

Metal-Free Photoredox-Catalyzed Hydrodefluorination of Fluoroarenes Utilizing Amide Solvent as Reductant

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Abstract: A metal-free photoredox-catalyzed hydrodefluorination of fluoroarenes was achieved by using N,N,N',N'tetramethyl-*para*-phenylenediamine (1) as a strong photoreduction catalyst. This reaction was applicable not only to electron-rich monofluoroarenes but also to polyfluoroarenes to afford non-fluorinated arenes. The experimental mechanistic studies indicated that the amide solvent NMP plays an important role for regeneration of the photocatalyst, enabling additive-free photoreduction catalysis.

Introduction

Reduction of carbon–halogen (C–X) bonds of aromatic compounds into corresponding carbon–hydrogen (C–H) bonds is one of the most fundamental reactions in organic chemistry, and has often been applied to detoxification of environmentally harmful haloarenes.^[1] Among them, hydrodefluorination (HDF) of fluoroarenes,^[2] which are incorporated into many drugs, agrochemicals, and functional materials, is an especially challenging topic due to the kinetic/thermodynamic stability of the C–F bonds and the more negative reduction potential of fluoroarenes compared with other haloarenes.^[3] Established protocols for the C–F bond cleavage rely on strong metallic reductants such as Na, Mg, Zn, etc.^[2,4] or transition metal catalysts combined with organic reductants like hydrogen, silanes, and alkoxides.^[2,5,6]

Nowadays, photoredox catalysis^[7] attracts significant attention in the community of organic synthesis in terms of the unique reactivity and environmental sustainability. There have been many photoredox catalysts suitable for hydrodehalogenation of haloarenes because of their highly reducing abilities upon excitation.^[1b] For instance, iodo- and bromoarenes are easily reducible by combination of common Ir photocatalysts and tertiary amines.^[8] Recently, hydrodechlorination of chloroarenes that are relatively difficult to accept an electron due to their larger negative reduction potentials was achieved through the development of highly reducing organic photocatalysts such as perylene diimide,^[9a] phenothiazine,^[9b] and acridine radical^[9c] under irradiation of near-UV or visible light (Scheme 1a). Concerning reduction of fluoroarenes, photoredoxcatalyzed partial HDF reactions and C-F functionalizations of polyfluoroarenes have been reported (Scheme 1b).^[10] However,

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Chem. Eur. J. 2021, 27, 1–8 Wiley Online Library 1 These are not the final page numbers! a) Organic photoredox-catalyzed hydrodechlorination of chloroarenes



b) Photoredox-catalyzed partial hydrodefluorination of polyfluoroarenes



c) **This work**: photoredox-catalyzed hydrodefluorination of monofluoroarenes



Scheme 1. Photoredox-catalyzed hydrodehalogenation of aryl chlorides and fluorides.

HDF of monofluoroarene derivatives with photoredox systems remains undeveloped due to their inertness towards singleelectron-transfer (SET),^[11] while several methods utilizing photoirradiation have recently been developed, which involve direct photoexcitation of fluoroarenes^[12a,b] and the use of stoichiometric amounts of strong photoreductants.^[12c,d]

To achieve photoredox-catalyzed HDF of monofluoroarenes of large negative reduction potentials, we have focused on



electron-rich aromatic amines as strongly reducing photocatalysts. It has long been known that aminobenzenes such as anilines and phenylenediamines exhibit highly electron-donating abilities in their excited states.^[13] In the context of photoredox catalysis, Akita and Koike et al. have recently developed novel diaminonaphthalene and diaminoanthracene derivatives as visible-light-responsive strongly reducing photocatalysts, although their oxidation potentials upon excitation seem to be still insufficient for reducing monofluoroarenes.^[14] We envisioned the use of para-phenylenediamine derivatives as represented by *N,N,N',N'*-tetramethyl-*para*-phenylenediamine (TMPD) (1), which was intensively employed for the study of photoinduced electron transfer in photochemistry.^[15] 1 can eject electrons easily from the lowest singlet excited state (S1),^{14d} and its oxidation potential upon excitation is almost equal to that of alkali metals.^[16,17] Although there are several reports using 1 as a stoichiometric photoreductant in organic synthesis,^[16,18] the use of 1 as a photocatalyst is still rare. It should be mentioned that while our work was in progress, Song et al. reported hydrodehalogenation of bromo-, chloro-, and polyfluoroarenes using 1 as a photoredox catalyst in MeCN combined with ⁱPr₂NEt as a reductant under irradiation of near-UV light, showcasing the usefulness of 1 as a photocatalyst.^[19] However, HDF of monofluoroarenes using 1 was not investigated. Herein, we present a metal-free HDF of monofluoroarenes employing 1 as a photoredox catalyst (Scheme 1c). Importantly, the reaction does not require the addition of alkyl amines such as ${}^{i}Pr_{2}NEt$ as sacrificial reductants. We found the common amide solvent, *N*-methyl-2-pyrrolidone (NMP), plays a crucial role for regeneration of the photocatalyst 1, which is significantly different from usual photoredox-catalyzed reactions.

