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C–C Bond activation with selective functionalization: preparation of unsymmetrical biaryls from benzonitriles

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Abstract—For the first time, benzonitriles have been shown to participate in metal-catalyzed cross coupling reactions via activation of the C–CN bond. Thus, reaction of a benzonitrile with an aryl Grignard derivative in the presence of a Ni catalyst can readily provide the corresponding unsymmetrical biaryl in high yield and with high selectivity. © 2001 Elsevier Science Ltd. All rights reserved.

We recently described the synthesis of unsymmetrical biaryls via Ni- and Pd-catalyzed cross coupling of aryl zincs[1a] and aryl Grignard reagents[1b] with functionally substituted aryl halides. For example, coupling of PhZnCl with 4-chlorobenzonitrile takes place at room temperature in the presence of a $Ni(acac)_2/PPh_3$ catalyst to afford 4-phenylbenzonitrile selectively and in high yield. During the course of catalyst optimization for this transformation, we found that use of Me_3P-based Ni catalysts resulted in phenyl coupling occurring at *both the C–Cl and C–CN bonds* of 4-chlorobenzonitrile to yield 4-chlorobiphenyl, 4-phenylbenzonitrile, *p*-terphenyl, and many other higher oligomers.[2] We now report that this heretofore unknown reactivity of benzonitriles[3] has been parlayed into an efficient synthesis of unsymmetrical biaryls via their Ni-catalyzed coupling with aryl Grignard reagents (Eq. (1)).

Reaction of 4-methoxybenzonitrile (2.0 mmol) with phenylzinc chloride (3.0 mmol, prepared in situ from PhMgCl and $ZnCl_2$) and $Cl_2Ni(PMe_3)_2$[4] (5 mol%) in THF at 60°C for 8 h 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).[6] Interestingly, substitution of PhMgCl for the corresponding zinc reagent in the otherwise same reaction gave negligible amounts of anisole and homocoupled side products, producing 4-methoxybiphenyl (1.42 mmol) and 4-methoxybenzophenone imine (0.36 mmol) in the amounts indicated. If this Grignard reagent is first treated with an alkoxide, however, its Ni-catalyzed cross coupling with benzonitriles can proceed selectively without significant imine formation or homocoupled side products. Thus, reaction of PhMgCl with LiOBu-*t* 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).[7] By comparison, similar derivatization of the PhMgCl with LiOEt prior to the coupling reaction gave the imine side product in slightly higher amounts. On the other hand, treatment of PhMgCl with LiSPh or the lithium salt of BHT resulted in only trace amounts, if any, of the corresponding imine being formed.

$$Ar^1CN + Ar^2MgX/\text{“}LiZR\text{”} \xrightarrow{Cl_2Ni(PMe_3)_2\ \text{catalyst}} Ar^1\text{–}Ar^2 \quad (1)$$

Several features of this biaryl synthesis are worth noting. First, use of 2 equiv. of aryl Grignard derivative relative to the benzonitrile substrate generally provides higher yields of biaryl product and lower amounts of imine byproduct. Second, use of LiSPh as Grignard modifier gives very high yields of biaryl products with virtually no imine formation. In addition, this reagent may be easily removed from the product mixture during workup via base extraction. Third, essentially equivalent results are obtained using an in situ-prepared catalyst derived from $Ni(acac)_2$ and PMe_3 (Table 1, entry 2). Use of Me_3P is important to the success of this cross coupling reaction; significantly lower yields are obtained from substitution of other phosphines.[9] Fourth, use of sodium- or potassium *t*-butoxide provides cross coupling results similar to those derived from use of LiOBu-*t* as Grignard modifier. Finally, from a preparative standpoint, the small amount of imine

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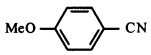
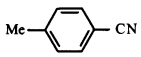
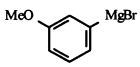
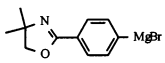
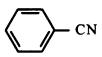
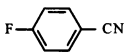
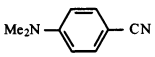
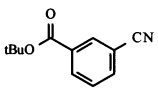
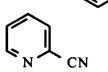
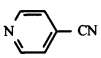
Table 1. Synthesis of biaryls via Ni-catalyzed coupling of benzonitriles with aryl Grignard derivatives[a]

Entry	Ar^1CN	Ar^2MgCl	"LiZR"	Reaction Temp/Time	Ar^1-Ar^2 Yield (%)[b]	Unreacted Ar^1CN (%)[b]
1		PhMgCl	LiOBu-t	60° C/2 h	91	0
2		PhMgCl	LiOBu-t	60° C/2 h[c]	88	0
3		PhMgCl	LiSPh[d]	60° C/2 h	97	0
4		PhMgCl	LiOBu-t	60° C/2 h	92	0
5			LiOBu-t	60° C/2 h	92	0
6			LiOBu-t	60° C/6 h	88	6
7		p-TolMgBr	LiOBu-t	60° C/2 h	88	<1
8		p-TolMgBr	LiOBu-t	60° C/2 h	82	0
9		PhMgCl	LiOBu-t	60° C/6 h	82	0
10		PhMgCl	LiSPh[d]	25° C/1 h	93	0
11		PhMgCl	LiOBu-t	25° C/24 h	85	0
12		PhMgCl	LiOBu-t	60° C/1 h[e]	69	0
13		PhMgCl	LiOBHT[f]	25° C/6 h	80	2
14		PhMgCl	LiOBHT[f]	25° C/6 h	75	0
15		PhMgCl	LiSPh[d]	25° C/2 h	86	8
16		p-TolMgBr	LiOBu-t	60° C/2 h	78	--[g]

