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Nickel catalyzed cross-coupling of modified alkyl and alkenyl Grignard reagents with aryl- and heteroaryl nitriles: activation of the C–CN bond

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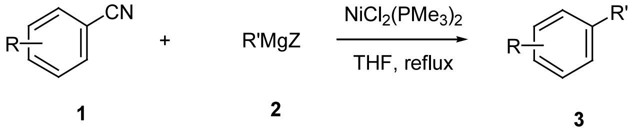
Abstract—The nickel catalyzed cross-coupling of alkyl and alkenyl Grignard reagents with aryl nitrile derivatives affords good yields of the corresponding aryl alkanes or aryl alkenes via activation of the C–CN bond. To prevent direct addition of the nucleophile to the nitrile group, the reactivity of the Grignard reagent was modulated by reaction with either LiO*t*-Bu or PhSLi prior to cross-coupling. The optimum catalyst was determined to be $NiCl_2(PMe_3)_2$, which is a convenient air stable commercially available complex. © 2003 Published by Elsevier Science Ltd.

Transition-metal (usually as Pd(0) or Ni(0) complexes) coupling reactions have taken a prominent role in the formation of C–C bonds. The cross-coupling of organozinc, organoborane, organomagnesium, and organostanannes with aryl or alkenyl halides are all standard procedures in modern organic synthesis.[1] In most cases the corresponding organohalide derivatives are utilized as the coupling partner. Recently, efforts have been made to expand the scope of the reaction and substrates which were previously deemed unreactive (e.g. aryl fluorides, carbamates, thioethers) have now been found to be suitable in transition-metal cross-coupling procedures.[2] Interestingly, the activation of the C–CN bond of benzonitriles using nickel catalysis has been previously described.[3] However, until our recent disclosure, this C–C bond cleavage reaction had not been exploited in a synthetically useful fashion. We reported last year that the $NiCl_2(PMe_3)_2$ mediated C–CN bond activation of benzonitriles could be parlayed into a useful preparation of unsymmetrical biaryls.[4] For example, the coupling of benzonitrile with *p*-tolMgCl/*t*-BuOLi in the presence of this nickel catalyst provides an 88% yield of the desired coupling product Ph-tol. The Grignard reagents were typically modified by the addition of either *t*-BuOLi or PhSLi to reduce the amount of nucleophilic addition to the nitrile group during the cross-coupling event. The purpose of this Letter is to expand the synthetic scope of this Ni-catalyzed coupling reaction to allow use of alkyl and alkenyl Grignard reagents (RMgX/*t*-BuOLi or PhSLi).

A survey of catalysts indicated that $NiCl_2(PMe_3)_2$ was generally superior to other Ni or Pd based catalyst systems.[5,6] It is interesting to note that palladium catalyst precursors ($Pd(dba)_2$, PMe_3) could participate in the cross-coupling of the nitrile substrates, however, the yields were too low for the reaction to have any synthetic value. For example, under the Pd(0) conditions described above, the reaction of 4-methoxybenzonitrile and 1-propenyl magnesium *tert*-butoxide provided a small amount (8/1 mixture of **1a** and **3a**) of the cross-coupling product **3a**.

The synthetic scope of the cross-coupling of various benzonitriles with modified Grignard reagents is illustrated in Table 1 and Scheme 1. As can be seen from the list of results the coupling procedure can be applied to benzonitrile derivatives with both electron donating substituents (entries 1–5) in the *para* position as well as electron withdrawing functionality (entry 13). In general, the alkenyl Grignard reagent **2a** (*E*/*Z* mixture)



Scheme 1. Nickel(0) promoted cross-coupling of alkyl- and alkenylmagnesium reagents and benzonitriles (see Table 1).

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Table 1. $NiCl_2(PMe_3)_2$ catalyzed cross-coupling of ArCN with organomagnesium reagents[d,e]

