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Improved synthesis of monodentate and bidentate 2- and 3-pyridylphosphines

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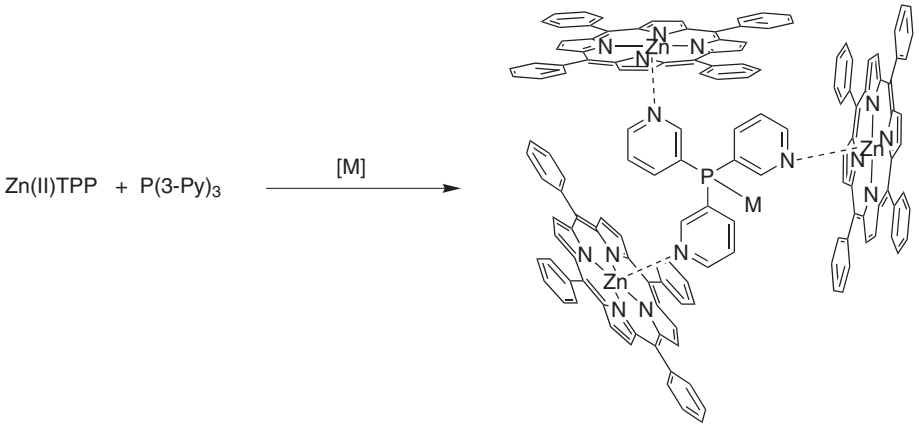
Abstract—Tris(pyridyl)phosphines (2- and 3-pyridyl) and 1,2-bis(di-3-pyridylphosphino)ethane were synthesized in 70–75% yield using a Grignard reagent. The product could be efficiently isolated by solid–liquid extraction with diethylamine.

Complexes of transition metals with pyridylphosphine ligands have been thoroughly investigated because of their interesting coordination behavior and catalytic activity.[1–6] Particular attention has been directed to the monopyridyl PPh_2(2-pyridyl), which has been successfully used in the construction of homo- and heterometallic complexes. Recently, the tris(pyridyl)phosphines (both 3- and 4-pyridyl, **1** and **2**, respectively) have been recognized as valuable building blocks for the construction of supramolecular structures. Particularly, the ability of such compounds to coordinate to hard metals via the pyridyl nitrogen and to a catalytically active transition metal via the phosphorus makes them ideal for building heterometallic architectures (Scheme 1).[7–9] This approach has been explored by our group to effectively encapsulate transition metal catalysts by, for example, Zn(II) *meso*-porphyrins and Zn(II)salphens, which has dramatic consequences for the activity (increases 10-fold) and the selectivity of the catalyst.[10] In addition, the preparation of supramolecular bidentate ligands by selective self-assembly has been used to prepare significantly large catalyst libraries, enabling a fast and efficient catalyst screening simply by changing the building blocks of the supramolecular bidentate.[11–15]



Scheme 1. Encapsulation of transition metal catalyst ([M]) by Zn(II)(*meso*-tetraphenyl porphyrine).

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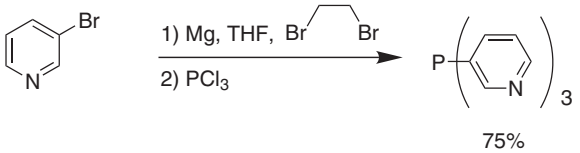
The syntheses of pyridylphosphines as published by Berners-Price et al.,[16] employ an organolithium compound to prepare the pyridyl lithium reagent, which is subsequently allowed to react with a PCl-compound (PCl_3 or $Cl_2PCH_2CH_2PCl_2$) to obtain the corresponding pyridylphosphine. Essential in the lithiation step are maintaining the low reaction temperature (−110 °C) and short reaction times to prevent isomerization of the parent pyridyl lithium compound. Besides the desired product also butyl phosphine compounds are formed, which need to be separated afterwards by column chromatography. According to the authors, multiple columns are required to obtain the pure tris(3-pyridyl)phosphines (isolated yield 45%).[16]

To circumvent these intensive purification steps and to satisfy the need for larger quantities of the pyridylphosphine compounds, a different procedure was explored using the Grignard reaction. Although some reports have appeared for the preparation of such compounds employing a Grignard reagent, the degree of success varies.[2] Particularly, the (3-pyridyl)- and (4-pyridyl)phosphine compounds are notoriously difficult to isolate. Here, we report a general route toward the synthesis of pyridylphosphines using Grignard reagents, giving high yields of the desired product. Since less stringent reaction conditions are required, and the work-up is considerably facilitated by reducing the number of byproducts, this reaction can easily be performed on a multigram scale.

For the preparation of the Grignard reagent, the pure 3-bromopyridine was added to a THF solution containing activated magnesium. Subsequently, the organomagnesium intermediate was allowed to react at −78 °C with PCl_3, forming the desired product (Scheme 2). An attempt to prepare a more pure Grignard reagent (without Wurtz-coupling product) based on the method often employed in dendrimer synthesis[17] yielded only a small amount of Grignard reagent, probably due to the low reactivity of bromopyridine.

From earlier studies it is known that the introduction of pyridyl groups to phosphines increases the solubility in aqueous solution of the corresponding phosphine ligand.[18] The presence of hard cations (such as Mg^{2+}) strongly increases the water-solubility of these compounds. Due to the stronger coordination of the desired product to the magnesium salts (compared to Li-salts) present in the reaction mixture, the standard work-up procedure (extraction with CH_2Cl_2 from aqueous layer) failed and a new one was developed. Several approaches were investigated such as the precipitation of the magnesium salts (by Na_2CO_3, NaOH or NH_4OH) or the chelating of the Mg^{2+}-ions by, for example, Na_2EDTA. None of these attempts were successful since, in every case, new (hard) cations are introduced that have a high tendency to coordinate to the pyridyl nitrogens. These complexes are too water soluble to extract with an organic solvent like dichloromethane or chloroform.



Scheme 2. The synthesis of the tris(3-pyridyl)phosphine via a Grignard reaction.

A suitable solution to this problem is the solid–liquid extraction of the phosphine (and phosphine oxide if formed) with diethylamine (Et_2NH) directly from the quenched and dried reaction mixture. The Et_2NH can successfully compete for the coordination sphere of the main group metal thereby liberating the desired product. The solubility of the Mg^{2+}-salts in pure Et_2NH is negligible and thus only organic products are collected. Since diethylamine is relatively cheap, has a low boiling point, and displays a relative low toxicity, it is ideal for such extractions and can be easily recycled. Of course, the formed phosphine oxide is also in the Et_2NH phase but this can be simply removed by flash column chromatography. Using this route, the reaction can be performed on a multi-gram scale with an overall yield of 75%. This procedure has also been applied to the synthesis of 1,2-bis(di-3-pyridylphosphino)ethane and tris(2-pyridine)phosphine and these compounds were isolated respectively in 70% and 71% yield.

An optimized synthesis of pyridylphosphines via a Grignard reaction has been reported. As is corroborated by the many literature reports, Mg-pyridyl reagents have a low tendency for isomerization and thus tolerate less stringent reaction conditions. The synthetic strategy and work-up procedure, that involves solid–liquid extraction with diethylamine, can be easily extended to other pyridylphosphines.

Acknowledgments

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Supplementary data

General experimental procedures, ^1H, ^{13}C, ^{31}P NMR spectra and GC–MS data are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.02.127.

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