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Preparation of Unsymmetrical Biaryls via Ni- or Pd-Catalyzed Coupling of Aryl Chlorides With Arylzincs

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Abstract: Unsymmetrical biaryls may be prepared in an efficient manner using aryl chlorides as substrates in Negishi-type cross-coupling reactions with arylzinc reagents via either Ni- or Pd-catalysis. Since a wide range of functional groups (e.g., nitrile, carbonyl, ester) tolerate arylzinc compounds, this methodology allows for the direct synthesis of biaryls from aryl chlorides possessing these moieties.

The synthesis of unsymmetrical biaryls via the Ni- and Pd-catalyzed coupling of arylzincs with aryl bromides or -iodides was first reported by Negishi more than 20 years ago.[1] Since that report, the reaction has been widely used as a preferred method for preparing biaryl compounds.[2] In view of the fact that biaryl-containing derivatives are becoming increasingly valuable in many applications, including use in liquid crystals and as components of pharmaceutically active compounds, their production via cost-effective methods is especially important. Although synthetic methods for preparing biaryls from the typically less reactive aryl chlorides, instead of the corresponding -bromides or -iodides, have recently been reported for both Stille[3] and Suzuki[4] biaryl protocols, the cross-coupling of arylzincs with aryl chlorides via the Negishi reaction has not been developed.[5]

We now report that inexpensive and readily available aryl chlorides can indeed be used as substrates in the Negishi biaryl synthesis, affording unsymmetrical biaryl products in high yield using either Ni or Pd catalysts (eq 1).

$$Ar^1Cl + Ar^2ZnX \xrightarrow{\text{Ni or Pd cat.}} Ar^1\text{-}Ar^2 \qquad (1)$$

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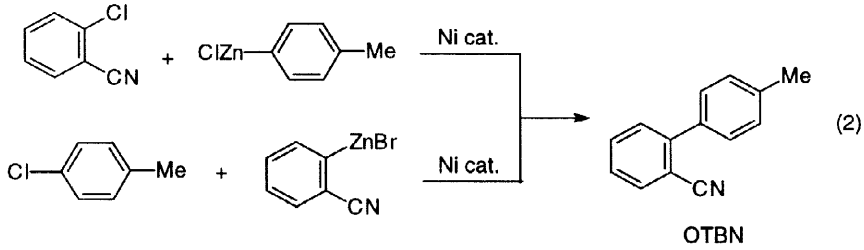
Moreover, since a variety of functional groups tolerate arylzinc compounds,[6] this procedure represents a direct and general method for the synthesis of functionally substituted biaryls from aryl chlorides without requiring accompanying protection/deprotection schemes.

The scope of the Ni- or Pd-catalyzed coupling of aryl chlorides with arylzinc compounds is illustrated in Table 1. For example, a mixture of phenylzinc chloride (1.25 equiv), 2-chlorobenzonitrile, $Ni(acac)_2$ (2 mol%), and 1,1'-bis(diphenylphosphino)ferrocene (dppf; 2.2 mol%) was stirred at room temperature for 18 h. Analysis of a hydrolyzed reaction sample by GC (using an internal reference standard) showed the formation of the cross-coupled biaryl, 2-phenylbenzonitrile, in 86% yield, with no remaining aryl chloride detected (entry 1). Minor amounts of the two homocoupled byproducts, biphenyl and 2,2'-dicyanobiphenyl, were also detected by GC analysis. As expected, when the analogous reaction was conducted using phenylmagnesium chloride directly, without prior transmetallation with $ZnCl_2$ to form phenylzinc chloride, the unsymmetrical biaryl product was produced in only 3% yield. The result illustrated by entry 1, as well as others contained in Table 1,[7] clearly demonstrate the tolerance of Grignard-sensitive funtionality (e.g., nitrile, ketone, ester groups) toward arylzinc compounds under the conditions used in this coupling reaction. It should be noted that arylzinc reagents are also readily prepared by other methods, including transmetallation of aryllithiums with $ZnCl_2$ (entry 7) and direct oxidative metallation of aryl halides (entry 14), and these arylzincs react analogously.

