$RhCl_3$/Amine-catalyzed Cyclotrimerization of Alkynes

Kenta Yoshida, Ichiro Morimoto, Koichi Mitsudo, and Hideo Tanaka*
Division of Chemistry and Biochemistry, Graduate School of Natural Science and Technology, Okayama University, 3-1-1 Tsushima-naka, Okayama 700-8530

(Received May 7, 2007; CL-070485; E-mail: tanaka95@cc.okayama-u.ac.jp)

$RhCl_3$/amine was found to be an efficient catalyst for the cyclotrimerization of alkynes. The [2 + 2 + 2] cyclotrimerization of internal alkynes proceeded smoothly to afford hexa-substituted benzenes regioselectively in moderate to high yields.

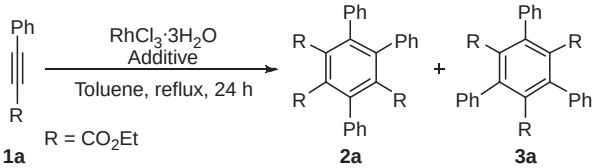
The transition-metal-catalyzed [2 + 2 + 2] cyclotrimerization of alkynes is a straightforward method to construct benzene derivatives in a one-pot process.[1] Although various transition metals (Ni,[2] Rh,[3] Pd,[4] Ru,[5] Co,[6] Ti,[7] and Mo[8]) catalyze alkyne cyclotrimerization, it has been not always easy to conduct intermolecular reactions regioselectively in high yields. In particular, the internal alkynes, which can be applied for the trimerization, have been often restricted to those bearing small or activated substituents such as acetylene dicarboxylate. For instance, the efficiency of the trimerization of internal alkynes bearing aryl and ester moieties, such as ethyl phenylpropiolate (PhC≡CCO_2Et), is quite low.[9] Therefore, a more general and efficient trimerization method has been in great demand.

Recently, we found that the combination of $RhCl_3$ and tertiary-alkylamines works as a unique catalyst. Herein, we report the $RhCl_3$/amine-catalyzed cyclotrimerization of alkynes, which can be widely applicable to internal alkynes. The cyclotrimerization of alkynes proceeded smoothly to afford hexa-substituted benzenes regioselectively in moderate to high yields.

In the presence of $RhCl_3 \cdot 3H_2O$ (8 mol %) and Et_3N (30 mol %), the cyclotrimerization of alkyne **1a** at reflux in toluene occurred to give **2a** in 67% yield in a virtually completely regioselective manner (Table 1, Entry 1). Without any amine, the cyclotrimerization of alkyne **1a** gave **2a** only in 20% yield (Entry 2). Various other *sec*- and *tert*-amines were applied to the $RhCl_3$-catalyzed trimerization reaction (Entries 3–11), and we found that *i*-Pr_2NEt, a highly electron-donating amine, was the most effective among them (Entry 5). With *i*-Pr_2NEt, the amount of Rh catalyst could be reduced to 3 mol % (Entry 7). The ratio of Rh/amine influenced the reactivity (Entries 6–8). With 1:3 of Rh/amine catalyst, the cycloadduct was obtained in the highest yield (93%, Entry 7). On the other hand, electron-deficient amine (e.g. Ph_3N) was found to be ineffective for the trimerization reaction (Entry 9). Pyridine was ineffective, and the starting material **1a** was recovered quantitatively, probably due to the generation of $Rh(py)_3Cl_3$ (Entry 10).[10] Using a bidentate amine ligand such as TMEDA, product **2a** was not obtained (Entry 11). The addition of an electron-donating monodentate amine might be essential for generation of the "active catalyst" in situ.

Next, the combination of $RhCl_3 \cdot 3H_2O$ with *i*-Pr_2NEt was successfully applied to the cyclotrimerization using a variety of alkynes (Table 2). Using internal alkynes, in many cases, the cyclotrimerization proceeded to give the corresponding cyclotrimerization products in high yields with good regioselectivities (Entries 1–5). The cyclotrimerization of alkynes **1a** or **1b** was highly regioselective (Entries 1–3).

