ORGANIC
LETTERS

2005
Vol. 7, No. 9
1711−1714

Iridium Complex-Catalyzed Reaction of 1,6-Enynes: Cycloaddition and Cycloisomerization

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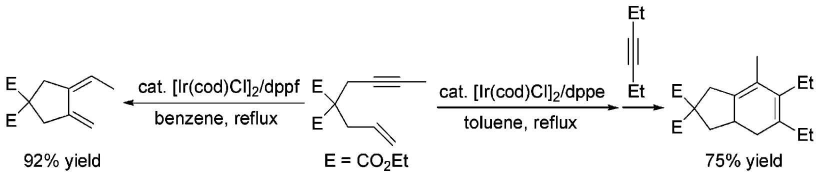
Received January 14, 2005

ABSTRACT



1,6-Enynes reacted with monoynes to give cyclohexadiene derivatives in the presence of a catalytic amount of [Ir(cod)Cl]$_2$/ligand. DPPE was most suitable for cycloaddition. Diastereoselective cycloaddition was also possible. In the absence of monoynes, 1,6-enynes cycloisomerized to (*Z*)-1-alkylidene-2-methylenecyclopentane derivatives. DPPF was most suitable for cycloisomerization. These results are the first examples of highly *Z*-selective cycloisomerization.

The cycloaddition of α,ω-enynes catalyzed by transition-metal complexes[1] is efficient, because it can be used to construct polycyclic compounds in a single step without any wasteful byproducts. For example, the Pauson−Khand reaction is useful for producing bicyclic cyclopentenones, which are a common structural component of naturally occurring and biologically active molecules.[2] The application of the Pauson−Khand reaction in the synthesis of natural products has been extensively studied.[2a] On the other hand, there is limited information available on the intermolecular cycloaddition of enynes with unsaturated molecules such as monoynes.[3] The cycloaddition of α,ω-enyne with monoynes gives cyclohexadiene derivatives. These compounds are used in the Diels−Alder reaction, which provides a rich and diverse chemistry.[4] This cycloaddition is the simplest route to a bicyclic cyclohexadiene framework. We previously reported that the [Ir(cod)Cl]$_2$/dppe-catalyzed cycloaddition of 1,6-heptadiynes with monoynes gave the corresponding indane derivatives in high yields.[5] In this study, we extended this chemistry to the reaction of 1,6-enynes. We found that [Ir(cod)Cl]$_2$ with a phosphine ligand was an efficient catalyst for the intermolecular cycloaddition of 1,6-enynes with monoynes and also that this catalyst is effective in the cycloisomerization of 1,6-enynes to (*Z*)-1-alkylidene-2-methylenecyclopentane derivatives.

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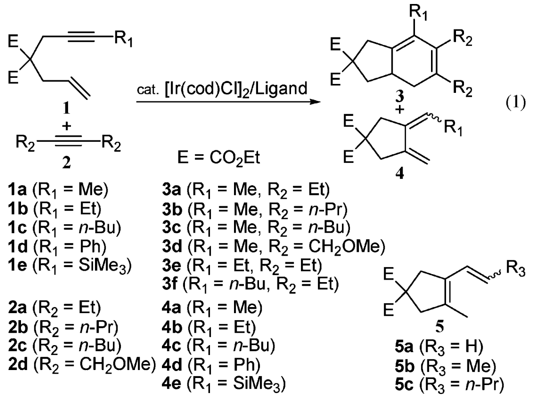
10.1021/ol050085e CCC: $30.25

Enyne **1a** (R_1 = Me) reacted with 3-hexyne (**2a**) to give a cyclohexadiene derivative **3a** and a cycloisomerization product **4a** (eq 1).