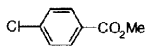
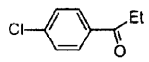
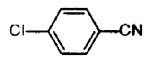
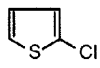
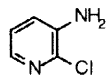
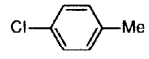
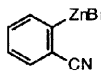
The ability of arylzincs to accommodate functionality in the reaction, both on the "nucleophilic" (arylzinc compound) and "electrophilic" (aryl chloride) substrates, provides for considerable flexability in the process. An illustration of this is demonstrated by the preparation of o-(p-tolyl)benzonitrile (OTBN) by the two possible modes of reaction (eq 2). Thus, 2-chlorobenzonitrile can serve as the "electrophilic" substrate and react (via Ni catalysis) with p-tolylzinc chloride to produce OTBN in high yield (89% by GC; entry 2). Conversely, the benzonitrile moiety may also serve as the "nucleophilic" reactant. Thus, o-cyanophenylzinc bromide, prepared from activated zinc and 2-bromobenzonitrile,[8] was treated with Ni catalyst and 4-chlorotoluene. After stirring for 5 h at 55° C, analysis by GC showed that OTBN had been formed in 75% yield (entry 14). The successful coupling of arylzincs with "unactivated" aryl chlorides, such as 4-chlorotoluene, is significant because it demonstrates that the reaction is not confined to aryl chlorides possessing an activating electron-withdrawing group (entries 13,14).



(2)

Arylzinc compounds also undergo coupling with aryl chlorides to form biaryls in the presence of Pd catalysts, with good cross-coupling results being provided by a Pd catalyst employing the dppf ligand. For example, the coupling of 4-chlorobenzonitrile with p-tolylzinc chloride (1.25 equiv), in the presence of $Cl_2Pd(dppf)\cdot CH_2Cl_2$ (5 mol%), in THF (reflux, 1 h) produced 4-phenylbenzonitrile in 82% yield with complete conversion of the aryl chloride (entry 8). Other phosphine-based Pd catalysts, such as those derived from Ph_3P, $(o\text{-}Tol)_3P$, and racemic BINAP, gave 4-phenylbenzonitrile in much lower yields under otherwise similar reaction conditions. The Ni- or Pd-catalyzed cross-coupling of 4-chlorobenzonitrile with diphenylzinc also proceeds readily, with both of the phenyl groups being transferred from Zn to yield 4-phenylbenzonitrile (entries 9 and 10).

Table 1. Synthesis of Biaryls via Ni- or Pd-Catalyzed Coupling of Arylzincs with Aryl Chlorides[a]

Entry	Ar^1Cl	Ar^2ZnCl (amount)	Catalyst (amount)	Added Ligand (amount)	Reaction Temp/Time	$Ar^1\text{-}Ar^2$ Yield (%)[b]	Unreacted Ar^1Cl (%)[b]
1		PhZnCl (1.25 equiv)	$Ni(acac)_2$ (2 mol%)	dppf (2.2 mol%)[c]	25° C/18 h	86	0
2		p-TolZnCl (1.5 equiv)	$Ni(acac)_2$ (7.5 mol%)	$(i\text{-}PrO)_3P$ (15 mol%)	40° C/6 h	89	<1
3		p-TolZnCl (1.25 equiv)	Pd cat. (5 mol%)[d]	--	Reflux/72 h	82	0
4		p-TolZnCl (1.25 equiv)	$Ni(acac)_2$ (5 mol%)[e]	PPh_3 (20 mol%)[e]	50° C/1.5 h	81	2
5		p-TolZnCl (1.25 equiv)	Pd cat. (5 mol%)[d]	--	Reflux/48 h	75	2
6		p-TolZnCl (1.25 equiv)	$Ni(acac)_2$ (5 mol%)[e]	PPh_3 (20 mol%)[e]	25° C/1 h	85	0
7		PhZnCl (1.25 equiv)[f]	$Ni(acac)_2$ (5 mol%)[e]	PPh_3 (20 mol%)[e]	25° C/1 h	81	0
8		p-TolZnCl (1.25 equiv)	Pd cat. (5 mol%)[d]	--	Reflux/1 h	82	0
9		Ph_2Zn (0.625 equiv)	Pd cat. (5 mol%)[d]	--	Reflux/4 h	80	2
10		Ph_2Zn (0.625 equiv)	$Ni(acac)_2$ (5 mol%)[e]	PPh_3 (20 mol%)[e]	25° C/1 h	84	0
11		p-TolZnCl (1.25 equiv)	$Ni(acac)_2$ (5 mol%)[e]	PPh_3 (20 mol%)[e]	25 ° C/1 h	63	0
12		PhZnCl (2.1 equiv)	$Cl_2Ni(PPh_3)_2$ (6 mol%)	--	25° C/3 h	(72)	--
13		PhZnCl (1.25 equiv)	$Cl_2Ni(PPh_3)_2$ (2 mol%)	PPh_3 (4 mol%)	50° C/24 h	75	5
14	 (1.25 equiv)[g]		$Cl_2Ni(PPh_3)_2$ (7.5 mol%)	PPh_3 (15 mol%)	55° C/5 h	75	3

