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Rhodium-Catalyzed Complete Regioselective Intermolecular Cross-Cyclotrimerization of Aryl Ethynyl Ethers and Nitriles or Isocyanates at Room Temperature

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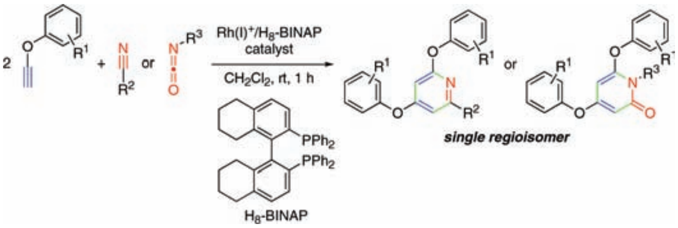
ABSTRACT



We have established that a cationic rhodium(I)/H$_8$−BINAP complex catalyzes the complete regioselective intermolecular cross-cyclotrimerization of aryl ethynyl ethers and nitriles or isocyanates leading to 2,4-diaryloxypyridines or 4,6-diaryloxy-2-pyridones at room temperature.

The transition-metal-catalyzed chemo- and regioselective intermolecular cross-cyclotrimerization has received much attention as a useful method for the synthesis of substituted arenes because of its high atom economy and convergent nature.[1] Although the intermolecular cross-cyclotrimerization involving alkynyl ethers is potentially attractive for the synthesis of aryl ethers, existing examples are quite limited.[2−6] For the reaction using a stoichiometric amount of a transition metal, Sato and co-workers reported the titanium-mediated regioselective cross-cyclotrimerization of cyclohexyl trimethylsilylethynyl ether and ethynyl tolyl sulfone.[2] For transition-metal-catalyzed reactions,[3−5] Saegusa and co-workers reported the nickel-catalyzed regioselective cross-cyclotrimerization of ethyl ethynyl ether and carbon dioxide.[3] Recently, Rovis and co-workers reported the neutral rhodium(I)/phosphoramidite complex-catalyzed regioselective cross-cyclotrimerization of terminal alkynes and isocyanates at elevated temperature (110 °C) that includes a single example using ethyl ethynyl ether as a terminal alkyne (38% isolated yield).[4] However, the corresponding reaction using nitriles has not been reported. In this paper, we disclose the cationic rhodium(I)/H$_8$-BINAP complex-catalyzed complete regioselective intermolecular cross-cyclotrimerization of aryl ethynyl ethers and nitriles as well as isocyanates at room temperature.

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[1] For a recent review, see: Galan, B. R.; Rovis, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 2830.

[2] (a) Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2001**, *123*, 7925. The zirconium-mediated cross-cyclotrimerization of ethyl ethynyl ether and 3-hexyne was also reported as a patent; see: (b) Takahashi, T. JP 11263737, 1999; *Chem. Abstr.* **1999**, *131*, 228541.

[3] Tsuda, T.; Kunisada, K.; Nagahama, N.; Morikawa, S.; Saegusa, T. *Synth. Commun.* **1989**, *19*, 1575.

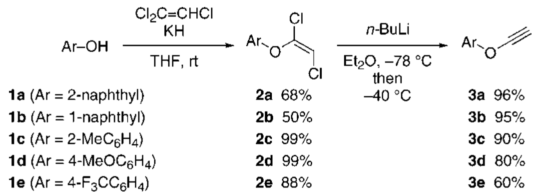
[4] Oberg, K. M.; Lee, E. E.; Rovis, T. *Tetrahedron* **2009**, *65*, 5056.

[5] Very recently, the nickel-catalyzed [3 + 2 + 2] cycloaddition of ethyl cyclopropylideneacetate and alkynyl ethers was reported; see: Yamasaki, R.; Terashima, N.; Sotome, I.; Komagawa, S.; Saito, S. *J. Org. Chem.* **2010**, *75*, 480.

