Rhodium-catalyzed [2+2+2] cycloaddition of various fluorine-containing alkynes—novel synthesis of multi-substituted fluoroalkylated aromatic compounds†

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Treatment of various fluorinated internal alkynes with 10 mol% of $RhCl_3 \cdot H_2O$ and 30 mol% of *i*-Pr_2NEt in toluene at the reflux temperature for 18 h gave the corresponding trimerization products as an isomeric mixture in high yields. Cycloaddition using 1.0 equiv. of fluorinated alkynes and 2.0 equiv. of non-fluorinated alkynes under the same reaction conditions as in the trimerization led to mono- and bis-fluoroalkylated benzene derivatives in high yields, together with small amounts of trimerization products. The reaction of fluorine-containing bispropargyl ether with non-fluorinated alkynes took place smoothly to afford the corresponding bicyclic molecules in good to high yields.

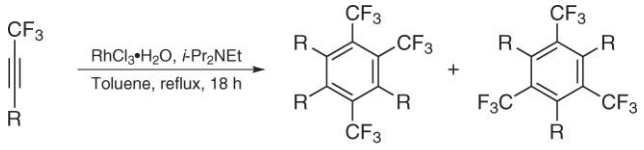
Introduction

The introduction of a fluoroalkyl group, such as a CF_3 group, into the benzene or heteroaromatic rings has been used quite often as one of the most efficient tools for modification of the lead molecules in view of biological activity.[1] Consequently, much effort has been put forth towards the development of a new synthetic approach to various classes of fluoroalkylated aromatic materials thus far.[2]

Transition metal-catalyzed [2+2+2] cycloaddition reactions are extremely valuable synthetic methods for the construction of six-membered carbocycles and heterocycles.[3] There have been accumulated studies on the reaction of *non-fluorinated alkynes* under the influence of various transition metals, such as Ni,[4] Rh,[5] Pd,[6] Ru,[7] Co,[8] Ti,[9] Mo,[10] Ir[11] and Mn[12] thus far. Despite of such great utility, *little attention has been paid to [2+2+2] cycloaddition of fluoroalkylated alkynes*.[13] Herein, we wish to describe a convenient and efficient approach to various types of fluoroalkylated aromatic compounds *via* [2+2+2] cycloaddition in detail.

Results and discussion

Initially, the trimerization of trifluoromethylated internal alkyne **1a**[14] (R = *p*-ClC_6H_4, Scheme 1) was examined as described in Table 1. Thus, treatment of **1a** in the presence of 3 mol% of $RhCl_3 \cdot H_2O$ and 9 mol% of *i*-Pr_2NEt in toluene (0.33 M) at reflux temperature for 18 h gave the desired trimerization product **2a** and **3a** in only 12% yield as an isomeric mixture (**2a** : **3a** = 83 : 17),[15] together with 83% recovery of **1a** (entry 1).[16] As shown in entry 2, an increase of the amount of Rh catalyst (10 mol%) as well as the amine (30 mol%) improved the yield to 59%. In this case, 16% of **1a** still remained unreacted. Then, the use of 20 mol% of Rh catalyst and 60 mol% of *i*-Pr_2NEt slightly decreased the yield,



R = *p*-ClC_6H_4 (**a**), Ph (**b**), *p*-$MeOC_6H_4$ (**c**), *p*-$EtO_2CC_6H_4$ (**d**)
o-ClC_6H_4 (**e**), *m*-ClC_6H_4 (**f**), *n*-$C_{10}H_{21}$ (**g**), CO_2Et (**h**)
$P(O)(OEt)_2$ (**i**), CH(OH)Ph (**j**)

Scheme 1 Trimerization of various trifluoromethylated alkynes **1**.

though the starting alkyne was completely consumed (entry 3). Changing the concentration from 0.33 to 0.5 M brought about a dramatic improvement of the yield, the trimerization products **2a** and **3a** being obtained in 85% yield in a ratio of 84 : 16. Increasing the concentration from 0.5 to 1.0 M resulted in a slight decrease of the yield (entry 5). Entries 6 and 7 show that the reaction could be carried out with a threefold lower loading of catalyst, though in the latter case, **1a** was recovered in significant amounts (53%). Reactions in *i*-PrOH, 1,2-dichloroethane, and 1,4-dioxane afforded the desired products in lower (31–44%) yields (entries 9–11). Several other attempts for improving the regioselectivity, such as the use of another rhodium catalyst, $[Rh(cod)_2]BF_4$ and $[RhCl(cod)_2]$ (entries 12 and 13), did not lead to satisfactory results.

With the optimized reaction conditions (entry 4 in Table 1), we next investigated the trimerization of various trifluoromethylated alkynes **1**. The results are summarized in Table 2.

As shown in entries 1–4, various trifluoromethylated alkynes with an electron-donating or an electron-withdrawing group on the benzene ring participated in the [2+2+2] cycloaddition successfully. On the other hand, the alkynes bearing *o*- or *m*-substituted benzene ring were found to be less reactive, the desired products being afforded in moderate yields (entries 5 and 6). In the case of a *m*-chlorophenyl group as R, the prolonged time (24 h) led to a satisfactory result (entry 6). However CO_2Et- or $P(O)(OEt)_2$-substituted alkynes (entries 8 and 9) and propargyl alcohol (entry

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Table 1 Investigation of the reaction conditions using **1a**

Entry	$RhCl_3 \cdot H_2O$/mol%	*i*-Pr_2NEt/mol%	Solvent/M	Yield of **2a**+**3a** (%)[a]	Ratio (**2a** : **3a**)[b]	Recovery of **1a** (%)[a]
1	3	9	Toluene/0.33	12	83 : 17	83
2	10	30	Toluene/0.33	59	83 : 17	16
3	20	60	Toluene/0.33	44	77 : 23	0
4	10	30	Toluene/0.5	85 (75)	84 : 16	0
5	10	30	Toluene/1.0	82[c,d]	84 : 16	0
6[e]	10	30	Toluene/0.5	54	83 : 17	0
7	3	9	Toluene/0.5	42	83 : 17	53
8[f]	10	30	Toluene/0.5	55	82 : 18	0
9	10	30	i-PrOH/0.5	31	82 : 18	3
10	10	30	DCE/0.5	44	77 : 23	17
11	10	30	1,4-Dioxane/0.5	40	84 : 16	8
12[g]	10	30	DCM	0	—	quant.
13[h]	10	30	DCM	0	—	quant.

[a] Determined by ^{19}F NMR. Value in parentheses is of combined yield of **2a** + **3a**. [b] Determined by ^{19}F NMR. [c] The yield was not reproducible. [d] 1.5 mmol scale. [e] Carried out for 4 h. [f] Carried out at 100 °C (bath temp.). [g] Carried out in the presence of $[Rh(cod)_2]BF_4$ at room temperature. [h] Carried out in the presence of $[RhCl(cod)_2]$ at room temperature.

