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Pd/C-catalyzed room-temperature hydrodehalogenation of aryl halides with hydrazine hydrochloride

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Abstract—Treatment of aryl and heteroaryl halides with catalytic amounts of Pd/C in the presence of hydrazine hydrochloride in basic medium (sodium hydroxide or sodium *t*-butylate) at room temperature leads to the corresponding hydrodehalogenation products with high selectivity. Aryl iodides, bromides, chlorides and fluorides can be reduced using this reagent combination. The reduction is compatible with various electron-donating or electron-withdrawing groups.

The conversion of aryl halides into arenes is a chemical transformation with important industrial applications. The detoxification of halogenated aromatic wastes, like polychlorinated biphenyls (PCBs), by catalytic hydrodehalogenation is indeed an environmentally friendly and cost-saving alternative to their traditional disposal by incineration, which can generate highly toxic dibenzofurans and dibenzodioxins.[1] This transformation has also been used for the selective deuterium or tritium labeling of arenes[2] and is of interest in organic synthesis, since a halogen atom can serve as a protecting group for an aryl site or direct electrophilic substitutions.[3]

A wide variety of hydrodehalogenating systems have been used over the years and this subject has recently been reviewed in detail.[4] Reduction is usually mediated by a transition-metal catalyst (Ni, Pd, Rh, Pt)[5] and is performed with molecular hydrogen, metal hydrides or hydrogen sources such as formic acid and its salts, hydrazine or alkoxides possessing a β-hydrogen. For safety and simplicity of operation, a liquid-phase process without using molecular hydrogen is more advantageous.

The Pd-catalyzed hydrogenolysis of carbon–halogen bonds with hydrazine as a hydrogen donor is a long-known method, but it is usually performed with large amounts of catalyst and/or reducing agent.[6,7] To our knowledge, no systematic study of the reaction has appeared in literature. Moreover, the use of catalytic palladium in combination with reduced amounts of hydrazine under mild conditions was only achieved by Balko et al. and is restricted to chlorophenols.[8] Thus, we decided to investigate the scope and limitations of this methodology and to establish the optimum reaction conditions.

We chose to use hydrazine as its hydrochloride salt for safety reasons, since this form is less dangerous and more easy to handle than the anhydrous or the hydrate forms. A preliminary survey of catalytic efficiency of different palladium sources was first undertaken on the model reaction involving 4-bromotrifluoromethylbenzene as the substrate, sodium *t*-butylate as the base and THF as the solvent (Table 1). Although effective protocols using metal catalysts in combination with sophisticated *N*-heterocyclic carbene ligands have been developed recently,[2b,5d] we preferred a methodology employing no additional ligand for economic reasons. Pd/C and $Pd_2(dba)_3$ allowed quasi selective hydrodehalogenations within 24 h at room temperature (Table 1, entries 1 and 2), while the use of palladium acetate favoured biaryl reductive coupling (entry 3). As expected, reactions performed without a palladium catalyst resulted in no detectable reduction product (entry 4). The less expensive and far more efficient Pd/C was

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Keywords: liquid-phase dehalogenation; palladium catalyst; heterogeneous catalysis; aryl halides; hydrazine.

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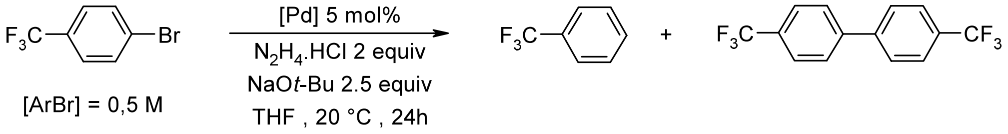
Table 1. Effect of palladium source on the reduction of 4-bromotrifluoromethylbenzene with hydrazine[a]



Entry	Catalyst	Arene yield (%)	Arene selectivity (%)[b]	Biaryl yield (%)
1	Pd/C	94	94	6
2	$Pd_2(dba)_3$	66	93	4
3	$Pd(OAc)_2$	38	38	62
4	–	0	–	0

[a] Yields determined by GC by obtaining the correction factors using authentic samples of the products.

[b] Arene yield divided by aryl bromide conversion.

