Tandem Catalysis Hot Paper

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Tandem Organocatalysis and Photocatalysis: An Anthraquinone-Catalyzed Indole-C3-Alkylation/Photooxidation/1,2-Shift Sequence**

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Dedicated to Professor Hans-Ulrich Reissig on the occasion of his 65th birthday

Abstract: *Quinones exhibit orthogonal ground- and excited-state reactivities and are therefore highly suitable organocatalysts for the development of sequential catalytic processes. Herein, the discovery of an anthraquinone-catalyzed thermal indole-C3-alkylation with benzylamines is described, which can be combined sequentially with a new visible-light-driven catalytic photooxidation/1,2-shift reaction. The one-flask tandem process converts indoles into 3-benzylindole intermediates, which are further transformed into new fluorescent 2,2-disubstituted indoline-3-one derivatives.*

In tandem catalysis, several fundamentally different catalytic reactions are combined in a one-flask protocol.[1] Ideally, one precatalyst is present at the outset of the process and each catalytic cycle is initiated by an external trigger such as addition of a reagent or switch in reaction conditions. A major challenge in this field is the precise separation of catalytic activities between the individual reaction steps and when a transition-metal catalyst is used, this is often achieved by in situ modification of the metal's ligand sphere,[2] or by temporal separation.[3] Herein, we describe the development of a tandem organocatalytic process which combines a thermal reaction with a photochemical one. Thus, separation of catalytic activities is achieved by exploiting a catalyst's orthogonal ground- and excited-state reactivities.

Quinones are among the most commonly used ground-state oxidants in synthesis[4] with the distinction that they also possess powerful and well-studied reactivity in the excited state.[5] This orthogonal reactivity renders them interesting candidate catalysts for the development of multistep sequential catalytic protocols. Our interest in quinone catalysis led to the development of such a sequence by combining two new catalytic reactions which we recently discovered. As depicted in Figure 1, an anthraquinone-catalyzed C3-alkylation of indoles **1** with benzylamines **2** was successfully sequenced with a visible-light-driven photooxidation/1,2-shift reaction to convert intermediate 3-benzylindoles **3** into new fluorescent 2,2-disubstituted indoline-3-one derivatives **4**. While the indole-C3-alkylation with amines constitutes the first organocatalytic variant of this type of reaction, the quinone-catalyzed photooxidation of substrates **3** was demonstrated to proceed with selectivity opposite to that found in the self-sensitized oxidation.

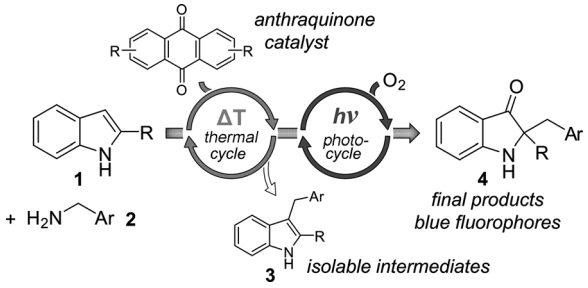
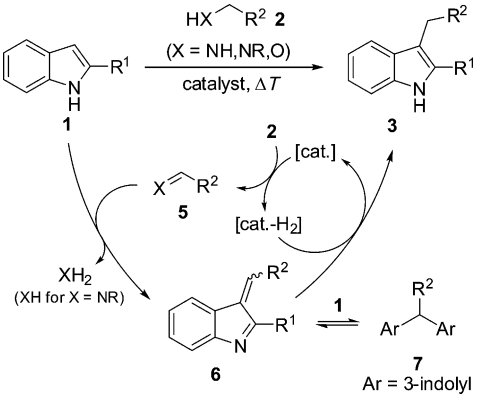


Figure 1. Tandem process for the synthesis of 2,2-disubstituted indoline-3-ones **4** by an anthraquinone-catalyzed indole-C3-alkylation/photooxidation/1,2-shift sequence.

Initially, we were interested in the C3-alkylation of indoles **1** with benzylamines **2** (Scheme 1), a reaction previously reported by Beller et al. using Shvo's ruthenium catalyst.[6a] The analogous process using benzyl and aliphatic alcohols has also been described employing catalytic Pt nanoclusters[6b] and stoichiometric hydroxide base.[6c] These high-temperature reactions (140–150 °C for 24 h) are initiated by dehydrogenation of the amine or alcohol to give an imine or aldehyde electrophile **5**, followed by nucleophilic addition–elimination of indoles **1** furnishing a putative 1-azadiene intermediate **6**. This is subsequently reduced to the saturated C3-alkylation product **3**, and the entire reaction can be regarded as



Scheme 1. Indole-C3-alkylation with amines or alcohols by catalytic H_2-transfer.

