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Pd/C–Et_3N-mediated catalytic hydrodechlorination of aromatic chlorides under mild conditions

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Abstract—A mild and efficient one-pot procedure for the hydrodechlorination of aromatic chlorides using a Pd/C–Et_3N system was developed. A variety of aromatic chlorides could be dechlorinated at room temperature and under ambient hydrogen pressure. Et_3N activates the catalysis and is likely to work as a single electron donor in this system.

1. Introduction

Much study has been devoted to developing new methods for the dehalogenation of aromatic halides from the synthetic[1] and environmental[2] points of view. It is well-known that aromatic chlorides are much less reactive than aromatic bromides and iodides and hence, the dechlorination of aromatic chlorides cannot readily be achieved.[3] Furthermore, the reduction of some persistent chlorinated aromatic pollutants such as DDT and PCB, which are difficult to degrade, has been a global issue. Therefore, the development of efficient dechlorination methods remains a topic of great interest. The dechlorination of aromatic chlorides is an underdeveloped methodology and few effective methods are available.[4] Existing techniques usually utilize hydride reduction,[5] hydrogenation,[3,6] catalytic transfer hydrogenation with formic acid,[7] formic acid salt,[8] or hydrazine,[9] dechlorination using metals,[10] photolysis,[11] oxidation,[12] electrolysis,[13] or supercritical water oxidation.[14] These reactions mostly require high heat, high pressure, radiation, stoichiometric reagents, vast amounts of catalyst, special equipment, and/or strong basic conditions and most of the reactions are frequently incomplete.

We have reported that addition of a nitrogen-containing base (e.g., NH_3, pyridine, ammonium acetate) to a Pd/C-catalyzed hydrogenation system as a weak catalyst poison chemoselectively inhibited the hydrogenolysis of a benzyl ether with smooth hydrogenation of other reducible functionalities such as olefin, Cbz, benzyl ester, azide, and so on. During the course of our further study on the chemoselective hydrogenation using a variety of Pd/C–amine systems, we found that the use of Et_3N remarkably and selectively enhanced the catalytic activity of Pd/C toward the hydrodechlorination of aromatic chlorides,[15] contrary to our expectation.[16] Kaneda et al. also reported a Pd-hydroxyapatite-catalyzed hydrodechlorination of aryl chlorides in the presence of Et_3N in 2004,[17] although our highly referential communications of hydrodechlorination published in 2002 (Refs. 16 and 18) were not properly cited in their paper. In this paper, we describe more details of the general procedure for the Pd/C-catalyzed hydrodechlorination of aromatic chlorides that operates under ambient hydrogen pressure at room temperature, together with the role of Et_3N in the system.

2. Results and discussion

2.1. General procedure for the Pd/C–Et_3N-mediated hydrodechlorination of aromatic chlorides

A control experiment on the Pd/C-catalyzed hydrodechlorination was performed using 4-chlorobiphenyl **1** as a substrate, which contains no reducible functional groups except an aromatic chloride, to investigate the effect of Et_3N as an additive. The hydrodechlorination of **1** using commercial 10% Pd/C (3% of the weight of **1**) and 1.2 equiv of Et_3N in MeOH was smoothly completed within 1 h under ambient hydrogen pressure (balloon) at room temperature to afford biphenyl **2** in 100% conversion yield (GC/MS) and triethylammonium chloride, whereas the dechlorination was incomplete even after 3 days when the reaction was carried out without Et_3N (Fig. 1 and Scheme 1).

To optimize the reaction conditions, a variety of nitrogen-containing bases were investigated (Table 1). The reaction was carried out under ordinary hydrogen pressure (balloon)

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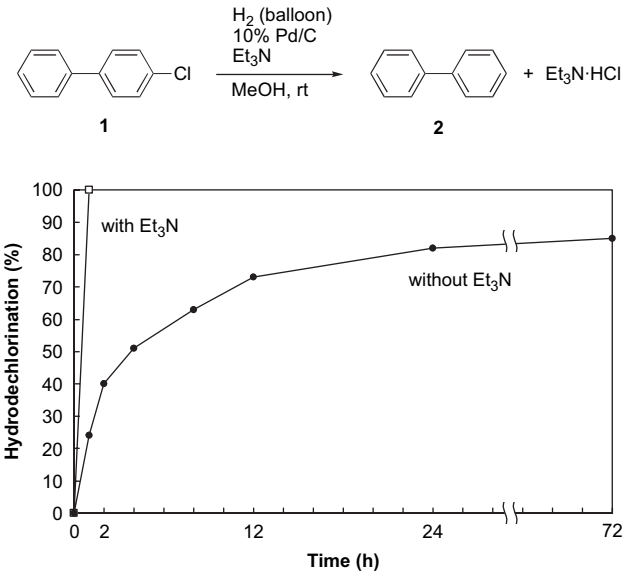


