Nickel Catalyzed Cross-Coupling and Amination Reactions of Aryl Nitriles

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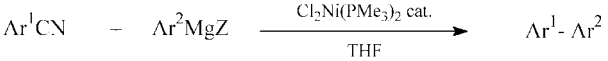
Abstract: Aryl nitriles have been found to participate in cross-coupling and amination reactions via nickel-catalyzed activation of the C–CN bond. With the development of these synthetically useful transformations, aryl nitriles can now be considered along with aryl halides and sulfonates as viable substrates for these types of reactions.

Key words: nitriles, nickel, cross-coupling, biaryls, aminations

Activation of the C–CN bond in aryl nitriles by transition metal complexes (Ni,[1] Pd,[1a] Pt,[1a,b,2] Mo,[3] Rh[4]) has been reported by several groups, including our own. Until now, however, these C–C bond activation processes have not been extended into synthetically useful reactions. With this goal in mind, we have recently developed efficient, novel procedures to prepare unsymmetrical biaryls,[1g] styrenes,[1i] and alkylated benzene derivatives[1i] via Ni-catalyzed cross-coupling reactions utilizing benzonitrile substrates. In theory, non-carbon nucleophiles could also participate in these cross-coupling reactions to afford hetero-substituted aromatic derivatives from aryl nitrile substrates. Indeed, we also report herein reaction conditions that for the first time allow Ni-catalyzed amination of the C–CN benzonitrile bond to take place and directly deliver the respective anilines. This paper presents an overview of this benzonitrile-based cross-coupling and amination chemistry.

During the course of catalyst optimization in our aryl halide-based unsymmetrical biaryl syntheses,[5] we observed that Me_3P-derived nickel catalysts delivered coupling products derived from activation of the C–CN bond when the aryl halide substrates also contained a nitrile functionality. Upon further examination of this novel aryl nitrile cross-coupling process, we observed that use of aryl zincs as coupling partners resulted in formation of significant amounts of homo-coupled and reductively decyanated byproducts besides the desired unsymmetrical biaryls. For example, reaction of 4-methoxybenzonitrile (2.0 mmol) with phenylzinc chloride (3.0 mmol; prepared in situ from PhMgCl and $ZnCl_2$) and $Cl_2Ni(PMe_3)_2$[6] (5 mol%) in THF at 60 °C for 8 hours gave a product mixture containing 4-methoxybiphenyl (0.90 mmol), 4,4′-dimethoxybiphenyl (0.23 mmol), biphenyl (0.82 mmol), anisole (0.38 mmol), and residual 4-methoxybenzonitrile (0.09 mmol).[7] Substitution of PhMgCl for the corresponding zinc reagent in the otherwise same reaction, however, gave negligible amounts of anisole and homo-coupled side products, producing 4-methoxybiphenyl (1.42 mmol) and 4-methoxybenzophenone imine (0.36 mmol) in the amounts indicated. Cross-coupling of aryl Grignard reagents with benzonitriles can proceed selectively without significant imine formation or homo-coupled side products if the Grignard reagent is first treated with a sterically bulky alkoxide (Scheme 1). Thus, reaction of PhMgCl with *t*-BuOLi in THF (60°C, 1 h), followed by treatment with 4-methoxybenzonitrile and $Cl_2Ni(PMe_3)_2$ catalyst under similar reaction conditions gave 4-methoxybiphenyl (1.59 mmol) and 4-methoxybenzophenone imine (0.05 mmol), along with residual 4-methoxybenzonitrile (0.12 mmol).[8] By comparison, similar derivatization of the PhMgCl with sterically smaller alkoxide reagents (e.g., LiOEt) prior to the coupling reaction gave the imine side product in higher amounts. On the other hand, treatment of PhMgCl with LiSPh, the lithium salt of BHT, or lithium diphenylphosphide resulted in only trace amounts, if any, of the corresponding imine being formed. Use of Me_3P ligand for the nickel catalyst is important to the success of this cross-coupling reaction; significantly lower yields are obtained from substitution of other phosphines.[10]



