Air-stable phosphine oxides as preligands for catalytic activation reactions of C–Cl, C–F, and C–H bonds*

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Abstract: Studies on the use of easily accessible heteroatom-substituted secondary phosphine oxides as preligands for cross-coupling reactions are described. These air-stable sterically hindered phosphine oxides allow for efficient palladium-catalyzed Suzuki- and nickel-catalyzed Kumada-coupling reactions using electronically deactivated aryl chlorides. In addition, they enable nickel-catalyzed coupling reactions of magnesium organyls with aryl fluorides at ambient temperature, and ruthenium-catalyzed coupling reactions of aryl chlorides via C–H bond activation. Finally, the application of modular diamino phosphine chlorides as preligands for a variety of transition-metal-catalyzed C–C and C–N bond formation reactions employing electron-rich aryl chlorides is presented.

Keywords: secondary phosphine oxide; cross-coupling; C–H bond activation; ruthenium; nickel; palladium.

INTRODUCTION

Transition-metal-catalyzed cross-coupling reactions of aryl halides are important tools for the synthesis of substituted biaryls (Scheme 1) [1]. While aryl iodides and activated aryl bromides can be converted using simple palladium and nickel salts, the transformation of aryl chlorides requires the use of recently developed stabilizing ligands [2]. Predominantly, electron-rich tertiary phophines are employed as ligands [3]. However, either these phosphines or their complexes are often prone to oxidation.
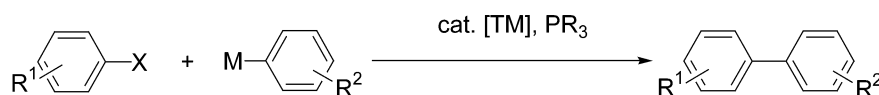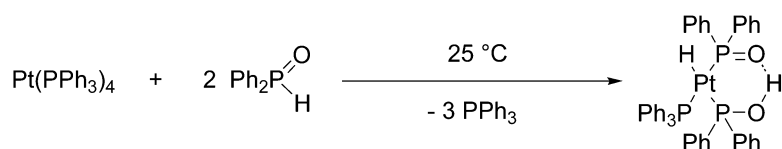

Scheme 1

A notable development was reported by Li, showing that alkyl-substituted phosphine oxides allow for the conversion of aryl chlorides in a variety of different cross-coupling reactions. It is noteworthy

that not only such secondary phosphine oxides, but also their complexes are air-stable [4]. Secondary phosphine oxides are in equilibrium with the corresponding phosphinous acid. In the presence of a late transition metal, this equilibrium is shifted by formation of a P-bound phosphinous acid complex [5]. An illustrative example was reported by Roundhill in the 1970s [6]. Here, the reaction of a secondary phosphine oxide with a platinum(0) precursor leads to the product of formal oxidative addition into the P–H bond of the preligand, which futhermore engages in an intramolecular H bond with another coordinated molecule of the phosphinous acid (Scheme 2).

Alkyl-substituted secondary phosphine oxides are usually prepared starting from the metallated alkyl, thereby limiting the scope of this approach, particularly with respect to the synthesis of enantiomerically enriched preligands [7]. Heteroatom-substituted secondary phosphine oxides, on the contrary, can be directly obtained from the corresponding diamines, diols, or amino alcohols and inexpensive PCl_3 in a one-pot procedure.
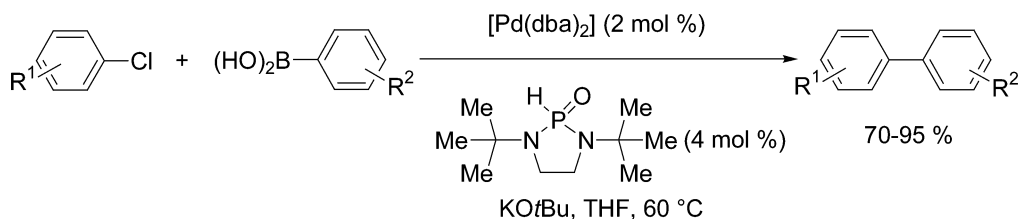

Scheme 2

RESULTS AND DISCUSSION

### Palladium-catalyzed Suzuki reactions with aryl chlorides

We synthesized a number of sterically hindered heteroatom-substituted secondary phosphine oxides and probed them in a variety of cross-coupling reactions. First, we studied their application to palladium-catalyzed Suzuki-type cross-coupling reactions with boronic acids (Scheme 3). We found that even electronically deactivated aryl chlorides are efficiently converted. Also, *ortho*-substituents on the aryl chloride and the boronic acid were tolerated. Heteroaromatic chlorides such as pyridine and isoquinoline derivatives were also efficiently converted [8].

