

# Ruthenium-Catalyzed Regioselective [2 + 2 + 2] Cyclotrimerization of Trifluoromethyl Group Substituted Internal Alkynes

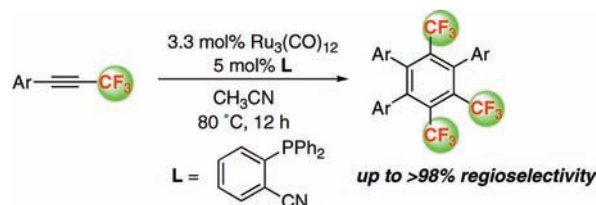
Motoi Kawatsura,\* Mitsuaki Yamamoto, Junya Namioka, Koji Kajita, Takuya Hirakawa, and Toshiyuki Itoh\*

Department of Chemistry and Biotechnology, Graduate School of Engineering, Tottori University, Koyama, Tottori 680-8552 Japan

kawatsur@chem.tottori-u.ac.jp; titoh@chem.tottori-u.ac.jp

Received December 20, 2010

## ABSTRACT



It found that the  $\text{Ru}_3(\text{CO})_{12}$  coordinated with 2-(diphenylphosphino)benzonitrile (2-DPPBN) to effectively catalyze the [2 + 2 + 2] cyclotrimerization of the trifluoromethyl group substituted internal alkynes in high yields with up to >98% regioselectivity. Isolation of a ruthenacyclopentadiene was successful and confirmed that the complex is a reaction intermediate.

Trifluoromethyl group substituted benzene derivatives exhibit several interesting biological activities, and the efficient construction of such a compound is very important.<sup>1</sup> One of the most efficient synthetic methods of the benzene derivatives is the transition metal-catalyzed [2 + 2 + 2] cycloaddition of alkynes, and several examples have been reported.<sup>2,3</sup> However, the [2 + 2 + 2] cycloaddition reaction of fluorine-containing alkynes is rare,<sup>4</sup> and there are only two examples of the synthesis of trifluoromethyl group substituted benzene derivatives by the transition metal-catalyzed [2 + 2 + 2] cyclotrimerization of this

group substituted internal alkynes.<sup>5</sup> In 2002, Jones and colleagues reported the first example of an intermolecular [2 + 2 + 2] cyclotrimerization reaction of a trifluoromethylated

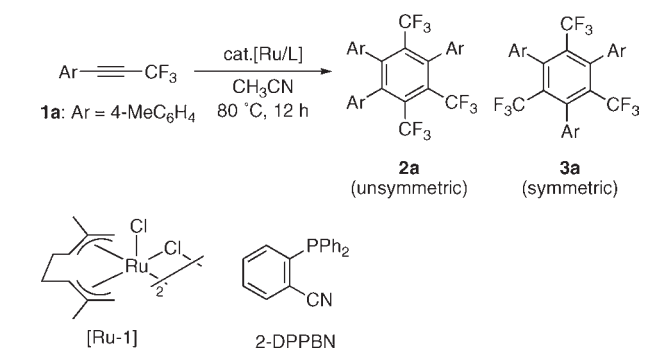
(1) (a) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303–319. (b) O'Hagan, D.; Rzepa, H. S. *Chem. Commun.* **1997**, 645–652.

(2) Recent reviews: (a) Galan, B. R.; Rovis, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 2830–2834. (b) Gandon, V.; Aubert, C.; Malacria, M. *Chem. Commun.* **2006**, 2209–2217. (c) Chopade, P. R.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307–2327. (d) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741–4767. (e) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901–2915. (f) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49–92.

(3) For ruthenium-catalyzed [2 + 2 + 2] cycloaddition and/or cyclotrimerization, see: (a) Cadierno, V.; García-Garrido, S. E.; Gimeno, J. *J. Am. Chem. Soc.* **2006**, *128*, 15094–15095. (b) Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125*, 12143–12160. (c) Rüba, E.; Schmid, R.; Kirchner, K.; Calhorda, M. J. *J. Organomet. Chem.* **2003**, *682*, 204–211. (d) Ura, Y.; Sato, Y.; Shiotsuki, M.; Kondo, T.; Mitsudo, T. *J. Mol. Catal. A: Chem.* **2004**, *209*, 35–39. (e) Yamamoto, Y.; Kinpara, K.; Saigoku, T.; Takagishi, H.; Okuda, S.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2005**, *127*, 605–613. (f) Yamamoto, Y.; Hattori, K.; Nishiyama, H. *J. Am. Chem. Soc.* **2006**, *128*, 8336–8340. (g) Yamamoto, Y.; Ishii, J.-i.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2004**, *126*, 3712–3713. (h) Varela, J. A.; Castedo, L.; Saá, C. *J. Org. Chem.* **2003**, *68*, 8595–8598. (i) Peters, J.-U.; Bleichert, S. *Chem. Commun.* **1997**, 1983–1984.

