCl_3$): 162.90 (t, $^{2'}J_{C-F}$=33.43Hz), 135.55, 133.78 (t, $^3J_{C-F}$=10Hz), 131.83, 129.17, 129.11, 128.66, 128.43, 128.23, 126.87 (t, $^2J_{C-F}$=28.06Hz), 122.19, 111.90 (t, $^1J_{C-F}$=243.81Hz), 93.61, 89.14, 63.01, 28.66, 13.65; ^{19}F NMR (376 MHz, $CDCl_3$): δ -91.80 (s, 2F); MS (ES-TOF) calculated $[M+H]^+$ for $C_{20}H_{16}F_2O2$: 327.1197, found: 327.3

5.27 (E)-(5,5,6,6,7,7,8,8,9,9,10,10-dodecafluorodec-3-en-1-yne-1,3-diyl)dibenzene (**3y**)

Pale yellow sticky liquid , yield: 70%, ^{1}H NMR (500 MHz, $CDCl_3$): δ7.5 (d, *J*=6.1Hz, 4H), 7.42-7.41 (m, 3H), 7.38-7.33 (m, 3H), 6.25 (t, *J*=15.25Hz, 1H).

5.28 (*E*)-2,2-difluoro-1-phenyl-4,6-bis(trimethylsilyl)hex-3-en-5-yn-1-one (**3z**)

Pale yellow sticky liquid , yield: 25%, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8 Hz, 2H), 7.60 (t, *J* = 7.25 Hz, 1H), 7.46 (t, *J* = 8Hz, 2H), 6.29 (t, *J* = 11 Hz, 1H), 0.166 (s, 9H), 0.108 (s, 9H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -94.75 (s, 2F)； HRMS (ESI-TOF) calculated [M+H]+ for $C_{26}H_{22}F_2OS$:351.1412 ， found：351.1402

5.29 (*E*)-2,2-difluoro-4-iodo-1-phenylnon-3-en-1-one(**4a**)

Pale yellow sticky liquid , yield: 65%, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.8 Hz, 2H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 6.62 (t, *J* = 11.9 Hz, 1H), 2.61 (t, *J* = 6.9 Hz, 2H), 1.55 (dt, J = 15.0, 7.4 Hz, 2H), 1.22 (dt, J = 14.6, 7.2 Hz, 2H), 0.89 (t, J = 7.2 Hz, 3H).

5.30 (*E*)-2,2-difluoro-4-iodo-1-phenyl-4-(trimethylsilyl)but-3-en-1-one(**4b**)

Pale yellow sticky liquid , yield: 50%, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.5 Hz, 2H), 7.63 (t, *J* = 7.25 Hz, 1H), 7.50 (t, *J* = 7.75Hz, 2H), 7.15 (t, *J* = 11.5 Hz, 1H), 0.216 (s, 9H).

5.31 Radical trapping experiment

An oven-dried tube was charged with K_3PO_4 (2.0 mmol, 2.0 equiv), and $Pd(PPh_3)_4$ (0.05 mmol, 5 mol %). The tube was evacuated and backfilled with nitrogen (repeated three times).Then, α,α-iododifluoroacetones **1a** (1.0 mmol, 1.0 equiv) dissolved in toluene (3.0 mL), the 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (1.2 mmol, 1.2eq) and phenylacetylene **2a** (2.0 mmol, 2.0 equiv) were added into the tube. The reaction mixture was stirring at 80 °C for 4-12h. ^{19}F NMR spectra of the reaction indicates the product distribution.