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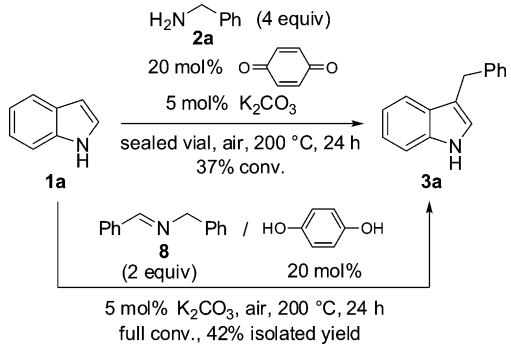
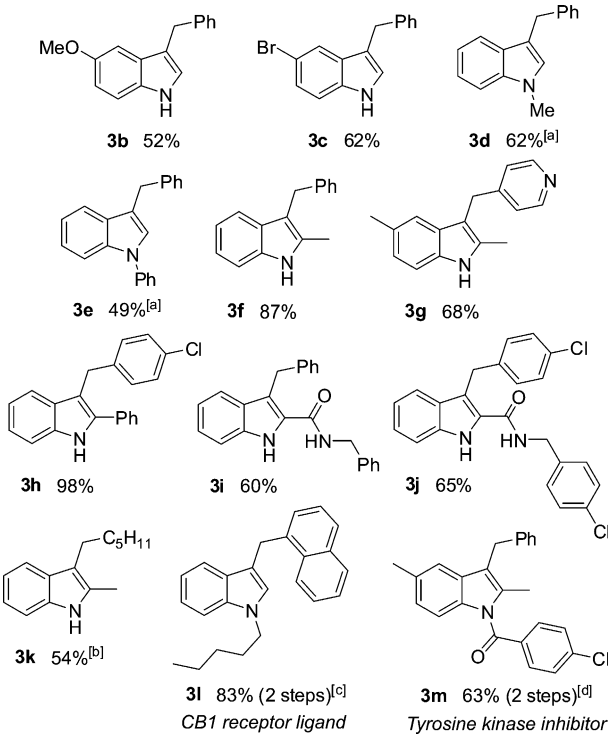
a catalytic hydrogen-transfer process. As quinone derivatives are known to catalyze the dehydrogenation of amines to imines both thermally[7] and photochemically,[8] we speculated they might also be suitable catalysts in the indole-C3-alkylation with benzylamines, provided the reduction of azadiene **6** by a second H_2-transfer step occurs. As shown in Scheme 2, we attempted the C3-alkylation of 1*H*-indole (**1a**)



Scheme 2. Benzoquinone-mediated C3-alkylation of indole (**1a**) with benzylamine (**2a**) and hydroquinone-mediated reaction of **1a** with imine **8**.

with benzylamine (**2a**) in the presence of K_2CO_3 using *p*-benzoquinone as the catalyst. The reaction furnished 3-benzylindole (**3a**) with 37% conversion using 20 mol% of benzoquinone and a fourfold excess of benzylamine **2a** under solvent-free conditions and when the mixture was heated to 200 °C for 24 h and under air (sealed vial). On the other hand, reacting indole **1a** with preformed imine **8** and replacing benzoquinone by hydroquinone led to full conversion and product **3a** was isolated in 42% yield. These results demonstrated that benzoquinone acted as a hydrogen shuttle in the overall process, which appears to proceed by a hydrogen-borrowing mechanism analogous to the known metal-based protocols.[6a,b,9]

Upon optimization,[10a] various benzo- and anthraquinone derivatives were found to catalyze the alkylation of indole **1a** with benzylamine (**2a**), of which 1,5-dichloroanthraquinone (DCAQ) offered the best results. When the reaction was conducted at the elevated temperature of 225 °C for 24 h, a reduced catalyst loading of 5 mol% was sufficient to achieve complete conversion and to afford product **3a** in 64% yield. A small library of 3-alkylated indole derivatives prepared by our method is depicted in Scheme 3. While 2-unsubstituted indoles were benzylated with moderate yields ranging from 50 to 60% (products **3b–e**), yields for 2-substituted derivatives were generally higher (products **3f–h**). When methyl 1*H*-indole-2-carboxylate was employed in the reaction, C3-benzylation was accompanied by formation of the C2-carboxyamide to provide products **3i** and **3j** with 60% and 65% overall yield, respectively. As expected, reactivity was lower for *N*-substituted indole substrates and also when benzylamines were replaced by aliphatic amines. In these cases, preparatively useful results were obtained with increased catalyst loading (20–30 mol% for products **3d**,**e**,**k**). The utility of the method was further demonstrated by the preparation of bioactive indoles **3l** and **3m**. Nanomolar



