Catalytic Umpolung Allylation of Aldehydes by π-Allylpalladium Complexes Containing Bidentate N-Heterocyclic Carbene Ligands

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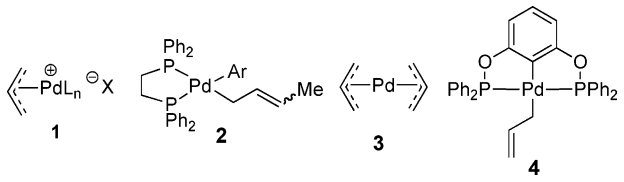
Summary: A series of π-allylpalladium complexes with neutral monodentate and bidentate ligands were prepared and examined for their ability to undergo stoichiometric umpolung allylation reactions with benzaldehyde. Neutral bidentate N-heterocyclic carbene ligands promote nucleophilic attack. Catalytic allylation reactions of aromatic and aliphatic aldehydes are reported.

π-Allylpalladium complexes (**1**, L_n = neutral ligand) most commonly behave as electrophiles, for example, as the key intermediates in Tsuji−Trost reactions.[1] It has recently been observed that replacing phosphine ligands with N-heterocyclic carbene (NHC) ligands decreases the electrophilicity of the allylpalladium complex and slows the rate of attack by nucleophiles.[2] This has been attributed to the strong σ-donating and weak π-accepting character of the NHC ligand.[3,4] We sought to determine whether NHC ligands are sufficiently electron-donating to impart nucleophilic character to allylpalladium complexes and promote attack on organic electrophiles such as aldehydes.



1 **2** **3** **4**

Nucleophilic reactivity of allylpalladium complexes is generally only observed with complexes such as **2**−**4** that contain anionic strongly σ-donating ligands that render the allyl fragment nucleophilic.[5] Kurosawa and co-workers demonstrated that allylpalladium species such as **2** serve as nucleophiles to attack electrophiles such as Br_2.[6,7] An anionic strong σ-donating aryl ligand was required in addition to a bidentate phosphine ligand to provide a nucleophilic allyl fragment. More recently, palladium-catalyzed allylations of aldehydes and imines by allylstannanes have been developed by Yamamoto and co-workers.[8] The key catalytic intermediate in the reactions is thought to be a bis-π-allylpalladium complex (**3**), which, upon coordination of aldehyde, undergoes intramolecular allylation.[9] Szabó and co-workers have utilized palladium pincer ligand complexes to catalyze similar allylation reactions of aldehydes and imines, and DFT calculations support the intermediacy of a nucleophilic η^1-allylpalladium complex (**4**).[10] Complexes **2**−**4** all contain anionic strongly σ-donating ligands that render the allyl fragment nucleophilic.[11,12] We report in this communication that allylpalladium complexes of general structure **1** are also nucleophiles that attack aldehydes when an electron-rich bidentate NHC is employed as ligand. This reactivity is in direct contrast to the reactivity demonstrated by the analogous phosphine-containing complexes.

To evaluate the ability of electron-rich monodentate and bidentate phosphine and NHC ligands to promote nucleophilic attack, we prepared a series of π-allylpalladium complexes according to literature procedures.[13,14] ^{1}H NMR spectroscopic data for complexes **1d**−**1m** are consistent with fluxional cationic η^3-allylpalladium complexes.[15] Single crystals of complex **1g** suitable for X-ray diffraction were obtained by slow diffusion of ether into a solution in DMF. The crystal structure contains considerable disorder; however it establishes that the NHC-pyridine ligand binds to palladium in a bidentate fashion with a bite angle of 87° (Figure 1).[16]

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(11) For other examples of reactions that are thought to proceed via nucleophilic allylpalladium intermediates, see: (a) Howell, G. P.; Minnaard, A. J.; Feringa, B. L. *Org. Biomol. Chem.* **2006**, *4*, 1278−1283. (b) Hopkins, C. D.; Malinakova, H. C. *Org. Lett.* **2006**, *8*, 5971−5974. (c) Hopkins, C. D.; Malinakova, H. C. *Org. Lett.* **2004**, *6*, 2221−2224.

