ORGANIC LETTERS

2008
Vol. 10, No. 6
1207−1210

Allylation of *N*-Heterocycles with Allylic Alcohols Employing Self-Assembling Palladium Phosphane Catalysts

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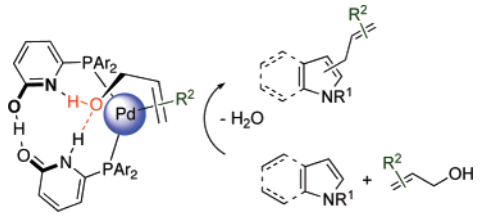
Received January 11, 2008

ABSTRACT



The first palladium catalyst system that allows the direct allylation of indoles with allylic alcohols as substrates with water being the only byproduct is presented. The application of self-assembing ligands based on complementary hydrogen bonding was the key to success.

N-Heterocycles are important building blocks and pharmacophores in natural products and synthetic drugs. As such, their synthesis and functionalization has been the subject of numerous studies.[1] However, catalytic processes which allow the construction of new C/C bonds between heterocycles and readily available bifunctional organic substrates which minimize the formation of a byproduct (salt etc.) are rare.[2] In this context, the transition-metal-catalyzed allylic alkylation could become an interesting alternative. Most frequently, allyl acetates and carbonates have been used as electrophiles in these reactions. However, use of these substrates is associated with the disadvantage of generating a stoichiometric amount of a couple product (carboxylate or alcohols/alcoholates and carbon dioxide). Furthermore, these starting materials have to be prepared in an extra step from the corresponding allylic alcohol. Thus, ideal substrates would be the allylic alcohols themselves, with water being the only byproduct in this case. Only a few studies have addressed this problem.[3] However, in order to employ *N*-heterocycles as nucleophiles, an additional activator (BEt_3) was required which results in the formation of boron-containing couple products.[4]

Recently, self-assembling ligand systems based on complementary hydrogen-bonding have been developed in our laboratory. This approach is intrinsically combinatorial and has potential for high throughput screening.[5] From these studies excellent catalysts have emerged for regioselective hydroformylation of terminal olefins,[6] asymmetric hydrogenation with Rh catalyst,[7] and Ru-catalyzed hydration of alkynes and nitriles.[8,9] The latter studies suggested that the hydrogen-bonding network of the self-assembling ligands might have the propensity for activation of protic nucleo-

(1) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell Science: Oxford, U.K., 2000.

(2) (a) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (b) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (c) Dyker, G. *Handbook of C-H activation Transformation*; Wiley-VCH: Weinheim, Germany, 2005; Vols. 1 and 2. (d) Ritleng, V.; Stirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (e) Campeau, L. C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (f) Alberico, D.; Scott, M. E.; Lautens, M. (g) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211.

(3) (a) Ozawa, F.; Okamoto, H.; Kawagishi, S.; Yamamoto, S.; Minami, T.; Yoshifuji, M. *J. Am. Chem. Soc.* **2002**, *124*, 10968. (b) Ozawa, F.; Ishiyama, T.; Yamamoto, S.; Kawagishi, S.; Murakami, H.; Yoshifuji, M. *Organometallics* **2004**, *23*, 1698. (c) Kayaki, Y.; Koda, T.; Ikariya, T. *J. Org. Chem.* **2004**, *69*, 2595. (d) Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2004**, *6*, 4085. (e) Utsunomiya, M.; Miyamoto, Y.; Ipposhi, J.; Ohshima, T.; Mashima, K. *Org. Lett.* **2007**, *9*, 3371.

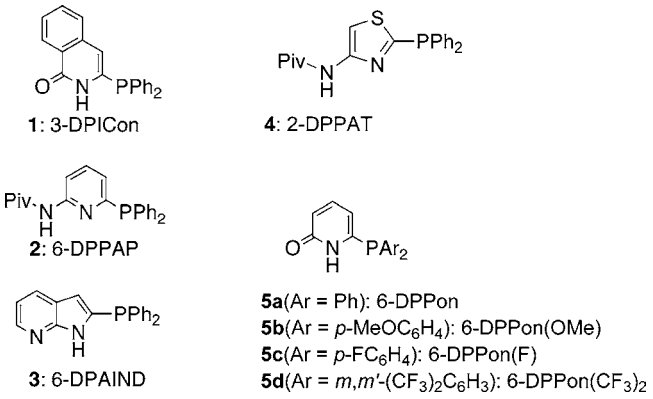
(4) (a) Kimura, K.; Furumata, M.; Mukai, R.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 4592. (b) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314.

