Pd/C(en) Catalyzed Chemoselective Hydrogenation in the Presence of Aryl Nitriles

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Aromatic nitriles are not only important components of natural products, pharmaceuticals, herbicides and agrochemicals but also a synthetic equivalent of various functionalities. The development of synthetic methods of aromatic nitriles have been increasing in terms of its usefulness. Since aromatic nitriles are susceptible to the hydrogenation, it has been desired for the development of chemoselective hydrogenation method with retention of nitrile groups. Pd/C is one of the most popular catalysts for hydrogenation and many of reducible functional groups such as multiple bonds, benzyl ethers, *N*-Cbzs, nitro groups and so on could be easily reduced under the conditions. Therefore, it is very difficult to achieve the chemoselective hydrogenation of substrates containing two or more reducible functional groups. We have found that a Pd/C catalyst formed an isolable complex with ethylenediamine (en) employed as catalytic poison, and the complex [Pd/C(en)] catalyzed chemoselective hydrogenation of a variety of reducible functionalities distinguishing *O*-benzyl, *N*-Cbz and *O*-TBDMS protective groups, benzyl alcohols and epoxides. In the course of these investigations, we found the aryl nitriles could survive under the Pd/C(en)-catalyzed hydrogenation conditions in THF whose choice is important for the effective suppression. This methodology could be applied to the selective hydrogenation of alkene and alkyne functionalities in the presence of aromatic nitrile.

Key words chemoselective hydrogenation; aromatic nitrile; Pd/C(en) catalyst; solvent effect; Pd/C

Nitriles are of substantial interest as useful ingredients of natural products, agrochemicals, pharmaceuticals, dyes and so on.[1] In addition, nitriles represent versatile precursors such as aldehydes, amines and carboxylic acids for organic synthesis.[2] However, aromatic nitriles are susceptive to hydrogenation conditions and easily reduced to amines.[3,4] To retain the nitriles under hydrogenation conditions lead to improve the usefulness of nitrile derivatives in organic syntheses. Recently, we found that the addition of a catalyst poison such as sulfur or nitrogen containing molecules depressed the catalyst activity of Pd/C and some chemoselective hydrogenation methods were established among several reducible functional groups.[5—11] As further expansion of the chemoselective hydrogenation methodology, we developed a novel hydrogenation catalyst, Pd/C-ethylenediamine complex {Pd/C(en) (Wako; 169-21443)},[12—16] which chemoselectively hydrogenated a variety of reducible functionalities distinguishing *O*-benzyl, *N*-Cbz and *O*-TBDMS protective groups, benzyl alcohols and epoxides. In this paper, we report the suppression of hydrogenation of aromatic nitriles under Pd/C(en)-catalyzed hydrogenation conditions in THF in the presence of other reducible functional groups such as alkenes and alkynes within a molecule.

It is well known that nitriles (especially aryl nitriles) were reduced and in part underwent the coupling reaction of the generated amine with the partially reduced (intermediary) imine as a side reaction under transition-metal-catalyzed hydrogenation conditions.[3,4] Therefore, we planned to apply the Pd/C(en) as a catalyst for the chemoselective hydrogenation with retention of nitriles. We first attempted to the hydrogenation of benzonitrile using 5% Pd/C(en) in MeOH. Although complete hydrogenation of nitriles and partial coupling reaction between the corresponding amine and intermediary imine were proceeded under the commercial 5% Pd/C (Aldrich; 205680)-catalyzed hydrogenation conditions in MeOH (Chart 1 and Table 1, entry 1), the hydrogenation of the nitrile was considerably suppressed (80% retention of benzonitrile, entry 2). Next, we examined the solvent effect since we have found that the choice of solvents remarkably affected to the catalyst activity in hydrogenation.[17] While the use of ethyl acetate or cyclohexane as a solvent exhibited moderate suppressive effect, nearly complete suppression was achieved in THF, 1,4-dioxane and MeCN (entries 5—7).[18] To optimize the suitable solvent, methyl 4-cyanobenzoate, a more reducible substrate, was used as a substrate in 1,4-dioxane and THF excluding MeCN which possesses a nitrile within the molecule. The use of THF as a solvent gave

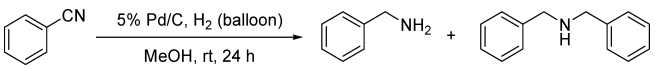
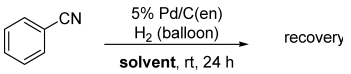


Chart 1

Table 1. Solvent Effect of Hydrogenation of Benzonitrile



Entry	Solvent	Purity (%)[a]
1[b]	MeOH	—
2	MeOH	80
3	AcOEt	72
4	Cyclohexane	75
5	THF	92
6	1,4-Dioxane	94
7	MeCN	94

a) Determined by ^{1}H-NMR. *b*) 5% Pd/C was used. Complete hydrogenation of the nitrile and partial coupling reaction between the corresponding amine and intermediary imine were observed.

