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Ni(II)/Zn Catalyzed Reductive Coupling of Aryl Halides with Diphenylphosphine Oxide in Water

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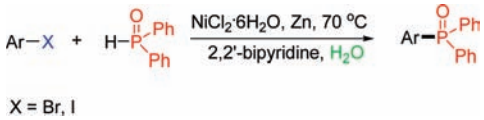
ABSTRACT



P-Arylation in water has been developed via cross-coupling of aryl halides with diphenylphosphine oxide ($Ph_2P(O)H$) and (R_P)-(−)-menthyl benzylphosphinate catalyzed by $NiCl_2 \cdot 6H_2O$/Zn under relatively mild conditions.

Aromatic organophosphorus compounds have attracted considerable interest due to their wide applications in organic synthesis,[1] polymers,[2] medicinal chemistry,[3] and photoelectric materials.[4] The most frequently employed method for their preparations is treatment of $Ph_2P(O)Cl$ with Li or Mg aromatics,[5] which suffers from a lack of tolerance for functional groups. The demand for functionalized aromatic phosphine oxides stimulated extensive studies on P−C bond-forming reactions catalyzed by transition metals,[6] e.g., Pd[7,8] and Cu,[9] but there is still a need for new methods that involve a cheap and environmentally

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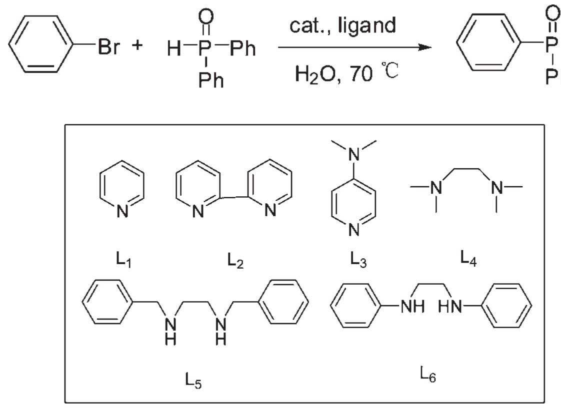
friendly catalyst system. Since nickel has been identified as a useful reagent and catalyst for cross-coupling reactions involving carbon–carbon bonds and carbon–heteroatom bonds,[10] it was suggested that it might provide a useful approach for P-arylation using diphenyl-phosphine oxide ($Ph_2P(O)H$) as a coupling partner.

Recently, the catalysis of organic reactions using water as a solvent has received much attention, and a broad variety of organometallic catalytic reactions have been successfully applied in water.[11,12] Considering this green solvent being cheap, nontoxic, safe, and environmentally benign, as compared with organic solvents, herein we disclose a simple and efficient approach for the synthesis of triarylphosphine oxides under relatively mild conditions by an aqueous reductive coupling of aryl halides, especially aryl bromides, with secondary phosphine oxides in the presence of an inexpensive nickel salt and zinc powder with corresponding ligands.

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	additive	ligand	base	yield (%)[b]
1	$NiCl_2 \cdot 6H_2O$	–	L_1	–	0
2	$NiCl_2 \cdot 6H_2O$	–	L_1	K_2CO_3	0
3	–	Zn	L_1	–	0
4	$NiCl_2 \cdot 6H_2O$	Zn	–	–	0
5	$NiCl_2 \cdot 6H_2O$	Zn	–	K_2CO_3	0
6	$NiCl_2 \cdot 6H_2O$	Zn	L_1	–	79
7	$NiCl_2 \cdot 6H_2O$	Zn	L_1	K_2CO_3	8
8	$NiCl_2 \cdot 6H_2O$	Zn	L_2	–	98
9	$NiCl_2 \cdot 6H_2O$	Zn	L_2	K_2CO_3	18
10	$NiCl_2 \cdot 6H_2O$	Zn	L_2	Et_3N	9
11	$NiCl_2 \cdot 6H_2O$	Zn	L_2	Cs_2CO_3	14
12	$Ni(NO_3)_2 \cdot 6H_2O$	Zn	L_2	–	15
13	$Ni(OAc)_2 \cdot 6H_2O$	Zn	L_2	–	33
14	$NiCl_2 \cdot 6H_2O$	Zn	L_3	–	62
15	$NiCl_2 \cdot 6H_2O$	Zn	L_4	–	36
16	$NiCl_2 \cdot 6H_2O$	Zn	L_5	–	87
17	$NiCl_2 \cdot 6H_2O$	Zn	L_6	–	5
18	$NiCl_2 \cdot 6H_2O$	Zn	L_2	–	97[c]

