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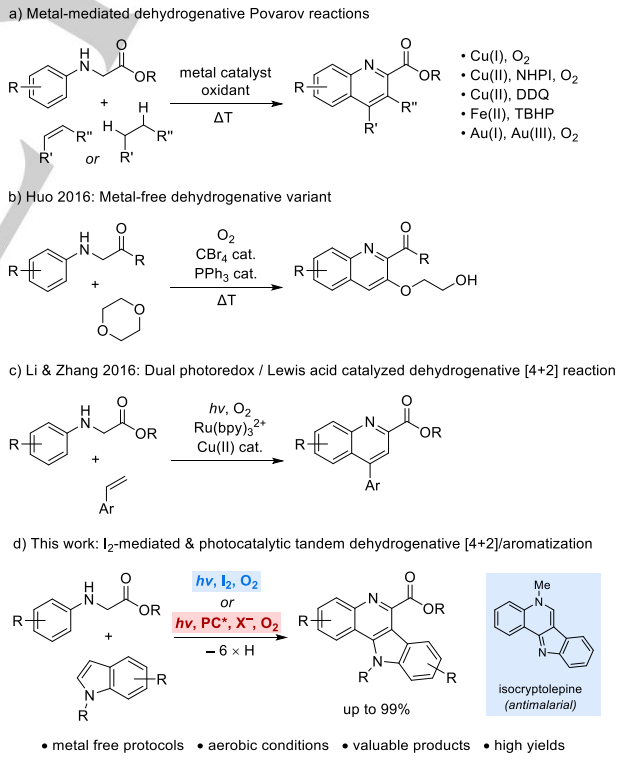
Visible light-mediated aerobic tandem dehydrogenative Povarov/aromatization reaction: synthesis of isocryptolepines

Eva Schendera,[a] Lisa-Natascha Unkel,[a] Phung Phan Huyen Quyen,[a] Gwen Salkewitz,[a] Frank Hoffmann,[b] Alexander Villinger[c] and Malte Brasholz*[a]

Abstract: A metal-free, photoinduced aerobic tandem amine dehydrogenation/Povarov cyclization/aromatization reaction between *N*-aryl glycine esters and indoles leads to tetracyclic 11*H*-indolo[3,2-*c*]quinolines under mild conditions and with high yield. The reaction can be performed using molecular iodine along with visible light, or combining an organic photoredox catalyst with halide anion. Mechanistic studies reveal that product formation occurs through a combination of radical-mediated oxidation steps with an iminium ion or *N*-haloiminium ion [4+2]-cycloaddition, and the *N*-heterocyclic products constitute new analogs of the antiplasmodial natural alkaloid isocryptolepine.

The Povarov reaction, i. e. the aza-Diels-Alder reaction of imines with electron rich alkenes, is a classical and versatile method for the synthesis of polysubstituted tetrahydroquinolines,[1] and the pivotal imine [4+2]-cycloaddition can be catalyzed by a range of Brønsted or Lewis acids[2]. In recent years, dehydrogenative Povarov reactions have been developed (Scheme 1a), where an amine-to-imine oxidation precedes the imine [4+2]-cycloaddition followed by aromatization to quinoline products. These protocols typically involve the use of metal catalysts like Cu(I) and Cu(II) salts as well as Fe(II) and Au(I) and Au(III) complexes along with DDQ, organic peroxides or O_2 as the stoichiometric oxidants.[3] A thermal double dehydrogenative variant of the Povarov reaction, including the parallel oxidation of an alkane as the precursor to the alkene 2π component, has also been introduced,[4] and Huo *et al.* remarkably could achieve such a process using the metal-free system of CBr_4 and PPh_3 (Scheme 1b).[5] In the arena of photochemistry, Li and Zhang developed a dual photoredox and Lewis acid-catalyzed dehydrogenative Povarov reaction between glycine esters and styrenes (Scheme 1c),[6] and later they also demonstrated the use of Eosin Y as an organic photocatalyst for the dehydrogenation of glycine esters in the Brønsted acid-mediated cycloaddition with dihydrofuran.[7] A single example of an aerobic photoinduced Cu(II)-mediated reaction has also been reported.[8]

We report here the tandem amine dehydrogenation/imine [4+2]-cycloaddition/aromatization of glycine esters with indoles. We developed two photoinduced aerobic and metal-free variants of this reaction, either using I_2 with blue light irradiation, or employing a system combing an organic photoredox catalyst with a source of halide anion X^- and visible light (Scheme 1d). 11*H*-indolo[3,2-c]quinoline products are obtained under mild conditions and with yields up to 99%. These tetracyclic compounds possess the core structure of the natural alkaloid isocryptolepine from the west-african flowering plant *Cryptolepis sanguinolenta*, which shows antimalarial activity against *plasmodium falciparum*.[9] Therefore, new derivatives of isocryptolepine have been of ongoing interest in medicinal chemistry research.[10]



Scheme 1. Methods for the tandem dehydrogenative Povarov/aromatization reaction

[a] Prof. Dr. Malte Brasholz
Institute of Chemistry – Organic Chemistry
University of Rostock
Albert-Einstein-Str. 3A, 18059 Rostock, Germany
E-mail: malte.brasholz@uni-rostock.de
Web: https://www.brasholz.chemie.uni-rostock.de
[b] Department of Chemistry – Institute of Inorganic Chemistry
University of Hamburg
Martin-Luther-King-Platz 6, 20146 Hamburg, Germany
[c] Institute of Chemistry – Inorganic Chemistry
University of Rostock
Albert-Einstein-Str. 3A, 18059 Rostock, Germany

