## [Ir(cod)Cl]<sub>2</sub>/FDPPE-Catalyzed Chemo- and Regioselective Cyclotrimerization of Two Different Terminal Alkynes To Give 1,3,5-Trisubstituted Benzenes

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**Abstract:**  $[Ir(cod)Cl]_2$  in combination with 1,2-bis(dipentafluorophenylphosphino)ethane catalyzes chemo- and regioselective cyclotrimerization of two different alkynes. The reaction of methyl propiolate with 1-hexyne gave methyl 3,5-di(*n*-butyl)benzoate as a single product in 88% yield.

Key words: iridium, cyclotrimerization, regioselectivity, alkynes, catalysis

Polysubstituted benzenes are a common structural component of naturally occurring biologically active molecules. The traditional synthesis of polysubstituted benzene is based on the stepwise introduction of substituents via electrophilic substitution.<sup>2</sup> This process is not atom-economical or environmentally benign, since a stoichiometric amount of waste is produced as a byproduct. To overcome these drawbacks, transition-metal-catalyzed cyclotrimerization to give benzene derivatives has been studied extensively.<sup>3</sup> The regioselective cyclotrimerization of two or three different monoynes is a new and efficient route to polysubstituted benzenes. However, it can be difficult to control the regioselectivity. There are limited examples of the successful regioselective cyclotrimerization of two or three different monoynes.<sup>4</sup> In the course of our study on iridium-catalyzed cycloaddition of alkynes,<sup>5</sup> we have previously reported the [Ir(cod)Cl]<sub>2</sub>catalyzed highly selective cycloaddition of dimethyl acetylenedicarboxylate (DMAD) with monoynes.<sup>5d</sup> In that study, we observed the unique reactivity of  $(C_6F_5)_2PCH_2CH_2P(C_6F_5)_2$  (FDPPE) as a ligand. We found that [Ir(cod)Cl]<sub>2</sub>/DPPE catalyzed the 2:1 coupling of DMAD with a monoyne, whereas [Ir(cod)Cl]<sub>2</sub>/FDPPE catalyzed the 1:2 coupling of DMAD with a monoyne. In this communication, we wish to report the  $[Ir(cod)Cl]_2/$ FDPPE-catalyzed chemo- and regioselective cyclotrimerization of two different terminal alkynes to give 1,3,5trisubstituted benzenes.

Methyl propiolate (1a) reacted with two molecules of 1hexyne (2a) to give 3aa in the presence of a catalytic amount of  $[Ir(cod)Cl]_2$  and FDPPE. Previously, we reported that DPPE was an efficient ligand for the  $[Ir(cod)Cl]_2$ -catalyzed cycloaddition of alkynes. Howev-

SYNLETT 2008, No. 5, pp 0755–0758 Advanced online publication: 26.02.2008 DOI: 10.1055/s-2008-1042810; Art ID: Y01807ST © Georg Thieme Verlag Stuttgart · New York er, the reaction of **1a** with **2a** catalyzed by [Ir(cod)Cl]<sub>2</sub>/ DPPE gave no product (3aa); [Ir(cod)Cl]<sub>2</sub>/PPh<sub>3</sub> and [Ir(cod)Cl]<sub>2</sub> alone were examined as catalysts. Only [Ir(cod)Cl]<sub>2</sub>/FDPPE gave **3aa**. Other transition-metal complexes combined with FDPPE were also examined for the reaction of 1a with 2a; [Rh(cod)Cl]<sub>2</sub>/FDPPE, Pd(dba)<sub>2</sub>/FDPPE and Ni(cod)<sub>2</sub>/FDPPE were inert as catalysts. The molar ratio of **1a** to **2a** affected the yield of **3aa**. The results are summarized in Table 1. The use of an excess amount of 2a to 1a is needed to give 3aa in good yield. The reaction using 3 equivalents of 2a gave 3aa in 88% yield (Table 1, entry 2). The use of 4 equivalents or 2.1 equivalents of **2a** to **1a** slightly decreased the yield of **3aa** (Table 1, entries 1 and 3). On the other hand, the use of 1 or 2 equivalents of 1a to 2a gave 3aa in poor yields (Table 1, entries 4 and 5).