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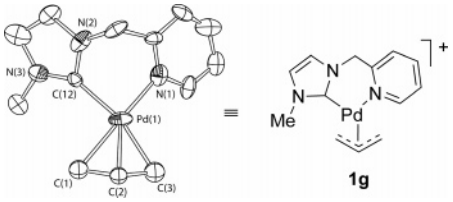
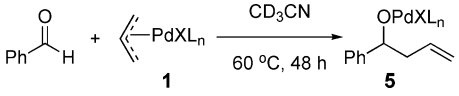
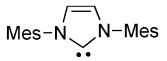
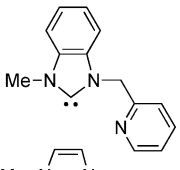
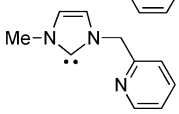
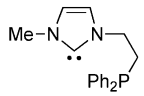
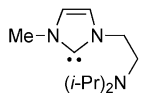


Figure 1. ORTEP diagram of **1g** showing 50% thermal ellipsoids.[17] Hydrogen atoms and BF_4^- counterion are omitted for clarity.

Table 1. Allylation of Benzaldehyde with Preformed π-Allylpalladium Complexes (1)[a]

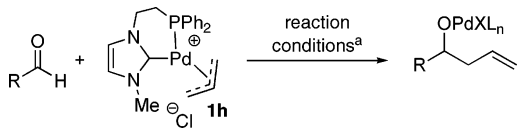


entry	ligand (L_n)	Pd complex (**1**)	conversion to **5** (%)[b]	unreacted **1** (%)[c]
1	(*R,R*)-BINAP	**1a** (X = Cl)	<5	>95
2	(*R,R*)-Me-DuPhos	**1b** (X = Cl)	19	<5
3		**1c** (X = Cl)	<5	>95
4		**1d** (X = Cl)	47	47
5		**1e** (X = Cl)	50	<5
6		**1f** (X = OAc)	41[d]	<5
7		**1g** (X = BF_4)	9	90
8		**1h** (X = Cl)	54	26
9		**1i** (X = OAc)	39[e]	30
10		**1j** (X = BAr_4^F)	12	75
11		**1k** (X = Cl)	51[f]	21
12		**1l** (X = OAc)	47	<5
13		**1m** (X = BF_4)	<5	>95

[a] Reaction conditions: 0.1 M Pd complex, 0.1 M benzaldehyde, TMS (internal standard) in 0.6 mL of CD_3CN at 60 °C. [b]Conversion to product **5**, as determined by ^{1}H NMR spectroscopy of the reaction mixture by comparison to TMS (internal standard). [c]Remaining palladium complex **1**, as determined by ^{1}H NMR spectroscopy. [d]Reaction performed at 50 °C. [e]Reaction performed at 70 °C. [f]Reaction performed at 85 °C. See Supporting Information for details.

With requisite palladium complexes in hand, we examined their stoichiometric reactions with aldehydes (Table 1). Palladium complexes **1** were dissolved in CD_3CN, benzaldehyde was added, and the mixtures were heated to 60 °C. The progress of the reactions was monitored by ^{1}H NMR spectroscopy using tetramethylsilane as an internal standard. Complexes prepared from bidentate phosphines such as BINAP did not react with benzaldehyde (entry 1). Complex **1b**, containing the more electron-rich bisphosphine ligand Me-DuPHOS, was more nucleophilic, but it underwent significant decomposition upon prolonged heating (entry 2).[18] Complex **1c**, using a monodentate NHC ligand, also did not afford desired product after 48 h (entry 3). Complexes containing bidentate NHC ligands (**1e**, **1h**, and **1k**) underwent reaction with benzaldehyde to afford **5** in 50, 54, and 51% conversion, respectively (entries 5, 8, and 11).[19] The less electron-rich benzimidazole-derived carbene also provided a nucleophilic palladium complex (entry 4).[20]

