# A Novel Self-Promoted Morita-Baylis-Hillman-Like Dimerization

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#### Abstract

While stable in  $CH_2Cl_2$ , hexane or THF, in the presence of MeOH, self-promoted dimerization of the tri-arylphosphine-alkene 1, a ligand for Pd-catalyzed reactions, produced an unusual racemic bis(phosphine) 2 in high yield. Reaction of 2 with Pd(dba)<sub>2</sub>, followed by oxidative addition of p-IC<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>, yields a trans-chelated Pd(II) aryl iodide complex.

Keywords: Phosphine, Ligand, Palladium, DFT calculations, Reaction mechanism

### **1. Introduction**

The Morita-Baylis-Hillman (MBH) reaction<sup>[1,2]</sup> is a useful and atom-economical carbon-carbon bond forming reaction (Scheme 1), which involves nucleophile catalyzed addition of an alkene, which is activated by an electron-withdrawing group, to an electrophile, typically an aldehyde or imine.<sup>[3]</sup> As it has been used for the synthesis of a variety of natural and unnatural products<sup>[4-6]</sup>, the MBH reaction has recently experienced an enormous growth in importance and use.<sup>[3, 7-19]</sup>

$$R \xrightarrow{\downarrow}_{H} F = C \text{ or } N$$

Scheme 1: Morita-Baylis-Hillman (MBH) Reaction. EWG: electron-withdrawing group.

However, the application of the MBH reaction had been limited in complex syntheses by slow reaction rates and low conversions<sup>[3, 20]</sup> as well as difficulty in controlling absolute stereochemistry.<sup>[8]</sup> Theoretical and experimental studies have provided insight into how to increase the rate of this reaction.<sup>[21-25]</sup>Often, nucleophilic catalysts such as DABCO, DBU, *n*-Bu<sub>3</sub>P are employed.<sup>[20]</sup> Slow reaction rates, <sup>[20]</sup> autocatalysis in the absence of proton donors, <sup>[22]</sup> formation of dioxanones, <sup>[26-27]</sup> and the rate acceleration observed in protic solvents, <sup>[28-32]</sup> are intriguing aspects of the MBH reaction, and recent DFT studies have begun to provide useful mechanistic insights.<sup>[33-35]</sup>

A few examples of dimerization reactions have been reported, but they require a catalyst, <sup>[36-39]</sup> or high temperature, <sup>[39]</sup> or high pressure. <sup>[40]</sup> We report herein the unusual case of a self-promoted dimerization of a triarylphosphine-substituted vinylphenyl-ketone **1**, which we have been exploring as a ligand in Pd-catalyzed reactions. <sup>[41-43]</sup>

### 2. Experiment and discussion



Scheme 2: Self-promoted dimerization.

The dimerization of **1** (Scheme 2) takes place under ambient conditions, in  $CH_2Cl_2/MeOH$  mixtures, requiring no additives, giving dimer **2** in ca. 80% isolated yield. *In situ* NMR experiments and DFT calculations, provide preliminary insight into the mechanism, including reaction order, solvent effects, etc.

Initially, we used different solvent combinations  $(CH_2Cl_2/hexane, THF/hexane, and CH_2Cl_2/MeOH)$  to grow crystals of **1**. We obtained crystals<sup>§</sup> of **1** (Figure 1, left) from  $CH_2Cl_2/hexane$  and THF/hexane, but were surprised to obtain crystals of the dimer, **2**, (Figure 1, right) from  $CH_2Cl_2/MeOH$ . Indeed, when pure **1** was dissolved in  $CH_2Cl_2$  (ca. 20 mg/mL) and layered with twice the amount of MeOH, crystals<sup>§</sup> of **2** were isolated in 81% yield after 4 d at room temperature. Compound **2** is clearly formed by dimerization of **1**, by a process related to the MBH reaction, although no catalyst, acid or base was added.



Figure 1: Molecular structures of **1** (left) and **2** (right) with phenyl H-atoms omitted for clarity and ellipsoids drawn at 30% probability.

