From Aniline to Phenol: Carbon-Nitrogen Bond Activation via Uranyl Photoredox Catalysis

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Abstract

Carbon-nitrogen bond activation, via uranyl photoredox catalysis with water, enabled the conversion from 40 protogenetic anilines, 8 N-substituted anilines, and 9 aniline-containing natural products/pharmaceuticals to the corresponding phenols at ambient environment. Single electron transfer process between protonated aniline and uranyl catalyst, which was disclosed by radical quenching experiments and Stern-Volmer analysis, facilitated the following oxygen atom transfer process between radical cation of protonated anilines and uranyl peroxide originating from water-splitting. ¹⁸O labelling and ¹⁵N tracking unambiguously depicted that the oxygen came from water and amino group leaved as ammonium salt. Hundredfold efficiency of flow operation demonstrated the great potential of the conversion process in industrial synthetic application.

Keywords: C-N Bond Activation, C-O Bond Formation, Uranyl Cations, Photoredox Catalysis
Introduction

$\text{Csp}^2$-$\text{N}$ bond activation remains an intractable challenge among the transformation of inert chemical bonds,$^1$-$^3$ due to the high bond dissociation energy [C-N BDE (PhNH$_2$) = 102.6 ± 1.0 kcal/mol],$^4$ the intense coordinating ability [$a^\text{TM}$ (amines) = 0-1.9 vs $a^\text{TM}$ (ethers) = -2.5-0.1],$^5$ and the inferior leaving ability [$\mu Ka$ (-NH$_2$) = 36]$^6$-$^7$ (Scheme 1a, left). Conventionally, prefunctionalization is the essential solution for C-N bond transformations in anilines, such as up-front operations to diazonium salts,$^8$-$^{10}$ quaternary ammonium salts,$^{11}$-$^{13}$ hydrazines, amines with vicinal directing groups,$^{14}$-$^{16}$ etc$^{17}$-$^{18}$ (Scheme 1a, right).

Akiyama et al. reported a pioneering progress of $\text{Csp}^2$-$\text{N}$ bond cleavage of undecorated aniline with stoichiometric palladium acetate.$^{19}$ Remarkably, the amino of 5-nitroanthranilic acid (5NAA), associated with tryptophan biosynthesis in living system, was transformed to hydroxyl group catalyzed by 5NAA-aminohydrolase at body temperature with water (Scheme 1b, left), which shed light on C-N activation.$^{20}$

Encouragingly, Nicewicz realized C-O bond activation via cation radical accelerating nucleophilic aromatic substitution (Scheme 1b, right).$^{21}$-$^{23}$ With the development of photocatalysis technique,$^{24}$-$^{28}$ it has been found that uranyl catalyst is characterized by ligand-to-metal charge transfer (LMCT) process and shows superior oxidative ability [$E^{\text{ox}}$ = +2.60 V vs SCE].$^{29}$-$^{36}$ Following our previous work on uranyl photoredox catalysis,$^{37}$-$^{38}$ C-N bond activation in protogenetic anilines was realized to generate corresponding phenols at ambient environment with water via synergistic process of single electron transfer (SET) and oxygen atom transfer (OAT) (Figure 1c).
(a) Catalytic Activation of C-N Bonds

**Challenge: Inert**

High bond dissociation energy\(^4\):
\[ \text{C(sp\(^3\))-N (102.6 ± 1.0 kcal/mol)} \]

Intense coordinating ability\(^2\):
\[ \alpha^{TM}\text{amines) = 0.1-1.9} \]

Inferior leaving ability\(^6,7\):
leaving groups (pKa of conjugated acid)
\[ \Gamma (-10) > \text{H}_2\text{O (-1.7)} > \text{NH}_3 (9.2) > -\text{NH}_2 (36) \]

(b) Proposed Solutions

**Inspiration from Biosynthesis\(^{28}\): Nucleophilic**

Variation on Activating Mode: Radical

\[ \text{Radical Accelerated } S_{\text{NAr}}: \]

Single electron transfer
Feasible nucleophilic addition
Low bond dissociation energy

(c) This Work

- C-N activation of protogenetic aniline
- Oxygen atom transfer from H\(_2\)O
- Sensitive and oxidizing phenol formation
- Hundredfold efficiency by flow apparatus

