

The Reagent

(Ph₃P)₂NiX₂ (X = Br, Cl) – A Mild Catalyst for C–C Coupling Reactions

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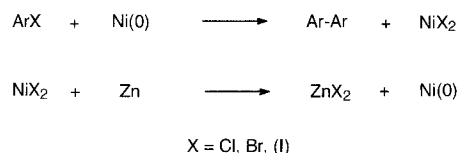
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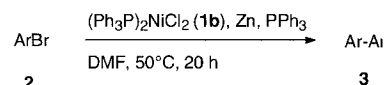
Bis(triphenylphosphine)nickel(II)bromide (**1a**) was first prepared by Venanzi in 1958 from NiBr₂ in the presence of triphenylphosphine [1]. On the basis of X-ray studies he showed that this compound, as well as its chloro analogue, is a pseudotetrahedral Ni(II) complex [2]. The bromo as well as the chloro complex are commercially available at a reasonable price; they are easy to handle although slightly moisture sensitive.

1 Biphenyl Formation

In 1971 Semmelhack found that several Ni(0) complexes (*e.g.* Ni(PPh₃)₄) are able to promote the homo-coupling reaction of aryl halides to biphenyls [3]. In contrast to the Ullmann reaction [4], which requires rather drastic conditions, the Ni(0) mediated procedure occurs under mild conditions. In order to avoid the handling of air sensitive Ni(0) reagents Kende reported a modification of Semmelhack's method, in which the reactive species was prepared *in situ* from easily accessible, air stable (Ph₃P)₂NiBr₂ (**1a**) by reduction with zinc dust [5]. It even is possible to run the reaction with catalytic amounts of the nickel precursor **1**, since the Ni(II) species resulting from the coupling reaction can be reduced again to regenerate the catalytically active species [6, 7].



Using the Ni(0) catalyzed reaction, various aryl halides can be coupled to obtain the corresponding biphenyls in good to excellent yields. Best results are obtained with catalyst amounts as low as 5 mol% with DMF as the most suitable solvent.

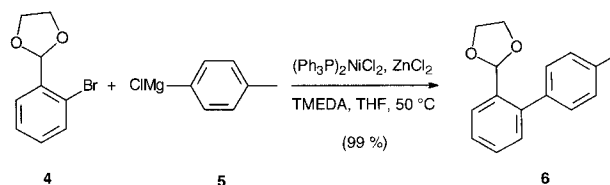
**Table 1** Ni(0)-catalyzed coupling of aryl halides **2** to form biphenyls **3**

aryl halide 2		yield of biphenyl 3 (%)	
bromobenzene	2a	89	3a
<i>p</i> -bromo methylbenzoate	2b	85	3b
<i>o</i> -bromo methylbenzoate	2c	33	3c
<i>o</i> -iodo methylbenzoate	2d	59	3d
<i>p</i> -bromo benzaldehyde	2e	70	3d

Bromobenzene (**2a**) for example is transformed to biphenyl (**3a**) in 89% yield within 20 h at 50 °C. However, in the case of *ortho*-substituted aryl halides yields dropped remarkably. Starting from *o*-bromo methylbenzoate (**2c**) only 33% of the corresponding biphenyl derivative **3c** is isolated. On the other hand, by using the corresponding *o*-iodo aryl compound **2d** and stoichiometric amounts of the nickel precursor the yield of the 2,2'-disubstituted biphenyl derivative **3d** is increased to 59%. Because of the mild reaction conditions this method offers the possibility to couple aryl halides **2** which bear functional groups such as ketones or even aldehydes to the corresponding biphenyls **3** as shown for the methyl-benzoates **2b–2d** and *p*-bromo benzaldehyde (**2e**).

2 Cross-Coupling of Aryl Halides

With the above described procedure only symmetrically substituted biphenyls can be obtained. In order to prepare unsymmetric biphenyl derivatives, a nickel catalyzed Grignard reaction can be used. This was demonstrated by Watanabe who described the preparation of 4-methyl-2'-(2,5-dioxolanyl)-biphenyl **6a** useful key intermediate for angiotensin II antagonists [8].

