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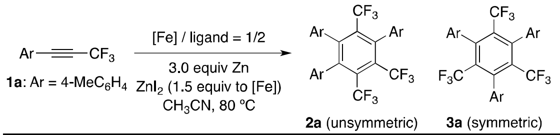
Iron-catalyzed [2+2+2] intermolecular cycloaddition of trifluoromethyl group substituted unsymmetrical internal alkynes afforded the corresponding the trifluoromethyl group substituted benzene derivatives in high yield with excellent selectivity.

Trifluoromethyl group (-CF_3) substituted benzene derivatives are important structural motifs due to its interesting biological activities.[1] One of the most efficient synthetic methods of benzene derivatives is transition metal-catalyzed [2+2+2] cycloaddition of alkynes.[2] Although various types of transition metal catalysts and substrates have been investigated to the inter- and intramolecular reactions,[2] iron-catalyzed [2+2+2] intermolecular cycloadditions have remained challenging topics.[3,4] To the best of our knowledge, there are no example of the CF_3-substituted benzene derivatives were produced via iron-catalyzed [2+2+2] cycloaddition.[2a,5] Previously, we reported that ruthenium-catalyzed [2+2+2] cyclotrimerization of CF_3-substituted internal alkynes.[5c] Here, we report the development of iron-catalyzed [2+2+2] cycloaddition of CF_3-substituted internal alkynes. The protocol gave access to arenes bearing CF_3 of important structural motifs.[1]

We initially examined the trimerization of CF_3-substituted unsymmetrical internal alkyne **1a** in the presence of iron catalyst under various reaction conditions (Table 1). The cyclotrimerization of CF_3-alkyne **1a** using FeI_2 (20 mol%) with DPPP as a ligand under Zn and ZnI_2 in CH_3CN at 80 °C for 12 h led to the corresponding CF_3-substituted benzene **2a** in 66% yield with a 92% regioselectivity (entry 1). The trimerization using $FeCl_2$ gave the desired product **2a** in 79% yield with a 94% regioselectivity (entry 2). Replacing $FeCl_2$ with $Fe(OTf)_2$ or $FeCl_3$, the decrease of desired product was observed (entries 3 and 4).[6] It was found that the cyclotrimerization of **1a** with 5 mol % of $FeCl_2$ for 36 h led to the desired product in 87% yield with a 95% regioselectivity without formation of byproducts (entry 5). The yield from trimerization **1a** was insufficient in the absence of ZnI_2 (entry 6). The combination of Zn/ZnI_2 is assumed to play an important role to promote such a process.[7] The reaction with DPPE, DPPB, or PPh_3 as a ligand resulted in lower yield of the desired product (entries 7-9). The catalytic amount of Zn was not effective in the reaction. The use of 3.0 equiv of Zn was necessary for the efficient cyclotrimerization.

Table 1. Iron-catalyzed Cyclotrimerization of 1-(4-Methyl-phenyl)-3,3,3-trifluoropropyne (**1a**)



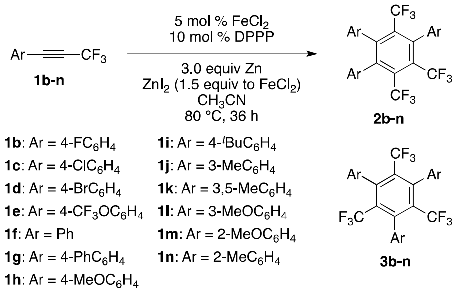
entry	[Fe] (mol %)	ligand	time (h)	yield (%)[a]	**2a**:**3a**[b]
1	FeI_2 (20)	DPPP	12	66	92:8
2	$FeCl_2$ (20)	DPPP	12	79	94:6
3	$Fe(OTf)_2$ (20)	DPPP	12	68	95:5
4	$FeCl_3$ (20)	DPPP	12	49	93:7
5	$FeCl_2$ (5)	DPPP	36	87	95:5
6[c]	$FeCl_2$ (5)	DPPP	36	10	95:5
7	$FeCl_2$ (5)	DPPE	36	21	94:6
8	$FeCl_2$ (5)	DPPB	36	<2	N.D.
9	$FeCl_2$ (5)	PPh_3[d]	36	<2	N.D.

