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Heterocycles

Visible-Light-Mediated Aerobic Tandem Dehydrogenative Povarov/Aromatization Reaction: Synthesis of Isocryptolepines

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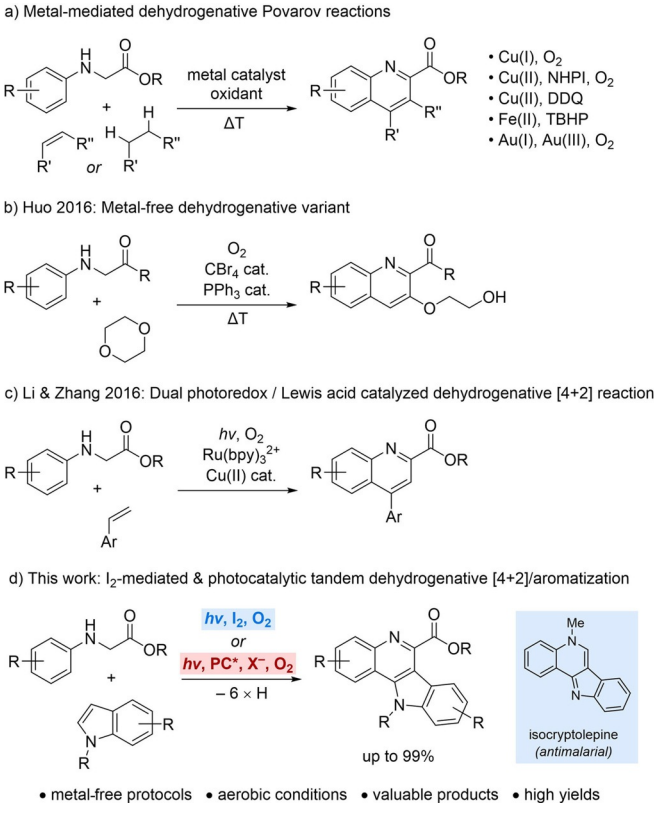
Abstract: A metal-free, photoinduced aerobic tandem amine dehydrogenation/Povarov cyclization/aromatization reaction between *N*-aryl glycine esters and indoles leads to tetracyclic 11*H*-indolo[3,2-*c*]quinolines under mild conditions and with high yields. The reaction can be performed by using molecular iodine along with visible light, or by combining an organic photoredox catalyst with a 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 analogues of the antiplasmodial natural alkaloid isocryptolepine.

Introduction

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 1 a), in which 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 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (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 1 b).[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 1 c),[6] and later they also demonstrated the use



Scheme 1. Methods for the tandem dehydrogenative Povarov/aromatization reaction.[5,6] NHPI = *N*-hydroxyphthalimid, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TBHP = *tert*-butyl hydroperoxide, PC = photocatalyst.

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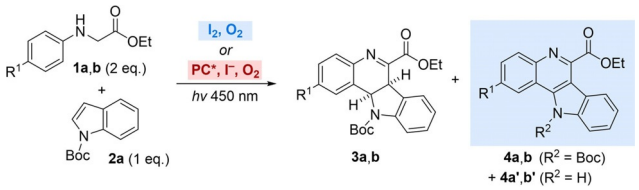
of Eosin Y as an organic photocatalyst for the dehydrogenation of glycine esters in the Brønsted acid mediated cycloaddition with dihydrofuran.[7] A single example of an aerobic photoinduced Cu^{II}-mediated reaction has also been reported.[8]

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 combining an organic photoredox catalyst with a source of halide anion X^- and visible light (Scheme 1 d). 11*H*-Indolo[3,2-*c*]quinoline products were 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]

Results and Discussion

Initially, we observed that reacting *p*-anisidinyl glycine ester **1a** with *N*-Boc-indole (**2a**) (Boc = *tert*-butoxycarbonyl) 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 a 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 (Table 1, 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 because 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′** (Table 1, entries 3–5), and using 50 mol% of I_2 under O_2 atmosphere fully converted indole **2a** within 48 hours, 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, Supporting Information); however, this resulted 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, whereas in the case of *p*-anisidinyl glycine ester **1a**, some product formation was also observed in the dark, which can be attributed to the particular ease of autoxidation of the highly electron-rich substrate **1a**. By comparison, the analogous dark reaction of the much less activated *p*-toluidinyl glycine ester **1b** gave only trace amounts of the corresponding product **4b** (<5%) (Table S1, Supporting Information). 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, whereas 1*H*-indole (**2d**) underwent decomposition to undefined products (entry 6).