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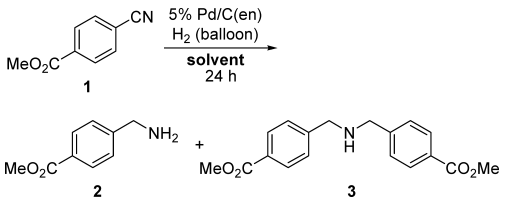
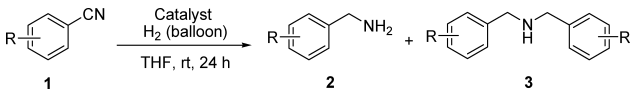
Table 2. Optimization of Solvent

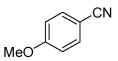
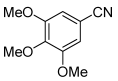


Solvent	Yield (%)[a]	
	1	**2+3**
THF	78	22
1,4-Dioxane	68	32

a) Determined by ^{1}H-NMR.

Table 3. Hydrogenation to Various Benzonitrile Derivatives Using Pd/C(en) or 5% Pd/C in THF



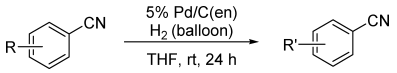
Entry	Substrate	Catalyst	Yield (%)[a]	
			1	**2+3**
1		5% Pd/C(en)	92	4
		5% Pd/C	0	96
2		5% Pd/C(en)	96	4
		5% Pd/C	0	89
3		5% Pd/C(en)	91	0
		5% Pd/C	52	0
4		5% Pd/C(en)	94	0
		5% Pd/C	0	96
5		5% Pd/C(en)	100	0
		5% Pd/C	100	0

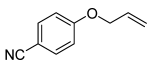
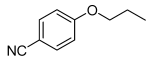
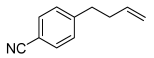
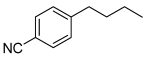
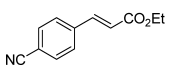
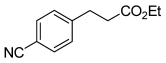
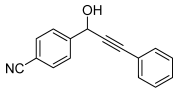
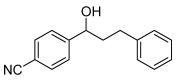
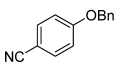
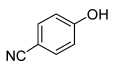
a) Yields were determined by ^{1}H-NMR.

better suppressive effect compare to 1,4-dioxane (Table 2). Various aromatic nitriles were applied to confirm the scope of the methodology and compare the reactivity between 5% Pd/C and 5% Pd/C(en) catalysts. As shown in Table 3, the hydrogenation of the substituted benzonitrile possessing electron-donating methoxy groups was almost completely suppressed under the 5% Pd/C(en)-catalyzed hydrogenation conditions in THF whereas the complete hydrogenation was occurred by the use of 5% Pd/C even in THF (Table 3, entries 2 and 4[19]) for 24 h. The Pd/C-catalyzed hydrogenation of 2-aminobenzonitrile was rather suppressed since the amino group might work as a weak catalyst poison (entry 3). On the other hand, dodecanenitrile, an aliphatic nitrile, never hydrogenated at all under even 5% Pd/C-catalyzed hydrogenation conditions (entry 5).

The chemoselective hydrogenation could be accomplished by employing benzonitrile derivatives bearing other reducible functional groups such as an alkene, alkyne or aromatic benzyl ether functionality within the molecule (Table 4). The hydrogenation of the alkene and alkyne proceeded smoothly with retention of the aromatic nitrile group and benzyl alcohol (Table 4, entries 1—4). The aromatic benzyl ether was also completely hydrogenolyzed under the conditions leaving the nitrile functionality intact (entry 5).[20] In the case of entry 5, the electron-withdrawing effect of cyano group led to the hydrogenolysis of the aromatic benzyl ether moiety, which was usually not reduced under the Pd/C(en)-catalyzed hydrogenation conditions in THF.[12—16]

Table 4. Chemoselective Hydrogenation with Retention of Aromatic Nitriles



Entry	Substrate	Product	Yield (%)[a]
1[b]	 23)	 23)	96
2[b]	 24)	 21)	84
3[b]	 25)	 26)	91
4			83
5	 21)	 21)	100

a) Isolated yield. *b*) Formation of trace amount (<3%) of the benzylamine was observed by NMR.