Results and Discussion

To initiate our study, HDF of fluorobenzene (2 a) to benzene (3 a) was investigated as a model system under photoirradiation conditions (Table 1, see Table S1 for details). Common photoredox catalysts such as $[Ir(ppy)_2(dtbbpy)]PF_6$ and fac- $Ir(ppy)_3$ with $^{1}Pr_2NEt$, which are effective for hydrodehalogenation of aryl halides and partial HDFs of polyfluoroarenes,^[8,10] did not afford 3 a at all under irradiation with blue LEDs (entries 1, 2). In contrast, the use of stoichiometric amounts of TMPD 1 or *para*-phenylenediamine (4) led to formation of 3 a in 73 and 63% yield, respectively, under irradiation with a mercury (Hg) lamp with heating in DMF (entries 3, 4), displaying the highly reducing ability of diaminobenzene derivatives in their excited states. In contrast, *N*,*N*,*N*',*N*'-tetraphenyl derivative 5 and *N*,*N*,*N*',*N*'-tetrabenzyl derivative 6 gave only trace amounts of 3 a



Chem. Eur. J. 2021, 27, 1–8 www.chemeurj.org 2 These are not the final page numbers! Full Paper doi.org/10.1002/chem.202101813



(entries 5, 6), suggesting that substituents on the amine moiety largely affect the reducing nature of the excited states of paraphenylenediamines. Lower concentration increased the yield of 3a up to 90% (entry 7). The reduction with 1 was driven by near-UV LEDs (365 nm) at room temperature (entry 8) but not by blue LEDs (425 nm) (Table S1, entry 17). Then, catalytic conditions using 1 as a photoredox catalyst were examined (entries 9-15). 1 was able to act catalytically (20 mol%) with excess amounts of ⁱPr₂NEt in polar solvents under irradiation with LEDs (365 nm) (entries 9, 10; Table S1, entries 22-25), and NMP gave the highest yield (95%) (entry 10). Surprisingly, even without addition of ⁱPr₂NEt the reduction proceeded catalytically to 1 when using NMP as a solvent (entry 11; Table S1, entries 26-30). This result is quite intriguing since common photoredox-catalyzed hydrodehalogenation reactions necessitate aliphatic amine additives as sacrificial electron donors.^[7] After further screening of the reaction conditions, we found HDF of 2a proceeded in 73% yield with 10 mol% catalyst loading of 1 under irradiation with a Hg lamp (entry 13; Table S1, entries 31–41).^[20,21] We confirmed the reaction did not proceed in the absence of 1 nor light irradiation (entries 14, 15). Thus, we considered two optimal reaction conditions for HDF of monofluoroarenes: one is using 1 (20 mol%) and ⁱPr₂NEt (5 eq.) in NMP under irradiation with LEDs (365 nm) (entry 10, Conditions A), and the other is using 1 (10 mol%) in NMP under irradiation with a Hg lamp (UV) (entry 13, Conditions B).

With the optimized conditions in hand, the substrate scope of monofluoroarenes 2 was examined (Table 2). Electron-rich fluorotoluenes 2b-d, fluoroanisoles 2e-g, and 3,4-dimethoxyfluorobenzene (2h) underwent HDF efficiently to afford corresponding arenes **3b-h** in good to excellent yields under Conditions A and B. Fluoroarenes 2i-k with amide and amine moieties gave HDF products 3i-k in moderate to high yields. The reaction conditions were also applicable to sterically hindered fluorobenzenes 21 and 2m with two methyl groups at the ortho-positions of the fluorine atom, showing the advantage of an outer-sphere SET reduction process over transition-metalcatalyzed reduction involving oxidative addition of C-F bonds. In contrast, 4-phenylfluorobenzene (2n) was almost inert to the HDF, and methyl 4-fluorobenzoate (2o) did not react at all. Similarly, other monofluoroarenes with electron-withdrawing substituents such as cyano, carbonyl, and trifluoromethyl groups did not undergo the HDF at all even using stoichiometric amounts of 1 (Chart S1). As discussed later, elimination of a fluoride anion from a fluoroarene anion radical would be slower in the case of electron-deficient fluoroarenes.