Figure 1. Kinetics plots on the hydrodechlorination of **1** using 10% Pd/C (3% of the weight of **1**) with or without Et_3N (1.2 equiv) in MeOH under ambient hydrogen pressure at room temperature.

using 1.2 equiv of an additive and 10% Pd/C (3% of the weight of **1**) in MeOH at room temperature for 1 h and the products were analyzed by GC/MS and ^1H NMR after simple extraction. Entries 3–10 in Table 1 indicate that the addition of relatively lipophilic amines greatly enhanced the efficiency of the reaction compared with the less lipophilic NH_3 or ethylendiamine (entries 2 and 11). In addition, the amines, which have aromatic substituents such as aniline and *N*,*N*-diethylaniline were effective additives (entries 9 and 10), whereas the aromatized heterocyclic bases such as pyridine or quinoline strongly suppressed the hydrodechlorination and no reaction was observed (entries 12 and 13). The addition of NaOH, an inorganic base, was also effective for the completion of the reaction (entry 15), although concern that the strong basicity and nucleophilicity of NaOH would narrow the applicability of this method excluded NaOH from the candidates.

Table 1. Assessment of bases in the dechlorination of 4-chlorobiphenyl (**1**)[a]

Entry	Additive	Yield of **2** (%)[b]
1	None	24
2	NH_3	67
3	Me_2NH	100
4	Me_3N	100
5	Et_3N	100
6	*i*-Pr_2NEt	100
7	*i*-Pr_3N	100
8	DBU	100
9	$PhNH_2$	100
10	$PhNEt_2$	100
11	$H_2N(CH_2)_2NH_2$	94
12	Pyridine	0
13	Quinoline	0
14	NaOH	100
15	NaOAc	10
16	$Et_3N\cdot HCl$	17

[a] All reactions were carried out under ordinary hydrogen pressure (balloon) using 1.2 equiv of additive and 10% Pd/C (3% of the weight of **1**) in MeOH at room temperature for 1 h.
[b] Yields were determined by GC/MS.

Among the nitrogen-containing bases, which worked well for the hydrodechlorination of **1**, Et_3N was selected as the best candidate for its cost-efficiency and its non-nucleophilicity.

The results of optimization of the solvent for the hydrodechlorination of aromatic chlorides are listed in Table 2. The use of an alcoholic solvent led to the completion of the reaction within an hour (entries 1, 3, and 4). When the reaction in such alcoholic solvent was carried out without hydrogen, no conversion to **2** was observed (entries 2 and 5) indicating that the hydrogen atom of alcoholic solvents cannot be a hydrogen source and hydrogen gas is indispensable for the hydrodechlorination system as a hydrogen donor. Using hexane as a solvent caused difficult stirring of the reaction mixture due to the poor solubility of the resulting $Et_3N\cdot HCl$ accompanied by the reaction progress (entry 8). When H_2O was used as a solvent, no reaction took place since H_2O could not dissolve **1** at all. Therefore, MeOH was chosen as a solvent for the hydrodechlorination.

The use of 10% Pd/C with more than 3% weight of **1** accomplished completion of the hydrodechlorination of **1**, although the reduction in weight of the catalyst to 1% weight of **1** resulted in incompletion of the reaction even after 24 h (Table 3, entries 1 and 2). The hydrodechlorination smoothly took place even under dark conditions (entry 3). Lowering the reaction temperature led to drastic decrease of the reaction efficiency (entry 4) and surprisingly, entirely no reaction was observed under reflux conditions (Table 3, entry 5). Detailed optimization of the reaction conditions eventually revealed that treatment of the methanol solution of **1** with 10% Pd/C

Table 2. Assessment of solvents in the dechlorination of **1**[a]

Entry	Solvent	Yield of **2** (%)[b]
1	MeOH	100
2[c]	MeOH	0
3	EtOH	100
4	*i*-PrOH	100
5[c]	*i*-PrOH	0
6	DMF	3
7	THF	43
8	Hexane	63
9	H_2O	0

[a] Reactions were carried out under ordinary hydrogen pressure (balloon) using 1.2 equiv of Et_3N and 10% Pd/C (3% of the weight of **1**) in a solvent at room temperature for 1 h.
[b] Yields were determined by GC/MS.
[c] Reaction was performed without hydrogen.

Table 3. Assessment of amount of 10% Pd/C and temperature in the dechlorination of **1**[a]

Entry	Amount of Pd/C[b]	Temperature	Yield of **2** (%)[c]
1	3 wt %	rt	100
2[d]	1 wt %	rt	98
3[e]	3 wt %	rt	100
4	3 wt %	−20 °C	4
5	3 wt %	Reflux	0

[a] Reactions were carried out under ordinary hydrogen pressure (balloon) using 1.2 equiv of Et_3N and 10% Pd/C in MeOH for 1 h.
[b] Amount of 10% Pd/C toward the weight of **1**.
[c] Yields were determined by GC/MS.
[d] The reaction was carried out for 24 h.
[e] Under dark conditions.