[6] The homo-cyclotrimerization of di-*tert*-butoxyacetylene was reported; see: Semmelhack, M. F.; Park, J. *Organometallics* **1986**, *5*, 2550.

10.1021/ol100182u

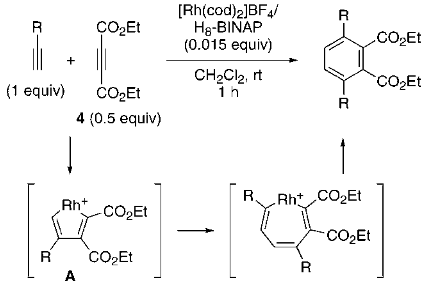
Scheme 1



1a (Ar = 2-naphthyl)	**2a** 68%	**3a** 96%
1b (Ar = 1-naphthyl)	**2b** 50%	**3b** 95%
1c (Ar = 2-MeC$_6$H$_4$)	**2c** 99%	**3c** 90%
1d (Ar = 4-MeOC$_6$H$_4$)	**2d** 99%	**3d** 80%
1e (Ar = 4-F$_3$CC$_6$H$_4$)	**2e** 88%	**3e** 60%

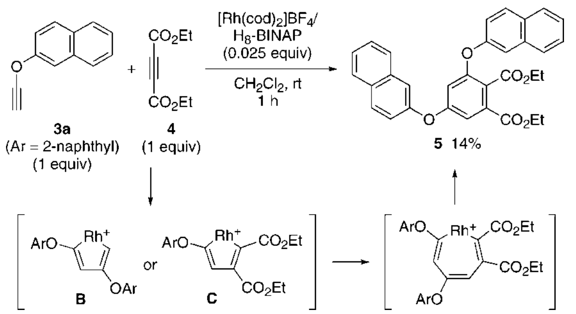
We recently reported that a cationic rhodium(I)/H$_8$-BINAP complex is able to catalyze the partially intramolecular cyclotrimerization of phenol-linked 1,6-diynes and alkynes or nitriles leading to substituted dibenzofurans or azadibenzofurans.[7] During the study, we were aware that aryl ethynyl ethers are stable compounds and can be readily handled without any special precautions. This feature is contrary to that of alkyl ethynyl ethers. These backgrounds prompted us to investigate the cationic rhodium(I)/bisphosphine complex-catalyzed intermolecular cyclotrimerization using aryl ethynyl ethers. Aryl ethynyl ethers **3a**−**e** were readily prepared by a two-step operation starting from commercially available naphthols **1a**,**b** or phenols **1c**−**e** via aryl dichloroethenyl ethers **2a**−**e** following our previous synthesis of phenol-linked 1,6-diynes (Scheme 1).[7] These alkynes **3a**−**e** could be purified by a silica gel column chromatography without decomposition.

Scheme 2



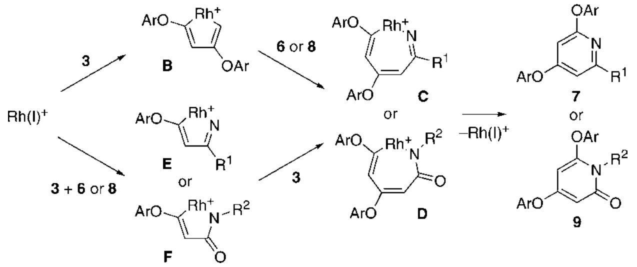
Our research group previously reported that the cationic rhodium(I)/H$_8$-BINAP complex catalyzes the intermolecular cross-cyclotrimerization of terminal alkynes and diethyl acetylenedicarboxylate (**4**) to yield 3,6-disubstituted phthalates in high yields with excellent regioselectivities as shown in Scheme 2.[8] A possible mechanism of this reaction is also shown in Scheme 2. Regioselective oxidative coupling of the terminal alkyne and **4** with rhodium leads to rhodacyclopentadiene intermediate **A**. Regioselective insertion of the terminal alkyne between the sterically less demanding rhodium−carbon bond followed by reductive elimination furnishes the 3,6-disubstituted phthalate.[8]