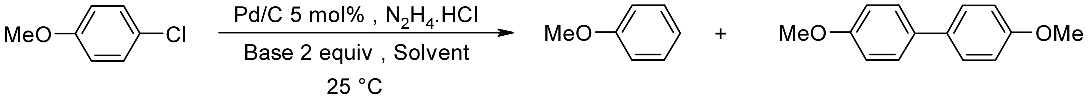
preferred to $Pd_2(dba)_3$ and used in experiments aimed at optimizing the hydrazine quantity and the nature of base and solvent (Table 2), employing the electron-rich 4-chloroanisole as a more challenging model substrate.

We found that the minimum amount of reducing agent compatible with a high ratio hydrodehalogenation/homocoupling (94%) was 0.75 equiv. relative to the aryl chloride (Table 2, entries 1–4). Lowering this amount to 0.5 equiv. also allowed a quantitative reduction of 4-chloroanisole but resulted in a decrease of the selectivity towards anisole (86%) and revealed rate-depressing (Table 2, entry 4). Interestingly, this experiment proved that the palladium catalyst generates 2 equiv. of hydrogen from 1 equiv. of hydrazine.

A variety of bases were then examined in THF with a reaction time fixed to 48 h. Of these, sodium hydroxide and sodium *t*-butylate were the most efficient (entries 5 and 6). K_3PO_4, KO*t*-Bu, LiO*t*-Bu, K_2CO_3 and Cs_2CO_3 all led to incomplete conversions of the starting material (Table 2, entries 7–11). These variations in yields imply that the role of base compounds is not limited to neutralization of halogenohydric acid. Due to its lower cost and its slightly higher selectivity in favour of the hydrodehalogenation product, sodium hydroxide[9] was chosen to investigate the effect of solvent on the reaction outcome. Toluene and THF were found to be the solvents of choice (Table 2, entries 12 and 13), allowing quasi quantitative conversion of 4-chloroanisole to anisole in less than 24 h. Reactions were slightly less selective in ethanol while poor yields were observed in acetonitrile or dichloromethane (entries 14–16).

Using the optimized reaction conditions (Table 2, entry 12), a broad sampling of functionalized substrates were

Table 2. Effect of hydrazine quantity and base or solvent nature on the hydrodehalogenation of 4-chloroanisole[a]



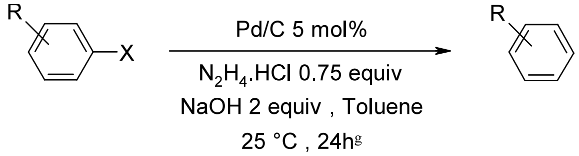
Entry	Base	Solvent	Time (h)	Equiv. $N_2H_4 \cdot HCl$	[ArX] (mol/L)	Anisole yield (%)	Anisole selectivity (%)[b]	4,4′-Bianisole yield (%)
1	NaO*t*-Bu	THF	55	2	0.5	100	100	0
2	NaO*t*-Bu	THF	24	1	0.5	94	94	6
3	NaO*t*-Bu	THF	24	0.75	0.5	94	94	6
4	NaO*t*-Bu	THF	24	0.5	0.5	86	86	14
5	NaOH	THF	48	0.75	0.5	99	99	1
6	NaO*t*-Bu	THF	48	0.75	0.5	94	94	6
7	K_3PO_4	THF	48	0.75	0.5	86	95	5
8	KO*t*-Bu	THF	48	0.75	0.5	73	97	2
9	K_2CO_3	THF	48	0.75	0.5	45	87	7
10	Cs_2CO_3	THF	48	0.75	0.5	29	84	6
11	LiO*t*-Bu	THF	48	0.75	0.5	17	84	4
12	NaOH	Toluene	24	0.75	1.0	>99	>99	<1
13	NaOH	THF	24	0.75	1.0	99	99	1
14	NaOH	EtOH	24	0.75	1.0	96	96	4
15	NaOH	CH_2Cl_2	24	0.75	1.0	15	100	0
16	NaOH	MeCN	24	0.75	1.0	2	100	0