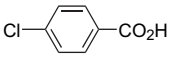
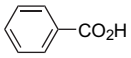
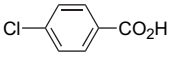
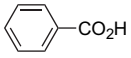
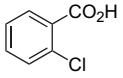
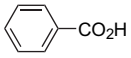
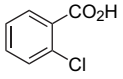
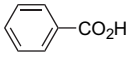
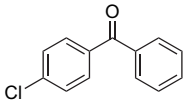
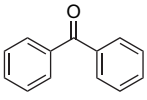
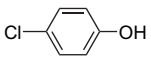
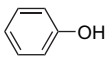
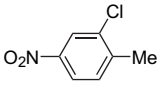
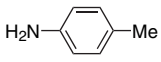
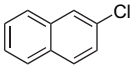
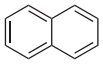
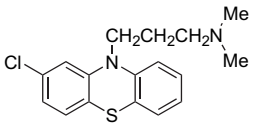
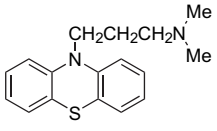
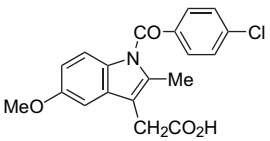
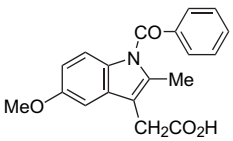
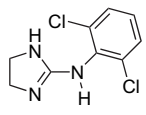
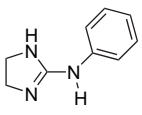
(more than 3% of the weight of **1**) and Et_3N (1.2 equiv) at room temperature under ordinary hydrogen pressure (balloon) is the best reaction conditions for the present hydrodechlorination.

To explore the scope of this method, the hydrodechlorination of a variety of aromatic chlorides was investigated (Table 4). The results shown in entries 1, 3, and 6 demonstrated that the reaction could be carried out in the presence of carboxylic acid and phenolic functionalities in the substrates. Absence of Et_3N in the reaction mixture diminished the efficiency of the hydrodechlorination (entries 2 and 4). Competitive reduction of the nitro moiety of 2-chloro-4-nitrotoluene was observed and 4-toluidine was isolated as the sole product (entry 7), while the aromatic ketone moiety of 4-chlorobenzophenone remained intact and the corresponding benzophenone was quantitatively generated (entry 5). In addition, some medicines (entries 9–15) were efficiently dechlorinated, although prolonged reaction time was required. In the hydrodechlorination of furosemide, the furan ring was competitively reduced to the corresponding tetrahydrofuran ring (entry 15).

2.2. Mechanism analysis of the Pd/C–Et_3N-mediated hydrodechlorination of aromatic chlorides

We demonstrated that the efficiency of the hydrodechlorination was greatly affected by the nature of amine. The use of

Table 4. Ten percent Pd/C–Et_3N-mediated dechlorination of aromatic chlorides[a]

Entry	ArCl	Time (h)	Product	Yield (%)[b]
1		6		100 (99)
2[c]		6		50
3		3		100 (100)
4[c]		3		60
5		1		100 (65)
6		3		100 (92)
7		2		100 (90)
8		1		100 (51)[d]
9[e]	 Chlorpromazine	24		100
10	 Indometacin	25		100 (44)
11[e]	 Clonidine	16		100

(*continued*)

Table 4. (*continued*)

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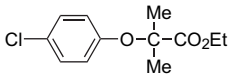
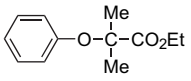
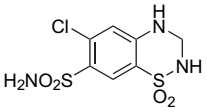
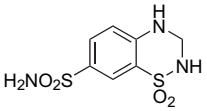
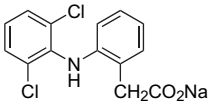
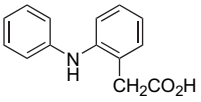
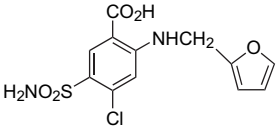
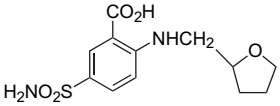
12	 Clofibrate	27		100 (71)
13	 Hydrochlorothiazide	22		100 (85)[f]
14[e]	 Dicrofenac sodium salt	22		100
15[e]	 Furosemide	6		100

[a] Reactions were carried out under ordinary hydrogen pressure (balloon) using Et_3N (1.2 equiv vs the number of chlorine atoms) and 10% Pd/C (3% of the weight of ArCl) in MeOH (ca. 1% solution of ArCl) at room temperature.
[b] Yields were determined by GC/MS and the isolated yields are indicated in parentheses. Hundred percent yield implied that no other products were detected by GC/MS.
[c] The reaction was carried out without Et_3N.
[d] The low isolated yield of the product is due to the low boiling point and volatile nature.
[e] The reaction was carried out using 10% Pd/C with 10% of the weight of ArCl.
[f] Product was contaminated with 10% of $Et_3N\cdot HCl$.