(4) (a) Arimitsu, S.; Fernández, B.; del Pozo, C.; Fustero, S.; Hammond, G. B. *J. Org. Chem.* **2008**, *73*, 2656–2661. (b) Tanaka, K.; Hara, H.; Nishida, G.; Hirano, M. *Org. Lett.* **2007**, *9*, 1907–1910. (c) Saito, S.; Kawasaki, T.; Tsuboya, N.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 796–802. (d) Saito, S.; Tanaka, T.; Koizumi, T.; Tsuboya, N.; Itagaki, H.; Kawasaki, T.; Endo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 1810–1811.

**Table 1.** Ruthenium-Catalyzed Cyclotrimerization of 1-(4-Methylphenyl)-3,3,3-trifluoropropyne (**1a**)<sup>a</sup>



entry	[Ru/L]	yield (%) <sup>b</sup> of <b>2a</b> and <b>3a</b>	<b>2a:3a</b> <sup>e</sup>
1	Cp <sup>*</sup> RuCl(cod)	<5	ND
2	[RuCp(CH <sub>3</sub> CN) <sub>3</sub> ]PF <sub>6</sub>	0	–
3	[RuCp <sup>*</sup> (CH <sub>3</sub> CN) <sub>3</sub> ]PF <sub>6</sub>	0	–
4	[Ru-1]	0	–
5	Ru <sub>3</sub> (CO) <sub>12</sub>	35	95:5
6	Ru <sub>3</sub> (CO) <sub>12</sub> /10% PPh <sub>3</sub>	7	95:5
7	Ru <sub>3</sub> (CO) <sub>12</sub> /5% PPh <sub>3</sub>	56	95:5
8	Ru <sub>3</sub> (CO) <sub>12</sub> /5% P <sup><i>n</i></sup> Bu <sub>3</sub>	32	90:10
9	Ru <sub>3</sub> (CO) <sub>12</sub> /5% DPPE	18	91:9
10	Ru <sub>3</sub> (CO) <sub>12</sub> /2.5% DPPE	42	78:22
11	Ru <sub>3</sub> (CO) <sub>12</sub> /5% 2-DPPBN	55	>98:2
12 <sup>d</sup>	Ru <sub>3</sub> (CO) <sub>12</sub> /5% 2-DPPBN	84 (95) <sup>e</sup>	>98:2
13	Ru <sub>3</sub> (CO) <sub>12</sub> /10% 2-DPPBN	45	97:3

<sup>a</sup> Reaction conditions: **1a** (0.2 mmol), 10 mol % for Cp<sup>\*</sup>RuCl(cod), [RuCp(CH<sub>3</sub>CN)<sub>3</sub>]PF<sub>6</sub> and [RuCp<sup>\*</sup>(CH<sub>3</sub>CN)<sub>3</sub>]PF<sub>6</sub>, 5 mol % for [Ru-1], 3.3 mol % for Ru<sub>3</sub>(CO)<sub>12</sub>, 0.4 mL of CH<sub>3</sub>CN (0.5 M). <sup>b</sup> Isolated yield. <sup>c</sup> Ratio was determined by <sup>1</sup>H and/or <sup>19</sup>F NMR of the crude materials. <sup>d</sup> CH<sub>3</sub>CN (0.1 mL, 2 M). <sup>e</sup> NMR yield is in parentheses.

internal alkyne.<sup>5a</sup> They reported that the reaction was catalyzed by a nickel catalyst, and the trifluoromethyl group substituted benzene derivatives were quantitatively formed with a 70% regioselectivity. Very recently, Konno and Ishihara discovered that the rhodium catalyst produced the cyclotrimerized benzene derivatives in moderate to good yields with up to an 88% regioselectivity.<sup>5b</sup> On the other hand, during the course of our research on ruthenium-catalyzed reactions<sup>6</sup> and the stereoselective reaction of fluorine-containing compounds,<sup>7</sup> we found that Ru<sub>3</sub>(CO)<sub>12</sub> coordinated with 2-(diphenylphosphino)benzonitrile (2-DPPBN) and effectively catalyzed a [2 + 2 + 2] cyclotrimerization of the trifluoromethyl group substituted internal alkynes in high yields with an almost perfect regioselectivity.