Scheme 3. DCAQ-catalyzed C3-alkylation of indoles **1** with amines **2**. Reaction conditions: 0.50 mmol indole **1**, 2.00 mmol amine **2**, 5 mol% DCAQ, 5 mol% K_2CO_3, sealed vial, air, 225 °C, 24 h. [a] 30 mol% DCAQ and no K_2CO_3 used. [b] 20 mol% DCAQ used. [c] *N*-alkylation: NaH, 1-bromopentane, DMF, RT. [d] *N*-benzoylation: NaH, 4-chlorobenzoyl chloride, DMF, 80 °C.

cannabinoid receptor ligand **3l**[11] was obtained in 83% yield after *N*-alkylation and low-micromolar tyrosine kinase inhibitor **3m**[12] was prepared by *N*-benzoylation in 63% over two steps. The only byproducts generally observed in these reactions were bisindolylmethanes **7** (Scheme 1). Kinetic analysis[10a] showed that their formation is initially fast, but since this side reaction is reversible **7** is subsequently converted into products **3**.

A distinct feature of the indole-C3-alkylation using DCAQ as the catalyst is the deep-red coloration of the resulting reaction mixtures. The benzylation of 2-phenylindole (**1b**) with benzylamine (**2a**) and catalytic DCAQ (10 mol%) was chosen as a model reaction for UV/Vis analysis (Figure 2). The absorption spectrum of the reaction mixture in acetic acid, after complete conversion of substrate **1b** (16 h), showed absorption bands characteristic for 3-benzyl-2-phenylindole (**3n**; $\lambda_{max} = 304$ nm) as well as a band in the visible region centered around 491 nm. This could be assigned to 1,5-bis(dibenzylamino)anthraquinone anil (**9a**) and was confirmed by comparison with a reference sample. Thus, DCAQ undergoes twofold chloride substitution by benzylamine **2a** during the process and anthraquinone anil **9a** appears as the key intermediate in the amine dehydrogenation step of the catalytic cycle, as well as the catalyst resting state after complete consumption of substrate **1b**. With this information at hand, we investigated possible photochemical reactions that could be performed sequentially with the indole-C3-alkylation. We found that irradiation of the crude

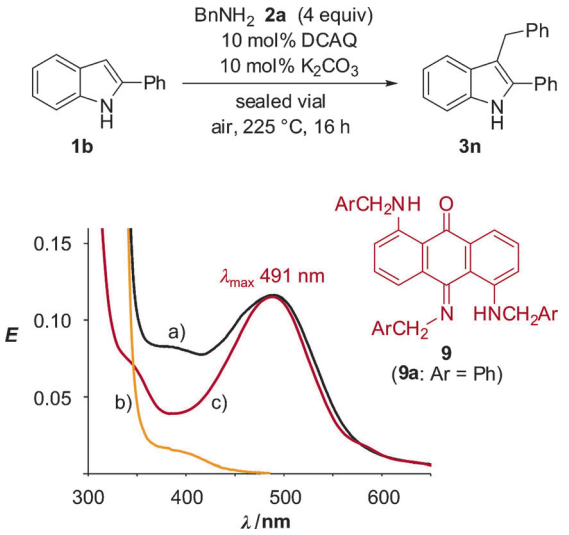
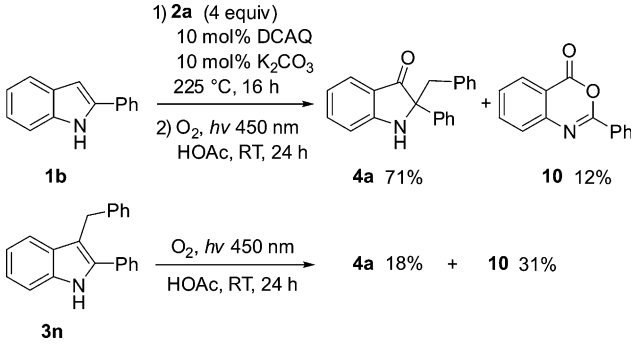


Figure 2. a) UV/Vis spectrum of the crude mixture obtained from the reaction of 2-phenylindole (**1b**) with benzylamine (**2a**) catalyzed by 10 mol% DCAQ; $c = 10^{-4}$ M in HOAc with respect to the indole component; b) absorption spectrum of 2-phenyl-3-benzylindole (**3n**; $c = 10^{-4}$ M in HOAc); c) absorption spectrum of anthraquinone anil **9a** ($c = 10^{-5}$ M, HOAc).