In summary, we have developed an effective and chemoselective hydrogenation method with retention of an aromatic nitrile group using Pd/C(en) as a catalyst in THF under which alkene, alkyne and electron-deficient aromatic benzyl ether functionalities were easily hydrogenated. This method is of practical for constructing the complex molecule including other reducible functionalities such as total synthesis.

Experimental

Procedure for Solvent Effect of Hydrogenation of Benzonitrile (Table 1, Entries 2—7) After two vacuum/H_2 cycles to replace air inside the reaction tube with hydrogen, the mixture of benzonitrile[21] (1.0 mmol) and 5% Pd/C(en) (10 wt% of the substrate (Wako; 169-231443)) in solvent (1.0 ml) was vigorously stirred at room temperature (*ca.* 20 °C) under 1 atm of hydrogen for 24 h. The reaction mixture was filtered using a membrane filter (Millipore, Millex-LH®, 0.45 μm), and the filtrate was concentrated to give the product.

Procedure for Solvent Effect of Hydrogenation of Benzonitrile (Table 1, Entry 1 and Chart 1) After two vacuum/H_2 cycles to replace air inside the reaction tube with hydrogen, the mixture of benzonitrile[21] (1.0 mmol) and 5% Pd/C (10 wt% of the substrate (Aldrich; 205680)) in MeOH (1.0 ml) was vigorously stirred at room temperature (*ca.* 20 °C) under 1 atm of hydrogen for 24 h. The reaction mixture was filtered using a membrane filter (Millipore, Millex-LH®, 0.45 μm), and the filtrate was concentrated to give the product. The complete conversion was observed and a mixture of benzylamine[21] and dibenzylamine[21] were obtained.

Procedure for the Optimization of Solvent (Table 2) After two vacuum/H_2 cycles to replace air inside the reaction tube with hydrogen, the mixture of methyl 4-cyanobenzoate[21] (1.0 mmol) and 5% Pd/C(en) (10 wt% of the substrate) in THF or dioxane (1.0 ml) was vigorously stirred at room temperature (*ca.* 20 °C) under 1 atm of hydrogen for 24 h. The reaction mix-

ture was filtered using a membrane filter (Millipore, Millex-LH®, 0.45 μm), and the filtrate was concentrated to give the product. A mixture of methyl 4-cyanobenzoate,[21] 4-methoxycarbonylbenzylamine[21] and bis(4-methoxycarbonylbenzyl)amine[22] was obtained. The ratio of the product was determined by ^{1}H-NMR.

General Procedure for the Hydrogenation to Various Benzonitrile Derivatives Using 5% Pd/C(en) or 5% Pd/C in THF (Table 3) After two vacuum/H_2 cycles to replace air inside the reaction tube with hydrogen, the mixture of substrate (1.0 mmol, commercially available) and 5% Pd/C (en) or 5% Pd/C (10 wt% of the substrate) in THF (1.0 ml) was vigorously stirred at room temperature (*ca.* 20 °C) under 1 atm of hydrogen for 24 h. The reaction mixture was filtered using a membrane filter (Millipore, Millex-LH®, 0.45 μm), and the filtrate was concentrated to give the product. A mixture of a benzylamine derivative and a dibenzylamine derivative were obtained. The ratio of the products was determined by ^{1}H-NMR. All of the compounds are commercially available except for dibenzylamine derivatives (**3**) in entries 2 and 4. The secondary amine (**3**) in entries 2 and 4 were known products in the literature; see references 27 and 28.