Table 2. Optimization of Allylation of Benzaldehyde with Complex 1h and Scope of the Allylation Reaction[a]



entry	R	solvent	time (h)	conversion (%)[b]
1	Ph	CD_3CN	96	81
2	Ph	CD_2Cl_2	72[c]	61
3	Ph	DMSO-d_6	48	59
4	Ph	THF-d_8	48	82
5	Ph	THF-d_8	4[d]	>95
6	4-$(NO_2)C_6H_4$	THF-d_8	2[d]	>95
7	4-(MeO)C_6H_4	THF-d_8	8[d]	>95
8	CH_2CH_2Ph	THF-d_8	8[d]	>95

[a] Reaction conditions: 0.1 M Pd complex, 0.1 M benzaldehyde, TMS (internal standard) in 0.6 mL solvent at 70 °C. [b]Conversion of the limiting reagent (**1h**) to homoallylic alcohol, as determined by ^{1}H NMR spectroscopy of the reaction mixture by comparison to TMS (internal standard). [c]Reaction was performed at 60 °C. [d]Reaction conditions: 0.1 M Pd complex, 1.0 M aldehyde (10 equiv), TMS (internal standard) in 0.6 mL of solvent at 70 °C. See Supporting Information for details.

The nature of the counterion (X^-) had a strong impact on the reactivity of the complexes. Coordinating counterions such as chloride and acetate afforded more reactive complexes than those containing noncoordinating counterions such as tetrafluoroborate or BAr_4^F (entries 5−13). This effect may be due to the increased ability of the counterion to coordinate to palladium to form the more nucleophilic[21] η^1-allylpalladium species.[22,23]

We focused our attention on nucleophilic complex **1h** because it consistently gave the highest conversion to alcohol **5** with the least amount of decomposition. Increasing the reaction temperature to 70 °C proved an optimal balance between allylation rate and rate of decomposition of the palladium complex (Table 2, entry 1). At higher temperatures, decomposition of the palladium complex began to predominate. Switching the solvent from acetonitrile to THF afforded a substantial increase in the rate of conversion to alcohol **5** (Table 2, entry 4).[24] Increasing the number of equivalents of aldehyde also provided a substantial increase in rate (entry 5). Under the

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(16) For the crystal structure of related complexes, see: (a) Tulloch, A. A. D.; Winston, S.; Danopoulos, A. A.; Eastham, G.; Hursthouse, M. B. *J. Chem. Soc., Dalton Trans.* **2003**, 699−708. (b) Reference 14c.

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(18) Phosphonium salts, formed by nucleophilic attack of phosphine ligand on the allylpalladium, are formed as the major decomposition products when nucleophilic phosphines are employed.

(19) Products that would arise from β-hydride elimination of the palladium alkoxide, such as 1-phenyl-3-butenone or 1-phenyl-2-butenone, were not observed.

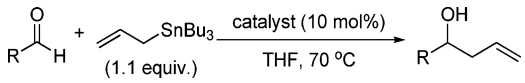
(20) See reference 3c.

(21) Kurosawa, H.; Urabe, A.; Kasai, N. *Organometallics* **1986**, *5*, 2002−2006.

(22) Braunstein, P.; Naud, F.; Dedieu, A.; Rohmer, M.-M.; DeCian, A.; Rettig, S. J. *Organometallics* **2001**, *20*, 2966−2981.

(23) For a review of halide effects in transition metal catalysis, see: Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26−47.

