Pergamon

Tetrahedron Letters 39 (1998) 4287–4290

TETRAHEDRON
LETTERS

Reusable Polymer-supported Palladium Catalysts : An Alternative to Tetrakis(triphenylphosphine)palladium in the Suzuki Cross-coupling Reaction[1]

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Received 5 March 1998; accepted 8 April 1998

Abstract : The Suzuki cross-coupling reaction of a boronic acid and a bromoaromatic compound requires palladium catalysis. Almost identical yields were obtained in the usual conditions, with 30 mequiv. of $Pd(PPh_3)_4$, and with 2 mequiv of a polymer-supported catalyst, which was easily prepared in two steps from Merrifield polymer. Recovery and reuse of the catalyst is easy, and only 0,60% of the initial amount of palladium is lost during a reaction. © 1998 Elsevier Science Ltd. All rights reserved.

The formation of aryl-aryl bonds is a crucial step in the synthesis of many biologically active compounds (e.g. Rosoxacin, Diflunisal) and of liquid crystals. Classical procedures such as the Ullmann or Gomberg-Bachmann reactions often lack selectivity or give only low yields. Therefore during the last twenty years they have been replaced by palladium-catalyzed coupling reactions, among which the most widely used is the Suzuki reaction where an arylboronic acid (or anhydride) reacts with an aryl halide or triflate in the presence of aqueous base[2]. Usually a soluble palladium catalyst such as $Pd(PPh_3)_4$ is used. However good results were reported a few years ago with palladium on carbon[3] and the recent publication by Jang[4] that polymer-supported palladium catalysts were highly effective prompts us to disclose our own results on the same topic.

In Pd(0) or Pd (II) catalyzed industrial processes, palladium catalysts are recovered by several methods (precipitation, use of water-soluble phosphine ligands, etc) or at least the metal itself is recovered by formation of insoluble complexes[5]. As an alternative, polymer-supported palladium catalysts have been used for allylic substitutions[6], oligomerizations[6c,7,8c], decarboxylations[6d], hydrogenations[8], isomerizations[9], telomerizations[10] and for the Heck reaction[8c,11]. These polymer supported catalysts can be seen as a borderline class of catalysts which retain the advantages of homogeneous catalysts while securing the ease of recovery and workup of heterogeneous catalysts[12]. However they can present also special properties : *e.g.* intramolecular reactions are favoured[6e], or the reaction becomes very sensitive to small differences of steric hindrance[6a,8c,10]. Different types of polymers have been used to support the palladium; the most common is polystyrene (crosslinked with divinylbenzene : DVB), which can bear different functional groups such as carboxylic acids, heterocyclic amines or phosphines[12]. A soluble Palladium salt or complex is then used for Pd introduction by an exchange reaction. For example, an heterogeneous catalyst for Heck reaction was easily prepared[13] in two steps from commercial Merrifield polymer by substitution with Ph_2PLi followed by an exchange reaction with

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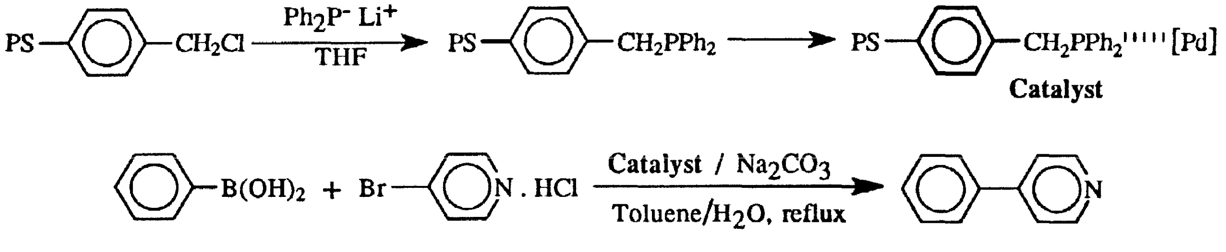
PII: S0040-4039(98)00757-6

$PdCl_2(PhCN)_2$. Hallberg and coworkers[11b] found that both the catalytic activity and the nature of the catalytic species were closely dependent of Pd/P ratios.

