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A COMPARATIVE STUDY OF SOME Pd-CATALYSED HECK REACTIONS IN POLAR- AND AQUEOUS BIPHASIC MEDIA

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A COMPARATIVE STUDY OF SOME Pd-CATALYSED HECK REACTIONS IN POLAR- AND AQUEOUS BIPHASIC MEDIA

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ABSTRACT

A comparative study of some Pd-catalysed reactions was carried out making use of various ligands and catalyst precursors in polar polar/aqueous biphasic media, the results of which assist in the judicious selection of the appropriate reaction conditions for such Heck reactions.

The advent of palladium catalysed reactions in aqueous or biphasic media has brought about a flurry of activity in the area. Various groups have worked in this sphere, and have made some decisive contributions. Primary among these are the contributions to water-soluble ligands.¹ Although most of the ligands revolve around suphonated aryl phosphines,² some other solutions to the problem of the solubilisation of the ligands have been forthcoming. These include cationic ammonium-based systems³ and

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carboxylated ligands.⁴ The recent seminal work of Beletskaya has shown that the need for polar ligands in aqueous reactions is not an absolute.⁵ In these latter cases, $Pd(OAc)_2$ was used without a ligand in pure water or in DMF/H_2O or $HMPA/H_2O$ mixtures. We herein wish to present a comparative study of various reaction conditions (including the presence or absence of ligands) on the outcome of a few Heck reactions in polar or biphasic solvents. This study was carried out as part of our interest in Pd-mediated reactions,⁶ and with the intention of extending some of this work to aqueous reaction media. However, we could find no comparative study in which certain reaction parameters were directly compared, and thus believed that such a study would contribute to the knowledge base of those in, or entering, this field.

As a basic reaction, we selected the Heck reaction between iodobenzene and butyl acrylate (Scheme 1).⁷ Various combinations of polar solvent, solvent-water mixtures, ligand and added base were tested. The results are shown in Table 1. (The arrangement in the table is primarily on the basis of catalyst, and secondarily on the basis of solvent.) The table shows that DMF or DMF/H₂O are almost invariably the solvents of choice for this reaction, and that the origin of the catalyst $[Pd(OAc)_2$ vs. Pd(dba)₂] made little difference to the yield of the reaction in most cases. (In some cases, however, Pd(OAc)₂ proved to be the superior catalyst precursor.)



A similar reaction set was attempted with bromobenzene without much success, presumably due to the lack in reactivity of the bromo-substrate under our reaction conditions. As a result, we made use of 4-bromobenzonitrile as a substrate in subsequent reactions (Scheme 2).⁸ (It is well known that electron-withdrawing substituents on the aryl halide enhance the rate of oxidative addition of the substrate to the Pd atom.)



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Yield Solvent Ligand Pd-catalyst Entry Base (%)TPPTS^b 20% NEt₃ 78 1 MeOH Pd(dba)₂ 2 **TPPTS 20%** MeOH/H₂O Pd(dba)₂ NEt₃ 55 3 MeOH Pd(dba)₂ K₂CO₃ 5 None 4 TPPTS 20% 23 CH₃CN Pd(dba)₂ NEt₃ 5 75 CH₃CN/H₂O **TPPTS 20%** Pd(dba)₂ NEt₃ 6 CH₃CN/H₂O Pd(dba)₂ K₂CO₃ 53 None 7 DMF **TPPTS 10%** Pd(dba)₂ NEt₃ 80 8 DMF/H₂O **TPPTS 10%** Pd(dba)₂ NEt₃ 75 9 **TPPTS 20%** 65 DMF Pd(dba)₂ NEt₃ 10 73 DMF/H₂O **TPPTS 20%** Pd(dba)₂ NEt₃ 75 11 DMF None Pd(dba)₂ NEt₃ 12 DMF/H₂O None Pd(dba)₂ NEt₃ 76 13 DMF/H₂O K₂CO₃ 23 None Pd(dba)₂ 40 14 MeOH **TPPTS 20%** Pd(OAc)₂ NEt₃ 15 **TPPTS 20%** 55 MeOH/H₂O Pd(OAc)₂ NEt₃ 16 MeOH Pd(OAc)₂ K₂CO₃ 15 None 17 **TPPTS 20%** 38 CH₃CN Pd(OAc)₂ NEt₃ 58 18 CH₃CN/H₂O TPPTS 20% Pd(OAc)₂ NEt₃ 19 CH₃CN/H₂O Pd(OAc)₂ K₂CO₃ 35 None 20 DMF **TPPTS 10%** Pd(OAc)₂ NEt₃ 58 NEt₃ 21 DMF/H_2O **TPPTS 10%** Pd(OAc)₂ 85 76 22 **TPPTS 20%** NEt₃ DMF Pd(OAc)₂ 23 TPPTS 20% 80 DMF/H₂O Pd(OAc)₂ NEt₃ 98 24 DMF None $Pd(OAc)_2$ NEt₃ 95 25 DMF/H₂O None $Pd(OAc)_2$ NEt₃ 26 DMF/H₂O Pd(OAc)₂ K₂CO₃ 73 None

Table 1. Reaction Conditions^a and Isolated Yields for the Heck Reaction

^a Standard reaction conditions: iodobenzene, butyl acrylate (1 eq.), solvent (mixtures are 1:1 v/v), base (1.5 eq.), catalyst (0.1 eq.), 80° C, 24 h.

^b TPPTS = trisodium 3,3',3''-phosphinidyne(benzenesulphonic acid).

The results of those reactions are displayed in Table 2. Reactions were carried out in DMF or in DMF/H₂O due to superiority of these solvents over the others tested. It is clear from the table that higher reaction temperatures were required to effect a satisfactory reaction. The difference in yield when increasing the temperature from 90 to 100 to 110° C was the most striking feature displayed in this comparison. Of equal mention is the lack of reactivity of the substrate in the absence of ligand (Entries 6–8).



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Table 2. Outcome of the Reaction^a of 4-bromobenzonitrile and Butyl Acrylate Under Pd-catalysis

Entry	Solvent	Ligand	Pd-catalyst	Temp. °C	Yield (%)
1	DMF	TPP ^b 20%	$Pd(OAc)_2$	90	29
2	DMF	TPP 20%	$Pd(OAc)_2$	100	74
3	DMF	TPP 20%	$Pd(OAc)_2$	110	83
4	DMF	TPPTS 20%	$Pd(OAc)_2$	110	64
5	DMF/H ₂ O	TPPTS 20%	$Pd(OAc)_2$	110	48
6	DMF	None	$Pd(OAc)_2$	110	10
7	DMF/H ₂ O	None	$Pd(OAc)_2$	110	5
8	DMF	None	$Pd(dba)_2$	110	4

^a Standard reaction conditions: bromobenzonitrile, butyl acrylate (1 eq.), solvent (mixtures are 1:1 v/v), base (1.5 eq.), catalyst (0.1 eq.), 24 h. ^b TPP = triphenylphosphine.

The results detailed above shed some light on the influence of certain variations in the reaction conditions on the Heck reaction in a polar or polar/aqueous medium. It seems as though DMF is universally the solvent of choice, and $Pd(OAc)_2$ the catalyst of choice. It is important to note that, while the elegant work of Beletskaya has shown that the presence of a ligand is not necessary in some cases, the current work indicates that a ligand is essential to a successful reaction when working with bromo substrates in polar or aqueous biphasic media. In this regard, some sensitivity in the reaction was shown with regard to the specific ligand employed (compare

TPP and TPPTS, Table 2).

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