Cycloaddition competed with cycloisomerization to give **4a**. Phosphine ligands affected the yields of the products. The results are shown in Table 1. Dppe gave the best results (entry 2). The reaction in refluxing toluene for 3 h gave **3a** in 75% yield. The reaction using dppm gave **3a** in 69% yield (entry 1). Dppp and dppb were less effective than dppe (entries 3 and 4). Reactions using 1,2-bis(diphenylphosphino)benzene and (*Z*)-1,2-bis(diphenylphosphino)ethylene gave **3a** in a yield comparable to that with dppm (entries 5 and 6). When the ligand was dppf, PPh_3, or $PMePh_2$, cycloisomerization was preferred to cycloaddition (entries 7−9). The reaction using dppf gave cycloisomerization product **4a** in 90% yield (vide infra) (entry 7).

Table 1. Effect of Ligands on Cycloaddition of **1a** with **2a**[a]

entry	ligand[b]	time (h)	yield of **3a** (%)[c]	yield of **4a** (%)[c]
1	dppm	5	69	3
2	dppe	3	75	10[d]
3	dppp	19	12	51
4	dppb	2	2	90[e]
5	1,2-bis(diphenylphosphino)benzene	8	51	23
6	(*Z*)-1,2-bis(diphenylphosphino)ethylene	10	65	3
7	dppf	1	0	90[f]
8	PPh_3	25	0	74[g]
9	$PMePh_2$	24	7	63[h]

[a] Mixture of **1a** (1 mmol), **2a** (3 mmol), Ir complex (0.02 mmol), ligand (P/Ir = 2), and toluene (5 mL) was stirred in refluxing toluene. [b] Abbreviations: dppm, 1,2-bis(diphenylphosphino)methane; dppe, 1,2-bis(diphenylphosphino)ethane; dppp, 1,2-bis(diphenylphosphino)propane; dppb, 1,2-bis(diphenylphosphino)butane; dppf, 1,1′-bis(diphenylphosphino)ferocene [c] Yields are isolated yields based on **1a**. [d] (*Z*)-**4a**/(*E*)-**4a**/**5a** = 89/7/4. [e] (*Z*)-**4a**/(*E*)-**4a**/**5a** = 94/3/3. [f] (*Z*)-**4a**/(*E*)-**4a**/**5a** = 95/4/1. [g] (*Z*)-**4a**/(*E*)-**4a**/**5a** = 50/45/5. [h] (*Z*)-**4a**/(*E*)-**4a**/**5a** = 56/39/5.

On the basis of these results, several internal monoynes were examined for $[Ir(cod)Cl]_2$/dppe-catalyzed cycloaddition (Table 2). Enyne **1a** reacted with **2b**−**d** under the same conditions as with **2a**. The yields of 1,3-cyclohexadienes (**3**) decreased with the use of 4-octyne (**2b**) and 5-decyne (**2c**) (entries 2 and 3 vs entry 1), but the reaction with 1,4-dimethoxy-2-butyne (**2d**) gave **3d** in 71% yield, which was comparable to that with 3-hexyne (**2a**) (entry 4). The reaction of **1a** with 1-alkynes such as 1-hexyne or propargylic alcohol did not give any cyclohexadiene derivatives. The starting material was recovered in quantitative yield. The substituent on the alkyne part of the enyne strongly affected the reaction. The reaction of an enyne substituted with other than a methyl group on the alkyne part with **2a** gave a cycloisomerization product as a major product (entries 5 and 6). These reactions gave cycloaddition products in low yields.

Table 2. Cycloaddition of **1** with **2**[a]

entry	enyne	alkyne	time (h)	yield of **3** (%)[b]	yield of **4** (%)[b]
1	**1a**	**2a**	3	75 (**3a**)	10 (**4a**)
2	**1a**	**2b**	6	53 (**3b**)	20 (**4a**)
3	**1a**	**2c**	14	39 (**3c**)	25 (**4a**)
4	**1a**	**2d**	24	71 (**3d**)	2 (**4a**)
5	**1b**	**2a**	3	15 (**3e**)	75 (**4b**)[c]
6	**1c**	**2a**	3	12 (**3f**)	73 (**4c**)[d]

