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1,2-Bis(diphenylphosphino)carborane As a Dual Mode Ligand for Both the Sonogashira Coupling and Hydride-Transfer Steps in Palladium-Catalyzed One-Pot Synthesis of Allenes from Aryl Iodides

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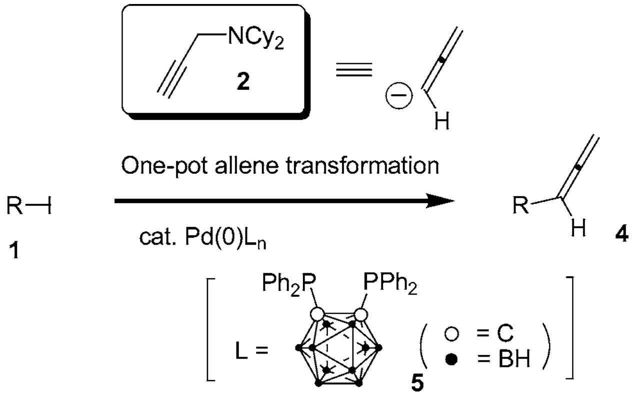
ABSTRACT



One-pot allene synthesis from aryl iodides 1 and propargyldicyclohexylamine 2 proceeded in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ catalyst (2.5 mol %), 1,2-bis(diphenylphosphino)carborane 5 (10 mol %), CuI (15 mol %), and Et_3N (150 mol %) to give the corresponding allenes 4 in good to high yields. Electron-deficient bidentate phosphines, such as 1,2-bis(diphenylphosphino)carborane 5 and $(C_6F_5)_2PC_2H_4P(C_6F_5)_2$, play the role of a dual mode ligand for both the Sonogashira coupling and hydride-transfer reactions.

The proper choice of ligands for transition-metal-catalyzed reactions is crucial for expanding the scope of reactions in organic synthesis.[1] We recently found the allene transformation from propargylic amines via palladium-catalyzed hydride-transfer reaction.[2] In this transformation, propargylic amines can be handled as an allenyl anion equivalent, which reacts with various aryl halides and heterocyclic halides through the Sonogashira coupling reaction to be transformed into allenes. Although trispentafluorophenylphosphine [$(C_6F_5)_3P$] was found to be a potent ligand for the palladium-catalyzed hydride-transfer reaction, it was not effective for the Sonogashira coupling step.[2a] Therefore, two separate steps were needed for the synthesis of allenes from organic halides (**1** → **3** → **4** pathway in Scheme 1). A carborane framework involves three-center two-electron

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[1] Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

[2] (a) Nakamura, H.; Kamakura, T.; Ishikura, M.; Biellmann, J.-F. *J. Am. Chem. Soc.* **2004**, *126*, 5958. (b) Nakamura, H.; Onagi, S.; Kamakura, T. *J. Org. Chem.* **2005**, *70*, 2357. (c) Nakamura, H.; Tashiro, S.; Kamakura, T. *Tetrahedron Lett.* **2005**, *46*, 8333. (d) Nakamura, H.; Onagi, S. *Tetrahedron Lett.* **2006**, *47*, 2539.

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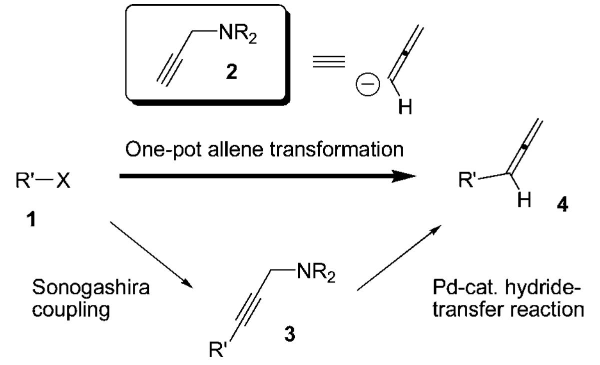
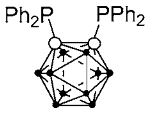
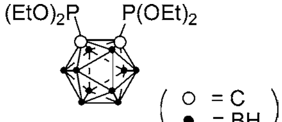
Scheme 1



bonding[3,4] and is thus known as an electron-deficient cluster. We utilized this framework for a skeleton of ligands (**5** and **6**) on palladium catalysts and found that 1,2-bis(diphenylphosphino)carborane **5**[5] plays the role of a dual mode ligand for both the Sonogashira coupling and hydride-transfer reactions (**1** → **4** pathway in Scheme 1). Herein we report the palladium-catalyzed one-pot synthesis of allenes[6] from organic iodides. Palladium-catalyzed direct coupling reactions of allenylic metals, such as allenylstannanes,[7] allenylindiums,[8] and allenylzincs,[9] with organic halides have been reported. The current transformation enables us to synthesize allenes from organic iodides without using a stoichiometric amount of metals.