[a] Isolated yield of **2a** and **3a**. [b] Ratio was determined by ^1H and/or ^{19}F NMR of the crude materials. [c] Without ZnI_2. [d] 20 mol%.

We next examined the iron-catalyzed [2+2+2] cyclotrimerization of various CF_3-alkynes **1b**-**m** under the optimized reaction conditions (Table 2). For the reaction of **1b**-**e**, which has an electron-withdrawing group at the *para*-position on the benzene ring, the corresponding CF_3-benzene derivatives **2b**-**e** were formed in up to

96% isolated yield with high regioselectivity (entries 1-4). In contrast, the cycloaddititión using **1h** and **1i** having an electron-donating group at the *para*-position on the benzene ring gave **2h** and **2i** with 93% regioselectivity in 73% and 65% yield, respectively (entries 7 and 8). The cycloaddition of **1j-l** also afforded **2j-l** in up to 92% isolated yield with 96% regioselectivity (entries 9-11). For the reaction of **1m** and **1o** bearing a functional group at the *ortho*-position on the benzene ring was not effective to give a small amount of products (entry 12 and 13). When the reaction was performed using 1-phenyl-1-propyne, 1-phenyl-2-trimethylsilyl acetylene, or ethyl phenyl propiolate, the trimerization did not proceed in the similar conditions.[8] A plausible mechanism is depicted in Scheme 1. The coordination of two CF_3-alkynes **1** to the Fe (0) complex is followed by an oxidative cyclometalation to give the ferracyclopentadiene **I**.[4,7] An additional insertion of CF_3-alkyne **1** and reductive elimination subsequently afford the regioselective cyclotrimerization product **2**.

Table 2. Iron-catalyzed Cyclotrimerization of CF_3-Alkynes **1b-n**

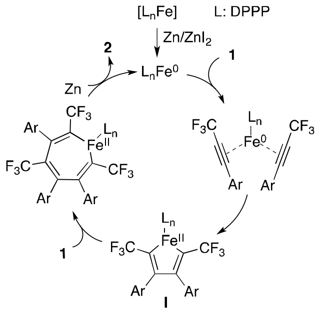


1b: Ar = 4-FC_6H_4
1c: Ar = 4-ClC_6H_4
1d: Ar = 4-BrC_6H_4
1e: Ar = 4-$CF_3OC_6H_4$
1f: Ar = Ph
1g: Ar = 4-PhC_6H_4
1h: Ar = 4-$MeOC_6H_4$
1i: Ar = 4-$^tBuC_6H_4$
1j: Ar = 3-MeC_6H_4
1k: Ar = 3,5-MeC_6H_4
1l: Ar = 3-$MeOC_6H_4$
1m: Ar = 2-$MeOC_6H_4$
1n: Ar = 2-MeC_6H_4

Entry	**1**	yield (%)[a]	**2**:**3**[b]
1	**1b**	96	95:5
2	**1c**	96	95:5
3[c,d]	**1d**	86	94:6
4	**1e**	80	94:6
5	**1f**	79	95:5
6[c]	**1g**	62	93:7
7[d]	**1h**	73	93:7
8[c]	**1i**	65	93:7
9	**1j**	92	96:4
10	**1k**	83	96:4
11	**1l**	84	96:4
12	**1m**	<2	N.D.
13	**1n**	<2	N.D.

[a] Isolated yield of **2** and **3**. [b] Ratio was determined by ^1H and/or ^{19}F NMR of the crude materials. [c] 60 h. [d] $FeCl_2$ (7.5 mol%), DPPP (15 mol%), ZnI_2 (11.3 mol%).

