

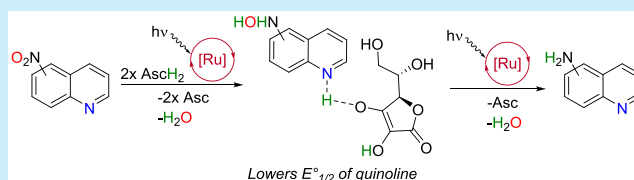
Visible-Light-Photocatalyzed Reductions of N-Heterocyclic Nitroaryls to Anilines Utilizing Ascorbic Acid Reductant

Aleksandar R. Todorov, Santeri Aikonen,[†] Mikko Muuronen,[†] and Juho Helaja*[‡]

Department of Chemistry, University of Helsinki, A.I. Virtasen aukio 1, 00014 Helsinki, Finland

Supporting Information

ABSTRACT: A photoreductive protocol utilizing [Ru(bpy)₃]²⁺ photocatalyst, blue light LEDs, and ascorbic acid (AscH₂) has been developed to reduce nitro N-heteroaryls to the corresponding anilines. Based on experimental and computational results and previous studies, we propose that the reaction proceeds via proton-coupled electron transfer between AscH₂, photocatalyst, and the nitro N-heteroaryl. The method offers a green catalytic procedure to reduce, e.g., 4-/8-nitroquinolines to the corresponding aminoquinolines, substructures present in important antimalarial drugs.

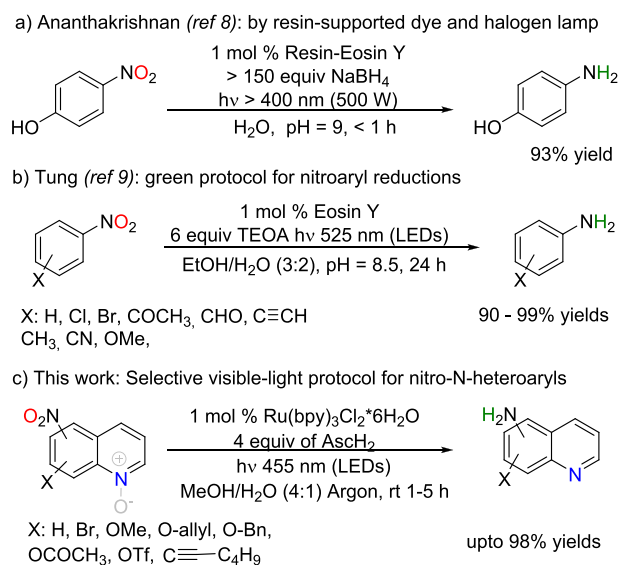


Reduction of an aromatic nitro compound is a prototypical way to prepare arylamines that are common substructures in pharmaceuticals, agrochemicals, dyes, and pigments and in a variety of other fine and specialty chemicals.¹ This fundamental transformation can be performed using a plethora of synthetic and catalytic protocols: conventional stoichiometric reagents, e.g., SnCl₂, TiCl₃, Raney Ni, Zn, Sn, Fe, and Na₂S, are appropriate for specific lab-scale conversion,² while transition-metal-catalyzed hydrogenations (e.g., Pd, Au, and Pt on various supports: C, TiO₂, etc.) dominate industrial applications.³ Lately, heterogeneous photocatalytic nitroarene reductions on various materials, e.g., semiconductors, nanoparticles, and nanocomposites, have also been under intensive development.⁴