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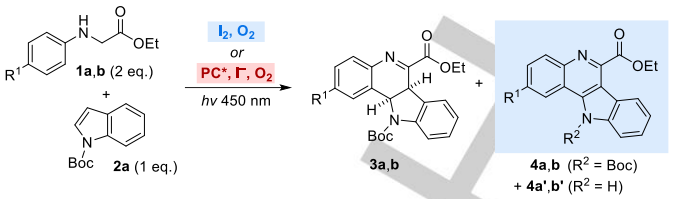
Initially, we observed that reacting *p*-anisidinyl glycine ester **1a** with *N*-Boc-indole (**2a**) in the presence of small amounts of molecular iodine and oxygen under blue light irradiation led to the aromatic *N*-Boc-protected 11*H*-indolo[3,2-*c*]quinoline-6-carboxylate **4a** in mixture with the Boc-deprotected derivative **4a'**, and the reaction was subsequently optimized as shown in Table 1, "method A" (see also Table S1, supporting information). Using 10 mol-% of I_2 in MeCN under air led to a combined yield of cycloadducts **4a**,**4a'** of 38% after 48 h (entry 1). When the same reaction was performed in the dark, the dihydro-11*H*-indolo[3,2-*c*]quinoline **3a** was formed in 12% yield along with 5% of product **4a**. The intermediacy of **3a** in the reaction was soon confirmed as its conversion to **4a**,**4a'** increased with prolonged reaction time. Increasing quantities of I_2 and oxygen both improved the yields of **4a** and **4a'** (entries 3-5), and using 50 mol-% of I_2 under O_2 atmosphere fully converted indole **2a** within 48 h, to give compound **4a** in a high yield of 70% after chromatography, along with 22% of its Boc-deprotected congener **4a'**. Br_2 could be used in place of I_2 (Table S1), however resulting in lesser conversion and a markedly decreased selectivity. Under the optimum conditions, no conversion occurred in the absence of I_2 and just 14% in the absence of O_2, while in the case of PMP-glycine ester **1a**, some product formation was also observed in the dark, which can be attributed to the particular ease of autoxidation of highly electron-rich substrate **1a**. By comparison, the analogous dark reaction of the much less activated *p*-tolyl glycine ester **1b** gave only trace amounts of the corresponding product **4b** (< 5%). (Table S1). Employing *N*-tosylindole (**2b**) in the reaction with **1a** under the optimum conditions, none of the corresponding indolo[3,2-*c*]quinolines could be detected. Using *N*-acetylindole (**2c**), its cycloadducts were formed in only 14% combined yield, while 1*H*-indole (**2d**) underwent decomposition to undefined products (entry 6).

Table 1. Reaction optimization.



#	R^1	conditions	conv. **2a** (%)[a]	**3** (%)[b]	**4** / **4'** (%)[b]
method A					
1	OMe	10 mol-% I_2, air, MeCN, 48 h	38	0	36 / 2
2	"	10 mol-% I_2, air, MeCN, 48 h, no light	22	12	5 / 0
3	"	20 mol-% I_2, air, MeCN, 48 h	38	8	21 / 8
4	"	50 mol-% I_2, air, MeCN, 48 h	82	8	56 / 26
5	"	50 mol-% I_2, O_2, MeCN, 48 h	100	0	74 / 26 (**70**[c] / **22**[c])
6	OMe	*N*-tosylindole (**2b**), *N*-acetylindole (**2c**), 1*H*-indole (**2d**)	n.d.	14% cycloadducts from **2c** only	
method B					
7	OMe	1 mol-% Acr^+-Mes•ClO_4, 10 mol-% TBAI, O_2, MeCN, 48 h	0	0	0 / 0
8	"	1 mol-% TPP•BF_4, 10 mol-% TBAI, O_2, MeCN, 48 h	0	0	0 / 0
9	"	1 mol-% TPP•BF_4, 10 mol-% TBAI, O_2, HFIP/DCE, 48 h	48	0	0 / 48
10	"	2 mol-% TPP•BF_4, 10 mol-% TBAI, O_2, HFIP/DCE, 48 h	68	12	22 / 30
11	"	1 mol-% TPP•BF_4, 10 mol-% TBAI, O_2, HFIP/DCE, 72 h	74	12	10 / 52 (55[c,d])
12	Me	1 mol-% TPP•BF_4, 10 mol-% TBAI, O_2, HFIP/DCE, 72 h	80	3	20 / 56 (**75**[c,d])

Reactions performed on 0.10 mmol scale of **2a**, irradiation with 36 W blue CFL, 450 ± 50 nm. [a] Conversion determined by ^{1}H-NMR analysis. [b] Yield determined by ^{1}H-NMR against CH_2Br_2 as internal standard. [c] Isolated yield after chromatography. [d] Reaction mixture treated with TFA before isolation. TPP•BF_4 = triphenylpyrylium tetrafluoroborate.

