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Reduction of Aryl Halides into Arenes with 2-Propanol Promoted by a Substoichiometric Amount of a *tert*-Butoxy Radical Source

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alkynylalkyl, alkenylalkyl, etc.

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Abstract Aryl halides are reduced into the corresponding arenes in high yields, using 2-propanol, cesium carbonate, and di-*tert*-butyl peroxide (or di-*tert*-butyl hyponitrite) as a reductant/solvent, a base, and a radical initiator, respectively. This simple system reduces a wide variety of aryl bromides, chlorides, and iodides through single-electron-transfer mechanism with high functional-group tolerance.

Key words reduction, radical chain mechanism, anion radical, ketyl, tert-butoxy radical

Reduction of aryl halides (ArX) into arenes (ArH) is an important transformation not only in organic synthesis but also in environmental protection since several harmful halogen-containing compounds (e.g., dioxins, polychlorobiphenyls) can be detoxified.^{1,2} Reduction using a combination of a hydride source and a transition-metal catalyst such as palladium is one of the most typical methods for the reduction.³ Although the transition-metal-catalyzed reductions achieve high tolerance towards various functional groups, it suffers from high cost of transition-metal catalysts and incompatibility with carbon-carbon unsaturated bonds. On the other hand, single-electron reduction is also effective for activation of ArX, in particular for those having a relatively low-lying LUMO. The successive elimination of X⁻ from the resulting anion radical, [ArX]⁻⁻, gives Ar⁻, which is readily reduced into ArH by a hydrogen donor. Bunnett and co-workers reported such a method using NaOMe and K₂S₂O₈, where formaldehyde ketyl generated through hydrogen abstraction from NaOMe by SO4- is considered to act as a single-electron reductant toward ArX and to be regenerated through hydrogen abstraction from NaOMe by Ar[•].⁴ However, the method employs a large excess amount of NaOMe and is applied merely to aryl iodides but not to bromides and chlorides. Here we report a simple reduction system consisting of 2-propanol, Cs₂CO₃, and a *t*-BuO[•] source,⁵ where aryl halides including bromides and chlorides are converted into the corresponding arenes with high functional-group tolerance.

One of the most effective protocols thus far examined is shown in entry 1 of Table 1. Treatment of 4-bromoanisole (1a) with Cs₂CO₃ (1.2 equiv) and *t*-BuOO*t*-Bu (0.2 equiv) in 2-propanol (80 equiv) at 120 °C for three hours gave anisole (2a) in 97% yield, where (*p*-methoxyphenyl)anisoles (3a) were produced as a regioisomeric mixture (o/m/p) = 60:40:<1) in 0.4% yield. Bianisoles **3a** are most likely to be produced through homolytic aromatic substitution on 1a by *p*-methoxyphenyl radical with H[•] followed by reduction of the bromoarene moieties.⁶ No reduction took place at 50 °C, at which temperature there is little homolysis of *t*-BuOOt-Bu, or in the absence of t-BuOOt-Bu.⁷ In contrast, even at 50 °C, the reduction took place by use of t-BuON=NOt-Bu, which readily undergoes thermal homolysis at this temperature to give *t*-BuO[•] and N₂ (Table 1, entry 4).⁸ All these results show that *t*-BuO[•] plays a crucial role in the reduction. The reaction in a decreased amount (30 equiv) of 2-propanol retarded the reduction and increased generation of **3a** to 0.4% (Table 1, entry 5), whereas use of an increased amount (2.4 equiv) of Cs_2CO_3 considerably suppress formation of **3a** to 0.2% (Table 1, entry 6). Use of other alkali metal carbonates was much less effective (Table 1, entries 7 and 8). Although the conditions in entry 4 (Table 1) scored a yield comparable to those in entry 1, we chose entry 1 as standard conditions because t-BuOOt-Bu is more readily available than t-BuON=NOt-Bu.

