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A HIGHLY EFFICIENT VERSION OF THE PALLADIUM-CATALYSED ARYLATION OF ALKENES WITH ARYL BROMIDES

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Summary

The palladium-catalysed arylation of alkenes with aryl bromides or iodides is shown to proceed in high yields at very low palladium concentration when carried out in a suitable strongly polar solvent with a carboxylate anion as base. The preferred combination is *N*, *N*-dimethylformamide with sodium acetate. The reaction is markedly dependent on the substituents in the aryl bromide, being favoured by electron-withdrawing groups. Turnover numbers up to 134,000 have been achieved.

Introduction

Mizoroki [1] and Heck [2] have reported the palladium-catalysed arylation of alkenes using aryl bromides and iodides. Heck has studied the reaction in detail and reviews are available [3,4]. These reactions were carried out at relatively high palladium concentrations, typically 1–2 mol% relative to the aryl halide, limiting the turnover numbers attained to a maximum of 100. As Heck has noted [3,4], practical application of the reaction under such conditions is not feasible as the cost would be prohibitive. In attempts to achieve higher turnover numbers, Heck had only limited success [3–5].

In view of the potential application of this reaction for the production of speciality organic chemicals, an improved version is extremely desirable.

We have now discovered a highly efficient variant of the Heck reaction [6] permitting in suitable cases the attainment of turnover numbers of up to 134,000, and we report here our findings.

Results

We have found that the Heck reaction can be carried out in high yields in short to moderate reaction times at palladium concentrations as low as 0.0005 mol% relative to aryl halide, by using an appropriate combination of base and solvent. The preferred bases are salts of carboxylic acids and are used in conjunction with

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strongly polar solvents, generally *N*,*N*-disubstituted amides. The combination normally used was anhydrous sodium acetate and *N*,*N*-dimethylformamide (DMF). The use of organic bases (tertiary amines) in DMF, or of sodium acetate in weakly polar solvents (alcohols, nitriles) did not lead to significant improvements. Palladium(II) acetate together with triphenylphosphine or tri(*o*-tolyl)phosphine was used as catalyst. In some cases (below) a phosphorus ligand was not needed.

Initial studies were carried out using the reaction of 4-bromobenzaldehyde and acrylonitrile as model system.

Table 1 shows the results obtained with various combinations of solvents and bases using 0.01 mol% diacetatobis[tri(*o*-tolyl)phosphine]palladium(II) as catalyst. Zero yields were obtained using sodium acetate in the solvents formamide, *N*-methylformamide, acetic acid, tetramethylurea and dimethylsulphoxide and with sodium bicarbonate, sodium trifluoroacetate or sodium phenoxide in DMF. On this basis, sodium acetate and DMF were chosen for further work.

Variation of the reaction temperature from 120°C to reflux gave best results at 130°C which was used in all subsequent experiments. A ten per cent excess of alkene and base relative to aryl halide was also found to give the best results. Variation of the concentration of the aryl halide over the range 1–5 *M* had little effect. A concentration of 2.5 *M* was generally used.

The effect of varying the phosphorus ligand is shown in Table 2. At 0.01 mol% palladium the effect is mainly on reaction time, but at 0.005 mol% tri(*o*-tolyl)phosphine gave the best results and was therefore preferred. As the differences are small, the phosphine dependence was again checked using the less reactive bromobenzene, this time with ethyl acrylate (Table 3). Here the beneficial effect of tri(*o*-tolyl)phosphine and triphenylphosphine is readily apparent.

Initial studies showed the reaction to be strongly dependent on the substituents present in the aryl group, electron withdrawing groups favouring the reaction and vice versa. This effect was far more noticeable at the low palladium concentrations

TABLE 1

DEPENDENCE OF THE PALLADIUM-CATALYSED ARYLATION OF ACRYLONITRILE BY 4-BROMOBENZALDEHYDE ON SOLVENT AND BASE (4-bromobenzaldehyde 25 mmol, acrylonitrile 27.5 mmol, base 27.5 mmol. $Pd(OAc)_2$ $[P(o\text{-}Tol)_3]_2$ 2.5 μmol, solvent 10 ml; 130°C

Solvent	Base	Time (h)	Yield (%)	Turnover number [a]
N,*N*-Dimethylformamide	NaOAc	4	88	8,800
N,*N*-Dimethylacetamide	NaOAc	8	58	5,800
N-Methylpyrrolidone	NaOAc	6	50	5,000
Hexamethylphosphortriamide	NaOAc	8	72	7,200
N,*N*-Dimethylformamide	LiOAc	8	65	6,500
N,*N*-Dimethylformamide	NaOBz [b]	5	74	7,400
N,*N*-Dimethylformamide	NaO_2CH	5	30	3,000

[a] Mol product formed/Mol catalyst used. [b] Bz is benzoyl.

