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Flexible Synthesis of Fused Benzofuran Derivatives by Rhodium-Catalyzed [2 + 2 + 2] Cycloaddition with Phenol-Linked 1,6-Diynes

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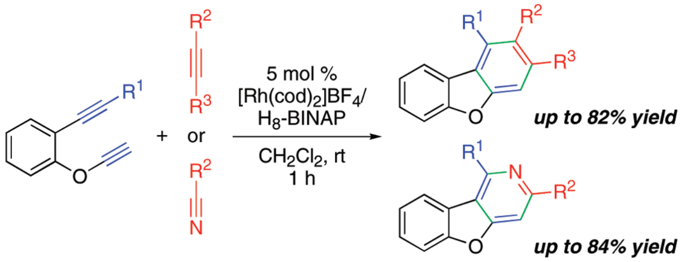
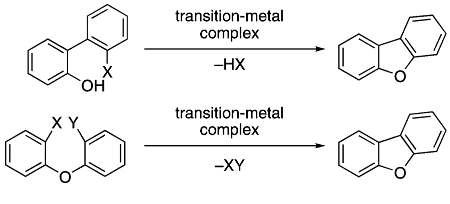
ABSTRACT



A flexible and convenient synthesis of fused benzofuran derivatives has been achieved under mild reaction conditions by cationic rhodium(I)/H_8−BINAP complex-catalyzed [2 + 2 + 2] cycloadditions of phenol-linked 1,6-diynes with alkynes and nitriles.

Fused benzofuran derivatives are an important class of compounds because of their utility in biologically active compounds including pharmaceutical ingredients.[1] Therefore, their convenient as well as flexible syntheses have attracted much attention. Two methods for the construction of fused benzofuran frameworks by metal-catalyzed or mediated coupling reactions have been developed as shown in Scheme 1. One is the intramolecular *O*-arylation of hydroxybiphenyl derivatives,[2] and the other is the intramolecular dehalogenation,[3] dehydrohalogenation,[4] dehydrocarboxylation,[5] and dehydrogenation[6] of diaryl ether derivatives. However, these reactions required harsh reaction conditions (high temperature and basic or acidic conditions), and thus an alternative

Scheme 1



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(1) For dibenzofuran derivatives, see: (a) Voigt, B.; Meijer, L.; Lozach, O.; Schächtele, C.; Totzke, F.; Hilgeroth, A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 823. For azadibenzofuran derivatives, see: (b) Oliveira, A. M. A. G.; Raposo, M. M. M.; Oliveira-Campos, A. M. F.; Machado, A. E. H.; Puapairoj, P.; Pedro, M.; Nascimento, M. S. J.; Portela, C.; Afonso, C.; Pinto, M. *Eur. J. Med. Chem.* **2006**, *41*, 367.

(2) (a) Liu, J.; Fitzgerald, A. E.; Mani, N. S. *J. Org. Chem.* **2008**, *73*, 2951. (b) Kawaguchi, K.; Nakano, K.; Nozaki, K. *J. Org. Chem.* **2007**, *72*, 5119. (c) Martınez, A.; Fernández, M.; Estevez, J. C.; Estevez, R. J.; Castedo, L. *Tetrahedron* **2005**, *61*, 1353. (d) Parmentier, M.; Gros, P.; Fort, Y. *Tetrahedron* **2005**, *61*, 3261. (e) Yue, W. S.; Li, J. J. *Org. Lett.* **2002**, *4*, 2201.

(3) Sanz, R.; Fernández, Y.; Castroviejo, M. P.; Perez, A.; Fananás, F. J. *J. Org. Chem.* **2006**, *71*, 6291.

(4) (a) Liu, Z.; Larock, R. C. *Tetrahedron* **2007**, *63*, 347. (b) Zhang, Y.-M.; Razler, T.; Jackson, P. F. *Tetrahedron Lett.* **2002**, *43*, 8235.

