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Cationic Rhodium(I)/BIPHEP Complex-Catalyzed Cross-Cyclotrimerization of Silylacetylenes and Unsymmetrical Electron-Deficient Internal Alkynes

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ARTICLE INFO

Article history:

Received

Received in revised form

Accepted

Available online

Keywords:

Alkynes

Alkynoates

Cyclotrimerization

Rhodium

Silylacetylenes

ABSTRACT

It has been established that a cationic rhodium(I)/BIPHEP complex catalyzes the chemo- and regioselective intermolecular cross-cyclotrimerization of silylacetylenes with unsymmetrical electron-deficient internal alkynes. Chemoselectivity was highly depending on steric bulk of the unsymmetrical electron-deficient internal alkynes used. Two molecules of sterically less demanding alkynoates and alkynone reacted with one molecule of the silylacetylene, on the contrary, one molecule of a sterically demanding alkynoate reacted with two molecules of the silylacetylene.

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The transition-metal-catalyzed intermolecular cross-cyclotrimerization of alkynes has been received much attention as a useful method for the synthesis of densely substituted benzenes.¹ Although a number of transition-metal complexes are capable of catalyzing alkyne cyclotrimerization, the transition-metal catalysts that can simultaneously control both chemo- and regioselectivities are limited in number.² In the last 15 years, several transition-metal complexes were found to catalyze the chemo- and regioselective intermolecular cross-cyclotrimerization of two or three different alkynes involving symmetrical internal alkynes.^{3,4} For example, our research group found in 2003 that a cationic rhodium(I)/H₈-BINAP complex catalyzes the intermolecular cross-cyclotrimerization of terminal alkynes and symmetrical internal alkynes (dialkyl acetylenedicarboxylates).^{4,5} After this report, the intermolecular cross-cyclotrimerization of terminal alkynes with unsymmetrical internal alkynes (alkynoates) has also been accomplished using a perfluoroalkylacetylene⁶ and aryl ethynyl ethers⁷ as terminal alkynes,⁸ and the cationic rhodium(I)/H₈-BINAP complex as a catalyst. In this paper, we have established that a cationic rhodium(I)/BIPHEP complex is capable of catalyzing the intermolecular cross-cyclotrimerization of silylacetylenes and unsymmetrical electron-deficient internal alkynes (alkynoates and an alkynone).

In our previous report, the cationic rhodium(I)/H₈-BINAP complex catalyzed the intermolecular cross-cyclotrimerization of trimethylsilylacetylene (**1a**) and diethyl acetylenedicarboxylate at room temperature to give the corresponding 2:1 (= **1a**/diethyl

acetylenedicarboxylate) reaction product in moderate yield (57%) with almost perfect regioselectivity along with the corresponding 1:2 reaction product in low yield (Scheme 1).

Scheme 1. The cationic rhodium(I)/H₈-BINAP complex-catalyzed intermolecular cross-cyclotrimerization of trimethylsilylacetylene (**1a**) and diethyl acetylenedicarboxylate.

On the other hand, the use of an unsymmetrical electron-deficient internal alkyne, ethyl 2-butynoate (**2a**), instead of diethyl acetylenedicarboxylate afforded not the corresponding 2:1 (= **1a**/**2a**) reaction products **A** but the corresponding 1:2 reaction products **3aa** and **4aa** as major products with good yield and regioselectivity (Table 1, entry 1). Screening of biaryl bisphosphine ligands (entries 1–4) revealed that the use of BIPHEP afforded **3aa** and **4aa** in the highest yield (entry 4). Sterically demanding biaryl bisphosphine ligand, tol-BINAP, was also tested, but the combined yield of **3aa** and **4aa** decreased significantly, although the improved regioselectivity was observed (entry 5). The ratio of **1a**/**2a** was examined, while the

combined yields of **3aa** and **4aa** were not improved (entries 6 and 7). Thus, the conditions employed in entry 4 were selected as the best conditions.

Table 1. Optimization of Reaction Conditions for Cationic Rhodium(I)/Biaryl Bisphosphine Complex-Catalyzed Cross-Cyclotrimerization of **1a** with **2a**^a

entry	ligand	time (h)	1a / 2a	A / % yield ^b	3-6aa / % yield ^b (3aa / 4aa / 5aa / 6aa)
1	H ₈ -BINAP	19	2:1	5	76 (71:29:0:0)
2	BINAP	20	2:1	8	79 (82:18:0:0)
3	Segphos	20	2:1	8	61 (83:16:1:0)
4	BIPHEP	16	2:1	12	85 (79:20:1:0)
5	tol-BINAP	16	2:1	10	50 (86:14:0:0)
6	BIPHEP	16	1.2	19	71 (82:14:4:0)
7	BIPHEP	16	5:1	21	74 (81:19:0:0)

^a [Rh(cod)₂]BF₄ (0.010 mmol), ligand (0.010 mmol), **1a** (0.10–0.50 mmol), **2a** (0.10–0.20 mmol), and (CH₂Cl)₂ (1.5 mL) were used.

