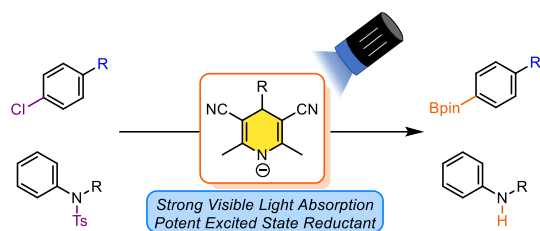# 1,4-Dihydropyridine Anions as Potent Single-Electron Photoreductants

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Supporting Information Placeholder

**ABSTRACT:** Organic anions offer a promising route for promoting difficult single-electron reductions, owing to their strongly reducing excited states that can be accessed under visible light irradiation. This report describes the use of simple 1,4-dihydropyridine anions as a general platform for promoting single-electron photoreductions. In the presence of a mild base, 1,4-dihydropyridines were shown to effectively promote the hydrodechlorination and borylation of aryl chlorides and the photodetosylation of N–Tosyl aromatic amines under visible light irradiation.

1,4-Dihydropyridines (DHPs) have emerged as a valuable class of reagents in organic synthesis, often used as reductants in catalytic hydrogenation reactions and more recently as a class of sacrificial single-electron reductants or as the hydrogen atom source in photoredox catalyzed reactions.[1] Further demonstrating the versatility of these reagents, 4-alkyl-1,4-DHPs have been extensively employed as precursors to alkyl radicals in C–C bond forming reactions.[2] A common theme in these methodologies is the requirement of some chemical entity to oxidize the DHP to the radical cation to ultimately furnish the alkyl radical, which is normally achieved using either a photocatalyst or through direct excitation of the DHP in the presence of an oxidant. In previous work from our lab, we demonstrated that, in the presence of a suitable base, 4-*tert*-alkyl-1,4-DHPs bearing cyano groups at C3 and C5 could be directly photolyzed under blue LED irradiation, which allowed for these DHPs to be used as *tert*-alkyl radical precursors in photochemical Giese reactions in the absence of a photocatalyst or external oxidant (Scheme 1A).[3] Mechanistic studies suggested that the reaction proceeds via excitation of the DHP anion, which possesses a significantly redshifted absorption in comparison to the neutral DHP. During the course of this work, we observed that 1,4-DHPs bearing secondary alkyl groups did not yield the corresponding Giese products, with reductive hydrogenation of the Michael acceptor being predominantly observed in these cases.[3] Inspired by this switch in mechanism afforded by a simple change in the substitution pattern at C4, we envisioned that these 1,4-DHPs, in the presence of a suitable mild base, could serve as a general platform for visible light mediated single-electron photoreduction reactions (Scheme 1B). Furthermore, as 1,4-DHPs are long established to be competent hydrogen atom donors,[1a] this strategy would eliminate the need for

separate chemical entities to promote the desired single-electron reduction and the subsequent hydrogen atom transfer, addressing a common drawback of many modern photochemical approaches in this space.

**Scheme 1. (A) Previous work: 4-*tert*-alkyl-1,4-DHP anions as radical precursors. (B) This work: 1,4-DHP anions as potent single-electron photoreductants.**

**(A)** *Previous work: 1,4-DHP anions as radical precursors*
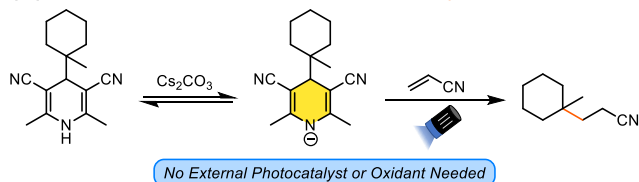


**(B)** *This work: 1,4-DHP anions as excited state reductants*
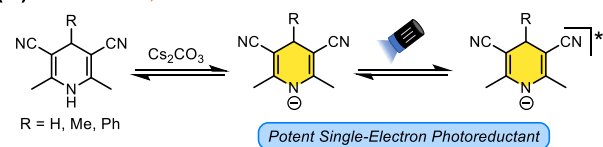


Our design plan was further motivated by the recent reports of organic anions serving as potent single-electron photoreductants upon visible light irradiation.[4] For example, Xia and coworkers, among others,[5] have shown that phenolate anions possess highly reducing excited states upon photoexcitation with visible light ($E_{ox}^* = -3.16$ V vs. SCE).[6] Furthermore, Melchiorre and coworkers recently reported that thiolate anions generated from the deprotonation of cyclic thioamides possess highly reducing excited states ($E_{ox}^* = -3.38$ V vs. SCE) capable