We also investigated multiple HDF of polyfluorobenzenes to obtain benzene **3a** without addition of ^{*i*}Pr₂NEt (Table 3), since complete HDF of polyfluoroarenes by photoredox catalysis has not been achieved yet due to the difficulty of reduction of less fluoro-substituted arenes.^[10] Double HDF of difluorobenzenes **2p-r** proceeded well to give **3a** in 56–76% yields. 1,2,4-Trifluorobenzene (**2s**) underwent triple HDF in moderate yield. However, the yields of **3a** decreased significantly with tetra-, penta-, and hexafluorobenzenes **2t-u** despite larger catalyst loadings. We confirmed generation of adducts of **1** and polyfluorobenzenes by GC-MS analysis in addition to partial



[a] All the reactions were carried out with **2** (0.1 mmol) in NMP (3 mL). The yields of **3** were determined by GC analysis. [b] TMPD (20 mol%). [c] 10 h. [d] 80 °C, 10 h. [e] The yields were determined by ¹H NMR analysis. [f] 80 °C.



HDF products for these substrates (Scheme S1), which might lower the efficiency of the multiple HDF reactions.





In order to clarify the mechanism of this photoredoxcatalyzed HDF, we conducted experimental studies mainly focusing on the following two processes: SET from excited photocatalyst 1* to fluoroarene 2 and regeneration of photocatalyst 1 in the absence of amine additives. Firstly we examined the physicochemical properties of 1 to probe the SET process (Figure 1). 1 exhibited intense absorption at 332 nm and fluorescence at 403 nm in DMF (Figure 1a). The absorption band spanned the near-UV regions up to 380 nm, which enables photoexcitation of 1 by 365 nm LEDs. Cyclic voltammetry (CV) of 1 showed a reversible oxidation wave at + 0.14 V vs. SCE in DMF (Figure S1). From these results, the oxidation potential of the lowest singlet excited state (S₁) of 1 is estimated



Figure 1. Mechanistic studies for the photo-induced SET step. a) Absorption and fluorescence spectra (λ_{ex} = 332 nm) of 1 in DMF. b) Stern-Volmer fluorescence quenching plots of 1 with addition of **2a** (red), **2o** (blue), and **3a** (black) in DMF. c) Proposed mechanism for generation of aryl radical from fluoroarene **2**. d) Trapping experiment of phenyl radical with **7**. The yields of **8** and **3a** were determined by ¹H NMR and GC analyses, respectively.

to be -2.94 V vs. SCE in DMF, which is slightly higher than the reported value of 1* (-3.25 V vs. SCE in MeCN).^[16,22] This value is almost equal to oxidation potentials of highly reducing alkali metals,^[9c] and is close to the reported value of the reduction potential of fluorobenzene 2a (-2.97 V vs. SCE in DMF).^[3a] In order to prove the SET step from 1* to fluoroarenes 2, Stern-Volmer fluorescence quenching experiments were conducted between 1 and arenes 2a, 2x, and 3a in DMF (Figure 1b). The fluorescence intensity of 1 was diminished by the addition of 2a efficiently. Since no significant change of the absorption spectra of 1 was observed in the presence of 2 a, the interaction between 1 and 2a in their ground states (e.g. forming a charge-transfer complex) is negligible. Therefore, this result clearly indicates that SET from the excited S₁ state of 1 to 2a is operative in the reaction conditions^[23] and confirms the utility of 1 as a powerful photoreductant. The fluorescence was also quenched by the addition of electron-deficient fluoroarene 2 o, which did not undergo HDF at all. Considering the general mechanism of hydrodehalogenation of haloarenes induced by SET,^[8] this defluorination reaction would proceed in a stepwise fashion through SET from 1* to fluoroarene 2 to give 1^{+•} and fluoroarene anion radical 2^{-•} followed by elimination of the fluoride anion to give an aryl radical (Figure 1c). In the case of electron-deficient fluoroarenes, the elimination of the fluoride anion would get slower since the electron density of anion radical 2^{-•} on the aryl ring is decreased by electron-withdrawing substituents. Instead, back electron-transfer from 2^{-•} to 1+* would be preferred, leading to recovery of the fluoroarenes 2. We also confirmed the HDF product 3a did not influence the fluorescence intensity of 1 at all (Figure 1b). In addition, the generation of phenyl radical from 2a was verified by a radical trapping experiment with excess amounts of Nmethylpyrrole (7) (Figure 1d). Corresponding coupling product 8 between phenyl radical and 7 was obtained along with 3a albeit in low yields. Other types of C-F bond functionalizations via phenyl radical such as borylation proceeded similarly in relatively low yields (Scheme S3).