Table 2 Trimerization of various trifluoromethylated alkynes **1**

Entry	Alkyne	Yield of **2**+**3**(%)[a]	Ratio (**2** : **3**)[b]	Recovery of **1** (%)[a]
1	**1a**	85 (75)	84 : 16	0
2	**1b**	69 (65)	81 : 19	0
3	**1c**	92 (90)	84 : 16	0
4	**1d**	68 (67)	84 : 16	0
5	**1e**	49 (40)	88 : 12[c]	0
6	**1f**	56	80 : 20	15
7[d]	**1f**	93 (80)	82 : 18	0
8	**1h**	n.d.[e]	—	0
9	**1i**	n.d.[e]	—	0
10	**1j**	n.d.[e]	—	0

[a] Determined by ^{19}F NMR. Values in parentheses are of the combined yield of **2** + **3**. [b] Determined by ^{19}F NMR. [c] Many atropisomers of **2e** and **3e** were detected. [d] Carried out for 24 h. [e] Not detected.

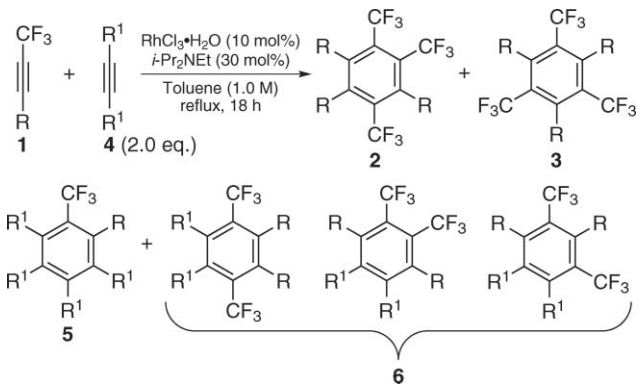
Table 3 [2+2+2] Cycloaddition of **1** with diphenylacetylene **4** (R^1 = Ph)

Entry[a]	Alkyne	Yield of **2**+**3** (%)[b] (**2** : **3**)	Yield of **5** (%)[c]	Yield of **6** (%)[b]
1[d]	**1a**	6 (83 : 17)	34	40 (38 : 15 : 47)
2[d,e]	**1a**	3 (67 : 33)	28	27 (31 : 15 : 52)
3	**1a**	8 (88 : 12)	51 (50)	41 (44 : 17 : 39)
4	**1b**	7 (86 : 14)	47 (32)	36 (39 : 14 : 47)
5	**1c**	7 (86 : 14)	45 (43)	37 (49 : 13 : 38)
6	**1d**	6 (83 : 17)	45 (31)	32 (37 : 16 : 47)
7	**1g**	0	41 (33)	32 (31 : 13 : 56)
8	**1h**	n.d.[f]	n.d.[f]	n.d.[f]
9	**1i**	n.d.[f]	16	n.d.[f]

[a] Unless otherwise noted, the reaction was performed using 2.0 equiv. of diphenylacetylene in a 1.0 M concentration. [b] Determined by ^{19}F NMR. [c] Determined by ^{19}F NMR. Values in parentheses are of the isolated yield. [d] Carried out in 0.5 M concentration. [e] 4 equiv. of diphenylacetylene was used. [f] Not detected.

10) did not give any desired products at all, although the starting alkynes were completely consumed.

Next, our attention was directed towards the [2+2+2] cycloaddition of **1** and non-fluorinated alkynes (Scheme 2). The results are summarized in Table 3.



Scheme 2 [2+2+2] Cycloaddition of **1** with various non-fluorinated alkynes.

Thus, treatment of 1.0 equiv. of **1a** and 2.0 equiv. of diphenylacetylene (R^1 = Ph) in the presence of 10 mol% of $RhCl_3 \cdot H_2O$ and 30 mol% of *i*-Pr_2NEt in toluene (0.5 M) at reflux temperature for 18 h gave the mono- and bis-trifluoromethylated benzene derivatives **5a** and **6a** in 34 and 40% yield, respectively,[17] together with 6% of trimerization products **2a** and **3a** (entry 1). In this case, **6a** was obtained as an inseparable isomeric mixture. In order to improve the yield of **5a** and **6a**, the reaction using 4.0 equiv. of diphenylacetylene was conducted, but no dramatic improvement was detected (entry 2). Increasing the concentration had a significant influence on the reaction with the mono- and bis-trifluoromethylated benzene derivatives being obtained in 51 and 41% yields, respectively. In this case, the trimerization product was still formed in 8% yield. With such reaction conditions, the cycloaddition of various fluoroalkylated alkynes with diphenylacetylene was carried out. As shown in entries 4–6, various fluorinated alkynes bearing an electron-donating group as well as an electron-withdrawing group on the benzene ring could be successfully applied for this reaction. Additionally, the alkyne bearing an alkyl group as R was also found to be a good substrate, **5g** and **6g** being obtained in 41 and 32% yield, respectively (entry 7). In this case, no trimerization product was detected. However, the use of CO_2Et or $P(O)(OEt)_2$ as R led to a complex mixture (entries 8 and 9).

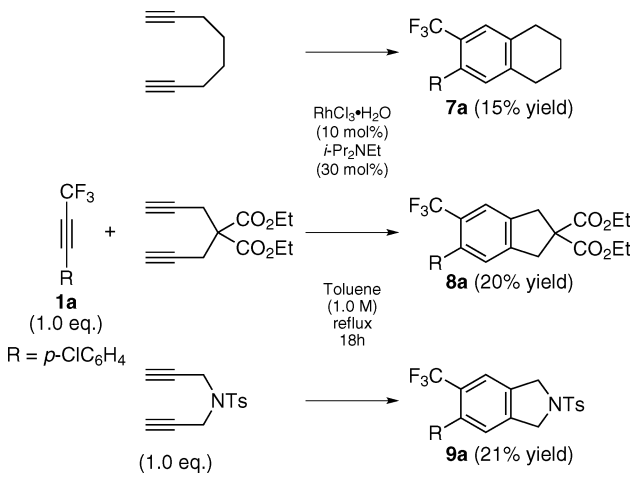
Table 4 [2+2+2] Cycloaddition of **1a** with various non-fluorinated alkynes **4**

Entry[a]	R^1	Product	Yield of **2**+**3** (%)[b] (**2** : **3**)	Yield of **5** (%)[c]	Yield of **6** (%)[b]
1	Ph	**a**	7 (88 : 12)	51 (50)	41 (44 : 17 : 39)
2	CO_2Me	**j**	52 (67 : 33)	17 (11)	17 (35 : 24 : 41)
3	TMS	**k**	47 (64 : 36)	n.d.[d]	n.d.[d]
4	*n*-Pr	**l**	10 (58 : 42)	21 (11)	69 (20 : 20 : 60)

[a] In all cases, **1a** was completely consumed. [b] Determined by ^{19}F NMR. [c] Determined by ^{19}F NMR. Values in parentheses are of the isolated yield. [d] Not detected.

