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Cascade Reactions

A Visible Light Photocatalytic Cross-Dehydrogenative Coupling/Dehydrogenation/6π-Cyclization/Oxidation Cascade: Synthesis of 12-Nitroindoloisoquinolines from 2-Aryltetrahydroisoquinolines

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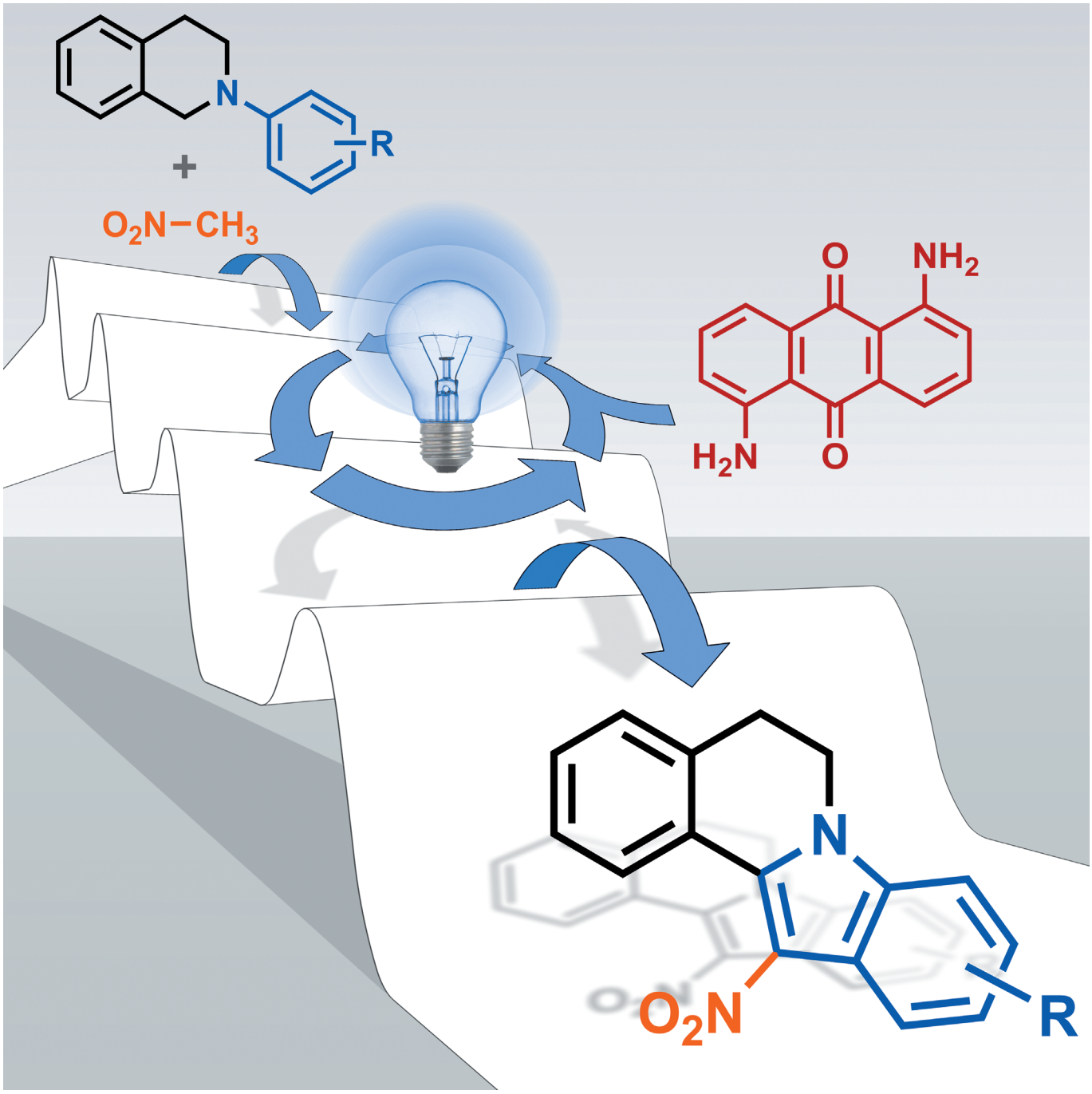
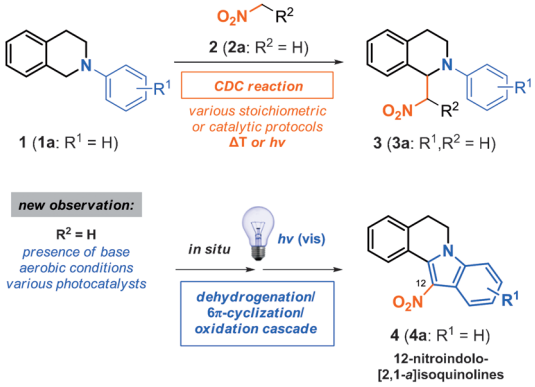