Table 1. Reaction optimization.[a]



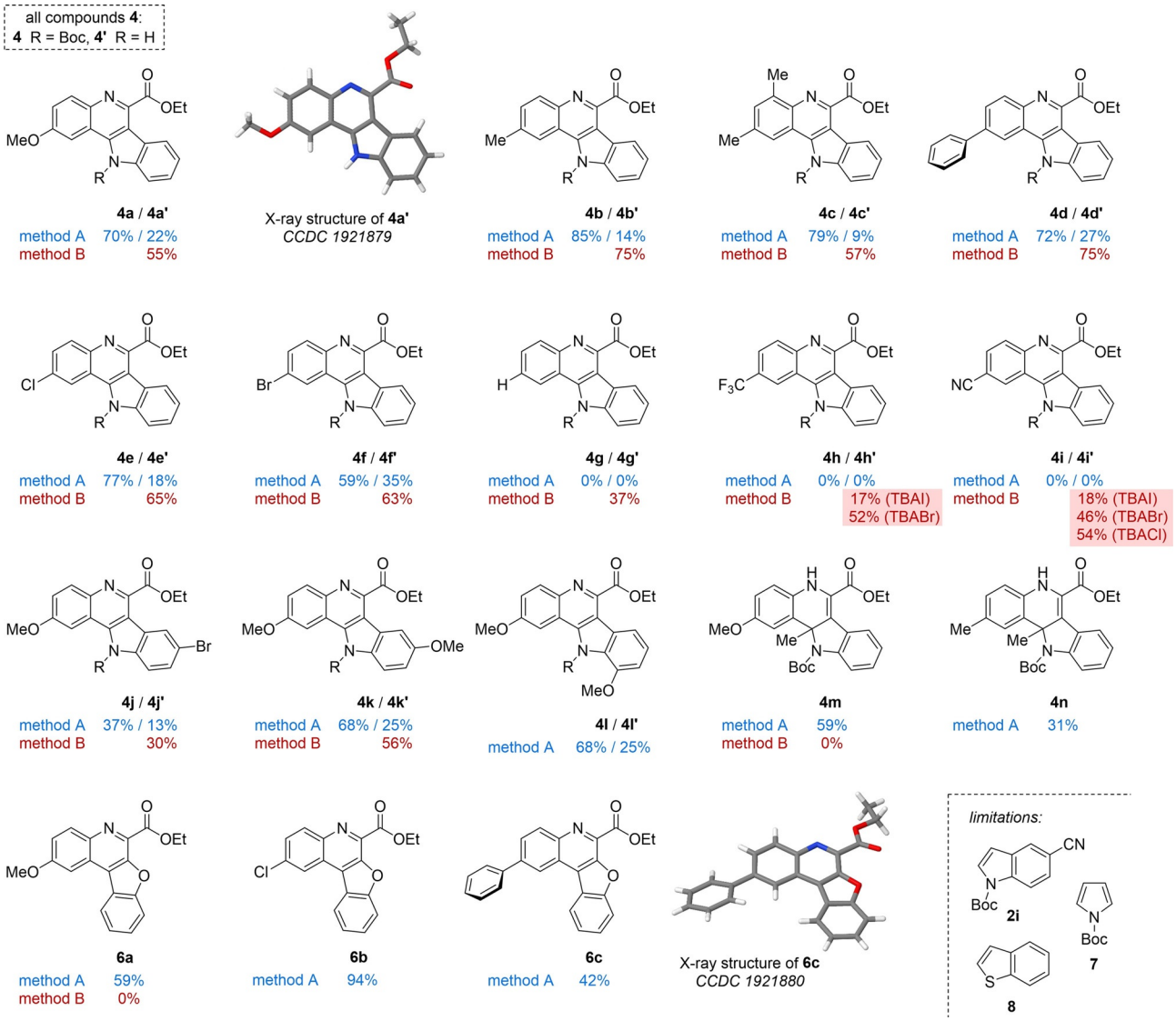
Entry	R^1	Conditions	Conv. **2a** [%][b]	**3** [%][c]	**4**/**4′** [%][c]
method A					
1	OMe	10 mol% I_2, air, MeCN, 48 h	38	0	36:2
2	"	10 mol% I_2, air, MeCN, 48 h, no light	22	12	5:0
3	"	20 mol% I_2, air, MeCN, 48 h	38	8	21:8
4	"	50 mol% I_2, air, MeCN, 48 h	82	8	56:26
5	"	50 mol% I_2, O_2, MeCN, 48 h	100	0	74:26 (**70**[d]:**22**[d])
6	OMe	*N*-tosylindole (**2b**), *N*-acetylindole (**2c**), 1*H*-indole (**2d**)	n.d.[e]	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[d,f])
12	Me	1 mol% TPP·BF_4, 10 mol% TBAI, O_2, HFIP/DCE, 72 h	80	3	20:56 (**75**[d,f])