aliphatic amines led to excellent conversion to the corresponding dechlorinated product, whereas the use of aromatized heterocyclic bases led to the complete recovery of the chlorinated starting material. As shown in entry 16 in Table 1, the presence of $Et_3N\cdot HCl$ in the reaction mixture seemed to delay the reaction rate rather than not to affect it in comparison with the absence of any additives (Table 1, entry 1). These results led us to presume that Et_3N does not work just for the removal of the generated HCl, which is suspected as a catalyst poison.

It is well-known that hydrogen chloride, which is generated during the Pd/C-catalyzed hydrodechlorination of aromatic chlorides decreases the efficiency of the reaction.[19] On the contrary, Angel and Benitez showed that the reaction rate of the hydrodechlorination of chlorobenezene in HCl media was boosted using their homemade Pd/C.[6h] To investigate the role of Et_3N in our system, we, first, studied the effect of HCl on the Pd/C-catalyzed hydrodechlorination of 4-chlorobiphenyl (**1**). As shown in Figure 2, HCl dose-dependently impeded the reaction progress. In each case, the hydrodechlorination started with a certain reaction rate, although the reaction rate gradually decreased as the reaction proceeded and eventually reached a plateau. These results suggest that Pd/C was time-dependently poisoned by the exposure to HCl. Furthermore, after pre-stirring of 10% Pd/C in the presence of HCl (1.2 equiv of **1**) in MeOH under hydrogen (balloon) at room temperature for 24 h, no hydrodechlorination of **1** was observed (Table 5, entry 2). On the other hand, the 1-h stirring of **1** under hydrogen atmosphere with the 10% Pd/C that was pre-treated without HCl afforded **2** in 12% yield (Table 5, entry 1). These results prove that HCl, which forms during the hydrodechlorination, time-dependently poisoned the commercial 10% Pd/C. Similar reaction conditions using $Et_3N\cdot HCl$ as an additive in place of HCl led to no hydrodechlorination of **1** (Table 5, entry 3). This result indicates that $Et_3N\cdot HCl$, which forms by neutralization of HCl generated from the reaction mixture, also

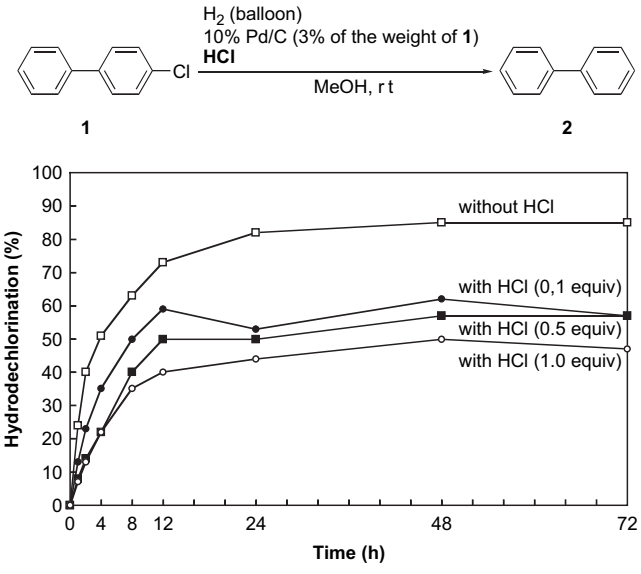
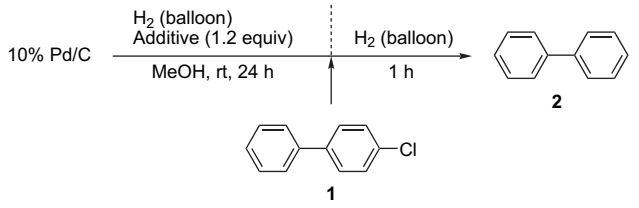


Figure 2. The effect of HCl on the hydrodechlorination of **1**.

Table 5. The effect of HCl and $Et_3N \cdot HCl$ on the hydrodechlorination of **1**[a]



Entry	Additive	Conversion (%)[b]
1	None	12
2	HCl	0
3	$Et_3N \cdot HCl$	0

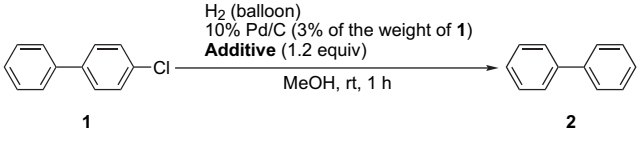
[a] All reactions were carried out by stirring 10% Pd/C (3% of the weight of **1**) with 1.2 equiv of additive in MeOH under ordinary hydrogen pressure (balloon) at room temperature for 24 h followed by the addition of **1**, reintroduction of hydrogen (balloon), and stirring the mixture for 1 h.
[b] Yields were determined by GC/MS.

suppresses the catalyst activity of Pd/C. It, therefore, seems sure that the great acceleration of the hydrodechlorination of aromatic chlorides by the addition of a certain amine is not achieved by just neutralization of HCl with the amine.