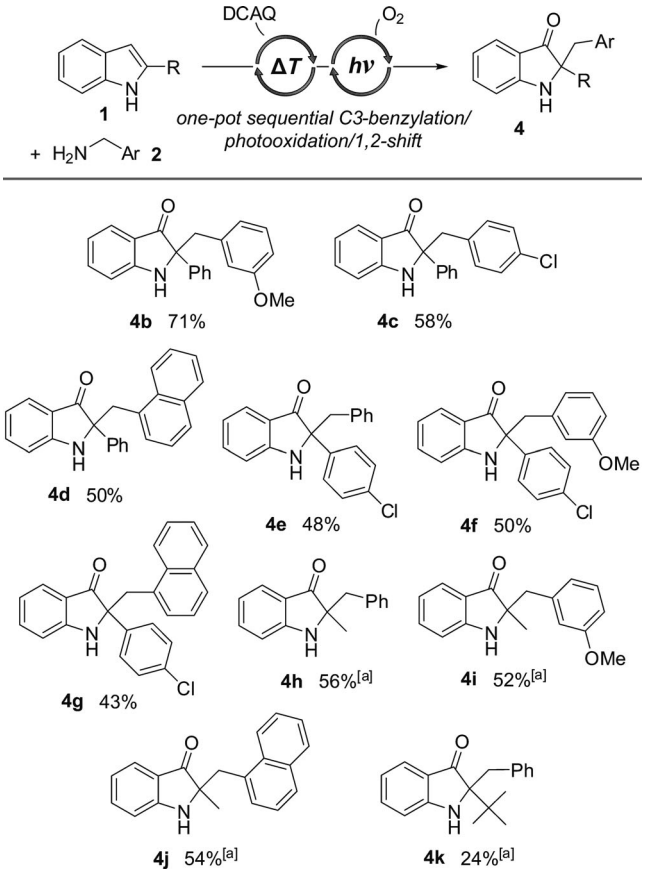
reaction mixture containing intermediate **3n** and quinone anil **9a** in acetic acid, under oxygen atmosphere and using blue fluorescent lamps, led to a photooxidation/1,2-shift reaction converting indole **3n** into 2-benzyl-2-phenylindoline-3-one (**4a**) with a high overall yield of 71% over two steps (Scheme 4). In this process, acetic acid traps excess benzylamine **2a** as its unreactive ammonium salt, and irradiation with blue light ensures selective excitation of the catalyst **9a**.[13]

A side product formed in this reaction is 2-phenylbenzoxazinone **10**, which was isolated with 12% yield. Its origin could be identified as a competing self-sensitized photooxidation:[14] Despite its very faint absorption in the visible region > 400 nm (Figure 2), when a sample of indole **3n** was reacted under similar photooxidation conditions but in the absence of quinone anil **9a**, oxazinone **10** was isolated as the major product along with a minor amount of indoline-3-one **4a**, both of which were obtained in low yields (Scheme 4).



Scheme 4. One-pot sequential conversion of 2-phenylindole (**1b**) into indoline-3-one **4a** and Type II photooxidation of 3-benzyl-2-phenylindole (**3n**).