of activating C–Cl, C–F, and C–O bonds as well as promoting the Birch reduction of unfunctionalized arenes.[7] Given this precedent, we set out to determine the excited state oxidation potentials of simple 1,4-DHP **I** to access the potential of the corresponding anions as potent single-electron photoreductants. UV-vis studies demonstrated that a significant redshift in the absorption of 1,4-DHP **I** is observed upon treatment with $Cs_2CO_3$, supporting the formation of the anion. Excitation of the anion resulted in an emission centered at ~490 nm, supporting the formation of an excited state upon irradiation of the anion. From these data, the $E_{0,0}$ of 2.69 eV could be inferred from the crossing point between the absorption and emission spectra (461 nm).[8] Using the ground state oxidation potential of 1,4-DHP **I** anion ($E_{p/2}$ = 0.01 V vs. SCE, see SI), an excited state oxidation potential [$E(DHP^•/[DPH^-]*)$] was estimated as –2.68 V vs. SCE using the Rehm–Weller equation.[9] Given the highly reducing nature of the excited state, we hypothesized that these 1,4-DHP anions could serve as a general platform for the single-electron photoreduction of C–Cl bonds of aryl halides[10] as well as the photodetosylation of N–Ts aromatic amines.[11]

**Scheme 2. (A) Absorption (black trace) and emission (orange trace) spectra of the 1,4-DHP I anion. (B) Summary of electrochemical and photophysical data for the 1,4-DHP I anion.**
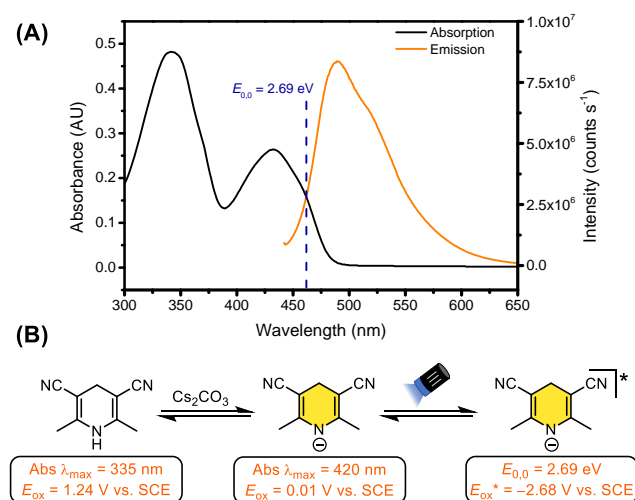


We began our investigation of 1,4-DHP anions as potent photoreductants by studying the hydrodechlorination of methyl 4-chlorobenzoate (**1**) as a model system (Table 1). Gratifyingly, hydrodechlorinated product **2** was observed in 60% yield using only 1 equiv of 1,4-DHP **I** in the presence of 5 equiv of $Cs_2CO_3$ in MeCN under 456 nm LED irradiation (Entry 1). Increasing the loading of 1,4-DHP **I** lead to a further increase in yield (entries 2, 3). Finally, running the reaction under more dilute conditions was found to be beneficial, providing **2** in 78% isolated yield (entry 4). Control experiments demonstrated that both $Cs_2CO_3$ and light were essential for promoting reactivity (entries 5, 6). Finally, we tested an alternative approach using Hantzsch ester (**II**) and *t*BuOK under 456 nm irradiation previously reported by Budén and coworkers,[12] which afforded **2** in only 22% yield under comparable reaction conditions (entry 7).

**Table 1. Hydrodechlorination optimization and control reactions.**



| entry | DHP | [MeCN] | base | yield 2 (%)[a] |
|---|---|---|---|---|
| 1 | **I**, 1.0 equiv | 50 mM | $Cs_2CO_3$ | 60 |
| 2 | **I**, 1.2 equiv | 50 mM | $Cs_2CO_3$ | 69 |
| 3 | **I**, 1.5 equiv | 50 mM | $Cs_2CO_3$ | 75 |
| 4 | **I**, 1.5 equiv | 62.5 mM | $Cs_2CO_3$ | 78[b] |
| 5 | **I**, 1.5 equiv | 62.5 mM | None | N.R. |
| 6 | **I**, 1.5 equiv | 62.5 mM | $Cs_2CO_3$ | N.R.[c] |
| 7 | **II**, 1.5 equiv | 62.5 mM | *t*BuOK[d] | 22 |

[a] Yield calculated by ^{1}H NMR using 1,3,5-trimethoxybenzene as an external standard. [b] Isolated yield. [c] No light. [d] 2.2 equiv. N.R.: no reaction.

