

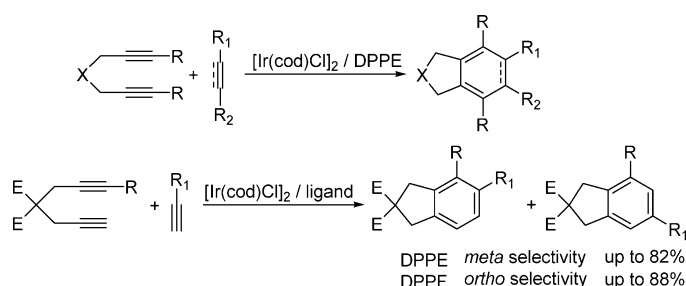
Iridium Complex-Catalyzed [2+2+2] Cycloaddition of α,ω -Diyne with Monoynes and Monoenes

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$[\text{Ir}(\text{cod})\text{Cl}]_2/\text{DPPE}$ was found to be a new catalyst for the cycloaddition of α,ω -diynes with monoynes to give polysubstituted benzene derivatives in high yields. Internal monoynes as well as terminal monoynes could be used. The reaction tolerates a broad range of functional groups such as alcohol, amine, alkene, ether, halogen, and nitrile. The reaction of 1,6-octadiyne derivatives with 1-alkynes gives ortho products and meta products. The regioselectivity could be controlled by the choice of ligand. The reaction with DPPE was meta selective, with meta selectivity of up to 82%. The reaction with DPPF was ortho selective, with ortho selectivity of up to 88%. We propose a mechanism to account for this regioselective cycloaddition. $[\text{Ir}(\text{cod})\text{Cl}]_2/\text{DPPE}$ also catalyzed the cycloaddition of α,ω -diynes with 2,5-dihydrofuran to give bicyclic cyclohexadiene derivatives. The reaction with 2,3-dihydrofuran and *n*-butyl vinyl ether gave benzene derivatives instead of cyclohexadiene derivatives. We also propose a mechanism to account for this novel aromatization that includes cleavage of the C–O bond.

Introduction

Cycloaddition is one of the most efficient methods for the synthesis of cyclic compounds from acyclic substrates. Multiple bond formation in a single operation is possible. Transition metal catalysts can be used for cycloadditions that would otherwise be difficult or impossible by conventional organic chemistry.¹

Since Reppe first reported the nickel complex-catalyzed cyclotrimerization of alkynes to give a benzene derivative,² the reaction has been extensively studied.³ Although the cyclotrimerization of alkynes is one of the most straightforward and atom economical routes to polysubstituted benzene derivatives,

the reaction is problematic with regard to the control of selectivity. To partially overcome this limitation, intramolecular modes of cyclotrimerization of alkynes have been developed: α,ω -diyne is used as one component and a monoynone is used as another component.⁴ α,ω -Diyne oxidatively adds to a metal center to give a metallacyclopentadiene. The reaction of the intermediate with a monoynone gives a benzene derivative. Müller first reported the stoichiometric reaction of rhodacyclopentadienes, which were formed by the reaction of $\text{RhCl}(\text{PPh}_3)_3$ with α,ω -diynes, and with monoynes to give benzene derivatives.⁵ Later, Vollhardt developed the catalytic cycloaddition of α,ω -

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diynes with monoynes to apply this chemistry to natural product synthesis. The reaction of α,ω -diyne with monoynes has been used as a benchmark reaction to evaluate the synthetic potential of a metallacyclopentadiene. Several transition-metal complexes such as those of Co,⁶ Ni,⁷ Rh,⁸ Pd,⁹ and Ru¹⁰ have been reported to be catalysts for this reaction. However, new catalysts are still valuable for expanding the reaction scope and selectivity.

In most cases, metallacycles including metallacyclopentadienes are intermediates for transition metal complex-catalyzed cycloaddition. The chemistry of metallacycles can be used to realize various useful cycloadditions. Collman et al. first prepared an iridacyclopentadiene by the reaction of IrCl(N₂)-

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(PPh₃)₂ with dimethyl acetylenedicarboxylate.¹¹ They found that a tetracarbomethoxyiridacyclopentadiene was a potential catalyst for the cyclotrimerization of dimethyl acetylenedicarboxylate. For example, the reaction of dimethyl acetylenedicarboxylate in the presence of a catalytic amount of a tetracarbomethoxyiridacyclopentadiene under refluxing toluene for 16 h gave hexacarbomethoxybenzene in 80% yield. However, cyclotrimerization was limited to dimethyl acetylenedicarboxylate. Although the structure and reactivity of iridacyclopentadienes have been studied¹² since their discovery, catalytic organic synthesis via iridacyclopentadienes has been less developed than that via rhodacyclopentadienes or cobaltacyclopentadienes. In the course of our study on iridium complex-catalyzed carbon-carbon bond formation,¹³ we found that [Ir(cod)Cl]₂/DPPE is an efficient catalyst for the [2+2+2] cycloaddition of α,ω -diynes with monoynes.^{14,15} We report here the full details of the [2+2+2] cycloaddition of α,ω -diynes with monoynes. Furthermore, we extended this chemistry to the [2+2+2] cycloaddition of α,ω -diynes with monoynes and found a novel aromatization reaction of α,ω -diynes with monoynes.

Results

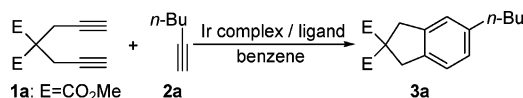
Diyne **1a** reacted with 3 equiv of 1-hexyne (**2a**) to give an indane derivative **3a** in the presence of a catalytic amount of [Ir(cod)Cl]₂ (Ir atom 4 mol %; cod = 1,5-cyclooctadiene). The catalytic activity depended on the ligand used. The results are summarized in Table 1. DPPE was found to be the most efficient

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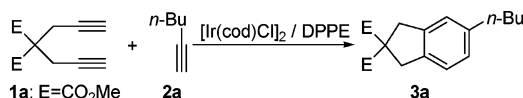
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TABLE 1. Effect of Ligands and Ir Complexes on the Reaction of **1a** with **2a**^a

entry	catalyst	ligand ^b	conditions	yield of 3a /%
1	[Ir(cod)Cl] ₂	PPh ₃	50 °C 24 h	45
2	[Ir(cod)Cl] ₂	DPPM	50 °C 24 h	45
3	[Ir(cod)Cl] ₂	DPPE	rt 20 min	84
4	[Ir(cod)Cl] ₂	DPPP	50 °C 24 h	68
5	[Ir(cod)Cl] ₂		50 °C 24 h	35
6	[Ir(cod)Cl] ₂	P(OPh) ₃	reflux 24 h	12
7	[Ir(cod)OMe] ₂	DPPE	50 °C 24 h	24
8 ^d	[Ir(cod) ₂]BF ₄	DPPE	50 °C 24 h	15
9 ^d	Ir(cod)(acac)	DPPE	50 °C 24 h	20
10 ^e	[Ir(cot) ₂ Cl] ₂	DPPE	50 °C 24 h	22

^a A mixture of **1a** (1 mmol), **2a** (3 mmol), Ir complex (0.02 mmol), ligand (P/Ir = 2), and benzene (5 mL) was stirred under Ar. ^b DPPM = bis(diphenylphosphino)methane; DPPE = 1,2-bis(diphenylphosphino)ethane; DPPP = 1,3-bis(diphenylphosphino)propane. ^c Isolated yield based on **1a**. ^d Ir complex (0.04 mmol). ^e cot = cyclooctene.

