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# Iron-catalyzed [2 + 2 + 2] cycloaddition of trifluoromethyl group substituted unsymmetrical internal alkynes<sup>†</sup>

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3,3,3-trifluoropropyne (1a)

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

Trifluoromethyl group (-CF<sub>3</sub>) substituted benzene derivatives are important structural motifs due to their interesting biological activities.1 One of the most efficient synthetic methods of benzene derivatives is transition metal-catalyzed  $\begin{bmatrix} 2 + 2 + 2 \end{bmatrix}$ cycloaddition of alkynes.<sup>2</sup> Although various types of transition metal catalysts and substrates have been investigated for interand intramolecular reactions,<sup>2</sup> iron-catalyzed [2 + 2 + 2] intermolecular cycloadditions have remained a challenging topic.<sup>3,4</sup> To the best of our knowledge, there are no examples of CF<sub>3</sub>substituted benzene derivatives that were produced via ironcatalyzed [2 + 2 + 2] cycloaddition.<sup>2a,5</sup> Previously, we reported ruthenium-catalyzed [2 + 2 + 2] cyclotrimerization of CF<sub>3</sub>substituted internal alkynes.<sup>5c</sup> Here, we report the development of iron-catalyzed [2 + 2 + 2] cycloaddition of CF<sub>3</sub>-substituted internal alkynes. The protocol gave access to arenes bearing the CF<sub>3</sub> group as important structural motifs.<sup>1</sup>

We initially examined the trimerization of CF<sub>3</sub>-substituted unsymmetrical internal alkyne **1a** in the presence of iron catalyst under various reaction conditions (Table 1). The cyclotrimerization of CF<sub>3</sub>-alkyne **1a** using FeI<sub>2</sub> (20 mol%) with DPPP as a ligand under Zn and ZnI<sub>2</sub> in CH<sub>3</sub>CN at 80 °C for 12 h led to the corresponding CF<sub>3</sub>-substituted benzene **2a** in 66% yield with a 92% regioselectivity (entry 1). The trimerization using FeCl<sub>2</sub> gave the desired product **2a** in 79% yield with a 94% regioselectivity (entry 2). Replacing FeCl<sub>2</sub> with Fe(OTf)<sub>2</sub> or FeCl<sub>3</sub>, the decrease of desired product was observed (entries 3 and 4).<sup>6</sup> 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.<sup>7</sup> The reaction with DPPE, DPPB, or PPh<sub>3</sub> 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.

We next examined the iron-catalyzed [2 + 2 + 2] cyclotrimerization of various CF<sub>3</sub>-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<sub>3</sub>-benzene derivatives **2b–e** were formed in up to 96% isolated yield with high

Table 1 Iron-catalyzed cyclotrimerization of 1-(4-methyl-phenyl)-

[Fe] / ligand = 1/2 3.0 equiv Zn **1a**: Ar =  $4 \cdot MeC_6H_4$  ZnI<sub>2</sub> (1.5 equiv to [Fe]) CH3CN, 80 °C 2a (unsymmetric) 3a (symmetric)  $2a: 3a^{b}$ Entry [Fe] (mol%) Ligand Time (h) Yield<sup>a</sup> (%) FeI<sub>2</sub> (20) DPPP 66 92:812 1 2 FeCl<sub>2</sub> (20) DPPP 12 79 94:6 3 Fe(OTf)<sub>2</sub> (20) DPPP 12 68 95:54 FeCl<sub>3</sub> (20) DPPP 1249 93:7 DPPP  $FeCl_2(5)$ 5 36 87 95:5 6<sup>*c*</sup> DPPP  $FeCl_2(5)$ 10 95:5 36 7  $FeCl_2(5)$ DPPE 36 21 94:6 8  $FeCl_2(5)$ DPPB 36 <2 N.D.  $FeCl_2(5)$  $PPh_3^d$ 9 36 <2N.D.

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

CF<sub>3</sub>

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Table 2 Iron-catalyzed cyclotrimerization of CF3-alkynes 1b-n



Entry	1	Yield <sup><i>a</i></sup> (%)	$2:3^{b}$
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 <sup><i>c</i></sup>	1g	62	93:7
7 <sup>d</sup>	1h	73	93:7
8 <sup>c</sup>	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.

