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Hydrogen bonding promoted simple and clean photo-induced reduction of C–X bond with isopropanol†

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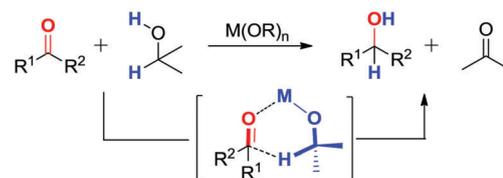
We herein report a simple and clean photo-induced metal-free reduction of C–X bond under an atmosphere of air at room temperature. Isopropanol is used as both the reducing reagent and solvent. Various functional groups (acids, esters, alcohols, anilines, phenols, indoles, pyridines, cyano and trifluoromethyl groups) and other heterocyclic compounds are tolerated. Different organic halides (including C–I, C–Br and C–Cl bonds) can be dehalogenated with moderate to excellent yields. Polyhalides are also reduced chemoselectively and efficiently. DFT calculation suggests a six-membered ring transition state *via* C–X···H–O hydrogen bonding to decrease the activation energy.

Reducing C–halogen bonds to C–H bonds is not only a fundamental organic transformation in organic synthesis¹ but also an important tool for detoxification of environmentally hazardous organic halides.² While classical methods utilized tributyltin hydride *via* radical reaction,³ a variety of alternative radical-based methods have been developed to avoid the toxicity of tin reagents.⁴ However, metal or metal organic chemicals are generally required for these transformations. In recent studies, transition-metal-free reduction of C–X bond was promoted by strong base,⁵ and sodium hydride was used as a hydride resource to reduce C–Br bond.⁶ Photo-induced metal catalyzed reduction⁷ and photo-induced organic photoredox catalyst-based reduction⁸ were also developed. Recently, photo-induced catalyst-free reductions of C–X bond were reported using BNAH (1-benzyl-1,4-dihydronicotinamide),⁹ TMSS (tristrimethylsilylsilane),¹⁰ borohydrides¹¹ and triethylamine¹² as reducing reagents, respectively. Nevertheless, all these methods require stoichiometric reducing reagents.

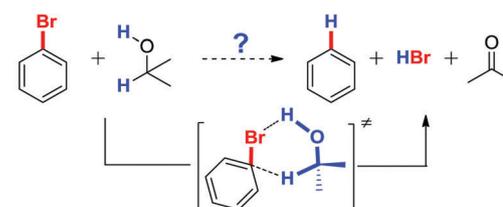
The Meerwein–Ponndorf–Verley (MPV) reduction is a classical reaction to reduce ketones to alcohols *via* hydrogen-transfer from isopropanol.¹³ This reaction was generally catalyzed by metal alkoxyl to form six-membered ring transition state (Scheme 1a). Inspired by this classical reaction, we hypothesized that organic halides can be irradiated by light to generate the excited state, which can form a six-membered ring transition state similar to the MPV reaction *via* a weak hydrogen bonding between the halogen and the hydroxyl group of isopropanol (Scheme 1b). Subsequent “intramolecular” hydrogen-transfer will generate the reduced product, with isopropanol being concurrently oxidized to form acetone.

To test the feasibility of this hypothesis, methyl 4-iodobenzoate (**1a**) was selected as a model substrate under UV (254 nm) irradiation in 1 mL of isopropanol solvent, using DBU as base under an argon atmosphere at room temperature (Table 1, entry 1). To our delight, 93% yield of the reduction product was detected! Encouraged by this result, different light sources (such as blue LED, CFL or without light) were

(a) Transition state of Meerwein–Ponndorf–Verley reduction



(b) The rationale of C–X bond reduction (*This work*)



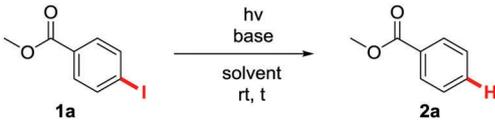
Scheme 1 The strategy for C–halogen reduction *via* hydrogen-transfer of isopropanol inspired by the Meerwein–Ponndorf–Verley reduction.