Table 1: Yield of 2 at different times vs.	$CH_2Cl_2$ / MeOH ratio
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CH <sub>2</sub> Cl <sub>2</sub> /MeOH ratio	20:80	33:67	66:34	90:10
24 hours	34%	34%	6%	0
4 days	81%	81%	20%	6%

The dimerization reaction can be carried out in air, in 20-33% CH<sub>2</sub>Cl<sub>2</sub>/CD<sub>3</sub>OD or in 20-33% THF/CD<sub>3</sub>OD; after 43 h in CH<sub>2</sub>Cl<sub>2</sub>/CD<sub>3</sub>OD, <sup>31</sup>P{<sup>1</sup>H} NMR spectroscopy showed no evidence for P=O, whereas in THF/CD<sub>3</sub>OD ca. 8% of phosphine oxide was observed. After 4 d, ca. 9 and 18% P=O species were observed in CH<sub>2</sub>Cl<sub>2</sub>/CD<sub>3</sub>OD and THF/CD<sub>3</sub>OD, respectively. Thus, although both **1** and **2** can be handled in air for brief periods without degradation, subsequent studies were carried out under N<sub>2</sub> via *in situ* <sup>31</sup>P{<sup>1</sup>H} NMR spectroscopy to monitor reaction progress. The reaction was ca. 4x faster in CH<sub>2</sub>Cl<sub>2</sub>/CD<sub>3</sub>OD than in THF/CD<sub>3</sub>OD, and ca. 70% yield of **2** was obtained within 2 d in the former case. As acids are known to promote MBH reactions, we examined both AR grade CH<sub>2</sub>Cl<sub>2</sub> as well as that which had been purified by washing with aq. Na<sub>2</sub>CO<sub>3</sub> followed by drying over CaCl<sub>2</sub> and distillation from CaH<sub>2</sub> under N<sub>2</sub>. There was no difference in the reaction rate in either case. We also examined the effect of the CH<sub>2</sub>Cl<sub>2</sub>/MeOH ratio over the range 20-90% CH<sub>2</sub>Cl<sub>2</sub> (Table 1). After 24 h, ca. 34% conversion was observed in either 20 or 33% CH<sub>2</sub>Cl<sub>2</sub>. In 66% CH<sub>2</sub>Cl<sub>2</sub>. Clearly, MeOH accelerates the reaction dramatically, and must play more than a spectator role in the reaction, *vide infra*. <sup>[39]</sup>

Traditional nucleophilic catalysts for the MBH reaction were examined against control reactions under identical conditions. n-Bu<sub>3</sub>P (in THF/MeOH, to avoid any reaction with CH<sub>2</sub>Cl<sub>2</sub>) had no significant effect on the rate, but DABCO (in CH<sub>2</sub>Cl<sub>2</sub>/MeOH) actually slowed down the reaction dramatically. Acids, i.e., PhOH and CH<sub>3</sub>COOH, had little if any effect on the rate.





Figure 2: Second order rate plots of the above reactions at the 4 different initial concentrations of monomer (1). Condition: 1) 15.3 mg of 1 was dissolved in 400  $\mu$ l of CD<sub>2</sub>Cl<sub>2</sub> + 200  $\mu$ l of CD<sub>3</sub>OD, [C]<sub>0</sub>= 0.06505 mol/L; 2) 30.6 mg of 1 was dissolved in 400  $\mu$ l of CD<sub>2</sub>Cl<sub>2</sub> + 200  $\mu$ l of CD<sub>3</sub>OD, [C]<sub>0</sub>= 0.1301 mol/L; 3) 45.9 mg of 1 was dissolved in 400  $\mu$ l of CD<sub>3</sub>OD, [C]<sub>0</sub>= 0.19515 mol/L; 4) 61.2 mg of 1 was dissolved in 400  $\mu$ l of CD<sub>2</sub>Cl<sub>2</sub> + 200  $\mu$ l of CD<sub>3</sub>OD, [C]<sub>0</sub>= 0.2602 mol/L; 4) 61.2 mg of 1 was dissolved in 400  $\mu$ l of CD<sub>2</sub>Cl<sub>2</sub> + 200  $\mu$ l of CD<sub>3</sub>OD, [C]<sub>0</sub>= 0.2602 mol/L.

