

Palladium-Catalyzed Allylation of Pronucleophiles with Alkynes at 50 °C – Remarkable Effect of 2-(Dicyclohexylphosphanyl)-2'-(dimethylamino)biphenyl as Ligand

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Keywords: Palladium / Alkynes / Pronucleophiles / Allylation / Biphenyl ligands / Lower temperatures

The allylation of various pronucleophiles **1a–i** with 1-phenylprop-1-yne (**2**) proceeded very smoothly at 50 °C in the presence of catalytic amounts of Pd₂(dba)₃·CHCl₃ (5 mol-%) and 2-(dicyclohexylphosphanyl)-2'-(dimethylamino)biphenyl (**I**; 20 mol-%) in toluene, whilst when Pd(PPh₃)₄ or Pd₂(dba)₃·

CHCl₃/PPh₃ were used, the reaction needed 100 °C for completion.

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Introduction

Palladium-catalyzed carbon–carbon and carbon–heteroatom bond-forming reactions are one of the most important research areas in organic synthesis, one example of these processes being the treatment of substrates with allylic compounds in the presence of Pd⁰ and a stoichiometric amount of a base (Tsuji–Trost reaction).^[1] All of these reactions are considered to be nucleophilic substitutions. In general, addition reactions^[2] are preferable to substitution reactions because they can be performed with 100% atom efficiency,^[3] without any waste formation. With this in mind, we have recently been investigating the allylation of carbon^[4] and heteroatom^[5] pronucleophiles with alkynes with the aid of a combined Pd⁰/carboxylic acid catalytic system. Since the products of this process were obtained through formal addition of pronucleophiles to alkynes, no waste elements were produced and, moreover, no base was needed, though a relatively high temperature (100 °C) was necessary in order to drive the reaction to completion. As a partial solution to this problem we later reported the allylation of some pronucleophiles with alkynes under microwave irradiation conditions in the absence of any solvent.^[6] As the reaction was carried out without any solvent, at least one substrate had to be a liquid in order for the reaction to be performed under homogeneous condition, so the method was not applicable when both substrates (pronucleophiles and alkynes) were solids. In the hope of finding milder and superior reaction conditions, we thus decided to pursue the search for alternative catalytic systems in these

allylation reactions, reasoning that suitable tuning of ligands attached to palladium might speed up the formation of the presumed π -allylpalladium complexes generated from alkynes, which would then be attacked by pronucleophiles, allowing us to perform the allylation at a lower temperature. We thus undertook a search for a suitable ligand and, after studying various ligands, found that the best results were given by the biphenyl ligand **I** in combination with Pd₂(dba)₃·CHCl₃, allowing us to allylate pronucleophiles at 50 °C. The detailed results of the work are reported here.

Results and Discussion

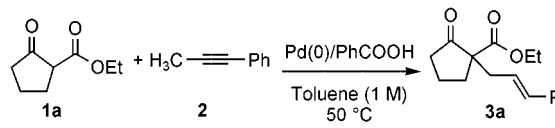
The results for various ligands are summarized in Table 1. Treatment of **1a** with 1-phenylprop-1-yne (**2**) at 50 °C in the presence only of Pd(PPh₃)₄ as catalyst did not yield any product, with the starting material being recovered (Table 1, Entry 1). The combination of Pd₂(dba)₃·CHCl₃ and PPh₃ at various stoichiometries at 50 °C also did not result in any product formation (Entries 2 and 3). Gratifyingly though, when ligand **I** was employed, the reaction proceeded smoothly and the desired product **3a** was obtained in an isolated yield of 90% (Entry 4). The use of its congener, biphenyl ligand **II**, also proved satisfactory, giving the product in 89% yield (Entry 5), but in the case of ligand **III** the yield was considerably lower (Entry 6). The optimal temperature for the reaction to occur is 50 °C; any further decrease in the reaction temperature results in lower yields.

