Highly efficient Heck olefin arylation in the presence of iminophosphine–palladium(0) complexes

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Abstract

The Heck coupling of aryl bromides with olefins such as styrene or butyl acrylate is efficiently catalysed by the iminophosphine–palladium(0) complex [Pd(dmfu)(P-N)] (dmfu = dimethyl fumarate; P-N = 2-(PPh$_2$)C$_6$H$_4$-1-CH=NC$_6$H$_4$OMe-4) (**1**) in polar solvents. With activated aryl bromides such as 4-bromoacetophenone turnover numbers of up to 20,000 can be achieved at 140 °C in 2 h. The presence of electron-donating groups leads to decreased reaction rates, nevertheless, high substrate conversions can be obtained in reasonable reaction times. Kinetic studies indicate that complex **1** is only a precursor of the actual catalytic species. Experiments aimed to demonstrate the intervention of metallic palladium did not lead to conclusive findings.
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1. Introduction

The Heck arylation reaction is one of the most important methods for the formation of new C–C bonds (Scheme 1) [1].

The most commonly used catalysts are palladium species in combination with phosphines [2] or other neutral ligands such as heterocyclic carbenes [3], and nitrogen [4] or sulfur ligands [5]. Alternatively, there is a wide variety of phosphorus [3b,6], nitrogen [7] and sulfur [8] containing palladacycles which are able to efficiently catalyse the reaction. For an industrial application, the development of "ligand-free" palladium catalytic systems appears particularly interesting [1c,9].

Recently, we have reported that the iminophosphine–palladium(0) complex **1** (Fig. 1) is an highly active catalyst for the Stille [10] and Suzuki [11] cross-coupling reactions.

Spurred by the analogies existing between all these reactions, we have extended our studies to assess the catalytic activity of **1** in the Heck arylation reaction. Herein we wish to report the results of our investigations on the catalytic activity of **1** in the coupling of aryl bromides with two model olefins such as styrene and butyl acrylate.

2. Experimental

All reactions, unless otherwise stated, were carried out under an inert atmosphere (argon). Commercial solvents (Aldrich or Fluka) were purified before the use according to standard procedures [12]. Bromobenzene, 4-bromotoluene, 4-chloroacetophenone, chlorobenzene, styrene, butyl acrylate, *n*-butylamine and thiophenol (Aldrich) were distilled before the use. 4-Bromoacetophenone (Aldrich) was recrystallised from methanol [12]. 4-Bromoanisole, 2-bromo-1,3,5-trimethylbenzene, triphenylphosphine were purchased from Aldrich and used as received. Anhydrous sodium acetate, anhydrous potassium carbonate, anhydrous sodium carbonate

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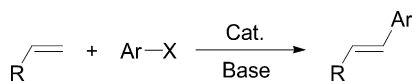
Scheme 1. The Heck reaction.

and mercury were obtained from Fluka. Complex **1** was prepared as described in the literature [13]. The coupling products were identified by their GC–MS and ^{1}H NMR spectra.

GLC analyses were performed on a Agilent 6850 gas chromatograph; GC–MS analyses were performed on a HP 5890 series II gas chromatograph interfaced to a HP 5971 quadrupole mass-detector. ^{1}H NMR spectra were registered on a Bruker Avance 300 NMR spectrometer operating at 300.11 MHz.

2.1. Catalytic experiments

The experiments were carried out in a magnetically stirred glass reactor (50 mL) having an inert gas inlet and a side arm closed with a rubber septum for the withdrawing of GLC samples. In a typical experiment (entry 9 of Table 1), under a nitrogen atmosphere, the reactor was charged with 995 mg (5.0 mmol) of 4-bromoacetophenone, 900 mg (7.0 mmol) of butyl acrylate, 450 mg (5.5 mmol) of NaOAc, 250 μL of a 10^{-3} M solution of complex **1** in dimethylacetamide and 5 mL of dimethylacetamide containing 128 mg (1.00 mmol) of naphthalene as GLC internal standard. The mixture was heated under stirring at 140 °C for 1 h, then it was rapidly cooled at room temperature and the liquid phase analysed by GLC.
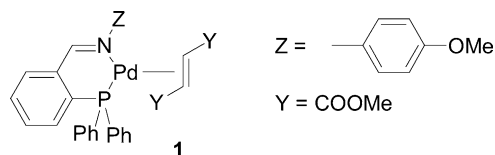
Fig. 1. Chemical structure of complex **1**.