Because of their analogy with PPh_3, we chosed these diphenylphosphinated DVB-crosslinked polystyrenes to prepare our catalysts. Their activity for Suzuki reactions was first measured on a "standard" reaction : the coupling of phenylboronic acid with 4-bromopyridine.



Scheme

Table 1. Comparison of different polymer-supported palladium catalysts in the coupling reaction of phenylboronic acid with 4-bromopyridine a)

Entry	Catalyst	Soluble Pd compound used for Pd introduction in catalyst	% Pd in catalyst	Pd/P ratio in catalyst	Nb of Pd mequiv. used in coupling reaction	Isolated yield c) of 4-phenyl-pyridine (%)
1	**1**	$PdCl_2$	3,7	0,51	45	75
2	**2**	"	2,1	0,26	25	76
3	**3**	"	0,8	0,09	30	75
4	"	"	0,8	0,09	10	60
5	**4**	"	11,1	0,90	135	72
6	**5**	1)$PdCl_2$; 2) PPh_3/N_2H_4	11,6	0,94b)	142	71
7	**6**	$Pd(PhCN)_2Cl_2$	5,3	0,81	30	89d)
8	**7**	"	1,9	0,24	22	80d)
9	**8**	"	0,5	0,06	6	55
10	**9**	$Pd(CH_3CN)_2Cl_2$	3,6	0,49	44	85
11	**10**	"	1,0	0,12	12	73
12	**11**	$Pd(PPh_3)_4$	5,1	0,35b)	30	94
13	**12**	"	1,1	0,07b)	30	95
14	**13**	"	0,3	0,04b)	10	94
15	"	"	0,3	0,04b)	1	90
16	**14**	$Pd(PPh_3)_2Cl_2$	1,1	0,16b)	2	90
17	**15**	$Pd(dba)_2$	0,8	0,11	10	90
18	"	"	0,8	0,11	2	86
19	**16**	Na_2PdCl_4	0,9	0,13	10	87
20	"	"	0,9	0,13	2	67

a) Under identical conditions, a 86% yield[14] was obtained with 30 mequiv. of $Pd(PPh_3)_4$.

b) During the exchange reaction, PPh_3 was quantitatively recovered in the liquid phase ; microanalyses confirmed that the phosphorus content of the polymer was not increased. Therefore all phosphorus present in the catalyst is polymer-bound.

c) The reaction was carried out at 80°C for 24 h under nitrogen in toluene/EtOH/H_2O (10:1:1) by using 4-bromopyridine hydrochloride (1 equiv.), phenylboronic acid (1,1 equiv.), Na_2CO_3 (3 equiv.) and the indicated amount of polymer-supported catalyst.

d) When these catalysts were reused in identical conditions, yields of 94% (entry 7) and 91 % (entry 8) were obtained.

In fact, diphenylphosphinated polystyrenes obtained from chloromethylated polystyrene (Merrifield polymer) are analogues of benzyldiphenylphosphine. We have also prepared polymer-supported analogues of triphenylphosphine itself by aromatic bromination of DVB-crosslinked polystyrene followed by reaction with Ph_2PLi. However, in all of our experiments, similar results were obtained for catalysts prepared with both phosphinated polymers. Therefore, we used Merrifield polymer as starting material, because it allowed a convenient synthesis of the catalysts in only two steps.

The results presented in Table 1 show that the Pd/P ratio has no influence on the activity of our catalysts (*e.g.* entries 1-3), which contrasts with the results obtained for similar catalysts in the Heck reaction[11b]. A critical factor for the catalytic activity is the nature of the soluble palladium salt or complex used to prepare the catalyst. With $PdCl_2$ or $Pd(RCN)_2Cl_2$ (entries 1-11) maximum yields were only obtained if at least *ca.* 20 mequiv. of polymer-bound palladium were used. Besides, entries 7-8 show that, when the catalysts were prepared with $Pd(RCN)_2Cl_2$, slightly better yields were obtained when the catalysts had been already used at least once. This was not observed with catalysts obtained from other palladium salts or complexes. It should be emphasized that activity of catalysts prepared with $PdCl_2$ is not modified by the reduction of Pd(II) in Pd(0) with $N_2H_4.H_2O$ / PPh_3 (entries 5-6). This reduction had been performed for the preparation of similar catalysts used for Heck reaction[8c] and for telomerization of butadiene[10]. However our result is not unexpected since the boronic acids used in the Suzuki reaction are known[15] to reduce Pd(II). The most active catalysts were obtained with $Pd(PPh_3)_4$: no significant yield decrease of the coupling reaction was observed when only 1 mequiv. of polymer-bound palladium (or even less) was engaged (entries 14-15). Entries 16-20 show that other palladium complexes afforded catalysts which were only slightly less active.