Scheme 3

Nickel-catalyzed Kumada reactions with aryl chlorides and fluorides

Next, we probed air-stable secondary phosphine oxides in the Kumada cross-coupling of aryl chlorides. In a thorough study of around 60 different preligands, Herrmann showed that an *N*-heterocyclic carbene precursor proved most efficient in nickel-catalyzed cross-coupling reactions with aryl chlorides at ambient temperature [9]. Compared with this preligand, a sterically hindered heteroatom-substituted phosphine oxide gave rise, under otherwise identical reaction conditions, to more efficient and more selective catalysis (Scheme 4) [10].
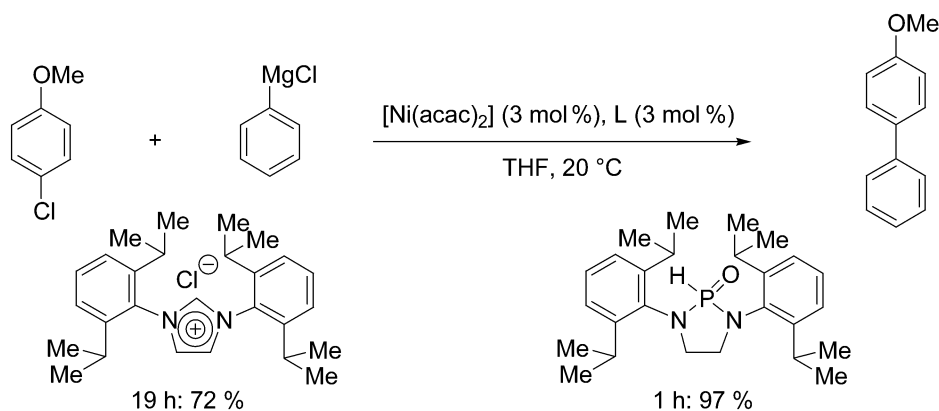
Scheme 4

The catalyst allowed for efficient conversion of a representative set of electron-rich aryl chlorides at ambient temperature. Also, the functionalization of heteroaromatic chlorides led to high yields of isolated products.

Cross-coupling reactions of aryl chlorides are useful transformations for synthetic organic chemistry. The conversion of aryl fluorides, however, is important for the fundamental understanding of the reactivity of very stable bonds, and the selective synthesis of partially fluorinated compounds. Therefore, we probed air-stable secondary phosphine oxides as preligands in Kumada cross-coupling reactions of aryl fluorides (Scheme 5).
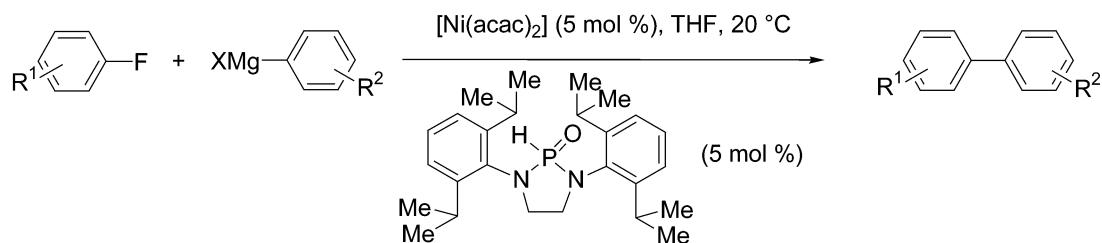
Scheme 5

