

Liquid Enol Ethers and Acetates as Gaseous Alkyne Equivalents in Rh-Catalyzed Chemo- and Regioselective Formal Cross-Alkyne Cyclotrimerization

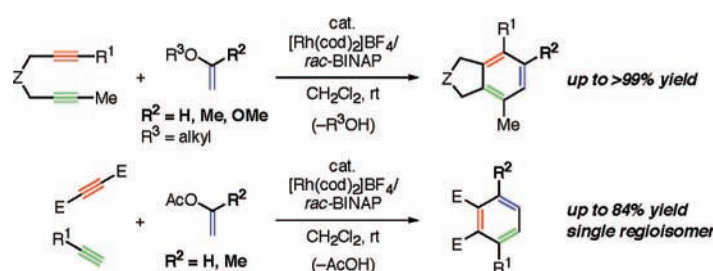
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ABSTRACT



A cationic rhodium(I)/*rac*-BINAP complex catalyzes chemo- and regioselective formal cross-cyclotrimerizations of alkynes with enol ethers or acetates. Commercially available and cheap liquid enol ethers and acetates could be used as convenient gaseous alkyne equivalents in the present rhodium catalyses.

Transition-metal-catalyzed [2 + 2 + 2] cycloadditions of alkynes have been shown to be a valuable method for the synthesis of substituted benzenes.¹ Although gaseous alkynes such as acetylene and propyne can be used for the transition-metal-catalyzed alkyne cyclotrimerization,² alternative liquid

reagents are more convenient to handle than gaseous alkynes using conventional laboratory equipment. As such, com-

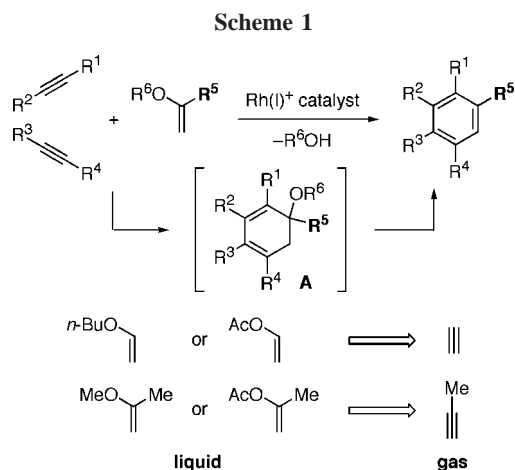
(1) For recent reviews of transition-metal-catalyzed [2 + 2 + 2] cycloadditions, see: (a) Agenet, N.; Buisine, O.; Slowinski, F.; Gandon, V.; Aubert, C.; Malacria, M. In *Organic Reactions*; Overman, L. E., Ed.; John Wiley & Sons: Hoboken, 2007; Vol. 68, p 1. (b) Chopade, P. R.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307. (c) Gandon, V.; Aubert, C.; Malacria, M. *Chem. Commun.* **2006**, 2209. (d) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741. (e) Yamamoto, Y. *Curr. Org. Chem.* **2005**, *9*, 503. (f) Robinson, J. E. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; p 129.

(2) For selected recent examples, see: (a) Heller, B.; Gutnov, A.; Fischer, C.; Drexler, H.-J.; Spannenberg, A.; Redkin, D.; Sundermann, C.; Sundermann, B. *Chem. Eur. J.* **2007**, *13*, 1117. (b) Ramana, C. V.; Salian, S. R.; Gonnade, R. G. *Eur. J. Org. Chem.* **2007**, 5483. (c) Young, D. D.; Senaiar, R. S.; Deiters, A. *Chem. Eur. J.* **2006**, *12*, 5563. (d) Yamamoto, Y.;

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(3) (a) Kezuka, S.; Tanaka, S.; Ohe, T.; Nakaya, Y.; Takeuchi, R. *J. Org. Chem.* **2006**, *71*, 543. For their first discovery of neutral iridium(I)/bisphosphine complex-catalyzed [2 + 2 + 2] cycloadditions, see: (b) Takeuchi, R.; Tanaka, S.; Nakaya, Y. *Tetrahedron Lett.* **2001**, *42*, 2991. (c) Takeuchi, R.; Nakaya, Y. *Org. Lett.* **2003**, *5*, 3659. (d) Kezuka, S.; Okado, T.; Niou, E.; Takeuchi, R. *Org. Lett.* **2005**, *7*, 1711.

