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Efficient Cross-Coupling of Functionalized Arylzinc Halides Catalyzed by a Nickel Chloride–Diethyl Phosphite System

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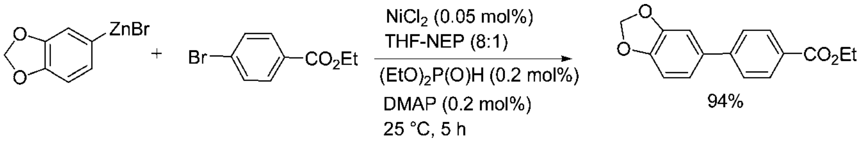
ABSTRACT



The combination of diethyl phosphite and DMAP as ligands for nickel in an 8:1 THF–*N*-ethylpyrrolidinone (NEP) mixture allows a very efficient cross-coupling reaction to be performed between various functionalized arylzinc halides and aryl bromides, triflates and activated chlorides. The reaction proceeds at 25 °C within 1–48 h and requires only 0.05 mol % of the nickel catalyst.

Transition-metal-catalyzed cross-couplings between aryl organometallics and aryl or heteroaryl halides are quite important in modern organic chemistry, and a number of the resulting biaryl products are of great industrial use.[1] Although arylboronic acids and derivatives[2] are favorite nucleophiles for performing such cross-couplings due to their good availability and excellent stability, in many cases polyfunctional aryl or heteroaryl zinc reagents are an attractive alternative.[3] The required arylzinc compounds can be prepared by transmetalation from the corresponding magnesium or lithium organometallics,[4] by direct zinc insertion[1] or by an I/Zn-exchange reaction.[2] Palladium-catalyzed cross-couplings require typically 1−3 mol % of a palladium phosphine complex. Both catalyst components (palladium and the phosphine) are expensive and complicate large-scale applications. In light of this, we have turned our attention to the use of nickel, an intrinsically more active metal. Various Ni-catalyzed Suzuki cross-coupling reactions have been described,[3] whereas only a few nickel-catalyzed cross-couplings of organozinc derivatives are known.[4,9] Herein, we wish to report a new highly efficient nickel-catalyzed cross-coupling between aryl and heteroaryl bromides, chlorides or sulfonates (**1**) and arylzinc reagents (**2**), using very small amounts of nickel salts (0.05 mol %) and

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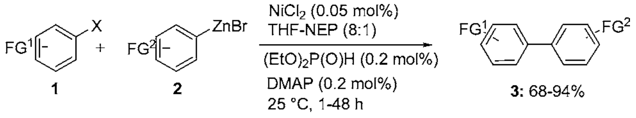
10.1021/ol051615+ CCC: $30.25

ligands (diethyl phosphite and DMAP, 0.2 mol % each) at room temperature in THF, using *N*-ethylpyrrolidinone (NEP) as cosolvent (Scheme 1).

Scheme 1. Ni-Catalyzed Cross-Coupling Reaction of Arylzinc Derivatives with Aryl Halides and Sulfonates



In preliminary studies, we investigated the cross-coupling reaction between 4-methoxyphenylzinc bromide and 4-bromotoluene and found that the reaction took place in the presence of 0.05 mol % of $NiCl_2$ at room temperature without a ligand when *N*-methylpyrrolidinone was used as a cosolvent (THF−NMP 5:2). Other polar solvents such as DMSO, DMAC, DMPU or Et_3N were not effective as cosolvents. Having examined various *N*-substituted pyrrolidinones, we observed that *N*-(2-methoxyethyl)- and especially *N*-ethylpyrrolidinone (NEP) gave much better results than with NMP (88% conversion in the presence of NEP within 6 h against 44% for NMP). We have further optimized the cosolvent ratio and found that 8:1 THF−NEP mixture gives the best results. We next screened this reaction with a broad number of ligands such as phosphines, diphosphines, phosphites and various *N*-heterocycles. Surprisingly, from all the ligands checked, diethyl phosphite gave the highest reaction rate and the minimum amount of the arylzinc homocoupling product. Interestingly, triphenylphosphine, also enhanced the coupling rate but did not inhibit the reaction even when present at 25-fold higher levels than Ni catalyst. Ratios of $NiCl_2$−$(EtO)_2P(O)H$ greater than 4:1 led to slower reaction rates and extensive homocoupling. Other dialkyl and diaryl phosphites were much less efficient.