We subsequently aimed at developing an alternative photoorganocatalytic variant of the reaction (Table 1, "method B"), which potentially would allow replacement of I_2 by iodide anion. While Fukuzumi's catalyst[11] along with a catalytic quantity of tetrabutylammonium iodide (TBAI) under O_2 in MeCN slowly converted glycine ester **1a** to the corresponding imine (56% conversion after 48 h) no cycloaddition products were detected (entry 7). The same reaction with the triphenylpyrylium (TPP^+) cation as organic photocatalyst gave a similar result, however with quantitative conversion of **1a** to the imine. Using 1 mol-% of TPP•BF_4 and 10 mol-% of TBAI in the protic solvent mixture of hexafluoroisopropanol (HFIP) and dichloroethane (DCE), conditions similar to those previously used by Muñiz *et al.* for photocatalytic Hofmann-Löffler type reactions,[12] glycine ester **1a** and *N*-Boc-indole (**2a**) were converted into the Boc-deprotected aromatic cycloadduct **4a'** with 48% yield after 48 h (entry 9). After further experimentation (entries 10-11 and Table S1), the best conditions were using 1 mol-% of TPP•BF_4 with irradiation for 72 h, to give **4a'** as the major product with 52% yield, accompanied by 10% of *N*-Boc-protected compound **4a**. To generate a single product, the reaction mixture was subsequently treated with TFA, to furnish compound **4a'** in an isolated yield of 55% after chromatography. Using glycine ester **1a**, a maximum conversion of indole **2a** of 74% could be obtained under these conditions, however, in case of *p*-tolyl-substituted **1b**, we could demonstrate that despite incomplete conversion of **2a** of 80% (entry 12), an isolated yield as high as 75% for compound **4b'** could be achieved. Further, we found that tetrabutylammonium bromide (TBABr) could be used in place of TBAI (Table S1).

The scope of the visible light-mediated tandem dehydrogenative Povarov/aromatization reaction is depicted in Scheme 2. Using method A, various donor-substituted *N*-aryl glycine esters **1a**-**1f** were employed in the reaction giving rise to clean and quantitative conversion of *N*-Boc-indole (**2a**) in all cases, and indolo[3,2-*c*]quinoline products **4a**-**4f** were isolated in high yields of 59-85%,

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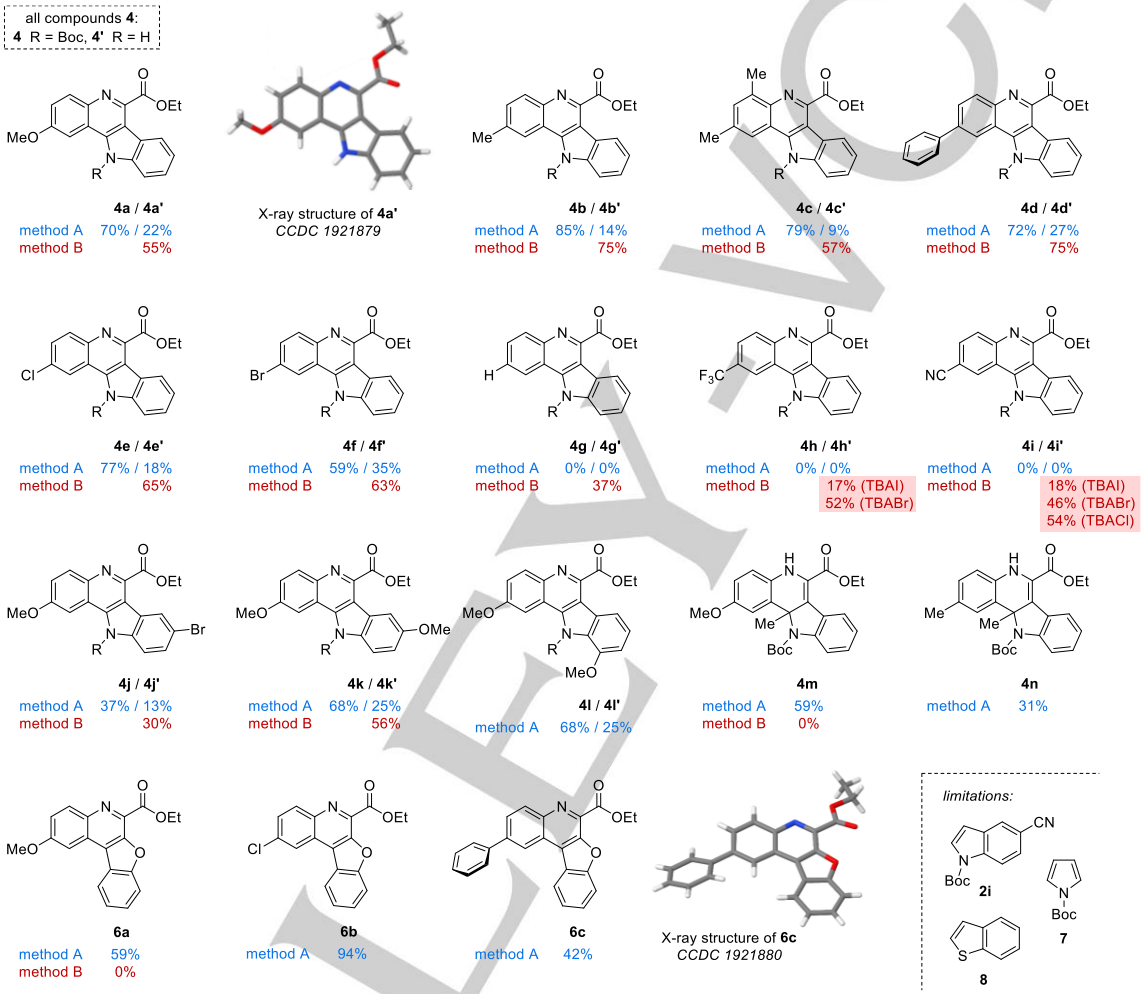
along with minor quantities of their *N*-deprotected analogs **4a'**-**4f'** (9-35%), which were readily separated by column chromatography.[13] Using method B, compounds **4a'**-**4f'** could be obtained in 55-75% yield after treatment of the crude product mixtures with TFA. Notably, the *N*-phenyl glycine ester **1g** did not provide products the **4g**,**4g'** under the conditions of method A (aromatic iodination of the aniline ring occurred), but using method B, derivative **4g'** could be prepared in 37% yield. Further, acceptor-substituted glycine esters like the 4-trifluoromethyl-phenyl and 4-cyanophenyl derivatives **1h** and **1i** did not react when employed under conditions A. However, using the photocatalyst TPP•BF_4 with halide anion, this limitation could be overcome. Thus, product **4h'** was formed in 17% with TPP^+/TBAI, and with a significantly improved yield of 57% with TBABr in place of TBAI. In case of 4-cyanophenyl glycine ester **1i**, the best result was achieved using the photocatalyst along with TBACl, to furnish product **4i'** in 54% yield.