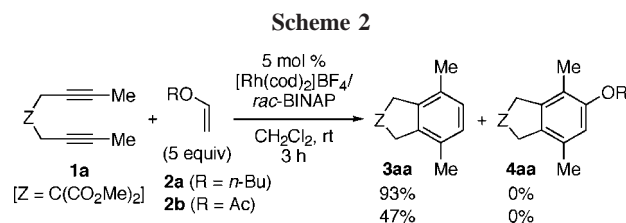
mercially available and cheap liquid enol ethers and acetates are possible gaseous alkyne equivalents as shown in Scheme 1.^{3,4} If a [2 + 2 + 2] cycloaddition of two alkyne units with



one enol ether or acetate could proceed, initially formed cyclohexadiene **A** would be aromatized to the corresponding substituted benzene through elimination of alcohol or acetic acid.^{3,4} Our research group already demonstrated that cationic rhodium(I)/BINAP-type bisphosphine complexes [BINAP = 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl]⁵ are highly effective catalysts for [2 + 2 + 2] cycloadditions of alkynes with not only monoynes⁶ but also monoenes.⁷ In this paper, we describe a cationic rhodium(I)/*rac*-BINAP complex-catalyzed chemo- and regioselective formal cross-cyclotrimerization of alkynes with enol ethers or acetates.

Recently, Takeuchi and co-workers reported that a neutral iridium(I)/dppf complex catalyzes a [2 + 2 + 2] cycloaddition of 1,6-diyne **1a** with *n*-butyl vinyl ether (**2a**) at elevated temperature (70 °C).³ However, the reaction furnished two aromatized products **3aa** and **4aa**, and **4aa** was generated as the major product.³ We anticipated that the high Lewis acidity of the cationic rhodium(I)/BINAP-type bisphosphine complexes would facilitate the elimination of *n*-butanol from the initially formed cyclohexadiene interme-

diolate, which may furnish tetrasubstituted benzene **3aa** as a sole product. We first investigated the reaction of **1a** with **2a** in the presence of a [Rh(cod)₂]BF₄/*rac*-BINAP complex (5 mol %). We were pleased to find that the reaction proceeded at room temperature to give the desired aromatized product **3aa** exclusively in high yield (Scheme 2). After screening various BINAP-type bisphosphine



ligands, the use of *rac*-BINAP furnished **3aa** in the highest yield. Although the reaction of **1a** with vinyl acetate (**2b**) was also examined, **3aa** was obtained in lower yield than that with **2a** (Scheme 2).

Thus, we explored the scope of this process using 5 equiv of enol ethers as shown in Table 1. Not only malonate- (**1a**, entry 1) but also tosylamide- (**1b**, entry 2) and oxygen-linked (**1c**, entry 3) 1,6-diyne could be employed for this reaction. With respect to enol ethers, the use of *n*-butyl vinyl ether (**2a**, entries 1–3) furnished the corresponding aromatized products **3aa–ca** in higher yields than **3ac–cc** obtained from isopropenyl methyl ether (**2c**, entries 4–6). Importantly, commercially available liquid ketene acetal **2d** could participate in this reaction as a gaseous ethynyl methyl ether equivalent, which furnished the corresponding bicyclic methoxybenzenes **3ad–cd** in high yield (entries 7, 9, and 10).⁸ When the amount of ketene acetal **2d** reduced to 1.1 equiv, the yield of the desired product **3ad** decreased to 65% (entry 8). Although a hexane solution of ethyl ethynyl ether is commercially available, it was unstable.⁹ The reaction of unsymmetrical 1,6-diyne **1d** bearing methyl and methoxy-carbonyl at each alkyne terminus with **2c** and **2d** furnished the corresponding pentasubstituted benzenes **3dc** and **3dd**, respectively, with perfect regioselectivity (entries 11 and 12).

A possible mechanism for the present regioselective [2 + 2 + 2] cycloaddition of **1d** with **2c** or **2d** is shown in Scheme 3. Diyne **1d** reacts with rhodium to form rhodacyclopentadiene **B**. Subsequent regioselective insertion of **2c** or **2d** forms intermediate **D** through intermediate **C**, which is stabilized by coordination of the carbonyl group and the methoxy group to the cationic rhodium. Reductive elimination of rhodium furnishes substituted benzene **3dc** or **3dd** and methanol.

The present success in the partial intramolecular cross [2 + 2 + 2] cycloaddition of 1,6-diyne with enol ethers

(4) Although palladium-catalyzed [2 + 2 + 2] cycloadditions of dimethyl acetylenedicarboxylate with vinyl ethers and vinyl esters were reported, the reactions require a large excess of the vinyl compounds (100 equiv) and a long reaction time (3–5 days), see: Stephan, C.; Munz, C.; Dieck, H. T. *J. Organomet. Chem.* **1993**, *452*, 223.