[a] Reaction conditions: bromobenzene (0.30 mmol), $Ph_2P(O)H$ (0.25 mmol), $NiCl_2 \cdot 6H_2O$ (0.025 mmol), zinc (0.50 mmol), ligand (0.05 mmol), base (0.25 mmol), H_2O (1.0 mL) at 70 °C in air, 15 h. [b] ^{31}P NMR yield. After 15 h, the mixture was concentrated, and 0.5 mL of DMSO was added, followed by ^{31}P NMR. [c] Under nitrogen atmosphere.

At the outset, coupling of bromobenzene with diphenylphosphine oxide was chosen as the model reaction using 0.1 equiv of $NiCl_2 \cdot 6H_2O$ as the catalyst for optimization of the reaction conditions. The influence of bases, ligands, and the source of nickel in the cross coupling reaction was investigated, and the screening of reaction conditions is summarized in Table 1. The reaction gave the desired product, triphenylphosphine oxide, in a 79% yield (^{31}P NMR yield) when the reaction mixture, bromobenzene (0.3 mmol) and diphenylphosphine oxide (0.25 mmol), was stirred in neat water (1 mL) at 70 °C in the presence of $NiCl_2 \cdot 6H_2O$ (10 mol %), zinc powder (0.50 mmol), and 0.05 mmol pyridine for 15 h (Table 1, entry 6). However, with the absence of $NiCl_2 \cdot 6H_2O$, zinc, or pyridine, no P-arylation occurred, even when K_2CO_3 was added to the reaction mixture (Table 1, entries 1–5). The choice of 2,2′-bipyridine (bpy) ligand greatly improved the reaction efficiency (98% yield, Table 1, entry 8). Under similar reaction conditions, various nitrogen ligands, including DMAP, *N,N*′-dibenzylethylenediamine, 1,2-dianilinoethane, and *N,N,N*′,*N*′-tetramethylethylenediamine were examined, which also showed catalytic activity for the reaction but provided coupling products in only 5–87% yields (Table 1, entries 14–17). When $Ni(NO_3)_2 \cdot 6H_2O$ and $Ni(OAc)_2 \cdot 6H_2O$ were used as the catalysts, 15 and 33% yields were obtained, respectively, under the same conditions (Table 1, entries 12 and 13). The effect of bases (Et_3N, K_2CO_3, and Cs_2CO_3) was also investigated, which indicated that bases were not necessary for these coupling reactions when water was the solvent (Table 1, entries 9–11). In addition, the reaction can also successfully proceed under a nitrogen atmosphere (Table 1, entry 18). When the temperature was increased from 70 to 90 °C, the reaction yield was not significantly improved. After optimization of the reaction conditions, we chose 10 mol % $NiCl_2 \cdot 6H_2O$ as the catalyst, 2 equiv of zinc powder as the reducing agent, 20 mol % bpy as the ligand, and water as the solvent at 70 °C without exclusion of air for the following P-arylations.

To explore the scope of this cross-coupling reaction catalyzed by our system, the reactions of a variety of aryl

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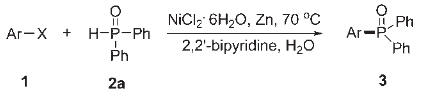
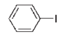
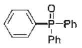
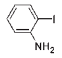
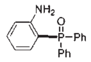
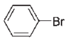
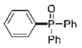
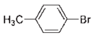
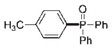
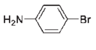
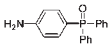
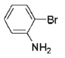
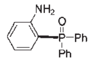
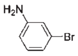
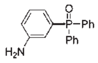
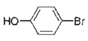
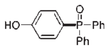
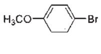
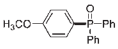
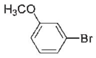
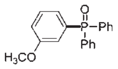
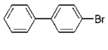
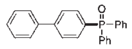
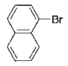
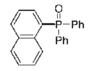
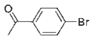
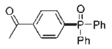
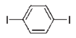
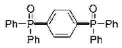
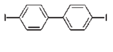
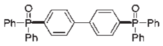
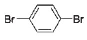
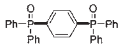
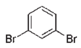
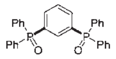
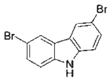
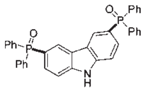
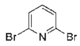
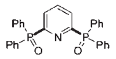
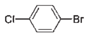
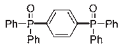
Table 2. Nickel-Catalyzed Cross-Coupling of Aryl Halides with Diphenylphosphine Oxide[a]