[a] Reactions performed on 0.10 mmol scale of **2a**, irradiation with 36 W blue compact fluorescent lamp (CFL), $\lambda = (450 \pm 50)$ nm. [b] Conversion determined by ^{1}H NMR spectroscopic analysis. [c] Yield determined by ^{1}H NMR spectroscopy against CH_2Br_2 as internal standard. [d] Yield of isolated products after chromatography. [e] n.d. = not determined. [f] Reaction mixture treated with TFA before isolation. Acr^+-Mes = 9-Mesityl-10-methylacridinium, TPP·BF_4 = triphenylpyrylium tetrafluoroborate.

We subsequently aimed at developing an alternative photo-organocatalytic variant of the reaction (Table 1, method B), which potentially would allow replacement of I_2 by the iodide anion. Although 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 the 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 (Table 1, entry 9). After further experimentation (Table 1, entries 10 and 11 and Table S1, Supporting Information), 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 trifluoroacetic acid (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% was obtained under these conditions; however, in the case of *p*-toluidinyl-substituted **1b**, we demonstrated that despite incomplete conversion of **2a** of 80% (Table 1, 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, Supporting Information).

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. The indolo[3,2-*c*]quinoline products **4a**–**4f** were isolated in high yields of 59–85%, along with minor quantities of their N-deprotected analogues **4a**′–**4f**′ (9–35%), which were readily separated by column chromatography.[13] Using method B, compounds **4a**′–**4f**′ were obtained in 55–75% yield after treatment of the crude product mixtures with TFA. Notably, the *N*-phenyl glycine ester **1g** did not provide the products **4g**,**4g**′ under the conditions of method A (aromatic iodination of the aniline ring occurred), but using method B, derivative **4g**′ was prepared in 37% yield. Further, acceptor-substituted glycine esters like the 4-trifluoromethylphenyl and 4-cyanophenyl derivatives **1h** and **1i** did not react when employed under conditions A. However, by using the photocatalyst TPP•BF_4 with a halide anion, this limitation could be overcome. Thus, product **4h**′ was formed in 17% yield with TPP^+/TBAI, and with a significantly improved yield of 52% with TBABr in place of TBAI. In the case of 4-cyanophenyl glycine ester **1i**, the best result was achieved by using the photocatalyst along with tetrabuty-

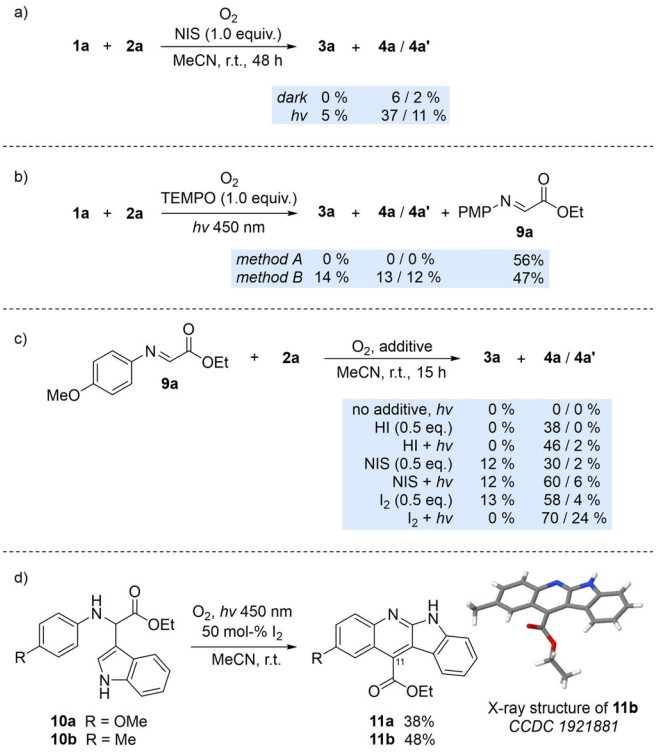


Scheme 2. Reaction scope. Yields after chromatography. Method A: 50 mol% I_2, O_2, *hv* 450 nm, MeCN, RT, 48 h. Method B: 1 mol% TPP•BF_4, 10 mol% TBAI, O_2, *hv* 450 nm, HFIP/DCE, RT, 72 h, then TFA, 50 °C, 6 h.

lammonium chloride (TBACl), to furnish product **4i′** in 54% yield.

