Nickel-Catalyzed Reductive Cross-Coupling of Aryl Halides

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Received: 27.12.2012; Accepted after revision: 28.01.2013

Abstract: This work highlights unsymmetrical biaryl compounds via direct nickel-catalyzed reductive coupling of two aryl halides. By tuning the ligand structures, the reaction of two electron-enriched aryl halides also provided the coupling product in good yields, with an excess of 1.4 equivalents of one of the halides. The mild reaction conditions display excellent functional-group tolerance and generally gave the coupling products in moderate to good yields. In addition to aryl bromides, activated aryl chlorides are effective.

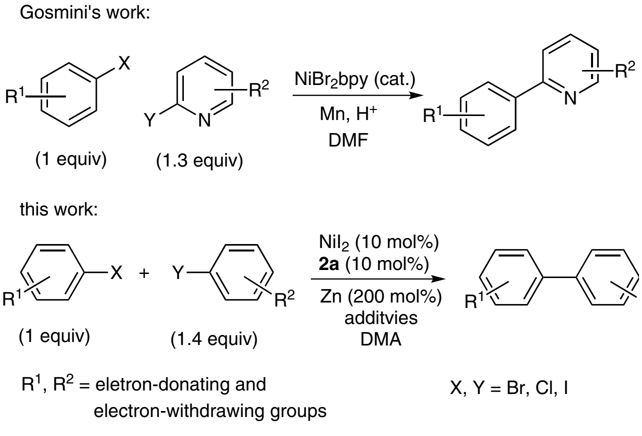
Key words: nickel, cross-coupling, biaryl, aryl halides

Aryl–aryl compounds are important organic units that are often found as part of skeletons in natural products[2] and have been intensively applied to several fields, including ligand design[3] and materials science.[4] As such, numerous methods have been developed in the synthesis of aryl–aryl bonds.[2,3,5] In particular, unsymmetrical biaryl compounds are generally obtained via conventional cross-coupling protocols involving organometallic reagents and aryl electrophiles.[2,3,5] In addition to direct coupling of aryl C–H bonds,[6] reductive coupling of two aryl electrophiles, in particular the Ni-catalyzed dimerization and oligomerization of aryl electrophiles, has also become a straightforward approach to aryl–aryl compounds in which the preparation of organometallic reagents can be avoided.[5]

However, direct reductive coupling of two unsymmetrical aryl electrophiles, for example, halides, is generally less effective due to intrinsic poor chemoselectivities between two structurally similar aryl coupling partners.[7] Although a variety of transition metals including Co, Ni, and Pd have been successfully employed, no general solutions have been achieved to overcome the poor selectivity issue.[5,7,8] Gosmini recently developed a relatively efficient cobalt-catalyzed method for the coupling of electron-deficient with electron-enriched aryl and heteroaryl halides.[7a] However, the reactions require the use of two equivalents of the second aryl halides, and generally moderate to good yields are obtained.

On the other hand, Gosmini further demonstrated that the Ni-catalyzed electrochemical and chemical coupling of aryl with pyridyl/pyrazinyl halides offered a facile synthetic route to unsymmetrical aryl–pyridyl or aryl–pyrazinyl compounds (Scheme 1).[7b] The use of Zn and Mn as the terminal reductant allowed the effective coupling of equimolar electron-poor 2-chloropyrimidine or 2-chloropyrazine with functionalized aryl halides. The high coupling efficiency appears to be a result of taking advantage of the gap of electronic properties between pyridine/pyrazine and benzene-derived aromatics. It should also be noted that bipyridine was the only ligand being investigated in the Ni-catalyzed protocols. In addition, both the cobalt and nickel methods suffer from limitations in substrate scope. For example, the coupling of two electron-enriched aryl halides has not been reported, and the nickel method is limited to N-heteroaryl halides with aryl iodides. It is therefore important to further optimize the nickel-catalyzed strategies, in particular the examination of other ligands so as to achieve higher compatibility for broader scope of substrates.