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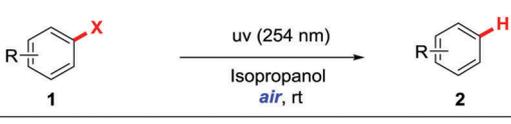
Table 1 Evaluation of various conditions^a


Entry	Light source	Base	Solvent (mL)	2a Yield ^b /%
1	UV (254 nm)	DBU	Isopropanol	93
2	Blue LED	DBU	Isopropanol	n.p.
3	CFL	DBU	Isopropanol	Trace
4		DBU	Isopropanol	n.p.
5	UV (254 nm)	DBU	DMSO	39
6	UV (254 nm)	DBU	DMF	58
7	UV (254 nm)	DBU	MeCN	21
8	UV (254 nm)	DBU	H ₂ O	Trace
9	UV (254 nm)		Isopropanol	89
10	UV (254 nm)		Isopropanol (1.5)	95
11	UV (254 nm)		Isopropanol (2)	96
12 ^c	UV (254 nm)		isopropanol (1.5)	72
13 ^d	UV (254 nm)		Isopropanol (1.5)	96
14 ^e	UV (254 nm)		Isopropanol (1.5)	95(89)

^a General conditions: **1a** (0.2 mmol), base (1.0 equiv.) and solvent (1.0 mL) at room temperature for 12 h under argon atmosphere. ^b Yields were determined by ¹H NMR using nitromethane as internal standard; isolated yields in brackets. ^c 6 h. ^d 24 h. ^e Under air.

examined, and only trace or no desired product was detected (Table 1, entries 2–4). These results indicate that the light resource is very important to this reaction. The influence of solvent was also investigated and showed that isopropanol is the best solvent (Table 1, entries 5–8). Interestingly, 89% yield of reduction product **2a** was also obtained without adding any base (Table 1, entry 9). When the volume of solvent was increased, the yield was slightly increased accordingly (Table 1, entries 10 and 11). For economical reason, 1.5 mL of solvent was chosen for subsequent studies. Reducing the reaction time to 6 h gave the product in 72% yield (Table 1, entry 12). However, prolonging the reaction time to 24 h did not change the yield (Table 1, entry 13). It is noteworthy that even when this reaction was performed under an atmosphere of air, almost the same excellent yield (95%) was obtained (Table 1, entry 14). Consequently, the reaction was carried out in 1.5 mL of isopropanol under UV irradiation (254 nm) utilizing quartz reactor (please see ESI[†]) under air at room temperature for 12 h.

With the optimized reaction conditions in hand, we explored the generality of this reaction (Table 2). Gratifyingly, a broad range of aryl halides containing either electron-donating or electron-withdrawing groups proved to be competent substrates, providing the reduction products in moderate to excellent yields. Notably, the reaction system also exhibited high chemoselectivity: various functional groups including ester (**1a–e**), carboxyl (**1f**), methoxy (**1g–l**), dimethoxy (**1m**), alkyl (**1n–q**), phenyl (**1r**), amine (**1t**), hydroxy (**1u–v**), hydroxymethyl (**1w–x**), trifluoromethyl (**1y**), cyano (**1z**) and heterocyclic compounds (**1ab–1ai**) were tolerated, thereby providing handles for further product diversifications. Among them, we also studied different halogen-substituted (–Cl, Br, I) substrates (**1a–c**, **1d–e**, **1h–j**, **1k–l**, **1o–p**, **1u–v**), all of them were reduced with high to excellent yields. It is noteworthy that 3.85 grams of compound **1a** was also successfully dehalogenated

Table 2 Reduction of different aryl halides^a


1a X = I 89%, 12 h 3.85 grams 73%, 36 h 1b X = Br 89%, 24 h 1c X = Cl 75%, 36 h ^b	1d X = I 90%, 12 h 1e X = Cl 91%, 36 h ^b	1f 94%, 12 h	1g 78% 18 h
1h X = I 80%, 18 h 1i X = Br 82%, 24 h 1j X = Cl 69%, 36 h ^b	1k X = I 74% 24 h 1l X = Br 68%, 36 h	1m 85%, 24 h	1n 83%, 24 h
1o X = I 85%, 18 h 1p X = Cl 82%, 36 h ^b	1q 88%, 24 h	1r R = Ph 94%, 36 h ^b 1s R = H 86%, 20 h ^c	1t 82%, 24 h
1u X = Br 94%, 24 h 1v X = Cl 89%, 36 h	1w 86%, 12 h	1x 92%, 36 h ^b	1y 80%, 36 h ^b
1z 89%, 36 h ^b	1aa 94%, 12 h	1ab 78%, 36 h	1ac 75%, 36 h
1ad 68%, 36 h	1ae 62%, 36 h ^b	1af 54%, 36 h ^b	
1ag 72%, 36 h ^b	1ah 78%, 36 h ^b	1ai 91%, 36 h ^b	

^a Reaction conditions: **1** (0.2 mmol), isopropanol (1.5 mL) at room temperature for 12 h under air. ^b 1.5 mL isopropanol and 0.5 mL DMF were used as a mixture solvent. ^c Yield was detected by GC.