2.2. Kinetic studies and poisoning experiments

In a typical experiment, the reactor was charged with 785 mg (5.0 mmol) of bromobenzene, 728 mg (7.0 mmol) of styrene, 450 mg (5.5 mmol) of NaOAc and 5 mL of NMP containing 128 mg (1.00 mmol) of naphthalene as GLC internal standard. The mixture was heated under stirring at 130 °C, then 500 μL of a 10^{-3} M solution of complex **1** in NMP was quickly introduced in the reactor from the side arm and the course of the reaction monitored by GLC until the substrate conversion was higher than 90%.

In the poisoning experiments, a bromobenzene–styrene reaction mixture prepared according to the procedure above described was allowed to react at 140 °C. After 1 h a sample of the reacting mixture was withdrawn and analysed by GLC to determine the substrate conversion, then the poison was added from the reactor side arm. Fifteen minutes later, the reacting mixture was analysed again in order to verify the progress of the coupling. Afterwards the reaction was monitored by GLC every 30 min for 2 h.

3. Results and discussion

To test the catalytic activity of **1** we used as the model reactions the coupling of 4-bromoacetophenone with styrene or butyl acrylate (Scheme 2).

Preliminary experiments in polar solvents such as dimethylacetamide (DMA) or *N*-methylpyrrolidinone
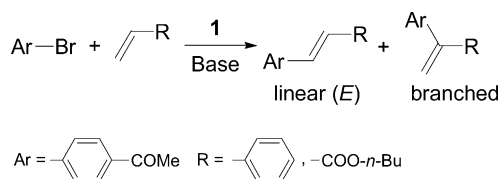
Scheme 2. Heck model reaction.

Table 1

Heck coupling of 4-bromoacetophenone with styrene or butyl acrylate in the presence of complex **1**

Entry	Solvent	Alkene	Base	Time (h)	T (°C)	Yield (%)[a]	TON[b]
1	NMP	Styrene	NaOAc	1	130	16.1[c]	3200
2	NMP	Styrene	NaOAc	1	140	73.7	14700
3	NMP	Butyl acrylate	NaOAc	1	140	63.1	12600
4	NMP	Butyl acrylate	K_2CO_3	1	140	50.4	10000
5	NMP	Butyl acrylate	Na_2CO_3	1	140	10.3	2000
6	NMP	Butyl acrylate	n-Bu$_3$N	1	140	48.7	9700
7	DMA	Styrene	NaOAc	1	140	43.1	8600
8	DMA	Styrene	NaOAc	2	140	98.8	19700
9	DMA	Butyl acrylate	NaOAc	1	140	40.2	8000
10	DMA	Butyl acrylate	NaOAc	2	140	82.4	16500
11	DMA	Butyl acrylate	NaOAc	3	140	99.8	19900
12	*o*-Xylene	Butyl acrylate	NaOAc	1	140	1.8	360

Reaction conditions. 4-Bromoacetophenone: 5.0 mmol; alkene: 7.0 mmol; cat.: 2.5×10^{-4} mmol; [ArBr]/[**1**] = 20,000; solvent: 5 mL; base: 5.5 mmol.

[a] Sum of the linear and branched products determined by GLC using naphthalene as internal standard.

[b] TON: mol of substrate converted/mol of catalyst.

[c] Cat.: 5.0×10^{-4} mmol; [ArBr]/[**1**] = 10,000.

Table 2
Influence of the nature of the aryl bromide

Entry	Aryl bromide	Alkene	Time (h)	Yield (%)[a]	TON[b]
1	C_6H_5Br	Styrene	3	97.7	9700
2	C_6H_5Br	Butyl acrylate	5	49.4	4900
3	C_6H_5Br	Butyl acrylate	24	81.6	8200
4	$4\text{-}CH_3C_6H_4Br$	Styrene	24	93.9	9400
5	$4\text{-}CH_3C_6H_4Br$	Butyl acrylate	24	72.3	7200
6	$4\text{-}CH_3OC_6H_4Br$	Styrene	24	75.5[c]	7500
7	$4\text{-}CH_3OC_6H_4Br$	Butyl acrylate	24	84.7[c]	8500
8	$2\text{-}Br\text{-}1,3,5\text{-}(CH_3)_3C_6H_2$	Styrene	24	2.3[c]	230
9	$2\text{-}Br\text{-}1,3,5\text{-}(CH_3)_3C_6H_2$	Butyl acrylate	24	1.5[c]	150

Reaction conditions. Aryl bromide: 5.0 mmol; alkene: 7.0 mmol; cat.: 5.0×10^{-4} mmol; [ArBr]/[**1**] = 10,000:1; solvent: NMP (5 mL); base: NaOAc (5.5 mmol); T: 140 °C.