Abstract: A visible light-induced photocatalytic dehydrogenation/6π-cyclization/oxidation cascade converts 1-(nitromethyl)-2-aryl-1,2,3,4-tetrahydroisoquinolines into novel 12-nitro-substituted tetracyclic indolo[2,1-*a*]isoquinoline derivatives. Various photocatalysts promote the reaction in the presence of air and a base, the most efficient being 1-aminoanthraquinone in combination with K_3PO_4. Further, the 12-nitroindoloisoquinoline products can be accessed directly from C1-unfunctionalized 2-aryl-1,2,3,4-tetrahydroisoquinolines by extending the one-pot protocol with a foregoing photocatalytic cross-dehydrogenative coupling reaction, resulting in a quadruple cascade transformation.



Scheme 1. CDC reaction between 2-aryl-1,2,3,4-tetrahydroisoquinolines **1** and nitroalkanes **2** and in situ dehydrogenation/6π-cyclization/oxidation cascade reaction leading to 12-nitro-substituted indoloisoquinolines **4**.

The cross-dehydrogenative coupling (CDC)[1] between 2-aryl-1,2,3,4-tetrahydroisoquinolines **1** and nitroalkanes **2** is a well-established method for the preparation of 1-(nitroalkyl)-2-aryl-tetrahydroisoquinolines **3**, and various reagents promote this transformation in high yields (Scheme 1, top). While the reaction can be performed under thermal conditions using stoichiometric oxidants such as DDQ,[2] $PhI(OAc)_3$[3] or catalytic $PtCl_2$[4] several visible-light photocatalytic methods have as well been developed, employing ruthenium(II)[5] and iridium(III)[6] photocatalysts, organic photocatalysts such as xanthene dyes[7] or 9,10-anthraquinone derivatives[8] as well as TiO_2.[9] However, despite the large number of methods available for the preparation of nitroalkyl amines **3**, these products have so far been void of any synthetic use, with the exception of a single report by Todd and co-workers who utilized compounds **3** in the synthesis of the anthelmintic praziquantel.[10]

As we investigated the photocatalytic CDC reaction **1a**→**3a** with nitromethane (**2a**, 5 equiv) in acetonitrile solution, under aerobic conditions and employing various photocatalysts, we observed that in the presence of a base and upon prolonged reaction times, initially formed 1-(nitromethyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (**3a**) undergoes an unprecedented subsequent oxidative transformation, in situ leading to 12-nitro-substituted tetracyclic indolo[2,1-*a*]isoquinoline **4a** (Scheme 1, bottom). The novel photocatalytic one-pot reaction **1a**+**2a**→[**3a**]→**4a** initially produced product **4a** in trace amounts only and consequently, we investigated this transformation in detail. It was further established that it may be classified as a photocatalytic CDC/dehydrogenation/6π-cyclization/oxidation cascade.

