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Nickel-catalyzed hydrogenolysis of unactivated carbon–cyano bonds†

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Selective hydrogenolysis of C–CN bonds can allow chemists to take advantage of *ortho*-directing ability, α -C–H acidity and electron withdrawing ability of the cyano group for synthetic manipulations. We have discovered hydrogenolysis of aryl and aliphatic cyanides under just 1 bar of hydrogen by using a nickel catalyst. This protocol was applied in the aryl cyanide directed functionalization reaction and α -substitution of benzyl cyanides.

Functional group assisted transformations are most widely used in synthetic chemistry.¹ In this regard, a cyano group has been found to be beneficial in terms of its α -acidity, electronwithdrawing properties and *ortho*-directing ability.^{2,3} Recently, using a locked long chain structural motif, *meta*-directing ability of a cyano group has been explored.⁴ Notably, during cross coupling reactions, the cyano group can alleviate metal-mediated steps *e.g.* oxidative addition, reductive elimination *etc.*⁵ By using the inherent stability and the electron withdrawing nature of the cyano group, otherwise unreactive arenes were fluorinated *via* Pd-catalyzed cross-coupling reaction.⁶ In this context, removal of a functional group that has fulfilled its obligation plays a key role in generation of the desired product.^{7–9}

High bond dissociation energy of C–CN bonds limits the easy removal of a cyano group;¹⁰ therefore earlier reports consisted of harsh reaction conditions using highly reactive alkali metals for removal of a cyano group.¹¹ On the other hand, newly developed transition metal catalyzed decyanation methods rely on hydrosilanes as hydride sources (Scheme 1).¹² The Enthaler group has introduced Grignard reagents as sources of hydride for hydrodecyanation reaction (Scheme 1).¹³ In this context, use of H₂ gas for C–CN bond cleavage is a superior choice since H₂ is extremely abundant and most importantly no extra waste is introduced into the reaction system.^{7,14} Earlier efforts devoted to utilization of H₂ as the reductant are limited to





either relatively active strained molecules^{14c,d} or harsh reaction conditions involving heterogeneous catalytic systems^{14e,f} or employing specially designed pincer ligands.^{14g} To date, only a few examples of reductive cleavage of unactivated C–C bonds using H₂ gas have been reported.^{14a,h,i}

Conversely, hydrogen is less nucleophilic compared to the carbon nucleophiles generated upon oxidative addition to C–CN and may thus lead to catalyst deactivation during decyanation of C–CN bonds.^{7*a*} Herein, we report the first hydrogenolysis of C–CN bonds using H_2 gas as the hydride source.

Recently we have reported a nickel catalyzed decyanation reaction using (Me₂SiH)₂O [tetramethyldisiloxane, TMDSO] as the hydride source.¹⁵ To develop hydrogenolysis of unactivated C-CN bonds, we started with 2-cyanonaphthalene using Ni(acac)2-PCy₃ combination under 1 bar pressure of H₂ which gave the desired product in 35% yield. Encouraged by our initial findings, different combinations of nickel catalyst-ligand systems were investigated along with different bases and additives.¹⁶ After extensive experimentations we have realized that catalytic Ni(COD)₂ in combination with PCy₃ (45-90 mol%) and AlMe₃ (3 equiv.) under 1 bar pressure of H₂ gas can produce the desired decyanated product in good yield. The role of AlMe₃ as an additive is found to be crucial. Firstly, as a Lewis acid it activates the inert C-CN bond for facile oxidative addition of Ni(COD)2.^{10q-t,15} Secondly, it can help to remove and consume the HCN gas produced under the reaction conditions.¹⁷ Although Ni-catalyzed aryl ether hydrogenolysis was unsuccessful with PCy₃ and required use of an expensive carbene ligand, decyanation reactions were effective with easily available and economical PCy₃.⁷ Furthermore no ring hydrogenation product from arene π -bonds was observed during the present study.¹⁸

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 Table 1
 Hydrogenolysis of aryl cyanides^{a 16,20}



^{*a*} Ar-CN (0.25 mmol), Ni(COD)₂ (30 mol%), PCy₃ (90 mol%), AlMe₃ (0.75 mmol), H₂ gas (1 bar), toluene (1 mL), 130 °C, 24 h. ^{*b*} Minor products and Ar-Me are depicted in parenthesis. ^{*c*} ArMe product isolated. ^{*d*} Ni(COD)₂ (15 mol%), PCy₃ (45 mol%). ^{*e*} 10–25% recovered starting materials (rsm). ^{*f*} 18% biphenyl.