^b Isolated yield.

Figure 1. Structures of biaryl bisphosphine ligands.

With the optimized reaction conditions in hand, the reaction scope was examined as shown in Table 2.⁹ With respect to silylacetylenes, not only trimethylsilylacetylene (**1a**, entry 1) but also sterically more demanding triethyl- (**1b**, entry 2), benzyldimethyl- (**1c**, entry 3), and *tert*-butyldimethyl- (**1d**, entry 4) silylacetylenes could be employed for this reaction, while lower product yields were observed. However, extremely bulky triisopropylsilylacetylene (**1e**, entry 5) failed to react with **2a**. With respect to unsymmetrical electron-deficient internal alkynes, not only ethyl and methyl 2-butynoates (**2a** and **2b**, entries 1 and 6) but also methyl 2-heptynoate and 2-undecynoate (**2c** and **2d**, entries 7 and 8) could be employed for this reaction, although product yields and regioselectivity were lower than those using **2a** and **2b**. Alkynyl ketone **2e** was also capable of reacting with **1a** to give the corresponding benzenes **3ae–5ae** in moderate yields, while the regioselectivity decreased significantly (entry 9). In all entries, 2:1 (= **1a/2a**) reaction products **B** were obtained as minor products in low yields (0–15%).

A preparative scale reaction was also conducted with one-half of the standard catalyst loading in five-fold greater substrate concentration to give **3aa–5aa** in 77% yield (Scheme 2).

Synthetic transformations of the cross-cyclotrimerization products are shown in Schemes 4–6. Treatment of three regioisomeric pentasubstituted benzenes **3aa–5aa** with

tetrabutylammonium fluoride (TBAF) afforded two regioisomeric tetrasubstituted benzenes **7** and **8** (Scheme 3), which cannot be accessible by our previously reported cationic rhodium(I)/H₈-BINAP complex-catalyzed intermolecular cross-cyclotrimerization of two molecules of the electron-rich terminal alkyne with one molecule of the dialkyl acetylenedicarboxylate.

Table 2. Cationic Rhodium(I)/BIPHEP Complex-Catalyzed Cross-Cyclotrimerization of **1a–e** with **2a–e**^a

entry	1 (Si)	2 (R ¹ , R ²)	B / % yield ^b	3-6 / % yield ^b (3 / 4 / 5 / 6)
1	1a (SiMe ₃)	2a (Me, OEt)	12	85 (79:20:1:0)
2	1b (SiEt ₃)	2a (Me, OEt)	4	45 (85:13:2:0)
3	1c (SiBnMe ₂)	2a (Me, OEt)	4	34 (84:12:4:0)
4	1d [Si(<i>t</i> -Bu)Me ₂]	2a (Me, OEt)	2	21 (69:28:3:0)
5	1e [Si(<i>i</i> -Pr) ₃]	2a (Me, OEt)	0	0
6	1a (SiMe ₃)	2b (Me, OMe)	13	77 (81:18:1:0)
7	1a (SiMe ₃)	2c (<i>n</i> -Bu, OMe)	7	50 (67:29:4:0)
8	1a (SiMe ₃)	2d (<i>n</i> -C ₈ H ₁₇ , OMe)	15	61 (63:27:3:7)
9	1a (SiMe ₃)	2e (Et, Me)	2	52 (59:30:11:0)

^a [Rh(cod)₂]BF₄ (0.10 mmol), BIPHEP (0.10 mmol), **1** (0.20 mmol), **2** (0.10 mmol), and (CH₂Cl)₂ (1.5 mL) were used.

^b Isolated yield.

Scheme 2. Preparative scale reaction of **1a** and **2a**.

Scheme 3. Desilylation of **3aa–5aa** with TBAF leading to tetrasubstituted benzenes **7** and **8**.

Scheme 4. Iodo-desilylation of **3aa–5aa** with ICl leading to iodobenzenes **9–11**.