TABLE 2

EFFECT OF PHOSPHORUS LIGANDS ON THE PALLADIUM-CATALYSED ARYLATION OF ACRYLONITRILE WITH 4-BROMOBENZALDEHYDE (4-bromobenzaldehyde 25 mmol, acrylonitrile 27.5 mmol, sodium acetate 27.5 mmol, DMF 10 ml; 130°C)

$Pd(OAc)_2$ (mol%) [a]	Ligand	Ratio P/Pd	Time (h)	Yield (%)	Turnover number
0.01	none	–	10	78	7,800
0.01	PPh_3	4	9	84	8,400
0.01	$P(o\text{-Tol})_3$	2	4	89	8,900
0.01	$P(o\text{-Tol})_3$	8	4	90	9,000
0.01	PBu^n_3	4	4	87	8,700
0.01	$P(OPh)_3$	4	6.5	85	8,500
0.005	$P(o\text{-Tol})_3$	4	8	87	17,400
0.005	PBu^n_3	4	7	72	14,400
0.005	$P(OPh)_3$	4	7	65	13,000

[a] Relative to aryl bromide.

used there than at 1–2 mol%, but it has previously been remarked upon by Heck [7]. In order to demonstrate more clearly this effect we have measured the initial rates (as catalytic activities) and the turnover numbers for an extended series of aryl bromides using ethyl acrylate as alkene (Table 4). Also included for purposes of comparison is the reaction of 4-chlorobromobenzene with ethyl acrylate using *p*-xylene as solvent and tri-n-butylamine as base. Although the initial catalytic activity here is just over sixteen times greater for DMF/sodium acetate than for *p*-xylene/tri-n-butylamine, comparison of the rates of oxidative addition of 4-chlorobromobenzene to tetrakis(triphenylphosphine)palladium(0) at 70°C in the two solvents gave a rate in DMF only three times that in *p*-xylene. No base was present in these stoicheiometric reactions.

As can be seen from Table 4, the initial activity varies by more than two orders of magnitude. 4-Bromonitrobenzene was originally included in this series but induction periods of 20–40 min were observed and it was therefore omitted. After the induction period, however, it reacted rapidly in high yields even without a phosphorus ligand as would be expected from the strongly electron-withdrawing nature of the nitro group. These reactions were carried out at an aryl bromide concentration of 1 *M* to ensure that the product remained in solution throughout the reaction. Methyl 4-bromo benzoate was omitted from the series as the product separated out

TABLE 3

EFFECT OF PHOSPHORUS LIGANDS ON THE PALLADIUM-CATALYSED ARYLATION OF ETHYL ACRYLATE BY BROMOBENZENE (Bromobenzene 25 mmol, ethyl acrylate 27.5 mmol, sodium acetate 27.5 mmol, palladium acetate 2.5 μmol, phosphorus ligand 10 μmol, 130°C, 8 h)

Ligand	Yield (%)	Turnover number
PPh_3	65	6,500
$P(o\text{-Tol})_3$	68	6,800
PBu^n_3	18	1,800
$P(OPh)_3$	11	1,100

TABLE 4

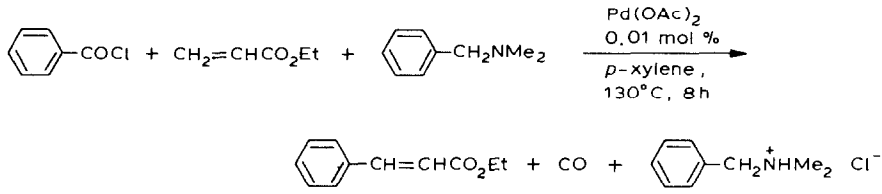
EFFECT OF SUBSTITUENTS ON THE PALLADIUM-CATALYSED ARYLATION OF ETHYL ACRYLATE WITH ARYL BROMIDES (Conditions, see Experimental)

Substituent	Time (h)	Yield [a] (%)	a_0 [b]	Turnover number
2-CN	4	78	245	7,800
3-CN	3	99	413	9,900
4-CN	1	97	466	9,700
4-CHO	1.67	94	301	9,400
4-Cl	7	76	228	7,600
4-F	24	53	72,2	5,300
H	24	50.5	38.3	5,050
4-Me	24	11.6	3.44	1,160
4-Cl [c]	7	6.5	14	650

[a] Determined by gas chromatography. [b] Initial catalytic activity (Mol product/mol catalyst/min). [c] In *p*-xylene with tri-n-butylamine as base.

even at this concentration. 4-Bromo-*N*,*N*-dimethylaniline gave under these conditions a yield of only 10% after 24 h. The initial activity was not measured. The significant reduction in a_0 for 2-bromobenzonitrile we attribute partly to steric effects and partly to coordination of the cyanide group to palladium.

