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Iridium Complex-Catalyzed Highly Selective Cross [2 + 2 + 2] Cycloaddition of Two Different Monoynes: 2:1 Coupling versus 1:2 Coupling

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ABSTRACT

Highly selective cross [2+2+2] cycloaddition of two different monoynes is achieved by using a catalytic amount of $[lr(cod)Cl]_2$ and ligand. The ligand had a considerable effect on the reaction. When 1,2-bis(diphenylphosphino)ethane was used, two molecules of dimethyl acetylenedicarboxylate (DMAD) reacted with one molecule of a monoyne to give the 2:1 coupling product. When 1,2-bis(dipentafluorophenylphosphino)ethane was used instead of dppe, one molecule of DMAD reacted with two molecules of a monoyne to give the 1:2 coupling product.

In the course of our study on iridium complex-catalyzed organic synthesis, we previously found that $[Ir(cod)Cl]_2/dppe$ is an efficient catalyst for [2+2+2]cycloaddition of α,ω -diynes with monoynes. We report here the extension of this chemistry to the highly selective cross [2+2+2] cycloaddition of two different monoynes (Scheme 1). The

[2+2+2] cycloaddition of monoynes is one of the most straightforward routes to polysubstituted benzenes, but the drawback of this route is selectivity. The highly selective cross [2+2+2] cycloaddition of two or three different monoynes is a challenging problem.³

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Scheme 1. 2:1 Coupling of DMAD with Monoynes

2h: R₁=H, R₂=SiMe₃

2i: R₁=H, R₂=CH₂NMe₂

2o: R₁=Ph, R₂=Me

The rich chemistry of metallacycles gives various useful transformations in selective organic synthesis.⁴ Both late and early transition metals can be used for this chemistry. Catalytic reactions via nickelacycles,⁵ palladacycles,⁶ cobaltacycles,⁷ rhodacycles⁸ and ruthenacycles⁹ have been extensively studied and used for the synthesis of cyclic compounds from an acyclic substrate. Since Collman et al. first reported the synthesis of an iridacyclopentadiene from the reaction of IrCl(N₂)(PPh₃)₂ with DMAD (1) in 1968,¹⁰ the reactivity and structure of iridacyclopentadiene have been studied.¹¹ However, there have been few reports on catalytic organic synthesis via iridacyclopentadiene.¹²

The reaction of **1** with 1-hexyne (**2a**) in the presence of a catalytic amount of [Ir(cod)Cl]₂/dppe gave **3a** and **4**.^{13,14} Product **3a** resulted from the 2:1 coupling of two molecules of **1** with one molecule of **2a**. Product **4** resulted from

Table 1. 2:1 Coupling of DMAD with 1-Hexyne (2a)^a

entry	1 (mmol)	2a (mmol)	time (h)	yield of $3a$ $(\%)^b$	yield of 4 $(\%)^b$
1	2	1	0.5	89	11
2	2	1.2	1	98	2
3	2	2	1	98	2
4	2	5	24	97	3

 a A mixture of 1, 2a, [Ir(cod)Cl]₂ (0.02 mmol), dppe (0.04 mmol), and toluene (5 mL) was stirred under refluxing toluene. b Isolated yield based on 1.

cyclotrimerization of **1**. The molar ratio of **1** to **2a** affected the yield of **3a**. The results are summarized in Table 1. The reaction using 0.6 equiv of **2a** gave **3a** in 98% yield (entry 2). Cyclotrimerization of **1** was not suppressed completely. Product **4** was obtained in 2% yield.

On the basis of these results, we examined the scope of the 2:1 coupling. The results are summarized in Table 2.

Table 2. 2:1 Coupling of DMAD with 2^a

entry	2	conditions	product	yield 3 $(\%)^b$	yield 4 (%) ^b
1	2b	toluene reflux 1 h	3b	96	2
2	2c	xylene reflux 20 h	3c	38	50
3	2d	toluene reflux 5 h	3d	86	3
4	2e	toluene reflux 5 h	3e	83	2
5^{c}	2f	THF reflux 12 h	3f	91	0
6^c	2g	THF reflux 0.5 h	3g	89	0
7^c	2h	THF reflux 20 h	3h	52	16
8^c	2i	dioxane reflux 20 h	3i	41	0
9^c	2 j	THF reflux 1 h	3j	90	0
10	2k	THF 50 °C 2 h	3k	98	0
11	21	THF 50 °C 1 h	31	93	0
12^d	2m	THF 50 °C 1 h	3m	89	10
$13^{d,e}$	2n	THF 50 °C 2 h	3n	73	11
$14^{d,f}$	2 o	THF 50 °C 3.5 h	3o	78	15

^a A mixture of 1 (2 mmol), 2 (1.2 mmol), [Ir(cod)Cl]₂ (0.02 mmol), dppe (0.04 mmol), and solvent (5 mL) was stirred.
^b Isolated yield based on 1.
^c [Ir(cod)Cl]₂ (0.03 mmol), dppe (0.06 mmol).
^d 2 (2 mmol).
^e Slow addition of 1 for 0.5 h.
^f Slow addition of 1 for 2 h.