(5) (a) Müller, C.; Lachicotte, R. J.; Jones, W. D. *Organometallics* **2002**, *21*, 1975–1981. (b) Konno, T.; Moriyasu, K.; Kinugawa, R.; Ishihara, T. *Org. Biomol. Chem.* **2010**, *8*, 1718–1724.

(6) (a) Kawatsura, M.; Kamesaki, K.; Yamamoto, M.; Hayase, S.; Itoh, T. *Chem. Lett.* **2010**, *39*, 1050–1051. (b) Kawatsura, M.; Ata, F.; Hirakawa, T.; Hayase, S.; Itoh, T. *Tetrahedron Lett.* **2008**, *49*, 4873–4875. (c) Kawatsura, M.; Ata, F.; Hayase, S.; Itoh, T. *Chem. Commun.* **2007**, 4283–4285. (d) Kawatsura, M.; Ata, F.; Wada, S.; Hayase, S.; Uno, H.; Itoh, T. *Chem. Commun.* **2007**, 298–300.

(7) (a) Kawatsura, M.; Hirakawa, T.; Tanaka, T.; Ikeda, D.; Hayase, S.; Itoh, T. *Tetrahedron Lett.* **2008**, *49*, 2450–2453. (b) Kawatsura, M.; Wada, S.; Hayase, S.; Itoh, T. *Synlett* **2006**, 2483–2485.

We screened ruthenium catalysis for [2 + 2 + 2] cycloaddition reaction of trifluoromethyl-substituted internal alkyne **1a** as the model substrate from among the commercial sources listed in Table 1.<sup>8</sup> Although [Ru-1] {dichlorobis(μ-chloro)bis[(1,2,3,6,7,8-η)-2,7-dimethyl-2,6-octadiene-1,8-diyl]diruthenium},<sup>3a</sup> Cp<sup>\*</sup>RuCl(cod),<sup>3b,d–g</sup> [RuCp(CH<sub>3</sub>CN)<sub>3</sub>]PF<sub>6</sub>,<sup>3c</sup> and [RuCp<sup>\*</sup>(CH<sub>3</sub>CN)<sub>3</sub>]PF<sub>6</sub><sup>3h</sup> are known as effective ruthenium catalysts for the trimerization of terminal alkynes, the reactions of **1a** by these ruthenium catalysts resulted in no reaction or very low yields (entries 1–4). On the other hand, we found that the Ru<sub>3</sub>(CO)<sub>12</sub> formed the desired benzene derivatives **2a** in 35% isolated yield with a 95% regioselectivity. The yield from the trimerization of **1a** was still insufficient, but the regioselectivity was higher than that of previous reports. On the basis of this preliminary result, we confirmed that Ru<sub>3</sub>(CO)<sub>12</sub> is a promising ruthenium precatalyst to produce the trifluoromethyl group substituted benzene derivative with a high regioselectivity. Therefore, we next attempted to optimize the reaction of **1a** by Ru<sub>3</sub>(CO)<sub>12</sub> with several phosphine ligands. Typically, the reaction was carried out as follows: in the presence of 3.3 mol % of Ru<sub>3</sub>(CO)<sub>12</sub> with a phosphine ligand (2.5, 5, or 10 mol %), an alkyne **1a** was mixed in CH<sub>3</sub>CN at 80 °C for 12 h. The reaction by the addition of 10 mol % of PPh<sub>3</sub> (Ru/PPh<sub>3</sub> = 1:1) decreased the yield to 7% (entry 6). However, an increased isolated yield (56%) was observed without reducing the regioselectivity when 5 mol % of PPh<sub>3</sub> (Ru/PPh<sub>3</sub> = 2:1) was added to the reaction mixture (entry 7).<sup>11</sup> Other phosphine ligands, for example P<sup>*n*</sup>Bu<sub>3</sub> or DPPE, were not effective for the cyclotrimerization of **1a** (entries 8–10). Finally, we found that the reaction with 2-(diphenylphosphino)benzonitrile (2-DPPBN) gave the best result for the desired cyclotrimerization. The reaction of 3.3 mol % of Ru<sub>3</sub>(CO)<sub>12</sub> with 5 mol % of 2-DPPBN exhibited the selective formation (>98% regioselectivity) of an unsymmetrical benzene derivative **2a** in 55% yield (entry 11). Changing the concentration of the reaction mixture from 0.5 to 2 M significantly increased the yield, and we thus succeeded in obtaining **2a** as a single regioisomer in an 84% isolated yield (95% NMR yield) (entry 12). Again, the reaction with 10 mol % of 2-DPPBN decreased both the yield and regioselectivity (entry 13), so the ratio of ruthenium to ligand (Ru/2-DPPBN = 2:1) is very important when forming the active ruthenium species.<sup>11</sup>