Scheme 1

The scope of this novel cross-coupling reaction is rather large, tolerating a wide variety of both benzonitrile and aryl Grignard substrates (Table 1). It is particularly noteworthy that all three cyanopyridines participate well in this biaryl forming reaction. Relative to the 2-, 3-, or 4-halopyridines, the corresponding cyanopyridines are considerably less expensive and are commercially available in their free base form (4-halopyridines may only be purchased as their respective hydrohalide salts). This fact should make cyanopyridines (vs. halopyridines) the preferred substrates from which to prepare pyridine-containing biaryls in pharmaceutical, fine chemical, or liquid crystal applications.[11]

We have also found that the scope of aryl nitrile based coupling reactions can be expanded to allow use of alkyl and alkenyl Grignard reagents, giving alkylated arenes and styrenes, respectively (Scheme 2). As shown in Table 2, this cross-coupling reaction accommodates a wide range of alkyl and alkenyl Grignard reagents, as well

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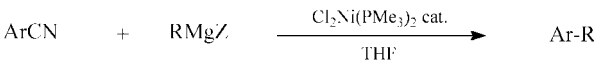
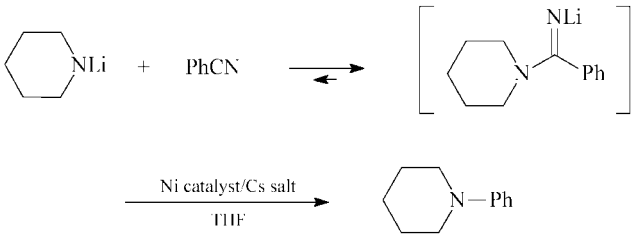
as a variety of aryl nitrile substrates. In general, alkenyl Grignard reagents can be expected to afford styrene adducts as mixtures of *E* and *Z* isomers. While the 1-propenyl Grignard derivative (entries 5, 7, 9, 10, 12, 13) was employed in these cross-couplings as an *E*/*Z* mixture and gave a mixture of stereoisomeric styrene products, Kumada has demonstrated that the coupling of stereodefined Grignard reagents under Ni-catalysis also produces a mixture of *E* and *Z* alkenes via isomerization of the nickel coordinated alkenyl magnesium reagent.[12] More sterically demanding alkenylmagnesium reagents also cross-couple efficiently under these reaction conditions to give synthetically useful yields of the desired styrene compounds (entries 1, 8). Cyclopropyl and other alkyl Grignard reagents also readily participate in this coupling reaction with aryl nitrile substrates.



