Available online at www.sciencedirect.com

Tetrahedron

Tetrahedron 61 (2005) 9663–9669

An evaluation of phosphine and carbene adducts of phosphite- and phosphinite-based palladacycles in the coupling of alkyl bromides with aryl boronic acids

Robin B. Bedford,[a,*] Michael Betham,[a] Simon J. Coles,[b] Robert M. Frost[c]
and Michael B. Hursthouse[b]

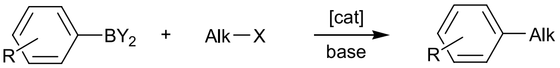
[a]*School of Chemistry, University of Bristol, Cantock's Close, Bristol, BS8 1TS, UK*
[b]*EPSRC National Crystallography Service, Department of Chemistry, University of Southampton, Highfield Road, Southampton, SO17 1BJ, UK*
[c]*Department of Chemistry, University of Exeter, Exeter, EX4 4QD, UK*

Received 12 May 2005; revised 14 July 2005; accepted 15 July 2005

Abstract—A range of palladacyclic catalysts and their phosphine and carbene adducts were tested in the Suzuki coupling of an alkyl bromide with phenylboronic acid and showed modest activity in some cases. Unlike with aryl halide substrates it appears that there is no particular benefit in the use of palladacycles as the palladium source. Initial data indicate that the rate determining step is not the oxidative addition of the alkyl halide substrate, but rather lies later in the catalytic cycle.

1. Introduction

Coupling reactions leading to the formation of new C–C bonds, typically catalysed by ubiquitous palladium complexes, form the bedrock of many contemporary syntheses.[1] Despite the undoubted usefulness of such processes, there are still holes in the general methodologies currently available that limit their applicability. Much research is focused on addressing these shortcomings and the last few years have seen substantial advances. One area that has proved particularly problematic is the extension of Suzuki coupling of aryl boron nucleophiles to alkyl halides bearing β-hydrogens (Scheme 1).[2]



Scheme 1. Suzuki coupling of aryl boron nucleophiles with alkyl halides.

The problems associated with this process are two-fold. Firstly, the oxidative addition of the C–X bond is believed to be more difficult for alkyl halides as a result of the higher bond strength compared with aryl halides.[3] Secondly, β-elimination of the Pd–alkyl complex formed after oxidative addition can lead to competitive alkene formation rather than subsequent coupling, depending on the relative rates of the two processes (Scheme 2).

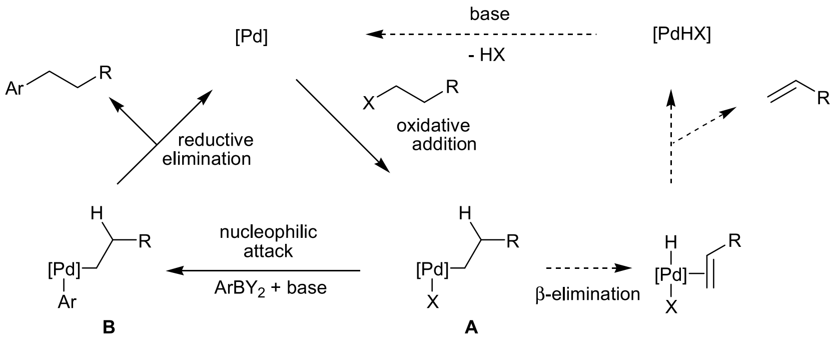
As long ago as 1992 Suzuki and co-workers showed that alkyl iodides could be coupled with alkyl- and aryl-(9-BBN) reagents (9-BBN = 9-borabicyclo[3.3.1]nonane) using [Pd(PPh$_3$)$_4$] as catalyst and K$_3$PO$_4$ as base at 60 °C, giving the coupled products in reasonable yield.[4] By contrast, no activity was seen with alkyl bromides. Fu and co-workers have focused on the problem of using substrates other than alkyl iodides and found that primary alkyl bromides can be coupled with both alkyl- and vinyl-(9-BBN) reagents at rt in THF using palladium acetate/tricyclohexylphosphine as the catalyst and potassium phosphate as a mild base.[5] When the base is replaced with cesium hydroxide and the reactions performed in dioxane at 90 °C, then primary alkyl chlorides can be used as coupling partners with alkyl-(9-BBN) reagents.[6] Both alkyl- and aryl-(9-BBN) reagents can be coupled with alkyl tosylates at 50 °C in dioxane using sodium hydroxide as base employing a catalyst formed in situ from palladium acetate and PMe(^{t}Bu)$_2$.[7] Caddick, Cloke and co-workers have shown that *N*-heterocyclic carbene adducts of palladium, formed in situ from palladium bis(dibenzylideneacetone) and the salt **1**, can

---

Keywords: Alkyl halide; Suzuki reaction; Palladacycles; Coupling; Catalysis.