Not only desilylation but also iodo-desilylation could be conducted. Treatment of silylbenzenes **3aa–5aa** with ICl¹⁰ afforded a mixture of iodobenzenes **9–11** in good yield (Scheme

4). The thus obtained iodobenzenes **9–11** were subjected to the palladium-catalyzed cross-coupling reactions with *p*-chlorophenylboronic acid and trimethylsilylacetylene to give biaryls **12–14** and alkynes **15–17**, respectively (Scheme 5).

Scheme 5. Palladium-catalyzed cross-coupling reactions of iodobenzenes **9–11** with *p*-chlorophenylboronic acid and trimethylsilylacetylene.

Interestingly, the reaction of **1a** and commercially available phenyl-substituted alkynoate **2f** afforded the corresponding 2:1 (= **1a/2f**) reaction product **18** in good yield with high regioselectivity along with a small amount of regioisomer **19** without formation of the corresponding 1:2 reaction products (Scheme 6).

Scheme 6. Cationic rhodium(I)/BIPHEP complex-catalyzed intermolecular cross-cyclotrimerization of **1a** and diethyl 3-phenylpropynoate (**2f**).

Scheme 7 A possible mechanism for the intermolecular cross-cyclotrimerization of **1a–d** and **2a–e**.

A possible mechanism for the chemo- and regioselective intermolecular cross-cyclotrimerization of **1a–d** and **2a–e** is shown in Scheme 7. In general, the rhodacycle generated from the alkynoate, in which the alkoxy carbonyl group is located in the α -position to rhodium, is preferable as a result of the

coordination of the carbonyl group to rhodium.⁶ Therefore, generation of regioisomers **3** and **4** from rhodacycles **C** and **D**, respectively, is more preferable than that from rhodacycle **E**, in which the alkoxy carbonyl group is located in the β -position to rhodium.

A possible mechanism for the chemo- and regioselective intermolecular cross-cyclotrimerization of **1a** and **2f** is shown in Scheme 8. The formation of rhodacycles **C** and **D** from two molecules of internal alkyne **2f** may be unfavorable due to large steric hindrance. Therefore, the formation of rhodacycle **F** from **1a** and **2f** followed by the reaction with **1a** giving regioisomers **18** and **19** is plausible, this mechanism is similar to that of the cationic rhodium(I)/H₈-BINAP complex-catalyzed intermolecular cross-cyclotrimerization of electron-rich terminal alkynes and dialkyl acetylenedicarboxylates.⁴

Scheme 8. A possible mechanism for the intermolecular cross-cyclotrimerization of **1a** and **2f**.

In conclusion, we have established that a cationic rhodium(I)/BIPHEP complex catalyzes the chemo- and regioselective intermolecular cross-cyclotrimerization of silylacetylenes with unsymmetrical electron-deficient internal alkynes.¹¹ Chemoselectivity was highly depending on steric bulk of the unsymmetrical electron-deficient internal alkynes used. Two molecules of sterically less demanding alkynoates and an alkynone reacted with one molecule of the silylacetylene, on the contrary, one molecule of a sterically demanding alkynoate reacted with two molecules of the silylacetylene.

Acknowledgments

This work was supported partly by ACT-C from the Japan Science and Technology Agency (Japan). We are grateful to Takasago International Corporation for the gift of Segphos, tol-BINAP, and H₈-BINAP, and Umicore for generous support in supplying the rhodium complex.

References and notes

- For selected recent reviews of transition-metal-catalyzed cyclotrimerization, see: (a) Tanaka, K.; Kimura, Y.; Murayama, K. *Bull. Chem. Soc. Jpn.* **2015**, *88*, 375. (b) *Transition-metal-mediated Aromatic Ring Construction*; Tanaka, K., Ed.; John Wiley & Sons: Hoboken, USA, 2013. (c) Okamoto, S.; Sugiyama, Y. *Synlett* **2013**, *24*, 1044. (d) Broere, D. L. J.; Ruijter, E. *Synthesis* **2012**, *44*, 2639. (e) Weding, N.; Hapke, M. *Chem. Soc. Rev.* **2011**, *40*, 4525. (f) Domínguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2011**, *40*, 3430. (g) Tanaka, K. *Chem. Asian J.* **2009**, *4*, 508. (h) Leboeuf, D.; Gandon, V.; Malacria, M. In *Transition metal-mediated [2+2+2] cycloadditions*, Handbook of Cyclization Reactions, 2010; p 367. (i) Hess, W.; Treutwein, J.; Hilt, G. *Synthesis* **2008**, 3537. (j) Shibata, T.; Tsuchikama, K. *Org. Biomol. Chem.* **2008**, *6*, 1317. (k) Agenet, N.; Buisine, O.; Slowinski, F.; Gandon, V.; Aubert, C.; Malacria, M.; In *Organic Reactions*; Overman, L. E., Eds.; John Wiley & Sons: Hoboken, USA, 2007; p. 1. (l) Chopade, P. R.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307. (m) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741.