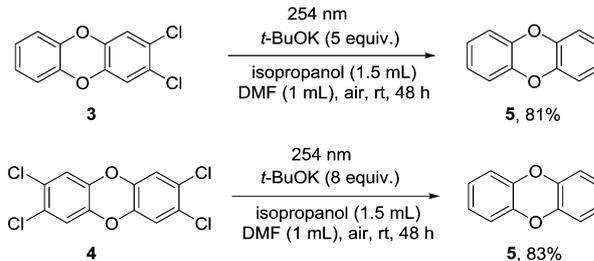
in 73% yield by prolonging the reaction time to 36 h. The substrates with methoxy group (**1g–1l**) generated slightly lower yields, due to isolation loss caused by the lower boiling points of these compounds. Much to our satisfaction, the substrates containing strong electron-withdrawing group, such as trifluoromethyl group (**1y**) and cyano group (**1z**) were tolerated and not reduced under our reaction system. 1-Iodonaphthalene (**1aa**) also furnished the desired products with excellent yield. Meanwhile, bromine-substituted indole substrates on different positions (**1ab–ad**) were dehalogenated in 68% to 78% yields, respectively. In addition, different halogen-substituted heterocyclic compounds (**1ae–ai**) could also be reduced with moderate to high yields.

To further investigate the scope of this reduction system, polyhalogen substituted substrates were tested, and the results

were summarized in Table 3. Polyhalides **1aj** and **1ak** can be chemo-selectively reduced to obtain the chlorinated products when we controlled the reaction time. It is noteworthy that different fluoroaryl compounds bearing iodo-, bromo- or chloro-group were reduced smoothly to generate the desired fluorinated compounds up to 89% yields (**1al-an**). To our delight, the iodo-substituted polyfluoroarene **1ao** could also be selectively reduced with high yield in 12 h.

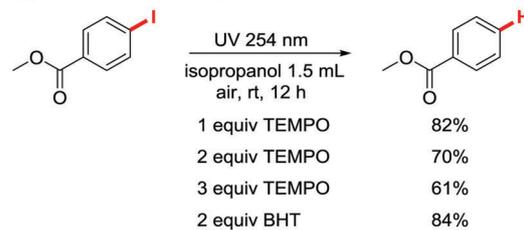
As is well known, dioxins are highly environmentally persistent organic pollutants. Detoxification of dioxins was investigated by our method. To our delighted, all of the C–Cl bonds of 2,3-dichlorodibenzo[*b,e*][1,4]dioxin (**3**) and the most dangerous dioxins 2,3,7,8-tetrachlorodibenzo[*b,e*][1,4]dioxin (TCDD)¹⁴ (**4**) were successfully reduced in the presence of strong base, and the detoxification compound dibenzo[*b,e*][1,4]dioxin (**5**) was obtained in this case with 81% and 83% yield (Scheme 2), respectively.

To understand the mechanism, free radical trap and deuterium experiments were performed (Scheme 3). When 1 to 3 equiv. of TEMPO were added to this reaction system under standard reaction conditions, the reaction still proceeded smoothly, to give 82% to 61% yields of the reduced product. The same result was obtained when 2 equiv. of BHT was added as the free radical trap (Scheme 3a). These experiments suggested the absence of free aryl radical during the course of this reaction. Deuterium product methyl 4-*d*-benzoate (**6**) was isolated when isopropanol-*d*₈ was used as solvent. To further exclude the possibility that the deuterium atom originated from hydroxyl group or methyl group of isopropanol. Normal water (0.4 mL) was added to the isopropanol-*d*₈. The product **6** was obtained in 85% yield with 100% deuteration at C-4 position (Scheme 3b).¹⁵ This result eliminated the possibility of deuterium originated from the hydroxyl group. 1,1,1,3,3,3-Hexafluoro-propanol-*d*₂ was also selected as solvent, the deuterated product **6** was also obtained. Combining these three deuterium experiments, we can speculate that the deuterium atom of product originated from C-2 position of isopropanol.

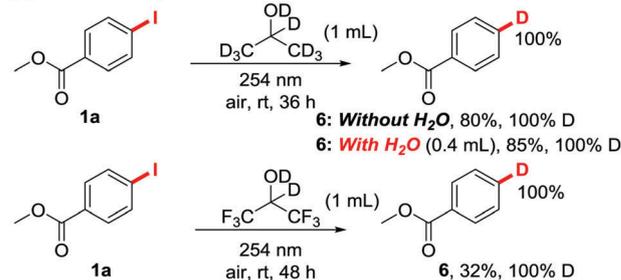


Scheme 2 Application of this method for detoxification of dioxins.

