First Application of Secondary Phosphines as Supporting Ligands for the Palladium-Catalyzed Heck Reaction: Efficient Activation of Aryl Chlorides

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Received: February 19, 2002; Accepted: March 28, 2002

Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de/

Abstract: Secondary dialkylphosphines were successfully used for the first time as efficient supporting ligands for the palladium-catalyzed Heck reaction of electron-rich and electron-poor aryl chlorides with olefins such as acrylate, ethylene, styrene, and *n*-butyl vinyl ether. The yields with HP(*t*-butyl)$_2$ and HP(adamantyl)$_2$ were comparable or better than those obtained with known systems of tertiary phosphines such as P(cyclohexyl)$_3$ and P(*t*-butyl)$_3$, especially at a catalyst loading of <1 mol %. In comparison with tertiary phosphines, the secondary phosphines have the advantage of being readily available at low cost on a technical scale, and are comparable with respect to handling and oxygen sensitivity.

Keywords: arylation; C-C coupling; Heck reaction; palladium; secondary phosphine

The palladium-catalyzed Heck reaction of aryl halides is an important method in organic synthesis, and many new catalysts have been developed in order to allow new transformations, to expand the scope of the reaction, use cheaper starting materials, or to improve the catalytic activity.[1] One crucial factor for a successful catalytic system is the choice of the ligand, and most frequently tertiary phosphines are used. The activation of aryl chlorides was studied intensely by several research groups in recent years.[2] Up to now, sterically hindered and electron-rich tertiary phosphines were the most successful ligands for the Heck reaction.[3] Despite considerable progress, the catalyst activity for the Heck reaction of aryl chlorides is still too low and improved systems are urgently needed.

In search of such new systems, we screened a wide variety of supporting ligands for the Heck reaction of 4-chloroanisole and 4-chlorobenzotrifluoride with butyl acrylate using a Chemspeed parallel synthesizer. Besides tertiary phosphines, also secondary phosphines were included.[4] Surprisingly, the palladium complexes of secondary dialkylphosphines gave highly active catalytic systems that were as efficient or better than those with tri-*t*-butylphosphine or tricyclohexylphosphine, and the liquid secondary phosphines were comparable to tertiary phosphines with respect to handling and oxygen sensitivity.

Secondary phosphines like HPNor$_2$ or **1** are easily synthesized from PH$_3$ and the corresponding olefins, and are available in bulk quantities at a relatively low price.[5] Reports about the application of such ligands in transition metal catalysis are very rare,[6] and no example is known for palladium-catalyzed reactions with aryl halides. Here we describe the first application of secondary phosphines as supporting ligands for a palladium-catalyzed reaction.

To demonstrate the efficiency of the secondary phosphines as ligands in the Heck reaction, we reacted butyl acrylate with the highly deactivated 4-chloroanisole as model substrate (Table 1). As Pd source, we used a 20% PdCl$_2$ solution in concentrated HCl. With 1 mol % Pd, the best secondary phosphines were slightly less active than P(*t*-Bu)$_3$, but significantly better than PCy$_3$. When we tried to lower the catalyst loading to 0.5 mol %, the reaction was often not reproducible. Replacing PdCl$_2$ by Pd(OAc)$_2$ solved this problem and at a catalyst loading of 0.5 mol %, the palladium

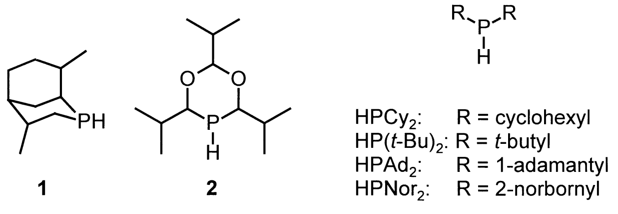
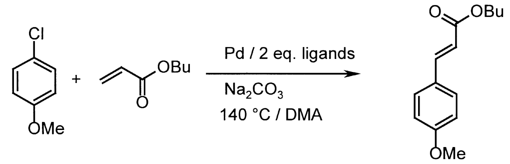


Figure 1. Secondary phosphine ligands used for the Heck reaction.

Table 1. Yields of butyl 4-methoxycinnamate in the Heck reaction of 4-chloroanisole with butyl acrylate using palladium complexes with different phosphines.[a]



Entry	Ligand	GC Yields [%][a]	
		$PdCl_2$[b] (1 mol %)	$Pd(OAc)_2$[c] (0.5 mol %)
1	PCy_3	40	15
2	$P(t\text{-}Bu)_3$	98	49
3	$HPCy_2$	39	17
4	$HP(t\text{-}Bu)_2$	86	53
5	$HPAd_2$	77	52
6	$HPNor_2$	78	34
7	**1**	24	0
8	**2**	64	27

[a] For reaction conditions, see experimental section and supporting information.

[b] Yields determined by GLC after 20 hours (internal standard method).

[c] Average of two runs.

complexes of $HP(t\text{-}Bu)_2$ and $HPAd_2$ gave yields comparable to the Pd-complex of $P(t\text{-}Bu)_3$, one of the most efficient systems currently known.[4a]

Since $HPAd_2$ showed the best performance, the scope of this secondary phosphine in the Heck reaction was investigated (Table 2). At a catalyst loading of 2 mol %, 80 – 100% conversion was observed with a wide variety of electron-poor and electron-rich aryl chlorides (Entries 1 – 9). *ortho*-Substituted aryl chlorides were also successfully coupled. However, they gave lower yields and required higher amounts of catalyst (Entries 10 and 11).