10.1021/ol800073v CCC: $40.75
Published on Web 02/27/2008

philes through hydrogen bonding.[10] This let us speculate, that the corresponding palladium catalysts of our self-assembling ligand systems might also allow for activation of unreactive allylic alcohols as substrates in the course of the palladium-catalyzed allylic substitution. Herein, we report on the application of self-assembling ligand-derived palladium catalysts for the allylic alkylation of indoles and pyrroles with allylic alcohols omitting the need for additives.

In our first experiments, we explored whether the principle of self-assembling of monodentate ligands through complementary hydrogen bonding is transferable to palladium catalysts. Thus, [Pd(cod)Cl_2] was reacted with 3-DPICon (**1**)[11] and 6-DPPAP (**2**)[11] in CH_2Cl_2 containing residual water to furnish the yellow crystalline palladium complex **6** (Scheme 1). From the X-ray plot of **6** depicted in Figure 1,

Scheme 1. Self-Assembling Ligands Employed in This Study



it is obvious that cis-coordinated 3-DPICon (**1**)/6-DPPAP (**2**) ligands form the expected hydrogen-bonded hetero dimer and act as a chelating ligand for the palladium metal center. Interestingly, an additional molecule of water was incorporated in the NH−N hydrogen bond system. Thus, we

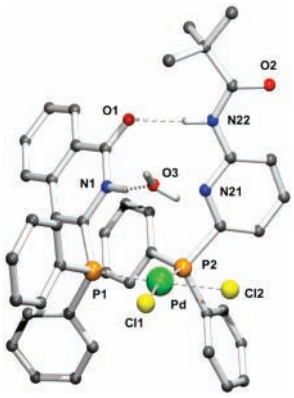
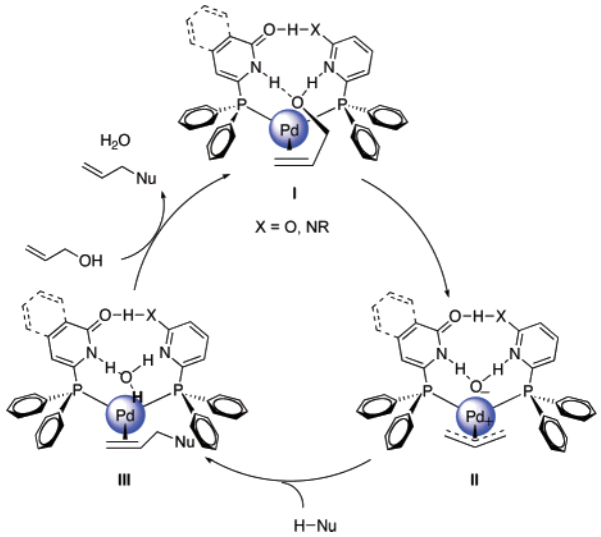


Figure 1. PLATON plot of [(3-DPICon·H_2O)(6-DPPAP)$PdCl_2$] (**6**) in the solid state. Selected interatomic distances (Å) and angles (deg): Pd−P1 2.2742(6), Pd−P2 2.2715(6), O1−N22 2.863(3), N1−O3 2.805(3), P1−Pd−P2 98.72(2), O1−H−N22 167(3), N1−H−O3 161(2). Pd = green, P = orange, Cl = yellow, O = red, N = blue. H atoms bound to C atoms are omitted for clarity.

speculated that water might be replaced in the course of a catalytic cycle by an allylic alcohol (see Scheme 2). This may allow for activation of the hydroxyl function to become a better leaving group in the course of an allylic substitution reaction.

Scheme 2. Proposed Reaction Mechanism



Unfortunately, complex **6** was not effective as a catalyst precursor to allylic substitution reaction (Table 1, entry 1). Also, when using π-allyl palladium chloride dimer as the catalyst precursor, although traces of the desired 3-allylation product **9a** could be observed, the result was unsatisfactory (entry 2). However, promising observations were made with [(η^3-allyl)Pd(cod)]BF_4 as the catalyst precursor in the presence of 5 mol % of each of the self-assembling ligands **1** and **2** (entry 3). After some experimentation the conditions