With our recent success in the nickel-catalyzed reductive coupling of alkyl halides with other electrophiles,[9–11] we reasoned that under nickel-catalyzed conditions, the efficiency of reductive coupling of two different aryl halides may be improved by tuning the reaction parameters such as ligand structures, solvent, and temperature, which may provide a complementary solution to the current methods. In this paper, we highlight the Ni-catalyzed reductive coupling of two different benzene-derived aromatic halides. The reactions were carried out at ambient temperature with a wide range of functional groups being tolerated (Scheme 1).



Scheme 1 Nickel-catalyzed chemically reductive synthesis of unsymmetrical biaryl compounds

After extensive investigation of the reaction conditions for the coupling of bromobenzene (100 mol%) and electron-enriched aryl bromide **1** (140 mol%), we identified that NiI$_2$ (10 mol%) as the precatalyst, 4,4′-dimethylbi-

SYNLETT 2013, 24, 0619–0624
Advanced online publication: 20.02.2013
DOI: 10.1055/s-0032-1318237; Art ID: ST-2012-W1102-L

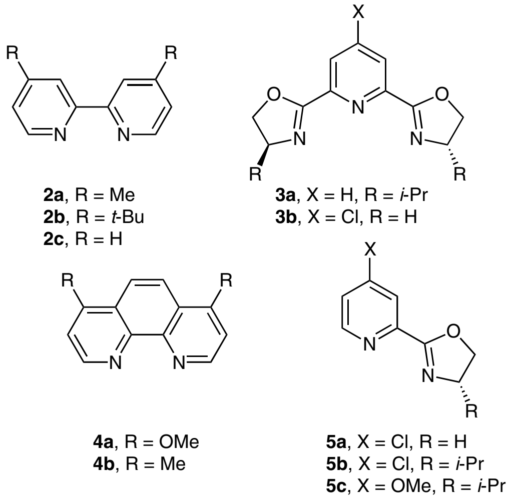
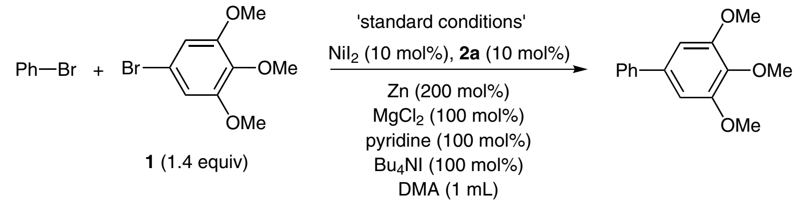


Figure 1 Structures of ligands

pyridine (10 mol%) as the ligand, zinc powder (200 mol%) as the reductant, in the presence of $MgCl_2$ (100 mol%), pyridine (100 mol%), and Bu_4NI (100 mol%) in DMA provided the coupling product in a best yield of 63% (Table 1, entry 1). The addition of Bu_4NI seems to be important as the yield decreased to 53% without it, possibly due to the removal of the salts on the zinc surface (Table 1, entry 2). In the initial search for the optimal conditions with no addition of Bu_4NI, other ligands such as tridentate pybox ligands **3a** and **3b**, bidentate ligands **2b**–**c**, **4a**–**b**, **5a**–**c** (Figure 1), other nickel sources such as $NiBr_2$ and $Ni(cod)_2$, and other solvent such as DMF were less effective (Table 1, entries 3–15). The use of other additives is also important. Without pyridine and Bu_4NI no product was observed (Table 1, entry 15). We reasoned that the role of $MgCl_2$ and Bu_4NI is probably to remove the salts on the zinc surface. The major side reaction arose from the homocoupling of aryl halides. On the other hand, the use of two equivalents of **1** decreased the yield (Table 1, entry 16).

