ORGANIC LETTERS

2003
Vol. 5, No. 9
1451−1454

Di-2-pyridylmethylamine-Based Palladium Complexes as New Catalysts for Heck, Suzuki, and Sonogashira Reactions in Organic and Aqueous Solvents[†]

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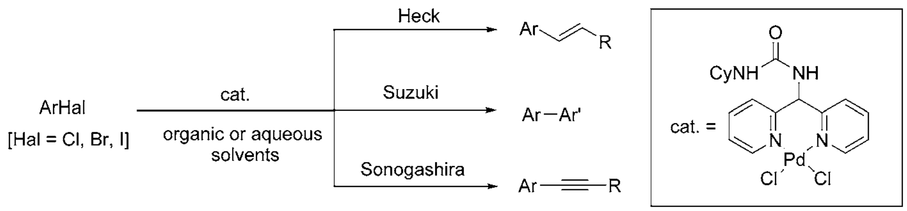
Received February 3, 2003

ABSTRACT



A new palladium−dipyridylmethylamine complex is an excellent catalyst for C−C bond-forming processes such as the Heck, Suzuki, and Sonogashira reactions in organic and aqueous solvents under homogeneous conditions.

The great importance of palladium-catalyzed carbon−carbon bond-forming reactions[1] has encouraged the chemical community to search for very active, and at the same time stable, palladium-based catalysts, which should also be versatile and efficient systems. This pertains particularly to the vinylation of aryl halides called the Heck−Mizoroki reaction,[2] the cross-coupling of aryl halides and boronic acids called the Suzuki−Miyaura reaction,[3] and the alkynylation of aryl halides called the Sonogashira−Hagihara reaction,[4] which are “classical” processes in organic synthesis and material science. Several goals have to be achieved for industrial applications such as

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[†] Dedicated to the memory of Prof. Antonio González.

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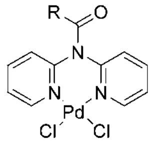
10.1021/ol0341849 CCC: $25.00

the use of aryl chlorides[1g] as substrates, the possibility of using aqueous conditions, and the recovery of the catalyst. Recent notable advances have been achieved by using bulky phosphanes,[5] phophites,[6] and phosphane oxides[7] as ligands. Palladium on carbon,[8] palladium N-heterocyclic carbene complexes,[9] and palladacycles[10] have also been used as catalysts. We have recently applied oxime-derived palladacycles as very stable and efficient precatalysts in several cross-coupling processes (even of deactivated aryl chlorides) in organic solvents (Heck, Suzuki, Stille, Sonogashira, Ullmann)[11] and in aqueous media (Suzuki).[12]

Palladium(II) salts with bidentate P,N-[13] and especially N,N-ligands[14] have proven to be efficient catalysts for C−C and C−N bond-forming reactions. The *N*-acyl-substituted dipyridyl-[14b] and dipyrimidylamines[14c,d] **1** and **2** form stable palladium complexes with $PdCl_2$. This type of ligand has been incorporated into a polymeric matrix via a ROMP process. All of these complexes present an excellent capacity for Pd^{2+} complexation,[14a−d] and no leaching of Pd was observed during any type of coupling reaction. Recently, *trans*-chelated complexes **3**, bearing a bidentate pyridine-containing ligand, have been described as catalysts for the Heck olefination of aryl iodides with *tert*-butyl acrylate under aerobic conditions but in triethylamine as a solvent.[15]

The activity of homogeneous catalysts **1**−**3** for the Heck reaction was only demonstrated in organic solvents. Polymer-supported reagents derived from complexes **1** and **2** showed greater activity than the monomeric complexes in Heck, Suzuki, and Sonogashira reactions even with chlorobenzene as a substrate.[14a−d] To study the activity of less-electron-rich ligands, we focused our attention on the 2,2-dipyridylmethylamine-based palladium complexes **4**.[16] The ligand can be easily prepared from commercially available di-2-pyridyl ketone or oxime, and the amino group can easily be acylated or anchored to a solid support and will not be involved in the chelation of palladium. In this letter, we describe the synthesis and activity of new complexes of type **4** as homogeneous catalysts in C−C bond-forming reactions not only in organic solvents but also in aqueous media.