(5) For alternative approaches to self-assembling ligand/catalyst systems, see: (a) Breit, B. *Angew. Chem.* **2005**, *117*, 6976; *Angew. Chem., Int. Ed.* **2005**, *44*, 6816. (b) Takacs, J. M.; Reddy, D. S.; Moteki, S. A.; Wu, D.; Palencia, H. *J. Am. Chem. Soc.* **2004**, *126*, 4494. (c) Slagt, V. F.; Roeder, M.; Kamer, P. C.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *J. Am. Chem. Soc.* **2004**, *126*, 4056. (d) Slagt, V. F.; van Leeuwen, P. W. N. M. *Angew. Chem.* **2003**, *115*, 5777; *Angew. Chem., Int. Ed.* **2003**, *42*, 5619. (e) Slagt, V. F.; van Leeuwen, P. W. N. M. *Chem. Commun.* **2003**, 2474. (f) Liu, Y.; Sandoval, C. A.; Yamaguchi, Y.; Zhang, X.; Wang, Z.; Kato, K.; Ding, K. *J. Am. Chem. Soc.* **2006**, *128*, 14212. (g) Sandee, A. J.; van der Burg, A. M.; Reek, J. N. H. *Chem. Commun.* **2007**, 864. (h) Rivillo, D.; Gulyas, H.; Benet-Buchholz, J.; Escudero-Adan, E. C.; Freixa, Z.; van Leeuwen, P. W. N. M. *Angew. Chem.* **2007**, *119*, 7385; *Angew. Chem., Int. Ed.* **2007**, *46*, 7247. (i) Hattori, G.; Hori, T.; Miyake, Y.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 12930.

(6) Breit, B.; Seiche, W. *J. Am. Chem. Soc.* **2003**, *125*, 6608.

(7) (a) Weis, M.; Waloch, C.; Seiche, W.; Breit, B. *Angew. Chem.* **2007**, *119*, 3097. *Angew. Chem., Int. Ed.* **2007**, *46*, 3037.

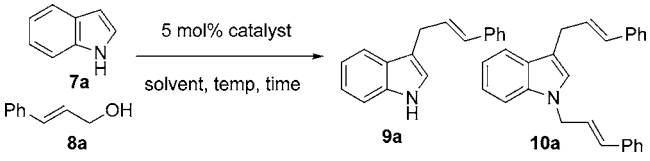
(8) Chevallier, F.; Breit, B. *Angew. Chem.* **2006**, *118*, 1629; *Angew. Chem., Int. Ed.* **2006**, *45*, 1599.

(9) Smejkal, T.; Breit, B. *Organometallics* **2007**, *26*, 2461.

(10) Oshiki, T.; Yamashita, H.; Sawada, K.; Utsunomiya, M.; Takahashi, K.; Takai, K. *Organometallics*, **2005**, *24*, 6287.

(11) 3-DPICon (1): 3-Diphenylphosphanylisoquinolone; 6-DPPAP (2): *N*-Pivaloyl-6-diphenylphosphanylaminopyridine; 6-DPAIND (3): 6-Diphenylphosphanyl-1*H*-7-azaindole; 2-DPPAT (4): *N*-Pivaloyl-2-diphenylphos-phanylaminothiazole; 6-DPPon (5): 6-Diphenylphos-phanylpyridone.

Table 1. Optimizing Reaction Conditions



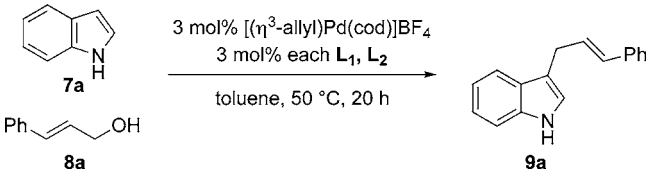
entry[a]	catalyst	solvent	T (°C)	t (h)	yield[b] (%)
1	**6**	PhCl	rt	65	0
2	[(η^3-allyl)PdCl]$_2$ 3-DPICon(**1**)/6-DPPAP(**2**)	PhCl	rt	65	trace
3	[(η^3-allyl)Pd(cod)]BF_4 3-DPICon(**1**)/6-DPPAP(**2**)	PhCl	rt	65	32 (0)
4[c]	[(η^3-allyl)Pd(cod)]BF_4 3-DPICon(**1**)/6-DPPAP(**2**)	toluene	50	20	84 (3)

[a] Pd/P (25/50 μmol), indole (0.50 mmol), and cinnamyl alcohol (0.55 mmol) were reacted in toluene (0.25 mL). [b] Determined from ^{1}H NMR employing t-Bu$_2$biphenyl (0.056 mmol = 2/18 mmol) as internal standard; yield of **10a** in parentheses. [c] Utilizing 3 mol % of catalyst and 0.50 mmol of cinnamyl alcohol.

shown in entry 4 were identified as best. Thus, employing 3 mol % of the self-assembling catalyst in toluene at 50 °C, 84% of the desired 3-allylated indole **9a** with only 3% of the easily separable bis-allylation product **10a** were obtained.