We then turned our attention to the mechanism of the regeneration of photocatalyst 1, the most intriguing process in this HDF reaction (Scheme 2). First the role of ⁱPr₂NEt as a sacrificial reductant was examined. The addition of ⁱPr₂NEt to cation radical of 1 $(1^{+\bullet}-PF_6)$, which is known as a stable, isolable organic radical, $^{\mbox{\tiny [24]}}$ led to facile formation of 1 in the dark (Scheme 2a). Therefore, ⁱPr₂NEt plays a role of a single electrondonor to 1^{+•} to regenerate 1, although this SET process seems to be thermodynamically somewhat unfavorable considering their redox potentials ('Pr₂NEt: $E_{ox} = +0.52 V_r^{[25]} 1^{+\bullet}$: $E_{red} = +$ 0.14 V vs. SCE in DMF). The use of such an alkyl amine additives as an electron-donor is quite common in photoredox-catalyzed reductions.^[7] In contrast, this HDF reaction proceeded catalytically to 1 in NMP even in the absence of ⁱPr₂NEt. To examine the unconventional feature of this reaction, HDF of 2a in NMP was monitored by ¹⁹F NMR analysis (Scheme 2b). We detected 5-fluoro-N-methyl-2-pyrrolidone (9)[26] in 23% yield along with HF in 55% yield, which indicates the involvement of NMP as a hydrogen atom donor to phenyl radical. It is worth noting that significant amounts of 9 was observed even in the presence of Full Paper doi.org/10.1002/chem.202101813





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Scheme 3. Proposed reaction mechanism.

Scheme 2. Mechanistic studies for the regeneration of photocatalyst 1. a) Reaction of 1^{++} -PF₆ with ⁱPr₂NEt under dark. The yield of 1 was determined by ⁱH NMR analysis. b) ¹⁹F NMR analysis of the HDF reaction of 2 a in NMP. The conversion of 2 a and the yields of 9 and HF were determined by ¹⁹F NMR analysis based on the amount of 2 a. The yield of 3 a was determined by GC analysis. c) Decomposition of 1. The isolated yields of coupling products 10a-10c are shown. Structures of the postulated NMP-derived radical intermediates 11 a-11 c are shown in the dotted box.

ⁱPr₂NEt, suggesting the important role of NMP as a reductant (Scheme S4). We also found photocatalyst 1 was completely consumed after the HDF reaction and was converted into NMP adducts 10a and 10b, which would be generated through the radical coupling reaction between $1^{+\bullet}$ and NMP-derived alkyl radicals 11a and 11b, respectively (Scheme 2c). The transformation of 1 by the reaction with the solvent would be the major deactivation pathway of the photocatalyst. Actually, 10a and 10b did not work well as photocatalysts for the HDF reactions under irradiation with LEDs (365 nm) (Scheme S5) because of their blue-shifted absorption wavelengths compared with that of 1 (10a: 313 nm; 10b: 315 nm; 1: 334 nm in NMP) (Figure S8). It should be noted that compound 10c, an adduct of 1 and NMP at the 5-position of the pyrrolidone ring, was not observed at all (Scheme 2c) while the generation of radical 11c in the reaction conditions was suggested by the observation of 9 (Scheme 2b).

