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

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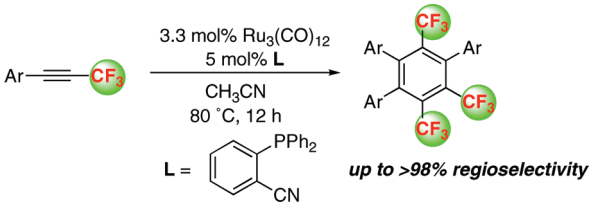
ABSTRACT



It found that the $Ru_3(CO)_{12}$ 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.[1] 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.[2,3] However, the [2 + 2 + 2] cycloaddition reaction of fluorine-containing alkynes is rare,[4] 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.[5] In 2002, Jones and colleagues reported the first example of a intermolecular [2 + 2 + 2] cyclotrimerization reaction of a trifluoromethylated

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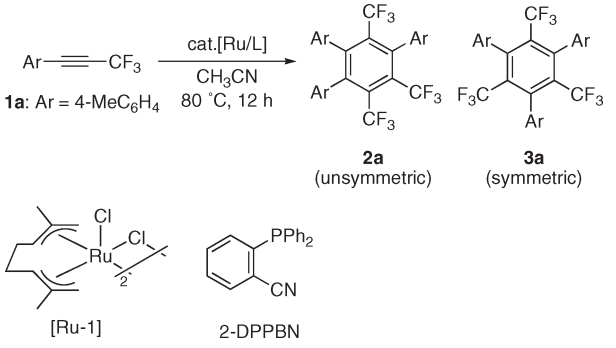
Table 1. Ruthenium-Catalyzed Cyclotrimerization of 1-(4-Methylphenyl)-3,3,3-trifluoropropyne (**1a**)[a]



entry	[Ru/L]	yield (%)[b] of **2a** and **3a**	**2a**:**3a**[c]
1	Cp*RuCl(cod)	<5	ND
2	$[RuCp(CH_3CN)_3]PF_6$	0	–
3	$[RuCp^*(CH_3CN)_3]PF_6$	0	–
4	[Ru-1]	0	–
5	$Ru_3(CO)_{12}$	35	95:5
6	$Ru_3(CO)_{12}$/10% PPh_3	7	95:5
7	$Ru_3(CO)_{12}$/5% PPh_3	56	95:5
8	$Ru_3(CO)_{12}$/5% P^nBu_3	32	90:10
9	$Ru_3(CO)_{12}$/5% DPPE	18	91:9
10	$Ru_3(CO)_{12}$/2.5% DPPE	42	78:22
11	$Ru_3(CO)_{12}$/5% 2-DPPBN	55	>98:2
12[d]	$Ru_3(CO)_{12}$/5% 2-DPPBN	84 (95)[e]	>98:2
13	$Ru_3(CO)_{12}$/10% 2-DPPBN	45	97:3

[a] Reaction conditions: **1a** (0.2 mmol), 10 mol % for Cp*RuCl(cod), $[RuCp(CH_3CN)_3]PF_6$ and $[RuCp^*(CH_3CN)_3]PF_6$, 5 mol % for [Ru-1], 3.3 mol % for $Ru_3(CO)_{12}$, 0.4 mL of CH_3CN (0.5 M). [b] Isolated yield. [c] Ratio was determined by ^1H and/or ^{19}F NMR of the crude materials. [d] CH_3CN (0.1 mL, 2 M). [e] NMR yield is in parentheses.

internal alkyne.[5a] 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.[5b] On the other hand, during the course of our research on ruthenium-catalyzed reactions[6] and the stereoselective reaction of fluorine-containing compounds,[7] we found that $Ru_3(CO)_{12}$ 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.

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.[8] Although [Ru-1] {dichlorobis(μ-chloro)bis[(1,2,3,6,7,8-η)-2,7-dimethyl-2,6-octadiene-1, 8-diyl]diruthenium},[3a] Cp*RuCl(cod),[3b,d−g] $[RuCp(CH_3CN)_3]PF_6$[3c] and $[RuCp^*(CH_3CN)_3]PF_6$[3h] 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 $Ru_3(CO)_{12}$[9,10] 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 $Ru_3(CO)_{12}$ 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 $Ru_3(CO)_{12}$ with several phosphine ligands. Typically, the reaction was carried out as follows: in the presence of 3.3 mol % of $Ru_3(CO)_{12}$ with a phosphine ligand (2.5, 5, or 10 mol %), an alkyne **1a** was mixed in CH_3CN at 80 °C for 12 h. The reaction by the addition of 10 mol % of PPh_3 (Ru/PPh_3 = 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_3 (Ru/PPh_3 = 2:1) was added to the reaction mixture (entry 7).[11] Other phosphine ligands, for example P^nBu_3 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 $Ru_3(CO)_{12}$ 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.[11]

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

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(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.