[a]All reactions were carried out in THF solvent. [b]Chemical yields are by GC analysis using an internal reference standard. Isolated yield is shown in parentheses. [c]dppf = 1,1'-Bis(diphenylphosphino)ferrocene. [d]Pd cat.= $Cl_2Pd(dppf)\cdot CH_2Cl_2$. [e]Catalyst derived from $Ni(acac)_2$, PPh_3, H_2O, and Vitride.[7] [f]PhZnCl in this entry was prepared by reaction of PhLi with $ZnCl_2$. [g]The zinc reagent was prepared from reaction of 2-bromobenzonitrile with activated Zn.[8]

In summary, unsymmetrical biaryl products are obtained in an efficient manner using aryl chlorides as substrates in a Negishi-type cross-coupling reaction with arylzinc reagents via either Ni- or Pd-catalysis. The inherently mild nature of the arylzinc reagents utilized in this chemistry makes the process particularly attractive for the synthesis of biaryl compounds containing "reactive" functionality (e.g., nitrile, carbonyl, ester groups). In addition, this biaryl synthesis is advantageous relative to the Stille or Suzuki biaryl protocols since the arylzinc reagents are not isolated prior to use, but instead (unlike typical procedures employing the aryltin and arylboron reagents[2]) are prepared and utilized in situ. Finally, since aryl chlorides are also suitable precursors to the respective arylzinc reagents (e.g., via transmetallation of the corresponding arylmagnesium chlorides with $ZnCl_2$), the biaryls (Ar^1-Ar^2) produced from this reaction may be totally derived from inexpensive and readily available aryl chloride starting materials (Ar^1Cl + Ar^2Cl).

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6. For a review on organozinc compounds in synthesis, see: Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117.
7. Representative procedure: [4-(4'-Methylphenyl)propiophenone; entry 6]. A solution of nickel acetylacetonate (0.128 g; 0.500 mmol; 5 mol%) and triphenylphosphine (0.523 g; 2.00 mmol; 20 mol%) in THF (5 mL) was treated with water (18 μL; 1.0 mmol; 10 mol%), cooled to 0° C, and further treated with Vitride (0.28 mL; 0.50 mmol; 5 mol%; 35 wt% in THF; ca 1.8 M). The dark reddish brown solution was stirred at 0° C for 10 min to complete the preparation of the nickel catalyst. In a separate flask, a solution of zinc chloride (1.77 g; 13.0 mmol) in THF (25 mL) was treated at 0° C with p-tolylmagnesium chloride (7.80 mL; 12.5 mmol; 1.60 M in THF), and the resulting mixture was warmed to room temperature and stirred for 15 min. The p-tolylzinc chloride obtained was treated at room temperature with the solution of nickel catalyst followed by 4-chloropropiophenone (1.68 g; 10.0 mmol). After stirring at room temperature for 1 h, a sample was withdrawn and quenched in a mixture of 1 N HCl and ether. GC analysis of the organic phase of the hydrolyzed reaction sample showed the presence of 8.5 mmol (85% yield) of 4-(4'-methylphenyl)propiophenone and no remaining 4-chloropropiophenone in the reaction mixture.
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