The protocol shown in entry 1 of Table 1 is applicable to reduction of various aryl bromides, chlorides, and iodides into the corresponding arenes.⁹ Phenyl bromides having no or alkyl substituents are reduced in high yields by treatment of Cs_2CO_3 (1.2 equiv) and *t*-BuOO*t*-Bu (0.2 equiv) in 2-

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Table 1 Reduction of 4-Bromoanisole^a

	MeOBr 1a	+ OH + OH + (80 equiv) + + + + + + + + + +	MeO A	i + MeO	Me
Entry	Base (equiv)	t-BuO' source	Temp (°C)	Conv. of 1a (%) ^b	Yield of 2a (%) ^b
1	Cs ₂ CO ₃ (1.2)	t-BuOOt-Bu	120	>99.9	97
2	Cs ₂ CO ₃ (1.2)	t-BuOOt-Bu	50	<0.1	<0.1
3	Cs ₂ CO ₃ (1.2)	none	120	<0.1	<0.1
4	Cs ₂ CO ₃ (1.2)	t-BuON=NOt-Bu	50	>99.9	96
5 ^c	Cs ₂ CO ₃ (1.2)	t-BuOOt-Bu	120	90	82
6	Cs ₂ CO ₃ (2.4)	t-BuOOt-Bu	120	>99.9	99
7	K ₂ CO ₃ (1.2)	t-BuOOt-Bu	120	20	19
8	Na ₂ CO ₃ (1.2)	t-BuOOt-Bu	120	2	0.5

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^a The reaction was carried out under a nitrogen atmosphere for 3 h using 4-bromoanisole (**1a**, 82 mg, 0.25 mmol), 2-PrOH (1.5 mL, 0.020 mol), a base (0.30 mmol), and t-BuO[•] source (0.050 mmol).

^b Determined by GC using decane as an internal standard.

^c A reduced amount (7.5 mmol) of 2-PrOH was used.

propanol (80 equiv) at 120 °C for 3 or 24 hours (Scheme 1, entries 1-3). Reduction of 2-bromonaphthalene (1e) under the standard conditions suffered from a relatively large amount (6%) of formation of 1,2'- and 2,2'-binaphthyls (3e), giving reduction product 2e only in 85% yield (Scheme 1, entry 4). This must be due to high reactivities of 1e and 2e towards radicals, accepting addition of 2-naphthyl radical more readily than monocyclic benzene derivatives. Use of an increased amount (240 equiv) of 2-propanol suppressed the side reaction to an acceptable level (1%) and raised the yield of 2e to 93% (Scheme 1, entry 5). In the reaction of 4bromo-*N*,*N*-dimethylaniline (**1f**) under the standard conditions (24 h), a large amount (8%) of a dimer of 1f. N.N'-dimethyl-*N*,*N*'-diphenylethylenediamine, was produced, probably through homocoupling of *N*-methyl-*N*-phenylaminomethyl radical. The side reaction was suppressed again by use of 240 equivalents of 2-propanol (Scheme 1, entry 6). The reduction is tolerant towards carboxylic acids and alkynes (Scheme 1, entries 7 and 8). Worthy of note is the stability of alkynes in this reaction as they are frequently incompatible with transition-metal-catalyzed reductions. Heteroaryl bromides are also reduced, though a larger amount (0.4 equiv) of t-BuOOt-Bu was required (Scheme 1, entries 9 and 10). As for hexabromobenzene (1k), all the bromine atoms are converted into hydrogen atoms, using appropriate amounts of the reagents (Scheme 1, entry 11). The reduction is applicable also to iodobenzene but is reluctant for chlorobenzene (8% yield with 13% conversion) (Scheme 1, entries 12 and 13), and thus selective reduction of aryl bromides over chlorides is possible (Scheme 1, entry 14). However, aryl chlorides are reduced when they have a low-lying LUMO as in the case with 3-chloropyridine (**1**"**m**) and 4-chlorobiphenyl (**1"n**), the LUMOs of which are lowered, respectively, by the electron-deficient character of the pyridine ring and a conjugating substituent (Scheme 1, entries 15 and 16). The result that a chlorine atom on biphenyl is removed shows that the reduction is a promising method to detoxify polychlorobiphenyls (PCB).¹

The reduction of the aryl bromides shown in Scheme 2 under the standard conditions induced side reactions other than the biaryl formation. Thus, ketone (**1o**), trifluoromethyl (**1p**), cyano (**1q**), alkene (**1r**), and thiazole (**1s**) moieties suffered, respectively, from reduction into alcohol (**1o**), hydrodefluorination (**1p**), conversion into amide (**1q**), hydrohydroxymethylation (**1r**), and nucleophilic aromatic substitution at 2-position (**1s**). All these side reactions are suppressed by lowering the reaction temperature from 120 °C to 50 °C by use of *t*-BuON=NO*t*-Bu as a *t*-BuO' source (cf. Table 1, entry 4), leading to high yields of the reduction products.