Recent advances in photoredox catalysis (e.g., metal complexes and organic dyes) have enabled new strategies for reductive organic conversions.⁵ The early photoreductions of nitrobenzenes to anilines were carried out under intense xenon lamp irradiation including UV wavelengths. In a pioneering example, Fukuzumi and co-workers used an excess of dihydroacridine as a reductant for triplet excited PhNO₂ in the presence of HClO₄/H₂O additives in MeCN.⁶ Later on, Hirao and co-workers developed a more convenient method, exploiting a Ru(bpy)₂(MeCN)₂(PF₆)₂ photosensitizer and hydrazine as reductant, while the most intense UV light was filtered out (<300 nm).⁷ Ananthakrishnan and co-workers employed visible light in 4-nitrophenol photoreduction using resin-supported eosin Y with a large excess of NaBH₄ (Scheme 1a).⁸ Tung and co-workers developed the method further to extend the substrate scope by utilizing green light-emitting diodes (LEDs) as a light source, eosin Y as a photosensitizer, and triethanolamine (TEOA) as a reductant (Scheme 1b).⁹

Our interest has been in the development of catalytic methods for quinoline modifications. Previously, we developed a protocol for photoreductive removal of *O*-benzyl groups from oxyarene N-heterocycles.¹⁰ At the beginning of the current study, we observed that even the eosin Y/TEOA photoreduction protocol (Scheme 1b) was widely tolerant for

Scheme 1. Visible Light Nitroaryl Photoreduction Reduction Protocols



nitrophenyl functional groups, the method was incompatible with nitroquinolines (Table S7). Therefore, we developed here a photocatalytic protocol for reducing nitro groups in *N*-(oxo)heterocyclic nitroaryls (Scheme 1c) leading to aminoquinoline structures present in many important antimalarial pharmaceuticals, e.g., in traditional chloroquine¹¹ and primaquine¹² as well as recently FDA-approved tafenoquine¹³ (Figure 1).

First, we studied the photoreduction of 2-methoxy-6-nitroquinoline 1a in the presence of ascorbic acid (AscH₂)

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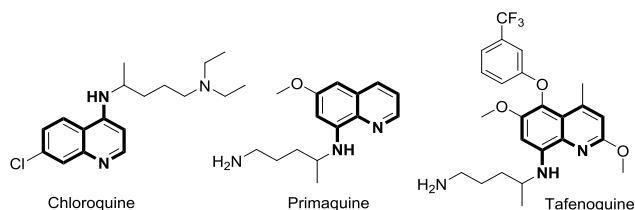
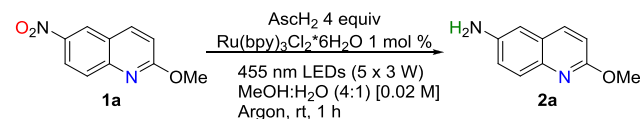


Figure 1. Examples of 4-/8-aminoquinoline-containing antimalarial drugs.

Table 1. Effect of Deviation from Standard Reaction Conditions^a



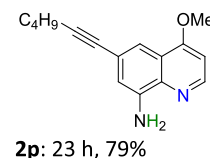
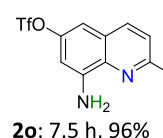
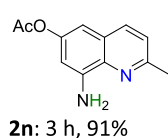
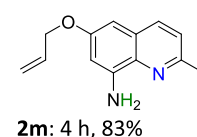
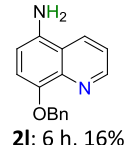
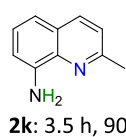
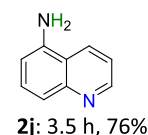
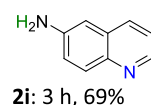
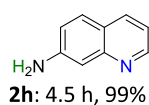
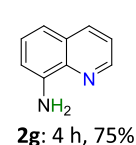
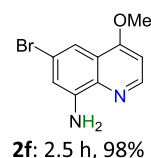
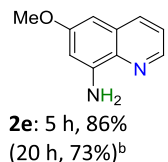
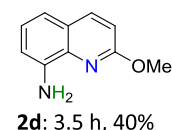
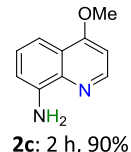
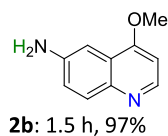
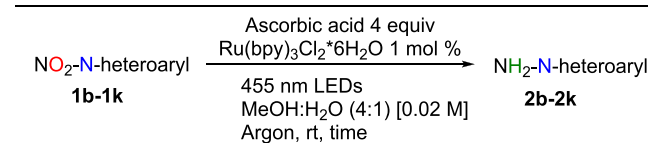
entry	variation from standard conditions	yield ^b (%)
1	none	83 (82) ^c
2	no light	0
3	air atmosphere	28
4	no photocatalyst	0
5	0.5% [Ru] loading	52
6	(Ir[dF(CF ₃)ppy] ₂ (dtbbpy))PF ₆ (1 mol %)	28
7	[Ir(dtbbpy)(ppy) ₂]PF ₆ (1 mol %)	16
8	no AsCH ₂	0
9	AsCH ₂ (2 equiv)	18
10	AsCH ₂ (3 equiv)	79
11	Na-ascorbate instead of AsCH ₂	0
12	30 min reaction time	36
13	MeOH	29
14	MeOH/H ₂ O (10:1)	41
15	MeOH/H ₂ O (6:1)	62
16	MeOH/H ₂ O (2:1)	71
17	EtOH/H ₂ O (1:1)	81
18	AcOH additive (10 vol %)	58
19	DMF	11
20	MeCN	0

