Tetrahedron 71 (2015) 4927–4932

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

The coupling reactions of aryl halides and phenols catalyzed by palladium and MOP-type ligands

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ARTICLE INFO

Article history:
Received 29 January 2015
Received in revised form 23 May 2015
Accepted 28 May 2015
Available online 4 June 2015

Keywords:
Palladium
Coupling reaction
Diaryl ether
Phosphines
o-Xylene

ABSTRACT

Palladium-catalyzed coupling reactions of aryl halides and phenols are described employing the bulky and electron-rich MOP-type ligands. When K_3PO_4 was used as base and toluene as solvent, the catalyst system exhibited high efficiency for the coupling reaction of the activated aryl halides. When NaH was used as base and *o*-xylene as solvent, unactivated aryl halides can be used as substrates.

1. Introduction

Diaryl ethers are common structural motifs in numerous natural products and biologically active compounds.[1] Traditionally, these ethers are prepared by the reaction of aryl halides with sodium or potassium aryl oxides promoted by copper reagents.[2] However, this protocol is often inhibited by high temperatures, stoichiometric amounts of copper, limited substrate scope, and poor functional group tolerance. The transition metal (Cu, Pd and Fe) catalyzed coupling reactions of aryl halides and phenols provide effective access to diaryl ethers.[3] In general, compared to copper catalysts, palladium catalysts are tuned more easily for activating aryl C–X bonds especially for aryl chlorides, and conduct the synthesis of diaryl ethers under relatively mild reaction conditions.[4] Hence, a lot of effort has been devoted to developing efficient palladium catalysts for the transformation.[5]

Using electron-rich, sterically bulky phosphines[6] or *N*-heterocyclic carbene ligands[7] is crucial to realize the palladium catalyzed the cross coupling of electron-deficient, electron-neutral, and electron-rich aryl halides with a variety of phenols. Despite these advances, poor conversions are observed for the coupling reactions of unactivated aryl halides and phenols without an *ortho*-substituent, and electron-deficient phenols were poor substrates.[8] To overcome these limitations, the more sterically hindered aryl dialkyl phosphines (Fig. 1) were synthesized and utilized in the formation of aryl C–O bonds.[9] Although these ligands succeeded in some difficult substrates, the high cost and difficult synthesis of these ligands would potentially prevent the utilization of these catalysts.[9c] In the coupling reaction, base and solvent are requisite components in the catalyst system and influence the catalytic activity.[10] Tuning of the base and solvent in the catalyst system may therefore, provide a readily accessible protocol for the difficult substrates.

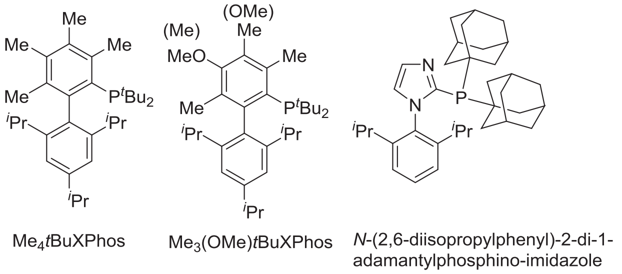

Fig. 1. Structures of sterically hindered phosphine ligands utilized in the palladium catalyzed formation of aryl C–O bonds.

The MOP-type ligands (2-(dialkyl-phosphino)-2′-alkoxy-1,1′-binaphthyls) that are bulky monodentate phosphines with a binaphthyl skeleton and a tunable alkoxy group at the adjacent position of phosphorus atom, have showed high effectiveness for

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http://dx.doi.org/10.1016/j.tet.2015.05.104
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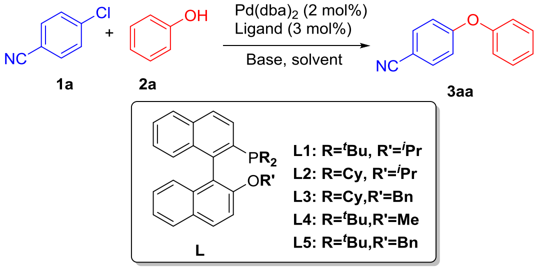
the palladium catalyzed formation of aryl C—N bonds.[11] Herein, we report the efficiency of the MOP-type ligands in the palladium-catalyzed coupling reaction of aryl halides and phenols and the effect of solvents and base in the catalyst system.