We have also observed that the addition of 4-(dimethylamino)pyridine (DMAP)[10] in equimolar ratio to the ligand amount provides a further rate acceleration, whereas DMAP itself as a ligand showed poor results. The optimized conditions allowed us to perform a broad range of cross-coupling reactions within 1−20 h at room temperature (Table 1). Thus, 4-methoxyphenylzinc bromide (**2a**, 1.2 equiv), obtained from the corresponding arylmagnesium reagent[11] by a transmetalation with $ZnBr_2$, reacted with 3-bromo-1-fluorobenzene (**1a**) in the presence of $NiCl_2$ (0.05 mol %), $(EtO)_2P(O)H$ (0.2 mol %) and DMAP (0.2 mol %) at 25 °C to give the cross-coupling product **3a** in 79% yield after 2 h (entry 1, Table 1). Similarly, the reaction of **2a** with ethyl 3-bromobenzoate (**1b**) furnished the expected product **3b** in 91% yield (entry 2) within a 6 h reaction time. We have noticed that electron-rich arylzinc reagents react especially well with aryl bromides under our conditions. Thus, the cross-coupling of ethyl 4-bromobenzoate (**1c**) with **2a** provided the biphenyl **3c** in 87% yield within a 6 h reaction time (entry 3). Aryl bromides, bearing a ketone function, are compatible with the mild cross-coupling conditions, and 4-bromobenzophenone reacted smoothly with **2a** leading to the ketone **3d** in 73% yield within a 3 h reaction time (entry 4). 4-Bromo-acetophenone (**1h**) reacted with **2b** within 2.5 h affording the methyl ketone **3g** in 77% yield (entry 8). Electron-poor aryl chlorides are also suitable electrophiles under the reaction conditions we are advocating. Thus, the reaction of **2a** with ethyl 4-chlorobenzoate gave the expected product **3c** within 48 h at 25 °C in 83% yield (entry 5). Heterocyclic halides such as 3-bromopyridine (**1f**) reacted with **2a** within 2 h at 25 °C, leading to the pyridine **3e** in 81% yield. Scaling up the reaction using 20 mmol (**1f**) provided the cross-coupling product **3e** in a comparable yield of 82%. By using 3-chloropyridine, the same cross-coupling reaction required 12 h and gave **3e** in 68% yield (entry 6). The presence of an electron-withdrawing group allowed cross-coupling of 2-chloropyridine derivatives. Thus, the reaction of methyl 6-chloronicotinate (**1g**) with 3-methoxyphenylzinc bromide (**2b**) furnished the pyridine **3f** in 74% yield after 24 h (entry 7). 3-Pyridylzinc bromide displayed a reduced reactivity and reacted with 2-bromobenzophenone only at 50 °C, giving the ketone **3h** in 76% yield within a 3 h reaction time (entry 9). Various substituted arylzinc reagents such as **2d** or **2e** reacted with 5-bromopyrimidine (**1f**), leading to the products **3i** (82%) and **3j** (60%). In the case of an electron-deficient arylzinc halide (**2e**) the reaction had to be performed at 50 °C within a 24 h reaction time (entries 10 and 11). Aryl nonaflates proved especially convenient substrates for the cross-coupling reaction as they were usually easier to purify and more reactive than the aryl triflates.[12] Thus, the reaction of the zinc reagent **2f** with the nonaflate **1k** provided the quinoline **3k** in 88% yield (entry 12). 2-Zincated *N*-methylpyrrole (**2g**) obtained from the corresponding lithium reagent[13] and $ZnBr_2$ underwent a smooth cross-coupling with 3-bromopyridine (**1f**) at 70 °C leading to β-nicotyrine **3l** in 62% yield (entry 13), a natural product with insecticidal activity[14] (Scheme 2).

Other arylzinc bromides such as **2h** or **2i** having a trifluoromethyl- or a 1,3-dioxolane group provided the corresponding biphenyls **3m**−**o** in 68−94% yields (entries 14−16). Finally, for the cross-coupling of triflate **1l**, we probed the effect of the nature of the halide in the arylzinc component. Thus, the cross-coupling reaction after the transmetalation of 1-naphthylmagnesium bromide with $ZnCl_2$

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[9] For Ni-catalyzed cross-coupling reactions, using other organometallics, see: (a) Han, J. W.; Tokunaga, N.; Hayashi, T. *Synlett* **2002**, 871. (b) Shirakawa, E.; Yamasaki, K.; Hiyama, T. *Synthesis* **1998**, 1544. (c) Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222. (d) Terao, J.; Nii, S.; Chowdhury, F. A.; Nakamura, A.; Kambe, N. *Adv. Synth. Cat.* **2004**, *346*, 905. (e) Percec, V.; Bae, J.-Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 6895−6903.