<sup>*a*</sup> Isolated yield of **2** and **3**. <sup>*b*</sup> Ratio was determined by <sup>1</sup>H and/or <sup>19</sup>F NMR of the crude materials. <sup>*c*</sup> 60 h. <sup>*d*</sup> FeCl<sub>2</sub> (7.5 mol%), DPPP (15 mol%), ZnI<sub>2</sub> (11.3 mol%).

regioselectivity (entries 1-4). In contrast, the cycloaddition using 1h and 1i having an electron-donating group at the paraposition 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 CF3-alkyne 1 and reductive elimination subsequently afford the regioselective cyclotrimerization product 2.

Furthermore, our reaction conditions of the iron-catalyzed cyclotrimerization using CF<sub>3</sub>-alkynes were applied to the [2 + 2 + 2] cycloaddition of CF<sub>3</sub>-alkyne **1c** with **1**,6-diyne **4a** (Table 3). Under the similar conditions, treatment of **1c** with **4a** afforded the corresponding CF<sub>3</sub>-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





Scheme 1 Proposed mechanism.

3).<sup>9</sup> No reaction was observed in 40 mol% of zinc (entry 4).<sup>10</sup> It should be noted that no reaction was observed in the absence of iron catalyst (entry 9).

Next, the cycloaddition of CF<sub>3</sub>-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<sub>3</sub>-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% vield. The cycloaddition 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.

We also performed the iron-catalyzed [2 + 2 + 2] carbocyclization of CF<sub>3</sub>-alkyne with unsymmetrical 1,6-diynes (eqn 1). The cycloaddition reaction of CF<sub>3</sub>-alkyne **1a** with unsymmetrical

Table 3Iron-catalyzed [2 + 2 + 2] carbocyclization of 1-(4-chlor-<br/>ophenyl)-3,3,3-trifluoropropyne (1c) with 1,6-diyne  $4a^{\alpha}$ 

	Ar $\longrightarrow$ CF <sub>3</sub> + EtO <sub>2</sub> C 1c: Ar = 4-ClC <sub>6</sub> H <sub>4</sub> $EtO_2$ C 4a	EIO <sub>2</sub> C additive CH <sub>3</sub> CN, 80 °C, 12 h EIO <sub>2</sub> C EIO <sub>2</sub> C	CF <sub>3</sub> Ar
Entry	[Fe] (mol%)	Additive (mol%)	Yield <sup>b</sup> (%)
1 <sup><i>c</i></sup>	$\operatorname{FeCl}_2(5)$	Zn/ZnI <sub>2</sub> (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

<sup>a</sup> Under air. <sup>b</sup> Isolated yield. <sup>c</sup> DPPP (10 mol%), CH<sub>3</sub>CN (0.3 mL), under nitrogen.

Table 4  $\,$  Iron-catalyzed [2 + 2 + 2] carbocyclization of CF3-alkynes 1 with symmetrical diynes  $4^a$ 



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 ESI†). The regiose-lectivity suggests that the iron-catalyzed cycloaddition of CF<sub>3</sub>-



Scheme 2 Proposed mechanism.

alkyne with 1,6-diyne follows a similar mechanism to that of well-established mechanism.<sup>4</sup> 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.<sup>11</sup>



#### 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<sub>3</sub>-alkyne with 1,6-diynes. A key intermediate in the selective iron-catalyzed [2 + 2 + 2] cycloadditions would be a ferracyclopentadiene intermediate.