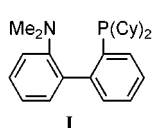
After the unique role of 2-(dicyclohexylphosphanyl)-2'-(dimethylamino)biphenyl (**I**) had been established, a few representative pronucleophiles were tested in this allylation reaction with 1-phenylprop-1-yne (**2**) as a standard alkyne. The results are summarized in Table 2. Treatment of 2-acetylcyclopentanone (**1b**) with **2** in the presence of Pd₂(dba)₃·

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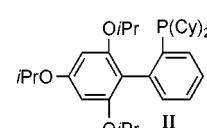
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Table 1. Allylation of **1a** with 1-phenylprop-1-yne (**2**) at 50 °C.^[a]

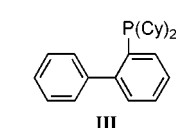
			
entry	Pd catalyst (5%)	ligand (mol%)	NMR yield (%) ^[b]
1	Pd(PPh ₃) ₄	-	0 ^[c]
2	Pd ₂ dba ₃ ·CHCl ₃	PPh ₃ (20)	0 ^[c]
3	Pd ₂ dba ₃ ·CHCl ₃	PPh ₃ (40)	0 ^[c]
4	Pd ₂ dba ₃ ·CHCl ₃	I (20)	92(90) ^[d]
5	Pd ₂ dba ₃ ·CHCl ₃	II (20)	89
6	Pd ₂ dba ₃ ·CHCl ₃	III (20)	52



I



II



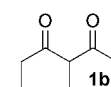
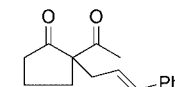
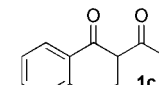
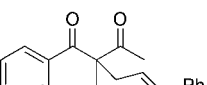
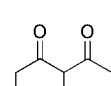
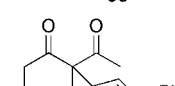
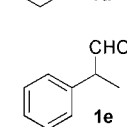
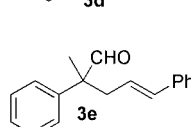
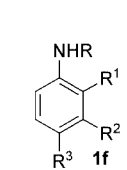
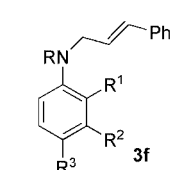
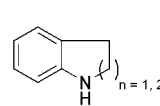
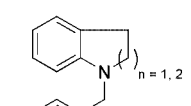
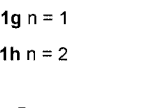
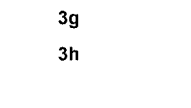
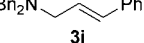
III

[a] Treatment of **1a** with alkyne **2** (1.1 equiv.) in the presence of Pd₂(dba)₃·CHCl₃ (5 mol-%), ligands (as specified in the table), and benzoic acid (10 mol-%) was carried out at 50 °C in toluene for 48 h. [b] Yields were determined by ¹H NMR spectroscopy with dibromomethane as an internal standard. [c] The starting material was recovered. [d] Isolated yields are shown in parentheses.

CHCl₃ (5 mol-%)/**I** (20 mol-%)/PhCOOH (10 mol-%) in toluene (1 M) at 50 °C gave the desired allylation product **3b** in 93% yield (Table 2, Entry 1). Similarly, the sterically constrained 1,3-diketones **1c** and **1d** reacted with **2** under standard reaction conditions to afford the corresponding allylation products **3c** and **3d** in 81% and 79% yields, respectively (Entries 2 and 3). Aldehyde **1e** was found to be a good substrate for this catalytic system, also undergoing smooth allylation (Entry 4).

We next turned out attention to the allylation of amines. As shown in Entries 5–9, anilines containing either electron-donating or electron-withdrawing groups on their aromatic rings smoothly underwent reaction with **2** to give the desired products in high yields. In the case of *p*-chloroaniline (Entry 10) only a 52% yield of product was obtained, unlike in our previously reported catalytic system,^[4d] in which the allylation had proceeded with quantitative formation of product, perhaps because of a side reaction in which oxidative insertion of the L–Pd complex into the Ar–Cl bond competes with the desired reaction.^[7] Indoline (**1g**) and tetrahydroquinoline (**1h**) also underwent smooth allylation, giving the corresponding products **3g** and **3h** in 91 and 99% yields, respectively (Entries 11–12). Dibenzylamine (**1i**) reacted with **2** quite sluggishly, giving the product **3i** in only 61% yield, indicating that bulky amines are not good nucleophiles in this catalytic system (Entry 13). The reasons for the high reactivity of this present catalytic