Table 1. Cyclotrimerization using several additives



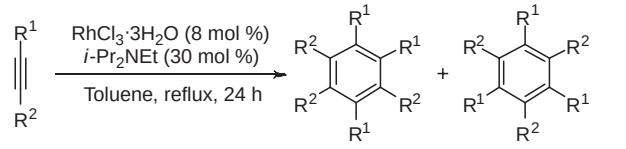
1a **2a** **3a**

Entry	Additive[a]	Yield/%[b]	**2a**:**3a**
1	Et_3N (8/30)	67	98:2
2	none	20	99:1
3	Et_2NH (8/30)	32	97:3
4	*i*-Pr_2NH (8/30)	69	95:5
5	*i*-Pr_2NEt (8/30)	91 (89)[c]	96:4 (99:1)[c]
6	*i*-Pr_2NEt (3/6)	74	96:4
7	*i*-Pr_2NEt (3/9)	93	97:3
8	*i*-Pr_2NEt (3/12)	84	96:4
9	Ph_3N (8/30)	26	97:3
10	Pyridine (8/30)	—	—
11	TMEDA (8/30)	—	—

[a]The values in parentheses are Rh/mol % and additive/mol %. [b]Isolated yield. [c]$RhCl_3$ was employed.

Decreasing the amount of $RhCl_3 \cdot 3H_2O$ (3 mol %) and *i*-Pr_2NEt (9 mol %), the yields and regioselectivities of **2** were almost the same. By GC analysis, it was revealed that the reaction was completed within 9 h to afford the cycloadduct quantitatively (Entry 2). When using alkyne **1c**, the cycloadduct was obtained quantitatively, while a slight decline of the regioselectivity was observed (Entry 4). When using symmetrical internal alkynes **1d** and **1e**, cycloadducts were obtained in 96 and 73% yields, respectively (Entries 5 and 6). Terminal alkynes also could be utilized in the Rh/amine-catalyzed trimerization (Entries 7–10). The trimerization of phenylacetylene, *p*-tolylacetylene, and 1-octyne gave the cycloadducts **2f**–**2h** in 98, 97, and 87% yields, respectively (Entries 7–9). Only in the case of ethyl propiolate (**1i**), the yield of the corresponding products was rather low (75%, Entry 10). In all cases, the unsymmetrical isomers **2a**–**2i** were obtained as the major products. The regioselectivity in the $RhCl_3$/amine-catalyzed cyclotrimerization was highly influenced by the substituents of alkynes. Especially, the reaction of alkynes bearing aryl groups proceeded with virtually complete regioselectivities. Blum and co-workers reported trimerization using $[R_4N]^+[RhCl_4]^-$, an anionic Rh^{III} catalyst, but the reactivity and regioselectivity of the cycloadducts were unsatisfactory[3f] and quite different from $RhCl_3$/*i*-Pr_2NEt catalyst. From this result, we proposed that $RhCl_3$ would be reduced by *i*-Pr_2NEt to generate Rh^I complexes coordinated by *i*-Pr_2NEt. Rh^I complexes bearing σ-donative trialkyl-

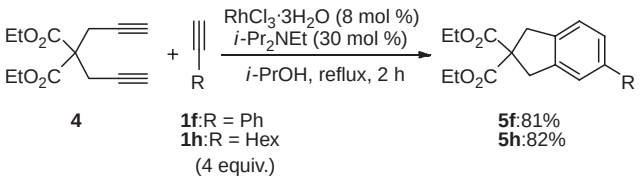
Table 2. Cyclotrimerization of several alkynes



1 2 3

Entry	R^1	R^2		Time/h	Yield/%[a]	**2**:**3**
1	Ph	CO_2Et	**1a**	24	91 (93)[b]	96:4
2	Ph	CO_2Et	**1a**	9	87 (99)[c]	96:4
3	Ph	Me	**1b**	24	87 (91)[b]	>99:<1
4	Me	CO_2Et	**1c**	24	95 (90)[b]	76:24
5	Pr	Pr	**1d**	24	96	—
6	Ph	Ph	**1e**	24	73	—
7	Ph	H	**1f**	12	98 (94)[b]	94:6
8	*p*-MeC_6H_4	H	**1g**	12	97	>99:<1
9	Hex	H	**1h**	12	87	67:33
10	EtO_2C	H	**1i**	12	75	74:26

[a]Isolated yield. [b]3 mol % of $RhCl_3 \cdot 3H_2O$ and 9 mol % of *i*-Pr_2NEt were employed. [c]GC yield.