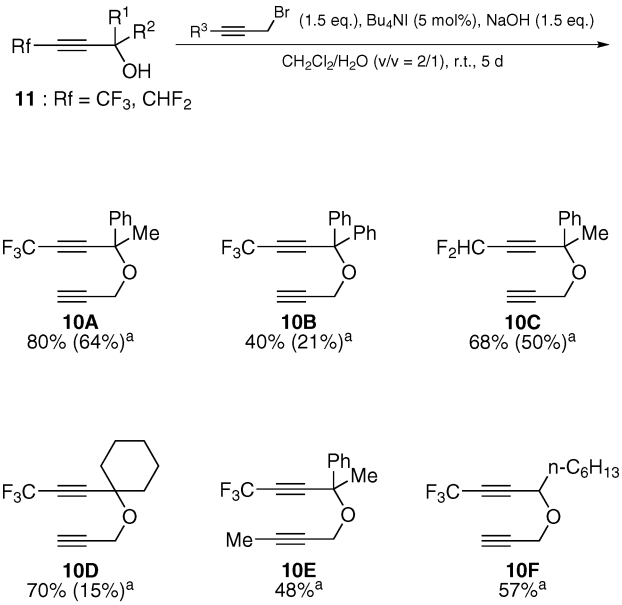
We also examined the cycloaddition of **1a** and various non-fluorinated alkynes as described in Table 4. As shown in entry 2, dimethyl acetylenedicarboxylate was found to be less reactive, the trimerization products of **1a** being obtained in 52% yield as the major product, together with 17% each of **5j** and **6j**. Similarly, the use of bis(trimethylsilyl)acetylene led to a favorable formation of the trimerization product (entry 3). In sharp contrast, the reaction with 4-octyne gave the bis-trifluoromethylated benzene derivatives **6l** in 69% as the major product (entry 4).

The cycloaddition of **1a** with various non-fluorinated diynes was also examined as shown in Scheme 3. Thus, treatment of 1.0 equiv. of **1a** with 1.0 equiv. of 1,7-octadiyne in the presence of 10 mol% of $RhCl_3 \cdot H_2O$ and 30 mol% of *i*-Pr_2NEt in toluene (1.0 M) at reflux temperature for 18 h afforded the corresponding benzene derivatives **7a** in only 15% yield. In this case, no starting CF_3–alkyne was detected at all. In order to improve the yield, several attempts were carried out; thus, the use of another rhodium catalyst, such as $[Rh(C_8H_{12})]BF_4$ and $RhCl(PPh_3)_3$, or changing the molecular ratio of the diyne, fluorinated alkyne and the catalyst. However, any significant improvement of the yield could not be observed at all. The use of diethyl bis(2-propyn-1-yl)malonate and bis(2-propyn-1-yl) *p*-toluenesulfonamide gave the corresponding benzene derivatives **8a** and **9a** in only 20 and 21% yield, respectively.



Scheme 3 [2+2+2] Cycloaddition of the trifluoromethylated alkyne **1a** with non-fluorinated diynes.

Next, our interest was directed towards the [2+2+2] cycloaddition of fluoroalkylated diynes and non-fluorinated alkynes. We selected fluoroalkylated bispropargyl ethers **10** as fluoroalkylated diynes and then attempted their synthesis. The usual etherification, such as Williamson synthesis, could not be applied for γ-fluoroalkylated propargyl alcohols. Thus, treatment of trifluoromethylated propargyl alcohol **11**, prepared according to the literature,[18] with NaH and propargyl bromide in THF led to a complex mixture. Any trace of the desired ether was not detected at all. After several attempts, we found that the etherification in the bi-phasic system using phase transfer catalyst gave the desired bispropargyl ether in good yields (Scheme 4). Thus, on treating γ-fluoroalkylated propargyl alcohol **11** with 1.5 equiv. each of propargyl bromide and NaOH in the presence of 5 mol% of tetrabutylammonium iodide in CH_2Cl_2–H_2O (v/v = 2 : 1) at room temperature for 5 d, the corresponding bis-propargyl ethers **10** were obtained in moderate to good yields.



a) Determined by ^{19}F NMR. Values in parentheses are of isolated yield.

Scheme 4 The synthesis of fluoroalkylated bispropargyl ether.

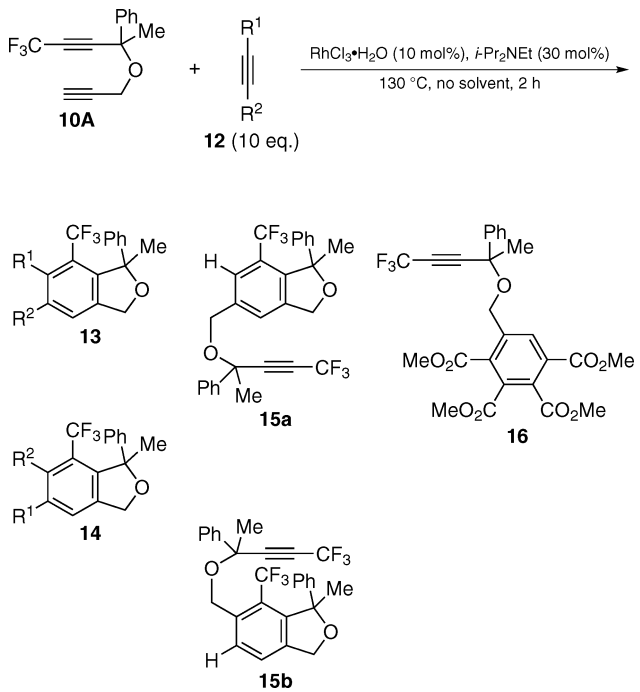
10D was very sensitive to silica gel as well as alumina, resulting in a very low isolated yield. **10E** and **10F** could not be completely separated from a small amount of byproduct. Therefore, **10E** and **10F**, which were not in pure form, were used for the next [2+2+2] cycloaddition without further purification.