[a] Sum of the linear and branched products determined by GLC using naphthalene as internal standard.

[b] TON: mol of substrate converted/mol of catalyst.

[c] Internal standard: *n*-undecane.

(NMP) showed that the reaction requires relatively high temperatures ($T > 120$ °C) in order to proceed with significant rates (see Table 1). At 140 °C the catalyst activity appears very good and the coupling of 4-bromoacetophenone with styrene proceeds giving turnover numbers (mol of substrate converted/mol of catalyst) of up to ca. 20,000 in 2 h. In the reaction of 4-bromoacetophenone with butyl acrylate exclusive formation of the linear (*E*) isomer is observed, instead the coupling of 4-bromoacetophenone with styrene affords a mixture of the linear (*E*) and of the branched isomer in a 95:5 molar ratio (Scheme 2). This ratio does not vary on changing either the solvent or the base used in the reaction.

The use of highly polar solvents is necessary in order to obtain high reaction rates (compare entries 3, 9 and 12 of Table 1), the highest activity being observed in NMP (compare entry 2 with entry 7 and entry 3 with entry 9 of Table 1). As far as the influence of the base is concerned, NaOAc gives the highest reaction rates (compare entries 3–6). Finally it is to remark that even if the catalyst itself is quite air stable, the reaction does not proceeds unless under an inert atmosphere.

In Table 2 are presented the results of coupling experiments of styrene or butyl acrylate with some other representative aryl bromides. As expected, with aryl bromides not bearing electron-withdrawing substituents the catalytic activity decreases; nevertheless remarkable reaction rates are obtained in the reaction of bromobenzene with styrene (entry 1 of Table 2: ca. 10,000 TON in 3 h). The presence of electron-donating groups on the aryl bromide such as a methyl or a methoxy moiety leads to lower reaction rates. However, even working with substrate/catalyst ratios of 10,000:1 high product yields can be achieved in reasonable reaction times (24 h). Only with the strongly deactivated and sterically hindered 2-bromo-1,3,5-trimethylbenzene the catalyst activity is exceedingly low. It is interesting to note that 4-bromoanisole reacts faster with butyl acrylate than with styrene, while the opposite reactivity pattern is observed with all the other aryl bromides.

There is a great interest in developing new catalytic systems able to activate aryl chlorides, owing to the low cost and availability of this class of substrates. Accordingly, as
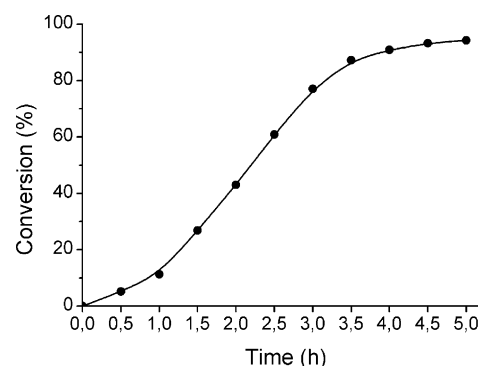

Fig. 2. Conversion vs. time plot for the reaction of bromobenzene with styrene in NMP at 130 °C (see Section 2).

a further step of our study, we investigated the activity of **1** in the coupling of styrene or butyl acrylate with 4-chloroacetophenone or chlorobenzene. Unfortunately, almost no reaction is observed: substrate conversions of ca. 1% are obtained by 24 h even using substrate/catalyst ratios of 500:1.

The reactivity pattern observed, i.e. very low reaction rates with aryl chlorides versus very high rates with aryl bromides bearing electron-withdrawing substituents is suggestive of a reaction mechanism in which the rate-determining step is the oxidative addition of the aryl halide to a Pd(0) species. However, complex **1** is likely only a precursor of the true catalytic species. In fact, preliminary kinetic studies of the coupling of bromobenzene with styrene (see Section 2) reveal that the reaction exhibits an induction period of about half hour during which the complex **1** likely transforms into the catalytically active species.