^aFull reaction optimization in Tables S1–S7. ^bGC yield: average of two runs. ^cIsolated yield by SiO₂ column chromatography

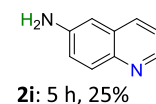
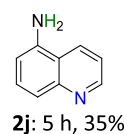
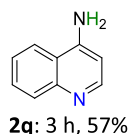
as the reductant and Ru(bpy)₃Cl₂ as the photosensitizer according to earlier successful protocols for reductions by us and others.¹⁴ Optimization of the reaction conditions, i.e., photocatalyst, reductant amount, solvent, concentration, and reaction time, provided aniline **2a** with 83% yield after 1 h irradiation with blue LEDs light (455 nm) in the presence of 4 equiv of AsCH₂ and 1 mol % of the [Ru] catalyst in MeOH/H₂O (0.02 M) at rt (Tables S1–S7). Varying the reaction conditions from the optimal shows that reaction does not take place without light, AsCH₂, or photocatalyst and the reaction is sensitive to air atmosphere (entries 2, 8, 4, and 3 Table 1). The reaction was also sensitive to the amount of reactants (entries 5, 9, and 10), and interestingly, the optimal solvent compositions proved to be 4:1 MeOH/H₂O and 1:1 EtOH/H₂O. The reaction proceeds poorly or not at all in polar aprotic solvents, e.g., DMF and MeCN, even though MeCN was employed as solvent in the previous AsCH₂ and [Ru]-photocatalyst studies.¹⁴

Next, we studied the scope of the reaction (Scheme 2); reduction of nitromethoxyquinolines **1b–1f** to the correspond-

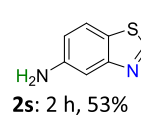
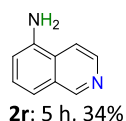
Scheme 2. Reaction Scope Study^a



From N-oxo quinolines



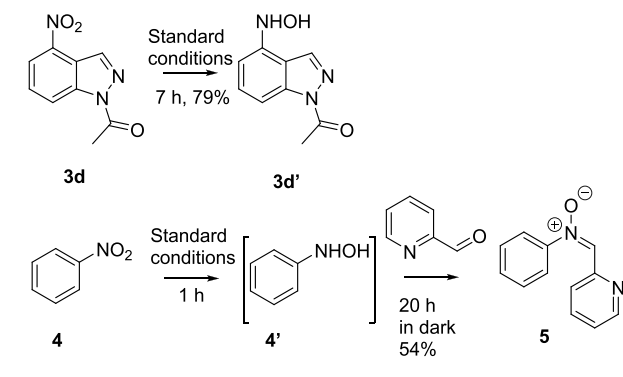
Other N-heterocycles



^aAverage isolated yields of two runs after SiO₂ chromatography. ^bUp-scaled (4 mmol) reaction under the same light source, 0.5 mol % of [Ru] catalyst.

ing amines **2b–2f** required slightly longer reactions times, 1.5–5 h, depending on the substituent positions. The obtained yields were, however, still high (86–97%) with **2d** being an exception by producing unidentified polymeric side products.