Scheme 2

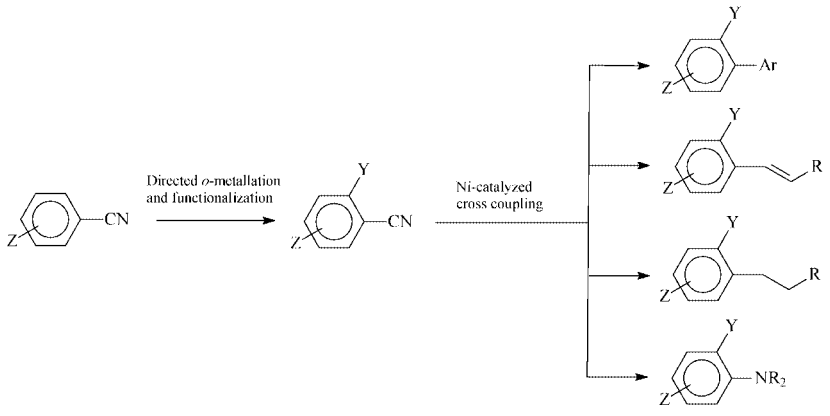
Ni[13] and Pd[14] catalyzed aminations of aryl halides and sulfonates are well established synthetic transformations. Since it is now apparent that aryl nitriles are also important substrates in carbon–carbon bond forming cross-coupling reactions, we have briefly examined the possibility of using aryl nitriles in similar amination reactions. Unfortunately, all attempts at aminating benzonitrile using $Cl_2Ni(PMe_3)_2$ as catalyst and otherwise 'typical amination conditions'[13,14] (i.e., secondary amine substrates and alkoxide bases) were unsuccessful and did not provide for more than trace amounts, if any, of the desired aryl amine products. Interestingly, when the secondary amine substrate (e.g., piperidine) was first deprotonated with BuLi and then allowed to react with benzonitrile in the presence of $Cl_2Ni(PMe_3)_2$ catalyst in refluxing THF, a small amount (<5% yield) of *N*-phenylpiperidine was produced after ca. 48 hours. By adding Cs_2CO_3 (1.5 equiv) to the same reaction mixture, the yield of *N*-phenylpiperidine was increased to 60% (via GC analysis) after reaction overnight. No *N*-phenylpiperidine was formed under comparable conditions in the absence of the Ni catalyst. This nitrile amination reaction possessed a long induction period (typically 4–8 h) during which little or no *N*-phenylpiperidine product was produced; the only product observed by GC analysis of the hydrolyzed reaction mixture during this time was the corresponding amidine derivative produced from addition of lithium piperidide to the nitrile moiety of benzonitrile (Scheme 3). It has not been established, however, whether this amidine adduct is truly a precursor to the aryl amination product.



Scheme 3

Upon further examination of this new aryl amination reaction, we found that nickel cyanide catalyst (without any added ligand) and CsF additive provided for a much more efficient amination medium. For example, reaction of lithium piperidide (2 equiv) with benzonitrile in the presence of $Ni(CN)_2 \cdot 4\,H_2O$ (5 mol%) and CsF (1.5 equiv) in refluxing THF gave *N*-phenylpiperidine in 73% yield after 8 h of reaction time. As opposed to the initial reaction conditions described above, there was relatively little 'induction period' observed under this protocol.

While this aryl nitrile amination reaction is still in an early stage of development, it is clear that its scope is certainly narrower than that of the corresponding amination of aryl halides. This limited scope is primarily due to the fact that the amine substrate must be employed as its 'preformed' lithium amide, which can lead to chemoselectivity issues in the reaction (e.g., metallation of acidic C–H bonds). However, as Table 3 shows, a reasonable variety of aryl nitriles and secondary amines may be utilized to deliver the respective aniline derivatives. While cyclic secondary amines work well in this amination reaction, product

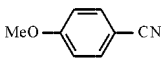
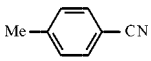
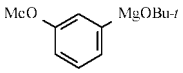
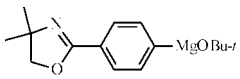
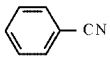
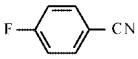
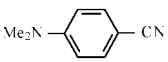
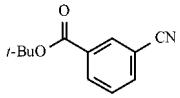
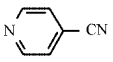


Scheme 4

yields are slightly lower when using acyclic amine substrates (entry 4). The reaction is completely regiospecific (entries 6–10), which, from a mechanistic standpoint, strongly disfavors the intermediacy of the respective benzynes. It is important to note that this reaction represents the first report of the direct conversion of aryl nitriles to their respective aniline derivatives.

