ChemComm

Highly chemo- and regio-selective [2 + 2 + 2] cycloaddition of unsymmetrical 1,6-diynes with terminal alkynes catalyzed by Cp*Ru(cod)Cl under mild conditions†

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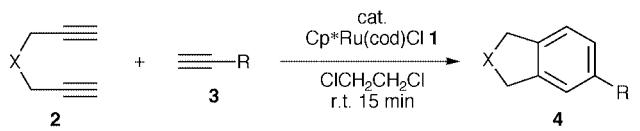
Received (in Cambridge, UK) 17th January 2000, Accepted 24th February 2000
Published on the Web 17th March 2000

Ru(II)-catalyzed cycloaddition of unsymmetrical 1,6-diynes gives the desired cycloadducts in high yields with a regioselectivity *meta*:*ortho* = 88:12–98:2.

Transition-metal catalyzed [2 + 2 + 2] cyclotrimerizations of alkynes has been recognized as a straightforward route to substituted benzenes.[1] The control of both the chemo- and regio-chemistries in the cyclotrimerization of two or three different alkyne components, however, have been a crucial problem. Although the selective cyclocotrimerization of three different alkynes was achieved using stoichiometric zirconocene reagent,[2] the regiochemistry problem has remained unsolved. In addition, catalytic reactions are ideal from both the environmental and economical points of view. The intramolecular cyclization of triynes was pioneered as a completely chemo- and regio-selective process by Vollhardt in work on the catalytic reactions of $CpCo(CO)_2$,[3] and subsequently, many triyne cyclizations have been applied for the syntheses of complex polycyclic systems.[4] Intermolecular couplings between a diyne and a monoalkyne have also been realized as a successful method to construct bicyclic frameworks.[3,5] At the expense of the complete regio- and chemo-selections, this partially intermolecular approach becomes more advantageous than the triyne methodology, because a wide variety of readily accessible or commercially available diynes and monoalkynes could directly be used. The chemoselectivity can be improved using an excess amount of a monoalkyne, although a satisfactory level of regiocontrol has not been achieved in previous diyne–monoalkyne couplings. Herein, we report the first Ru-catalyzed regioselective cycloaddition between unsymmetrical 1,6-diynes and monoalkynes.

Recently, we have found that Cp*Ru(cod)Cl **1**: (Cp* = pentamethylcyclopentadienyl, cod = cycloocta-1,5-diene) effectively catalyzes the selective intermolecular coupling of 1,6-heptadiynes with 2,5-dihydrofuran.[6] In order to extend the catalytic utility of the ruthenium complex **1**, we further explored the catalyzed cross-cyclotrimerization of 1,6-diynes with monoalkynes. To the best of our knowledge, ruthenium-catalyzed [2 + 2 + 2] cyclotrimerizations of monoalkynes has scarcely been investigated so far,[7] and no example of co-cyclotrimerization of different alkynes was found in previous reports.[1,8] At the outset, dimethyl dipropargylmalonate **2a** [X = $C(CO_2Me)_2$] and 2 equiv. of hex-1-yne **3a** (R = Bu) were treated with 1 mol% of **1** in 1,2-dichloroethane at *ambient* temperature (Scheme 1). The



Scheme 1

† Electronic supplementary information (ESI) available: experimental procedures and analytical data for **4** and **6**. See http://www.rsc.org/suppdata/cc/b0/b000466i/

starting diyne **2a** was completely consumed within 15 min, and silica-gel column chromatography of the crude reaction mixture gave the desired indan derivative **4a** in 89% yield (TOF = 356 h^{-1}; Table 1, entry 1). The undesired competitive dimerization and trimerization of **2a** were effectively suppressed (11%), and the cyclotrimerization of **3a** was not detected in the crude reaction mixture by ^1H NMR spectroscopy. The yield and the selectivity were slightly improved using 4 equiv. of **3a** (entry 2). The reaction of phenyl acetylene **3b** (R = Ph) required a longer reaction time (14 h) even using 3 mol% of **1a** (entry 3). A biphenyl derivative **4b** was obtained in 74% yield. In contrast to these results, a terminal alkyne possessing a bulky substituent, *tert*-butyl acetylene **3c** (R = Bu^t) gave the corresponding cycloadduct **4c** only in low yield (entry 4). In this case, substantial amounts of the dimer and the trimer of **2a** were formed. In addition to terminal alkynes, the parent acetylene **3d** (R = H) was found to be an effective monoalkyne component for our catalyzed cycloaddition. The diyne **2a** was treated with **1** at 0 °C for 1 h under acetylene gas (balloon) to afford **4d** in 84% yield (entry 5).