Indeed, sigmoidal-shaped kinetics such as the one in Fig. 2 can be taken as evidence of the in situ formation of metallic palladium [14], i.e. that the catalysis is actually heterogeneous. During our experiments we did not observe the formation of palladium black, but it is known that often is very difficult to distinguish between homogeneous and heterogeneous catalytic systems, in particular when colloidal metallic nanoparticles are the active catalytic species. In this connection, it is worth to note that when Pd(OAc)$_2$ [9b,9f] or some

palladacycles [6c,7f–h,15] are employed as catalysts in the Heck reaction, there are strong evidences indicating that the actual catalytic species are ligand-free colloidal palladium nanoparticles or clusters and that the starting palladium complex just acts as a catalyst precursor. Therefore, in order to substantiate the intervention of colloidal palladium species in the present case, we deemed appropriate to get a deeper insight on the nature of the catalysis with some poisoning experiments (for a leading review of this subject, see Ref. [14]). Indeed, if the actual catalytic species is a metal particle it would be expected that the addition of a Hg drop or of neutral molecules such as PPh$_3$, CS$_2$ or thiophene, able to strongly bind to the particle surface, would stop the reaction [14].

Unfortunately, our experiments led to conflicting results leaving the question about the nature of the true catalytic species without a clear-cut answer. In fact, the addition of a small Hg drop (ca. 600 or 1000 equivalents with respect to complex **1**) to a reacting mixture of bromobenzene and styrene leads to immediate suppression of the catalysis supporting the possible intervention of metal nanoparticles. On the other hand, no effect follows the addition of PPh$_3$ (0.05 or 0.10 equivalents) or of thiophenol [16] (0.05 or 0.10 equivalents) to reacting mixtures of bromobenzene and styrene.

4. Conclusions

In conclusion, the iminophosphine–palladium complexes are highly active catalyst precursors for the Heck coupling of aryl bromides with terminal olefins. The catalyst efficiency compares well with that of other highly active catalysts, even if the catalysis appears particularly sensitive to steric hindrance on the aryl group. Further studies are in progress in order to determine the effect of the structure of the catalyst (effect of the nature of the groups Z and Y in Fig. 1) and gain evidences on the nature of the actual catalytic species and the reaction mechanism.

Acknowledgements

References

[1] Leading reviews on the Heck reaction: (a) R.F. Heck, in: B.M. Trost, I. Fleming (Eds.), Comprehensive Organic Synthesis, vol. 4, Pergamon Press, Oxford, 1991;
(b) S. Bräse, A. de Meijere, in: F. Dieterich, P.J. Stang (Eds.), Metal Catalyzed Cross Coupling Reactions, Wiley, New York, 1998 (Chapter 3);
(c) G.T. Crisp, Chem. Soc. Rev. 27 (1998) 427;
(d) I.P. Beletskaya, A.V. Cheprakov, Chem. Rev. 100 (2000) 3009;
(e) C.E. Tucker, J.G. de Vries, Top. Catal. 19 (2002) 111;