The inherent advantage of the self-assembly approach is its implemented combinatorial flexibility for optimization. Thus, next we decided to identify the best self-assembly platform in order to achieve optimal results in the title transformation. Thus, replacing aminopyridine **2** by the thiazole **4**, which has recently been shown to be an ideal system for rhodium-catalyzed hydroformylation,[6b] did not lead to a better catalyst (Table 2, entry 2), neither did the

Table 2. Identifying the Best Self-assembling Ligand System

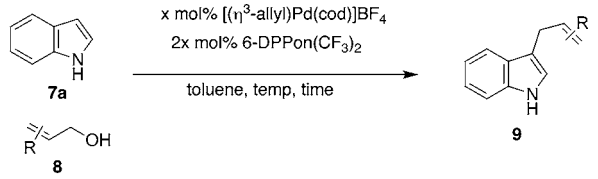


entry	L_1/L_2	yield[a] (%)	entry	L_1/L_2	yield[a] (%)
1	**1/2**	84 (3)	7[c]	**5a/5a**	10 (0)
2	**1/4**	76 (4)	8[c]	**5b/5b**	22 (0)
3	**3/2**	0	9[c]	**5c/5c**	41 (3)
4	**5a/5a**	79 (6)	10[c]	**5d/5d**	40 (0)
5[b]	**1/2**	42 (0)	11[b]	**5d/5d**	80
6[b]	**5a/5a**	60 (0)			

[a] Estimated from ^{1}H NMR with use of t-Bu$_2$biphenyl (0.056 mmol = 2/18 mmol) as internal standard; yield of **10a** in parentheses. [b] Utilizing allyl alcohol (**8b**) instead of cinnamyl alcohol (**8a**). [c] Utilizing allyl alcohol (**8b**) instead of cinnammyl alcohol (**8a**) at rt.

replacement of the isoquinolone **1** by the azaindole ligand **3**. However, the simplest self-complementary 6-DPPon ligand **5a** provided a rather active catalyst (entry 4). Notably, replacing cinnamyl alcohol **8a** by the less reactive parent allyl alcohol **8b**, the 6-DPPon derived catalyst performed best (compare entries 5 and 6) although the overall yields were still unsatisfactory. Hence, in a second stage we decided

Table 3. Scope of Allylic Alcohol



entry	allylic alcohol	x	t [°C]	t [h]	yield [%][a]
1	**8b**	3	50	22	**9b** (80)
2	**8c**	5	50	24	**9c** (32), **9d** (33)
3	**8d**	5	50	24	**9c** (40), **9d** (50)
4[b]	**8e**	5	90	64	**9e** (0), **9f** (58)
5[b]	**8f**	5	80	24	**9e** (12), **9f** (75)
6[c]	**8a**	3	50	20	**9a** (79)
7[c]	**8g**	3	50	20	**9a** (87)
8[b,d]	**8h**	3	90	20	**9g** (94)

[a] Isolated yield. [b] 3 equiv of allylic alcohol (**8b**) was utilized. [c] Employed 3 mol % of **1**, **2** as ligands. [d] Utilizing *N*-methylindole (**7d**) instead of *N*-unsubstituted indole (**7a**).

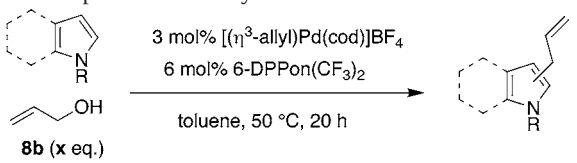
to optimize the most simple 6-DPPon system by variation of the electronic properties of the phosphine donors. It has previously been shown that the electrophilicity and hence reactivity of a palladium π-allyl intermediate toward nucleophiles can be increased on increasing the π-acceptor strength of the ligands attached to palladium.[12] Accordingly, we observed increased catalyst activity when increasing the π-acceptor strength of the phosphine donors attached to the pyridone platform (entries 7−11) with the bis-*m*-trifluoromethyl-substituted phosphine **5d** furnishing the best catalyst (entries 7−10). Thus, good yield and excellent chemoselectivity for the C3-allylation product were obtained (entry 11).