With the above bis-propargyl ether, we investigated the [2+2+2] cyclization in detail (Table 5, Scheme 5). Thus, treatment of **10A** with 1.0 equiv. of diphenylacetylene in the presence of 10 mol% of $RhCl_3 \cdot H_2O$ and 30 mol% of *i*-Pr_2NEt in toluene (0.5 M) at reflux temperature for 18 h gave the desired adduct in only 12% (entry 1). In this case, the starting diyne was not detected at all. As shown in entry 2, increasing an amount of diphenylacetylene from 1 to 4 equiv. led to a dramatic improvement of the yield, the desired product being obtained in 32% yield. Furthermore, the use of 10 equiv. of diphenylacetylene increased the yield to 55% (entry 3). On the other hand, the cycloaddition with 4.0 equiv. of diphenylacetylene without solvent at 130 °C also gave the adduct in 60% yield (entry 4). Additionally, the adduct was afforded in 58% yield even when the reaction was carried out for only 2 h (entry 5). Finally, it was found that the reaction with

Table 5 [2+2+2] Cycloaddition of fluoroalkylated diyne **10A** and monoynes

Entry[a]	R^1	R^2	Product	Yield of **13**+**14** (%)[b]	[**13**] : [**14**]	Yield of **15a**+**15b** (%)[b]	[**15a**] : [**15b**]
1[c]	Ph	Ph	**a**	12	—	0	—
2[d]	Ph	Ph	**a**	32	—	0	—
3[e]	Ph	Ph	**a**	55	—	0	—
4[f]	Ph	Ph	**a**	60	—	0	—
5[g]	Ph	Ph	**a**	58	—	0	—
6	Ph	Ph	**a**	73 (68)	—	0	—
7	Pr	Pr	**b**	49 (31)	—	51	[77 : 23]
8	TMS	TMS	**c**	10	—	57	[70 : 30]
9	CO_2Me	CO_2Me	**d**	47 (35)[h]	—	0	—
10	H	Ph	**e**	99 (86)[i]	[71 : 29]	0	—
11	H	n-$C_{10}H_{21}$	**f**	87 (80)[i]	[79 : 21]	0	—
12[j]	H	TMS	**g**	16	—	46	[76 : 24]
13	Me	Ph	**h**	48	[60 : 40]	32	[81 : 19]

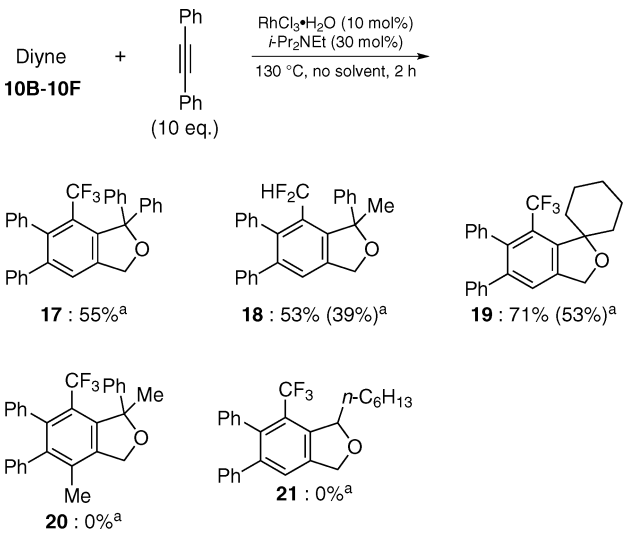
[a] Unless otherwise noted, the reaction with 10 equiv. of monoalkyne was carried out without solvent at 130 °C. [b] Determined by ^{19}F NMR. Values in parentheses are of isolated yield. Isomeric ratios in brackets are also determined by ^{19}F NMR. [c] Carried out using 1.0 equiv. of diphenylacetylene in 0.5 M toluene solution at the reflux temperature for 18 h. [d] Carried out using 4.0 equiv. of diphenylacetylene at the reflux temperature in 0.5 M toluene solution for 18 h. [e] Carried out in 0.5 M toluene solution at the reflux temperature for 18 h. [f] Carried out using 4.0 equiv. of diphenylacetylene for 18 h. [g] Carried out using 4.0 equiv. of diphenylacetylene. [h] 16 was obtained in 41% (^{19}F NMR yield) (isolated yield: 31%). [i] Values in parentheses are of combined yield of **13** + **14**. [j] Carried out in a sealed tube.



Scheme 5 [2+2+2] Cycloaddition of trifluoromethylated diyne **10A** with monoynes.

10 equiv. of diphenylacetylene without solvent at 130 °C for 2 h proceeded smoothly to give the corresponding benzene derivative **13** (**14**) in 73% yield (entry 6). With such reaction conditions, [2+2+2] cycloaddition using various non-fluorinated monoynes was investigated. The use of 4-octyne instead of diphenylacetylene had a significant effect on the outcome with **13** (and **14**) being obtained in only 49% yield (entry 7). In this case, **15a** and **15b**, formed *via* [2+2+2] cyclization of two molecules of **10A**, were obtained in 51% yield. Similarly, **15a** and **15b** were obtained in 57% yield in the case of bis(trimethylsilyl)acetylene (entry 8). In the case of dimethyl acetylenedicarboxylate, only the desired benzene derivatives were obtained in 47% yield (entry 9). As described in entries 10 and 11, terminal alkynes, such as phenyl acetylene and 1-decyne, were found to be very reactive, intermolecular cyclization products being obtained in high yields as an isomeric mixture,[19] though trimethylsilylacetylene was less reactive (entry 12). Additionally, 1-phenyl-1-propyne was also less reactive, **13** and **14** being afforded in only 48% yield, together with 32% of **15a** and **15b** (entry 13).

We also investigated the cycloaddition of other diynes **10** and diphenylacetylene as described in Scheme 6. **10B**, **10C**, and **10D** were found to be good substrates for the present reaction, the cycloaddition products **17**, **18**, **19** being obtained in good yields. Only in the case of **10B**, the byproducts **22**, **23** and **24** being obtained in 19, 8, and 16% yields, respectively (Fig. 1). The reactions of **10E** and **10F** failed to afford any product at all.



Scheme 6 [2+2+2] Cycloaddition of various fluoroalkylated diynes with diphenylacetylene.

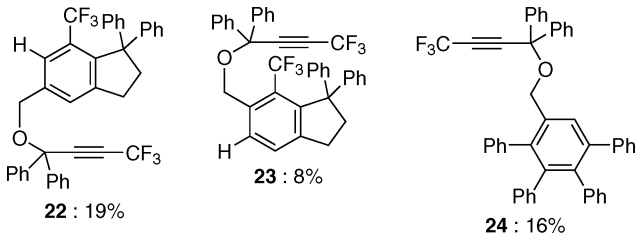
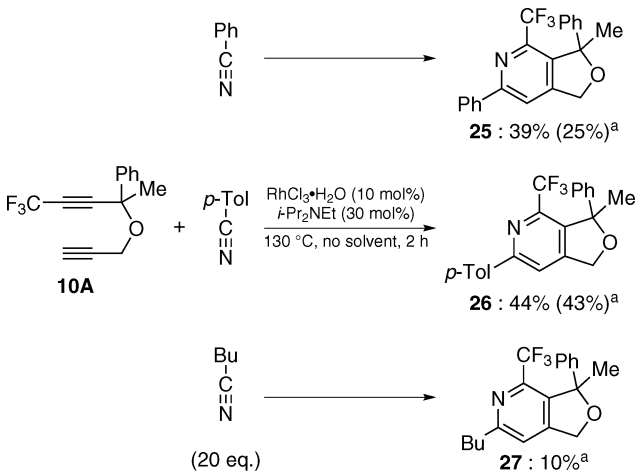


Fig. 1 Byproducts.