The reduction is considered to proceed through a mechanism similar to that proposed by Bunnett and co-workers.⁴ As shown in Scheme 3, thermal homolysis of *t*-BuOO*t*-Bu gives *t*-BuO', which abstracts H' from cesium isopropoxide (steps *a* and *b*). Single-electron transfer (SET) from the resulting acetone ketyl I to ArX 1 gives anion radical, $Cs^{+}[ArX]^{-}$ II, which undergoes homolysis to give Ar' III and CsX (step *c* and *d*). Ar' III abstracts H' from cesium isopropoxide to be converted into reduction product 2 and regenerate ketyl I (step *e*). Otherwise, Ar' III reacts with ArX 1, and in some cases also with ArH 2, to give ArAr 3. Thus, the selectivity for 2 over 3 should depend on reaction rates of step *e* and addition of Ar' to the aromatic rings. Actually, the selectivity is higher when concentration of cesium iso-

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Scheme 1 Reduction of aryl halides using *t*-BuOOt-Bu as a radical initiator. *Reagents and conditions*: The reaction was carried out under a nitrogen atmosphere at 120 °C for 3 or 24 h using an aryl halide **1** (0.25 mmol), 2-PrOH (1.5 mL, 0.020 mol), Cs_2CO_3 (0.30 mmol), and *t*-BuOOt-Bu (0.050 mmol). The yields were determined by GC using decane as an internal standard. For products having a relatively high boiling point, the yields of the isolated products are given (entries 7, 8, 10, and 16). ^a 2-PrOH (4.6 mL, 60 mmol) was used. ^b *t*-BuOOt-Bu (0.10 mmol) was used. ^c *t*-BuOOt-Bu (0.20 mmol) and Cs_2CO_3 (1.8 mmol) were used.



Scheme 2 Reduction of aryl halides using *t*-BuON=NOt-Bu as a radical initiator. *Reagents and conditions*: The reaction was carried out under a nitrogen atmosphere at 50 °C for 3 h using an aryl bromide **1** (0.25 mmol), 2-PrOH (1.5 mL, 0.020 mmol), Cs_2CO_3 (0.30 mmol), and *t*-BuON=NOt-Bu (0.050 mmol). The yields were determined by GC using decane as an internal standard. ^a 2-PrOH (4.6 mL, 60 mmol) was used.

proxide is higher (cf. Table 1, entries 1 vs. 5 and 6 vs. 1). The reactivity order of aryl halides is fairly consistent with SET mechanism (step c): aryl iodides and bromides are more re-

active than aryl chlorides, which are reduced only when their LUMO energy levels are lowered (cf. Scheme 1, entries 13, 15, and 16). D

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Scheme 3 A plausible reaction mechanism

In conclusion, we have developed a simple method to reduce aryl halides into arenes with high functional-group tolerance, where a radical chain mechanism initiated by *t*-BuO[•] is operative, employing 2-propanol and Cs₂CO₃ as a reductant/solvent and a base, respectively. This method is expected to be utilized for detoxification of harmful halogencontaining compounds such as PCB.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561342.

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- (6) *p*-Methoxyphenyl radical possibly reacts also with anisole (2a). However, it would give *p*-(*p*-methoxyphenyl)anisole in addition to *ortho* and *meta* isomers. No generation of the *para* isomer shows that such a reaction hardly took place under the reaction conditions.
- (7) The half-life of *t*-BuOO*t*-Bu is reported to be more than 1000 h even at 80 °C. See: Walling, *C. Tetrahedron* **1985**, *41*, 3887.
- (8) *t*-BuON=NO*t*-Bu is reported to undergo decomposition into *t*-BuO' and N₂ with $t_{1/2}$ = 29 min at 65 °C. See: Kiefer, H.; Traylor, T. G. *Tetrahedron Lett.* **1966**, 7, 6163.

(9) General Procedure

To a 3 mL vial equipped with a stir bar in a glove box were added successively an aryl halide **1** (0.25 mmol), 2-PrOH (1.5 mL, 0.020 mol), Cs_2CO_3 (97.7 mg, 0.30 mmol), and *t*-BuOOt-Bu (8.8 mg, 0.050 mmol). The vial was taken out of the glove box and stirred at 120 °C for 3 or 24 h. Decane was added to the reaction mixture as an internal standard for GC analysis. After dilution with EtOAc (1.0 mL), an aliquot was subjected to GC analysis. For products having a boiling point that is high enough not to be lost in evacuation process, addition of H₂O (20 mL) was followed by extraction with EtOAc (3 × 20 mL). The combined organic layer was dried over MgSO₄, filtered, and concentrated in vacuo. The residue was subjected to silica gel chromatography (PTLC) to give the corresponding arene **2**.