Experiment 4

Palladium Catalysed Cross Coupling Reactions

Third Year Advanced Practical Organic Chemistry

EXPERIMENT 4:

PALLADIUM CATALYSED CROSS COUPLING REACTIONS

Aims of the experiment

To prepare a diarylalkyne from an aryl halide and monosubstituted alkyne using palladium catalysis.

Techniques used/learned:

Transition metal catalysis; preparative vacuum sublimation for the isolation of the product.

Introduction

Transition metal mediated reactions are becoming increasingly important in organic synthesis as organic chemists become familiar with the myriad of organometallic mechanisms involved in these processes.¹

Palladium is by far the most developed and used as far as application to organic synthesis is concerned² and indeed homogeneous palladium catalysts are used in the commercial production of acetaldehyde, cinnamates and other products. Palladium undergoes many reactions with organic systems and, apart from the well known hydrogenation and oxidation (Wacker and other²) processes, it acts as a catalyst for many key C—C bond forming reactions.

Three areas are particularly important: the reaction of π -allyl-(η^3 -allyl)palladium cations with nucleophiles, the cross coupling of organometallic reagents (such as organotin, organoboron and organozinc reagents) with organic halides, and the reaction of organic halides (usually aryl/alkenyl halides) with alkenes - the Heck reaction. The first of these was extensively developed by Trost,³ the second by Kumada⁴ and later by Stille,⁵ Suzuki⁶ and others and the last by Heck himself.⁷ The catalytically active component in these reactions is frequently a Pd(0) species. However, the added material is often a Pd(II) salt as in these cases the Pd(0) is generated *in situ* by reduction with the organometal reagent, solvent or some other species in the reaction mixture.

A full account of this fascinating and widely used area of chemistry, including the generally accepted mechanisms, can be culled from the references cited (1-7). It is important to note that the ready oxidative addition of the aryl halides and triflates to the Pd(0) species reverses the conventional concepts of reactivity in aryl systems: in nucleophilic displacement processes, as normally encountered, the alkyl halides are the more reactive. In the palladium catalysed reactions, the alkyl halides are the unreactive species.

In this experiment, 4-nitrobromobenzene is cross coupled with phenylacetylene to give the mixed diarylalkyne.



The product is conveniently purified by vacuum sublimation, a clean and much underused technique.

HAZARD DATA - READ THIS BEFORE GOING ANY FURTHER!

PHENYLACETYLENE:

IRRITATING TO EYES AND RESPIRATORY SYSTEM

FLAMMABLE

Colourless liquid, b.p. 142°C. Immiscible with water. Avoid breathing vapour and skin contact.

Toxic effects:	Harmful by ingestion in quantity. May irritate skin and eyes.
Fire hazard:	Flash point 31°C; extinguish fire with CO ₂ .
Hazardous reactions: Spillage & disposal:	Can react vigorously with oxidising agents Wear face shield, goggles and gloves. Absorb bulk quantities on sand, shovel into containers and remove to a chemical disposal skip. Wash site of spillage with plenty of water and detergent.

1-BROMO-4-NITROBENZENE:

TOXIC BY INHALATION, INGESTION AND BY SKIN CONTACT

Colourless crystals, m.p. 126°C. Immiscible with water. Avoid breathing vapour and skin contact.

Toxic effects:	Very harmful by ingestion in quantity. Irritant of skin and eyes. Danger of cumulative effects.
Hazardous reactions: Spillage & disposal:	May react with oxidising agents Wear face shield, goggles and gloves. Absorb bulk quantities on sand, shovel into containers and remove to a chemical disposal skip. Wash site of spillage with plenty of water and detergent.

TRIETHYLAMINE:

HIGHLY FLAMMABLE IRRATATING TO EYES AND RESPIRATORY SYSTEM

Colourless liquid, ammoniacal odour, b.p. 89°C. Miscible with water. Avoid breathing vapour and skin contact. OEL 40 mgm⁻³.

Toxic effects: Harmful by ingestion causing internal irritation and damage. Extremely irritating to skin and eyes and respiratory system.

Hazardous reactions: Reacts vigorously with oxidising agents.

Spillage & disposal: Wear goggles, laboratory coat, and gloves. Absorb bulk quantities on sand, shovel into containers and remove to a chemical disposal skip. Wash site of spillage with plenty of water.

TRIPHENYLPHOSPHINE:

HARMFUL BY INGESTION AND SKIN CONTACT

Colourless crystals, m.p. 80°C. Insoluble in water. Avoid skin contact. May cause sensitization after skin contact

 Toxic effects:
 Harmful by inhalation, in contact with skin and if swallowed. May cause sensitization with skin contact. Danger of serious health damage after prolonged exposure

Spillage & disposal: Wear goggles, laboratory coat, and gloves. Collect into containers and remove to a chemical disposal skip. Wash site of spillage with plenty of water and detergent.

Experimental Procedure

In a 100 ml 3-necked flask are placed 4-bromonitrobenzene (2.02 g 10 mmol), phenylethyne (1.53 g, 1.65 ml, 1.5 eq.), palladium (II) acetate (2.8 mg, 0.12 mol%), triphenylphosphine (6.6 mg, 0.25 mol%), triethylamine (20 ml) and a magnetic stirrer bar. The flask is fitted with a condenser, attached to a N₂ supply with a pressure relief bubbler, and the two remaining ports stoppered after the flask has been purged with N₂. The solution is stirred and heated gently to 100°C for 75 min. The exothermic reaction will initially cause vigorous boiling, but this will subside as the reaction nears completion.

The reaction mixture is cooled to room temperature and 2*M* hydrochloric acid (42 ml) added. The insoluble product is collected by filtration and dried in a drying pistol overnight. The product is then sublimed at ~115°C at 2-3 mmHg. The sublimate is dissolved in ~70% ethanol/water and left in a fridge overnight to complete crystallisation. The crystals are finally collected and dried *in vacuo*. Record the yield, m.p., i.r. and n.m.r. spectra and give full interpretations of the spectral data.

Write up

The write up should conform to *Organic and Biomolecular Chemistry* style (Title, Abstract, Introduction, Results and Discussion, Experimental, References). Your introduction must include discussion of the following points:

- **1.** The mechanism of the reaction, including a proposal for the initial conversion of palladium (II) to palladium (0).
- 2. One recent (2003 or later) example from the primary literature of the applications of a Heck-type reaction.

References and Notes

- 1. For an excellent general account, see '*Principles and Applications of Organotransition Metal Chemistry*' by J.P. Collman, L.S. Hegedus, J.R. Norton and R.G. Finke, University Science Books/OUP, 1987.
- **2.** For a comprehensive account of palladium in organic synthesis, including full experimental details, see '*Palladium Reagents in Organic Synthesis*' by R.F. Heck, Academic Press, 1985.
- **3.** B.M. Trost and T.R. Verhoeven, in '*Comprehensive Organometallic Chemistry*', eds G. Wilkinson, F.G.A. Stone and E.W. Abel, Pergamon Press, 1982, vol. 8, pp. 799-938.
- 4. T. Hayashi, M. Konishi and M. Kumada, *Tetrahedron Lett.*, 1979, 1871
- 5. J.K. Stille, Angew. Chem. Int. Ed. Engl., 1986, 25, 508.
- 6. N. Miyaura, K. Yamada, H. Suginome and A. Suzuki, *J. Am. Chem. Soc.*, 1985, 107, 972.
- 7. G. Wu, I. Shimoyama and E.I. Negishi, *J. Org. Chem.*, 1991, **56**, 6506.