Scheme 1. Activation of carbon-nitrogen bond in aniline. (a) Catalytic activation of C-N bonds. (b) Proposed solutions. (c) This work.
Result and Discussion

We commenced the study with 4-(tert-butyl)aniline as reactant and uranyl nitrate hexahydrate as photoredox catalyst irradiated by blue light (460 nm) at room temperature. Lewis and Brønsted acids, considered as coactivator (Table 1, entries 1-8), were added to the system respectively, in which trifluoroacetic (TFA) supplied the optimal result with 85% isolated yield of the desired product. Compared with uranyl ion, Ir(ppy)3dtbpy·PF6 [E1/2 = +1.21 V vs SCE], Ru(bpy)3Cl2·6H2O [E1/2 = +0.77 V vs SCE], or riboflavin tetra-acetate [E = +1.67 V vs SCE] were inefficient for the transformation (Table 1, entry 9). Solvents also played a crucial role, in which acetonitrile was the best choice (Table 1, entries 10 and 11). Control experiments further demonstrated that UO2(NO3)2·6H2O, TFA and light were all essential conditions (Table 1, entries 12-14).

Table 1. Optimatization conditions. General conditions: 1a (0.2 mmol), UO2(NO3)2·6H2O (4 mol%), acid (0.2 mmol), and H2O (0.6 mmol) were stirred in solvent (2 mL) at room temperature for 24 hours under blue light (460 nm.). 1H NMR yields with CH2Br2 as the internal standard. [a] Acid (30 mmol%). [b]
Isolated yields. [c] Ir\{dF(CF\textsubscript{3})ppy\}\textsubscript{2}dtbpy\cdot PF\textsubscript{6}, Ru\{bppy\}\textsubscript{2}Cl\textsubscript{2}·6H\textsubscript{2}O or Riboflavin tetraacetate instead of UO\textsubscript{2}(NO\textsubscript{3})\textsubscript{2}·6H\textsubscript{2}O. [d] Without UO\textsubscript{2}(NO\textsubscript{3})\textsubscript{2}·6H\textsubscript{2}O. [e] No light. NR = No reaction.