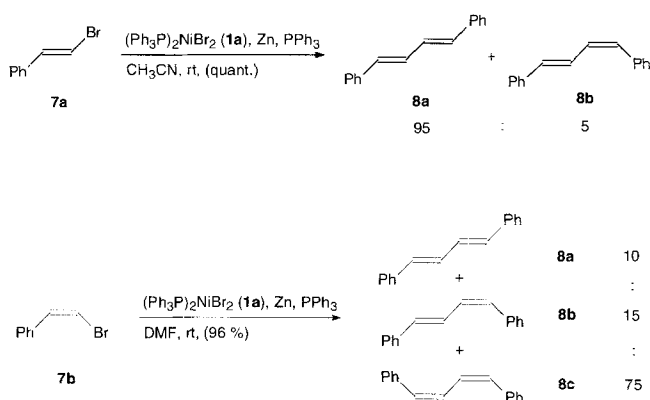


The aryl Grignard reagent **5** reacts with the substituted bromo aryl derivative **4** in the presence of bis(triphenylphosphine)nickel(II)chloride (**1b**), and the desired cross-coupling product **6** is generated in quantitative yield. Instead of the dioxolanyl group several other functional groups (*e.g.* cyano) are tolerated [8].

In a related reaction the Grignard addition to alkylsilanes also can be catalyzed by $(\text{Ph}_3\text{P})_2\text{NiCl}_2$ (**1b**) [9, 10].

3 Coupling of Alkenyl Halides

The use of $(\text{Ph}_3\text{P})_2\text{NiBr}_2$ (**1a**)/Zn is not limited to biphenyl formation. Conjugated dienes are generated if 1-alkenyl halides are coupled [11, 12]. The reaction proceeds smoothly upon addition of PPh_3 (two fold excess to $(\text{Ph}_3\text{P})_2\text{NiBr}_2$ (**1a**)) to give the product in excellent yields. Furthermore the reaction is highly stereoselective.



As an example, (*E*)- β -bromostyrene (**7a**) in acetonitrile as solvent at ambient temperature is transformed into the coupling product 1,4-diphenyl-1,3-butadien (**8**). The (*E*, *E*) **8a**:(*E*, *Z*) **8b**:(*Z*, *Z*) **8c**-ratio is 95:5:0 and the yield quantitative. In the case of (*Z*)- β -bromostyrene (**7b**) isomerisation is observed. Starting from (*Z*)- β -bromostyrene (**7b**) the reaction furnishes the dien as a mixture of the three possible isomers **8a**–**8c**. The best selectivities are obtained in DMF as solvent with a ratio of the stereoisomers 10:15:75 (**8a**:**8b**:**8c**). The original configuration of the double bonds in the reaction of (*E*)-1-alkenyl halides is retained in the products, whereas isomerisation occurs in the (*Z*)-1-alkenyl halides. Para-substituents (chloro, methyl) at the aromatic rings do not significantly influence the reactivity [12].

4 Homo-Coupling of Benzyl Halides

So far several examples are presented where Ni(0) complexes exhibit the ability for reductive coupling of aryl or alkenyl halides. In particular the in situ reduction of $(\text{Ph}_3\text{P})_2\text{NiX}_2$ ($\text{X} = \text{Br}$ **1a**, Cl **1b**) with zinc powder generates simple and convenient catalysts for this purpose. Although many methods for the reductive coupling of benzyl halides are known [13] the Ni(0) catalyzed procedure provides an

alternative for the synthesis of bibenzyls because it occurs under very mild conditions. This is shown by Iyoda who couples a series of benzyl halides with $(\text{Ph}_3\text{P})_2\text{NiBr}_2$ (**1a**), Zn and Et_4NI at room temperature in THF to obtain the corresponding bibenzyls [14].