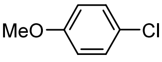
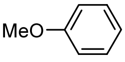
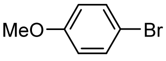
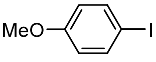
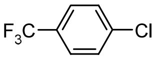
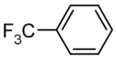
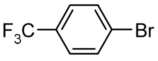
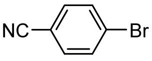
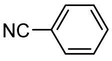
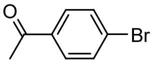
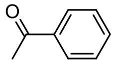
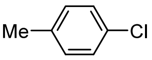
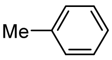
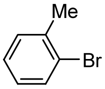
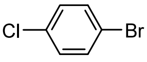
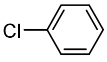
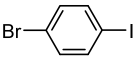
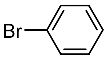
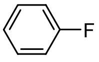
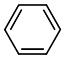
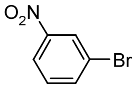
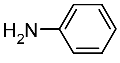
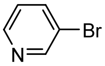
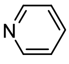
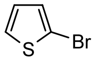
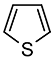
[a] Yields determined by GC by obtaining the correction factors using authentic samples of the products.

[b] Anisole yield divided by chloroanisole conversion.

hydrodehalogenated with good to excellent yields (Table 3).[10] Electron-rich (entries 1 and 2), electron-poor (entries 6–9) and sterically hindered (entry 11) aryl chlorides or bromides were reduced to the corresponding arenes with equal efficiency within 24 h. Heteroaromatics such as 3-bromopyridine or 2-bromothiophene (Table 3, entries 17 and 18) behaved similarly. We found that the ratio hydrodehalogenation/homocou-

Table 3. Palladium-catalyzed hydrodehalogenation of aromatic and heteroaromatic halides



Entry	Aryl halide	Product	[ArX] (mol/L)	CG yield (%)	Selectivity (%)[h]	Biaryl GC yield (%)
1			1.0	> 99	> 99	< 1
2		"	"	97	97	3
3		"	1.0	78	78	22
4			0.5	83	83	17
5[a]			1.0	29	29	71
6			1.0	99	99	1
7		"	"	96	96	3
8			"	94	94	3
9			"	82[b]	99	< 1
10[a]			"	98	98	2
11[a]		"	"	95	95	5
12[f]			"	53[e]	86	~ 2
13[f]			"	42	64	~ 7
14			"	51	100	0
15[c]			"	74	74[d]	0
16			1.0	90	90	10
17			0.5	96	96	4
18			0.5	96	96	4

[a] In THF.

[b] After hydrolysis of the reaction mixture with 35% HCl at rt.

[c] With 6 equiv. of NaOH and 2.5 equiv. of N_2H_4·HCl.

[d] 21% azobenzene were formed.

[e] Reaction time: 30 h.

[f] With 0.5 equiv. of N_2H_4·HCl.

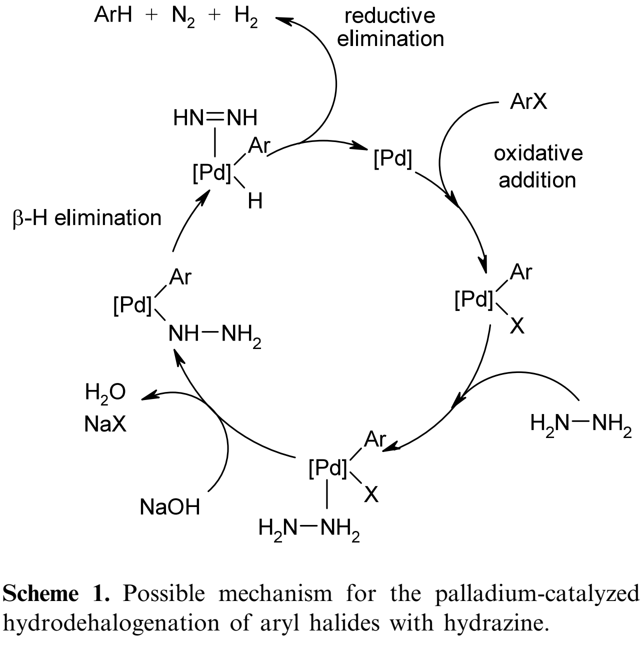
[g] Reaction times are not optimized.

[h] Arene yield divided by aryl halide conversion.

pling was sensitive to the nature of halogen and decreased when going from chlorine to iodine. Thus, 4-chloranisole and 4-bromoanisole were reduced to anisole with >99 and 97% yield respectively, while 4-iodoanisole afforded 78% anisole along with 22% 4,4′-bianisole (entries 1–3). In the latter case, using THF instead of toluene as the solvent further decreased the yield of anisole to 29% (entry 5). As expected, the incidence of biaryl coupling could be reduced by diluting the reaction mixture (compare entries 4 and 16 with entries 5 and 17).

