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## Construction of Bidentate Arsenic Ligand Library Starting from a Cyclooligoarsine

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Bidentate ligand is, needless to say, pivotal in  $\frac{1}{2}$ organometallic chemistry. In contrast to phosphorus ligands, 3 4 practical synthetic protocols for the arsenic analogues remain to be developed, resulting in lack of bidentate 5 arsenic ligands. Herein the methods that we have recently 6 developed were applied for the bidentate arsenic ligands whose frameworks are well known in phosphorus ligand systems such as dppe, dppp, dppf, xantphos, etc. The 8 ġ palladium dichloride complexes of the obtained ligands were synthesized and used for the Suzuki-Miyaura coupling reaction.

#### 12 Keywords: Arsenic, Bidentate ligand, Cyclooligoarsine, 13 Palladium complex, Coupling reaction

14 In the early 20th century, coordination chemistry of 15 arsenic ligands was an active field; organoarsenic chemistry was studied for medical and military purposes during and 16 just after the World War I.<sup>1</sup> However, arsenic ligands were 17 then overtaken by the phosphorus analogues because of 18 superior coordination ability of phosphorus ligands to hard 19 metals, and of development of <sup>31</sup>P-NMR technique. 20 21 Numerous kinds of phosphorus ligands have been developed 22 and are commercially available. Needless to say, they 23 currently play primary roles in coordination chemistry, 24 particularly in the field of transition metal catalysts. In 25 contrast, a lineup of available arsenic ligands is very poor. 26 This is because typical synthetic precursors for 27 organoarsenic compounds, e.g., arsenic hydrides and 28 chlorides, are volatile and toxic. Miserably, such kinds of 29 compounds were misused as chemical weapons: Adamsite, 30 Luisite, sneezing gas, etc.<sup>2</sup> Serious concern to the danger of 31 their hazardous natures has made people avoid experimental 32 studies on organoarsenic chemistry in this century.

33 It is known that arsenic atom has bulkiness and poor  $\sigma$ -34 donation to transition metals compared with phosphorus 35 atom.<sup>1</sup> Accordingly, arsenic ligands enhance reactivity and/or selectivity from those of the phosphorus analogues in 36 some catalytic reactions.<sup>3-6</sup> For example, a significant rate 37 38 acceleration was observed in Pd-catalyzed Stille coupling 39 reaction by changing the ligand from triphenylphosphine to triphenylarsine.<sup>3</sup> Nishibayashi developed an arsenic-40 41 nitrogen-arsenic pincer ligand for a ruthenium catalyst 42 giving high selectivity.<sup>4</sup> It was reported that triphenylarsine 43 is beneficial for copper-free Sonogashira coupling for porphyrin substrates.<sup>5</sup> It is evidential that arsenic ligands 44 45 have great potential in coordination chemistry, especially in catalytic chemistry. Nevertheless, there are few studies on 46 47 structure-catalytic activity relationship in arsenic ligand

systems due to lack of the practical synthetic methods; only 48 49 monodentate-type ligands have been examined.<sup>7,8</sup>

50 Meanwhile, our research group has broken through the 51 synthetic barrier via development of practical routes towards 52 arsenic ligands (Scheme 1).9 Cyclooligoarsines, in which 53 five (1: R = Me) or six (2: R = Ph) arsenic atoms are linked 54 through As-As bonds, are key intermediates because they 55 are readily prepared by reduction of non-volatile inorganic arsenic precursors.<sup>10</sup> As-As bond cleavage reactions by 56 57 iodine (I<sub>2</sub>) generates diiodoarsines in situ, and subsequent 58 reactions with nucleophiles give As-C bonds (Scheme 1a). 59 <sup>11</sup> This strategy has contributed to studies on functional organoarsenic molecules and polymers.<sup>12,13</sup> Reactions of 60 cyclooligoarsines with organometallic reagents such as 61 62 organolithium or Grignard reagents generate arsenic nucleophiles, which can be utilized for syntheses of 63 asymmetric and bidentate organoarsenic ligands (Scheme 64 1b).<sup>14</sup> Furthermore, As-C bonds can be cleaved by halogen 65 reagents such as iodine and iodine monochloride. In this 66 67 reaction, a methyl group substituted to an arsenic atom is 68 converted to a halogen group, and substituent conversion is 69 attained by the subsequent substitution reaction (Scheme 70 1c).<sup>15</sup>





74 These accumulated synthetic tools motivated us to 75 construct organoarsenic library. We previously reported 76 monodentate ligands for Mizoroki-Heck reaction by 77 employing the route shown in Scheme 1a.8 Herein, bidentate 78 ligands, which have particularly contributed advancement of 79 transition metal catalysts, are focused. In phosphorus 80 coordination chemistry, various ligands have been utilized: 81 dppe, dppp, dppf, xantphos, etc. (Chart 1). In this work,

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arsenic analogues of traditional bidentate phosphorus
ligands were synthesized by employing our practical
methods. We, for the first time, systematically studied the
structures and catalytic activities of the palladium(II)
dichloride complexes having the bidentate arsenic ligands.