Scheme 3. Synthesis of Hydroxylamine and Nitrone



The excellent yield of **2f** demonstrates that halogen substituents in the nitro/amino aryl ring are also well tolerated. In addition, the monosubstituted 5-, 6-, 7-, or 8-nitroquinolines are converted into amines **2g–2j** with up to quantitative yields, and the 2-methyl substituent improved the 8-aminoquinoline yield from 75 to 90% (**2g** vs **2k**). Importantly, the protocol proved to be scalable: reduction of **1e** on a larger 4 mmol (vs 0.2 mmol) scale with reduced catalyst loading ([Ru] 0.5 mol %) yielded 73% of **2e** after 24 h reaction time.

A poor yield of 16% received for **2l** indicates that the combination of 6-nitro-8-ether substitution is unfavorable for the reaction. On the other hand, 2-methyl-8-nitroquinolines with allyl ether, acyl, or triflyl at the 6-position gave high yields of 83%, 91%, and 96% for **2m**, **2n**, and **2o**, respectively, although the TfO compound (**2o**) required longer reaction time (7.5 h). The chemoselectivity of the method was further

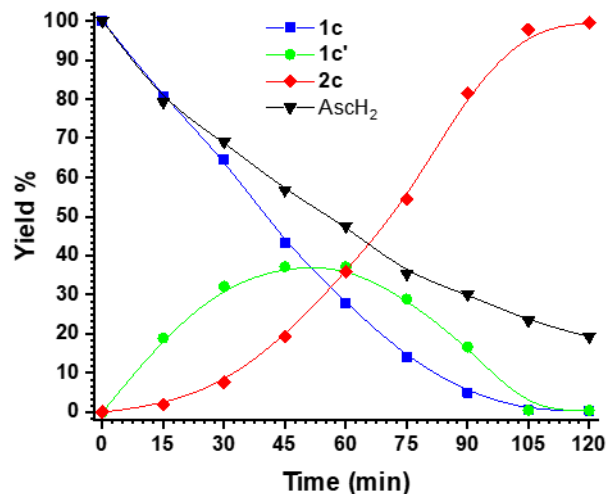


Figure 3. Conversion of **1c** to **2c** via observed hydroxylamine intermediate **1c'** followed by ^1H NMR monitoring (SI). Structures are presented in Figure 2a.

highlighted with a 79% yield of 6-alkyne-substituted 8-amino-4-methoxyquinone **2p** after 23 h reaction time.

Another attractive class of target molecules is 4-nitroquinolines (Scheme 2), which are commonly prepared by nitration of *N*-oxoquinolines and require the use of trivalent phosphorus compounds for removal of the *N*-oxo groups.¹⁵ Our received yields of 57%, 35%, and 25% for **2q**, **2i**, and **2j**, respectively, using *N*-oxo compounds as starting materials are therefore highly encouraging.

