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Synthesis of Perfluoroalkylated Benzenes and Pyridines through Cationic Rh(I)/Modified BINAP-Catalyzed Chemo- and Regioselective [2 + 2 + 2] Cycloaddition

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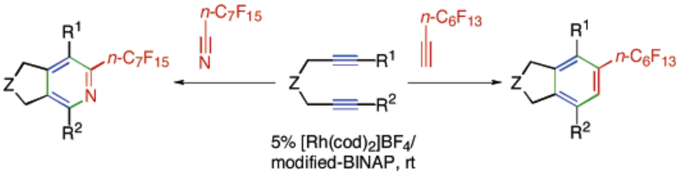
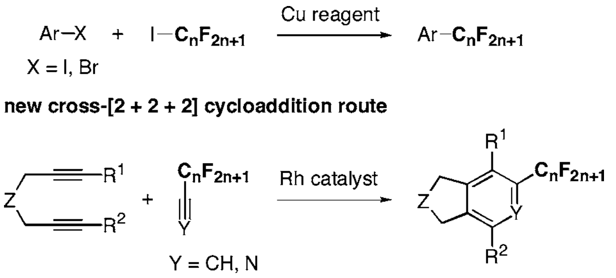
ABSTRACT



A convenient synthesis of perfluoroalkylated benzenes and pyridines has been achieved by a cationic Rh(I)/modified BINAP-complex-catalyzed chemo- and regioselective [2 + 2 + 2] cycloaddition of alkynes with a perfluoroalkylacetylene and a perfluoroalkylnitrile.

Fluorous chemistry[1,2] has received much attention as an environmentally benign recycling process and an efficient tool for combinatorial synthesis.[3] Perfluoroalkylated aromatic compounds are important building blocks for the synthesis of various fluorous catalysts, reagents, and substrates used for the above-mentioned fluorous chemistry, so the development of convenient synthetic approaches to them is highly attractive. The most frequently employed regioselective method is a Cu-mediated cross-coupling reaction of perfluoroalkyl iodides and aryl halides developed by McLoughlin and Thrower (Scheme 1).[4] However, this method requires harsh reaction conditions, excess Cu reagents, and regioselective preparation of aryl halides. On the other hand, a transition-metal-catalyzed chemo- and regioselective [2 + 2 + 2] cycloaddition[5] of alkynes with perfluoroalkylacetylenes, which are commercially available and can be readily prepared from perfluoroalkyl iodides,[6] would be an attractive method (Scheme 1). Although a transition-metal-catalyzed homo-[2 + 2 + 2] cycloaddition of a perfluoroalkylacetylene leading to triperfluoroalkylbenzenes by using Mo(CO)$_3$ as a

Scheme 1



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[1] (a) Horváth, I. T.; Rabái, J. *Science* **1994**, *266*, 72. (b) Gladysz, J. A. *Science* **1994**, *266*, 55.

[2] For reviews of fluorous chemistry, see: (a) Cornils, B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2057. (b) Horváth, I. T. *Acc. Chem. Res.* **1998**, *31*, 641. (c) Curran, D. P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1174. (d) Fish, R. H. *Chem.—Eur. J.* **1999**, *5*, 1677. (e) Barthel-Rosa, L. P.; Gladysz, J. A. *Coord. Chem. Rev.* **1999**, *190−192*, 587. (f) de Wolf, E.; van Koten, G.; Deelman, B.-J. *Chem. Soc. Rev.* **1999**, *28*, 37. (g) Curran, D. P. *Synlett* **2001**, 1488. (h) Yoshida, J.; Itami, K. *Chem. Rev.* **2002**, *102*, 3693. (i) Otera, J. *Acc. Chem. Res.* **2004**, *37*, 288. (j) Gladysz, J. A., Curran, D. P., Horváth, I. T., Eds. *Handbook of Fluorous Chemistry*; Wiley-VCH: Weinheim, Germany, 2004. (k) For a review of fluorous ligands and catalysts, see: Pozzi, G.; Shepperson, I. *Coord. Chem. Rev.* **2003**, *242*, 115.