It appears that the reaction is self-promoted, i.e., that the nucleophilic catalyst is the phosphine itself. Reactions carried out under otherwise identical conditions but with four different starting concentrations show that the rate depends on the initial concentration of the monomer. Plots of  $[1]^{-1}$  vs. time, obtained from in situ <sup>31</sup>P{<sup>1</sup>H} NMR spectroscopy, were linear (R<sup>2</sup> > 0.987 in all cases) with similar slopes (Figure 2), suggesting that the reaction is second order in [1].



Figure 3: Dideuteration of **2** from reaction in  $CD_3OD$ .

When the reaction was carried out in CD<sub>2</sub>Cl<sub>2</sub>/CD<sub>3</sub>OD, D<sub>2</sub>-dimer was obtained exclusively, with the two diastereotopic protons at position 2a ( $\alpha$  to the carbonyl, Figure 3) of **2** being deuterated. The <sup>1</sup>H NMR spectrum showed that the two doublets of doublets at 3.63 and 3.14 ppm, normally observed for the gem H<sub>2</sub> group, disappeared and the quartet (due to coupling to 2 protons and to <sup>31</sup>P) for H(2b) at 5.75 ppm collapsed to a doublet. The deuteration level (>90% D<sub>2</sub>) was confirmed by MS and HRMS(ESI+): m/z calcd. for C<sub>54</sub>H<sub>40</sub><sup>2</sup>H<sub>2</sub>O<sub>2</sub>P<sub>2</sub> (M+H)<sup>+</sup> 787.28584, found 787.28645. As both protons are potentially enolizable, in order to determine whether proton exchange occurred during or after the reaction, **2** was dissolved in CH<sub>2</sub>Cl<sub>2</sub>/CD<sub>3</sub>OD. Within 4 h, only the signal at 3.63 ppm disappeared,

whereas the signal at 3.14 ppm collapsed to a doublet and the signal at 5.75 ppm collapsed to a triplet. Thus, only one of the two diastereotopic H's in **2** undergoes rapid enolization and D exchange, and this did not change within 3 d, as confirmed by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy and ESI-MS. Clearly, the other H at position 2a must become deuterated during the course of the dimerization reaction rather than after **2** is formed, again indicating the important role of MeOH/D in the reaction. <sup>[34]</sup>



Transition	ΔE (gas phase)	$\Delta E (CH_3OH)$	Correction to	Correction to	Relative ∆G
state	(Hartrees)	(Hartrees)	∆H (Hartrees)	$\Delta G$	(MeOH)
				(Hartrees)	(kcal/mol)
1-ts	-2916.116616	-2916.140660	0.849402	0.713482	0.0
2-ts	-2916.064854	-2916.093403	0.849320	0.708860	26.7
3-ts	-2916.063781	-2916.090888	0.846320	0.708457	28.0
4-ts	-3031.843496	-3031.869767	0.906054	0.758819	6.2
CH <sub>3</sub> OH	-115.7144050	-115.7224202	0.05571	0.028749	

Figure 4: Preliminary DFT studies of the dimerization reaction mechanism

Preliminary DFT studies (B3LYP/6-31G\*) of the reaction pathway clearly indicate that intramolecular activation via attack of the phosphorus atom on the carbon  $\beta$ -to the C=O group (C1b in Scheme 2) is prohibitively high in energy due to ring strain (formation of a 4-membered ring), whereas intermolecular attack of the phosphorus atom on C1b of a second molecule, while entropically disfavored, is enthalpically favorable, consistent with the observed 2<sup>nd</sup> order dependence of the reaction rate on [1]. The free energy of activation for the formation of the new C-C bond via a 6-membered ring transition state was computed to be ca. 27 kcal/mol lower than via intermolecular nucleophilic attack (Figure 4). In addition, the calculations show that MeOH plays an important role in the key proton transfer step, as noted previously (Figure 4).<sup>[34]</sup> Assistance of MeOH lowers  $\Delta G^{\ddagger}$  for the proton transfer step by ca. 22 kcal/mol. Further comprehensive DFT studies (MPWpw91, 6-31+G\*) of the mechanism of the dimerization, including solvent effects and all possible diastereomeric transition states, are ongoing.