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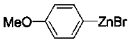
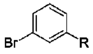
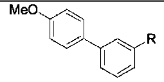
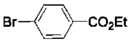
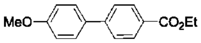
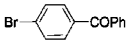
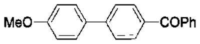
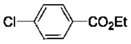
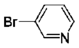
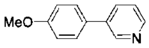
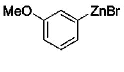
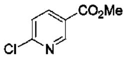
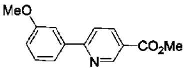
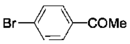
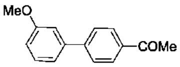
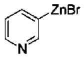
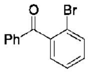
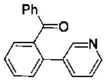
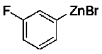
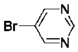
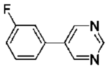
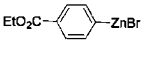
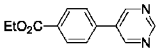
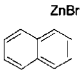
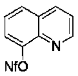
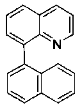
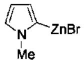
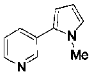
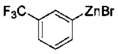
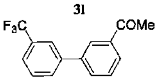
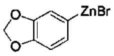
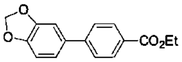
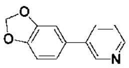
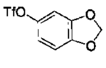
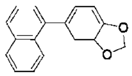
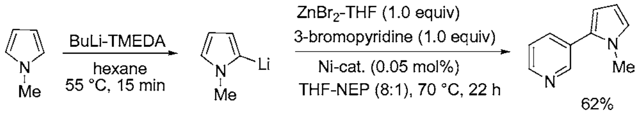
Table 1. Cross-Coupling Products of Type 3, Obtained by a Nickel-Catalyzed Cross-Coupling between Aryl Halides and Sulfonates with Functionalized Arylzinc Compounds in the Presence of $(EtO)_2P(O)H$ and DMAP

Entry	Arylzinc of type **2**	Aryl halide of type **1**	Product of type **3**	Reaction time (h)[a]	Yield (%)[b]
					
1	**2a**	**1a** : R=F	**3a** : R=F	2	79
2	**2a**	**1b** : R=CO_2Et	**3b**: R=CO_2Et	6	91
3	**2a**	 **1c**	 **3c**	6	87
4	**2a**	 **1d**	 **3d**	3	73
5	**2a**	 **1e**	**3c**	48	83
6	**2a**	 **1f**	 **3e**	2 (12)[c]	81 (68)[c] (82)[g]
7	 **2b**	 **1g**	 **3f**	24	74
8	**2b**	 **1h**	 **3g**	2.5	77
9	 **2c**	 **1i**	 **3h**	3	76[d]
10	 **2d**	 **1j**	 **3i**	1	82
11	 **2e**	**1j**	 **3j**	24	60
12	 **2f**	 **1k**	 **3k**	24	88
13	 **2g**	**1f**	 **3l**	22	62[e]
14	 **2h**	**1h**	 **3m**	18	68
15	 **2i**	**1e**	 **3n**	5	94
16	**2i**	**1f**	 **3o**	5	83
17	**2f**	 **1l**	 **3p**	24	79 (77)[f]

[a] Reaction time at 25 °C. [b] Yield of analytically pure product. [c] Reaction time and yield, obtained by using 3-chloropyridine as a substrate. [d] Reaction performed at 50 °C. [e] Reaction performed at 70 °C. [f] Yield obtained by using 1-naphthylzinc chloride as a reagent. [g] 20 mmol scale reaction.

Scheme 2. Synthesis of β-Nicotyrine



or $ZnBr_2$ proceeded with practically the same yields (77–79%, entry 17).

In many cases, our cross-coupling reaction can be performed with even much lower catalyst loadings. For instance, the cross-coupling between 4-methoxyphenylzinc bromide and ethyl 4-bromobenzoate or 5-bromopyrimidine were complete at room temperature in the presence of $NiCl_2$ (0.0025 mol %), $(EtO)_2P(O)H$ (0.01 mol %), DMAP (0.01 mol %) catalyst after 24 h. In these cases, even nickel that was present as an admixture in commercial $ZnBr_2$ (about 1 ppm, measured by atomic absorption spectroscopy method) caused the formation of significant amounts of the cross-coupling products. The source of such high efficiency of $(EtO)_2P(O)H$ and the role of DMAP in the ligand complex is not yet clear, and the reaction mechanism is currently under further investigation in our laboratory.

In summary, we have developed an efficient Ni-catalyzed cross-coupling reaction of arylzinc halides with aryl bromides, triflates and activated chlorides, using very small amount of $NiCl_2$ (0.05 mol %) with $(EtO)_2P(O)H$ and DMAP (0.2 mol % each) as ligands. The reaction scope is broad and most of the cross-couplings proceed at room temperature.

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Supporting Information Available: Experimental procedures and full characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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