Finally, we attempted [2+2+2] cycloaddition of **10A** with various nitrile compounds as described in Scheme 7. Unfortunately, the cycloaddition under the same reaction conditions as in the reaction of **10A–E** and non-fluorinated monoynes proceeded sluggishly, the desired pyridine derivatives being obtained in poor yields. After several attempts, we found that treatment of **10A** with 20 equiv. of benzonitrile or toluonitrile in the presence of 10 mol% of $RhCl_3 \cdot H_2O$ and 30 mol% of *i*-Pr_2NEt at 130 °C for 2 h gave the desired adducts in 39% or 44% yield, respectively.[19,20] However, aliphatic nitrile was found to be much less reactive, the desired adduct being obtained in only 10% yield in the case of butyronitrile. Additionally, the same phenomenon was observed in the case of acetonitrile (yield: <10%).

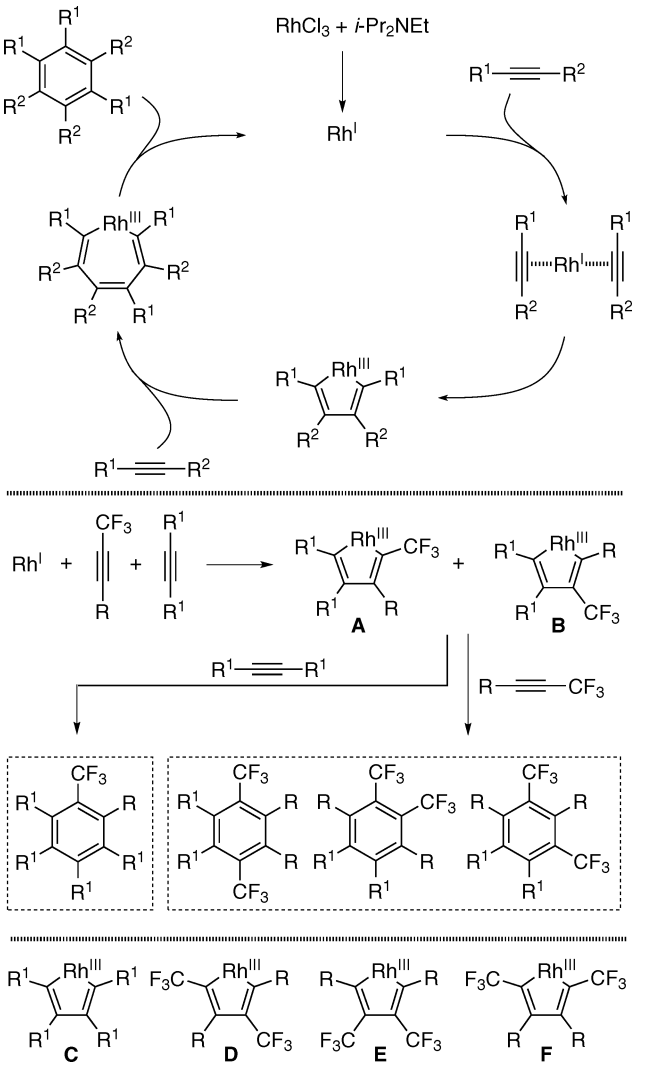


a) Determined by ^{19}F NMR. Values in parentheses are of isolated yield.

Scheme 7 The synthesis of various trifluoromethylated pyridine derivatives.

A plausible reaction mechanism is described in Scheme 8. First, $RhCl_3$ would be reduced by *i*-Pr_2NEt to produce a Rh(I) species. Thus generated electron-rich Rh(I) species might interact with two alkynes by strong π-back donation to form a rhodacyclopentadienyl complex. Then, the insertion of another alkyne to the complex may take place, followed by the subsequent reductive elimination, affording the corresponding cyclized product.

Considering that [2+2+2] cycloaddition of fluorinated alkynes (1.0 eq.) and non-fluorinated alkynes (2.0 eq.) gave the isomeric mixture of **5** and **6** in good yields (shown in Scheme 2), it is highly possible that the cycloaddition, except for trimerization, proceed *via* the rhodacycles **A** and **B**, not **C–F**. Thus, the rhodacycles **A** and **B**, which are produced *via* the coordination and the following oxidative addition of rhodium(I) into one molecule each of fluorinated and non-fluorinated alkyne, generates faster than



Scheme 8 A plausible reaction mechanism.

the other rhodacycle does, to react with another non-fluorinated alkyne and/or fluorinated alkyne, giving the corresponding mono- and/or bis(trifluoromethyl)benzene derivatives. In this case, the fact that a small amount of trimerization product is obtained, and that additionally **5** and **6** are produced in a ratio of an approximately 1 : 1, despite of the use of 2.0 equiv. of non-fluorinated alkynes, strongly suggest that fluorinated alkynes can coordinate with rhodium faster than non-fluorinated alkynes can.

The detailed reaction mechanism for the [2+2+2] cycloaddition as well as the regioselectivity in trimerization remains unclear at present, and an exact explanation for the whole mechanism must await further investigation.

In conclusion, we investigated the [2+2+2] cycloaddition of fluoroalkylated alkynes or fluoroalkylated bispropargyl ether with various non-fluorinated alkynes. Trimerization of fluoroalkylated alkynes took place smoothly to give the corresponding adducts in high yields. Additionally, the intermolecular cycloaddition of fluoroalkylated alkynes and non-fluorinated alkynes also proceeded smoothly to afford the mono- and bis(trifluoromethylated)benzene derivatives in good to high yields. The reaction of fluoroalkylated bispropargyl ether with non-

fluorinated alkynes or nitriles proceeded relatively smoothly to give the corresponding bicyclic materials in moderate to good yields.