Scheme 1. Cycloaddition of diyne and alkynes.

amines assumed to interact with alkynes by strong back-donation to promote the reductive cyclization to give rhodacyclopentadiene. The high-regioselectivity of Rh/amine system might be caused by the regioselective construction of the rhodacycle.

Finally, the combination of $RhCl_3 \cdot 3H_2O$ with *i*-Pr_2NEt was applied to the [4 + 2] cycloaddition of a diyne and alkynes (Scheme 1). The cycloaddition of diyne **4** and phenylacetylene (**1f**) or 1-octyne (**1h**) gave the cycloadducts **5f** and **5h** in 81 and 82% yields, respectively.

In summary, we have developed the $RhCl_3$/amine-catalyzed [2 + 2 + 2] cyclotrimerization of alkynes, which can be widely applicable for various alkynes, providing tri- or hexa-substituted benzenes regioselectively in moderate to high yields. The [4 + 2] cycloaddition of diynes and alkynes has also been developed based on the use of the Rh/amine complex, providing benzene derivatives in high yields. Further investigation of the structure and catalytic activity of Rh/amine complex is currently in progress in our laboratory.

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References and Notes

1 For reviews see: a) S. Kotha, E. Brahmachary, K. Lahiri, *Eur. J. Org. Chem.* **2005**, 4741. b) S. Saito, Y. Yamamoto, *Chem. Rev.* **2000**, *100*, 2901. c) D. B. Grotjahn, in *Comprehensive Organometallic Chemistry* II, **1995**, Vol. 12, (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson, L. Hegedus), Pergamon, Oxford, pp. 741–770. d) R. Boese, A. P. V. Sickle, K. P. C. Vollhardt, *Synthesis* **1994**, 1374. e) N. E. Shore, in *Comprehensive Organic Synthesis*, **1991**, Vol. 5 (Ed.: B. M. Trost, I. Fleming), Pergamon, Oxford, pp. 1129–1162.

2 a) C. Müller, R. J. Lachicotte, W. D. Jones, *Organometallics* **2002**, *21*, 1975. b) A. Jeevanandam, R. P. Korioi, I-w. Huang, C.-H. Cheng, *Org. Lett.* **2002**, *4*, 807. c) S. Saito, T. Kawasaki, N. Tsuboya, Y. Yamamoto, *J. Org. Chem.* **2001**, *66*, 796. d) Y. Sato, K. Ohashi, M. Mori, *Tetrahedron Lett.* **1999**, *40*, 5231. e) Y. Saito, T. Nishimata, M. Mori, *Heterocycles* **1997**, *44*, 443. f) Y. Sato, T. Nishimata, M. Mori, *J. Org. Chem.* **1994**, *59*, 6133. g) G. P. Chiusoli, L. Pallini, G. Terenghi, *Transition Met. Chem.* **1983**, *3*, 189.

3 a) K. Tanaka, K. Toyoda, A. Wada, K. Shirasaki, M. Hirano, *Chem. Eur. J.* **2005**, *11*, 1145. b) L. Dufková, L. Císarová, P. Stepnicka, M. Kotora, *Eur. J. Org. Chem.* **2003**, 2882. c) H. Kinoshita, H. Shinokubo, K. Oshima, *J. Am. Chem. Soc.* **2003**, *125*, 7784. d) Q. Sun, X. Zhou, K. Islam, D. J. Kyle, *Tetrahedron Lett.* **2001**, *42*, 6495. e) I. Ojima, A. T. Vu, J. V. McCullagh, A. Kinoshita, *J. Am. Chem. Soc.* **1999**, *121*, 3230. f) I. Amer, T. Bernstein, M. Eisen, J. Blum, K. P. C. Volhardt, *J. Mol. Catal.* **1990**, *60*, 313. g) R. Grigg, R. Scott, P. Stevenson, *Tetrahedron Lett.* **1982**, *23*, 2691. h) E. Müller, *Synthesis* **1974**, 761. i) J. P. Collman, J. W. Kang, W. F. Little, M. F. Sullivan, *Inorg. Chem.* **1968**, *7*, 1298.