5.32 Experiment for ratio of **1a** and **2a** with 1: 0.5.

An oven-dried tube was charged with K_3PO_4 (2.0 mmol, 2.0 equiv), and $Pd(PPh_3)_4$ (0.05 mmol, 5 mol %). The tube was evacuated and backfilled with nitrogen (repeated three times).Then, α,α-iododifluoroacetones **1a** (1.0 mmol, 1.0 equiv) dissolved in toluene (3.0 mL), and Phenylacetylene (0.5 mmol, 0.5equiv) were added into the tube. The reaction mixture was stirring at 80 °C for 0.5 h. After completion of the reaction (as indicated by TLC), the reaction is quenched with the appropriate amount of water, and the reaction mixture was extracted with ethyl acetate (3*10 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, concentrated in vacuum and the crude residue was purified by silica-gel column chromatography (petroleum ether/EtOAc =200:1) to afford desired the product **6**

5.33 Coupling reaction of the adduct product **6** and **2a**

An oven-dried tube was charged with K_3PO_4 (2.0 mmol, 2.0 equiv), and $Pd(PPh_3)_4$ (0.05 mmol, 5 mol %). The tube was evacuated and backfilled with nitrogen (repeated three times).Then, The compound **6** (0.8 mmol, 1.0 equiv) dissolved in toluene (3.0 mL), and Phenylacetylene (0.96 mmol, 1.2equiv) were added into the tube. The reaction mixture was stirring at 80 °C for 4-6h. After completion of the reaction (as indicated by TLC), the reaction is quenched with the appropriate amount of water, and the reaction mixture was extracted with ethyl acetate (3*10 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, concentrated in vacuum and the crude residue was purified by silica-gel column chromatography (petroleum ether/EtOAc =200:1) to afford desired the product **3a**.

Appendix A. Supplementary data

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References and notes

[1] (a) Müller. K, Faeh. C, Diederich. F, *Science*. 317 (2008) 1881-1888;
(b) O'Hagan. D. *Chem. Soc. Rev*. 37 (2008) 308-320;
(c) Purser, S.; Moore, P. R.; Swallow, S. Gouverneur, V. *Chem. Soc. Rev*. 37 (2008) 320-330;
(d) Jian.W, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S, Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev*. 114 (2004) 2432−2506;
(e) R. Berger, G, Resnati, P. Metrangolo, E. Weber, J. Hulliger. *Chem. Soc. Rev*. 40 (2011) 3496–3508.

[2] (a) E. G. Skolnik, W. E. Jones, *Chem Rev*. 76 (1976) 565-592;
(b) M. John, *Chem. Soc. Rev.* 16 (1987) 381-436;
(c) Y. Zhu, J. L. Han, J. D. Wang, Norio Shibata,, M. Sodeoka, , V. A. Soloshonok, J. A. S. Coelho, F. D. Toste. *Chem. Rev.* 118 (2018) 3887−3964.

[3] (a) O'Hagan. D, W. Yi, S. Maciej, M. Z. S. Alexandra, *Pure Appl. Chem.* 84 (2012) 1587–1595;
(b) C. Fang, Fanhong. Wu, *Adv Mater Res*. 881-883 (2014) 196-200;
(c) Z. Feng, Y. L. Xiao, X. G. Zhang, *Acc. Chem. Res.* 51 (2018) 2264−2278.

[4] (a) W. X. Sha, W. Z. Zhang, S. Y. Ni, H. B. Mei, J. L. Han, Y. Pan, *J. Org. Chem.* 82 (2017) 9824-9831;
(b) H. G Huang, Y. Li, *J. Org. Chem.* 82 (2017) 4449-4457;
(c) H. Y. Zhao, Z. Feng, Z. J. Luo, X. G. Zhang, *Angew. Chem. Int. Ed*. 55 (2016), 10401-10405;
(d) N. N. Yi, H. Zhang, C. H. Xu, W. Deng, R. J. Wang, D. M. Peng, Z. B. Zeng, J. N. Xiang, *Org. Lett.* 18 (2016) 1780-1783;
(e) Y. Arai, R. Tomita, G. Ando, T. Koike, M. Akita, *Chem. Eur. J*. 22 (2016) 1262-1265;
(f) G. B. Ma, W. Wan, J. L. Li, Q. Y. Hu, H. Z. Jiang, S. Z. Zhu, J. Wang, J. Hao, *Chem. Commun*. 50 (2014), 9749-9752.