Experimental

Typical procedure for the synthesis of 3,5,6-tris(4-chlorophenyl)-1,2,4-tris(trifluoromethyl)benzene (2a) and 2,4,6-tris(4-chlorophenyl)-1,3,5-tris(trifluoromethyl)benzene (3a) (trimerization)

To a suspension of $RhCl_3 \cdot 3H_2O$ (13 mg, 0.05 mmoL) in toluene (1.0 mL) were added *i*-Pr_2NEt (24 mg, 0.15 mmol) and 3,3,3-trifluoro-1-(4-chlorophenyl)-1-propyne (103 mg, 0.50 mmol), and then the mixture was stirred at reflux temperature for 18 h. After being cooled to room temperature, the residue was purified by column chromatography on silica gel to afford the inseparable isomeric mixture of fluoroalkylated benzene derivatives (281 mg, 0.43 mmol, 85% yield). Isomeric ratio = 84 : 16; HRMS (FAB) calcd for (M^+) $C_{27}H_{12}ClF_9$: 611.9874, Found 611.9861; ^{1}H NMR ($CDCl_3$) δ = 6.87–7.43 (m, 12H); **2a**: ^{19}F NMR ($CDCl_3$) δ = –51.52 (q, J = 16.2 Hz, 3F), –50.27 (q, J = 16.2 Hz, 3F), –48.36 (s, 3F); **3a**: ^{19}F NMR ($CDCl_3$) δ = –46.76 (s, 9F).

Typical procedure for the synthesis of 2-(4-chlorophenyl)-1-trifluoromethyl-3,4,5,6-tetraphenylbenzene (5a), 2,4-bis(4-chlorophenyl)-1,3-bis(trifluoromethyl)-5,6-diphenylbenzene, 2,3-bis(4-chlorophenyl)-1,4-bis(trifluoromethyl)-5,6-diphenylbenzene, and 3,6-bis(4-chlorophenyl)-1,2-bis(trifluoromethyl)-4,5-diphenylbenzene (6a)

The reaction was carried out under the reaction conditions similar to that in trimerization, except for the use of 0.5 eq. of 3,3,3-trifluoro-1-(4-chlorophenyl)-1-propyne and 1.0 eq. of diphenylacetylene. **2-(4-Chlorophenyl)-1-trifluoromethyl-3,4,5,6-tetraphenylbenzene (5a)**. Yield: 34%; m.p. 176–178 °C; HRMS (FAB) calcd for (M^+) $C_{37}H_{24}ClF_3$: 560.1514, Found 560.1519; ^{1}H NMR ($CDCl_3$) δ = 6.77–6.87 (m, 15H), 7.08–7.15 (m, 9H);^{13}C NMR ($CDCl_3$) δ = 125.66, 125.76, 125.87, 126.50, 126.56, 126.63, 126.78, 127.00 (q, J = 25.6 Hz), 127.06, 128.91 (q, J = 285.9 Hz), 130.04 (q, J = 1.7 Hz), 130.45, 130.79, 130.84, 131.42 (q, J = 1.6 Hz), 137.79, 138.78, 138.84 (q, J = 1.6 Hz), 138.93, 139.05, 139.25, 140.33 (q, J = 1.6 Hz), 142.50, 142.90, 144.51; ^{19}F NMR ($CDCl_3$) δ = –47.96 (s, 3F); IR (KBr) 1493, 1441, 1407, 1342, 1235, 1176, 1121, 806, 745, 697, 564 cm^{-1}. **2,4-Bis(4-chlorophenyl)-1,3-bis(trifluoromethyl)-5,6-diphenylbenzene, 2,3-bis(4-chlorophenyl)-1,4-bis(trifluoromethyl)-5,6-diphenylbenzene** and **3,6-bis(4-chlorophenyl)-1,2-bis(trifluoromethyl)-4,5-diphenylbenzene (6a).** Combined yield: 40%, Isomeric ratio = 38 : 15 : 47; HRMS (FAB) calcd for (M^+) $C_{32}H_{18}Cl_2F_6$: 586.0690, Found 586.0690; ^{1}H NMR ($CDCl_3$) δ = 6.87–7.43 (m, 18H); (Isomer 1): ^{19}F NMR ($CDCl_3$) δ = –47.61 (s, 3F), –47.44 (s, 3F); (Isomer 2): ^{19}F NMR ($CDCl_3$) δ = –50.33 (s, 6F); (Isomer 3): ^{19}F NMR ($CDCl_3$) δ = –49.01 (s, 6F).

Typical procedure for the synthesis of diethyl 6-(4-chlorophenyl)-5-trifluoromethyl-1*H*-indene-2,2(3*H*)-dicarboxylate (8a)

To a suspension of $RhCl_3 \cdot 3H_2O$ (13 mg, 0.05 mmol) in toluene (0.5 mL) were added *i*-Pr_2NEt (24 mg, 0.15 mmol) and 3,3,3-trifluoro-1-(4-chlorophenyl)-1-propyne (103 mg, 0.50 mmol), diethyl bis(2-propyn1yl)malonate (118 mg, 0.50 mmol). The mixture was stirred at reflux temperature for 18 h. After being cooled to room temperature, the residue was purified by column chromatography on silica gel to afford diethyl 6-(4-chlorophenyl)-5-trifluoromethyl-1*H*-indene-2,2(3*H*)-dicarboxylate (**8a**) in 20% ^{19}F NMR yield. HRMS (FAB) calcd for (M+H) $C_{22}H_{21}F_3ClO_4$: 441.1071, Found 440.1080; ^{1}H NMR ($CDCl_3$) δ = 1.30 (t, J = 7.2 Hz, 6H), 3.65 (s, 2H), 3.69 (s, 2H), 4.25 (q, J = 6.8 Hz, 4H), 7.13 (s, 1H), 7.24 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.58 (s, 1H); ^{13}C NMR ($CDCl_3$) δ = 13.97, 40.08, 40.26, 60.30, 61.98, 121,96 (q, J = 5.8 Hz), 124.10 (q, J = 273.6 Hz), 127.37 (q, J = 30.6 Hz), 127.67, 127.87; ^{19}F NMR ($CDCl_3$) δ = –57.02 (s, 3F); IR (KBr) 3467, 2982, 2318, 1906, 1732, 1597, 1485, 1297, 1135, 911 cm^{-1}.