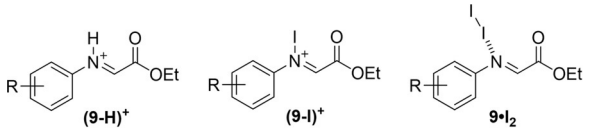
In addition to *N*-Boc-indole (**2a**), *N*-Boc-5-bromoindole (**2e**) as well as the 5- and 7-methoxylated *N*-Boc-indoles **2f** and **2g** were used, giving rise to polysubstituted indoloquinolines **4j**,**4j′**–**4l**,**l′**. Further, 2-methyl-*N*-Boc-indole (**2h**) was successfully employed, leading to the cycloadducts **4m** and **4n** with 59 and 31% yields, respectively, 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 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 form 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, whereas 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 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) (Scheme 3b). Although no cycloaddition occurred, 56% of the imine **9a** was formed, indicating its role as a key intermediate. The same experiment under the conditions of method B also showed radical quenching, even though to a slightly lesser extent (compare with Table 1, entry 11).



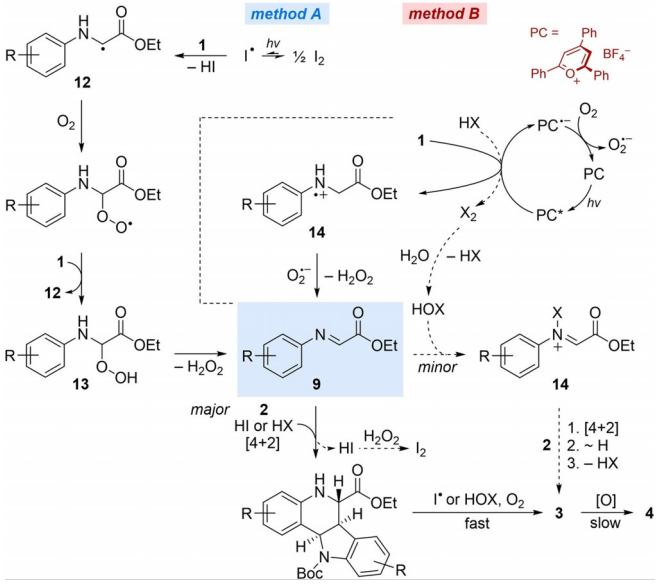
Scheme 3. Mechanistic control experiments.

Imine **9a**, derived from glycine ester **1a** by dehydrogenation, was generally present in all crude reaction mixtures as evident from NMR spectroscopic 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, Supporting Information), we reacted imine **9a** with indole **2a** under various conditions. Although 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), NIS as well as I_2, to find that the cycloaddition occurred in all cases, even in the dark. These results showed that the imine could be activated by 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 did not generate 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]

On the basis of 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] Converse-



Scheme 4. Proposed mechanism.

ly, using TPP^+ and X^- (method B), photoelectron transfer (PET) between the excited-state catalyst ($E^*_{red} = +2.55$ V vs. the standard calomel electrode (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 the 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, Supporting Information), 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*-haloiminium ion **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 the 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**).

Conclusion

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 analogues of the antimalarial natural alkaloid isocryptolepine, and thus they may be of value in medicinal research.

Experimental Section

Typical procedures: synthesis of compounds 4b and 4b′

Method A: In a 10 mL crimp cap vial, *N*-aryl glycine ester **1b** (40.2 mg, 208 μmol) and *N*-Boc-indole (**2a**, 22.6 mg, 104 μmol) were dissolved in MeCN (3.50 mL). I_2 (13.2 mg, 52.0 μmol) was added, and the vial was sealed and fitted with an O_2-balloon (with the septum pierced by a 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 compounds **4b** (35.8 mg, 85%) and **4b′** (4.4 mg, 14%).