Scheme 2. Reaction scope. Yields after chromatography. Method A: 50 mol-% I_2, O_2, *hv* 450 nm, MeCN, r.t., 48 h. Method B: 1 mol-% TPP•BF_4, 10 mol-% TBAI, O_2, *hv* 450 nm, HFIP/DCE, r.t., 72 h, then TFA, 50 °C, 6 h.

In addition to *N*-Boc-indole (**2a**), *N*-Boc-5-bromoindole (**2e**) as well as the 5- and 7-methoxylated *N*-Boc-indoles **2f** and **2g** could be used, giving rise to polysubstituted indoloquinolines **4j**,**4j'**-**4l**,**l'**. Further, 2-methyl-*N*-Boc-indole (**2h**) could successfully be employed, leading to the cycloadducts **4m**-**4n** with 59% and 31% yields, but using I_2 only. Finally, benzofuran (**5**) was identified as another viable 2π component, to generate the benzofuro[2,3-*c*]quinoline-6-carboxylates **6a**-**6c** in yields of 42-94%, and the observed reversal of regioselectivity in these cycloaddition reactions was unambiguously confirmed by the single crystal X-ray structure of compound **6c**.[13] Again, products **6a**-**6c** were accessible only under the conditions of method A. We have further attempted to use *N*-Boc-pyrrole (**7**) and benzothiophene (**8**) in the reaction, however, no cycloaddition occurred and both substrates were mostly recovered. The reaction between glycine ester **1a** and 5-cyano-*N*-Boc-indole (**2i**) was also not feasible.

With regard to the reaction mechanism, we conducted the control experiments summarized in Scheme 3. The reaction to products **4a**,**4a'** starting from glycine ester **1a** and *N*-Boc-indole (**2a**) could also be promoted by *N*-iodosuccinimide (NIS) with blue light irradiation, while almost no conversion occurred in the dark, which proved the contribution of radical intermediates (Scheme 3a). Additionally, the standard reaction between **1a** and **2a** using I_2 was largely quenched in the presence of an equimolar amount of

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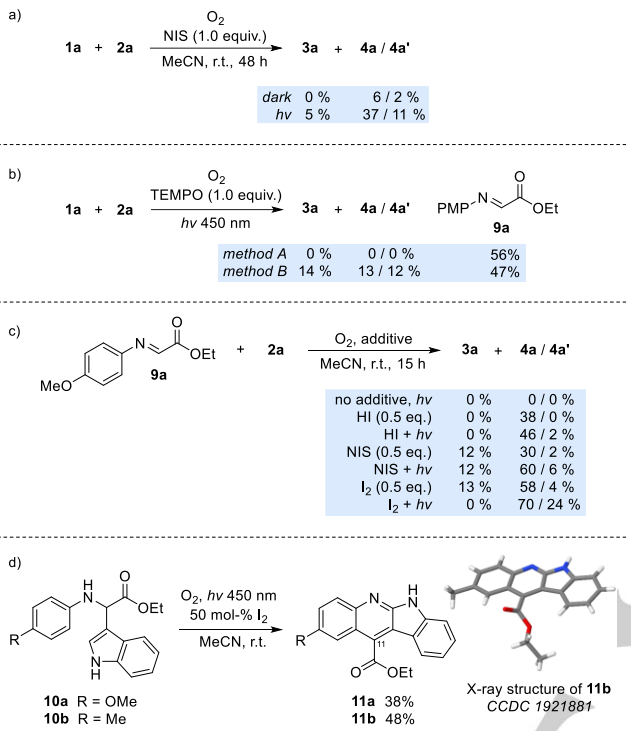
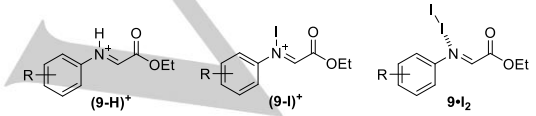
TEMPO (Scheme 3b). While no cycloaddition occurred, 56% of the imine **9a** were formed, indicating its role as a key intermediate. The same experiment under the conditions of method B also showed radical quenching, even though to slightly lesser extent (compare Table 1, entry 11).