As previously stated in literature,[2b] the reactivity of aryl halides was found to follow the order of bond strength: ArI>ArBr>ArCl, as deduced from entries 12 and 13. 4-Chlorobromobenzene was reduced to chlorobenzene (53% yield, 86% selectivity), along with benzene (6%) and chlorinated biaryl compounds (~3%). Iodine removal from 4-iodobromobenzene took place preferentially, affording bromobenzene as the main product (42% yield, 64% selectivity). 2% benzene and ~9% brominated biaryl compounds were also formed in this case.[11] Due to the high strength of the carbon–fluorine bond, aryl fluorides usually exhibit a relative inertness in metal-catalyzed reactions.[4,5d,e] Therefore, we were pleased to find that they were also prone toward our room-temperature hydrodehalogenation protocol. Benzene was obtained from fluorobenzene as the sole product in 51% yield within 24 h (Table 3, entry 14).

Nitrile and ketone functions (Table 3, entries 8 and 9) were not reduced by hydrazine, attesting the functional group compatibility offered by the present method. In the case of 4-bromoacetophenone (entry 9), the crude reaction mixture had to be treated with concentrated HCl at room temperature to hydrolyze the azines formed from the reaction of hydrazine with two acetophenone molecules. We could reduce both nitro and bromine groups of 3-bromonitrobenzene using 2.5 equiv. of hydrazine relative to the aryl halide (Table 3, entry 15). Aniline was obtained with a 74% yield and the incompletely reduced azobenzene was formed as a side product (21%).



Scheme 1. Possible mechanism for the palladium-catalyzed hydrodehalogenation of aryl halides with hydrazine.

A possible pathway for hydrodehalogenations mediated by the system $Pd/C/N_2H_4/NaOH$ is depicted by Scheme 1. The first step involves oxidative addition of the aryl halide to a zerovalent palladium complex[5b] (generated from Pd/C with hydrazine), followed by base-assisted displacement of the halogen atom by hydrazine. Decomposition of the palladium-bonded hydrazide into diimine[12] N_2H_2 via β-H elimination leads to a palladium hydride complex from which the Pd(0) catalyst is regenerated by reductive elimination of the arene. The likely evolved dihydrogen also takes part to this process in a similar fashion, accounting for the fact that a 0.5 equiv. of hydrazine can reduce 1 equiv. amount of aryl halide to the corresponding arene.

In summary, we have shown that the conversion of aryl iodides, bromides, chlorides and even fluorides to the corresponding arenes can be efficiently performed in toluene at room temperature in the presence of a slight excess of hydrazine as a cheap hydrogen donor, sodium hydroxide and catalytic amounts of Pd/C without supporting ligand. Worthy of note is the fact that some sensitive functional groups like nitrile and ketone are tolerated on the aryl halides. The method is mild, operationally simple (no pressure apparatus is required) and enjoys benefits associated with heterogeneous catalysis.

Acknowledgements

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7. New examples were reported after the completion of this work. See: (a) Rodriguez, J. G.; Lafuente, A. *Tetrahedron Lett.* **2002**, *43*, 9645–9647; (b) Rodriguez, J. G.; Lafuente, A. *Tetrahedron Lett.* **2002**, *43*, 9581–9583.
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9. Used as 20–40 mesh beads (Aldrich Chem. Co.).
10. *Typical procedure*: Under an atmosphere of dry and pure nitrogen, an oven-dried Schlenk tube equipped with a magnetic stir bar was charged with 10% w/w Pd/C (26 mg, 0.025 mmol Pd, Fluka), hydrazine hydrochloride (26 mg, 0.375 mmol), sodium hydroxide (40 mg, 1 mmol) and the aryl halide (0.5 mmol), if a solid. The tube was capped with a rubber septum. If a liquid, the aryl halide was added via syringe, followed by anhydrous toluene (1 mL). The septum was removed and the tube was sealed under a positive pressure of nitrogen. The slurry was allowed to stir for 24 h at room temperature. The reaction mixture was then diluted with dichloromethane (5 mL) and a known volume of internal standard was added. A small sample of this mixture was filtered through a plug of Celite®, washed three times with water and analyzed by gas chromatography.
11. No attempts were made to optimize the reduction of dihalogenated aromatics.
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