Typical procedure for the synthesis of 5-trifluoromethyl-3-methyl-3,6,7-triphenyl-1,3-dihydroisobenzofuran (13a). To a suspension of $RhCl_3 \cdot 3H_2O$ (8 mg, 0.03 mmol) were added *i*-Pr_2NEt (14 mg, 0.09 mmol) and 4,4,4-trifluoro-1-methyl-1-phenyl-2-butyn-1-yl 2-propyn-1-yl ether (**10A**) (76 mg, 0.30 mmol), diphenylacetylene (0.530 g, 3.0 mmol). The mixture was stirred at 130 °C (bath temp.) for 2 h. After being cooled to room temperature, the residue was purified by column chromatography on silica gel to afford 5-trifluoromethyl-3-methyl-3,6,7-triphenyl-1,3-dihydroisobenzofuran (**13a**) in 68% isolated yield (88 mg, 0.20 mmol). m.p. 165–166 °C; HRMS (FAB) calcd for (M+Na) $C_{28}H_{21}F_3NaO$: 453.1449, Found 453.1442; ^{1}H NMR ($CDCl_3$) δ = 2.13 (s, 3H), 5.11 (d, J = 12.8 Hz, 1H), 5.16 (d, J = 12.4 Hz, 1H), 6.99–7.01 (m, 3H), 7.03–7.17 (m, 7H), 7.33–7.35 (m, 5H), 7.46 (s, 1H); ^{13}C NMR ($CDCl_3$) δ = 24.62 (q, J = 4.1 Hz), 69.91, 91.27, 123.78 (q, J = 276.9 Hz), 124.73 (q, J = 29.7 Hz), 125.72, 126.07, 126.67, 126.94, 127.50, 127.52, 128.04, 129.56, 130.51 (q, J = 1.7 Hz), 130.63 (q, J = 1.6 Hz), 137.91, 140.15 (q, J = 2.4 Hz), 140.41, 141.61, 142.89 (q, J = 2.2 Hz), 143.87 (q, J = 1.6 Hz), 144.06; ^{19}F NMR ($CDCl_3$) δ = –49.94 (s, 3F); IR (KBr) 2963, 2345, 1654, 1261, 1095 cm^{-1}.

Typical procedure for the synthesis of 6-(4-methylphenyl)-4-trifluorometyl-2-methyl-2-diphenyl-1,3-dihydrofuro[3,4-*c*]pyridine (26)

To a suspension of $RhCl_3 \cdot 3H_2O$ (8 mg, 0.03 mmol) were added *i*-Pr_2NEt (14 mg, 0.09 mmol) and 4,4,4-trifluoro-1-methyl-1-phenyl-2-butyn-1-yl 2-propyn-1-yl ether (**10A**) (76 mg, 0.30 mmol) and benzonitrile (689 mg, 6.0 mmol). The mixture was stirred at 130 °C (bath temp.) for 2 h. After being cooled to room temperature, the residue was purified by column chromatography on silica gel to afford 6-(4-methylphenyl)-4-trifluorometyl-2-methyl-2-diphenyl-1,3-dihydrofuro[3,4-*c*]pyridine (**26**) in 44% yield (47 mg, 0.13 mmol). ^{1}H NMR ($CDCl_3$) δ = 2.07 (s, 3H), 2.44 (s, 3H), 5.13 (d, J = 14.0 Hz, 1H), 5.18 (d, J = 14.0 Hz, 1H), 7.26–7.36 (m, 7H), 7.83 (s, 1H), 8.00 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ = 21.33, 24.74 (q, J = 2.4 Hz), 69.95, 89.26, 115.19, 121.28 (q, J = 275.2 Hz), 1256.31, 127.00, 127.99, 128.11, 129.66, 134.62, 137.67, 140.08, 141.83, 142.83, 153.99, 156.62; ^{19}F NMR ($CDCl_3$) δ = –63.68 (s, 3F); IR (neat) 2923, 2372, 1609, 1560, 1446, 1376, 1325, 1224, 1190, 1136, 1047 cm^{-1}.

References

1 For reviews, see: (*a*) C. Isanbor and D. O'Hagan, *J. Fluorine Chem.*, 2006, **127**, 303–319; (*b*) D. O'Hagan and H. S. Rzepa, *Chem. Commun.*, 1997, 645–652.

2 M. A. McClinton and D. A. McClinton, *Tetrahedron*, 1992, **48**, 6555–6666.

3 For reviews, see: (*a*) T. Shibata and K. Tsuchikama, *Org. Biomol. Chem.*, 2008, **6**, 1317–1323; (*b*) S. Kotha, E. Brahmachary and K. Lahiri, *Eur. J. Org. Chem.*, 2005, 4741–4767; (*c*) V. Gandon, C. Aubert and M. Malacria, *Chem. Commun.*, 2006, 2209–2217; (*d*) B. R. Galan and T. Rovis, *Angew. Chem., Int. Ed.*, 2009, **48**, 2830–2834.

4 (*a*) H. A. Duong and M. J. Cross Louie, *J. Am. Chem. Soc.*, 2004, **126**, 11438–11439; (*b*) Y. Sato, T. Nishimata and M. Mori, *J. Org. Chem.*, 1994, **59**, 6133–6135.

5 (*a*) G. Nishida, K. Noguchi, M. Hirano and K. Tanaka, *Angew. Chem., Int. Ed.*, 2008, **47**, 3410–3413; (*b*) K. Tanaka, Y. Otake, H. Sagae, K. Noguchi and M. Hirano, *Angew. Chem., Int. Ed.*, 2008, **47**, 1312–1316; (*c*) G. Nishida, K. Noguchi, M. Hirano and K. Tanaka, *Angew. Chem., Int. Ed.*, 2007, **46**, 3951–3954; (*d*) K. Tanaka, K. Takeishi and K. Noguchi, *J. Am. Chem. Soc.*, 2006, **128**, 4586–4587; (*e*) P. A. Evans, K. W. Lai and J. R. Sawyer, *J. Am. Chem. Soc.*, 2005, **127**, 12466–12467; (*f*) K. Tanaka, G. Nishida, A. Wada and K. Noguchi, *Angew. Chem., Int. Ed.*, 2004, **43**, 6510–6512; (*g*) K. Tanaka and K. Shirasaka, *Org. Lett.*, 2003, **5**, 4697–4699; (*h*) H. Kinoshita, H. Shinokubo and K. Oshima, *J. Am. Chem. Soc.*, 2003, **125**, 7784–7785.

6 S. Saito, T. Kawasaki, N. Tsuboya and Y. Yamamoto, *J. Org. Chem.*, 2001, **66**, 796–802.

7 (*a*) Y. Yamamoto, K. Hattori and H. Nishiyama, *J. Am. Chem. Soc.*, 2006, **128**, 8336–8340; (*b*) V. Cadierno, S. E. García-Garrido and J. Gimeno, *J. Am. Chem. Soc.*, 2006, **128**, 15094–15095; (*c*) Y. Yamamoto, K. Kinpara, T. Saigoku, H. Takagishi, S. Okuda, H. Nishiyama and K. Itoh, *J. Am. Chem. Soc.*, 2005, **127**, 605; (*d*) Y. Yamamoto, J. Ishii, H. Nishiyama and K. Itoh, *J. Am. Chem. Soc.*, 2004, **126**, 3712–3713; (*e*) J. A. Varela, L. Castedo and C. Saß, *J. Org. Chem.*, 2003, **68**, 8595–8598.