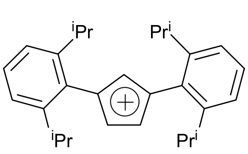
* Corresponding author. Fax: +44 117 925 1295;
e-mail: r.bedford@bristol.ac.uk

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.07.097

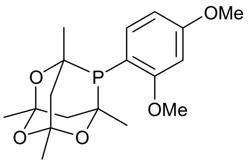


Scheme 2. Simplified catalytic cycles for competing coupling and β-elimination pathways.

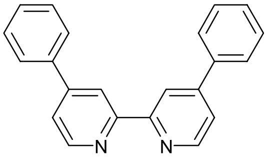
also be used to couple primary alkyl bromides with alkyl- and vinyl-(9-BBN) reagents, using potassium *tert*-butoxide as base at 40 °C in THF.[8]



1



2



3

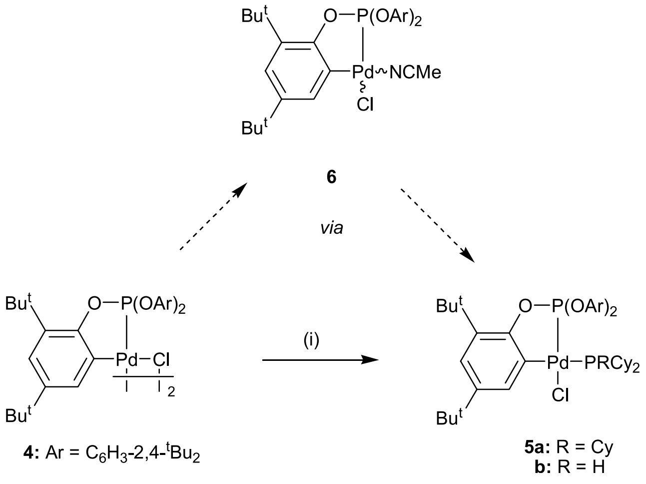
While such reactions are useful, the low commercial availability of alkyl- and aryl-(9-BBN) reagents and their air-sensitivity limits their appeal. In contrast aryl boronic acids reagents are widely available and easily handled. Therefore, Fu and co-workers investigated the possibility of using them as coupling partners with alkyl halides.[9] They found that the catalyst formed in situ from $Pd(OAc)_2$/$PMe(^tBu)_2$ couples primary alkyl bromides with aryl- and vinyl-boronic acids at rt when KO^tBu is used as the base in *tert*-amyl alcohol. Capretta and co-workers recently demonstrated that palladium catalysts containing the phosphaadamantyl ligand **2** can be used to good effect in the rt coupling of primary alkyl bromides and chlorides with aryl boronic acids, using potassium *tert*-butoxide in dioxane.[10] Interestingly, they even found that a moderate yield of coupled product results when the secondary alkyl bromide bromocyclohexane is used as a substrate. Zhou and Fu have also investigated the coupling of secondary alkyl halides with aryl- and vinyl-boronic acids and find that optimum activity is obtained with a nickel-based catalyst formed in situ from $[Ni(COD)_2]$ and bathophenanthroline, **3**, in *sec*-butanol using potassium *tert*-butoxide as base.[11]

We have been interested in the use phosphite- and phosphinite-based palladacyclic catalysts and their phosphine and carbene adducts in a range of Suzuki couplings of aryl halides with aryl and alkyl boronic acids.[12,13] Often the phosphines tested show far better activity when used in conjunction with palladacyclic precursors than classical palladium sources such as palladium acetate or palladium dibenzylideneacetone complexes.[14] We were interested to see whether this would hold true in the Suzuki coupling of alkyl halides with aryl boronic acids (Scheme 1, Y = OH), the results of an evaluative study are presented below.

2. Results and discussion

2.1. Synthesis and characterisation of catalysts

We have previously found that the reaction of the palladacyclic phosphite complex **4** with tricyclohexylphosphine at rt in dichloromethane leads to the formation of the phosphine adduct **5a**. However, under these conditions, the reaction does not go to completion, but rather gives a mixture of **4**, **5a** and PCy_3.[12b] Pure complex **5a** can be synthesized by the reaction of **4** with PCy_3CS_2, however, we wished to design a synthesis that exploits the free phosphine. This proves to be straightforward; the use of acetonitrile as solvent gives clean **5a** from **4** and PCy_3, presumably via the intermediate formation of a mononuclear acetonitrile complex **6** (Scheme 3).



Scheme 3. Synthesis of phosphine adducts of a phosphite palladacycle. Conditions: (i) $PRCy_2$, MeCN, rt, 18 h.