Table 1 Cp*Ru(cod)Cl-catalyzed cycloaddition of 1,6-diynes **2a–c** with terminal alkynes **3**[a]

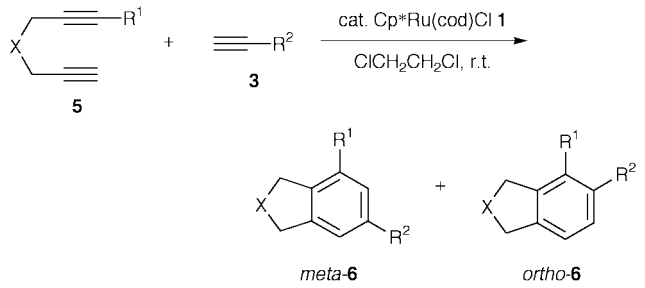
					Yield[b] (%)	
Entry	X	R	Catalyst (mol%)	*t*	**4**	Dimer + trimer
1	$C(CO_2Me)_2$	Bu	1	15 min	**4a**, 89	11
2	$C(CO_2Me)_2$	Bu[c]	1	15 min	**4a**, 94	5
3	$C(CO_2Me)_2$	Ph	3	14 h	**4b**, 74	21
4	$C(CO_2Me)_2$	Bu^t	1	30 min	**4c**, 21	53
5	$C(CO_2Me)_2$	H[d]	1	1 h	**4d**, 84	9
6	NTs	Bu	1	10 min	**4e**, 80	—
7	O	Bu	1	12 h	**4f**, 68	18

[a] All reactions were carried out with a terminal alkyne (2 equiv.) in 1,2-dichloroethane at r.t. [b] Isolated yield. [c] 4 equiv. [d] Under acetylene gas (balloon) at 0 °C.

Furthermore, this novel protocol using the Ru(II)-catalyst was successfully applied to other heterocyclic species. The cycloaddition of *N*,*N*-dipropargyl tosylamide **2b** (X = NTs) with hex-1-yne **3a** was complete within 10 min at ambient temperature to afford an isoindoline derivative **4e** as the sole product in 80% yield (entry 6). A phthalan derivative **4f** was obtained in 68% yield along with the dimer and trimer of **2c** (entry 7).

We next investigated the regiochemistry in the cycloaddition of a series of unsymmetrical 1,6-diynes **5** (Scheme 2). The regiochemistry of the cyclotrimerization key steps have been examined only to a limited degree: a few examples of regioselective cycloaddition using $ClRh(PPh_3)_3$ have been reported, but these were limited to alkynes possessing a hydroxyl group.[5f,k] In fact, the reaction of a malonate derivative **5a** [X = $C(CO_2Me)_2$, R^1 = Me] with hexyne **3a** at 60 °C for 3 days using 5 mol% $ClRh(PPh_3)_3$ gave a 5,7-disubstituted indan derivative *meta*-**6a** and its 5,6-disubstituted isomer *ortho*-**6a** in

DOI: 10.1039/b000466i



Scheme 2

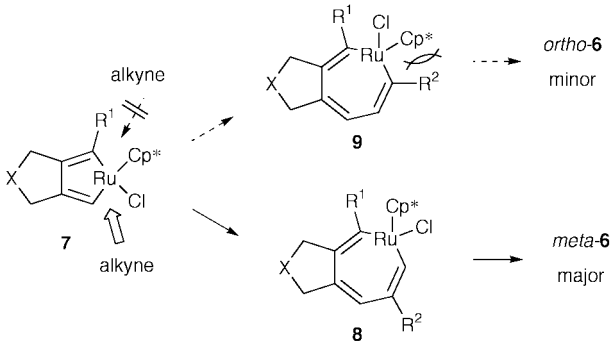
Table 2 Cp*Ru(cod)Cl-catalyzed cycloaddition of 1,6-diynes **5a–c** with terminal alkynes **3**[a]