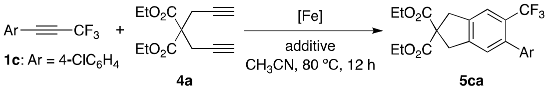
Scheme 1. Proposed Mechanism



Furthermore, our reaction conditions of the iron-catalyzed cyclotrimerization using CF_3-alkynes were applied to the [2+2+2] cycloaddition of CF_3-alkyne **1c** with 1,6-diyne **4a** (Table 3). Under the similar conditions, treatment of **1c** with **4a** afforded the corresponding CF_3-benzene **5ca** in 17% yield (entry 1). The reaction without a ligand increased the yield of the desired product to give **5ca** in 75% yield (entry 2). We were pleased to find that the reaction of **1c** with **4a** under air conditions successfully promoted the formation of **5ca** in 90% yield (entry 3).[9] No reaction was observed in 40 mol % of zinc (entry 4).[10] It should be noted that no reaction was observed in the absence of iron catalyst (entry 9).

Next, the cycloaddition of CF_3-alkynes **1** with 1,6-diynes **4** was performed in the optimized reaction conditions (Table 4). The reaction of **1a** and **1h** bearing an electron-donating group at the *para*-position on the benzene ring with **4a** gave the corresponding CF_3-benzene derivative **5aa** and **5ha** in 92% and 94% yield, respectively (entries 1 and 5). For the reaction of **1c** or **1n**, which has an electron-withdrawing group at the *para*-position on the benzene ring with **4a**, cycloadduct **5ca** and **5na** was formed in 90% and 94% yield, respectively. (entries 2 and 8). The carbocyclization of **1j** bearing an electron-donating group at the *meta*-position on the benzene ring with **4a** afforded **5ja** in 88% yield. The cycloaddtion of **1m** bearing an electron-donating group at the *ortho*-position on the benzene ring took place to give **5ja** in 82% yield. The reaction of **1h** with various 1,6-diynes **4b-e** proceeded in the similar conditions to afford **5hb-e** in up to 97% isolated yield.

Table 3. Iron-catalyzed [2+2+2] Carbocyclization of 1-(4-Chlorophenyl)-3,3,3-trifluoropropyne (**1c**) with 1,6-Diyne **4a**[a]

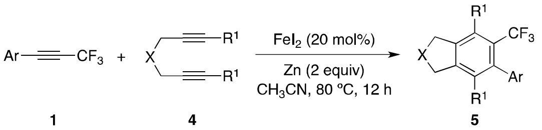


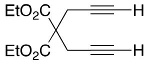
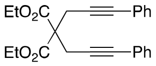
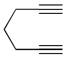
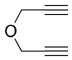
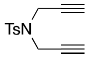
entry	[Fe] (mol %)	additive (mol %)	yield (%)[b]
1[c]	$FeCl_2$ (5)	Zn/ZnI_2 (300/7.5)	17
2	FeI_2 (20)	Zn (200)	75
3	FeI_2 (20)	Zn (200)	90
4	FeI_2 (20)	Zn (40)	0
5	$FeCl_2$ (20)	Zn (200)	83
6	$FeBr_2$ (20)	Zn (200)	<1
7	$Fe(OTf)_2$ (20)	Zn (200)	0
8	$FeCl_3$ (20)	Zn (200)	67
9	–	Zn (200)	0

[a] Under air. [b] Isolated yield. [c] DPPP (10 mol%), CH_3CN (0.3 mL), under nitrogen.