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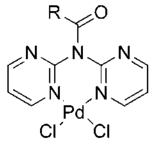

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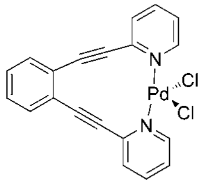

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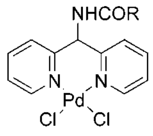

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The starting amine **6**[17] was prepared from ketone **5** in 78% overall yield by zinc-mediated reduction of its oxime, and it was immediately subjected to acylation with acetic anhydride or with cyclohexyl isocyanate giving ligands **7a** and **7b** in 88 and 84% yields, respectively. Palladium(II) complexes **4a** and **4b** were prepared by reaction with H_2PdCl_4 in 73 and 94% yields, respectively, as described by Buchmeiser et al.[14a−d] for complexes **1** and **2** (Scheme 1).

Complexes **4a** and **4b** are only soluble in very polar organic solvents such as DMSO or DMF. Complex **4a** was characterized by X-ray analysis (Figure 1) and crystallizes in the monoclinic space group $P2_1/c$ with the Pd center in a square planar enviroment and with unique N−Pd bond lengths of 2.017 and 2.029 Å. These bonds are slightly shorter than in complexes **1** (R = Me, 2.041 and 2.039 Å) and **2** (R = Me, 2.031 and 2.048 Å).

Preliminary catalytic studies of complexes **4a** and **4b** in a model Heck reaction between iodobenzene and *n*-butyl acrylate at 140 °C (bath temperature) in DMF and with Bu_3N as a base showed that they have similar efficiencies (TON $= 10^5$, TOF $= 10^4$ h^{-1}) (Table 1, entries 1 and 2). This activity was superior to that of other pyridine complexes such as **1** (TON = 14 100, TOF = 156 h^{-1}),[14c] **2** (TON = 6600, TOF = 91 h^{-1})[14d] and **3** (TON $= 8 \times 10^4$, TOF = 1596 h^{-1})[15] and also superior to the activity of $PdCl_2(PhCN)_2$ (TON 4790, TOF = 99 h^{-1}).

Complex **4b** was considered to be a more robust catalyst compared to **4a**, especially for working under aqueous conditions at high temperatures. First, the Heck reaction was studied with iodo-, bromo-, and chlorobenzene together with acrylates or *p*-chlorostyrene as olefinic counterparts. The reactions with acrylates were performed in DMF, NMP/H_2O (3/1), and H_2O. Diisopropylamine was used as a base under

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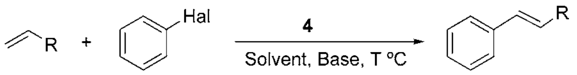
Table 1. Heck Coupling Reactions Catalyzed by **4**[a]