[5] (a) Z. Feng, Y. L. Xiao, X. G. Zhang, *Acc. Chem. Res.* 51 (2018) 2264−2278;
(b) Y. L. Li, J. Liu, S. Zhao, X. Z. Du, M. J. Guo, W. T. Zhao, X. Y. Tang, G. W. Wang, *Org. Lett.* 20 (2018) 917−920;
(c) W. Q. Fu, Q. L. Song, *Org. Lett.* 20 (2018) 393−396;
(d) J. W. Gu, Q. Q. Min, L. C. Yu, X. G. Zhang, *Angew. Chem. Int. Ed*. 55 (2016) 12270 –12274;
(e) M. L. Ke, Q. L. Song, *J. Org. Chem*.,81 (2016) 3654−3664;
(f) G. Li, T. Wang, F. Fei, Y. M. Su, Q. Lan, X. S. Wang, *Angew. Chem. Int. Ed*. 55 (2016) 3491 –3495;
(g) Y. L. Xiao, W. H. Guo, G. Z. He, Q. Pan, X. S. Wang, *Angew. Chem. Int. Ed*. 53 (2014) 9909 –9913;
(h) X. L. Nie, C. G. Cheng, G. G. Zhu, *Angew. Chem. Int. Ed.* 56 (2017) 1898 –1902.
(i) Y. Gu. X. B. Leng, Q. L. Shen. *Nat. Commun*., 2014, 5, 5405
(j) C. H. Lu, Y. Gu, J. Wu, Y. C. Gu, Q. L. Shen. *Chem. Sci*., 2017, 8, 4848
(k) C. H. Lu, H. Lu, J. Wu, H. Shen, T. S. Hu, Y. C. Gu, Q. L. Shen. *J. Org. Chem.* 2018, 83, 1077.
(l) W. H. Guo, H. Y. Zhao, Z. J. Luo, S. Zhang, X. G. Zhang. *ACS Catal*. 2019, 9, 38-43
(m) W. H. Guo, Z. J. Luo, W. B. Zeng, X. G. Zhang. *ACS Catal*. 2017, 7, 896-901.

[6] (a) X. Huang, S. M. Ma, *Acc. Chem. Res.* 52 (2019) 1301−1312;
(b) A. M. Haydl, B. Breit, T. Liang, M. J. Krische, *Angew. Chem. Int. Ed*. 56 (2017) 11312 – 11325;
(c) P. B. Mi, L. R. He, T. X. Shen, J. Z. Sun, H. Zhao, *Org. Lett.* 21 (2019) 6280-6284;
(d) A. Hazra, J. Chen, G. Lalic, *J. Am. Chem. Soc*. 141 (2019) 12464-12469;
(e) T. Inami, T. Takahashi, T. Kurahashi, S. Matsubara, *J. Am. Chem. Soc*, 141 (2019) 12541-12544;
(f) Y. H. Lv, W. Y. Pu, L. H. Shi, *Org. Lett.* 21 (2019) 6034−6039;

(g) Y. Wang, R. Guan, P. Sivaguru, X. F. Cong, X. H. Bi, *Org. Lett*. 21 (2019)4035−4038;
(h) M. K. Armstrong , G. Lalic, *J. Am. Chem. Soc*. 141 (2019) 6173−6179.

[7] Z. Li, A. García-Domínguez, C. Nevado, *J. Am. Chem. Soc.* 137 (2015) 11610-11613.

[8] S. Domański, W. Chaładaj, *ACS Catal*. 6 (2016) 3452-3456;

[9] Y.-T. He, Q. Wang, L.-H. Li, X.-Y. Liu, P.-F. Xu, Y.-M. Liang, *Org. Lett.* 17 (2015) 5188-5191.

[10] J. Q. Liang, G. Z. Huang, P. Peng, T. Y. Zhang, J. J. Wu, F. H. Wu, *Adv. Synth. Catal*. 360 (2018) 2221-2228.

[11] X. X. Qi, H. J. Ai, C. X. Cai, J. B. Peng, F. Zheng, X. F. Wu, Eur. *J. Org. Chem*. (2017) 2940–2943.