In view of the limited reactivity of aryl bromides not having electron-withdrawing substituents, palladium-catalysed arylation of alkenes with such aryl derivatives at low palladium concentration is in many cases better carried out using the corresponding aroyl chloride (Blaser reaction), a reaction which we have previously reported [8]. Thus the following reaction may be compared with that of bromobenzene in Table 4.



This reaction achieves a turnover number of 8100, the initial activity being 68.3 min^{-1}.

The arylation of various activated alkenes with 4-bromobenzonitrile is compared in Table 5. The initial activity was very strongly dependent on the activating group, though the yields were in all cases reasonable. Table 6 shows the kind of turnover numbers that can be achieved. They are high enough for the palladium price to be a negligible factor in these reactions.

The products of these reactions are exclusively the *E*-isomers, with the exception of those derived from acrylonitril, where up to one third of the product has the *Z*-structure. The factors controlling the stereochemistry of palladium-catalysed arylations have been discussed elsewhere [7,9].

Heck has also reported the reaction of aryl bromides with ethylene to give styrene derivatives [10]. The corresponding stilbenes were also formed. We have shown that,

TABLE 5

PALLADIUM-CATALYSED ARYLATION OF ACTIVATED ALKENES BY 4-BROMOBENZONITRILE (Conditions, see Experimental)

Alkene	Time (h)	Yield [a] (%)	a_0 [b]	Turnover number
CH_2=$CHCO_2Et$	1	97	466	9,700
CH_2=CHCN	3	87	118	8,700
CH_2=CHC_6H_5	4	61	60.5	6,100

[a] Determined by gas chromatography. [b] See Table 4.

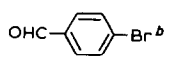
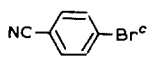
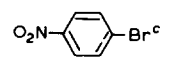
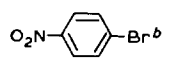
using aroyl chlorides, the reaction can be steered by control of the ethylene pressure to give either stilbene or styrene derivatives with good selectivity [11]. A similar situation was found here. At normal pressure, stilbene derivatives were formed almost exclusively. At raised pressure, the styrene derivatives predominate. The substituent effect in the aryl group is similar to that with activated alkenes (Table 7).

Whereas the formation of stilbenes and the arylation of the activated alkenes described above proceeded cleanly and reproducibly, with the exception on the induction periods observed with 4-bromonitrobenzene, the formation of styrene derivatives did not. Reactions under ethylene pressure generally showed induction periods, gave yields of unsatisfactory reproducibility, were rapid once started but ceased well before complete conversion of the aryl bromide had occurred. The latter point is an especial problem, as we have found no convenient, efficient method for separating the resultant styrene from its parent aryl bromide. The formation of styrene derivatives by this method is therefore of rather limited practical value at the moment.

Some of these reactions have been carried out on scales of up to five moles,

TABLE 6

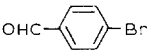
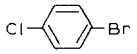
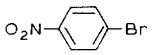
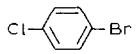
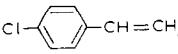
PALLADIUM-CATALYSED ARYLATIONS OF ACTIVATED ALKENES WITH ARYL BROMIDES AT VERY LOW CATALYST CONCENTRATION (Aryl bromide 50 mmol, alkene 55 mmol, sodium acetate 55 mmol, palladium acetate (see table), tri(*o*-tolyl)phosphine (P/Pd = 4), DMF (see notes *b* and *c*), 130°C)

Aryl bromide	Alkene	$Pd(OAc)_2$ (mol%) [a]	Time (h)	Yield (%)	Turnover number
 [b]	CH_2=CHCN	0.001	24	79	79,000
 [c]	CH_2=CHC_6H_5	0.001	32	65	65,000
 [c]	CH_2=$CHCO_2Et$	0.001	5	81	81,000
 [b]	CH_2=$CHCO_2Et$	0.0005	6	67	134,000

[a] Relative to aryl bromide. [b] Aryl bromide 2.5 *M*. [c] Aryl bromide 1 *M*.

TABLE 7

PALLADIUM-CATALYSED ARYLATION OF ETHYLENE GIVING STILBENE AND STYRENE DERIVATIVES (Aryl bromide 50 mmol, ethylene (see table), sodium acetate 55 mmol, palladium acetate 5 μmol, tri(*o*-tolyl)phosphine 20 μmol, DMF 20 ml; 130°C)

Aryl bromide	Ethylene pressure (atm)	Time (h)	Product	Yield (%)	Turnover number
	1 [a]	8	Stilbene deriv.	75	15,000
	1 [a]	8	Stilbene deriv.	78	15,600
	1 [a]	8	Stilbene deriv.	91	18,200
	10 [b]	6		52	5,200

[a] Absolute pressure. [b] Gauge pressure (at 130°C).

without alteration of performance. Aryl iodides also reacted extremely well under these conditions, but were not studied in detail in view of their much higher cost.