Scheme 3



The use of aryl ethynyl ether **3a** as a terminal alkyne in a cross-cyclotrimerization with **4** was examined using the cationic rhodium(I)/H$_8$-BINAP catalyst. Contrary to our expectation, a homocyclotrimerization of **3a** proceeded predominantly and a large amount of **4** was recovered. Furthermore, the unexpected diethyl 3,5-diaryloxyphthalate **5**, not the expected diethyl 3,6-diaryloxyphthalate, was obtained in 14% yield as a major regioisomer (Scheme 3).[9] We anticipated that the selective formation of intermediate **B** by oxidative coupling of two aryl ethynyl ethers **3a** with rhodium might account for the observed selective formation of **5** and the rapid homocyclotrimerization of **3a** rather than that of **4** (Scheme 3). Alternatively, the selective formation of intermediate **C** by oxidative coupling of **3a** and **4** with rhodium might also account for the observed selectivity (Scheme 3).

Scheme 4



Based on the above mechanistic consideration, the regioselective intermolecular cross-cyclotrimerization of aryl ethynyl ethers and nitrogen-containing unsaturated com-

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(7) Komine, Y.; Kamisawa, A.; Tanaka, K. *Org. Lett.* **2009**, *11*, 2361.

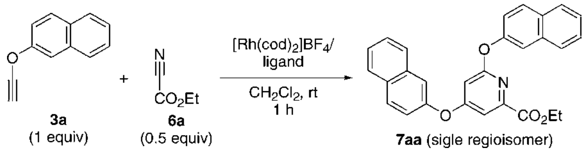
(8) (a) Tanaka, K.; Shirasaka, K. *Org. Lett.* **2003**, *5*, 4697. (b) Tanaka, K.; Toyoda, K.; Wada, A.; Shirasaka, K.; Hirano, M. *Chem.*−*Eur. J.* **2005**, *11*, 1145.

(9) Other regioisomers were generated in <5% yields. A cross-cyclotrimerization product of one molecule of **3a** and two molecules of **4** was not detected at all.

(10) Deiters and co-workers successfully overcame the regioselectivity problem in the cobalt-catalyzed intermolecular cross-cyclotrimerization of terminal alkynes and nitriles by employing the solid-supported reaction system; see: Senaiar, R. S.; Young, D. D.; Deiters, A. *Chem. Commun.* **2006**, 1313.

(11) The cobalt-catalyzed regioselective cross-cyclotrimerization of *tert*-butylacetylene and trimethylacetonitrile leading to 2,4,6-tri-*tert*-butylpyridine was reported; see: Heller, B.; Sundermann, B.; Buschmann, H.; Drexler, H.-J.; You, J.; Holzgrabe, U.; Heller, E.; Oehme, G. *J. Org. Chem.* **2002**, *67*, 4414.

Table 1. Effect of Ligands for Rh-Catalyzed Intermolecular Cross-Cyclotrimerization of Aryl Ethynyl Ether **3a** and Nitrile **6a**[a]



entry	ligand	catalyst (equiv)	yield[b] (%)
1	H_8-BINAP	0.05	75
2	Segphos	0.05	53
3	BINAP	0.05	39
4	BIPHEP	0.05	39
5[c]	H_8-BINAP	0.025	64[d]

[a] $[Rh(cod)_2]BF_4$ (0.010 mmol), ligand (0.010 mmol), **3a** (0.20 mmol), **6a** (0.10 mmol), and CH_2Cl_2 (2.0 mL) were used. [b] Determined by ^1H NMR using 1,4-dimethoxybenzene as an internal standard. [c] **3a** (0.40 mmol) and **6a** (0.20 mmol) were used. [d] Isolated yield.