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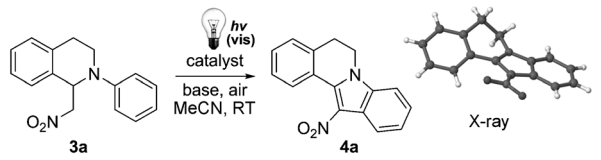
The crucial role of the base in the reaction **1a**+**2a**→**4a** was recognized at an early stage, as product **4a** was never detected in its absence. In a preliminary screening, amine bases, carbonates as well as strong bases such as guanidine, DBU, KO*t*Bu and K_3PO_4 were employed in the reaction, along with $Ru(bpy)_3^{2+}$ as the photocatalyst. These early experiments showed that Cs_2CO_3 and K_3PO_4 are suitable bases while DBU, KO*t*Bu and Et_3N failed to afford product **4a**. However, yields for the overall transformation **1a**+**2a**→[**3a**]→**4a** remained low (~10–15%), for which we decided to investigate the second half reaction **3a**→**4a** first, and Table 1 shows a catalyst screening in MeCN solution. Metal-based photocatalysts $Ru(bpy_3)^{2+}$ and $Ir(dtbbpy)(ppy)_2^+$ convert compound **3a** into product **4a** with 47 and 41% isolated yield (reaction times of 39 and 31 h, respectively), in the presence of 2 equivalents of K_3PO_4, under air and using blue LED irradiation (entries 1 and 2). Using green LED irradiation under otherwise unchanged reaction conditions, organic photocatalysts eosin Y and nile red produce product **4a** in 19 and 6% yield, at low conversion even after 40 h reaction time (entries 3 and 4). Methylene blue along with red LED light irradiation (entry 5) was found to be ineffective. Finally, various anthraquinone derivatives[11] were employed in the reaction, with blue fluorescent lamp irradiation (450±50 nm). While alizarin gives low conversion and produces **4a** with only 11% isolable yield after 93 h reaction time (entry 6), 1,5-dichloroanthraquinone (DCAQ) offers full conversion of substrate **3a** and leads to **4a** with 32% yield after 40 h (entry 7). Finally, the red dye 1-aminoanthraquinone (1-AAQ, 5 mol%, λ_{max}=465 nm, ε=8000) emerged as the optimal catalyst as it gives rise to product **4a** with 62% isolated yield, with full consumption of starting material **3a** after 40 h reaction time and under aerobic conditions (entry 8).

As mentioned above for the reaction **1a**→**4a**, the reaction **3a**→**4a** does not proceed in the absence of base (entry 12), and a reduction of the amount of K_3PO_4 or catalyst loading results in a decreased yield of **4a** (entries 10 and 11). While no conversion is observed in the dark (entry 13), the reaction proceeds to some minor extent when irradiated in the absence of catalyst and under air (17% yield after 48 h, entry 14). When oxygen is excluded, uncatalyzed conversion of **3a** is minimal

Table 1. Optimization of the photocatalytic reaction **3a**→**4a**.[a]



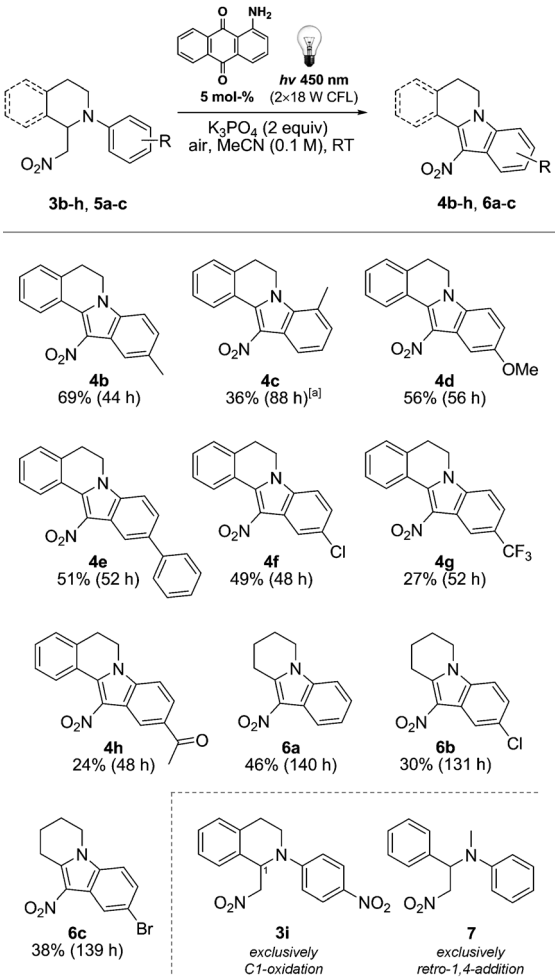
3a **4a**

#	Catalyst (mol%)	Light source	Base	*t* [h]	Yield [%][b]
1	$Ru(bpy)_3(BF_4)_2$ (1)	blue LED	K_3PO_4 (2)	39	47
2	$Ir(dtbbpy)(ppy)_2(PF_6)$ (1)	blue LED	K_3PO_4 (2)	31	41
3	eosin Y (5)	green LED	K_3PO_4 (2)	40	19
4	nile red (5)	green LED	K_3PO_4 (2)	40	6
5	methylene blue (5)	red LED	K_3PO_4 (2)	88	trace
6	Alizarin (5)	blue CFL	K_3PO_4 (2)	93	11
7	DCAQ[c] (5)	blue CFL	K_3PO_4 (2)	40	32
8	**1-AAQ[d] (5)**	**blue CFL**	**K_3PO_4 (2)**	**40**	**62**
9	1-AAQ (5)	blue CFL	Cs_2CO_3 (2)	22	52
10	1-AAQ (1)	blue CFL	K_3PO_4 (2)	45	36
11	1-AAQ (5)	blue CFL	K_3PO_4 (1)	48	15
12	1-AAQ (5)	blue CFL	–/–	48	0
13	1-AAQ (5)	–/–	K_3PO_4 (2)	48	0
14	–/–	blue CFL	K_3PO_4 (2)	48	17
15	–/–	blue CFL	K_3PO_4 (2)	48	8[e]