Table 1Effect of Molar Ratio on the Reaction of 1a with  $2a^a$ 

CO <sub>2</sub> Me    + 1a	       2a	Bu [Ir(cod)Cl] <sub>2</sub> /FDPP THF, reflux	E n-Bu 3aa	łu
Entry		1a (mmol)	2a (mmol)	Yield of <b>3aa</b> (%) <sup>b</sup>
1		1	4	83
2		1	3	88
3		1	2.1	71
4		2	2	34 <sup>c</sup>
5		4	2	14 <sup>c</sup>

<sup>a</sup> A mixture of **1a**, **2a**, [Ir(cod)Cl]<sub>2</sub> (0.02 mmol), FDPPE (0.04 mmol), and THF (5 mL) was stirred under refluxing THF for 2 h.

<sup>b</sup> Yields were isolated yields based on **1a**.

<sup>c</sup> Yields were isolated yields based on 2a.

We examined the scope of the cross-cyclotrimerization.<sup>6</sup> All of the reactions listed in Table 2 gave a single product.<sup>7</sup> Methyl propiolate (**1a**) smoothly reacted with various 1-alkynes (**2b**–**h**) to give **3** in high yields. The results are summarized in Table 2. The reactions with 1-octyne (**2b**) and 1-decyne (**2c**) gave the corresponding products in high yields (Table 2, entries 1 and 2). Conjugated enynes could be used for the reaction. The reaction with phenylacetylene (**2d**) required a longer reaction time than that with ethynylcyclohexene (**2e**). Teraryl **3ad** was obtained in 85% yield (Table 2, entry 3). This reaction is useful for the synthesis of teraryl compounds. The reaction of **1a** with **2e** gave **3ae** in 72% yield (Table 2, entry 4). Methyl propiolate reacted smoothly with **2f**, in which the phenyl group is away from a triple bond, as in **2a** or **2b**, to give **3af** in 88% yield (Table 2, entry 5). The reaction with monoynes bearing a functional group, such as a chloro or cyano group, gave **3ag** and **3ah** in high yields (Table 2, entries 6 and 7). The reaction of ethynyl *p*-tolyl sulfone (**1b**) with various 1-alkynes (**2a,c,d,g**) gave the corresponding products in high yields (Table 2, entries 8– 11).

Table 2Reaction of 1 with  $2^a$ 



Entr	уE	R	Time (h)	Prod. <b>3</b>	Yield (%) <sup>b</sup>
1	CO <sub>2</sub> Me ( <b>1a</b> )	<i>n</i> -Hex ( <b>2b</b> )	16	3ab	96
2	CO <sub>2</sub> Me ( <b>1a</b> )	<i>n</i> -Oct ( <b>2c</b> )	5	3ac	84
3°	CO <sub>2</sub> Me ( <b>1a</b> )	Ph ( <b>2d</b> )	14	3ad	85
4	CO <sub>2</sub> Me ( <b>1a</b> )	1-cyclohexenyl (2e)	6	3ae	72
5°	CO <sub>2</sub> Me ( <b>1a</b> )	$Ph(CH_2)_3 (\mathbf{2f})$	4	3af	88
6	CO <sub>2</sub> Me ( <b>1a</b> )	$Cl(CH_2)_3$ ( <b>2g</b> )	5	3ag	82
7	CO <sub>2</sub> Me ( <b>1a</b> )	NC(CH <sub>2</sub> ) <sub>3</sub> ( <b>2h</b> )	4	3ah	90
8	SO <sub>2</sub> <i>p</i> -Tol ( <b>1b</b> )	<i>n</i> -Bu ( <b>2a</b> )	24	3ba	66
9	SO <sub>2</sub> <i>p</i> -Tol ( <b>1b</b> )	<i>n</i> -Oct ( <b>2c</b> )	5	3bc	90
10	SO <sub>2</sub> <i>p</i> -Tol ( <b>1b</b> )	Ph ( <b>2d</b> )	2	3bd	58
11	SO <sub>2</sub> <i>p</i> -Tol ( <b>1b</b> )	$Cl(CH_2)_2$ (2g)	5	3bg	95

<sup>a</sup> A mixture of **1** (1 mmol), **2** (3 mmol), [Ir(cod)Cl]<sub>2</sub> (0.02 mmol), FD-PPE (0.04 mmol), and THF (5 mL) was stirred under refluxing THF. <sup>b</sup> Yields were isolated yields based on **1**.

<sup>c</sup> Conditions: **1a** (2 mmol), **2** (6 mmol), [Ir(cod)Cl]<sub>2</sub> (0.04 mmol), FD-PPE (0.08 mmol), THF (10 mL).