We next examined the [2 + 2 + 2] cyclotrimerization of various trifluoromethylated internal alkynes **1b–i** under the optimized reaction conditions, and the results are summarized in Table 2. For the reaction of **1c–e**, which has an electron-withdrawing group at the *para*-position on the benzene ring, small amounts of symmetrical products **3c–e** were formed

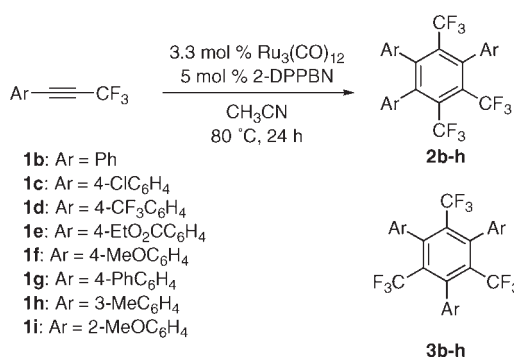
(8) Konno, T.; Chae, J.; Kanda, M.; Nagai, G.; Tamura, K.; Ishihara, T.; Yamanaka, H. *Tetrahedron* **2003**, *59*, 7571–7580.

(9) Ru<sub>3</sub>(CO)<sub>12</sub> is known to react with hexafluoro-2-butyne and forms cyclopentadienone-ruthenium complex, see: Bruce, M. I.; Knight, J. R. *J. Organomet. Chem.* **1968**, *12*, 411–413.

(10) Ru<sub>3</sub>(CO)<sub>12</sub> is also an active catalyst for several types of [2 + 2 + 2] cycloadditions, see: Yamamoto, Y.; Itoh, K. In *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH: Weinheim, 2004; pp 95–128.

(11) The ratio of Ru to phosphine (2:1) is crucial to attain both a high yield and regioselectivity, but the details are unknown at this time.

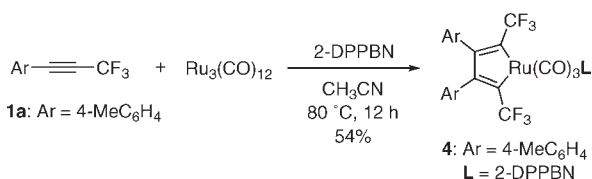
**Table 2.** Ru<sub>3</sub>(CO)<sub>12</sub>/2-DPPBN-catalyzed Cyclotrimerization of Trifluoromethylated Alkynes **1b–i**<sup>a</sup>



entry	<b>1</b>	yield (%) <sup>b</sup> of <b>2</b> and <b>3</b>	ratio <sup>c</sup> of <b>2</b> : <b>3</b>
1	<b>1b</b>	92	>98:2
2	<b>1c</b>	77	93:7
3	<b>1d</b>	81	93:7
4	<b>1e</b>	78	95:5
5	<b>1f</b>	81	>98:2
6	<b>1g</b>	84	>98:2
7	<b>1h</b>	85	>98:2
8	<b>1i</b>	trace	ND

<sup>a</sup> Reaction conditions: **1** (0.2 mmol), Ru<sub>3</sub>(CO)<sub>12</sub> (0.0066 mmol), and 2-DPPBN (0.010 mmol) in CH<sub>3</sub>CN (0.1 mL) at 80 °C for 24 h. <sup>b</sup> Isolated yield. <sup>c</sup> Ratio was determined by <sup>1</sup>H and/or <sup>19</sup>F NMR of the crude materials.