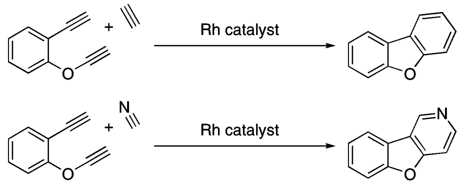
(5) (a) Wang, C.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194. (b) Voutchkova, A.; Coplin, A.; Leadbeater, N. E.; Crabtree, R. H. *Chem. Commun.* **2008**, 6312.

10.1021/ol900802d CCC: $40.75

method that can be carried out under mild reaction conditions (low temperature and neutral conditions) is highly desirable.

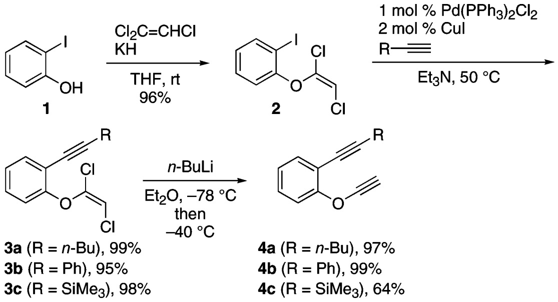
Our research group already demonstrated that cationic rhodium(I)/biaryl bisphosphine complexes are highly effective catalysts for [2 + 2 + 2] cycloadditions, leading to substituted benzenes and pyridines.[7−10] In this paper, we describe a flexible and convenient synthesis of fused benzofuran derivatives by cationic rhodium(I)/H_8−BINAP complex-catalyzed [2 + 2 + 2] cycloadditions of phenol-linked 1,6-diynes[11,12] with alkynes and nitriles (Scheme 2).[13]

Scheme 2



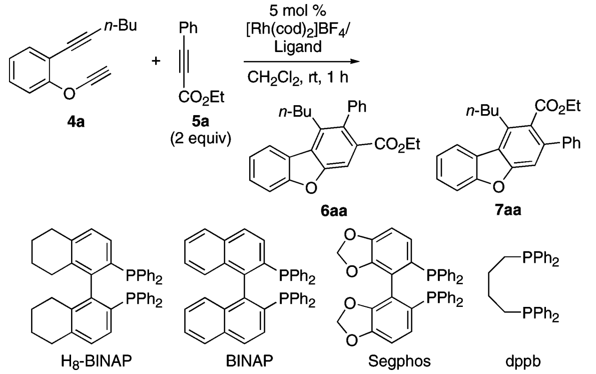
We first examined the synthesis of phenol-linked 1,6-diynes. They could be readily prepared in three steps as shown in Scheme 3. The reaction of a potassium salt of 2-iodophenol (**1**) with 1,1,2-trichloroethylene proceeded to give aryl alkenyl ether **2** in 96% yield.[14] Sonogashira coupling between iodide **2** and terminal alkynes proceeded to give phenol-linked 1,6-enynes **3** in excellent yields. Treatment of **3** with *n*-butyl lithium at −40 °C formed phenol-linked 1,6-diynes **4** in moderate to high yields.

Scheme 3



Thus obtaining the targeted 1,6-diynes, a rhodium-catalyzed [2 + 2 + 2] cycloaddition of 1,6-diyne **4a** and unsymmetrical monoyne **5a** was attempted. Pleasingly, the reaction proceeded to give the corresponding trisubstituted dibenzofurans **6aa** and **7aa** in moerate yield by using a cationic rhodium(I)/H_8−BINAP complex as a catalyst, although poor regioselectivity was observed (Table 1, entry 1). The use of other bisphosphine ligands significantly decreased the product yields (entries 2−4).

Table 1. Effect of Ligands on Yield and Regioselectivity[a]

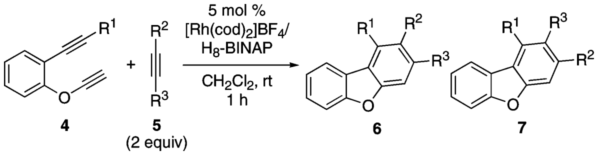


entry	ligand	yield (%)[b]	6aa/7aa
1	H_8−BINAP	56	39:61
2	BINAP	35	34:66
3	Segphos	33	61:39
4	dppb	16	31:69

[a] $[Rh(cod)_2]BF_4$ (0.0050 mmol), H_8−BINAP (0.0050 mmol), **4a** (0.10 mmol), **5a** (0.20 mmol), and CH_2Cl_2 (2.0 mL) were used. [b] Determined by ^1H NMR using 1,4-dimethoxybenzene as an internal standard.

