FULL PAPERS

Iridium Complex-Catalyzed Cross-Coupling Reaction of Terminal Alkynes with Internal Alkynes *via* C–H Activation of Terminal Alkynes

Tomotaka Hirabayashi, Satoshi Sakaguchi, Yasutaka Ishii*

Department of Applied Chemistry, Faculty of Engineering, Kansai University, Suita, Osaka 564-8680, Japan Fax: (+81)-6-6339-4026, e-mail: ishii@ipcku.kansai-u.ac.jp

Received: November 25, 2004; Accepted: March 8, 2005

Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: The cross-dimerization of an electron-rich terminal alkyne with an electron-deficient internal alkyne was promoted by an iridium complex to produce a 1:1 adduct in high regio- and stereoselectivities. This reaction was extended to various combinations of terminal alkynes with internal alkynes such as alkynyl esters and alkynyl aldehydes. The selectivity of the reaction was found to markedly depend on the ligands used. When dppe was used as a ligand,

the 1:2 cross-cyclotrimerization reaction took place to form substituted benzene derivatives. A plausible reaction path was suggested based on a labeling experiment. This reaction provides a method for the production of complicated enynes which are difficult to be prepared by conventional methods.

Keywords: alkynes; C–H activation; catalysis; crosscoupling; dimerization; iridium complex

Introduction

The C-C bond-forming reaction is one of the most important reactions in organic synthesis. In particular, the dimerization of alkynes is a very useful method for forming compounds such as enynes from simple alkynes.^[1] Transition metal-catalyzed coupling reactions of alkynes constitute an effective method for forming synthetically useful compounds.^[2] However, the catalytic intermolecular dimerization of alkynes has not yet been developed,^[3] since the homo- and cross-dimerizations of two different alkynes take place simultaneously to result in a complex mixture of products like homodimers,^[4] trimers,^[5] and oligomers in addition to the desired cross-dimers. Trost et al. have reported the selective cross-addition of terminal alkynes (donor alkynes) to activated internal alkynes (acceptor alkynes) by the use of palladium acetate in the presence of an electron-rich, sterically encumbered ligand like tris(2,6-dimethoxyphenyl)phosphine.^[6] Quite recently, Yi and co-worker have reported a similar cross-dimerization of unactivated internal alkynes using a ruthenium-vinylidene complex as the catalyst.^[7] Furthermore, there have been several studies on the synthesis of enyne compounds from halogenated alkenes and alkynes catalyzed by a Cu complex and from alkynes and a stoichiometric amount of a Ti complex.^[8]

In the course of our studies to develop a new coupling reaction of alkynes using an iridium complex as a catalyst,^[9] we have now found that terminal alkynes add selectively to activated internal alkynes in the presence of a catalytic amount of $[IrCl(cod)]_2$ combined with bidentate ligands such as (rac)-BINAP, 1,4-bis(diphenylphosphino)butane (dppb) and 1,1'-bis(diphenylphosphino)ferrocene (dppf).

Results and Discussion

In the first place, we examined the cross-addition of 1octyne (1a) with methyl phenylpropiolate (2a) using $[IrCl(cod)]_2$ (cod = cycloocta-1,5-diene) combined with various phosphines [Eq. (1) and Table 1].



A typical reaction was carried out as follows. To a solution containing $[IrCl(cod)]_2$ (0.035 mmol) and dppb (0.07 mmol) in toluene was added a 1:1 mixture of **1a** (0.5 mmol) and **2a** (0.5 mmol). The reaction was carried

DOI: 10.1002/adsc.200404359

Entry	Ir Complex	Ligand	Conversion [%] ^[b]	Yield [%] ^[c]	
1	$[IrCl(cod)]_2$	dppb	69	35	9
2	$[IrCl(cod)]_2$	none	8	n.d.	n.d.
3	$[IrCl(cod)]_2$	PPh ₃	48	<1	2
4	$[IrCl(cod)]_2$	PCy ₃	89	n.d.	n.d.
5	$[IrCl(cod)]_2$	$P(OBu-n)_3$	3	<1	n.d.
6	$[IrCl(cod)]_2$	dppf	>99	62	12
7	$[IrCl(cod)]_2$	(rac)-BINAP	>99	83	2
8	$[Ir(cod)_2]^+BF_4^-$	(rac)-BINAP	4	n.d.	n.d.
9	IrCl ₃	(rac)-BINAP	No reaction		

Table 1. The cross-dimerization of 1a with 2a catalyzed by [IrCl(cod)]₂ under various conditions.^[a]

^[a] Alkyne **1a** (0.5 mmol) was reacted with **2a** (0.5 mmol) in the presence of [IrCl(cod)]₂ (0.035 mmol) and ligand (0.07 mmol) in toluene (1 mL) at 80 °C for 3 h.

^[b] The conversion was based on **2a**.