We described that the addition of pyridine or quinoline instead of Et_3N completely blocked the hydrodechlorination (Table 1, entries 12 and 13 or Table 6, entries 2 and 3). Furthermore, addition of either pyridine or quinoline to the Pd/C–Et_3N system suppressed the hydrodechlorination efficiency (Table 6, entries 4 and 5), and no reaction was observed when quinoline was added to the reaction mixture (entry 5). There is little doubt that Et_3N is not only an HCl scavenger but also plays some vital role as a strong accelerator in the Pd/C-catalyzed hydrodechlorination process. Moreover, addition of TCNE (tetracyanoethylene) or TCNQ (7,7,8,8-tetracyanoquinodimethane), a single electron capture, to the hydrodechlorination reaction mixture in the presence of Et_3N thoroughly suppressed the reaction (entries 6 and 7), suggesting the participation of a single electron transfer (SET) mechanism in the simple catalytic process.

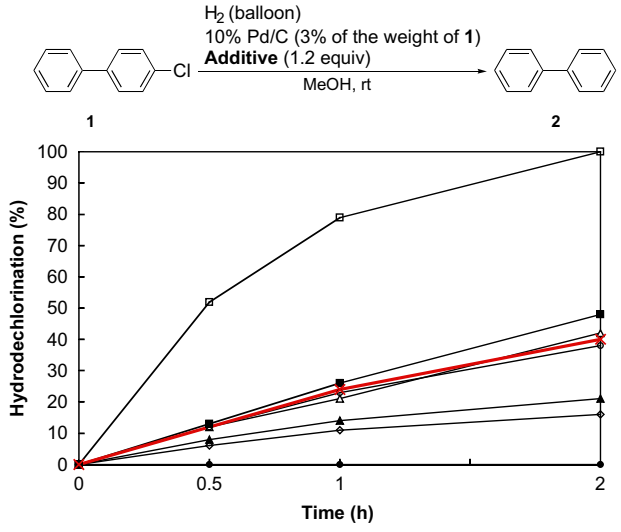
Et_3N has been reported as an initiator (single electron donor) of the photochemical dechlorination of aryl chlorides.[11a–f] It seems reasonable to consider that an SET from aliphatic amines such as Et_3N to aromatic chlorides initiated the hydrodechlorination in our system and each pyridine or quinoline may have worked as an electron acceptor to inhibit the electron transfer to aromatic chlorides. Hydrodechlorination of **1** using pyridine or a variety of substituted pyridines as an additive was investigated (Fig. 3): (1) use of 2-methyl- or 4-methylpyridine caused very sluggish hydrodechlorination of **1**, although use of pyridine caused no hydrodechlorination; (2) use of 2,6-dimethylpyridine, 4-methoxypyridine, or 4-*tert*-butylpyridine allowed the reaction to proceed at a rate similar to that of the reaction without additives; (3) the addition of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) expedited the reaction to completion. Tabner and Yandle reported the half-wave potentials ($E_{1/2}$) of a series of nitrogen-containing heterocyclic compounds in DMF: the potentials of quinoline, pyridine, 2-methylpyridine, 4-methylpyridine, and 2,6-dimethylpyridine are −2.18, −2.76, −2.80, −2.86, and −2.85 V [vs a saturated calomel electrode (SCE)], respectively.[20] The $E_{1/2}$ of 4-chlorobiphenyl (**1**) in DMF was also reported to be −2.37 V (vs SCE).[13b] The $E_{1/2}$ of quinoline is much greater than that of **1**, while the potentials of pyridine analogs are lower than that of **1** and are very close. It is, therefore, reasonable to think quinoline accepted an electron exclusively from Pd(0) or Et_3N to block the hydrodechlorination of **1** (Table 6, entries 3 and 5).[21] On the contrary, both the comparison between pyridines and **1** and the similarity of pyridines in $E_{1/2}$ seem to make it difficult to explain our results in Figure 3 with a simple SET mechanism. We reported that less sterically hindered pyridine inhibited more the hydrogenolysis of aliphatic benzyl ethers[22] and these results suggested some interaction, possibly complexation, between pyridines and palladium metal delayed the reaction rate. Combining the substituent effect on the pyridine ring as a catalyst poison with the SET mechanism, the results in Figure 3 could be rationally explained: (1) pyridine interacted with palladium metal to block the hydrogenation and even in the presence of Et_3N as an additive (the deactivation of catalysis was observed, Table 6, entry 1 vs entry 4); (2) mono-substituted pyridines such as 2-methyl- and