[a] Reactions were run on 0.2 mmol scale at RT in MeCN ($c = 0.1$ M), conversion monitored by T.L.C. [b] Isolated yield after chromatography. [c] 1,5-Dichloroanthraquinone. [d] 1-Aminoanthraquinone. [e] Reaction performed under N_2 atmosphere. LED setup used: 5.4 W/0.87 cd/450 ± 25 nm or 560 ± 25 nm; CFL lamps used: 2×18 W/2×2.73 cd/450 ± 50 nm.

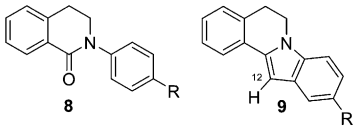
(8% yield after 48 h, entry 15). Finally, the optimum conditions (5 mol% 1-AAQ, 2 equiv K_3PO_4, blue CFL irradiation) were also tested in polar solvents other than acetonitrile, and runs in MeOH, DMSO or DMF (not shown in the table) gave comparable results to MeCN, hence solvent influence on the reaction is marginal.

Applying the optimum reaction conditions, various indoloisoquinolines **4b–h** could be prepared from nitroalkyl amines **3b–h**[12] (Scheme 2). Reactions of donor-substituted substrates efficiently lead to tetracycles **4b–f** with yields from 36–69% in reaction times of 44–88 h. In all cases, conversion was near quantitative, with the exception of sterically hindered *ortho*-substituted compound **4c** (77% conversion after 88 h). In addition, the reaction **3c**→**4c** is more efficiently carried out using 15 mol% of 1,5-diaminoanthraquinone (1,5-AAQ, $\lambda_{max} = 475$ nm, $\varepsilon = 21\,800$) instead of 1-AAQ.[13] In case of substrates **3g** and **3h** bearing electron acceptor substituents, cyclization is less efficient and products **4g,h** are isolated in yields of 27% (after 52 h) and 24% (after 48 h), respectively. Interestingly, the reaction of 4-nitro-substituted substrate **3i** does not lead to any tetracyclic product, but oxidative C,C-cleavage at C-1 occurs exclusively in this case, to give the corresponding dihydroisocarbostyryl. Open-chain substrate **7** in turn undergoes quantitative retro-1,4-addition under the standard reaction conditions. Finally, in addition to substrates **3**, *N*-aryl piperidine nitroalkyl amines **5**[12] can as well be cyclized, and tricyclic indole products **6a–c** are obtained in 30–46% yield, with full conversion of substrates after elongated reaction times of 131–140 h.



Scheme 2. Reaction scope; yields refer to isolated yields after chromatography. [a] Compound **4c** was prepared using 15 mol% 1,5-AAQ instead of 5 mol% 1-AAQ.

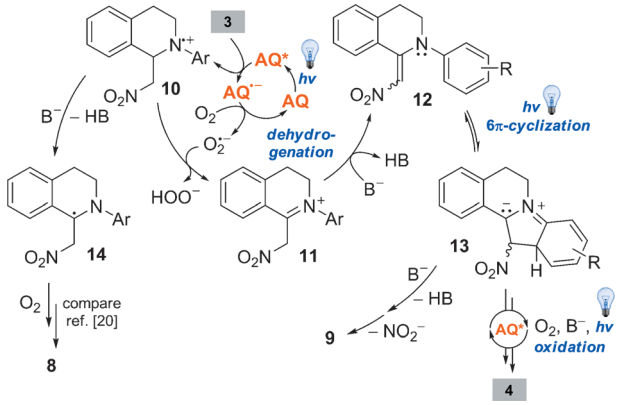
The cyclization reactions of nitroalkyl amines **3** shown in Scheme 2 generally produce two isolable side products in addition to the tetracyclic products **4**. Dihydroisocarbostyryls **8** are obtained in 10–30% yield from substrates **3a–h** (and exclusively in the case of substrate **3i**). Notably, when air is replaced by oxygen, yields of compounds **8** increase.[14] As for the second side reaction, 12*H*-substituted indoloisoquinolines **9** are isolated in trace amounts (up to 5%).