[12] S. L. Iverson and J. P. Uetrecht, *Chem. Res. Toxicol.* 14 (2001) 175-181.

[13] (a) Y. N. Yang, J. L. Jiang, H. Z. Yu, J. Shi, *Chem. Eur. J*. 24 (2008), 178-186;
(b) R. Kumar, E. Tamai, A. Nishimura, Y. Hoshimoto, M. Ohashi, S. Ogoshi, *Synthesis* .48 (2016) A–F;
(c) Y. M. Huang, J. D. Pozo, S. Torker, A. H. Hoveyda, *J. Am. Chem. Soc.* 140 (2018) 2643−2655;
(d) Y. Y. Zhou, X. X. Chen, D. L.Yin, Y. Ling, S. F. Wang, X. X. Zhang, W. D. Rao, *Eur. J. Org. Chem.* 5 (2019), 999-1007;
(e) K. D. Nguyen, D. Herkommer, M. J. Krische, *J. Am. Chem. Soc*. 138 (2016) 5238-524;
(f) K. F. Zhang, K. J. Bian, C. Li, J. Sheng, X. S. Wang, *Angew. Chem. Int. Ed*, 58 (2019) 5069-5074;
(g) S. Gao, H. Liu, C. Yang, Z. F. Fu, H. Q. Yao, A. J. Lin, *Org. Lett.* 19 (2017) 4710−4713.

[14] (a) J. P. John, D. A. Colby, *J. Org. Chem.* 76 (2011) 9163−9168;
(b) H. Chen, J. X. Wang, J. J. Wu, Y. J. W. Huang, F. H. Wu, *J .Fluorine. Chem* 200 (2017) 41–46;
(c) P. Peng, J. J. Wu, J. Q. Liang, T. Y. Zhang, J. W. Huang, F. H. Wu, *RSC Adv*., 7 (2017) 56034–56037;
(d) J. X. Wang, J. J. Wu, H. Chen, S. W. Zhang, F. H. Wu, *Chin Chem Lett.* 26 (2015) 1381–1384.
(e) D. F. Wang, J. J. Wu, J. W. Huang, J. Q. Liang, P. Peng, H. Chen, F. H. Wu, *Tetrahedron* 73 (2017) 3478-3484;
(f) P. Peng, G. Z. Huang, Y. X. Sun, X. Wang, J. J. Wu, F. H. Wu, *Org. Biomol. Chem.*17 (2019) 6426–6431

[15] (a) Z. D. Li, A. García-Domínguez, C. Nevado, *J. Am. Chem. Soc*. 137 (2015) 11610-11613;
(b) Z. D. Li, E. Merino, C. Nevado, Top *Catal*. 60 (2017) 545-553;
(c) S. Domański, W. Chaładaj, *ACS Catal*., 6 (2016) 3452-3456;
(d) Y. T. He, L. H. Li, Q. Wang, W. S. Wu, Y. M. Liang, *Org. Lett*. 18 (2016) 5158;
(e) Y. T. He, Q. Wang, L. H. Li, X. Y. Liu, P. F. Xu, Y. M. Liang, *Org. Lett*. 17 (2015) 5188-5191;
(f) Q. Wang, Y. T. He, J. H. Zhao, Y. F. Qiu, L. Zheng, J. Y. Hu, Y. C. Yang, X. Y. Liu, Y. M. Liang, *Org. Lett.* 18 (2016) 2264-2267;
(g) P. B. Zhang, J. X. Ying, G. Tang, Y. F. Zhao, *Org. Chem. Front*. 4 (2017) 2054-2057.

Highlights:

The alkyne difunctionalization of fluoroalkyl species is still a challenge task. In this work, we reported a palladium-catalyzed one-pot difunctionalization of alkynes with α,α-iododifluoroacetones for the synthesis of difluorinated 1,3-enynes. The reaction proceeds through the radical addition of $RCOCF_2$ radical to alkynes and subsequent Sonogashira coupling with the same alkynes to give the 1,3-enyne products with high regio and stereoselectivity.

Declaration of interest statement

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted