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Ni(II)/Zn-Mediated Chemoselective Arylation of Aromatic Aldehydes: Facile Synthesis of Diaryl Carbinols

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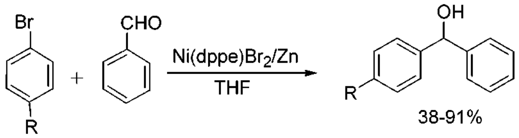
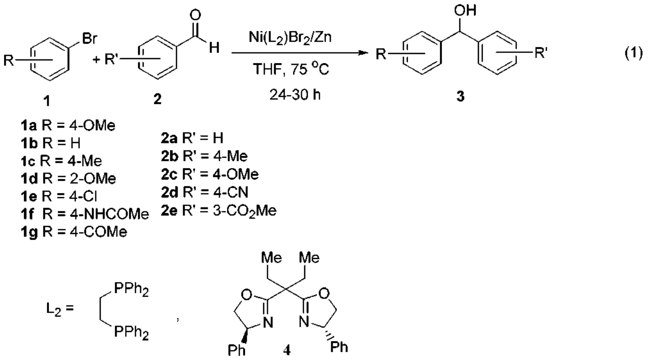
ABSTRACT



Direct arylation of aromatic aldehydes with aryl bromides in the presence of Ni(II)/Zn was investigated. The choice of ligand in this nickel-catalyzed coupling was critical to the formation of the secondary alcohols. Monodentate phosphine ligands were ineffective, whereas NiBr$_2$(dppe)/Zn successfully catalyzed this reductive coupling reaction. The reaction conditions were mild and diarylcarbinols with a variety of functional groups such as ketone, ester, amide, and nitrile groups were readily prepared.

Arylation of aldehydes is one of the most important C−C bond-forming reactions in organic synthesis.[1,2] Conventional methods employ aryllithium or Grignard reagents as the arylating agents.[3,4] However, this widely used technique is limited to substrates without sensitive functional groups such as ketone, ester, or cyano groups. The use of organochromium(III) reagents,[5,6] (the *Nozaki−Hiyama−Kishi reaction*, N−H−K) offers an attractive advantages over other conventional organometallic addition reagents, particularly in the presence of sensitive functionalities, but the reaction requires greater than stoichiometric amount of divalent chromium salt. The electrochemical method provides an alternative for the use of catalytic amounts of Cr(II) salt.[7] The reaction is still limited to laboratory scale preparations. We wish to report herein our initial results as a partial solution to these problems, a direct arylation of aromatic aldehydes with aryl bromides to afford diarylcarbinols in high yields using catalytic NiL$_2$Br$_2$ in the presence of Zn powder (eq 1). This nickel-catalyzed new simple coupling reaction requires specifically a bidentate ligand and proceeds with high chemoselectivity.



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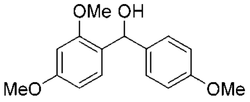
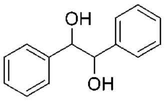
Our initial studies were focused on a search for optimal reaction conditions including reaction temperature, solvent, and nickel precursors for the arylation of benzaldehyde (**1a**) with 4-bromoanisole (**2a**), producing diarylcarbinol **3a**. The reaction temperature is important for the selectivity and yield. At refluxing temperature of THF, the arylation reaction is slow, giving **3a** in 52% yield. Significant amount of pinacol **5** (22%) was formed via the reductive homo coupling of benzaldehyde. At 110 °C the yield of **5** decreased greatly and diarylcarbinol **3a** in 67% yield was obtained. In addition, a new product, diaryl ketone **6** in 23% yield, was formed. The optimum temperature with respect to selectivity and yield was ca. 75 °C.



3l



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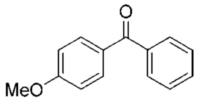

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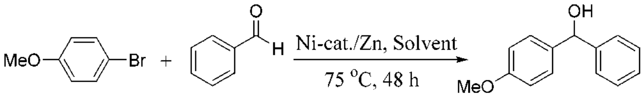
The nature of phosphine ligands influences drastically the rate of reaction and product yields (Table 1). Several monodentate phosphine complexes, $Ni(PPh_3)_2Br_2$, $Ni(P\textit{n}\text{-}Bu_3)_2Br_2$, $Ni(PPh_2Me)_2Br_2$, and $Ni(PCy_3)_2Br_2$, were tested as catalysts for the reaction. Either no arylation product or a trace of **3a** was detected using these nickel complexes. In contrast, the reaction was efficiently catalyzed by nickel(II) complexes bearing a bidentate phosphine ligand, such as $Ni(dppp)Br_2$, $Ni(dppb)Br_2$, $Ni(chiraphos)Br_2$, and $Ni(dppe)Br_2$ (Table 1, entries 7−15). The catalyst containing 1,2-bis(diphenylphosphino)ethane (dppe) ligand provided clean chemistry with 4-bromoanisole at 75 °C, giving 91% of **3a**. Nitrogen-containing ligands, 2,2′-bipyridyl and 1,10-phenanthroline, did not give any expected product; however, bisoxazoline **4**[8] provided **3a** in 82% yield although no chirality was observed (entry 16). Solvents also play a crucial role in the reaction. The use of highly polar solvents, DMF and acetonitrile, caused low yields along with several byproducts (entries 11−12). In a low polarity solvent, 1,2-dichloroethane or toluene, the reaction was incomplete even after 48 h and gave poor yields (entries 13 and 15). An ether-type solvent is most suitable for this nickel-catalyzed reaction. The reaction afforded **3a** in 56% yield in 1,2-dimethoxyethane and 91% in THF (entries 10 and 14).

Table 1. Reaction of 4-bromoanisole with Benzaldehyde under Various Conditions[a]



entry	catalyst	solvent	isolated yield (%)
1	no	THF	0
2	$Ni(PPh_3)_2Br_2$	THF	trace
3	$Ni(P^nBu_3)_2Br_2$	THF	0
4	$Ni(PPh_2Me)Br_2$	THF	0
5	$Ni(BINAP)Cl_2$	THF	0
6	$Ni(BINAP)Br_2$	THF	8
7	$Ni(dppp)Br_2$	THF	22
8	$Ni(chiraphos)Br_2$	THF	32
9	$Ni(dppb)Br_2$	THF	18
10	$Ni(dppe)Br_2$	THF	91
11	$Ni(dppe)Br_2$	CH_3CN	43
12	$Ni(dppe)Br_2$	DMF	38
13	$Ni(dppe)Br_2$	toluene	6
14	$Ni(dppe)Br_2$	DME	56
15	$Ni(dppe)Br_2$	DCE	8
16	$Ni(bisoxazoline)Br_2$	THF	82

[a] Reactions of 4-bromoanisole (1.25 mmol) with benzaldehyde (1.00 mmol) were carried out at 75 °C for 48 h in 4 mL of solvent by using 10 mol % of Ni-catalysts and Zn (2.75 mmol). Isolated yields are based on benzaldehyde used.

The catalytic arylation also nicely applied to a set of aryl bromides and aldehydes. As shown in Table 2, 4-bromoanisole and 4-bromotoluene reacted smoothly with benzaldehyde to give the corresponding diarylcarbinols in high yields.[9] Aryl bromides with Cl, MeCONH-, MeCO- substituents reacted with benzaldehyde slowly and afforded low yields of the corresponding diarylcarbinol **3** (entries 9−11). 4-Nitrobromobenzene and 4-cyanobromobenzene did not give any arylation product. The position of substituent on aryl bromide influences greatly the yield of the reaction. Ortho-substituted aryl bromides are generally less reactive and give lower yields of diarylcarbinols than the corresponding para-substituted ones (entries 1 and 8). An ortho effect was markedly observed in the case of 2-bromo-*m*-xylene and 2-bromomesitylene; no arylation product was detected even after 48 h.

In contrast to the behavior of aryl bromides, electron-donating substituents on the aromatic ring of aldehydes reduces the yields of diarylcarbinol **3**, while electron-withdrawing groups favor formation of these products. The reaction of 4-methoxybenzaldehyde with 4-bromoanisole gives product **3c** in 57% yield. When 2,4-dimethoxybenzaldehyde was treated with 4-bromoanisole, the corresponding carbinol **3l** was isolated in only 12% and no arylation product was detected when 3,4,5-trimethoxybenzaldehyde was used. On the other hand, the reaction of 4-cyanobenzadehyde and

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(5) Reviews: (a) Cintas, P. *Synthesis* **1992**, 248. (b) Saccomano, N. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, pp 173−209. Synthesis of natural products: (a) Kishi, Y. *Pure Appl. Chem.* **1992**, *64*, 343. (b) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH Publishers Inc.: Weinheim, 1996; pp 712−717 and references therein.

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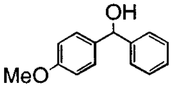
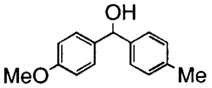
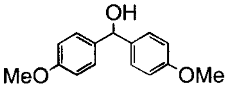
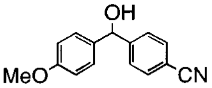
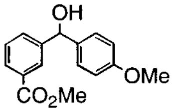
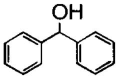
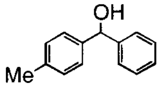
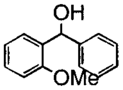
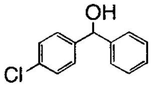
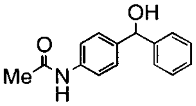
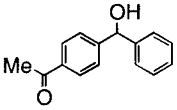
(9) **General procedure for the arylation of aldehydes**: $Ni(dppe)Br_2$ (62 mg, 0.1 mmol) and Zn (180 mg, 2.75 mmol) were placed in a screw-capped vial. The vial was sealed with septum and flashed several times with N_2. 4-Bromoanisole (234 mg, 1.25 mmol), benzaldehyde (106 mg, 1.0 mmol), and THF (4 mL) were added to the reaction mixture via syringe. The septum was removed, and the vial was sealed with a screw cap quickly under N_2. The reaction mixture was stirred at 75 °C for 24 h. The crude reaction mixture was diluted with ether, filtered through a thin Celite pad, and washed several times with ether. The solution was concentrated in vacuo. The residue was chromatographed on a silica gel column (hexane/EtOAc = 85/15) to give 195 mg (91%) of **3a**.

Table 2. Nickel-Catalyzed Arylation of Aromatic Aldehydes

Entry	1	2	Product		Yield (%)[a]
1	**1a**	**2a**		**3a**	91[b]
2	**1a**	**2b**		**3b**	87[b]
3	**1a**	**2c**		**3c**	57[b]
4	**1a**	**2d**		**3d**	71[b]
5	**1a**	**2e**		**3e**	75[b]
6	**1b**	**2a**		**3f**	58[c]
7	**1c**	**2a**		**3g**	65[c]
8	**1d**	**2a**		**3h**	72[b]
9	**1e**	**2a**		**3i**	42[c]
10	**1f**	**2a**		**3j**	38[c]
11	**1g**	**2a**		**3k**	43[c]

[a] Isolated yields; yields are based on aldehydes used. [b] Reactions were run for 24 h. [c] Reactions were run for 30 h.

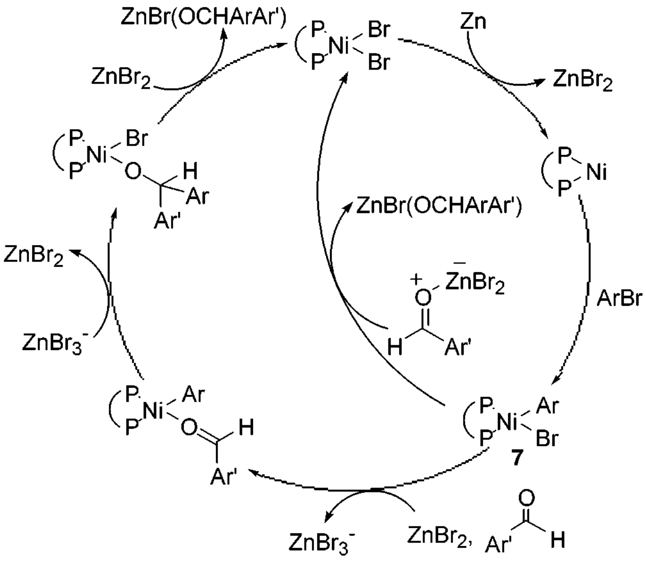
3-methoxycarbonylbenzaldehyde with 4-bromoanisole required a shorter reaction time and afforded the corresponding carbinols **3d** and **3e** in 71 and 75% yields, respectively. For comparison, the yield for the reaction of benzaldehyde with 4-bromoanisole is 91%.

The present catalytic reaction is compatible with several sensitive functional groups such as ester, ketone, amide, or nitrile in both the aryl bromide and aldehyde (entries 4−5 and 10−11). It should be noted that conventional methods via Grignard reagents or organolithiums frequently require the protection of these functional groups. As a whole, the desired products **3** were contaminated with small amounts of biaryls **4** and pinacol **5**, but the isolation was easy through column chromatography. Traces of biaryl formation are due to homo coupling of aryl bromides[10] in the presence of Ni(0), and a small amount of pinacol formation[11] is caused by the presence of $ZnBr_2$ formed in situ under the reaction conditions.

Several control experiments were performed in order to understand the mechanism of this catalytic reaction. In the absence of nickel complex, no reaction of 4-bromoanisole and benzaldehyde was observed. No arylation product was detected when a stoichiometric amount of $Ni(COD)_2$ and dppe was treated with 4-bromoanisole and benzaldehyde, but in the presence of $ZnBr_2$, the arylation proceeds smoothly to provide **3a**. Preformed ArZnCl upon treatment with benzaldehyde also did not give any arylation product with or without Ni-catalyst. Either trace or no arylation product was obtained when monodentate phosphine ligands were used.

On the basis of the above observations and the known nickel and zinc chemistry, a catalytic cycle is proposed as shown in Scheme 1. Reduction of Ni(II) to Ni(0) by zinc metal is likely the first step which is followed by oxidative addition of aryl bromide to nickel(0) species to yield nickel(II) intermediate **7**. Substitution of aldehyde for the bromide in **7**, migration of the aryl group to the carbonyl carbon in the aldehyde, and transmetalation with zinc bromide gives the final zinc alkoxide and regenerates $Ni(dppe)Br_2$.

Scheme 1



The requirement of a bidentate ligand in this catalytic reaction and that fact that monodentate ligands are ineffective indicates that both the aryl group and aldehyde should coordinate to the nickel center in a cis manner to facilitate coupling of these two groups. Because of steric hindrance, monodentate phosphine ligands in general favor the formation of the trans isomer of the nickel complex Ni $L_2(Ar)X$, where L = phosphine, thus preventing the direct couplig of aryl group and aldehyde. The requirement of $ZnBr_2$ for the coupling reaction of 4-bromoanisole and benzaldehyde in

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(10) (a) Semmelhack, M. F.; Helquist, P.; Jones, L. D.; Keller, L.; Mendelson, L.; Ryono, L. S.; Smith, J. G.; Stauffer, R. D. *J. Am. Chem. Soc.* **1981**, *103*, 6460. (b) Yamamoto, T.; Wakabayashi, S.; Osakada, K. *J. Organomet. Chem.* **1992**, *428*, 223.

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the presence of a stoichiometric amount of Ni(COD)$_2$ and dppe suggests a ZnBr$_2$-assisted substitution of the bromide ligand in Ni(dppe)ArBr by aldehyde or a Lewis-assisted addition of Ni−Ar to aldehyde (Scheme 1).

In conclusion, the present procedure provides a convenient and synthetically useful method for the arylation of aromatic aldehydes in a mild and chemoselective way. This Ni(II)/Zn-mediated arylation reaction may be an alternative to the N−H−K reaction. Further work on the precise mechanism for these reactions and an asymmetric version of this reaction is actively underway.

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