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Hiroaki Imoto, Chieko Yamazawa, Susumu Tanaka, Takuji Kato, and Kensuke Naka*

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A Practical Screening Strategy of Arsenic Ligands for a Transition Metal-Catalyzed Reaction

Hiroaki Imoto, Chieko Yamazawa, Susumu Tanaka, Takuji Kato and Kensuke Naka*
Faculty of Molecular Chemistry and Engineering, Graduate School of Science and Technology, Kyoto Institute of Technology, Goshokaido-cho, Matsugasaki, Sakyo-ku, Kyoto 606-8585, Japan.

(E-mail: kenaka@kit.ac.jp)

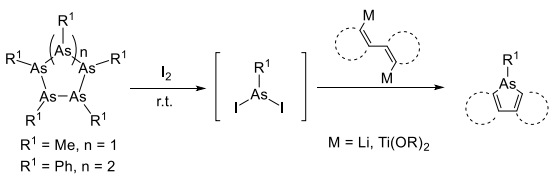
Organoarsenic ligands were synthesized via a safe and easy procedure, superior to the conventional synthetic methodologies. Diiodophenylarsine was prepared in-situ, and readily converted to diarylphenylarsines. Pd-catalyzed Mizoroki-Heck reaction was investigated using the obtained arsenic ligands. It was found that bulky and electron-donating ligands were effective for the reaction, meaning the success in screening of arsenic ligand structures based on the present facile strategy.

Transition metal-catalyzed coupling reactions are, needless to say, absolutely essential tools in the field of organic synthesis. Accompanied with the growing demand for the development of catalytic systems, ligand structure has been varied and polished. Among various kinds of ligands, trivalent phosphorus compounds have been extensively studied.[1,2] Structural effects of phosphorus ligands on catalytic activity have been fully investigated to date, and the widespread knowledge has been accumulated. Obviously, challenging matters in organic reactions still remain, and further variation of ligands is required. To embark on a new stage of catalytic chemistry, the incorporation of other basic building blocks should be effective.

An arsenic atom acts as a poorer σ-donor and π-acceptor, and has larger steric hindrance compared to a phosphorus atom.[3] It is reported that arsenic ligands accelerate reaction rate[4] and improve selectivity[5] in some cases. Copper-free Sonogashira-Hagihara coupling reaction needs triphenylarsine ($AsPh_3$) as a ligand.[6] Moreover, a trivalent arsenic atom is much more stable in the air than phosphorus atom. While phosphorus ligands are often subjected to oxidation during reaction and storage, arsenic analogues could be treated under the ambient air. Because of these potential functions and advantages, organoarsenic compounds are promising candidates as a novel class of ligands for transition metal-catalysts.

However, structure-activity relationship of arsenic ligands has been rarely investigated in researches on organic reactions. This is because there is concern to the toxicity and volatility of arsenic intermediates, e.g., arsenic chlorides and hydrides, which are typically exploited in conventional synthetic procedures for arsenic ligands.[7] Actually, some of these low molecular weight arsenic compounds were tragically abused in World War I. The practical utilities of the reported As−C bond formation reactions without volatile arsenic intermediates are still limited; narrow applicable ranges and/or severe reaction conditions.[8] Synthetic barrier of arsenic compounds should be overcome for further advancement of transition metal-catalyst.

Cyclooligoarsines such as *cyclo*-$(AsMe)_5$ and *cyclo*-$(AsPh)_6$ are synthesized from nonvolatile arsenics, methylarsonic acid[9a] and phenylarsonic acid,[9b] respectively. Recently, we have working on developing practical synthetic routes for As−C bond formation using these cyclooligoarsines as precursors.[10] In the series of these studies, it has been found that cyclooligoarsines are readily converted to diiodoarsines by addition of iodine,[10,11] and subsequent substitution reaction with nucleophiles can lead to various kinds of arsenic compounds (Scheme 1). As a result, we have succeeded in the experimental studies on functional organoarsenic compounds such as arsafluorene, arsole, and dithienoarsoles, and disclosed the intriguing nature of an arsenic atom.[10,12] Therefore, we assumed that this synthetic protocol can be applied to the development of arsenic ligands for transition metal-catalyzed reactions. In this work, strategy for the construction of arsenic ligand library is proposed in order to enable systematic studies on structure-activity relationship. Mizoroki-Heck reaction[13] was herein chosen for the structural screening of the arsenic ligands, and the obtained arsenic ligands were tested. In addition, oxidative resistance was investigated to demonstrate the advantage of the arsenic ligands over a phosphorus analogue, triphenylphosphine (PPh_3).