8 **9**

Mechanistically, we propose that the reaction **3**→**4** is initiated by photoelectron transfer between amine **3** (exemplary compound **3d** shows $E_{ox} = +0.82$ V vs. SCE in MeCN)[15] and the triplet-excited anthraquinone catalyst AQ* to give amine radical cation **10**, which is converted into iminium ion **11** via H-abstraction by superoxide radical anion (Scheme 3). Facile

deprotonation of iminium ion **11** generates nitroenamine **12** which undergoes photoinduced conrotatory 6π-electrocyclic ring closure[16,17] to azomethine ylide **13**. Rearomatization of ylide **13** followed by catalytic oxidation leads to 12-nitroindoloisoquinoline **4**. Consequently, the proposed overall reaction pathway **3**→**4** may be classified as a dehydrogenation/6π-cyclization/oxidation cascade[18] and visible light excitation sustains each of the three individual steps.

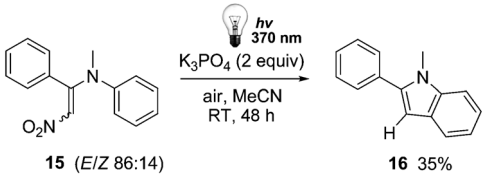


Scheme 3. Proposed mechanism of the dehydrogenation/6π-cyclization/oxidation cascade of nitroalkyl amines **3** to products **4**.

As for the formation of the 12*H*-substituted indoloisoquinolines **9**, we propose an elimination of nitrite anion (NO_2^-) from intermediate **13**.[19] The second side reaction leading to dihydroisocarbostyryls **8** is likely to be initiated by the deprotonation of radical cation **10** to give α-amino radical **14**, which adds molecular oxygen to give a C1-peroxide intermediate. Its subsequent CC-cleavage to products **8** is in close analogy to the known autoxidation of Reissert compounds.[20]

To further support our mechanistic proposal, we prepared model nitroenamine **15**[21] ($\lambda_{max}=355$ nm, $\varepsilon=15\,000$) and subjected it to UVA irradiation (370±30 nm) in the presence of air and K_3PO_4. As shown in Scheme 4, compound **15** undergoes photoinduced cyclization to 1-methyl-2-phenylindole (**16**) in 35% yield, which is in analogy to the proposed 6π-cyclization/elimination **12**→**9** shown in Scheme 3. In addition, a conceivable radical reaction pathway via an intramolecular cyclization of the radical cation derived from nitroenamine **15** appeared unlikely, as enamine **15** shows an oxidation potential $E_{ox}=+1.32$ V in cyclic voltammetry (vs. SCE in MeCN).[15] This would render its one-electron oxidation by $Ru(bpy)_3^{2+*}$ thermodynamically impossible ($E^*_{red}=+0.77$ V vs. SCE),[22] however, the reaction **3a**→**4a** is quite efficiently promoted by this catalyst (Table 1, entry 1).

After we succeeded in the one-step photocatalytic synthesis of diverse products **4** and **6** with good yield starting from the corresponding nitroalkyl amines **3** and **5** (Scheme 2), we re-examined the initially attempted one-step synthesis of 12-nitroindoloisoquinolines **4** starting from the parent 2-aryltetrahydroisoquinolines **1** and nitromethane (**2a**). Table 2 summarizes our experiments towards the desired one pot reaction **1**+**2a**→

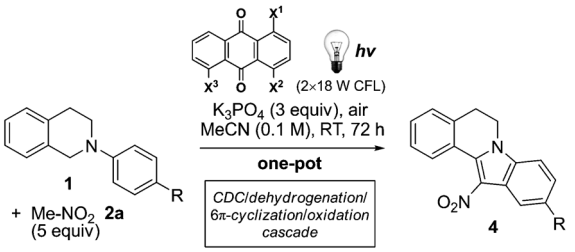


Scheme 4. 6π-Cyclization/elimination reaction of nitroenamine **15**.