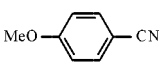
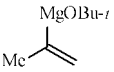
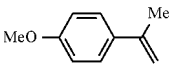
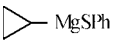
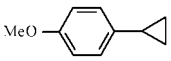
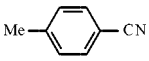
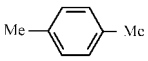
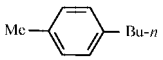
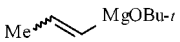
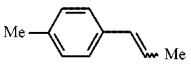
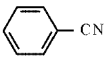
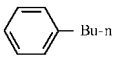
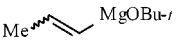
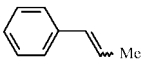
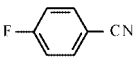
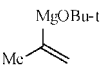
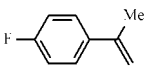
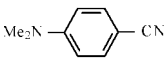
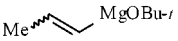
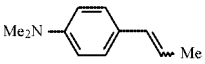
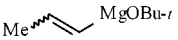
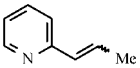
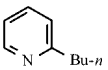
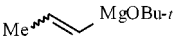
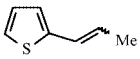
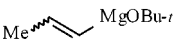
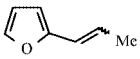
The nitrile moiety is a rather common aromatic substituent, and, as noted above, certain classes of aryl nitriles are significantly less expensive and more readily available than the corresponding aryl halides. Moreover, the nitrile group can allow for proximal aromatic functionalization-either by directly facilitating *ortho* aromatic metallation reactions[15] or by being easily derived from other useful directive metallation functionalty.[16,17] Taken together, the potential for *ortho* functionalization of an aromatic ring and participation in subsequent cross-coupling reactions further distinguishes aryl nitriles from aryl halides as attractive substrates upon which to base a synthetic scheme (Scheme 4). At the least, this new aryl nitrile-based cross-coupling and amination chemistry should represent a useful synthetic complement to similar aryl halide and sulfonate based chemistry.

Table 1 Synthesis of Biaryls via Ni-Catalyzed Coupling of Benzonitriles with Aryl Grignard Derivatives[a]

Entry	Ar^1CN	Ar^2MgZ	Reaction temp (°C) /time (h)	Ar^1–Ar^2 Yield (%)[b]
1		PhMgOBu-*t*	60/2	91
2		PhMgOBu-*t*	60/2[c]	88
3		PhMgSPh[d]	60/2	97
4			60/2	92
5			60/6	88[f]
6		*p*-TolMgOBu-*t*	60/2	88
7		*p*-TolMgOBu-*t*	60/2	82
8		PhMgOBu-*t*	60/6	82
9		PhMgSPh[d]	25/1	93
10		PhMgOBu-*t*	25/24	85
11		PhMgOBHT[e]	25/6	80[g]
12		PhMgSPh[d]	25/2	86[h]
13		*p*-TolMgOBu-*t*	60/2	78

[a] All reactions were carried out with stoichiometries, catalyst loadings, etc., as illustrated in the representative procedure.
[b] Chemical yields are by GC analysis using an internal reference standard and based on aryl nitrile. Unless otherwise indicated, starting nitrile was fully consumed in all cases.
[c] The catalyst was derived in situ from use of $Ni(acac)_2$ (5 mol%) and PMe_3 (10 mol%).
[d] Commercial 1 M solution of PhSLi in THF (Aldrich) was used to prepare this reagent.
[e] Prepared from treatment of a solution of 2,6-di-*tert*-butyl-4-methylphenol (BHT) in THF at 0 °C with an equimolar amount of BuLi.
[f] A small amount (6%) of starting aryl nitrile remained unreacted.
[g] A small amount (2%) of starting aryl nitrile remained unreacted.
[h] A small amount (8%) of starting aryl nitrile remained unreacted.

Table 2 Synthesis of Styrenes and Alkylated Aromatics via Ni-Catalyzed Coupling of Benzonitriles with Grignard Derivatives[a]

Entry	ArCN	RMgZ	Ar–R Product	Ar–R Yield (%)[b]
1				56[c]
2				64
3		MeMgOBu-*t*		66
4		BuMgOBu-*t*		43
5				80[c]
6		BuMgSPh		53[d]
7				77[c]
8				46
9				55[c]
10				59[c]
11		BuMgOBu-*t*		68
12				46[c]
13				46[c]

[a] All reactions were carried out with stoichiometries, catalyst loadings, etc., as illustrated in the representative procedure, and run overnight (15–18 h) at 60 °C.
[b] Chemical yields are by GC analysis using an internal reference standard and based on aryl nitrile. Starting aryl nitrile was fully consumed in all cases.
[c] The styrene product was obtained as a mixture of *E* and *Z* isomers.
[d] The imine byproduct (derived from direct attack of the Grignard reagent on the nitrile moiety of the benzonitrile substrate) was formed in 7% yield.
[e] The reaction was carried out overnight at 23 °C.