pounds, nitriles and isocyanates, were investigated. In general, the regioselective intermolecular cross-cyclotrimerization of terminal alkynes and nitriles[10−14] or isocyanates[4,15] is difficult to proceed presumably due to the lack of regioselectivity in the oxidative coupling and/or insertion step.[16] On the other hand, as shown in Scheme 4, if nitrile **6** is able to react with intermediate **B**, insertion of the cyano group between the sterically less demanding rhodium−carbon bond might regioselectively furnish intermediate **C** through the formation of the bond between the nitrogen atom and the cationic rhodium. Reductive elimination would furnish 2,4-diaryloxypyridine **7** and regenerate the rhodium catalyst. The reaction using isocyanate **8** would furnish 4,6-diaryloxy-2-pyridone **9** through the regioselective formation of intermediate **D**. Alternatively, the selective formation of intermediate **E** or **F** by oxidative coupling of aryl ethynyl ether **3** and nitrile **6** or isocyanate **8** instead of diethyl acetylenedicarboxylate (**4**) with rhodium followed by regioselective insertion of **3** would also furnish intermediate **C** or **D**, respectively (Scheme 4).

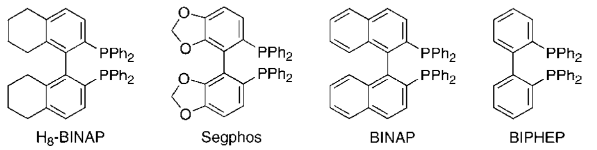
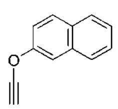
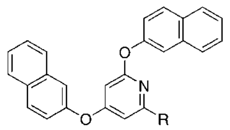
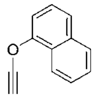
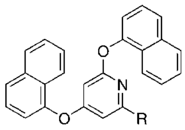
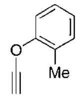
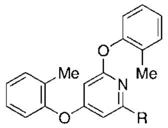
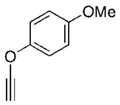
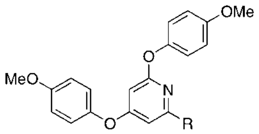
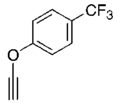
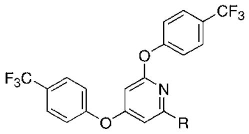


Figure 1. Structures of biarylbisphosphine ligands.

Thus, we investigated an intermolecular cross-cyclotrimerization of aryl ethynyl ether **3a** and ethyl cyanoacetate (**6a**) in the presence of the cationic rhodium(I)/H_8-BINAP catalyst.[14] Pleasingly, the expected cross-cyclotrimerization

Table 2. Rh-Catalyzed Intermolecular Cross-Cyclotrimerizations of Aryl Ethynyl Ethers **3a**−**e** and Nitriles **6a**−**f**[a]

entry	3	6 (R, equiv)	7 (% yield[b])
			
1	**3a**	**6a** (CO_2Et, 0.5)	**7aa** (64)
2	**3a**	**6b** (CH_2CN, 0.5)	**7ab** (68)
3	**3a**	**6c** (Ac, 0.5)	**7ac** (45)
4	**3a**	**6d** (Bz, 0.5)	**7ad** (42)
5	**3a**	**6a** (CO_2Et, 1)	**7aa** (82)
6	**3a**	**6e** (Ph, 5)	**7ae** (47)
7	**3a**	**6f** (CH_3, 10)	**7af** (32)
			
8	**3b**	**6a** (CO_2Et, 0.5)	**7ba** (74)
9	**3b**	**6b** (CH_2CN, 0.5)	**7bb** (66)
			
10	**3c**	**6a** (CO_2Et, 0.5)	**7ca** (61)
11	**3c**	**6b** (CH_2CN, 0.5)	**7cb** (59)
			
12	**3d**	**6a** (CO_2Et, 0.5)	**7da** (55)
13	**3d**	**6b** (CH_2CN, 0.5)	**7db** (57)
			
14	**3e**	**6a** (CO_2Et, 0.5)	**7ea** (67)
15	**3e**	**6b** (CH_2CN, 0.5)	**7eb** (62)

[a] Reactions were conducted using $[Rh(cod)_2]BF_4$ (0.010 mmol), H_8−BINAP (0.010 mmol), **3a**−**e** (0.40 mmol), **6a**−**f** (0.20−4.0 mmol), and CH_2Cl_2 (2.0 mL) at rt for 1 h. [b] Isolated yield.