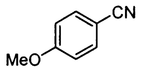
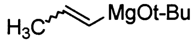
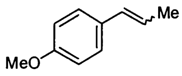
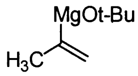
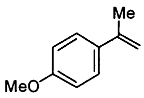
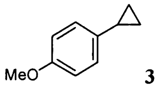
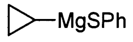
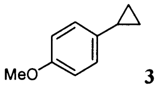
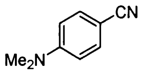
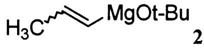
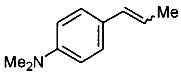
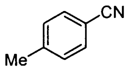
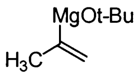
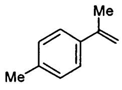
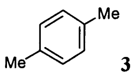
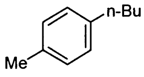
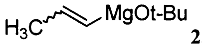
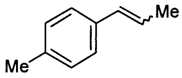
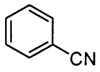
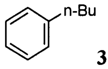
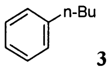
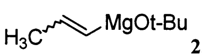
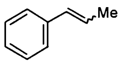
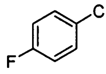
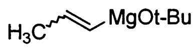
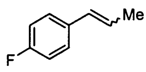
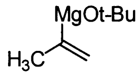
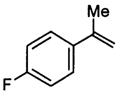
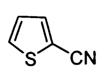
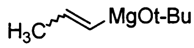
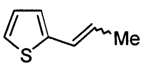
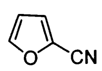
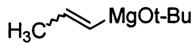
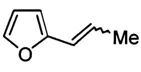
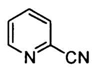
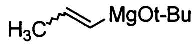
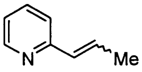
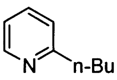
Entry	Aromatic Nitrile	Grignard	Product	Temperature (°C)	Yield %
1	 **1a**	 **2a**	 **3a**	60	70%[a]
2		 **2b**	 **3b**	60	56%
3		 **2c**	 **3c**	60	33%
4		 **2d**	 **3c**	60	64%[d]
5	 **1b**	 **2a**	 **3d**	60	55%[a]
6	 **1d**	 **2b**	 **3e**	60	53%
7		CH₃MgOt-Bu **2e**	 **3f**	60	66%
8		n-BuMgO-tBu	 **3g**	60	43%
9		 **2a**	 **3h**	60	80%[a]
10	 **1i**	n-BuMgSPh **2g**	 **3i**	60	53%[b]
11		n-BuMgOt-Bu **2f**	 **3i**	60	51%[c]
12		 **2a**	 **3j**	60	77%[a]

Table 1. (Continued)

13	 **1e**	 **2a**	 **3k**	60	66%^{a,f}
14		 **2b**	 **3l**	60	46%^{f}
15	 **1f**	 **2a**	 **3m**	60	46%^{a}
16	 **1g**	 **2a**	 **3n**	60	46%^{a}
17	 **1h**	 **2a**	 **3o**	23	59%^{a}
18		n-BuMgOt-Bu **2f**	 **3p**	23	68%

(a) E/Z mixture.

(b) The addition product of the Grignard to benzonitrile was formed in 7% yield.

(c) The addition product of the Grignard to benzonitrile was formed in 26% yield.

(d) For representitive procedure see reference 8. All cross-coupling reactions were run overnight (15-18 h).

(e) All yields were determined by GC using an internal standard.

(f) Activation of the C-F bond also occurs in the reaction of 4-fluorobenzonitrile with the modified alkenylmagnesium Grignard. The resulting cross-coupling provided trace amounts (5%) of the 1,4-dialkenylbenzene derivative by GC/MS.

provides styrene adducts (**3a**, **d**, **h**, **j**, **m**–**o**) as a mixture of *E* and *Z* isomers. Kumada has demonstrated that the coupling of stereodefined Grignard reagents under Ni(0)-catalysis produces a mixture of (*E*) and (*Z*) alkenes via isomerization of the nickel coordinated alkenyl magnesium reagent.[7] More sterically demanding organomagnesium reagents such as (**2b**) are also compatible to the Ni catalyzed cross-coupling methodology affording synthetically useful yields of the desired styrene compounds (**3b**,**e**, and **l**). The cyclopropyl Grignard reagent couples efficiently, however, the yield of the reaction is superior if the thiophenoxide derivative (**2d**) is used as the cross-coupling partner (compound **3c**, entries 3 and 4). In addition, heterocyclic nitrile compounds such as 2-thiophene carbonitrile **1f** and 2-furan carbonitrile **1g** are also effective substrates in this nickel catalyzed carbon–carbon bond forming procedure (entries 15 and 16). This Ni(0)-catalyzed method is ideal for the construction of alkylarenes via the coupling of benzonitriles with modified alkyl Grignard reagents. Thus, the coupling of either MeMgO*t*-Bu or *n*-BuMgO*t*-Bu with *p*-methylbenzonitrile **1d** provides the desired arene compounds *p*-xylene and *n*-butyltoluene in 66% and 43% yield respectively (entries 7 and 8).