Under the optimal conditions, the scope of undecorated anilines was investigated comprehensively (Scheme 2). Diverse anilines with electron-rich substitutions produced corresponding phenols in an effective way, despite which were prone to be oxidized (2a-2e). Subsequently, we found electron-neutral substituted aniline could be transformed smoothly (2f and 2g). For electron-deficient substrates (2h-2p), HFIP was found to be a more helpful solvent, due to its ability to stabilize cation radicals.\textsuperscript{40} Noteworthily, halides were well tolerated under this condition (2h-2k), especially for commonly light-sensitive iodo-group (2k). Easily hydrolytic cyano- (2l) and carboxylic ester (2m and 2m) were preserved in this water-involving reaction. Furthermore, various active C-H bonds were well tolerated, such as acetyl (2p) and dually activated benzyl (2q-2s). Due to the steric and electronic effects, polysubstituted phenol synthesis is always challenging but imperative, in which while phenols with 2,6-diisopropyl- (2t), 2,4,6-tri tertbutyl (2u) and 3,5-dimethyl (2v) groups were successfully achieved in our system with sterically bulky hinderance. Besides, multiple substituents with distinct electronic properties, such as bromo- (2w), nitro- (2x and 2y), carboxylic ester (2z) and acid (2aa) groups, were compatible. Michael acceptor containing motif (2ab) was well preserved. Remarkably, when only one amino group of p-phenylenediamine was protected, highly selective conversion of the unprotected amino group occurred, which yielded 82% paracetamol, a clinically applied antipyretic and analgesic drug (2ac). Undecorated or substituted hydroxyl (2ad and 2ae) and thioethers with electron-rich or -deficient substituent group (2af and 2ag) were all compatible during C-N activation. Amino group on condensed cyclicity (2ah) and heterocyclicity (2ai-2ak) were smoothly activated, in spite of high electron density or coordinating effect. Moreover, a series of diphenylaminos could be transformed to diphenols successfully (2al-2ao). X-ray diffraction of 2ao (CCDC 2043527) further confirmed its structure. The applicability and compatibility of C-N activation were demonstrated in natural products and pharmaceuticals. Terpenoid (borneol and menthol) derivatives and amino acids-containing molecules (valine and phenylalanine) were
transformed to corresponding phenols (2ap-2as) in moderate yields. Subsequently, ibuprofen, a non-steroidal anti-inflammatory drug, was proved to have 70% yield (2at). Late-stage modification of oxaprozin (2au) and indometacin (2av and 2aw) were achieved in spite of highly active sites on heterocycles. X-ray diffraction (CCDC 2050763) further confirmed the structure of 2av. Phenylpiperidine, N, N-dimethylanilines, and phenyl-morpholine analogous yielded corresponding phenol efficiently, fulfilling the tough target in traditional cross coupling (Scheme 3).
Scheme 2. Scope of anilines. Standard conditions: 1 (0.2 mmol), UO₂(NO₃)₂·6H₂O (4 mol%), TFA (0.2 mmol) and H₂O (0.6 mmol) were stirred in CH₃CN (2 mL) at room temperature under blue LED (460 nm) in the air, isolated yields. [a] UO₂(OAc)₂·2H₂O (4 mol%), N₂. [b] TFA (0.4 mmol). [c] HFIP (2 mL). [d] TFA (0.4 mmol), HFIP (2 mL), N₂. [e] CH₃NO₂ (2 mL). [f] UO₂(OAc)₂·2H₂O (4 mol%), HFIP (2 mL), N₂. [g] UO₂(OAc)₂·2H₂O (8 mol%), TFA (0.4 mmol), HFIP (2 mL), N₂. [h] UO₂(NO₃)₂·6H₂O (8 mol%), TFA (0.4 mmol), HFIP (2 mL), N₂. [i] TFA (0.4 mmol), CH₃NO₂ (2 mL). [j] 1 (0.1 mmol), HFIP (2 mL), N₂. [k] 1 (0.1 mmol), HFIP (1 mL), N₂. [l] 1 (0.1 mmol), CH₃NO₂ (2 mL), N₂. [m] 1 (0.1 mmol), CH₃CN (2 mL), N₂.
Scheme 3. Transformation of tertiary anilines. Standard conditions: 1 (0.2 mmol), UO$_2$(NO$_3$)$_2$·6H$_2$O (4 mol%), TFA (0.2 mmol) and H$_2$O (0.6 mmol) were stirred in HFIP (2 mL) at room temperature under blue light (460 nm), isolated yields. [a] UO$_2$(NO$_3$)$_2$·6H$_2$O (8 mol%), TFA (0.4 mmol), N$_2$. [b] UO$_2$(OAc)$_2$·2H$_2$O (4 mol%), TFA (0.4 mmol). [c] UO$_2$(NO$_3$)$_2$·6H$_2$O (8 mol%). [d] N$_2$. [e] UO$_2$(OAc)$_2$·2H$_2$O (8 mol%), TFA (0.6 mmol).

To further demonstrate the application potential of anilines, flow reactions were conducted, which was (0.68 mmol/h for 2a, 20 mmol scale) more efficient than that with parallel reactors (0.04 mmol/h for 2a, 10 mmol scale). It is noteworthy that clinically applied pharmaceuticals, i.e., propofol and paracetamol by flow reactions could be at most 315 times as efficient as by tube operation, though the residue volume of flow pipeline was only about 4.7 mL (less than 1/10 of the total volume) (Scheme 4).
Scheme 4. Flow reaction. Standard conditions: 1 (20 mmol), UO$_2$(NO$_3$)$_2$·6H$_2$O (2 mol%), TFA (40 mmol) and H$_2$O (60 mmol) were stirred in CH$_3$CN/HFIP (25 mL/25 mL) at room temperature irradiated with blue light (435nm) in the air, isolated yields. [a] TFA (60 mmol), HFIP (50 mL). [b] UO$_2$(NO$_3$)$_2$·6H$_2$O (3 mol%), TFA (60 mmol), CH$_3$CN/HFIP (25 mL/45 mL).