[a] Mixture of **1** (1 mmol), **2** (3 mmol), Ir complex (0.02 mmol), ligand (P/Ir=2), and toluene (5 mL) was stirred in refluxing toluene. [b] Yields are isolated yields based on **1**. [c] (*Z*)-**4b**/(*E*)-**4b**/**5b** = 74/2/24. [d] (*Z*)-**4c**/(*E*)-**4c**/**5c** = 66/11/23.′

The cycloisomerization of enynes has been extensively studied as a unique tool for the synthesis of various types of cyclic compounds.[6] Several transition metal complexes such as Pd,[7] Rh,[8] Ru,[9] Co,[10] and Ti[11] have been reported to be catalysts for this reaction. However, new catalysts are still needed to expand the scope and selectivity of this reaction.

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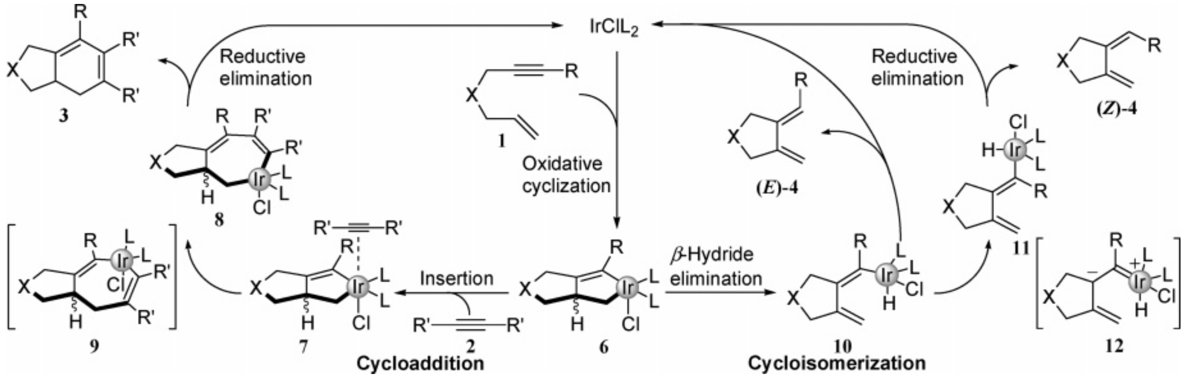
Scheme 1



A single example of iridium complex-catalyzed cycloisomerization of 1,6-enynes was reported in 2001.[12a] As described above, cycloisomerization product **4a** was obtained as a byproduct of the cycloaddition of **1a**. We next focused on the cycloisomerization of 1,6-enynes. *The results described below represent the first examples of the highly Z-selective cycloisomerization of 1,6-enynes.* The stereochemistry of an alkylidene group in similar cycloisomerizations has been reported to be *E*.[7b,c,f−j,8,9,10b,c,11,12a] The presence of phosphine ligands affected the yield and selectivity of cycloisomerization (Table 3). The cycloisomerization of **1a** gave (*Z*)-**4a**, (*E*)-**4a**, and **5a**.

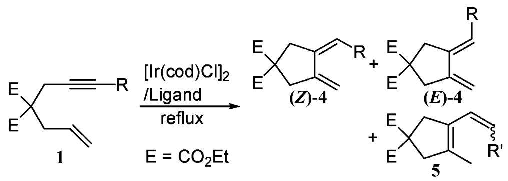
Table 3. Effect of Ligands on Cycloisomerization of **1a**[a]

entry	ligand[b]	time (h)	yield (%)[c]	(*Z*)-**4a**:(*E*)-**4a**:**5a**
1	dppm	3	18[d]	14:85:1
2	dppe	3	45[d]	85:6:9
3	dppp	3	83	89:9:2
4	dppb	1	82	94:4:2
5	dpph	45	49[e]	48:46:4
6	PMePh$_2$	21	53	45:47:8
7	2,2′-bis(diphenyl-phosphino)-1,1′-biphenyl	1	88	91:4:5
8	1,2-bis(dipentafluoro-phenylphosphino)ethane	1	87	91:2:7
9	dppf	0.5	92	96:3:1
10[f]	dppf	2	88	98:2:0
11[g]	dppf	2	92	99:1:0

[a] Mixture of **1a** (1 mmol), Ir complex (0.02 mmol), ligand (P/Ir = 2), and toluene or benzene (5 mL) was stirred in refluxing solvent. [b] Abbreviation: dpph, 1,2-bis(diphenylphosphino)hexane [c] Yields are isolated yields based on **1a**. [d] Conversion was 100%. Other products were not identified. [e] **1a** was recovered. [f] Reaction temperature: 80 °C. [g] Benzene was used.