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Chart 1. Representative bidentate phosphorus ligands.

8 Six bidentate arsenic ligands were synthesized by 9 using an arsenic nucleophile and bifunctional electrophiles (Scheme 2). Synthesis of alkylene-linked arsenic ligands 10 11  $(Ph_2As-(CH_2)_n-AsPh_2)$  was carried out: n = 1 (dpam), 2 12 (dpae), 3 (dpap), 4 (dpab). Hexaphenylcyclohexaarsine 2 13 was reacted with phenyllithium to generate diphenylarsino 14 lithium (Ph2AsLi) in situ, and then addition of alkyl dihalides gave the corresponding bidentate ligands dpam, 15 dpae,<sup>14</sup> dpap, and dpab. The same protocol was applied to 16 the reaction with cis-1,2-dichloroethylene and 2,3-17 dichloroquinoxaline offered  $dpav^{14}$  and dpaq, respectively. 18



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20 Scheme 2. Syntheses of bidentate ligands using diphenylarseno lithium.

21 а previous paper, we reported In that 22 iododiphenylarsine (Ph2AsI) can be generated by addition of 23 iodine (I<sub>2</sub>) to a solution of methyldiphenylarsine (MePh<sub>2</sub>As), which is prepared from Ph<sub>2</sub>AsLi and iodomethane.<sup>14</sup> The 24 25 halogenation proceeds via removal of iodomethane under 26 heating condition. The obtained solution of Ph2AsI was used 27 for the reaction with dilithiated ferrocene and 9,9-28 dimethylxanthene to produce **dpaf** and **xantas**, respectively 29 (Scheme 3).







33 Scheme 4. Synthesis of palladium(II) dichloride complexes with the
34 bidentate ligands.

35 Palladium(II) dichloride complexes of the bidentate using 36 ligands were synthesized cis-37 bis(benzonitrile)palladium(II) chloride (cis-[PdCl<sub>2</sub>(PhCN)<sub>2</sub>]) 38 as shown in Scheme 4. The chemical structures of the complexes were determined by NMR spectroscopy. 39 40 Unfortunately, the complex of **dpam** was not isolated due to 41 the unidentified impurities. Single crystals of six complexes suitable for X-ray crystallography were prepared: 42 43 [PdCl<sub>2</sub>(dpae)], [PdCl<sub>2</sub>(**dpap**)], [PdCl<sub>2</sub>(dpab)],  $[PdCl_2(dpaq)], [PdCl_2(dpaf)], and [PdCl_2(xantas)].^{16,17}$ 44 45 Electron-donation ability is crucial for catalytic activity, and 46 was evaluated based on the *trans*-influence of the Pd-Cl 47 bond lengths. Besides, a bite angle of a bidentate ligand is 48 an important structural parameter in reaction yield and/or 49 selectivity of catalytic reactions. Judging from the shorter Pd-As and longer Pd-Cl bond lengths, triaryl type ligands 50 51 dpaf and xantas are less electron-donating than diaryl type ligands dpae, dpap, and dpab. In the case of dpaq, the 52 53 Pd–As bond lengths were shortest because of the strong  $\pi$ -54 acceptance due to the quinoxaline moiety. 55

Table 1. Selected bond lengths and angles of palladium dichloride
complexes with bidentate arsenic ligands

Complex	Bond length [Å]		Angle [°]
	Pd-As	Pd-Cl	As-Pd-As
[PdCl <sub>2</sub> ( <b>dpae</b> )]	2.344(2)	2.345(2)	9E 70(2)
	2.339(2)	2.334(3)	65.70(Z)
[PdCl <sub>2</sub> ( <b>dpap</b> )]	2.352(2)	2.334(2)	80.62(4)
	2.339(2)	2.346(2)	69.62(1)
[PdCl <sub>2</sub> ( <b>dpab</b> )]	2.358(5)	2.331(5)	02 72/4)
	2.341(4)	2.335(6)	92.73(4)
[PdCl <sub>2</sub> ( <b>dpaq</b> )]	2.328(1)	2.341(2)	07.07(0)
	2.327(1)	2.338(1)	07.07(2)
[PdCl <sub>2</sub> ( <b>dpaf</b> )]	2.3840(7)	2.333(1)	07 64(2)
	2.3691(6)	2.334(1)	97.64(2)
[PdCl <sub>2</sub> (xantas)]	2.3769(5)	2.315(1)	00 47(2)
	2.3927(5)	2.333(1)	99.47(Z)