^[c] The yield was based on **2a** used.

out at 80 °C for 3 h, giving a regioisomeric mixture of cross-addition products, **3aa** (35%) and **4aa** (9%) (Entry 1). In the absence of a ligand, most of **2a** was recovered (Entry 2). Monodentate phosphines, PPh₃ and PCy₃, and phosphite P(OBu-n)₃, resulted in **3aa** in poor yields (Entries 3 to 5), while the reaction using a bidentate phosphine like dppf gave **3aa** in fair yield (62%) (Entry 6). When (*rac*)-BINAP was employed as a ligand, **3aa** was produced in the highest yield (83%) (Entry 7). This is the first successful 1:1 cross-addition of alkynes catalyzed by iridium complexes. The cationic iridium complex [Ir(cod)₂]⁺BF₄⁻ and IrCl₃ were inert in this reaction (Entries 8 and 9).

On the basis of these results, the cross-dimerization of various terminal alkynes (1b-f) with internal alkynes was examined [Eq. (2) and Table 2].



Trimethylsilylacetylene (1b), phenylacetylene (1c), *tert*butyl 1-methyl-2-propynyl ether (1d) and 1-ethynyl-1cyclohexanol (1e) reacted with 2a under these conditions to give the corresponding cross-addition products, 3ba, 3ca, 3da and 3ea, respectively, in fair to good yields (Entries 1 to 4). The reaction of methyl propiolate (1f) as the electron-deficient terminal alkyne with 2a did not form a cross-adduct, but rather afforded small amounts of the cyclotrimerization products of 1f, trimethyl 1,2,4and 1,3,5-benzenecarboxylates (7) (Entry 5). When 1a was allowed to react with 2b under the standard conditions, the desired product (3ab) consisting of a 1:1 mixture of *E*- and *Z*-isomers was obtained in 56% yield (En-

Table 2.	The	cross-dimerization	of	two	different	monoynes
catalyze	d by	$[IrCl(cod)]_2$. ^[a]				-

Entry	Terminal alkyne		Internal alkyne		ne	Product (Yield $[\%]^{[b]}$)	
Linuy	R		R^1 R^2				
1	TMS	(1b)		2a		3ba (73 (99 /1)) 4ba (2)	
2	Ph	(1c)		2a		3ca (79 (99 / 1)) 4ca (2)	
3	t-BuO	(1d)		2a		3da (73 (99 / 1)) 4da (1)	
4	OH → OH	(1e)		2a		3ea (59 (99 / 1)) 4ea (6)	
5	CO ₂ Me	(1f)		2a		7 (12)	
6 ^[c]	1a		<i>n</i> -Pn	CO ₂ Me	(2b)	3ab (56 (50 / 50))	
7 ^[c]	1c			2b		3cb (57 (51 / 49))	
8 ^[d]	1d		<i>n-</i> Hex	CO₂Me	(2c)	3dc (62 (55 / 45))	
9 ^[c,e]	1d		<i>n</i> -Pn	СНО	(2d)	3dd (32)	
10 ^[c]	1a		Ph	Ph	(2e)	3ae (16)	
11 ^[1]	1a	C	O ₂ Me	CO₂Me	(2 f)	6af (38)	

^[a] Alkyne 1 (0.5 mmol) was reacted with 2 (0.5 mmol) in the presence of [IrCl(cod)]₂ (0.035 mmol) and (*rac*)-BINAP (0.07 mmol) in toluene (1 mL) at 80 °C for 3 h.

^[b] The yield was based on **2** used, and the number in parenthesis shows the E/Z ratio.

^[c] Dppf was used instead of (*rac*)-BINAP.

^[d] Dppb was used instead of (*rac*)-BINAP.

^[e] 3-(3-*tert*-Butoxybut-1-ynyl)-oct-3-enal (**5dd**) was obtained in 22% yield.

^[f] See text.

try 6). The reaction of **1c** with **2b** and **1d** with **2c** provided the corresponding cross-adducts **3cb** (57%) and **3dc** (62%), respectively (Entries 7 and 8). Alyknyl ether **1d** reacted with alkynyl aldehyde (**2d**), giving **3dd** (32%) MeO₂C

1a. 1b and 1d

2 mmol

2f

1 mmol

CO₂Me

along with 3-(3-*tert*-butoxybut-1-ynyl)-oct-3-enal (**5dd**) (22%) (Entry 9). The reaction of **1a** with diphenylacetylene (**2e**) formed a 1:1 cross-adduct **3ae** in low yield (16%) (Entry 10). However, dimethyl acetylenedicarboxylate (**2f**) reacted with **1a** to give the [2+2+2] cyclotrimerization product (**6af**) of **1a:2f**=1:2 in 38% yield, but not the desired product **3af** (Entry 11). Recently, Takeuchi and co-workers have reported the iridium-catalyzed the [2+2+2] cyclotrimerizations of **1c** and **2f**.^[10] We found that the cross-cyclotrimerization is also promoted by [IrCl(cod)]₂ by the use of dppe as a ligand in the presence of a small amount of Na₂CO₃ under mild conditions [Eq. (3)].