The scope of dibenzofuran synthesis is shown in Table 2.[15] Not only *n*-butyl-(**4a**) but also phenyl- and trimethylsilyl-

Table 2. Synthesis of Substituted Dibenzofurans by RhodiumCatalyzed [2 + 2 + 2] Cycloadditions[a]



entry	**4** (R^1)	**5**(R^2, R^3)	**6**/**7** (% yield)[b]
1	**4a** (*n*-Bu)	**5a** (Ph, CO_2Et)	**6aa** (17)/**7aa** (32)
2	**4b** (Ph)	**5a** (Ph, CO_2Et)	**6ba**/**7ba** (78, **6**/**7** = 66:34)
3	**4c** ($SiMe_3$)	**5a** (Ph, CO_2Et)	**6ca** (36)/**7ca** (36)
4	**4b** (Ph)	**5b** (Me, CO_2Et)	**6bb** (63)/**7bb** (19)
5	**4b** (Ph)	**5c** (Me, CH_2OH)	**6bc** (44)/**7bc** (24)
6[c]	**4b** (Ph)	**5d** (CH_2OH, CH_2OH)	**6bd** (65)
7[c]	**4a** (*n*-Bu)	**5d** (CH_2OH, CH_2OH)	**6ad** (48)
8[c]	**4c** ($SiMe_3$)	**5d** (CH_2OH, CH_2OH)	**6cd** (69)
9	**4b** (Ph)	**5e** (CH_2OMe, CH_2OMe)	**6be** (45)

[a] $[Rh(cod)_2]BF_4$ (0.010 mmol), H_8−BINAP (0.010 mmol), **4** (0.20 mmol), **5** (0.40 mmol), and CH_2Cl_2 (2.0 mL) were used. [b] Isolated yield. [c] Solvent: THF.

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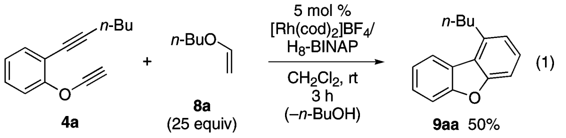
(6) (a) Lee, B. D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008**, *73*, 5022. (b) De Lombaert, S.; Blanchard, L.; Stamford, L. B.; Tan, J.; Wallace, E. M.; Satoh, Y.; Fitt, J.; Hoyer, D.; Simonsbergen, D.; Moliterni, J.; Marcopoulos, N.; Savage, P.; Chou, M.; Trapani, A. J.; Jeng, A. Y. *J. Med. Chem.* **2000**, *43*, 488.

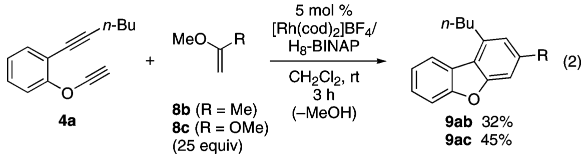
(7) For our accounts, see: (a) Tanaka, K. *Synlett* **2007**, 1977. (b) Tanaka, K.; Nishida, G.; Suda, T. *J. Synth. Org. Chem. Jpn.* **2007**, *65*, 862.

(8) For the pioneering work on $RhCl(PPh_3)_3$-catalyzed [2 + 2 + 2] cycloadditions of 1,6-diynes with monoynes, see: (a) Grigg, R.; Scott, R.; Stevenson, P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1357. For the stoichimetric reaction, see: (b) Müller, E. *Synthesis* **1974**, 761.

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

substituted 1,6-diynes **4b** and **4c** could also participate in this reaction (entries 1−3). With respect to monoynes, a variety of functionalized monoynes **5b**−**e** reacted with **4a**−**c** to give the corresponding trisubstituted dibenzofurans **6** and **7** in moderate to high yields (entries 4−9).