(a) Free radical trap experiments

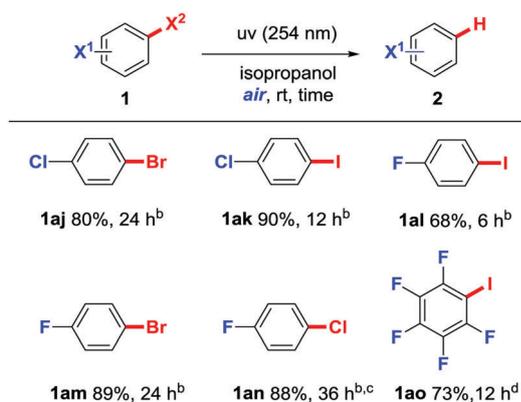


(b) Deuterium experiments



Scheme 3 Control experiments.

Table 3 Chemoselective reduction of organic halides^a



^a Reaction conditions: **1** (0.2 mmol), isopropanol (1.5 mL) at room temperature under air, reaction time were shown under the structure.

^b Yields were determined by GC-MS. ^c 1.5 mL isopropanol and 0.5 mL DMF were used as a mixture solvent. ^d Yield was determined by ¹⁹F NMR using fluorobenzene as internal standard.

Based on the mechanistic studies above, we proposed a plausible reaction mechanism, and corresponding density functional theory (DFT) calculations were also carried out at M06-2X¹⁶/6-31+G(d,p)/IEFPCM¹⁷ (2-propanol) level of theory. As described in Fig. 1 (for the whole free energy profile, please see ESI,† Fig. S1), the ground state bromobenzene goes through UV light excitation and intersystem crossing (isc) successively to form the first triplet excited state PhBr (**T1**). Both “intra-” and intermolecular pathways are investigated (black and grey, respectively). For the “intramolecular” pathway (black), hydrogen atom transfer (HAT) and C–Br bond cleavage can take place synchronously in **TS1** with a six-membered ring structure to generate the radical **IM3** and reduced product benzene. For the intermolecular pathway (grey), homo-cleavage of C–Br bond in PhBr (**T1**) will form benzene radical. Then, HAT occurs *via* **TS1'** to form the reduced product benzene and radical **IM3**.

DFT calculation shows that there is 14.7 kcal mol^{−1} free energy increase from PhBr (**T1**) to **TS1'** in the grey pathway. In comparison, the black pathway only has 5.1 kcal mol^{−1} free energy change from PhBr (**T1**) to **TS1**. The result indicates that the black pathway is more favorable than the grey pathway.

This stabilization may be due to the larger dipole moment of **TS1** (please see ESI,† Table S2). With the existence of O–H⋯Br–C

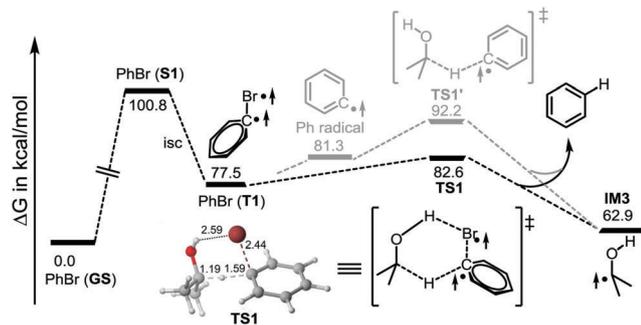


Fig. 1 DFT calculation of the reaction mechanism and partial potential energy surface of the **black pathway** and the **grey pathway**. Some intermediates are omitted. The Gibbs free energies of PhBr (**GS**) and isopropanol were set to 0.0 kcal mol⁻¹ as reference. Distances are in Å.

hydrogen bond of **TS1**, there is apparent charge separation (large red and blue clouds), leading to large dipole moment. In contrast, there is less charge separation in **TS1'** (please see ESI,† Fig. S2).

In conclusion, we have developed a simple and clean metal-free reduction of C–X bond under air at room temperature. Isopropanol was used as both reducing reagent and solvent. A wide range of functional groups, such as acids, esters, alcohols, anilines, phenols, indoles, pyridines, cyano group, trifluoromethyl group and heterocyclic compounds, were all tolerated. Different organic halides comprising C–I, C–Br and C–Cl bonds were reduced with good to excellent yields. Polyhalides were also chemoselectively reduced. DFT calculation showed that a six-member ring transition state containing C–Br···H–O hydrogen bonding has lower energy. This strategy provides greener approach for C–halogen bond reduction and detoxification of environmentally hazardous organic halides.

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Conflicts of interest

There are no conflicts to declare.

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