Table 6. The effect of additional additive on the hydrodechlorination of **1**[a]



Entry	Additive	Yield of **2** (%)[b]
1	Et_3N	100
2	Pyridine	0
3	Quinoline	0
4	Et_3N+pyridine	90
5	Et_3N+quinoline	0
6	Et_3N+TCNE	0
7	Et_3N+TCNQ	0

[a] All reactions were carried out under ordinary hydrogen pressure (balloon) using 1.2 equiv of additive and 10% Pd/C (3% of the weight of **1**) in MeOH at room temperature for 1 h.
[b] Yields were determined by GC/MS.

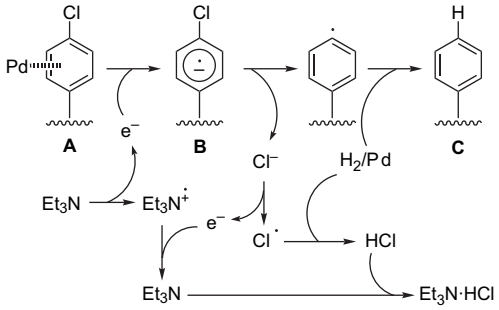


pyridine (●), 2-methylpyridine (◇), 4-methylpyridine (▲), 2,6-dimethylpyridine (○), 4-methoxypyridine (△), 4-*tert*-butylpyridine (■), DTBMP (□), without additive (×)

Figure 3. The effect of substituted pyridine as an additive on the hydrodechlorination of **1**.

4-methylpyridines could interact with palladium metal and deactivated Pd/C less than pyridine; (3) bulky pyridines such as 2,6-dimethylpyridine, 4-methoxypyridine, and 4-*tert*-butylpuridine were hard to interact with palladium metal and did not interfere in the catalyst activity for the hydrodechlorination; (4) the bulkiest DTBMP never interacts with palladium metal, but acts as an electron donor, as well as Et_3N.

These experimental results suggest that an SET mechanism is involved in the dechlorination using the Pd/C–Et_3N system (Scheme 1). Initial single electron transfer from Et_3N to the palladium-activated chlorobenzene ring of **A** affords an anion radical **B**, which then could be converted to the dechlorinated benzene ring of **C** by the elimination of the chloride anion and subsequent hydrogenation of the corresponding benzene radical.



Scheme 1. Proposed mechanism of the hydrodechlorination of aromatic chlorides.

3. Conclusion

We have developed a mild and efficient one-pot method for the hydrodechlorination of aromatic chlorides that proceeds at room temperature and under ordinary hydrogen pressure. The presence of Et_3N is crucial for the reaction and Et_3N works not only as a scavenger of hydrogen chloride but also as an electron donor to expedite the reaction. The reaction is general for a variety of aromatic chlorides. The simplicity and reliability of this method make it an attractive tool for organic and environmental chemists.

4. Experimental[23]

4.1. General

Pd/C (10%) was purchased from Sigma–Aldrich (cat. no. 205699) and Et_3N was purchased from Wako Pure Chemical Industries, Ltd. Analytical thin-layer chromatography (TLC) was carried out on pre-coated Silica Gel 60 F_{254} plates (Merck, Art 5715) and visualized with UV light. Column chromatography was accomplished using Merck Silica Gel 60 (230–400 mesh). For reversed phase column chromatography Waters Sep-Pak® C_{18} cartridge was used. ^1H NMR spectra were recorded on a JOEL JNM EX-400 NMR spectrometer (400 MHz). Chemical shifts (δ) are expressed in parts per million and are internally referenced (0.00 ppm for tetramethylsilane—$CDCl_3$, 4.79 ppm for D_2O, or 3.31 ppm for CD_3OD). Mass spectra and high-resolution mass spectra were taken on a JMS-SX 102A spectrometer at the Mass Spectrometry Laboratory at Gifu Pharmaceutical University.