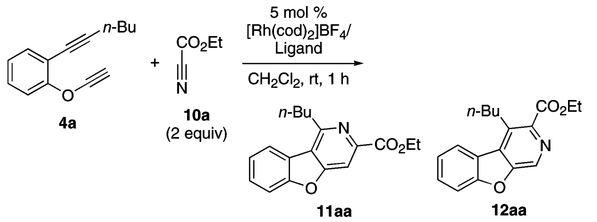




As we have recently reported that enol ethers can be used as gaseous alkyne equivalents in the cationic rhodium(I)/biaryl bisphosphine complex-catalyzed [2 + 2 + 2] cycloadditions,[16,17] the use of enol ethers instead of monoynes was investigated.[15] The reaction of **4a** with *n*-butyl vinyl ether (**8a**) furnished monosubstituted dibenzofuran in moderate yield (eq 1). In the reactions of **4a** with 1,1-disubstituted enol ether **8b** and ketene acetal **8c**, the corresponding *meta*-disubstituted dibenzofurans were obtained with perfect regioselectivities (eq 2).[18]

The present success in the [2 + 2 + 2] cycloadditions of phenol-linked 1,6-diynes with monoynes or enol ethers, leading to substituted dibenzofurans, prompted our investigation into [2 + 2 + 2] cycloadditions of those with nitriles,[19,20] leading to substituted azadibenzofurans. Fortunately, activated nitrile **10a** reacted with 1,6-diyne **4a** to give the corresponding *meta*-disubstituted azadibenzofuran **11aa** in good yield with excellent regioselectivity (Table 3, entry 1).[21,22] The use of other bisphosphine ligands significantly decreased the product yields (entries 2−4).

Table 3. Effect of Ligands on Yield and Regioselectivity[a]

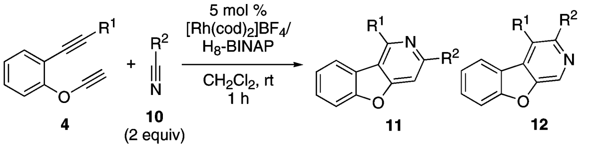


entry	ligand	yield (%)[b]	**11aa/12aa**
1	H_8−BINAP	72	>98:2
2	BINAP	58	>98:2
3	Segphos	57	>98:2
4	dppb	9	>98:2

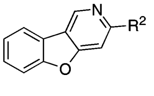
[a] $[Rh(cod)_2]BF_4$ (0.0050 mmol), H_8−BINAP (0.0050 mmol), **4a** (0.10 mmol), **10a** (0.20 mmol), and CH_2Cl_2 (2.0 mL) were used. [b] Determined by ^1H NMR using 1,4-dimethoxybenzene as an internal standard.

The scope of azadibenzofuran synthesis is shown in Table 4.[15] Not only *n*-butyl- (entry 1) but also phenyl-substituted 1,6-diyne **4b** could participate in this reaction furnishing the corresponding *meta*-disubstituted azadibenzofuran in good yield with excellent regioselectivity (entry 2).[21,22] On the

Table 4. Synthesis of Substituted Azadibenzofurans by RhodiumCatalyzed [2 + 2 + 2] Cycloadditions[a]



entry	**4** (R^1)	**10** (R^2, equiv)	**11–13** (% yield[b])
1	**4a** (*n*-Bu)	**10a** (CO_2Et, 2)	**11aa** (67)
2	**4b** (Ph)	**10a** (CO_2Et, 2)	**11ba** (69)
3	**4c** ($SiMe_3$)	**10a** (CO_2Et, 2)	**13ca** (38) / **12ca** (21)
4	**4b** (Ph)	**10b** (CH_2CN, 2)	**11bb** (84)
5	**4b** (Ph)	**10c** (Bz, 2)	**11bc** (75)
6	**4b** (Ph)	**10d** (Ac, 2)	**11bd** (81)
7	**4b** (Ph)	**10e** (Ph, 5)	**11be** (77)
8	**4a** (*n*-Bu)	**10e** (Ph, 5)	**11ae** (75)
9	**4c** ($SiMe_3$)	**10e** (Ph, 5)	**13ce** (20)
10	**4b** (Ph)	**10f** (Me, 10)	**11bf** (46)