5



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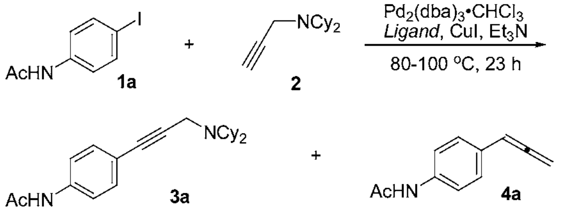
We first examined the one-pot allene synthesis from 4-iodoacetanilide **1a** and propargyldicyclohexylamine **2**[2c] using various phosphine ligands as shown in Table 1. The reaction was carried out at 80 °C for 3 h and monitored by TLC to confirm the generation of **3a**, then the reaction temperature was raised to 100 °C. The reaction proceeded in the presence of $Pd_2(dba)_3 \cdot CHCl_3$ catalyst (2.5 mol %), PPh_3 (20 mol %), CuI (15 mol %), and Et_3N (150 mol %) to give the allene **4a** in 23% yield along with the Sonogashira coupling product **3a** in 70% yield (entry 1). The use of $P(OPh)_3$ as a ligand increased the yield of **4a** (40%, entry 2). However, the reaction did not proceed in the presence of $P(C_6F_5)_3$ ligand, which is effective for the palladium-catalyzed hydride-transfer step (entry 3).[2a] Although the reactions failed with various bidentate phosphine ligands, such as bis(diphenylphosphino)methane (dppm), 1,2-bis(diphenylphosphino)ethane (dppe), and 1,1′-bis(diphenylphosphino)ferrocene (dppf), $(C_6F_5)_2PC_2H_4P(C_6F_5)_2$ was found to be effective for both the Sonogashira coupling and hydride-transfer steps and **4a** was obtained in 87% yield, exclusively (entry 4). This result indicates that an electron deficient bidentate phosphine may be suitable for the one-pot synthesis of allenes. It occurred to us that use of a carborane cluster as a skeleton of ligands would be more effective for the current reaction. We synthesized the diphosphinocarborane ligands **5** and **6** from 1,2-dilithiocarborane[3,10] with $ClPPh_2$

Table 1. Optimization of Reaction Conditions[a]



entry	ligand	solvent	yields[b,c] of **3a/4a** [%]
1	PPh_3	CH_3CN	70/23
2	$P(OPh)_3$	CH_3CN	53/40
3	$P(C_6F_5)_3$	CH_3CN	−/− (99)
4	$(C_6F_5)_2PC_2H_4P(C_6F_5)_2$	CH_3CN	−/87
5	**5**	CH_3CN	−/87
6	**6**	CH_3CN	−/50
7	**5**	dioxane	−/57 (37)
8	**5**	$CHCl_3$	−/33 (67)

[a] All reactions were carried out in the presence of $Pd_2(dba)_3 \cdot CHCl_3$ catalyst (2.5 mol %), ligand (20 mol % of monodentate ligands (entries 1−3) or 10 mol % of bidentate ligands (entries 4−8)), CuI (15 mol %), and Et_3N (150 mol %) at 80 °C for 3 h, and then the temperature was increased to 100 °C for 20 h. [b] Isolated yield based on **1a**. [c] Recovery of **1a** is indicated in parentheses.