[a] All reactions were carried out with stoichiometries, catalyst loadings, etc. as illustrated in the representative procedure[11].
[b] Chemical yields are by GC analysis using an internal reference standard.
[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 in THF (Aldrich).
[e] A solution of 3-cyanopyridine in THF was added dropwise at 60°C over a 10–15 min period to a mixture of PhMgCl/LiOBu-*t* and Ni catalyst.
[f] Prepared from treatment of a solution of 2,6-di-*t*-butyl-4-methylphenol ('BHT') in THF at 0°C with an equimolar amount of BuLi.
[g] Due to its volatility, 2-furonitrile could not be observed by GC analysis.

byproduct is easily removed from 'neutral' organic biaryl products via extraction with dilute acid (e.g. 1 M HCl).

As shown in Table 1, the scope of this novel cross coupling reaction is rather large, tolerating a wide variety of both benzonitrile and aryl Grignard substrates. Thus, the reaction proceeds readily whether the benzonitrile substrate is substituted with electron donating or withdrawing groups. In addition, the reaction conditions tolerate the presence of many functionalities, including ether and ester groups, basic nitrogen-containing substrates, and heterocyclic derivatives. Concerning the latter, 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 stable and available in their free base form (4-halopyridines are only available commercially as the corresponding hydrohalide salts).

The cleavage of the benzonitrile C–CN bond and its subsequent selective functionalization is unprecedented and truly remarkable. Clearly, this new methodology represents a valuable addition to the aryl halide and

-sulfonate substrates typically employed in cross coupling reaction schemes to prepare unsymmetrical biaryls.[10] From a conceptual viewpoint, Ni-catalyzed activation of this same C–CN bond followed by alternate means of functionalization has the potential to produce a host of other useful products. We are vigorously pursuing these additional synthetic possibilities in our laboratories.

Acknowledgements

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References

1. (a) Miller, J. A.; Farrell, R. P. *Tetrahedron Lett*. **1998**, *39*, 6441; (b) Miller, J. A.; Farrell, R. P. *Tetrahedron Lett*. **1998**, *39*, 7275.
2. Also, detected in the reaction mixture by GCMS analysis were 4,4′-dichlorobiphenyl, 4-(4′-chlorophenyl)benzonitrile, 4-cyano-*p*-terphenyl, 4-chloro-*p*-terphenyl, *p*-tetraphenyl, 4-cyano-*p*-tetraphenyl, and 4-chloro-*p*-tetraphenyl.
3. The reversible insertion of the benzonitrile C–CN bond by a Ni(0) species has recently been described: Garcia, J. J.; Jones, W. D. *Organometallics* **2000**, *19*, 5544.
4. A slightly modified procedure relative to that in the literature[5] was used to prepare this catalyst: A mixture of anhydrous nickel chloride (2.80 g, 21.6 mmol) in anhydrous ethanol (35 mL, containing 5% methanol and 5% isopropanol) was degassed via nitrogen purge and heated to 60°C. The yellow slurry was treated with trimethylphosphine (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 ethanol (50 mL). The clear, dark solution was refrigerated overnight, and the crystalline product was filtered and washed with cold ethanol followed by cold ether. The yield of dichlorobis(trimethylphosphine)nickel (as purple needles) was 1.67 g (mp = 195–200°C, lit. mp[5] = 199–200°C).
5. Mathis, M.; Harsha, W.; Hanks, T. W.; Bailey, R. D.; Schimek, G. L.; Pennington, W. T. *Chem. Mater*. **1998**, *10*, 3568.
6. These results were obtained by GC analysis of a reaction sample (containing tridecane as an internal standard) quenched in a mixture of 1 M sodium citrate (aq) and ether.
7. A 'spot test'[8] confirmed the presence of cyanide ion in the aqueous phase of the quenched reaction mixture.
8. Feigl, F.; Anger, V. *Analyst* **1966**, *91*, 282.
9. Among phosphines screened, the relative order of effectiveness in this cross coupling reaction is: $Me_3P >> Me_2PPh \approx Et_3P > MePPh_2 \approx Me_2PCH_2CH_2PMe_2 > Ph_3P > (C_6H_{11})_3P$.
10. For a review of biaryl syntheses, see: Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263.
11. Representative procedure: (4-phenylanisole, entry 1). A solution of lithium *t*-butoxide in THF (4.4 mL of 1.0 M solution, Aldrich) was treated at room temperature 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 room temperature, 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 1 M sodium citrate (aq) and ether. GC analysis of the organic phase of the hydrolyzed reaction sample showed the presence of 1.82 mmol (91% yield) of 4-phenylanisole, 0.06 mmol of 4-methoxybenzophenone imine, and no remaining 4-methoxybenzonitrile in the reaction mixture.