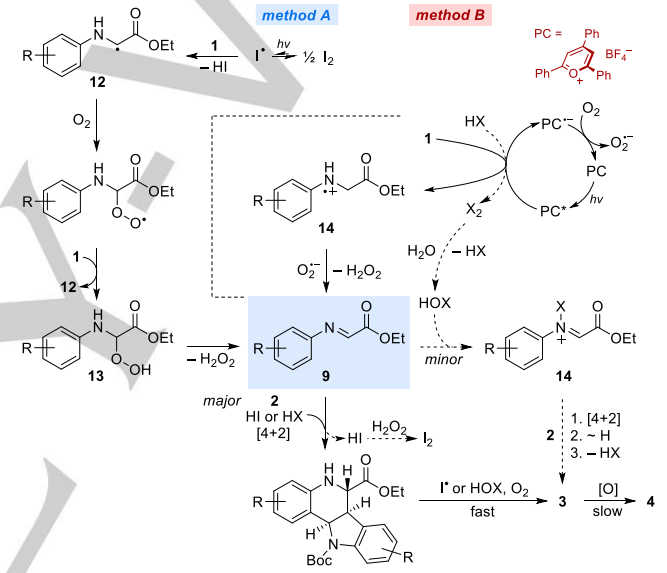


Scheme 3. Mechanistic control experiments.

Imine **9a**, derived from glycine ester **1a** by dehydrogenation, was generally present in all crude reaction mixtures as evident from NMR analysis. When glycine ester **1a** was reacted alone, imine **9a** was generated exclusively, both under the conditions of methods A and B. As shown in Scheme 3c (and Table S2), we reacted imine **9a** with indole **2a** under various conditions. While irradiation of imine **9a** in MeCN under O_2 with indole **2a** alone gave no conversion, its reactions under both conditions of methods A and B delivered the products **3a**, **4a** and **4a'**. In order to establish which species actually activates imine **9a** in the [4+2]-cycloaddition, we added hydroiodic acid (HI), *N*-iodosuccinimide (NIS) as well as I_2, to find that formation of products **3a** and **4a**,**4a'** occurred in all cases, even in the dark. These results showed that the imine could be activated *via* a number of alternative pathways, including protonation by HI to the iminium ion **(9-H)$^+$** as well as *N*-iodination with NIS or I_2 to give the *N*-iodoiminium ion **(9-I)$^+$**, and possibly also by halogen bonding-activation of **9** in a complex **9•I_2** under these model conditions.[14]



However, when using HI, NIS and I_2 under irradiation, a further significant increase in conversion was observed, which proved an additional strong contribution of light-induced radical pathways in the subsequent oxidation steps to the final products **4a**,**4a'**. Finally, in order to rule out a conceivable reaction pathway consisting of a tandem cross-dehydrogenative coupling (CDC) between glycine ester **1a** and indole, followed by 6π-electron cyclization and aromatization, we subjected the independently prepared CDC products **10a** and **10b** to the typical conditions of method A (Scheme 3d). These reactions however generated none of products **3** and **4**,**4'**, but the deeply rearranged[15] 6*H*-indolo[2,3-b]quinoline-11-carboxylates **11a** and **11b** were formed as the only products and isolated in moderate yields of 38% and 48%, respectively, their constitution being confirmed by single crystal X-ray analysis of product **11b**.[13]



Scheme 4. Proposed mechanism.

Based on our observations we propose the mechanism depicted in Scheme 4. Under the conditions of method A, photolysis of I_2 generates the iodine radical I• which abstracts a hydrogen atom from glycine ester **1**, to give HI and the α-amino radical **12**, which is trapped by O_2. The resulting peroxyl radical can react with another molecule of glycine ester **1** in a chain propagation step.[5a] Elimination of H_2O_2 from hydroperoxide **13** gives the imine **9**, which undergoes a Brønsted-acid-mediated [4+2]-cyclization with HI followed by 1,4-hydrogen shift, and a fast oxidation mediated by I• and O_2 leads to the dihydroquinoline **3**. The regeneration of the I_2 catalyst can occur through the reaction between HI and H_2O_2.[16] Conversely, using TPP^+ and X^- (method B), photoelectron transfer (PET) between the excited state catalyst (E^*_{red} = +2.55 V vs.SCE)[17] and glycine esters **1** (E_{ox} ranging from +0.82 to +1.59 V vs. SCE)[18] generates the radical cation **14** which can react with superoxide to give imine **9**. In the protic medium, the major product-forming pathway similarly is the acid-mediated [4+2]-cycloaddition and oxidation to **3**, however, control experiments showed that the presence of the halide ion X^- contributes to 30-

35% of total conversion to products **3** and **4** (Table S1), indicating the existence of a second minor reaction pathway. We propose that PET between PC* and HX generates X_2,[19,20] which in the presence of trace amounts of H_2O gives hypohalite,[12] to convert imine **9** into the *N*-haloiminiumion **14**. The subsequent [4+2]-cyclization followed by elimination of HX leads to intermediate **3**. The final comparatively slow oxidation of **3** gives the aromatic product **4**, which undergoes *N*-Boc-deprotection by HX, the rate of which depends on the actual acid concentration under the reaction conditions A or B. Generally, the protic medium of method B also facilitates an autoxidative product formation in case of highly electron rich glycine esters like **1a** or **1b**; this is however much less pronounced for less activated and acceptor-substituted systems. In the presence of TPP^+, all incident light is absorbed by the photocatalyst.

The orientation of the C3-nucleophilic indole **2** and imine **9** in the [4+2]-cycloaddition is polarity-matched, yet it also avoids a steric clash between the *N*-Boc-group of the indole and the carboethoxy function of the imine (such steric hindrance does not occur in cycloadditions with benzofuran (**5**) which reacts through a regioisomeric orientation, which is also in agreement with its higher charge density at C2).[21] The failure of benzofuran (**5**) to undergo the imine [4+2]-cycloaddition under conditions B likely results from a competing photoelectron transfer to the excited photocatalyst (E_{ox} of **5** = +1.20 V vs. SCE)[22] impeding further conversion, and which evidently does not occur with *N*-Boc-indole (**2a**).