CO₂Me

[IrCl(cod)]₂ (0.05 mmol) dppe (0.1 mmol)

Na₂CO₃ (0.1 mmol)

toluene (2 mL)

60 °C, 15 h

R

ÇO₂Me

ĊO₂Me 6af: 90 % 6bf: 82 %

6df: 67 %

CO₂Me

°CO₂Me

(3)



phenylacetylene- d_1 (1c- d_1) with 2a. The ¹H NMR spec-

trum of the resulting product showed that the reaction



In order to obtain mechanistic information about the present cross-addition, we attempted the reaction of

These results suggest that the reaction proceeds *via* the following reaction pathway (Scheme 1). First, the oxidative addition of terminal alkyne $1c \cdot d_1$ to an iridium complex leads to an alkynyl-iridium complex (**A**). The coordination of an internal alkyne (**2a**) to **A** followed by insertion gives a vinyliridium complex (**C**). The oxidative

 $Pn \stackrel{O}{\longrightarrow} CO_2Me$ $Pn \stackrel{O}{\longrightarrow} Pn$ $Pn \stackrel{O}{\longrightarrow} CO_2Me$ $Pn \stackrel{Vinyl proton shift}{\bigcap} O_{Pn} \stackrel$

Figure 1. ¹H NMR spectrum of the product from the reaction of $1c-d_1$ with 2a.

asc.wiley-vch.de



Scheme 1. A plausible reaction pathway for the cross-dimerization of alkynes.

addition of alkyne to C followed by reductive elimination produces the enyne $3ca - d_1$, and the complex A may be regenerated.

Conclusion

We have found a catalytic cross-dimerization between terminal alkynes and internal alkynes, catalyzed by an iridium complex. This reaction provides a method for the production of various complicated enyne compounds.

Experimental Section

General Remarks

¹H and ¹³C NMR were measured at 270 and 67.5 MHz, respectively, in CDCl₃ with TMS as the internal standard. Infrared (IR) spectra were measured as thin films on NaCl plate or KBr pressed disks. GLC analysis was performed with a flame ionization detector using a 0.2 mm \times 25 m capillary column (OV-17). Mass spectra were determined at an ionizing voltage of 70 eV. All starting materials, catalysts, and initiators were purchased from commercial sources and used without further treatment. The yields of products were estimated from the peak areas based on the internal standard technique.

Typical Procedure for the Cross-Coupling of 1-Octyne (1a) and Methyl Phenylpropiolate (2a)

To a solution containing $[IrCl(cod)]_2$ (0.035 mmol) and dppb (0.07 mmol) in toluene (1 mL) was added a 1:1 mixture of **1a** (0.5 mmol) and **2a** (0.5 mmol). The reaction was carried out at 80 °C for 3 h. Removal of the solvent under reduced pressure afforded a cloudy solution, which was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 10/1) to give the corresponding product. The products were characterized by ¹H and ¹³C NMR, IR, and GC-MS, respectively.

Procedure for the Cyclotrimerization of 1a and Methyl Propiolate (2f)

To a solution containing $[IrCl(cod)]_2$ (0.05 mmol), dppe (0.1 mmol) and Na₂CO₃ (0.1 mmol) in toluene (2 mL) was added a 2:1 mixture of **1a** (2 mmol) and **2f** (1 mmol). The reaction was carried out at 60 °C for 15 h. Removal of the solvent under reduced pressure afforded a cloudy solution, which was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 9/1) to give the corresponding product. The products were characterized by ¹H and ¹³C NMR, IR, and GC-MS, respectively.

Supporting Information

Characterization data for products 3.

Acknowledgements

This work was partially support by a Grant-Aid for Scientific Research (KAKENHI) (S) (No. 13853008) from Japan Society for the Promotion of Science (JSPS), and DAICEL Chemical Industries, Ltd.