1 2a 3

X = Cl, Br, I

entry	1		2	3		yield[b]
1		1a	2a		3a	92
2		1b	2a		3b	81
3		1c	2a		3a	92
4		1d	2a		3c	92
5		1e	2a		3d	89
6		1f	2a		3b	76
7		1g	2a		3e	86
8		1h	2a		3f	83
9		1i	2a		3g	97
10		1j	2a		3h	95
11		1k	2a		3i	91
12		1l	2a		3j	88
13		1m	2a		3k	94
14		1n	2a		3l	88
15		1o	2a		3m	88
16		1p	2a		3l	85
17		1q	2a		3n	78
18		1r	2a		3o	75
19		1s	2a		3p	81
20		1t	2a		3l	75

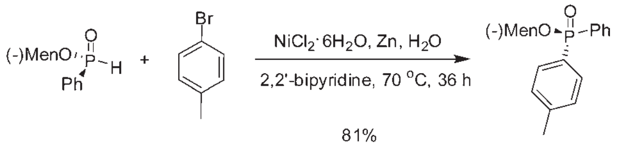
[a] Reaction conditions: for entries 1–13, **1** (0.60 mmol), **2** (0.50 mmol), $NiCl_2 \cdot 6H_2O$ (0.05 mmol), zinc (1.0 mmol), bpy (0.10 mmol), H_2O (1.0 mL) at 70 °C for 15 h; for entries 14–20, **1** (0.50 mmol), **2** (1.20 mmol), $NiCl_2 \cdot 6H_2O$ (0.10 mmol), zinc (2.0 mmol), bpy (0.20 mmol), H_2O (1.5 mL) at 70 °C for 24 h. [b] Isolated yield.

halides and organophosphorus compounds containing P–H were examined. As shown in Table 2, the substrates bearing different leaving groups (iodide, bromide) were all efficiently coupled under these reaction conditions to afford the corresponding P-arylated derivatives with good isolated yields. A variety of functional groups, such as hydroxyl, alkoxyl, carbonyl, and amino groups, would be incorporated, leading to the corresponding reductive coupling products in good to excellent yields. Substituted bromobenzenes with electron-donating hydroxyl, amino, and methoxy groups reacted with **2a** to provide products **3b**–**3h** in 76–97% yields (Table 2, entries 2–10). Similarly, the reaction of 4-acetyl-bromobenzene (**1m**) with **2a** gave **3k** in 94% yield (Table 2, entry 13). For most cases, electron-donating groups (Table 2, entries 4–10) or an electron-withdrawing group (Table 2, entry 13) on the aryl halides did not change the yields of the P–C cross-coupling products significantly. However, the ortho-substituted steric effect caused some reduction in yields from 89% to 76% (Table 2, entries 5, 6).

The bis-coupling products from bis-substituted aryl halides were also obtained (Table 2, entries 14–20) in moderate yields; this protocol undoubtedly provides a powerful tool for the preparation of the valuable P-arylated motifs. Such molecules can serve as host materials in the emissive layer of blue electrophosphorescent organic devices.[4a]

It is worth noting that the nickel-catalyzed cross-coupling reaction can be also applied in the preparation of enantiomerically pure P-chiral diarylphosphinate **3q** (Scheme 1) from the easily accessible optically pure H-phosphinate ((R_P)-(−)-menthyl benzylphosphinate) (**2b**)[13] with retention of configuration at the phosphorus atom (Figure 1).