TABLE 2. Effect of Solvents on the Reaction of **1a** with **2a**^a

entry	solvent	conditions	yield of 3a /%
1	benzene	rt 20 min	84
2	EtOH	reflux 8 h	60
3	THF	rt 20 min	79
4	dioxane	rt 1 h	80
5	acetone	50 °C 5 h	64
6	1,2-dichloroethane	rt 8 h	68

^a A mixture of **1a** (1 mmol), **2a** (3 mmol), [Ir(cod)Cl]₂ (0.02 mmol), DPPE (0.04 mmol), and solvent (5 mL) was stirred under Ar. ^b Isolated yield based on **1a**.

ligand (entry 3). The reaction was completed in 20 min at room temperature to give **3a** in 84% yield. DPPP, DPPM, and PPh₃ were all inferior to DPPE. Reactions with DPPP, DPPM, or PPh₃ as a ligand gave **3a** only upon heating, and the yield of **3a** decreased (entries 1, 2, and 4). [Ir(cod)Cl]₂ without any ligand gave **3a** in 35% yield (entry 5). We previously reported that P(OPh)₃ was an efficient ligand for [Ir(cod)Cl]₂-catalyzed allylic substitution.^{13c–i} However, P(OPh)₃ was a less efficient ligand than DPPE for [2+2+2] cycloaddition (entry 6). The catalytic activities of several iridium complexes combined with DPPE as a ligand were examined (entries 7–10). The catalytic activities of these complexes were lower than that of [Ir(cod)Cl]₂ combined with DPPE, and the yield of **3a** decreased.

The solvent also affected the reaction (Table 2). Benzene was the solvent of choice (entry 1). Reactions with THF or dioxane gave a slightly decreased yield of **3a** compared to that with benzene (entries 3 and 4). EtOH has been reported to be a general solvent for RhCl(PPh₃)₃-catalyzed [2+2+2] cycloaddition.^{8b,p,q} However, the reaction in EtOH did not proceed at room temperature. The reaction under refluxing EtOH gave **3a**, but

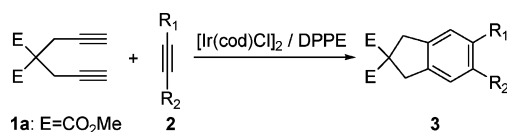
(14) For preliminary work described here, see: (a) Takeuchi, R.; Tanaka, S.; Nakaya, Y. *Tetrahedron Lett.* **2001**, *42*, 2991. Related reactions, see: (b) Kezuka, S.; Okado, T.; Niou, E.; Takeuchi, R. *Org. Lett.* **2005**, *7*, 1711. (c) Takeuchi, R.; Nakaya, Y. *Org. Lett.* **2003**, *5*, 3659.

(15) Iridium complex-catalyzed enantioselective [2+2+2] cycloaddition has been reported, see: Shibata, T.; Fujimoto, T.; Yokota, K.; Takagi, K. *J. Am. Chem. Soc.* **2004**, *126*, 8382.

the yield was less than that in benzene (entry 2). A similar [2+2+2] cycloaddition catalyzed by RuCp*(cod)Cl has been reported to proceed at room temperature in 1,2-dichloroethane.^{10a–c,e} In our reaction, 1,2-dichloroethane was less efficient than benzene (entry 6).

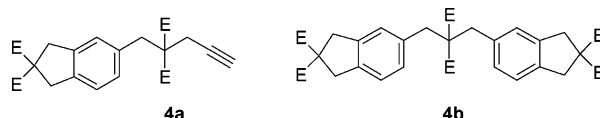
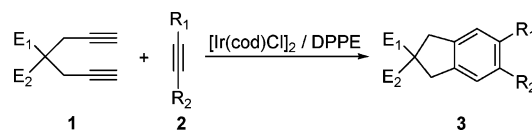
Diyne **1a** reacted with 3 equiv of monoynes **2** to give indane derivatives **3** in good to excellent yields. Various functionalized monoynes could be used. The results are summarized in Table 3. The optimal reaction conditions depended on the monoynone component used. Diyne **1a** reacted with 1-decyne (**2b**), 5-phenyl-1-pentyne (**2c**), and 5-chloro-1-pentyne (**2d**) at room temperature to give **3b**, **3c**, and **3d** in excellent yields (entries 1–3). The reaction with phenylacetylene (**2e**) required more demanding conditions. The reaction with **2e** under refluxing dioxane for 2 h gave **3e** in 85% yield (entry 4). Conjugated enyne (**2f**), propargylic ether (**2g**), propargylic alcohol (**2h**), and 3-butyn-1-ol (**2j**) could each be used as a monoynone component (entries 5–7 and 9). Reactions with **2f** and **2g** gave the corresponding products in decreased yields compared to those with **2a–e** (entries 5 and 6). The reaction with a tertiary carbon-substituted monoynone gave a product in high yield. The reaction with 2-methyl-3-butyn-2-ol (**2i**) gave **3i** in 86% yield (entry 8). In contrast, the Ni(0)-mediated reaction of 1,6-heptadiyne derivative with **2i** has been reported to give the corresponding product in 12% yield.^{7k} Interestingly, the reaction with *N,N*-dimethylpropargylic amine (**2l**) gave **3l** in 65% yield (entry 10). The reaction of α,ω -diyne with **2l** has been reported to require a stoichiometric amount of a Ni(0) complex.^{7h} It is well-known that a cyano group reacts with α,ω -diyne or two molecules of monoynone to give a pyridine derivative.¹⁶ Diyne **1a** reacted smoothly with 5-cyano-1-pentyne (**2m**) at the carbon–carbon triple bond to give an indane derivative **3m** exclusively. The reaction required a longer time for completion than those with other monoynes (entry 11). No pyridine derivative was obtained. Internal monoynes could also be used for the reaction of **1a**. Diyne **1a** reacted with 3-hexyne (**2o**) at room temperature to give **3o** in 15% yield. Dimer **4a** and trimer **4b** were obtained in respective yields of 43% and 40%. To suppress self-dimerization or -trimerization of **1a**, diyne **1a** was added to a reaction mixture containing a catalyst and a monoynone for 7 h. Slow addition of **1a** increased the yield of **3o** up to 82% (entry 12). The same reaction catalyzed by Cp*Ru(cod)Cl has been reported to give **3o** in 13% yield.^{10b} When 5,7-dodecadiyne (**2p**) was used as a monoynone component, the reaction took place at one of two carbon–carbon triple bonds. Alkynyl substituent was successfully introduced to the aromatic ring.^{7c} Slow addition of **1a** was effective to give indane **3p** in 61% yield. The reaction with internal monoynes gave at a yield comparable to that of the

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TABLE 3. The Reaction of **1a** with **2**^a

entry	monoyne	solvent	conditions	product	yield of 3 / ^b
1	2b (R ₁ = <i>n</i> -Oct, R ₂ = H)	benzene	rt 20 min	3b	82
2	2c (R ₁ = CH ₂ CH ₂ CH ₂ Ph, R ₂ = H)	benzene	rt 1 h	3c	81
3	2d (R ₁ = CH ₂ CH ₂ CH ₂ Cl, R ₂ = H)	benzene	rt 30 min	3d	86
4	2e (R ₁ = Ph, R ₂ = H)	dioxane	reflux 2 h	3e	85
5	2f (R ₁ = 1-cyclohexenyl, R ₂ = H)	benzene	reflux 6 h	3f	65
6	2g (R ₁ = CH ₂ OMe, R ₂ = H)	benzene	reflux 10 h	3g	66
7	2h (R ₁ = CH ₂ OH, R ₂ = H)	dioxane	reflux 8 h	3h	85
8	2i (R ₁ = CMe ₂ OH, R ₂ = H)	dioxane	reflux 3 h	3i	86
9	2j (R ₁ = CH ₂ CH ₂ OH, R ₂ = H)	dioxane	reflux 6 h	3j	77
10 ^c	2l (R ₁ = CH ₂ NMe ₂ , R ₂ = H)	dioxane	reflux 2 h	3l	65
11	2m (R ₁ = CH ₂ CH ₂ CH ₂ CN, R ₂ = H)	dioxane	reflux 17 h	3m	71
12 ^d	2o (R ₁ = R ₂ = Et)	benzene	rt 7 h	3o	82 ^e
13 ^d	2p (R ₁ = <i>n</i> -Bu, R ₂ = ≡- <i>n</i> -Bu)	benzene	rt 7 h	3p	61

^a A mixture of **1a** (1 mmol), **2** (3 mmol), [Ir(cod)Cl]₂ (0.02 mmol), DPPE (0.04 mmol), and solvent (5 mL) was stirred under Ar. ^b Isolated yield based on **1a**. ^c [Ir(cod)Cl]₂ (0.03 mmol), DPPE (0.06 mmol). ^d Diyne **1a** was added by a syringe pump for 7 h. ^e Dimer **4a** was obtained in 5% yield. Trimer **4b** was obtained in 10% yield.