Mechanism study was carried out to understand the process. Firstly, radical quenching experiments with 2,2,6,6-tetramethyl-1-piperinedinylxyloxy (TEMPO) and butylated hydroxytoluene (BHT) suggested the radical property of this system (Scheme 5a, SI, ...
Section IV-1. UV-vis absorption between catalyst and each component demonstrated that uranyl salt served as a photosensor. The addition of aniline salt to uranyl solution enhanced the absorption efficiency, illustrating the interaction between the uranyl species and aniline complex (Scheme 5b, SI, Section IV-2). Active uranyl cation was quenched by aniline/TFA complex as was detected by Stern-Volmer analysis (Scheme 5c, SI, Section IV-3), and energy transfer process was ruled out considering the lower value of lowest triplet energy of uranyl cation ($E_T = 58.5$ kcal/mol) compared with that of anilines.\(^{41,42}\) Meanwhile, the ammonium salt was instantaneously generated, as was monitored by $^1$H NMR experiments before C-N bond activation (Scheme 5d, SI, Section IV-4). Furthermore, quenching effect between uranyl species and protonated anilines was much stronger than those with Ir[dF(CF\(_3\))ppy]\(_2\)dtbpyPF\(_6\), Ru(bpy)\(_3\)Cl\(_2\)6H\(_2\)O, and Riboflavin tetraacetate, revealing the unique interaction property between uranyl ion and substrate in the transformation (SI, Section IV-3).

Labeling experiments with H\(_2\)\(^{18}\)O and \(^{18}\)O\(_2\) unambiguously demonstrated that the oxygen atom of the product phenols originated from water rather than oxygen atmosphere (Scheme 6a, SI, Section IV-5). According to the previous studies,\(^{38,43,44}\) uranyl peroxide complexes was obtained from uranyl photolysis of water, which is responsible for the oxygen atom transfer. \(^{15}\)N NMR tracking experiments showed that only ammonium trifluoroacetate was obtained, which indicated that amino group on anilines left in the form of ammonia followed by neutralization with TFA. (Scheme 6b, SI, Section IV-6). In addition, both on-off experiments (SI, Section IV-6) and the quantum yield of 8.4 (SI, Section IV-7) elucidated the existence of a radical chain propagation process during the transformation.
Scheme 5. Mechanistic studies of SET mode. (a) Radical quenching experiments. (b) UV-vis experiments. (c) Stern-Volmer analysis. (d) $^1$H NMR experiments in CD$_3$CN.
Scheme 6. Mechanistic studies. (a) Oxygen labeling experiments. (b) $^{15}$N NMR experiments.

Based on the mechanistic study, a possible reaction pathway was depicted as shown in Scheme 7. Under blue light, uranyl photoredox catalysis was stimulated and generated
*UO$_2^{2+}$* through ligand-to-metal charge transfer (LMCT) process. Then, single electron transfer process between *UO$_2^{2+}$* and protonated anilines A brought forth UO$_2^+$ and radical cation B. Another uranyl peroxide dimer was generated from water-splitting, capturing B with C-O bond formation and C-N bond fracture to get radical cation of phenol C. Single electron transfer between C and UO$_2^+$ afforded the desired product 2 and regenerated the catalyst. Meanwhile, radical chain propagation process was also in progress during this transformation owing to the higher oxidation potential of intermediate C ($E_{1/2} = 1.56$ V) compared with protonated anilines A ($E_{1/2} = 0.89$ V).

![Scheme 7. Proposed mechanism.](https://academic.oup.com/nsr/advance-article-doi/10.1093/nsr/nwab156/6355461)

**Conclusion**

In summary, oxygen atom transfer from water to organic molecules via uranyl photoredox catalysis was discovered in photoredox circulation. Accordingly, C-N bond activation in undecorated anilines was systematically established at ambient conditions, generating a series of sensitive and fragile phenols. Hundredfold efficiency of flow setup
indicated the industrial application potential of the strategy. Radical trapping experiments, Stern-Volmer analysis and \(^1\)H NMR experiments demonstrated the interaction between active uranyl species and protonated anilines. Further studies on uranyl catalysis are on-going in our laboratory.

**Founding**

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**Author contributions**

X. J. proposed and supervised the project. X. J. and D. H. conceived and designed the experiments. D. H. performed the experiments and analyzed the data. X. J., D. H. and Y. Z. prepared the manuscript. All authors discussed the results and participated in analyzing the experimental results.

**Conflict of interest**

The authors declare no conflict of interest.

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