Scheme 3: Reaction to form compound 3.

Compound **2** contains two P-donors separated by seven carbon atoms, and has one chiral carbon center. Thus, we decided to explore its potential as a ligand. When **2** was reacted with  $Pd(dba)_2$  followed by addition of excess p-IC<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>, the Pd(II) oxidative addition product **3** formed in essentially quantitative yield, as determined by in situ <sup>31</sup>P{<sup>1</sup>H} NMR spectroscopy, and was isolated in 73% yield (Scheme 3).

The <sup>31</sup>P{<sup>1</sup>H} NMR spectrum of 3 was strongly 2<sup>nd</sup> order even on a 700 MHz spectrometer, giving rise to an AB multiplet centred at 19.5 ppm with  $J_{P-P}$  of ca. 400 Hz, clearly indicating a trans-disposition of the two P atoms, which was confirmed by X-ray diffraction (Figure 5).<sup>§</sup> As oxidative additions of ArX to Pd(0) are believed to be concerted processes leading initially to cis-products, <sup>[44-46]</sup> it is likely that one arm of the ligand dissociates prior to oxidative addition.



Figure 5: Molecular structure of **3** with phenyl H-atoms and disorder omitted for clarity and ellipsoids drawn at 30% probability. Selected bond distances (Å): Pd-I 2.6977(5), Pd-P(1) 2.327(1), Pd-P(2) 2.334(1), Pd-C(1) 2.003(3).

§ Crystal data at T = 120 K: C<sub>27</sub>H<sub>21</sub>OP (1),  $M_r = 392.41$ , monoclinic, space group  $P2_1/n$ , a = 15.0231(9), b = 7.5594(5), c = 18.8798(11) Å,  $\beta = 101.263(8)^\circ$ , V = 2102.8(2) Å<sup>3</sup>, Z = 4; C<sub>54</sub>H<sub>42</sub>O<sub>2</sub>P<sub>2</sub> (2),  $M_r = 784.82$ , monoclinic, space group  $P2_1/c$ , a = 10.6118(7), b = 20.8716(16), c = 18.5327(14) Å,  $\beta = 94.12(1)^\circ$ , V = 4094.1(5) Å<sup>3</sup>, Z = 4; C<sub>60</sub>H<sub>46</sub>INO<sub>4</sub>P<sub>2</sub>Pd·½C<sub>6</sub>D<sub>6</sub>·1.65 CH<sub>2</sub>Cl<sub>2</sub> (3) (the content of disordered CH<sub>2</sub>Cl<sub>2</sub> is uncertain),  $M_r = 1322.42$ , triclinic, space group *P*-*I*, a = 11.8555(6), b = 12.8611(8), c = 21.8617(11) Å,  $\alpha = 79.13(2)$ ,  $\beta = 75.98(2)$ ,  $\gamma = 65.15(3)^\circ$ , V = 2920.3(3) Å<sup>3</sup>, Z = 2;  $R_F = 0.038$ , 0.039 and 0.044 for 3967, 6936 and 10477 unique reflections with I > 2 (*I*), respectively. Supplementary data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data\_request/cif, CCDC 703071 (1), 703072 (2) and CCDC 703073 (3).

### **3** Conclusion and future works

In conclusion, we have observed the unusual self-promoted dimerization of a phosphine-alkene ligand leading to a new bis-phosphine capable of *trans*-chelation. Preliminary kinetic and mechanistic studies indicate a  $2^{nd}$  order process which is triggered by the nucleophilic attack of one phosphorus on the carbon  $\beta$ -to the carbonyl group of another molecule, and which only takes place in the presence of a protic solvent (i.e., MeOH). Further experimental and theoretical studies of the mechanism of the reaction and of the chemistry of the dimeric ligand are in progress.

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#### Author Brief Introduction:

Qiang Li, Male, Ph.D candidate for Organic Chemistry, interested in Ligand design, synthesis and application of the ligand on the field of Pd chemistry.