4 a) J. S. Cheng, H. F. Jiang, *Eur. J. Org. Chem.* **2004**, 643. b) M. F. N. N. Carvalho, F. M. T. Almeida, A. M. Galvão, A. J. L. Pombeiro, *J. Organomet. Chem.* **2003**, *679*, 143. c) Y. Yamamoto, A. Nagata, H. Nagata, Y. Ando, Y. Arikawa, K. Tatsumi, K. Itoh, *Chem. Eur. J.* **2003**, *9*, 2469. d) J. Li, H. Jiang, M. Chen, *J. Org. Chem.* **2001**, *66*, 3627. e) A. K. Jhingan, W. F. Maier, *J. Org. Chem.* **1987**, *52*, 1161.

5 a) Y. Yamamoto, K. Kinpara, T. Saigoku, H. Takagishi, S. Okuda, H. Nishiyama, K. Itoh, *J. Am. Chem. Soc.* **2005**, *127*, 605. b) Y. Yamamoto, J. Ishii, H. Nishiyama, K. Itoh, *J. Am. Chem. Soc.* **2004**, *126*, 3712. c) Y. Ura, Y. Sato, M. Shiotsuki, T. Kondo, T. Mitsudo, *J. Mol. Catal. A: Chem.* **2004**, *209*, 35. d) E. Rüba, R. Schmid, K. Kirchner, M. J. Calhorda, *J. Organomet. Chem.* **2003**, *682*, 204. e) Y. Yamamoto, T. Arakawa, R. Ogawa, K. Itoh, *J. Am. Chem. Soc.* **2003**, *125*, 12143. f) J.-U. Peters, S. Blechert, *Chem. Commun.* **1997**, 1983.

6 a) N. Saino, F. Amemiya, E. Tanabe, K. Kase, S. Okamoto, *Org. Lett.* **2006**, *8*, 1439. b) V. Gandon, C. Aubert, M. Malacria, *Chem. Commun.* **2006**, 2209. c) G. Hilt, T. Vogler, W. Hess, F. Galbiati, *Chem. Commun.* **2005**, 1474. d) L. Yong, H. Butenschön, *Chem. Commun.* **2002**, 2852. e) M. S. Sigman, A. W. Fatland, B. E. Eaton, *J. Am. Chem. Soc.* **1998**, *120*, 5130. f) S. H. Lecker, N. H. Nguyen, K. P. C. Vollhardt, *J. Am. Chem. Soc.* **1986**, *108*, 856.

7 a) F. T. Ladipo, V. Sarveswaran, J. V. Kingston, R. A. Huyck, S. Y. Bylikin, S. D. Carr, R. Watts, S. Parkin, *J. Organomet. Chem.* **2004**, *689*, 502. b) O. V. Ozerov, B. O. Patrick, F. T. Ladipo, *J. Am. Chem. Soc.* **2000**, *122*, 6423. c) O. V. Ozerov, F. T. Ladipo, B. O. Patrick, *J. Am. Chem. Soc.* **1999**, *121*, 7941. d) E. S. Johnson, G. J. Balaich, P. E. Fanwick, I. P. Rothwell, *J. Am. Chem. Soc.* **1997**, *119*, 11086.

8 a) Y. Sato, T. Nishimata, M. Mori, *J. Org. Chem.* **1994**, *59*, 6133. b) N. Kaneta, T. Hirai, M. Mori, *Chem. Lett.* **1995**, 627.

9 a) M. Toganoh, Y. Matsuo, E. Nakamura, *J. Organomet. Chem.* **2003**, *683*, 295. b) H. Yan, A. M. Beatty, T. P. Fehlner, *Organometallics* **2002**, *21*, 5029. c) P. Cioni, P. Diversi, G. Ingrosso, A. Lucherini, P. Ronca, *J. Mol. Catal.* **1987**, *40*, 337. d) S. T. Flynn, S. E. Hasso-Henderson, A. W. Parkins, *J. Mol. Catal.* **1985**, *32*, 101. e) R. Diercks, H. tom Dierk, *Z. Naturforsch., B: Chem. Sci.* **1984**, *39B*, 180. f) W. Hübel, C. Hoogzand, *Chem. Ber.* **1960**, *93*, 103.

10 J. P. Collman, H. F. Holtzclaw Jr., *J. Am. Chem. Soc.* **1958**, *80*, 2054.

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