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(12) The ruthenium-catalyzed regioselective cross-cyclotrimerization of methyl propiolate and electron-deficient nitriles leading to 2,3,6-trisubstituted pyridines was reported; see: (a) Varela, J. A.; Carlos, L.; Saá, C. *J. Org. Chem.* **2003**, *68*, 8595. (b) Yamamoto, Y.; Kinpara, K.; Saigoku, T.; Takagishi, H.; Okuda, S.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2005**, *127*, 605.

(13) For the regioselective cross-cyclotrimerization of terminal alkynes and nitriles using a stoichiometric amount of a transition metal, see: (a) Suzuki, D.; Nobe, Y.; Watai, Y.; Tanaka, R.; Takayama, Y.; Sato, F.; Urabe, H. *J. Am. Chem. Soc.* **2005**, *127*, 7474. (b) Takahashi, T.; Tsai, F.-Y.; Li, Y.; Wang, H.; Kondo, Y.; Yamanaka, M.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*, 5059.

(14) For the rhodium-catalyzed intermolecular cross-cyclotrimerization of a terminal alkyne and an activated nitrile leading to two regioisomeric pyridines, see: Tanaka, K.; Suzuki, N.; Nishida, G. *Eur. J. Org. Chem.* **2006**, 3917.

(15) Our research group reported the rhodium-catalyzed intermolecular cross-cyclotrimerization of terminal alkynes and isocyanates, but the regioselectivities vary depending on the alkynes used; see: Tanaka, K.; Wada, A.; Noguchi, K. *Org. Lett.* **2005**, *7*, 4737.

(16) For recent reviews of the transition-metal-catalyzed cyclotrimerization for the synthesis of nitrogen heterocycles, see: (a) Varela, J. A.; Saá, C. *Synlett* **2008**, 2571. (b) Heller, B.; Hapke, M. *Chem. Soc. Rev.* **2007**, *36*, 1085. (c) Yamamoto, Y. *Chim. Oggi* **2007**, *25*, 108. (d) Chopade, P. R.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307. (e) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (f) Varela, J. A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787.

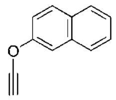
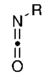
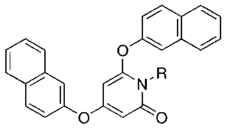
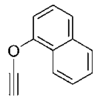
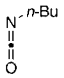
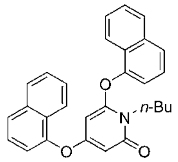
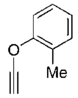
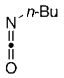
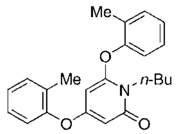
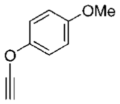
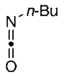
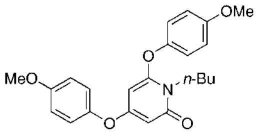
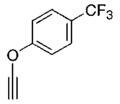
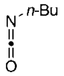
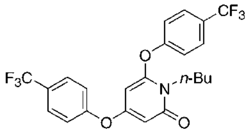
proceeded at room temperature for 1 h to yield 2,4-diaryloxypyridine **7aa** as a single regioisomer in good yield (Table 1, entry 1).[17] The effect of biarylbisphosphine ligands (Figure 1) was then examined, which revealed that the use of electron-rich ligands (entries 1 and 2) furnished **7aa** in higher yields than that of electron-deficient ligands (entries 3 and 4). The catalyst loading could be reduced to 0.025 equiv when H_8-BINAP was used as a ligand (entry 5).