Entry	X	R^1	R^2	Catalyst (mol%)	Yield[b] (%) t	(*meta*:*ortho*)[c]
1	$C(CO_2Me)_2$	Me	Bu	1	1 h	**6a**, 85 (93:7)
2	$C(CO_2Me)_2$	Me	Me[d]	3	18 h	**6b**, 80 (94:6)
3	$C(CO_2Me)_2$	Me	CH_2OMe	1	3 h	**6c**, 86 (94:6)
4	$C(CO_2Me)_2$	Me	Ph	3	24 h	**6d**, 82 (88:12)
5	$C(CO_2Me)_2$	Ph	Bu	10	24 h	**6e**, 80 (95:5)
6	$C(CO_2Me)_2$	$SiMe_3$	Bu	5	7 h	**6f**, 94 (98:2)
7	NTs	Me	Bu	1	10 min	**6g**, 82 (93:7)
8	O	Me	Bu	1	30 min	**6h**, 75 (95:5)

[a] All reactions were carried out with a terminal alkyne (2 equiv.) in 1,2-dichloroethane at r.t. [b] Isolated yield. [c] Ratios in parentheses were determined by GC analyses of isolated products. [d] Under propyne gas (balloon).

61% total yield with a low regioselectivity *meta*:*ortho* = 65:35. In our hands, **5a** regioselectively reacted with 2 equiv. of **3a** in the presence of the catalyst **1** (1 mol%) to afford *meta*-**6a** and *ortho*-**6a** in 85% total yield with an excellent regioselectivity *meta*:*ortho* = 93:7 (Table 2, entry 1). The importance of the bulky Cp* ligand of **1** was clearly demonstrated by the fact that the reaction of **5a** and **3a** conducted using CpRu(cod)Cl bearing a smaller Cp ligand gave cycloadduct **6a** in 76% yield with lower selectivity (*meta*:*ortho* = 87:13). Similarly, the reaction of **5a** with propyne gas **3e** (R^2 = H; balloon) or propargyl methyl ether **3f** (R^2 = CH_2OMe) gave **6b** and **6c** in 80 and 86% yields, respectively with high *meta*-selectivities (entries 2 and 3). The ether functionality at the propargylic position in **3f** did not decrease both the yield and regioselectivity. Cycloaddition with the less reactive aromatic alkyne, phenylacetylene **3b**, was conducted using an increased amount of the catalyst, and biphenyl derivatives **6d** were obtained in a comparable total yield (82%) with somewhat lower selectivity (entry 4). Similar biphenyl derivatives **6e** were also obtained from the reaction of a 1,6-diyne possessing a phenyl group as a terminal substituent **5b** (entry 5). In this case, the increased amount of the catalyst (10 mol%) was again found to be effective. The highest yield and regioselectivity were achieved in the reaction of a diyne **5c** having a bulky trimethylsilyl substituent at the terminal position with **3a** (entry 6). The corresponding indan derivatives **6f** were obtained in 94% total yield with an isomer ratio of *meta*:*ortho* = 98:2. The regioselective syntheses of highly substituted heterocycles were also realized using nitrogen- or oxygen-tethered unsymmetrical diynes **5d** and **5e**. An isoindoline derivative **6g** and a phthalan derivative **6h** were obtained in 82 and 75% yields, respectively, with high *meta*-selectivities (entries 7 and 8).

The origin of the high *meta*-selectivity can be explained by the insertion mechanism depicted in Scheme 3. A ruthenacyclopentadiene **7** formed from **1** and **5** can be proposed as a key intermediate.[9] In order to avoid the steric interaction with the terminal substituent R^1, a monoalkyne **3** is selectively inserted into the less substituted Ru–C single bond to form ruthenacycloheptatriene intermediates **8** or **9**. At this stage, the bulky Cp* ligand directs formation of **8** because the steric repulsion between Cp* and R^2 is obviously greater in **9** and reductive elimination from **8** gives a *meta*-isomer *meta*-**6** as the major product.