1,3,5-Trisubstituted benzenes have attracted considerable attention as basic components in dendrimers.<sup>8</sup> The central core, the surface unit and the branching propagating unit need this structure. The synthetic approach to 1,3,5-trisubstituted benzene via traditional electrophilic substitution requires long synthetic sequences. For example, 3,5-dialkyl benzoate, which is the surface unit of dendrimer, can be prepared in three steps from benzoate: meta-selective bromination of benzoate, Sonogashira coupling with 1-alkyne and hydrogenation of a carbon–carbon triple bond.<sup>9</sup> Our cyclotrimerization provides the most efficient route to 3,5-disubstituted benzoate.

Aromatic aldehydes are a very useful class of products, since the highly reactive aldehyde group can be readily

used in numerous carbon–carbon and carbon–nitrogen bond-forming reactions as well as other transformations. We first attempted to carefully reduce **3aa** to **4aa** with DIBAL-H, but instead obtained a mixture of alcohol and aldehyde **4aa**. We then tried reduction–in situ manganese dioxide alcohol oxidation (Table 3).<sup>7,10</sup> Various 3,5-disubstituted benzaldehydes **4** were obtained from 3,5-disubstituted benzoates by this procedure without isolation of the intermediate alcohols.

Table 3 Reduction-in Situ Manganese Dioxide Alcohol Oxidation<sup>a</sup>



<sup>a</sup> A mixture of **3** (1 mmol),  $LiAlH_4$  (1.5 mmol), and  $Et_2O$  (5 mL) was stirred at r.t. Then, a mixture of crude alcohol,  $MnO_2$  (10 mmol), and  $CH_2Cl_2$  (5 mL) was stirred.

8

9

58

4ah

<sup>b</sup> Yields were isolated yields based on **3**.

NC(CH<sub>2</sub>)<sub>3</sub> (3ah)

7°

<sup>c</sup> A mixture of **3ah** (1 mmol), DIBAL-H (3 mmol), and THF (5 mL) was stirred at -78 °C. Then, a mixture of crude alcohol, MnO<sub>2</sub> (10 mmol), and CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was stirred.

It is reasonable to consider that the reaction proceeds via iridacyclopentadiene<sup>11</sup> as an intermediate. Iridacyclopentadiene can be produced as an intermediate either from two molecules of 2 or from 1 and 2. To obtain additional mechanistic information, we examined the cyclotrimerization of 1-hexyne. The cyclotrimerization of 1-hexyne under refluxing toluene in the presence of [Ir(cod)Cl]<sub>2</sub> (Ir atom 4 mol%) and FDPPE gave no benzene derivative. The formation of an iridacyclopentadiene from two molecules of 1-hexyne is unlikely. The regioselectivity of the reaction can be explained by the selective formation of an iridacyclopentadiene from 1 and 2. The reaction of 1 with 2 can give iridacyclopentadiene 5 and 6 (Scheme 1). The second molecule of 2 reacts with 5 or 6 to give 3 as a final product. Due to steric considerations, the more hindered  $\alpha$ -carbon of **5** and **6** smoothly couples with unsubstituted alkyne carbon to give 3. The regioselectivity of the formation of metallacyclopentadiene has been reported. The reaction of diphenylacetylene cobalt Cp complex with methyl propiolate gave a cobaltacyclopentadiene complex, in which a carbomethoxy group occupied the  $\alpha$ -position.<sup>12</sup> On this basis, an iridacyclopentadiene **5** is a more

likely intermediate.  $[Ir(cod)Cl]_2/FDPPE$  gave no cyclotrimerization of two molecules of **1** with one molecule of **2**. The coordination of two molecules of methyl propiolate (**1a**) or ethynyl *p*-tolyl sulfone (**1b**) to Ir(FDPPE)Cl species gives an electron-deficient species. Since an electron-rich species is more favorable for oxidative addition, the oxidative cyclization of **1** and **2** to give an iridacyclopentadiene is preferred over that of two molecules of **1** to give an iridacyclopentadiene.



Scheme 1 Formation of iridacyclopentadiene

In conclusion, we have found chemo- and regioselective cyclotrimerization of one molecule of 1 with two molecules of 2. This reaction provides a practical synthesis of 3,5-disubstituted benzoates and 3,5-disubstituted phenyl *p*-tolyl sulfone. These 1,3,5-trisubstituted benzenes have various synthetic applications and should be useful building blocks. For example, such structural units are needed in the synthesis of dendrimer. We are currently extending the scope of the reaction and performing mechanistic studies.