The scope of the 2,4-diaryloxypyridine synthesis was then examined under the above optimal reaction conditions (Table 2).[17] Not only ethyl cyanoacetate (**6a**) but also a series of activated nitriles **6b**−**d** could react with **3a** to give the corresponding diaryloxypyridines in moderate to good yields with perfect regioselectivity without using excess nitriles (0.5 equiv, entries 1−4). Consistent with the mechanism shown in Scheme 4, increasing the amount of **6a** to 1 equiv, which would suppress the competitive homocyclotrimerization of **3a**, improved the yield of pyridine **7aa** (entry 5).[18] Not only activated nitriles **6a**−**d** but also benzonitrile (**6e**) and acetonitrile (**6f**) could participate in this reaction, although excess nitriles were used (entries 6 and 7). With respect to aryl ethynyl ethers, sterically and electronically diverse alkynes could equally react with activated nitriles **6a**,**b** in good yields with perfect regioselectivity (entries 8−15).

Regioselective intermolecular cross-cyclotrimerizations of aryl ethynyl ethers and isocyanates were also investigated using the cationic rhodium(I)/H_8-BINAP catalyst (Table 3).[15,17] Pleasingly, *n*-butyl isocyanate (**8a**) reacted with aryl ethynyl ether **3a** at room temperature for 1 h to yield the corresponding 4,6-diaryloxy-2-pyridone **9aa** with perfect regioselectivity, although the product yield was moderate (entry 1). Increasing the amount of **8a** to 2 equiv improved the yield of 2-pyridone **9aa** (entry 2).[18] Not only *n*-butyl isocyanate (**8a**) but also benzyl isocyanate (**8b**, entry 3) could react with **3a** to yield the corresponding pyridone with perfect regioselectivity, albeit in lower yield. With respect to aryl ethynyl ethers, sterically and electronically diverse alkynes **3b**−**e** could participate in this reaction, although the product yields were lower than that using **3a** (entries 4−7).

In conclusion, we have established that a cationic rhodium(I)/H_8-BINAP complex catalyzes the complete regioselective intermolecular cross-cyclotrimerization of aryl ethynyl ethers and nitriles or isocyanates leading to 2,4-diaryloxypyridines or 4,6-diaryloxy-2-pyridones at room temperature.

Table 3. Rh-Catalyzed Intermolecular Cross-Cyclotrimerizations of Aryl Ethynyl Ethers **3a**−**e** and Isocyanates **8a**,**b**[a]

entry	**3**	**8** (R, equiv)	**9** (% yield[b])
			
1	**3a**	**8a** (*n*-Bu, 1)	**9aa** (43)
2	**3a**	**8a** (*n*-Bu, 2)	**9aa** (53)
3	**3a**	**8b** (Bn, 2)	**9ab** (36)
			
4	**3b**	**8a** (2)	**9ba** (31)
			
5	**3c**	**8a** (2)	**9ca** (31)
			
6	**3d**	**8a** (2)	**9da** (16)
			
7	**3e**	**8a** (2)	**9ea** (33)

[a] Reactions were conducted using $[Rh(cod)_2]BF_4$ (0.010 mmol), H_8−BINAP (0.010 mmol), **3a**−**e** (0.40 mmol), **8a**,**b** (0.40−0.80 mmol), and CH_2Cl_2 (2.0 mL) at rt for 1 h. [b] Isolated yield.

Future studies will focus on the utilization of aryl ethynyl ethers in various transition-metal-catalyzed reactions.

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

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(17) Homo-cyclotrimerization products of **3a**−**e** were generated as byproducts in the reactions of Tables 1−3.

(18) Although the slow addition of aryl ethynyl ether **3a** to nitrile **6a** or isocyanate **8a** and the Rh catalyst over 30 min was also examined, the yields of the corresponding pyridine **7aa** and 2-pyridone **9aa** were not increased.