4.2. General procedure (Fig. 1)

After two vaccum/H_2 cycles to remove air from a round-bottom flask, a suspension of 4-chlorobiphenyl (100 mg, 0.53 mmol), 10% Pd/C (3.0 mg), and Et_3N (89 μL, 0.64 mmol) in MeOH (10 mL) was vigorously stirred using a stir bar under hydrogen atmosphere (balloon) at ambient temperature (ca. 20 °C). At a given time point, the reaction mixture (1 mL) was sampled using a syringe, filtered through a 0.2-μL Millipore membrane filter (Millipore), and concentrated in vacuo. The residue was partitioned between hexanes (10 mL) and H_2O (10 mL) and the organic layer was washed with brine (10 mL), dried ($MgSO_4$), and filtered. An aliquot (1 mL) was taken from the filtrate, diluted with hexanes (19 mL), and analyzed by a Hewlett Packard 5891 series II gas chromatograph equipped with a Hewlett Packard 5972 mass-selective detector (Hewlett Packard) and a Neutrabond-5 capillary column (30 m×0.25 m, 0.4 μm film thickness; GL Science). Helium was employed as carrier gas with a flow rate of 1.0 mL/min. Injector and detector temperatures were 230 and 250 °C, respectively. The column temperature was programmed to ramp from 150 °C (5 min hold) to 250 °C (3 min hold) at a rate of 5 °C/min. The retention times of 4-chlorobiphenyl and biphenyl were 8.86 min and 4.81 min, respectively. The products were identified by their retention times on GC/MS or their ^1H NMR spectra in comparison with those of commercial authentic samples.

4.2.1. Optimization of base for the hydrodechlorination of 4-chlorobiphenyl (1) (Table 1). According to the general procedure, the reaction was carried out for 1 h using another base in place of Et_3N. The reaction mixture was filtered through a 0.2-μL Millipore membrane filter and concentrated in vacuo. The residue was partitioned between hexanes (10 mL) and H_2O (10 mL) and the organic layer was washed with brine (10 mL), dried ($MgSO_4$), and filtered. The filtrate was concentrated in vacuo. An aliquot (1 mg) was taken from the residue, dissolved in hexanes (20 mL), and analyzed as described in Section 4.2.

4.2.2. Optimization of solvent for the hydrodechlorination of 1 (Table 2). According to the general procedure, the reaction was carried out for 1 h using another solvent in place of MeOH. The reaction mixture was treated and analyzed in the same manner as described in Table 1.

4.2.3. Optimization of amount of Pd/C and temperature for the hydrodechlorination of 1 (Table 3). According to the general procedure, the reaction was carried out for 24 h using 1 mg of 10% Pd/C (1% weight of **1**) in place of 3 mg of 10% Pd/C or the reaction was carried out for 1 h at −20 °C or reflux in place of room temperature. Aluminum foil was used for the reaction under dark conditions. The reaction mixture was treated and analyzed in the same manner as described in Table 1.

4.3. Hydrodechlorination of aromatic chlorides (Table 4)

According to the general procedure, the reaction was carried out using 100 mg of a substrate. After the starting chloride

disappeared, the reaction mixture was filtered through a 0.2-μL Millipore membrane filter and concentrated in vacuo. The residue was partitioned between Et_2O (10 mL) and H_2O (10 mL) and the organic layer was washed with brine (10 mL), dried ($MgSO_4$), and filtered. If necessary, the residue was purified by silica gel column chromatography or reversed phase column chromatography.

4.3.1. 10-[3-(Dimethylamino)propyl]phenothiazine [CAS Registry Number 58-40-2] (entry 9).[24] ^{1}H NMR ($CDCl_3$) δ 2.19 (5H, m), 2.42 (6H, s), 2.76 (2H, t, J=6.4 Hz), 4.00 (2H, t, J=6.4 Hz), 6.89–6.96 (4H, m), 7.17 (4H, m); MS (EI) m/z 284 (M^+), 58 (83), 198 (45), 238 (42), 284 (100); HRMS (EI) Calcd for $C_{17}H_{20}N_2S$ (M^+) 284.1347; Found 284.1356.

4.3.2. 1-Benzoyl-5-methoxy-2-methylindole-3-acetic acid [CAS Registry Number 1601-19-0] (entry 10).[25] ^{1}H NMR ($CDCl_3$) δ 2.38 (3H, s), 3.71 (2H, s), 3.83 (3H, s), 6.65 (1H, d, J=9.3 Hz), 6.87 (1H, d, J=9.3 Hz), 6.95 (1H, s), 7.49 (2H, t, J=7.6 Hz), 7.62 (1H, t, J=7.6 Hz), 7.70 (2H, d, J=7.6 Hz); MS (EI) m/z 357 (M^+), 77 (61), 105 (100), 158 (25), 323 (76); HRMS (EI) Calcd for $C_{19}H_{17}NO_4$ (M^+) 323.1158; Found 323.1146.

4.3.3. 2-(Phenylamino)imidazoline [CAS Registry Number 1848-75-5] (entry 11).[26] ^{1}H NMR (D_2O) δ 3.62 (4H, s), 7.18 (2H, s), 7.26 (1H, t, J=7.3 Hz), 7.36 (2H, t, J=7.3 Hz); MS (EI) m/z 161 (M^+), 77 (29), 104 (33), 160 (40); HRMS (EI) Calcd for $C_9H_{11}N_3$ (M^+) 161.0953; Found 161.0949.