Scheme 3

In conclusion, an Ru(II) complex possessing a bulky planar ligand, Cp*Ru(cod)Cl, catalyzed the cycloaddition of 1,6-diynes with terminal alkynes at or below room temperature. Satisfactory chemoselectivity can be achieved using 2 equiv. of a monoalkyne. Excellent *meta*-selectivity was observed for the reaction of unsymmetrical diynes.

We gratefully acknowledge financial support (09305059, 10132222, and 11119223) from the Ministry of Education, Science, Sports, and Culture, Japan.

Notes and references

1 D. B. Grotjahn, in *Comprehensive Organometallic Chemistry II*, ed. L. S. Hegedus, E. W. Abel, F. G. A. Stone and G. Wilkinson, Pergamon, Oxford, 1995, vol. 12, p. 741; N. E. Shore, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, vol. 5, p. 1037.
2 T. Takahashi, Z. Xi, A. Yamazaki, Y. Liu, K. Nakajima and M. Kotora, *J. Am. Chem. Soc.*, 1998, **120**, 1672.
3 K. P. C. Vollhardt, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 539.
4 S. J. Neeson and P. J. Stevenson, *Tetrahedron*, 1989, **45**, 6239; P. Phansavath, C. Aubert and M. Malacria, *Tetrahedron Lett.*, 1998, **39**, 1561; I. G. Stará, I. Stary, A. Kollárovic, F. Teply, D. Saman and M. Tichy, *J. Org. Chem.*, 1998, **63**, 4046; I. G. Stará, I. Stary, A. Kollárovic, F. Teply, S. Vyskocil and D. Saman, *Tetrahedron Lett.*, 1999, **40**, 1993.
5 (*a*) E. Müller, *Synthesis*, 1974, 761; (*b*) R. Grigg, R. Scott and P. Stevenson, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1357; (*c*) P. Bahataran and E. H. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2603; (*d*) P. Bahataran and E. H. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2163; (*e*) D. M. Duckworth, S. Lee-Wong, A. M. Z. Slawin, E. H. Smith and D. J. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1996, 815; (*f*) F. E. McDonald, H. Y. H. Zhu and C. R. Holmquist, *J. Am. Chem. Soc.*, 1995, **117**, 6605; (*g*) Y. Sato, T. Nishimata and M. Mori, *Heterocycles*, 1997, **44**, 443; (*h*) Y. Sato, K. Ohashi and M. Mori, *Tetrahedron Lett.*, 1999, **40**, 5231; (*i*) S. Kotha and E. Brahmachary, *Tetrahedron Lett.*, 1997, **38**, 3561; (*j*) A. Bradley, W. B. Motherwell and F. Ujjainwalla, *Chem. Commun.*, 1999, 917; (*k*) B. Witulski and T. Stengel, *Angew. Chem., Int. Ed.*, 1999, **38**, 2426.
6 Y. Yamamoto, H. Kitahara, R. Ogawa and K. Itoh, *J. Org. Chem.*, 1998, **63**, 9610.
7 Ru-catalysed cyclotrimerization of electron-deficient alkynes has been reported, see: E. Lindner, R.-M. Jansen, H. A. Mayer, W. Hiller and R. Fawzi, *Organometallics*, 1989, **8**, 2355.
8 T. Naota, H. Takaya and S. Murahashi, *Chem. Rev.*, 1998, **98**, 2599; H. Butenschön, in *Organic Synthesis Highlights III*, ed. J. Mulzer, H. Waldman, Wiley-VCH, Weinheim, 1998, p. 96.
9 M. O. Albers, D. J. A. de Waal, D. C. Liles, D. J. Robinson, E. Singleton and M. B. Wiege, *J. Chem. Soc., Chem. Commun.*, 1986, 1680; B. K. Campion, R. H. Heyn and T. D. Tilley, *Organometallics*, 1990, **9**, 1106; M. I. Bruce and G. A. Koutsantonis, *Aust. J. Chem.*, 1991, **44**, 207; C. S. Yi, J. R. Torres-Lubian, N. Liu, A. L. Rheingold and I. A. Guzei, *Organometallics*, 1998, **17**, 1257; C. Ernst, O. Walter, E. Dinjus, S. Arzberger and H. Görls, *J. Prakt. Chem.*, 1999, **341**, 801.

Communication b000466i