Table 3 Synthesis of Aryl Amines via Ni-Catalyzed Coupling of Benzonitriles with Secondary Amines[a]

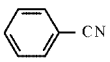
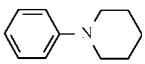
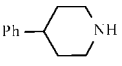
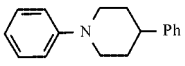
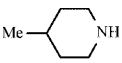
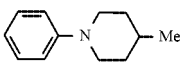
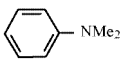
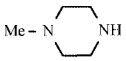
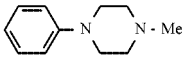
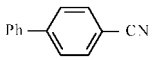
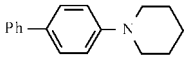
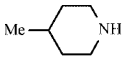
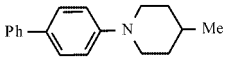
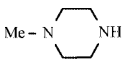
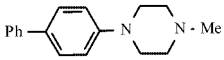
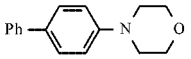
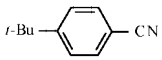
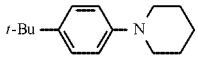
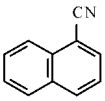
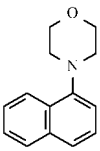
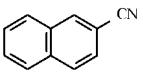
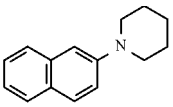
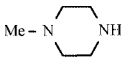
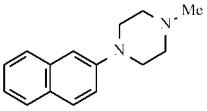
Entry	ArCN	R_2NH	Reaction Time (h)[c]	$ArNR_2$ Product	$ArNR_2$ Yield (%)[b]
1			8		73
2			<24[d]		61
3			6		69
4		Me_2NH	6.5		38

Table 3 Synthesis of Aryl Amines via Ni-Catalyzed Coupling of Benzonitriles with Secondary Amines[a] (continued)

Entry	ArCN	R_2NH	Reaction Time (h)[c]	$ArNR_2$ Product	$ArNR_2$ Yield (%)[b]
5			6		60
6			5		79
7			6		56
8			4.5		71
9			7		44[e]
10			6.5		44
11			6		49[e]
12			3		42[e]
13			3		77[e]

[a] All reactions were carried out with stoichiometries, catalyst loadings, etc., as illustrated in the representative procedure.
[b] Chemical yields are by GC analysis using an internal reference standard and based on aryl nitrile. Starting aryl nitrile and intermediate amidine adduct were consumed in all cases.
[c] Reaction time indicates the time required for full consumption of the amidine intermediate by GC analysis.
[d] The actual time needed for full conversion of amidine intermediate was not determined in this run.
[e] A reduced amount (1.5 equiv) of the lithium piperidide reagent (R_2NLi) was used.

All reactions were conducted under a nitrogen atmosphere. All chemicals and anhyd solvents were obtained from Aldrich Chemical Co. or VWR, except $Ni(CN)_2 \cdot 4\,H_2O$ which was purchased from Alfa Aesar and used without purification. Solutions of Grignard reagents and BuLi were titrated prior to use.[18] Chemical yields were obtained by GC analysis of a hydrolyzed reaction sample (using tridecane as an internal standard in the reaction mixture). The identity of all products were confirmed by NMR and/or mass spectrometry, and compared with commercially available samples when possible.