TABLE 4. The Reaction of **1b–g** with **2**^a

entry	diyne	monoyne	conditions	product	yield of 3 / ^b
1	1b (E ₁ = E ₂ = Ac)	2a (R ₁ = <i>n</i> -Bu, R ₂ = H)	rt 1 h	3q	73
2	1c (E ₁ = Ph, E ₂ = CO ₂ Me)	2a	rt 1 h	3r	91
3 ^c	1c	2h (R ₁ = CH ₂ OH, R ₂ = H)	dioxane reflux 6 h	3s	77
4	1d (E ₁ = SO ₂ Me, E ₂ = CO ₂ Me)	2a	rt 1 h	3t	59
5	1e (E ₁ = E ₂ = CH ₂ OMe)	2a	rt 4 h	3u	67
6 ^c	1e	2h	dioxane reflux 12 h	3v	78
7 ^d	1f (E ₁ = E ₂ = CH ₂ OAc)	2a	rt 3 h	3w	73
8	1g (E ₁ = E ₂ = H)	2a	rt 8 h	3x	41

^a A mixture of **1** (1 mmol), **2** (3 mmol), [Ir(cod)Cl]₂ (0.02 mmol), DPPE (0.04 mmol), and benzene (5 mL) was stirred under Ar. ^b Isolated yield based on **1**. ^c Solvent was dioxane (5 mL). ^d A mixture of **1** (0.5 mmol), **2** (1.5 mmol), [Ir(cod)Cl]₂ (0.01 mmol), DPPE (0.02 mmol), and benzene (5 mL) was stirred under Ar.

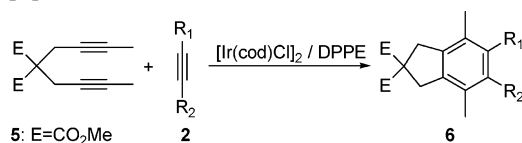
reaction with terminal monoynes. Internal monoynes as well as terminal monoynes could be used as a monoyne component.

1,6-Heptadiyne derivatives with various functional groups at the 4-position were subjected to cycloaddition. The results are summarized in Table 4. Reactions with **2a** proceeded at room temperature. The reaction of ketone **1b** with **2a** gave **3q** in 73% yield (entry 1). Introduction of a phenyl group at the 4-position increased the yield up to 91% (entry 2). The reaction of sulfone **1d** with **2a** gave a product in a slightly decreased yield compared to that of **1a** (entry 4). A substituent other than a carbonyl group is also effective for this cycloaddition. Methoxymethyl- and acetoxymethyl-substituted diynes (**1e** and **1f**) reacted with **2a** to give **3u** and **3w** in respective yields of 67% and 73% (entries 5 and 7). Diyne with no substituent at the 4-position gave a product in decreased yield compared to other 4,4-disubstituted-1,6-heptadiyne derivatives. The reaction of 1,6-heptadiyne (**1g**) gave **3x** in 41% yield (entry 8). The low yield of the product could be due to the lack of a Thorpe–Ingold effect.¹⁷ When propargylic alcohol (**2h**) was used as a monoyne component

instead of **2a**, the reaction of **1c,e** required heating to give a product in good yield (entries 3 and 6).

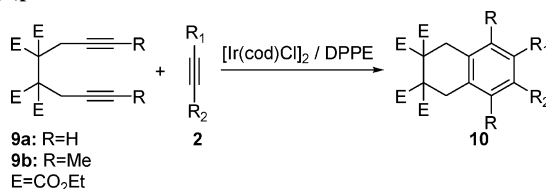
As described above, 1,6-heptadiyne derivatives reacted smoothly with a monoyne to give a product in good to high yield. We examined the reaction of 2,7-nonadiyne **5** with monoynes. The results are summarized in Table 5. Diyne **5** reacted smoothly with monoynes. Internal monoynes as well as terminal monoynes could be used for the reaction of **5**. Diyne **5** reacted with 1-hexyne (**2a**) and propargyl ether (**2g**) to give **6a** and **6g** in respective yields of 87% and 79% (entries 1 and 3). The reaction with phenylacetylene (**2e**) gave **6e** in a decreased yield compared to those of **6a** and **6g** (entry 2). Reactions with internal monoynes proceeded at room temperature to give products in high yields (entries 4–6). The cycloaddition of terminally disubstituted diynes with monoynes

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TABLE 5. The Reaction of **5** with **2a,e,g,o,p,q**^a

entry	monoynone	conditions	product	yield of 6 / ^b
1	2a (R ₁ = <i>n</i> -Bu, R ₂ = H)	toluene reflux 7 h	6a	87
2	2e (R ₁ = Ph, R ₂ = H)	toluene reflux 3 h	6e	55
3	2g (R ₁ = CH ₂ OMe, R ₂ = H)	toluene reflux 5 h	6g	79
4	2o (R ₁ = R ₂ = Et)	benzene rt 2 h	6o	87
5	2p (R ₁ = <i>n</i> -Bu, R ₂ = ≡- <i>n</i> -Bu)	benzene rt 30 min	6p	86
6	2q (R ₁ = R ₂ = CH ₂ OMe)	benzene rt 30 min	6q	94

^a A mixture of **5** (1 mmol), **2** (3 mmol), [Ir(cod)Cl]₂ (0.02 mmol), DPPE (0.04 mmol), and benzene (5 mL) was stirred under Ar. ^b Isolated yield based on **5**.

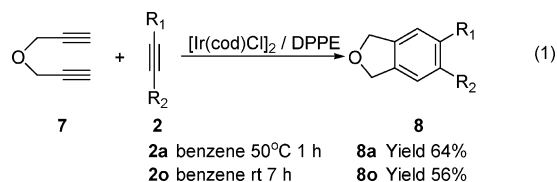
TABLE 6. The Reaction of **9a,b** with **2a,o,p**

entry	diyne	monoynone	conditions	product	yield of 10 / ^b
1 ^a	9a	2a (R ₁ = <i>n</i> -Bu, R ₂ = H)	benzene reflux 2 h	10a	53
2 ^a	9b	2a	toluene reflux 1 h	10b	45
3 ^c	9b	2o (R ₁ = R ₂ = Et)	benzene 50 °C 1 h	10c	92
4 ^d	9b	2p (R ₁ = <i>n</i> -Bu, R ₂ = ≡- <i>n</i> -Bu)	benzene 40 °C 1 h	10d	95

^a A mixture of **9** (1 mmol), **2** (6 mmol), [Ir(cod)Cl]₂ (0.03 mmol), DPPE (0.06 mmol), and solvent (5 mL) was stirred under Ar. ^b Isolated yield based on **9**. ^c A mixture of **9b** (1 mmol), **2o** (5 mmol), [Ir(cod)Cl]₂ (0.02 mmol), DPPE (0.04 mmol), and benzene (5 mL) was stirred under Ar. ^d A mixture of **9b** (1 mmol), **2p** (3 mmol), [Ir(cod)Cl]₂ (0.02 mmol), DPPE (0.04 mmol), and benzene (5 mL) was stirred under Ar.

has been studied less than that of terminally unsubstituted diynes. The Cp*Ru(cod)Cl-catalyzed reaction of **5** with **2o** has been reported to require 15 mol % of catalyst and 10 equiv of **2o** to give **6o** in 66% yield.^{10b} Iridium catalyst is more suitable for the cycloaddition of terminally disubstituted diyne with internal monoynes than other transition-metal catalysts.