In summary, we developed two metal-free protocols for the photoinduced aerobic tandem amine dehydrogenation/Povarov cyclization/aromatization reaction between *N*-aryl glycine esters and indoles as well as benzofuran, to furnish the corresponding aromatic [4+2]-cycloadducts with high selectivity and yield. The indolo[3,2-*c*]quinoline products resemble new analogs of the antimalarial natural alkaloid isocryptolepine, and thus they may be of value in medicinal research.

Experimental section

Typical procedures: synthesis of compounds **4b**,**4b'**

Method A: In a 10 mL crimp cap vial, 40.2 mg (208 µmol) of *N*-aryl glycine ester **1b** and 22.6 mg (104 µmol) *N*-Boc-Indole (**2a**) were dissolved in MeCN (3.50 mL). I_2 (13.2 mg, 52.0 µmol) was added, the vial was sealed and fitted with an O_2-balloon (septum pierced by needle). The mixture was irradiated between two blue CFL lamps (2×18 W, 450±50 nm) with rapid stirring for 48 h. The mixture was poured into $NaHCO_3$ aq. and $Na_2S_2O_3$ aq. followed by extraction with EtOAc (3×). The combined organic layers were dried with Na_2SO_4, filtered and evaporated to dryness. Column chromatography (silica, Et_2O/heptane 1:1) furnished compound **4b** (35.8 mg, 85%) and **4b'** (4.4 mg, 14%).

Method B: In a 10 mL crimp cap vial, 44.1 mg (228 µmol) of *N*-aryl glycine ester **1b**, 24.8 mg (114 µmol) *N*-Boc-Indole (**2a**), 4.2 mg (11.0 µmol) TBAI and 0.5 mg (1.0 µmol) TPP•BF_4 were dissolved in DCE (1.90 mL) and HFIP (1.90 mL). The vial was sealed and fitted with an O_2-balloon (septum pierced by needle). The mixture was irradiated between two blue CFL lamps (2×18 W, 450±50 nm) with rapid stirring for 72 h. TFA (169 µL, 2.21 mmol) was added and the mixture was stirred at 50 °C for 6 h. The mixture was poured into $NaHCO_3$ aq. and $Na_2S_2O_3$ aq. followed by extraction with EtOAc (3×). The combined organic layers were dried with Na_2SO_4, filtered and evaporated to dryness. Column chromatography (silica, Et_2O/heptane 1:1) furnished **4b'** (26.0 mg, 75%).

4b: Colorless solid, m.p. 103 °C, R_f 0.57 (Et_2O/heptane 1:1). ^{1}H-NMR (600 MHz, $CDCl_3$) δ = = 1.56 (t, ^3J = 7.2 Hz, 3 H, CH_3), 1.72 (s, 9 H, ^{t}Bu), 2.62 (s, 3 H, Ar-CH_3), 4.70 (q, ^3J = 7.2 Hz, 2 H, CH_2), 7.45 (ddd, ^4J = 1.1 Hz, ^3J = 7.2, 8.2 Hz, 1 H, 8-H), 7.54-7.60 (m, 2 H, 3-H, 9-H), 8.07 (s, 1 H, 1-H), 8.21 (dt, ^4J = 0.9 Hz, ^3J = 8.4 Hz, 1 H, 10-H), 8.23 (d, ^3J = 8.6 Hz, 1 H, 4-H), 8.44 (dt, ^4J = 1.0 Hz, ^3J = 7.9 Hz, 1 H, 7-H) ppm. ^{13}C-NMR (150 MHz, $CDCl_3$) δ = 14.5 (q, CH_3), 22.4 (q, Ar-CH_3), 28.1 (q, ^{t}Bu), 62.6 (t, CH_2), 85.8 (s, ^{t}Bu), 114.4 (d, C-10), 117.1 (s, C-6a), 119.1 (s, C-4a), 123.0 (s, C-6b), 123.4 (d, C-7), 123.8 (d, C-1), 124.0 (d, C-8), 127.7 (d, C-9), 130.8 (d, C-4), 131.2 (d, C-3), 136.9 (s, C-2), 140.3 (s, C-10a), 141.1 (s, C-11a), 144.2 (s, C-6), 144.9 (s, C-11b), 150.9 (s, NCO), 167.1 (s, CO_2R) ppm. IR: $\tilde{\nu}$ = 2980, 2935 (=C-H, -C-H), 1740 (CO), 1250 (C=C), 1150, 1095, 750 cm^{-1}. HRMS (ESI+): *m/z* calc.: $C_{24}H_{24}N_2O_4$ $[M+H]^+$: 405.1809, found: 405.1825.