2. Results and discussion

We initially chose the coupling reaction of *p*-chlorobenzonitrile (**1a**), an activated aryl chloride, and phenol as the model reaction to examine the use of the MOP-type ligands in the palladium catalyzed formation of aryl C—O bonds. When di-*tert*-butyl(2′-isopropoxy-[1,1′-binaphthalen]-2-yl) phosphane (**L1**) was used as ligand with NaH as base and toluene as solvent, the desired product, 4-phenoxybenzonitrile (**3aa**), was obtained in only 38% yield, and 4,4′-di-CN-biphenyl was formed as the main byproduct (Table 1, entry 1). Replacing NaH with Cs_2CO_3 or K_2CO_3 increased the yield of the diaryl ether (**3aa**) to 95% (entries 2 and 3). When Na_2CO_3 was used as base, a decreased conversion of *p*-chlorobenzonitrile was observed (entry 4). To our surprise, nearly exclusive formation of the diaryl ether (**3aa**) was observed when K_3PO_4 was used as base (entry 5). Using an ethereal solvent such as, THF and DME (dimethoxyethane), resulted in a slightly decreased yield of **3aa**. When $PdCl_2(CH_3CN)_2$ was used as precatalyst, the high activity of the catalyst system remained (entry 9).

Table 1
Optimization of reaction conditions for coupling reaction of *p*-chlorobenzonitrile (**1a**) with phenol (**2a**)[a]



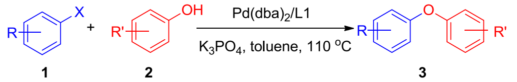
Entry	Ligand	Base	Solvent	Conv. (%)	Yield[b] (%)
1	L1	NaH	Toluene	>99	38
2	L1	Cs_2CO_3	Toluene	>99	95
3	L1	K_2CO_3	Toluene	>99	96
4	L1	Na_2CO_3	Toluene	85	69
5	L1	K_3PO_4	Toluene	>99	>99
6	L1	K_3PO_4	THF[c]	92	84
7	L1	K_3PO_4	Dioxane[d]	>99	72
8	L1	K_3PO_4	DME[e]	>99	82
9[f]	L1	K_3PO_4	Toluene	>99	>99
10	L2	K_3PO_4	Toluene	44	29
11	L3	K_3PO_4	Toluene	<1	<1
12	L4	K_3PO_4	Toluene	>99	>99
13	L5	K_3PO_4	Toluene	>99	>99

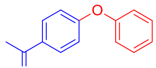
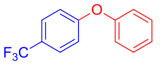
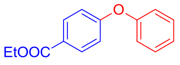
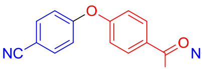
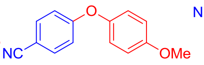
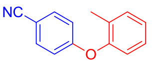
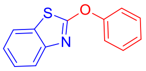
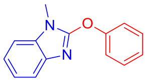
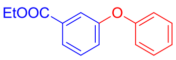
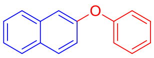
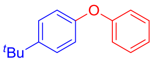
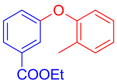
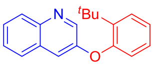
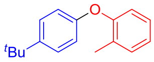
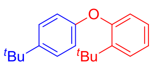
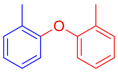
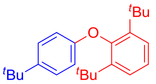
[a] *p*-Chlorobenzonitrile (**1a**) (1.0 mmol), phenol (**2a**) (1.2 mmol), $Pd(dba)_2$ (2 mol %), ligand (3 mol %), base (2.0 mmol), solvent (2.5 mL), 110 °C, 18 h.
[b] Yields determined by GC analysis.
[c] Reaction temperature: 65 °C.
[d] Reaction temperature: 101 °C.
[e] Reaction temperature: 85 °C.
[f] $PdCl_2(CH_3CN)_2$ (2 mol %).