Method B: In a 10 mL crimp cap vial, *N*-aryl glycine ester **1b** (44.1 mg, 228 μmol), *N*-Boc-indole (**2a**, 24.8 mg, 114 μmol), TBAI (4.2 mg, 11.0 μmol), and $TPP{\cdot}BF_4$ (0.5 mg, 1.0 μmol) were dissolved in DCE (1.90 mL) and HFIP (1.90 mL). The vial was sealed and fitted with an O_2-balloon (with the septum pierced by a 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%).

Compound 4b: Colorless solid; m.p. 103 °C; $R_f = 0.57$ (Et_2O/heptane 1:1); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.56$ (t, $^3J = 7.2$ Hz, 3H, CH_3), 1.72 (s, 9H, *t*Bu), 2.62 (s, 3H, Ar-CH_3), 4.70 (q, $^3J = 7.2$ Hz, 2H, CH_2), 7.45 (ddd, $^4J = 1.1$ Hz, $^3J = 7.2$, 8.2 Hz, 1H, 8-H), 7.54–7.60 (m, 2H, 3-H, 9-H), 8.07 (s, 1H, 1-H), 8.21 (dt, $^4J = 0.9$ Hz, $^3J = 8.4$ Hz, 1H, 10-H), 8.23 (d, $^3J = 8.6$ Hz, 1H, 4-H), 8.44 ppm (dt, $^4J = 1.0$ Hz, $^3J = 7.9$ Hz, 1H, 7-H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 14.5$ (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 ppm (s, CO_2R); IR: $\tilde{\nu}$ = 2980, 2935 (=C–H, –C–H), 1740 (CO), 1250 (C=C), 1150, 1095, 750 cm^{-1}; HRMS (ESI+): *m/z* calcd $C_{24}H_{24}N_2O_4$ $[M+H]^+$: 405.1809, found: 405.1825.

Compound 4b′: Colorless solid; m.p. 276 °C (dec.); $R_f = 0.57$ (Et_2O/heptane 3:1); ^{1}H NMR (600 MHz, [D$_6$]acetone): $\delta = 1.50$ (t, $^3J = 7.2$ Hz, 3H, CH_3), 2.62 (s, 3H, Ar-CH_3), 4.62 (d, $^3J = 7.1$ Hz, 2H, CH_2), 7.35 (ddd, $^4J = 1.1$ Hz, $^3J = 7.1$, 8.2 Hz, 1H, 8-H), 7.52 (ddd, $^4J =$

1.2 Hz, ^{3}J = 7.1, 8.2 Hz, 1H, 9-H), 7.65 (dd, ^{4}J = 1.9 Hz, ^{3}J = 8.5 Hz, 1H, 3-H), 7.73 (dt, ^{4}J = 1.0 Hz, ^{3}J = 8.2 Hz, 1H, 10-H), 8.12 (d, ^{3}J = 8.5 Hz, 1H, 4-H), 8.30–8.34 (m, 1H, 1-H), 8.53 (dd, ^{4}J = 1.0 Hz, ^{3}J = 8.2 Hz, 1H, 7-H), 11.9 ppm (s, 1H, NH); ^{13}C NMR (150 MHz, [D$_6$]acetone): 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 ppm (s, CO_2R); 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* calcd $C_{19}H_{16}N_2O_2$ $[M+H]^+$: 305.1290, found: 305.1292.

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Conflict of interest

The authors declare no conflict of interest.

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[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. d) For general studies of the reaction mechanism, see: 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. Heterocycl. 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; c) 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, F. Zhuanli Shenqing, CN 103910723 A Jul 09, **2014**.

[9] a) P. T. Parvatkar, S. G. Tilve, *Bioactive heterocycles* (Eds.: K. L. Ameta, R. P. Pawar, A. J. Domb), Nova, New York, **2013**, pp. 217–234; 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; *Angew. Chem.* **2017**, *129*, 8117–8121.

[13] CCDC 1921879, 1921880, and 1921881 (**4a′**, **6c**, and **11b**, respectively) contain the supplementary crystallographic data for this paper. These data are provided free of charge by 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 the 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; *Angew. Chem.* **2018**, *130*, 12843–12847; b) S. Rohe, A. O. Morris, T. McCallum, L. Barriault, *Angew. Chem. Int. Ed.* **2018**, *57*, 15664–15669; *Angew. Chem.* **2018**, *130*, 15890–15895.

[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, *Comprehensive Heterocyclic Chemistry III, Vol. 3* (Eds.: A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. Taylor), Elsevier, Amsterdam, **2008**, pp. 407–496; 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, *Eur. Polym. J.* **2005**, *41*, 1654–1661.

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