Selective hydrogenolysis of C–CN bonds over C–OMe bonds^{7,9,19} was observed under the present conditions (entries **1g**, **1h** and **2c**). Tolerance towards ester (**1i** and **1m**) groups is also advantageous because the use of a Grignard reagent as a hydride source might be difficult for such compounds.¹³ For substrates bearing dicyano groups, monodecyanation resulted in the formation of the major product (**1k**). It should be noted that, sequential removal of cyano groups is possible from a dicyano substrate by employing our present protocol (entries **1k** and **1l**).

Aryl cyanides with hydroxyl (ArOH, 1c), amide (1d), keto (1e), trifluoromethyl (1f), ester (1i and 1m) and fluoro (1j) groups underwent hydrogenolysis of cyano groups in good yield (Table 1).

In order to further explore the substrate scope, heterocyclic cyanide compounds (HetAr-CN) were reacted under the optimized reaction conditions. In general, irrespective of the position of the cyano group, good to excellent yields of the desired decyanated products were obtained for different HetAr-CN compounds (Table 2). Of note is that indole derivatives with cyano groups at 3- and 4-positions were decyanated (entries 2e and 2d, respectively). Furthermore, 2- and 3-cyanobenzothiophene can be employed successfully (entries 2f and 2g, respectively) under the present reaction conditions. Five membered heterocyclic cyanide with two heteroatoms (e.g. entry 2k) was also decyanated effectively. A 73% yield was obtained with the dibenzo[b,d]thiophene containing substrate. We found that 2a can be obtained in 93% yield with 30 mol% of catalyst, whereas 15 mol% of catalyst gave 78% product. Also, hydrogenolysis was successful with cyanoarenes with sterically demanding orthosubstituents (entries 2a, 2b and 2c) or with ortho-directing groups (entries 2j and 2m). Therefore, a desired transformation can be carried out at the 6-position of the arene by using a cyano group as a temporary protecting group at the 2-position.

Benzyl cyanides without β -hydrogen gave the desired product in preparatively useful yield (entries **3a** and **3c**). Different alkyl cyanides with β -hydrogens were examined as the β -hydride



 a Ar–CN (0.25 mmol), Ni(COD)₂ (30 mol%), PCy₃ (90 mol%), AlMe₃ (0.75 mmol), H₂ gas (1 bar), toluene (1 mL), 130 °C, 24 h. b Ni(COD)₂ (15 mol%). c 12% methylated product. d 9% methylated product.

elimination is a major problem for aliphatic substrates when involved in metal mediated oxidative addition reactions.²¹ Interestingly, benzyl cyanides (**3d**) and aliphatic nitrile (**3b**) with β -hydrogen underwent smooth hydrogenolysis with only 1 bar H₂ gas (Table 3).

In complex molecular set up only desired hydrogenolysis of cyano groups was observed without reduction of internal alkene in the cholesterol core (Scheme 2, **4b**). Using α -acidity of cyano groups alkylation is possible for benzyl cyanide (Scheme 2, **4i**). In a similar manner, cyano directed *ortho*-arylation²² (Scheme 2, **4c**) and *ortho*-alkoxylation²³ (Scheme 2, **4e** and **4g**) can be implemented in a molecule of interest. After its beneficial use, the cyano group can be removed effectively by using the current hydrogenolysis protocol (Scheme 2, entries **4d**, **4f**, **4h** and **4j**).

In summary, an alternate and general protocol for nickelcatalyzed hydrogenolysis of aryl and alkyl cyanides by using cheaper, greener and milder hydrogen gas as the hydride source has been developed. Different electronic and steric substituents as well as substrates with β -hydrogen were successfully reacted using



 a Reaction conditions: Ar–CN (0.25 mmol), Ni(COD)₂ (30 mol%), PCy₃ (90 mol%), AlMe₃ (0.75 mmol), H₂ gas (1 bar), toluene (1 mL), 130 °C, 24 h. b Minor products and Ar–Me are depicted in parenthesis. c GC yield. d Ni(COD)₂ (15 mol%), PCy₃ (45 mol%). e ArMe product isolated.



Scheme 2 Synthetic applicability. ^a Ni(COD)₂ (30 mol%). ^b 8% methylated product. ^c Ni(COD)₂ (15 mol%).

this protocol. This decyanation reaction can be conducted without reduction of arenes. Cyano directed *ortho*-arylation, *ortho*-alkoxylation, α -C-H acidity and electron withdrawing properties can temporarily be used for synthetic manipulations.

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