2. For a review of the transition-metal-catalyzed intermolecular cross-cyclotrimerization of alkynes, see: Galan, B. R.; Rovis, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 2830.
3. For Ni(0), see: (a) Mori, N.; Ikeda, S.-I.; Odashima, K. *Chem. Comm.* **2001**, 181. For Ru(II), see: (b) Ura, Y.; Sato, Y.; Shiotsuki, M.; Kondo, T.; Mitsudo, T. *J. Mol. Catal. A* **2004**, *209*, 35. (c) Kotha, S.; Seema, V.; Mobin, S. M. *Synthesis* **2011**, 1581. (d) Ura, Y.; Sato, Y.; Tsujita, H.; Kondo, T.; Imachi, M.; Mitsudo, T. *J. Mol. Catal. A: Chem.* **2005**, *239*, 166. (e) Wu, C.-Y.; Lin, Y.-C.; Chou, P.-T.; Wang, Y.; Liu, Y.-H.; *Dalton Trans.* **2011**, *40*, 3748. For Rh(I), see: (f) Konno, T.; Moriyasu, K.; Kinugawa, R.; Ishihara, T. *Org. Biomol. Chem.* **2010**, *8*, 1718. (g) Tanaka, K.; Nishida, G.; Ogino, M.; Hirano, M.; Noguchi, K. *Org. Lett.* **2005**, *7*, 3119. For Ir(I), see: (h) Takeuchi, R.; Nakaya, Y. *Org. Lett.* **2003**, *5*, 3659. (i) Onodera, G.; Matsuzawa, M.; Aizawa, T.; Kitahara, T.; Shimizu, Y.; Kezuka, S.; Takeuchi, R. *Synlett* **2008**, 755.
4. (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.
5. For reviews involving the rhodium-catalyzed intermolecular cyclotrimerization, see: (a) Shibata, Y.; Tanaka, K. *Synthesis* **2012**, *44*, 323. (b) Tanaka, K. *Heterocycles* **2012**, *85*, 1017. See also refs 1a and 1b.
6. Tanaka, K.; Hara, H.; Nishida, G.; Hirano, M. *Org. Lett.* **2007**, *9*, 1907.
7. Komine, Y.; Miyauchi, Y.; Kobayashi, M.; Tanaka, K. *Synlett* **2010**, 3092.
8. The transition-metal-catalyzed cross-cyclotrimerization involving propylates has been reported. See: Abdulla, K.; Booth, B. L.; Stacey, C. *J. Organomet. Chem.* **1985**, *293*, 103. See also ref 3a.
9. The reaction of alkylacetylene **1f** and **2a** (**1f** / **2a** = 2:1) was also examined, while poor chemo- and regioselectivity were observed.

$n\text{-C}_{10}\text{H}_{21}\text{C}\equiv\text{CH}$ (1f, 2 equiv) + $\text{Me-C}\equiv\text{C-CO}_2\text{Et}$ (2a)

10 mol % $[\text{Rh}(\text{cod})_2]\text{BF}_4 / \text{BIPHEP}$
 CH_2Cl_2 , rt, 16 h

Product 1: $n\text{-C}_{10}\text{H}_{21}\text{C}_6\text{H}_8\text{CO}_2\text{Et}$ (56%, 4 regioisomers, rs = 51:30:14:5)
 Product 2: $n\text{-C}_{10}\text{H}_{21}\text{C}_6\text{H}_8(\text{CO}_2\text{Et})_2$ (31%, 3 regioisomers, rs = 75:17:8)
10. (a) Foster, R. W.; Tame, C. J.; Hailes, H. C.; Sheppard, T. D. *Adv. Synth. Catal.* **2013**, *355*, 2353. (b) Ihara, H.; Sugimoto, M. *J. Am. Chem. Soc.* **2009**, *131*, 7502.
11. The cationic rhodium(I)/(R)-tol-BINAP complex-catalyzed highly chemo-, regio-, and enantioselective cross-cyclotrimerization of silylacetylenes, di-*tert*-butyl acetylenedicarboxylate, and acrylamides has been reported. See: Hara, J.; Ishida, M.; Kobayashi, M.; Noguchi, K.; Tanaka, K. *Angew. Chem., Int. Ed.* **2014**, *53*, 2956.