With the optimized conditions in hand, the limitation and scope of the aryl halides were examined (Table 2). In contrast to **1**, reaction of bromobenzene with electron-enriched 1-bromo-3,4-dimethoxybenzene and 1-bromo-4-methoxybenzene provided the coupling products in 56%

Table 1 Optimization of the Reaction Conditions



Entry	Deviation from the standard conditions	Yield (%)[a]
1	none	63
2	without Bu_4NI	53
3	**2b** instead of **2a**, without Bu_4NI	48
4	**2c** instead of **2a**, without Bu_4NI	48
5	*i*-Pr-Pybox **3a** instead of **2a**, without Bu_4NI	trace
6	Cl-Pybox **3b** instead of **2a**, without Bu_4NI	22
7	**4a** instead of **2a**, without Bu_4NI	trace
8	**4b** instead of **2a**, without Bu_4NI	36
9	**5a** instead of **2a**, without Bu_4NI	<10
10	**5b** instead of **2a**, without Bu_4NI	trace
11	**5c** instead of **2a**, without Bu_4NI	trace
12	$NiBr_2$ and **2b** instead of NiI_2 and **2a**, without Bu_4NI	35
13	$Ni(cod)_2$ and **2b** instead of NiI_2 and **2a**, without Bu_4NI	trace
14	DMF instead of DMA, without Bu_4NI	39
15	**2b** instead of **2a**, 100 mol% $MgCl_2$, without pyridine, without Bu_4NI	n.d.
16	PhBr/**1** = 1:2	22

[a] Isolated yields.

and 28% yield (Table 2, entries 1 and 2), suggesting a more electron-rich aromatic ring with respect to benzene promote the coupling efficiency. However, the coupling efficiency of bromobenzene with 1-bromo-4-methoxybenzene can be boosted when 4,4′-di-*tert*-butylbipyridine (**2b**) was used as the ligand. Interestingly, coupling of 1-bromo-4-methoxybenzene with **1** generated the desired product in 60% yield (Table 2, entry 3). The use of 1-chloro-4-methoxybenzene was comparable to the bromo analogue (Table 2, entry 4). The use of benzyl 4-bromophenylcarbamate as the limiting reagent, coupling with 1-bromo-4-methoxybenzene offered the biaryl product in 54% yield, although a relatively acidic NH was present (Table 2, entry 5). In addition, 1-bromo-3-methoxybenzene appeared to be as efficient as 1-bromo-4-methoxybenzene (Table 2, entry 6). Coupling of bromobenzene with electron-deficient aryl bromides and chlorides also provided the coupling products higher than 60% (Table 2, entries 7–9). When the electron-deficient aryl chlorides and bromides were employed as the limiting reagents, coupling with **1**, bromobenzene, and other electron-deficient aryl chlorides or bromides usually resulted in low yields (Table 2, entries 10–14), although a 52% yield was observed for the coupling of methyl 4-bromobenzoate and bromobenzene (Table 2, entry 11). Finally, coupling of electron-enriched 5-iodo-1,2,3-trimethoxybenzene and 5-bromo-1,2,3-trimethoxybenzene with methyl 4-iodobenzoate and 1-(4-bromophenyl)ethanone, provided the products in 55% and 57% yield, respectively (Table 2, entries 15 and 16). The electron-enriched 1-iodo-4-methoxybenzene and its bromo analogue, on the other hand, only delivered 32% and trace yields of the coupling product with methyl 4-bromobenzoate and 1-(4-bromophenyl)ethanone, respectively (Table 2, entries 17 and 18), suggesting that certain difference of electron properties between the coupling partners is important for the high coupling efficiency.

