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# Alkynylation of benzonitriles via nickel catalyzed C–C bond activation

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**Abstract**—The scope of synthetically useful nickel catalyzed cross coupling reactions of benzonitriles has now been expanded to allow alkynylation. Thus, the cross coupling of benzonitriles with alkynylzinc reagents occurs readily in the presence of Ni/$PMe_3$ based catalysts to afford the respective aryl alkynes in high yields.

We have recently demonstrated that the C–CN bond in benzonitriles can undergo nickel catalyzed activation and functionalization to give the corresponding unsymmetrical biaryls,[1,2] styrenes,[2,3] alkylated benzenes,[2,3] and anilines.[2] These new aryl nitrile based cross coupling and amination reactions offer useful synthetic alternatives to the more commonly practiced reactions that employ aryl halides as starting materials. Interestingly, our initial attempts at expanding the scope of benzonitrile cross coupling reactions to include Ni-catalyzed alkynylation were unsuccessful. Since the Pd-catalyzed alkynylation of aryl halides via Negishi[4] or Sonogashira[5] protocols are well established and important synthetic methods, we reexamined the alkynylation of aryl nitrile substrates. We now wish to report an efficient, general procedure for the synthesis of aryl alkynes from the corresponding benzonitriles and terminal alkynes.

Attempted cross coupling of benzonitrile with phenylethynylmagnesium bromide (2 equiv) in the presence of 5 mol% $Cl_2Ni(PMe_3)_2$ catalyst led to total consumption of the aryl nitrile but formation of only a negligible amount (<5%) of the desired product, diphenylacetylene, after reaction overnight in refluxing THF. The reaction mixture also contained an appreciable amount of diphenylbutadiyne, derived from homocoupling of the alkynyl Grignard reagent. Prior derivatization of the Grignard reagent with lithium *t*-butoxide or lithium thiophenoxide[1–3] did not increase the yield of diphenylacetylene, and byproducts derived from alkynylation of the nitrile moiety were not detected by GC analysis. On the other hand, use of the corresponding alkynylzinc reagent under otherwise similar reaction conditions gave diphenylacetylene in much higher yield (50% yield after 4 days; 27% remaining benzonitrile). The yield of diphenylacetylene in the same reaction could be further improved by use of additional catalyst [10 mol% $Cl_2Ni(PMe_3)_2$; 41 h reaction time: 79% diphenylacetylene, 10% benzonitrile] or additional ligand [5 mol% $Cl_2Ni(PMe_3)_2$, 10 mol% $PMe_3$; 44 h reaction time: 72% diphenylacetylene, 18% benzonitrile). Alkyl substituted alkynylzincs are considerably more reactive than their aryl substituted counterparts. For example, reaction of benzonitrile with 1-hexynylzinc bromide (2 equiv) in refluxing THF in the presence of 5 mol% $Cl_2Ni(PMe_3)_2$ gave the alkynylation product, 1-phenyl-1-hexyne, in 95% yield after 20 h.

The superior cross coupling performance of alkynylzincs relative to the corresponding magnesium reagents seems to be rather general in this alkynylation reaction and has provided the reaction with applicability toward a broad scope of substrates (Eq. 1).[6] As shown in Table 1,

$$\mathrm{ArCN} + \mathrm{R}{-}{\equiv}{-}\mathrm{ZnX} \xrightarrow[\text{THF}]{\mathrm{Cl_2Ni(PMe_3)_2}\ \text{cat.}} \mathrm{Ar}{-}{\equiv}{-}\mathrm{R} \tag{1}$$

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**Table 1.** Synthesis of aryl alkynes via Ni-catalyzed alkynylation of aryl nitriles[a]