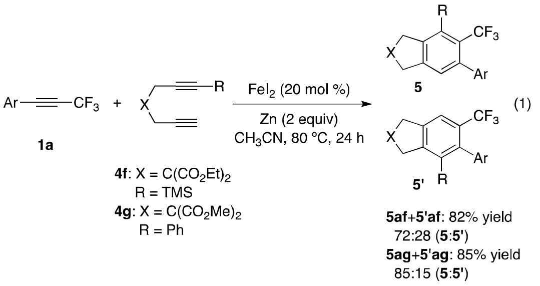
We also performed the iron-catalyzed [2+2+2] carbocyclization of CF_3-alkyne with unsymmetrical 1,6-diynes (eq 1). The cycloaddition reaction of CF_3-alkyne **1a** with unsymmetrical 1,6-diyne **4f** gave cycloadduct **5af** and **5'af** in 82% yield as a 72:28 (**5**:**5'**) mixture of regioisomers. The cycloaddition of **1a** with **4g** afforded **5ag** and **5'ag** in 85% yield as a 85:28 (**5**:**5'**) mixture of regioisomers. The structure of major product was confirmed in X-ray analysis of **5ag** (See supporting information). The regioselectivity suggests that the iron-catalyzed cycloaddition of CF_3-alkyne with 1,6-diyne follows a similar mechanism to that of well-established mechanism.[4] A plausible mechanism is depicted in Scheme 2. The coordination of 1.6-diyne **4** to the Fe (0) complex is followed by an oxidative cyclometalation to give the ferracyclopentadiene **II**. Insertion of CF_3-alkyne **1** and reductive elimination subsequently afford the cycloadduct **5**. In the carbocyclization, CH_3CN may act as a ligand.[11]

Table 4. Iron-catalyzed [2+2+2] Carbocyclization of CF_3-Alkynes **1** with Symmetrical Diynes **4**[a]

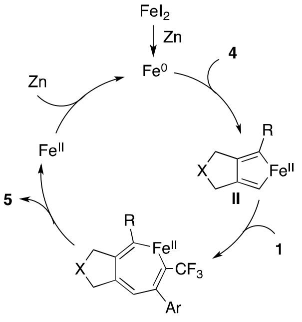


Entry	1	4	yield (%)[b]
1	**1a**: Ar = 4-MeC_6H_4	 **4a**	92
2	**1c**: Ar = 4-ClC_6H_4	**4a**	90
3	**1f**: Ar = Ph	**4a**	92
4	**1g**: Ar = 4-PhC_6H_4	**4a**	90
5	**1h**: Ar = 4-$MeOC_6H_4$	**4a**	94
6	**1j**: Ar = 3-MeC_6H_4	**4a**	88
7	**1m**: Ar = 2-$MeOC_6H_4$	**4a**	82
8	**1n**: Ar = 4-$CF_3C_6H_4$	**4a**	94
9[c]	**1h**	 **4b**	97
10[d]	**1h**	 **4c**	79
11[c]	**1h**	 **4d**	75
12[e]	**1h**	 **4e**	76

[a]Under air. [b]Isolated yield. [c]24 h. [d]FeI_2 (25 mol%). [e]48 h.



Scheme 2. Proposed Mechanism



Conclusions

We demonstrated the iron-catalyzed [2+2+2] intermolecular cyclotrimerization of trifluoromethyl-substituted internal alkynes to give the corresponding trifluoromethylated benzene derivatives in high yield with excellent regioselectivity. We also succeeded in the iron-catalyzed [2+2+2] carbocyclization of the CF_3-alkyne with 1,6-diynes. A key intermediate in the selective iron-catalyzed [2+2+2] cycloadditions would be a ferracyclopentadiene intermadiate.

Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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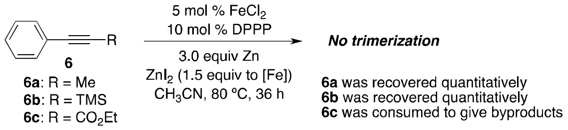

9 The reaction under O_2 atmosphere did not proceed in the similar conditions.

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11 In the carbocyclization other solvents such as DMF, dioxane, toluene, THF, and dichloroethane led to trace of desired product or no reaction.