Discussion

Heck has proposed a mechanism for the reaction [3] involving oxidative addition of the aryl bromide to palladium(0), insertion of alkene into the palladium–aryl bond, elimination of a palladium(II) hydride with formation of the product and regeneration of palladium(0) by reaction of the hydride with the base.

The substituent effect in the aryl bromides is similar to that previously observed qualitatively for the oxidative addition of aryl halides to tetrakis(triphenylphosphine)palladium(0) [12]. The use of stoicheiometric reactions as models for catalytic processes is decidedly questionable, but the relative rates of the stoicheiometric oxidative addition of 4-chlorobromobenzene in the two-solvents compared with the relative catalytic rates and the fact that both sodium acetate and DMF were needed to produce the catalytic activities and turnover numbers reported here suggest that the oxidative addition is not the limiting factor. Attempts to follow the alkene insertion and subsequent steps in stoicheiometric reactions were prevented by the insolubility of some of the complexes involved.

In addition to its function as base, acetate is a good ligand, and is present in large excess over catalyst. A polar solvent such as DMF would also favour ionic ligand exchange reactions. DMF is a poor ligand but against this must be set the fact that it is present in solvent concentration. The final stage of the mechanism involving the reaction of a palladium(II) hydride with the base to give palladium(0) might be expected to proceed more rapidly with tri-n-butylamine, which has a pK value some two units higher than acetate. However, in the case of acetate, this reaction may well be intramolecular, whereas the coordinating ability of tertiary amines is so low as to make this unlikely for tri-n-butylamine.

As regards the remaining steps of the mechanism, it is difficult to speculate usefully on the effect of DMF and sodium acetate on the alkene insertion and subsequent product elemination steps and a detailed kinetic study may be necessary to resolve the matter fully.

Finally, the difference between the reactions carried out under ethylene pressure and the rest must be stressed. Although we have prepared several styrene derivatives by this method, we have restricted ourselves to one example in Table 7 in view of their limited reproducibility. Ethylene is a far better ligand for palladium(0) than the activated alkenes used and in styrene formation it is used under pressure. It may well be that in this case the palladium(0) species undergoing oxidative addition is an ethylene complex, whereas in other cases only phosphorus ligands are present.

Experimental

Palladium acetate was obtained from Engelhard. Tri(*o*-tolyl)phosphine was prepared by the literature method [13]. Other chemicals were from Fluka or EGA. ^{1}H NMR spectra were recorded with a Varian XL-100, IR spectra with a Perkin–Elmer 157 and mass spectra with Varian CH 5 and CH 7 instruments. Elemental analyses were carried out by the Microanalytical Laboratory at Ciba-Geigy. All products were fully characterised. Gas chromatographic studies were performed with a Varian 3700 instrument using OV 101 and OV 225 columns, and equipped with a Shimadzu Chromatopac ElA integrator.

Except for the work-up of reaction mixtures, all operations were carried out under argon. In view of the low catalyst concentrations, stock solutions were used. These were freshly prepared for each reaction and used only once.

General procedure

(Preparation of ethyl 4-cyanocinnamate, Table 4). Catalyst solution: To *N*,*N*-dimethylformamide (20 ml) was added under argon palladium acetate (0.02244 g, 10^{-4} mol) and tri(*o*-tolyl)phosphine (0.1216 g, 4×10^{-4} mol). The mixture was stirred at room temperature until homogeneous (ca. 5 min) and was then ready for use.

Reaction mixture: A reflux apparatus, having a three-necked flask equipped with a thermometer and an argon inlet-tube, an argon bubbler for the condenser and arranged for magnetic stirring was used. To *N*,*N*-dimethylformamide (49 ml) was added diethyleneglycol di-n-butylether (2 g, GC standard) 4-bromobenzonitrile (9.1 g, 50 mmol), anhydrous sodium acetate (4.51 g, 55 mmol) and ethyl acrylate (5.96 g, 55 mmol). After 5 min, the inlet-tube was replaced by a stopper and argon was passed over the condenser. The reaction mixture was then heated to 130°C and catalyst solution (1 ml) was added by pipette. Circa 0.2 ml samples were removed as required for gas chromatography.

In reactions where it was not intended to measure the initial activity, the GC standard was omitted and the catalyst solution was added to the reaction mixture at room temperature. Work-up was achieved by pouring the reaction mixture at room temperature into an excess of water, extracting with methylene chloride or diethyl ether, and drying with magnesium sulphate. After removal of the extraction solvent and DMF, the products were purified by distillation or recrystallisation.

Reactions involving ethylene at normal pressure or above were carried out as previously described [11].

Yields quoted are of the isolated, pure compound, unless otherwise stated.

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