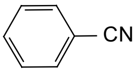
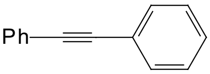
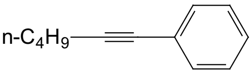
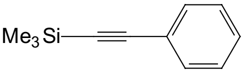
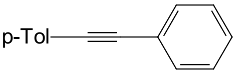
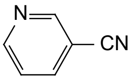
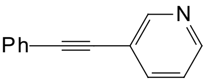
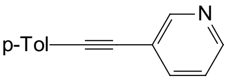
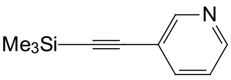
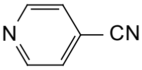
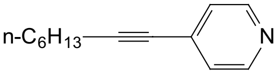
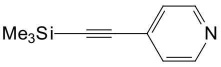
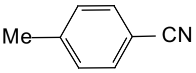
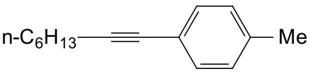
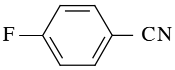
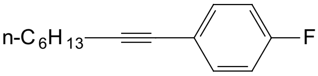
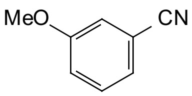
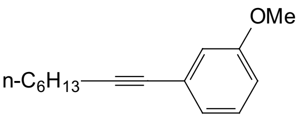
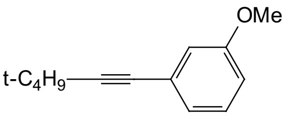
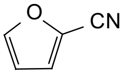
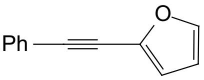
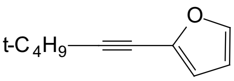
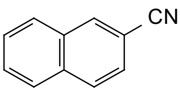
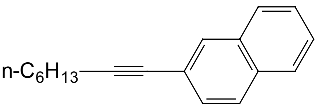
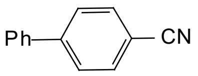
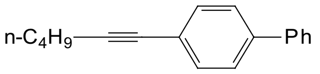
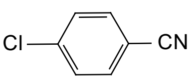
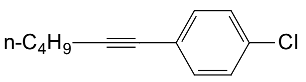
| Entry | ArCN | R—≡—ZnBr | Reaction time (h) | R—≡—Ar | Product yield (%)[b] |
|---|---|---|---|---|---|
| 1 |  | Ph—≡—ZnBr | 41 |  | 79[e] |
| 2 | | $n$-$C_4H_9$—≡—ZnBr | 20 |  | 95[f] |
| 3 | | $Me_3Si$—≡—ZnBr | 23 |  | 87 |
| 4 | | p-Tol—≡—ZnBr | 42 |  | 81[g] |
| 5 |  | Ph—≡—ZnBr | 20 |  | 45[c] |
| 6 | | p-Tol—≡—ZnBr | 18 |  | 75 |
| 7 | | $Me_3Si$—≡—ZnBr | 20 |  | 50 |
| 8 |  | $n$-$C_6H_{13}$—≡—ZnBr | 21 |  | 80[c,d] |
| 9 | | $Me_3Si$—≡—ZnBr | 20 |  | 56 |
| 10 |  | $n$-$C_6H_{13}$—≡—ZnBr | 46 |  | 83[h] |
| 11 |  | $n$-$C_6H_{13}$—≡—ZnBr | 45 |  | 67[c] |
| 12 |  | $n$-$C_6H_{13}$—≡—ZnBr | 17 |  | 80 |
| 13 | | $t$-$C_4H_9$—≡—ZnBr | 16 |  | 92 |
| 14 |  | Ph—≡—ZnBr | 18 |  | 74 |
| 15 | | $t$-$C_4H_9$—≡—ZnBr | 16 |  | 91 |
| 16 |  | $n$-$C_6H_{13}$—≡—ZnBr | 22 |  | 98[c] |

**Table 1** (*continued*)

| Entry | ArCN | R—≡—ZnBr | Reaction time (h) | R—≡—Ar | Product yield (%)[b] |
|---|---|---|---|---|---|
| 17 |  | $n$-C$_4$H$_9$—≡—ZnBr | 20 |  | 80 |
| 18 |  | $n$-C$_4$H$_9$—≡—ZnBr | 20 |  | 65[i] |

[a] All reactions were carried out with stoichiometries, catalyst loadings, etc., as illustrated in the representative procedure[6].

[b] Chemical yields are by GC analysis using an internal reference standard.

[c] $Cl_2Ni(PMe_3)_2$ (5 mol%) was used.

[d] The reaction was carried out at 23 °C.

[e] Benzonitrile (10%) remained unreacted.

[f] Benzonitrile (4%) remained unreacted.

[g] Benzonitrile (12%) remained unreacted.

[h] *p*-Tolunitrile (5%) remained unreacted.