(f) A.B. Dounay, L.E. Overman, Chem. Rev. 103 (2003) 2945.
[2] (a) D.H. Valentine, J.H. Hillhouse, Synthesis (2003) 2437, and references therein;
(b) I. Kondolff, H. Doucet, M. Santelli, Tetrahedron Lett. 44 (2003) 8487;
(c) A.F. Littke, G.C. Fu, Angew. Chem. Int. Ed. 41 (2002) 4177, and references therein;
(d) A.F. Littke, G.C. Fu, J. Am. Chem. Soc. 123 (2001) 6989;
(e) A. Zapf, M. Beller, Chem. Eur. J. 7 (2001) 2908;
(f) V.P.W. Bohm, W.A. Herrmann, Chem. Eur. J. 6 (2000) 1017.
[3] (a) H. Palencia, F. Garcia-Jimenez, J.M. Takacs, Tetrahedron Lett. 45 (2004) 3849;
(b) W.A. Herrmann, K. Öfele, D. von Preysing, S.K. Schneider, J. Organomet. Chem. 687 (2003) 229, and references therein;
(c) A.C. Hillier, S.P. Nolan, Platinum Met. Rev. 46 (2002) 50, and references therein;
(d) K. Selvakumar, A. Zapf, M. Beller, Org. Lett. 4 (2002) 3031.
[4] (a) S. Iyer, G.M. Kulkarni, C. Ramesh, Tetrahedron 60 (2004) 2163;
(b) G.A. Grasa, R. Singh, E.D. Stevens, S.P. Nolan, J. Organomet. Chem. 687 (2003) 269, and references therein;
(c) S.B. Park, H. Alper, Org. Lett. 5 (2003) 3209.
[5] (a) D. Yang, Y.-C. Chen, N.-Y. Zhu, Org. Lett. 6 (2004) 1577;
(b) A.S. Gruber, D. Pozebon, A.L. Monteiro, J. Dupont, Tetrahedron Lett. 42 (2001) 7345.
[6] (a) M.-H. Huang, L.-C. Liang, Organometallics 23 (2004) 2813;
(b) M.E. van der Boom, D. Milstein, Chem. Rev. 103 (2003) 1759, and references therein;
(c) C.S. Consorti, M.L. Zanini, S. Leal, G. Ebeling, J. Dupont, Org. Lett. 5 (2003) 983;
(d) J. Dupont, M. Pfeffer, J. Spencer, Eur. J. Inorg. Chem. (2001) 1917, and references therein;
(e) T. Rosner, J. Le Bars, A. Pfaltz, D.G. Blackmond, J. Am. Chem. Soc. 123 (2001) 1848;
(f) S. Gibson, D.F. Foster, G.R. Eastham, R.P. Tooze, D.J. Cole-Hamilton, Chem. Commun. (2001) 779.
[7] (a) C.S. Consorti, G. Ebeling, F.R. Flores, F. Rominger, J. Dupont, Adv. Synth. Catal. 346 (2004) 617;
(b) A.K. Gupta, C.H. Song, C.H. Oh, Tetrahedron Lett. 45 (2004) 4113;
(c) L. Botella, C. Najera, Tetrahedron Lett. 45 (2004) 1833;
(d) A. Schnyder, A.F. Indolese, M. Studer, H.-U. Blaser, Angew. Chem. Int. Ed. 41 (2002) 3668;
(e) G.A. Grasa, A.C. Hillier, S.P. Nolan, Org. Lett. 3 (2001) 1077;
(f) R.B. Bedford, C.S.J. Cazin, M.B. Hursthouse, M.E. Light, K.J. Pike, S. Wimperis, J. Organomet. Chem. 633 (2001) 173;
(g) I.P. Beletskaya, A.N. Kashin, N.B. Karlstedt, A.V. Mitin, A.V. Cheprakov, G.M. Kazankov, J. Organomet. Chem. 622 (2001) 89;
(h) M. Nowotny, U. Hanefeld, H. van Koningsveld, T. Maschmeyer, Chem. Commun. (2000) 1877.
[8] (a) V.V. Thakur, N.S.C. Ramesh Kumar, A. Sudalai, Tetrahedron Lett. 45 (2004) 2915;
(b) A.S. Gruber, D. Zim, G. Ebeling, A.L. Monteiro, J. Dupont, Org. Lett. 2 (2000) 1287;
(c) D.E. Bergbreiter, P.L. Osburn, A. Wilson, E.M. Sink, J. Am. Chem. Soc. 122 (2000) 9058.
[9] (a) C.E. Willans, J.M.C.A. Mulders, J.G. de Vries, A.H.M. de Vries, J. Organomet. Chem. 687 (2003) 494;
(b) A.H.M. de Vries, J.M.C.A. Mulders, J.H.M. Mommers, H.J.W. Henderickx, J.G. de Vries, Org. Lett. 5 (2003) 3285;
(c) Q. Yao, E.P. Kinney, Z. Yang, J. Org. Chem. 68 (2003) 7528, and references therein;
(d) K. Kohler, R.G. Heidenreich, J.G.E. Krauter, J. Pietsch, Chem. Eur. J. 8 (2002) 622;
(e) A. Biffis, M. Zecca, M. Basato, Eur. J. Inorg. Chem. (2001) 1131;
(f) M.T. Reetz, E. Westermann, Angew. Chem. Int. Ed. 39 (2000) 165, and references therein.

[10] A. Scrivanti, U. Matteoli, V. Beghetto, S. Antonaroli, B. Crociani, Tetrahedron 58 (2002) 6881.

[11] A. Scrivanti, V. Beghetto, U. Matteoli, S. Antonaroli, A. Marini, F. Mandoj, R. Paolesse, B. Crociani, Tetrahedron Lett. 45 (2004) 5861.

[12] W.L.F. Armarego, D.D. Perrin, Purification of Laboratory Chemicals, 4th ed., Butterworths-Heinemann, 1996.

[13] S. Antonaroli, B. Crociani, J. Organomet. Chem. 560 (1998) 137.

[14] J.A. Widegren, R.G. Finke, J. Mol. Catal. A 198 (2003) 317.

[15] (a) M.R. Eberhard, Org. Lett. 6 (2004) 2125, and references therein;
(b) C. Rocaboy, J.A. Gladysz, Org. Lett. 4 (2002) 1993.

[16] We used thiophenol in the poisoning experiments owing to its high boiling point which ensures its permanence in the reaction solution at 140 °C..