4b': Colorless solid, m.p. 276 °C (dec.), R_f 0.57 (Et_2O/heptane 3:1). ^{1}H-NMR (600 MHz, acetone-d_6) δ = 1.50 (t, ^3J = 7.2 Hz, 3 H, CH_3), 2.62 (s, 3 H, Ar-CH_3), 4.62 (d, ^3J = 7.1 Hz, 2 H, CH_2), 7.35 (ddd, ^4J = 1.1 Hz, ^3J = 7.1, 8.2 Hz, 1 H, 8-H), 7.52 (ddd, ^4J = 1.2 Hz, ^3J = 7.1, 8.2 Hz, 1 H, 9-H), 7.65 (dd, ^4J = 1.9 Hz, ^3J = 8.5 Hz, 1 H, 3-H), 7.73 (dt, ^4J = 1.0 Hz, ^3J = 8.2 Hz, 1 H, 10-H), 8.12 (d, ^3J = 8.5 Hz, 1 H, 4-H), 8.30-8.34 (m, 1 H, 1-H), 8.53 (dd, ^4J = 1.0 Hz, ^3J = 8.2 Hz, 1 H, 7-H), 11.9 (s, 1 H, NH) ppm. ^{13}C-NMR (150 MHz, acetone-d_6) δ = 14.7 (q, CH_3), 21.9 (q, Ar-CH_3), 62.2 (t, CH_2), 112.5 (d, C-10), 113.4 (s, C-6a), 118.4 (s, C-4a), 121.5 (d, C-1), 121.7 (d, C-8), 122.3 (s, C-10a), 124.2 (d, C-7), 126.9 (d, C-9), 131.0 (d, C-4), 131.6 (d, C-3), 138.2 (s, C-2), 140.5 (s, C-6b), 142.2 (s, C-11a), 143.8 (s, C-11b), 145.6 (s, C-6), 168.1 (s, CO_2R) ppm. IR: $\tilde{\nu}$ = 2972 (=C-H, -C-H), 1720 (C=O), 1588 (C=N, C-N, NH), 1299, 1239, 1175, 816, 739 (C-H) cm^{-1}. HRMS (ESI+): *m/z* calc.: $C_{19}H_{16}N_2O_2$ $[M+H]^+$: 305.1290, found: 305.1292.

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Keywords: Aerobic oxidation • Dehydrogenation • Cycloaddition • Photochemistry • Heterocycles

[1] Reviews: a) J. S. Bello Forero, J. Jones Jr., F. M. da Silva, *Curr. Org. Synth.* **2016**, *13*, 157-179. b) V. V. Kouznetsov, *Tetrahedron* **2009**, *65*, 2721-2750. c) V. A. Glushkov, A. G. Tolstikov, *Russian Chem. Rev.* **2008**,

77, 137-159. For a general studies of the reaction mechanism, see: d) L. R. Domingo, M. J. Aurell, J. A. Sáez, S. M. Mekelleche, *RSC Adv.* **2014**, *4* ,25268-25278. e) S. Hermitage, J. A. K. Howard, D. Jay, R. G. Pritchard, M. R. Probert, A. Whiting, *Org. Biomol. Chem.* **2004**, *2*, 2451-2460.

[2] a) G. Bianchini, P. Ribelles, D. Becerra, M. T. Ramos, J. C. Menéndez, *Org. Chem. Front.* **2016**, *3*, 412-422. b) J. McNulty, R. Vemula, C. Bordón, R. Yolken, L. Jones-Brando, *Org. Biomol. Chem.* **2014**, *12*, 255-260. c) H. Huang, H. Jiang, K. Chen, H. Liu, *J. Org. Chem.* **2009**, *74*, 5476-5480. d) M. J. Alves, N. G. Azoia, A. G. Fortes, *Tetrahedron* **2007**, *63*, 727-734. e) D. Osborne, P. J. Stevenson, *Tetrahedron Lett.* **2002**, *43*, 5469-5470. f) E. Borrione, M. Prato, G. Scorrano, M. Stivanello, V. Lucchini, *J. Heterocyclic Chem.* **1988**, *25*, 1831-1835.

[3] a) M. Ni, Y. Zhang, T. Gong, B. Feng, *Adv. Synth. Catal.* **2017**, *359*, 824-831. b) Z. Xie, J. Jia, X. Liu, L. Liu, *Adv. Synth. Catal.* **2016**, 358, 919-925.

[4] a) W. Jiang, S. Wan, Y. Su, C. Huo, *J. Org. Chem.* **2019**, *84*, 8232-8241. b) W. Jiang, Y. Wang, P. Niu, Z. Quan, Y. Su, C. Huo, *Org. Lett.* **2018**, *20*, 4649-4653. b) C. Huo, F. Chen, Y. Yuan, H. Xie, Y. Wang, *Org. Lett.* **2015**, *17*, 5028-5031.

[5] a) C. Huo, H. Xie, F. Chen, J.Tang, Y. Wang, *Adv. Synth. Catal.* **2016**, *358*, 724-730. b) C. Huo, H. Xie, M. Wu, X. Jia, X. Wang, F. Chen, J. Tang, *Chem. Eur. J.* **2015**, *21*, 5723-5726.

[6] X. Yang, L. Li, Y. Zhang, *J. Org. Chem.* **2016**, *81*, 12433-12442.

[7] Y. He, B. Yan, H. Tao, Y. Zhang, Y. Li, *Org. Biomol. Chem.* **2018**, *16*, 3816-3823.

[8] L. Wu, Q. Meng, T. Lei, X. Gao, J. Zhong, M. Xiang, B. Chen, Z. Tong, Faming Zhuanli Shenqing, CN 103910723 A Jul 09, **2014**.

[9] a) P. T. Parvatkar, S. G. Tilve in *Bioactive heterocycles*, K. L. Ameta, R. P. Pawar, A. J. Domb, Eds.; pp. 217-234, *Nova Science Publishers* **2013**. b) P. T. Parvatkar, P. Parameswaran, S. G. Tilve, *Curr. Org. Chem*. **2011**, *15*, 1036-1057. c) S. van Miert, S. Hostyn, B. U. W. Maes, K. Cimanga, R. Brun, M. Kaiser, P. Mátyus, R. Dommisse, G. Lemière, A. Vlietinck, L. Pieters, *J. Nat. Prod.* **2005**, *68*, 674-677.