DMAD smoothly reacted with 0.6 equiv of various monoynes (2) under mild conditions. The reaction with 1-decyne (2b) proceeded at room temperature to give a product in high yield (entry 1). The reaction with phenylacetylene (2c)

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required more demanding conditions and a longer reaction time and gave 3c in 38% yield (entry 2). DMAD reacted smoothly with 2d, in which the phenyl group is away from a triple bond, to give 3d in 86% yield (entry 3). The reaction with monoynes bearing a functional group such as a chloro, cyano, or ether group gave 3e-g in excellent yields (entries 4-6). The steric hindrance of a trimethylsilyl group decreased the product yield (entry 7). The reaction with propargylic amine 2i gave 3i in 41% yield (entry 8). Introducing an electron-withdrawing group on the nitrogen atom increased the yield. The reaction with *N*-propargylic carbamate 2j gave 3j in 90% yield (entry 9). Internal alkynes could also be used for the reaction (entries 10-14). The reaction with 2n gave an alkynyl group-substituted benzene in 73% yield (entry 13).

DMAD reacted with propargylic alcohols (5a-c) to give lactone as a product (Scheme 2). Lactone would be formed

Scheme 2. 2:1 Coupling of DMAD with Propargylic Alcohols

by transesterification.^{3d} In these reactions, the cyclotrimerization of 1 did not occur at all.

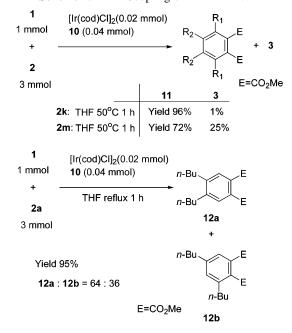
Methyl 2-octynoate (7), an unsymmetrical monoyne, reacted with 2k at 50 °C (Scheme 3). Two 2:1 coupling

Scheme 3. 2:1 Coupling of Methyl 2-Octynoate with 2k

products were obtained in 82% yield. The selectivity of the major product 8 was 93%.

The 1:2 coupling was possible by using 1,2-bis(dipentafluorophenylphosphino)ethane (10) instead of dppe (Scheme 4). The reaction of 1 with 3 equiv of 2k gave 11k, the 1:2 coupling of one molecule of 1 with two molecules of 2k, in 96% yield. Similarly, the reaction of 1 with 2m gave 11m

Scheme 4. 1:2 Coupling of DMAD with 2



in 72% yield. DMAD smoothly reacted with a terminal monoyne **2a** to give two 1:2 coupling products. A 64:36 mixture of **12a** and **12b** was obtained in 95% yield.

It is reasonable to consider that the reaction proceeds via iridacyclopentadiene as an intermediate. When the ligand is dppe, the coordination of 1 to an iridium center would be much faster than with other monoynes. It leads to the formation of tetracarbomethoxy-substituted iridacyclopentadiene (13). The reaction of this intermediate with the second monoyne gives the final product. The use of the ligand 10 gave a different result. Since 1 and 10 are both electron-withdrawing, the coordination of two molecules of 1 to Ir-(cod)(10)Cl gives an electron-deficient species. Oxidative cyclization of this species would be a relatively difficult process. When the ligand is 10, oxidative cyclization of Ir-(cod)(10)Cl with two molecules of 2 to give 14 is preferred.

Figure 1.

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In conclusion, we have found a highly selective cross [2 + 2 + 2] cycloaddition of two different monoynes catalyzed by $[Ir(cod)Cl]_2$ /ligand under mild conditions. The reaction is quite useful and practical for the synthesis of polysubstituted benzene derivatives. The experimental procedure for the reaction is quite simple. Monoynes are added to the solution of a catalyst, and then DMAD (1) is added. Slow addition of the substrate using a syringe pump is unnecessary except when 2n or 20 is used. Extension of the scope of this reaction and mechanistic studies are underway.

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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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