The preparations of catalysts **1-16** were very reproducible : for example, several batches of catalyst **13** were independently prepared during this work (from different batches of commercial Merrifield polymer) and showed identical activities in the coupling reaction. On the contrary, exchange reactions with $Pd(OAc)_2$ afforded, in an irreproducible way, catalysts of different activities which were therefore not studied further.

Whereas $Pd(PPh_3)_4$ is known to be heat- and air-sensitive, our catalysts were stable at least for more than a year when stored in air at 20°C. They were reused more than 5 times without any activity decrease. The amount of precious metal lost from the polymer-supported catalyst during the reaction is a very important factor which conditions both the life expectancy of the catalyst and the presence of palladium impurities in the product. When the coupling reaction was run using 10 mequiv of catalysts **12**, **13** or **14**, only 0,60-0,65% of the initial amount of palladium was lost (*ca.* 0.06 mequiv.). The Pd losses were found to be independent of the value of the Pd/P ratio in the range studied. Nevertheless, we chosed the catalyst **13** with the lowest Pd/P ratio to replace $Pd(PPh_3)_4$ in the coupling reactions of several bromoaromatics with phenylboronic acid[16]. The yields obtained

Table 2. Comparison of different catalysts in coupling reactions of phenylboronic acid with bromoaromatics[a)]

Bromoaromatic	Reaction yield (%) with 2 mequiv of catalyst **13**	Reaction yield (%) with 30 mequiv of catalyst **6**	Reaction yield (%) with 30 mequiv $Pd(PPh_3)_4$
2-Bromo-5-nitropyridine	90	44	93
3-Bromoquinoline	78	60	93
4-Bromoaniline	56	36	39
4-Bromoacetanilide	76	65	77
1-Bromo-4-methoxybenzene	80	59	80
4-Bromoacetophenone	98	68	92

[a)] The reaction was carried out at 80°C for 24 h under nitrogen in toluene/EtOH/H_2O (10:1:1) by using the bromoaromatic (1 equiv.), phenylboronic acid (1,1 equiv.) , Na_2CO_3 (2 equiv.) and the indicated amount of catalyst.

(see Table 2) confirm that catalyst **13** is considerably more active than, for example **6**. In our opinion, catalyst **13** is an interesting alternative to $Pd(PPh_3)_4$ in the Suzuki reaction.

Acknowledgement. We are grateful to Drs D. Clérin and O. Jentzer (ICMD, Mulhouse) for helpful discussions, to the Centre National de la Recherche Scientifique (UPRES-A Q7015), for financial support, and to the undergraduate students who worked with enthusiasm and dedication during the early stages of this project : E. Banchereau, V. Laplace, P. Masson, P. Schott, and specially, M.L. Delahaye and J.L. Grieneisen.

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16. Preparation of catalyst 13 : A solution of $LiPPh_2$ (70 mmol) in THF (50 mL) was added to a suspension of Merrifield polymer (10 g, crosslinked with 2% DVB, Fluka, 0.89 mmol Cl/g by analysis) in THF (100 mL). After 24 h at 25°C under N_2, acetone/H_2O (3:1, 80 mL) was added; the polymer was recovered by filtration, washed successively with H_2O, acetone, $CHCl_3$, benzene and ether. A suspension of this polymer in 100 mL ethanol/benzene (2:1) was then refluxed for 24 h. After filtration this treatment was repeated 4 times with fresh volumes of solvent to ensure complete removal of the soluble fractions of the polymer. The polymer was then dried at 60°C under vacuum. It contained 2,15% P (0.69 mmol/g) and less than 0.2% Cl. To a suspension of 10 g of this polymer in benzene, $Pd(PPh_3)_4$ (0.35 g, 0.30 mmol) was added and the mixture was heated at reflux under N_2 for 26 h. After filtration the yellow polymer was washed successively with ethanol, ether and dried.