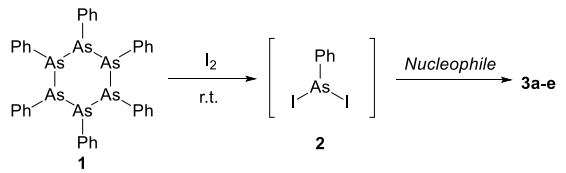


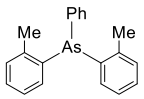
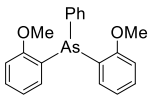
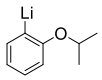
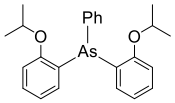
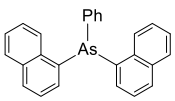
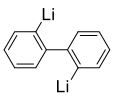
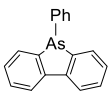
Scheme 1. Syntheses of functional arsenic compounds via in-situ generation of diiodoarsines.[10,12]

Diarylphenylarsines PhR_2As (**3a-e**) were synthesized as described in Table 1. A solution of iodine was added to a dispersion of hexaphenylhexaarsine **1** for the in-situ preparation of diiodophenylarsine **2**, and subsequently the solution of **2** was added to solutions of nucleophiles without isolation. Organolithium or Grignard reagents were used as a nucleophile, and column chromatography and recrystallization gave arsenic compounds **3a-e** in moderate isolated yields (41-89%).[14] The newly synthesized compounds **3a-d** were characterized with ^1H and ^{13}C NMR spectra and mass analysis.

For the observation of the structural features of the ligands, the X-ray diffraction data of their palladium complexes ($[PdCl_2(ligand)_2]$) were collected.[15] The single crystals suitable for the X-ray analysis were successfully

Table 1. Syntheses of arsenic ligands.



Run	Nucleophile	Product	Yield[a] [%]
1		 **3a**	41
2		 **3b**	70
3		 **3c**	72
4		 **3d**	55
5[b]		 **3e**	89

[a]Isolated yield. [b]Reported in the reference 10.

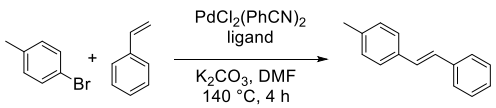
obtained in the cases of **3a-c** and **3e**. The palladium dichloride complexes [$PdCl_2$(ligand)$_2$] were synthesized as follows. *cis*-Bis(benzonitrile)palladium(II) dichloride ([$PdCl_2(PhCN)_2$)]) and a ligand were reacted in chlorobenzene under reflux condition overnight. The slow diffusion of dichloromethane solutions of the complex to methanol gave the single crystals of [$PdCl_2$(ligand)$_2$] (ligand = **3a-c** and **3e**). The isolated complexes adopt *trans* configuration in the crystalline state. Thus, to work as a catalyst, *trans-cis* isomerization and/or transformation to mono-arsine state should occur. The As−Pd bond lengths are approximately the same (2.40-2.43 Å) as shown in Table 2. The cone angles are estimated based on the

Table 2. X−Pd (X = As or P) bond length and cone angle of [$PdCl_2$(ligand)$_2$]

Ligand	X−Pd (X = As or P) bond length [Å]	Cone angle[a] [°]
3a	2.430(2)	182
3b	2.404(3)	191
3c	2.432(4)	203
3e	2.4172(9)	139
PPh_3[b]	-	145

[a]Estimated by Tolman's method.[16] [b]Cited from reference 16.

Tolman's method.[16] The cone angles of **3a-c** and **3e** are 182°, 191°, 203°, and 139°, respectively. The ligands **3a-c** have much larger values in comparison with the reported data of PPh_3 (145°),[16] while **3e** has smaller steric hindrance. It has been shown that wide variety of steric hindrance was induced into the prepared arsenic ligands. Pd-catalyzed Mizoroki-Heck reaction was investigated to determine the effect of the arsenic ligands. In addition to **3a-e**, PPh_3, and $AsPh_3$ were examined as commercially available ligands. For the evaluation of the catalytic activity, the relatively challenging Mizoroki-Heck reaction of *p*-bromotoluene and styrene was selected (Scheme 2) in reference to the previous literature.[8c] These substrates are not activated for Mizoroki-Heck reaction, and suitable for comparing the catalytic activity. Palladium catalyst was loaded as the mixture of [$PdCl_2(PhCN)_2$)] and ligand. For the confirmation of the repeatability, each ligand was examined several times, and the results were summarized in Figure 1. The *o*-isopropoxy-substituted ligand **3c** showed the highest activity (43%), while in the case of **3e**, the yield (22%) was significantly lower than those of others (30-43%). These results suggest that sterically hindered structures, which were confirmed by the X-ray diffraction, are advantageous in the reaction. From the view point of electron-donation ability, the activities of the alkoxy-substituted ligands **3b** and **3c** were relatively high (38% and 43%, respectively), meaning that the more electron-donating the ligand, the higher the catalytic activity. Reductive elimination and oxidative addition steps are promoted by steric hindrance and electron-donation, respectively. This is well corresponding to general phosphine ligand systems.[17] Especially, in the case of **3c**, the yield (43%) is compatible to that of the reported arsenic ligand (44%),[8c] whose structure is optimized based on Buchwald-type biphenyl backbone. It has been demonstrated that the systematic study on arsenic ligand structures can be carried out based on the facile synthetic strategy.