References and Notes

- [1] a) B. M. Trost, Angew. Chem. Int. Ed., 1995, 34, 259;
 b) B. M. Trost, Science 1991, 254, 1471.
- [2] Recent reviews: a) G. W. Parshall, S. D. Ittel, Homogeneous Catalysis, 2nd edn., Wiley: New York, 1992; b) H. Bönnemann, W. Brijoux, in: Applied Homogeneous Catalysis with Organometallic Compounds, (Eds.: B. Cornils, W. A. Herrmann), VCH, New York, 1996, Vol. 2, p. 1102; c) N. E. Schore, in: Comprehensive Organic Synthesis, (Ed.: B. M. Trost), Pergamon Press: New York, 1990, Vol. 5.
- [3] D. B. Grotjahn, in: Comprehensive Organometallic Chemistry II, (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson), Pergamon Press: New York, 1994, Vol. 12.
- [4] For Ru: a) Y. Wakatsuki, H. Yamazaki, N. Kumegawa, T. Satoh, J. Y. Satoh, J. Am. Chem. Soc. 1991, 113, 9604; b) C. Bianchini, M. Peruzzini, F. Zanobini, P. Frediani, A. Albinati, J. Am. Chem. Soc. 1991, 113, 5453; c) Y. Sasaki, P. H. Dixneuf, J. Chem. Soc. Chem. Commun. 1986, 790 and references cited therein; for Rh: d) M. Schäfer, N. Mahr, J. Wolf, H. Werner, Angew. Chem. Int. Ed. 1993, 32, 1315; e) W. T. Boese, A. S. Goldman, Organometallics 1991, 10, 782; for Ni: f) M. Ishikawa, J. Ohshita, Y. Ito, A. Minato, J. Chem. Soc. Chem. Commun. 1988, 804; for Pd: g) F. A. Selimov, O. G. Rutman, U. M. Dzhemilev, J. Organomet. Chem. 1988, 346, C58; for Cu: h) M. Rubina, V. Gevorgyan, J. Am. Chem. Soc. 2001, 123, 11107; for Ir: i) T. Ohmura, S. Yorozuya, Y. Yamamoto, N. Miyaura, Organometallics 2000, 19, 365; others: j) A. K. Dash, M. S. Eisen, Org. Lett. 2000, 2, 737; k) T. Straub, A. Haskel, M. S. Eisen, J. Am. Chem. Soc.

Adv. Synth. Catal. 2005, 347, 872-876

asc.wiley-vch.de

1995, *117*, 6364; I) M. Nishiura, Z. Hou, J. Mol. Catal. A: Chemical, **2004**, *213*, 101.

[5] For no catalyst: a) K. P. C. Vollhardt, Angew. Chem. Int. Ed. Engl. 1984, 23, 539; b) L. D. Field, A. Ward, Aust. J. Chem. 1999, 52, 1085; for Ni: c) Y. Sato, T. Nishimata, M. Mori, J. Org. Chem., 1994, 59, 6133; for Rh: d) F. E. McDonald, H. Y. H. Zhu, C. R. Holmquist, J. Am. Chem. Soc. 1995, 117, 6605; e) R. Witulski, T. Stengel, Angew. Chem. Int. Ed. Engl. 1999, 38, 2426; for Pd: f) Y. Yamamoto, A. Nagata, Y. Arikawa, K. Tatsumi, K. Itoh, Organometallics, 2000, 19, 2403; for Ru: g) J.-U. Peters, S. Blechert, Chem. Commun. 1997, 1983; h) Y. Yamamoto, R. Ogawa, K. Itoh, Chem. Commun. 2000, 549; for Ir: i) R. Takeuchi, Synlett 2002, 12, 1954; j) C. Bianchini, K. G. Caulton, C. Chardon, O. Eisenstein, K. Folting, T. J. Johnson, A. Meli, M. Peruzzini, D. J. Rauscher, W. E. Streib, F. Vizza, J. Am. Chem. Soc. 1991, 113, 5127; for Zr: k) T. Takahashi, Z. Xi, A. Yamazaki, Y. Liu, K. Nakajima, M. Kotora, J. Am. Chem. Soc. 1998, 120, 1672.

- [6] a) B. M. Trost, C-J. Li, Synthesis 1994, 1267; b) B. M. Trost, M. C. McIntosh, J. Am. Chem. Soc. 1995, 117, 7255; c) B. M. Trost, M. T. Sorum, C. Chan, A. E. Harms, G. Rhter J. Am. Chem. Soc. 1997, 119, 698; d) B. M. Trost, A. J. Frontier, J. Am. Chem. Soc. 2000, 122, 11727.
- [7] C. S. Yi, N. Liu, Organometallics 1998, 17, 3158.
- [8] a) T. Mandai, Y. Tsujiguchi, S. Matsuoka, J. Tsuji, *Tetrahedron Lett.* 1993, 34, 7615; b) U. Lcking, A. Pfaltz, *Synlett* 2000, 1261; c) C. Delas, H. Urabe, F. Sato, *Chem. Commun.* 2002, 272; d) C. G. Bates, P. Saejueng, D. Venkataraman, *Org. Lett.* 2004, 6, 1441.
- [9] a) Y. Ishii, S. Sakaguchi, Bull. Chem. Soc. Jpn. 2004, 77, 909; b) S. Sakaguchi, T. Kubo, Y. Ishii, Angew. Chem. Int. Ed. 2001, 40, 2534.
- [10] R. Takeuchi, Y. Nakaya, Org. Lett. 2003, 5, 3659.