With the optimized conditions in hand, we examined the scope of compatible aryl chlorides (Scheme 3). To facilitate product isolation, we employed slightly modified conditions to afford the corresponding borylated products by adding bis(pinacolato)borane (($Bpin)_2$). For the borylation of aryl chlorides, it was also found that using 1,4 DPH **III** with a methyl group at C4 was beneficial, as it reduced the amount of hydrodechlorinated byproduct (see SI for full reaction optimization). Aryl chlorides possessing electron-withdrawing groups (**3**-**5**) were efficiently photoreduced, giving the corresponding borylated products in moderate to good yields. Chlorobenzene (**6**) and 4-chlorobiphenyl (**7**) were also found to be compatible substrates, which was anticipated based on the measured reduction potential of **7** ($E_{p/2}$ = −2.34 V vs. SCE, see SI). Aryl chlorides bearing electron-donating groups did not undergo photoreduction, which was expected as the reduction potentials required exceeded the excited state oxidation potential of the 1,4-DHP **III** anion ($E(DHP^•/[DPH^-]*)$ = –2.63 V vs. SCE, see SI).[11a]

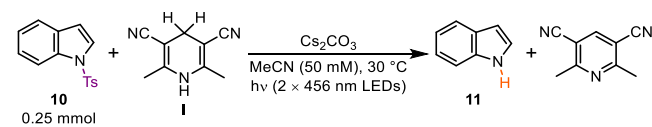**Scheme 3. Reaction scope for the borylation of aryl chlorides.[a]**
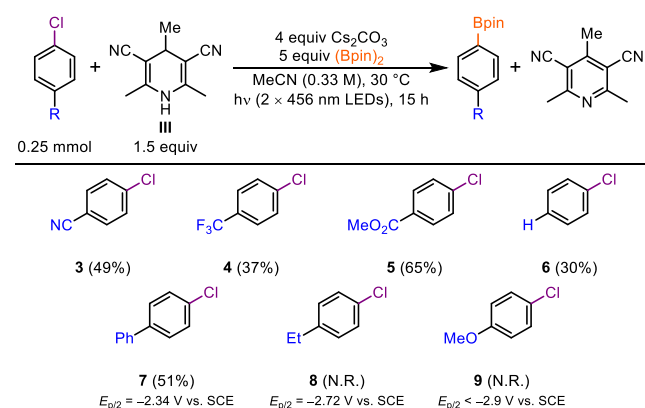


[a] Yields of isolated, purified products after 15 h of irradiation using the optimized conditions (see General Procedure C3 in the Supporting Information).

Next, we examined the potential of 1,4-DHP anions for the photodetosylation of N–Ts aromatic amines, given the similarities in the reported reduction potentials of these substrates in

comparison to aryl chlorides.[11a, 13] As a model reaction, we examined the photodetosylation of N–Ts indole (**10**) using 1,4-DHP **I** as the excited state anionic photoreductant. In an initial attempt using only 1 equiv of DHP **I** in the presence of 5 equiv of Cs$_2$CO$_3$ in MeCN, detosylated indole **11** was observed in 72% yield after 18 h of 456 nm irradiation (Table 2, entry 1). Varying the loadings of DHP **I** and Cs$_2$CO$_3$ revealed that 1.2 equiv of DHP **I** and 4 equiv of Cs$_2$CO$_3$ were optimal, giving **11** in 99% yield (entries 2-4). Control reactions demonstrated that light and Cs$_2$CO$_3$ were essential for reactivity (entries 5 and 6). Finally, a time course revealed that the reaction was complete in 12 h, giving 97% yield of **11** (entries 7 and 8).

**Table 2. Photodetosylation optimization and control reactions.**



| entry | DHP I | equiv Cs$_2$CO$_3$ | Time | yield 11 (%)[a] |
|-------|-------|------------------|------|------------------|
| 1 | 1.0 equiv | 5.0 | 18 h | 72 |
| 2 | 1.2 equiv | 5.0 | 18 h | 81 |
| 3 | 1.5 equiv | 5.0 | 18 h | 83 |
| 4 | 1.2 equiv | 4.0 | 18 h | 99 |
| 5 | 1.2 equiv | None | 18 h | N.R. |
| 6 | 1.2 equiv | 4.0 | 18 h | N.R.[b] |
| 7 | 1.2 equiv | 4.0 | 8 h | 89 |
| 8 | 1.2 equiv | 4.0 | 12 h | 97 |

[a] Yields calculated by $^1$H NMR using 1,3,5-trimethoxybenzene as an external standard. [b] No light. Ts: tosyl; N.R.: no reaction.

