Stereochemistry at the Phosphorus Atom during Palladium-catalysed Formation of Carbon–Phosphorus Bonds and Mechanistic Implications

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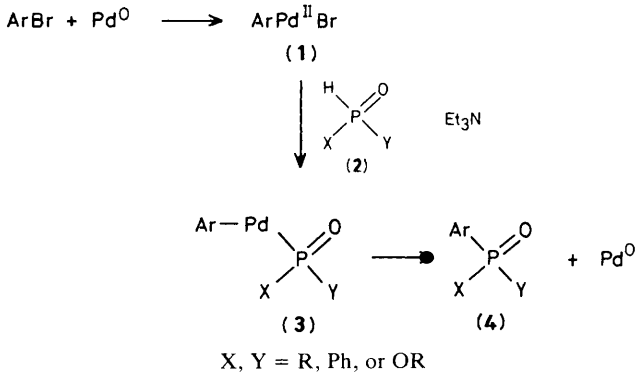
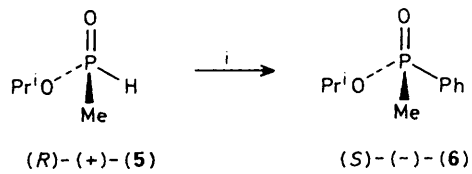
The reaction of (*R*)-(+)-isopropyl methylphosphinate (**5**) with bromobenzene in the presence of Pd^0 catalyst and triethylamine to afford (*S*)-(−)-isopropyl methylphenylphosphinate (**6**) proceeds with complete retention of configuration *via* a front-sided attack by phenylpalladium bromide on the phosphorus nucleophile.

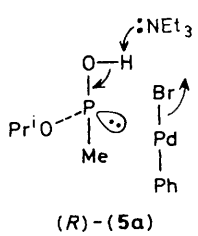
Recently, it has been shown that aryl- and alkenyl-phosphonates,[1] arylphenylphosphinates,[2] alkylarylphosphinates,[3] alkylarylphenylphosphine oxides,[4] alkenylmethyl- and alkenylaryl-phosphinates,[5] as well as alkenyldiphenyl- and alkenylbenzylphenyl-phosphine oxides[6] can be synthesised *via* palladium-catalysed formation of carbon–phosphorus bonds. Moreover, benzoxaphosphacycloalkane derivatives[7] and α-methylenephospholactones[8] have also been synthesized *via* an intramolecular version of this palladium-catalysed route. The formation of the carbon–phosphorus bond is assumed to occur *via* the pathway depicted in Scheme 1.[2] The palladium(0) species undergoes oxidative addition with aryl bromide to give the arylpalladium complex (**1**). Attack of the phosphorus nucleophile (**2**) at the arylpalladium complex in the presence of triethylamine results in the elimination of hydrogen bromide to give the intermediate (**3**) which then undergoes reductive elimination to afford the final product (**4**) and regenerate the Pd^0 species. However, the reaction mode of (**1**) with (**2**) remained unclear in this mechanism. We have therefore studied the stereochemistry of the carbon–phosphorus bond formation in this type of process in order to shed light on the reaction mechanism involved.



Scheme 1. Phosphine ligands are omitted for clarity.



Scheme 2. *Reagents and conditions:* i, PhBr, $Pd(PPh_3)_4$ (5 mol %), Et_3N, 90 °C, 0.5 h.



(*R*)-(+)-Isopropyl methylphosphinate (**5**) {$[\alpha]_D$ +32.32°, lit.,[9] (*R*)-(+), $[\alpha]_D^{27}$ +32.25°} (100% optical purity), which was prepared according to known procedures,[9–11] on treatment with bromobenzene in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium and triethylamine at 90 °C, afforded (*S*)-(−)-isopropyl methylphenylphosphinate (**6**) in 93% optical purity {$[\alpha]_D^{10}$ −50.26°, lit.,[11] (*R*)-(+), $[\alpha]_D^{25}$ +35.7°, 66% optical purity} and in 88% yield (Scheme 2). This clearly demonstrates that the palladium-catalysed formation of carbon–phosphorus bonds occurs with complete retention of configuration at the chiral phosphorus atom.

If the reductive elimination with formation of the carbon–phosphorus bond from intermediate (**3**) in Scheme 1 is assumed to occur in a mode akin to that of the carbon–carbon bond formation which is known to proceed with retention of configuration,[12] then this indicates that attack of the phosphorus nucleophile (**2**) at the arylpalladium complex also takes place with retention of configuration. Consequently, it can be assumed that the reaction of (*R*)-(**5**) with the arylpalladium complex occurs by a front-sided replacement of hydrogen in (*R*)-(**5**), presumably *via* its trico-ordinated tautomer (*R*)-(**5a**).† In other words, the lone electron pair of (*R*)-(**5a**) attacks the Pd atom in the arylpalladium complex, thus facilitating the loss of a proton from (*R*)-(**5a**) and a bromide ion from the arylpalladium complex with the aid of triethylamine; this results in the formation of triethylamine hydrobromide and an intermediate of type (**3**). Reductive elimination then takes place to yield the final product (**6**).

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† It has been reported that the hydrogen in optically active isopropyl methylphosphinate underwent exchange with deuterium in MeOD with retention of configuration *via* a front-sided attack, see ref. 10.