Scheme 1. Nickel-Catalyzed Cross-Coupling of Aryl Bromide with Optically Pure H-Phosphinate



2b 1d 3q

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[13] Xu, Q.; Zhao, C. Q.; Han, L. B. *J. Am. Chem. Soc.* **2008**, *130*, 12648.

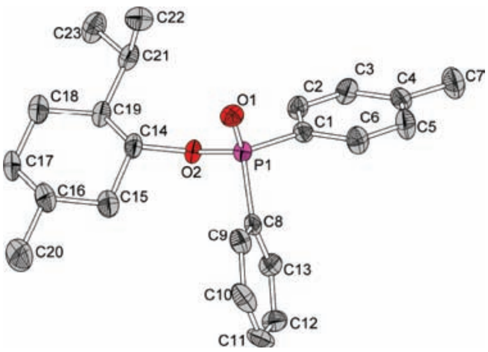
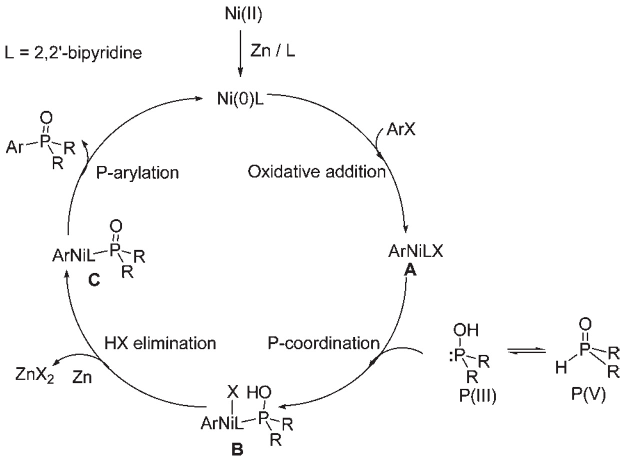


Figure 1. Single-crystal X-ray structure of compound **(*S*p)-3q** (ellipsoids at the 50% probability level). Some of the hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [deg]: P1−O1 1.475(2), P1−O2 1.590(2), P1−C1 1.791(3), P1−C8 1.796(3), C14−O2 1.468(3), O1−P1−O2 114.90(13), O1−P1−C1 115.10(15), O2−P1−C1 101.62(13), O1−P1−C8 111.08(14), O2−P1−C8 106.55(15), C1−P1−C8 106.73(15), C14−O2−P1 119.79(16).

A possible mechanism is proposed in Scheme 2 based on the palladium-catalyzed cross-coupling reactions.[14a] The active catalytic species Ni(0),[14b,c] generated from $NiCl_2 \cdot 6H_2O$ in the presence of zinc powder in water, undergoes oxidative addition with aryl halides to afford an intermediate **A**. Subsequent P(III)-coordination and HX elimination with the help of Zn lead to the formation of the intermediate **C**. The final P−C bond formation *via* reductive elimination completes the catalytic cycle by regenerating Ni(0) as a catalytically active species. The proposed mechanism is supported by DFT calculations.[15]

Scheme 2. Proposed Mechanism for Nickel-Catalyzed P-Arylation



In conclusion, we have developed an efficient nickel-catalyzed method for the cross-coupling of various aryl halides with diphenylphosphine oxide in water. This method avoids the use of air sensitive reagents and the reaction can therefore be performed under air, rendering the experimental procedure very simple. It is noteworthy that a wide range of groups could be tolerated. Therefore, this protocol will have wide application for the construction of biologically active molecules, catalytic ligands, and organophosphorus compounds.

Acknowledgment. We acknowledge financial support from the Chinese National Natural Science Foundation (20732004, 20972130) and the Ministry of Science and Technology (2011CB808504).

Supporting Information Available. General experimental procedure and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] (a) Montchamp, J. L.; Dumond, Y. R. *J. Am. Chem. Soc.* **2001**, *123*, 510. (b) Ueda, M.; Ichikawa, F. *Macromolecules* **1990**, *23*, 926. (c) Ananikov, V. P.; Gayduk, K. A.; Starikova, Z. A.; Beletskaya, I. P. *Organometallics* **2010**, *29*, 5098.

[15] See Supporting Information for details.