With the optimized conditions in hand, we explored the scope of compatible aromatic amines and heterocycles for the photodetosylation reaction (Scheme 4). N–Ts heterocycles such as indoles (**11**, **12**), benzimidazole (**13**) and carbazole (**14**) could all be photodetosylated in excellent yields using this method, and no loss in reactivity was observed when the detosylation was performed at 1 mmol scale. Secondary N–Ts anilines **15**-**17** were also effectively photodetosylated using this protocol. N–Ts melatonin (**18**) also underwent photodetosylation in 55% yield. Remarkably, 1,4-DHP **I** was able to mediate the selective deprotection of an N–Ts group in the presence of both Boc (**19**) and Cbz (**20**) protecting groups, highlighting the potential utility of this method for selective deprotections of aromatic amines in organic synthesis.

**Scheme 4. Reaction scope for the photodetosylation of *N*-Ts aromatic amines.[a]**
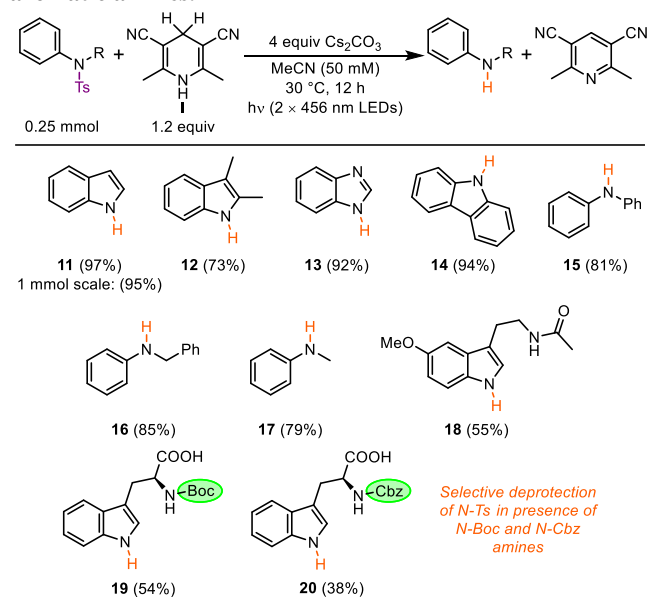


[a] Yields of isolated, purified products after 12 h of irradiation using the optimized conditions (see General Procedure C4 in the Supporting Information).

While secondary N–Ts anilines underwent photodetosylation efficiently, photodetosylation of primary N–Ts aniline (**21**) were found to be significantly proved challenging under our standard conditions, despite the reaction being thermodynamically favorable based on the reported reduction potential of N–Ts aniline.[11a] We posited that the decreased reactivity was attributed to the poor stability of the resulting anilide anion leaving group. After further optimization (see SI), we found that a reasonable yield (53%) of **21** could be obtained using 1,4-DHP **IV** with a phenyl group at C4 and using water as a co-solvent to stabilize the leaving group (Scheme 5). We posited that adding the phenyl group to the C4 position of the 1,4-DHP helped facilitate the initial single-electron transfer by enabling the pre-association of **IV** with the Ts group in the ground state,[14] which was corroborated using UV-vis studies (see SI). Finally, aliphatic N–Ts amines were found to be unreactive using our approach.

**Scheme 5. Photodetosylation of *N*-Ts aniline.**
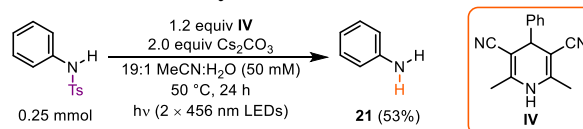


In summary, simple 1,4-DHPs, which can be deprotonated using a mild base to form the corresponding anion, can serve as a general platform for visible light mediated single-electron reductions. Through a combination of electrochemical and photophysical studies, the excited state oxidation potentials of 1,4-DHP anions were estimated to be ~ –2.6 V vs. SCE, which was shown to be sufficiently reducing to promote the borylation of aryl chlorides and the photodetosylation of N–Ts aromatic amines. Furthermore, 1,4-DHP anions can effectively play the role of both single-electron donor and hydrogen atom donor as exemplified in the hydrodechlorination reaction of an aryl chloride. Given the highly reducing excited states that can be

accessed under mild conditions and the wide array of substrates that can be reduced at these potentials, we anticipate that 1,4-DHPs could find widespread use as photoreductants in organic synthesis.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, reaction optimization, compound characterization, cyclic voltammetry studies, absorption and fluorescence studies and NMR spectra (PDF)

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### Notes

The authors declare no competing financial interests.

## ACKNOWLEDGMENT

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