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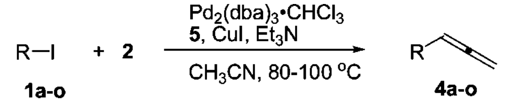
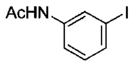
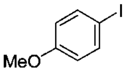
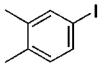
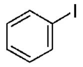
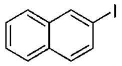
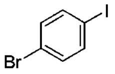
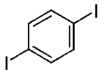
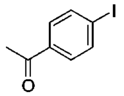
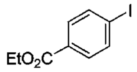
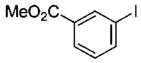
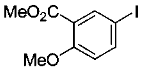
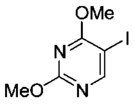
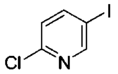
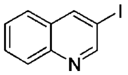
and ClP(OEt)$_2$, respectively. The reaction proceeded with 1,2-bis(diphenylphosphino)-*o*-carborane **5** to give only **4a** in 87% yield, although the yield of **4a** was lower in the case of 1,2-bis(diethoxyphosphino)-*o*-carborane **6** (entries 5 and 6). We also examined the reactions using **5** as a ligand in various solvents, such as dioxane (entry 7), CHCl$_3$ (entry 8), dimethoxyethane, THF, toluene, and dimethylformamide; however, **4a** was obtained in low yields (22−57%).

With optimized conditions established, we next investigated the one-pot synthesis of various allenes from the corresponding aryl iodides using 1,2-bis(diphenylphosphino)-*o*-carborane **5**. The results are summarized in Table 2. The aryl iodides, which have an electron-donating group such as AcNH− (**1a** and **1b**), MeO− (**1c**), and dimethyl (**1d**), underwent the one-pot allene transformation to give the corresponding allenes **4a**−**d** in high yields (entries 1−4). Although allenylbenzene **4e** was produced from iodobenzene **1e** quantitatively (entry 5), 2-iodonaphthalene **1f** gave **4f** in 60% yield (entry 6). The use of $(C_6F_5)_2PC_2H_4P(C_6F_5)_2$ as a ligand for the reactions gave the allenes in lower yields (i.e., **4b** 44%, **4d** 67%, and **4e** 59%). In the case of 4-bromoiodobenzene **1g**, the reaction took place at the iodo-substituted position, selectively, to afford 4-bromoalleneylbenzene **4g** in 68% yield, whereas 1,4-diiodobenzene **1h** gave 1,4-diallenylbenzene **4h** in 65% yield (entries 7 and 8). It is noted that the current transformation takes place selectively at an iodide group. The aryl iodides, which have an electron-withdrawing group such as acetyl (**1i**) and esters (**1j**−***l***), gave the corresponding allenes **4i**−***l*** in 74−99% yields (entries 9−12). It is noted that $(C_6F_5)_2PC_2H_4P(C_6F_5)_2$ is a suitable ligand for the reactions of **1i** and **1j**. We also demonstrated the one-pot allene transformation from iodoheterocycles (**1m**−**o**). The reactions of 5-iodo-2,4-dimethoxypyrimidine **1m**, 2-chloro-5-iodopyridine **1n**, and 3-iodoquinoline **1o** proceeded in the presence of Pd$_2$(dba)$_3$•CHCl$_3$ catalyst (2.5 mol %), $(C_6F_5)_2PC_2H_4P(C_6F_5)_2$ (10 mol %), CuI (15 mol %), and Et$_3$N (150 mol %) in chloroform to give the corresponding allenes **4m**−**o** in 67−99% yields (entries 13−15). The combination of $(C_6F_5)_2PC_2H_4P(C_6F_5)_2$ with chloroform as a solvent was effective for the synthesis of heterocyclic allenes.[2b]

To clarify the reaction rate and mechanism of this one-pot allene transformation, we monitored the concentration of **1b**, **3b**, and **4b** during the reaction for 11 h by HPLC analysis (Figure 1). Within 20 min after addition of **2** at 80 °C, **1b** was consumed and the Sonogashira coupling product **3b** was produced in 25% yield along with the allene **4b** in 3% yield. The consumption of **1b** and generation of **3b** and **4b** plateaued after 3 h. When the reaction temperature was raised to 100 °C, the yield of **4a** increased along with consumption of **1b** and **3b**. We do not know why the reaction stopped after 3 h; however, it was essential to heat the reaction to 100 °C to achieve allene transformation with high yields. The reaction carried out at 100 °C after addition of **2** did not complete the Sonogashira coupling step due to the decomposition of catalysts. According to our proposed mechanism reported previously, the anionic palladium hydride species generated by a hydride transfer from the cyclohexyl carbon of **3** would be a key intermediate.[2b] Therefore, a certain extent of reactivity at the oxidative addition step in addition to an ability to stabilize the palladium hydride intermediate was required of a potent ligand for one-pot allene transformation. In this regard, the electron-deficient bidentate ligands such as the diphosphino-