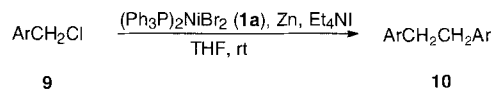
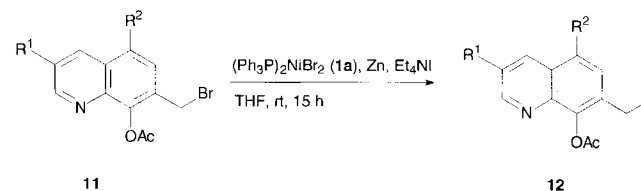


Table 2 Ni(0)-catalyzed coupling of benzyl chlorides **9** to form bibenzyls **10** (* stoichiometric reaction)

benzyl chloride 9	yield of bibenzyl 10 (%)
<i>o</i> -methyl 9a	89 10a
<i>m</i> -methyl 9b	85 10b
<i>p</i> -methyl 9c	96 10c
<i>p</i> -nitro 9d	28* 10d
5-bromo-3,4-dimethoxy 9e	73 10e
4-CO ₂ Me 9f	82 10f

Under these conditions the *o*-, *m*- and *p*-methyl substituted bibenzyls **9** are generated in good to excellent yields. However, yields are poor if the benzyl halides bear electron withdrawing groups such as nitro or cyano. As an example, 1,2-di(4-nitrophenyl)ethane (**10d**) (28% yield) only can be obtained if equimolar amounts of the nickel precursor **1a** are used. On the other hand, the before mentioned coupling of aryl halides to the biphenyl systems can not be observed in THF [6, 7]. This chemoselectivity allows the generation of the natural product 1,2-di(3-bromo-4,5-dimethoxy)ethane (**10e**) in 73% yield.

This mild and convenient Ni(0) catalyzed homo benzyl coupling reaction also enables the preparation of ethylene-bridged di(8-hydroxyquinoline) derivatives which are building blocks for metallo-supramolecular chemistry [15, 16]. The key step of the ligand synthesis is the homo-coupling of a 7-bromomethyl quinoline derivative **11** to afford the corresponding ligand precursor **12**. All attempts to prepare the molecule *via* Wurtz-type coupling chemistry failed even if the protecting groups were changed from phenol acetates to phenylmethylethers. The occurring problems seem to be due to the ease of dehalogenation (reduction) at the benzylic position.



Using the above described Ni(0) catalyzed procedure the ethylene linked ligand precursors **12** were obtained. Isolated yields of pure coupling product range from 42% to 65% depending on the nature of the substitution pattern. As a side reaction dehalogenation of the benzyl bromide is observed but the protecting group is stable under the reaction conditions. In addition to the ligands with ethylene links in 7-

Table 3 Ni(0)-catalyzed preparation of ethylene-bridged di(8-acetoxyquinoline) derivatives **12**

	R ¹	R ²	yield of 12 (%)
11a	H	H	45
11b	<i>n</i> -Bu	H	42
11c	<i>n</i> -Dec	H	65
11d	<i>n</i> -Dec	<i>n</i> -Dec	45

position those with links in 2- or 3-position can be obtained *via* the nickel catalyzed route.

As was shown (Ph₃P)₂NiBr₂ (**1a**) and (Ph₃P)₂NiCl₂ (**1b**) are precursors for many Ni(0) catalyzed reactions, namely homo-coupling of aryl, alkenyl and benzyl halides. In most cases the reactions proceed smooth and under very mild conditions. With this reagent one can expect more useful transformations to be developed especially in the field of cross coupling reactions. Besides the presented examples there are many more applications using (Ph₃P)₂NiX₂ (X = Br **1a**, Cl **1b**) as catalyst, *e.g.* for aldol-type condensations of enol ethers, reductions of aryl mesylates or triflates, living polymerisations and so on [17–19].

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