In summary, the nickel catalyzed cross-coupling of aryl nitriles and Grignard reagents provides an efficient method for the preparation of styrene and alkyl arene derivatives via activation of the C–CN bond by Ni catalysis. We are continuing to pursue other related transformations of this novel chemistry in our laboratories.

Acknowledgements

The authors would like to thank Professor B. M. Trost (Stanford University) for helpful discussions concerning this work.

References

1. For general references, see: (a) Negishi, E.-i.; Liu, F. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp. 1–48; (b) Farina, V. In *Comprehensive Organometallic Chemistry II*; Abel, E. W.; Stone, F. G. A.; Wilkinson, G.; Hegedus, L. S., Eds.; Pergamon: Oxford, 1995; Vol. 3.4, pp. 161–

240. (c) For a review on nickel catalyzed cross-coupling of Grignard reagents and aryl halides, see: Kumada, M. *Pure Appl. Chem.* **1980**, *52*, 669.

2. (a) For an example of C–F bond activation of aryl fluorides, see: Bohm, V. P. W.; Gstottmayer, C. W. K.; Weskamp, T.; Herrmann, W. A. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 3387; (b) For an example using a carbamate leaving group, see: Sengupta, S.; Leite, M.; Rasland, D. S.; Quesnelle, C.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 4066; (c) For an example using a thioalkyl leaving group, see: Tiecco, M.; Testaferri, L.; Tingoli, M.; Chianelli, D.; Wenkert, E. *Tetrahedron Lett.* **1982**, *23*, 4629.
3. (a) Morvillo, A.; Turco, A. *J. Organomet. Chem.* **1981**, *208*, 103; (b) Abla, M.; Yamamoto, T. *J. Organomet. Chem.* **1997**, *532*, 267; (c) Garcia, J. J.; Brunkan, N. M.; Jones, W. D. *J. Am. Chem. Soc.* **2002**, *124*, 9547.
4. Miller, J. A. *Tetrahedron Lett.* **2001**, *42*, 6991.
5. $NiCl_2(PMe_3)_2$ is now commercially available from Aldrich (catalog number 56,767-1).
6. It was determined that 5 mol% $Ni(acac)_2/2PMe_3$ was an equally effective catalyst system in these cross-coupling reactions. Phosphine ligands with larger cone angles were found to be less effective. For example, $NiCl_2(PEt_3)_2$ will indeed activate the C–CN bond; however, the scope of the reaction with this catalyst is not general and the yields are inferior versus $NiCl_2(PMe_3)_2$. The application of $Ni(acac)_2$/1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride or the Buchwald ligand (2-(dicyclohexylphosphino)-2′-methylbiphenyl) failed to provide any of the desired styrene adduct **3a** resulting in complete recovery of the benzonitrile starting material (**1a**). $Pd(t\text{-}Bu_3P)_2$ was also found to be ineffective as a catalyst in this cross-coupling reaction. A combination of 5 mol% $Pd(OAc)_2$ and 2-(dicyclohexylphosphino)-2′-methylbiphenyl (7.5 mol%) afforded small amounts of the desired styrene compound with the starting benzonitrile as the major component (1/9.8 **3a**/**1a** by GC).
7. Tamao, K.; Sumitani, K.; Kiso, Y.; Zembayashi, M.; Fujioka, A.; Kodama, S.-i.; Nakajima, I.; Minato, A.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1958.
8. Representative procedure: (1-cyclopropyl-4-methoxybenzene **3c**, entry 4). A solution of lithium thiophenoxide in THF (4.0 mL, 4.0 mmol, Aldrich) was treated at 0°C with cyclopropyl magnesium bromide (7.5 mL, 3.75 mmol, Aldrich) and the resulting solution was initially warmed to room temperature (for 30 min) and then heated at 60°C for 1 h. The solution of **2d** was cooled to room temperature and added to a solution of 4-methoxybenzonitrile **1a** (249 mg, 1.875 mmol), $NiCl_2(PMe_3)_2$ (29 mg, 0.103 mmol) and tridecane (196 mg, 1.07 mmol) in THF (2 mL). The reaction was heated to 60°C for 15 h. An aliquot was withdrawn and quenched with 1 M solution of sodium citrate. GC analysis indicated the formation of **3c** (1.21 mmol, 64%) and the cyclopropyl(4-methoxyphenyl)-methanone (0.21 mmol).