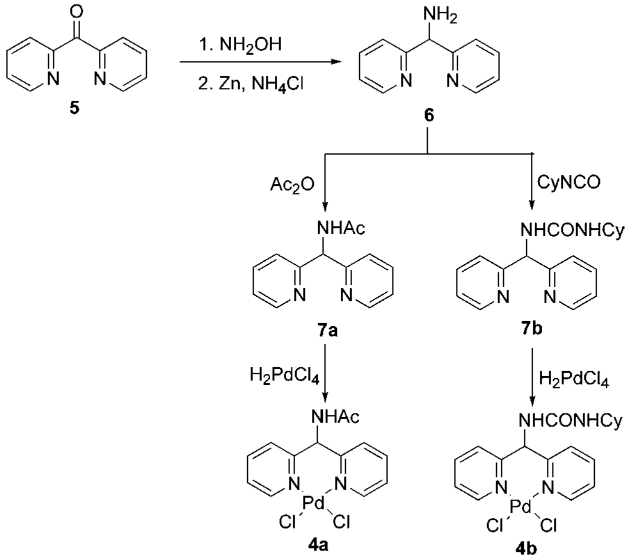
entry	R	Hal	mol % Pd	solvent	base	additive	T (°C)[b]	t (h)	yield (%)[c,d]	TON	TOF (h^{-1})
1	CO_2Bu^n	I	**4a** (0.001)	DMF	Bu_3N		140	4	>99 (99)	10^5	2.5×10^4
2	CO_2Bu^n	I	**4b** (0.001)	DMF	Bu_3N		140	5	>99 (89)	10^5	2×10^4
3	CO_2Bu^t	I	**4b** (0.001)	NMP/H_2O[e]	*i*-Pr_2NH		140	142	74	74 000	521
4	CO_2Bu^t	I	**4b** (0.001)	H_2O	*i*-Pr_2NH		140	142	>99[f]	10^5	704
5	CO_2Bu^n	Br	**4b** (0.01)	DMF	Bu_3N	TBAB	140	19	90	9000	473
6	CO_2Bu^t	Br	**4b** (0.01)	NMP/H_2O[e]	*i*-Pr_2NH	TBAB	140	92	93	9300	101
7	CO_2Bu^t	Br	**4b** (0.01)	H_2O	*i*-Pr_2NH	TBAB	140	158	98 (78)[f]	9800	62
8	4-ClC_6H_4	I	**4b** (0.01)	DMF	Bu_3N		140				
9	4-ClC_6H_4	I	**4b** (0.01)	NMP/H_2O[e]	*i*-Pr_2NH		160	32	>99 (97)[g]	10^4	312
10	4-ClC_6H_4	I	**4b** (0.01)	H_2O	*i*-Pr_2NH		140	31	95[h]	9500	306
11	4-ClC_6H_4	Br	**4b** (0.01)	DMF	K_2CO_3	TBAB	160	116	77[i]	7700	66
12	4-ClC_6H_4	Br	**4b** (0.01)	NMP/H_2O[e]	*i*-Pr_2NH	TBAB	160	47	97[j] (81)[k]	9700	206
13	4-ClC_6H_4	Br	**4b** (0.01)	H_2O	*i*-Pr_2NH	TBAB	160	110	12	1200	11
14	4-ClC_6H_4	Cl	**4b** (0.5)	NMP/H_2O[e]	*i*-Pr_2NH	TBAB	160	150	40[l] (34)[m]	80	

[a] Reaction conditions: 1.0 equiv of ArHal, 1.5 equiv of alkene, 3 equiv of DIA or 1.4 equiv of Bu_3N, and 0.5 equiv of TBAB. [b] Bath temperature. [c] Determined by GC, based on the ArHal using decane as an internal standard. [d] In parentheses isolated yield after flash chromatography. [e] Mixture (3/1). [f] Cinnamic acid was isolated. [g] 1-(4-Chlorophenyl)-1-phenylethene (2%) was also obtained. [h] Mixture of regioisomers (13:1). [i] Mixture of regioisomers (29:1). [j] 1-(4-Chlorophenyl)-1-phenylethene (8%) was also obtained. [k] Mixture of regioisomers (15:1). [l] Mixture of regioisomers (3:11). [m] 1-(4-Chlorophenyl)-1-phenylethene (5%) was also obtained.