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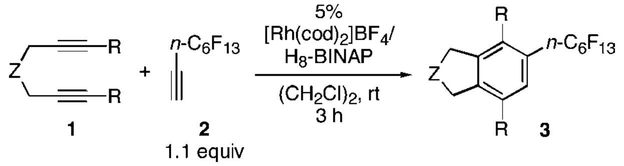
catalyst was reported,[7−9] a cross-[2 + 2 + 2] cycloaddition involving a perfluoroalkylacetylene has not been reported to date.[10]

Our research group demonstrated that a cationic rhodium(I)/modified BINAP complex catalyzes cross-[2 + 2 + 2] cycloadditions involving various unsaturated compounds with high chemo- and regioselectivity.[11−13] In this communication, we describe a convenient synthesis of perfluoroalkylated benzenes and pyridines through a cationic rhodium(I)/modified BINAP-complex-catalyzed chemo- and regioselective [2 + 2 + 2] cycloaddition of alkynes with a perfluoroalkylacetylene and a perfluoroalkylnitrile.

First the reaction of malonate-derived internal 1,6-diyne **1a** and perfluoroalkylacetylene **2** (1.1 equiv) was examined in the presence of various cationic rhodium(I)/modified BINAP complexes. We were pleased to find that desired cross-[2 + 2 + 2] cycloaddition product **3a** was obtained in high yield at room temperature by using 5% $[Rh(cod)_2]BF_4$/H_8-BINAP [2,2′-bis(diphenylphosphino)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl][14] as a catalyst (Table 1, entry 1). Thus, a series of 1,6-diynes was subjected to this optimal reaction condition. Internal 1,6-diynes **1a** and **1b** reacted with **2** to give the corresponding perfluoroalkylated benzenes in high yield (entries 1 and 2), but the use of terminal 1,6-diyne **1c** significantly lowered the yield of the desired product due to the competitive homo-[2 + 2 + 2] cycloaddition of **1c** leading to a dimer (entry 3). Not only electron-rich internal 1,6-diynes but electron-deficient internal 1,6-diynes **1d**−**g** possessing alkoxycarbonyl groups at alkyne termini could be employed for this reaction (entries 4−7).

Table 1. $Rh(I)^+/H_8$-BINAP-Catalyzed [2 + 2 + 2] Cycloaddition of 1,6-Diynes **1** with Perfluoroalkylacetylene **2**



entry	**1**	Z	R	**3**	yield[a] (%)
1	**1a**	$C(CO_2Me)_2$	Me	**3a**	85
2	**1b**	NTs	Me	**3b**	94
3	**1c**	NTs	H	**3c**	21
4	**1d**	$C(CO_2Me)_2$	CO_2Et	**3d**	89
5	**1e**	NBn	CO_2Me	**3e**	72
6	**1f**	O	CO_2Et	**3f**	75
7	**1g**	CH_2	CO_2Me	**3g**	99

[a] Isolated yield based on **1**.

Next, we investigated a complete intermolecular cross-[2 + 2 + 2] cycloaddition of monoalkynes with **2**.[15] In our previous report, two molecules of terminal monoalkynes reacted with one molecule of dialkylacetylene dicarboxylates, furnishing 3,6-disubstituted phthalates in high yield with excellent regioselectivity upon treatment with a catalytic amount of $[Rh(cod)_2]BF_4$/H_8-BINAP.[11a,c] On the contrary, one molecule of **2** reacted with two molecules of dimethyl acetylenedicarboxylate (**4**) in the presence of 5% $[Rh(cod)_2]BF_4$/H_8-BINAP to give the corresponding perfluoroalkylated benzene **5** in high yield (eq 1). The reaction of an unsymmetrical electron-deficient monoalkyne, ethyl phenylpropiolate (**6**), with **2** also proceeded to give 1,2-teraryl compound **7** in moderate yield as a single regioisomer (eq 2).

Interestingly, in the case of ethyl 2-butynoate (**8**), two molecules of **2** reacted with one molecule of **8** in the presence of 5% $[Rh(cod)_2]BF_4$/H_8-BINAP to give the corresponding

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(9) For $Pd(PPh_3)_4$-catalyzed homo-[4 + 2] cycloaddition of 2-perfluoroalkyleneynes, see: Saito, S.; Tanaka, T.; Koizumi, T.; Tsuboya, N.; Itagaki, H.; Kawasaki, T.; Endo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 1810.

(10) For co-cyclotrimerization of perfluoroalkyleneynes with acetylene gas and (trimethylsilyl)acetylene, see ref 8.

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(13) For a review of the rhodium-catalyzed [2 + 2 + 2] cycloaddition, see: Fujiwara, M.; Ojima, I. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, Germany, 2005; Chapter 7, p 129.