The mechanism for this additive-free photoredox-catalyzed HDF reaction is proposed based on the experimental results (Scheme 3). 1 is excited under irradiation of UV light to form the strongly reducing S_1 state 1*. SET from 1* to fluoroarene 2 affords stable cation radical $1^{+\bullet}$ and fluoroarene anion radical

 $2^{-\bullet}$. $2^{-\bullet}$ eliminates a fluoride anion to give the aryl radical, which abstracts a hydrogen atom from NMP to yield the desired arene 3. Three kinds of α -amino and α -carbonyl hydrogen atoms with relatively small C-H bond dissociation energies can be abstracted from NMP to give radicals 11 a-c. In the presence of ⁱPr₂NEt, regeneration of photocatalyst 1 can proceed via SET from ${}^{i}Pr_{2}NEt$ to 1^{+•}. In contrast, bulky α -amino radical 11c can work as a single electron-donor to $1^{+\bullet}$ in the absence of ^{*i*}Pr₂NEt, since oxidation potentials of α -amino radicals of amides are calculated to be relatively low (+0.12 V vs. SCE for N-methylacetamide).^[27] However, less reducing α -carbonyl radical **11a** and less-hindered α -amino radical **11b** directly couple with **1**^{+•} prior to SET, leading to the formation of undesired deactivated products 10a and 10b, respectively. The iminium cation generated from 11c is trapped by the fluoride anion to give fluorinated NMP 9.9 would be gradually converted into HF and enamide 12, which was detected by GC-MS analysis.

Here the solvent NMP plays a critical role as a hydrogen and electron donor for the photoredox catalysis. Other highly polar solvents such as DMF, DMA, DMSO, and MeCN did not work well for the HDF reaction of **2a** with catalytic amounts of **1** in the absence of ^{*i*}Pr₂NEt (Table S1, entries 26–29), where full conversions of **1** and generation of adducts of **1** and the solvents were confirmed by GC-MS analysis. The facile generation of α -amino radical **11c** from NMP, possessing both the appropriate reducing ability for **1**^{+•} and the steric bulkiness to avoid attacking **1**^{+•}, seems to be the key to realize this unique additive-free photoredox-catalyzed HDF reaction. Additionally, the relatively weak acidity of in situ generated HF would also be important for the catalysis. Chlorobenzene and bromobenzene, which usually undergo photoredox-catalyzed hydrodehalogena-

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Chem. Eur. J. 2021, 27, 1–8 www.chemeurj.org 5
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tion reactions more easily than fluorobenzene, did not yield benzene **3a** efficiently (<20%) without ${}^{i}Pr_{2}NEt$ under Conditions B (Scheme S6, S7). The strong acidity of HCl and HBr would protonate **1** completely, leading to deactivation.

Conclusion

We have developed a metal-free HDF reaction of fluoroarenes 2 by using 1 as a photocatalyst, which is the first example of a photoredox-catalyzed reduction of monofluoroarenes. In contrast to the reported photoredox-catalyzed hydrodehalogenations, this reaction proceeded catalytically in NMP even without the addition of alkyl amines as sacrificial reductants. The experimental mechanistic investigations revealed SET from highly reducing 1* to 2 and the essential role of NMP as a hydrogen and electron donor in this HDF reaction. This is a rare example of photoredox catalysis using an amide as a reductant instead of an amine. We believe this study offers not only a simple reduction procedure for fluoroarenes but also a novel insight into the design of efficient photoredox catalysis. Further work to develop C–F bond functionalization of fluoroarenes with this strategy is now ongoing in our laboratory.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: amides · hydrodefluorination · metal-free · phenylenediamine · photocatalysis

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- [23] The possibility of direct excitation of fluoroarene 2 and successive SET from 1 to 2* cannot be excluded when using a Hg lamp. However, we think SET from from 1* to 2 is dominant because of the quite shorter absorption wavelength of 2 (< 250 nm) and the low transparency of the Pyrex reaction vessels in the UVC region.
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FULL PAPER



A metal-free photoredox-catalyzed hydrodefluorination of fluoroarenes was realized by using *N*,*N*,*N'*,*N'*tetramethyl-*para*-phenylenediamine as a catalyst under UV light irradiation. This reaction does not necessitate aliphatic amine additives as sacrificial reductants. The mechanistic studies indicated that the amide solvent NMP plays a critical role as a hydrogen and electron donor for this photoredox catalysis. Dr. N. Toriumi, K. Yamashita, Prof. Dr. N. Iwasawa*

1 – 8

Metal-Free Photoredox-Catalyzed Hydrodefluorination of Fluoroarenes Utilizing Amide Solvent as Reductant