13ca (R^2 = CO_2Et)
13ce (R^2 = Ph)

[a] $[Rh(cod)_2]BF_4$ (0.010 mmol), H_8−BINAP (0.010 mmol), **4** (0.20 mmol), **10** (0.40 mmol), and CH_2Cl_2 (2.0 mL) were used. [b] Isolated yield.

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(10) For recent reviews of transition-metal-catalyzed [2 + 2 + 2] cycloadditions, see: (a) Tanaka, K. *Chem. Asian J.* **2009**, *4*, 508. (b) Shibata, T.; Tsuchikama, K. *Org. Biomol. Chem.* **2008**, 1317. (c) Agenet, N.; Buisine, O.; Slowinski, F.; Gandon, V.; Aubert, C.; Malacria, M. *Organic Reactions*; RajanBabu, T. V., Ed.; John Wiley & Sons: Hoboken, 2007; Vol. 68, p 1. (d) Gandon, V.; Aubert, C.; Malacria, M. *Chem. Commun.* **2006**, 2209. (e) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741. (f) Gandon, V.; Aubert, C.; Malacria, M. *Curr. Org. Chem.* **2005**, *9*, 1699. (g) Yamamoto, Y. *Curr. Org. Chem.* **2005**, *9*, 503.

(11) [2 + 2 + 1] Cycloadditions of ynol ethers with $Fe(CO)_5$ giving Fe complexes of 3-oxocyclopentadienes and subsequent cycloadditions of those with alkynes were reported; see: Imbriglio, J. E.; Rainier, J. D. *Tetrahedron Lett.* **2001**, *42*, 6987.

(12) For rhodium(I)-catalyzed [2 + 2 + 2] cycloadditions of diynes with alkynyl ethers, see: (a) Clayden, J.; Moran, W. J. *Org. Biomol. Chem.* **2007**, *5*, 1028. (b) Alayrac, C.; Schollmeyer, D.; Witulski, B. *Chem. Commun.* **2009**, 1464.

(13) For the pioneering works on the syntheses of substituted indolines and carbazoles by $RhCl(PPh_3)_3$-catalyzed [2 + 2 + 2] cycloadditions using nitrogen-bridged 1,6-diynes, see: (a) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 2426. (b) Witulski, B.; Alayrac, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3281. (c) See also ref 12b. For cobalt or iron-mediated formal [2 + 2 + 2] cycloadditions using nitrogen-bridged 1,6-diynes, see: (d) Rainier, J. D.; Imbriglio, J. E. *J. Org. Chem.* **2000**, *65*, 7275. (e) Rainier, J. D.; Imbriglio, J. E. *Org. Lett.* **1999**, *1*, 2037. For iridium(I)/PPh_3-catalyzed analogous [2 + 2 + 2] cycloadditions of silicon-bridged 1,6-diynes with monoynes, leading to substituted siloles, see: (f) Matsuda, T.; Kadowaki, S.; Goya, T.; Murakami, M. *Org. Lett.* **2007**, *9*, 133.

(14) For the synthesis of an *O*-ethynyl-2-naphthol derivative, see: Moyano, A.; Charbonnier, F.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 2919.

(15) Homo-[2 + 2 + 2] cycloadditions of 1,6-diynes **4** proceeded other than the desired cross-[2 + 2 + 2] cycloadditions.

(16) Hara, H.; Hirano, M.; Tanaka, K. *Org. Lett.* **2008**, *10*, 2537.