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- (6) Typical Experimental Procedure for the Reaction of Methyl Propiolate (1a) with 1-Hexyne (2a) Catalyzed by [Ir(cod)Cl]<sub>2</sub>/FDPPE and Spectral Data of Methyl 3,5-Di(*n*-butyl)benzoate (3aa)

Into a two-necked flask with a stirring bar were placed [IR (cod)Cl]<sub>2</sub> (13.6 mg, 0.02 mmol) and FDPPE (30.9 mg, 0.040 mmol). The flask was evacuated and filled with Ar. Then, anhydrous THF (5.0 mL) was added to the flask. To the stirred solution was added 1-hexyne (2a, 243 mg, 3.0 mmol). Methyl propiolate (1a, 83.3 mg, 1.0 mmol) was then added dropwise to the reaction mixture. The reactor was immersed in an oil bath, which was kept at 75 °C. The reaction mixture was heated under reflux for 1 h. The progress of the reaction was monitored by GLC. After the reaction was completed, the solvent was concentrated in vacuo. Column chromatography of the residue gave 3aa as a colorless oil (nhexane-EtOAc = 99:1, 219 mg, yield 88%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta = 0.93$  (t, J = 7.3 Hz, 6 H), 1.35 (sext, J = 7.3 Hz, 4 H), 1.58–1.64 (m, 4 H), 2.62 (t, J = 7.8 Hz, 4 H), 3.90 (s, 3 H), 7.18 (s, 1 H), 7.68 (d, J = 1.8 Hz, 2 H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta = 13.9 (2 \text{ C}), 22.3 (2 \text{ C}), 33.6 (2 \text{ C}),$ C), 35.4 (2 C), 51.9, 126.9 (2 C), 130.1, 133.4, 143.1 (2 C), 167.6. Anal. Calcd for C<sub>16</sub>H<sub>24</sub>O<sub>2</sub>: C, 77.38; H, 9.74; O, 12.88. Found: C, 77.49; H, 9.74.

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- (10) Typical Procedure for the Reaction of 3aa To Give 3,5-Di(*n*-butyl)benzaldehyde (4aa) and Spectral Data of 4aa A flask was charged with LiAlH<sub>4</sub> (57 mg, 1.5 mmol). The flask was evacuated and filled with argon. To the flask was added Et<sub>2</sub>O (3 mL). An ether solution (3.0 mL) of benzoate **3aa** (248 mg, 1 mmol) was added dropwise to the reaction mixture. The mixture was stirred at r.t. for 4 h. The progress of the reaction was monitored by TLC. After the reaction was complete, the mixture was poured into 2 M HCl, and the

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aqueous layer was extracted with Et<sub>2</sub>O. The combined organic layers were washed with a solution of sat. aq NaHCO<sub>3</sub> and dried with Mg<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated in vacuo. Another flask was charged with MnO<sub>2</sub> (869 mg, 10 mmol). The flask was evacuated and filled with argon. Then, CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added to the flask. The CH<sub>2</sub>Cl<sub>2</sub> solution (3 mL) of the residue was then added to the stirred reaction mixture. The reaction mixture was stirred at r.t. for 30 h. The progress of the reaction was monitored by GLC and TLC. After the reaction was complete, the mixture was filtered through a Celite pad. The solution was evaporated in vacuo. Column chromatography of the residue gave **4aa** as a colorless oil (*n*-hexane–EtOAc = 99:1, 192 mg, yield 88%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta = 0.94$  (t, J = 7.3 Hz, 6 H), 1.36 (sext, J = 7.3 Hz, 4 H), 1.59–1.65 (m,

4 H), 2.66 (t, J = 7.8 Hz, 4 H), 7.26 (s, 1 H), 7.51 (d, J = 1.4 Hz, 2 H), 9.97 (s, 1 H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta = 13.9$  (2 C), 22.3 (2 C), 33.4 (2 C), 35.3 (2 C), 127.1 (2 C), 135.0, 136.6, 143.8 (2 C), 192.8. HRMS: m/z calcd for C<sub>15</sub>H<sub>22</sub>O [M<sup>+</sup>]: 218.1671; found: 218.1651.

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