Table 2 Examples of the Synthesis of Unsymmetrical Biaryl Compounds

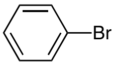
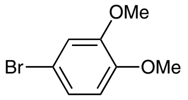
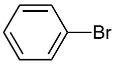
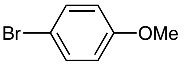
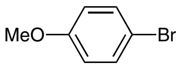
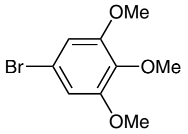
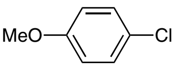
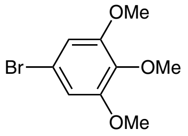
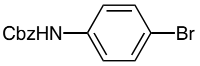
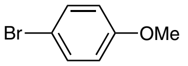
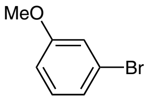
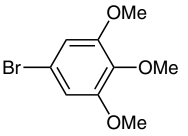
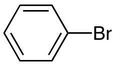
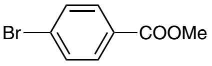
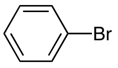
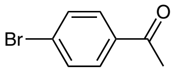
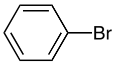
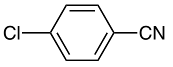
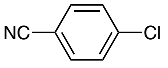
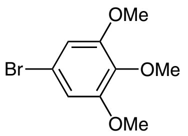
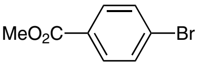
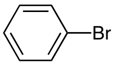
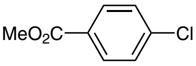
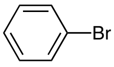
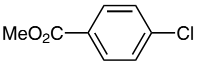
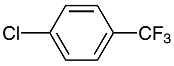
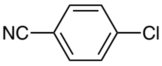
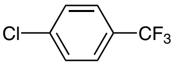
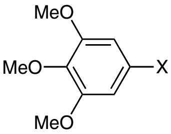
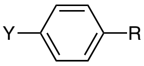
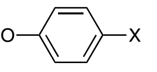
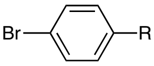
Entry	Ar^{1}X (1 equiv)	Ar^{2}Y (1.4 equiv)	Yield of Ar^{1}Ar^2 (%)[a]
1			56
2			28 (55)[b]
3			60
4			58
5			54
6			61
7			65
8			64
9			60
10			43

Table 2 Examples of the Synthesis of Unsymmetrical Biaryl Compounds (continued)

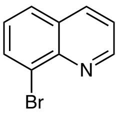
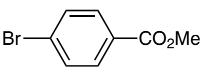
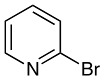
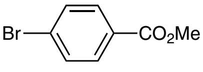
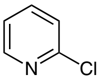
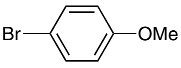
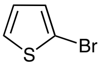
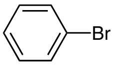
Entry	Ar^1X (1 equiv)	Ar^2Y (1.4 equiv)	Yield of Ar^1Ar^2 (%)[a]
11			52
12			40
13			48
14			30
15 16	 X = I, Br	 Y = I, R = CO_2Me Y = Br, R = C(O)Me	55 57
17 18	 X = I, Br	 R = CO_2Me R = C(O)Me	32 trace

[a] Isolated yields.

[b] 4,4′-Di-*tert*-butylbipyridine (**2b**) was used.

To further test the compatibility of this unsymmetrical biaryl formation method, we used heteroaromatic halides as substrates for the coupling with aryl bromides (Table 3). To our surprise, 8-bromoquinoline gave the coupling product in excellent yield, implying that coordination of 1-nitrogen to the nickel center played an important role (Table 3, entry 1). The coupling of pyridine derivatives such as 2-bromo- and 2-chloropyridine with methyl 4-bromobenzoate and 1-bromo-4-methoxybenzene delivered the coupling products in 68% and 52% yield, respectively (Table 3, entries 2 and 3). Reaction of 2-bromothiophene with bromobenzene did not generate the desired product.