General Procedure for the Chemoselective Hydrogenation (Table 4) After two vacuum/H_2 cycles to replace air inside the reaction tube with hydrogen, the mixture of the substrate (1.0 mmol) and 5% Pd/C(en) (10 wt% of the substrate) in THF (1.0 ml) was vigorously stirred at room temperature (*ca.* 20 °C) under 1 atm of hydrogen for 24 h. The reaction mixture was filtered using a membrane filter (Millipore, Millex-LH®, 0.45 μm), and the filtrate was concentrated to give the product. All of the starting materials and products are reported in literature except for 1-(4-cyanophenyl)-3-phenyl-2-propyn-1-ol and 1-(4-cyanophenyl)-3-phenylpropan-1-ol in entry 5.

1-(4-Cyanophenyl)-3-phenyl-2-propyn-1-ol To a diethyl ether (70 ml) solution of phenylacetylene (2.88 g, 28.2 mmol) and triethylamine (2.85 g, 28.2 mmol) were added a diethyl ether (70 ml) solution of $InBr_3$ (10.0 g, 28.2 mmol) and the reaction mixture was stirred for 1 h at room temperature (*ca.* 20 °C) under argon. To the solution benzaldehyde (1.85 g, 14.1 mmol) was added dropwise. The mixture was stirred for 2 h at room temperature (*ca.* 20 °C). To the reaction mixture dichloromethane (150 ml) was added, the solution was washed with 1 N HCl (175 ml) and water (120 ml). The organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure. The crude product was purified by recrystallization (*n*-hexane and ethyl acetate) to afford 1-(4-cyanophenyl)-3-phenyl-2-propyn-1-ol (2.55 g, 78% yield) as a pale yellow solid. mp 91.0—92.0 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J=8.1 Hz, 2H), 7.65 (d, J=8.1 Hz, 2H), 7.45—7.43 (m, 2H), 7.35—7.29 (m, 3H), 5.73 (s, 1H), 2.98 (br s, 1H). ^{13}C-NMR δ: 145.5, 132.3, 131.6, 128.8, 128.3, 127.1, 121.7, 118.5, 111.8, 87.5, 87.4, 64.1. MS (EI) m/z: 233 (M^+), 216, 204, 102. *Anal.* Calcd for $C_{16}H_{11}NO$: C, 82.61; H, 4.96; N, 6.02. Found: C, 82.38; H, 4.75; N, 6.00.

1-(4-Cyanophenyl)-3-phenylpropan-1-ol To a round-bottom flask with a stir bar were added 1-(4-cyanophenyl)-3-phenyl-2-propyn-1-ol (233.2 mg, 1.00 mmol), 5% Pd/C(en) (23 mg, 10 wt% of the substrate), and THF (1.00 ml). The air in the flask was replaced with hydrogen by two vacuum/H_2 cycles and the mixture was vigorously stirred at room temperature (*ca.* 20 °C) under ambient pressure of hydrogen (balloon). The reaction mixture was filtered through a filter paper and the filtrate was concentrated under reduced pressure to afford 1-(4-cyanophenyl)-3-phenylpropan-1-ol (196.4 mg, 83% yield) as a pale yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.53 (d, J=8.1 Hz, 2H), 7.40 (d, J=8.1 Hz, 2H), 7.27—7.24 (m, 2H), 7.19—7.14 (m, 3H), 4.70—4.67 (m, 1H), 2.87 (br s, 1H), 2.72—2.65 (m, 2H), 2.04—1.98 (m, 2H). ^{13}C-NMR δ: 150.3, 141.0, 131.9, 128.2, 128.1, 126.3, 125.8, 118.6, 110.6, 40.4, 31.6. MS (EI) m/z: 237 (M^+), 219, 132, 105, 92. *Anal.* Calcd for $C_{16}H_{15}NO$: C, 80.73; H, 6.39; N, 5.93. Found: C, 80.98; H, 6.37; N, 5.90.

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18) Ikawa T., Hattori K., Sajiki H., Hirota K., *Tetrahedron*, **60**, 6901—6911 (2004).
19) A mixture of the starting material (3,4,5-trimethoxybenzonitrile (**1**), 3,4,5-trimethoxybenzylamine (**2**) and bis(3,4,5-trimethoxybenzyl)-amine (**3**) was obtained for even shorter reaction time (6 h, **1**:**2**+**3**=68:32).
20) A mixture of 4-hydroxybenzonitrile (**A**), 4-methylphenol (**B**) and 4-hydroxybenzylamine (**C**) was obtained (**A**:**B**:**C**=15:68:17) by the use of 5% Pd/C as a catalyst.
21) Commercially available.
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