Table 2. One-Pot Synthesis of Various Allenes **4** from Aryl Iodides **1** with Propargyldicyclohexylamine **2**[a]



entry	**1**, R-I		time (h)	yield of **4** (%)[b]
1	**1a**		23	87
2	**1b**		24	>99
3	**1c**		36	96
4	**1d**		36	86
5	**1e**		43	>99
6	**1f**		48	60
7	**1g**		48	68
8	**1h**		48	65[c]
9	**1i**		43	74[d]
10	**1j**		48	74[d]
11	**1k**		23	99
12	**1l**		22	90
13	**1m**		24	67[d,e]
14	**1n**		8	72[d,e]
15	**1o**		24	99[d,e]

[a] All reactions were carried out in the presence of Pd$_2$(dba)$_3$•CHCl$_3$ catalyst (2.5 mol %), **5** (10 mol %), CuI (15 mol %), and Et$_3$N (150 mol %) at 80 °C for 3 h, and then the temperature was increased to 100 °C. [b] Isolated yield based on **1**. [c] The diallene product was obtained exclusively. [d] $(C_6F_5)_2PC_2H_4P(C_6F_5)_2$ was used instead of **5**. [e] The reaction was carried out in CHCl$_3$.

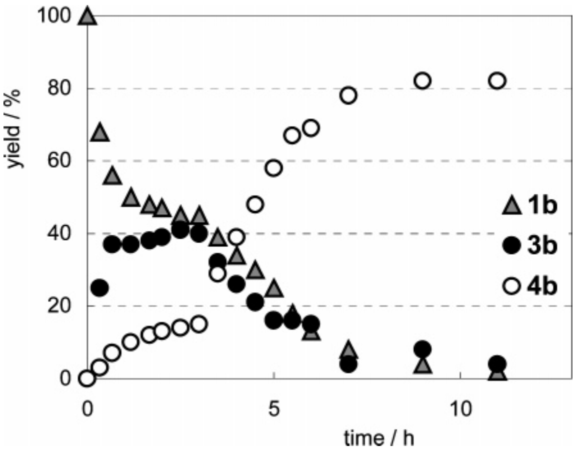


Figure 1. Concentrations of **3b** and **4b** with time during the reaction of **1b** and **2** for 0−11 h. The reaction was carried out in the presence of $Pd_2(dba)_3 \cdot CHCl_3$ catalyst (2.5 mol %), **5** (10 mol %), CuI (15 mol %), and Et_3N (150 mol %) at 80 °C and the reaction temperature was raised to 100 °C after 3 h. The amounts (yields) of **1b**, **3b**, and **4b** were determined by HPLC analysis.

carborane ligands **5** and $(C_6F_5)_2PC_2H_4P(C_6F_5)_2$ were suitable for both catalytic cycles of the Sonogashira coupling and hydride-transfer steps.

In conclusion, we succeeded in the synthesis of allenes from the corresponding organic iodides via the Sonogashira coupling followed by the hydride-transfer reaction in one pot. In the current transformation, the use of 1,2-bis(diphenylphosphino)carborane **5** as well as $(C_6F_5)_2PC_2H_4P(C_6F_5)_2$ was found to be effective as dual mode phosphine ligands for both the Sonogashira coupling and hydride-transfer steps. It is a first example to utilize carboranylphosphine ligands for transition-metal-catalyzed coupling reactions, although hydrogenation has been studied with use of rhodium-*nido*-carborane complexes.[5c,11] Since many attempts have been made to introduce an allenic moiety into the backbone of certain pharmacologically active molecules to develop new biological and pharmacological properties,[2d,12] we believe that the current finding would be influential not only in development of new transition-metal-catalyzed synthetic methods but also in development of pharmacologically active allenes in organic synthesis.

Supporting Information Available: Detailed experimental procedures and characterization data for compounds **4b**, **4d**, **4f−i**, **4k**,***l***, **4n**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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