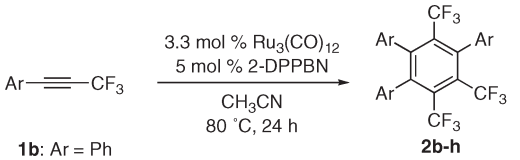
(8) Konno, T.; Chae, J.; Kanda, M.; Nagai, G.; Tamura, K.; Ishihara, T.; Yamanaka, H. *Tetrahedron* **2003**, *59*, 7571–7580.

(9) $Ru_3(CO)_{12}$ 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) $Ru_3(CO)_{12}$ 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.

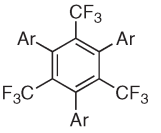
(11) The ratio of Ru to phosphine (2:1) is crucial to attain both a high yield and regioselectivity, but the details are unknown at this time.

Table 2. $Ru_3(CO)_{12}$/2-DPPBN-catalyzed Cyclotrimerization of Trifluoromethylated Alkynes **1b**−**i**[a]



2b-h

1b: Ar = Ph
1c: Ar = 4-ClC_6H_4
1d: Ar = 4-$CF_3C_6H_4$
1e: Ar = 4-$EtO_2CC_6H_4$
1f: Ar = 4-$MeOC_6H_4$
1g: Ar = 4-PhC_6H_4
1h: Ar = 3-MeC_6H_4
1i: Ar = 2-$MeOC_6H_4$

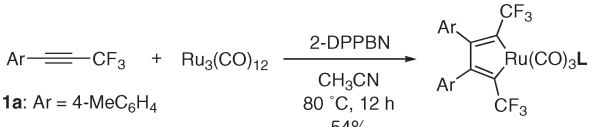


3b-h

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

[a] Reaction conditions: **1** (0.2 mmol), $Ru_3(CO)_{12}$ (0.0066 mmol), and 2-DPPBN (0.010 mmol) in CH_3CN (0.1 mL) at 80 °C for 24 h. [b] Isolated yield. [c] Ratio was determined by ^1H and/or ^{19}F NMR of the crude materials.

Scheme 1. Synthesis of Ruthenacyclopentadiene **4**



1a: Ar = 4-MeC_6H_4

4: Ar = 4-MeC_6H_4
L = 2-DPPBN

(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).[12]

We further examined the isolation of the reaction intermediate, which might be a ruthenacyclopentadiene.[13] To our delight, we succeeded in obtaining a ruthenium complex **4** by the mixing of $Ru_3(CO)_{12}$, 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.

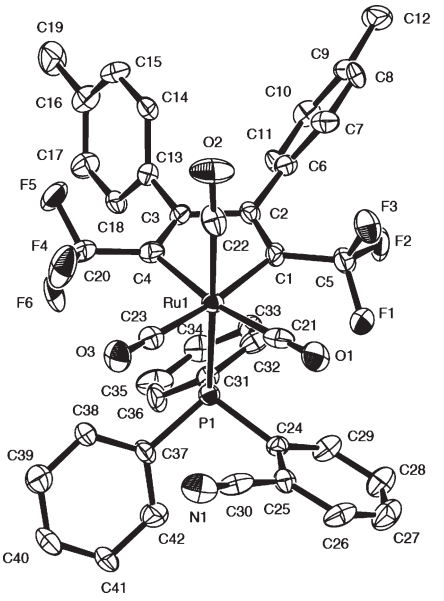
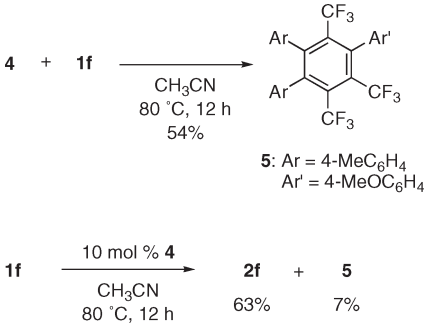


Figure 1. X-ray structure of ruthenacyclopentadine **4**. Hydrogen atoms have been omitted for clarity.

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 $Ru_3(CO)_{12}$/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 $Ru_3(CO)_{12}$/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.