**Scheme 1.** Synthesis of Ruthenacyclopentadiene **4**

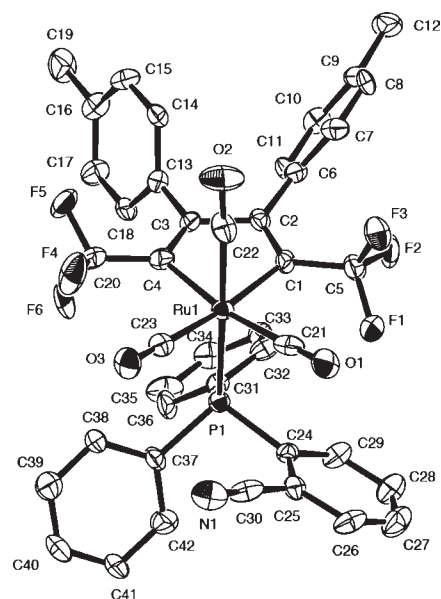


(entries 2–4). On the other hand, the reaction of **1f–h** produced unsymmetrical benzene derivatives **2f–h** selectively in good yield (entries 5–7). Unfortunately, the reaction of **1i**, bearing an *ortho*-substituted aromatic group, gave only a trace amount of the trimerization product (entry 8).<sup>12</sup>

We further examined the isolation of the reaction intermediate, which might be a ruthenacyclopentadiene.<sup>13</sup> To our delight, we succeeded in obtaining a ruthenium complex **4** by the mixing of Ru<sub>3</sub>(CO)<sub>12</sub>, 2-DPPBN and the alkyne **1a** (Scheme 1), then solved the structure based on an X-ray crystallographic analysis (Figure 1). In the complex, the 2-DPPBN ligand coordinated with the ruthenium metal as a monodentate ligand, while the nitrile group was not coordinated to the ruthenium. We ran the stoichiometric reaction of **4** with the alkyne **1f**, then succeeded in obtaining the expected benzene derivative **5** in 47% isolated yield (Scheme 2). The

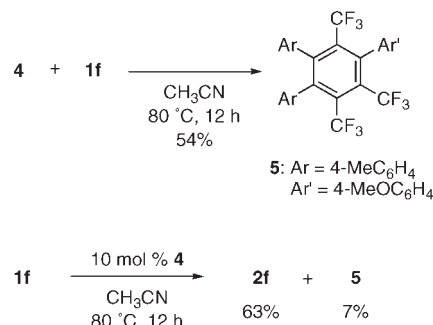
(12) The reaction of 1-phenyl-1-propyne gave a trace amount of trimerization products with a low regioselectivity.

(13) Zhou, L.; Li, S.; Kanno, K.-i.; Takahashi, T. *Heterocycles* **2010**, *80*, 725–738.



**Figure 1.** X-ray structure of ruthenacyclopentadiene **4**. Hydrogen atoms have been omitted for clarity.

**Scheme 2.** Stoichiometric Reaction of Ruthenacyclopentadiene **4** with **1f**, and Complex **4** Catalyzed Cyclotrimerization of **1f**



yield was slightly low, but these results support the fact that the ruthenacyclopentadiene **4** is a reaction intermediate in the Ru<sub>3</sub>(CO)<sub>12</sub>/2-DPPBN catalyzed intermolecular [2 + 2 + 2] cyclotrimerization of the trifluoromethylated internal alkynes **1a**. Furthermore, we confirmed that the complex **4** works as a catalyst for the cyclotrimerization reaction.

In conclusion, we demonstrated the Ru<sub>3</sub>(CO)<sub>12</sub>/2-DPPBN catalyzed [2 + 2 + 2] intermolecular cyclotrimerization of trifluoromethylated alkynes and obtained the trifluoromethylated benzene derivatives in good yields with a high regioselectivity. We also succeeded in isolating a ruthenacyclopentadiene and confirmed that the complex is a reaction intermediate.

**Supporting Information Available.** Experimental details, characterization data and X-ray crystallographic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.