Dichlorobis(trimethylphosphine)nickel

A slightly modified procedure relative to that in the literature[19] was used to prepare this catalyst. A mixture of anhyd nickel chloride (2.80 g; 21.6 mmol) in anhyd EtOH (35 mL; containing 5% MeOH and 5% *i*-PrOH) was degassed via nitrogen purge and heated to 60 °C. The yellow slurry was treated with Ph_3P (25 mL; 1 M solution in toluene), and the mixture stirred at 60 °C for 1 h. After cooling gradually to –10 °C, the mixture was filtered to remove unreacted nickel chloride. The dark purple mother liquor was concentrated and the residue redissolved (with heating) in EtOH (50 mL). The clear, dark solution was refrigerated overnight, and the crystalline product was filtered and washed with cold EtOH followed by cold Et_2O to give dichlorobis(trimethylphosphine)nickel. Yield: 1.67 g; purple needles; mp 195–200 °C (Lit.[19] 199–200 °C).

4-Phenylanisole (Table 1, Entry 1); Unsymmetrical Biaryls from Aryl Nitriles; Representative Procedure

A solution of lithium *t*-butoxide in THF (4.4 mL of 1.0 M solution; Aldrich) was treated at r.t. with phenylmagnesium chloride (2.8 mL; 4.0 mmol; 1.40 M in THF) and the resulting solution heated at 60 °C for 1 h. After cooling to r.t., the reaction solution was treated with a solution of 4-methoxybenzonitrile (0.27 g, 2.0 mmol), dichlorobis(trimethylphosphine)nickel (0.028 g; 5 mol%), and tridecane (0.18 g, 1.0 mmol; internal GC standard) in THF (2 mL). The reaction mixture was heated to 60 °C and stirred for 2 h. A sample was withdrawn and quenched in a mixture of aq sodium citrate (1 M) and Et_2O. GC analysis of the organic phase of the hydrolyzed reaction sample showed the presence of 4-phenylanisole (1.82 mmol, 91%), 4-methoxybenzophenone imine (0.06 mmol), and no remaining 4-methoxybenzonitrile in the reaction mixture.

1-Cyclopropyl-4-methoxybenzene (Table 2, Entry 2); Styrenes and Alkylated Aromatics from Aryl Nitriles; Representative Procedure

A solution of lithium thiophenoxide in THF (4.0 mL of 1.0 M solution; Aldrich) was treated at 0 °C with cyclopropylmagnesium bromide (7.5 mL; 3.75 mmol; 0.50 M in THF) and the resulting solution was stirred at r.t. for 30 min and then heated at 60 °C for 1

h. The reaction solution was cooled to r.t. and added to a solution of 4-methoxybenzonitrile (0.249 g, 1.88 mmol), dichlorobis(trimethylphosphine)nickel (0.029 g, 5.5 mol%) and tridecane (0.196 g, 1.07 mmol; internal GC standard) in THF (2 mL). The reaction mixture was then heated at 60 °C for 15 h. A sample was withdrawn from the reaction and quenched with sodium citrate (1 M) and Et_2O. GC analysis of the organic phase of the hydrolyzed reaction mixture indicated the presence of 1-cyclopropyl-4-methoxybenzene (1.21 mmol, 64%) and cyclopropyl-(4-methoxyphenyl)methanone (0.21 mmol).

***N*-Phenylpiperidine (Table 3, Entry 1); Amines from Aryl Nitriles; Representative Procedure**

A stirred mixture of $Ni(CN)\cdot 4\,H_2O$ (0.054 g, 0.30 mmol), CsF (1.37 g, 9.0 mmol), and piperidine (1.0 g, 12 mmol) in anhyd THF (15 mL) was treated with BuLi (4.80 mL of 2.5 M solution; 11.7 mmol; Aldrich) at r.t.. After stirring the mixture for 10 min, benzonitrile (0.62 g, 6.0 mmol) and tridecane (0.55 g, 3.0 mmol; internal GC standard) were added and the resultant dark brown reaction mixture was heated to reflux. After stirring for 8 h at reflux, a sample was withdrawn from the reaction and quenched in a mixture of sodium citrate (1 M) and methyl *tert*-butyl ether. GC analysis of the organic phase of the hydrolyzed reaction mixture indicated the presence of *N*-phenylpiperidine (4.4 mmol, 73%), and no remaining benzonitrile or the corresponding amidine adduct.

Acknowledgements

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