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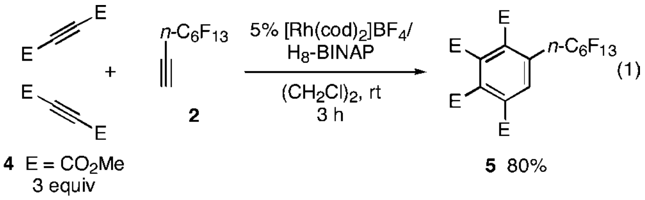
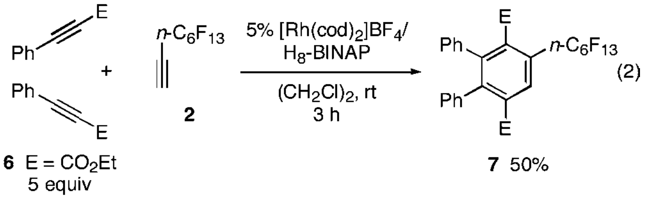
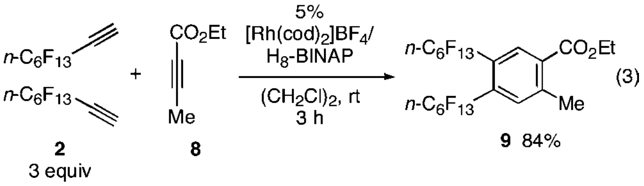
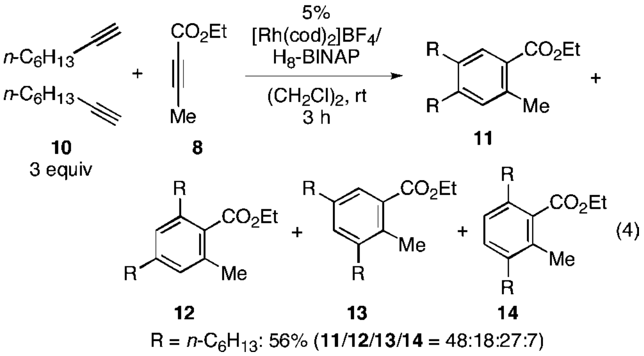




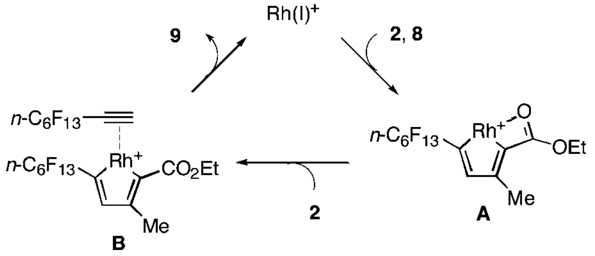




diperfluoroalkylbenzene **9** in high yield as a single regioisomer (eq 3). On the other hand, the reaction of 1-octyne (**10**) and **8** furnished a mixture of regioisomers in moderate yield (eq 4). In these complete intermolecular cross-[2 + 2 + 2] cycloadditions of monoalkynes shown in eqs 1−4, the use of 1 equiv of each reactant furnished the same cycloaddition products as major products.

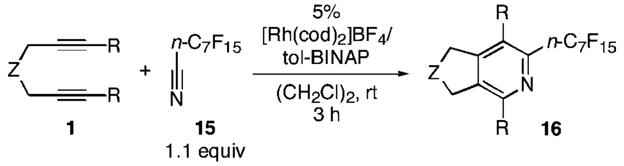
Scheme 2 depicts a possible mechanism for the selective formation of **9**. Because cyclotrimerization of perfluoroalkylacetylene **2** is sluggish under the present reaction conditions shown in eq 3, formation of metallacyclopentadiene from two molecules of **2** may not be involved. Accordingly, chemo- and regioselectivity may be determined by preferential formation of metallacycle **A** from **2** and **8** through coordination of the carbonyl group to rhodium followed by the coordination of **2** to form complex **B**.[16] Regioselective coordination of **2** may be explained by the interaction of two perfluoroalkyl groups. Reductive elimination of rhodium gives **9** and regenerates the rhodium catalyst.