(5) 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.

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(7) For examples, see: (a) Tsuchikama, K.; Kuwata, Y.; Shibata, T. *J. Am. Chem. Soc.* **2006**, *128*, 13686. (b) Tanaka, K.; Nishida, G.; Sagae, H.; Hirano, M. *Synlett* **2007**, 1426. (c) Shibata, T.; Kawachi, A.; Ogawa, M.; Kuwata, Y.; Tsuchikama, K.; Endo, K. *Tetrahedron* **2007**, *63*, 12853.

(8) The reaction of a malonate-linked terminal 1,6-diyne with ketene acetal **2d** (5 equiv) was also examined, but the yield of the desired cross-[2 + 2 + 2] cycloaddition product was significantly decreased (ca. 30%) due to the rapid homo-[2 + 2 + 2] cycloaddition of the diyne.

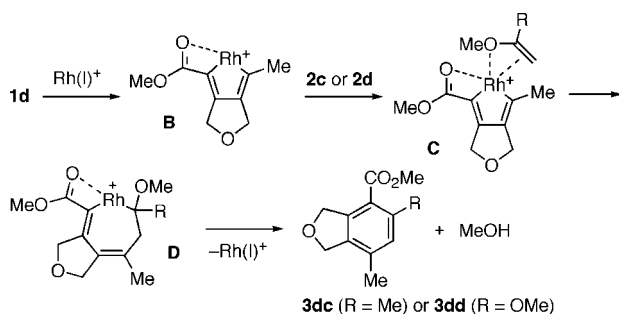
(9) A cationic rhodium(I)/BINAP complex-catalyzed [2 + 2 + 2] cycloaddition of diynes with alkynyl ethers towards the synthesis of aryl ethers, see: Clayden, J.; Moran, W. J. *Org. Biomol. Chem.* **2007**, *5*, 1028.

Table 1. Rh(I)⁺/*rac*-BINAP-Catalyzed [2 + 2 + 2] Cycloaddition of 1,6-Diynes **1** with Enol Ethers **2**^a

entry	1 (Z)	2	3 yield (%) ^b
1	1a [Z = C(CO ₂ Me) ₂]	2a (n-BuO)	3aa 93
2	1b (Z = NTs)	2a	3ba 96
3 ^c	1c (Z = O)	2a	3ca 95
4	1a [Z = C(CO ₂ Me) ₂]	2c (MeO)	3ac 85
5	1b (Z = NTs)	2c	3bc 74
6	1c (Z = O)	2c	3cc 76
7	1a [Z = C(CO ₂ Me) ₂]	2d (OMe)	3ad >99
8 ^d	1a [Z = C(CO ₂ Me) ₂]	2d	3ad 65
9	1b (Z = NTs)	2d	3bd 71
10	1c (Z = O)	2d	3cd 91
11 ^{c,e,f}	1d (O)	2c	3dc 60
12 ^{c,e}	1d	2d	3dd 69

^a Reactions were conducted using [Rh(cod)₂]BF₄ (0.015 mmol, 5 mol %), *rac*-BINAP (0.015 mmol, 5 mol %), **1** (0.30 mmol), **2** (1.50 mmol, 5 equiv), and CH₂Cl₂ (2.0 mL) at rt for 3 h. ^b Isolated yield. ^c For 16 h. ^d **2d**: 1.1 equiv. ^e At 80 °C in (CH₂Cl)₂. ^f **2c**: 25 equiv.

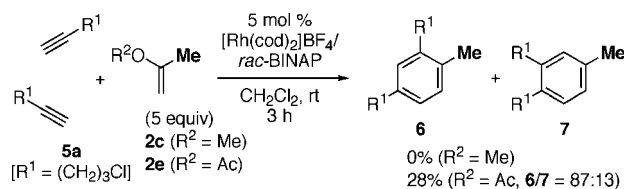
Scheme 3



prompted our investigation into a complete intermolecular cross [2 + 2 + 2] cycloaddition of monoynes with enol ethers. Interestingly, although terminal monoyne **5a** failed

to react with enol ether **2c** in the presence of the same rhodium catalyst, the reaction of **5a** with enol ester **2e** proceeded to give the corresponding trisubstituted benzenes in 28% yield as a mixture of two regioisomers **6** and **7** (Scheme 4). The reactions of an electron-deficient internal