aqueous conditions in order to avoid ester hydrolysis. In the case of bromo- or chlorobenzene, tetrabutylammonium bromide (TBAB) had to be added. In the case of iodobenzene (Table 1, entries 2−4 and 8−10), TON of 10^5 was achieved for acrylates and 10^4 for *p*-chlorostyrene. For bromobenzene 10^{-2} mol % catalyst **4b** was used (Table 1, entries 5−7 and 11−13). In the arylation reactions of *p*-chlorostyrene a small amount of the regioisomer 1-(*p*-chlorophenyl)-1-phenylethylene was obtained in some cases (Table 1, entries 10−13). Chlorobenzene only reacted with *p*-chlorostyrene in NMP/H_2O at 160 °C using 0.5 mol % catalyst, giving a 3:11 mixture of the two regioisomers, *p*-chlorostilbene and 1-(*p*-chlorophenyl)-1-phenylethylene (Table 1 entry 14). For the preparation of cinnamate, the alkenylation took place faster in DMF than in aqueous solvents. However, for stilbene formation, the use of aqueous solvents gave better results.

Cross-coupling reactions of aryl bromides or chlorides with phenylboronic acid were carried out with K_2CO_3 as a base in DMF/H_2O (95/5) at 110 °C (Table 2, entries 1, 6, and 8) or under reflux in water (Table 2, entries 2, 4, 7, and 9). The reaction with aryl chlorides had to be run in the presence of TBAB as an additive. In general, reactions in water took place faster and more efficiently. In the case of 4-bromophenol and 4-chloroaniline, couplings in DMF/H_2O failed. Alternatively, the reaction can be performed in MeOH/H_2O (2/3) at room temperature (Table 2, entries 3 and 5). In general, better results were obtained in water as a solvent.

Scheme 1. Synthesis of Dipyridylmethylamine-Based Palladium Complexes **4**



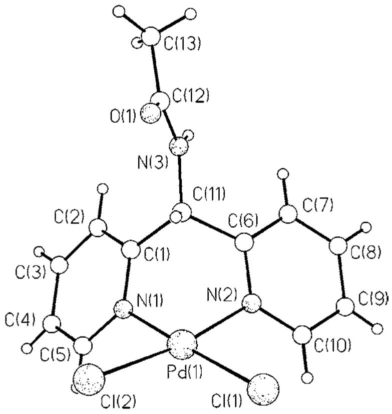
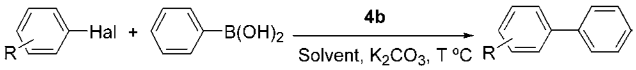


Figure 1. X-ray structure of complex **4a**.

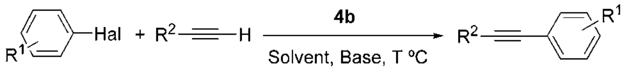
Table 2. Suzuki Coupling Reactions Catalyzed by Complex **4b**[a]



entry	R	Hal	mol % Pd	solvent	T (°C)[b]	t (h)	yield (%)[c,d]	TON	TOF (h^{-1})
1	4-MeCO	Br	0.01	DMF/H_2O[e]	110	3.5	87	8700	2486
2	4-MeCO	Br	0.001	H_2O	100	1	>99 (91)	10^5	10^5
3	4-MeCO	Br	0.2	MeOH/H_2O[f]	rt	6	82	68	41
4	4-OH	Br	0.00076	H_2O	100	2	95 (82)	125 000	62 500
5	4-OH	Br	0.1	MeOH/H_2O[f]	rt	120	75	6	6.25
6	4-Me_2N	Br	1	DMF/H_2O[e]	110	48	96 (84)	96	2
7	4-Me_2N	Br	0.1	H_2O	100	17	37	370	22
8	4-MeCO	Cl	0.1	DMF/H_2O[e]	130	120	88 (69)	880	7
9	4-MeCO	Cl	0.1	H_2O[g]	100	7.5	>99	10^3	133
10	4-NH_2	Cl	1	DMF/H_2O[e]	130				
11	4-NH_2	Cl	1	H_2O[g]	100	7.5	73 (52)	73	10

[a] Reaction conditions: 1.0 equiv of ArHal, 1.5 equiv of phenylboronic acid, and 2 equiv of base. [b] Bath temperature for aqueous DMF. [c] Determined by GC, based on the ArHal using decane as an internal standard. [d] In parentheses is shown the isolated yield after flash chromatography. [e] Mixture (95/5). [f] Mixture (2/3) and KOH as a base. [g] TBAB (0.5 equiv) was added.