[**3**]→**4**, that is, a photochemical CDC/dehydrogenation/6π-cyclization/oxidation quadruple cascade. In order to achieve this transformation in synthetically useful yields, a catalyst needed to be identified which additionally displays high productivity in the upstream CDC reaction, and several donor-substituted anthraquinone derivatives were probed as catalysts. Reaction of 2-(4-methylphenyl)-1,2,3,4-tetrahydroisoquinoline (**1b**) with 5 equiv of nitromethane (**2a**) and 5 mol% of 1-AAQ in MeCN solution, under 450 nm irradiation for 72 h in the presence of air and 3 equiv of K_3PO_4 leads to full consumption of substrate **1b** but conversion of intermediate nitroalkyl amine **3b** into product **4b** is largely incomplete (Table 2, entry 1). Increasing the catalyst loading to 15 mol% slightly improves conversion of intermediate **3b** and product **4b** can be isolated in 27% yield after 72 h (entry 2). It was hypothesized that triplet–triplet quenching between the excited ^{3}AQ* catalyst and the emerging product **4b** ($\lambda_{max}=380$ nm, $\varepsilon=14\,300$) could be the cause of the incomplete conversion of intermediate **3b**. Thus, the reaction was attempted using 1,4-diaminoanthraquinone (1,4-AAQ) as catalyst, which possesses long-wave absorption ($\lambda_{max}=545$ and 580 nm) along with 530–630 nm irradiation (entry 3). Yet, under these conditions, conversion of tetrahydroisoquinoline substrate **1b** into nitroalkyl amine **3b** is minimal and no tetracyclic product **4b** can be detected. Next, short-wave absorbing catalyst 1,5-dichloroanthraquinone (1,5-ClAQ, $\lambda_{max}=345$ nm) was employed along with 370 nm excitation, where 6π-cyclization of putative nitroenamine intermediate **12** should occur at a faster rate than at 450 nm (entry 4). However, the conversion of **3b** into **4b** could not be improved compared to 1-AAQ (entry 2). Gratifyingly, we found that 1,5-AAQ, (15 mol %) offered full conversion in the CDC reaction combined with 80% conversion of intermediate nitroalkyl amine **3b**, and product **4b** could be isolated in an attractive 53% yield. Applying these conditions, various indoloisoquinolines **4a**–**e** could as well be prepared in one-pot fashion, in satisfactory to good yields of 28–44% (entries 7–10).

In summary, a visible light-induced aerobic photocatalytic dehydrogenation/6π-cyclization/oxidation cascade was discovered to convert 1-(nitromethyl)-2-aryltetrahydroisoquinolines into tetracyclic 12-nitroindolo[2,1-*a*]isoquinoline products. The cascade reaction can be further extended to encompass an upstream cross-dehydrogenative coupling (CDC) between the parent 2-aryltetrahydroisoquinolines and nitromethane, resulting in a quadruple cascade transformation. This operationally very simple one-pot protocol provides new and valuable indoloisoquinoline products in good overall yields and amino-substituted anthraquinones appear as the ideal organic photocatalysts.

Table 2. Optimization and examples of the one pot cascade reaction **1** + **2a** → **4** catalyzed by donor-substituted anthraquinones.



#	R	Catalyst[a]	Mol %	λ_{exc} [nm]	Rel. ratio [%][b] **1:3:4:8:9**	Yield ([%])[c]
1	CH_3	1-AAQ	5	450 ± 50	0/52/28/15/5	**4b** (19)
2	CH_3	1-AAQ	15	450 ± 50	8/39/38/12/3	**4b** (27)
3	CH_3	1,4-AAQ	15	530-630	92/5/0/3/0	–/–
4	CH_3	1,5-ClAQ	15	370 ± 30	0/41/30/19/10	n.d.
5	**CH_3**	**1,5-AAQ**	**15**	**450 ± 50**	**0/21/59/18/2**	**4b** (53)
6	CH_3	1,5-AAQ	30	450 ± 50	10/19/55/14/2	n.d.
7	**H**	1,5-AAQ	15	450 ± 50	26/11/45/18/0	**4a** (34)
8	**OMe**	1,5-AAQ	15	450 ± 50	8/22/58/12/0	**4d** (43)
9	**Ph**	1,5-AAQ	15	450 ± 50	10/16/51/23/0	**4e** (44)
10	**Cl**	1,5-AAQ	15	450 ± 50	17/11/33/39/0	**4f** (28)

[a] 1-AAQ = 1-aminoanthraquinone, 1,5-ClAQ = 1,5-dichloroanthraquinone, 1,4-AAQ = 1,4-diaminoanthraquinone, 1,5-AAQ = 1,5-diaminoanthraquinone. [b] Determined by ^{1}H NMR. [c] Isolated yield after chromatography.

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Keywords: cascade reactions · heterocycles · organocatalysis · photocatalysis

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