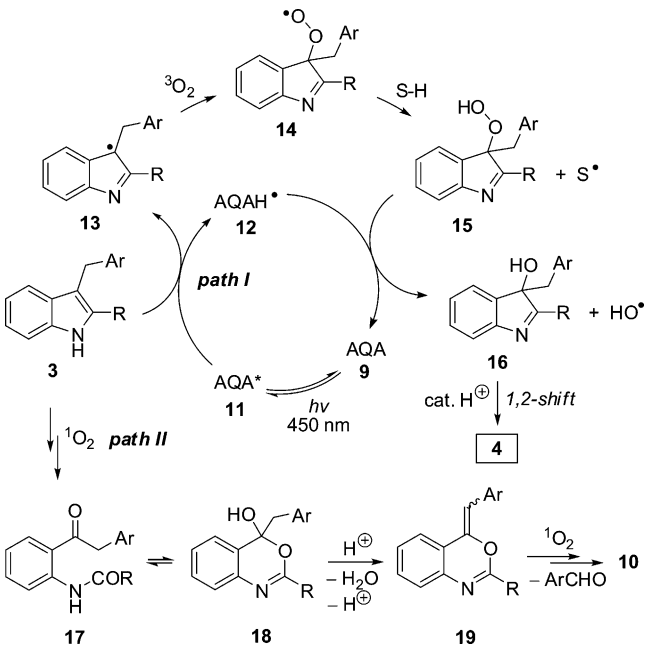
Thus, photooxidation **3n**→**4a** catalyzed by quinone anil **9a** overrides the inherent Type II reactivity of substrate **3n** offering a highly useful selectivity in favor of pseudo-indoxyl product **4a**. Using green LED light [$\lambda = (560 \pm 25)$ nm] instead of blue fluorescent lamps [$\lambda = (450 \pm 50)$ nm) leads to complete suppression of the formation of oxazinone **10** through the Type II path;[15] however, conversion **3n**→**4a** was much slower with the commercial LED assembly (5.4 W total) than with the blue fluorescent lamps (2 × 18 W) as the former have considerably lower power than the latter. Despite the many factors influencing the course of the tandem reaction, such as the type of the anthraquinone anil **9** formed by variation of the benzylamine, the 1,2-migration propensity of the C3-substituent in intermediates **3**, and the more or less stabilizing contribution by the C2-substituent, a number of indoline-3-one derivatives **4** could be synthesized in a sequential fashion with consistently good yields over two steps (Scheme 5). For 2-aryl-substituted 1*H*-indole derivatives, yields ranged from 43 to 71% (examples **4a–g**). Changing the C2-substituent to a methyl group slows down the photooxidation reaction. However, when irradiation was extended to a duration of 48 h, also these substrates provided appreciable yields of 52–56% of indoline-3-one products (**4h–j**). Even when 2-*tert*-butyl-1*H*-indole was employed in the sequence, product **4k** could be isolated in 24% yield.



Scheme 5. Tandem indole-C3-alkylation/photooxidation/1,2-shift reaction. Conditions: step 1: 0.25 mmol indole **3**, 4 equiv benzylamine **2**, 10 mol% DCAQ, 10 mol% K_2CO_3, sealed vial, air, 225 °C, 16 h; step 2: O_2, HOAc, *hv* 450 nm, RT, 24 h. [a] Irradiation for 48 h in step 2.

Novel pseudo-indoxyls **4a–k** all displayed blue fluorescence around 430 nm, a property of these materials which may find future applications.[10a,b]

A tentative mechanism for the photooxidation of substrates **3** is depicted in Scheme 6. The anthraquinone anil (AQA)-catalyzed reaction (path I) is initiated by H-abstraction from 1*H*-indole substrate **3** by the excited catalyst **11**.[16] The resulting benzylic radical **13** reacts with molecular oxygen to generate indole-3-peroxyradical **14**, which is converted into 3-hydroperoxyindolenine **15** by H-abstraction, possibly from acetic acid.[17] Reduction of **15** by the semiquinone radical **12** furnishes 3-hydroxyindolenine **16** by cleavage of the peroxide bond and regenerates catalyst **9**. Indolenine **16** subsequently undergoes acid-assisted 1,2-migration to product **4**.[18] In contrast to path I, path II involves reaction of substrate **3** with self-sensitized singlet oxygen generating keto amide **17** through dioxetane formation and scission of the C2–C3 bond.[19] Intramolecular cyclization to intermediate **18** followed by acid-catalyzed elimination[20] leads to 4-alkylidene oxazine **19** which is converted into benzoxazinone derivative **10** by [2+2] cycloaddition with singlet oxygen and subsequent dioxetane cleavage.[21]



Scheme 6. Proposed mechanism for the Type I and Type II photooxidation of substrates **3**.

In summary, two new anthraquinone-catalyzed reactions were combined in a tandem process leading to pseudo-indoxyls **4** by way of a photooxidation/1,2-shift reaction of the intermediate 3-benzylindoles **3**, which proceeds with selectivity that is opposite that of a competing Type II reaction.

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