[10] a) P. Aroonkit, C. Thongsornkleeb, J. Tummatorn, K. Jumreang, M. Suppachai, M. Mungthin, S. Ruchiwarat, *Eur. J. Med. Chem.* **2015**, *94*, 56-62. b) N. Wang, K. J. Wicht, K. Imai, M.-Q. Wang, T. Anh Ngoc, R. Kiguchi, M. Kaiser, T. J. Egan, T. Inokuchi, *Bioorg. Med. Chem.* **2014**, *22*, 2629-2642. c) L. R. Whittell, K. T. Batty, R. P. M. Wong, E. M. Bolitho, S. A. Fox, T. M. E. Davies, P. E. Murray, *Bioorg. Med. Chem.* **2011**, *19*, 7519-7525. d) J. Lavrado, R. Moreira, A. Paolo, *Curr. Med. Chem.* **2010**, *17*, 2348-2370.

[11] S. Fukuzumi, K. Ohkubo, *Org. Biomol. Chem.* **2014**, *12*, 6059-6071.

[12] P. Becker, T. Duhamel, C. J. Stein, M. Reiher, K. Muñiz, *Angew. Chem. Int. Ed.* **2017**, *56*, 8004-8008.

[13] CCDC 1921879 contains the supplementary crystallographic data for compound **4a'**. CCDC 1921880 contains the supplementary crystallographic data for compound **6c**. CCDC 1921881 contains the supplementary crystallographic data for compound **11b**. These data can be obtained from The Cambridge Crystallographic Data Centre.

[14] a) Review: D. Bulfield, S. M. Huber, *Chem. Eur. J.* **2016**, *22*, 14434-14450; b) For an account on halogen-bonding activation by I_2, see: M. Breugst, E. Detmar, D. von der Heiden, *ACS Catal.* **2016**, *6*, 3203-3212. c) For halogen-bonding activation of imines, see: M. Kaasik, A. Metsala, S. Kaabel, K. Kriis, I. Järving, T. Kanger, *J. Org. Chem.* **2019**, *84*, 4294-4303. d) X.-S. Wang, M.-Y. Yin, W. Wang, S.-J. Tu, *Eur. J. Org. Chem.* **2012**, 4811-4818.

[15] The mechanism of this reaction is currently under investigation.

[16] G. Schmitz, *Phys. Chem. Chem. Phys.* **2001**, *3*, 4741-4746.

[17] R. Akaba, H. Sakuragi, K. Tokumaru, *J. Chem. Soc., Perkin Trans. 2* **1991**, *3*, 291-297.

[18] J. Kabatc, Z. Kucybała, M. Pietrzak, F. Ścigalski, J. Pączkowski, *Polymer* **1999**, *40*, 735-745.

[19] For recent examples of generation of halogen radicals from halide anions by photoredox catalysis, see: a) H.-P. Deng, Q. Zhuo, J. Wu, *Angew. Chem. Int. Ed.* **2018**, *57*, 12661-12665. b) S. Rohe, A. O. Morris, T. McCallum, L. Barriault, *Angew. Chem. Int. Ed.* **2018**, *57*, 15664-15669.

[20] The excited-state reduction potential of TPP^+ is sufficient for the one-electron oxidation of chloride to $Cl^{\bullet}$ (E_{ox} of Cl^- = +2.19 V vs. SCE), see: D. A. Armstrong, R. E. Huie, S. Lymar, W. H. Koppenol, G. Merényi, P. Neta, D. M. Stanbury, S. Steenken, P. Wardman, *BioInorg. React. Mech.* **2013**, *9*, 59-61.

[21] a) H. N. C. Wong, K.-S. Yeung, Z. Yang in *Comprehensive Heterocyclic Chemistry III*; A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. Taylor, Eds.; Vol. 3, pp. 407-496; *Elsevier* **2008**. b) G. F. Krainova, Y. O. Chudinova, A. A. Gorbunov, O. A. Mayorova, V. A. Glushkov, *Mendeleev Commun.* **2012**, *22*, 201-202.

[22] J. Xu, G. Nie, S. Zhang, X. Han, S. Pu, L. Shen, Q. Xiao, *European Polymer Journal* **2005**, *41*, 1654-1661.

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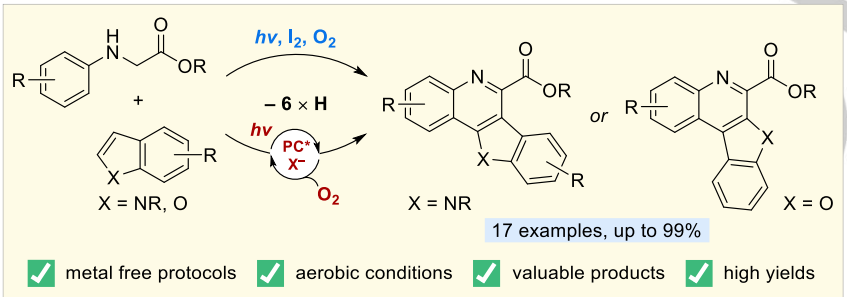

*Eva Schendera, Lisa-Natascha Unkel, Phung Phan Huyen Quyen, Gwen Salkewitz, Frank Hoffmann, Alexander Villinger, Malte Brasholz**

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Visible light-mediated aerobic tandem dehydrogenative Povarov/aromatization reaction: synthesis of isocryptolepines

All metal-free: A photoinduced tandem amine dehydrogenation/Povarov cyclization/aromatization reaction leads to isocryptolepine analogs with high yield, using molecular iodine under visible light, or combining an organic photoredox catalyst with halide anion.