Heteroaryl chlorides were tested with mixed success. 3-Chloropyridine reacted smoothly with butyl acrylate (Entry 12), but 2-chloropyridine gave low conversion. In this case, the main product was the homo-coupled 2,2′-bipyridyl (Entry 13). For unknown reasons, no reaction was observed with 2-chloropyrimidine (Entry 14). With 2-chlorothiophene the conversion was fairly high, however, the product was isolated in only 15% yield, probably due to instability (Entry 15). Other olefins such as butyl vinyl ether, styrene, and ethylene were also successfully reacted with 4-chlorotoluene (Entries 16 – 18).

Table 2. Scope of the Heck reaction with $HPAd_2$ as the ligand.[a]

Entry	Chloroarenes	Olefins[b]	Conversion [%][c]	Isolated yield [%]
1	4-chlorobenzaldehyde	A	100	71
2	4-chloroacetophenone	A	100	66
3	4-chloronitrobenzene	A	100	82
4	3-chlorodimethylaniline	A	100	90
5	ethyl 3-chlorobenzoate	A	100	55 (18)[d]
6	1-chloro-4-(trifluoromethyl)benzene	A	80	76
7	chlorobenzene	A	98	75[e]
8	4-chlorotoluene	A	93	87
9	4-chloroanisole	A	89	71
10	2-chlorobenzonitrile[f]	A	84	50
11	1-chloronaphthalene	A	57	38
12	3-chloropyridine	A	100	84
13	2-chloropyridine[f]	A	53	10 (31)[g]
14	2-chloropyrimidine	A	0	–
15	2-chlorothiophene	A	87	22
16	4-chlorotoluene[f, h]	B	94	74[i]
17	4-chlorotoluene	styrene	76	79
18	4-chlorotoluene	ethylene[j]	94	70[e]

[a] For reaction conditions see experimental section and supporting information.

[b] A: butyl acrylate; B: butyl vinyl ether.

[c] Conversion was determined by GLC (internal standard).

[d] In parentheses: isolated yield of butyl 3,3-diarylacrylate.

[e] Purified by distillation.

[f] With 4 mol % catalyst.

[g] In parentheses: isolated yield of 2,2′-bipyridyl.

[h] With KOAc as base.

[i] Isolated yields of all Heck products. According to GLC, the reaction mixture contained 40% *E*, 15% *Z*, and 19% *p*-methylacetophenone.

[j] With 30 bar ethylene.

The high efficiency of the secondary phosphines is surprising, since secondary phosphines have a much lower basicity and are less sterically hindered than P(*t*-Bu)$_3$. According to the results of Littke and Fu[3c] this should drastically decrease the activity of the catalyst and raises of course questions about the nature of the active palladium catalyst. Various explanations are possible: Even though mononuclear palladium complexes with secondary phosphine ligands are known,[7] palladium can also form phosphido-bridged di- and polynuclear compounds.[8] Moreover, it is well known that secondary phosphines react with aryl halides in the presence of palladium catalysts to form aryl phosphines.[9] Under the reaction conditions, this would result in a Pd complex with a tertiary phosphine of the Alkyl$_2$P-Aryl type. Last but not least, the secondary phosphines might react with the butyl acrylate in a Michael-type reaction to form a P-Alkyl$_3$ type ligand. At the present time, the structure of the active catalyst remains an open question.

In conclusion, we have reported the first palladium-catalyzed reaction with secondary phosphines as supporting ligands. The activity of these catalysts is comparable with the best systems known up to date for the Heck reaction of aryl chlorides. The secondary phosphines are commercially available in bulk quantities at a relatively low price. Therefore, they are an interesting alternative to the tertiary phosphines as ligands for technical applications. Moreover, the rich complex chemistry of secondary phosphines opens up a totally new field of opportunities for the transition metal catalysis since they display a much more diverse coordination chemistry than tertiary phosphines.

Experimental Section

For a detailed description of the experiments, see supporting information.

General Procedure for the Experiments in Tables 1 and 2

To Na$_2$CO$_3$ (0.81 g, 7.6 mmol) and diadamantylphosphine (60.6 mg, 0.2 mmol) in a 50-mL Schlenk tube under argon, DMA (*N,N*-dimethylacetamide, 4 mL), the chloroarene (5 mmol), and *n*-butyl acrylate (0.70 g, 5.5 mmol) were added and the reaction mixture was heated in a oil bath to 140 °C. After 5 minutes, the catalyst solution [0.1 mmol Pd(II) in 0.4 mL DMA prepared by diluting 53 mg of a 20% Pd (w/w) solution in concentrated HCl with 0.35 mL DMA, or by dissolving 22 mg Pd(OAc), in 0.4 mL DMF]. The reaction mixture was stirred for additional 20 hours at 140 °C oil bath temperature. After cooling to room temperature, the reaction mixture was poured into water, and extracted twice with *t*-butyl methyl ether. The organic phases were washed with water, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude material was purified by column chromatography (silica gel, mixtures of EtOAc/hexanes as eluent). For details, see supporting information.

Acknowledgements

*This work was supported by the Novartis Forschungsstiftung. We thank our colleagues Hans-Ulrich Blaser and Benoit Pugin (Solvias AG), Matthias Beller and Wolfgang Mägerlein (IfOK, Rostock, Germany) for general discussion, and Lars Troendlin and Andrea Marti for there careful experimental work. Compounds **1** and **2** were generously provided by Cytec Industries, Niagara Falls, USA (Al Robertson and Olivier Rouher).*

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