We examined the reaction of an oxygen atom-tethered diyne (eq 1). Dipropargyl ether **7** reacted with 3 equiv of 1-hexyne



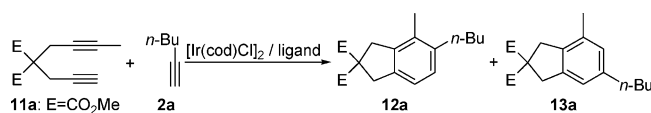
(**2a**) at room temperature for 23 h to give **8a** in 25% yield. Increasing the amount of 1-hexyne (**2a**) and heating increased the yield. The reaction of **7** with 8 equiv of **2a** at 50 °C gave **8a** in 64% yield. When 3-hexyne (**2o**) was used instead of 1-hexyne (**2a**), the slow addition of **7** to a reaction mixture containing a catalyst and **2o** for 7 h at room temperature gave **8o** in 56% yield.

As mentioned above, the [Ir(cod)Cl]₂/DPPE catalyst system is efficient for the formation of five-membered rings from either 1,6-heptadiyne derivatives **1** or 2,7-nonadiyne derivatives **5**. We next examined the possibility of six-membered ring formation from 1,7-octadiyne derivative **9a** and 2,8-decadiyne derivative **9b** (Table 6).¹⁸ The results are summarized in Table 6. Diyne **9a**, which has two quaternary carbon centers on the tether chain,

reacted with 3 equiv of **2a** under refluxing benzene for 2 h in the presence of 4 mol % of catalyst to give **10a** in 30% yield. Increasing the amount of catalyst and **2a** improved the yield up to 53%. The reaction of 2,8-decadiyne **9b** gave good results. The reaction of **9b** with 3-hexyne (**2o**) and 5,7-dodecadiyne (**2p**) gave **10c** and **10d** in respective yields of 92% and 95%. This cycloaddition is useful for the formation of six-membered rings.

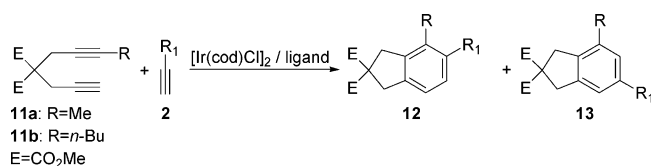
The cycloaddition of unsymmetrical α,ω-diyne with 1-alkyne gives two isomers. The control of regioselectivity is a challenging problem. Limited examples of regioselective cycloaddition of unsymmetrical α,ω-diyne with 1-alkyne have been reported. The Cp*Ru(cod)Cl-catalyzed reaction of 4,4-disubstituted 1,6-octadiyne with 1-alkyne has been reported to be meta selective.^{10b,e} The RhCl(PPh₃)₃-catalyzed reaction of oxygen-tethered diyne with 1-alkynes has also been reported to be meta selective.⁸ⁿ However, the RhCl(PPh₃)₃-catalyzed reaction of nitrogen-tethered diyne was reported to be ortho selective, and the ortho selectivity was up to 90%.^{8l} This is the only example of ortho-selective cycloaddition. To the best of our knowledge, there is no previous report of the selective synthesis of either ortho or meta products from the same substrate. It is well-known that the electronic and steric nature of a ligand affects the catalytic activity and selectivity. The regioselectivity of cycloaddition can be controlled by a ligand. A systematic survey of ligands showed that regioselective cycloaddition was controlled by the ligand. The results are summarized in Table 7. Diyne **11a** reacted with 1-hexyne (**2a**) to give ortho-product **12a** and meta-product **13a**. DPPE and

(18) Six-membered ring formation, see ref 7i.

TABLE 7. Effect of the Ligand on the Reaction of **11a** with **2a**^a

entry	ligand ^b	conditions	yield/% ^c	ratio ^d 12a/13a
1	DPPM	benzene reflux 5 h	84	26/74
2	DPPE	benzene rt 30 min	93	20/80
3	DPPP	benzene reflux 1 h	82	43/57
4	DPPB	benzene reflux 1 h	89	59/41
5	DPPH	benzene reflux 24 h	10	70/30
6	1,2-bis(diphenylphosphino)ethylene	benzene rt 3 h	74	19/81
7	DPPF	benzene reflux 1 h	84	88/12
8	(<i>R</i>)-(<i>S</i>)-BPPFOAc	toluene reflux 3 h	72	78/22
9	PPh ₃	toluene reflux 3 h	32	81/19

^a A mixture of **11a** (1 mmol), **2a** (3 mmol), [Ir(cod)Cl]₂ (0.02 mmol), ligand (0.04 mmol), and solvent (5 mL) was stirred under Ar. ^b DPPB = 1,4-bis(diphenylphosphino)butane; DPPH = 1,6-bis(diphenylphosphino)hexane; DPPF = 1,1'-bis(diphenylphosphino)ferrocene; (*R*)-(*S*)-BPPFOAc = (*R*)-1-[(*S*)-1',2-bis(diphenylphosphino)ferrocenyl]ethyl acetate. ^c Isolated yield based on **11a**. ^d Determined by ¹H NMR.

TABLE 8. Cycloaddition of **11a,b** with **2**^a

entry	diyne	monoene	ligand	conditions	product	yield/% ^b	ratio ^c 12/13
1	11a	2a (R ₁ = <i>n</i> -Bu, R ₂ = H)	DPPE	benzene rt 0.5 h	12a, 13a	92	20/80
2	11a	2b (R ₁ = <i>n</i> -Oct, R ₂ = H)	DPPE	benzene rt 1 h	12b, 13b	80	19/81
3	11a	2f (R ₁ = 1-cyclohexenyl, R ₂ = H)	DPPE	toluene reflux 9 h	12c, 13c	92	39/61
4	11a	2k (R ₁ = CH ₂ CH ₂ CH ₂ OH, R ₂ = H)	DPPE	benzene rt 12 h	12d, 13d	75	18/82
5	11a	2n (R ₁ = Me ₃ Si, R ₂ = H)	DPPE	toluene reflux 2 h	12e, 13e	74	42/58
6	11a	2a	DPPF	benzene reflux 1 h	12a, 13a	84	88/12
7	11a	2b	DPPF	benzene reflux 1 h	12b, 13b	83	86/14
8	11a	2f	DPPF	toluene reflux 8 h	12c, 13c	68	76/24
9	11a	2k	DPPF	benzene reflux 2 h	12d, 13d	86	84/16
10	11a	2n	DPPF	toluene reflux 1 h	12e, 13e	52	74/26
11	11b	2a	DPPE	benzene rt 3 h	12f, 13f	76	14/86
12	11b	2a	DPPF	toluene reflux 3 h	12f, 13f	80	59/41

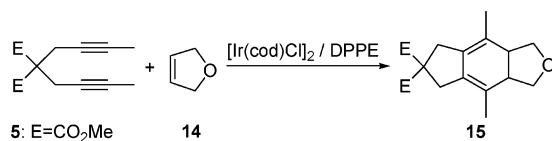
^a A mixture of **11** (1 mmol), **2** (3 mmol), [Ir(cod)Cl]₂ (0.02 mmol), ligand (0.04 mmol), and solvent (5 mL) was stirred under Ar. ^b Isolated yield based on **11**. ^c Determined by ¹H NMR.