Product **5a** resulted from the further double-bond isomerization of **4a**. The reaction using dppe in refluxing toluene for 3 h gave an 85:6:9 mixture of (*Z*)-**4a**, (*E*)-**4a**, and **5a** in 45% yield (entry 2). Dppp and dppb improved the yield and selectivity of (*Z*)-**4a** (entries 3 and 4). On the other hand, dpph and PMePh$_2$ decreased the yield of the products (entries 5 and 6). By using dppf and lowering the reaction temperature, we increased the selectivity of (*Z*)-**4a** up to 99% (entry 10). A previous example of iridium complex-catalyzed cycloisomerization of 1,6-enynes required acetic acid as an additive to give a product in high yield.[12a] In contrast, our cycloisomerization gave the product in high yield without acetic acid.

The cycloisomerization of various 1,6-enynes catalyzed by [Ir(cod)Cl]$_2$/dppf was examined (eq 2).



(2)

R = Et (**1b**)	benzene	2.5 h	85%	98 : 1 : 1 (R′ = Me)
R = *n*-Bu (**1c**)	benzene	2.5 h	81%	98 : 1 : 1 (R′ = *n*-Pr)
R = Ph (**1d**)	toluene	8 h	69%	77 : 23
R = SiMe$_3$ (**1e**)	toluene	17 h	73%	0 : 100

The reactions of **1b**,**c** were also highly *Z*-selective. The reaction of 1,6-enynes **1d** containing a phenyl group on the alkyne part gave a 77:23 mixture of (*Z*)-**4d** and (*E*)-**4d**. Unlike the reaction of **1a**−**d**, the reaction of **1e** containing a trimethylsilyl group on the alkyne part exclusively gave (*E*)-**4e**. These results suggest that the steric bulkiness of the substituent on the alkyne part was important for the stereocontrol of the alkylidene group (vide infra).

A proposed mechanism is given in Scheme 1. Oxidative cyclization of **1** gives iridacyclopentene **6**. Monoyne coordinates to a vacant site on the iridium. Insertion of a monoyne into the Ir−C bond followed by reductive elimination gives **3**. There are two possibilities for the insertion into **7**; one is insertion into a Csp^2−Ir bond, and the other is insertion into a Csp^3−Ir bond. The former insertion involves steric repulsion between a substituent on an incoming monoyne and a substituent on the carbon adjacent to iridium. Actually, the yield of the cycloaddition products was decreased with the use of enyne **1b** and **1c** (Table 2). These observations

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(12) (a) Chatani, N.; Inoue, H.; Morimoto, T.; Muto, T.; Murai, S. *J. Org. Chem.* **2001**, *66*, 4433. Cycloisomerization of dieneynes, see: (b) Shibata, T.; Takasaku, K.; Takesue, Y.; Hirata, N.; Takagi, K. *Synlett* **2002**, 1681.

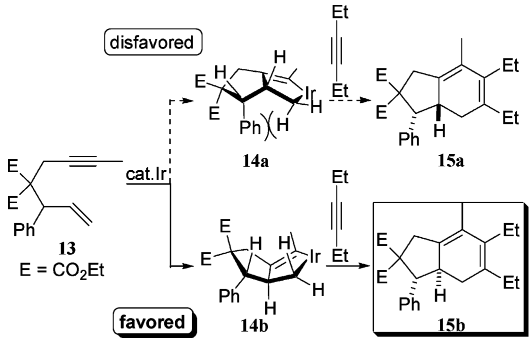
suggest that an incoming monoyne is inserted into a Csp^2−Ir bond in **7**. The regioselectivity of the insertion can be explained by the fact that the insertion product **8** is more stable than **9** due to the presence of a conjugated dienyl unit.