Table 3 Coupling of Hetereoaromatic Halides

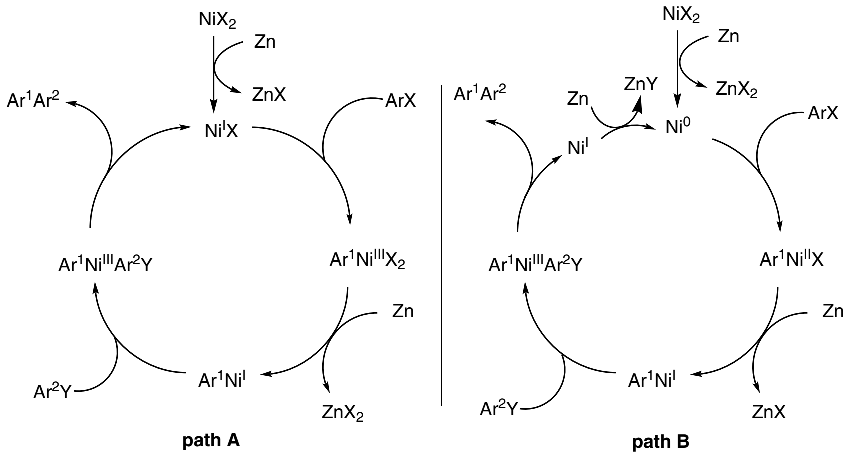
Entry	$HetAr^1X$	Ar^2Y	Yield of $HetAr^1Ar^2$ (%)[a]
1			86
2			68
3			52
4			n.d.[b]

[a] Isolated yields.

[b] n.d. = not detected.

To test whether the reaction proceeds through an in situ Negishi process, we first conducted the cross-coupling of the halides as in entries 3 and 11 in Table 2, using the optimized conditions but in the absence of ligand. Only recovered aryl bromides were isolated, suggesting that in the absence of ligand under the Ni/Zn conditions neither electron-rich nor electron-poor aryl bromides were converted into organozinc reagents. In addition, coupling of dimethyl 4-bromophthalate-derived organozinc·LiCl with **1** using the optimized conditions, without zinc powder, did not generate the cross-coupling product but recovered aryl bromide **1**. Therefore, the in situ Negishi process is excluded.

Gosmini's mechanistic proposal for the Co-catalyzed biaryl formation, a Co^{I} to Co^{III} process was discussed without in situ formation of organo-Mn reagents followed by Negishi-type reaction.[7a] Also in line with the studies on the catalytic and stiochiometric Ni^{I}-catalyzed dimerization of aryl halides leading to symmetric biaryl compounds[5,12] we proposed a similar Ni^{I}/Ni^{III} catalytic process in the current method. $Ni^{II}X_2$ was first reduced to $Ni^{I}X$ by single-electron reduction with Zn, which then oxidatively adds to ArX to form an $Ar^1Ni^{III}X_2$ complex. Subsequent reduction of the $Ar^1Ni^{III}X_2$ complex with Zn generates an Ar^1Ni^{I} intermediate, which undergoes oxidative addition to Ar^2Y, forming an $Ar^1Ni^{III}Ar^2Y$ species prior to the product formation (Scheme 2). Alternatively, Ni^0 could be generated by two-electron reduction of $Ni^{II}X_2$ with Zn. Oxidative addition of aryl halide to Ni^0 generates an $Ar^1Ni^{II}X$ intermediate, which then undergoes a one-electron reduction to give an Ar^1Ni^{I} species (path B, Scheme 2).[12c,13] Similar to pathway A, an oxidative addi-



Scheme 2 Proposed catalytic cycle

tion of Ar^2Y to Ar^1Ni^I is followed by reductive elimination to give a second Ni^I, which is reduced to Ni^0.

In conclusion, we have optimized the Ni-catalyzed reductive coupling of two aryl halides by tuning the reaction parameters. With the present reaction conditions, reasonably good coupling results could be achieved for the electron-enriched aryl halides, wherein one of the coupling aryl halides requires only 1.4 equivalents excess. The coupling of electron-deficient pyridyl and quinoline bromides with benzene-based aryl halides also offered the coupling products in good to excellent yields. The mild reaction conditions also display excellent functional-group tolerance.