DPPM were meta-selective ligands (entries 1 and 2). The reaction with DPPE gave products in 93% yield with 80% meta selectivity. Increasing the methylene length between the two phosphorus atoms increased the ortho selectivity. DPPH gave 70% ortho selectivity, but the product yield was only 10% (entry 5). The reactions with ferrocenyl phosphine ligands were ortho selective. The reaction with DPPF gave products in 84% yield with 88% ortho selectivity (entry 7). (*R*)-(*S*)-BPPFOAc was less ortho selective than DPPF (entry 8). PPh₃ was an ortho-selective ligand, but the product yield was only 32% (entry 9).

On the basis of these results, we developed the regioselective cycloaddition of **11a** with 1-alkynes. The results are summarized in Table 8. Reactions with DPPE were meta selective, while those with DPPF were ortho selective. Various 1-alkynes including alcohol **2k** could be used for regioselective cycloaddition. Good meta selectivities were observed for the reaction with **2a,b,k** (entries 1, 2, and 4). Reactions with enyne **2f** and trimethylsilylacetylene **2n** were less meta selective than that with **2a,b,k**. For reactions with DPPF, good ortho selectivities were observed in all cases (entries 6–10). The introduction of a longer alkyl substituent to the alkyne part in the unsymmetrical diyne affected the regioselectivity. When the ligand was DPPE, the reaction of **11b** with **2a** was more meta selective than that of

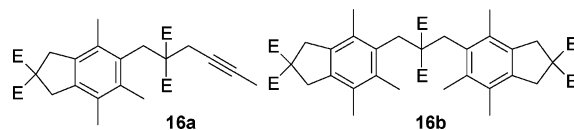
11a with **2a** (entry 11). Meta selectivity was 86%. The reaction with DPPF gave products in 80% yield with 59% ortho selectivity, which is less ortho selective than the reaction of **11a** with **2a** (entry 12).

Cycloaddition of α,ω -Diyne with Monoenes. The cycloaddition of α,ω -dienes with monoynes was efficiently catalyzed by [Ir(cod)Cl]₂/DPPE. If a monoene is used instead of a monoene, a cyclohexadiene derivative will be obtained as a product.¹⁹ A polycyclic cyclohexadiene structure can be constructed by using iridium catalysis. Cyclohexadienes are used in the Diels–Alder reaction, which provides a rich and diverse chemistry.²⁰ This cycloaddition is the simplest route to a bicyclic cyclohexadiene framework. To examine this possibility, we carried out the cycloaddition of α,ω -dienes with monoenes. We examined the reaction of **1a** with monoenes such as 1-octene, acrylonitrile, styrene, and 2,5-dihydrofuran. Although diyne **1a** was consumed completely, no cyclohexadiene derivative was obtained. Only the self-dimerization of **1a** occurred. The terminal alkyne part of **1a** would be more reactive than the monoenes used. We used 2,7-nonadiyne **5** instead of **1a** to suppress the self-dimerization of a diyne component, since internal alkynes should be less reactive than terminal alkynes

TABLE 9. Effect of Molar Ratio on the Reaction of **5** with **14**^a

entry	molar ratio 14/5	solvent (mL)	time/h	yield of 15 ^b	yield of 16a ^b
1	66	none	2	76	13
2	50	THF (1.2 mL)	2	79	19
3	50	dioxane (1.2 mL)	1	62	24
4	50	1,2-dimethoxyethane (1.2 mL)	6	54	20
5	50	benzene (1.2 mL)	2	69	20
6	50	1,2-dichloroethane (1.2 mL)	1	67	16
7	50	EtOH (1.2 mL)	13	58	17
8	30	THF (2.7 mL)	2	58	33
9	10	THF (4.2 mL)	2	40	36

^a A mixture of **5** (1 mmol), **14**, [Ir(cod)Cl]₂ (0.01 mmol), DPPE (0.02 mmol), and solvent was stirred at 70 °C under Ar. ^b Isolated yield based on **5**.

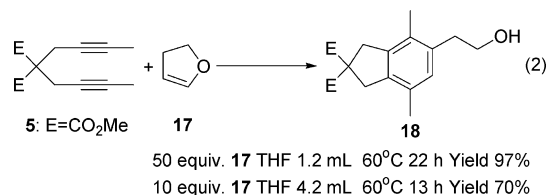


due to steric reasons. Diyne **5** reacted with 2,5-dihydrofuran (**14**) under reflux in the presence of a catalytic amount of [Ir(cod)Cl]₂/DPPE (Ir atom 4 mol %). The results are summarized in Table 9. When 2,5-dihydrofuran was used as a solvent, cyclohexadiene **15** was obtained in 76% yield along with the self-dimerization product **16a** in 13% yield (entry 1). Self-trimerization product **16b** was not obtained at all. The molar ratio of 2,5-dihydrofuran (**14**) to diyne **5** strongly affected the yield of **15**. A molar ratio of **14** to **5** of 50 gave **15** in 79% yield (entry 2). The effect of the solvent was examined at a molar ratio of 50 (entries 2–7). THF gave the best result (entry 2). A molar ratio of 30 or 10 decreased the yield of **15** (entries 8 and 9). A large excess of 2,5-dihydrofuran (**14**) is necessary for a high yield of **15**.

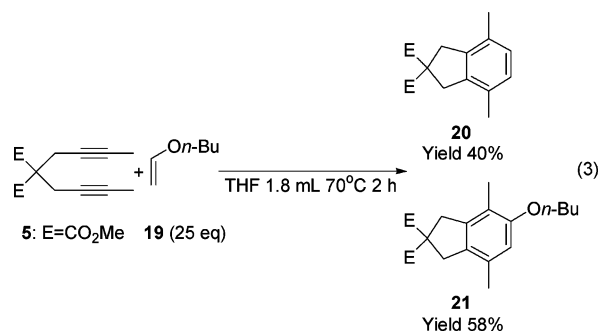
Diyne **5** reacted smoothly with 2,5-dihydrofuran (**14**) to give **15**. Analogous to the iridium-catalyzed reaction of **5** with **14**, the [2+2+2]cycloaddition of 1,6-heptadiyne with 2,5-dihydrofuran catalyzed by ruthenium complex has been reported.^{19d,h} The coordination of the allylic oxygen atom to the ruthenium center plays an important role. On the basis of this result, we examined the reaction of **5** with allyl acetate, allyl *n*-propyl ether,

and diallyl ether. Reactions were carried out under reflux for 24 h. No products were obtained.

A novel aromatization reaction including cleavage of a C–O bond was found in the reaction of **5** with 2,3-dihydrofuran (**17**) (eq 2). Diyne **5** reacted with 50 equiv of 2,3-dihydrofuran (**17**)



in the presence of a catalytic amount of [Ir(cod)Cl]₂/DPPE (Ir atom 4 mol %) at 60 °C for 22 h to give aromatic alcohol **18** in 97% yield. When the amount of **17** was reduced to 10 equiv, the yield of **18** decreased to 70%. The aromatization reaction could be extended to the reaction with an acyclic vinyl ether such as *n*-butyl vinyl ether (**19**) (eq 3). The reaction of **5** with 25 equiv of **19** at 70 °C for 2 h gave **20** and ether **21**. The combined yield was nearly quantitative.