4.3.4. Ethyl 2-methyl-2-phenoxypropanoate [CAS Registry Number 18672-04-3] (entry 12).[27] ^{1}H NMR ($CDCl_3$) δ 1.25 (3H, t, J=7.1 Hz), 1.60 (6H, s), 4.23 (2H, q, J=7.1 Hz), 6.84 (2H, d, J=8.0 Hz), 6.98 (1H, t, J=8.0 Hz), 7.24 (2H, t, J=8.0 Hz); MS (EI) m/z 208 (M^+), 77 (18), 94 (100), 135 (54); HRMS (EI) Calcd for $C_{12}H_{16}O_3$ (M^+) 208.1099; Found 208.1101.

4.3.5. 7-Sulfamoyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide [CAS Registry Number 23141-82-4] (entry 13).[28] ^{1}H NMR (CD_3OD) δ 3.46 (2H, s), 4.89 (2H, s), 7.01 (1H, d, J=8.9 Hz), 7.85 (1H, d, J=8.9 Hz), 8.14 (1H, s); MS (EI) m/z 263 (M^+), 171 (58), 187 (36); HRMS (EI) Calcd for $C_7H_9N_3O_4S_2$ (M^+) 263.0034; Found 263.0038.

4.3.6. 2-(Phenylamino)benzeneacetic acid [CAS Registry Number 70172-33-7] (entry 14).[29] ^{1}H NMR (CD_3OD) δ 3.53 (2H, s), 6.70 (1H, t, J=7.6 Hz), 6.77 (2H, d, J=7.6 Hz), 6.87 (1H, t, J=7.6 Hz), 7.05–7.10 (3H, m), 7.13–7.17 (2H, m); MS (EI) m/z 227 (M^+), 167 (10), 180 (100), 209 (54); HRMS (EI) Calcd for $C_{14}H_{13}NO_2$ (M^+) 227.0946; Found 227.0956.

4.3.7. 5-Sulfamoyl-*N*-(tetrahydrofurfuryl)anthranilic acid [CAS Registry Number 4818-84-2] (entry 15).[30] ^{1}H NMR (CD_3OD) δ 1.80–1.93 (1H, m), 1.99–2.10 (2H, m), 3.42–3.49 (2H, m), 3.86 (1H, m), 4.01 (1H, m), 4.23 (1H, m), 6.86 (1H, d, J=8.8 Hz), 7.81 (1H, d, J=8.8 Hz), 8.51 (1H, s); MS (EI) m/z 300 (M^+), 71 (57), 81 (73), 211 (100), 229 (42); HRMS (EI) Calcd for $C_{12}H_{16}N_2O_5S$ (M^+) 300.0780; Found 300.0785.

4.4. Hydrodechlorination of 1 in the presence of HCl (Fig. 2)

According to the general procedure, the reaction was carried out using 0.1 M HCl in MeOH (0, 0.1, 0.5, or 1.0 equiv) in place of Et_3N and analyzed.

4.5. Hydrogenation of 1 after pre-treatment of Pd/C with additive (Table 5)

A suspension of 10% Pd/C (3 mg) and an additive (0.64 mmol) was stirred under hydrogen (balloon) for 24 h. 4-Chlorobiphenyl (100 mg, 0.53 mmol) was added and the mixture was stirred under hydrogen (balloon) for 1 h. The reaction mixture was treated and analyzed in the same manner as described in Table 1.

4.6. Hydrogenation of 1 in the presence of Et_3N and an additional additive (Table 6)

According to the general procedure, the reaction was carried out for 1 h in the presence of Et_3N (89 μL, 0.64 mmol) and an additive (0.64 mmol). The reaction mixture was treated and analyzed in the same manner as described in Table 1.

4.7. Hydrogenation of 1 in the presence of pyridine analog (Fig. 3)

According to the general procedure, the reaction was carried out using a substituted pyridine (0.64 mmol) in place of Et_3N and analyzed.

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23. The residual palladium assay of biphenyl: after two vaccum/H_2 cycles to replace air inside a round-bottom flask with H_2, a solution of 4-chlorobiphenyl (1.89 g, 10 mmol), 10% Pd/C (56.7 mg), and Et_3N (1.67 mL, 12 mmol) in MeOH (35 mL) was vigorously stirred using a stir bar under hydrogen atmosphere (balloon) at ambient temperature (ca. 20 °C) for 24 h. Simple filtrations of the reaction mixture using Millipore membrane filters (0.45 μL Millex®-LH and then 0.20 μL Millex®-LG) without any rinse with additional MeOH gave Pd/C-free filtrate. The filtrate was concentrated in vacuo and the resulting white solid (1.34 g) was assayed. Residual palladium (3.5 ppm) was detected by an ICP-MS (Agilent 7500CE, Agilent Technologies). The leaching of palladium into the reaction mixture in the presence of Et_3N was reported: Zhao, F.; Bhanage, B. M.; Shirai, M.; Arai, M. *Chem.—Eur. J.* **2000**, *6*, 843–848.
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