### Notes and references

- (a) K. Müller, C. Faeh and F. Diederich, Science, 2007, 317, 1881–1886; (b) W. K. Hagmann, J. Med. Chem., 2008, 51, 4359–4369; (c) C. Isanbor and D. O'Hagan, J. Fluorine Chem., 2006, 127, 303–319; (d) D. O'Hagan and H. S. Rzepa, Chem. Commun., 1997, 645–652.
- 2 (a) T. Konno, Synlett, 2014, 25, 1350–1370; (b) B. R. Galan and T. Rovis, Angew. Chem., Int. Ed., 2009, 48, 2830–2834; (c)
  V. Gandon, C. Aubert and M. Malacria, Chem. Commun., 2006, 2209–2217; (d) P. R. Chopade and J. Louie, Adv. Synth. Catal., 2006, 348, 2307–2327; (e) S. Kotha, E. Brahmachary and K. Lahiri, Eur. J. Org. Chem., 2005, 4741–4767; (f) S. Saito and Y. Yamamoto, Chem. Rev., 2000, 100, 2901–2915; (g) M. Lautens, W. Klute and W. Tam, Chem. Rev., 1996, 96, 49–92.
- 3 (a) C. Wang and B. Wan, Chin. Sci. Bull., 2012, 57, 2338–2351;
  (b) X. Bu, Z. Zhang and X. Zhou, Organometallics, 2010, 29, 3530–3534;
  (c) C. Breschi, L. Piparo, P. Pertici, A. M. Caporusso and G. Vitulli, J. Organomet. Chem., 2000, 607, 57–63;
  (d) Y. Liu, X. Yan, N. Yang and C. Xi, Catal. Commun., 2011, 12, 489–492;
  (e) B. R. D'Souza, T. K. Lane and J. Louie, Org. Lett., 2011, 13, 2936–2939;
  (f) N. Saino, D. Kogure, K. Kase and S. Okamoto, J. Organomet. Chem., 2006, 691, 3129–3136;
  (g) N. Saino, D. Kogure and S. Okamoto, Org. Lett., 2005, 7, 3065–3067.

- 4 (*a*) C. Wang, X. Li, F. Wu and B. Wan, *Angew. Chem., Int. Ed.*, 2011, **50**, 7162–7166; (*b*) C. Wang, D. Wang, F. Xu, B. Pan and B. Wan, *J. Org. Chem.*, 2013, **78**, 3065–3072; (*c*) T. K. Lane, B. R. D'Souza and J. Louie, *J. Org. Chem.*, 2012, **77**, 7555–7563.
- 5 (a) C. Müller, R. J. Lachicotte and W. D. Jones, Organometallics, 2002, 21, 1975–1981; (b) T. Konno, K. Moriyasu, R. Kinugawa and T. Ishihara, Org. Biomol. Chem., 2010, 8, 1718–1724; (c) M. Kawatsura, M. Yamamoto, J. Namioka, K. Kajita, T. Hirakawa and T. Itoh, Org. Lett., 2011, 13, 1001–1003.
- 6 (a) T. Konno, J. Chae, T. Tanaka, T. Ishihara and H. Yamanaka, Chem. Commun., 2004, 690–691; (b) T. Konno, T. Daitoh, A. Noiri, J. Chae, T. Ishihara and Yamanaka, Tetrahedron, 2005, 61, 9391-9404; (c) H. T. Konno, T. Daitoh, A. Noiri, J. Chae, T. Ishihara and H. Yamanaka, Org. Lett., 2004, 6, 933-936; (d)S. S. Karpiniec, D. S. McGuinness, G. J. P. Britovsek and Patel, Organometallics, 2012, 31, 3439-3442; (e) I. A. Joosten, M. Soueidan, C. Denhez, D. Harakat, F. Hélion, L.-J. Namy, L.-J. Vasse and J. Szymoniak, Organometallics, 2008, 27, 4152-4157.
- 7 (a) G. Hilt, W. Hess, T. Vogler and C. Hengst, J. Organomet. Chem., 2005, 690, 5170–5181; (b) G. Hilt, T. Vogler, W. Hess and F. Galbiati, Chem. Commun., 2005, 1474–1475; (c) M. Achard, A. Tenaglia and G. Buono, Org. Lett., 2005, 7, 2353–2356; (d) Y. Chen, R. Kiattansakul, B. Ma and J. K. Snyder, J. Org. Chem., 2001, 66, 6932–6942.



- 9 The reaction under O<sub>2</sub> atmosphere did not proceed in the similar conditions.
- 10 C.-C. Wang, P.-S. Lin and C.-H. Cheng, J. Am. Chem. Soc., 2002, 124, 9696–9697.
- 11 In the carbocyclization other solvents such as DMF, dioxane, toluene, THF, and dichloroethane led to trace of desired product or no reaction.