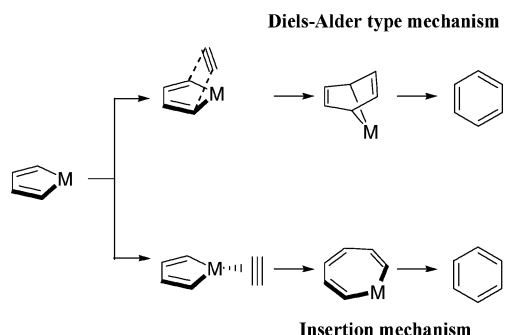
Discussion

Metallacyclopentadiene is a common intermediate in the cyclotrimerization of alkynes.³ It is generally accepted that there are two mechanisms for the reaction of metallacyclopentadiene with alkynes (Scheme 1): a Diels–Alder type mechanism and

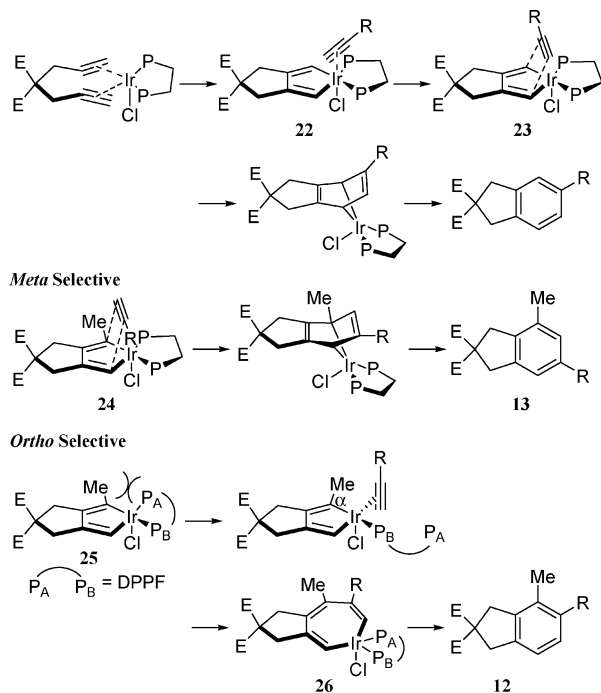
(19) Cycloaddition of diynes or two molecules of monoynes with monoenes to give cyclohexadienes, see: (a) Wu, M.-S.; Rayabarapu, D. K.; Cheng, C.-H. *Tetrahedron* **2004**, *60*, 10005. (b) Sambaiah, T.; Li, L.-P.; Huang, D.-J.; Lin, C.-H.; Rayabarapu, D. K.; Cheng, C.-H. *J. Org. Chem.* **1999**, *64*, 3663. (c) Eichberg, M. J.; Dorta, R. L.; Lamottke, K.; Vollhardt, K. P. C. *Org. Lett.* **2000**, *2*, 2479. (d) Yamamoto, Y.; Kitahara, H.; Ogawa, R.; Kawaguchi, H.; Tatsumi, K.; Itoh, K. *J. Am. Chem. Soc.* **2000**, *122*, 4310. (e) Ikeda, S.; Kondo, H.; Mori, N. *Chem. Commun.* **2000**, 815. (f) Mori, N.; Ikeda, S.; Sato, Y. *J. Am. Chem. Soc.* **1999**, *121*, 2722. (g) Yamamoto, Y.; Kitahara, H.; Hattori, R.; Itoh, K. *Organometallics* **1998**, *17*, 1910. (h) Yamamoto, Y.; Kitahara, H.; Ogawa, R.; Itoh, K. *J. Org. Chem.* **1998**, *63*, 9610. (i) Ikeda, S.; Watanabe, H.; Sato, Y. *J. Org. Chem.* **1998**, *63*, 7026. (j) Ikeda, S.; Mori, N.; Sato, Y. *J. Am. Chem. Soc.* **1997**, *119*, 4779. (k) Balaich, G. J.; Rothwell, I. P. *J. Am. Chem. Soc.* **1993**, *115*, 1581. (l) Zhou, Z.; Costa, M.; Chiusoli, G. P. *J. Chem. Soc., Perlin Trans. I* **1992**, 1399. (m) Zhou, Z.; Battaglia, L. P.; Chiusoli, G. P.; Costa, M.; Nardelli, M.; Pelizzi, C.; Predieri, G. *J. Chem. Soc., Chem. Commun.* **1990**, 1632. (n) Macomber, D. W.; Verma, A. G.; Rogers, R. D. *Organometallics* **1988**, *7*, 1241. (o) Brown, L. D.; Itoh, K.; Suzuki, H.; Hirai, K.; Ibers, J. A. *J. Am. Chem. Soc.* **1978**, *100*, 8232. (p) Suzuki, H.; Itoh, K.; Ishii, Y.; Simon, K.; Ibers, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 8494.

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SCHEME 1



SCHEME 2



an insertion mechanism to give metallacycloheptatriene. Iridacyclopentadiene formed by the oxidative cyclization of α,ω -diynes is an intermediate for cycloaddition (Scheme 2). The catalytic activity of our iridium catalyst strongly depended on the ligand used, and $[\text{Ir}(\text{cod})\text{Cl}]_2/\text{DPPE}$ was the most catalytically active. The reaction of $[\text{Ir}(\text{cod})\text{Cl}]_2$ with DPPE gives the mononuclear species $\text{Ir}(\text{cod})\text{Cl}(\text{dppe})$. Oxidative cyclization of diynes with $\text{Ir}(\text{cod})\text{Cl}(\text{dppe})$ would give iridacyclopentadiene **22**. The reaction of **22** with monoalkyne followed by reductive elimination gives a final product. The efficiency of DPPE suggests that a Diels–Alder type mechanism²¹ is involved in this case. Bidentate coordination of DPPE produces a vacant coordination site above the plane of iridacyclopentadiene **22**. Coordination of a monoalkyne at this position²² would facilitate a Diels–Alder type process via intermediate **23**. Coordination of DPPE to iridium forms a five-membered ring, which gives the most stable chelation. The stability of the intermediate coordinated by DPPE would lead to high catalytic activity.

(21) Reaction of iridacyclopentadiene with a monoalkyne via a Diels–Alder type process, see: ref 12j,k. Reaction of cobaltacyclopentadiene with a monoalkyne via a Diels–Alder type process, see: (a) Hardesty, J. H.; Koerner, J. B.; Albright, T. A.; Lee, G.-Y. *J. Am. Chem. Soc.* **1999**, *121*, 6055. (b) McAlister, D. R.; Bercaw, J. E.; Bergman, R. G. *J. Am. Chem. Soc.* **1977**, *99*, 1666.