The sterically congested preligand allowed for efficient conversion of electron-rich aryl fluorides and heteroaromatic fluorides even at ambient temperature (Chart 1) [10].
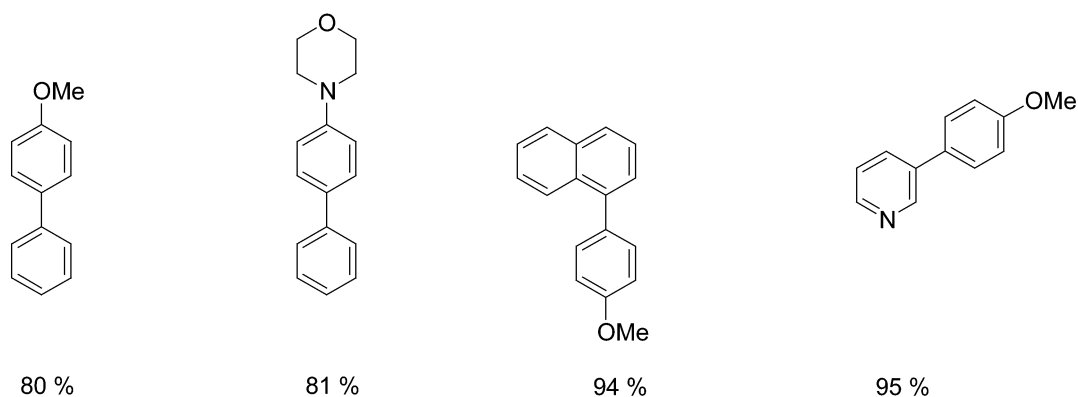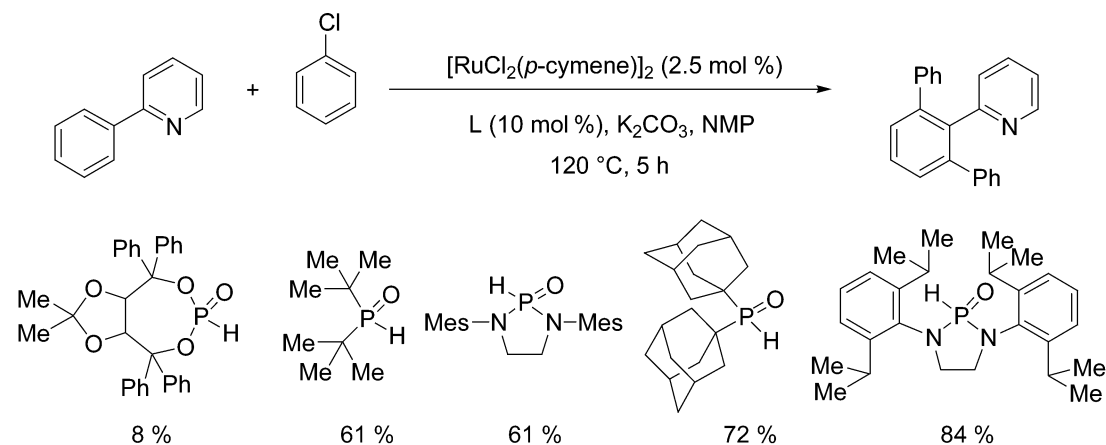
Chart 1

OMe 80 %   81 %   94 %   95 %

Ruthenium-catalyzed arylation via C–H bond functionalization using aryl chlorides

Traditional transition-metal-catalyzed cross-coupling reactions employ organometallic reagents such as organoboron, -magnesium, or -tin species as nucleophiles [1]. These organometallic starting materials are frequently not commercially available, expensive, and give rise to undesired by-products. These problems can potentially be circumvented with protocols for the direct cross-coupling of organic compounds via C–H bond functionalization. Oi, Inoue, and coworkers described a ruthenium-catalyzed regioselective arylation of pyridine and imine derivatives employing PPh$_3$ as ligand [11–13]. While these reaction conditions allowed for the conversion of aryl bromides, a general protocol for ruthenium-catalyzed arylations employing inexpensive, but less reactive aryl chlorides proved elusive.

We found that the use of air-stable phosphine oxides as preligands enabled unprecedented general ruthenium-catalyzed arylation reactions of pyridines through C–H bond activation using aryl chlorides. Sterically hindered preligands proved most efficient (Scheme 6) [14].

$$\text{[RuCl}_2(p\text{-cymene})]_2 \text{ (2.5 mol \%)}$$
$$\text{L (10 mol \%), K}_2\text{CO}_3\text{, NMP}$$
$$120\ °C, 5\ h$$