[i] 1,4-Bis(1′-hexynyl)benzene (5%) was also present in the reaction mixture; no 4-(1′-hexynyl)benzonitrile was detected.

a variety of aryl nitriles and terminal alkynes participate efficiently in this alkynylation reaction. For example, electron donating and withdrawing groups are accommodated on the aromatic ring of the nitrile substrate, although the former substrates tend to lead to longer reaction times. Heteroaromatic nitrile substrates, such as cyanopyridines and cyanofurans also participate well in this cross coupling reaction. Superior results are obtained from accessing the alkynylzinc halide reagent via transmetallation of the respective alkynyl lithium intermediate with $ZnX_2$ versus use of the alkynyl Grignard reagent as a precursor to the alkynylzinc halide. However, the nature of the halide ligand 'X' does not appear to be critical in this cross coupling reaction; thus, zinc chloride and zinc bromide may both be used to prepare the alkynyl zinc halide reagent via transmetallation of the respective alkynyl lithium. Use of the corresponding bis(alkynyl)zinc reagent (i.e., that derived from use of 2 equiv of alkynyl lithium per mole of $ZnX_2$) also produces an effective alkynyl coupling partner for this aryl nitrile alkynylation reaction.

The preformed nickel complex '$Cl_2Ni(PMe_3)_2$'[7] and the species derived in situ from $Ni(acac)_2$ and $PMe_3$ serve as efficient catalysts for this alkynylation reaction. Depending upon the reactivity of the particular substrates, it may be beneficial to employ excess $PMe_3$ ligand with either the preformed complex or in situ derived catalyst. The use of $PMe_3$ as ligand in this reaction is imperative; no other phosphine ligand surveyed (e.g., $Ph_3P$, $Et_3P$, *i*-$Pr_3P$, $Me_2PCH_2CH_2PMe_2$) delivered the desired alkynylation products in more than minor yields.

The selectivity toward cross coupling at the nitrile moiety in 4-chlorobenzonitrile (Table 1, entry 18) is remarkable. Thus, cross coupling of this bifunctional substrate with excess 1-hexynylzinc bromide afforded 1-chloro-4-(1′-hexynyl)benzene as the only mono-alkynylation product detected by GC analysis; none of the corresponding monoalkynylation adduct derived from cross coupling at the aryl chloride group was observed. For at least this substrate, the reactivity of the C–CN bond toward the nickel catalyst is far greater than that of the C–Cl bond.

With efficient reaction conditions now established for the alkynylation of benzonitriles, the scope of useful C–C and C–N bond forming reactions from these substrates has been further expanded. This new alkynylation methodology should provide for increased flexibility in designing a synthetic route utilizing an aromatic alkynylation step since aryl nitriles can now be considered as substrates along with the aryl halides commonly employed in Negishi or Sonogashira alkynylation protocols.

## Acknowledgements

We thank Prof. B. M. Trost (Stanford University) for helpful discussions concerning this chemistry.

## References and notes

1. Miller, J. A. *Tetrahedron Lett.* **2001**, *42*, 6991.
2. Miller, J. A.; Dankwardt, J. W.; Penney, J. M. *Synthesis* **2003**, 643.
3. Miller, J. A.; Dankwardt, J. W. *Tetrahedron Lett.* **2003**, *44*, 1907.
4. Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979.
5. Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46.
6. *Representative procedure*: (1-Hexynylbenzene; entry 2). A solution of 1-hexyne (0.450 mL, 0.329 g, 4.00 mmol) in THF (2 mL) was treated at 0 °C with *n*-butyllithium (1.6 mL, 4.0 mmol, 2.5 M in hexanes) and the resulting solution was allowed to warm to room temperature and stirred for 15 min. The solution was cooled to 0 °C, then treated with a solution of $ZnBr_2$ (0.901 g, 4.00 mmol) in THF (2 mL) and allowed to warm to room temperature and stirred for 30 min. The solvent was removed in vacuo, and the resulting residue was dissolved in THF (2 mL). This solution was then added at room temperature to a solution of benzonitrile (0.204 mL, 0.206 g, 2.00 mmol), dichlorobis(trimethylphosphine)nickel (0.0564 g, 10 mol%), and tridecane (0.244 mL, 0.184 g, 1.00 mmol, internal GC standard) in THF (2 mL). The

reaction mixture was then heated at 65 °C for 20 h, and then a sample was withdrawn and quenched in a mixture of 1 M sodium citrate (aq) and MTBE. GC analysis of the organic phase of the hydrolyzed reaction sample showed the presence of 1.90 mmol (95% yield) of 1-hexynylbenzene and 0.08 mmol of benzonitrile remaining in the reaction mixture.

7. This catalyst was prepared as described previously.[1] Alternatively, it can be purchased from Aldrich (catalog number 56,767-1).