Regioselectivity of Cycloaddition. The regioselectivity of the cycloaddition of **11** with 1-alkynes could be controlled by the ligand. DPPE was a meta-selective ligand, whereas DPPF was an ortho-selective ligand. Meta selectivity is outlined in Scheme 2. 1-Alkyne coordinates to the vacant coordination site above the plane of the iridacyclopentadiene formed by the oxidative cyclization of **11a**. The orientation of the incoming 1-alkyne is directed to avoid steric interaction between the methyl group on iridacyclopentadiene **24** and the substituent on 1-alkyne. Therefore, meta-product **13** is obtained as a major product. To explain the ortho selectivity, we should propose another mechanism. Important results are shown in Table 7. Increasing the length of the carbon chain between the two phosphorus atoms in diphosphine increased the ortho selectivity (Table 7, entries 2–5). Triphenylphosphine also showed high ortho selectivity (Table 7, entry 9). The results with DPPH and triphenylphosphine are important for considering the mechanism of ortho selectivity (Table 7, entries 5 and 9). These ligands gave low yields of products, but gave high ortho selectivity. Coordination of DPPH to the iridium center forms a nine-membered ring in which chelation is not tight.²³ One of the two phosphorus atoms in DPPH easily dissociates from the iridium center to give a vacant coordination site. Triphenylphosphine also easily dissociates from the metal center compared to bidentate ligands. The high ortho selectivities given by DPPH and PPh_3 suggest that the generation of a vacant coordination site is important. Ortho selectivity is outlined in Scheme 2. DPPF was found to be the best ligand for ortho selectivity (Table 7, entry 7). Since DPPF has a large bite angle,^{23d} it is reasonable to consider that similar dissociation takes place in intermediate **25** coordinated by DPPF. The steric hindrance between a methyl group and PPh_2 moiety induces the dissociation of P_A to give a vacant coordination site on the iridium center. Coordination of a monoalkyne at this position followed by insertion gives intermediate **26**. Reductive elimination from **26** gives the product. In this insertion step, the iridium moiety, which is more bulky than the C_α moiety, adds to the less-hindered site of two acetylenic carbons²⁴ to give iridacycloheptatriene **25** **26**. Thus, ortho product **12** is obtained as a major product.

Cycloaddition with Monoenes to Give Cyclohexadiene Derivatives. A possible mechanism is outlined in Scheme 3. Coordination of 2,5-dihydrofuran (**14**) to a vacant coordination site above the plane of iridacyclopentadiene **27** is followed by a Diels–Alder type process to give **29**. Reductive elimination from **29** gives **15**.

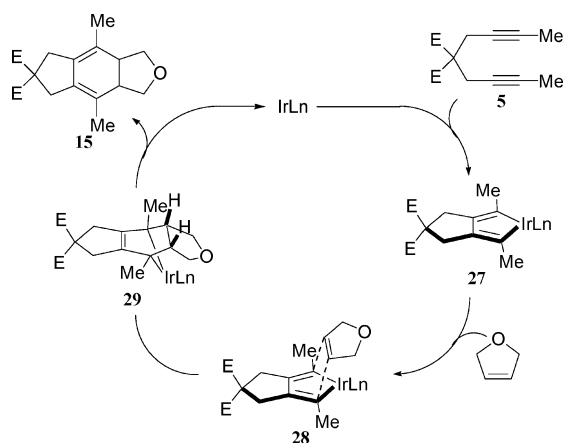
Cycloaddition with Monoenes to Give Benzene Derivatives. Diyne **5** reacted with 2,3-dihydrofuran to give benzene derivative **18** (eq 2). The reaction involves the cleavage of a C–O bond in 2,3-dihydrofuran. A possible mechanism is outlined in Scheme 4. Iridacyclopentadiene **27** reacts with 2,3-dihydrofuran to give intermediate **31** via a Diels–Alder type process. Reductive elimination of **31** gives diene intermediate

(22) Cobaltacyclopentadiene bearing an alkyne ligand is isolated, see: (a) Dosa, P. I.; Whiteener, G. D.; Vollhardt, K. P. C.; Bond, A. D.; Teat, S. J. *Org. Lett.* **2002**, *4*, 2075. (b) Diercks, R.; Eaton, B. E.; Gürtzgen, S.; Jalisatgi, S.; Matzger, A. J.; Radde, R. H.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1998**, *120*, 8247.

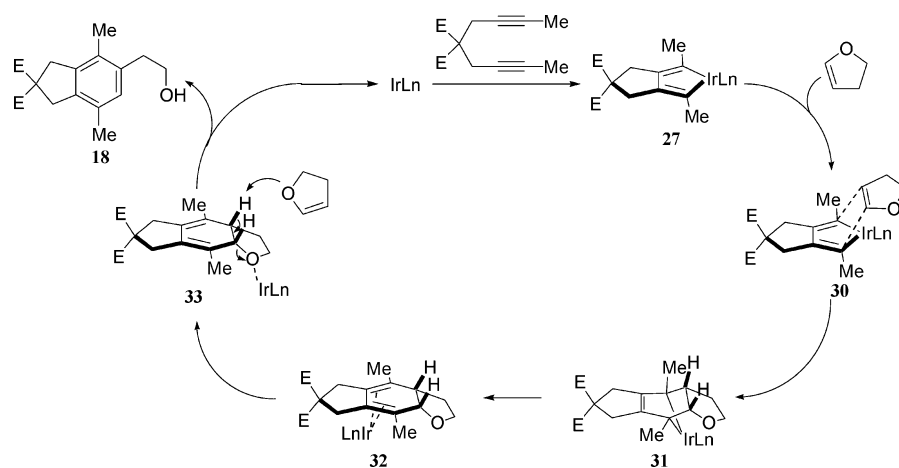
(23) The effect of bite angle, see: (a) Freixa, Z.; van Leeuwen, P. W. N. M. *Dalton Trans.* **2003**, 1890. (b) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741. (c) Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Acc. Chem. Res.* **2001**, *34*, 895. (d) Dierkes, P.; van Leeuwen, P. W. N. M. *J. Chem. Soc., Dalton Trans.* **1999**, 1519.

(24) The regioselectivity of the insertion is governed by the steric demands of both the metal center and the alkyne.

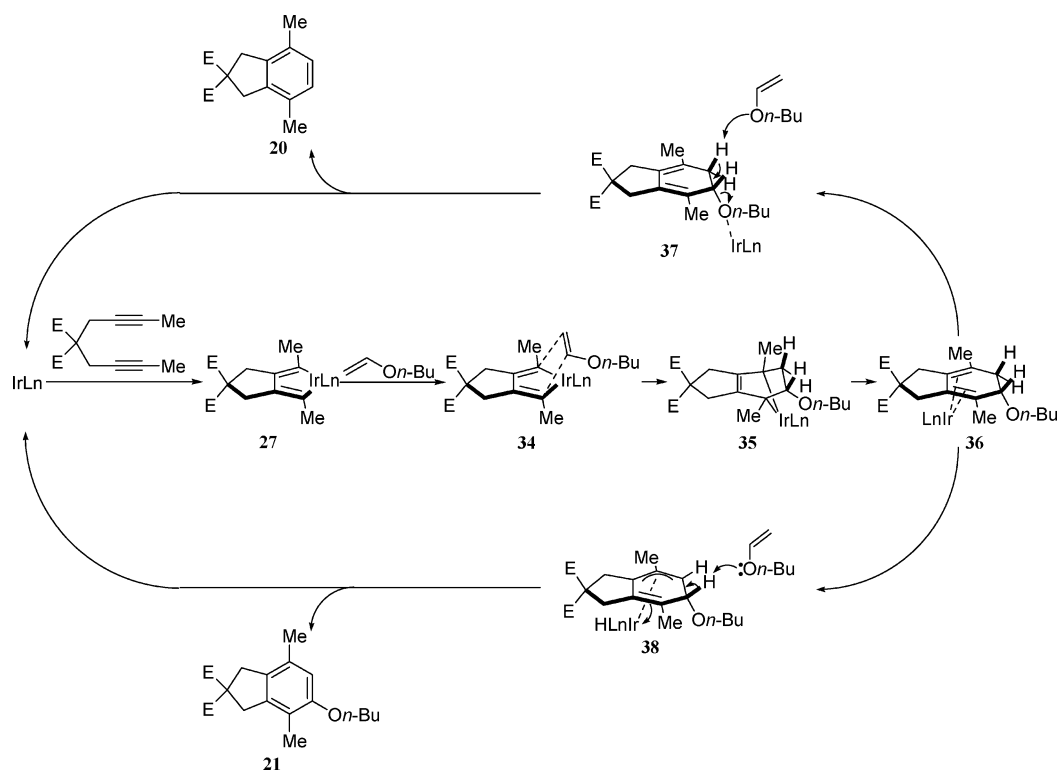
SCHEME 3



SCHEME 4



SCHEME 5



32. The iridium moiety moves to an oxygen atom to give intermediate **33**. E2 elimination from **33** gives product **18** and regenerates an iridium active species. The reaction of **5** with *n*-butyl vinyl ether gave two benzene derivatives **20** and **21** (eq 3). A possible mechanism is outlined in Scheme 5. A process similar to that discussed above takes place in this case. The reaction of **27** with *n*-butyl vinyl ether gives diene **36**. The iridium moiety moves to an oxygen atom to give intermediate **37**. E2 elimination from **37** gives product **20** and regenerates an iridium active species. Another reaction pathway is possible for diene **36**. The oxidative addition of the allylic C–H bond to the iridium center gives π -allyl iridium hydride intermediate **38**.²⁶ Anti β -hydride elimination²⁷ assisted by *n*-butyl vinyl ether gives **21** and regenerates an iridium active species.