Table 2. Allylation of various pronucleophiles with **2** at 50 °C.^[a]

entry	substrate (1)	product (3) ^[b]	yield (%) ^[c]
1	 1b	 3b	93
2	 1c	 3c	81
3	 1d	 3d	79
4	 1e	 3e	89
	 1f	 3f	
5	1fa R = -CH ₃ , R ¹ = R ² = R ³ = H	3fa	91
6	1fb R = -Ts, R ¹ = R ² = R ³ = H	3fb	92
7	1fc R = R ³ = H, R ¹ = R ² = CH ₃	3fc	86
8	1fd R = R ² = R ³ = H, R ¹ = -CN	3fd	88
9	1fe R = R ² = R ³ = H, R ¹ = -COOMe	3fe	87
10	1ff R = R ² = H, R ¹ = -CH ₃ , R ³ = Cl	3ff	52
	 1g n = 1	 3g	91
12	 1h n = 2	 3h	99
13	 1i	 3i	61

[a] The reactions of pronucleophiles **1** with 1-phenylprop-1-yne (**2**, 1.1 equiv.) in the presence of Pd₂dba₃·CHCl₃ (0.05 mmol), **I** (0.2 equiv.), and benzoic acid (0.1 equiv.) were carried out at 50 °C in toluene (1 M) until the disappearance of the starting material **1** was observed. [b] All products obtained were identified as (*E*) isomers by ¹H NMR spectroscopy. [c] Isolated yields.

system are not completely understood: several structural features of biphenyl–Pd complexes may contribute to their effectiveness.^[8]

The catalytic cycle for the allylation reactions is presumably similar to that reported previously and depicted in Figure 1. Although the reasons for the high reactivity of the

current catalytic system are not completely understood, we believe that the main reason for the rate enhancement might be acceleration of the β -elimination.^[9] Palladium metal coordinated to a bulky ligand should act as good leaving group in the β -elimination process to form phenylallene (**6**) and subsequently π -allylpalladium complex **7**. The rate of transformation of **5** to **7** should thus increase, which should in turn enhance the overall reaction rate.

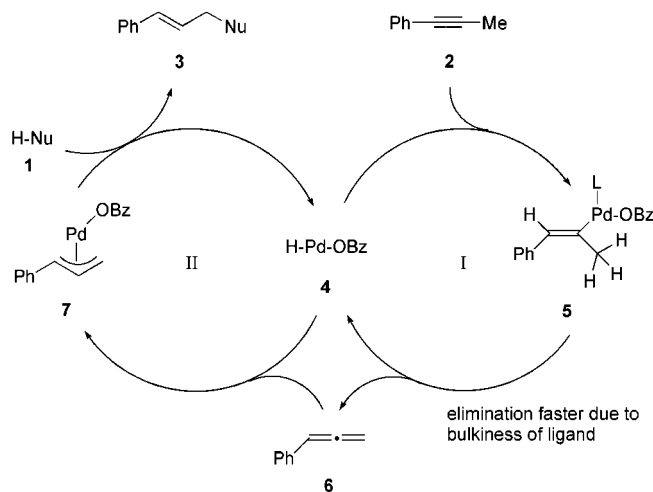


Figure 1. Plausible mechanism.

Conclusion

We have discovered a remarkable effect of 2-(dicyclohexylphosphanyl)-2'-(dimethylamino)biphenyl as a ligand in the palladium-catalyzed allylation of various pronucleophiles with alkynes at 50 °C and are now in a position to allylate various pronucleophiles at 50 °C instead of 100 °C. Potential applications of biphenyl ligands for cross-coupling reactions are known,^[10] but to the best of our knowledge the unique role of these ligands in accelerated palladium-catalyzed reactions involving π -allylpalladium chemistry have not been reported until now.^[11]

Experimental Section

General Procedure: 1-Phenylprop-1-yne (**2**, 0.21 mmol) and 2-(dicyclohexylphosphanyl)-2'-(dimethylamino)biphenyl (**I**, 20 mol-%) were added under argon to a toluene solution (1 M) of the pronucleophile **1** (0.2 mmol), Pd₂(dba)₃·CHCl₃ (5 mol-%), and benzoic acid (10 mol-%). The solution was stirred at 50 °C in a screw-capped vial until the disappearance of the starting material was observed, the reaction mixture was cooled to room temperature, filtered through a short silica gel pad, and concentrated, and the residue was purified by column chromatography (silica gel, hexane/AcOEt) to afford the allylation product **3** in good yield.

Supporting Information (see footnote on the first page of this article). Experimental details, characterization data for newly synthesized compounds **3g** and **3h**, ¹H NMR spectra of all compounds.

Acknowledgments

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