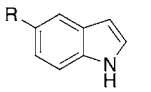
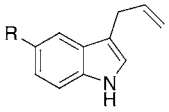
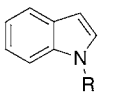
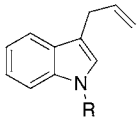
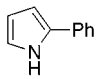
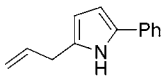
(12) Kuhn, O.; Meyr, H. *Angew. Chem.* **1999**, *111*, 356; *Angew. Chem., Int. Ed.* **1999**, *38*, 343.

More substituted allylic alcohols **8c**−**h** can be applied as substrates as well, and the corresponding 3-indole monoallylation products **9** were obtained selectively and in good yields (Table 3, entries 1−7). The results obtained for the unsymmetrical π-allyl systems (entries 2−7) suggest the presence of a π-allylpalladium intermediate. For the methallylic alcohol substrate the bismethallylation product at C3 and N was isolated. On the other hand, when the *N*-methylindole was employed the C3-allylation product **9g** could be isolated in 94% yield.

Furthermore, several substituted indole derivatives **7b**−**f** as well as pyrrole (**11)** were successfully allylated employing the new self-assembly catalyst to give the corresponding products in good to excellent yields (Table 4). We also briefly

Table 4. Scope of *N*-Heterocycles



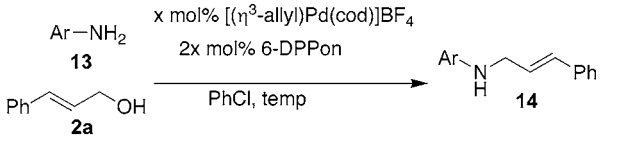
N-heterocycle	x equiv	product	yield[a]
 **7b**: R = OH **7c**: R = OMe	1.0		**9h**: (R = OH) 84% **9i**: (R = OMe) 85%
 **7d**: (R = Me) **7e**: (R = Bn) **7f**: (R = Boc)	3.0		**9j**: (R = Me) 90%[b] **9k**: (R = Bn) 96% **9l**: (R = Boc) n.r.[c]
 **11**	1.0		**12**: 61 %[d]

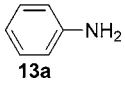
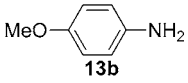
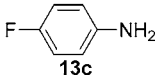
[a] Isolated yield. [b] 36 h. [c] No reaction. [d] 85% conversion.

looked into nitrogen nucleophiles such as aniline derivatives, which gave excellent yields of the monoallylation products as well (Table 5).

Although the exact details of the reaction mechanism have not been clarified yet, we propose the following rational (Scheme 2). In agreement with the experimental observation that water can be incorporated into the ligand hydrogen-bonding network (Figure 1), we suggest that the hydroxy function of an allyl alcohols may be bound in a similar manner to give alkene complex **I**. As a result, the hydroxy substituent may become a better leaving group and thus facilitates the formation of the π-allylpalladium intermediate

Table 5. Nitrogen Nucleophiles



N-nucleophile	x	*t* [°C]	*t* [h]	yield[a]
 **13a**	0.5	90	8	88% (5% dimer) **14a**
 **13b**	0.5	90	21	95% **14b**
 **13c**	1.0	80	10	92% **14c**

[a] Isolated yield.

II. Nucleophile attack and proton transfer lead to product alkene complex **III** which undergoes ligand exchange with the allylic alcohol substrate liberating the allylation product and water as the only byproduct.

In conclusion, we have developed the first palladium catalyst system that allows the direct allylation of indoles with allylic alcohols as substrates with water being the only byproduct. Key to success was the application of self-assembling ligands based on complementary hydrogen-bonding. We propose that the ligand hydrogen-bonding network goes beyond its role in ligand structure determining and suggest that the hydrogen-bonding system assists the hydroxy group to become a better leaving group in the course of this allylic substitution process. Hence, this is an example of a dual transition metal/organocatalysis, which opens up numerous possibilities for the application of these self-assembling ligands to homogeneous catalysis including asymmetric versions.

Acknowledgment. This work was supported by the Fonds der Chemischen Industrie, the DFG via the International Research Training Group "Catalysts and Catalytic Reactions for Organic Synthesis" (GRK 1038), and the Alfried Krupp Award for young university teachers of the Krupp foundation (to B.B.).

Supporting Information Available: Expermental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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