Scheme 2



In the cationic rhodium(I)/modified BINAP-complex-catalyzed [2 + 2 + 2] cycloaddition of alkynes with nitriles, electron-deficient nitriles showed high reactivity.[12c] Therefore, we anticipated that this complex would catalyze the [2 + 2 + 2] cycloaddition of alkynes with commercially available electron-deficient perfluoroalkylnitrile **15**, leading to perfluoroalkylated pyridines.[17−19] Indeed, the reaction of 1,6-diyne **1a** and **15** (1.1 equiv) in the presence of 5% [Rh(cod)$_2$]BF$_4$/tol-BINAP proceeded at room temperature to give the corresponding pyridine **16a** in high yield (Table 2, entry 1). Terminal 1,6-diyne **1h** and electron-deficient internal 1,6-diyne **1d** could also participate in this reaction, although lower yields were observed (entries 2 and 3). Not

Table 2. Rh(I)$^+$/tol-BINAP-Catalyzed [2 + 2 + 2] Cycloaddition of 1,6-Diynes **1** with Perfluoroalkylnitrile **15**



entry	1	Z	R	16	yield[a] (%)
1	**1a**	C(CO$_2$Me)$_2$	Me	**16a**	85
2[b]	**1h**	C(CO$_2$Me)$_2$	H	**16h**	62
3	**1d**	C(CO$_2$Me)$_2$	CO$_2$Et	**16d**	55
4[c]	**1b**	NTs	Me	**16b**	92
5	**1i**	O	Et	**16i**	86
6	**1j**	CH$_2$	Et	**16j**	85

[a] Isolated yield based on **1**. [b] Reaction time: 2 h. [c] Reaction time: 1 h.

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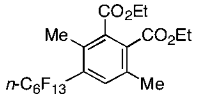
(16) A pentasubstituted benzene (shown below) was generated in a trace amount as a single regioisomer. Because cyclotrimerization of **8** is also sluggish under the present reaction conditions, formation of metallacyclopentadiene from two molecules of **8** may not be involved. Accordingly, the regioselective formation of this compound can be explained by the reaction of rhodacycle **B** with **8** instead of **2**.



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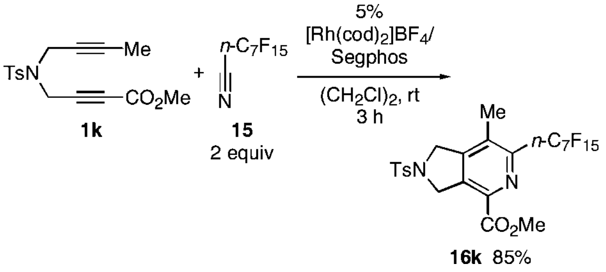
only malonate-derived 1,6-diyne **1a** but also tosylamide (**1b**, entry 4), ether (**1i**, entry 5), and methylene (**1j**, entry 6) linked 1,6-diynes also reacted with **15** to give the corresponding perfluoroalkylated pyridines **16** in high yields.

The regioselectivity of the present pyridine synthesis was then investigated using unsymmetrical 1,6-diyne **1k** bearing methyl and methoxycarbonyl at each terminal position. The reaction of **1k** and **15** in the presence of 5% $[Rh(cod)_2]BF_4$/Segphos [(4,4′-bi-1,3-benzodioxole)-5,5′-diylbis(diphenylphosphine)][20] at room temperature afforded the corresponding pyridine **16k** as a single regioisomer (eq 5).



(5)

In conclusion, we have demonstrated that a cationic Rh(I)/modified BINAP-complex-catalyzed chemo- and regioselective [2 + 2 + 2] cycloaddition of alkynes with a perfluoroalkylacetylene and a perfluoroalkylnitrile represents a versatile new method for the synthesis of perfluoroalkylated benzenes and pyridines, respectively.[21]

Acknowledgment. We thank Takasago International Corporation for the gift of modified BINAP ligands, and Asahi Glass Corporation for the gift of a perfluoroalkyl iodide.

Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Synthesis of perfluoroalkylated pyridines from perfluoroalkylnitriles via formation of 3-(perfluoroalkyl)-2-azadienes: Palacious, F.; Alonso, C.; Rodriguez, M.; de Marigorta, E. M.; Rubiales, G. *Eur. J. Org. Chem*. **2005**, 1795.

(20) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal*. **2001**, *343*, 264.

(21) In the present study, n-$C_6F_{13}CCH$ (**2**) and n-$C_7F_{15}CN$ (**15**) were used because of their commercial availability, their low toxicity, and their high solubility in $(CH_2Cl)_2$. The effect of alkyl chain length will be investigated in due course.