59 Among alkylene-linked ligands dpae, dpap, and dpab, 60 the bite angle got bigger as the chain was longer. 61 Interestingly, the bite angle of **xantas** 99.47(2)° was slightly 62 smaller than that of the phosphorus analogue xantphos (natural bite angle:108°18a and estimated P-Pd-P angle of 63 64 the palladium(II) dichloride complex:  $101.64^{\circ 18b}$ ). 65 Coordination direction of an arsenic atom is flexibly 66 changed due to the s-character of the lone pair, and hence 67 the coordination angles around the square planar palladium

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1 center can be adjusted to be close to 90°. This means that 2 arsenic atoms can reduce the distortion derived from the 3 ligand skeletons.

4 To demonstrate the effect of the arsenic ligands on 5 catalytic activity, Suzuki-Miyaura coupling reaction was 6 carried out. p-Bromotoluene and phenylboronic acid were 7 reacted in the presence of the palladium catalysts having the 8 arsenic ligands (Scheme 5). Comparing the alkylene-linked ligands, bite angle drastically affected the catalytic activity. 9 The larger the bite angle, the higher the reaction yield,<sup>19</sup> and 10 11 **dpab** gave the best yield (60%) among the alkylene-linked ligands. This is because large bite angle in general 12 accelerates a reductive elimination step.<sup>20</sup> In addition, the 13 relatively electron-donating ligands dpam, dpae, dpap, and 14 dpab gave lower catalytic activity than dpaq, dpaf, and 15 16 **xantas**. These results mean that the reductive elimination is 17 the rate-determining step of this reaction system as shown 18 by the computational calculation below (Figure 1); the 19 activation energies for the oxidative addition were 6.1 20 (dpae) and 6.3 (dppe) kcal/mol, while those for the reductive elimination were 12.7 (dpae) and 13.5 (dppe) 21 22 kcal/mol.





26 Finally, we conducted density functional theory (DFT) 27 calculations to answer the question of the difference 28 between arsenic and phosphorus bidentate ligands in the 29 oxidative addition and reductive elimination processes of 30 the Suzuki-Miyaura coupling (Figure 1). For the evaluation, 31 dpae and dppe were selected for the reaction of pbromotoluene and phenylboronic acid.21 As a result, 32 33 negligible differences between the dpae and dppe systems 34 were observed in the activation energies and heat of 35 formation for the oxidative addition and reductive elimination processes. This computational evaluation well 36 37 accords to the experimental results of our previous work on 38 monodentate arsenic ligands; bulky and electron-rich 39 ligands were beneficial for a coupling reaction as known in 40 catalytic systems of phosphorus ligands.<sup>8</sup> It is implied that 41 the accumulated knowledge on design of phosphorus 42 ligands can be applied for that of arsenic ligands.



 Figure 1. Optimized geometries for local minima, corresponding to reactants, intermediates, and products in (I) oxidative addition and (II) reductive elimination processes.

47 In conclusion, we demonstrated that various kinds of 48 bidentate arsenic ligands can be synthesized from cyclooligoarsine. Notably, volatile arsenic precursors, which 49 50 should be used in the conventional synthetic routes, were 51 circumvented the present in protocols. X-ray 52 crystallography revealed the conformational and electronic 53 differences between the palladium dichloride complexes of 54 the obtained ligands, and their catalytic activity for Suzuki-55 Miyaura coupling reaction was shown. This is the first 56 systematic study on bidentate arsenic ligands for a 57 transition-metal catalyst. The bidentate arsenic ligand library that is constructed by the practical synthetic routes 58 59 will lead to remarkable expansion of abundance of metal 60 complexes. Further development of arsenic ligands and 61 investigation on advanced functions of the complexes are 62 now under way.



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- 70 17 In the cases of [PdCl<sub>2</sub>(**dpae**)] and [PdCl<sub>2</sub>(**dpaf**)], solvent 71 72 73 74 75 76 77 78 79 80 81 molecules found in the voids could not be modeled to an acceptable level, and therefore, SQUEEZE was applied.
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84 21 We conducted Suzuki-Miyaura coupling reaction with dppe 85 under the same condition as Scheme 5. The NMR yield was 75%, 86 which was higher than that of dpae. This difference might be 87 caused by the stronger coordination ability of the phosphorus 88 atoms than that of the arsenic ones; the catalyst with dppe is 89 more durable than that of dpae under the heating condition. To 90 understand the difference between arsenic and phosphorus 91 systems, further investigation is under way.