Table 3. Scope of Catalytic Allylation Reactions of Aldehydes[a]



entry	R	catalyst	time (h)	isolated yield (%)[b]
1	Ph	**1e**	1.5	88
2	Ph	**1h**	17	69
3	Ph	**1k**	3	91
4	4-(MeO)C_6H_4	**1e**	10	85
5	CH_2CH_2Ph	**1e**	9	79

[a] Reaction conditions: 0.01 M Pd complex, 0.1 M aldehyde, 0.11 M allyltributylstannane in THF at 70 °C. [b]Isolated yield of homoallylic alcohol after silica gel chromatography. See Supporting Information for details.

optimized conditions, alcohol **5** was generated in quantitative conversion from palladium complex **1h** after only 4 h.

Several aromatic aldehydes undergo allylation reactions with acceptable reaction times (Table 2). Electron-deficient aldehydes reacted most quickly; *p*-nitrobenzaldehyde reacted to provide quantitative conversion of palladium complex **1h** to product after 2 h (entry 6). Electron-rich aldehydes reacted more slowly (entry 7). We were particularly encouraged to see that aliphatic aldehydes are also tolerated: hydrocinnamaldehyde afforded complete conversion to the desired homoallylic alcohol (entry 8).

To demonstrate the ability of these palladium complexes to participate in catalytic reactions, we examined allylation of benzaldehyde under reaction conditions reported by Yamamoto for umpolung allylation reactions (Table 3). In these transformations it is proposed that a nucleophilic allylpalladium complex attacks the aldehyde, and subsequent transmetalation with allyltributylstannane regenerates the catalyst. Treatment of benzaldehyde with allyltributylstannane in the presence of 10 mol % of palladium complexes **1e**, **1h**, and **1k** afforded homoallylic alcohol in good yields. Of the three complexes, complex **1e**, containing the NHC-pyridine ligand, was the most reactive.[25,26] As was observed in the stoichiometric allylation, electron-rich *p*-methoxybenzaldehyde reacts, as does the enolizable aliphatic aldehyde, hydrocinnamaldehyde.

We have demonstrated that allylpalladium complexes with bidentate NHC ligands are umpolung nucleophiles that attack aromatic and aliphatic aldehydes. Strongly σ-donating anionic ligands such as aryl ligands are not required to activate the allyl ligand to attack nucleophiles. These complexes catalyze allylation of aldehydes with allylstannane. Investigation of the mechanism of this reaction and further development of catalytic reaction manifolds featuring these reactive intermediates are ongoing in our laboratories.

Acknowledgment. This work was supported by PRF 46043-G1. Amgen and Eli Lilly Foundation are gratefully acknowledged for additional research support. Dr. Joseph Ziller is acknowledged for the crystal structure of complex **1g**. Dr. John Greaves is acknowledged for mass spectrometric data.

Supporting Information Available: Experimental procedures, details of reaction conditions, and spectroscopic data for the complexes **1d**−**1n**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) The cause of this effect is under investigation and is presumably due to the differing ability of the solvents to coordinate to palladium complex **1h**. (a) Ketz, B. E.; Cole, A. P.; Waymouth, R. M. *Organometallics* **2004**, *23*, 2835−2837. (b) Solin, N.; Szabó, K. J. *Organometallics* **2001**, *20*, 5464−5471.

(25) This trend may be due to the differing rates of transmetalation of the palladium alkoxides with allyltributylstannane. In related allylation reactions a decrease in rate with increasing electron-donating ability of pincer ligands has been attributed to a decrease in the rate of transmetalation: Solin, N.; Kjellgren, J.; Szabó, K. J. *J. Am. Chem. Soc.* **2004**, *126*, 7026−7033.

(26) At this time we are unable to rule out an alternate Sakurai-type mechanism, where the palladium complex functions as a Lewis acid catalyst to activate the aldehyde toward addition of allylstannane. (a) For a discussion, see ref 10c. (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763−2793. (c) Trost, B. M.; King, S. A. *J. Am. Chem. Soc.* **1990**, *112*, 408−422.