Table 3. Sonogashira Coupling Reactions Catalyzed by **4b**[a]



entry	R^1	Hal	R^2	mol % Pd	solvent	base	additive	T (°C)[b]	t (h)	yield (%)[c,d]	TON
1	Cl	I	Ph	0.1	NMP	TBAA		110	1	97[e] (88)	970
2	Cl	I	Ph	0.1	H_2O	pyrrolidine	TBAB	100	6	>99	10^3
3	MeO	I	Ph	0.1	NMP	TBAA		110	1	96 (71)	960
4	MeO	I	Ph	0.1	H_2O	pyrrolidine	TBAB	100	7	>99[f]	10^3
5	Cl	I	n-C_4H_9	0.1	NMP	TBAA		110	1.5	97[g] (88)	970
6	MeO	I	i-Pr_3Si	0.1	H_2O	pyrrolidine	TBAB	100	17	89[h] (65)	890
7	Cl	Br	Ph	0.2	NMP	TBAA		110	2	69[i] (59)	345
8	Cl	Br	Ph	0.2	H_2O	pyrrolidine	TBAB	100	4	96[j]	480
9	Me	Br	Ph	0.2	H_2O	pyrrolidine	TBAB	100	50	>99[k] (76)	500

[a] Reaction conditions. (a) In NMP: 1.0 equiv of ArHal, 1.5 equiv of alkyne, 1.5 equiv of TBAA, 110 °C. (b) In H_2O: 1.0 equiv of ArHal, 1.5 equiv of alkyne, 2 equiv of pyrrolidine, 1 equiv of TBAB, 100 °C. [b] Bath temperature in the case of NMP. [c] Determined by GC, based on the ArHal using decane as an internal standard. [d] In parentheses is the isolated yield after flash chromatography. [e] Diyne (6%). [f] Diyne and enyne (8%). [g] Diyne and enyne (<2%). [h] Diyne and enyne (10%). [i] Diyne and enyne (8%). [j] Diyne and enyne (20%). [k] Enyne (20%) due to the addition of 1 equiv of phenylacetylene after 1 day.

The Sonogashira coupling of iodo and bromoarenes with terminal acetylenes in organic solvents could be carried out under the copper- and amine-free conditions we set up recently for oxime-derived palladacycles.[11d] The reaction was performed in NMP with tetrabutylammonium acetate (TBAA) as a base at 110 °C (Table 3, entries 1, 3, 5, and 7). When this alkynylation reaction was carried out in refluxing water, pyrrolidine (2 equiv) as a base and TBAB (0.5 equiv) as an additive were used (Table 3, entries 2, 4, 6, 8, and 9). As secondary products, some amounts of diyne and enyne corresponding to the homocoupling of the starting alkyne were obtained due to the use of an excess of acetylene. In general, reactions were faster in NMP than in water.

In conclusion, dipyridylmethylamine-based palladium complexes are stable catalysts for different types of carbon–carbon bond-forming reactions, which can be carried out in air and in organic or aqueous solvents. Further studies on their versatility as catalysts as well as on reusability through the utilization of an appropriate solid support are underway.

Acknowledgment. We thank DGES of the Spanish Ministerio de Ciencia y Tecnologia (MCyT) (BQU2001-0724-C02-01 and BQU2002-00554) for financial support. S.K. thanks the Stiftelsen Bengt Lundquists minne (Sweden), the Swedish Institute, and the Spanish Ministerio de Asuntos Exteriores for postdoctoral fellowships. J.G.M. thanks MCyT for a predoctoral fellowship.

Supporting Information Available: Experimental procedures for the synthesis of palladium complexes **4** and catalytic processes and data for the X-ray structure of compound **4a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL0341849