Scheme 2. Mizoroki-Heck reaction.

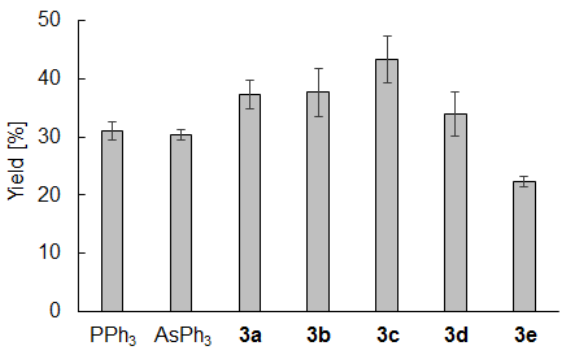


Figure 1. Yields of the Mizoroki-Heck reaction. The yields were estimated by the ^{1}H NMR spectra (Figure S13 in Supporting Information[18]).

The Mizoroki-Heck reaction was performed under an open-air atmosphere to show oxidative resistance of the arsenic ligand system. PPh_3, $AsPh_3$, and **3c** were employed for the reaction of Scheme 2 with adopting an open-air condition (Figure S14 in Supporting Information[18]). It is worth nothing that $AsPh_3$ and **3c** showed no significant difference; under N_2, 30% ($AsPh_3$) and 43% (**3c**), and under the open-air atmosphere, 32% ($AsPh_3$) and 41% (**3c**). In contrast, PPh_3 may be oxidized during the reaction under the open-air atmosphere, and the yield was lowered from 31% (N_2) to 23% (open-air). Then, we performed an oxidative resistance test; chloroform solutions of PPh_3, $AsPh_3$, and **3c** were subjected to dry air-bubbling for 8 h at room temperature. In the ^{1}H NMR spectra of $AsPh_3$ and **3c**, the oxidation was not observed. However, approximately 5% amounts of PPh_3 were oxidized to triphenylphosphine oxide. This implies that catalytic systems using the arsenic ligands are highly tolerant to air oxidation. This is great advantage of the arsenic ligands over phosphorus analogues in practical use.

Finally, the activity of **3c**, which showed the highest yield in Scheme 2, was evaluated in the Mizoroki-Heck reaction using traditional substrates. The results are posted in Table 3. Halobenzenes having electron-donating and withdrawing groups were applied to the coupling reaction with styrene, and *n*-butyl acrylate was used as a substrate. The isolated yields were high (79-96%),[19] suggesting that **3c** works as an active ligand for Mizoroki-Heck reaction. Notably, even under an open-air condition, the catalytic activity was never suffered (Run 1).

Table 3. Scope of substrates for ligand **3c**.

Run	**4**		**5**	*t*	Yield[a]
	R^1	X		[h]	[%]
1	CN	Br	Styrene	2	95 (99)[b]
2	OCH_3	I	Styrene	24	86
3	$COCH_3$	Br	*n*-Butyl acrylate	2.5	79
4	$COCH_3$	Br	Styrene	2.5	96

[a]Isolated yields. [b]Result of the reaction under an open-air atmosphere is in bracket.

In conclusion, we have demonstrated the structural variation of organoarsenic ligands based on a practical synthetic strategy. Diiodophenylarsine, which was safely and easily prepared in-situ from the nonvolatile precursors, was employed to obtain various arsenic ligands. The activity for the Pd-catalyzed Mizoroki-Heck reaction was improved by electron-donating and sterically hindered structure, corresponding to the phosphorus chemistry.[17] In spite of the simple structure of **3c**, the reaction yield was compatible to the Buchwald-type arsenic ligands.[8c] Notably, the arsenic ligands were highly tolerant to oxidation under an open-air atmosphere, compared with a phosphorus analogue, PPh_3. This is the first report on the systematic study of arsenic ligand structure based on a practical synthetic strategy. Further development of arsenic ligands and more widely applicable synthetic route are under investigation.

Acknowledgement

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14 The isolated yields of **3a** and **3d** were relatively low. The ^{1}H-NMR spectrum of **3a** in the crude state indicated that the reaction proceeded quantitatively. Thus, recrystallization process should lower the isolated yield of **3a** due to its low crystallinity. On the other hand, the ^{1}H-NMR spectrum of **3d** in the crude state showed that the mono-substituted by-product may be contained.

15 Crystallographic data reported in this manuscript have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1525695-1525698. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

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18 Supporting Information is also available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

19 The isolated yields in run 2 and 3 were relatively low (86% and 79%, respectively) probably because the products were lost during the isolation process. Actually, in their ^{1}H-NMR spectra in the crude states, no signals derived from the substrates **4** were

observed, and only small amounts of unidentified impurities were included.