8 (*a*) A. Gutnov, B. Heller, C. Fischer, H.-J. Drexler, A. Spannennberg, B. Sundermann and C. Sundermann, *Angew. Chem., Int. Ed.*, 2004, **43**, 3795–3797; (*b*) V. Gandon, D. Leca, T. Aechtner, K. P. C. Vollhardt, M. Malacria and C. Aubert, *Org. Lett.*, 2004, **6**, 3405–3407.

9 (*a*) F. T. Ladipo, V. Sarveswaran, J. V. Kingston, R. A. Huyck, S. Y. Bylikin, S. D. Carr, R. Watts and S. Parkin, *J. Organomet. Chem.*, 2004, **689**, 502–514; (*b*) O. V. Ozerov, B. O. Patrick and F. T. Ladipo, *J. Am. Chem. Soc.*, 2000, **122**, 6423–6431.

10 (*a*) Y. Sato, T. Nishimata and M. Mori, *J. Org. Chem.*, 1994, **59**, 6133–6135; (*b*) N. Kaneta, T. Hirai and M. Mori, *Chem. Lett.*, 1995, 627–628.

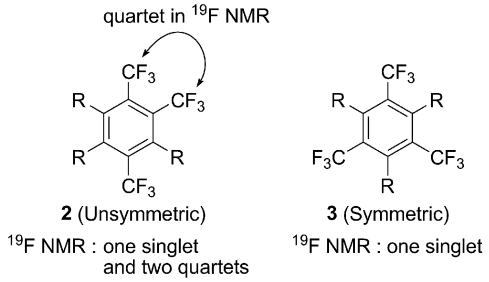
11 (*a*) T. Shibata and K. Tsuchikama, *Chem. Commun.*, 2005, 6017–6019; (*b*) T. Shibata, T. Fujimoto, K. Yokota and K. Takagi, *J. Am. Chem. Soc.*, 2004, **126**, 8382–8383; (*c*) T. Shibata, K. Tsuchikama and M. Otsuka, *Tetrahedron: Asymmetry*, 2006, **17**, 614–619.

12 (*a*) H. Tsuji, K. Yamagata, T. Fujimoto and E. Nakamura, *J. Am. Chem. Soc.*, 2008, **130**, 7792–7793.

13 There have been several reports on the synthesis of fluoroalkylated benzene or pyridine derivatives: (*a*) K. Tanaka, H. Hara, G. Nishida and M. Hirano, *Org. Lett.*, 2007, **9**, 1907–1910; (*b*) S. Saito, T. Tanaka, T. Koizumi, N. Tsuboya, H. Itagaki, T. Kawasaki, S. Endo and Y. Yamamoto, *J. Am. Chem. Soc.*, 2000, **122**, 1810–1811; (*c*) S. Arimitsu, B. Fernández, C. del Pozo, S. Fustero and G. B. Hammond, *J. Org. Chem.*, 2008, **73**, 2656–2661.

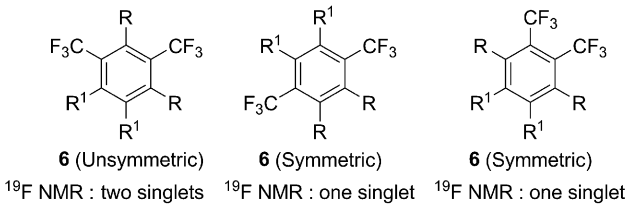
14 Various fluoroalkylated alkynes were prepared according to the literature: (*a*) T. Konno, A. Morigaki, K. Ninomiya, T. Miyabe and T. Ishihara, *Synthesis*, 2008, 564–572; (*b*) T. Konno, G. Nagai and T. Ishihara, *J. Fluorine Chem.*, 2006, **127**, 510–518; (*c*) T. Konno, J. Chae, M. Kanda, G. Nagai, K. Tamura, T. Ishihara and H. Yamanaka, *Tetrahedron*, 2003, **59**, 7571–7580; (*d*) B. C. Hamper, *Org. Synth.*, 1991, **70**, 246–253.

15 The determination of the structure for the compounds **2** and **3** was carried out based on ^{1}H NMR and ^{19}F NMR. Especially, in ^{19}F NMR were observed two pairs of signal peaks; one is three sets of peaks, one singlet and two quartet peaks with an integration ratio of 1 : 1 : 1 and the other is only one singlet peak. This fact strongly suggests that the former is the asymmetric compound **2** and the latter is the symmetric compound **3**. The detail is described in the ESI† .



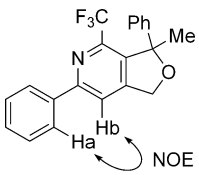
16 The similar rhodium-catalyzed cycloaddition has been reported thus far. See: (*a*) K. Yoshida, I. Morimoto, K. Mitsudo and H. Tanaka, *Tetrahedron*, 2008, **64**, 5800–5807; (*b*) K. Yoshida, I. Morimoto, K. Mitsudo and H. Tanaka, *Chem. Lett.*, 2007, **36**, 998–999.

17 The determination of the structure for the compounds **6** was carried out based on ^{1}H NMR and ^{19}F NMR. Especially, in ^{19}F NMR were observed three pairs of signal peaks; the first one is two sets of singlet peaks with an integration ratio of 1 : 1 and the others are only one singlet peak. This fact strongly suggests that the first is the asymmetric compound (Isomer 1) and the others are the symmetric compounds (Isomer 2 and 3). The exception is in the case of the reaction of **1b**; three sets of singlet peaks were observed because all of **6b** is symmetric. The detail is described in the ESI† .



18 For the preparation of various fluoroalkylated propargyl alcohols, see: (*a*) T. Yamazaki, K. Mizutani and T. Kitazume, *J. Org. Chem.*, 1995, **60**, 6046–6056; (*b*) K. Mizutani, T. Yamazaki and T. Kitazume, *J. Chem. Soc., Chem. Commun.*, 1995, 51–52.

19 The structure of **25** was determined on the basis of the NOESY experiment. Thus, the cross peak between *ortho* proton Ha and vinylic proton Hb, as described below, could be observed, strongly suggesting that [2+2+2] cycloaddition of trifluoromethylated diyne with nitriles proceeds, avoiding a steric repulsion between a CF_3 group and a substituent (Ph, *p*-Tol, Bu) in the nitrile to afford 2-CF_3 pyridine derivatives, not 3-CF_3 ones. This hypothesis could be applied for the determination of the compounds **13** and **14**.



20 We have done the cycloaddition of fluoroalkylated diyne **10A** with benzonitrile under the various reaction conditions; thus changing the amount of benzonitrile, the concentration, and so on. However, the carbocyclic compunds, **15a** and **15b** were given as byproducts, in addition to the desired pyridine derivatives. Even when the best yield of **25** was obtained, **15a** and **15b** were afforded in 52% combined yield in a ratio of 56 : 44.