Ligands affected whether intermediate **6** undergoes insertion leading to cycloaddition or β-hydride elimination leading to cycloisomerization. Dppm, dppe, 1,2-bis-(diphenylphosphino)benzene, and (*Z*)-1,2-bis(diphenylphosphino)ethylene favor insertion, whereas dppp, dppb, and dppf favor β-hydride elimination, even in the presence of an alkyne. Since a ligand with a smaller bite angle occupies less space around the iridium center, it stabilizes six-coordinated intermediate **7** compared to a ligand with a large bite angle. The stabilization of **7** promotes insertion to increase the yield of the cycloaddition product.

In the absence of monoyne, intermediate **6** undergoes β-hydride elimination to give **10**, which suffers from steric repulsion between the iridium moiety and the cis substituent on the alkene. Isomerization of **10** to **11** via the zwitterionic carbene intermediate **12** releases steric repulsion.[13] Reductive elimination from **11** gives (*Z*)-**4**. Dppb and dppf were good ligands for *Z*-selective cycloisomerization. Their large bite angles[14] increase the steric bulkiness of the iridium moiety to promote the isomerization of **10** to **11**. Compound **1e** gives unique results. The reaction of **1e** exclusively gave (*E*)-**4e**. The steric bulkiness of a trimethylsilyl group plays a crucial role. The steric repulsion between a trimethylsilyl group and the cis substituent on the alkene in **11** is stronger than that between the iridium moiety and the cis substituent on the alkene in **10**. Therefore, **11** (R = $SiMe_3$) is sterically more congested than **10** (R = $SiMe_3$). Isomerization of **10** to **11** leading to **(*Z*)-4e** does not occur. A phenyl group is more bulky than a primary alkyl group and less bulky than a trimethylsilyl group. Intermediate **10** (R = Ph) undergoes both isomerization to give (*Z*)-**4d** and reductive elimination to give (*E*)-**4d**. Thus, a mixture of (*E*)- and (*Z*)-**4d** is obtained.

Diastereoselective cycloaddition of enynes with monoynes was possible. The $[Ir(cod)Cl]_2$/dppe-catalyzed reaction of enyne **13**, bearing a phenyl group at the allylic position, with 3-hexyne (**2a**) in refluxing toluene for 7 h gave **15b** in 62% yield (>99% de). The diastereoselectivity of this cycloaddition reaction could be explained in Scheme 2. The oxidative cyclization of enyne **13** preferentially gives **14b**, because intermediate **14a** suffers from serious steric hindrance between phenyl group and hydrogen.

Scheme 2



In conclusion, we have demonstrated that $[Ir(cod)Cl]_2$/diphosphine is an effective catalyst for both cycloaddition with a monoyne and cycloisomerization. Our catalyst system shows unique reactivity and selectivity compared to related reactions catalyzed by other late transition metal complexes. Further synthetic applications and mechanistic studies of these reactions are under investigation in our laboratory.

Acknowledgment. This research was supported in part by Grants-in-Aid for Scientific Research (C) and for Scientific Research on Priority Areas (A) "Exploitation of Multi-Element Cyclic Molecules" from the Japan Society for the Promotion of Science and the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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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[13] Similar isomerization of alkenylmetal complexes has been proposed in catalytic reactions. The driving force of the isomerization is to release steric repulsion; see: (a) Ojima, I.; Clos, N.; Donovan, R. J.; Ingallina, P. *Organometallics* **1990**, *9*, 3127. (b) Tanke, R. S.; Crabtree, R. H. *J. Am. Chem. Soc.* **1990**, *112*, 7984. Isomerization of alkenylmetal complexes was observed; see: (c) Huggins, J. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 3002.

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