Scheme 4



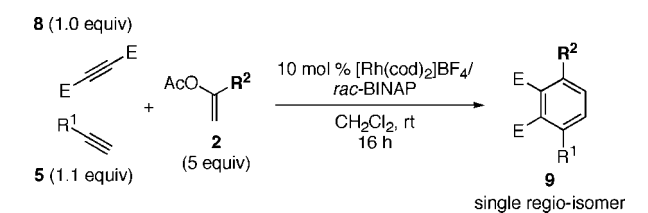
monoyne, dimethyl acetylenedicarboxylate (**8a**), with enol ether **2c** and enol ester **2e** were also examined, but both **2c** and **2e** failed to react with **8a** in the presence of the [Rh(cod)₂]BF₄/*rac*-BINAP catalyst.⁴ On the other hand, we have already reported that two molecules of terminal monoyne **5** react with one molecule of dialkyl acetylenedicarboxylate **8** in the presence of the [Rh(cod)₂]BF₄/H₈-BINAP catalyst to give the corresponding tetrasubstituted benzene in high yield with high regioselectivity.^{6a,c}

Because enol ester **2e** showed no reactivity to electron-deficient internal monoyne **8a** and moderate reactivity to terminal monoyne **5a**, cross [2 + 2 + 2] cycloaddition of **2e**, **8a**, and 1-dodecyne (**5b**) was investigated in the presence of the [Rh(cod)₂]BF₄/*rac*-BINAP catalyst.^{10,11} We were pleased to find that the desired three-component coupling proceeded at room temperature to give the corresponding tetrasubstituted benzene **9abe** in good yield with perfect regioselectivity (Table 2, entry 1). Thus, we explored the scope of this process as shown in Table 2. With respect to terminal monoynes, alkyl- (**5b**, entry 1), chloroalkyl- (**5a**, entry 3), benzyl- (**5c**, entry 4), phenyl- (**5d**, entry 5), and trimethylsilyl-substituted (**5e**, entry 6) terminal monoynes could participate in this reaction to give the corresponding tetrasubstituted benzenes in moderate to good yields with perfect regioselectivity. Not only dimethyl (**8a**, entry 1) but

(10) For examples of transition-metal-catalyzed intermolecular three-component cocyclotrimerization, see: (a) Mori, N.; Ikeda, S.; Sato, Y. *J. Am. Chem. Soc.* **1999**, *121*, 2722. (b) Mori, N.; Ikeda, S.; Odashima, K. *Chem. Commun.* **2001**, 181. (c) Chouraqui, G.; Petit, M.; Aubert, C.; Malacria, M. *Org. Lett.* **2004**, *6*, 1519. (d) Yamamoto, Y.; Ishii, J.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2004**, *126*, 3712. (e) Ura, Y.; Sato, Y.; Tsujita, H.; Kondo, T.; Imachi, M.; Mitsudo, T. *J. Mol. Catal. A* **2005**, *239*, 166. (f) Deng, L.; Giessert, A. J.; Gerlitz, O. O.; Dai, X.; Diver, S. T.; Davies, H. M. L. *J. Am. Chem. Soc.* **2005**, *127*, 1342. (g) Yamamoto, Y.; Ishii, J.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2005**, *127*, 9625. (h) Komagawa, S.; Saito, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2446.

(11) For examples of intermolecular three-component cocyclotrimerization using stoichiometric transition-metal complexes, see: (a) Wakatsuki, Y.; Aoki, K.; Yamazaki, H. *J. Am. Chem. Soc.* **1979**, *101*, 1123. (b) Takahashi, T.; Kotora, M.; Xi, Z. *J. Chem. Soc., Chem. Commun.* **1995**, 361. (c) Takahashi, T.; Xi, Z.; Yamazaki, A.; Liu, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **1998**, *120*, 1672. (d) Takahashi, T.; Tsai, F.-Y.; Li, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **1999**, *121*, 11093. (e) Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2001**, *123*, 7925. (f) Takahashi, T.; Tsai, F.-Y.; Li, Y.; Wang, H.; Kondo, Y.; Yamanaka, M.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*, 5059. (g) Tanaka, R.; Nakano, Y.; Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2002**, *124*, 9682.