8 %   61 %   61 %   72 %   84 %

Scheme 6

The optimized catalyst allowed for quantitative conversion of both electron-poor and -rich aryl chlorides with good to excellent yields of isolated products. Importantly, a wide variety of important functional groups, such as an ester, a cyano group, and an enolizable ketone, were tolerated by the catalytic system. Given the practical importance of imines for organic synthesis, phosphine oxides were

probed as preligands in ruthenium-catalyzed functionalization of differently substituted ketimines with aryl chlorides. Subjection of ketimines and aryl chlorides to the reaction conditions yielded selectively the mono-arylated products. The corresponding ketones were isolated after hydrolysis in high yields. Again, electron-poor as well as -rich aryl chlorides could be employed. Not only *meta-*, but also *ortho-*substituted aryl chlorides were efficiently converted (Chart 2). The functional group tolerance of the catalytic system constitutes a valuable asset of the present protocol.
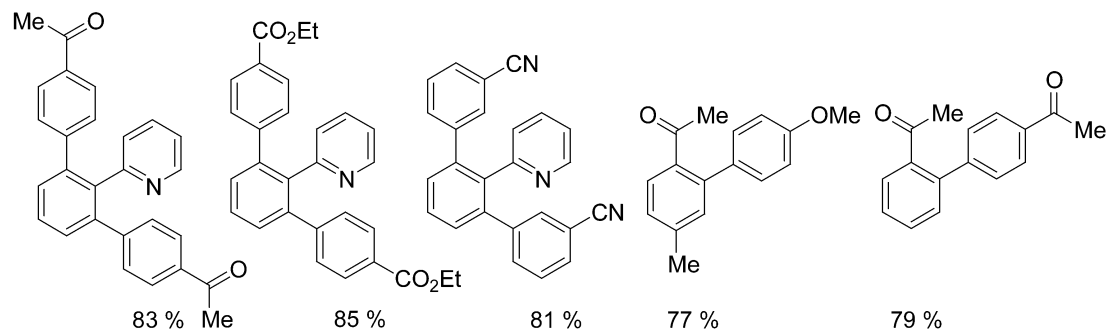

83 %   85 %   81 %   77 %   79 %

Chart 2

Diamino phosphine chlorides as preligands for coupling reactions of aryl chlorides

Finally, we studied the use of heteroatom-substituted phosphine chlorides for cross-coupling reactions. The unprecedented use of a diaminophosphine chloride as a ligand precursor in palladium- and nickel-catalyzed C–C and C–N bond-forming reactions of aryl chlorides was demonstrated (Scheme 7) [8].
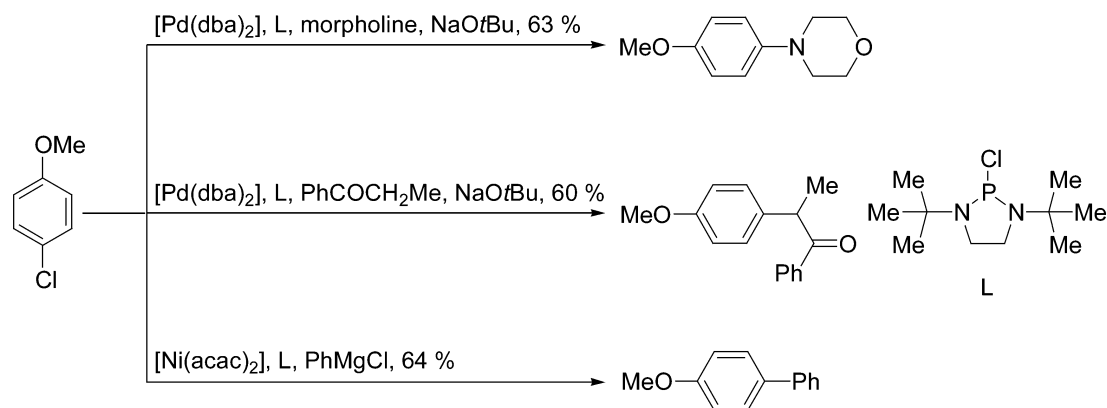
Scheme 7

SUMMARY

Our recent efforts to develop novel preligands for cross-coupling reactions led to a modular set of air-stable diamino- and dioxophosphine oxides that are easily accessible and allow for efficient catalytic activation reactions of C–Cl, C–F and C–H bonds. Studies on the application of these preligands to further transition-metal-catalyzed reactions, such as the Negishi cross-coupling reaction, are in progress.

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