Next, the structural influence of ligands on the catalytic activity was explored. The substituents on the phosphorus atom of the ligands significantly influenced the activity of the catalyst. When the ligand with a dicyclohexylphosphino group (**L2** or **L3**) was used, the catalytic activity decreased greatly (Table 1, entries 10 and 11), while the ligands with bulky di *tert*-butylphosphino group were highly efficient for the formation of aryl C—O bonds (entries 5 and 12, 13). The sterics of the alkyl substituents on the oxygen atom did not appear to affect the catalytic activity. When the alkyl group was isopropyl (**L1**), methyl (**L4**), or benzyl (**L5**), high conversions and yields of the diaryl ether were obtained. This result is in contrast to palladium-catalyzed formation of aryl C—N and C—C bonds in which increasing the steric profile of the dialkylphosphino group or alkoxy group led to an increase in catalyst activity.[11] This difference may be attributed to the absence of hemilabile coordination of the oxygen to the palladium center in the rate-determining step of the coupling of aryl halides and phenols.

Under the optimized conditions in which $Pd(dba)_2$ and **L1** were used as the catalyst, K_3PO_4 as the base, and toluene as the solvent, the scope and limitations of the catalytic system were explored. As shown in Table 2, the activated aryl halides including the chlorides and the bromides were coupled with phenols to generate the desired diaryl ether (**3**) in excellent yield. Even the coupling of the electron-deficient methyl 4-hydroxybenzoate (**2b**) with *p*-bromobenzonitrile occurred in 92% yield. The bulky *o*-methyl phenol was coupled with chlorobenzonitrile (**1a**) to generate the corresponding diaryl ether (**3ad**) in 98% yield. Moreover, the catalytic system showed the good tolerance for functional groups such as ketones, esters, and heterocycles. Reaction of 2-chlorobenzo[*d*]thiazole (**1e**) proceeded smoothly to give the desired product (**3ea**) in 86% yield. However, the coupling reaction provided low yields for electron-neutral aryl halides or aryl halides with electron-withdrawing groups at the *meta*-position. Coupling of ethyl 3-chlorobenzoate (**1g**) with phenol gave the diaryl ether (**3ga**) in 21% yield, while the diaryl ether (**3da**) was obtained in 97% yield when ethyl 4-chlorobenzoate (**1d**) was coupled. The results are similar with that obtained from the reported palladium catalyzed the formation of aryl C—O bonds.[6,8] But the existence of *ortho*-substituent in the substrates, either aryl halides or phenols, increased the yield of diaryl ether significantly regardless of the electronic nature of the aryl halide. Ethyl 3-(*o*-tolyloxy)benzoate (**3ge**) was obtained in 85% yield in the reaction of ethyl 3-chlorobenzoate (**1g**) with *o*-methyl

Table 2
Coupling reactions of aryl halides (**1**) with phenols (**2**) catalyzed by $Pd(dba)_2$/**L1** using K_3PO_4 as base and toluene as solvent[a]



 X=Cl, **3ba**: 94% [b]	 X=Cl, **3ca:** 86%[b]	 X=Cl, **3da:** 97%
 X=Br, **3ab**: 92%	 X=Cl, **3ac:** 98%	 X=Cl, **3ad:** 98%
 X=Cl, **3ea:** 86%	 X=Cl, **3ka:** 46%	 X=Br, **3fa**: 32%
 X=Cl, **3ga**: 21%	 X=Br, **3ha:** 39%	 X=Cl, **3ia:** 7%
 X=Cl, **3ge:** 85%	 X=Br, **3ff:** 93%	 X=Cl, **3ie:** 86% X=Br 96%
 X=Cl, **3if:** 97%	 X=Cl, **3je:** 93% X=Br, 97%	 X=Cl, **3ig:** 20%

[a] Aryl halide (**1**) (1.0 mmol), phenol (**2**) (1.2 mmol), $Pd(dba)_2$ (2 mol%), **L1** (3 mol%), K_3PO_4 (2.0 mmol), toluene (2.5 mL), 18 h, and isolated yield was gave.
[b] $Pd(dba)_2$ (1.0 mol%), Ligand (1.5 mol%).