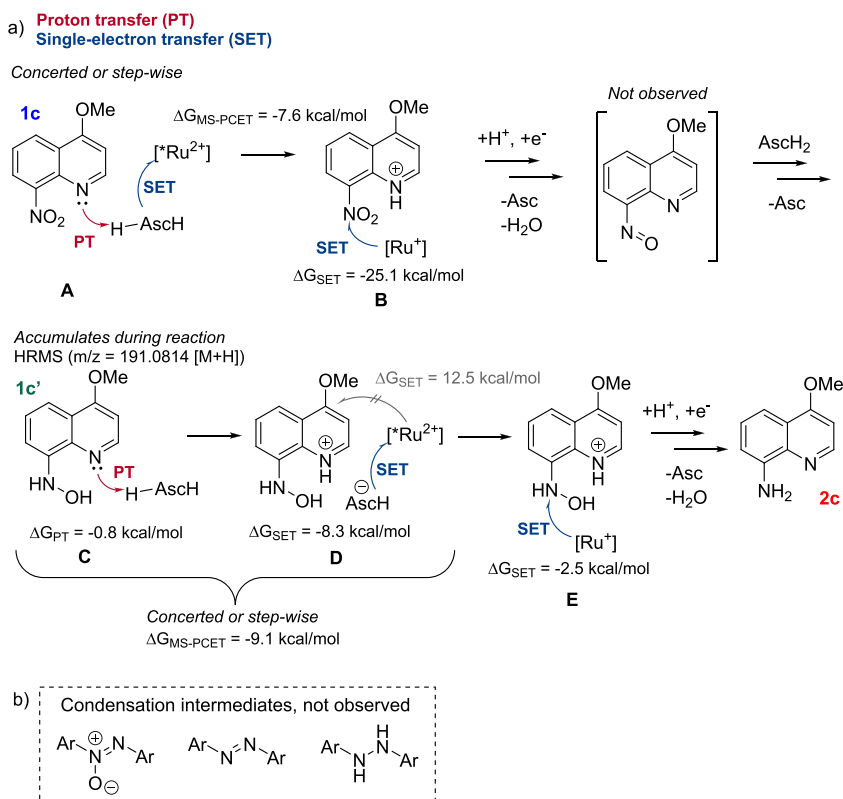


Figure 2. (a) Schematic representation of the nitro reduction to amine. (b) Condensation intermediates.

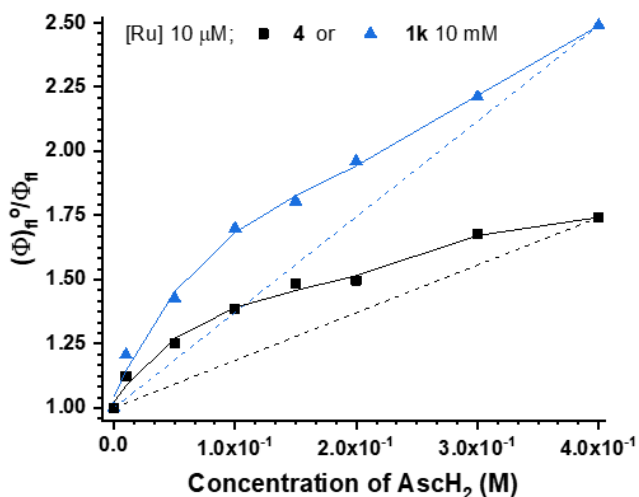


Figure 4. Modified Stern–Volmer titration, where [Ru] and quencher **1k** or **4** were kept constant and AscH₂ quencher was varied.

Last, we also tested the substrate scope for producing 6-aminoisoquinoline **2r** and 5-aminobenzothiazole **2s**, which worked with decent to good yields (Scheme 2). Other tested N-heterocycles fell into the category of unsuitable substrates (**3a–3h**, SI), being either unreactive, stopping at hydroxylamine intermediate stage (**3d**, Scheme 3), or leading to side products and oligomerization, which limit the scope of the method.

Interestingly, for 1-acyl-4-nitroindazole **3d** and nitrobenzene **4**, very good yields (79%) of hydroxylamine **3d'** and (54%) nitron **5**, respectively, were obtained instead of their amine products (Scheme 3). Therefore, we decided to study the reaction mechanism to understand why the reaction is not driven to amine formation in these cases.

First, the mechanism of the photoreduction was studied by monitoring the conversion of **1c** to **2c** with NMR. Hydroxylamine intermediate (**1c'**) was increasingly formed and consumed in the course of the reaction (Figures 2a and 3 and SI) in accordance with the previously proposed mechanism for the nitrobenzene reduction.^{16,17} The acquired NMR data showed no traces of other species, indicating that the reduction proceeds via the direct route (Figure 2a and SI) rather than through the condensation of hydroxylamine and nitroso intermediates (Figure 2b).