Table 2. Rh(I)⁺/*rac*-BINAP-Catalyzed [2 + 2 + 2] Cycloaddition of Two Different Monoynes **8** and **5** with Enol Esters **2**^a



entry	8 (E)	5 (R ¹)	2 (R ²)	9	yield ^b (%)
1	8a (CO ₂ Me)	5b (<i>n</i> -C ₁₀ H ₂₁)	2e (Me)	9abe	69
2	8b (CO ₂ <i>t</i> -Bu)	5b (<i>n</i> -C ₁₀ H ₂₁)	2e (Me)	9bbe	66
3	8a (CO ₂ Me)	5a [Cl(CH ₂) ₃]	2e (Me)	9aae	41
4	8a (CO ₂ Me)	5c (Bn)	2e (Me)	9ace	44
5	8a (CO ₂ Me)	5d (Ph)	2e (Me)	9ade	51
6	8a (CO ₂ Me)	5e (Me ₃ Si)	2e (Me)	9aee	73
7 ^c	8a (CO ₂ Me)	5e (Me ₃ Si)	2e (Me)	9aee	60
8 ^d	8a (CO ₂ Me)	5e (Me ₃ Si)	2e (Me)	9aee	63
9	8a (CO ₂ Me)	5b (<i>n</i> -C ₁₀ H ₂₁)	2b (H)	9abb	49
10	8a (CO ₂ Me)	5e (Me ₃ Si)	2b (H)	9aeb	84

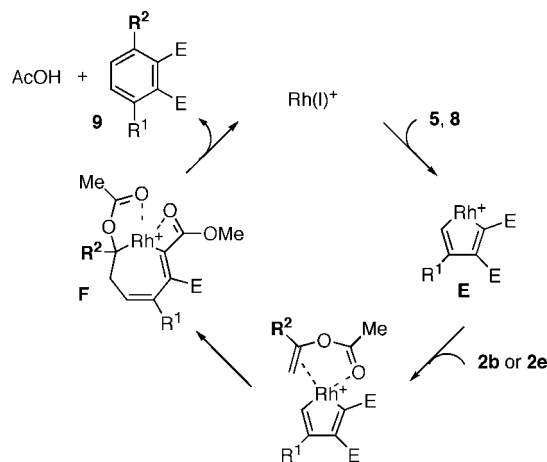
^a [Rh(cod)₂]BF₄ (0.030 mmol), *rac*-BINAP (0.030 mmol), **8** (0.30 mmol), **5** (0.33 mmol), **2** (1.50 mmol), and CH₂Cl₂ (2.0 mL) were used. ^b Isolated yield. ^c **2e**: 1.1 equiv. ^d Catalyst: 5 mol %.

also di-*tert*-butyl acetylenedicarboxylate (**8b**, entry 2) could be employed for this reaction. Furthermore, the use of vinyl acetate (**2b**) furnished the corresponding trisubstituted benzenes in good yields with perfect regioselectivity (entries 9 and 10). Although the yield of the desired product decreased, the reaction could be carried out using 1.1 equiv of enol ester **2e** (entry 7) or 5 mol % of the rhodium catalyst (entry 8).

A possible mechanism for the present chemo- and regioselective cross [2 + 2 + 2] cycloaddition of two different monoynes with enol esters is shown in Scheme 5. Terminal monoynone **5** and electron-deficient internal monoynone **8** react with rhodium to form rhodacyclopentadiene **E** due to the steric repulsion between R¹ and the BINAP ligand. Coordination of enol ester **2b** or **2e** followed by regioselective insertion forms intermediate **F**, which is stabilized by coordination of the carbonyl groups to the cationic rhodium. Reductive elimination of rhodium furnishes substituted benzene **9** and acetic acid.

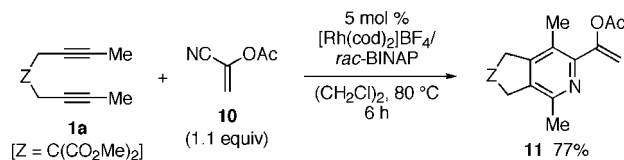
As our previous report demonstrated that a chemoselective [2 + 2 + 2] cycloaddition of the cyano group of acrylonitrile with a 1,6-diyne proceeded to give a bicyclic 2-vinylpyridine

Scheme 5



in good yield,¹² chemoselectivity of a [2 + 2 + 2] cycloaddition of commercially available 1-cyanovinyl acetate (**10**) with 1,6-diyne **1a** is of interest. Like acrylonitrile, the cyano group of **10** selectively reacted with **1a** to give bicyclic 2-(1-acetoxyvinyl)pyridine **11** in high yield (Scheme 6).

Scheme 6



Future studies will focus on the further application of these catalyses to the convenient synthesis of a wide variety of aromatic compounds.

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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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