All experiments were carried out under dry nitrogen atmosphere. DMA (anhyd and 99.5% ultra pure, Acros), NiI_2 (anhyd, Alfa Aesar), anhyd $MgCl_2$ (Alfa Aesar), other chemicals were purchased from Aldrich Chemical company and were used without purification.

General Experimental Procedure
To a flame-dried Schlenk tube equipped with a stir bar was loaded ligand (10 mol%), zinc powder (200 mol%), and Bu_4NI (100 mol%). The tube was moved to a dry glove box, at which point NiI_2 (10 mol%) and $MgCl_2$ (100 mol%) were added. The tube was capped with a rubber septum, and it was moved out of the glove box. DMA (1 mL), aryl Ar^1X (0.15 mmol), Ar^2Y (0.21 mmol), and pyridine (100 mol%) were then added via syringe. After the reaction mixture was allowed to stir for 12 h under N_2 atmosphere at 25 °C, it was directly loaded onto a silica column without workup. The residue in the reaction vessel was rinsed with small amount of CH_2Cl_2. Flash column chromatography provided the product as a solid or oil.

Benzyl[4′-methoxy-(1,1′-biphenyl)-4-yl]carbamate (Table 2, Entry 5)
According to the general procedure, this compound was obtained as a white solid; mp 184–187 °C. IR (KBr): $\nu_{max} = 3327$ (O=CNH, ν_{NH}), 1702 [OC(O)N, $\nu_{C=O}$), 1229 (=$COCH_3$, ν_{CO}). ^1H NMR (500 MHz, $CDCl_3$): $\delta = 3.87$ (3 H, s), 5.25 (2 H, s), 6.74 (1 H, s), 6.99 (2 H, dt, $J = 8.7$, 2.8 Hz), 7.35–7.42 (2 H, m), 7.43–7.48 (4 H, m), 7.50–7.54 (4 H, m). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 55.7$, 67.4, 114.6 (2 C), 119.4 (2 C), 127.6 (2 C), 128.2, 128.7 (2 C), 128.8 (2 C), 129.0 (2 C), 133.5, 136.4, 136.5, 136.8, 154.1, 159.3. HRMS (EI): *m/z* calcd for $C_{21}H_{19}NO_3$: 333.1365; found: 333.1369 [$M^+ + 1$].

3,4,3′,5-Tetramethoxybiphenyl (Table 2, Entry 6)
According to the general procedure, this compound was obtained as a white solid; mp 89–92 °C. IR (KBr): $\nu_{max} = 2997$ (OCH_3, ν_{CH}), 2938 (OCH_3, ν_{CH}), 2834 (OCH_3, ν_{CH}), 1258 (=$COCH_3$, ν_{CO}). ^1H NMR (500 MHz, $CDCl_3$): $\delta = 3.87$ (3 H, s), 3.89 (3 H, s), 3.92 (6 H, s), 6.77 (2 H, s), 6.89 (1 H, dd, $J = 8.2$, 2.5 Hz), 7.09 (1 H, t, $J = 2.3$ Hz), 7.14 (1 H, m), 7.35 (1 H, t, $J = 7.9$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 55.4$, 56.2 (2 C), 60.9, 104.5 (2 C), 112.3, 113.2, 119.6, 129.8, 137.1, 137.7, 142.9, 153.4 (2 C), 159.9. HRMS (EI): *m/z* calcd for $C_{16}H_{18}O_3$: 258.1256; found: 274.1204 [$M^+ + 1$].

Acknowledgment

Financial support was provided by the Chinese NSF (Nos. 2097209 and 21172140), the general research grant (No. 10YZ04), and the Program for Professor of Special Appointment (Eastern Scholar) at Shanghai Institutions of Higher Learning Shanghai Education Committee. Dr. Hongmei Deng (Shanghai University) is thanked for help in the NMR facility.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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