Initially, we considered the first step of the mechanism to be reduction of substrate, or protonation of the substrate followed by its reduction. However, Stern–Volmer measurements pointed out that a 1:1 mixture of **1k**/AscH₂ was a superior quencher of [*Ru²⁺] compared to either of the components alone, indicating their cooperative role (SI). Furthermore, the computed oxidation potentials indicate oxidation of ascorbic acid with [*Ru²⁺] to be an endergonic process (17.5 kcal/mol, SI), and neither do the experimentally observed yields correlate with the computed reduction potentials of the protonated or nonprotonated substrates (see SI for E_{red}^o and E_{red,H+}^o values). Therefore, we propose the mechanism depicted in Figure 2a: (A) the reaction is initiated by a multisite proton-coupled electron transfer (MS-PCET)¹⁸ between the nitro quinoline, AscH₂, and [*Ru²⁺], i.e., proton and electron are transferred from one donor to two separate acceptors. This is supported by Stern–Volmer titrations for **1k**

and nitrobenzene (**4**), in which concentrations of these substrates were fixed and the amount of AscH₂ was varied (Figure 4). The nonlinear behavior in both cases indicates an MS-PCET-type reaction as suggested by Qiu and Knowles.^{18b} Next, (B) the protonated nitro substrate is reduced by [Ru⁺]: reduction of protonated nitro compound with [Ru⁺] is a more exergonic process (ΔG ≤ −15.9 kcal/mol) than with [*Ru²⁺] (−12.7 [**1g**] ≤ ΔG ≤ −0.9 [**3d**] kcal/mol), and reduction of [*Ru²⁺] to [Ru⁺] by AscH[−] is an exergonic process (−8.3 kcal/mol). The protonation energies of reactive nitro substrates by AscH₂ were calculated to vary between thermoneutral (0.7 kcal/mol for **1c**) and endergonic (15.4 kcal/mol for **3d**), where the endergonicity of protonation does not exclude hydrogen-bonding interactions between acid and base, which in turn can facilitate MS-PCET reactions.¹⁸

The protonation of hydroxylamine (C) and the subsequent reduction of [*Ru²⁺] to [Ru⁺] by AscH[−] (D) are required for the reduction of the substrate by [Ru⁺] (E, Figure 2a), as the reduction of electron-rich hydroxylamine quinolines would be endergonic with *Ru(bpy)₃²⁺ (ΔG ≥ 27.9 kcal/mol, SI). The pK_{aH} values for unreactive hydroxylamine intermediates of **3d** and **4** indicates that the protonation is endergonic: 10.1 kcal/mol for **3d'** and 8.9 kcal/mol for **4'**. In turn, the reactive hydroxylamine intermediates are easily protonated (C, Figure 2a) with free energies of −0.8, 2.4, and 2.0 kcal/mol for **1c**, **1d**, and **1g**, respectively. The reduction of protonated hydroxylamine quinolines would be endergonic with [*Ru²⁺] (4.8 ≤ ΔG ≤ 12.5 kcal/mol, SI), while the process is exergonic with the obtained ground state [Ru⁺] (ΔG ≤ −2.5 kcal/mol, SI).

In summary, we have developed a chemoselective and green photoreductive protocol for reduction of nitro N-heteroaryls that exploits AscH₂ as hydrogen source. The method complements the existing photoredox catalysis protocols, extending their applicability for the N-heteroaryls.

■ ASSOCIATED CONTENT

§ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01205.

Experimental procedures, full reaction optimization tables, ¹H NMR reaction monitoring, computational procedures and details, and ¹H and ¹³C NMR spectra for all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: juho.helaja@helsinki.fi.

ORCID

Santeri Aikonen: 0000-0003-2675-7290

Mikko Muuronen: 0000-0001-9647-7070

Juho Helaja: 0000-0001-8645-617X

Present Address

†(M.M.) BASF SE, Carl-Bosch-Str. 38, 67056 Ludwigshafen, Germany.

Notes

The authors declare no competing financial interest.

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