Conclusion

In conclusion, we developed the iridium complex-catalyzed cycloaddition of diynes with monoynes and monoenes. The reactions proceeded under mild conditions to give polysubstituted benzene derivatives and cyclohexadiene derivatives in good to excellent yields. The experimental procedures are quite simple. A phosphine ligand is crucial for high catalytic activity and high selectivity. In alkyne cycloaddition chemistry, Cp or Cp* metal complexes such as CpCo(CO)₂, CpRh(ethylene)₂, and Cp*Ru(cod)Cl have been used as catalysts. In such cases, it can be difficult to control the reaction by tuning the steric and electronic effects of the Cp ligand since the introduction of substituents to the Cp ligand requires considerable synthetic operations. In contrast, our catalyst is convenient for controlling the reaction, since various phosphine ligands are available. It is important to note that [Ir(cod)Cl]₂ is a commercially available, air-stable, and easily handled complex. The results described here should lead to new opportunities for the application of organoiridium chemistry in cycloaddition.

Experimental Section

General Procedure for the Cycloaddition of Diyne with Monoynone at Room Temperature. A typical procedure is described for the reaction of **1a** with 1-hexyne (**2a**) (Table 1; entry 3). Into a two-necked flask with a stirring bar were placed diyne **1a** (208 mg, 1.0 mmol), [Ir(cod)Cl]₂ (13.4 mg, 0.02 mmol), and DPPE (15.9 mg, 0.04 mmol). The flask was evacuated and filled with Ar. Benzene (5.0 mL) was added to the flask. To the stirred solution was added 1-hexyne (**2a**) (246 mg, 3.0 mmol). The mixture was stirred at room temperature for 20 min. The solvent was evaporated in vacuo. Column chromatography (*n*-hexane/AcOEt = 98/2) of the residue gave **3a** as a colorless oil (244 mg; yield 84%).

General Procedure for the Cycloaddition of Diyne with Monoynone at Elevated Temperature. A typical procedure is described for the reaction of **1a** with propargyl alcohol (**2h**) (Table 1; entry 7). Into a two-necked flask with a stirring bar were placed diyne **1a** (208 mg, 1.0 mmol), [Ir(cod)Cl]₂ (13.4 mg, 0.02 mmol), and DPPE (15.9 mg, 0.04 mmol). The flask was evacuated and filled with Ar. Dioxane (5.0 mL) was added to the flask. To the stirred solution was added propargyl alcohol (**2h**) (168 mg, 3.0 mmol) at room temperature. The reactor was immersed in an oil bath at room temperature, and then heating was begun. The reaction mixture was heated under refluxing dioxane for 8 h. After the reaction was completed, the solvent was evaporated in vacuo. Column chromatography of the residue gave **3h** (*n*-hexane/AcOEt = 70/30, 225 mg, yield 85%).

General Procedure for the Slow Addition of Diyne. A typical procedure is described for the reaction of **1a** with **2o** (Table 3; entry 12). Into a two-necked flask with a stirring bar were placed [Ir(cod)Cl]₂ (13.4 mg, 0.02 mmol) and DPPE (15.9 mg, 0.04 mmol). The flask was evacuated and filled with Ar. Benzene (3.0 mL) was added to the flask. To the stirred solution was added 3-hexyne (**2o**) (246 mg, 3.0 mmol). A benzene solution (2.0 mL) of **1a** (208 mg, 1.0 mmol) was added dropwise to the reaction mixture over 7 h by a syringe pump with stirring at room temperature. After the reaction was completed, the solvent was evaporated in vacuo. Column chromatography of the residue gave **3o** (*n*-hexane/AcOEt = 98/2, 238 mg, yield 82%), **4a** (*n*-hexane/AcOEt = 80/20, 11 mg, yield 5%), and **4b** (*n*-hexane/AcOEt = 50/50, 21 mg, yield 10%).

General Procedure for the Cycloaddition of **5 with **14**.** A typical procedure is described for the reaction in THF (Table 9; entry 2). Into a two-necked flask with a stirring bar were placed [Ir(cod)Cl]₂ (6.8 mg, 0.01 mmol) and DPPE (8.0 mg, 0.02 mmol). The flask was evacuated and filled with Ar. THF (1.2 mL) was added to the flask. To the stirred solution was added 2,5-

dihydrofuran (**14**) (3.505 g, 50 mmol), and **5** (236 mg, 1.0 mmol) was then added to the stirred solution. The reactor was immersed in an oil bath, which was kept at 70 °C. The reaction mixture was heated at 70 °C for 2 h. After the reaction was completed, the solvent was evaporated in vacuo. Column chromatography of the residue gave **15** and **16a** as a mixture (*n*-hexane/AcOEt = 90/10, 289 mg). The yield of each product was determined by ¹H NMR. Products were purified by recycling preparative HPLC.

Cycloaddition of **5 with **17**.** Into a two-necked flask with a stirring bar were placed [Ir(cod)Cl]₂ (6.8 mg, 0.01 mmol) and DPPE (8.0 mg, 0.02 mmol). The flask was evacuated and filled with Ar. THF (1.2 mL) was added to the flask. To the stirred solution was added 2,3-dihydrofuran (**17**) (3.505 g, 50 mmol), and **5** (236 mg, 1.0 mmol) was then added to the stirred solution. The reactor was immersed in an oil bath, which was kept at 60 °C. The reaction mixture was heated at 60 °C for 22 h. After the reaction was completed, the solvent was evaporated in vacuo. Column chromatography of the residue gave **18** (*n*-hexane/AcOEt = 70/30, 297 mg, yield 97%).

Cycloaddition of **5 with **19**.** Into a two-necked flask with a stirring bar were placed [Ir(cod)Cl]₂ (6.8 mg, 0.01 mmol) and DPPE (8.0 mg, 0.02 mmol). The flask was evacuated and filled with Ar. THF (1.8 mL) was added to the flask. To the stirred solution was added *n*-butyl vinyl ether (**19**) (2.504 g, 25 mmol), and **5** (236 mg, 1.0 mmol) was then added to the stirred solution. The reactor was immersed in an oil bath, which was kept at 70 °C. The reaction mixture was heated at 70 °C for 2 h. After the reaction was completed, the solvent was evaporated in vacuo. Column chromatography of the residue gave **20** and **21** as a mixture (*n*-hexane/AcOEt = 98/2, 299 mg). The yield of each product was determined by ¹H NMR. Products were purified by recycling preparative HPLC.

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Supporting Information Available: Experimental details, compound characterization data, and ¹H and ¹³C NMR spectra for compounds **3a**, **3e**, **3l**, **3t**, **3w**, **3x**, **4a**, **4b**, **6p**, **8a**, **10b**, **10d**, and **16a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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