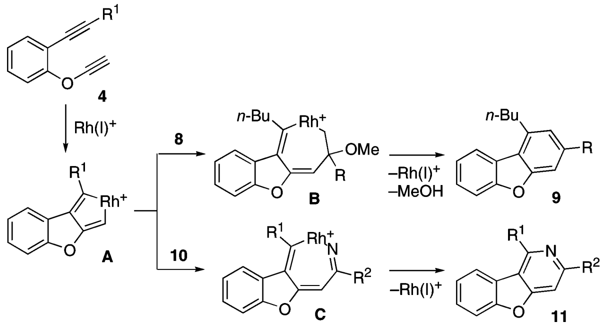
(17) For the pioneering work on a transition-metal-catalyzed [2 + 2 + 2] cycloaddition of a 1,6-diyne with an enol ether, see: Kezuka, S.; Tanaka, S.; Ohe, T.; Nakaya, Y.; Takeuchi, R. *J. Org. Chem.* **2006**, *71*, 543.

(18) In the reaction of **4a** and **8b**, the choice of biaryl bisphosphine ligands did not affect the product yield and regioselectivity. [Yields of **9ab** determined by ^1H NMR using 1,4-dimethoxybenzene as an internal standard: 34% (H_8-BINAP), 34% (BINAP), 33% (Segphos)].

other hand, the reaction of trimethylsilyl-substituted 1,6-diyne **4c** with **10a** furnished desilylated product **13ca** along with *ortho*-disubstituted product **12ca** in moderate yield (entry 3). With respect to nitriles, a variety of activated (**10b-d**) and unactivated (**10e** and **10f**) nitriles reacted with **4a-c** to give the corresponding *meta*-disubstituted azadibenzofurans **11** or desilylated product **13ce** in fair to high yields with excellent regioselectivities (entries 4−10).[21,22]

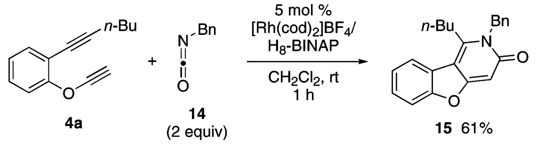
A possible mechanism for the highly regioselective [2 + 2 + 2] cycloadditions of phenol-linked 1,6-diynes **4** with enol ethers **8** and nitriles **10** is shown in Scheme 4. Oxidative coupling of two alkyne moieties of **4** with rhodium leads to rhodacyclopentadiene intermediate **A**. Regioselective insertions of the double bond of **8** and the cyano group of **10** between the sterically less demanding rhodium−carbon bond furnish intermediates **B** and **C**, respectively. The electronically negative sp^2 carbon atom β to the methoxy group of **8** and the nitrogen atom of **10** preferentially form the bonds with the cationic rhodium. Reductive eliminations furnish dibenzofuran **9** and azadibenzofuran **11**, respectively.

Scheme 4



Finally, the reaction of **4a** with isocyanate **14** was investigated, which revealed that the expected 2-pyridone-fused benzofuran **15** was obtained in good yield as a single regioisomer (eq 3).[15,23] The observed high regioselectivity can be explained by preferential bond formation of nitrogen atom of **14** with the cationic rhodium, which is similar to the mechanism shown in Scheme 4.

In conclusion, we have achieved a flexible and convenient synthesis of fused benzofuran derivatives by cationic rhodium(I)/H$_8$−BINAP complex-catalyzed [2 + 2 + 2] cycloadditions with phenol-linked 1,6-diynes. Applications of the present catalysis in the synthesis of ladder-type and helically chiral molecules are currently underway in our laboratory.



(3)

Acknowledgment. This work was supported partly by a Grant-in-Aid for Scientific Research (No. 20675002) from MEXT, Japan. We are grateful to Takasago International Corporation for the gift of H$_8$−BINAP and Segphos, and Umicore for generous supports in supply of a rhodium complex.

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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(19) For cationic rhodium(I)/biaryl bisphosphine complex-catalyzed [2 + 2 + 2] cycloadditions of alkynes with nitriles, see: (a) Tanaka, K.; Suzuki, N.; Nishida, G. *Eur. J. Org. Chem.* **2006**, 3917. (b) Wada, A.; Noguchi, K.; Hirano, M.; Tanaka, K. *Org. Lett.* **2007**, *9*, 1295. (c) Tanaka, K.; Hara, H.; Nishida, G.; Hirano, M. *Org. Lett.* **2007**, *9*, 1907. For neutral rhodium(I) complex-catalyzed [2 + 2 + 2] cycloadditions of alkynes with nitriles, see: (d) Cioni, P.; Diversi, P.; Ingrosso, G.; Lucherini, A.; Ronca, P. *J. Mol. Catal.* **1987**, *40*, 337. (e) Cioni, P.; Diversi, P.; Ingrosso, G.; Lucherini, A.; Ronca, P. *J. Mol. Catal.* **1987**, *40*, 359. (f) Diversi, P.; Ermini, L.; Ingrosso, G.; Lucherini, A. *J. Organomet. Chem.* **1993**, *447*, 291.

(20) For recent reviews involving the synthesis of nitrogen heterocycles by transition-metal-catalyzed [2 + 2 + 2] cycloadditions, see: (a) Varela, J. A.; Saá, C. *Synlett* **2008**, 2571. (b) Hess, W.; Treutwein, J.; Hilt, G. *Synthesis* **2008**, 3537. (c) Heller, B.; Hapke, M. *Chem. Soc. Rev.* **2007**, *36*, 1085. (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.

(21) Similar regioselectivities were observed in ruthenium- and cobalt-catalyzed [2 + 2 + 2] cycloadditions of unsymmetrical 1,6-diynes with nitriles. For Ru(II), see: (a) Yamamoto, Y.; Kinpara, K.; Ogawa, R.; Nishiyama, H.; Itoh, K. *Chem.−Eur. J.* **2006**, *12*, 5618. (b) Yamamoto, Y.; Kinpara, K.; Nishiyama, H.; Itoh, K. *Adv. Synth. Catal.* **2005**, *347*, 1913. (c) Yamamoto, Y.; Kinpara, K.; Saigoku, T.; Takagishi, H.; Okuda, S.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2005**, *127*, 605. (d) Yamamoto, Y.; Okuda, S.; Itoh, K. *Chem. Commun.* **2001**, 1102. (e) Yamamoto, Y.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2001**, *123*, 6189. For Co(I), see: (f) Goswami, A.; Ohtaki, K.; Kase, K.; Ito, T.; Okamoto, S. *Adv. Synth. Catal.* **2008**, *350*, 143. (g) Kase, K.; Goswami, A.; Ohtaki, K.; Tanabe, E.; Saino, N.; Okamoto, S. *Org. Lett.* **2007**, *9*, 931. (h) Hrdina, R.; Starà, I.; Dufkovà, L.; Mitchel, S.; Cisarovà, I.; Kotora, M. *Tetrahedron* **2006**, *62*, 968. (i) Gutnov, A.; Heller, B.; Fischer, C.; Drexler, H.-J.; Spannenberg, A.; Sundermann, B.; Sundermann, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3795.

(22) The regioisomeric *ortho*-disubstituted azadibenzofurans **12** were not generated at all or generated in only trace amounts (<3% yields).

(23) For cationic rhodium(I)/biaryl bisphosphine complex-catalyzed [2 + 2 + 2] cycloadditions of alkynes with isocyanates, see: (a) Tanaka, K.; Wada, A.; Noguchi, K. *Org. Lett.* **2005**, *7*, 4737. (b) Tanaka, K.; Takahashi, Y.; Suda, T.; Hirano, M. *Synlett* **2008**, 1724. For neutral rhodium(I) complex-catalyzed [2 + 2 + 2] cycloadditions of alkynes with isocyanates, see: (c) Flynn, S. T.; Hasso-Henderson, S. E.; Parkins, A. W. *J. Mol. Catal.* **1985**, *32*, 101. (d) Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2782. (e) Kondo, T.; Nomura, M.; Ura, Y.; Wada, K.; Mitsudo, T. *Tetrahedron Lett.* **2006**, *47*, 7107. (f) Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 12370. (g) Lee, E. E.; Rovis, T. *Org. Lett.* **2008**, *10*, 1231.